
## Agenda

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|---|---|
| **9:00 AM PDT** | **Introduction**<br>*Eunjoo Pacifici, PharmD, PhD*<br>USC, SC-CTSI, School of Pharmacy I Chair & Associate Professor, Dept. of Reg. & Quality Sciences<br>Associate Director, DK Kim International Center for Regulatory Science |
| **9:15 AM PDT** | **Genomics and Regulation**<br>*Nancy Pire-Smerkanich, DRSc*<br>USC, SC-CTSI, School of Pharmacy I Assistant Professor, Dept. of Reg. & Quality Sciences |
| **10:00 AM PDT** | **Novel Regulatory Science Paradigms Based on Data and Analytics**<br>*Klaus A. Romero Cepeda, MD, MS, FCP*<br>C-Path Institute I Chief Science Officer & Executive Director, Clinical Pharmacology and Quantitative Medicine |
| **11:00 AM PDT** | **Break** |
| **11:15 AM PDT** | **Pharmacogenomics**<br>*Scott Mosley, PharmD*<br>USC, School of Pharmacy I Assistant Professor of Titus Department of Clinical Pharmacy |
| **12:15 AM PDT** | **Lunch** |
| **1:15 PM PDT** | **Big Data and Genomics**<br>*Jerry SH Lee, PhD*<br>USC, Keck School of Medicine & Viterbi School of Engineering I Associate Professor<br>USC, Lawrence J. Ellison Institute for Transformative Medicine I Chief Science and Innovation Officer |
| **2:15 PM PDT** | **Applied Genomics and Target Identification**<br>*Robert Pacifici, PhD*<br>CHDI Foundation I Chief Scientific Officer |
| **3:15 PM PDT** | **Break** |
| **3:30 PM PDT** | **Panel Discussion** |
| **4:00 PM PDT** | **Wrap-Up**<br>*Eunjoo Pacifici, PharmD, PhD*<br>USC, SC-CTSI, School of Pharmacy I Chair & Associate Professor, Dept. of Reg. & Quality Sciences<br>Associate Director, DK Kim International Center for Regulatory Science |

# Regulatory Science Symposium:

## *Innovation to Translation: Role of Genomics in Medical Product Development*

# Speaker Bios

**Eunjoo Pacifici, PharmD, PhD**, is the Chair and Associate Professor of Regulatory and Quality Sciences and Associate Director of the International Center for Regulatory Science at USC. Dr. Pacifici received a BS in Biochemistry from the University of California Los Angeles followed by a PharmD and PhD in Toxicology from USC. She conducted her graduate research in the laboratory of Dr. Alex Sevanian in the Institute for Toxicology where she studied the mechanism of oxidative damage and repair in endothelial cell membrane. Before returning to USC as faculty, Dr. Pacifici worked at Amgen and gained experience in conducting clinical research with a special focus on the Asia Pacific and Latin America regions. She initially worked in the clinical development group managing U.S. investigational sites and central laboratories and then went on to work in the Asia Pacific / Latin America group interfacing with local clinical and regulatory staff in Japan, the People's Republic of China, Taiwan, and Mexico. She represented regional clinical and regulatory views on therapeutic product development teams and led satellite task forces in order to align local efforts with U.S. activities. Her additional professional experiences include community pharmacy practice in various settings and clinical pharmacy practice at the Hospital of the Good Samaritan in Los Angeles. Her current focus is on developing the next generation of regulatory scientists and pharmacy professionals with the knowledge, tools, and skills to expedite the development of innovative, safe, and effective biomedical products. epacific@usc.edu

**Nancy Smerkanich, DRSc**, **MS,** is an Assistant Professor in the Department of Regulatory and Quality Sciences, School of Pharmacy at USC. Dr. Smerkanich holds a Doctorate and master's degree in Regulatory Science from USC and a Bachelor of Science Degree in Microbiology and a Bachelor of Arts in Russian from the University of Connecticut. Dr. Smerkanich received her faculty appointment after successfully completing her Doctoral Dissertation on "Benefits Risk Frameworks – Implementation in Industry" in 2015. In addition to teaching courses related to drug development and clinical trials, she provides regulatory guidance to industry peers. Nancy brings many years of practical regulatory knowledge and experience to academia where she participated in all regulatory aspects of product development, having served as Regulatory Liaison, US Agent, and Global Regulatory Lead across varied therapeutic areas. Known for her dedication to education and mentoring across industry, Nancy continues to be recognized for her ability to provide accurate, relevant and dynamic instruction on both the technical and strategic aspects of global regulatory affairs and for her service to professional organizations such as the Drug Information Association (DIA) and The Organization for Professionals in Regulatory Affairs (TOPRA). piresmer@usc.edu

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International Center for Regulatory Science

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**Klaus Romero, MD, MS, FCP,** is a Chief Science Officer and Executive Director of Clinical Pharmacology and Quantitative Medicine at the Critical Path Institute. Dr. Romero, a clinical pharmacologist and epidemiologist with more than 17 years of experience in academic and pharmaceutical clinical research, translational sciences, pharmacometrics, modeling and simulation and pharmacoepidemiology, has been with C-Path since December 2007 where he has helped lead clinical pharmacology, pharmacoepidemiology and modeling and simulation projects in Alzheimer's disease, polycystic kidney disease (PKD), tuberculosis, type 1 diabetes, Parkinson's disease, Duchenne muscular dystrophy, kidney transplantation, Huntington's disease, and cardiovascular drug safety. His work has helped to achieve major milestones, including the first regulatory endorsement by the U.S. Food and Drug Administration and European Medicines Agency of a clinical trial simulation tool for mild and moderate Alzheimer's disease and the regulatory qualification of the first imaging biomarker for PKD. Dr. Romero is a fellow of the American College of Clinical Pharmacology, a founding member of the International Society of Pharmacometrics, as well as a member of the American Society for Clinical Pharmacology and Therapeutics, and the International Society for Pharmacoepidemiology. Dr. Romero is also a Research Associate Professor at the University of Arizona College of Medicine, Adjunct Professor at the College of Health Solutions at Arizona State University, Adjunct Professor at the USC School of Pharmacy and serves on the Scientific Board of Pharos Dx. Dr. Romero received his medical degree from Pontifical Xavierian University, completed his training in Clinical Pharmacology at Columbia National University and holds an MS degree in Epidemiology from the Columbia School of Medicine. kromero@c-path.org

**Scott Mosley, PharmD,** is an Assistant Professor in the Titus Department of Clinical Pharmacy, School of Pharmacy at USC. His research is focused on pharmacogenomics implementation, which incorporates genetic information with other clinical factors to optimize drug selection. Dr. Mosley received a B.S. in Biochemical/Biophysical Science from the University of Houston in 2006, then worked as an analytical chemist in a core pharmacology lab for MD Anderson Cancer Center in Houston, TX. He received his PharmD degree from the University of Texas in 2013, and then took a position as a pharmacist with MD Anderson Cancer Center. Dr. Mosley completed a postdoctoral research fellowship at the University of Florida College of Pharmacy in the Center for Pharmacogenomics during which he carried out a research protocol to assess the value of utilizing CYP2D6 genotype to guide opioid selection for patients with cancer pain. samosley@usc.edu

**Jerry S.H. Lee, PhD** is the Chief Science and Innovation Officer for the Lawrence J. Ellison Institute for Transformative Medicine and Associate Professor of Clinical Medicine and Chemical Engineering & Material Sciences at the USC. Prior to USC, Dr. Lee served as a Health Sciences Director within the National Cancer Institute's Office of the Director. Through direct support and use of public-public/public-private partnerships, he deployed programs focused on the integration of advanced technologies, trans-disciplinary approaches, infrastructures, and standards, to accelerate the creation of publicly available, broadly accessible, multi-dimensional data, knowledge, and tools to empower the entire cancer research continuum for patient benefit. In 2016, Dr. Lee was assigned to Office of the Vice President to serve as the Director for Cancer Research and Technology for the White House Cancer Moonshot Task Force. A few key efforts he helped coordinate include the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network, international collaborations to share molecular characterization datasets, the Blood Profiling Atlas in Cancer pilot, as well as co-chairing an interagency group focused on cancer data and technology policy issues. Dr. Lee's research involves elucidating the interplay between biophysical and biochemical drivers of age-related diseases. He is a member of the Department of Veterans Affairs' National Research Advisory Council, the National Academies Board on Science, Technology, and Economic Policy's Innovation Policy Forum, and the Health and Environmental Sciences Institute's Board of Trustees. Dr. Lee earned his BS in biomedical engineering and PhD in chemical and biomolecular engineering from Johns Hopkins University. dr.jerry@usc.edu

**Robert Pacifici, PhD,** is Chief Scientific Officer of CHDI Foundation, a private, not-for-profit research organization working to accelerate therapeutics development for Huntington's disease. Dr. Pacifici has served as Site Director and Chief Scientific Officer at the Research Triangle Park Laboratories of Eli Lilly where he oversaw the company's global screening and quantitative-biology efforts, and Vice President of Discovery Technologies at Xencor, a privately held biotechnology company that applied rational design principles to the development of protein therapeutics. At Amgen for nearly ten years, he held positions of increasing leadership for their automation, high throughput screening, and information technologies groups. Dr. Pacifici participates in several external boards and advisory committees including: an adjunct appointment at the USC Department of Molecular Pharmacology and Toxicology; Council member for National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) from 2011 to 2014; and Panel of Experts for National Center for Advancing Translational Sciences at NIH. Dr. Pacifici previously served as Chair of the NIH/NINDS Spinal Muscular Atrophy Project's Scientific Steering Committee; Advisor to the Marigold Foundation for Myotonic Dystrophy, the Cooperative International Neuromuscular Group (CINRG), and the Center for Genetic Medicine Research at the Children's National Medical Center (CNMC); and Member of the Science Advisory Board for Edison Pharmaceuticals, the TREAT ALS Steering Committee; the Pathogenesis of Facioscapulohumeral Muscular Dystrophy advisory board, the Spinal Muscular Atrophy Foundation Scientific Advisory Board; and the DART Rx Scientific Advisory Board. He received a BS in Biochemistry from the University of Massachusetts, Amherst, and a PhD in Biochemistry from USC. robert.pacifici@chdifoundation.org

## Regulatory Science Symposium

# Innovation to Translation: Role of Genomics in Medical Product Development

## Introduction

**Eunjoo Pacifici, PharmD, PhD**
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

# SC CTSI Clinical Research Support (CRS)

**Lily Jara, BS**
Clinical Research Supervisor, COVID-19 Biorepository Project Manager, CRS

**Contact Information:**
crs@sc-ctsi.org

**A single stop for accessing all services an investigator and research team needs to develop, activate, conduct, and report results for human subject research studies**

**Initial focus on investigator-initiated trials (non-cancer)**

- **Services:**
  - **Clinical research coordinators for hire**
  - **Research navigation**
  - **Recruitment support**
  - **Budget preparation support**
- **Clinical Trials Unit (CTU):**
  - **Skilled research and nursing staff**
  - **Services to support highly-complex human subjects research studies**
  - **Specimen processing lab**
- **Voucher program:**
  - **Awards up to $3,000 to generate new data for development of clinical and/or community research projects**

**https://sc-ctsi.org/about/groups/clinical-research-support**

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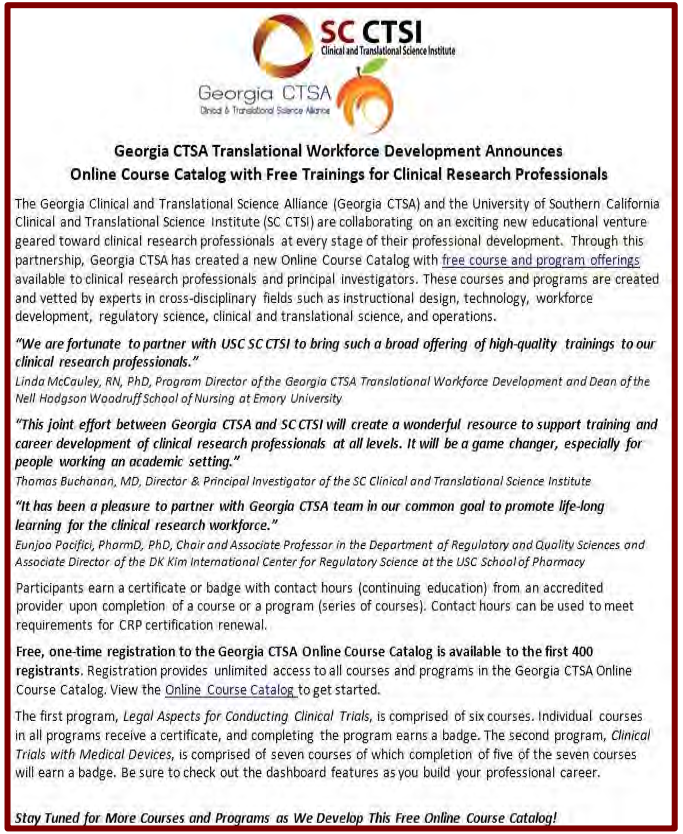
# Clinical Trial Quality Training Series


1. Go to: *https://uscregsci.remote-learner.net*
2. Click ***create new account*** (right-hand side)
3. Type in your information and click ***Create my new account*** (bottom of page)
4. Open your email and click the link to confirm your account
5. Click ***courses*** (middle of page)
6. Scroll down and click the desired module
7. Click ***Enroll me*** (middle of page)

# Georgia CTSA and SC CTSI: Online Course Catalog

- Free trainings for clinical research workforce
- Free, one-time registration to the first 400 registrants
- Registration provides unlimited access to all courses and programs in the Online Course Catalog
- Participants earn a certificate or badge with contact hours upon completion of a course or program
- Contact hours can be used for CRP certification renewal
- To get started: **https://twd.ce.emorynursingexperience.com/**



SC CTSI Clinical and Translational Science Institute

Georgia CTSA Clinical & Translational Science Alliance

**Georgia CTSA Translational Workforce Development Announces Online Course Catalog with Free Trainings for Clinical Research Professionals**

The Georgia Clinical and Translational Science Alliance (Georgia CTSA) and the University of Southern California Clinical and Translational Science Institute (SC CTSI) are collaborating on an exciting new educational venture geared toward clinical research professionals at every stage of their professional development. Through this partnership, Georgia CTSA has created a new Online Course Catalog with free course and program offerings available to clinical research professionals and principal investigators. These courses and programs are created and vetted by experts in cross-disciplinary fields such as instructional design, technology, workforce development, regulatory science, clinical and translational science, and operations.

***"We are fortunate to partner with USC SC CTSI to bring such a broad offering of high-quality trainings to our clinical research professionals."***
*Linda McCauley, RN, PhD, Program Director of the Georgia CTSA Translational Workforce Development and Dean of the Nell Hodgson Woodruff School of Nursing at Emory University*

***"This joint effort between Georgia CTSA and SC CTSI will create a wonderful resource to support training and career development of clinical research professionals at all levels. It will be a game changer, especially for people working an academic setting."***
*Thomas Buchanan, MD, Director & Principal Investigator of the SC Clinical and Translational Science Institute*

***"It has been a pleasure to partner with Georgia CTSA team in our common goal to promote life-long learning for the clinical research workforce."***
*Eunjoo Pacifici, PharmD, PhD, Chair and Associate Professor in the Department of Regulatory and Quality Sciences and Associate Director of the DK Kim International Center for Regulatory Science at the USC School of Pharmacy*

Participants earn a certificate or badge with contact hours (continuing education) from an accredited provider upon completion of a course or a program (series of courses). Contact hours can be used to meet requirements for CRP certification renewal.

**Free, one-time registration to the Georgia CTSA Online Course Catalog is available to the first 400 registrants.** Registration provides unlimited access to all courses and programs in the Georgia CTSA Online Course Catalog. View the Online Course Catalog to get started.

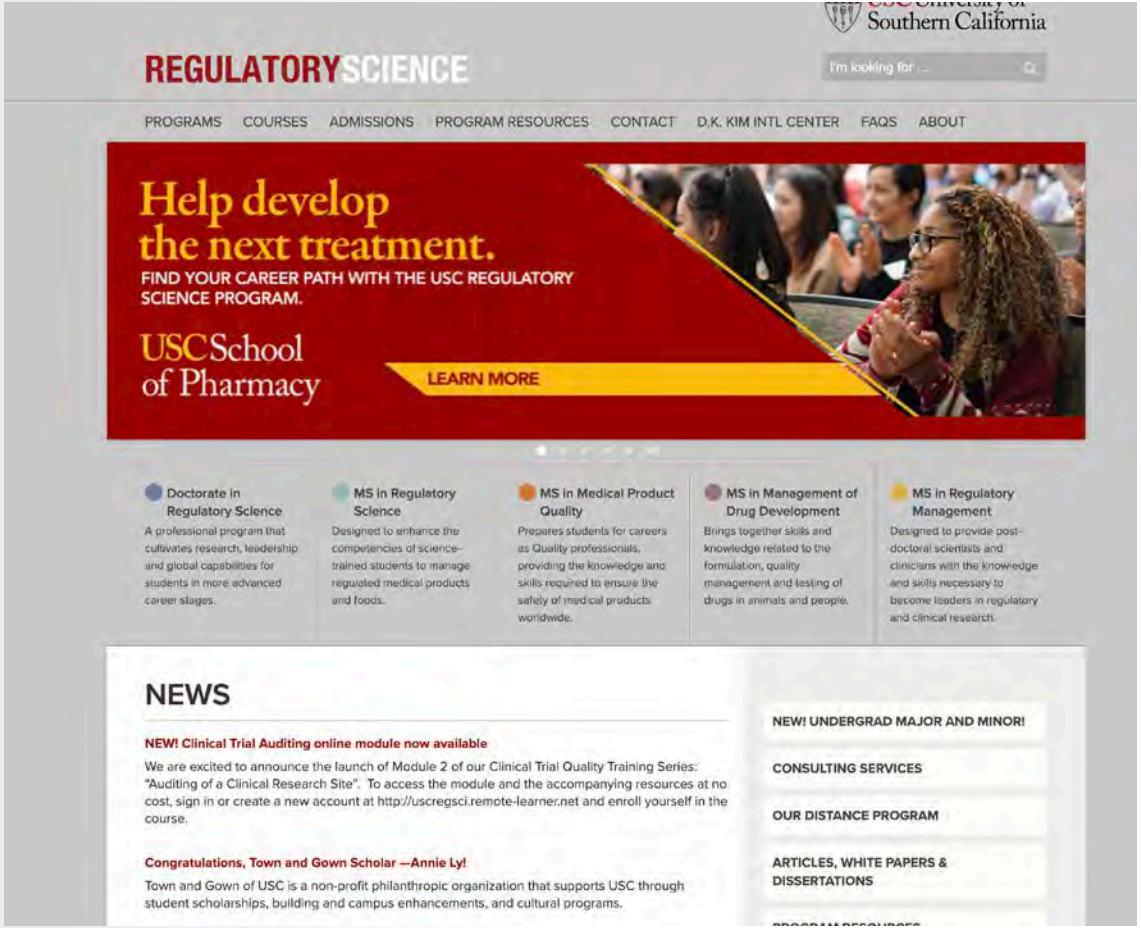
The first program, *Legal Aspects for Conducting Clinical Trials*, is comprised of six courses. Individual courses in all programs receive a certificate, and completing the program earns a badge. The second program, *Clinical Trials with Medical Devices*, is comprised of seven courses of which completion of five of the seven courses will earn a badge. Be sure to check out the dashboard features as you build your professional career.

***Stay Tuned for More Courses and Programs as We Develop This Free Online Course Catalog!***

USC School of Pharmacy
DK Kim International Center for Regulatory Science

SC CTSI

# Find us on our website: https://regulatory.usc.edu/






SC CTSI

# Degree Programs

## Five Graduate Streams

- DRSC
- **MS Regulatory Science**
- MS Regulatory Management
- MS Management of Drug Development
- MS Medical Product Quality

## Certificates

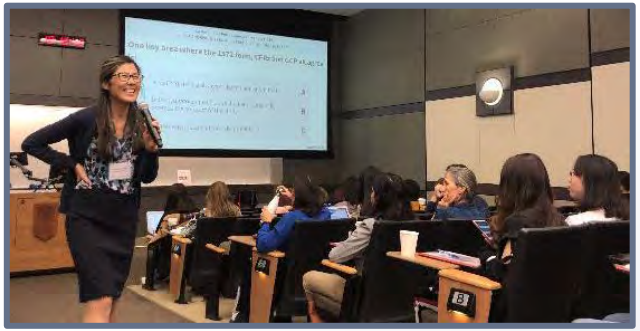
- Food safety
- Regulatory Science
- Early Drug Development
- **Clinical Design and Management**
- Patient and Product Safety

**Nancy Smerkanich DRSc, MS**

Assistant Professor
Department of Regulatory and Quality Sciences

piresmer@usc.edu

# Symposiums



- **2015 -** Clinical Trial Hurdles
- **2016 Spring** - Clinical Trial Startup
- **2016 Fall** - Monitoring and Auditing
- **2017 Spring** - Clinical Trials in Special Populations
- **2017 Fall** - Clinical Trials in Era of Emerging Technologies and Treatments
- **2018 Spring** - Regulatory Aspects of Clinical Trial Design
- **2018 Fall** - Pharmacovigilance and Safety Reporting
- **2019 Spring** - Patient-Centered Drug Development and Real World Evidence/Data
- **2019 Summer** - Clinical Trials with Medical Devices
- **2019 Fall** - Legal Aspects of Conducting Clinical Trials
- **2020 Spring** - Quality by Design in Clinical Trials
- **2020 Fall –** Diversity in Clinical Trials in the Time of COVID-19
- **2021 Spring** – Clinical Research Career Pathways (half-day)
- **2021 Spring** – Principles of Global Clinical Research for Medical Devices
- **2021 Fall** – Innovation to Translation: Role of Genomics in Medical Product Development
- **2022 Spring** - TBD

Symposium recordings are easily accessible for viewing on the SC CTSI's online educational library *https://sc-ctsi.org/training-education/courses?audience=researchProfessionals*


USC School of Pharmacy
Department of Regulatory and Quality Sciences
SC CTSI
Regulatory Science Symposium
Innovation to Translation:
Role of Genomics in Medical
Product Development
FRIDAY, SEPT. 24, 2021
9AM - 4PM PDT
HOSTED ONLINE VIA ZOOM

# Agenda

| | |
|---|---|
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Presented by the USC School of Pharmacy International Center for Regulatory Science and the Southern California Clinical and Translational Science Institute

*This certifies that*

Before the end of today's symposium, you will receive a link to take the program evaluation.

**Follow this link to the Survey:**
Take the Survey

Please complete the program evaluation to receive a certificate of completion by Friday, October 8, 2021.

Eunjoo Pacifici, PharmD, PhD
Director
International Center for Regulatory Science

Thomas A. Buchanan, MD
Director
Southern California Clinical and Translational Science Institute

USC School of Pharmacy
*DK Kim International Center for Regulatory Science*

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# Thank You!


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Twitter: @SoCalCTSI

USC School of Pharmacy
*DK Kim International Center for Regulatory Science*

regulatory.usc.edu
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Email: regsci@usc.edu
Facebook: @RegSci

# Genomics and Regulation

Nancy Pire-Smerkanich, DRSc, MS

USC School of Pharmacy
Department of Regulatory and Quality Sciences
SC CTSI

# Agenda

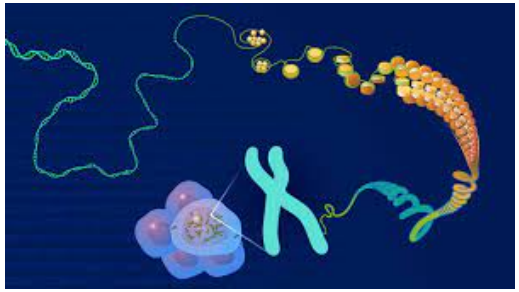
1. Regulations for the tests that are performed

2. Regulations for the products developed based on testing/biomarkers

# Definitions

## Genomics

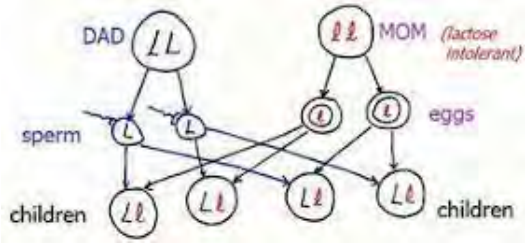
The branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes (Oxford Dictionary)



## Personalized or <u>Precision Medicine</u>

Practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease (NIH)

# Definitions




**Genotype:**
**What makes you – you!**

**Genomic Biomarker:**
A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.

**Pharmacogenomics(PGx):**
The study of how an individual's entire genetic makeup determines the body's response to drugs.

**Pharmacogenetics(PGt):**
The study of how sequence variation within specific candidate genes affects an individual's drug responses.

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Department of Regulatory and Quality Sciences

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# The Testing We Will Be Talking About

In vitro diagnostic (IVD) products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3]

# Regulatory Authority

IVDs are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to section 351 of the Public Health Service Act.

- Like other medical devices, IVDs are subject to premarket and post-market controls.
- IVDs are generally also subject to categorization under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88)

# Genetic Testing

## Different Types of IVD Testing

- In vitro diagnostics (IVDs) that are marketed directly to consumers without the involvement of a health care provider are called direct-to-consumer tests (also referred to as DTC).
- These tests generally require the consumer collect a specimen, such as saliva or urine, and send it to the company for testing and analysis.
- Direct-to-consumer testing is expanding the number of people who are able to get genetic testing of their DNA (or genome)

  (Example: 23andMe)

# Genetic Testing
# DCT Testing

- Direct-to-consumer tests have varying levels of evidence that support their claims.
  - Some direct-to-consumer tests have a lot of scientific and clinical data to support the information they are providing, while other tests do not have as much supporting data
- Some DCTs are reviewed by the FDA while others are not.
  - DCTs tests for non-medical, general wellness, or low risk medical purposes are not reviewed by the FDA before they are offered.
  - DCTs for moderate to high risk medical purposes are (generally) reviewed by the FDA to determine the validity of test claims

# DCT Genetic Testing

## FDA Review is based on…

- Whether a test can accurately and reliably measure what it claims to measure (analytical validity);
- Whether the measurement is predictive of a certain state of health (clinical validity); and
- What a company says about their test and how well it works (claims)

# Regulatory Pathway(s)

## Some specific/relevant examples:

1. Carrier Screening Tests (21 CFR 866.5940):
   - These tests can be used to determine whether a healthy person carries a genetic variant that could be passed on to their potential future child(ren)
   - Carrier screening tests are exempt from FDA premarket review, but they do need to follow specific requirements that are described in the regulation for this type of test.

2. Genetic Health Risk (GHR) Tests (21 CFR 866.5950):
   - GHR tests are intended to provide information on an individual's genetic risk for certain medical diseases or conditions
   - Companies that offer DTC GHR tests are required to obtain FDA clearance prior to offering their first test

# Regulatory Pathway(s)

## Some specific/relevant examples:

3. Cancer Predisposition Tests (CFR 21 866.6090):
   - These tests provide information about an individual's risk of getting certain types of cancer
   - These tests are considered moderate to high risk and are required to come to FDA for premarket review and clearance

4. Pharmacogenetics Tests (21 CFR 862.3364):
   - Pharmacogenetics tests provide information regarding the role genetics may play in an individual's reaction to drug
   - Companies that offer DTC pharmacogenetic tests are required to come to FDA for premarket review and clearance.
   - Currently the FDA has not authorized any DTC pharmacogenetic tests that predict whether an individual is likely to respond to or have adverse reactions from any specific therapeutic drug.

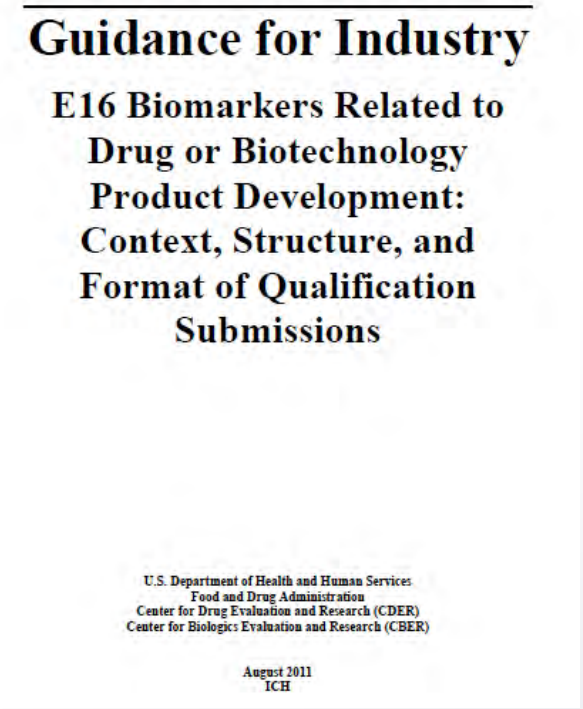
# Proprietary/Specialized Genetic Testing - Biomarkers

A biomarker is something that can be objectively measured and is a sign of a normal or abnormal process, or a condition or disease.

- A biomarker can be a molecule found in the blood or other body fluids or tissues.
- A biomarker is a genetic signature or "fingerprint"—a pattern of activity in a set of genes that reveals some biological condition

*"The development of biomarkers can benefit the availability of new medical therapies by helping translate scientific discoveries into clinical applications."*

# Guidance for Biomarkers (US)



**Guidance for Industry**

**E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions**

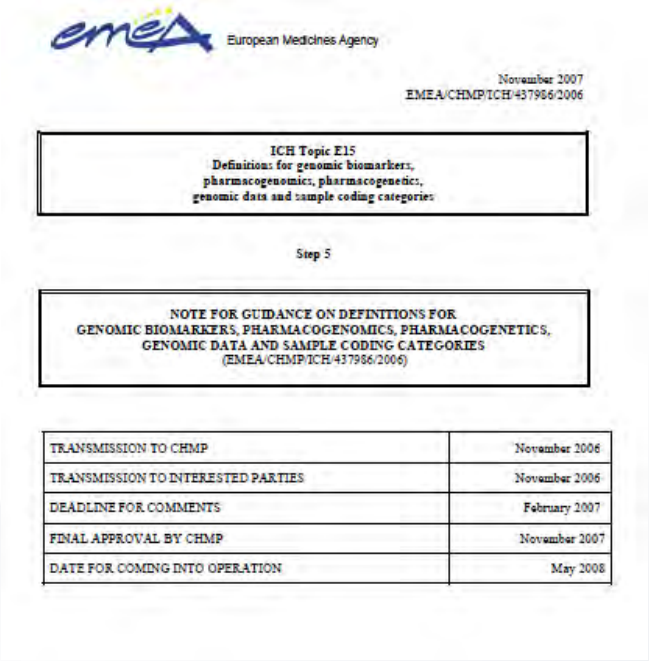
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
ICH

FDA E16 (2011)

- Describes recommendations re: Context (of use),
- structure and format of regulatory submission for qualification (Ref: ICH E15)
- Notes that “qualification” is a conclusion

# Guidance for Biomarkers/PGx and PGt Data (EU)



European Medicines Agency

November 2007
EMEA/CHMP/ICH/437986/2006

**ICH Topic E15**
**Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories**

Step 5

**NOTE FOR GUIDANCE ON DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES**
(EMEA/CHMP/ICH/437986/2006)

| | |
|---|---|
| TRANSMISSION TO CHMP | November 2006 |
| TRANSMISSION TO INTERESTED PARTIES | November 2006 |
| DEADLINE FOR COMMENTS | February 2007 |
| FINAL APPROVAL BY CHMP | November 2007 |
| DATE FOR COMING INTO OPERATION | May 2008 |

ICH Topic E15[EMEA 2007]:

- Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories
- Provides a harmonized definition for the coding of these samples and their associated data will facilitate use in research and development of new medicines.

## ICH E15 reflects EU Priority re: Confidentiality and Privacy

There are four general categories of coding:

- identified,
- coded,
- anonymized
- anonymous

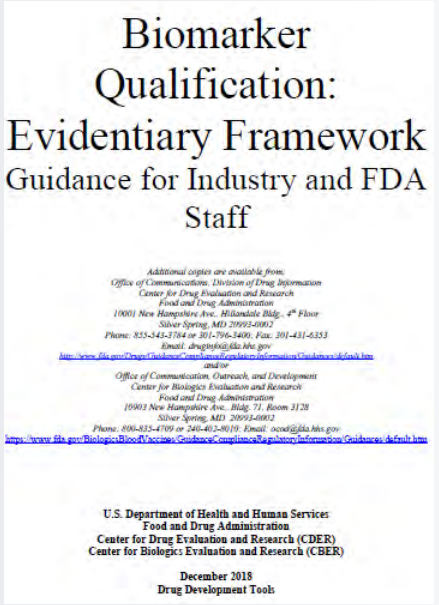
Coded data or samples can be single or double coded

**Table 1: Summary of Genomic Data and Sample Coding Categories**

| Sample Coding Category | | LINK BETWEEN SUBJECT'S PERSONAL IDENTIFIERS AND GENOMIC BIOMARKER DATA | Traceability Back to the Subject (Actions possible, including e.g. sample withdrawal or return of individual genomic results at subject's request) | Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data | Extent of Subject's Confidentiality and Privacy Protection |
|---|---|---|---|---|---|
| *Identified* | | Yes (direct)<br>Allows for subjects to be identified | Yes | Yes | Similar to general healthcare confidentiality and privacy |
| *Coded* | *Single* | Yes (indirectly)<br>Allows for subjects to be identified (via single, specific coding key) | Yes | Yes | Standard for clinical research |
| | *Double* | Yes (very indirectly)<br>Allows for subjects to be identified (via the two specific coding keys) | Yes | Yes | Added privacy and confidentiality protection over single code |
| *Anonymised* | | No<br>Does not allow for subjects to be re-identified as coding key(s) have been deleted | No | No | Genomic data and samples no longer linked to subject as coding key(s) have been deleted |
| *Anonymous* | | No<br>Identifiers never collected and coding keys never applied<br><br>Does not allow for subjects to be identified | No | No | Genomic data and samples never linked to subject |

# Biomarker Development

There is guidance and a program for this!



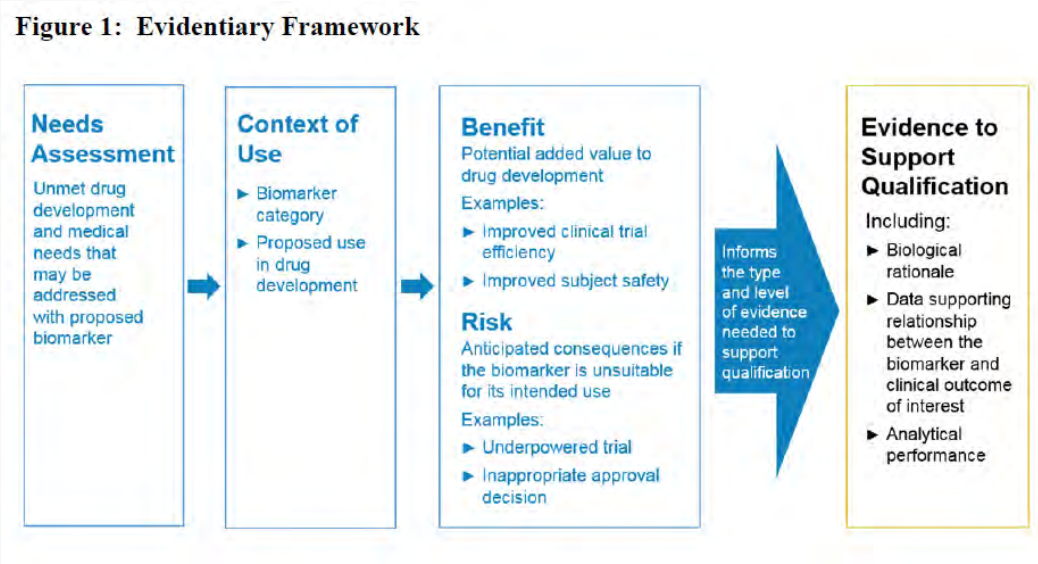
Biomarker Qualification: Evidentiary Framework

Guidance for Industry and FDA Staff

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2018
Drug Development Tools

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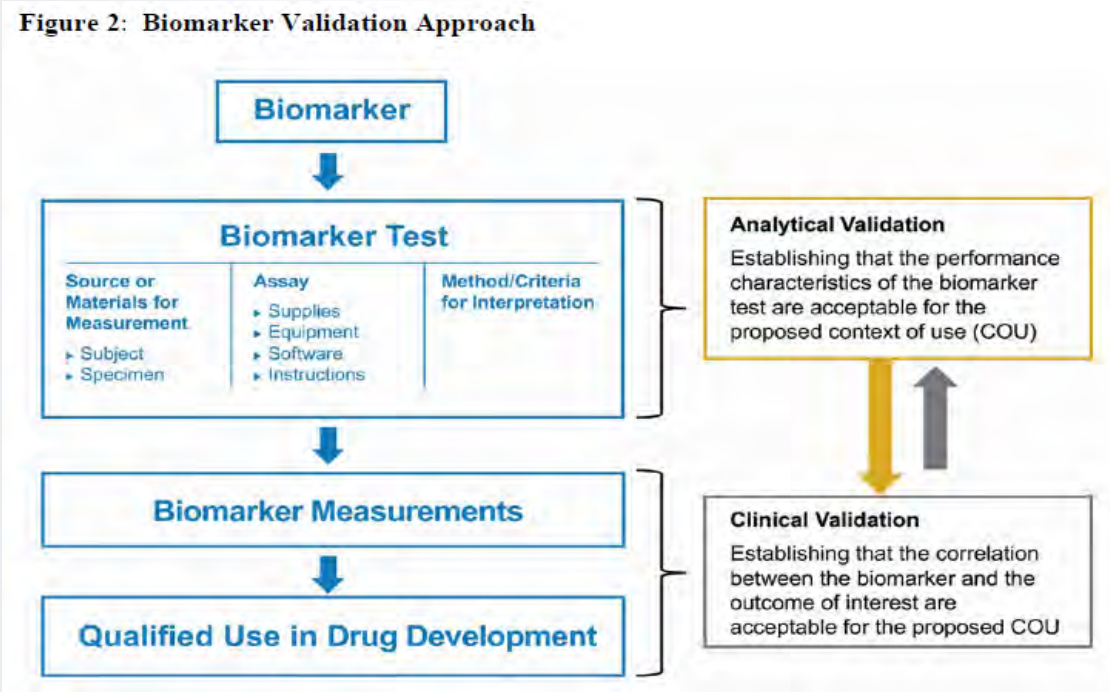
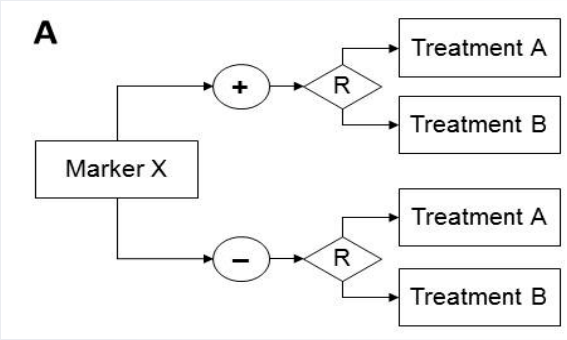
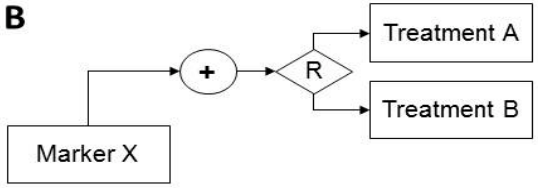
# Biomarker Development

**Figure 2: Biomarker Validation Approach**



# Biomarkers based CT designs




+ Obtain information from all subjects
+ Assess predictive vs. prognostic
+ May include futility analysis
+ May stack enrollment toward biomarker positive (e.g., 80/20)
+ Large trial

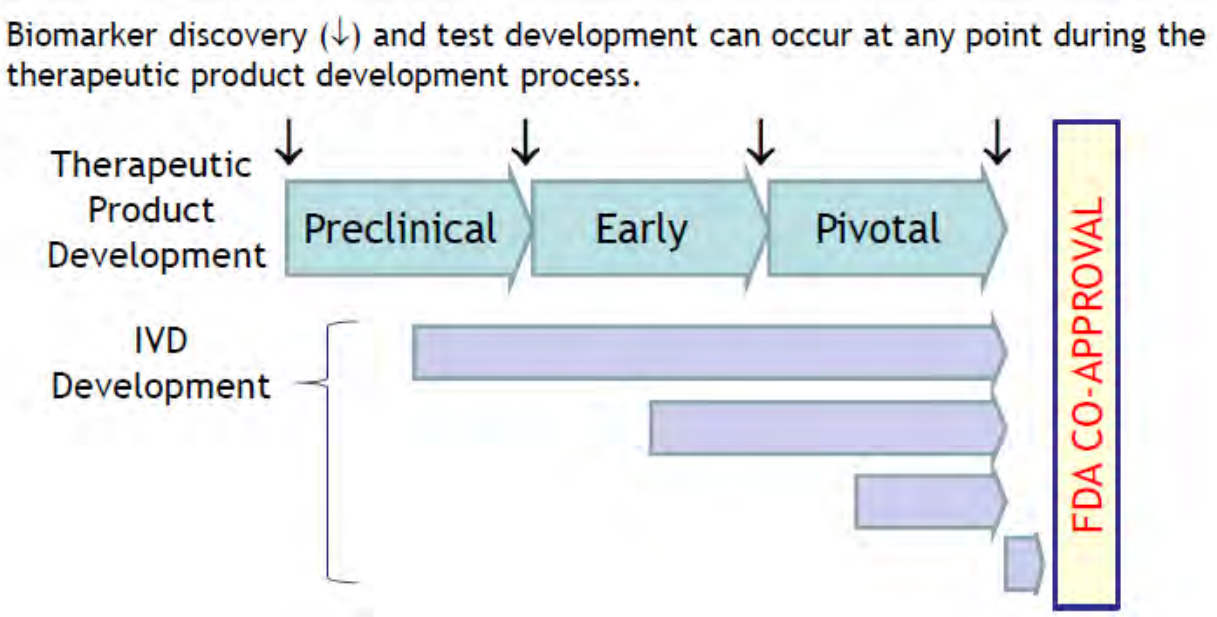
+ More efficient (if biomarker is predictive or prognostic)
+ Potentially exposes fewer patients to ineffective therapy
+ May hinder enrollment
+ No information about marker-negative

# Biomarkers v. Companion Diagnostics

How are companion diagnostic tests different from biomarkers?

- A companion diagnostic test is essentially a biomarker test that enables better decision making on the use of a therapy.
- It is a diagnostic test that is specifically linked to a therapeutic drug

# Biomarkers as CoDx



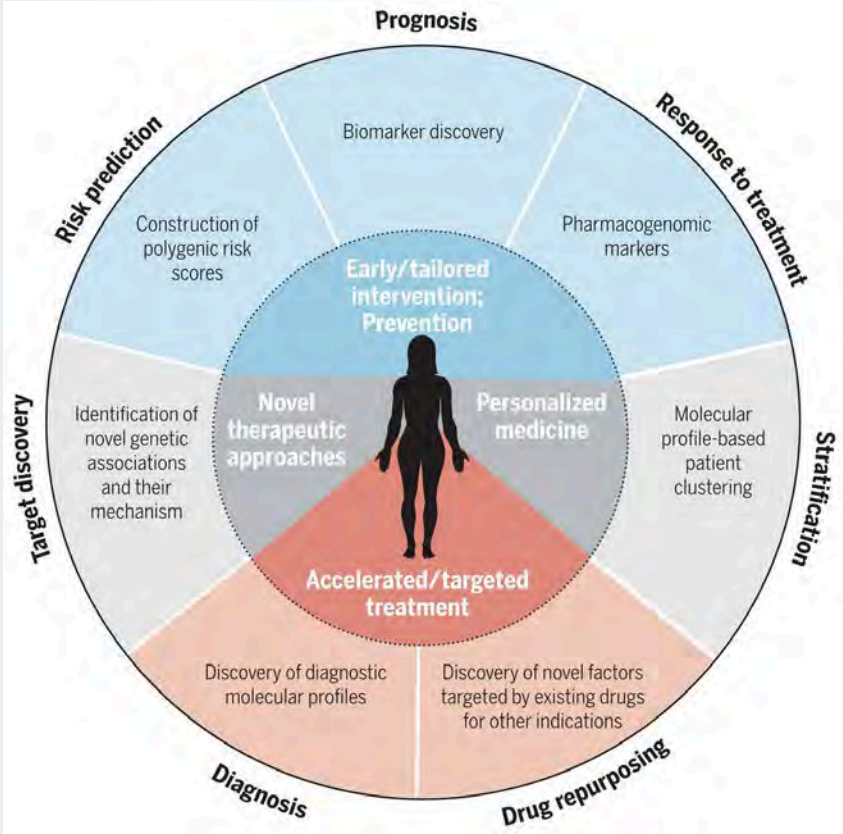
# In Vitro/Companion Diagnostics

- The FDA issued final guidance "In Vitro Companion Diagnostic Devices" Aug. 2014
- Defined companion diagnostic (CoDx) as IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product
- Described CoDx uses:
  - Identify population most likely to benefit or most at risk of adverse reaction.
  - Monitor response to adjust treatment.
  - Identify population for whom product is known to be safe and effective.
- Clarified that, in general, the FDA expects contemporaneous regulatory approvals of the CoDx and therapeutic product
- Described other regulatory requirements (labeling, etc.)

# Companion Diagnostics

- When a clinical trial is properly designed to establish the safety and effectiveness of a therapeutic product in a population based on measurement or detection of a (bio)marker, the results of the clinical trial can also be used to establish the clinical validity of the IVD companion diagnostic
- Considerations:
  - Mechanistic rationale for selecting the marker
  - The nature of the disease
  - Level of characterization in the test-negative population
  - Prospective-retrospective analyses

# The translational potential of complex disease genomics
## REF: Zeggini et al. Science 27Sept2019

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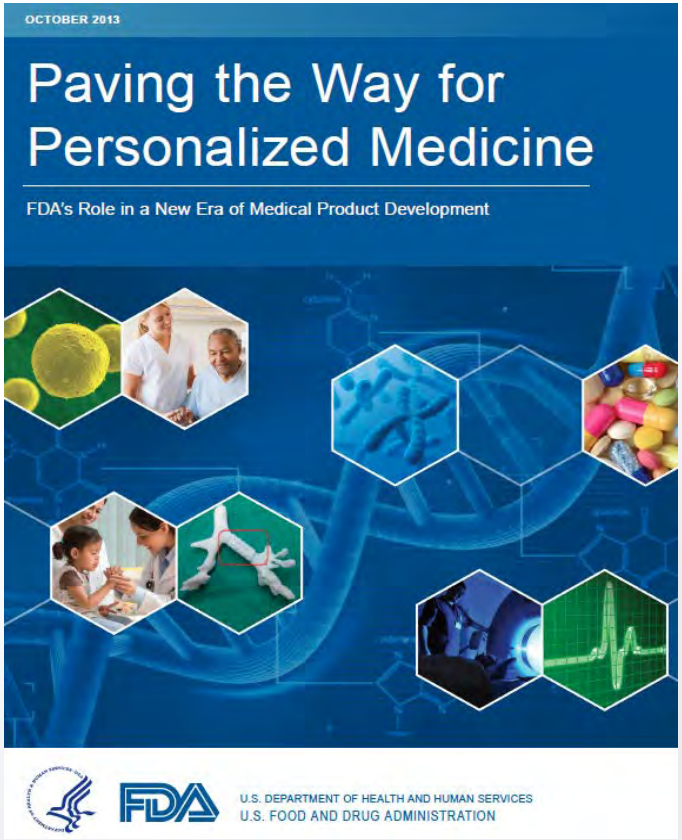
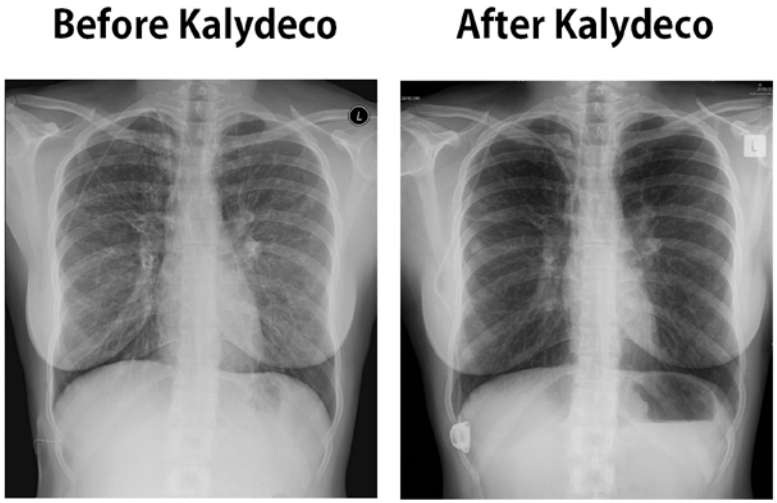
FDA Report from 2013 describes the (still) evolving regulatory processes in response to scientific developments that are critical for the development of personalized therapeutics and diagnostics and how to bridge developments in genomics and other relevant sciences to clinical practice by advancing the tools necessary for evaluating targeted therapeutics and bringing them to market more efficiently.



# CASE STUDY:
# Kalydeco™(ivacaftor)

- Approved January 2021 for Cystic Fibrosis patients with G551D genetic mutation
- This gene helps regulate the transport of salt and water in the body
- Ivacaftor restores the function of the protein that is made by the mutated gene allowing the proper flow of salt and water on the surface of the lungs and helps prevent the buildup of sticky mucus that occurs and can lead to life-threatening lung infections and digestive problems



# PERSONALISED MEDICINE

## PREVENTION

**Early detection of patients at risk, Improve preventive measures (individual/collective)**

## DIAGNOSIS


**Accurate disease diagnosis enabling individualized treatment strategy**

## TREATMENT


**Improved outcomes through targeted treatments and reduced side effects**

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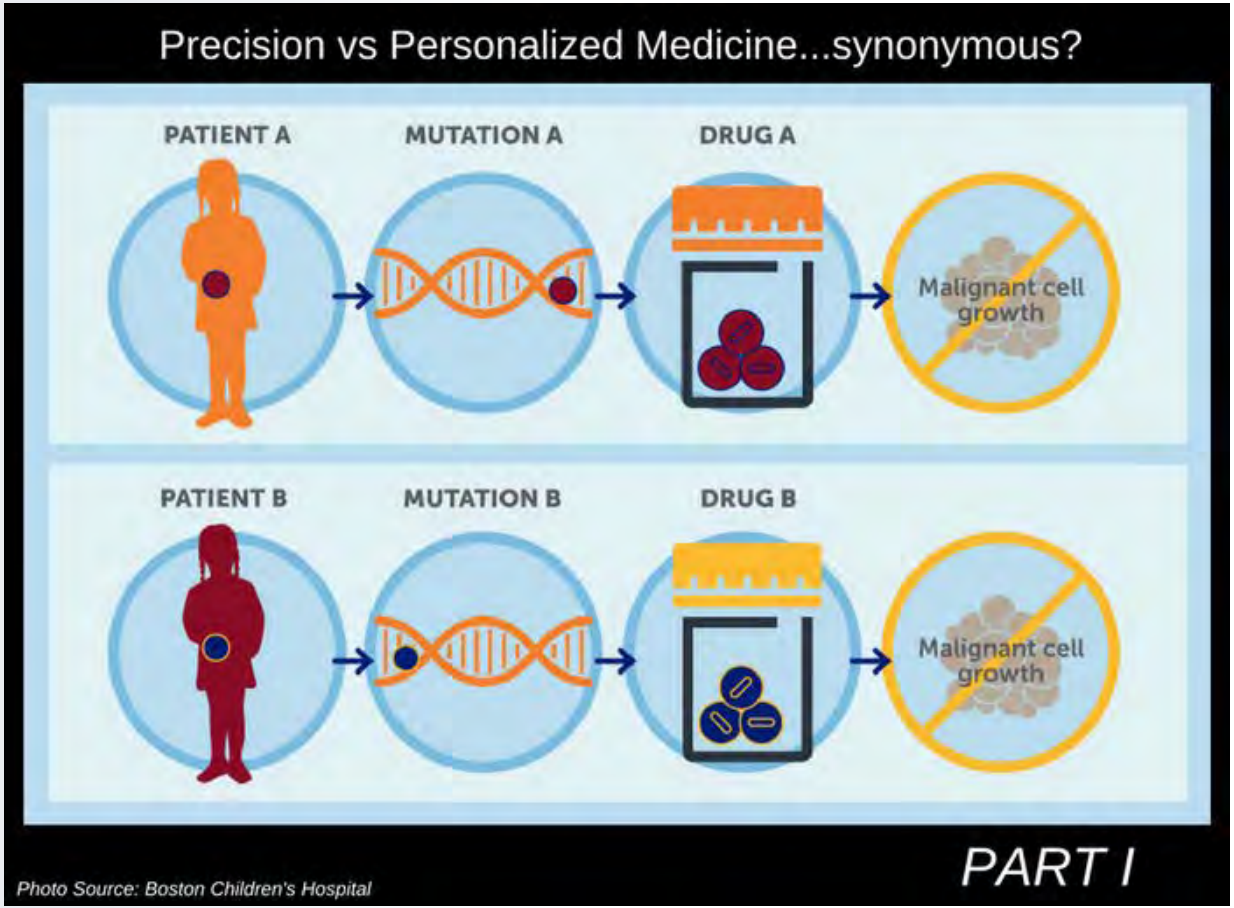
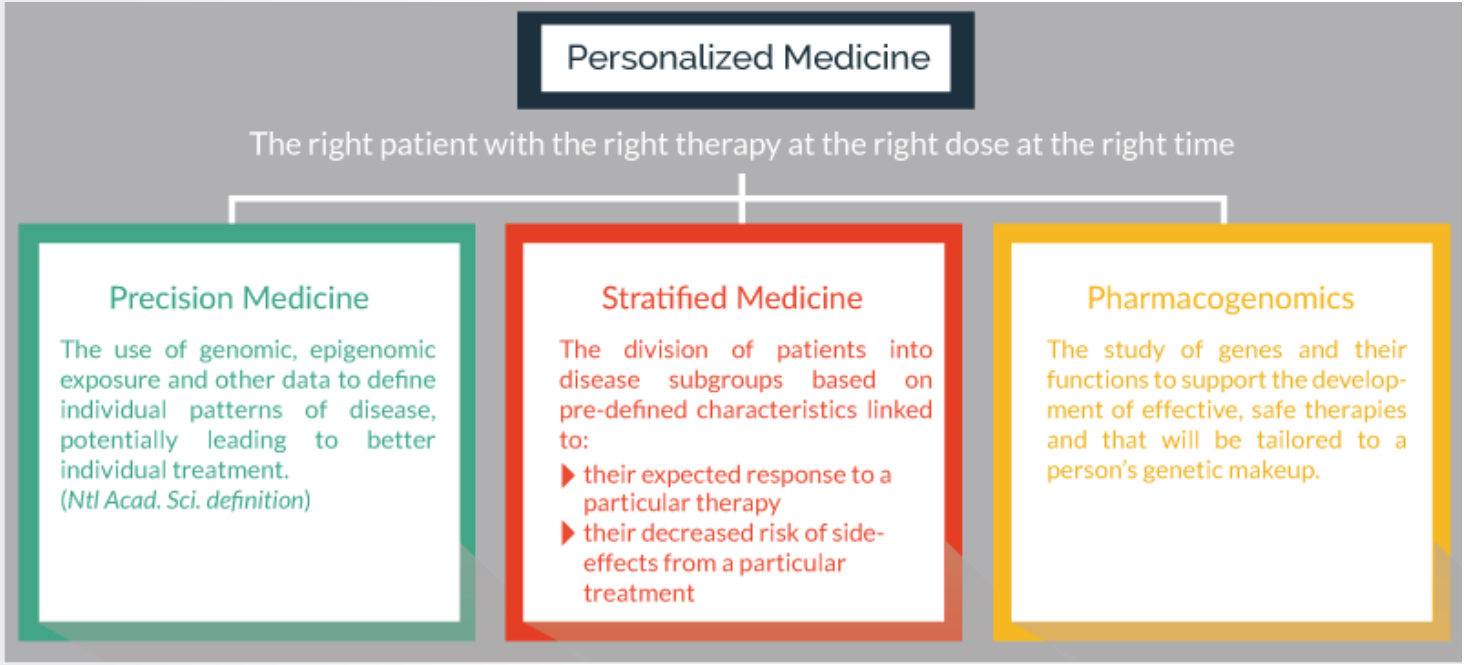
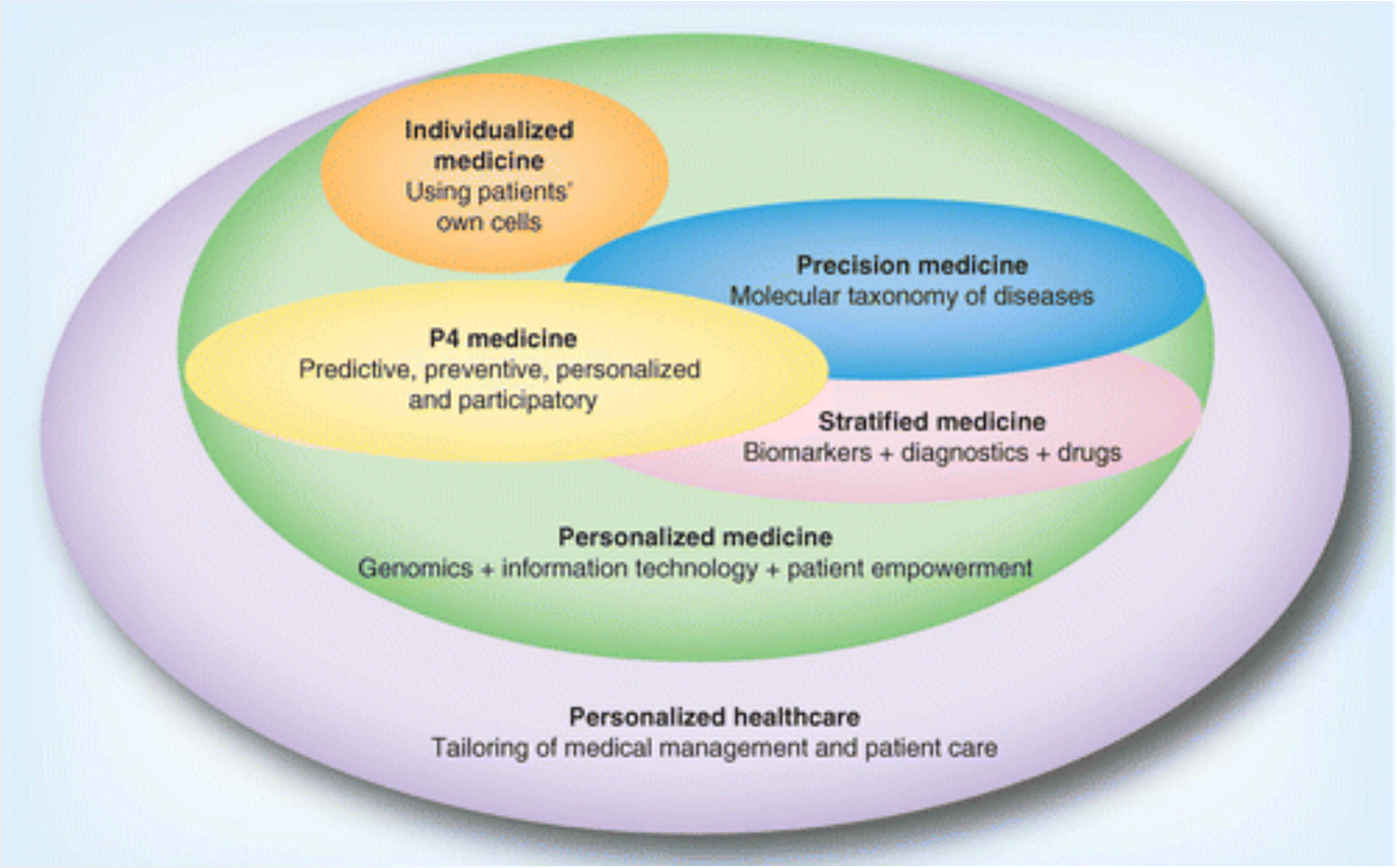

Precision vs Personalized Medicine...synonymous?
PATIENT A
MUTATION A
DRUG A
Malignant cell growth
PATIENT B
MUTATION B
DRUG B
Malignant cell growth
PART I
Photo Source: Boston Children's Hospital

# (More) Terminology – Clarified?




Individualized medicine
Using patients' own cells
Precision medicine
Molecular taxonomy of diseases
P4 medicine
Predictive, preventive, personalized and participatory
Stratified medicine
Biomarkers + diagnostics + drugs
Personalized medicine
Genomics + information technology + patient empowerment
Personalized healthcare
Tailoring of medical management and patient care

# The Innovation to Translational Science

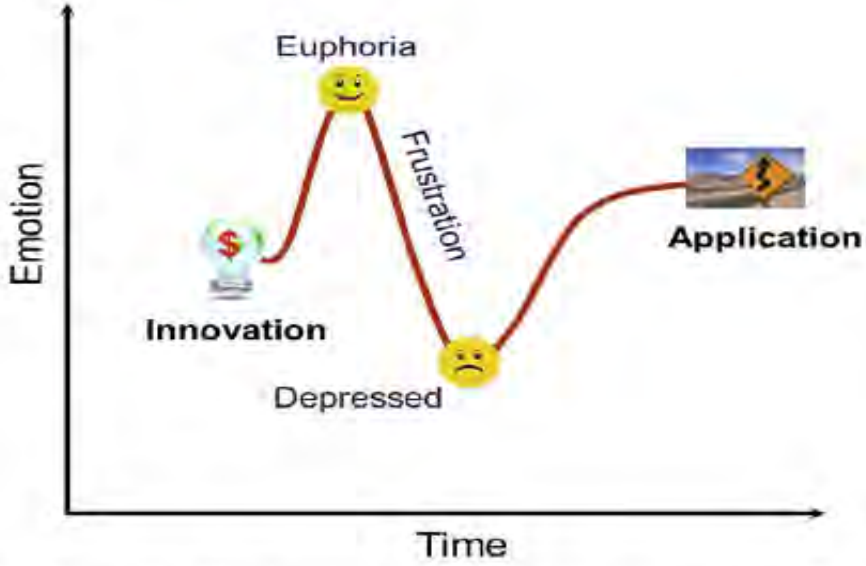
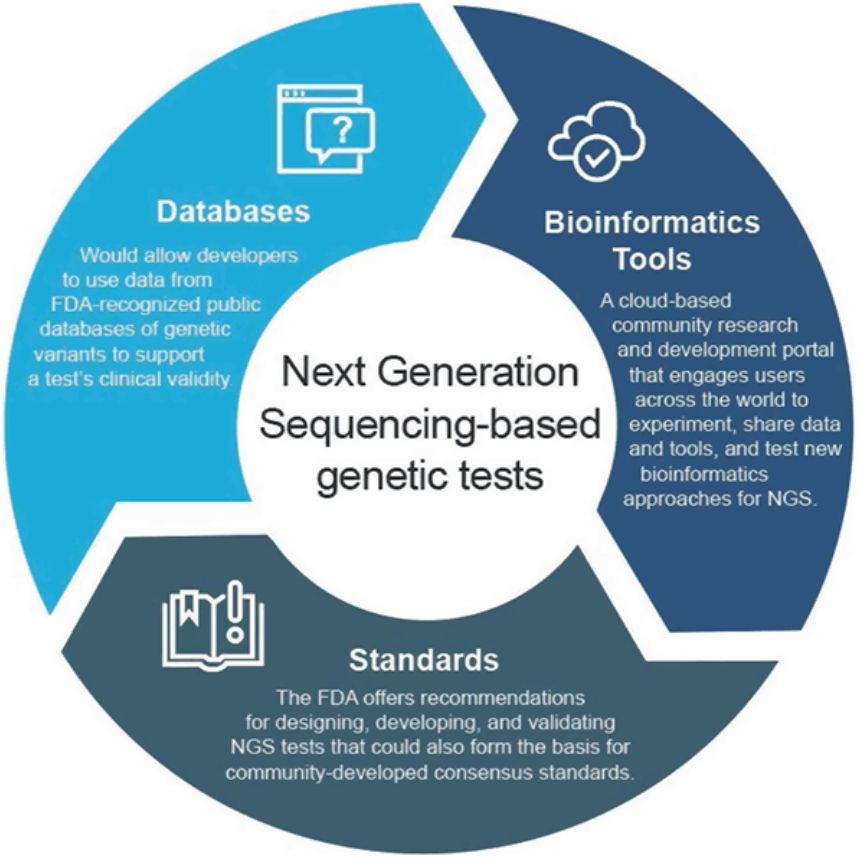



**Fig. 1.** An illustration of the innovation-to-application process. It usually takes 10–20 years to translate innovation to regulatory application. Therefore, one of the objectives of Regulatory Science Research is to expedite the translation process for innovation by optimizing its reproducibility, standardizing the analysis protocols and promoting data sharing.

Ref: Tong et al.,
Regulatory Tox and Pharm(2015)

# More to Follow from Our Other Speakers…



# Genomics and Personalized Medicine

## A view from a drug development and regulatory science perspective

**Klaus Romero MD MS FCP**
Chief Science Officer, Critical Path Institute

CRITICAL PATH INSTITUTE

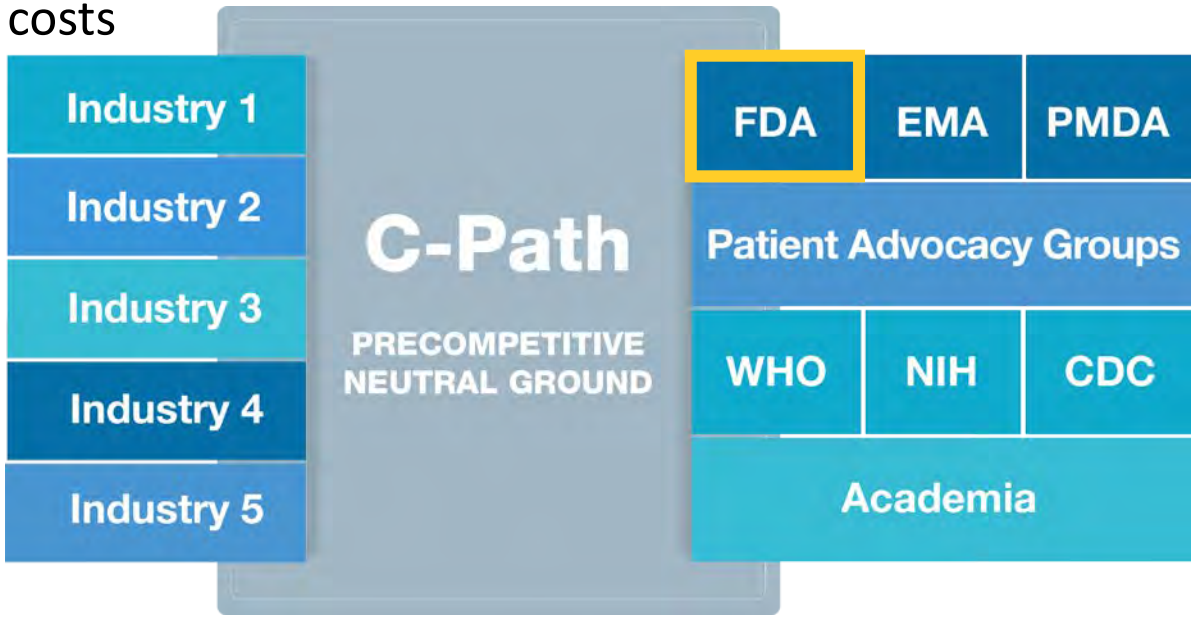
# How C-Path came about

In response to the Critical Path Initiative, the **Critical Path Institute** was formed as an independent 501(c)3 in 2005

***"… to foster development of new evaluation tools to inform medical product development."***

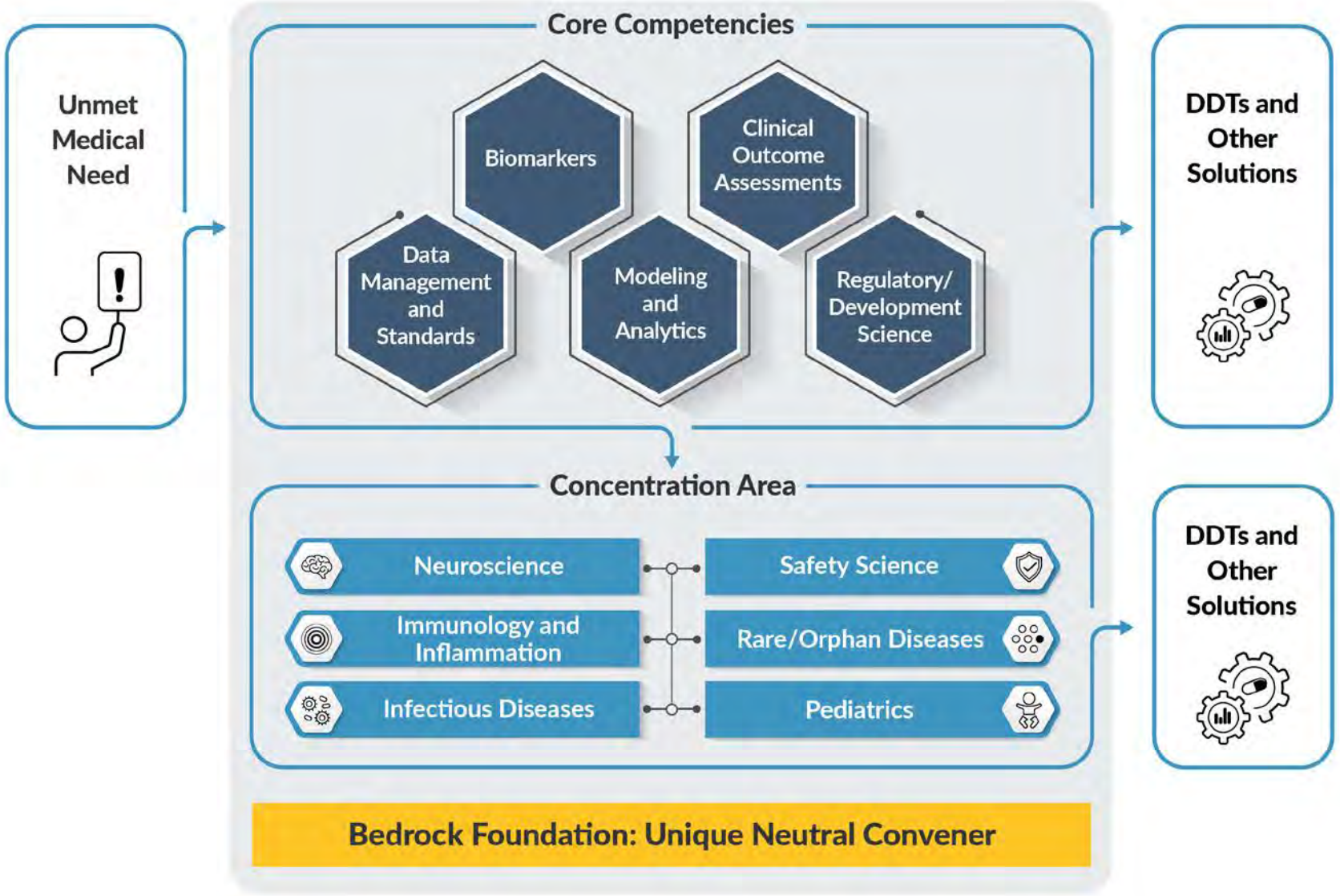
# How C-Path Works: Public-Private Partnerships

- Acts as a trusted, neutral third party
- Convenes scientific collaborations of industry, academia and government for sharing of data and expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs
- Enable iterative FDA/EMA/PMDA participation in developing new methods to assess the safety and efficacy of medical products




**Official regulatory endorsement of novel methodologies and drug development tools**

# C-Path generates actionable solutions (in interesting packages)



# Active C-Path Consortia & Programs

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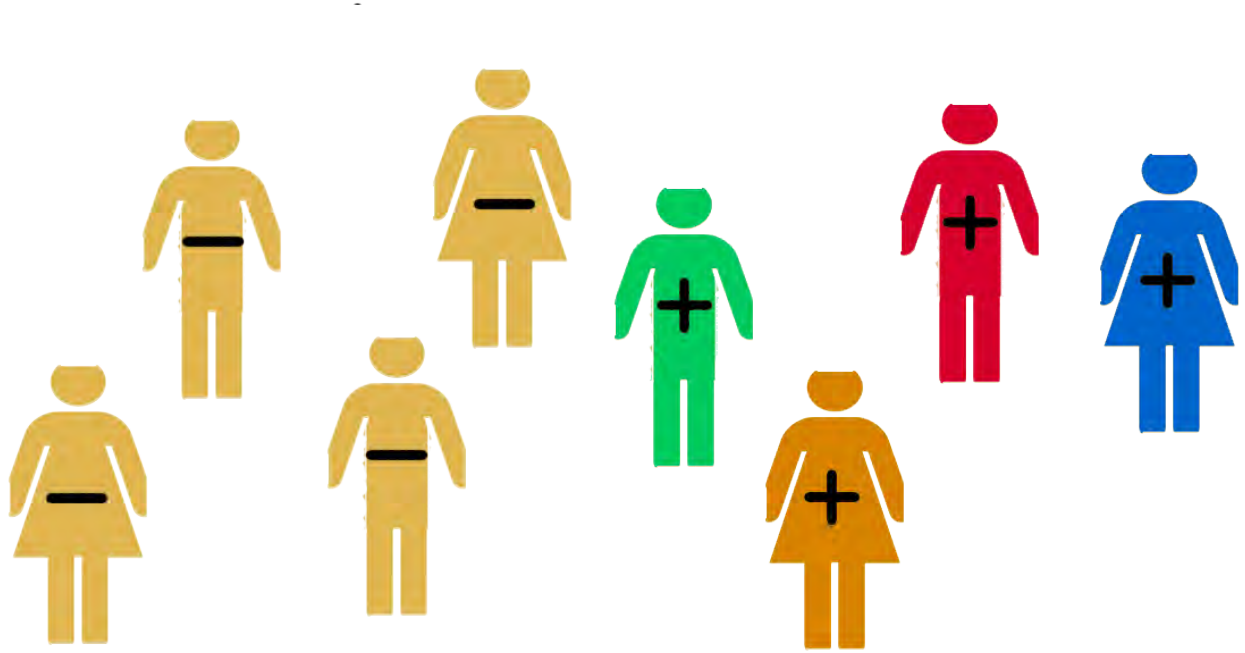
## Active Consortia/Programs

| | |
|---|---|
| **BmDR** | Biomarker Data Repository |
| **CDRC** | Cure Drug Repurposing Collaboratory |
| **CPAD** | Critical Path for Alzheimer's Disease |
| **CPP** | Critical Path for Parkinson's Disease |
| **CPTA** | Critical Path to Therapeutics for the Ataxias |
| **CPTR** | Critical Path to TB Drug Regimens |
| **CP-SCD** | Critical Path for Sickle Cell Disease |
| **DCC** | Data Collaboration Center |
| **D-RSC** | Duchenne Regulatory Science Consortium |
| **ePRO Consortium** | Electronic Patient-Reported Outcome Consortium |
| **ERA4TB** | European Regimen Accelerator for Tuberculosis* |
| **HD-RSC** | Huntington's Disease Regulatory Science Consortium |
| **INC** | International Neonatal Consortium |
| **MSOAC** | Multiple Sclerosis Outcome Assessment Consortium |
| **PKDOC** | Polycystic Kidney Disease Outcomes Consortium |
| **PredicTox KE** | PredicTox Knowledge Environment |
| **PRO Consortium** | Patient-Reported Outcome Consortium |
| **PSTC** | Predictive Safety Testing Consortium |
| **QuantMed** | Quantitative Medicine |
| **RDCA-DAP** | Rare Disease Cures Accelerator- Data and Analytics Platform |
| **RD-COAC** | Rare Disease Clinical Outcome Assessment Consortium |
| **T1D** | Type 1 Diabetes Consortium |
| **TOMI-T1D** | Trial Outcome Markers Initiative in T1D Consortium |
| **TTC** | Transplant Therapeutics Consortium |
| **UNITE4TB** | Worldwide Accelerator for Tuberculosis* |

* C-Path Ltd.

# Critical questions for trial design

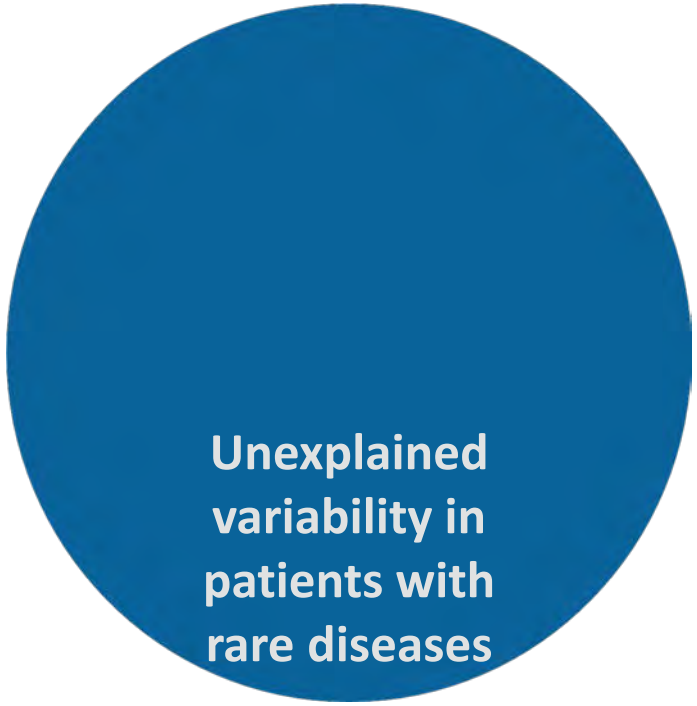
- How many patients should be recruited to properly power the trial?
- What should be the inclusion criteria?
- Can the control arm be optimized?
- What types of progression rates are expected for different subpopulations?
- What measures of progression are most adequate, at which stages of the disease continuum?
- How long should the trial duration be?
- How often should I assess?
- What is the time-varying probability of dropouts, and what are their predictors?

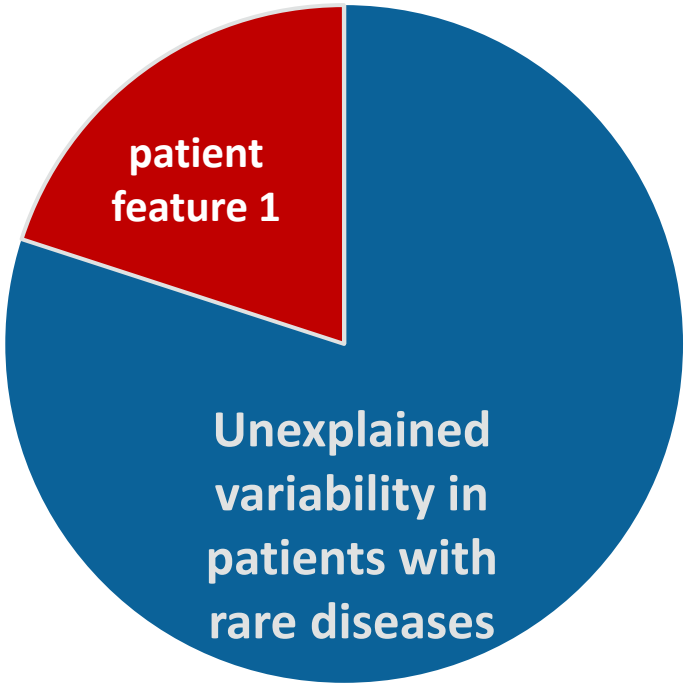


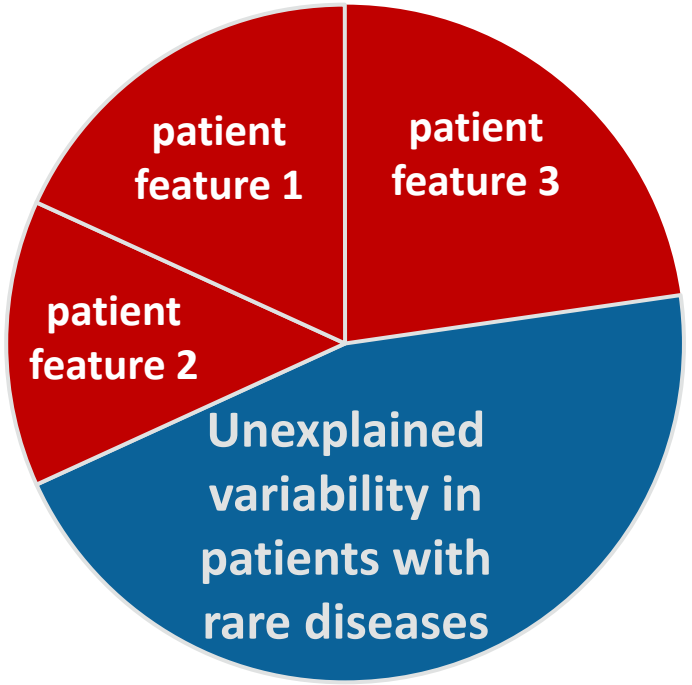
How should one go about providing sound quantitative answers to these questions?

# Answer 1: Quantifying variability

Quantifying multiple sources of variability simultaneously within the patient population reduces overall unexplained variability



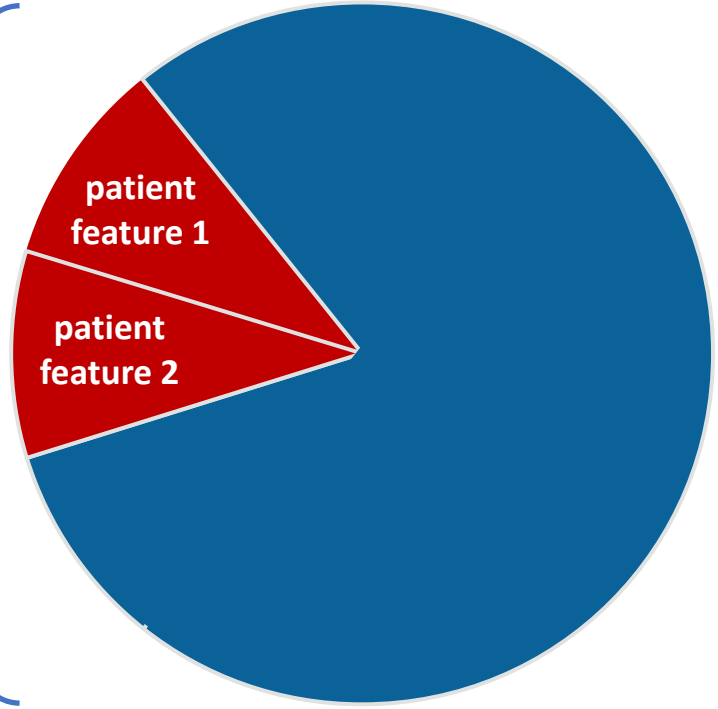



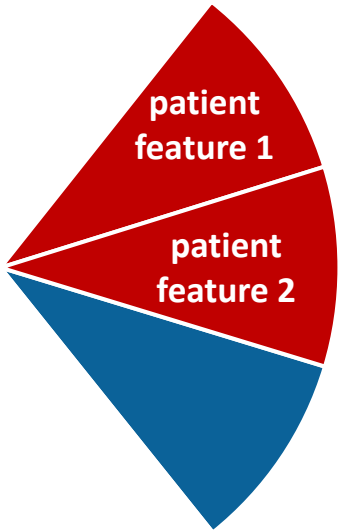

Result: The ability to predict more accurate progression rates for heterogeneous subpopulations of patients in clinical trials

# Answer 2: Multiple data sources

Understanding the 'universe' of a given disease's heterogeneity

**Unexplained variability in <u>ALL</u> patients with rare diseases**

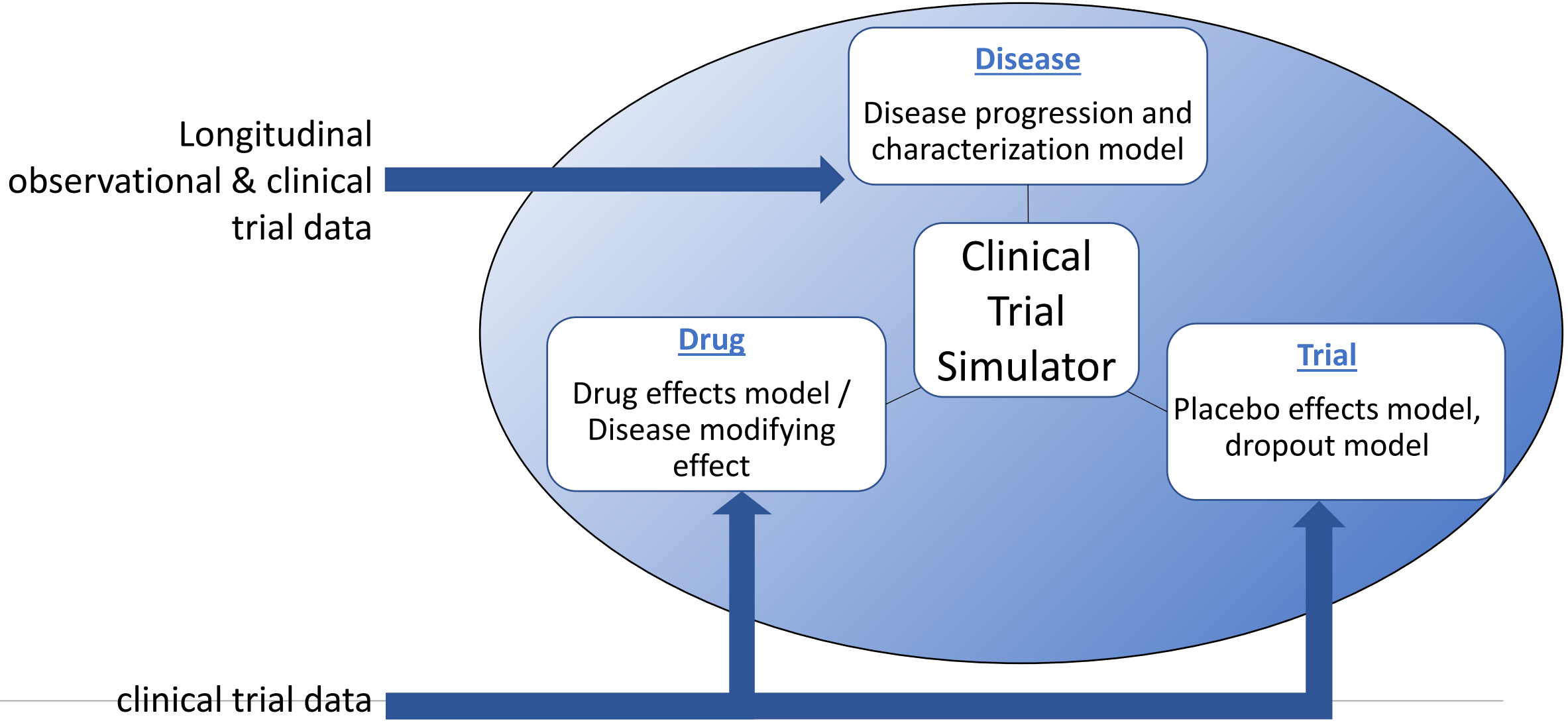


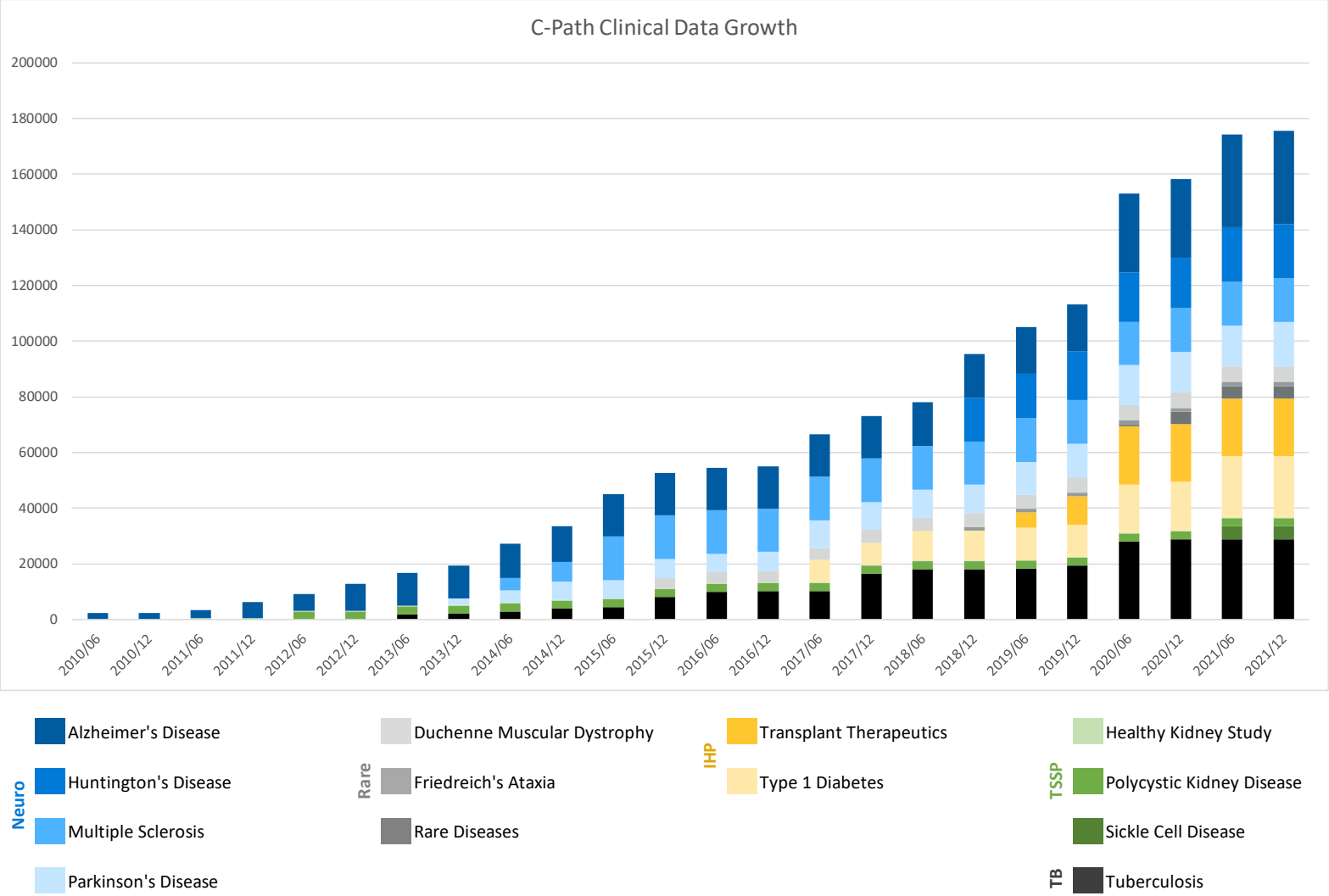

**Unexplained variability in patients with rare diseases from <u>a single study</u>**

Result: The ability to more accurately account for the heterogeneity in rare diseases and avoid biased conclusions on few data sources

# Answer 3: Drug-disease-trial modeling



# Clinical Data Contributed to C-Path




| | Clinical Data | Nonclinical Data |
|---|---|---|
| Studies | 235 | 162 |
| Subjects | 175,401 | 19,726 |
| | | |
| ReSeqTB isolates: | | 9,215 |

# Data Science and Quantitative Medicine

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**Actionable drug development solutions**

- Clinical Trial Data
- Registry Data
- Natural History Data
- RMT/3DT Data
- Biomarker Data
- Translational Data
- Genetic Data
- Other Novel Data

## C-Path Data Collaboration Center

Data Vault

Curation

Metadata Annotation

Standardization

**Data for Analysis**

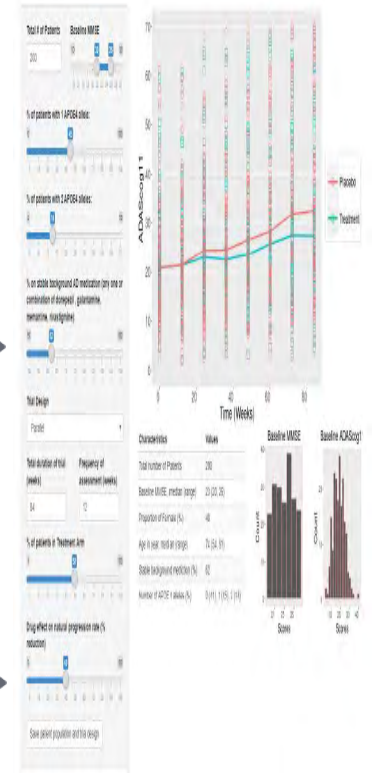
Data Lake

Data Warehouse

User Friendly, Secure Cloud Interface

C-Path Quantitative Medicine Program

Other Researchers



# Building Quantitative Drug Development Tools Based on Standardized Integrated Data

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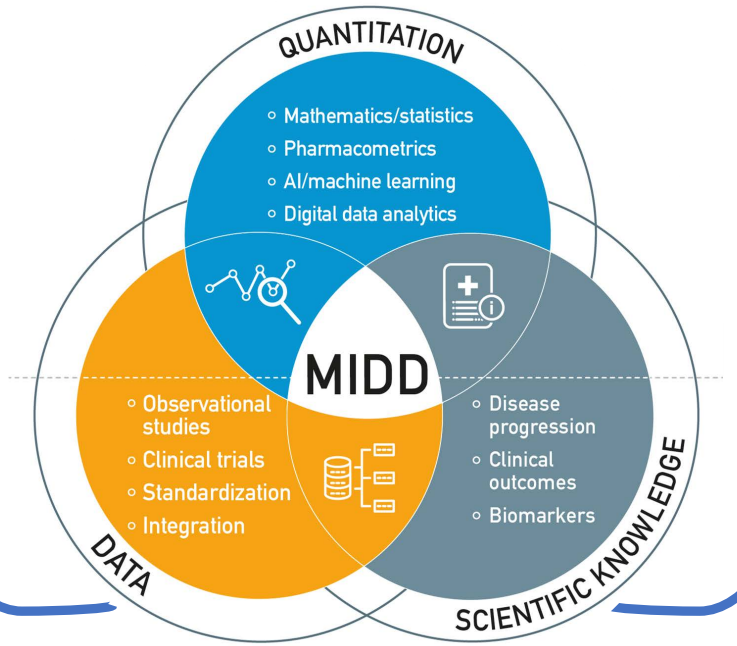
Model-Informed Drug Development (MIDD) serves as the approach to generate drug development tools

QUANTITATIVE MEDICINE




DATA COLLABORATION® CENTER

Rare Disease

CRITICAL PATH INSTITUTE

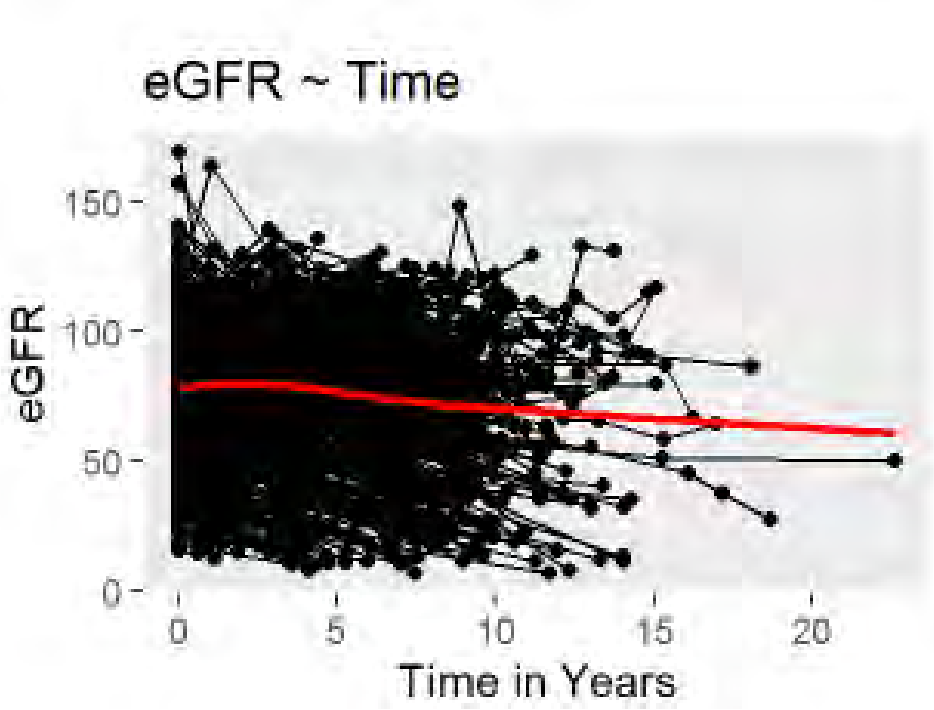
NORD® National Organization for Rare Disorders

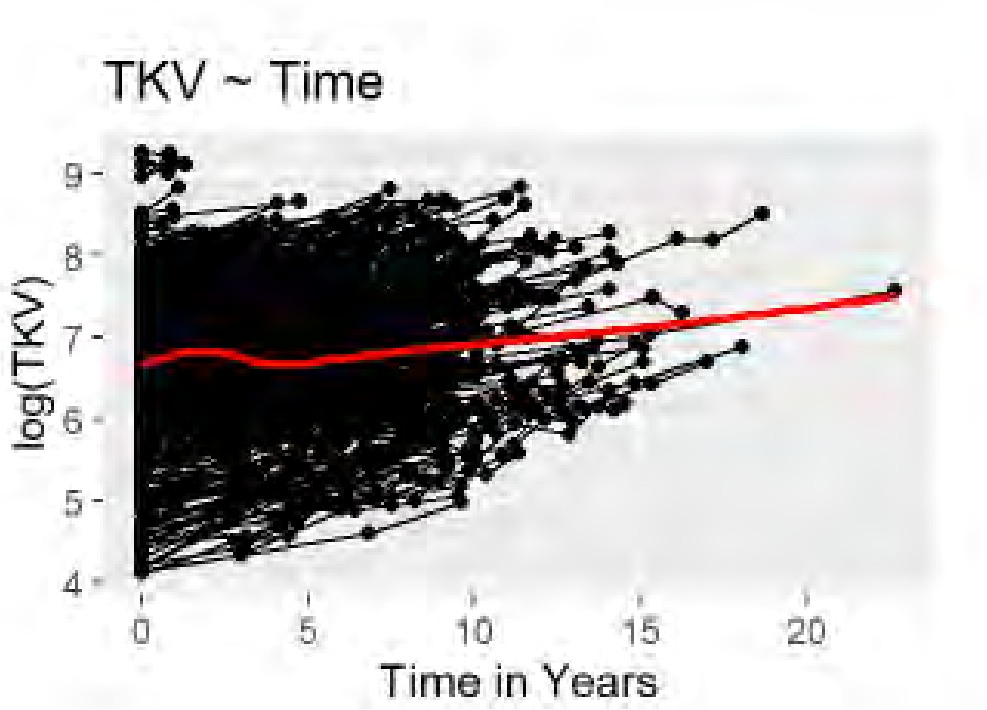
RARE DISEASE CURES ACCELERATOR-DATA AND ANALYTICS PLATFORM

PKD

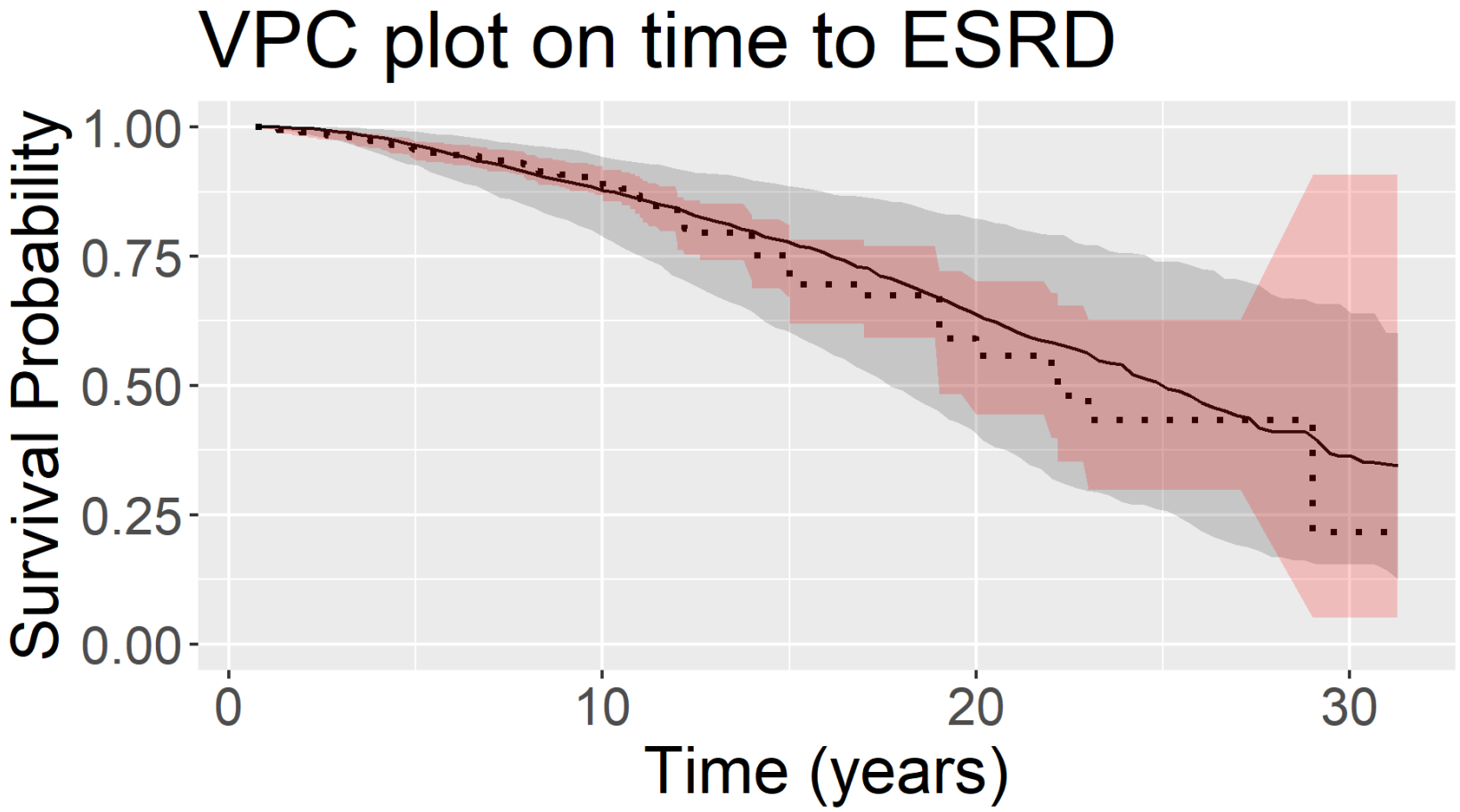
POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM

# Multivariate TKV/eGFR model



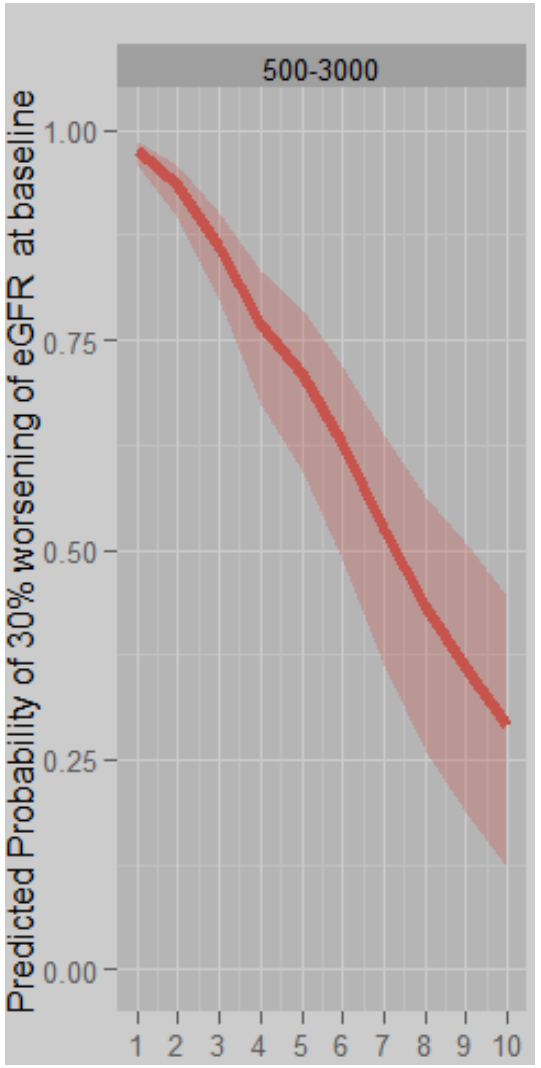
# Joint survival model for ESRD



# Underlying model developed on the data

- Joint model:
  - TKV progression model (continuous model endpoint over time)
  - Survival model (time-varying probability of reaching a 30% decline in eGFR)
  - Including covariates such as baseline eGFR and age

| Age | TKV | Follow-Up Period | 1-Probability of 30% Worsening of eGFR | | |
|---|---|---|---|---|---|
| | | | Median | Lower | Upper |
| Baseline age=30yrs | Baseline TKV 1.7L | 1 | 0.98 | 0.96 | 0.99 |
| | | 2 | 0.93 | 0.90 | 0.96 |
| | | 3 | **0.86** | 0.80 | 0.90 |
| | | 4 | 0.77 | 0.67 | 0.83 |
| | | 5 | 0.71 | 0.59 | 0.79 |
| | | 6 | 0.63 | 0.49 | 0.72 |
| | | 7 | 0.52 | 0.36 | 0.64 |
| | | 8 | 0.43 | 0.26 | 0.56 |
| | | 9 | 0.36 | 0.19 | 0.51 |
| | | 10 | 0.29 | 0.12 | 0.45 |



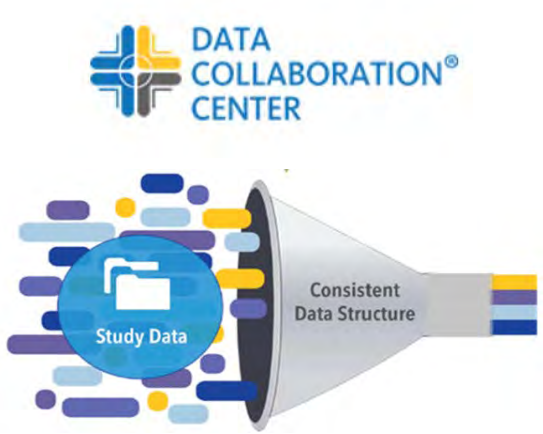
# So…

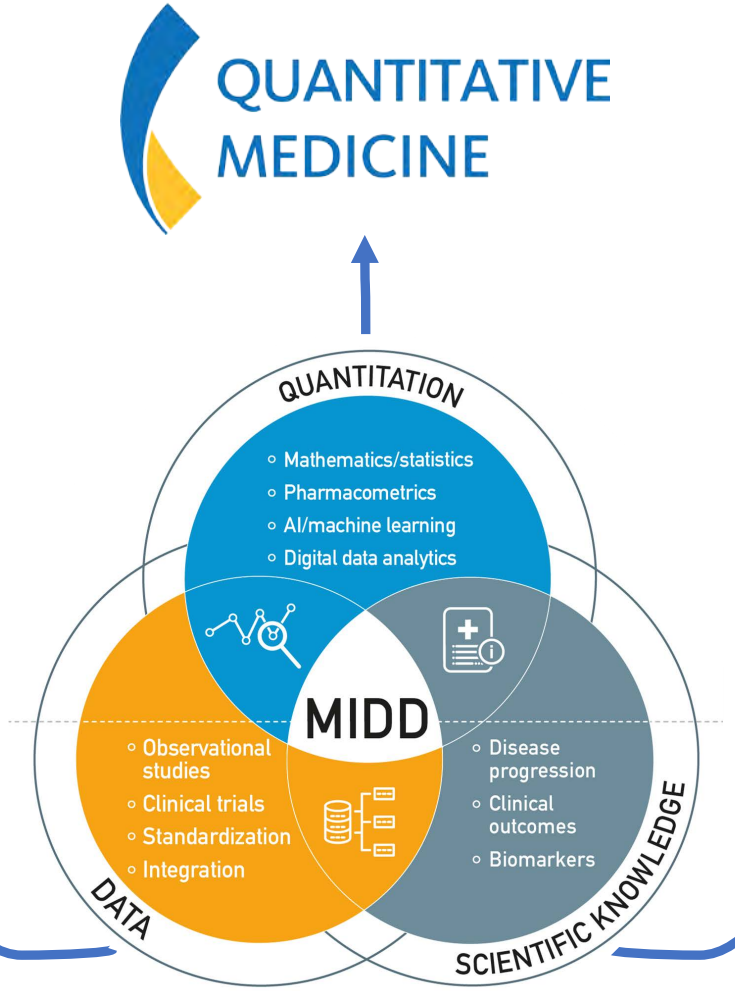
- Collaborative science transformed the landscape of drug development for PKD:
  - First-ever drug approval to slow/halt disease progression
  - Pipeline of over 14 drugs in development
- Expand the PKD-OC database, leveraging the functionality of RDCA-DAP
- Leverage C-Path's QuantMed Program, in collaboration with PKD-OC members, to expand the development of the CTS platform with additional mutation-specific data
- Leverage the collaborative framework and regulatory connectivity of the PKD-OC do drive the regulatory strategy for the clinical trial simulation platform

# Building Quantitative Drug Development Tools Based on Standardized Integrated Data

CRITICAL PATH INSTITUTE

Model-Informed Drug Development (MIDD) serves as the approach to generate drug development tools



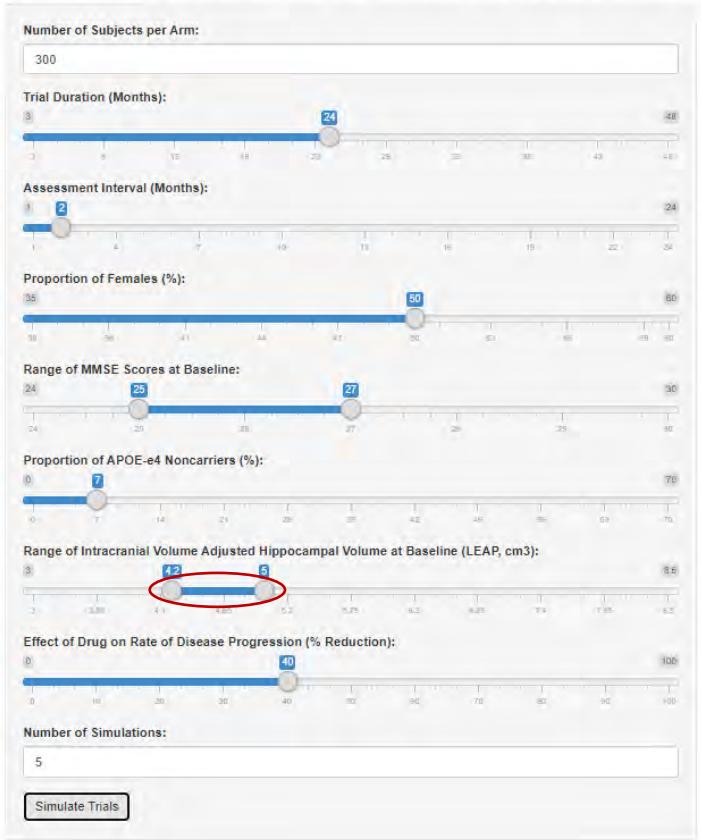



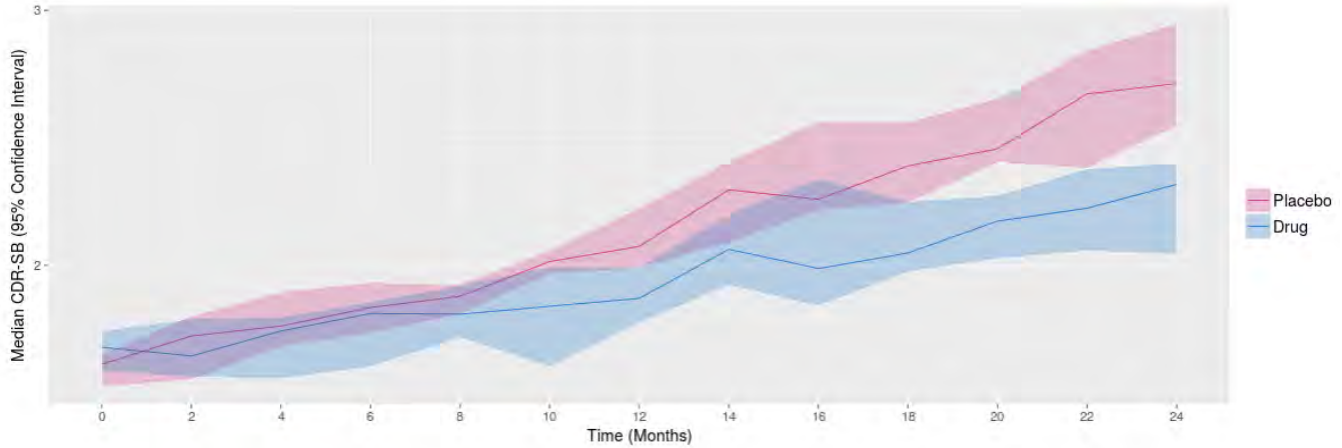

CPAD
CRITICAL PATH FOR ALZHEIMER'S DISEASE

## Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

CPAD

Simulate clinical trials on patients with amnestic mild cognitive impairment




| Characteristics | Values |
|---|---|
| Study Design | Placebo-Controlled Parallel Group |
| Total Number of Subjects | 600 |
| Study Duration (Months) | 24 |
| Assessment Interval (Months) | 2 |
| Effect of Drug on Rate of Disease Progression (% Reduction) | 40 |
| Proportion of Female (%) | 50 |
| Range of MMSE Scores at Baseline | [25, 27] |
| Proportion of APOE-e4 Noncarrier (%) | 7 |
| Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3) | [4.2, 5] |
| Median Age at Baseline (95% Confidence Interval) (Years) | 74 (74, 74) |
| Median MMSE Score at Baseline (95% Confidence Interval) (Points) | 26 (26, 26) |
| Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3) | 4.7 (4.7, 4.7) |
| Number of Simulations | 5 |
| Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%) | 0 |
| Statistical Power (%, 95% Confidence Interval) | 100 (47.8, 100) |

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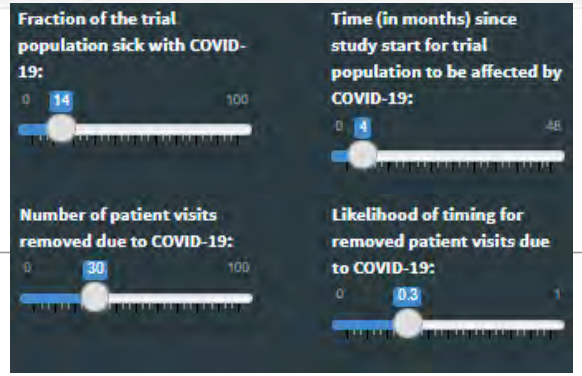
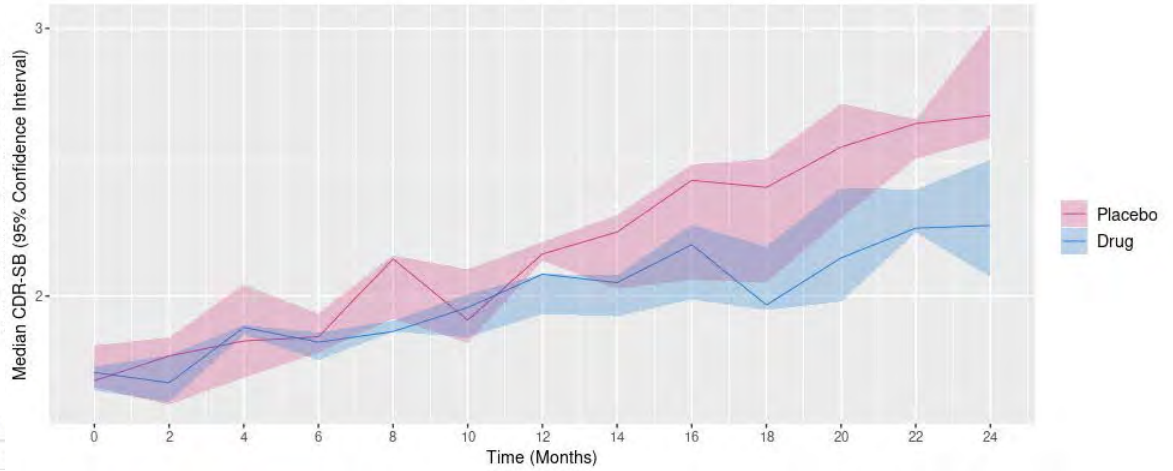
## Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

Simulate clinical trials on patients with amnestic mild cognitive impairment

CPAD

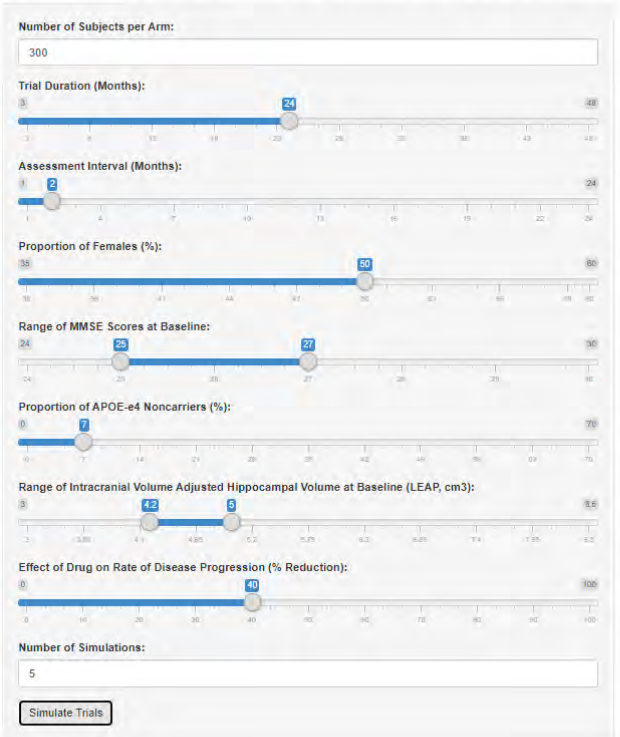



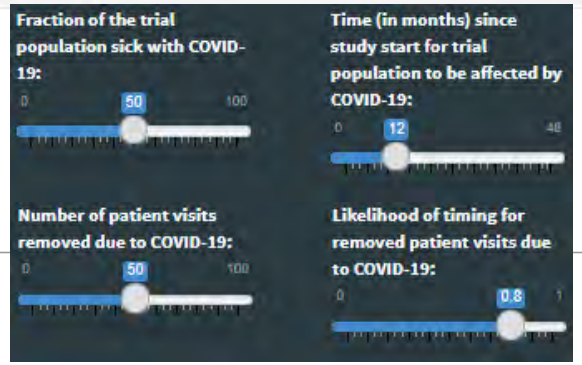

| | |
|---|---|
| Total Number of Subjects | 600 |
| Study Duration (Months) | 24 |
| Assessment Interval (Months) | 2 |
| Effect of Drug on Rate of Disease Progression (% Reduction) | 40 |
| Proportion of Female (%) | 50 |
| Range of MMSE Scores at Baseline | [25, 27] |
| Proportion of APOE-e4 Noncarrier (%) | 7 |
| Range of Intracranial Volume Adjusted Hippocampal Volume at Baseline (cm3) | [4.2, 5] |
| Median Age at Baseline (95% Confidence Interval) (Years) | 74 (74, 74) |
| Median MMSE Score at Baseline (95% Confidence Interval) (Points) | 26 (26, 26) |
| Median Intracranial Volume Adjusted Hippocampal Volume at Baseline (95% Confidence Interval) (cm3) | 4.7 (4.7, 4.7) |
| Number of Simulations | 5 |
| Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%) | 0 |
| Statistical Power (%, 95% Confidence Interval) | 100 (47.8, 100) |

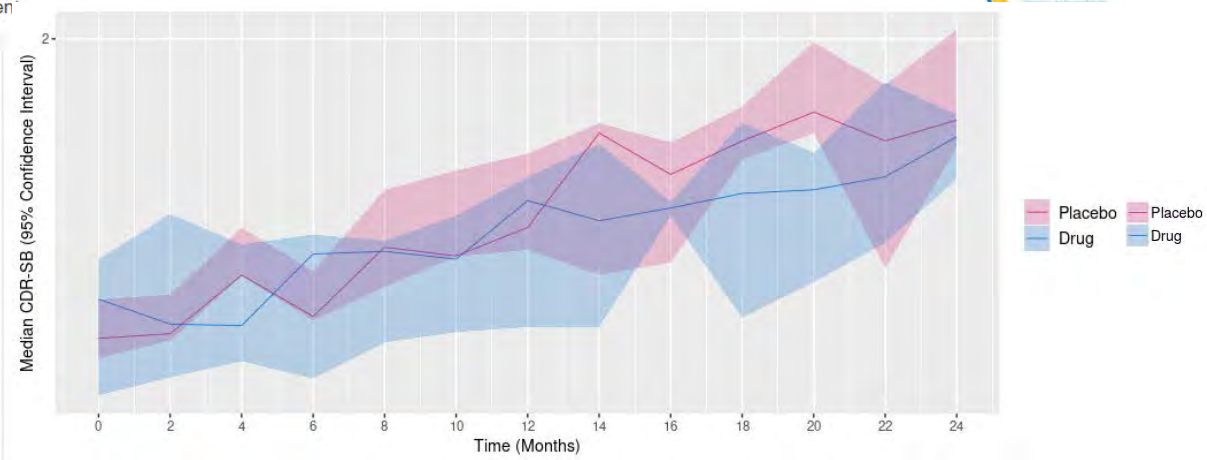
## Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator

CPAD

Simulate clinical trials on patients with amnestic mild cognitive impairmen

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| Monte-Carlo Standard Error for Calculation of Confidence Interval for Statistical Power (%) | 0 |
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# So…

- Collaborative science transformed the landscape of drug development for AD:
  - News headlines aside, the first new drug approval represents a milestone
  - Pipeline of over 21 drugs in development
- Expand the CPAD database, leveraging the functionality of DCC
- Leverage C-Path's QuantMed Program, in collaboration with CPAD members, to expand the development of the CTS platform with additional mutation-specific dominant AD data
- Leverage the collaborative framework and regulatory connectivity of CPAD do drive the regulatory strategy for the clinical trial simulation platform

# TTE Disease Progression Model for T1D Prevention Trials

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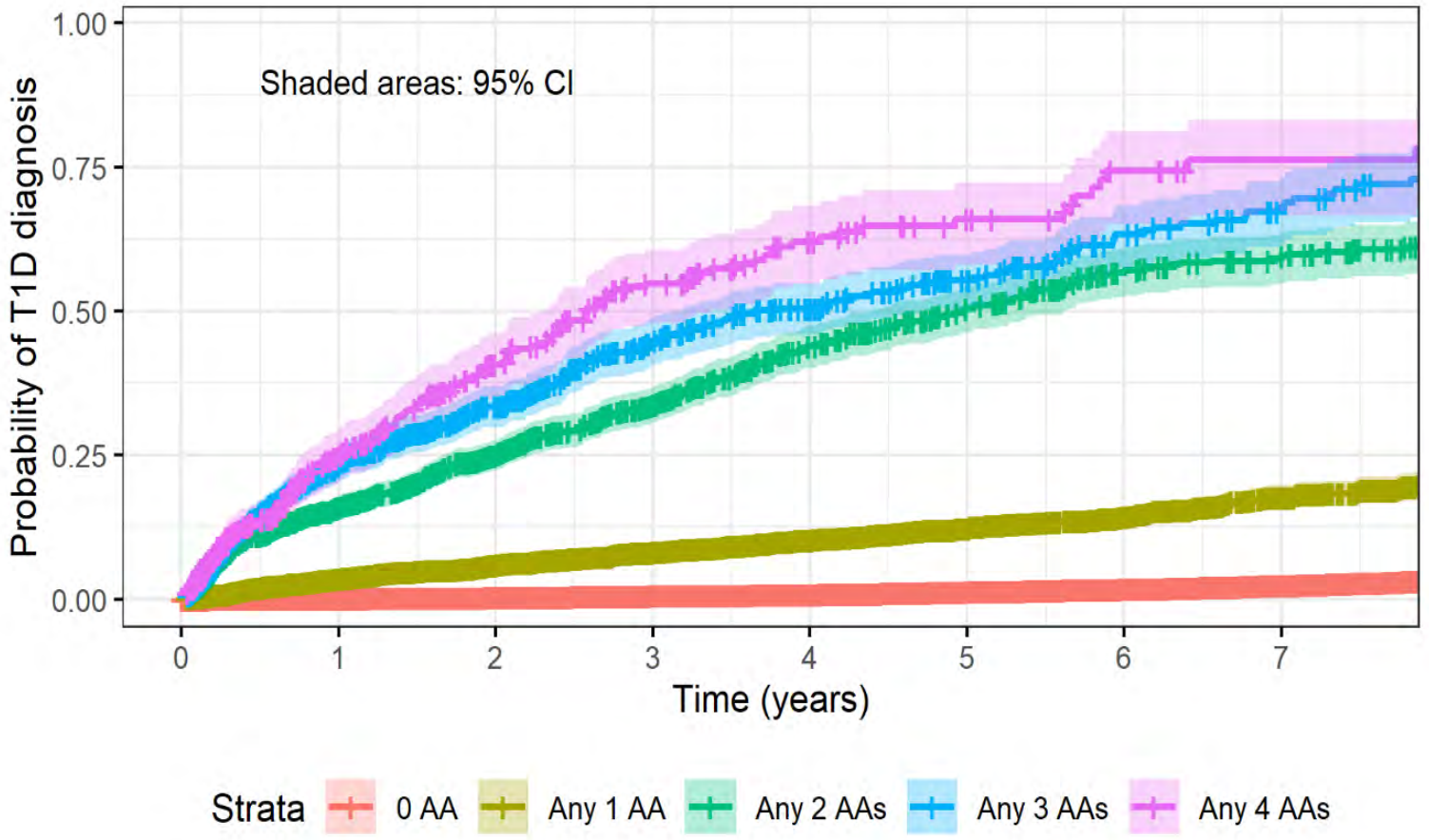
Risk of T1D diagnosis stratified by the number of islet AAs present at the first patient record (including zero)



# So…

- Collaborative science is transforming the landscape of drug development for T1D prevention:
  - Challenges, the first new drug review represents a milestone
  - Pipeline getting interesting, with over 9 drugs in development
- Expand the T1D-C database, leveraging the functionality of DCC
- Leverage C-Path's QuantMed Program, in collaboration with T1D-C members, to expand the development of the disease progression models, with HLA genetic data
- Leverage the collaborative framework and regulatory connectivity of the T1D-C do drive the regulatory strategy for the disease progression models

# Thank you.

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# Pharmacogenomics Considerations for Clinical Research and Implementation

Scott Mosley, PharmD
Assistant Professor of Clinical Pharmacy
University of Southern California, School of Pharmacy

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# Objectives

- Explain how genetic variation influences response to drug therapy
- Introduce approaches to discover pharmacogenetic associations and to evaluate the clinical utility of pharmacogenomics in clinical practice
- Summarize *CYP2C19* genetic variability in ACS patients receiving clopidogrel post PCI
- Review available resources and guidelines to design best practices for discovering and translating pharmacogenetic (PGx) research

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"Here's my DNA sequence."

Aaron Bacall's "Here's my DNA sequence" cartoon published in 2000. Licensed for publication in JAPhA by www.CartoonStock.com.
Ready or not, here it comes: Direct-to-consumer pharmacogenomic testing and its implications for community pharmacists. Gammal, Roseann S. et al. Journal of the American Pharmacists Association, Volume 59, Issue 5, 646 - 650

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# Precision Medicine and Pharmacogenomics

I am a responder

I am a non-responder

An alternative therapy is most appropriate for me

I am at risk for an adverse event

I should receive an increased dose

I should receive an decreased dose

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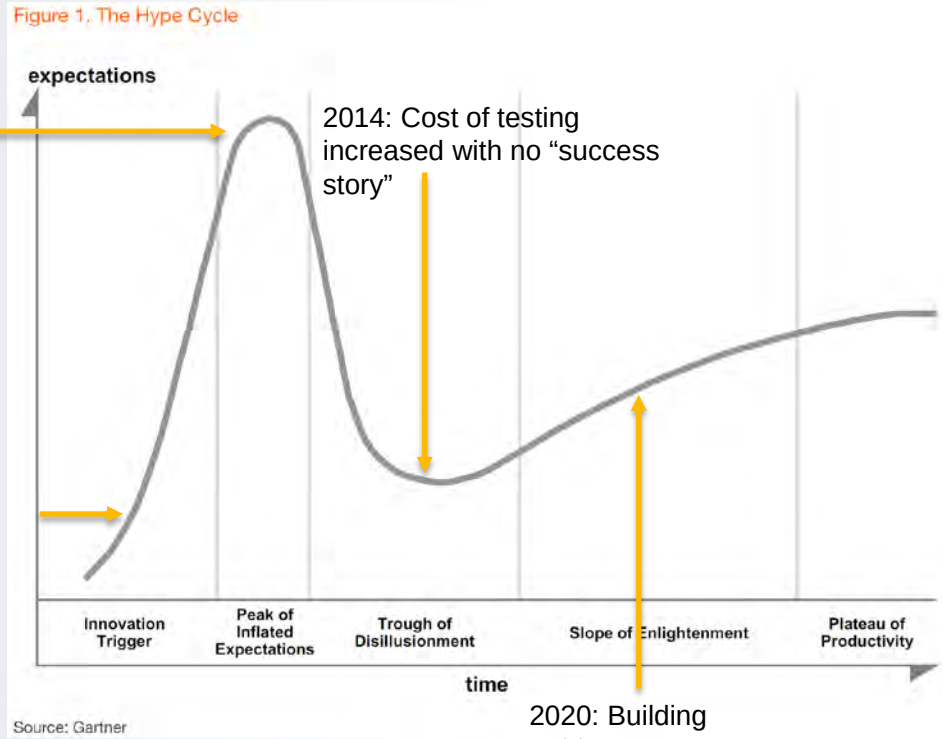
# Gartner's Hype Cycle

2013: COAG trial published in JAMA

2003: Human Genome Project complete




2014: Cost of testing increased with no "success story"

2020: Building Evidence

https://www.gartner.com/en

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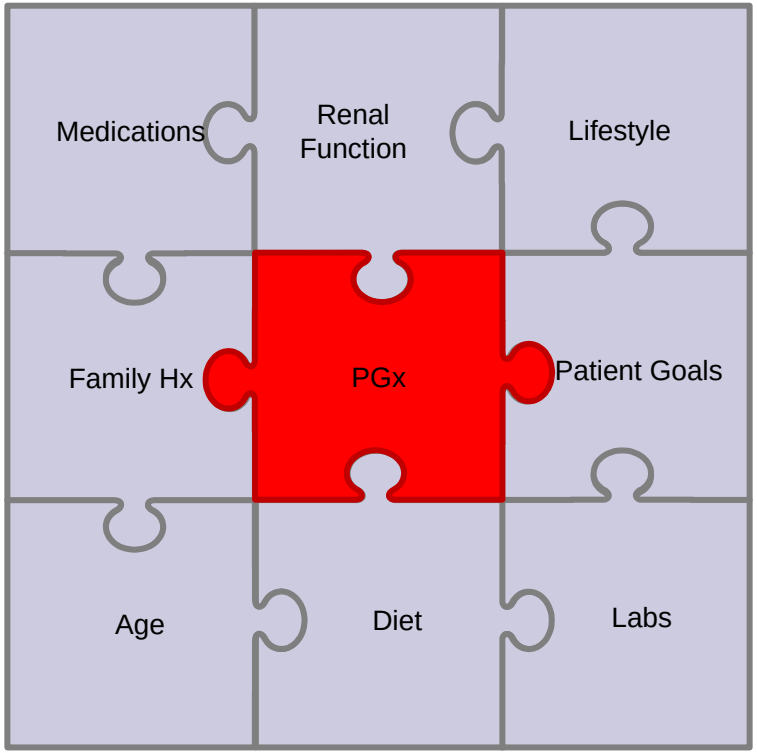
# The Reality…

- Not all PGx knowledge merits clinical action
- Two factors influence the clinical implementation of a PGx test:

1. Clinical Validity
   - Test accurately detects phenotype
2. Clinical Utility (Implementation)
   - Likelihood that a test will alter therapy and outcomes

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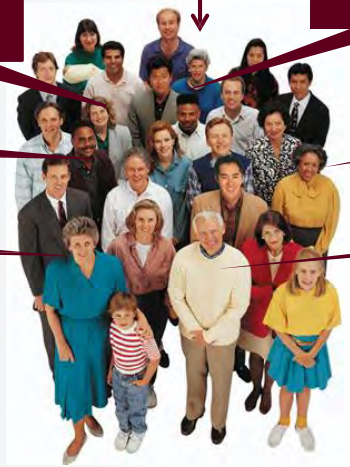



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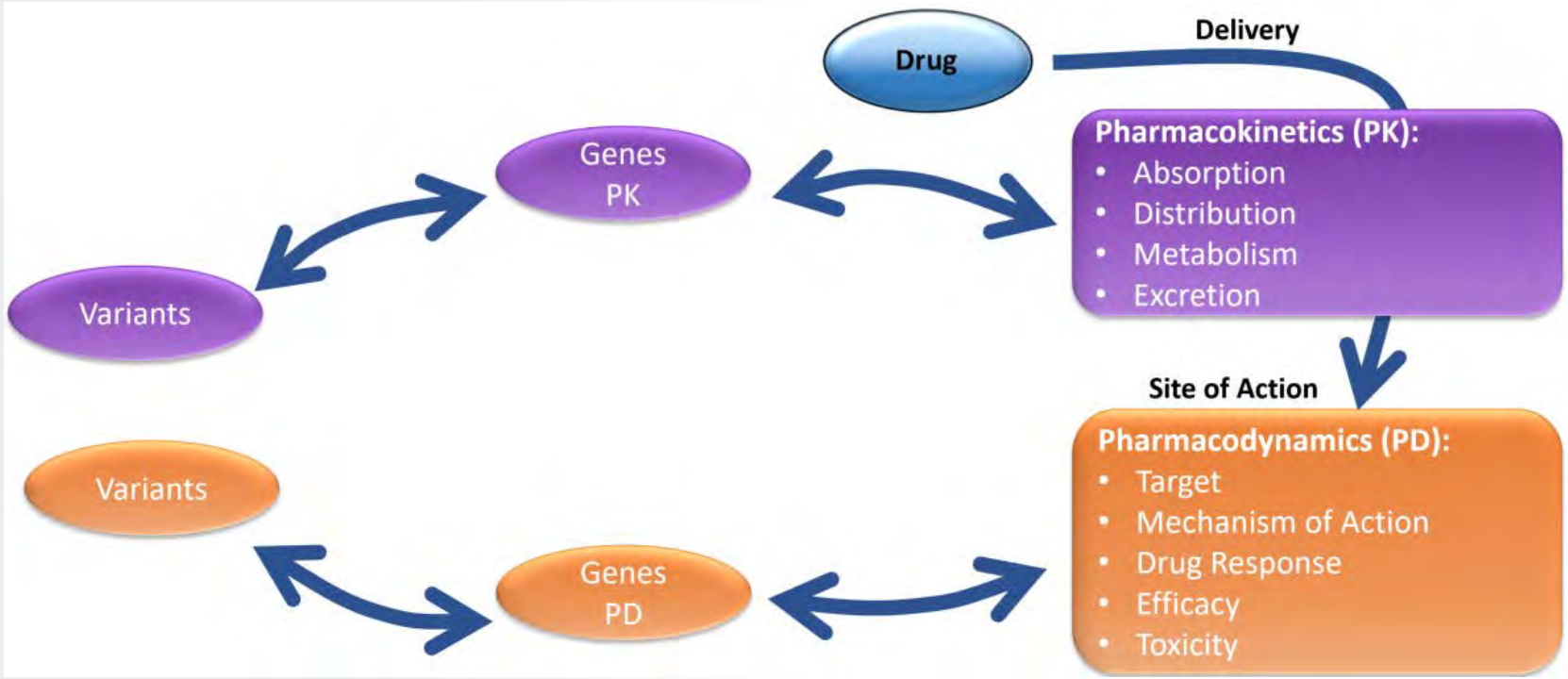
# Pharmacokinetics and Pharmacodynamics




Modified from PharmGKB

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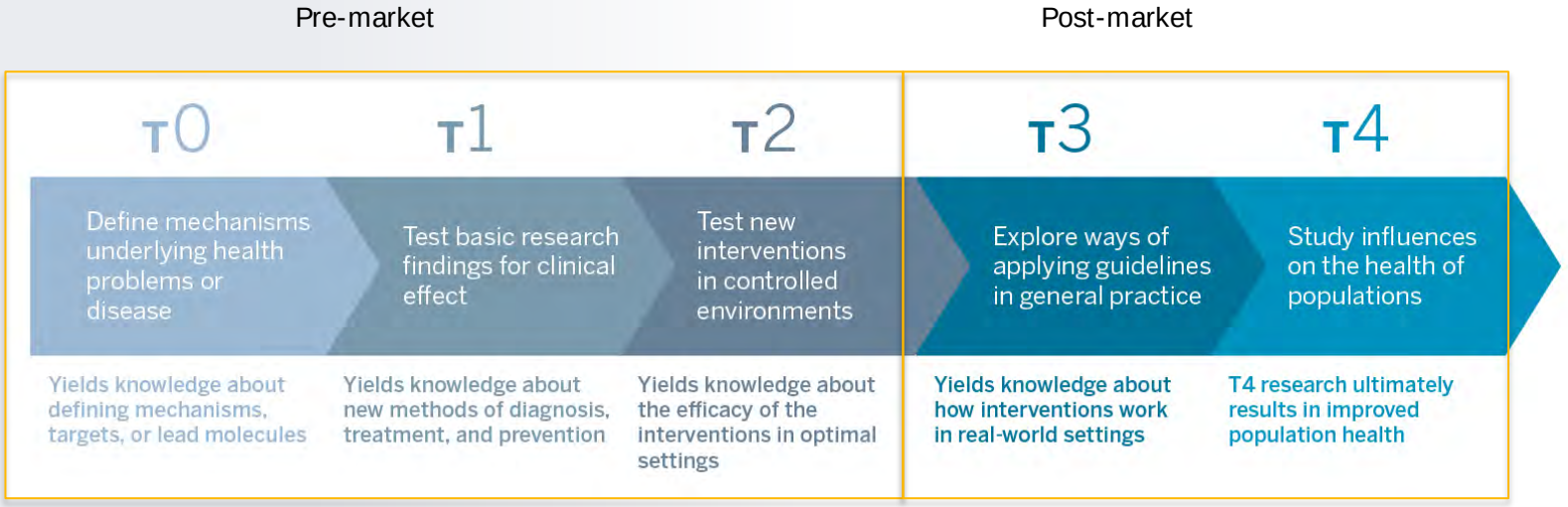
# Translational Research




https://med.nyu.edu/departments-institutes/clinical-translational-science/about-us

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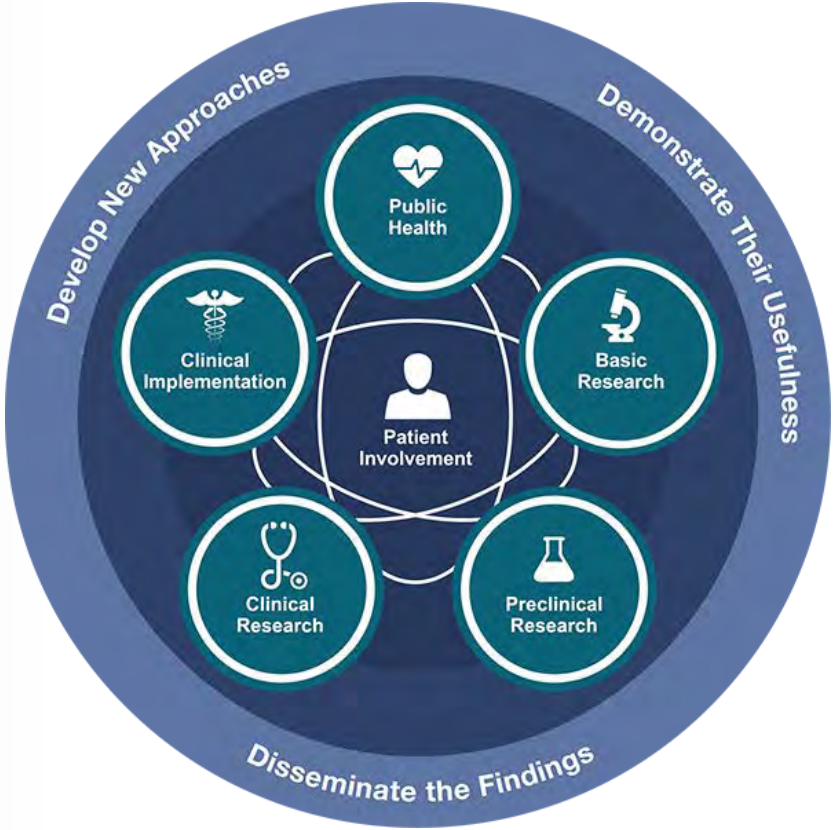
# Translational Research




https://ncats.nih.gov/translation/spectrum

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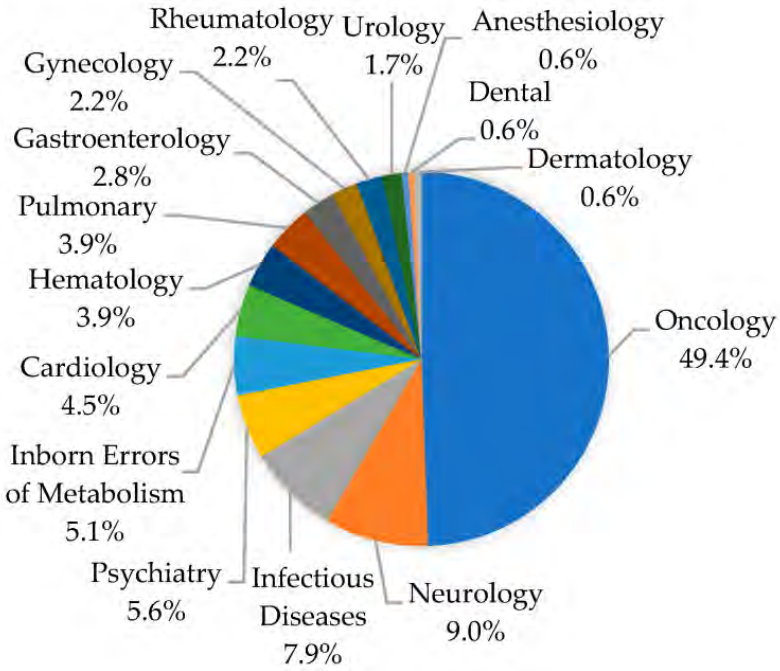
# US FDA Approval of New Drugs

- 694 drug approvals over past 20 years
- 178 (26%) of those have PGx labeling




Kim, Jeeyun A et al. "Pharmacogenomic Biomarkers in US FDA-Approved Drug Labels (2000-2020)." *Journal of personalized medicine* vol. 11,3 179. 4 Mar. 2021, doi:10.3390/jpm11030179

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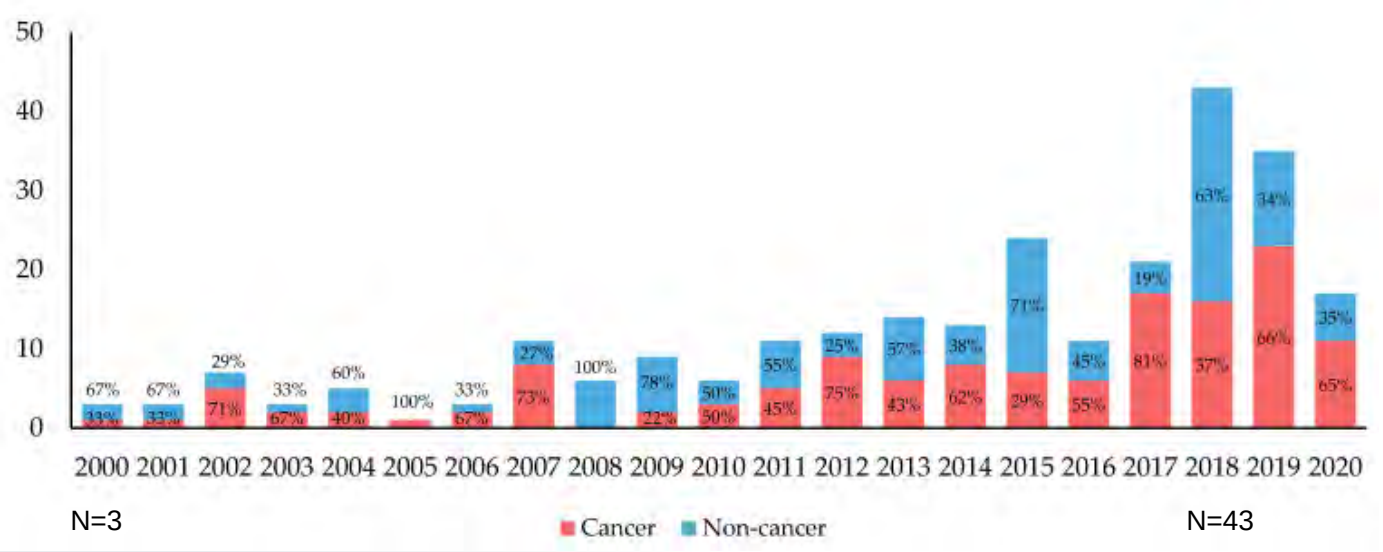
# Biomarker–drug pairs approved per year




Kim, Jeeyun A et al. "Pharmacogenomic Biomarkers in US FDA-Approved Drug Labels (2000-2020)." *Journal of personalized medicine* vol. 11,3 179. 4 Mar. 2021, doi:10.3390/jpm11030179

# Pre-market Considerations

- FDA has guidance (2013)
  - **Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling**

- Consider collecting DNA during drug development when:
  - High variability in PK or PD
  - Metabolism via polymorphic enzymes (e.g., CYP2D6 or CYP2C19)
  - Biological activation (prodrugs)
  - Significant side effect profile or poor tolerability
  - Serious adverse events

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacogenomics-premarket-evaluation-early-phase-clinical-studies-and-recommendations

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# Post-market Considerations

- Genetic sub-studies
- Randomized clinical studies
- Clinical implementation and feasibility studies (pragmatic)

Let's explore the *gene* – drug case for ***CYP2C19* – Clopidogrel**

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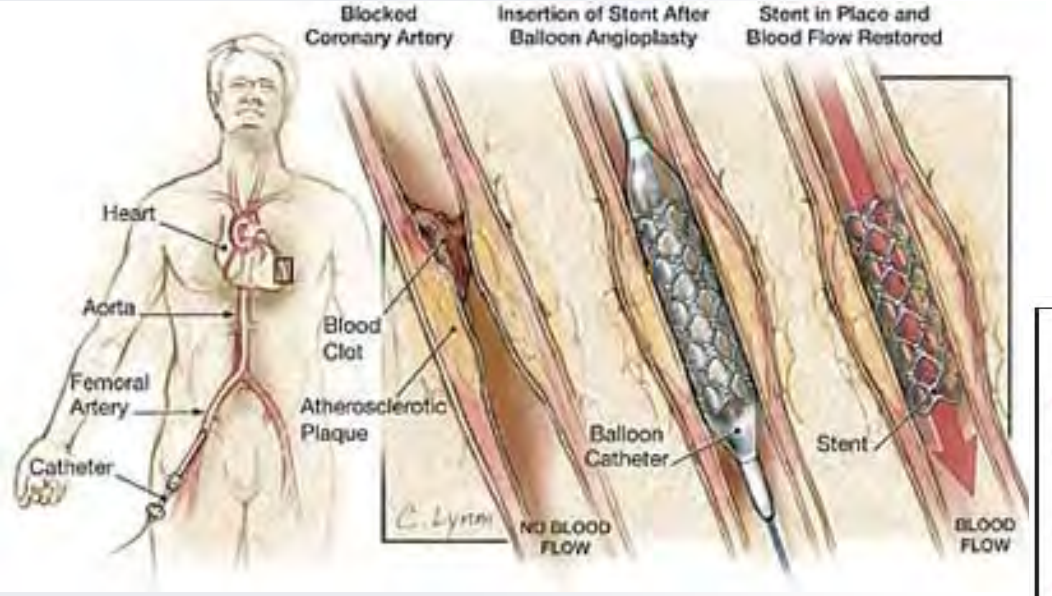
# Percutaneous Coronary Intervention (PCI)





**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

*See full prescribing information for complete boxed warning.*

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

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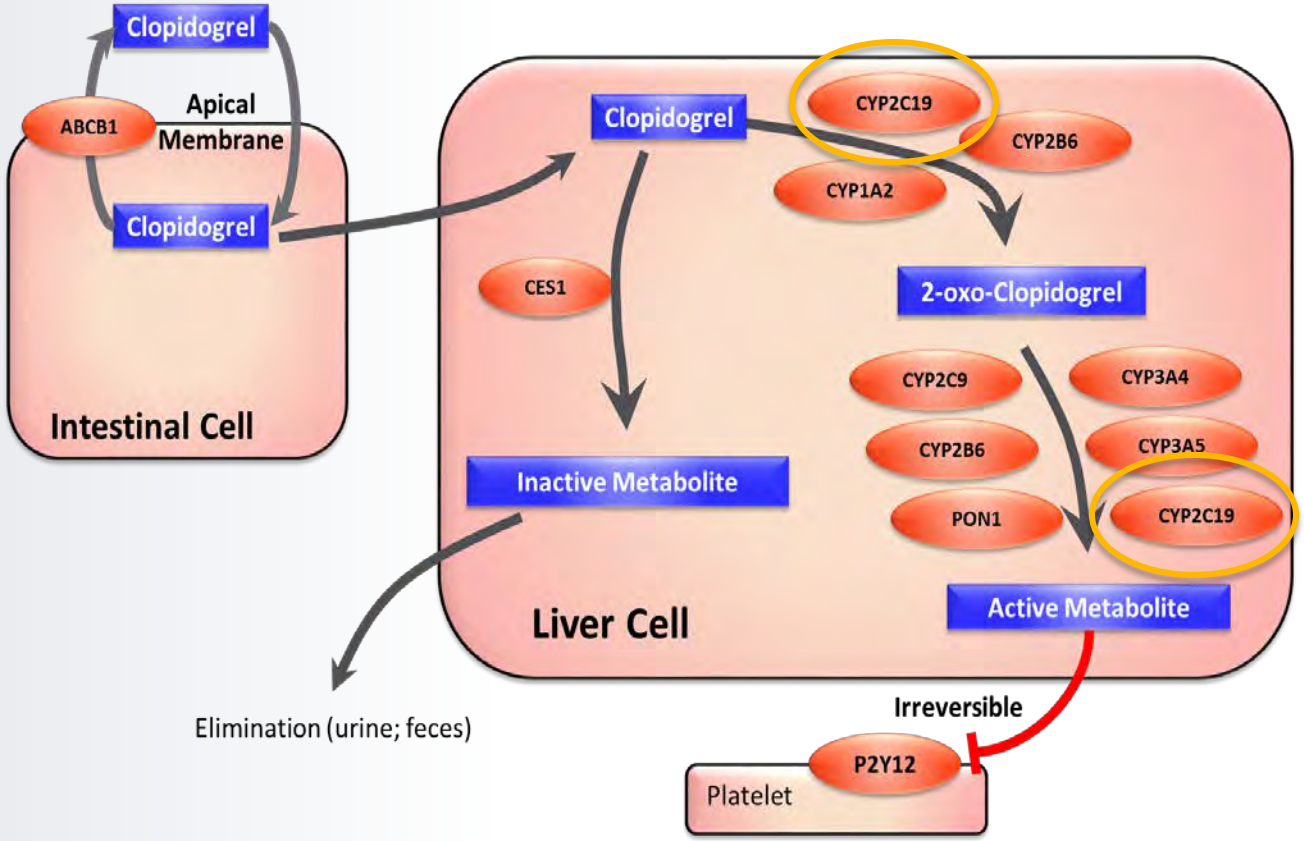
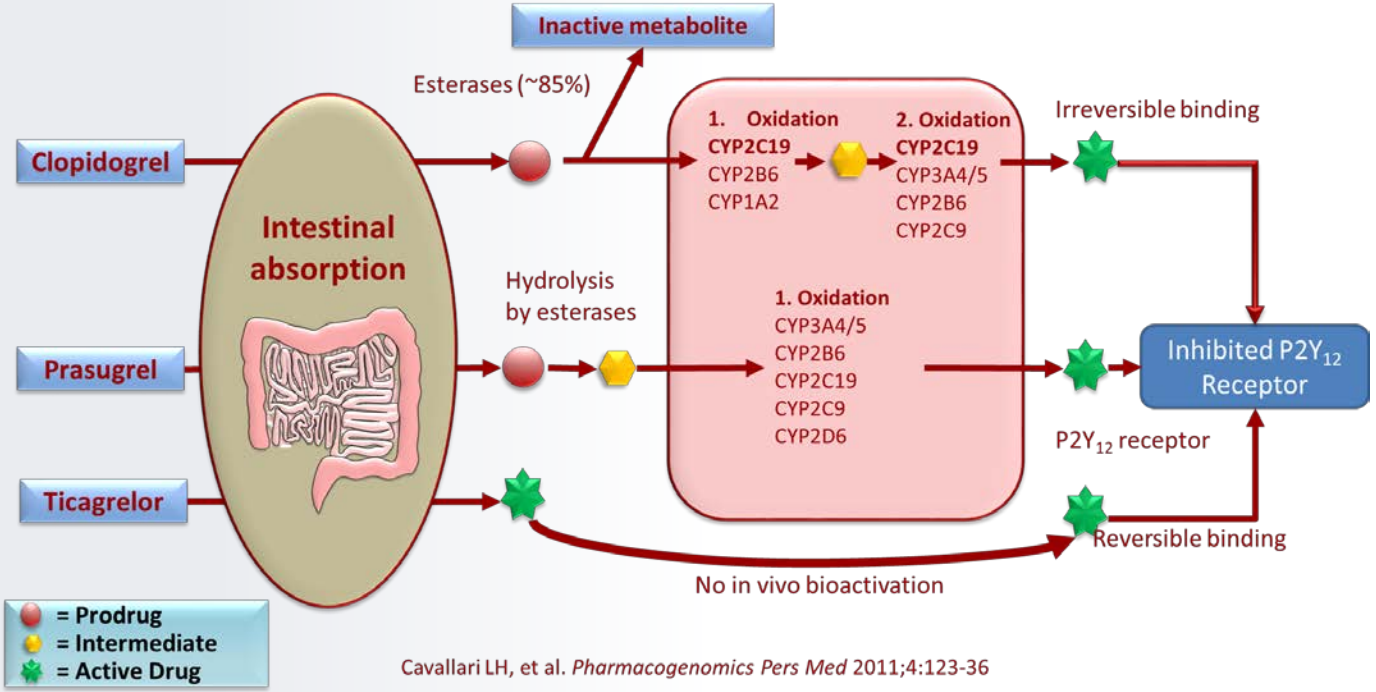
# Clopidogrel Metabolism




Sangkuhl K et al. "Clopidogrel pathway" *Pharmacogenet Genomics* (2010). Copyright to PharmGKB.

# Alternatives to Clopidogrel




Cavallari LH, et al. *Pharmacogenomics Pers Med* 2011;4:123-36

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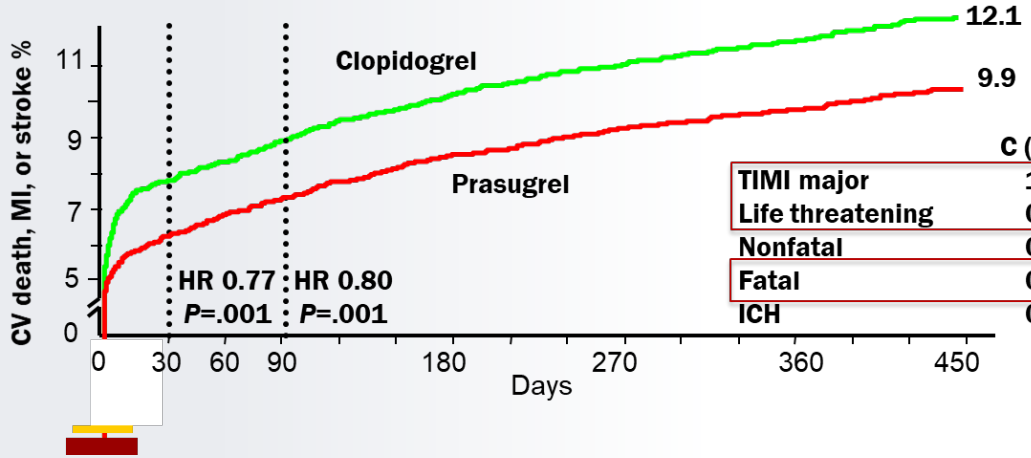
# Genetic Sub-studies

# Prasugrel Evidence: Secondary Prevention

## Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)

- **13,608 patients with high-risk ACS scheduled for PCI randomized to:**
  - **clopidogrel (300 mg LD and 75 mg MD)**
  - **OR**
  - **prasugrel (60 mg LD and 10 mg MD)**

**Prasugrel reduces ischemic events with a higher rate of bleeding**




**Bleeding Events**

| | C (%) | P (%) | *P-value* |
|---|---|---|---|
| TIMI major | 1.8 | 2.4 | .03 |
| Life threatening | 0.9 | 1.4 | .01 |
| Nonfatal | 0.9 | 1.1 | .23 |
| Fatal | 0.1 | 0.4 | .002 |
| ICH | 0.3 | 0.3 | .74 |

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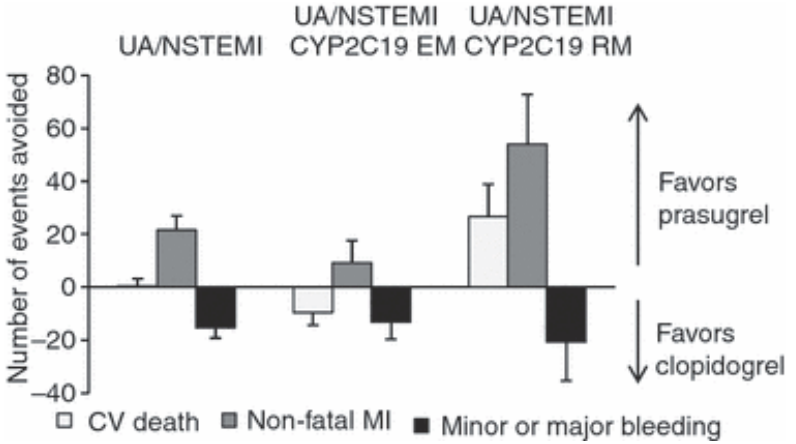
# Prasugrel vs Clopidogrel by Genotype: Genetic Sub-study of TRITON TIMI-38

| Event (and group) | Prasugrel [% (95% CI)] | Clopidogrel [% (95% CI)] | Relative risk* (95% CI) |
|---|---|---|---|
| **CV death, non-fatal MI, or non-fatal stroke** | | | |
| CYP2C19 EM | 9.6 (8.3 – 10.8) | 9.8 (8.3 – 11.3) | 0.98 (0.80 – 1.20) |
| CYP2C19 RM | 8.5 (6.2 – 11.4) | 15.0 (11.6 – 18.8) | 0.57 (0.39 – 0.83) |
| **CV death** | | | |
| CYP2C19 EM | 1.9 (1.2 – 2.5) | 0.9 (0.3 – 1.7) | 2.07 (0.96 – 5.66) |
| CYP2C19 RM | 1.6 (0.6 – 3.2) | 4.2 (2.2 – 6.1) | 0.36 (0.13 – 0.96) |
| **Non-fatal MI** | | | |
| CYP2C19 EM | 7.4 (6.4 – 8.5) | 8.3 (7.0 – 9.6) | 0.89 (0.72 – 1.11) |
| CYP2C19 RM | 6.2 (4.2 – 8.5) | 11.6 (8.7 – 14.8) | 0.53 (0.34 – 0.81) |
| **Major or Minor Bleeding** | | | |
| CYP2C19 EM | 4.7 (3.7 – 5.7) | 3.4 (2.6 – 4.2) | 1.38 (1.00 – 1.93) |
| CYP2C19 RM | 5.5 (3.6 – 8.1) | 3.5 (2.0 – 5.5) | 1.60 (0.8 – 3.1) |

EM=Extensive Metabolizer (NM/RM/UM)
RM=Reduced Metabolizer (IM/PM)

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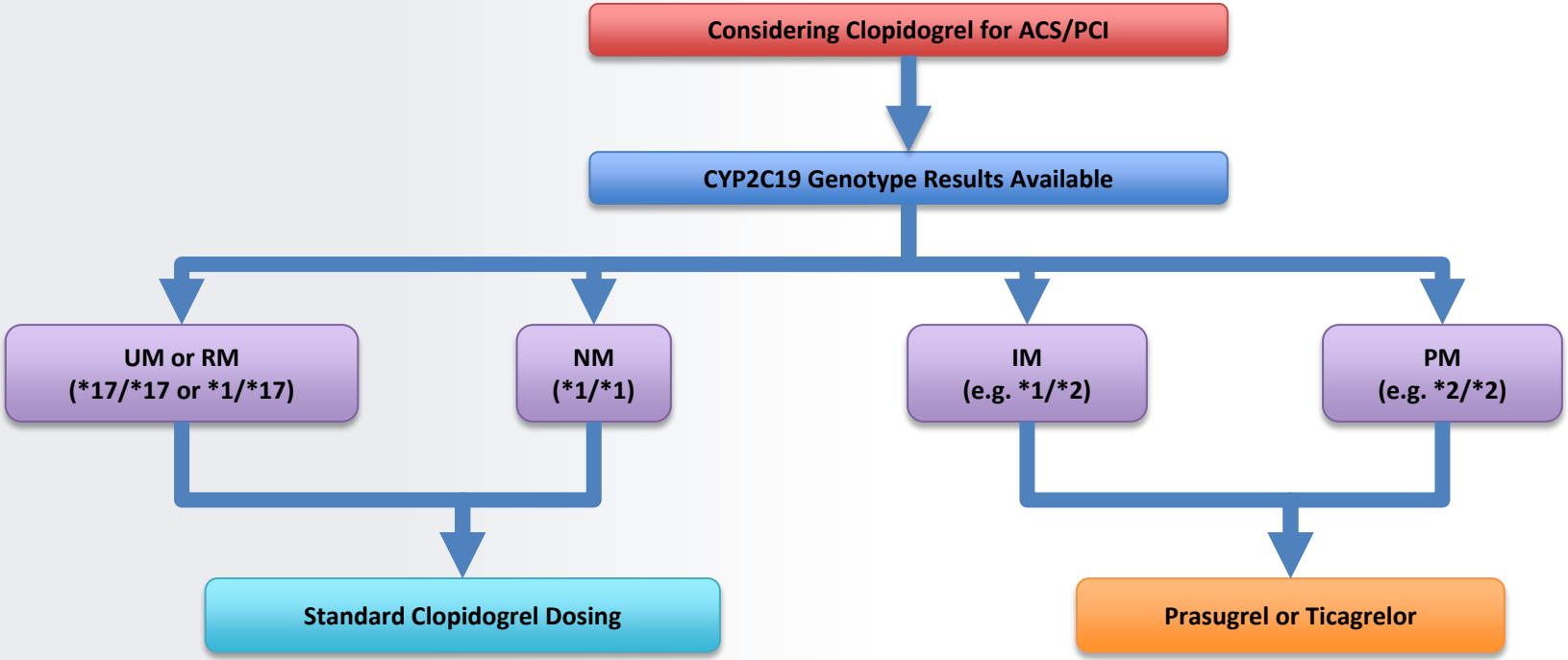
# CPIC Guidelines




CPIC, Clinical Pharmacogenetics Implementation Consortium
Scott SA et al. *Clin Pharmacol Ther* 2013;94:317-23.

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# Genetic Sub-studies Benefits and Limitations

- Help determine effect of genetic markers in selected populations
  - responder vs non responder
  - Outliers (toxicity)
- Insights into clinical utility of testing to diagnose or treat a condition

- Secondary analyses, dependent on the quality of the original study design and execution
- Usually low number of subjects with genetic variation of interest

Sorich et al. *J Thromb Haemost* 2010;8:1678-84.

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# Randomized Clinical Studies

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- Different strategies to test value of incorporating PGx into clinical care
  - Superiority
  - Non-Inferiority

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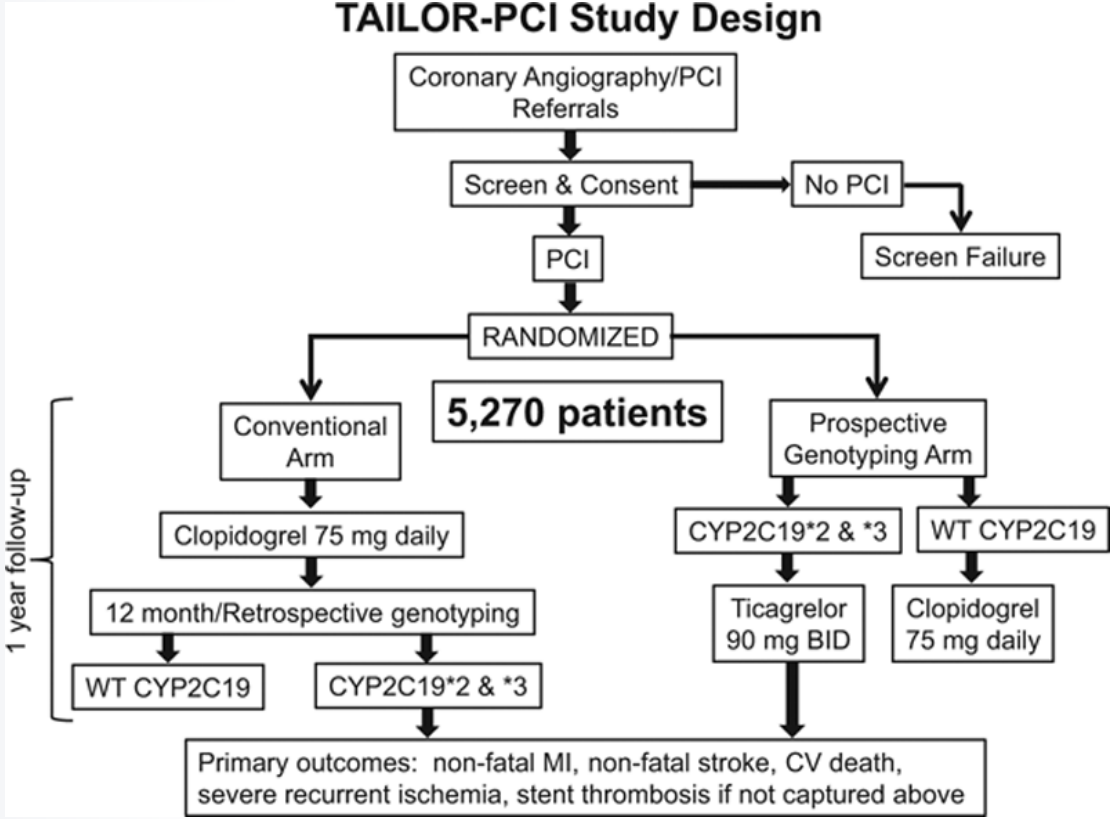
# Randomized Clinical Studies

TAILOR-PCI STUDY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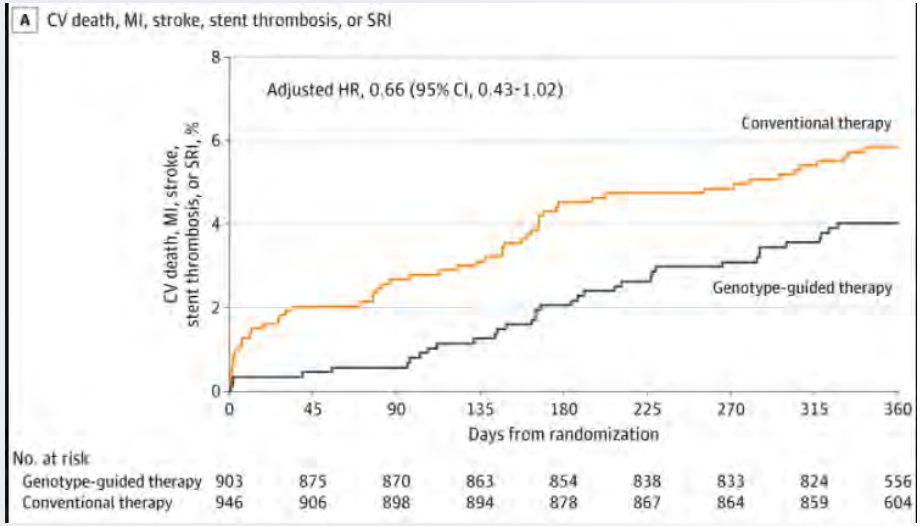
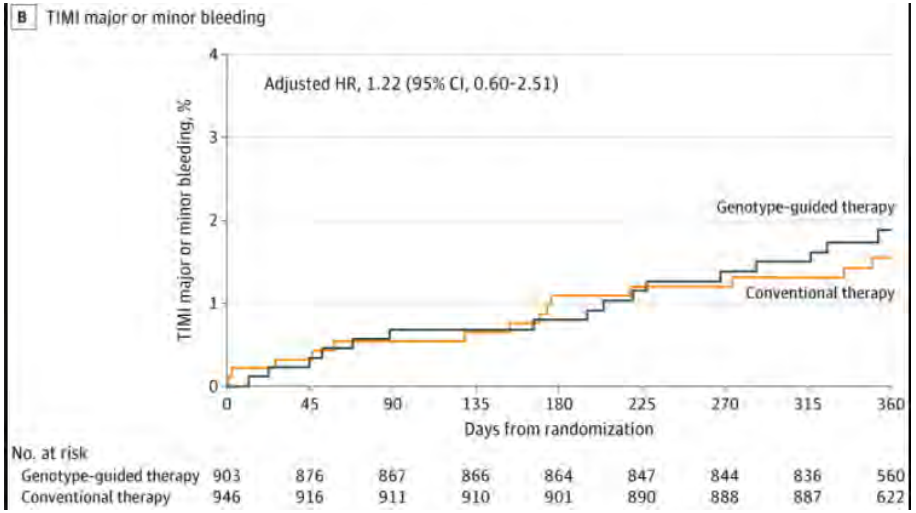
# TAILOR-PCI : RESULTS

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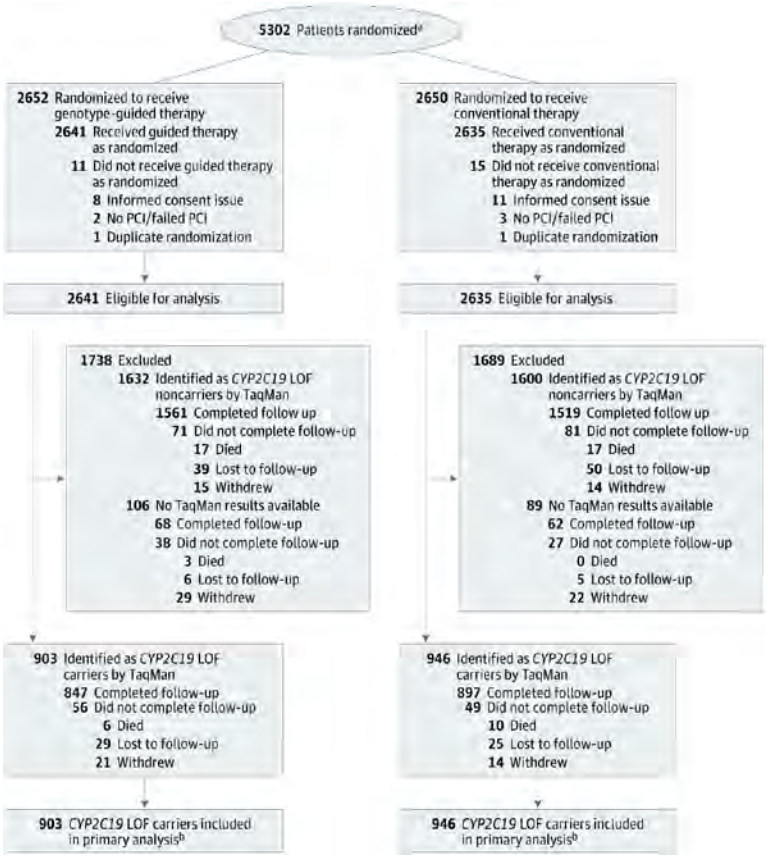
# Randomized Clinical Studies

**Table. TAILOR-PCI Inclusion and Exclusion Criteria**

| |
|---|
| Inclusion criteria |
| Patient ≥18 y of age |
| Patient presents with ACS or stable CAD |
| Patient is eligible for PCI |
| Patient is willing and able to provide informed written consent |
| Exclusion criteria |
| Patient not able to receive 12 mo of dual antiplatelet therapy |
| Failure of index PCI |
| Patient or physician refusal to enroll in the study |
| Patient with known *CYP2C19* genotype before randomization |
| Planned revascularization of any vessel within 30 d post-index procedure or of the target vessel(s) within 12 mo post-procedure |
| Anticipated discontinuation of clopidogrel or ticagrelor within the 12-mo follow-up period, example for elective surgery |
| Serum creatinine >2.5 mg/dL within 7 d of index procedure |
| Platelet count <80 000 or >700 000 cells/mm$^3$ or white blood cell count <3000 cells/mm$^3$ if persistent (at least 2 abnormal values) within 7 d before index procedure |
| History of intracranial hemorrhage |
| Known hypersensitivity to clopidogrel or ticagrelor or any of its components |
| Inability to take aspirin at a dosage of ≤100 mg |

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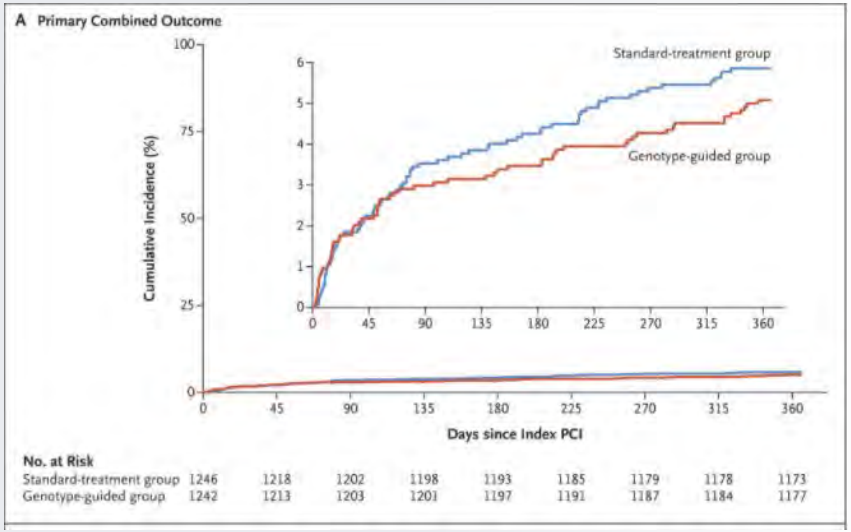
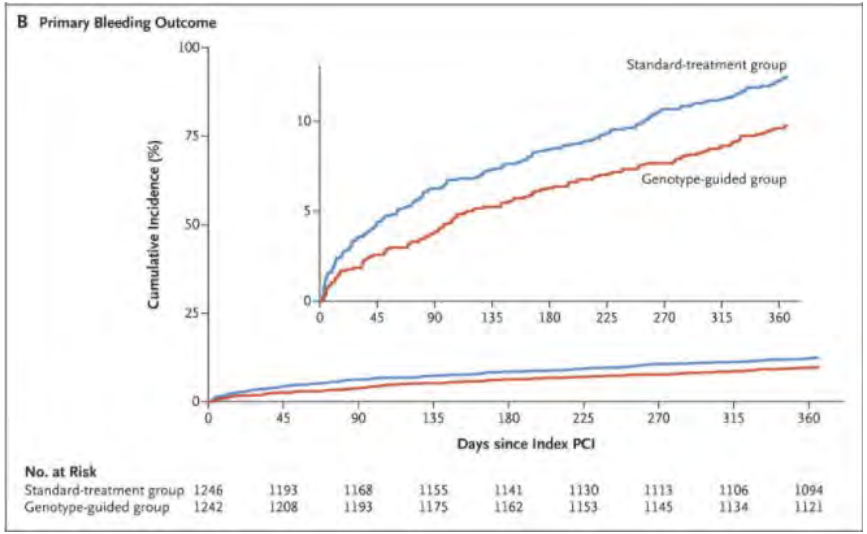
# POPular Genetics: Results



# Randomized Clinical Studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## A Genotype-Guided Strategy for Oral $P2Y_{12}$ Inhibitors in Primary PCI

Daniel M.F. Claassens, M.D., Gerrit J.A. Vos, M.D., Thomas O. Bergmeijer, M.D.,

**Conclusions:**

In patients undergoing primary PCI, a *CYP2C19* genotype–guided strategy for selection of oral P2Y12 inhibitor therapy was **non-inferior** to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding.

**Table 2. Primary Combined Outcome and Secondary Thrombotic Outcomes.***

| Outcome | Genotype-Guided Group (N=1242) | Standard-Treatment Group (N=1246) | Absolute Difference (95% CI)† | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|
| | no. of patients (%) | | percentage points | | |
| **Primary combined outcome‡** | | | | | |
| Noninferiority analysis | 63 (5.1) | 73 (5.9) | −0.7 (−2.0 to 0.7) | | <0.001§ |
| Superiority analysis | 63 (5.1) | 73 (5.9) | | 0.87 (0.62 to 1.21) | 0.40 |
| **Secondary thrombotic outcomes** | | | | | |
| Combined ischemic outcome of death from vascular causes, myocardial infarction, definite stent thrombosis, or stroke | | | | | |
| Noninferiority analysis | 34 (2.7) | 41 (3.3) | −0.3 (−1.4 to 0.8) | | |
| Superiority analysis | 34 (2.7) | 41 (3.3) | | 0.83 (0.53 to 1.31) | |
| Combined ischemic outcome of death from vascular causes, acute coronary syndrome, definite stent thrombosis, stroke, or urgent TVR | 57 (4.6) | 59 (4.7) | | 0.97 (0.67 to 1.40) | |
| Death from any cause | 19 (1.5) | 19 (1.5) | | 1.00 (0.53 to 1.89) | |
| Death from vascular causes | 9 (0.7) | 10 (0.8) | | 0.90 (0.37 to 2.22) | |
| Acute coronary syndrome | 43 (3.5) | 43 (3.5) | | 1.00 (0.66 to 1.53) | |
| Myocardial infarction | 19 (1.5) | 26 (2.1) | | 0.73 (0.41 to 1.32) | |
| Stroke | 8 (0.6) | 11 (0.9) | | 0.73 (0.29 to 1.82) | |
| Ischemic | 7 (0.6) | 10 (0.8) | | 0.70 (0.27 to 1.85) | |
| Hemorrhagic | 1 (0.1) | 1 (0.1) | | 1.00 (0.06 to 16.1) | |
| Definite stent thrombosis | 2 (0.2) | 3 (0.2) | | 0.67 (0.11 to 4.01) | |
| Definite, probable, or possible stent thrombosis | 9 (0.7) | 11 (0.9) | | 0.73 (0.29 to 1.81) | |
| Urgent TVR | 15 (1.2) | 15 (1.2) | | 1.00 (0.49 to 2.05) | |

* All outcomes were confirmed by an independent adjudication committee. The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. TVR denotes target-vessel revascularization.
† Integrated differences were used to calculate the absolute differences at 12 months for the two Kaplan–Meier curves. Therefore, these values differ from the absolute difference in the cumulative incidence at 12 months.
‡ The primary combined outcome was death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes criteria.
§ The P value was not adjusted to account for the assessment of two primary outcomes.

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# Randomized Clinical Studies Benefits and Limitations

- Good randomization will "wash out" any selection bias
- Can determine causality
- Help guide decisions for allocation of healthcare resources

- Not clinically feasible or necessary for many pharmacogenomic applications
- Rigorously designing a scientific trial is not always ethical
- $$$$$$$$$$$

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# Clinical implementation and feasibility studies (pragmatic trial)

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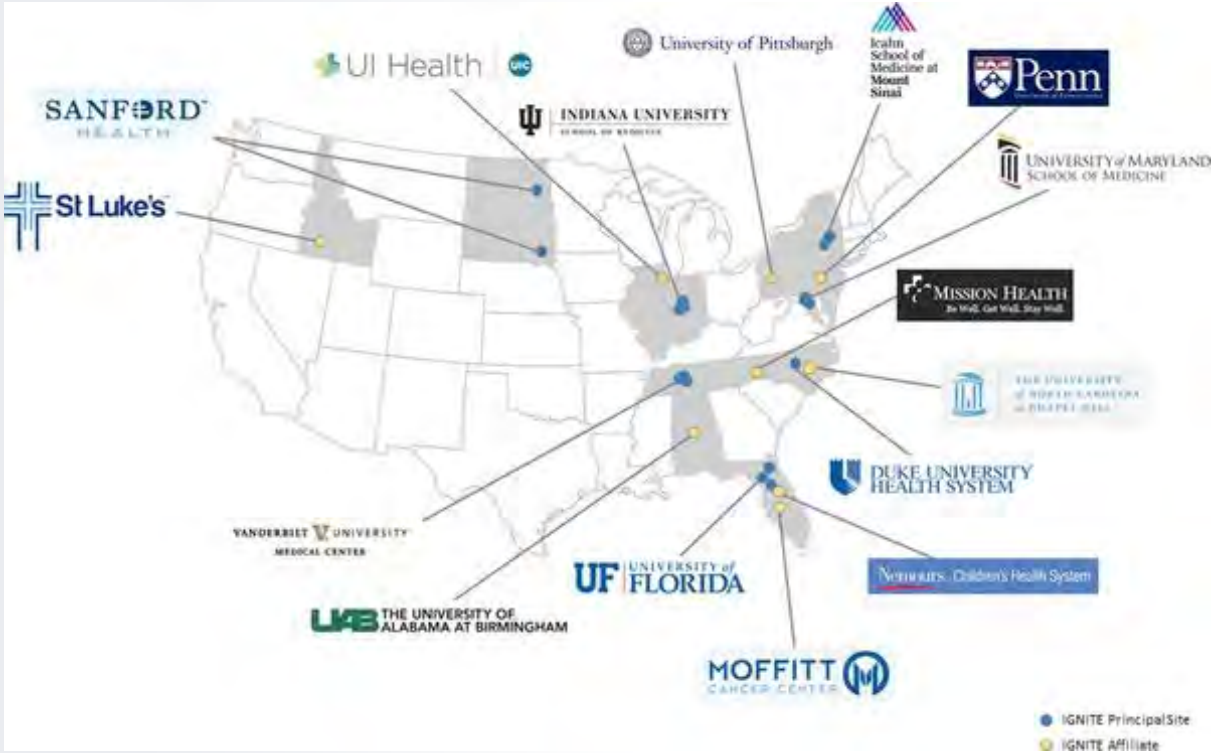
# IGNITE: Pharmacogenetics Working Group

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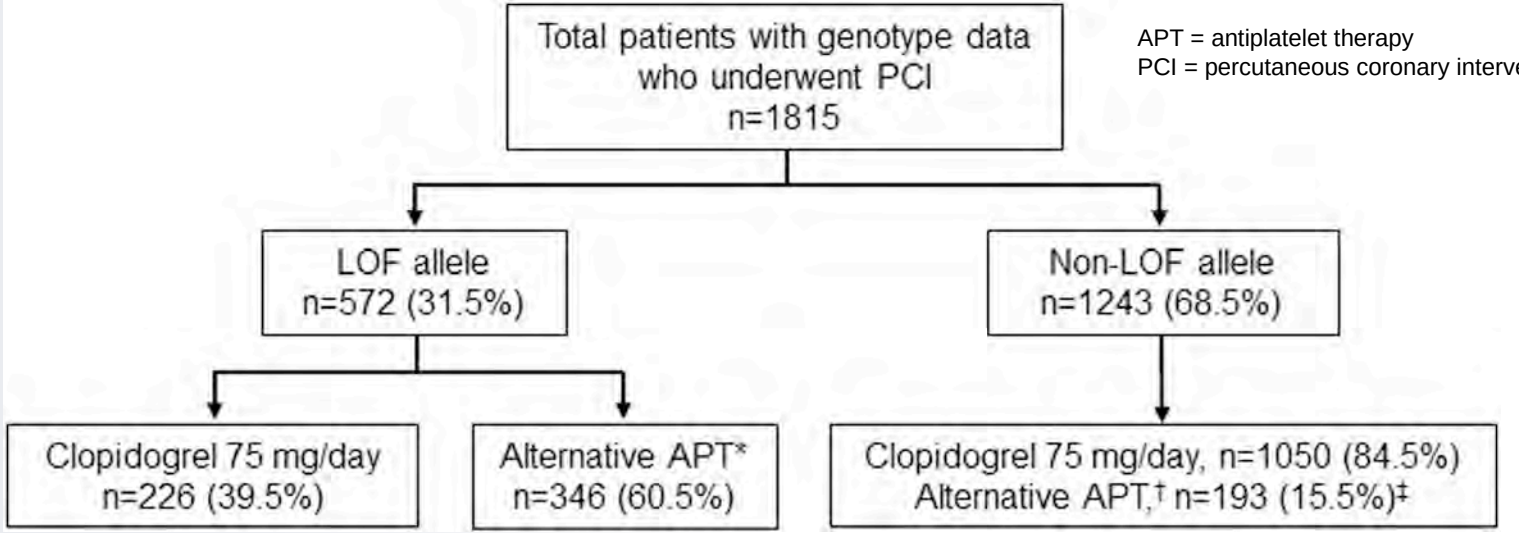
# Real-World Evidence




APT = antiplatelet therapy
PCI = percutaneous coronary intervention

*Cavallari et al., "Multisite Investigation of Outcomes with Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy after Percutaneous Coronary Intervention," JACC Cardiovasc Interv, vol. 11, no. 2, pp. 181-191, Jan 22 2018.*

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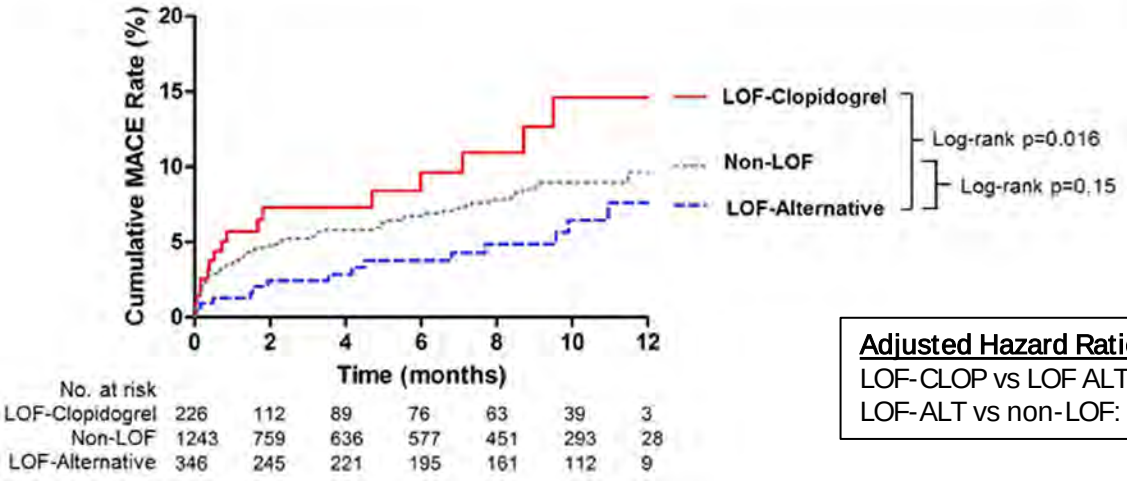
# Results

Clinical Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy after PCI at 7 U.S. Institutions

↓

Kaplan-Meier Survival Estimates of MACE in Relation to *CYP2C19* Genotype and Antiplatelet Therapy




**Adjusted Hazard Ratio**

LOF-CLOP vs LOF ALT: 2.21 (1.13-4.33) p=0.021

LOF-ALT vs non-LOF: 0.81 (0.48-1.35) p=0.41

*Cavallari et al., "Multisite Investigation of Outcomes with Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy after Percutaneous Coronary Intervention," JACC Cardiovasc Interv, vol. 11, no. 2, pp. 181-191, Jan 22 2018.*

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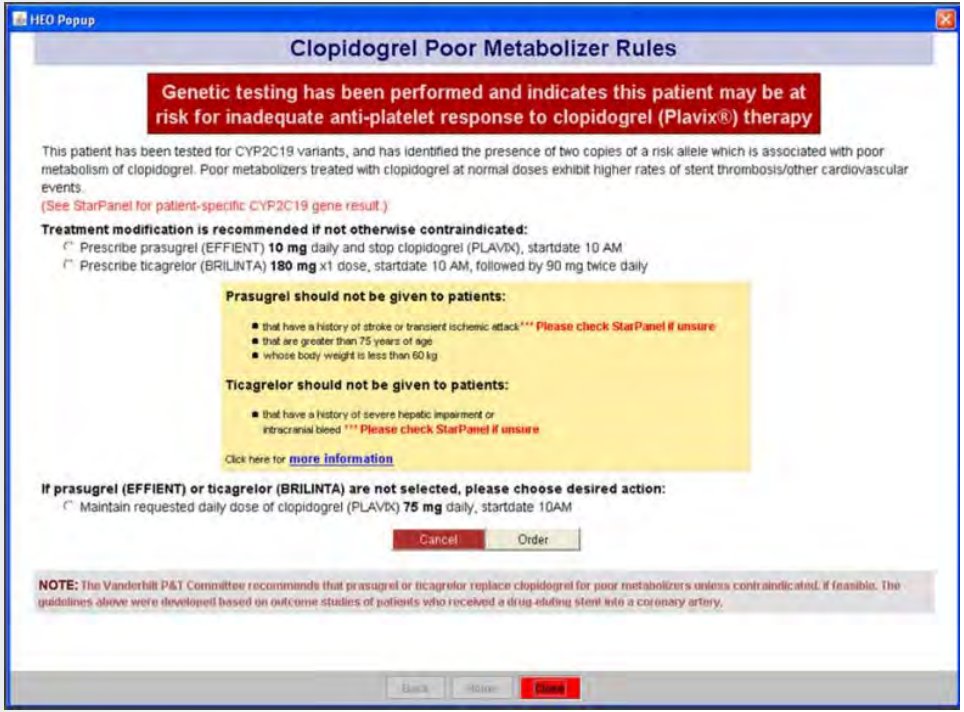
# Clinical Decision Support Example



# Clinical implementation and feasibility studies (pragmatic) Benefits and Limitations

- Broad view of an intervention, including approaches to improve its effectiveness (different from efficacy)
- Allows for economic analysis
- Identifies systematic, personnel, and technological barriers

- Could be overestimating benefits and underestimating harm
- Frequently include complex interventions
- Investigators to take responsibility for recruitment, treatment, and follow-up of participants

N Engl J Med 2016;375:454-63.

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# Pharmacogenomics Research Resources


https://cpicpgx.org/


https://www.pharmgkb.org/


https://www.pgrn.org/

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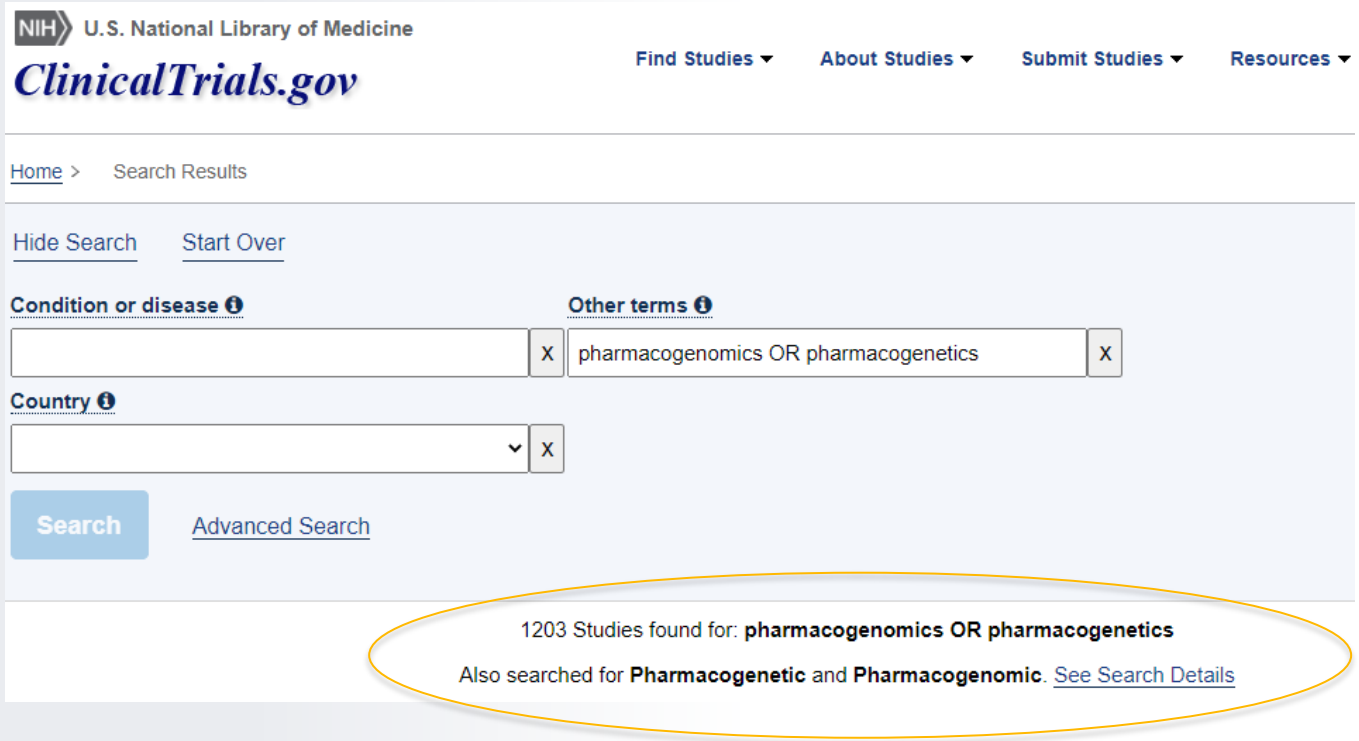
# Registered Clinical Studies




https://clinicaltrials.gov/ct2/home

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# Summary

- PGx can be used to guide specific drugs with clinical evidence
- Resources, like **PharmGKB** and **CPIC** guidelines, can help with PGx considerations for research design and clinical recommendations
- Opportunity to advance PGx research throughout translational spectrum
- Clinical studies are warranted in diverse patients populations to determine the utility for pharmacogenomics and deliver reliable care

# Thank You!

**SC CTSI** | www.sc-ctsi.org Phone: (323) 442-4032 Email: info@sc-ctsi.org Twitter: @SoCalCTSI

**Cite us:** This work was supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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# Big Data and Genomics

**Jerry S.H. Lee, PhD**
Associate Professor of Clinical Medicine, Chemical Engineering, and Material Sciences
University of Southern California

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# Disclosure Statement

- Consultant, Murtha Cancer Center, Henry M. Jackson Foundation
- Scientific Advisory Board, AtlasXomics, Inc.
- Board of Trustees, Health and Environmental Sciences Institute
- Chief Science and Innovation Officer, Lawrence J. Ellison Institute for Transformative Medicine of USC

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# My Perspective

## PhD in Chemical and Biomolecular Engineering (JHU)

***Nuclear and Cellular Mechanics: Implications for Laminopathies and Cancer***

### Ellison Institute & University of Southern California

- **Associate Professor of Clinical Medicine, Chemical Engineering, and Material Sciences** **(2018 – Present)**
- **Chief Science and Innovation Officer, Lawrence J. Ellison Institute for Transformative Medicine of USC** **(2018 – Present)**
- Member, Murtha Cancer Center, Walter Reed National Medical Center, Dept. of Defense (2019 – Present)
- National Research Advisory Council, VA ORD, Dept. of Veterans Affairs (2018 – Present)
- Biden-Harris Transition Team, JBRPT (2020 – 2021)

### National Cancer Institute

- **Office of the Director** **(2006 – 2018)**
- **Cancer Moonshot Task Force, WH OVP** **(2016 – 2017)**
- Adjunct Associate Professor, Dept. of Chem. & Biomolecular Eng, Johns Hopkins University (2008 – 2018)
- Data Research Health Scientist, DC VAMC, Dept. Veterans Affairs (2013 – 2018)

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# How Did We Get Here?

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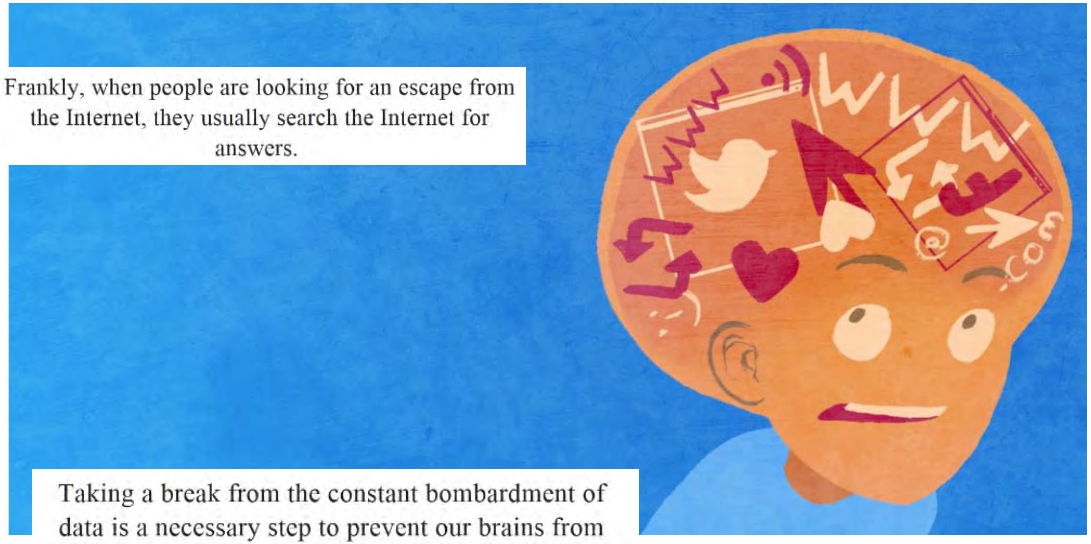
The Daily Dot

# The struggle against Internet overload is real




"Since the **dawn of civilization**, roughly 12,000 B.C., to 2003 A.D., **only 5 exabytes (5,000 PB)** of data has been created.

Now, with the rise of the Internet's influence in our daily lives, we produce this amount of data ***every two days***."

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https://www.dailydot.com/via/internet-overload-the-struggle-against-is-real/

GEN3 DATA COMMONS

# 9/24/2021

**783,126** Total Subjects | **33,086,052** Total Files | **14.03 PB** Total File Size

## NIH NATIONAL CANCER INSTITUTE Cancer Research Data Commons

83,709 Subjects
622 Attributes
5,226,838 Files
Total Size 3.71 PB

## NIH National Institute of Allergy and Infectious Diseases — AccessClinicalData@NIAID

2,096 Subjects
145 Attributes
5 Files
Total Size 1.51 MB

## GenoMEL the Melanoma Genetics Consortium

1,390 Subjects
387 Attributes
6,555 Files
Total Size 31.6 TB

## ACCOUNT

1,516 Subjects
985 Attributes
5,661 Files
Total Size 7.77 TB

## CANINE Data Commons

1,499 Subjects
1,008 Attributes
3,802 Files
Total Size 1.88 TB

## NIH HEAL INITIATIVE | Justice Community Opioid Innovation Network (JCOIN)

237 Subjects
854 Attributes
163 Files
Total Size 410.18 MB

## BDGC

107,418 Subjects
784 Attributes
11,287 Files
Total Size 3.76 TB

## BloodPAC BLOOD PROFILING ATLAS IN CANCER

4,839 Subjects
888 Attributes
33,825 Files
Total Size 27.91 TB

## VPO Veterans Precision Oncology Data Commons

163,695 Subjects
1,606 Attributes
352,783 Files
Total Size 2.18 TB

## CHICAGOLAND COVID-19 COMMONS

53,728 Subjects
1,456 Attributes
282,082 Files
Total Size 117.64 TB

## Gabriella Miller Kids First Pediatric Research Program Data Resource Center

21,833 Subjects
622 Attributes
633,305 Files
Total Size 6.1 PB

## NIH National Heart, Lung, and Blood Institute | BioData CATALYST

240,460 Subjects
739 Attributes
641,162 Files
Total Size 3.55 PB

## MIDRC MEDICAL IMAGING AND DATA RESOURCE CENTER

5,356 Subjects
510 Attributes
1,356,018 Files
Total Size 486.03 GB

## Environmental Data Commons

265 Attributes
24,355,516 Files
Total Size 70.51 TB

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https://stats.gen3.org


Microhabitats save mammals, but not birds, from warming pp. 553 & 633
Gut microbiota modulate immunotherapy pp. 573, 595, & 602
Physically distanced quantum gates pp. 576 & 614
Science
$15
5 FEBRUARY 2021
sciencemag.org
AAAS
SPECIAL ISSUE
HUMAN GENOME AT
20


The international journal of science / 11 February 2021
nature
GENOME REVOLUTION
How 20 years of the human genome sequence have helped reshape science
Coronavirus
The power and pitfalls of rapid tests for COVID-19
Into the unknown
Quantum technology offers boost to the hunt for dark matter
The hear and now
Sounding out how the middle ear evolved in mammals

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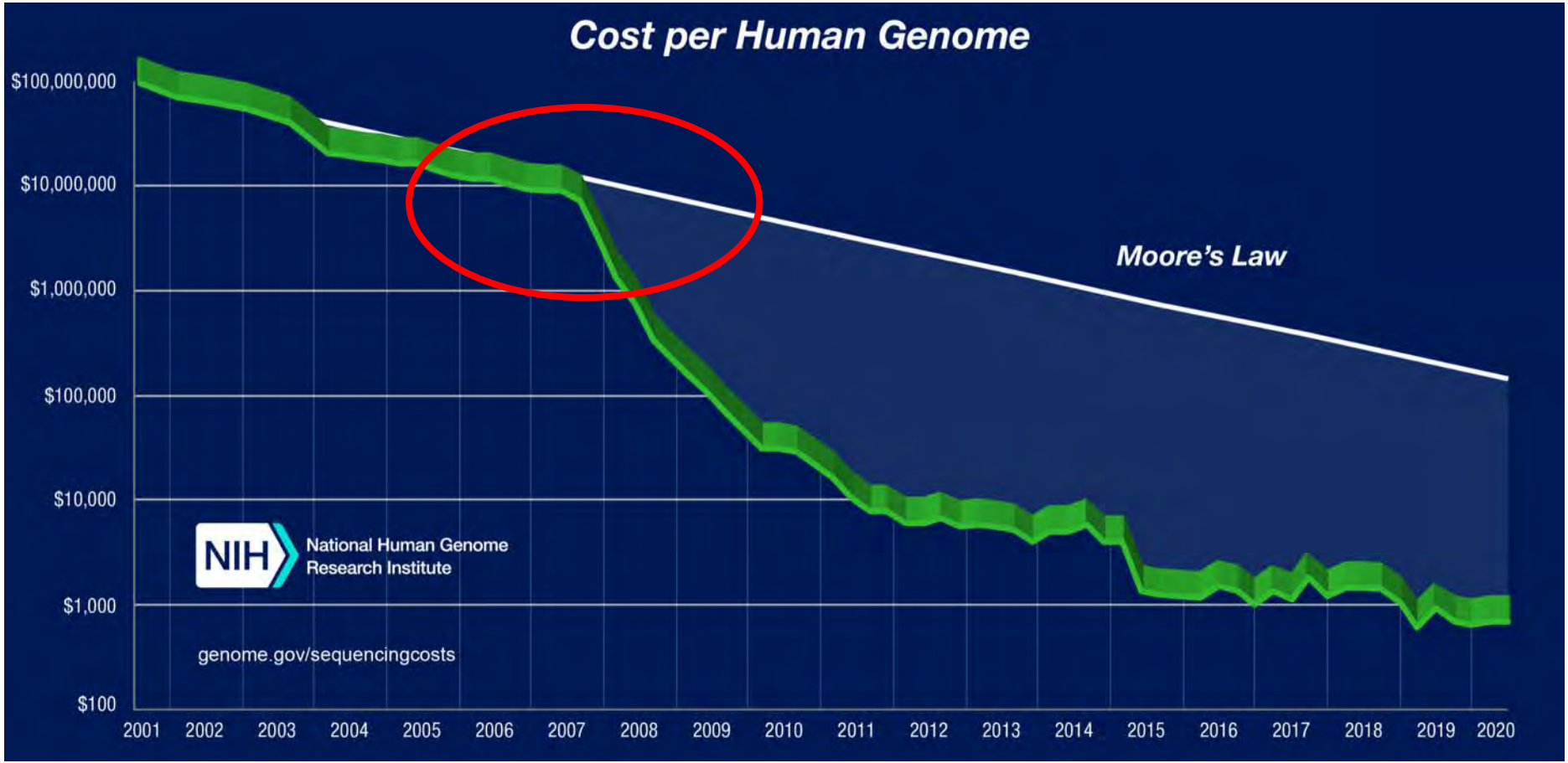


https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

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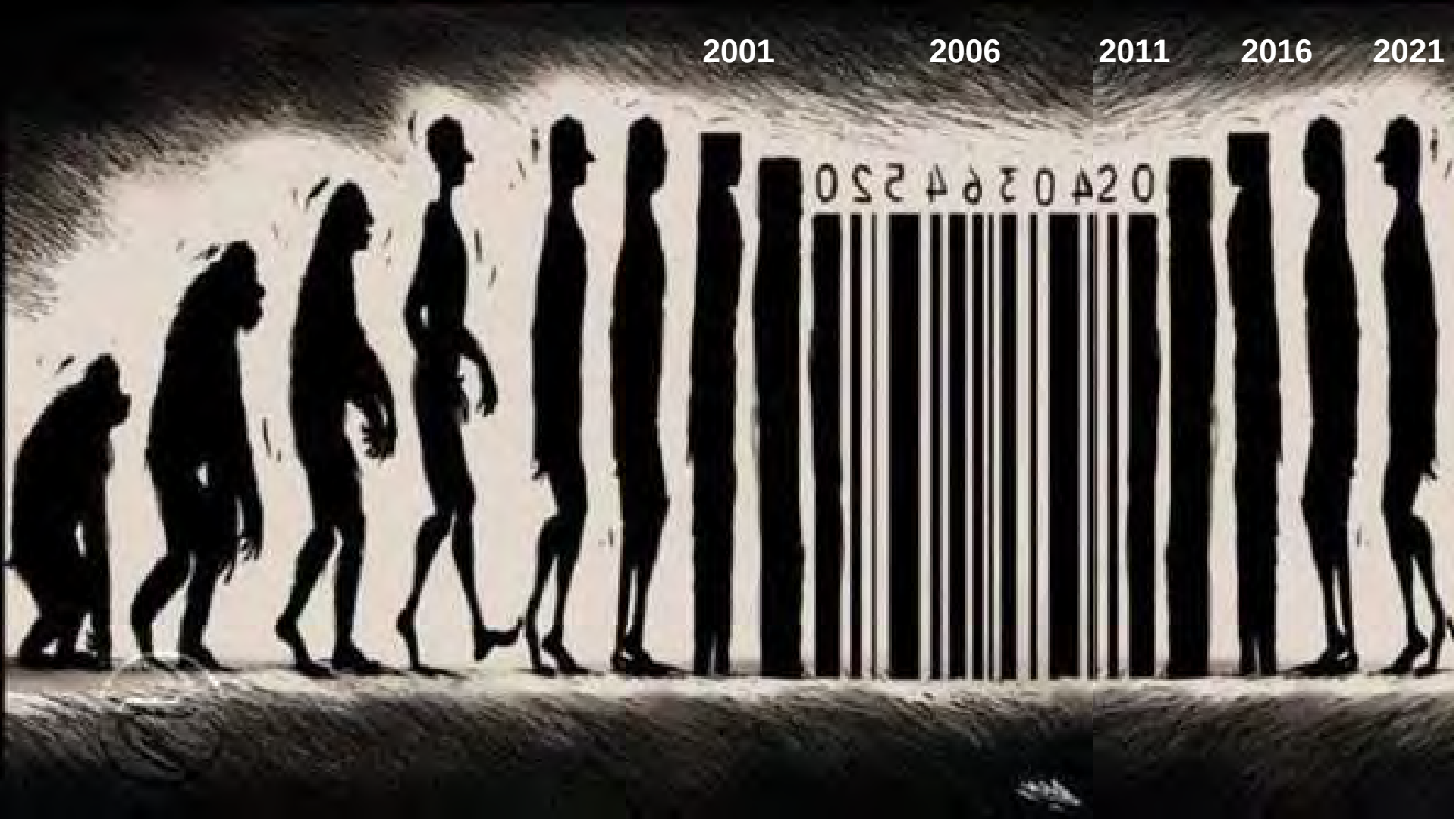
2001
2006
2011
2016
2021


**9/28/2006**

# NIH Announces Two Integral Components of The Cancer Genome Atlas Pilot Project

The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health (NIH), today announced another two of the components of The Cancer Genome Atlas (TCGA) Pilot Project, a three-year, $100 million collaboration to test the feasibility of using large-scale genome analysis technologies to identify important genetic changes involved in cancer. Lung, brain (glioblastoma), and ovarian cancers have been chosen as the tumors for study by TCGA Pilot Project.

"…the Data Coordinating Center will make TCGA data **publicly accessible**…and access to all TCGA data will be provided in a manner that meets the highest standards for **protection** and **respect** of the **research participants**…."

https://www.nih.gov/news-events/news-releases/nih-announces-two-integral-components-cancer-genome-atlas-pilot-project

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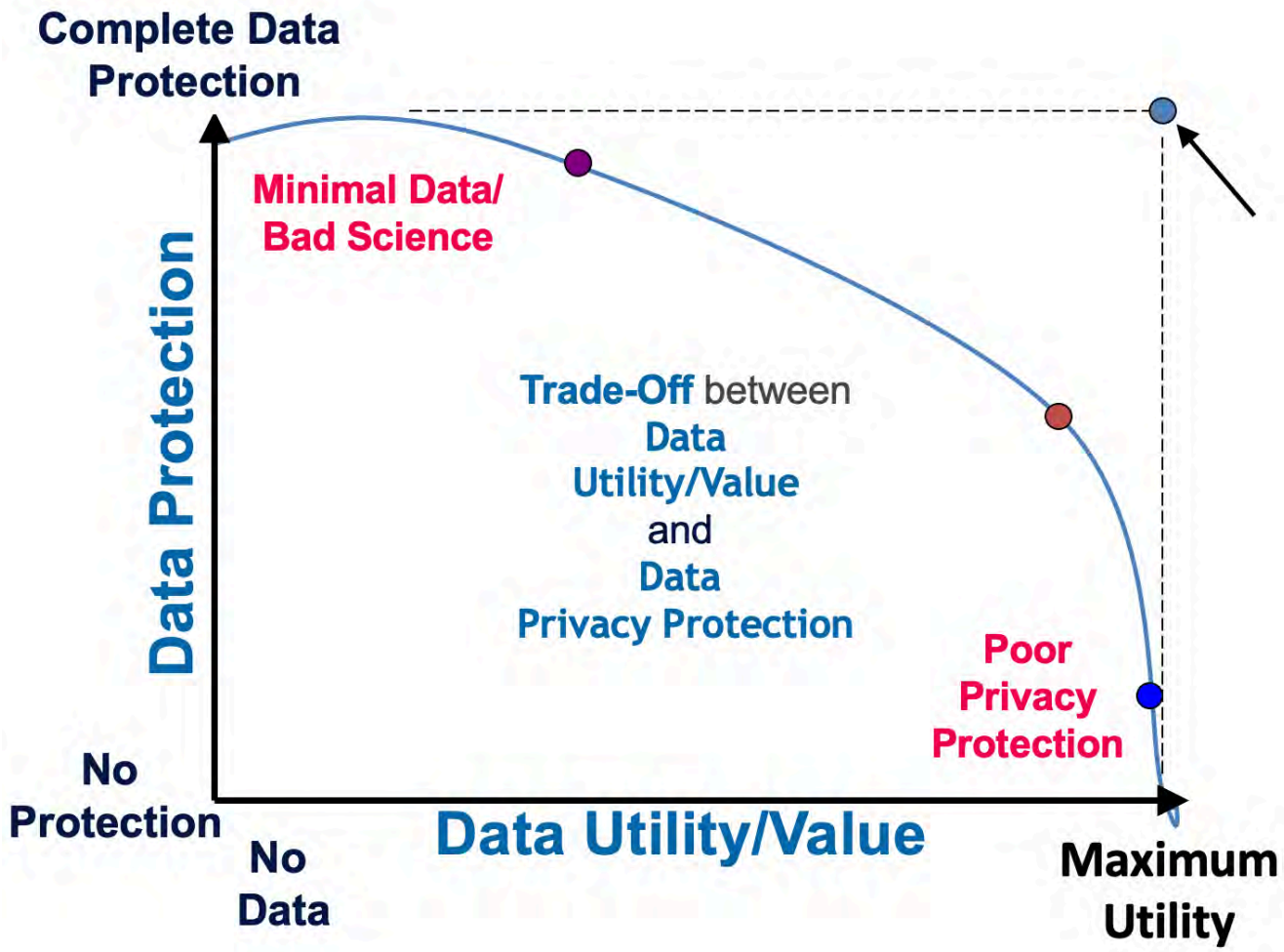


Daniel C. Barth-Jones, M.P.H., Ph.D. (Columbia University), IAPP 2017

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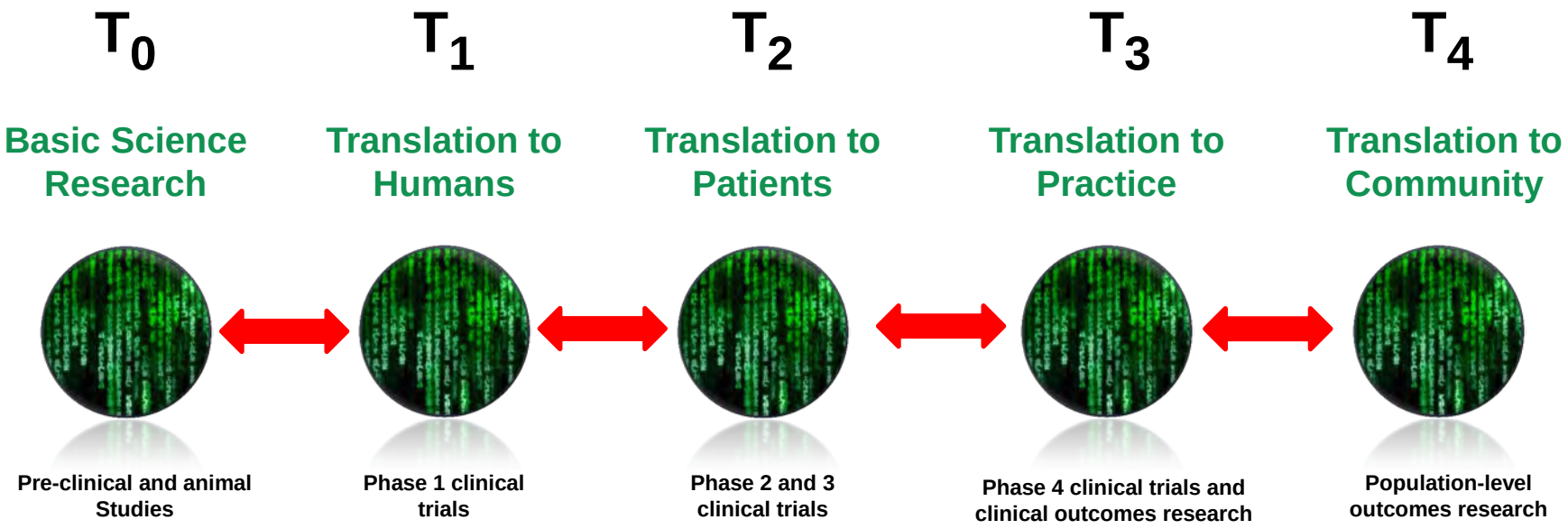
# Translation Data Spheres




When analyses are conducted **without understanding the basic science or clinical context of data capture**, there is a risk of ***inappropriate interpretation***, ***lack of clinical relevance***, or ***lack of feasible implementation*** for broader impact.

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# Making Data FAIR & Transparent

**F**indable

**A**ccessible

**I**nteroperable

**R**eusable

https://www.force11.org/group/fairgroup/fairprinciples

The Washington Post



Speaking Of Science

# Londoners accidentally pay for free Wi-Fi with a firstborn, because no one reads anymore



35

By Rachel Feltman September 29 Follow @rachelfeltma



Courtesy of John Wilbanks

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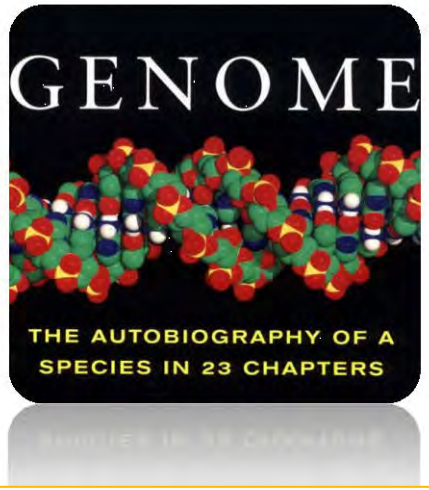
# Visualization of Genome

Genome = A Book

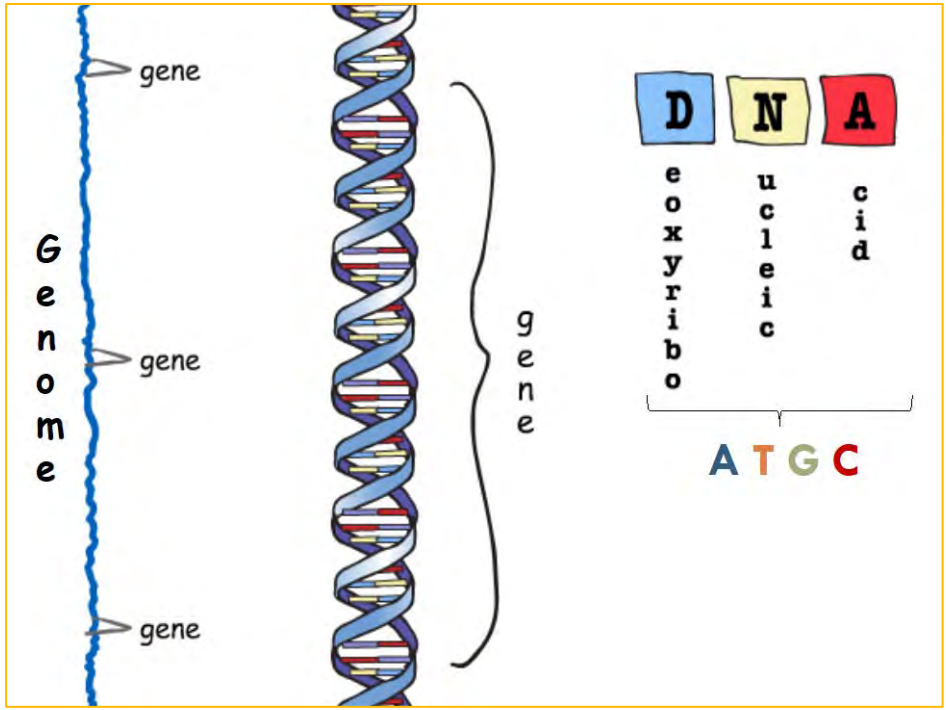
Written in 4 letters of nucleotides – A T G C

23 Chromosomes = 23 Chapters

Genes = Stories in each chapter




~3 billion DNA base pairs



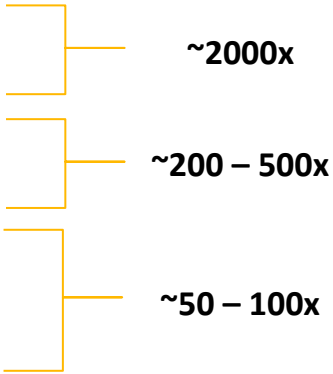

Courtesy of Dhawal Verma

**9/16/2021**

# Human Autocorrect Works (Mostly)

| Cell Type | Turnover Time |
|---|---|
| small intestine epithelium | 2-4 days |
| white blood cells | 2-5 days |
| platelets | 10 days |
| skin cells | 10-30 days |
| sperm (male gametes) | 2 months |
| red blood cells | 4 months |
| liver cells | 0.5 – 1 year |
| fat cells | 8 years |
| heart cells | 0.5-10% per year |
| skeleton | 10% per year |
| central nervous system | life time |
| oocytes (female gametes) | life time |

**Cell Divisions (18.5 yrs)**




Modified from http://book.bionumbers.org/how-quickly-do-different-cells-in-the-body-replace-themselves/

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# Single Nucleotide Polymorphisms (SNPs)

- SNPs are variations that involve a change in just one nucleotide.

THE RAT CAN RUN FAST

THE CAT CAN RUN FAST

Courtesy of Dhawal Verma

SC CTSI

# Copy Number Variants (CNVs)

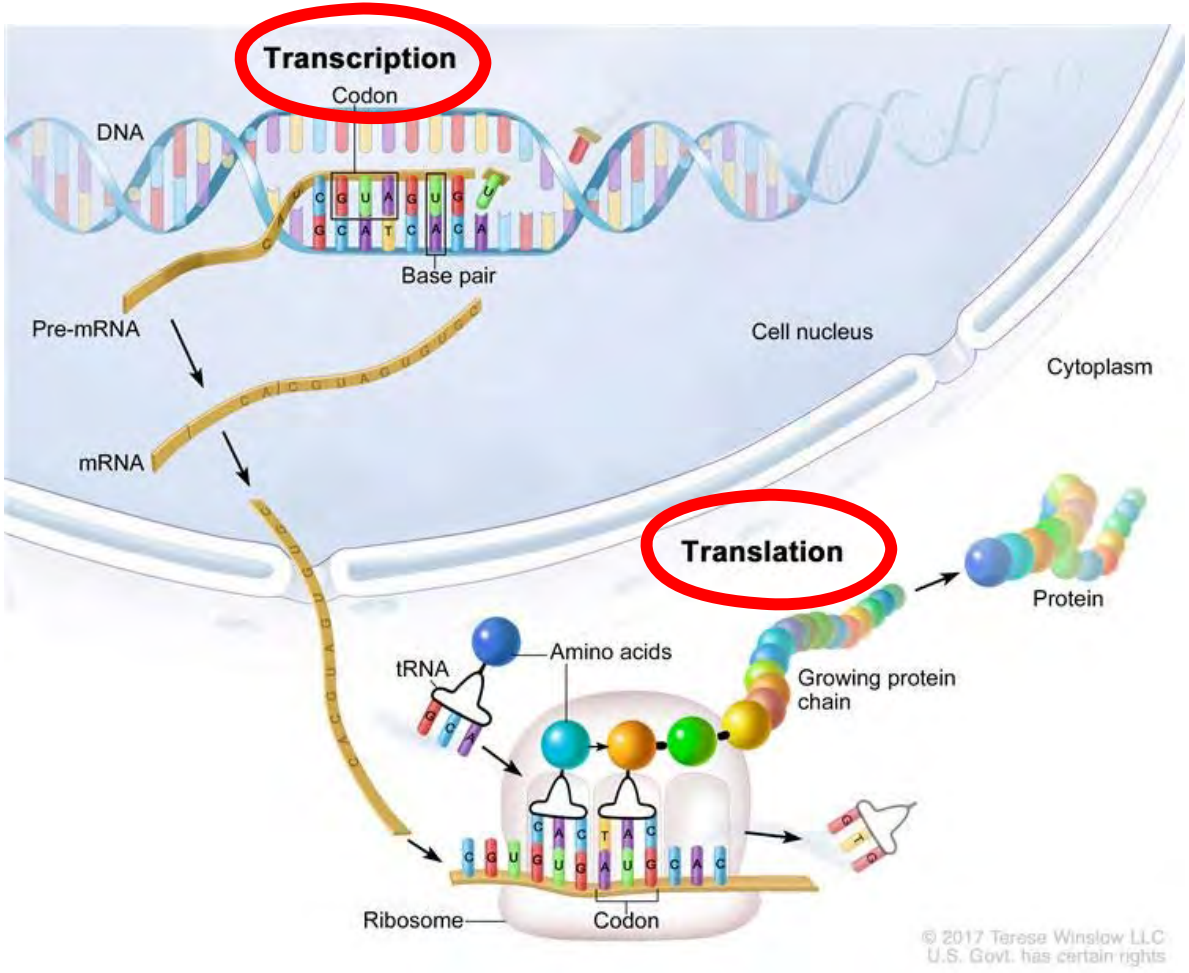
- CNVs are defined as chromosomal segments, at least 1000 bases (1 kb) in length that vary in number of copies from human to human.
- CNVs are large chunks of DNA that are deleted, copied, flipped or otherwise rearranged in combinations that can be unique for each individual.

YOU CAN RUN FAST

YOU CAN RUN RUN RUN FAST

SC CTSI

Courtesy of Dhawal Verma




**Read/Write Error**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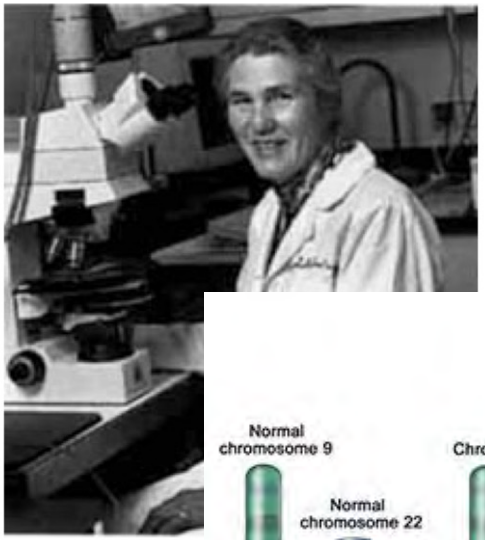
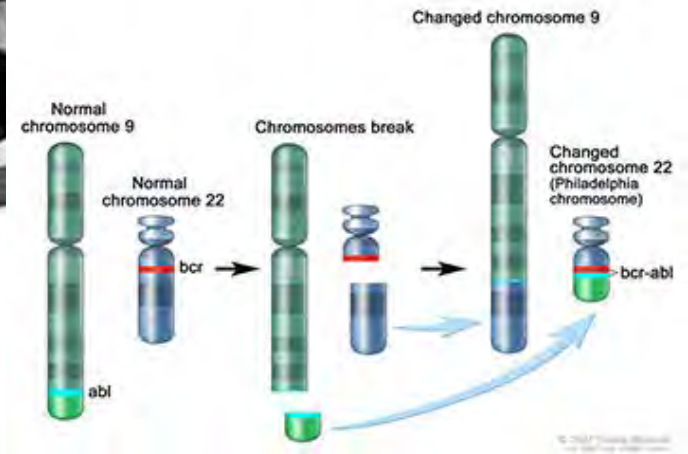
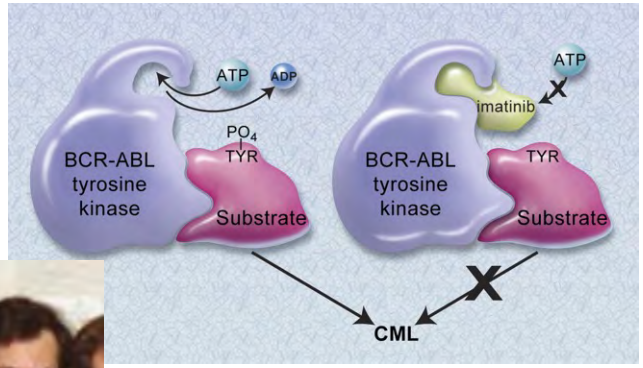
**Early 1970's, Janet Rowley's microscopy studies of leukemia cell chromosomes suggested that specific alterations led to cancer**






**"By early 1999, six months after beginning the phase 1 study…virtually all of our patients were responding and experiencing few, if any, side effects… Internet chat rooms were a new phenomenon, and patients were describing their experiences with imatinib even before we had presented clinical data or published our results…"- Brian Druker, MD**

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Courtesy of Yao Fu, NCI, and Nature Medicine

**Initial sequencing and analysis of the human genome**

International Human Genome Sequencing Consortium*

2/15/2001

Herceptin

9/25/1998

Gleevac

5/10/2001


iTunes Music Store


4/28/2003

(~3 yrs old)

1997

2002

2007

2012

2017

YouTube

4/23/2005

(~5 yrs old)

Spotify

4/23/2006

twitter

7/15/2006

facebook

9/26/2006

(~6 yrs old)

iPhone

(EDGE, 16 GB max)

1/9/2007

(~7 yrs old)

Gmail

2/7/2007

iPad

(EDGE, 64 GB max)

4/3/2010

(~10 yrs old)

Instagram

10/6/2010

UBER

7/1/2012

(~12 yrs old)

iPhone5

(LTE, 128 GB max)


9/12/2012

(~12 yrs old)

HTC VR Headset


4/5/2016

(~16 yrs old)

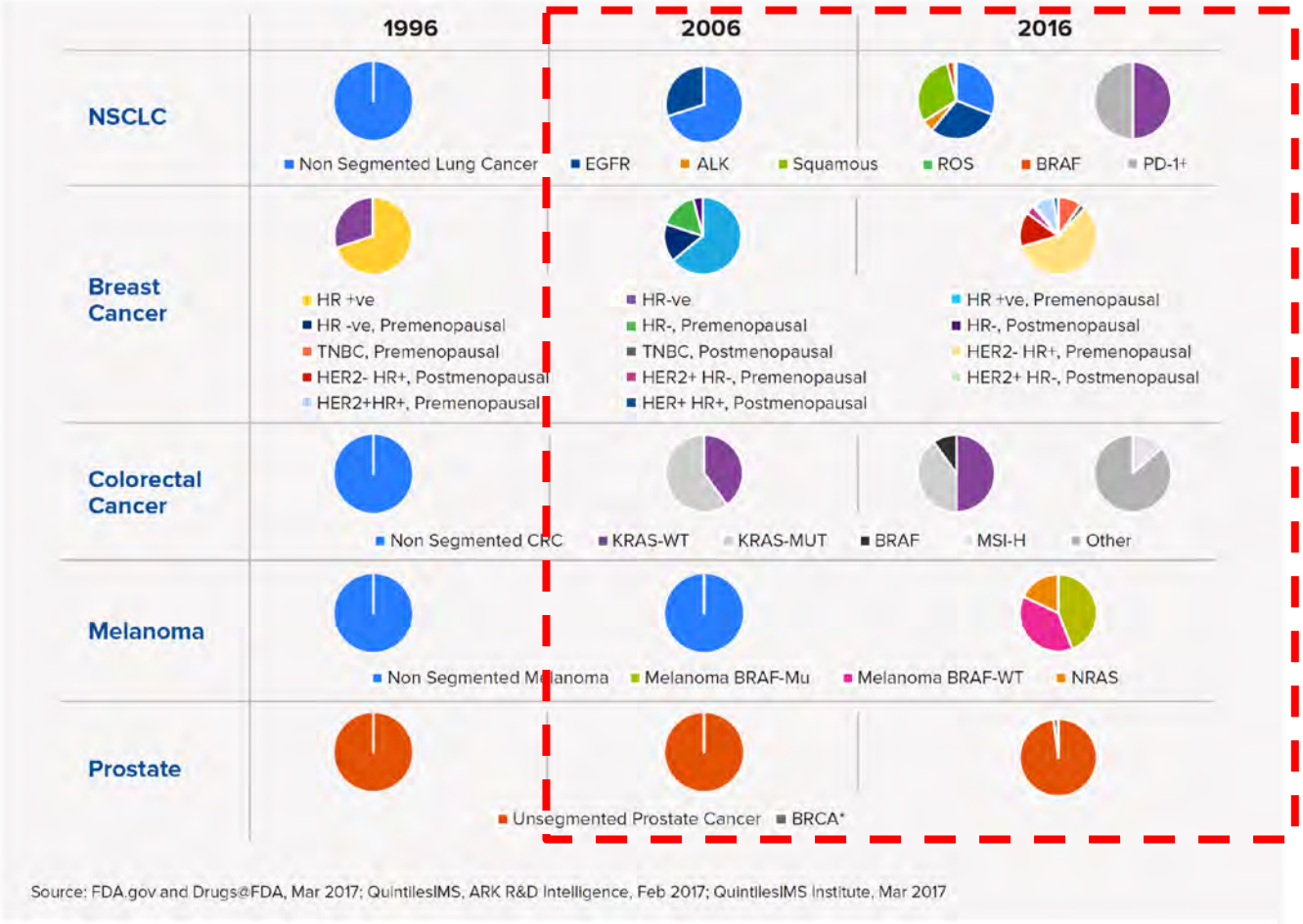
AI beats human at Go

AlphaGo

3/15/2016

***Next Gen***

# Cancer has been progressively redefined over the past 20 years




Source: FDA.gov and Drugs@FDA, Mar 2017; QuintilesIMS, ARK R&D Intelligence, Feb 2017; QuintilesIMS Institute, Mar 2017

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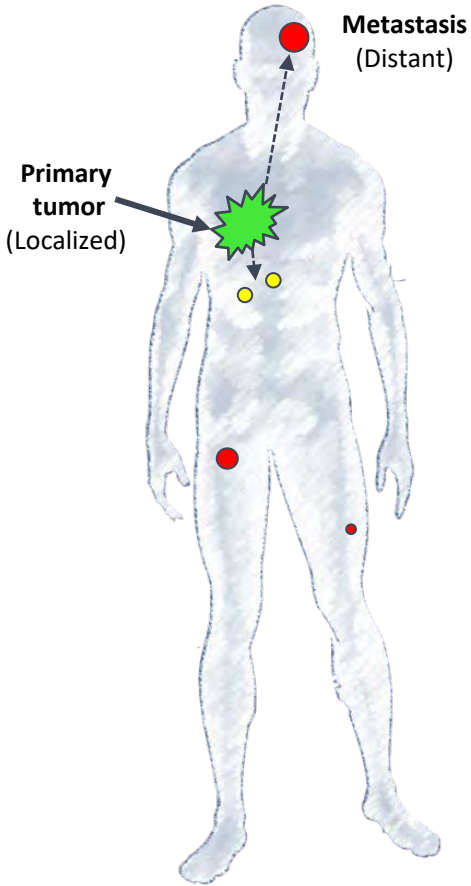
# **Tumor, Cancer, and Metastasis:** Length-scale and Time-scale Matter




*5 year Relative Survival Rates (2021 report of 2010-2016 data)*

| Organ Site | All Stages | Localized | Regional | Distant |
|---|---|---|---|---|
| Prostate | 98 | **>99** | >99 | **30** |
| Breast | 90 | **99** | 86 | **28** |
| Ovary | 49 | **93** | 75 | **30** |
| Uterine Cervix | 66 | **92** | 58 | **17** |
| Melanoma | 93 | **99** | 66 | **27** |
| Urinary Bladder | 77 | **69** | 37 | **6** |
| Kidney | 75 | **93** | 70 | **13** |
| Colorectum | 65 | **90** | 72 | **14** |
| Esophagus | 20 | **47** | 25 | **5** |
| Lung | 21 | **59** | 32 | **6** |
| Liver | 20 | **34** | 12 | **3** |
| Pancreas | 10 | **39** | 13 | **3** |

***"…>90% of deaths are caused by disseminated disease or metastasis…"***

Siegel et. al. *CA Cancer J Clin*, Jan/Feb 2021

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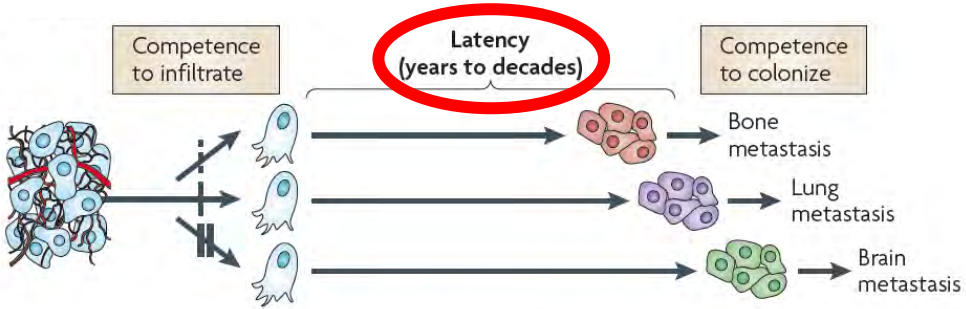
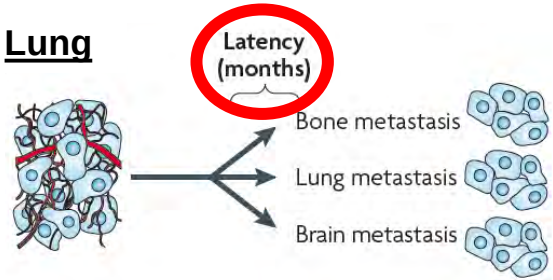
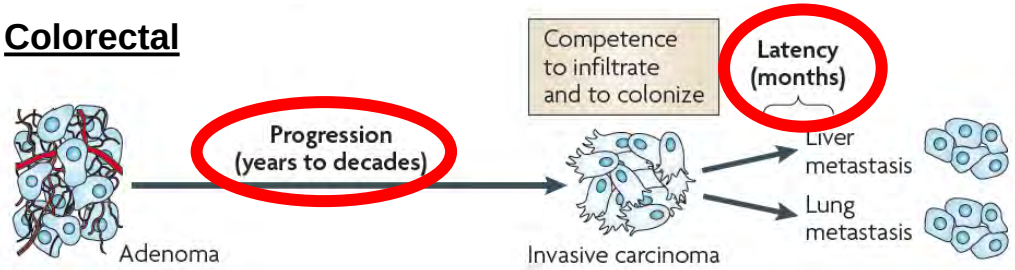
## Breast




## Lung




## Colorectal




Nguyen et. al. *Nat.Rev. Cancer*, April 2009, Aparicio et. al., *NEJM* Feb 2013

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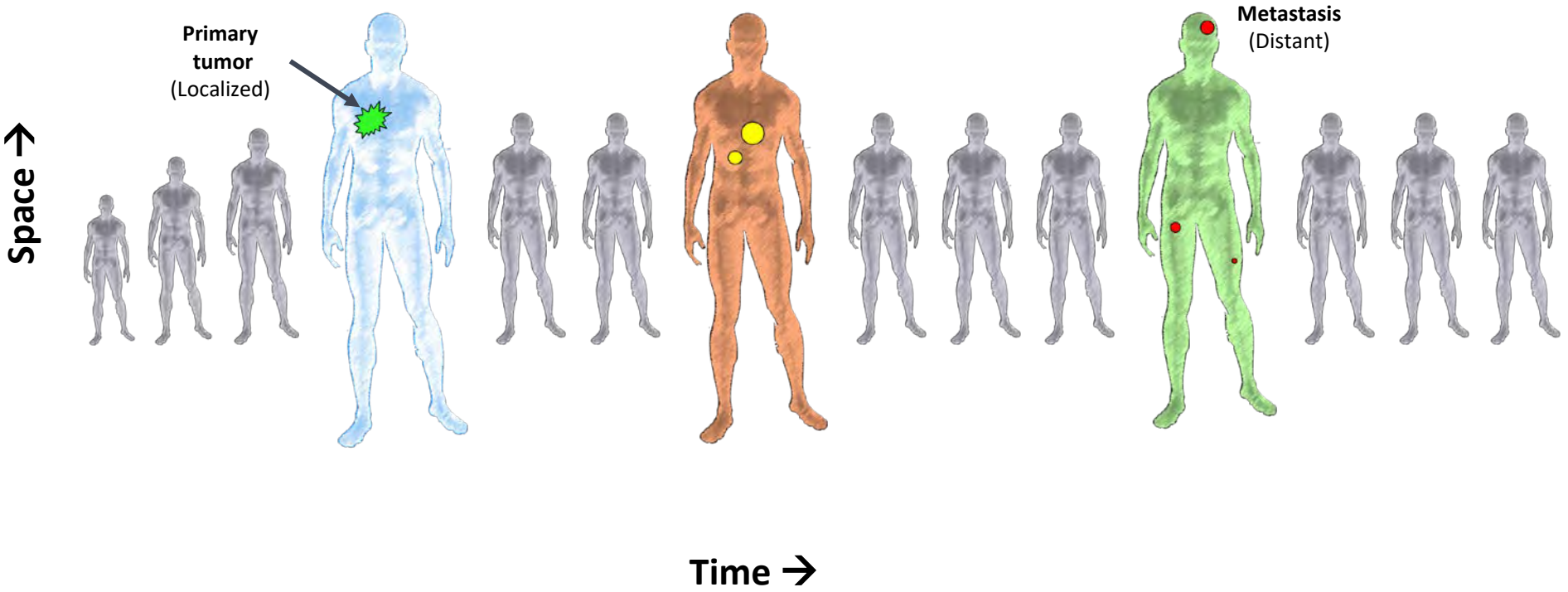
# Engineer's Dream: Develop A Continuum

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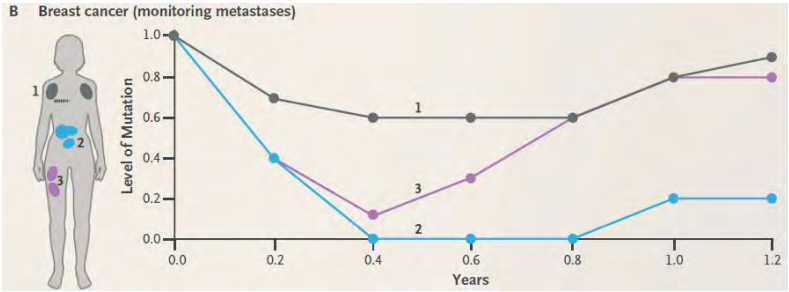
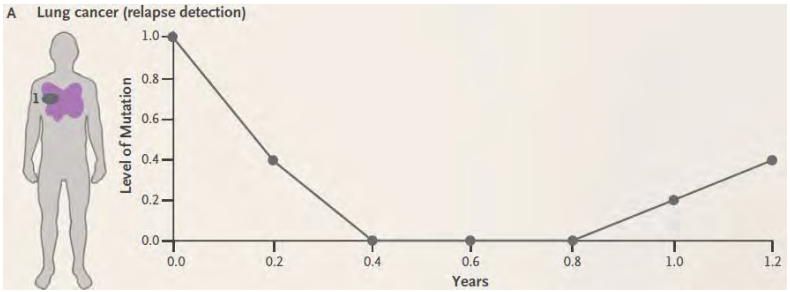
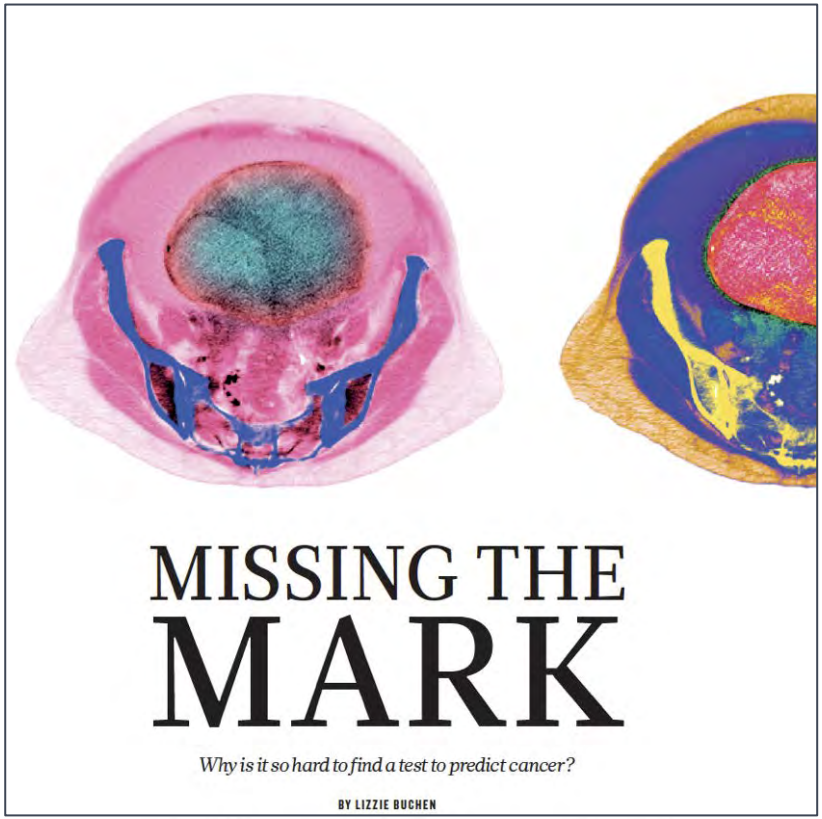
# Potential Use of New Technologies




Aparicio et. al., *NEJM* Feb 2013

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# Early Years


On 23 June 2008, LabCorp announced the availability of the OvaSure test.

Jean McKibben, an ovarian-cancer survivor, rushed to take OvaSure on the first day it was available, and **her results showed a 0.00 chance of cancer**. A week later, scans showed that her cancer was back. **She was crushed**.

FDA on 7 August 2008 sent a letter to LabCorp saying that the test 'has not received adequate clinical validation, and may harm the public health'.

A second letter, sent on 29 September 2008, alleged that LabCorp did not have the necessary marketing clearance or approval for the test from the FDA.

LabCorp replied to the FDA on 20 October 2008, disagreeing with the agency's assertions, but agreed to **pull OvaSure from the market**.

# Milestones, Highlights, & Lessons Learned

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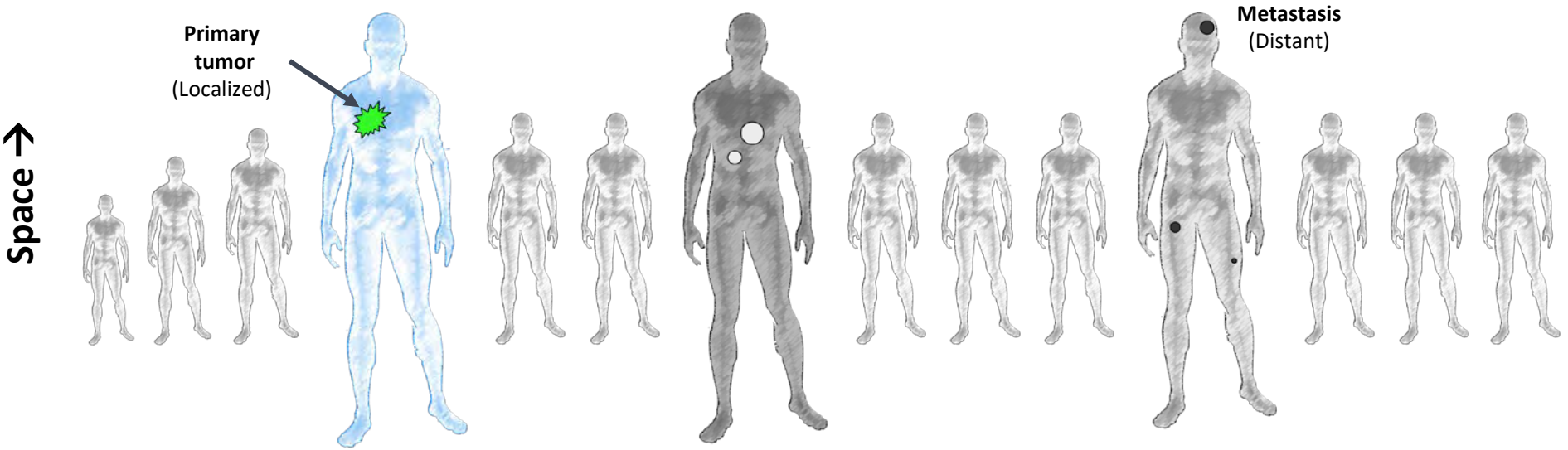
# 2006-2015: A Decade of Illuminating the Underlying Causes of Primary Untreated Tumors




The Cancer Genome Atlas

Clinical Proteomic Tumor Analysis Consortium

Cancer Imaging Archive

(12,000+ patient tumors)

SC CTSI

Science

# An Open Letter to Cancer Researchers

"…the unstated goal of the Human Cancer Genome Project (HCGP) is to ***accelerate*** **the discovery of cures for cancers**. The question we need to answer is not whether the information generated will be useful, but whether, **if given $1.5 billion in "new" cancer money, would the HCGP be the best application of that money toward the goal of cancer cures**…"

– Oct 21, 2005

SC CTSI

# First Pass at Cancer Genome Reveals Complex Landscape

Science

8 SEPTEMBER 2006

"…to conduct this mini–cancer-genome project, a **29-person** team, resequenced…**11** breast cancer samples and **11** colon cancer samples…then winnowed out more than **99%** of the mutations by **removing errors**…and **changes that didn't alter a protein**.

…this yielded a total of 189 "candidate" cancer genes. Although some are familiar…most had **never been found mutated** in cancer before. The results…are a **'treasure trove'**…

…the relatively small number of new genes **common to the tumors** reinforces concerns about [NIH] The Cancer Genome Atlas…

…despite such doubts, the atlas project gets under way next week. NIH will announce the three cancers to be studied in the pilot phase…the project is on an **extremely aggressive timeline**…"

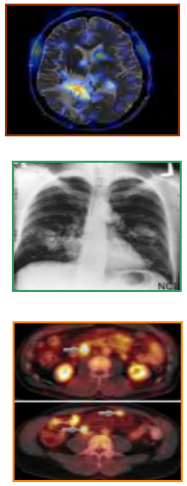
# The Cancer Genome Atlas

## Three Cancers- Pilot

glioblastoma multiforme (brain)

squamous carcinoma (lung)

serous cystadenocarcinoma (ovarian)



Biospecimen Core Resource with more than 13 Tissue Source Sites

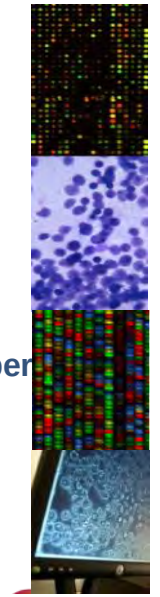
7 Cancer Genomic Characterization Centers

3 Genome Sequencing Centers

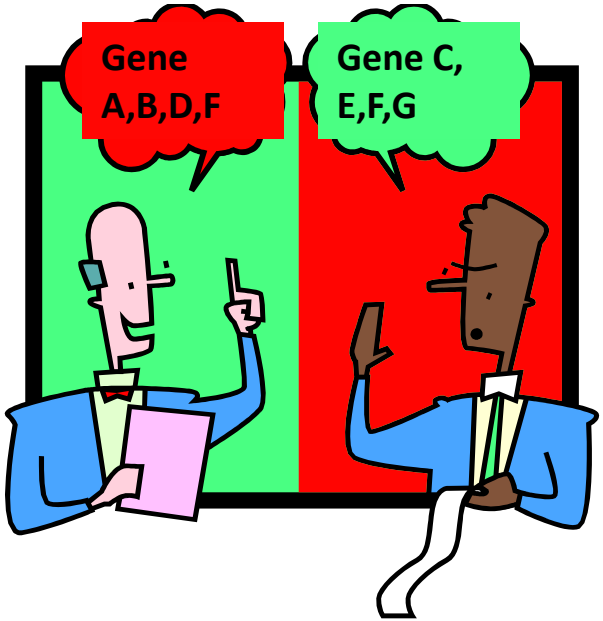
Data Coordinating Center

## Multiple data types

- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic status
- Tissue anatomic site
- Surgical history
- Gene expression
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence



# Adding an Engineering Perspective




**Anna Barker, PhD**
NCI Deputy Director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# Potential Sources of Variability

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# Platforms Only

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# Maturity and Heterogeneity of Platforms

454

Illumina

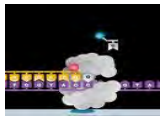
SOLiD

Complete Genomics

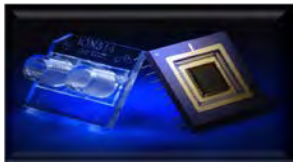
Complete Genomics

Helicos

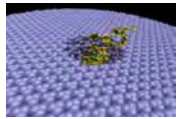
Visigen



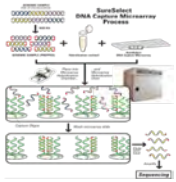
PacBio



Ion-Torrent

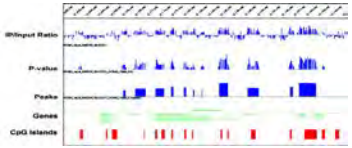


Oxford Molecular



Agilent

Nimblegen



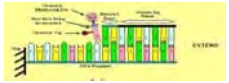
LaserGen

ZSGenetics

NABsys

Raindance

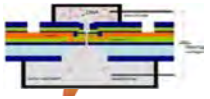
Febit

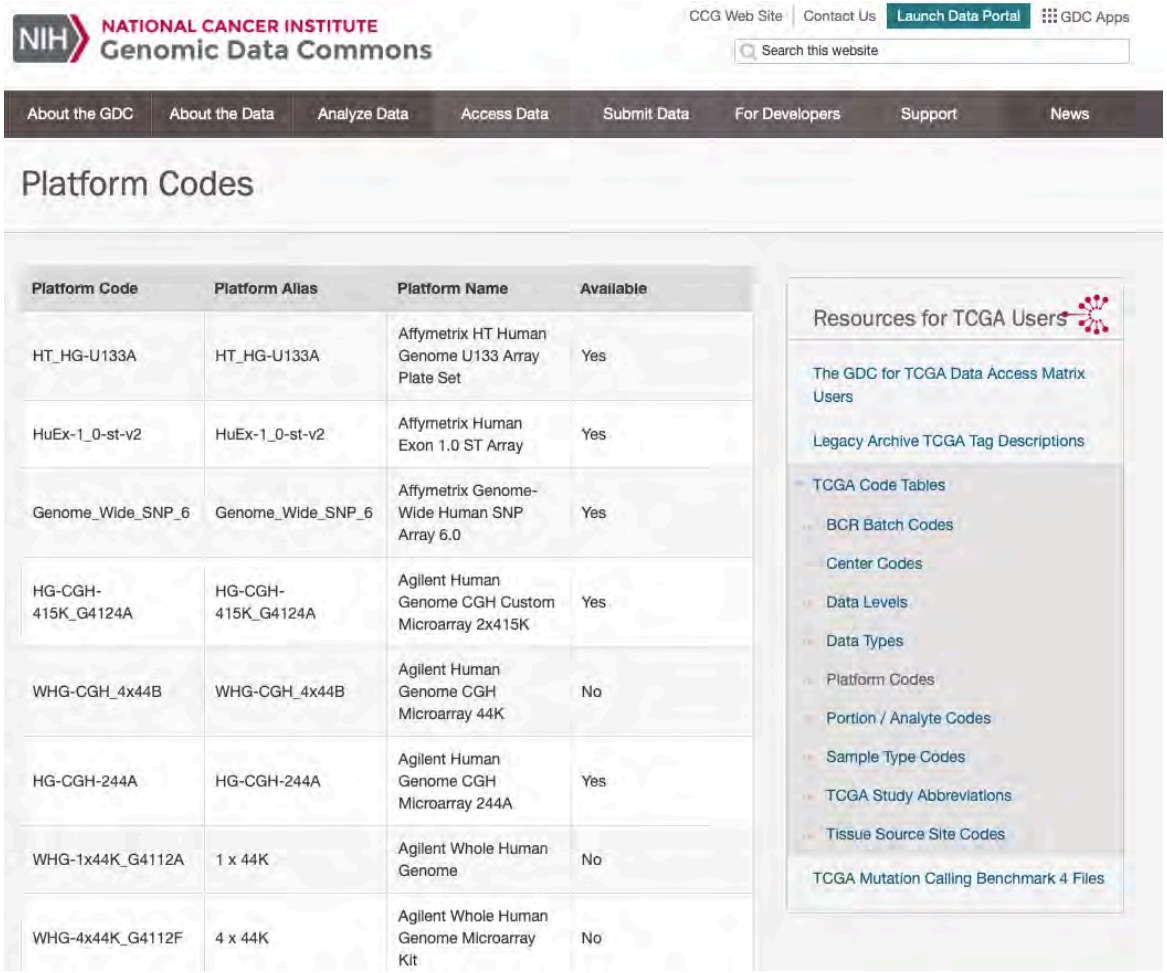


Intelligent Biosystems

Halycon

IBM






**~ 60 different hardware platforms**

- Illumina (30)
- Agilent (14)
- Affymetrix (8)
- ABI (8)

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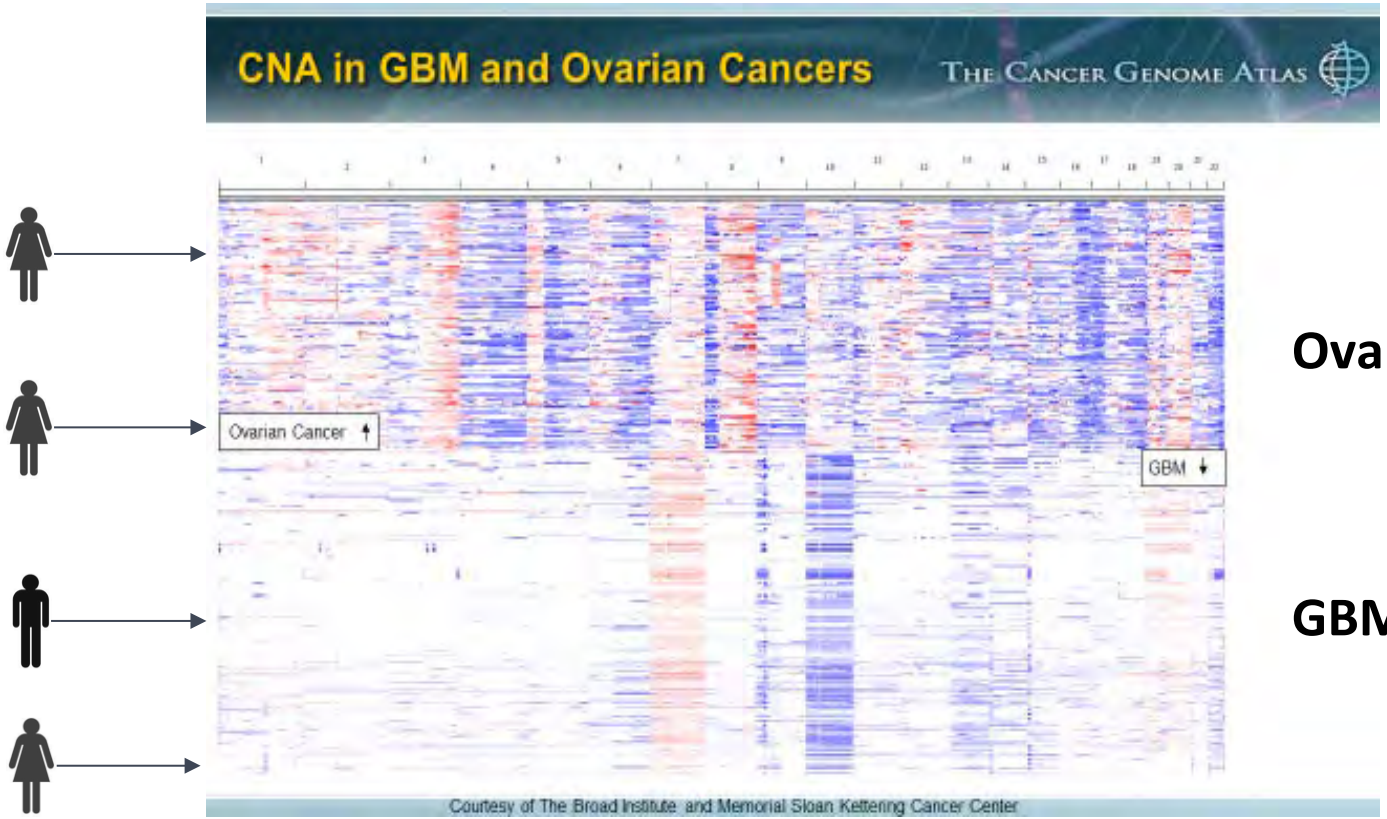
# 2008/9




**Ovarian**

**GBM**

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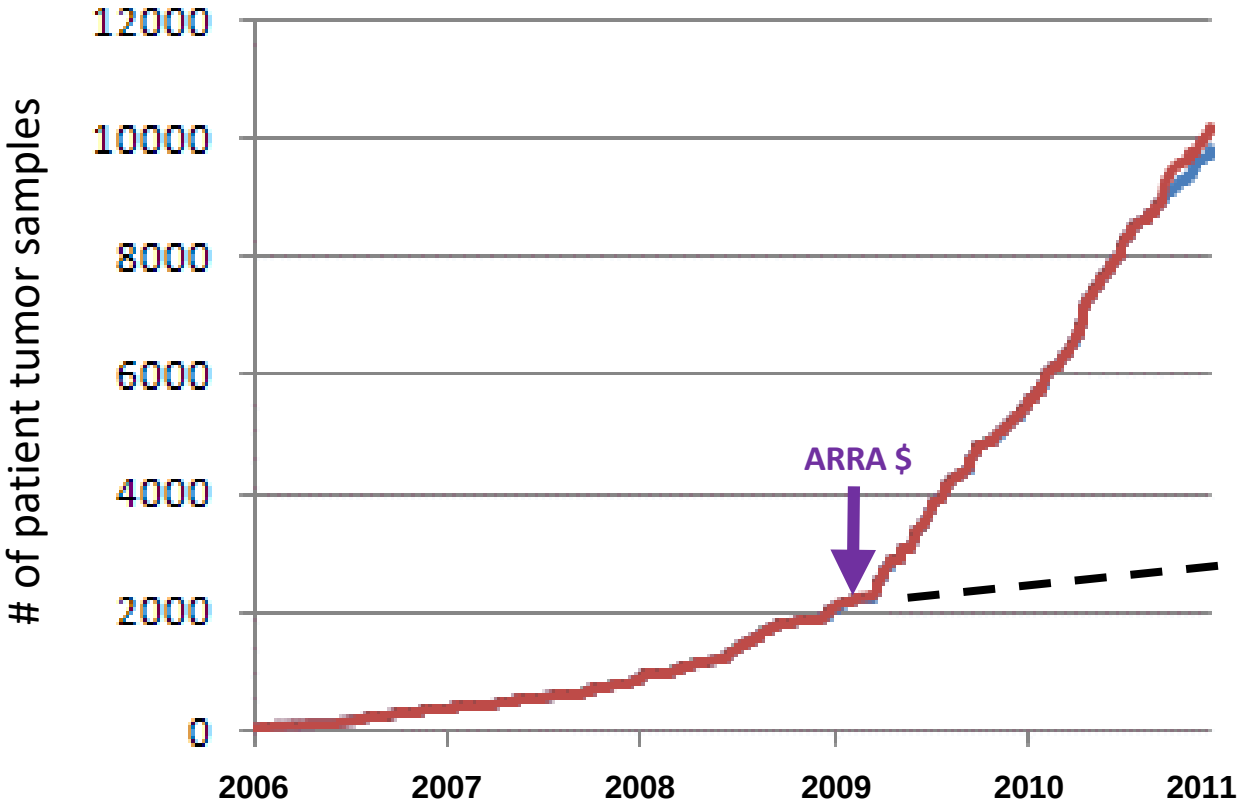
# Rapid Acceleration from Stimulus Funding (2009-2011)

Former President Obama at NIH 9/30/2009

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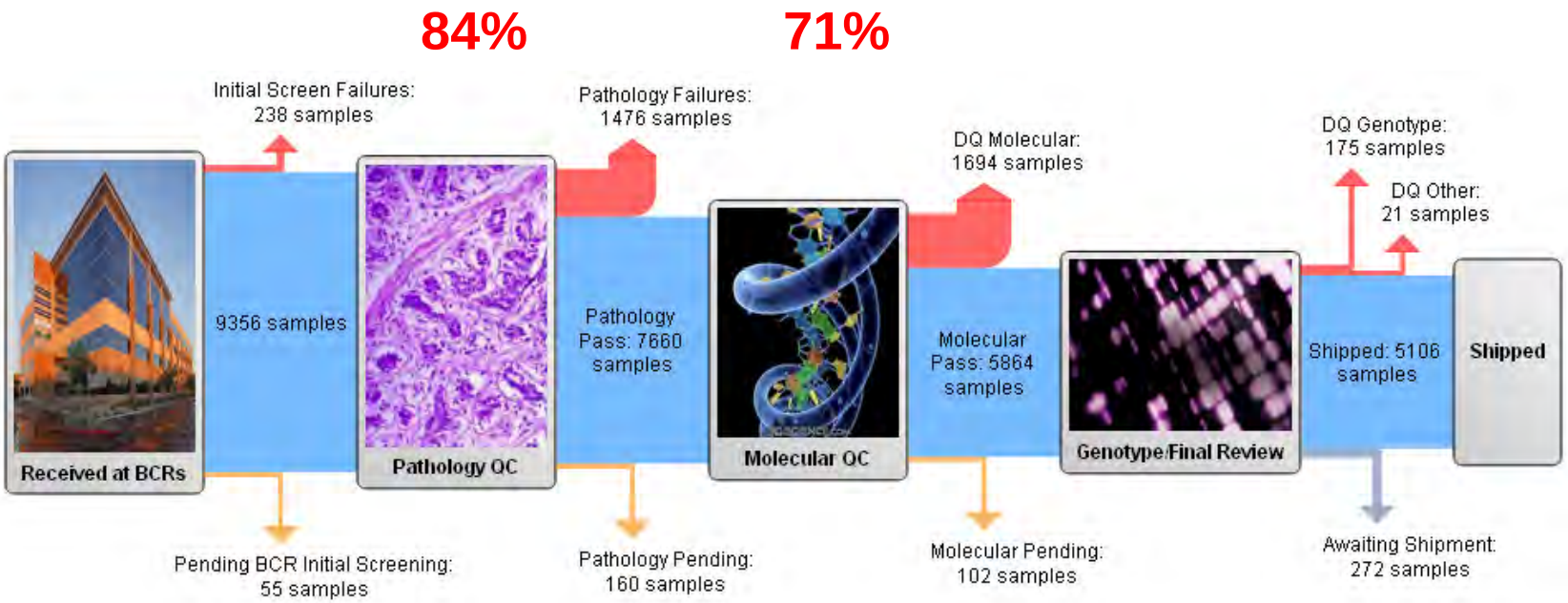
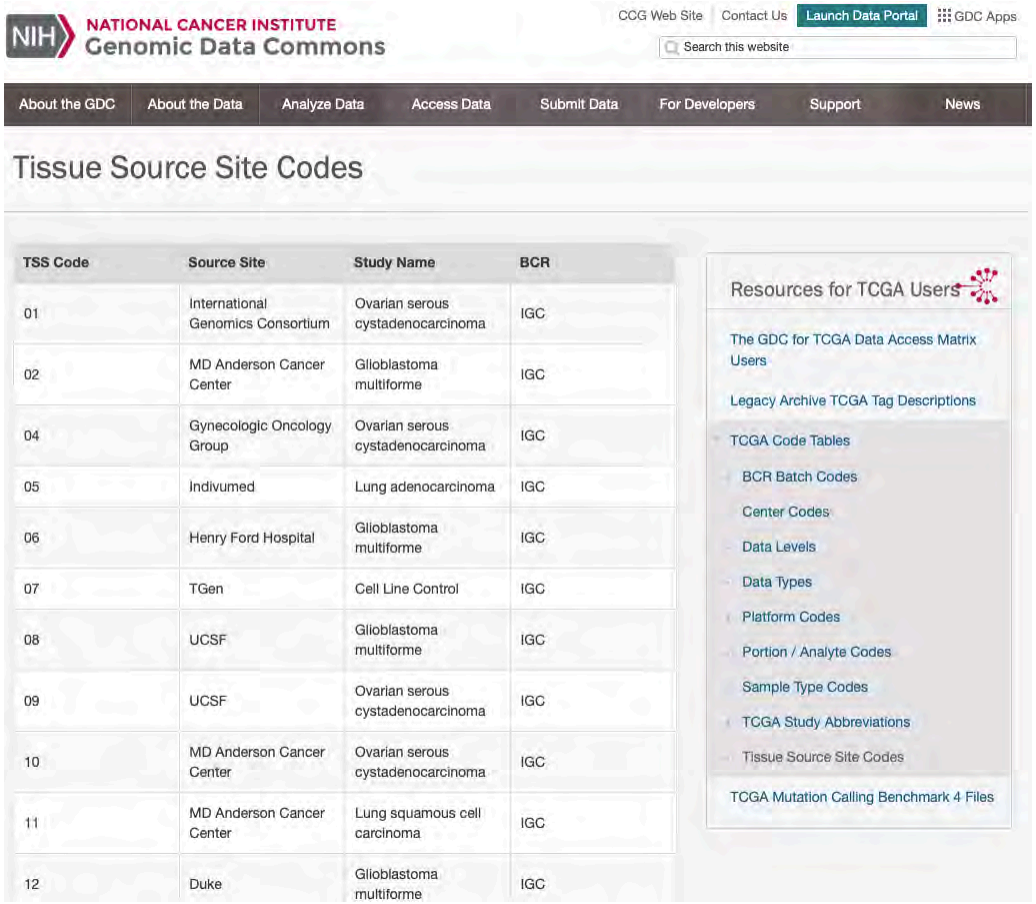
# QA, QC, and Optimization: Metadata Matters




**Overall = 58%**




**~ 830 different site codes**

- Colorectal (44)
- Breast (42)
- Liver (39)
- Pancreatic (38)
- Lung adeno (37)
- Bladder (36)

- Lung squamous (42)
- Ovarian (26)
- GBM (21)

- Uveal melanoma (8)
- AML (7)
- CML (1)

# Not All Bad News…

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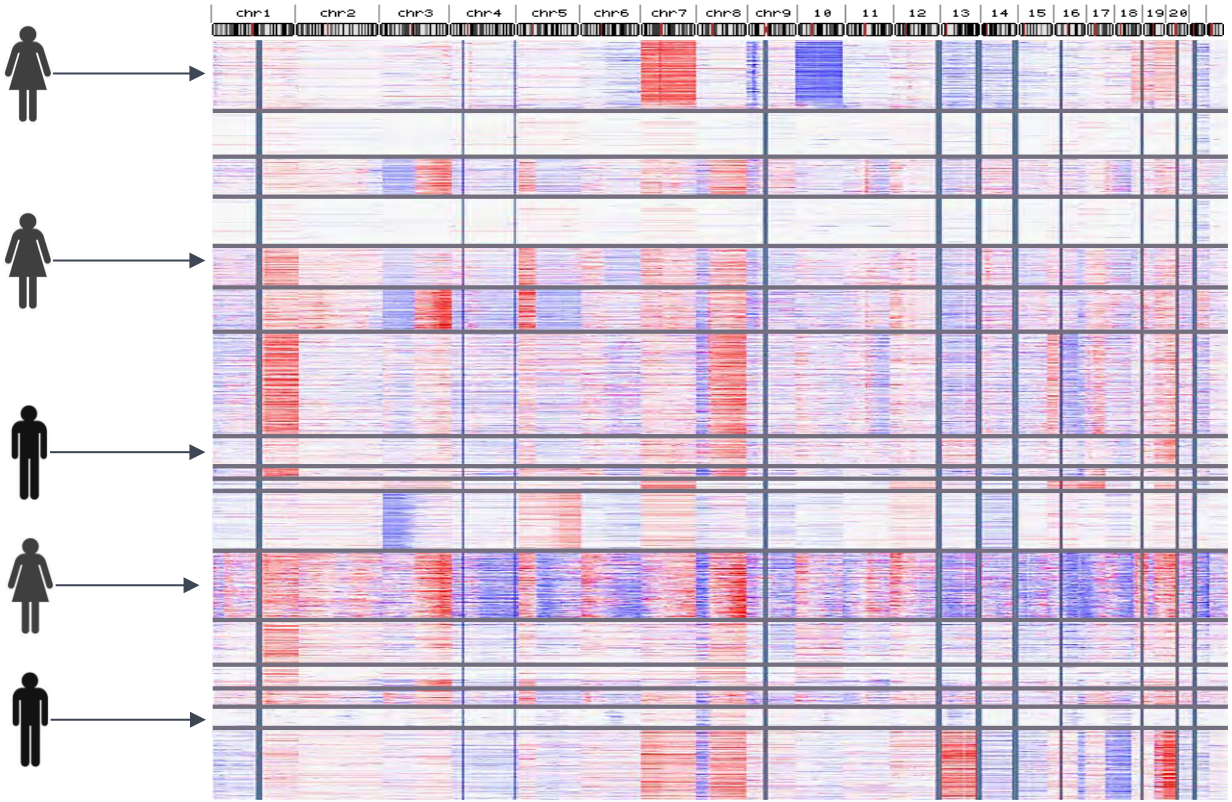
# The Cancer Genome Atlas




| | |
|---|---|
| Glioblastoma: | 563 |
| Brain lower grade glioma: | 180 |
| Head & neck: | 306 |
| Thyroid carc: | 401 |
| Lung adeno: | 356 |
| Lung squamous: | 343 |
| Breast carc: | 866 |
| Stomach adeno: | 237 |
| Liver hep. carc: | 97 |
| Kidney pap. cell carc: | 103 |
| Kidney clear cell carc: | 493 |
| Ovarian serous: | 559 |
| Uterine corpus end. carc: | 492 |
| Cervical carc: | 102 |
| Bladder carc: | 135 |
| Prostate adeno: | 171 |
| Colon/rectum adeno: | 575 |
| **Total:** | **5,979** |

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Source: UCSC Cancer Genomic Heatmaps (CopyNumber GISTIC2) [https://genome-cancer.ucsc.edu/] Compiled by Jerry S.H. Lee, PhD, March 2013

2013

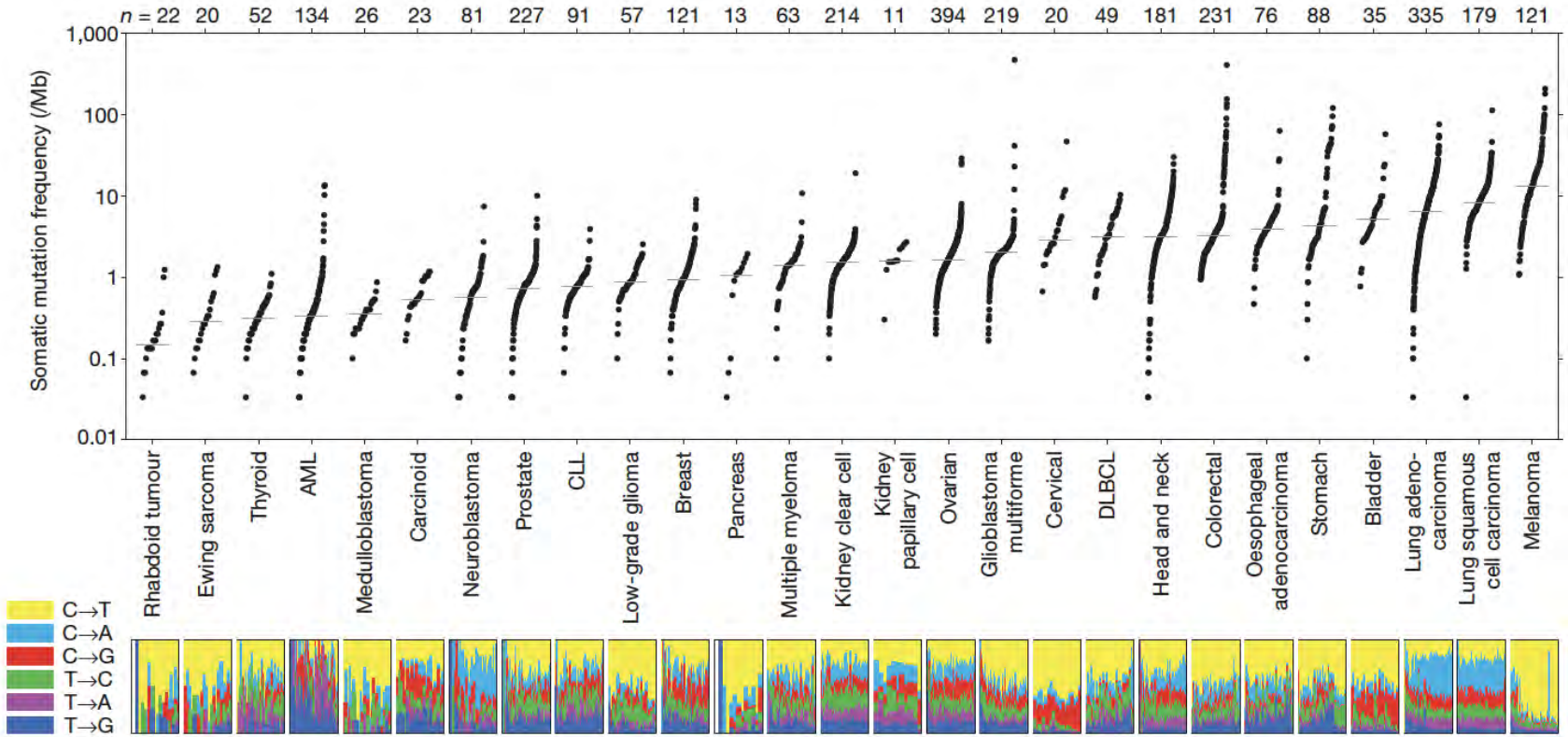



**Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.** Each dot corresponds to a tumour–normal pair, with such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also

SC CTSI

Lawrence et. al., Nature, 2013

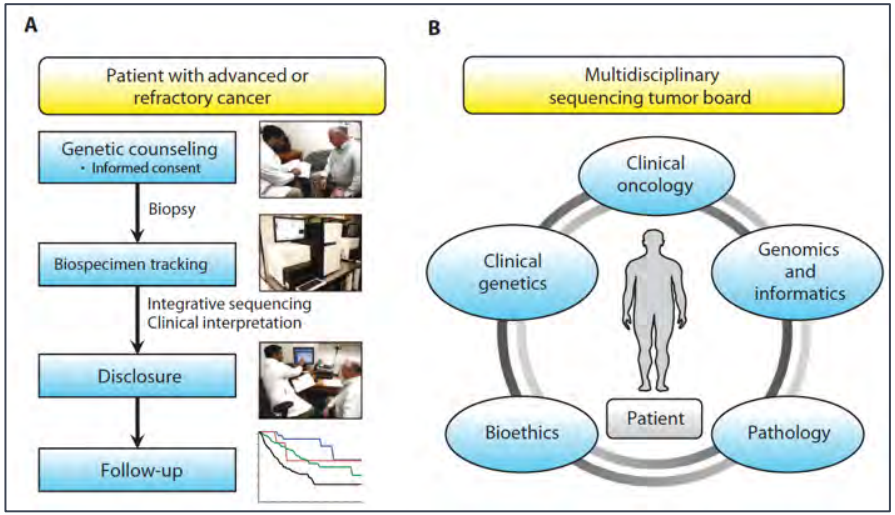
11/30/2011

# Personalized Oncology Through Integrative High-Throughput Sequencing: A Pilot Study

Sameek Roychowdhury,[1,2*] Matthew K. Iyer,[1,3*] Dan R. Robinson,[1,4*] Robert J. Lonigro,[1,3] Yi-Mi Wu,[1,4] Xuhong Cao,[1,4,5] Shanker Kalyana-Sundaram,[1,4,6] Lee Sam,[1,3] O. Alejandro Balbin,[1,3] Michael J. Quist,[1,4] Terrence Barrette,[1,4] Jessica Everett,[7] Javed Siddiqui,[1,4] Lakshmi P. Kunju,[1,4] Nora Navone,[8] John C. Araujo,[8] Patricia Troncoso,[8] Christopher J. Logothetis,[8] Jeffrey W. Innis,[9] David C. Smith,[2,10] Christopher D. Lao,[2,10] Scott Y. Kim,[11] J. Scott Roberts,[11,12] Stephen B. Gruber,[2,10] Kenneth J. Pienta,[1,2,10,13] Moshe Talpaz,[2,10] Arul M. Chinnaiyan[1,3,4,5,13†]

"…Translating high-throughput sequencing for biomarker-driven clinical trials for personalized oncology presents unique logistical challenges, including:

(i) the identification of patients who could **benefit**,
(ii) the development of an informed consent process that includes a way to deal with **incidental findings**,
(iii) the implementation of **efficient and integrative computational pipelines** for data analysis,
(iv) the selection of the results that should be **disclosed to patients**, and
(v) the completion of the sequencing analysis in a **cost-effective** and **clinically relevant** time frame…"




SC CTSI

Roychowdhury et. al., Science Translational Medicine, 2011

# Still Learning: ACMG Secondary Findings v3.0 [2021]

| Phenotypes | Gene(s) |
|---|---|
| **Cancer (28)** | **v1.0 [2013]:** TP53, APC, RET, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, MEN1, MUTYH, NF2, STK11, PTEN, RB1, TSC1, TSC2, VHL, WT1, SDHD, SDHAF2, SDHC, SDHB<br><br>**v.2.0 [2016]:** BMPR1A, SMAD4<br><br>**v3.0 [2021]: PALB2, MAX, TMEM127** |
| **Cardiovascular (33)** | **v1.0 [2013]:** FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYH11, PKP2, DSP, DSC2, TMEM43, DSG2, RYR2, TNNT2, LMNA, COL3A1, LDLR, APOB, PCSK9, MYH7, MYBPC3, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, MYL2, KCNQ1, KCNH2, SCN5A<br><br>**v3.0 [2021]: CASQ2, TRDN, FLNC, TTN** |
| **Metabolism (4)** | **v1.0 [2013]:** GLA<br><br>**v.2.0 [2016]:** OTC<br><br>**v3.0 [2021]: GAA, BTD** |
| **Miscellaneous (8)** | **v1.0 [2013]:** RYR1, CACNA1S<br><br>**v.2.0 [2016]:** ATP7B<br><br>**v3.0 [2021]: HFE, ACVRL1, ENG, HNF1A, RPE65** |

Modified from Miller et. al. *Genetics in Medicine*, 2021

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# Drug Discovery and Development

2011


- **Accelerate the *translation* of patient *genomic data* into *clinical application***
  - Innovate integration of computational mining of large-scale genomic data analysis
  - Identify and confirm new therapeutic target candidates
    - Existing therapeutics and /or orphan drugs
  - Identify and confirm novel modulators
    - Small molecules
    - siRNAs
- **Share models, reagents, analysis tools, and data with scientific community**

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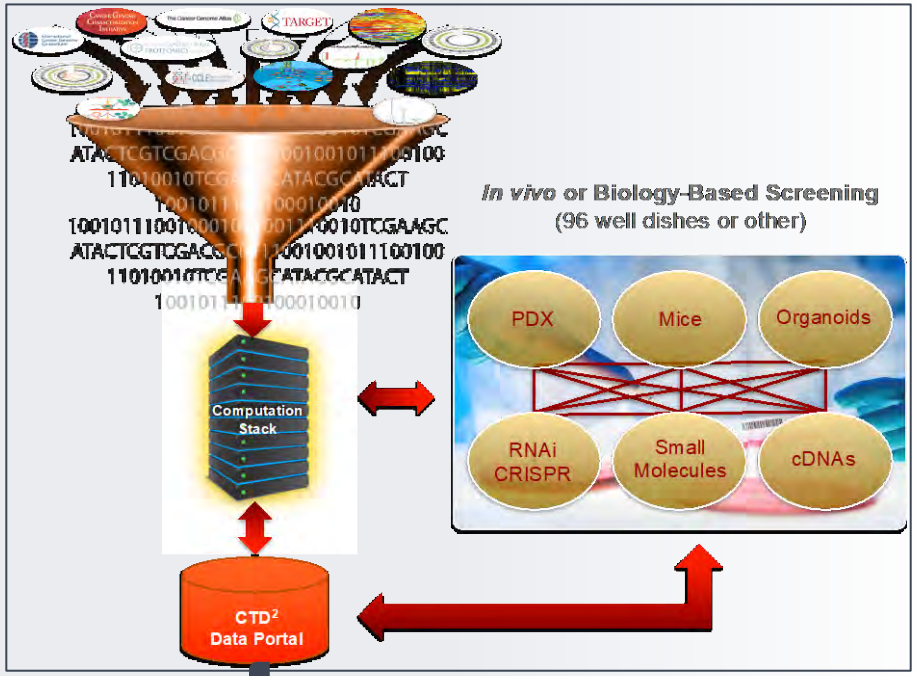
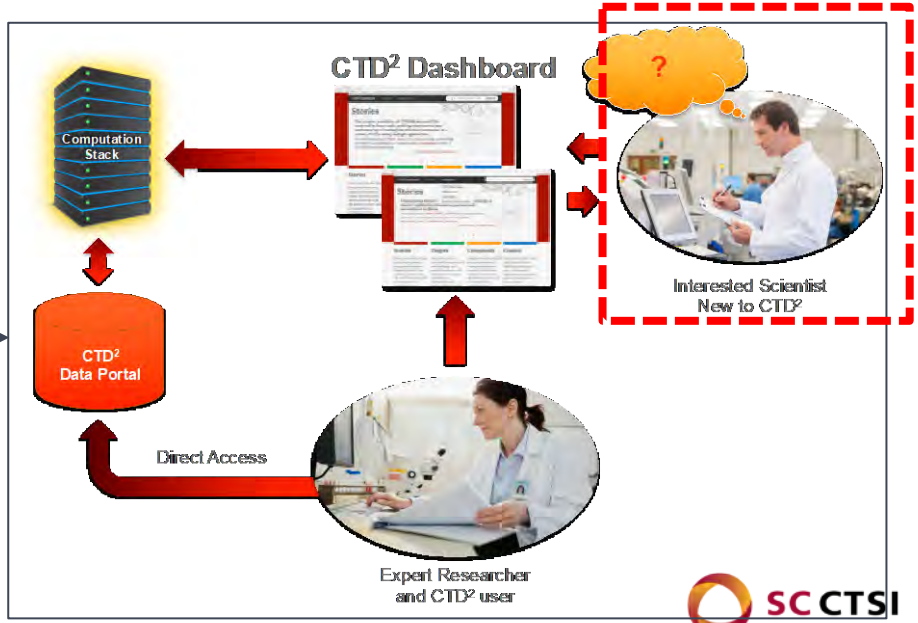



CTD² Cancer Target Discovery and Development




http://ocg.cancer.gov/programs/ctd2

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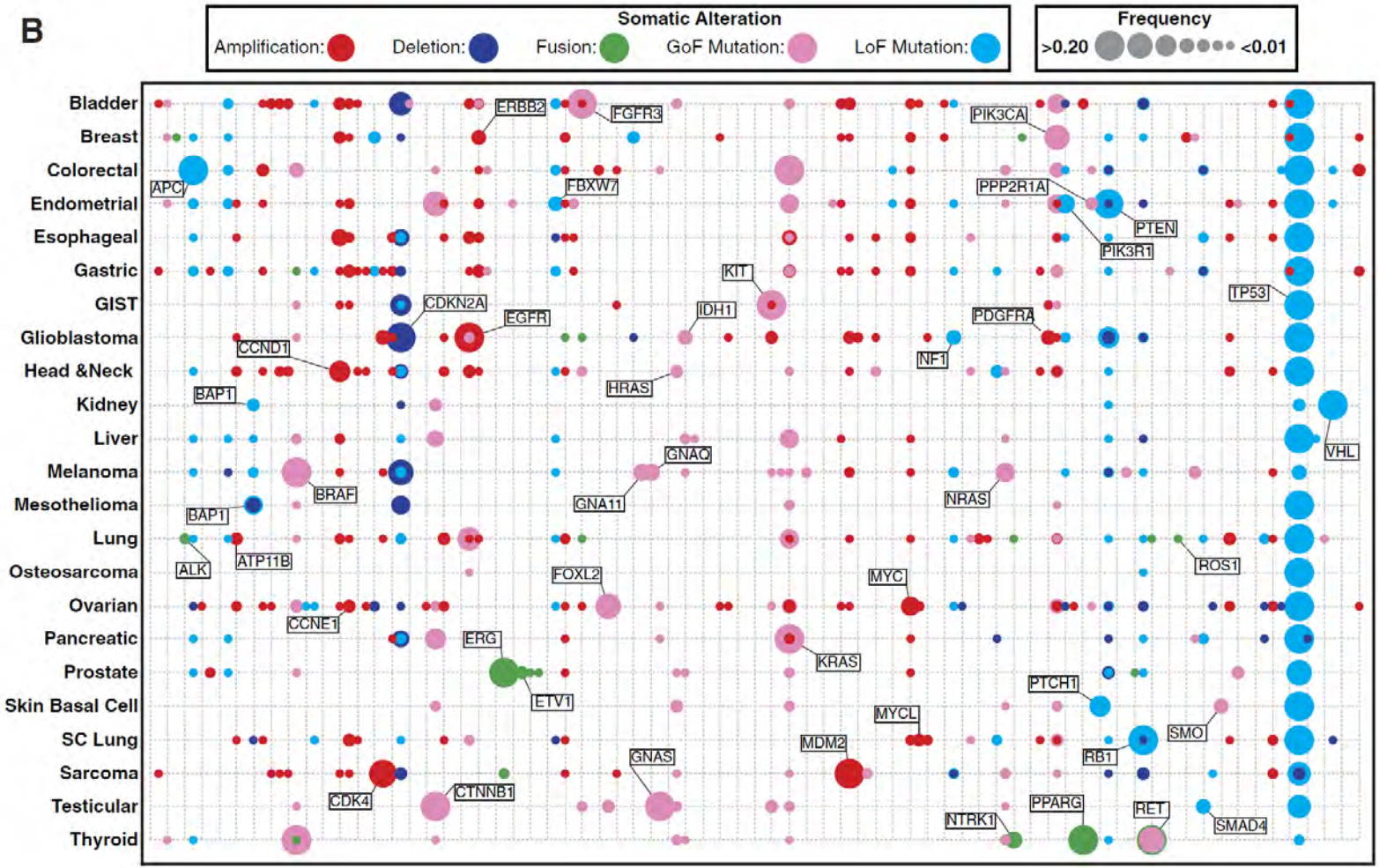



Hovelson et. al, Neoplasia, 2015

SC CTSI

# NATIONAL CANCER INSTITUTE
# NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

**NCI-MATCH* IS FOR ADULTS WITH:**

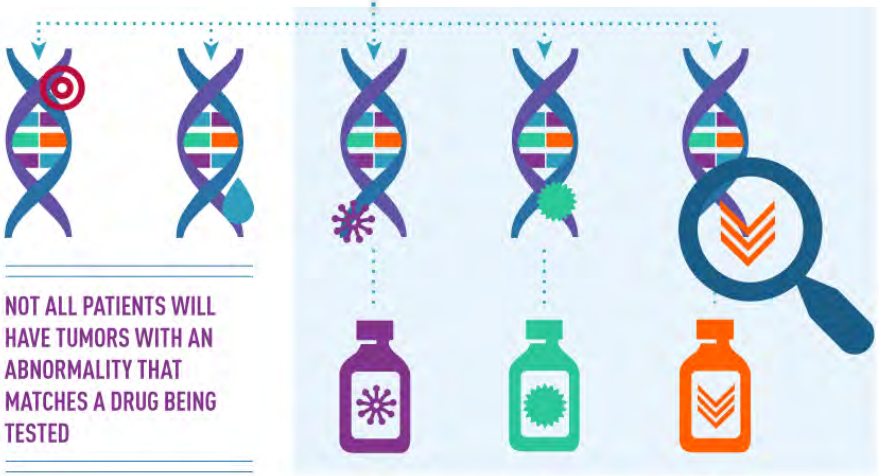
- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment

ABOUT 5,000 CANCER PATIENTS WILL BE SCREENED WITH A TUMOR BIOPSY

GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

THE BIOPSIED TUMOR TISSUE WILL UNDERGO GENE SEQUENCING

IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH



NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY

*NCI-Molecular Analysis for Therapy Choice

www.cancer.gov/nci-match

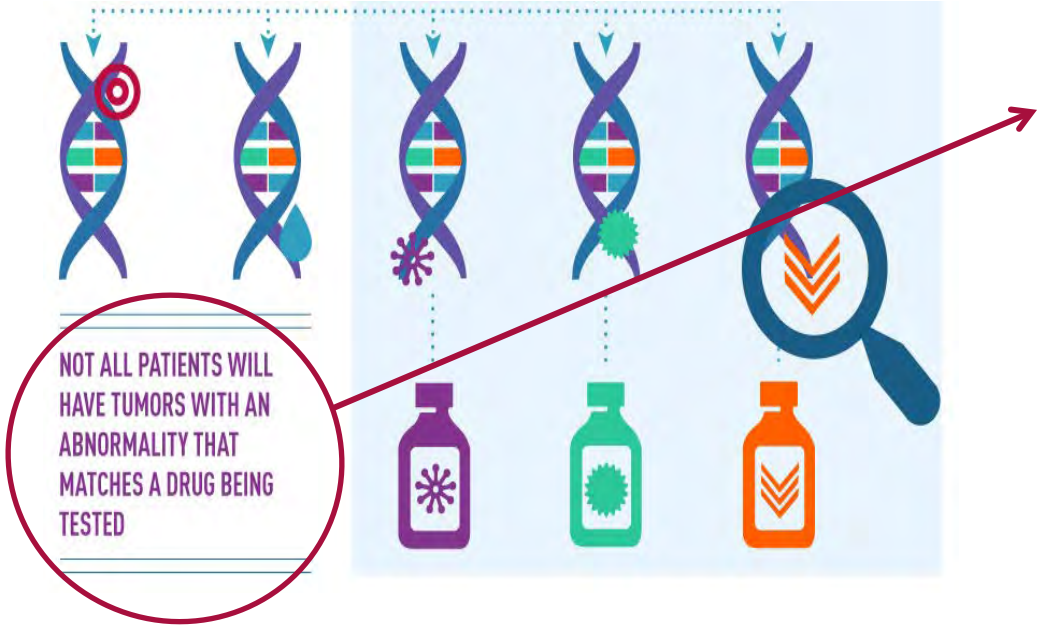
To learn more, call 1-800-4-CANCER

NCI National Clinical Trials Network

**August 2015**

11/16/2017

# NCI-MATCH Central Screening Summary




**6,397** patients registered
**5,962** samples (93% seq success rate)

- Overall match rate: **18%**
  - Patients with a tumor gene abnormality that matched to one of the 30 treatment arms (992/5560 with testing completed)
- Enrollment rate: **69%**
  - Patients with a treatment assignment who enrolled (689/992)

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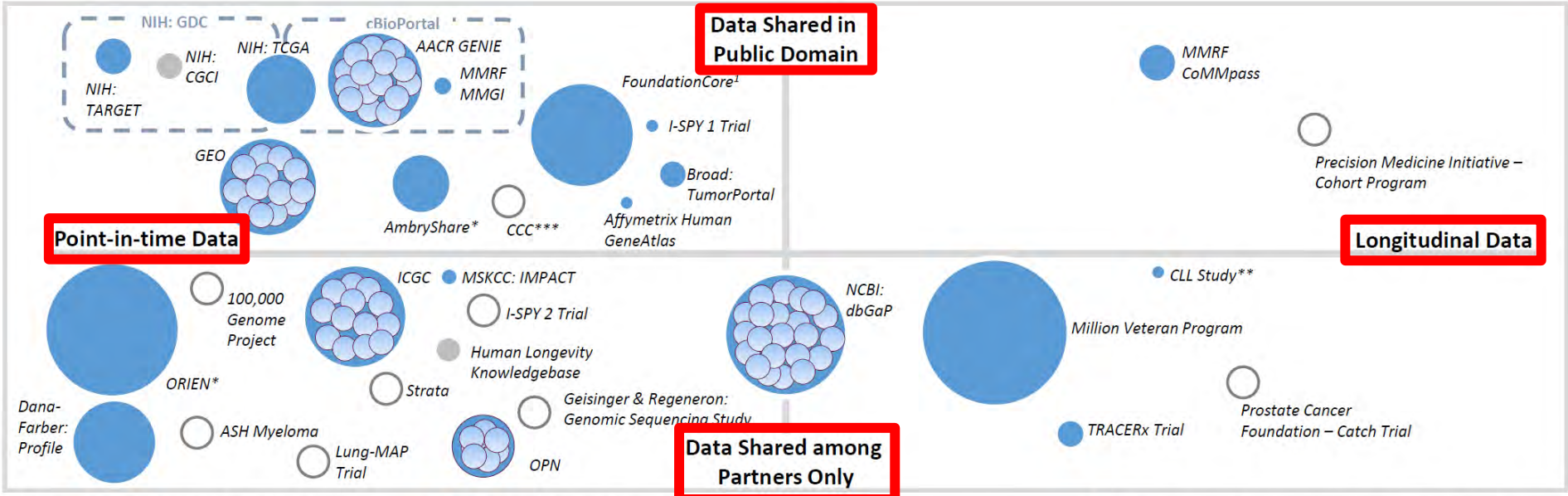
2016




Bubble size = estimated size of available dataset
Note: Representative selection of landscape, not all inclusive

Available datasets, size known
Available datasets, size unknown
Dataset in development
Available datasets that comprise multiple smaller datasets
Portals that are currently active/utilized in the public domain

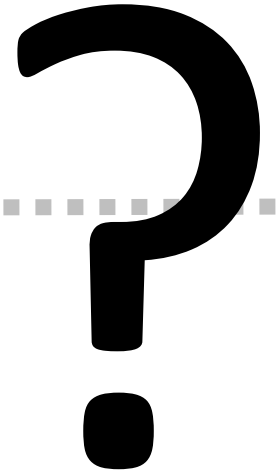
***Opportunity exists to generate publicly available longitudinal data to drive understanding of genetic mutations and find Precision Medicine cures***

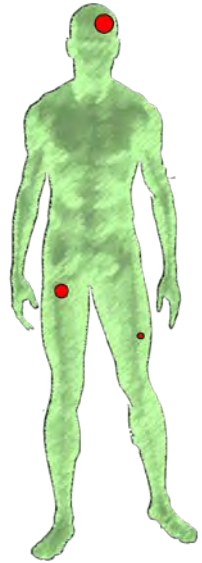
*Datasets have potential to include longitudinal data in the future
**Public/private information not available
***Serves as a portal also, has potential to include longitudinal data in the future

1. FoundationCore's pediatric cancer data has been made public

HARVARD BUSINESS SCHOOL
Kraft Precision Medicine Accelerator

SC CTSI





The Cancer Genome Atlas

CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM

MSKCC IMPACT

NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL

AACR GENIE

ORIEN

## 2006 - 2009

THE CANCER GENOME ATLAS

**Pilot Phase (3 years)**

- 3 tumor types
  - Brain (n = 206)
  - Ovarian (n = 489)
  - Lung (n = 178)

## 2009 - 2014

The Cancer Genome Atlas

**Expansion Phase (5 years)**

- Original plan 10 tumor types
  - 2,500 cases (250 / tumor type)
- Accelerated plan ~30 tumor types
  - 10,000 cases (~500 / tumor type)

NIH NATIONAL CANCER INSTITUTE GDC Legacy Archive

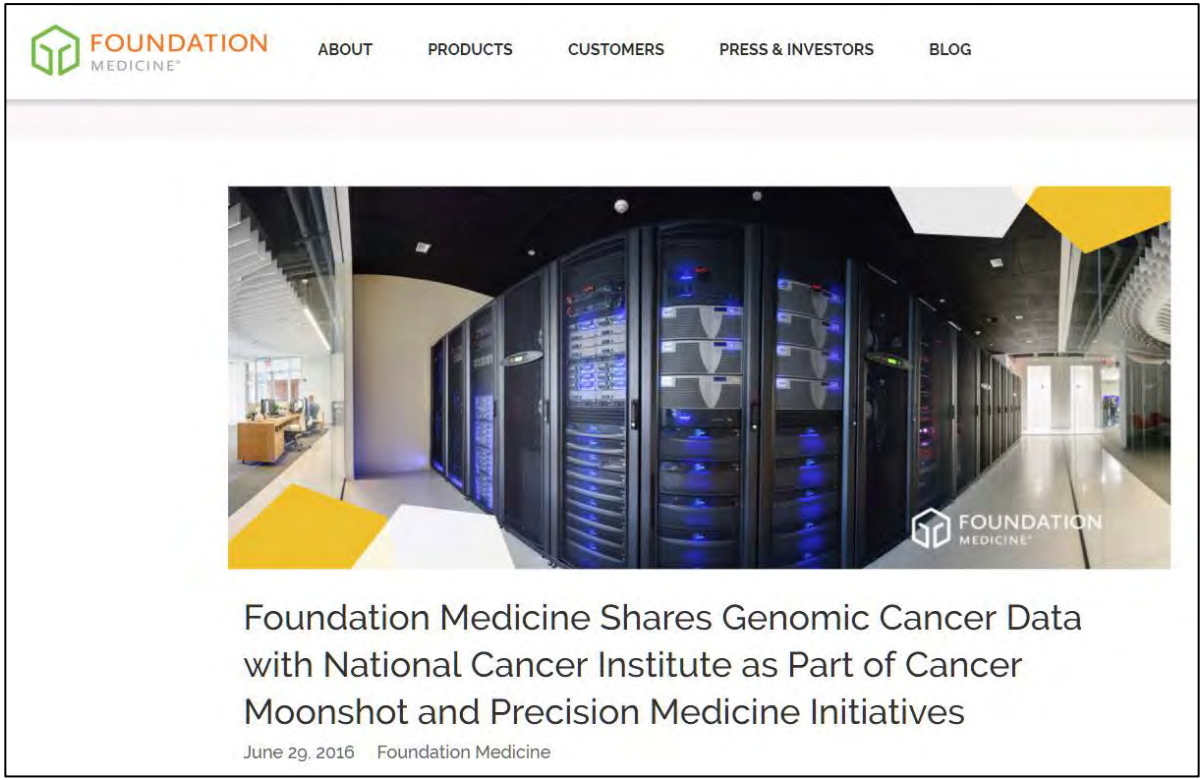
Legacy TCGA data (2.6 PB)

## 2014 - 2016

NIH NATIONAL CANCER INSTITUTE Genomic Data Commons

**Pilot Phase (3 years)**

- Launched 6/2016
- Harmonized TCGA data (1.5 PB)




**At the June 29th Cancer Moonshot Summit, *Foundation Medicine* announced the release of 18,000 genomic profiles to the NCI GDC**

NATIONAL CANCER INSTITUTE
Genomic Data Commons

10/17/2017

**Current**

- TCGA — 11,353 cases
- TARGET — 3,178 cases

**Coming soon**

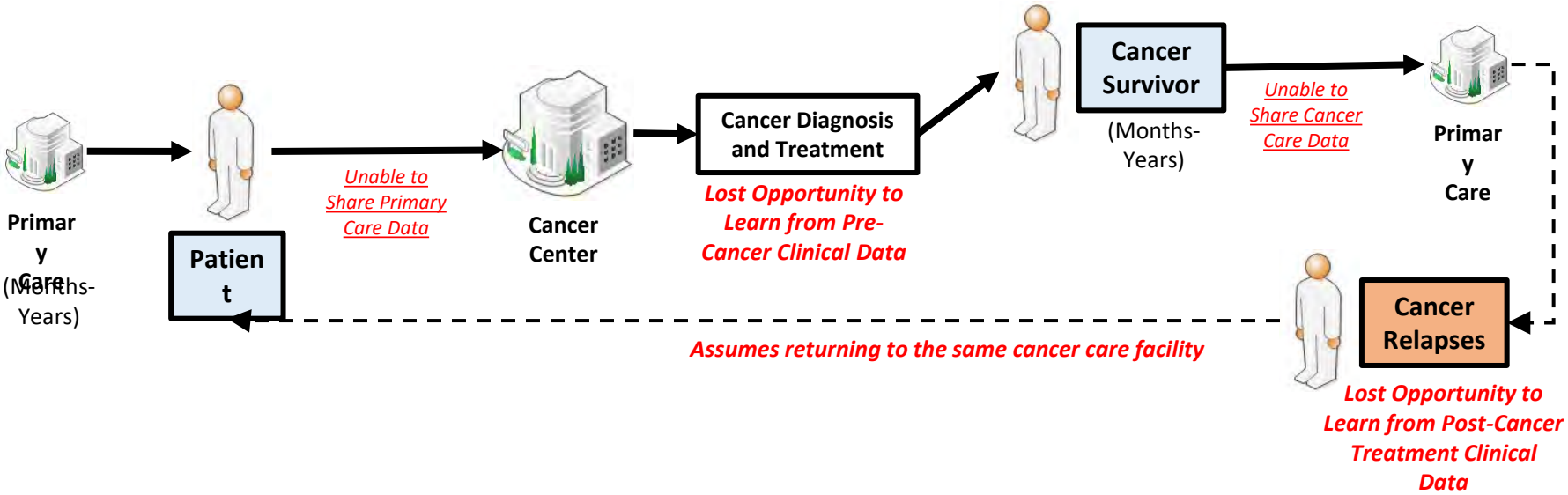
- Foundation Medicine — 18,000 cases
- Cancer studies in dbGaP — ~4,000 cases
- Multiple Myeloma RF — ~1,000 cases
- AACR GENIE — 59,000 cases

**Planned (1-3 years)**

- NCI-MATCH — ~3,000 cases
- Clinical Trial Sequencing Program — ~3,000 cases
- NCI-CPTAC — ~1,000 cases
- Cancer Driver Discovery Program — ~5,000 cases
- Human Cancer Models Initiative — ~1,000 cases
- **APOLLO – VA and DoD** — **~8,000 cases**

**~117,000 cases**

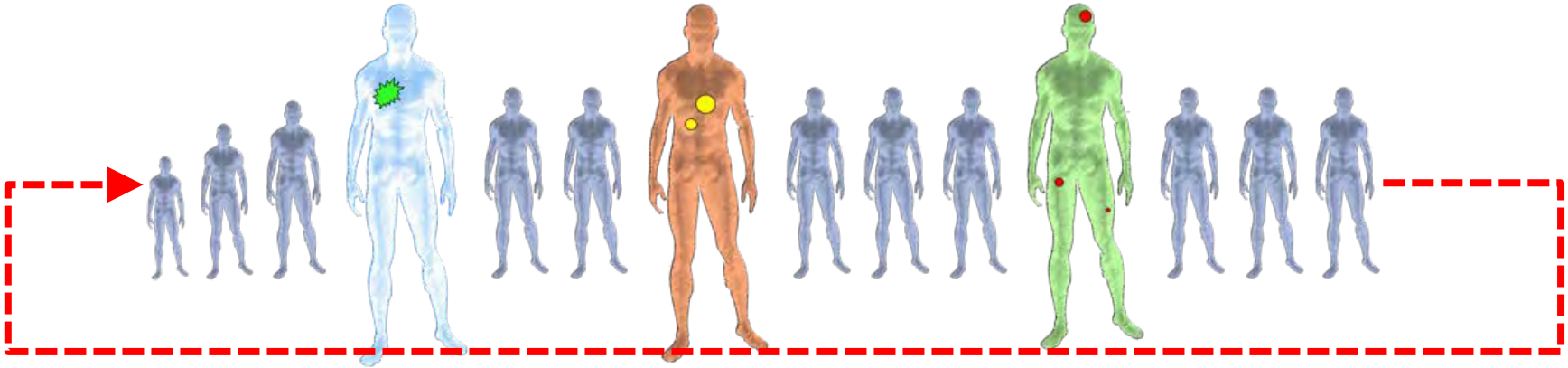
# Without a National Learning Healthcare System for Cancer




**"~85% of cancer patients are first diagnosed and treated in community setting"**

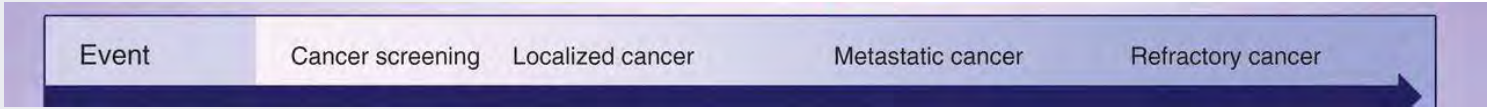
Copur et. al. J. Onc. Practice, 2015

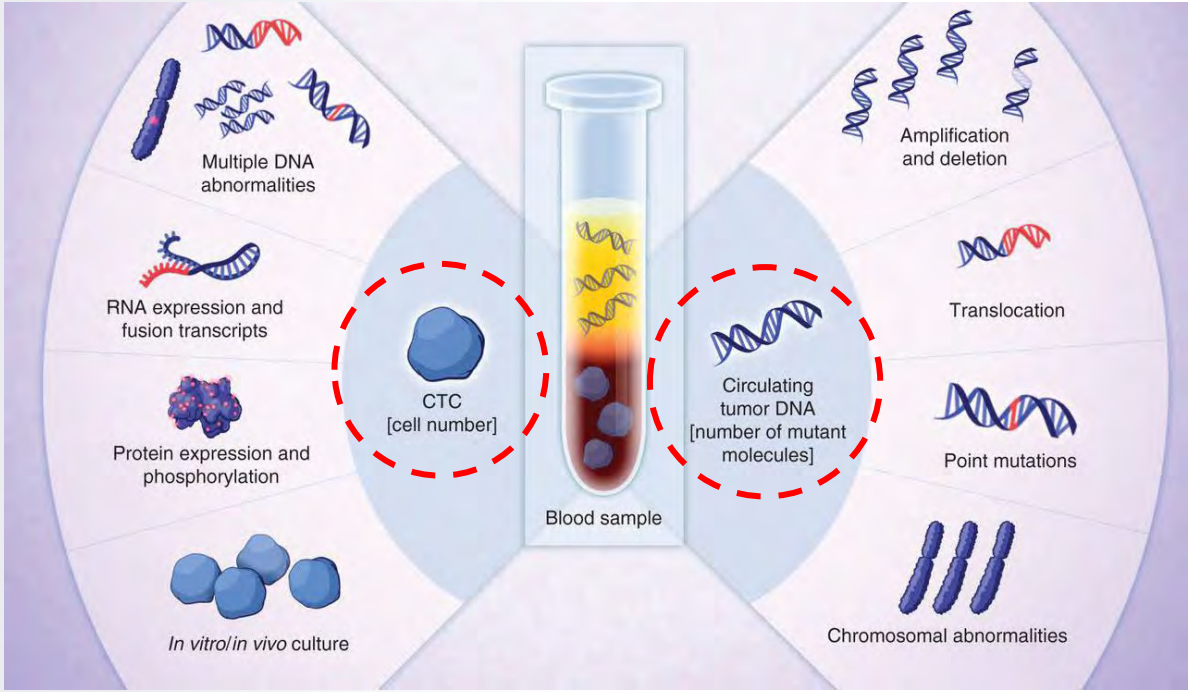
**The nation's first integrated molecular driven cancer care early discovery-to-clinical health care implementation system for active duty (AYAs), beneficiary, and veteran cancer patients.**



RWE Bootcamp, 2019 SC CTSI

# What about liquid biopsies?



HISTORY

BloodPAC
BLOOD PROFILING ATLAS IN CANCER

# White House Cancer Moonshot

On October 17, 2016, in response to the Vice President's call to action and in alignment with the goals of the White House Cancer Moonshot, representatives from government, academic, pharmaceutical and diagnostic companies launched the Blood Profiling Atlas in Cancer pilot in pursuit of creating an open database for liquid biopsies to potentially accelerate the development of safe and effective blood profiling diagnostic technologies for patient benefit.

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Courtesy of Lauren Leiman

## BLOODPAC COLLABORATORS


lauren@bloodPAC.org

Courtesy of Lauren Leiman

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# BloodPAC Pre-Analytical Requirements


April 2020

## Minimum Technical Data Elements for Liquid Biopsy Data Submitted to Public Databases

Phillip G. Febbo[1,†], Anne-Marie Martin[2,†], Howard I. Scher[3,†], J. Carl Barrett[4], Julia A. Beaver[5], Paul J. Beresford[6], Gideon M. Blumenthal[4], Kelli Bramlett[7], Carolyn Compton[8], Ryan Dittamore[9], David A. Eberhard[1], Daniel Edelstein[10], James Godsey[1], Andrew Gruen[11], Sean E. Hanlon[12], James Hicks[13], Daniel Hovelson[14], Melanie Hullings[3], Donald Johann[15], Justin Johnson[4], Anand Kolatkar[13], Peter Kuhn[13], Rebecca Levine[16], Jean-Francois Martini[17], Daniel P. Miller[18], Carissa Moore[19], Bryan Moy[11], Anand Pathak[20], Reena Philip[20], David Reese[21], Wendy Royalty[19], Matthew Ryder[10], Hakan Sakul[17], Lea M. Salvatore[22], Andrew Schade[23], Angela Silvestro[24], John K. Simmons[25], Jonathan Simons[16], Seema Singh Bhan[26], Matthew D. Smalley[27], Stella B. Somiari[28], AmirAli Talasaz[29], Muneesh Tewari[14], Hsian-Rong Tseng[27], Jake Vinson[30], Walt Wells[22], Allison Welsh[26], Robert L. Grossman[18,*,†], Jerry S. H. Lee[13,‡] and Lauren C. Leiman[31,‡]

http://bit.ly/BloodPACMTDE

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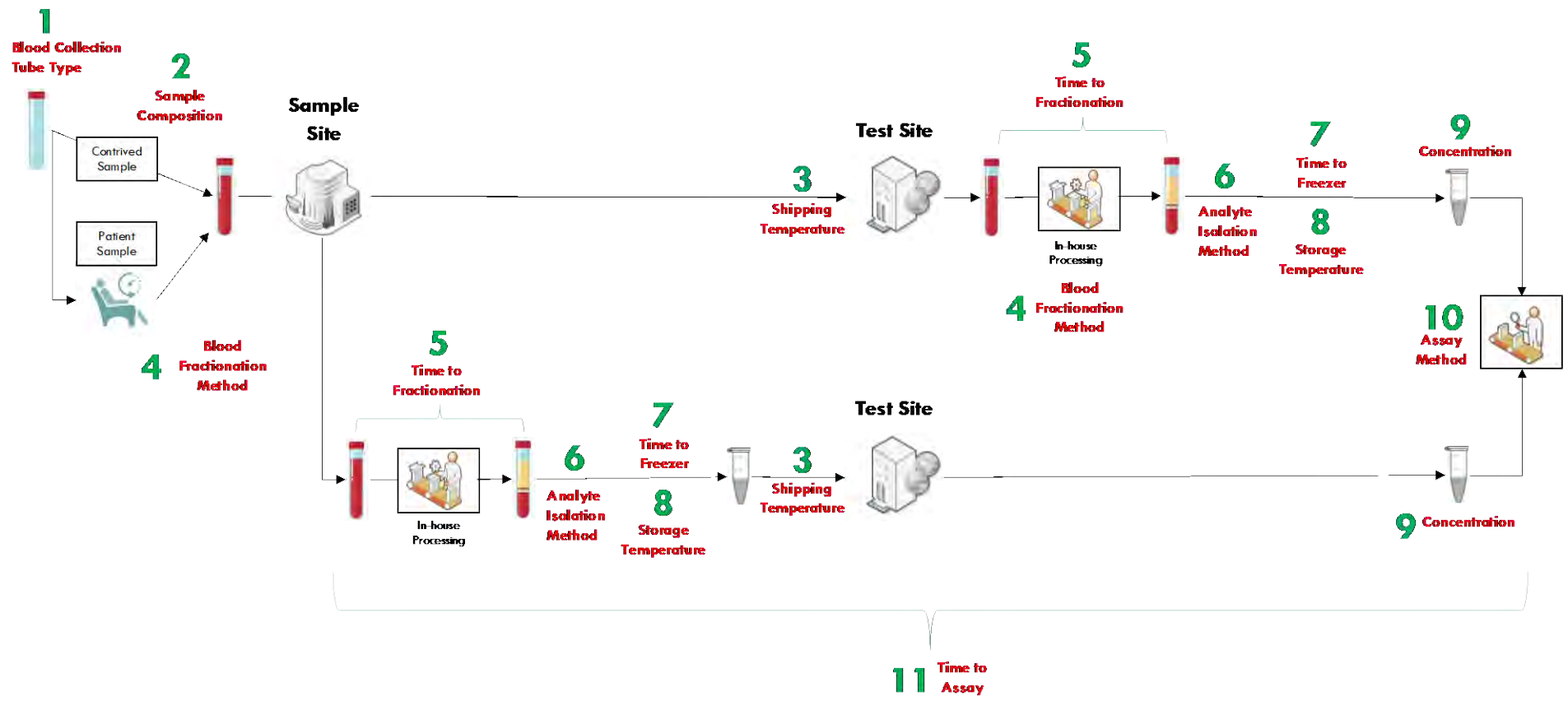
1
Blood Collection Tube Type
2
Sample Composition
Contrived Sample
Patient Sample
4
Blood Fractionation Method
Sample Site
3
Shipping Temperature
Test Site
5
Time to Fractionation
In-house Processing
4
Blood Fractionation Method
6
Analyte Isolation Method
7
Time to Freezer
8
Storage Temperature
9
Concentration
10
Assay Method
5
Time to Fractionation
In-house Processing
6
Analyte Isolation Method
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8
Storage Temperature
3
Shipping Temperature
Test Site
9
Concentration
11
Time to Assay

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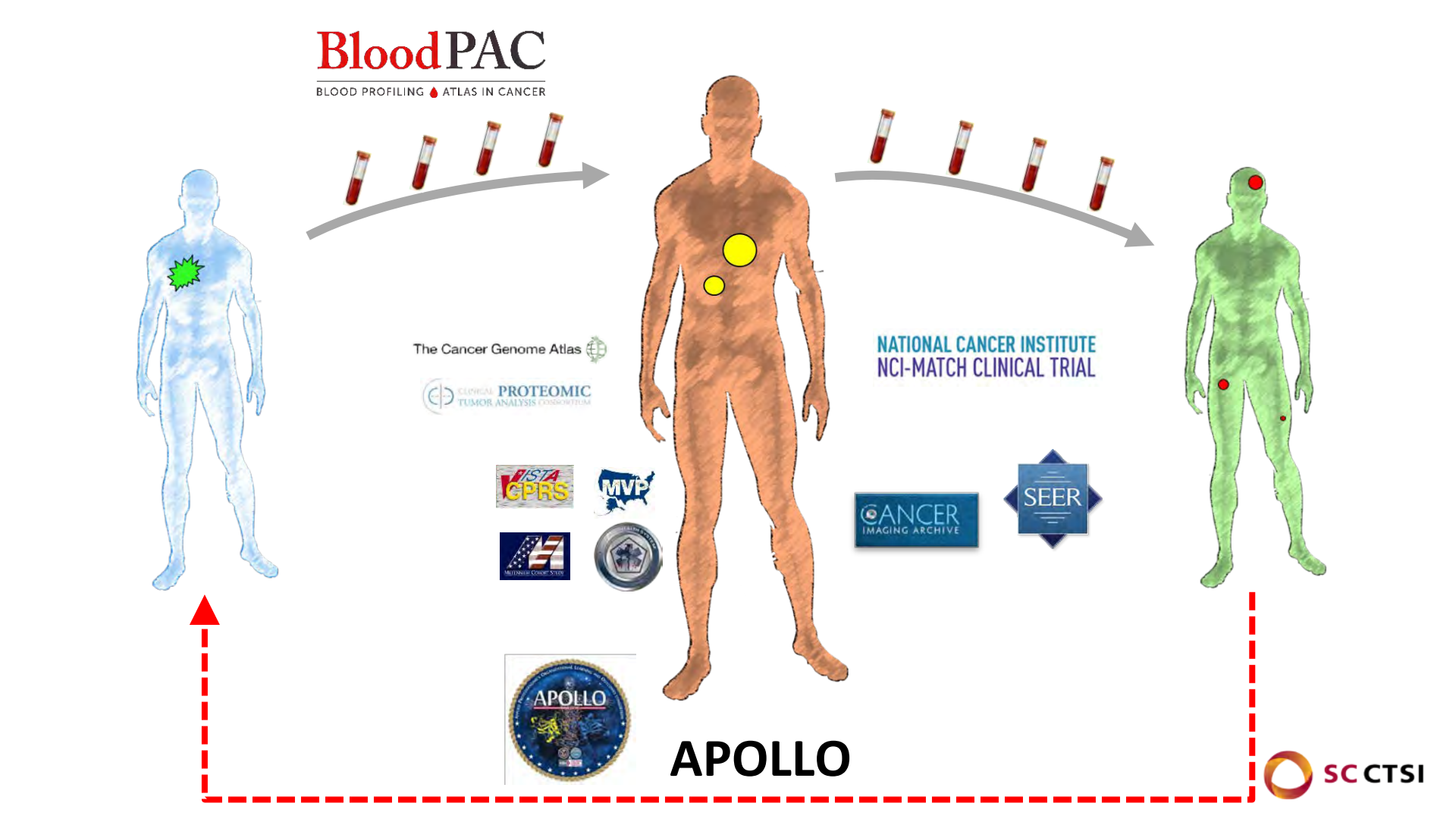
BloodPAC
BLOOD PROFILING ATLAS IN CANCER
The Cancer Genome Atlas
CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM
NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL
VISTA CPRS
MVP
CANCER IMAGING ARCHIVE
SEER
APOLLO
APOLLO
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# 2017 and beyond

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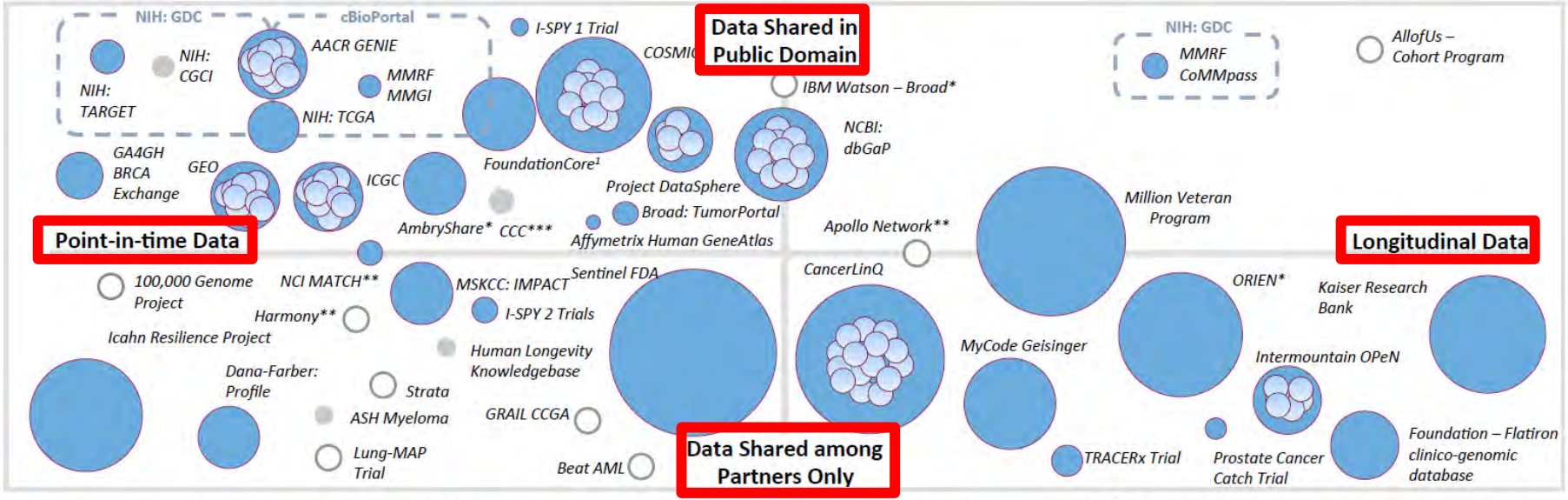
# Oncology Precision Medicine Data Landscape:
# December 2016 Update




Bubble size = estimated size of current dataset
Note: Representative selection of landscape, not all inclusive
Note: Dataset selection focused on oncology specific and oncology-inclusive datasets

Available datasets, size known
Available datasets, size unknown
Data initiative announced. Recruiting planned
Independent initiatives as part of larger dataset
Portals that are currently active/utilized in the public domain

***Opportunity exists to generate publicly available longitudinal data to drive understanding of genetic mutations and find Precision Medicine cures***

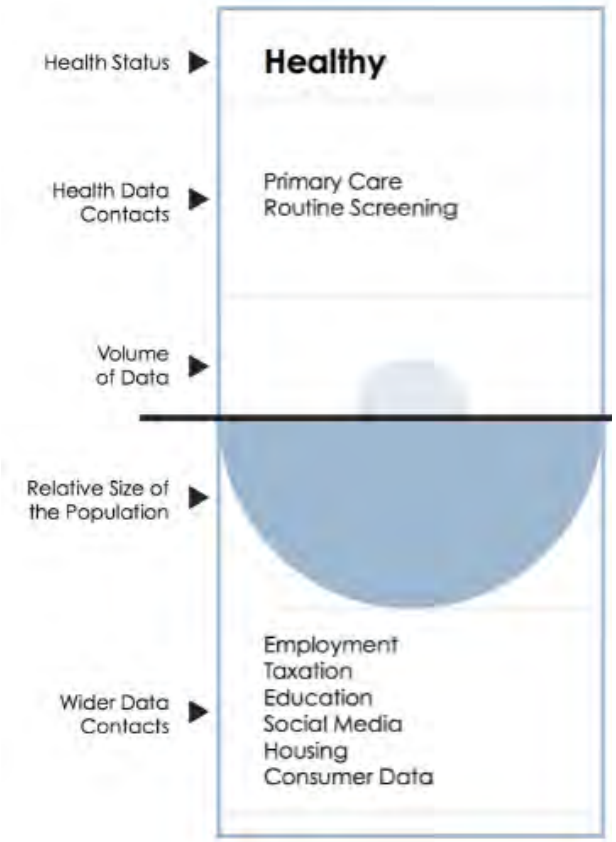
*Datasets have potential to include longitudinal data in the future
**Public/private information not available
***Serves as a portal also, has potential to include longitudinal data in the future

1. FoundationCore's pediatric cancer data has been made public

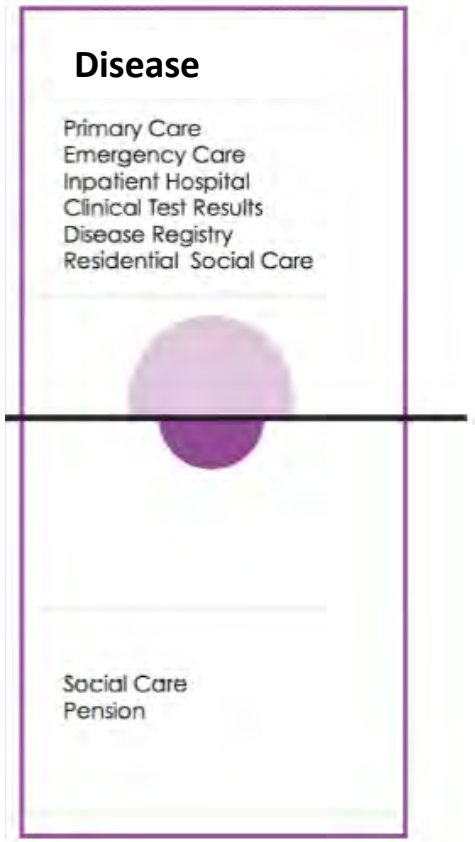


HARVARD BUSINESS SCHOOL
Kraft Precision Medicine Accelerator

# Precision Health

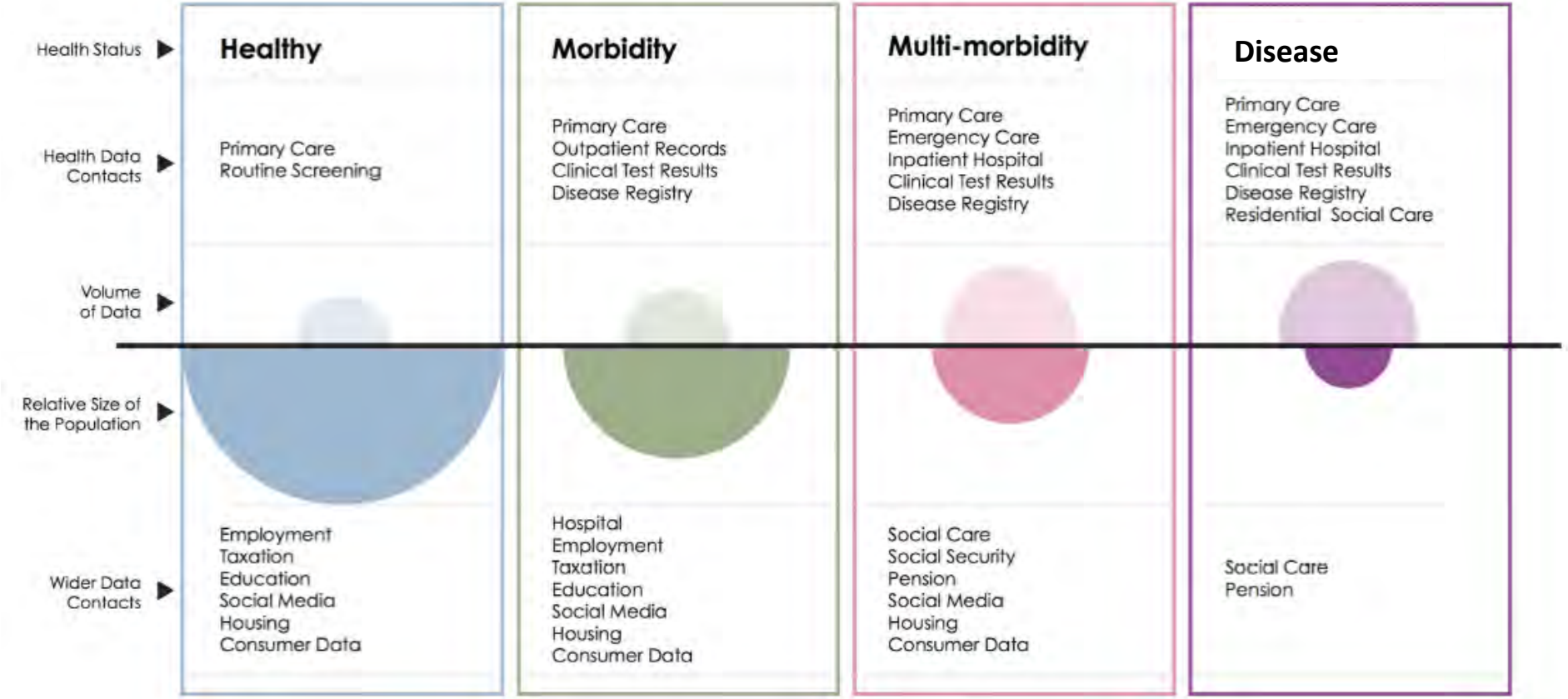



# Precision Oncology



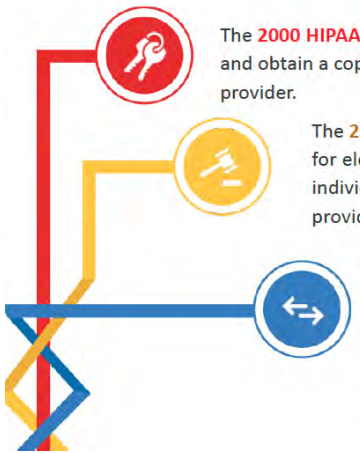

Denny and Steventon. *BMJ,* 2015

# Precision Health **Reality** Precision Oncology




Denny and Steventon. *BMJ*, 2015

# Promote **patient access** to their health information in a "**single, longitudinal** format that is **easy to understand, secure**, and **updated automatically.**"



The **2000 HIPAA Privacy Rule** established an individual's right to access, inspect, and obtain a copy of health records, upon request, from a covered health care provider.

The **2009 HITECH Act** directs HHS to adopt certification standards for electronic health record systems (EHRs), including methods for individual access, and to create rules for providers to use EHRs to provide access under Medicare enhanced payment programs

The **2016 Cures Act** directs HHS to develop the Trusted Exchange Framework and Common Agreement (TEFCA) for EHI exchange through health information networks (HINs) (Sec 4003), to require certified HIT to publish application programming interfaces (Sec 4002), & to educate stakeholders about how EHI exchange can support individual access (Sec 4006)

Supports two types of API-enabled services:

- Services for which a **single patient's data** is the focus
- Services for which **multiple patients' data** are the focus

https://www.healthit.gov/NPRM

HL7® FHIR®

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Lye et. al. *JAMIA* 2018

# 2017




# 2018




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# 2019


FDA

IN THIS SECTION

FDA NEWS RELEASE

**FDA approves third oncology drug that targets a key genetic driver of cancer, rather than a specific type of tumor**

*FDA also approves drug for second indication in a type of lung cancer*

For Immediate Release:
August 15, 2019


U.S. FOOD & DRUG ADMINISTRATION

**FDA In Brief: FDA launches new digital tool to help capture real world data from patients to help inform regulatory decision-making**


U.S. FOOD & DRUG ADMINISTRATION

FRAMEWORK FOR FDA'S
**REAL-WORLD EVIDENCE PROGRAM**

December 2018
www.fda.gov


U.S. FOOD & DRUG ADMINISTRATION

**FDA's MyStudies Application (App)**

The U.S. Food and Drug Administration (FDA) is posting computer code and a technical roadmap that will allow researchers and developers to customize and use the FDA's newly created MyStudies app. The FDA MyStudies App is designed to facilitate the input of real world data directly by patients which can be linked to electronic health data supporting traditional clinical trials, pragmatic trials, observational studies and registries. It was developed by the FDA and private sector partners, but open source code and technical documentation are being released to the public, so the app and patient data storage system can be reconfigured by organizations conducting clinical research. The app bore the FDA brand while its functionality was tested in a pilot study, but it can now be rebranded by researchers and developers who would like to customize and rebrand the app.

# 2020


CMS.gov

Newsroom

Press release

**CMS Expands Coverage of Next Generation Sequencing as a Diagnostic Tool for Patients with Breast and Ovarian Cancer**

Jan 27, 2020 | Coverage

Share

Today the Centers for Medicare & Medicaid Services (CMS) took action to cover FDA approved or cleared laboratory diagnostic tests using Next Generation Sequencing (NGS) for patients with germline (inherited) ovarian or breast cancer.

**FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers**

Share Tweet LinkedIn Email Print

On October 26 and November 6, 2020, the Food and Drug Administration approved the liquid biopsy next-generation sequencing-based FoundationOne Liquid CDx test (Foundation Medicine, Inc.) as a companion diagnostic device for multiple additional biomarkers detected in cell free-DNA isolated from plasma specimens.

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# Patient Trajectory Comprised of All Relevant Cancer Case and Cofactor Trajectories

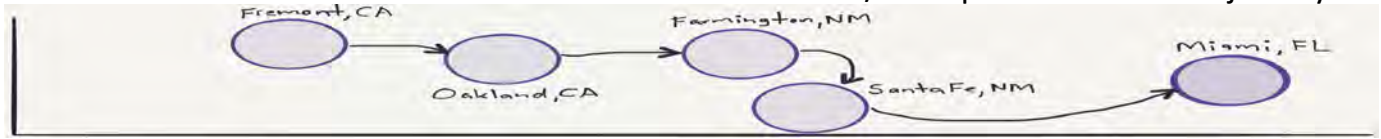
Cancer Case #1 Trajectory



Cancer Case #2 Trajectory

Comorbidity Cofactor Trajectory


Residence / Geospatial Cofactor Trajectory




Courtesy of Paul Fearn

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# Your Insights Matter and Are Critical

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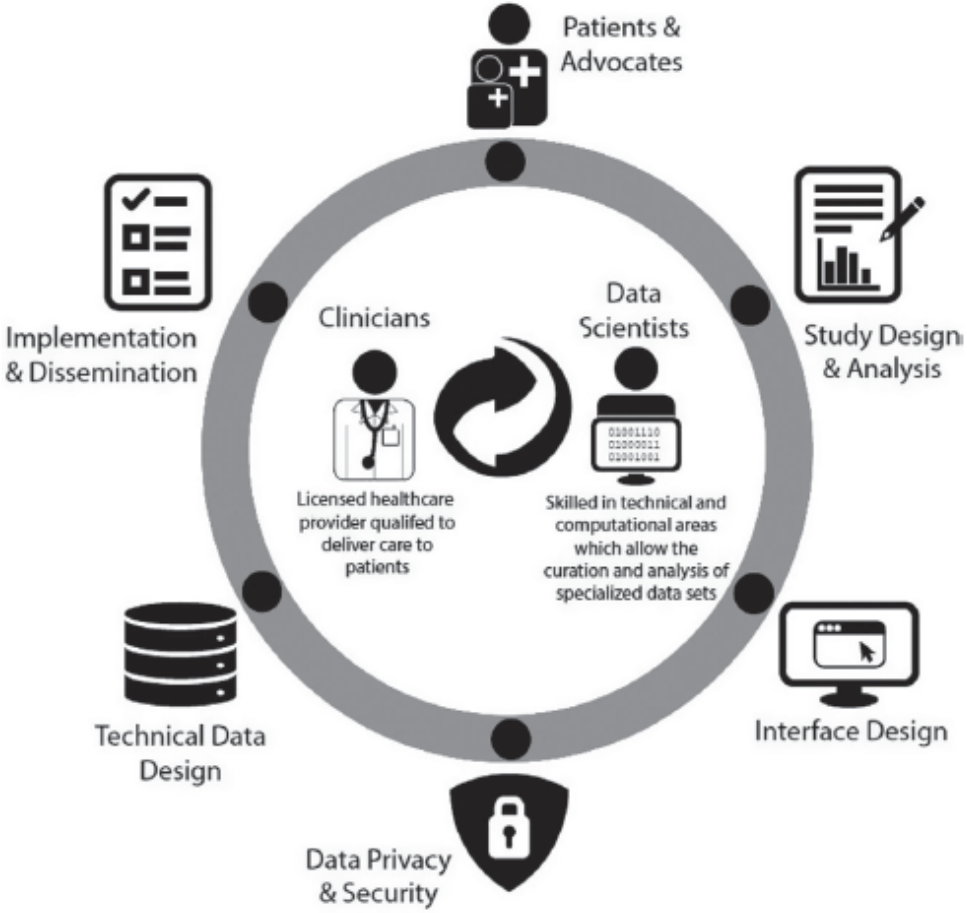
# Harnessing the Power of Collaboration and Training Within Clinical Data Science to Generate Real-World Evidence in the Era of Precision Oncology

Donna R. Rivera[1,*], Jerry S. H. Lee[2,3,4], Elizabeth Hsu[5], Muin J. Khoury[6], Frank Meng[7,8], Ofelia Olivero[9], Lynne Penberthy[1] and Georgia D. Tourassi[10]



# Making Data FAIR & Transparent

**F**indable

**A**ccessible

**I**nteroperable

**R**eusable

https://www.force11.org/group/fairgroup/fairprinciples

# An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics

4/2018

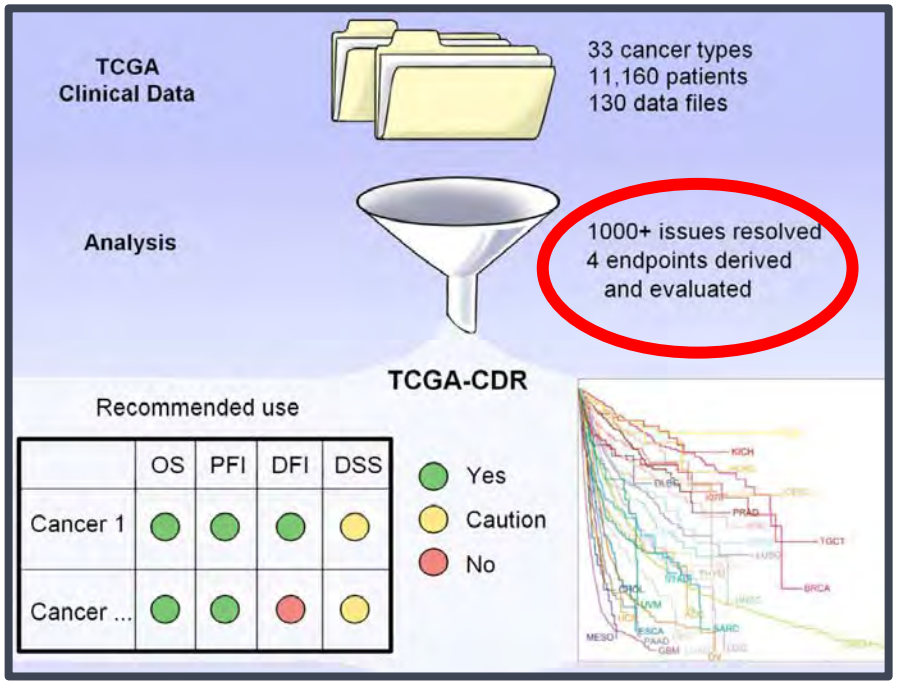



**Table 3. Assessment and Recommended Use of the Endpoints of OS, PFI, DFI, and DSS**

| | | OS (Accurately Defined) | | | PFI (Accurately Defined) | | | DFI (Accurately Defined) | | | DSS (Approximately Defined) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Type | N | Use | Event | Censored | Use | Event | Censored | Use | Event | Censored | Use | Event | Censored |
| ACC | 92 | ● | 34 | 58 | ● | 49 | 43 | ◐ | 14 | 39 | ● app. | 30 | 60 |
| BLCA | 412 | ● | 181 | 231 | ● | 177 | 235 | ● | 32 | 157 | ● app. | 124 | 274 |
| BRCA | 1097 | ◐ | 151 | 946 | ● | 145 | 952 | ● | 84 | 869 | ◐ App.* | 83 | 995 |
| CESC | 307 | ● | 71 | 236 | ● | 71 | 236 | ● | 26 | 150 | ● acc. | 54 | 249 |
| CHOL | 45 | ● | 22 | 23 | ● | 23 | 22 | ◐ | 10 | 18 | ◐ app.* | 18 | 24 |
| COAD | 459 | ● | 102 | 357 | ● | 123 | 336 | ● | 24 | 166 | ● app. | 64 | 379 |
| DLBC | 48 | ○ | 9 | 39 | ◐ | 12 | 36 | ○ | 4 | 24 | ○ | 4 | 44 |
| ESCA | 185 | ● | 77 | 108 | ● | 87 | 98 | ● | 23 | 66 | ● app. | 51 | 132 |
| GBM | 596 | ● | 491 | 105 | ● | 506 | 90 | ○ | 2 | 1 | ● app. | 445 | 110 |
| PCPG | 179 | ○ | 6 | 173 | ○ | 21 | 158 | ○ | 4 | 156 | ○ | 4 | 175 |
| PRAD | 500 | ◐ | 10 | 490 | ● | 93 | 407 | ● | 30 | 310 | ○ | 5 | 493 |
| READ | 170 | ◐ | 26 | 144 | ● | 39 | 131 | ○ | 7 | 41 | ◐ app.* | 15 | 149 |

Liu et. al. *Cell*, 2018

# Tempus and Leidos Biomedical Research Inc. Launch Effort to Enhance The Cancer Genome Atlas

**6/11/2019**

CHICAGO, June 11, 2019 (GLOBE NEWSWIRE) — Tempus, a technology company advancing precision medicine through the collection and analysis of molecular and clinical data at scale announced today that it was selected by Leidos Biomedical Research Inc. (Leidos Biomed) to abstract and structure follow-up clinical data for The Cancer Genome Atlas (TCGA) Project for submission to the National Cancer Institute's Genomic Data Commons (GDC).

There are 230 distinct investigators that contributed samples to TCGA, with 10,000 cases represented by 100 contributing institutions. While the genomic data from TCGA has been transformative for research, continuing to enrich the dataset can increase its usefulness for researchers and clinicians. To make the TCGA resource even more useful, Tempus is working with Leidos Biomed on behalf of the NCI to obtain up-to-date medical records for clinical data abstraction.

As part of this collaboration, Tempus will reach out to these contributors and/or their institutions to obtain up-to-date medical records for clinical data abstraction. Then, using its Tempus O platform, which employs a sophisticated combination of technologies, such as optical character recognition and natural language processing algorithms, along with qualified healthcare professionals, Tempus will clean and structure the collected data, which will then get paired with the corresponding molecular data. This 'upgraded' TCGA dataset will then be made publicly available for researchers around the world, as the current TCGA data is today.

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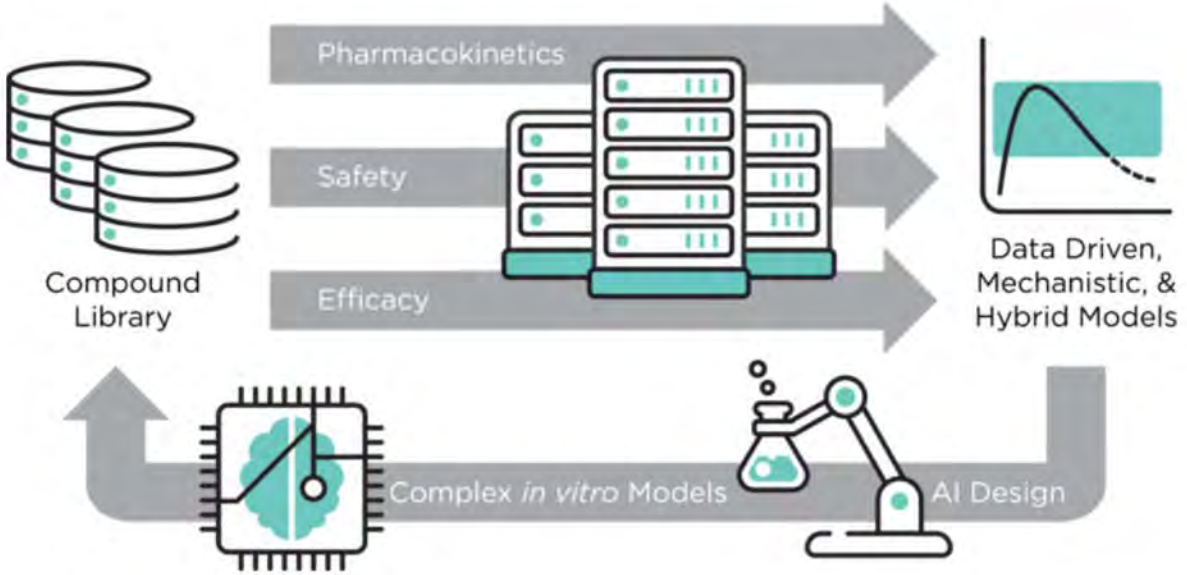
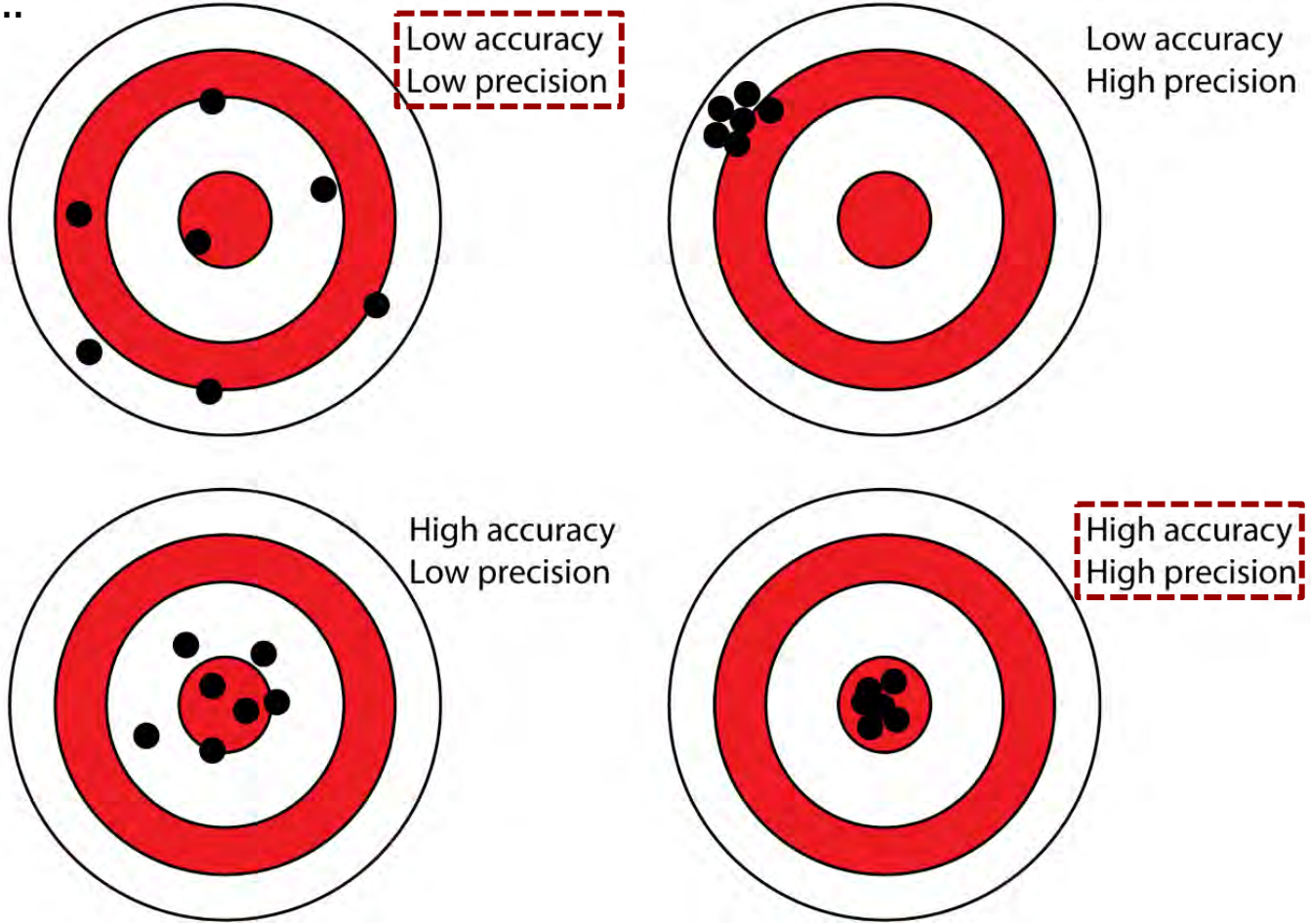



**For more information:**


- **Eric Stahlberg, Ph.D.**
  ATOM Co-lead & Director, Biomedical Informatics & Data Science
  Frederick National Laboratory
  Eric.Stahlberg@nih.gov

## Final thought…




http://www.antarcticglaciers.org/glacial-geology/dating-glacial-sediments-2/precision-and-accuracy-glacial-geology/

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# Questions?


dr.jerry@usc.edu

***Service to others is the rent you pay for your room here on earth*** – **Muhammad Ali**

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# Thank You!

**SC CTSI** | www.sc-ctsi.org Phone: (323) 442-4032 Email: info@sc-ctsi.org Twitter: @SoCalCTSI

**Cite us:** This work was supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

# Recommended References


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- Roychowdhury S, Iyer MK, Robinson DR, Lonigro RJ, Wu YM, Cao X, Kalyana-Sundaram S, Sam L, Balbin OA, Quist MJ, Barrette T, Everett J, Siddiqui J, Kunju LP, Navone N, Araujo JC, Troncoso P, Logothetis CJ, Innis JW, Smith DC, Lao CD, Kim SY, Roberts JS, Gruber SB, Pienta KJ, Talpaz M, Chinnaiyan AM. **Personalized oncology through integrative high-throughput sequencing: a pilot study.** Sci Transl Med. 2011

# Innovation to Translation:

## Role of Genomics in Medical Product Development

Robert E. Pacifici, Ph.D.
Chief Scientific Officer
CHDI Foundation

SC CTSI


Accelerating therapeutic development for Huntington's disease

USC University of Southern California

# Innovation to Translation:

## *Role of Genomics in Medical Product Development*

# *Applied Genomics and Target Identification*

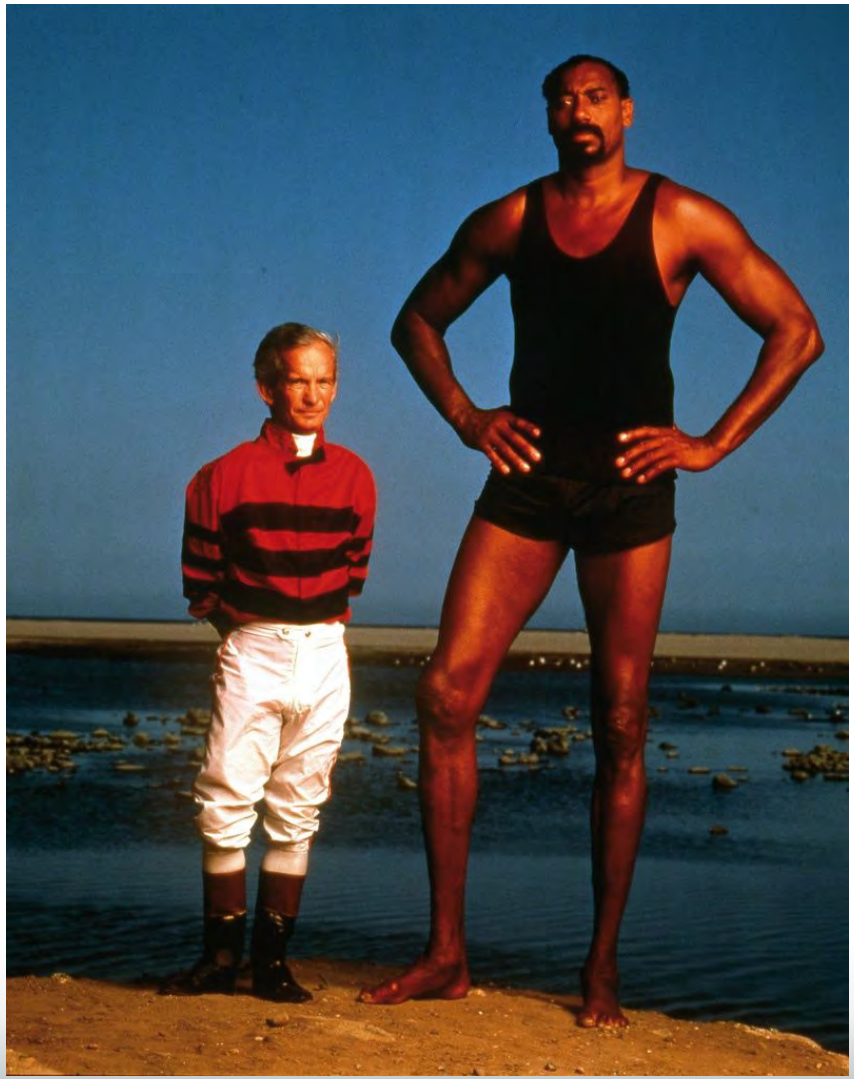
***Robert E. Pacifici, Ph.D.***

*Chief Scientific Officer*

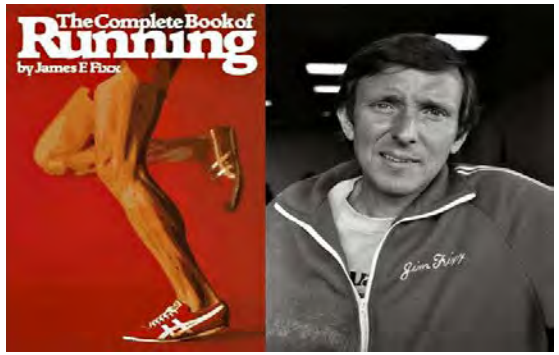
*CHDI Foundation, Inc/ CHDI Management, Inc.*

# We all share the same genome, but…

…small changes can make a big difference!



Phenotypes go beyond appearance and can also dramatically impact health

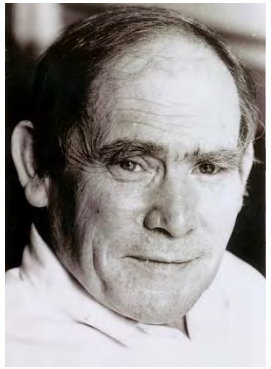



1932 -1984
52 years

“Unlucky genes”

1874 -1965
90 years

“Lucky genes”



Sydney Brenner

MB427: *Biotechnology and its Social Impact*
Princeton Course ~1995
“Uncle Winston’s Genome”

“Identifying Disease genes is fundamental—the opportunity for new medicines is finding the genes for luck”

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# Very lucky (modifier) genes!



nature biotechnology

## Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

Genetic studies of human disease have traditionally focused on the detection of disease-causing mutations in afflicted individuals. Here we describe a complementary approach that seeks to identify healthy individuals resilient to highly penetrant forms of genetic childhood disorders. A comprehensive screen of 874 genes in 589,306 genomes led to the identification of 13 adults harboring mutations for 8 severe Mendelian conditions, with no reported clinical manifestation of the indicated disease. Our findings demonstrate the promise of broadening genetic studies to systematically search for well individuals who are buffering the effects of rare, highly penetrant, deleterious mutations. They also indicate that incomplete penetrance for Mendelian diseases is likely more common than previously believed. The identification of resilient individuals may provide a first step toward uncovering protective genetic variants that could help elucidate the mechanisms of Mendelian diseases and new therapeutic strategies.

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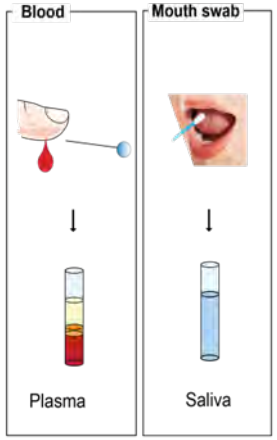
# *Innovation* in DNA Sequencing technology is driving a revolution in *Translation*

- Comprehensive
  - Unbiased whole genome sequencing
  - Databases populated from large number of individuals

- Non-invasive
  - Unlike other biopsies, very easy to obtain DNA
  - A little bit goes a long way


- Continuous improvement on all metrics
  - ↓Cost, ↑Throughput, ↓Cycle-time, ↑Quality
- Genomics can impact drug discovery & development at all stages in a myriad of ways
  - Diagnosis
  - Target Identification
  - Prognosis
  - Stratification

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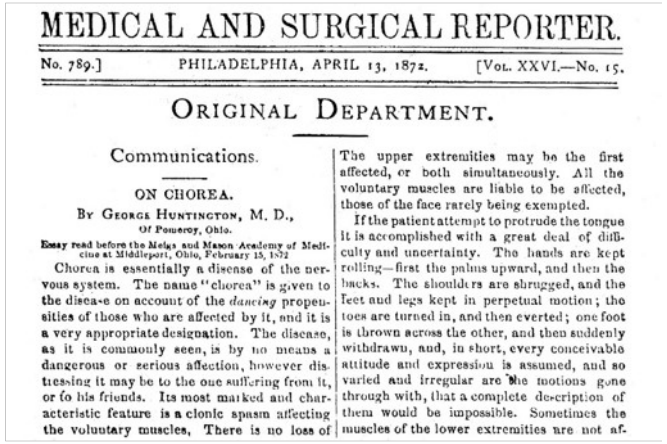
# Huntington's Disease: What I work on & a good example!



MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

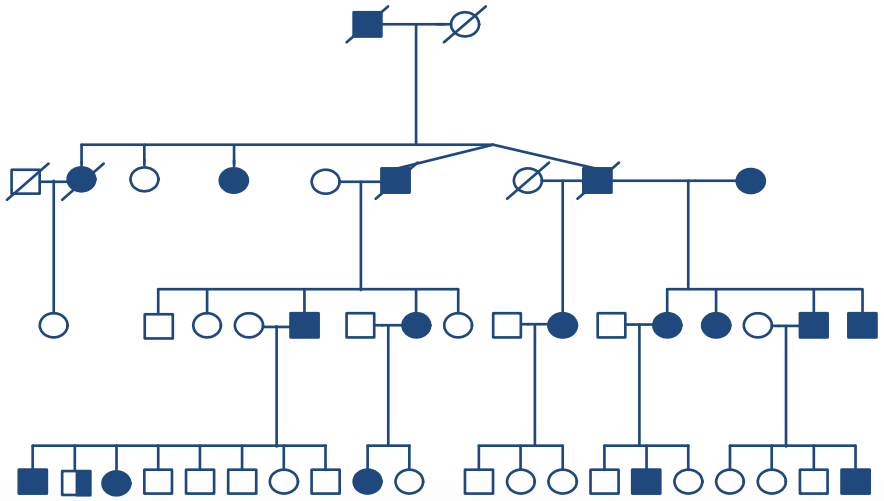
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-



- George Huntington
  - Family doctor on Long Island
- Publishes his one and only paper in 1872
  - Describes the movement disorder as chorea
- HD is a hereditary disease
  - It runs in families
  - You don't "catch" it
  - You are not possessed by demons
- Autosomal dominant
  - Males and females have same chance
  - No "recessive" carriers
  - Children have a 50:50 chance

# The Hunt Begins to Clone the Causal Gene


Short Arm of Chromosome 4 (4p16.3)

**A polymorphic DNA marker genetically linked to Huntington's disease**

James F. Gusella*, Nancy S. Wexler†‖, P. Michael Conneally†, Susan L. Naylor§, Mary Anne Anderson*, Rudolph E. Tanzi*, Paul C. Watkins*¶, Kathleen Ottina*, Margaret R. Wallace‡, Alan Y. Sakaguchi§, Anne B. Young‖, Ira Shoulson†, Ernesto Bonilla† & Joseph B. Martin*

*Neurology Department and Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA
† Hereditary Disease Foundation, 9701 Wilshire Blvd, Beverley Hills, California 90212, USA
‡ Department of Medical Genetics, Indiana University Medical Center, Indianapolis, Indiana 46223, USA
§ Department of Human Genetics, Roswell Park Memorial Institute, Buffalo, New York 14263, USA
‖ Venezuela Collaborative Huntington's Disease Project*

- Monogenic with 100% penetrance
  - Everyone that has the "bad" gene will get HD
  - Everyone that gets HD has the "bad" gene
- Relatively rare disease (1:10,000)
  - Meets with orphan designation
  - Familial link allows ID of concentrated cohorts
  - Second disease gene to be positionally cloned
- Linkage analysis finds the marker in 1983
- Full gene sequence in 1993

Cell Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

**A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes**

The Huntington's Disease Collaborative Research Group*

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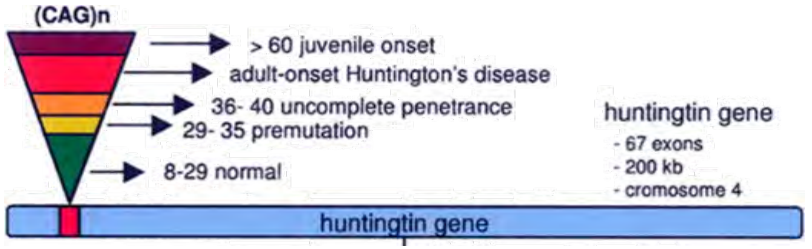
# Big deal, you know the gene…so what?

- Huntington's disease isn't caused by a point mutation
  - Polymorphic expansion of $(CAG)_n$
  - Trinucleotide repeat or poly glutamine disorder
  - (Still) unknown function
  - Probably gain of tox versus loss of function
    - Heterozygotes (Dx and KO), Homozygotes
- Enables genetic testing (diagnostic)
  - Predict who is going to get it
  - Estimate age of onset




# Big deal, you know the gene…so what?

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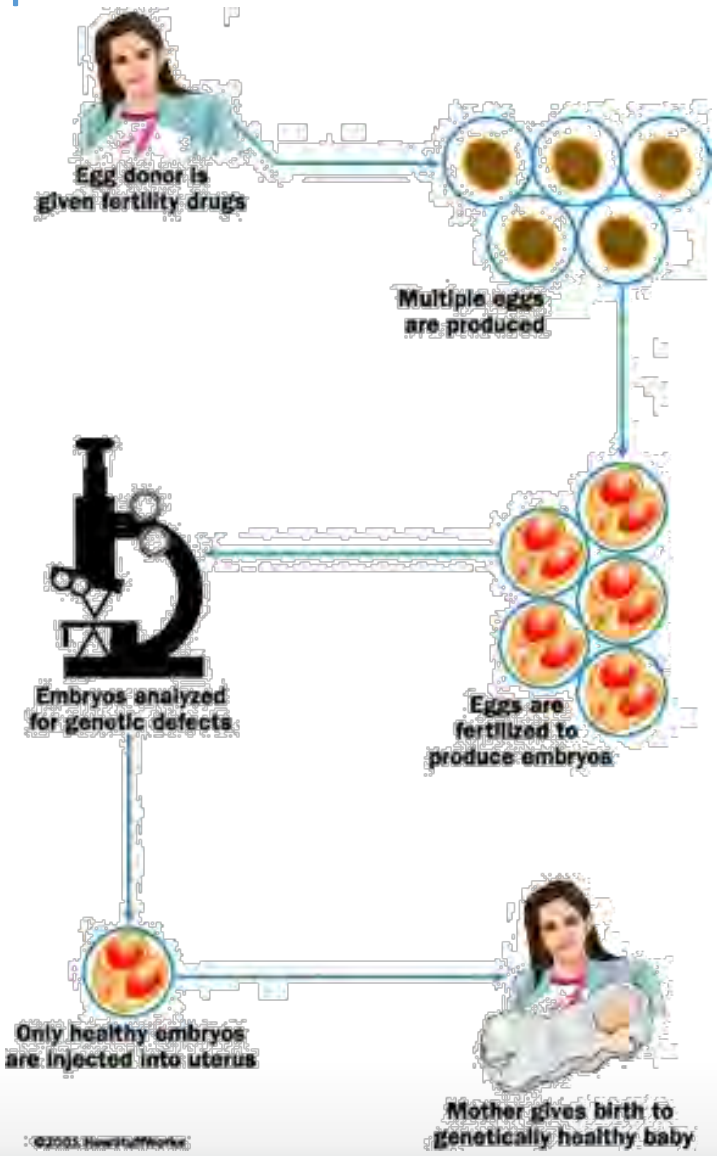
- You can do family planning
  - Do I want to take a 50% risk?
  - Pre-Implantation Genetic Diagnosis



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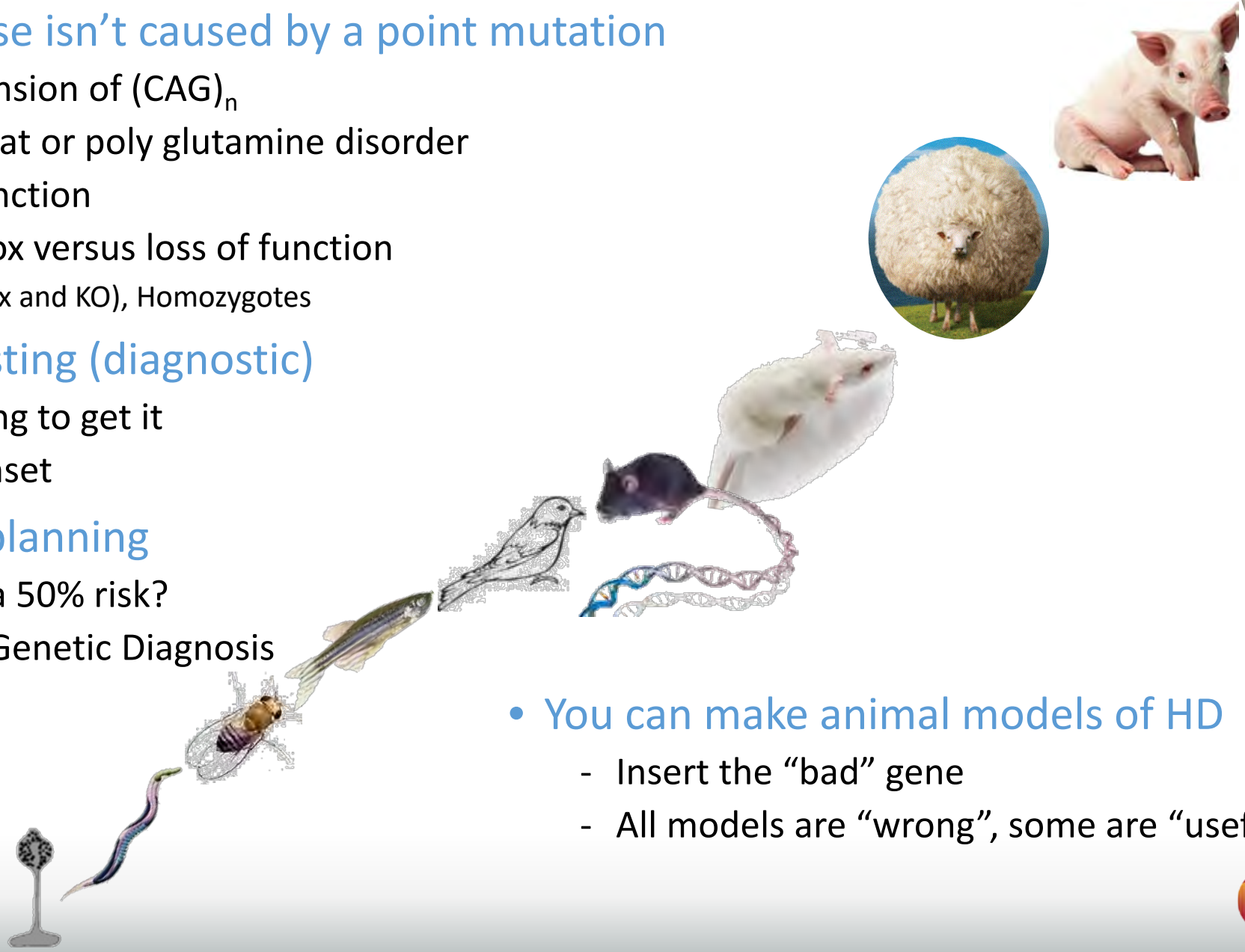

- You can make animal models of HD
  - Insert the "bad" gene
  - All models are "wrong", some are "useful"

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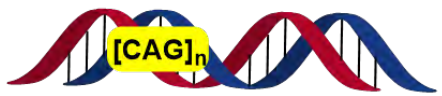
# Directly enable discovery of HTT lowering drugs




- *AAV-ZFP*
- *CRISPR-Cas9*
- *Small molecule transcription blocker*

Roche

*Transcription*

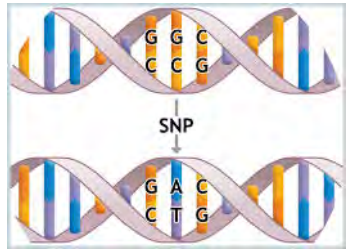

- *AAV-miRNA*
- *ASO*
- *siRNAs*
- *Small molecule translation blocker*

uniQure

*Translation*


- *Degradation enhancers*

WAVE LIFE SCIENCES




*Aggregation*

IONIS PHARMACEUTICALS

UC San Diego

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Neuron
Article

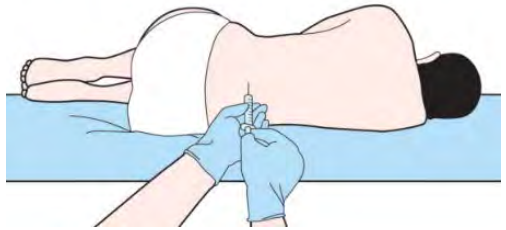
Cell PRESS

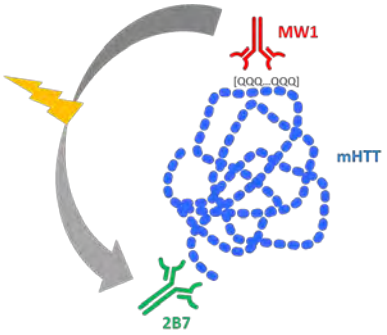
**Sustained Therapeutic Reversal of Huntington's Disease by Transient Repression of Huntingtin Synthesis**

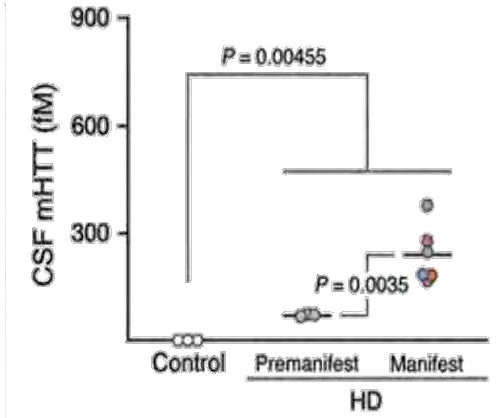
Holly B. Kordasiewicz,[1] Lisa M. Stanek,[2] Edward V. Wancewicz,[3] Curt Mazur,[3] Melissa M. McAlonis,[1] Kimberly A. Pytel,[1] Jonathan W. Artates,[1] Andreas Weiss,[4] Seng H. Cheng,[2] Lamya S. Shihabuddin,[2] Gene Hung,[3] C. Frank Bennett,[3] and Don W. Cleveland[1,*]
[1]Ludwig Institute for Cancer Research and Department of Cellular and Molecular Medicine, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
[2]Genzyme Corporation, 49 New York Avenue, Framingham, MA 01760, USA
[3]Isis Pharmaceuticals, 2588 Gazelle Court, Carlsbad, CA 92010, USA
[4]Novartis Institutes for BioMedical Research, CH-4002 Basel, Switzerland
*Correspondence: dcleveland@ucsd.edu
DOI 10.1016/j.neuron.2012.05.009

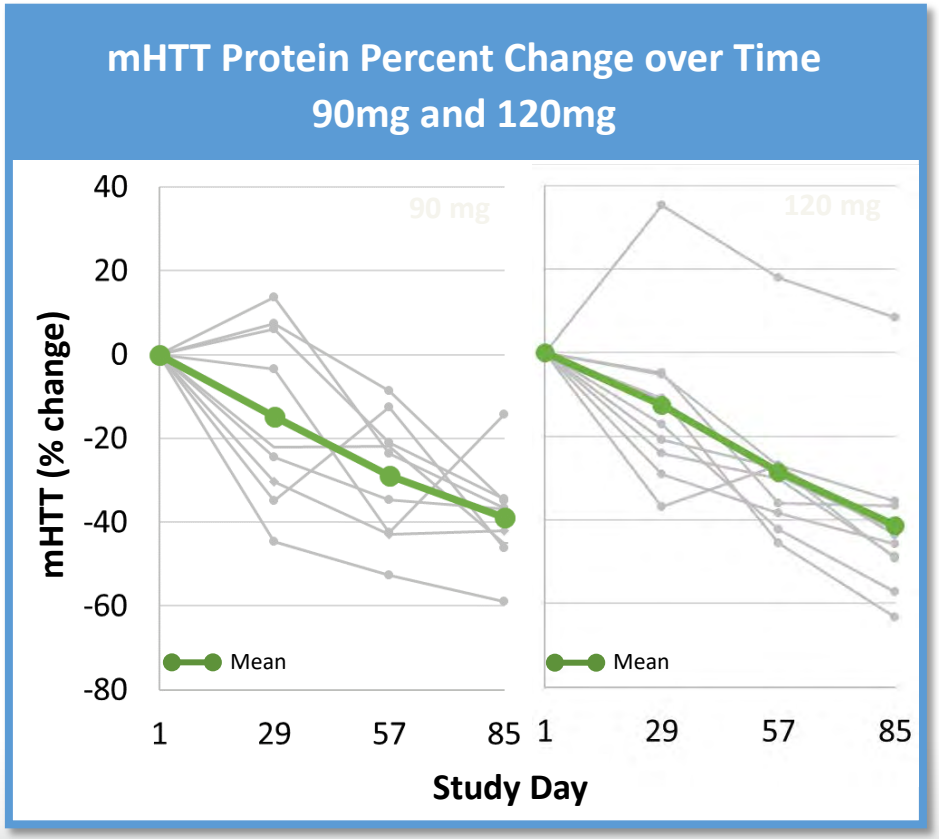
NOVARTIS

# Development of pharmacodynamic biomarkers






From 2018 HDSA Annual Convention

Genentech
*A Member of the Roche Group*

Roche

16 September 2018

**Update on RG6042 (formerly known as IONIS-HTT$_{Rx}$) Huntington's disease global development programme: Two clinical studies to begin by end of 2018**

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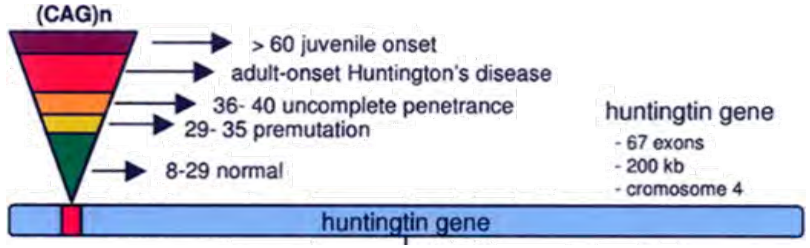
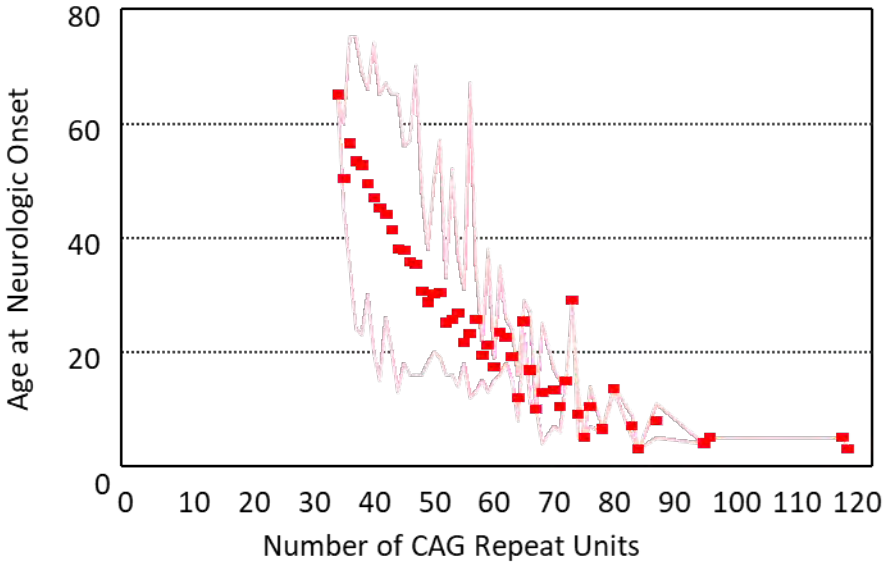
# Back to HD Genetics




- Huntington's disease isn't caused by a point mutation
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- Inverse correlation between size and onset
  - Small = later / Bigger = earlier

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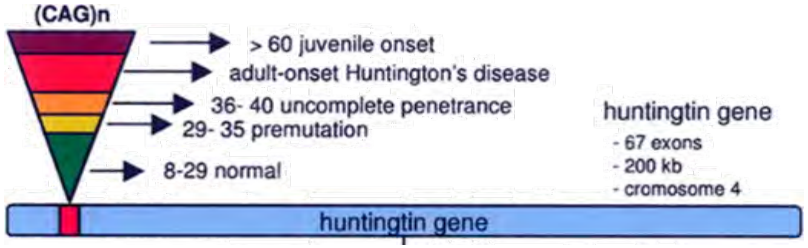
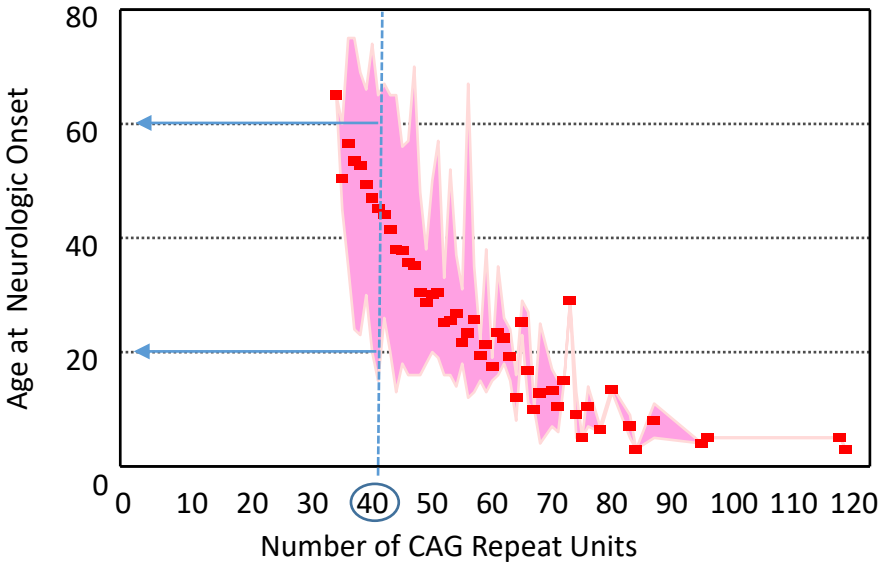
# Back to the patients & families and their genetics

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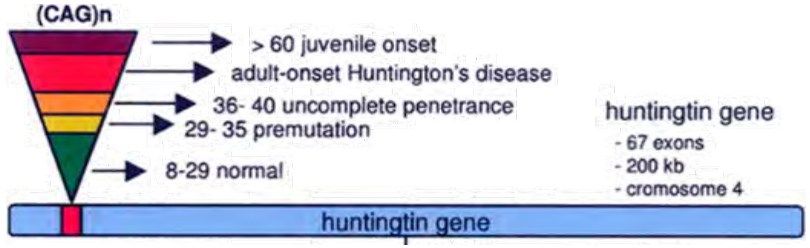


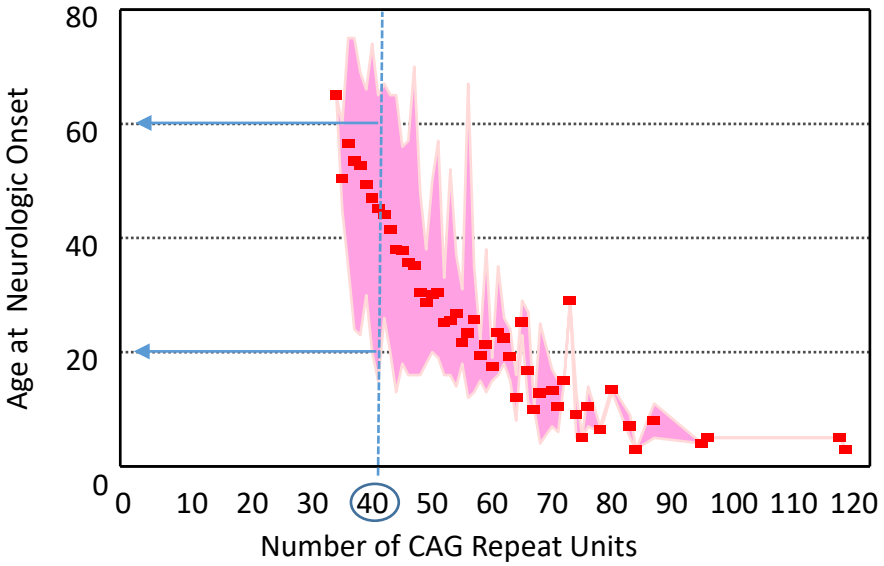


GenomeMedicine

Review

**Huntington's disease: the case for genetic modifiers**

James F Gusella and Marcy E MacDonald

Address: Molecular Neurogenetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, 02114, USA.

Correspondence: James F Gusella. E-mail: gusella@helix.mgh.harvard.edu

- Huntington's disease isn't caused by a point mutation
  - Expansion of $(CAG)_n$
- Inverse correlation between size and onset
  - Small = later / Bigger = earlier
- $(CAG)_n$ accounts for about 2/3 of age of onset
  - There must be other factors in play
- The propensity to be "late" or "early" is also heritable
  - Modifier genes!
  - Need big numbers
- Imagine a drug that delays onset for 40 years!

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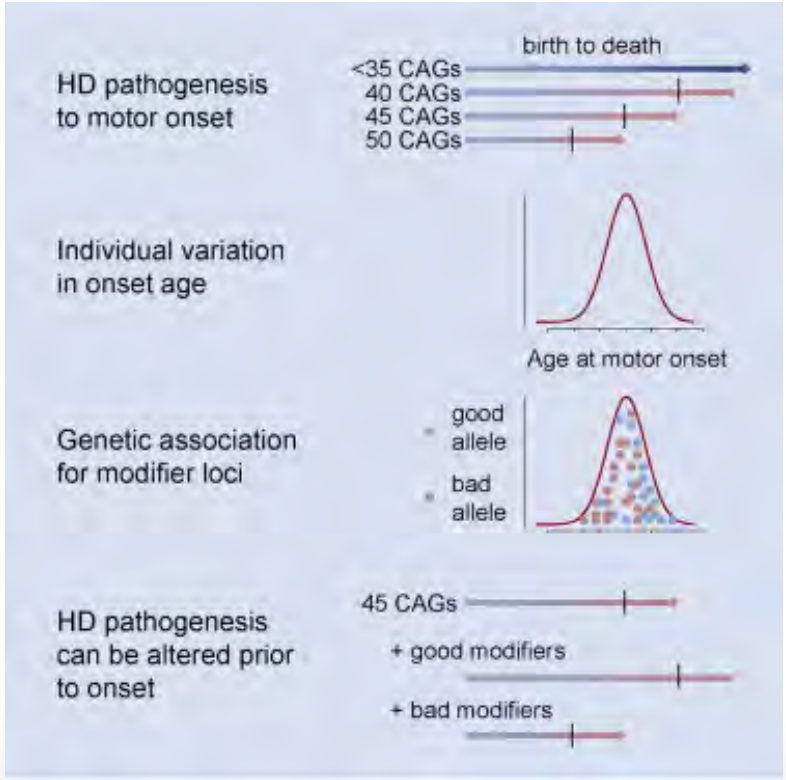
# Genome Wide Association Studies (GWAS):Can be used to identify causal genes which modify disease onset and rate of progression

## Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease

Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium*
*Correspondence: gusella@helix.mgh.harvard.edu
http://dx.doi.org/10.1016/j.cell.2015.07.003




- A massive collaborative effort
  - 9000 patients and family members

# Huntington's patients continue to provide the keys

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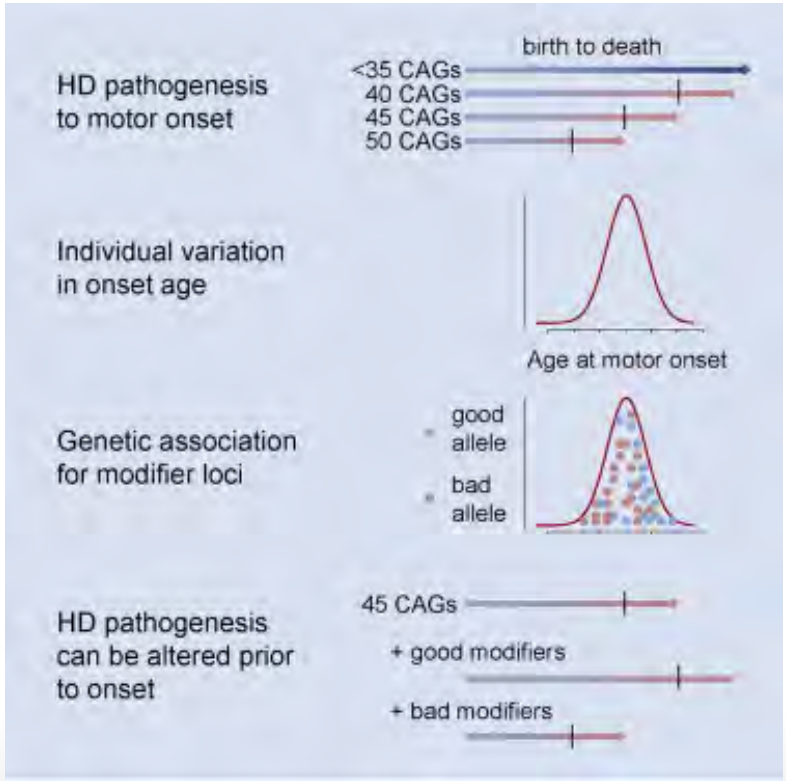
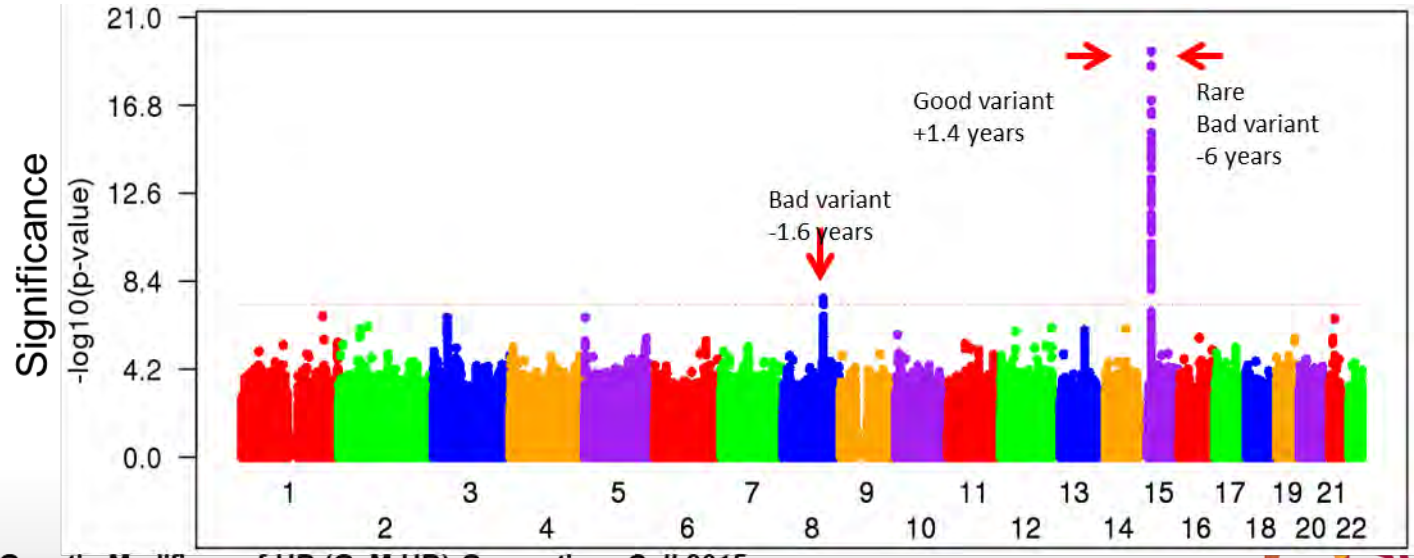
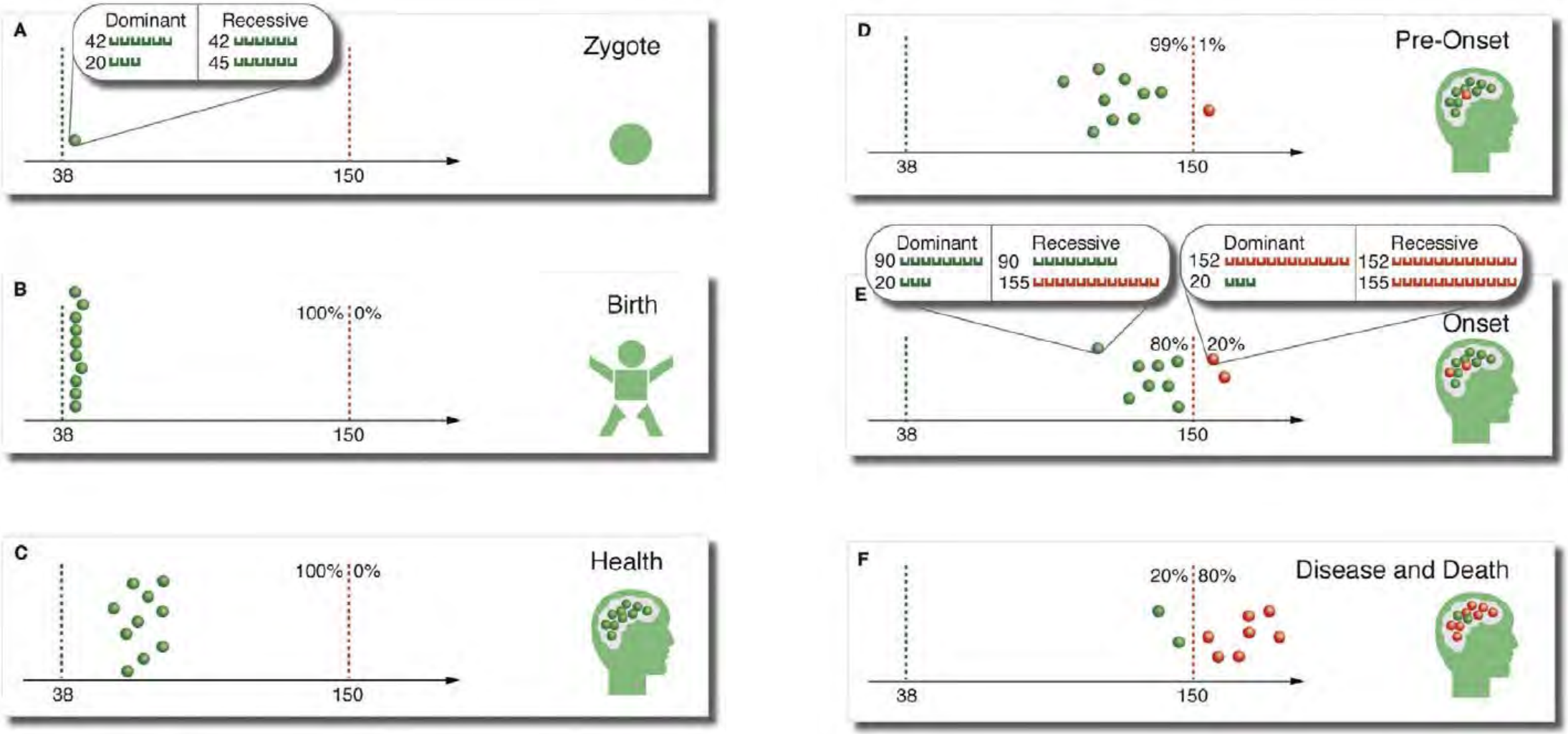



- A massive collaborative effort
  - 9000 patients and family members
- Several candidate causative genes identified
  - "Bad" accelerator variants
  - "Good" retarding genes
- Many genes related to DNA
  - Remarkable converging
  - Somatic instability theory

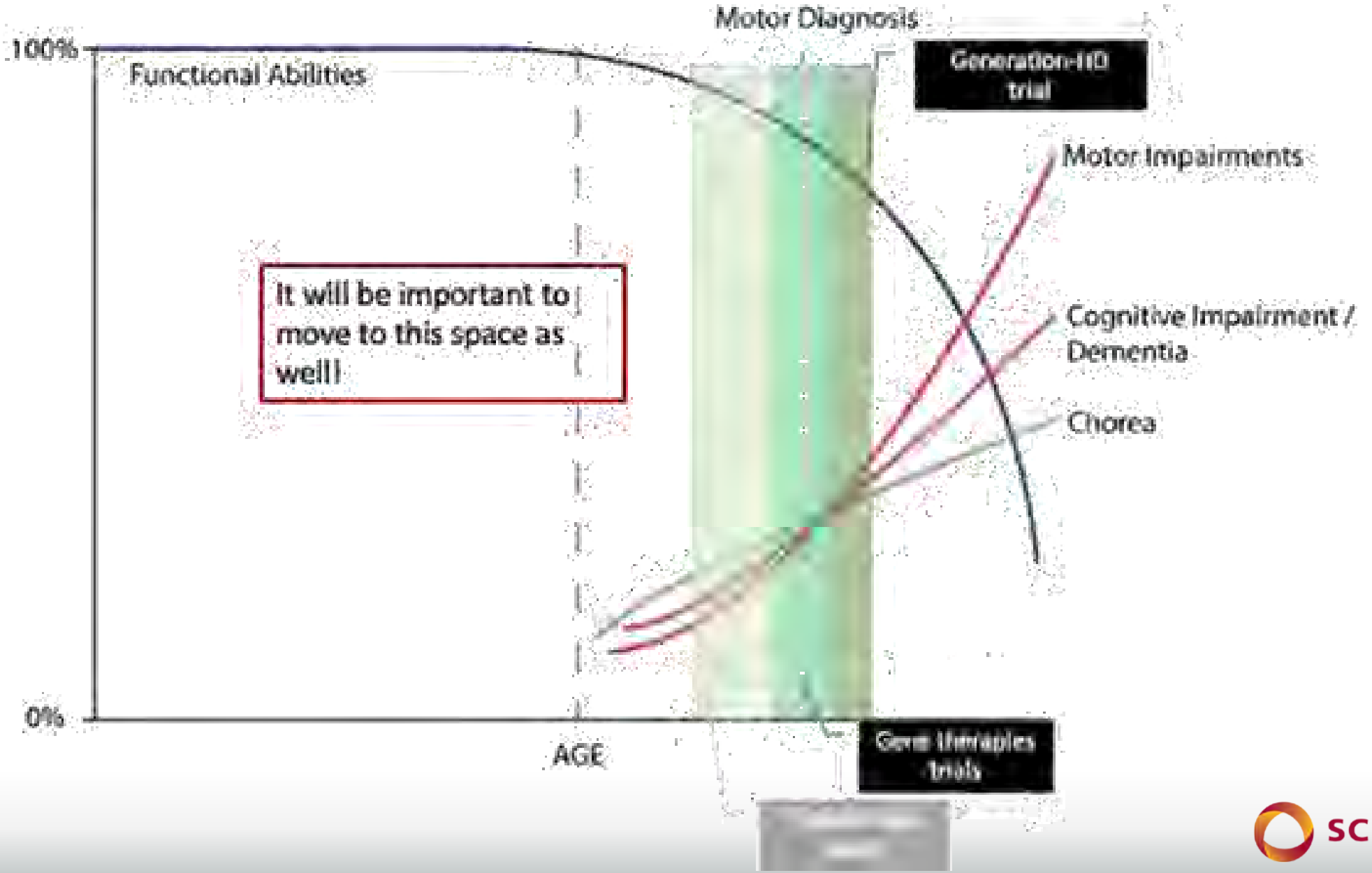



Genetic Modifiers of HD (GeM-HD) Consortium *Cell 2015*
Modifier of HD onset at *MLH1* locus *HMG 2017*

# Modulating rates of Somatic Instability



# Stratify (prodromal) Clinical Trial Populations: $(CAG)_n$ & Modifiers



# A Few Take Aways

- The revolution in genomics is having a profound impact on drug discovery
  - Diagnosis
  - Prognosis
  - Stratification
  - Target identification
  - Biomarkers
  - Therapeutic candidates


- Many additional examples beyond HD

  across multiple therapeutic areas
  - PCSK9 → Repatha (Evolocumab) and Praluent (Alirocumab)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# Thank You!

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**Cite us:** This work was supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## Regulatory Science Symposium

# Innovation to Translation: Role of Genomics in Medical Product Development

## Wrap-Up!

**Eunjoo Pacifici, PharmD, PhD**
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

UC IRVINE ICTS from lab to life.
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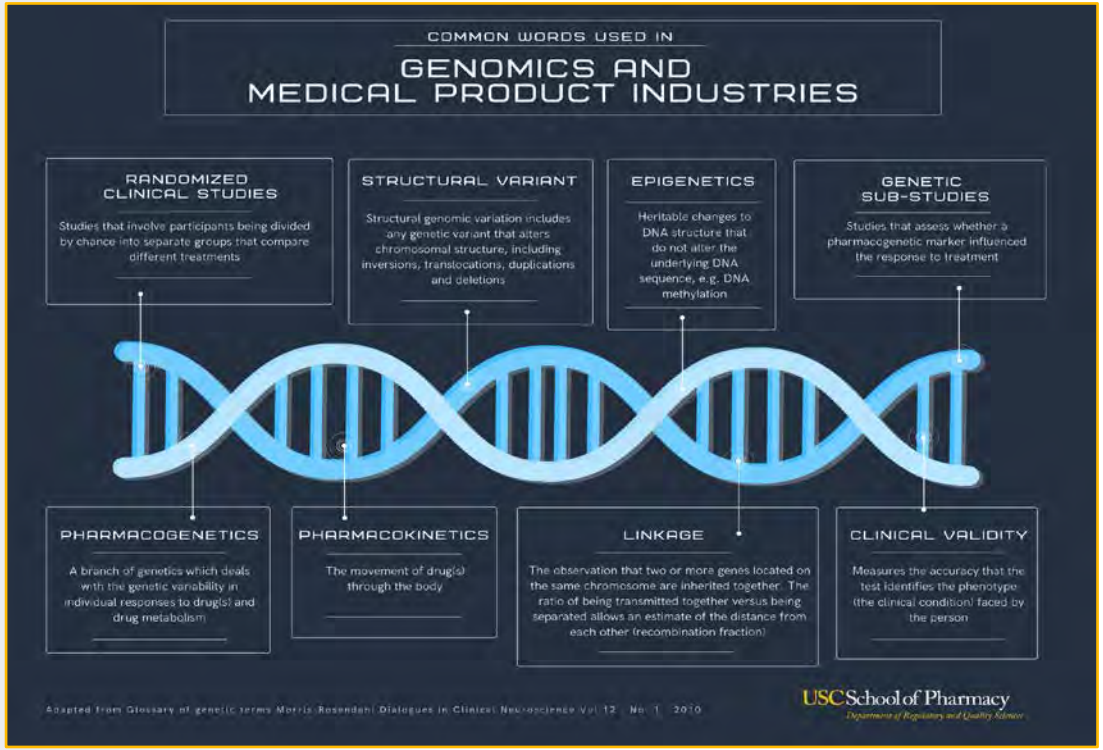
# Resource



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# Thank You!


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