Business Need of RWD Utilization

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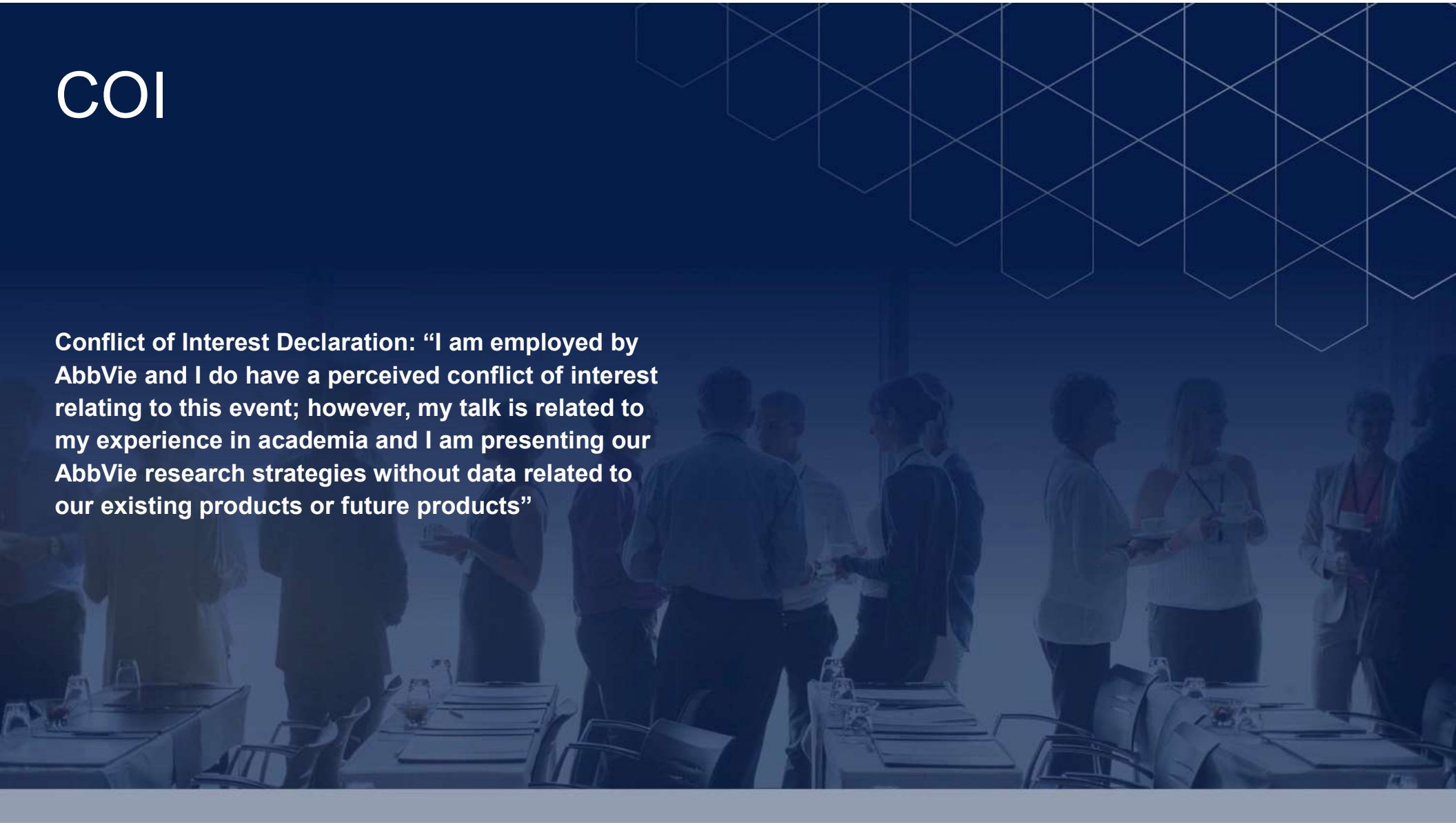
Drug Discovery Science and Technology
Distinguished Research Fellow
Member of the AbbVie Scientific Governing Board

COI



Conflict of Interest Declaration: “I am employed by AbbVie and I do have a perceived conflict of interest relating to this event; however, my talk is related to my experience in academia and I am presenting our AbbVie research strategies without data related to our existing products or future products”

Overview

- The need for changing drug development and developing precision medicine
- Genomes, genome sequencing and building blueprints
- Building better medicines using genome sequencing, genome editing, iPSC
- Moving to Precision Medicine through Computational Biology and Bioinformatics

Why is the rate of attrition across pharma pipelines constant?

- In medicine, knowledge in estimated to be doubling every 18 months
- There must be a better understanding of pathobiology in these data
- How can knowledge be doubling and pharma's success rate staying constant?
- There must be better ways to treat disease and manage healthcare with data

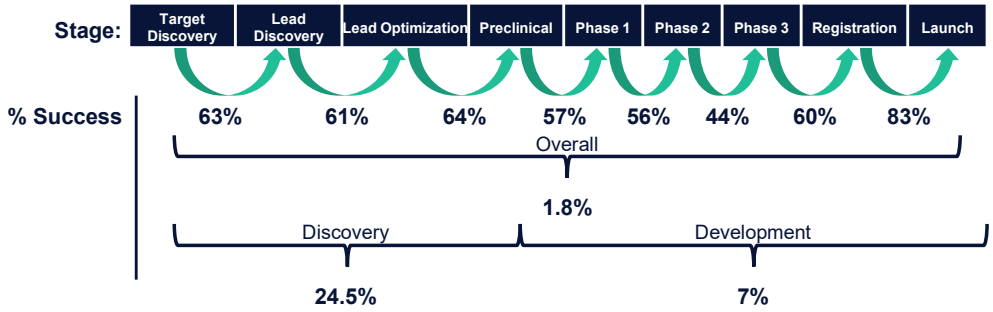
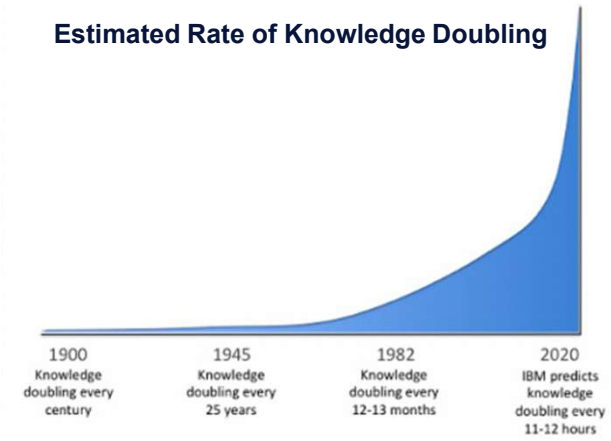
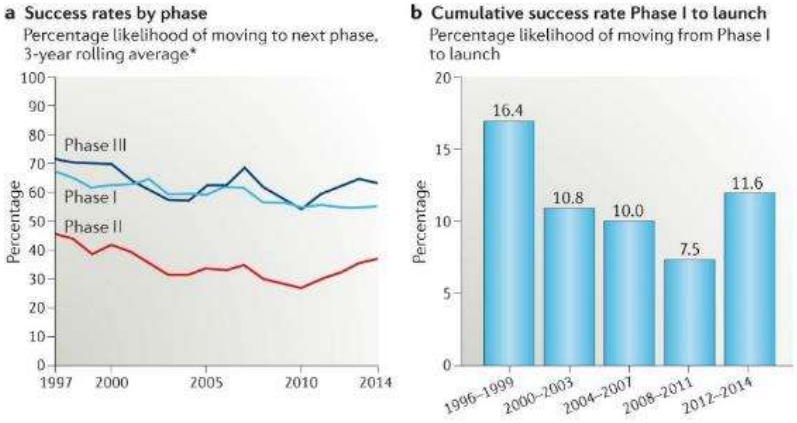


Figure1, Attrition Across the Pipeline.[1]





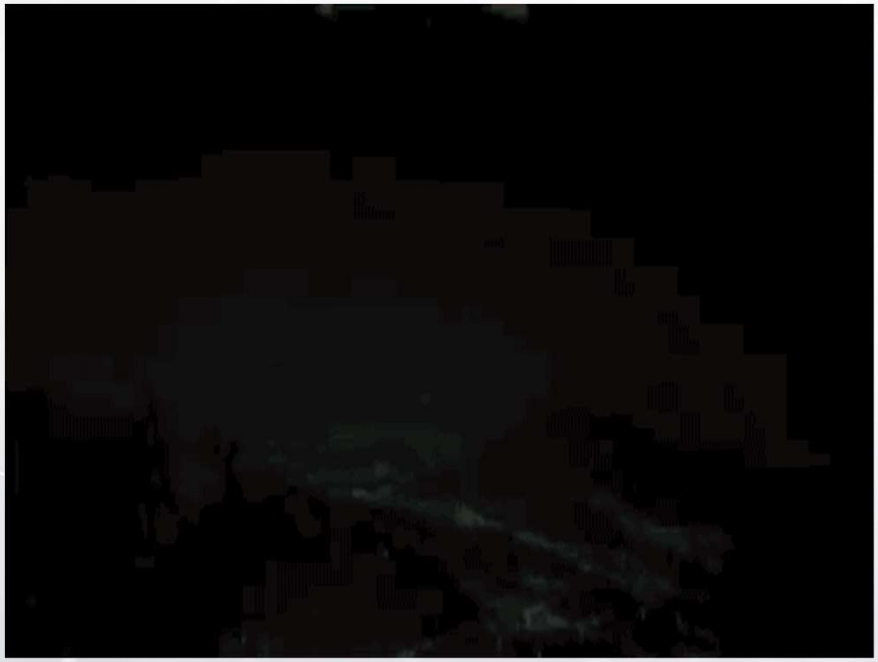
Nature Reviews Drug Discovery June 2016, Vol 15. pg. 379

Aircraft engine

IT-Enabled revolution in aviation

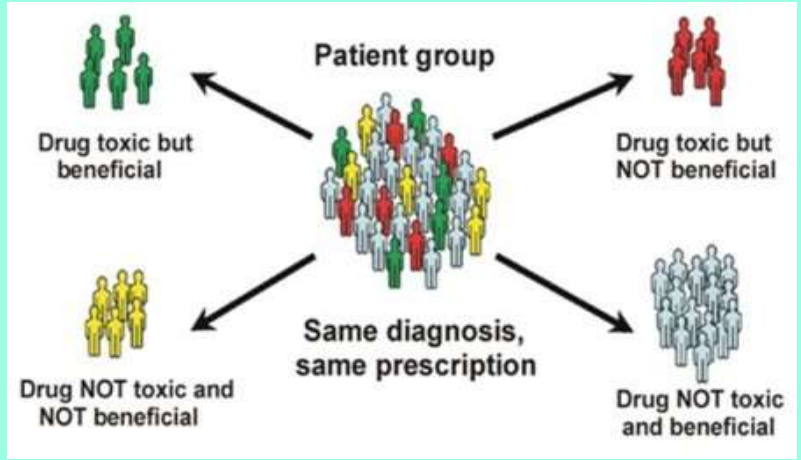
Trial & Error

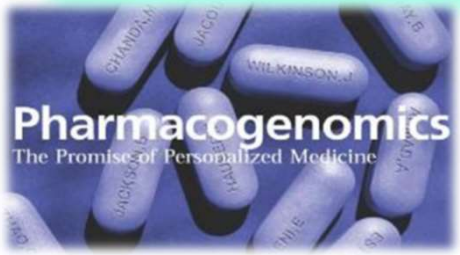
VS.



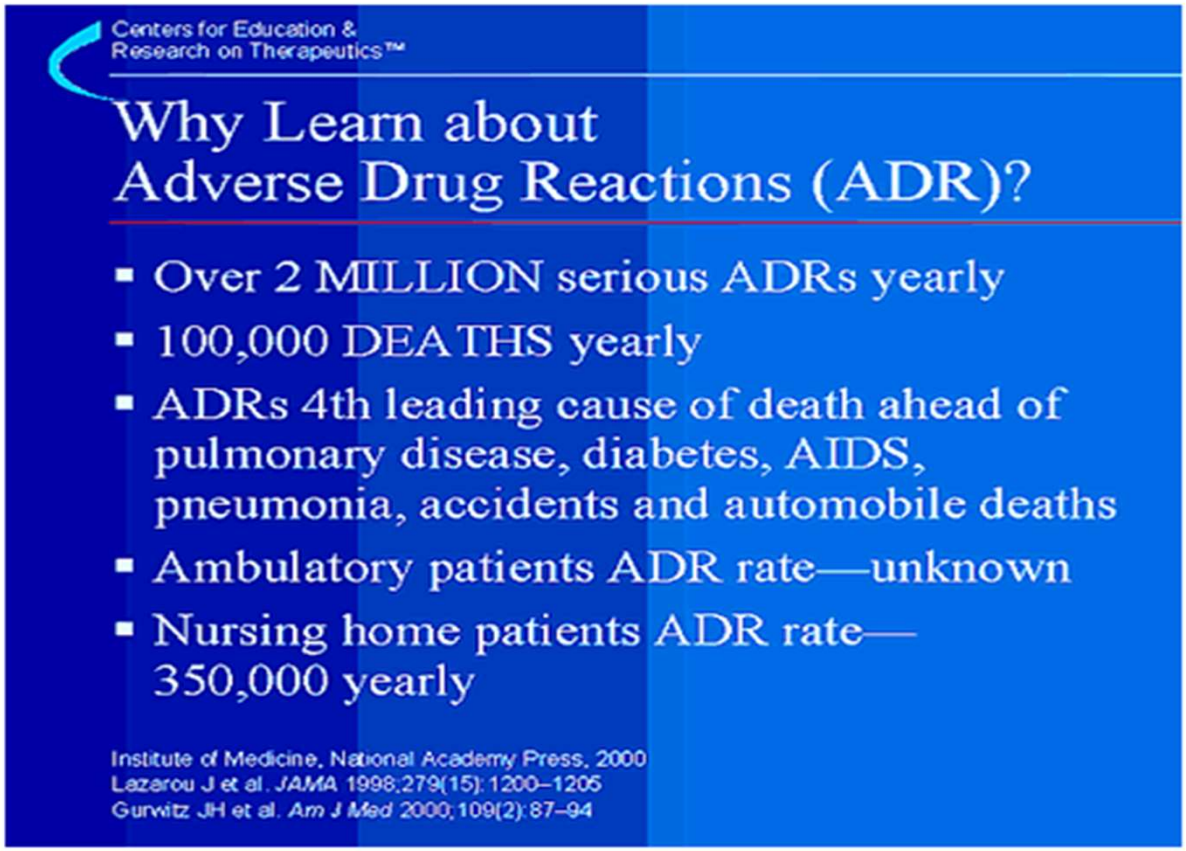
Blueprint & Knowledge

Pharmacogenomics





Adverse Drug Reactions



Your doctor has no blueprint

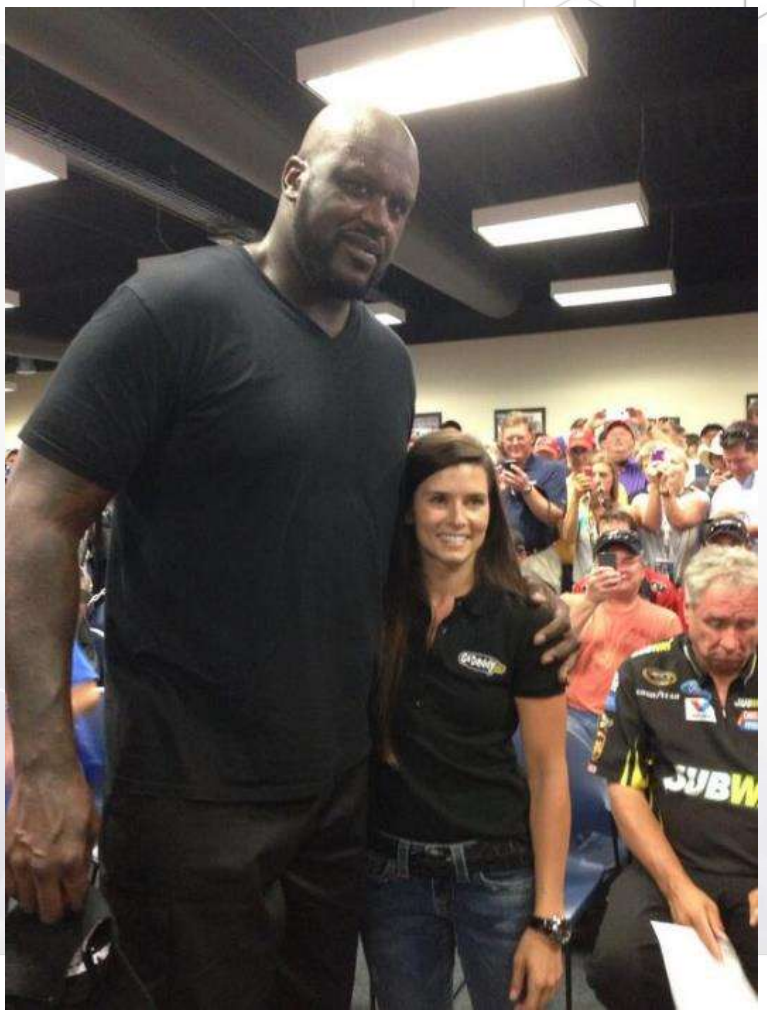
Healthcare is about taking averages

Adults: Take 2 aspirin

Shaq =
4 aspirin

Danica =
1 aspirin

Out of **6 billion** chemical units in their DNA, they differ at only **4M to 6M** places

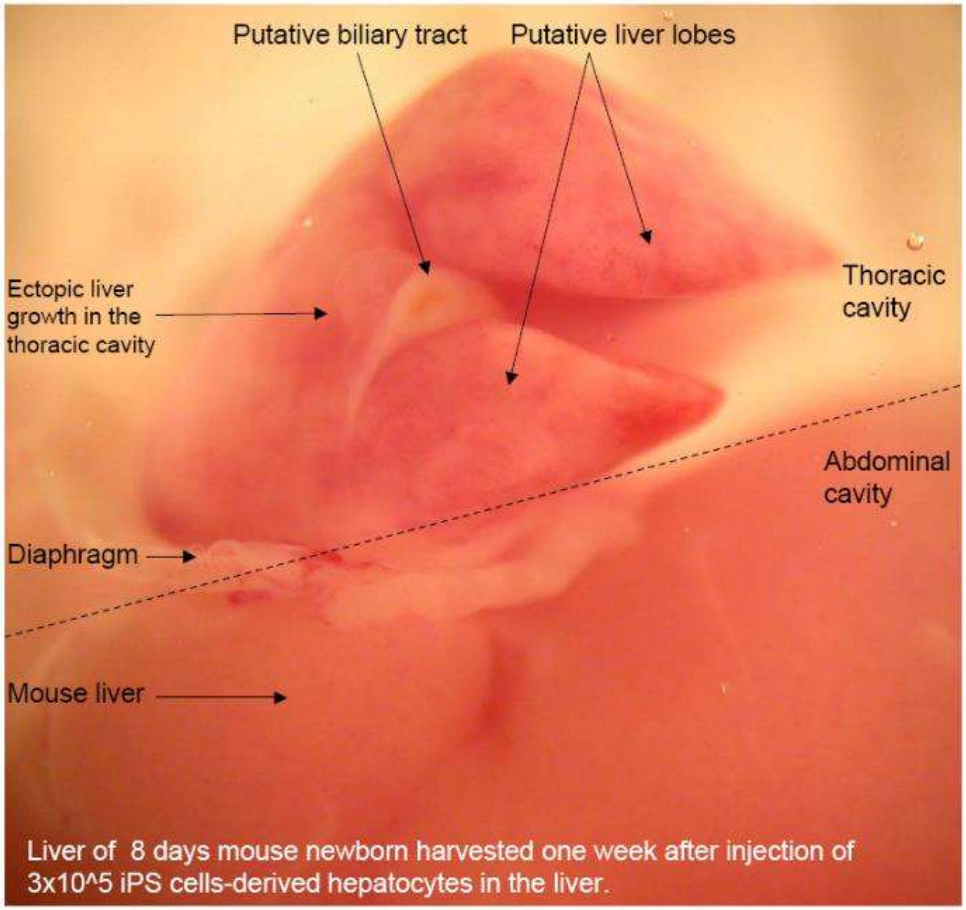


DNA and Art

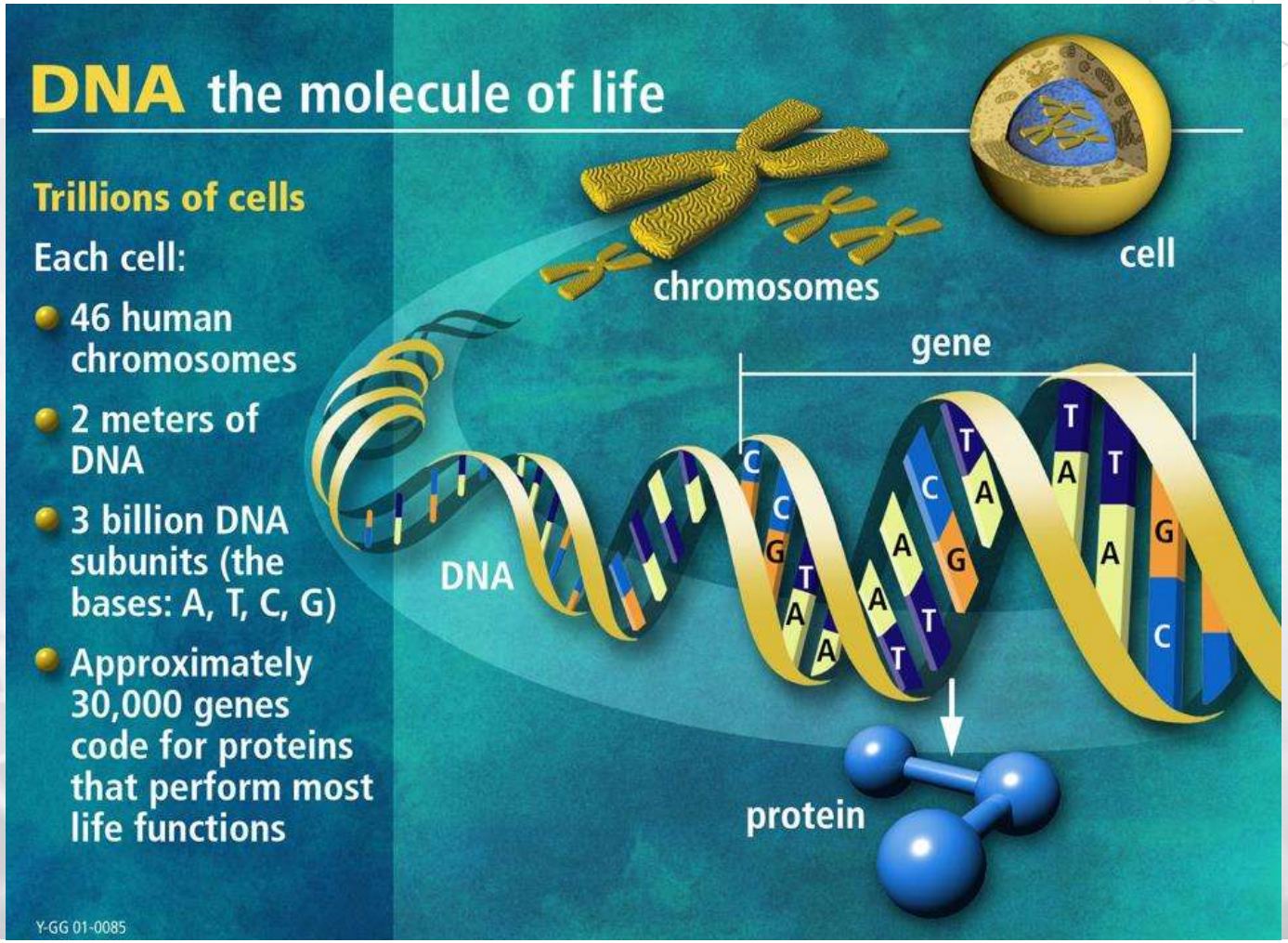
Heather Dewey Hagborg

http://deweyhagborg.com/projects/stranger-visions

Building organs with a blueprint



Stephen Duncan
MUSC



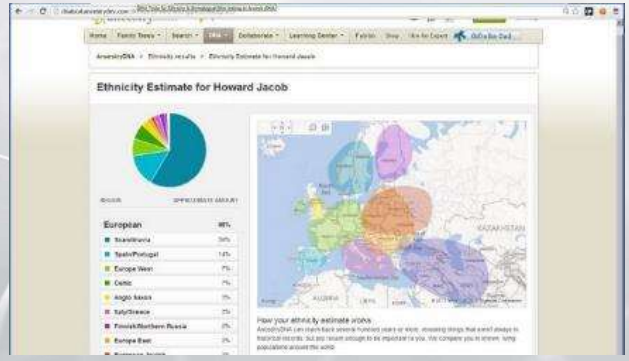
Source: U.S. Dept. of Energy. Human Genome Project, https://web.ornl.gov/sci/techresources/Human_Genome/index.shtml

Reading (sequencing) DNA has been possible since 1970's

Sequencing the Human Genome took **10 years**, **$1B** and was complete in **2002**

The **Human Genome Project** created the ability to build **blue prints** for **humans**

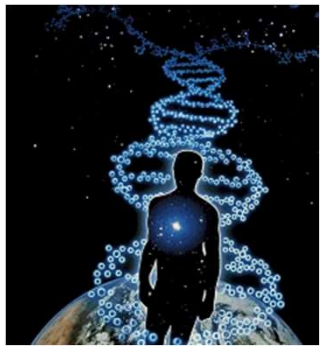
Sequencing the human genome has hit **main stream**



Source: https://www.genome.gov/human-genome-project/Timeline-of-Events

How Long is All the DNA In Your Body?

2m X 100,000,000,000,000 cells = 2 $x10^{14}$m



The earth to the sun is 150,000,000,000m ($1.5x10^{11}$)

$2x10^{14}/1.5x10^{11}$ = **1333 trips**
Or **666.5 round trips**

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Nic Volker

First patient to be treated after diagnosis with genome sequencing

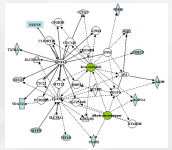
Why genetics/genomics research?

Genetics and genomics research is a critical tool to help us better understand the molecular underpinnings of human disease biology

Potential impact from target discovery to clinical trial process

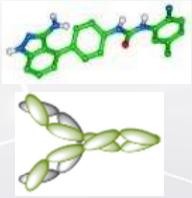
Start here

Right biology



Right target

Right molecule



Right dose

Right patients

Target Discovery → Target Validation → Lead Generation → Lead Optimization → Preclinical Development → Phase I and II → Pivotal Trials

Picking a target without human genetics is slightly better than a random pick of a target

SCIENTIFIC REPORTS
nature research

"Observed success rate was only slightly greater than expected for a random pick from the sample space."

"Genetic studies conducted at much larger scale, with greater resolution of disease end-points, e.g. by connecting genomics and electronic health record data within healthcare systems has the potential to produce radical improvement in drug development success rate."

Scientific Reports | (2019) 9:18911 | https://doi.org/10.1038/s41598-019-54849-w 1

nature genetics

"We estimate that selecting genetically supported targets could double the success rate in clinical development."

Nature Genetics, 47, 856-860(2015)

PLOS | GENETICS

Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval

Emily A. King, J. Wade Davis, Jacob F. Degner

Published: December 12, 2019 https://doi.org/10.1371/journal.pgen.1008489

Building a genomics capability at AbbVie

Since 2016, we have invested in people, technology, and cohorts totaling over $100M to date

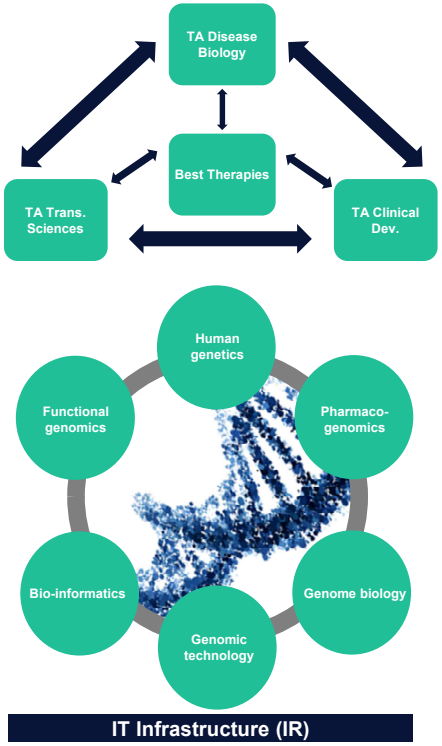
AbbVie is acquiring over 1 million genomes

Genomics is now impacting:

- Discovery in all three therapeutic areas
- Development in all areas
- Process sciences to improve our CHO cells ability to make biologics
- Governance starting in March 2020
- Corporate Strategy: what indications, what targets, what companies
- Commercial: we are testing if Omics can be used to identify the best drug

The Genomics Research Center (GRC)

Six functional teams
Supports all therapeutic areas
Connects across R&D

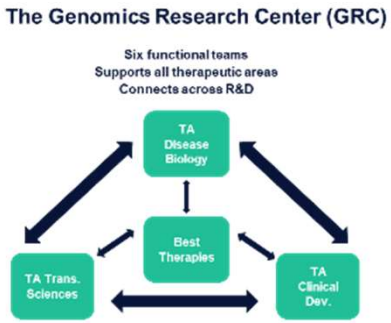


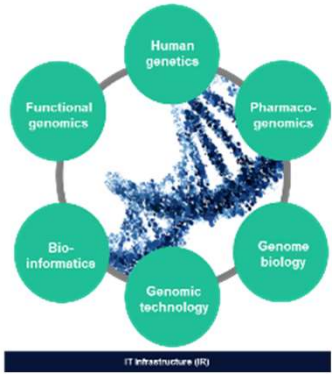
Massive data sets from:

- Real world data (~350M claims)
- Large cohorts
  - 10% of Finland
  - ~1% of Ireland
  - 500,000 UK biobank
  - 30,000 cancer patients
- Whole genome sequencing
- Single cell transcriptomics
- Epigenetics
- Imaging
- Wearables
- Longitudinal data
- EHRs: 150 million (globally)
- Whole genome CRISPR screens in cell lines, iPCS from patients, and in vivo models

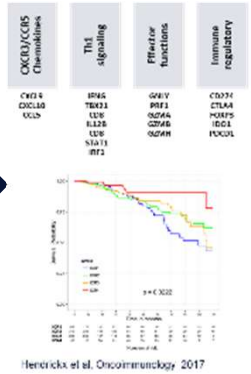
- Today we are working from the single patient with deep phenotyping and molecular fingerprinting to national level healthcare data
- Creating the need to re-think our data strategy and pipeline
- Doubled the number of clinically validated targets

Building a genomics capability at AbbVie

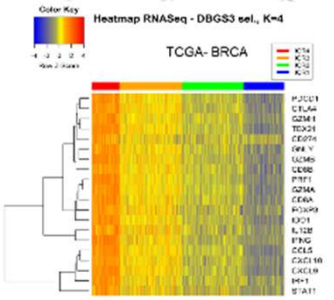




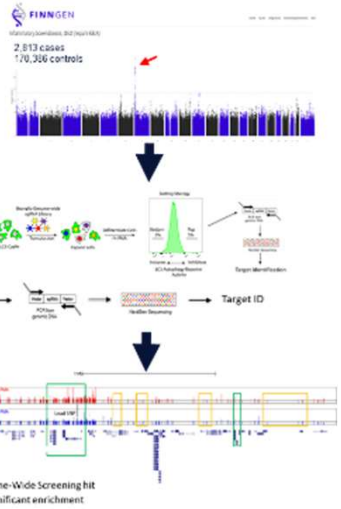
Stratify Patients



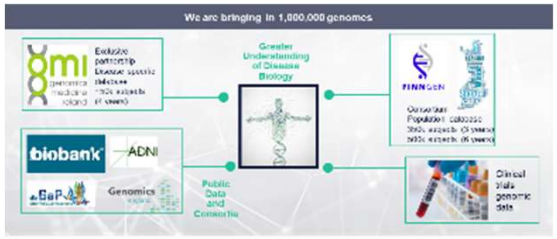
Oncology



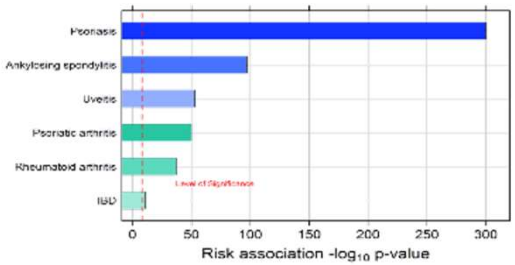
Immunology
Target ID and Confirmation



Population cohorts for new Indications,Target ID and Confirmation



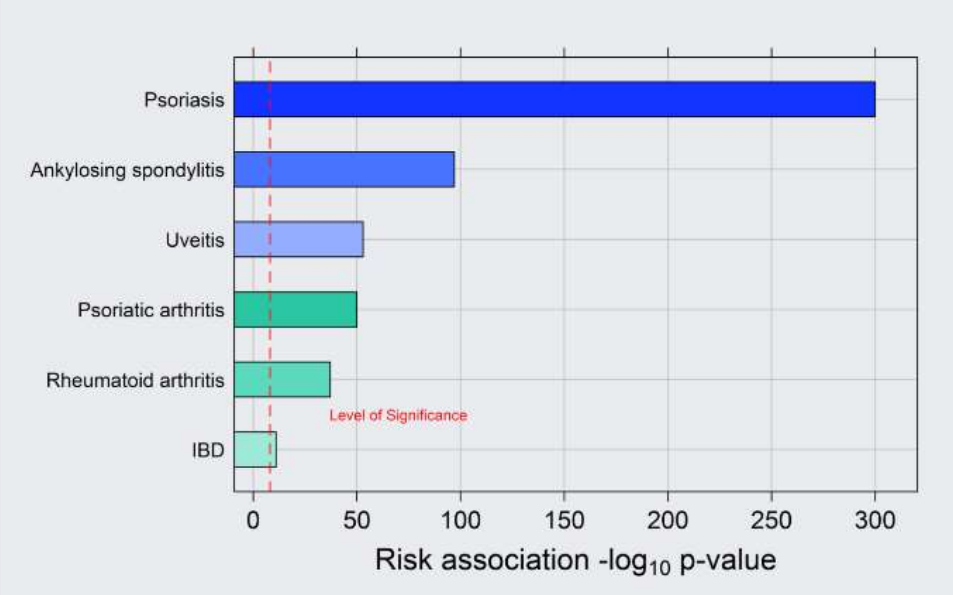
New Indications, TNF example



In silico testing of adjacencies

- How well does the 500,000 UK Biobank data set “predict” clinical indications?
- While not previously available, and thus retrospective, these data suggest a powerful resource for assessing targets.

Clinical Phenotypes associated with TNFα



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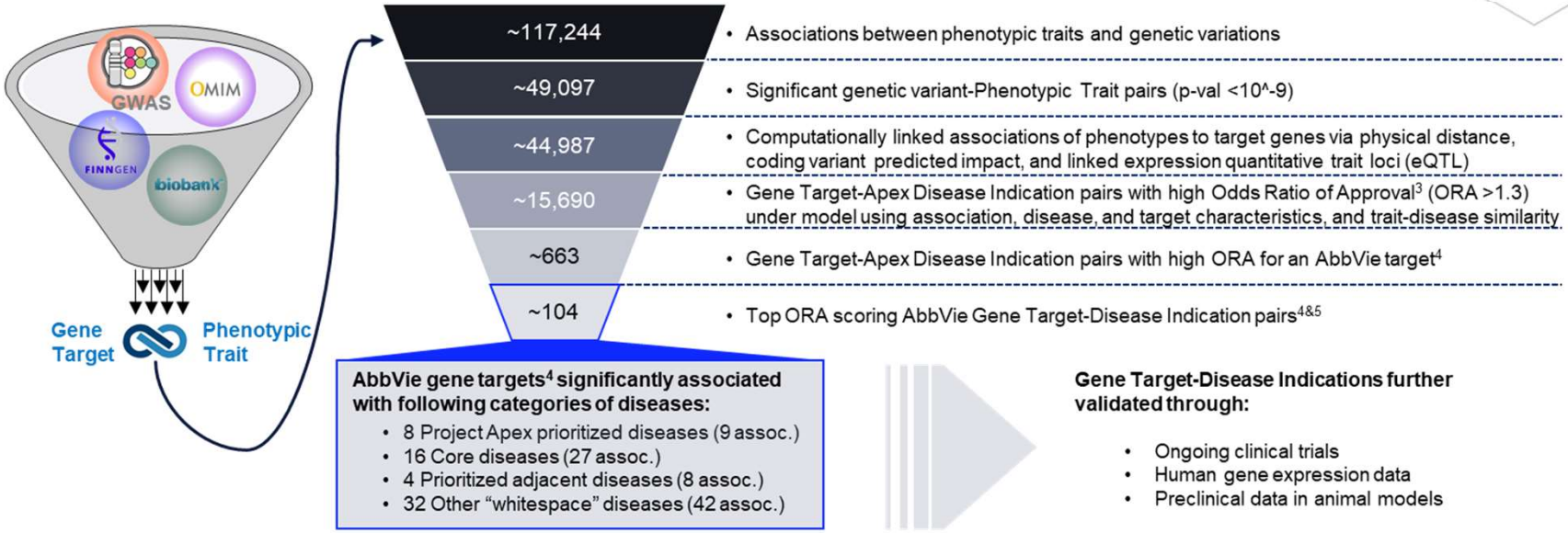
GRC
GENOMICS RESEARCH CENTER

Using human genetics to select gene targets *in silico*



Using >500,000 genomes to evaluate large numbers of targets *in silico*
Increase accuracy and reduce time to identify

Leveraging Real World Data

- M2Gen ORIEN: Real world cancer patients enrolled among 19 nation's leader cancer centers under M2Gen Total Cancer Care protocol.
- Abbvie as one of the five industry sponsors get access to all clinical data, raw and processed molecular data.
- Contracted till 2022 for a total cohort of ~30,000 patients.
- Data used to support all oncology discovery and development projects.
- Other RWD data: Syapse, Tempus, Guardant health, etc.

- 986 patients
- ~5700 controls
- **174** genes
- Rare disease in **21 (2.1%)** patients

Data freeze 1

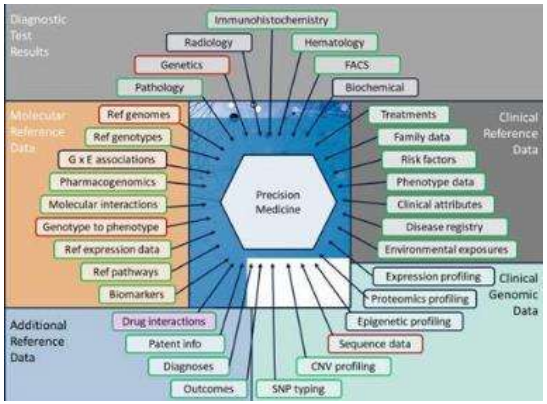
RWD (HEOR)

- 13,000 MS patients*
- Confirmation of similar prevalence of rare diseases
- 11 additional diseases**

- 4511 patients
- ~11000 controls
- **271** genes
- Rare disease in **152 (3.4%)** patients

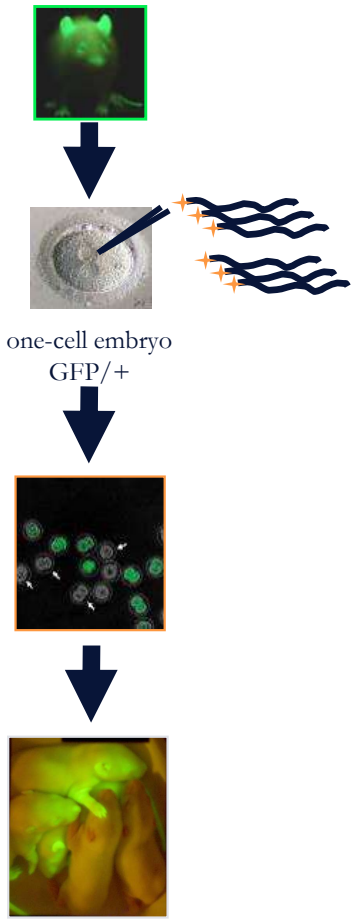
Data freeze 3

*RWD: 2011-2018 Truven Commercial/Medicare age and gender matched
** inherited muscular dystrophy, dystonia, cerebral arteritis, disorders of basal ganglia, optic atrophy ...

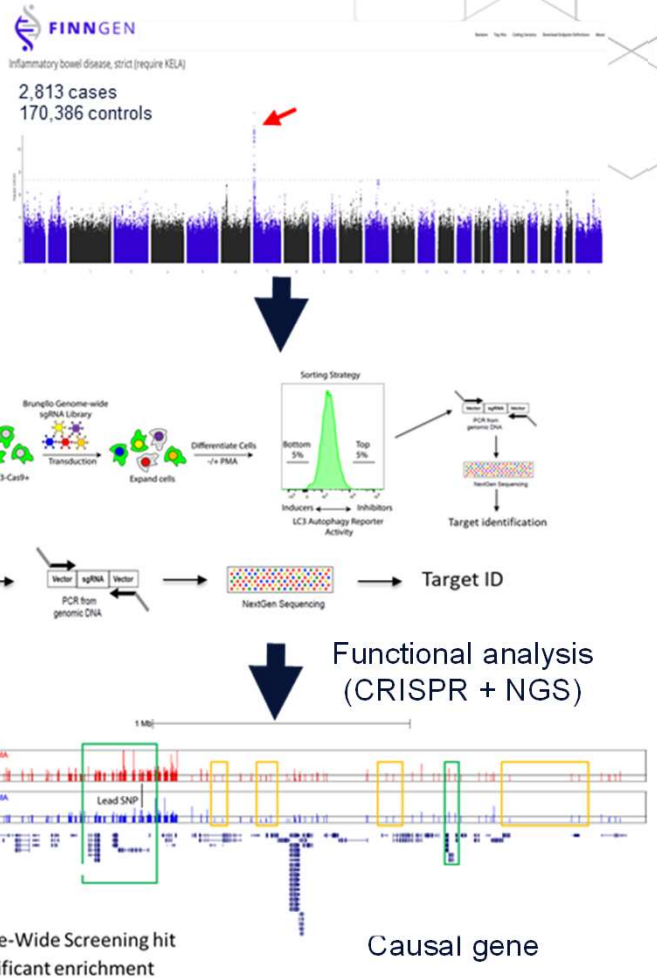


Reading and Writing DNA

How Gene Editing Works



CRISPR/CAS9—current technology



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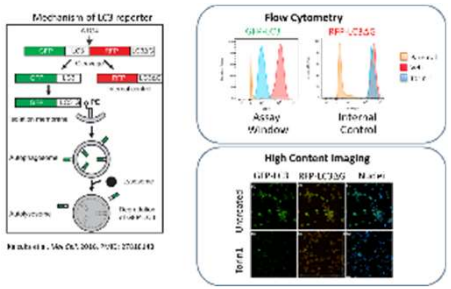
Functional genomics: Ongoing projects

IBD Target Discovery

Immunology

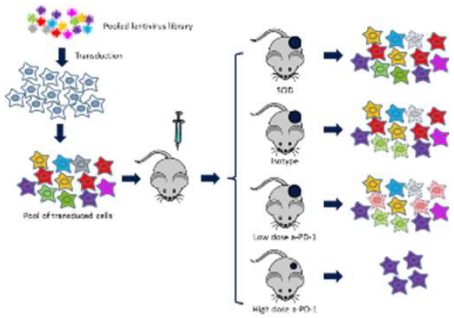
- **Overview:** Integrated genomics and genomics approach to IBD target discovery (genome-wide CRISPR screens, GWAS and clinical expression profiling)
- **Outcome:** 3 new targets entering Immunology Discovery pipeline
- **Status:** Additional target validation efforts ongoing with human primary macrophage and *in vivo* approaches



In vivo Syngeneic Tumor Cell IO CRISPR Screens

Oncology

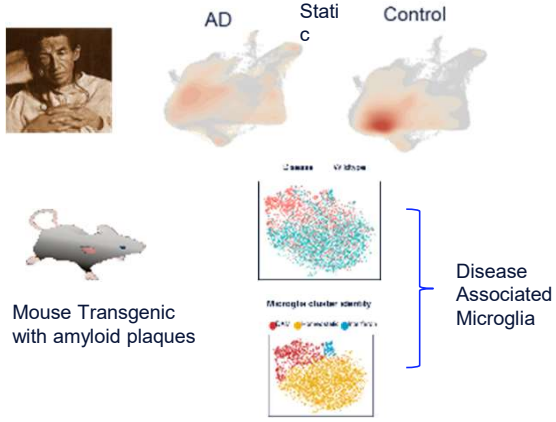
- **Overview:** *In vivo* CRISPR screens using multiple syngeneic tumor models to identify tumor cell targets under immune surveillance
- **Outcome:** Feasibility demonstrated for MC38 colon cancer model
- **Status:** Multiple new screens planned for 2020; additional model development in progress



Microglia Alzheimer Disease Target Discovery

Neuroscience

- **Overview:** Human AD vs Mouse APP transgenic – select targets from man and back-translate
- **Outcome:** sNuc/cell-Seq enables use of archived human AD brains. Major regulatory pathways identified
- **Status:** Target validation ongoing



Innovation projects and new initiatives

Epigenetics

- Identify functional target (gene/s) of sequence variant nominated from FinnGen by mapping enhancers, promoters (ChIP-seq) and generation of 3D DNA interactions with Hi-C,PLAC-seq
- Deconvolute the GWAS hits in patients with IBD by utilizing ATAC-seq, Hi-C, PLAC-seq, proteomics, and RNA-seq data from gut tissue samples in healthy individuals, non-inflamed individuals, and inflamed individuals

Image-based morphological profiling (Cell Painting)

- Multiple cellular features imaged simultaneously using fluorescent dyes
- Cellular signatures derived via automated feature extraction and machine-learning assisted image analysis
- Clustering of signatures to categorize phenotypically similar genetic or chemical perturbations

CHOmics: SUPERCHO expression platform

- Collaboration with Process Science team at ABC (Operations S&T)
- Leverage 'omics platforms to improve biologics product quality, yield, manufacture process
- CHO lipase KO to support Risankizumab production completed in 2019; unbiased epigenetic characterizations, additional gene editing and screening projects in line for 2020

CRISPR Screening in Single Cells

- Link genotype to molecular phenotype at high throughput.
- Utilize the conventional CRISPR/Cas9 loss-of-function (LoF) screen.
- Couple with single-cell RNA-Seq (scRNA-Seq).

Deep mutational Scanning (MITE-seq)

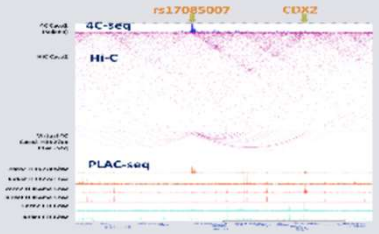
- Implement saturation mutagenesis approach to comprehensively assess the effect of nonsynonymous mutations on BCL-2 and its role in development of resistance to ABT-199.
- Confirm/discover findings as it correlates with novel mutations arising in the clinic.

Lenti-MPRA

- Functionalization of GWAS non-coding variants using lentivirus based massively parallel reporter assay (Lenti-MPRA) in disease-relevant cells.
- POC with 225 SNPs in IBD overlapping with H3K27Ac PLAC-seq data in Caco-2 cells, 38 SNPs from PANTS anti-TNFα response/ non-response in Chr12 and 45 SNPs from FinnGen IBD GWAS Chr7 TNRC18 locus

Linking non-coding variant to gene

- Implement 3C (chromosome conformation capture) methods to link non-coding variants (IBD GWAS) to their target genes in disease-relevant cell system



Coordination center for development of animal models for all of AbbVie

- Utilizing knock-in, knock-out, CRISPR/Cas, BAC transgenesis etc. 13 genetically modified strains were delivered and 9 new one were started in 2019

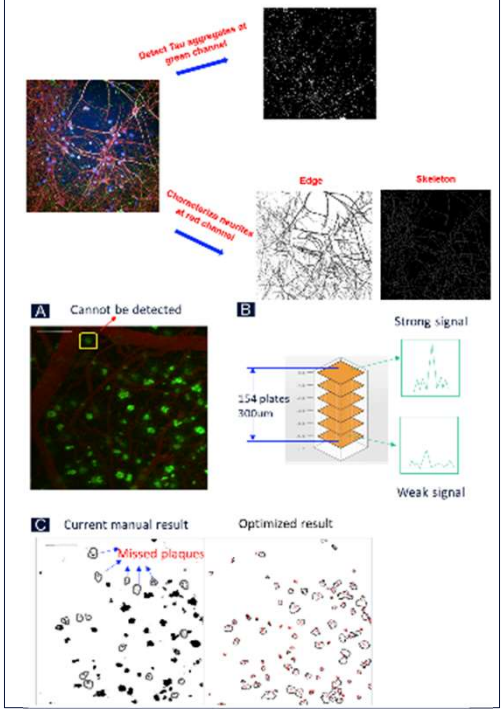
Computational Genomics Contributions to Discovery

New Targets

- Partnered with key external leaders to jointly call UK Biobank whole exome data with > 100K gnomAD samples and process in unified manner
- Executed UK Biobank PheWAS on 200K whole exomes and 500K genotyped subjects for 2200 phenotypes, with single variant analyses and gene burden tests
- Developed UKB and FinnGen results browser

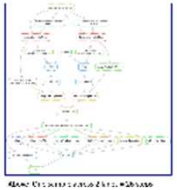
Target Biology

Automation of a manual image processing for tau aggregate assays, reducing processing time from weeks to minutes.

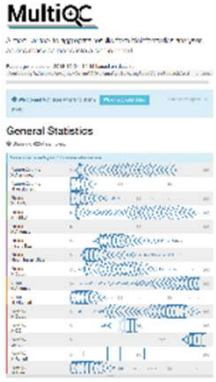


Core Functionality

Partnered with Genomic Technologies to drive use of unique molecular identifiers to improve signal and reduce wasted reads from RNA-seq & other NGS workflows by developing automated bioinformatic pipeline

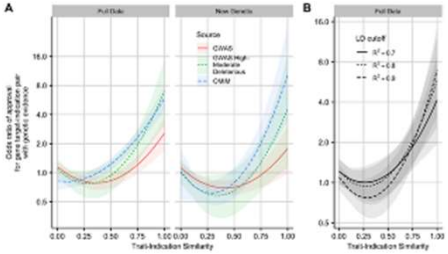


Developed automated QC reporting process that generates key statistics and plots for all scientists to use to evaluate NGS run quality



Pipeline Strategy

Published widely cited paper on evaluating how genetic evidence supports drug approval success rate using independent data sets and advanced statistical modeling

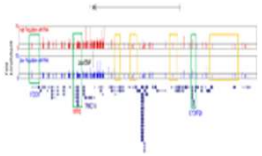


Key contributions made to the data and methods for selecting on new target and indications

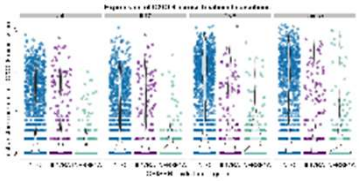
Computational Genomics Contributions to Discovery

Target Screening Methods

- Standardized and improved computational methodology for pooled CRISPR screening (R package GRCmeta w/ manuscript) after discovering flaw in widely used software
- Developed data analysis methods for tiling CRISPR experiments with focus on variant-to-function interrogation

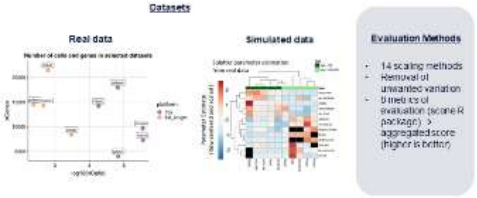


- Developed analysis process for single-cell CRISPR (CRISTomics)

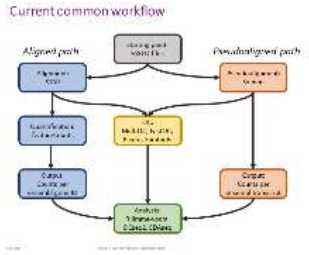


RNA-oriented Improvements

Co-led global AbbVie-wide single-cell RNAseq methods group to evaluate and select best techniques in the field, w/ experts at UC-Berkeley



Led working group across AbbVie to standardize bulk RNA-seq data process and statistical modeling



New Methods

Improved existing widely used SAIGE method for variant association at large-scale via code optimization with C++, smarter compression schemes, and better data structures to improve run times 6-fold. Poster at ASHG 2019 meeting and manuscript submitted.

Developed new method for colocalization when you don't have access to all data or summary statistics. No current tools address this problem. 2019 ASHG Poster

Pipeline Support

- Data analysis for CRISPR screening of all varieties as needed and serve as subject matter experts for data analysis for CRISPR experiments
- GWAS/PheWAS data analysis support for internal and external data
- Gene expression expertise as needed (single-cell RNAseq, bulk RNA-seq, gene expression microarrays, Nanostring, etc)
- Epigentic data analysis expertise for ATAC-seq, Hi-C, 4C, PLAC-seq, ChiP-seq, and various DNA methylation assays
- Advanced modeling using machine learning and other modeling paradigms to extract knowledge from data
- Provide ad hoc analyses as needed to support experiments critical to the pipeline

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Your medical record

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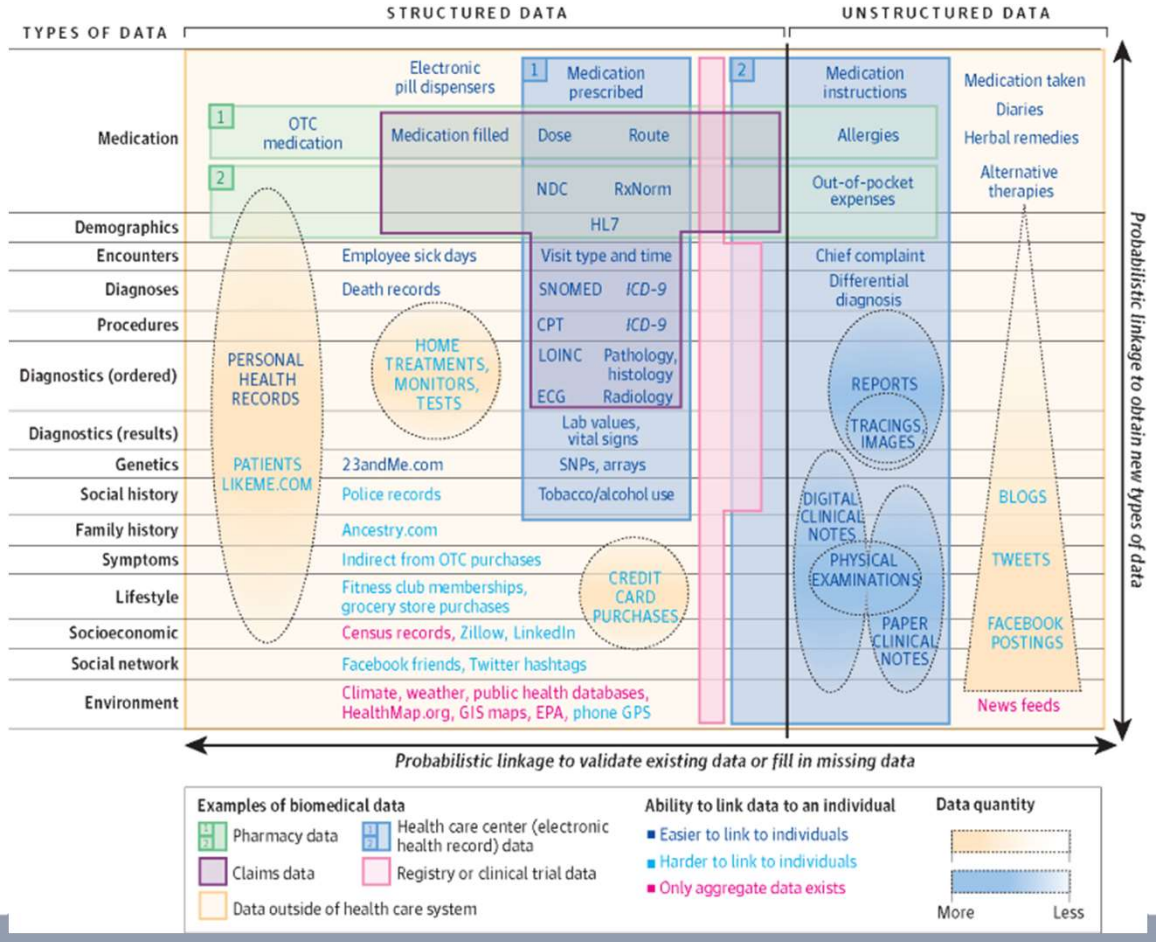
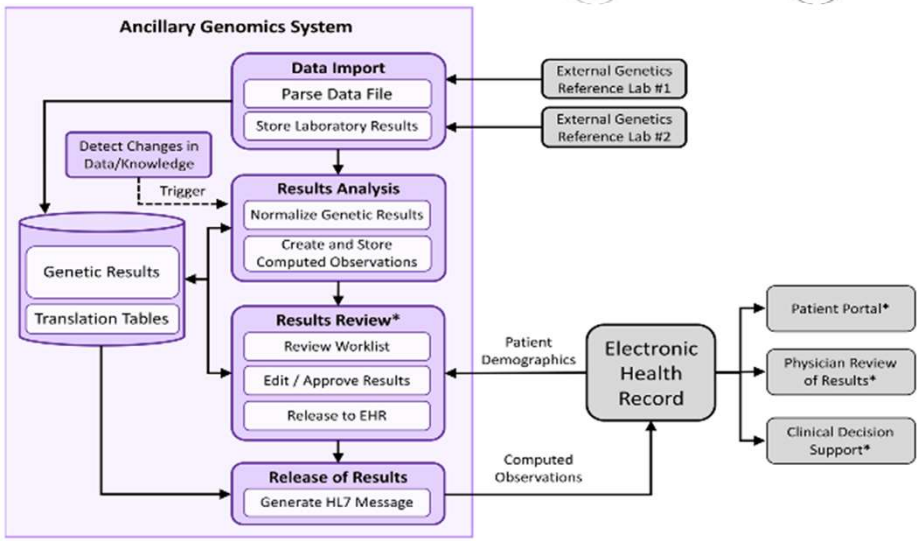
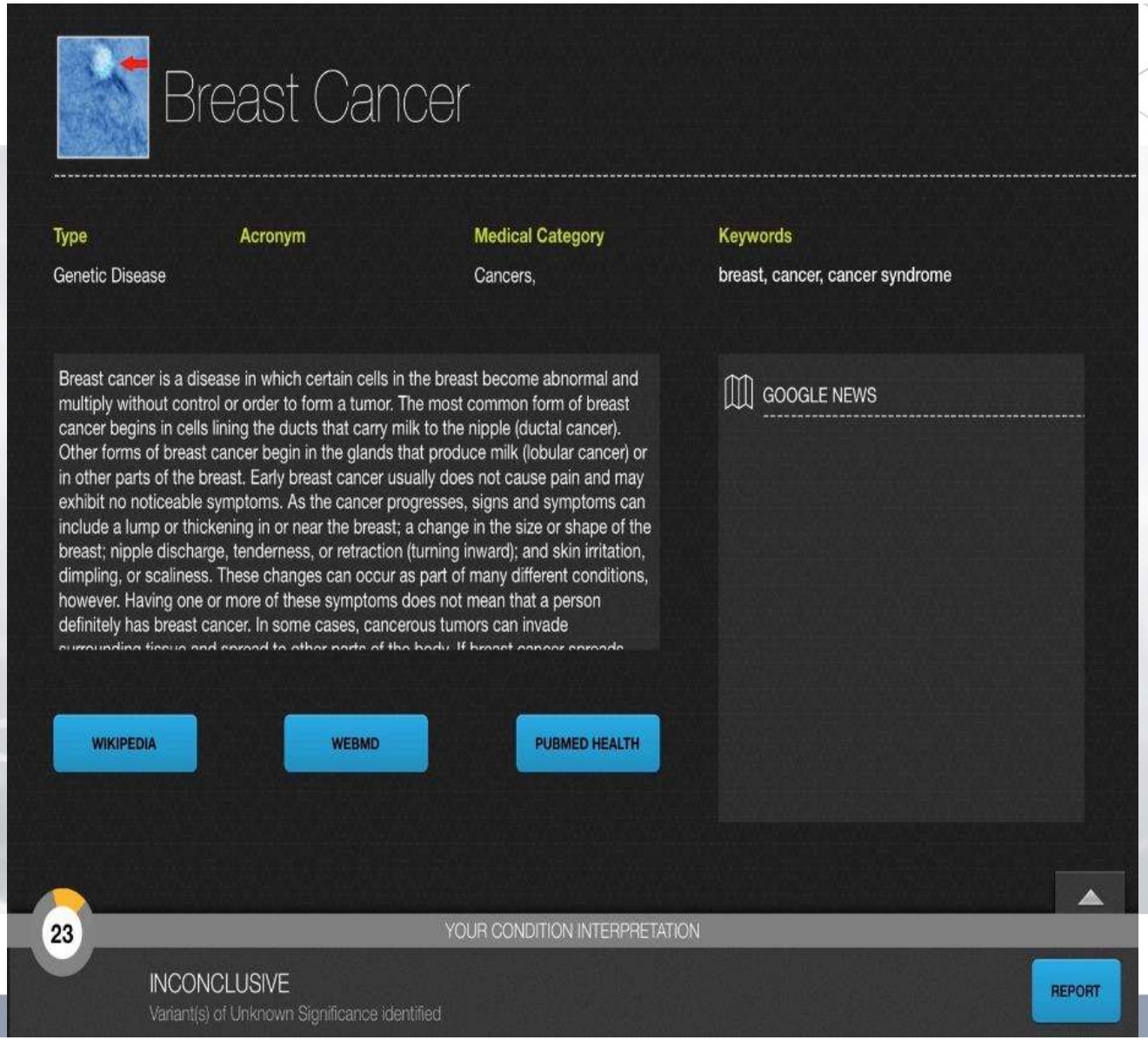
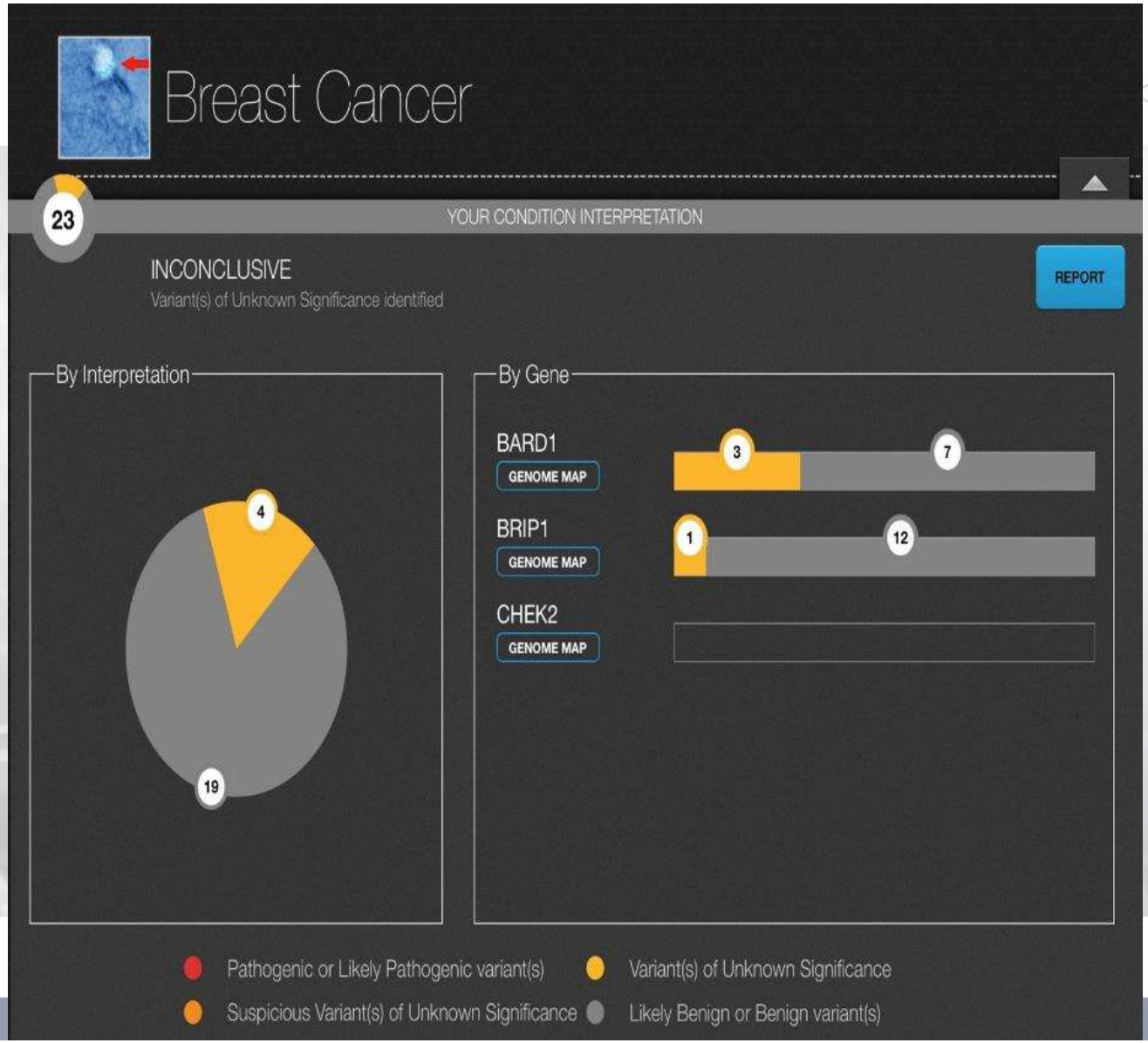
Clinical phenotypes are messy but large numbers and integrated data are powerful

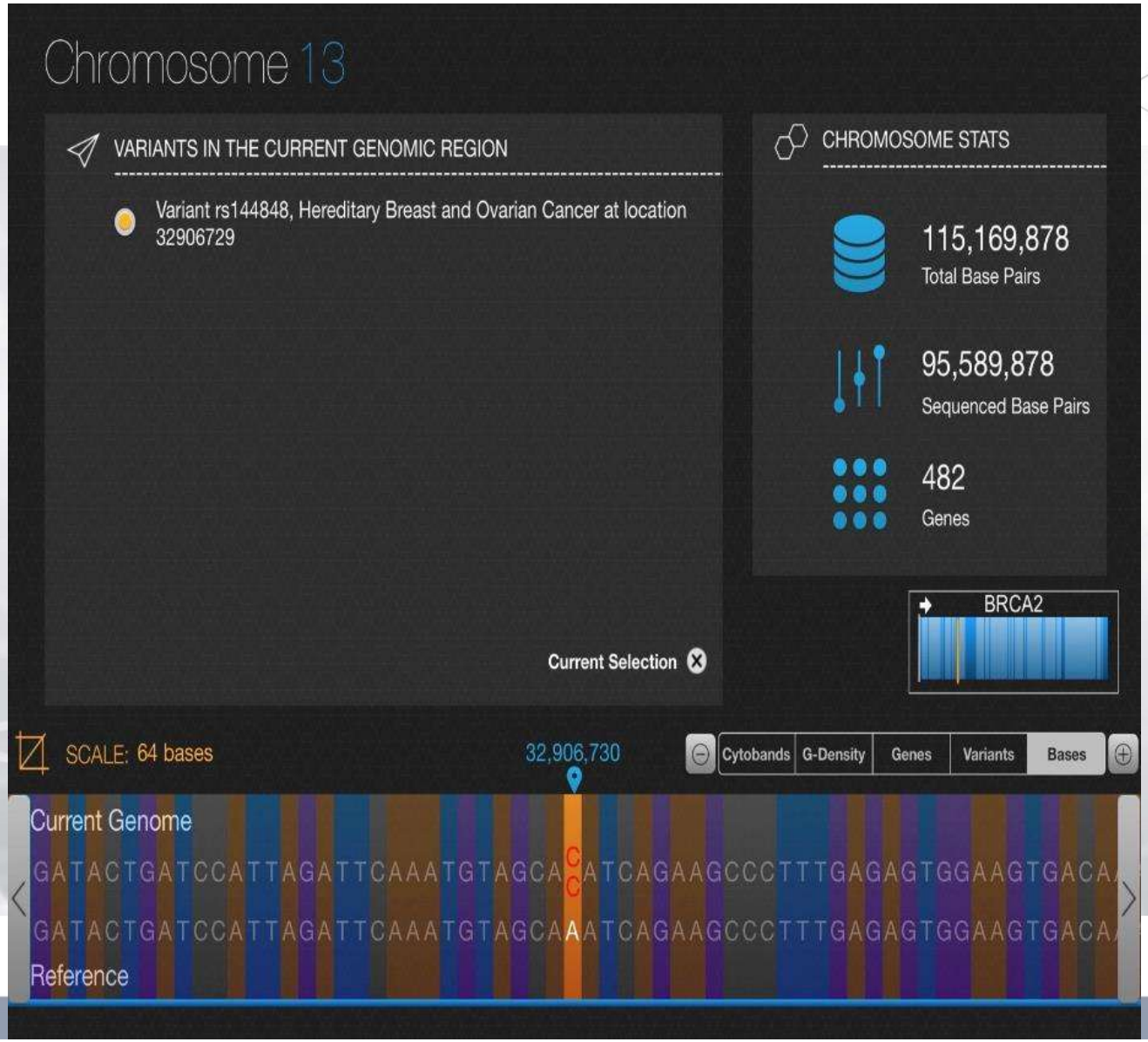


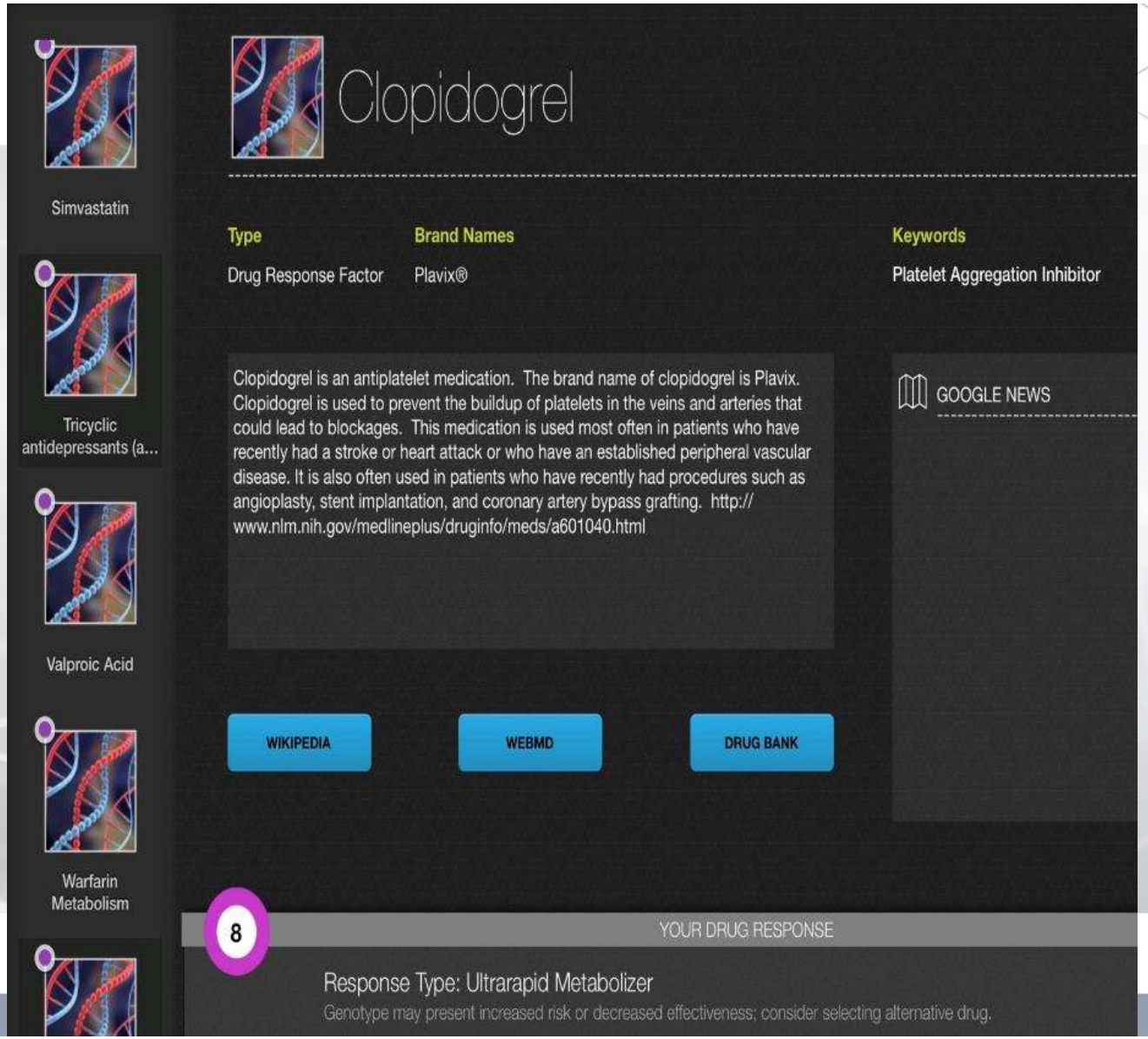


From Abel Kho's presentation to the RDLT workshop on R&D Data Strategy


Breast Cancer
Type
Genetic Disease
Acronym
Medical Category
Cancers,
Keywords
breast, cancer, cancer syndrome
Breast cancer is a disease in which certain cells in the breast become abnormal and multiply without control or order to form a tumor. The most common form of breast cancer begins in cells lining the ducts that carry milk to the nipple (ductal cancer). Other forms of breast cancer begin in the glands that produce milk (lobular cancer) or in other parts of the breast. Early breast cancer usually does not cause pain and may exhibit no noticeable symptoms. As the cancer progresses, signs and symptoms can include a lump or thickening in or near the breast; a change in the size or shape of the breast; nipple discharge, tenderness, or retraction (turning inward); and skin irritation, dimpling, or scaliness. These changes can occur as part of many different conditions, however. Having one or more of these symptoms does not mean that a person definitely has breast cancer. In some cases, cancerous tumors can invade
GOOGLE NEWS
WIKIPEDIA
WEBMD
PUBMED HEALTH
23
YOUR CONDITION INTERPRETATION
INCONCLUSIVE
Variant(s) of Unknown Significance identified
REPORT


Breast Cancer
23
YOUR CONDITION INTERPRETATION
INCONCLUSIVE
Variant(s) of Unknown Significance identified
REPORT
By Interpretation
4
19
By Gene
BARD1
GENOME MAP
3
7
BRIP1
GENOME MAP
1
12
CHEK2
GENOME MAP
Pathogenic or Likely Pathogenic variant(s)
Variant(s) of Unknown Significance
Suspicious Variant(s) of Unknown Significance
Likely Benign or Benign variant(s)


Chromosome 13
VARIANTS IN THE CURRENT GENOMIC REGION
Variant rs144848, Hereditary Breast and Ovarian Cancer at location 32906729
Current Selection
CHROMOSOME STATS
115,169,878
Total Base Pairs
95,589,878
Sequenced Base Pairs
482
Genes
BRCA2
SCALE: 64 bases
32,906,730
Cytobands
G-Density
Genes
Variants
Bases
Current Genome
GATACTGATCCATTAGATTCAAATGTAGCACATCAGAAGCCCTTTGAGAGTGGAAGTGACA
GATACTGATCCATTAGATTCAAATGTAGCAATCAGAAGCCCTTTGAGAGTGGAAGTGACA
Reference


Simvastatin
Tricyclic antidepressants (a...
Valproic Acid
Warfarin Metabolism
Clopidogrel
Type
Drug Response Factor
Brand Names
Plavix®
Keywords
Platelet Aggregation Inhibitor
Clopidogrel is an antiplatelet medication. The brand name of clopidogrel is Plavix. Clopidogrel is used to prevent the buildup of platelets in the veins and arteries that could lead to blockages. This medication is used most often in patients who have recently had a stroke or heart attack or who have an established peripheral vascular disease. It is also often used in patients who have recently had procedures such as angioplasty, stent implantation, and coronary artery bypass grafting. http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601040.html
GOOGLE NEWS
WIKIPEDIA
WEBMD
DRUG BANK
8
YOUR DRUG RESPONSE
Response Type: Ultrarapid Metabolizer
Genotype may present increased risk or decreased effectiveness; consider selecting alternative drug.

Convergence

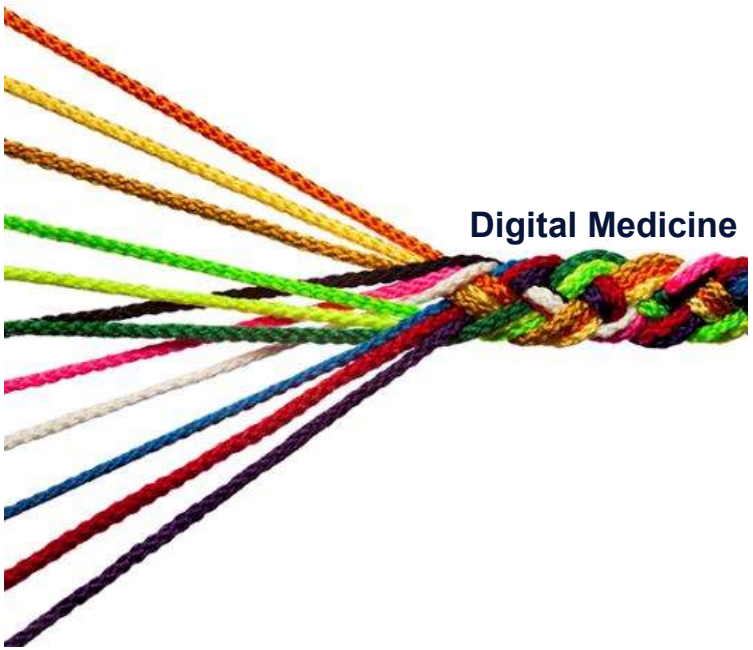
Life Sciences

Health Care

Mathematics

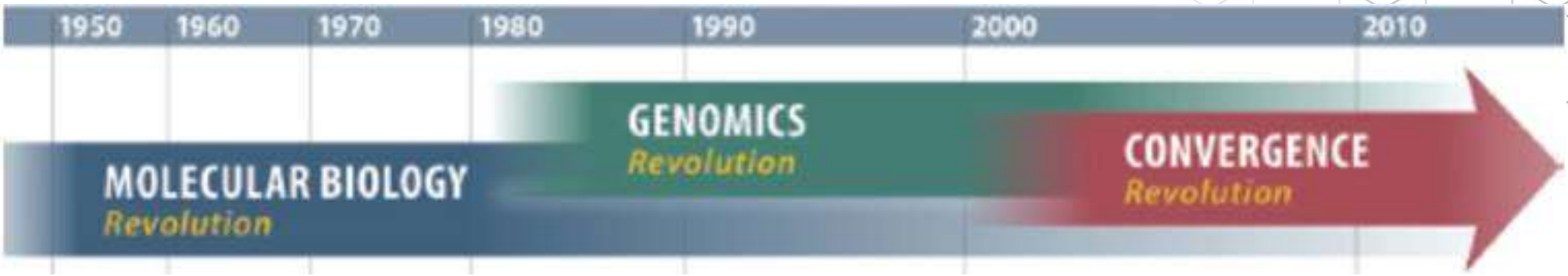
Engineering

Data Sciences



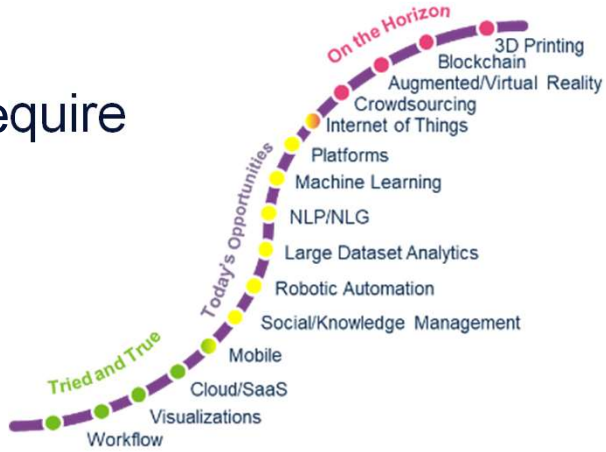
con·ver·gence
: integration of historically distinct disciplines and technologies into a unified whole that creates fundamentally new opportunities for life science and medical practice

The Three Revolutions in Life Science



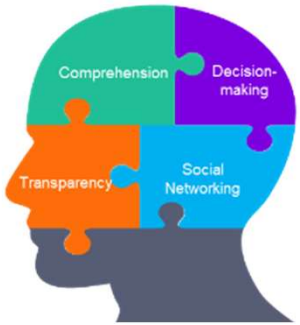
Will require

Technology



Data

Behaviors



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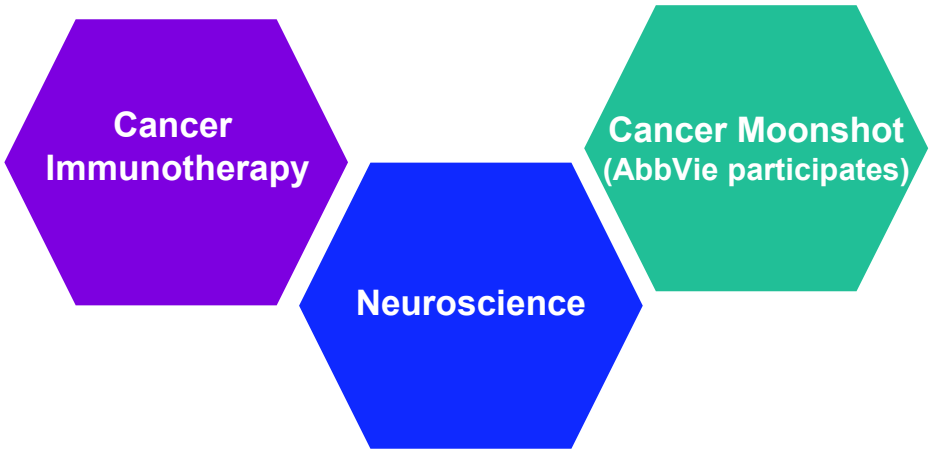
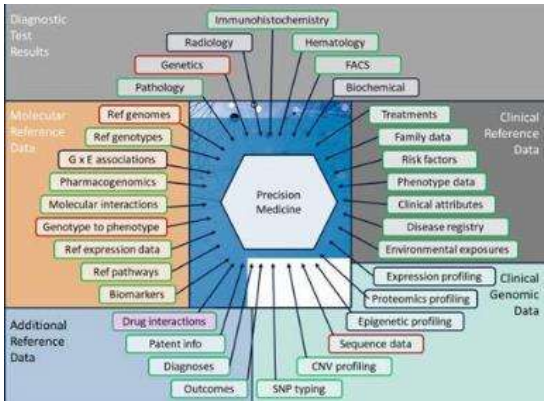
GRC
GENOMICS RESEARCH CENTER

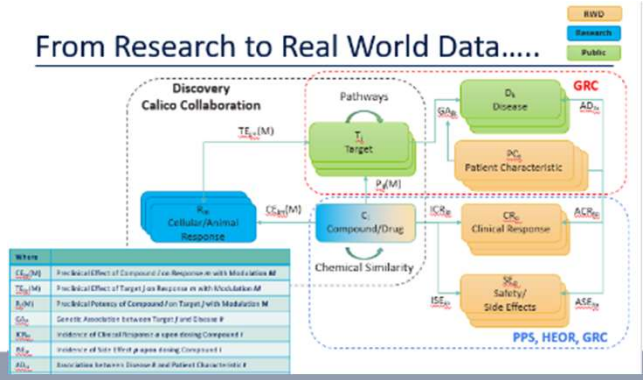
Convergence at AbbVie

Should our R&D Data Strategy Center on Convergence?

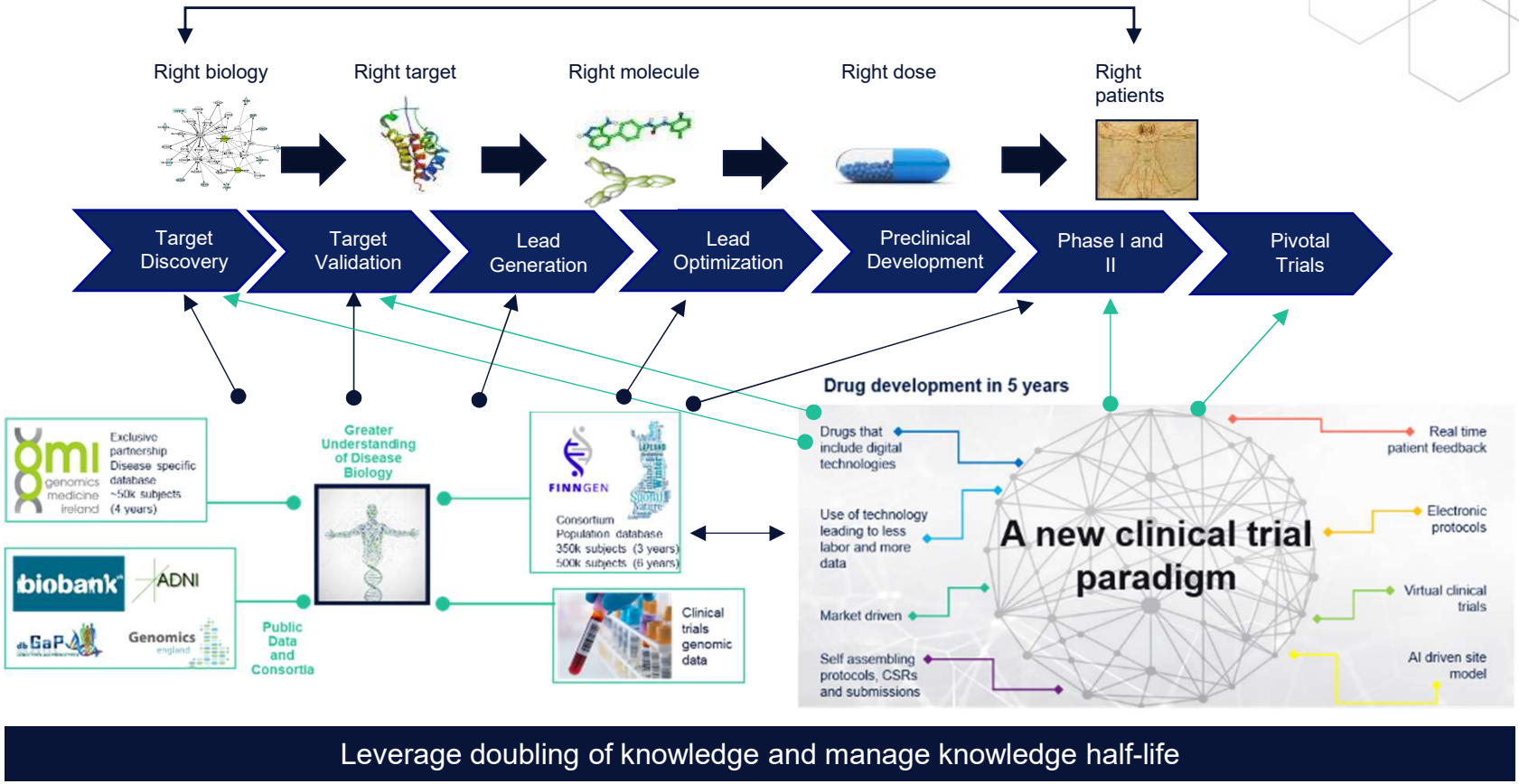




"The Precision Medicine Initiative create a million-person cohort to collect and analyze genetic, environmental, and other medical data for comparison across the largest patient database ever created." AbbVie is bringing in one million genomes.



Convergence: disrupting the discovery and development paradigm



Leverage doubling of knowledge and manage knowledge half-life

What does this innovation mean for AbbVie?

- We can start our discovery pipeline with knowledge from human data
  - Real world data
  - EHR data or clinical trial data
  - Omics data
  - Molecular fingerprints
- The ability to gene edit in the cell, tissue and animal has changed our discovery platform
- Reduce our failure rates and accelerate the pipeline by using human data most of the time
- Increase the effectiveness of our treatments
- Move into new indications faster
- Produce better biologics faster
- Help physicians and patients use our medications

Acknowledgements for Genomics Research Center

Pharmacogenetics

- Aparna Vasanthakumar
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- Sanjana Singh
- Lindsey Stolzenburg
- Jeff Waring

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- Sahar Esmaeeli
- Bridget Riley-Gillis
- Nizar Smaoui
- Jeff Waring

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- Kari Barlan
- Celso Espinoza

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