HIMSS18 The leading health information and technology conference

WHERE THE WORLD CONNECTS FOR HEALTH

Conference & Exhibition | March 5–9, 2018

Las Vegas | Venetian – Palazzo – Sands Expo Center

Going From the Trail to the Summit in Precision Medicine

Precision Medicine Preconference Symposia, Las Vegas

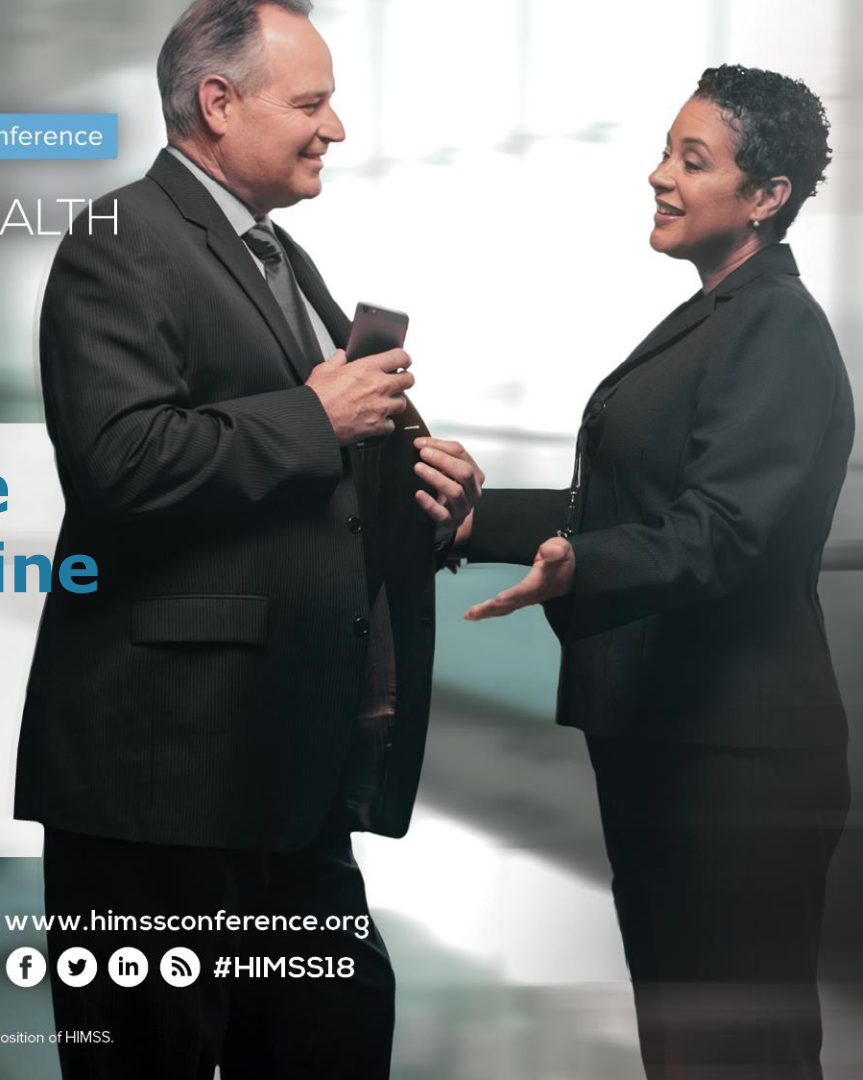
Venetian – Palazzo 4400, 3:15pm – 4:15pm

March 5, 2018

Steven N. Kalkanis, MD

Medical Director, Henry Ford Cancer Institute

COMMITMENT



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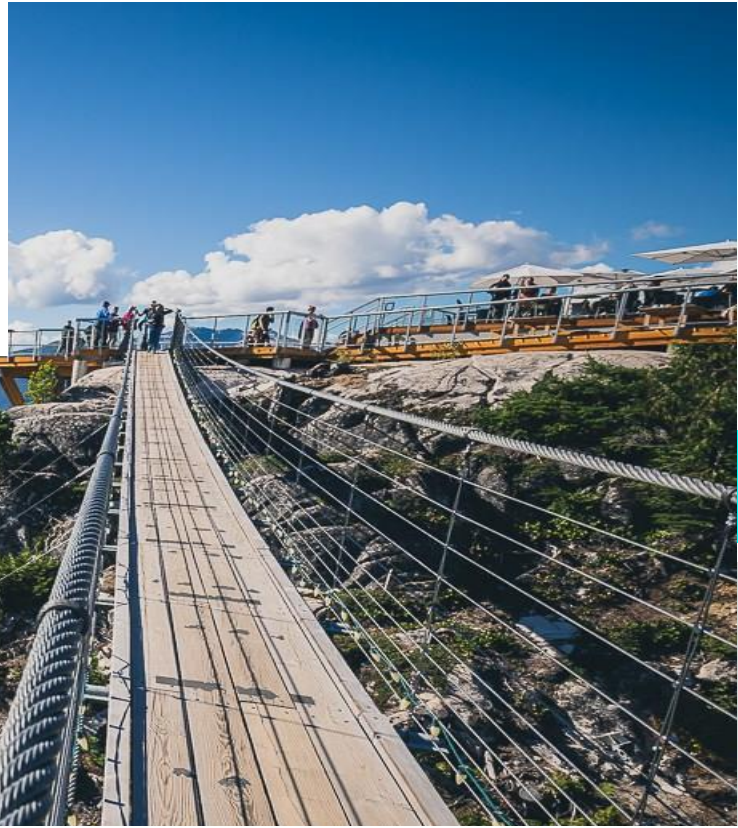
#HIMSS18

Going From the Trail to the Summit in Precision Medicine



HIMSS18 Precision Medicine Symposium
March 5, 2018
Las Vegas, Nevada

Steven N. Kalkanis, MD
Medical Director, Henry Ford Cancer Institute
Chair, Department of Neurosurgery
Henry Ford Health System

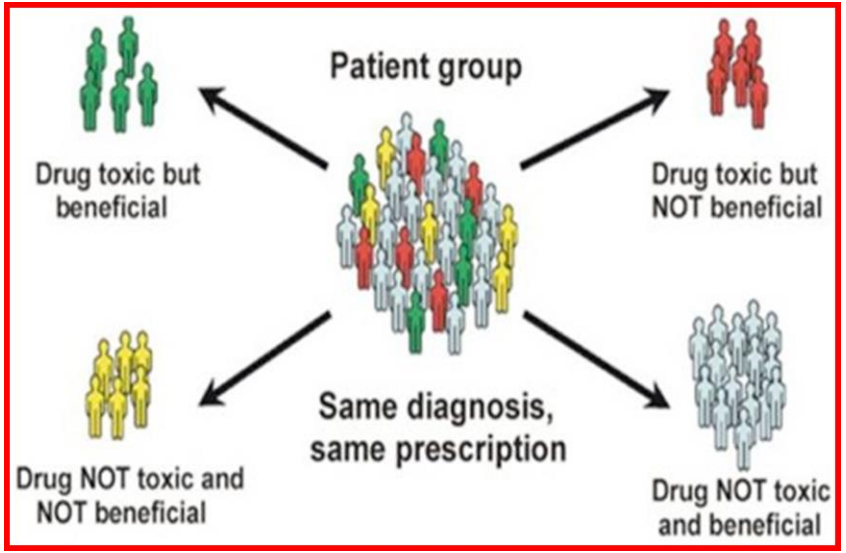
Conflict of Interest

Steven Kalkanis, MD

Has no real or apparent conflicts of interest to report.

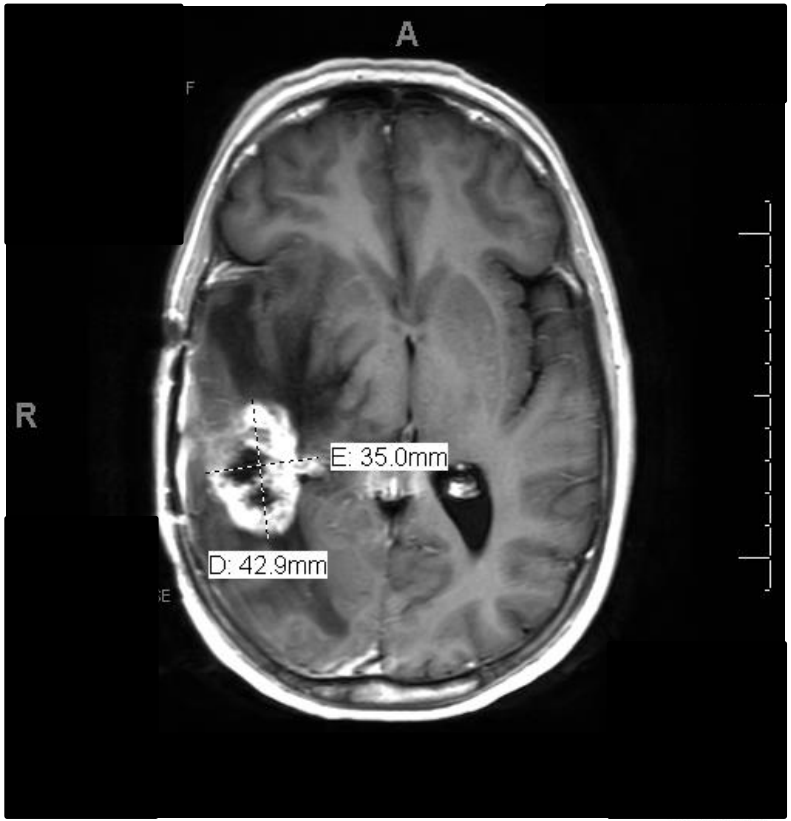
Learning Objectives

- Explore precision medicine capabilities on the horizon
- Identify challenges of building a scalable precision medicine program that delivers at the point of care
- Summarize the convergence of research and routine clinical care in precision medicine



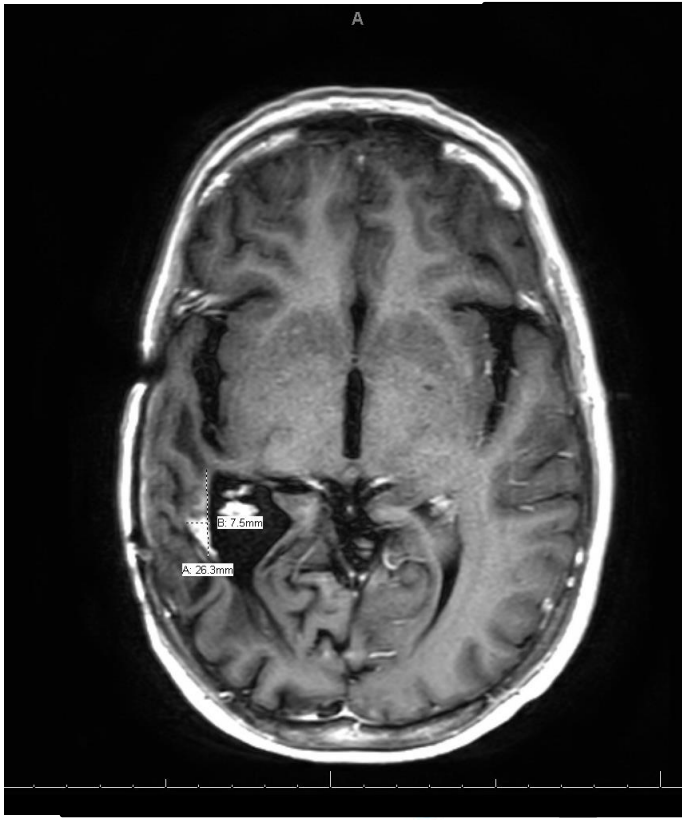
Patient Story - Glioblastoma

- 35 yo woman presents with headaches; found to have a right temporal lobe brain tumor: *Glioblastoma, WHO IV*
- Patients with this aggressive tumor (Ted Kennedy, Bo Biden, John McCain) have a median survival of 15 months
- Patient underwent standard of care: brain tumor resection plus 6 weeks radiation & temozolomide chemo
- Tumor recurs 6 months later

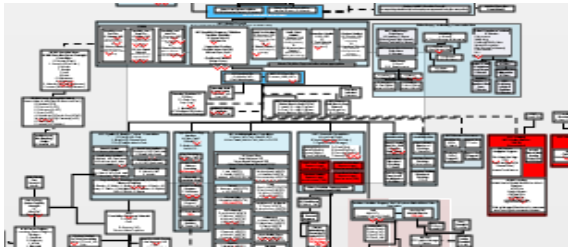


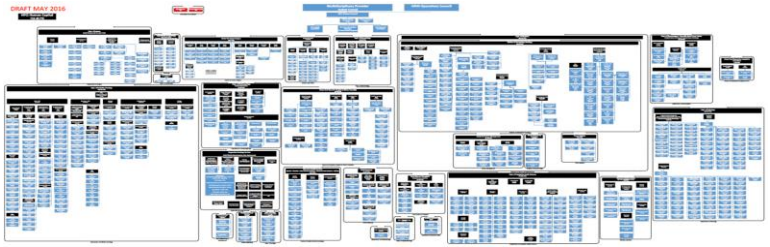
Patient Story - Glioblastoma

- Patient presents for 2nd opinion to Hermelin Brain Tumor Center at Henry Ford Hospital
- Personalized pathology analysis performed to identify molecular markers
- Patient enrolled in clinical trial specifically based on her tumor marker: EGFRviii mutation
- Patient receives IV immunotherapy for this specific marker
- Her tumor stabilizes, starts shrinking
- Patient continues to do well after 30 months



Henry Ford Cancer Institute





HFCI North West

HFCI North East

HFCI Detroit Destination Cancer Center

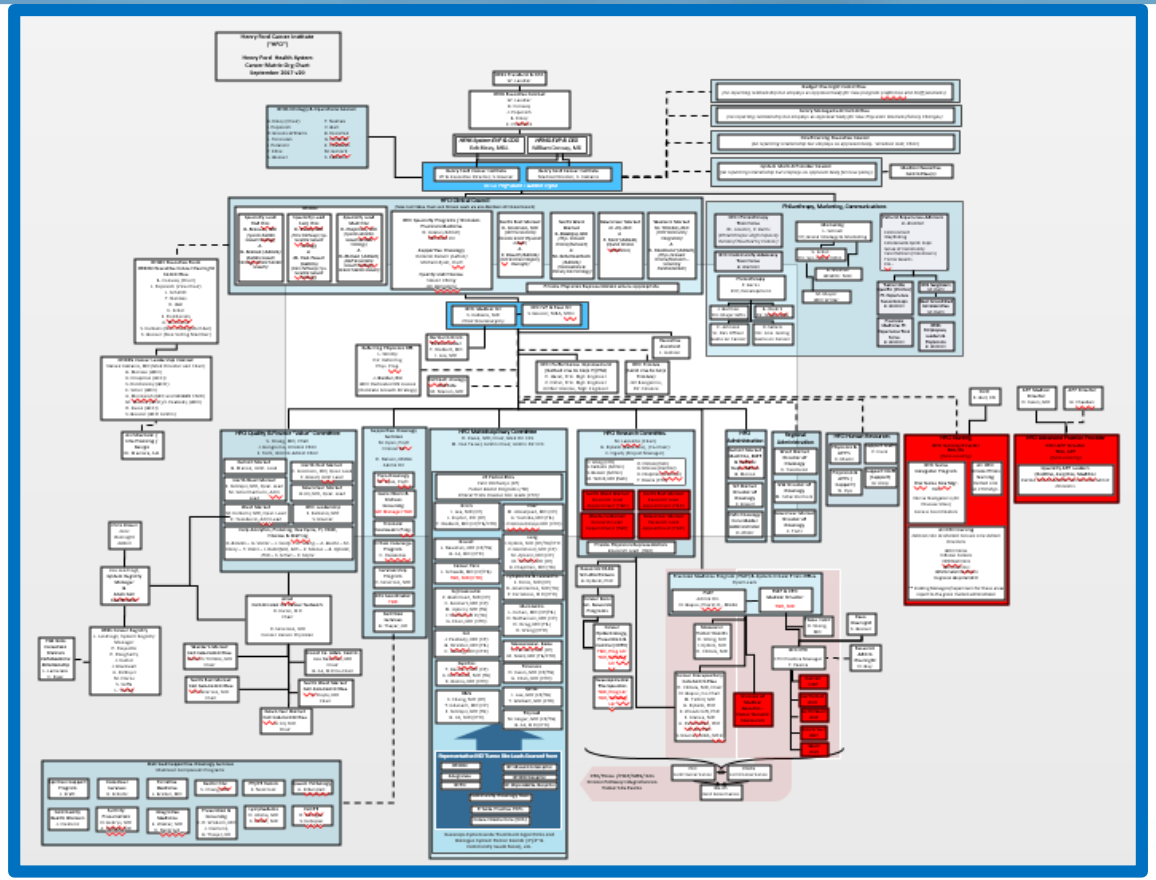
HFCI West

HFCI Downriver

Creating a coordinated, personalized "All for You" Henry Ford Cancer experience at all locations

HFCI Organizational Structure

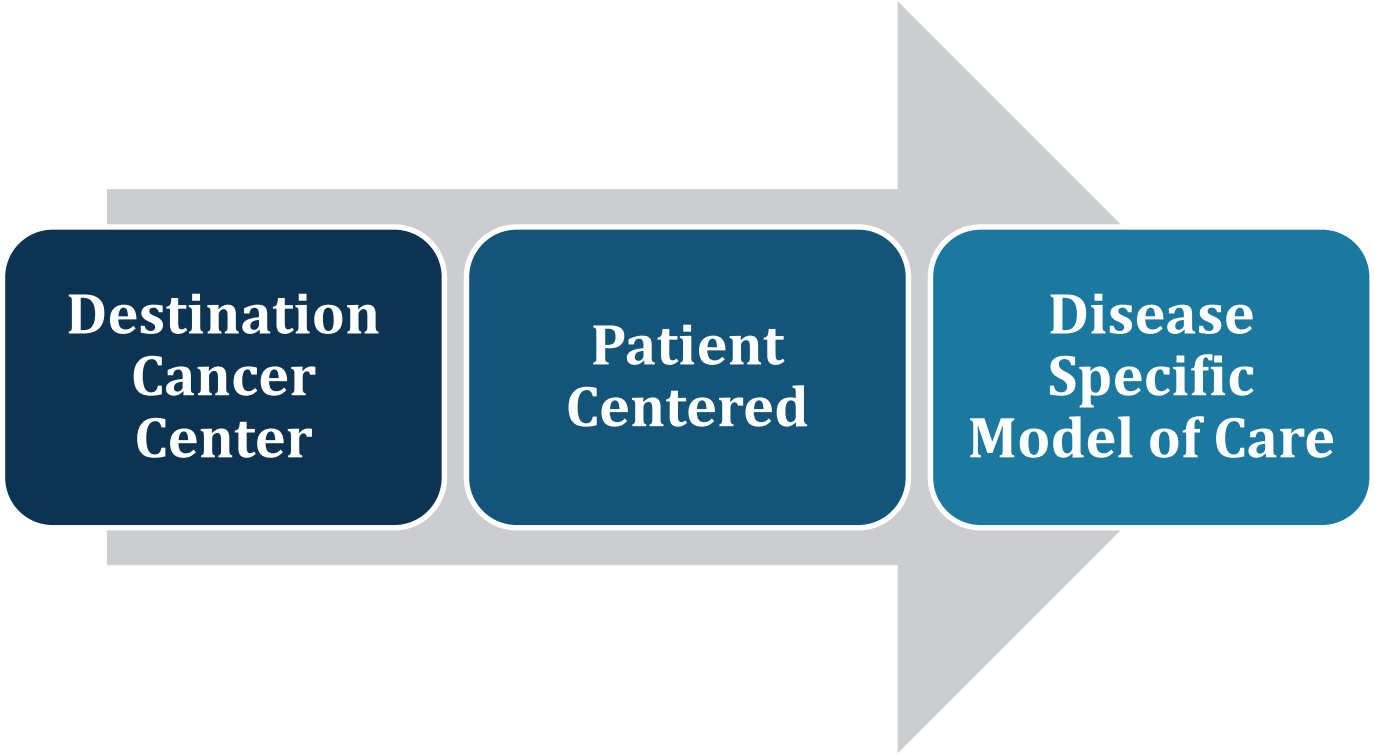
- 1300 FTEs
- $1.2 Billion
- Over 7,500 analytic cases each year



Henry Ford Health System
Henry Ford Cancer Institute


HENRY FORD CANCER INSTITUTE
BRIGITTE HARRIS CANCER PAVILION

Design Vision



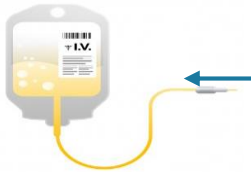
A cancer patient navigates through a seamless experience – via a HFCI Care Pathway

Patients who may benefit from molecular testing are identified, ensuring patients with advanced disease receive molecular profiling to determine their eligibility for a targeted therapy

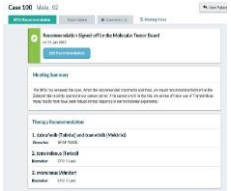
HFHS' internationally renowned pathology laboratory performs next gen sequencing with a turnaround time of 2-3 days

Molecular tumor boards can easily review cases & make recommendations based on real-world treatment and outcomes data across multiple institutions in the Oncology Precision Network (OPeN) through Syapse

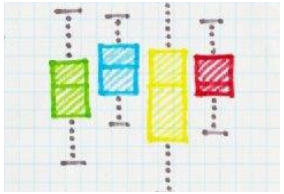
Molecular tumor boards interact with experts on our 15 disease specific tumor boards



Molecular testing increases access to clinical trials, or assists in creating targeted cancer treatment



All treatment information and recommendations are sent back to the referring physician



Researchers collect outcomes data to see which targeted therapies work best – for current and future treatments

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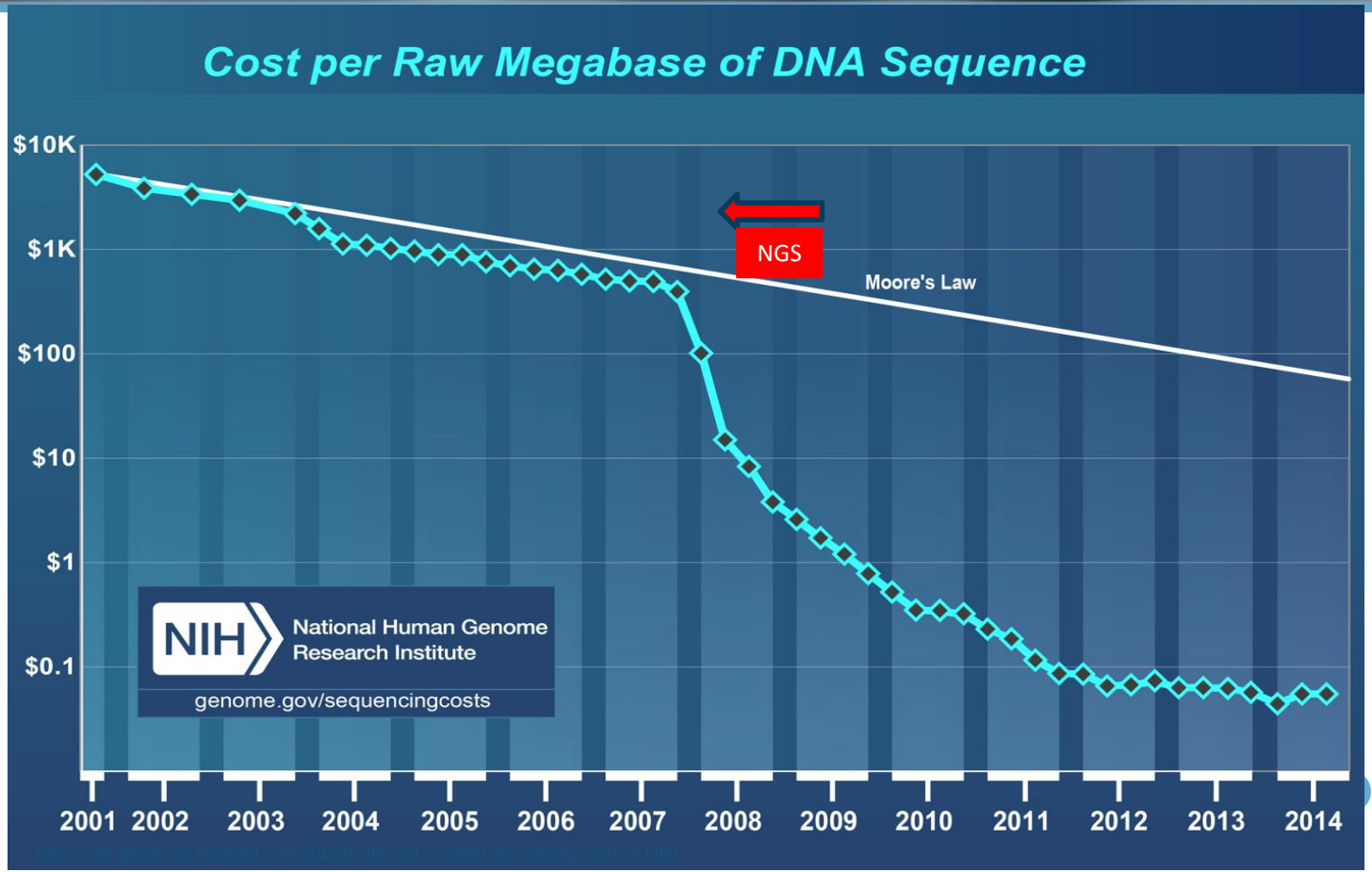
- Cost of lab testing
- Scalability within a system
  - Germline and Somatic
  - Universal adoptability across disease sites/departments
  - Quality Measurements
- Data storage
- Data analytics
- Clinical bioinformatics expertise


Cost per Raw Megabase of DNA Sequence
$10K
$1K
$100
$10
$1
$0.1
NGS
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
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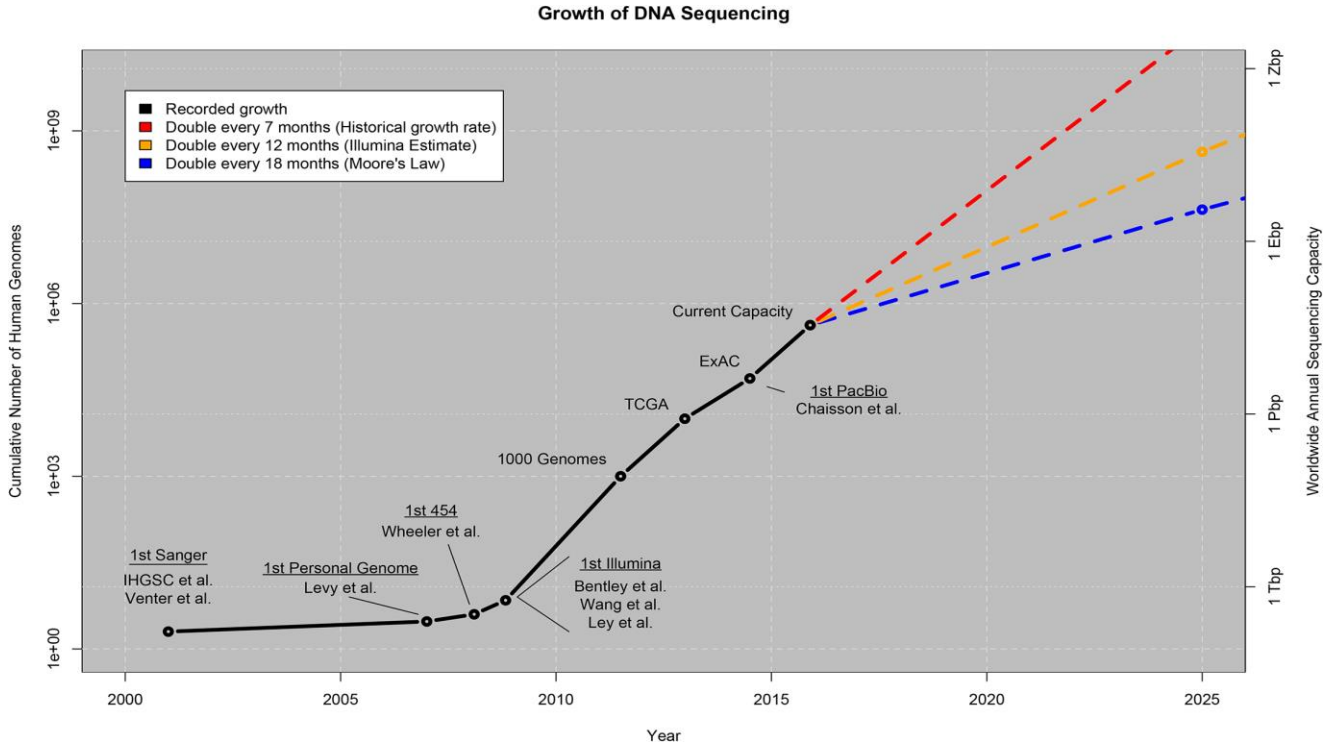
Growth of DNA Sequencing



Stephens ZD, Lee SY, Faghri F, Campbell RH, Zhai C, et al. (2015) Big Data: Astronomical or Genomical?. PLOS Biology 13(7): e1002195. https://doi.org/10.1371/journal.pbio.1002195

Germline vs Somatic Mutations

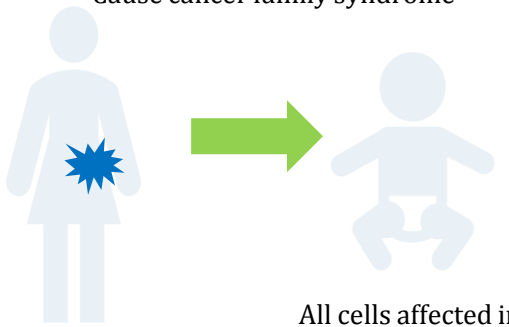
Somatic Mutations

- Occur in nongermline tissues
- Cannot be inherited

Mutation in tumor only (for example, breast)

Germline Mutations

- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome



All cells affected in offspring

Mutation in egg or sperm

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Henry Ford Cancer Institute

Adapted from the National Cancer Institute and the American Society of Clinical Oncology

Consistent practice across an institution

Disease Site Name: Lung

Physician Lead: Rybkin

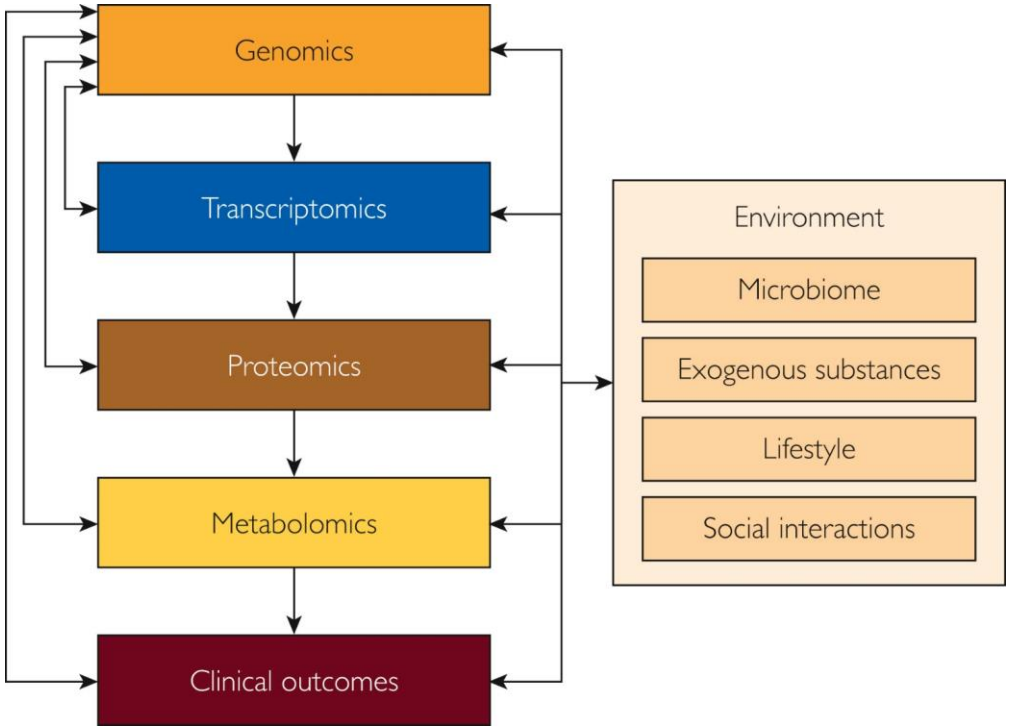
Staging	Routine Tests	Reimbursement	Tier	Available Treatment(s)	
per AJCC	Test name (i.e. EGFR, Her 2 mutation, etc.)	Yes = SOC (w/ or w/o prior auth) No = Not SOC and not approved by MTB HAP = Yes if the DTB or MTB deems the test appropriate	1 = Test requested by treating physician 2 = Test is requested by DTB 3 = Test is requested by MTB	On Label FDA approved drug(s)	Off Label FDA approved drug(s)
I -IIIa	no routine tests	HAP	2	none	none
IIIb, IV	EGFR (pm/del, including T790) [PCR/NGS-D] *	Yes	1	Erlotinib Afatinib Gefitinib Necitumumab	
	EGFR (T790M); ctDNA [PCR/NGS-D] *	Yes	1	Osimertinib	
	KRAS (pm) [PCR/NGC-D] *		1	none	none
	NRAS (pm) [PCR/NGS-D] *		1	none	none
	BRAF (pm) [PCR/NGS-D] * #		1	Vemurafenib Dabrafenib Trametinib	
	MET (pm/del/ins) [PCR/NGS-D] * #		1	none	Crizotinib Cabozantinib Capmatinib
	MET (ampl/rearrang) [FISH/NGS-R] $	HAP	1	none	Crizotinib Cabozantinib Capmatinib
	ERBB2 (pm/del/ins) [PCR/NGS-D] * #	HAP	1	Afatinib Lapatinib	
	ALK (rearrang) [FISH */NGS-R $]	HAP	1	Crizotinib Ceritinib Alectinib Brigatinib	
	ROS1 (rearrang) [FISH */NGS-R $]				
	RET1 (rearrang) [FISH */NGS-R $]				
	PD-L1 immunocytochemistry $	HAP	1		
	MSI [ICC */ NGS $]	HAP	2	Nivolumab Pembrolizumab Avelumab	
	Experimental Clinical Trial NGS Panel */$	HAP	3	none	none

Data Generated

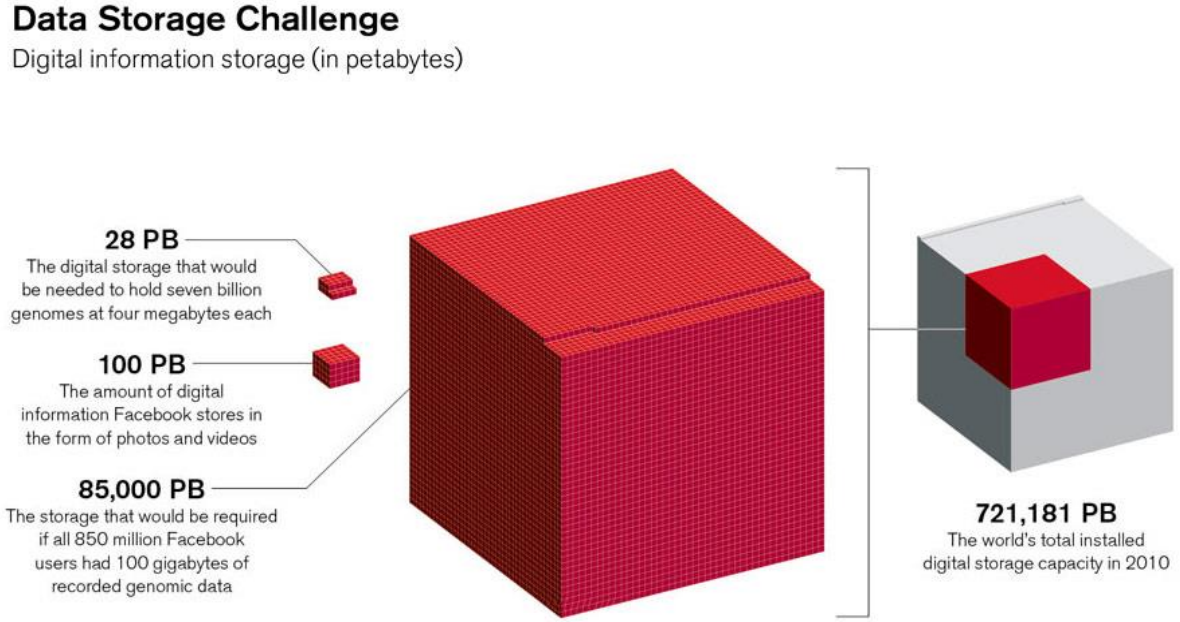
These groups are used to create contiguous sequences containing both forward (blue) and reverse (purple) reads.

Contiguous sequences are then aligned against the reference genome and variant alleles (differ from the reference allele) are identified.

The "Personalome"



Data Storage



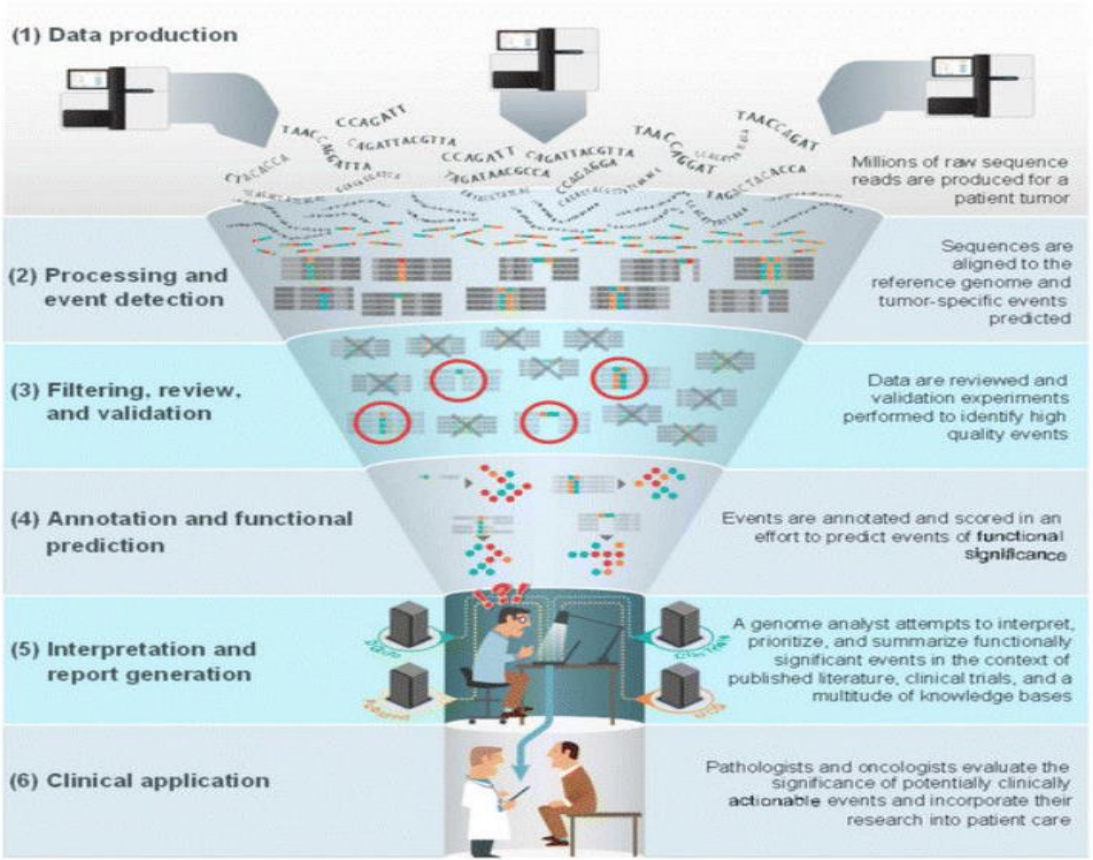
Source: Illumina, Facebook, IDC
https://www.technologyreview.com/s/427720/bases-to-bytes/

Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year
Analysis	In situ data reduction	Topic and sentiment mining	Limited requirements	Heterogeneous data and analysis
	Real-time processing	Metadata analysis		Variant calling, ~2 trillion central processing unit (CPU) hours
	Massive volumes			All-pairs genome alignments, ~10,000 trillion CPU hours
Distribution	Dedicated lines from antennae to server (600 TB/s)	Small units of distribution	Major component of modern user's bandwidth (10 MB/s)	Many small (10 MB/s) and fewer massive (10 TB/s) data movement

doi:10.1371/journal.pbio.1002195.t001

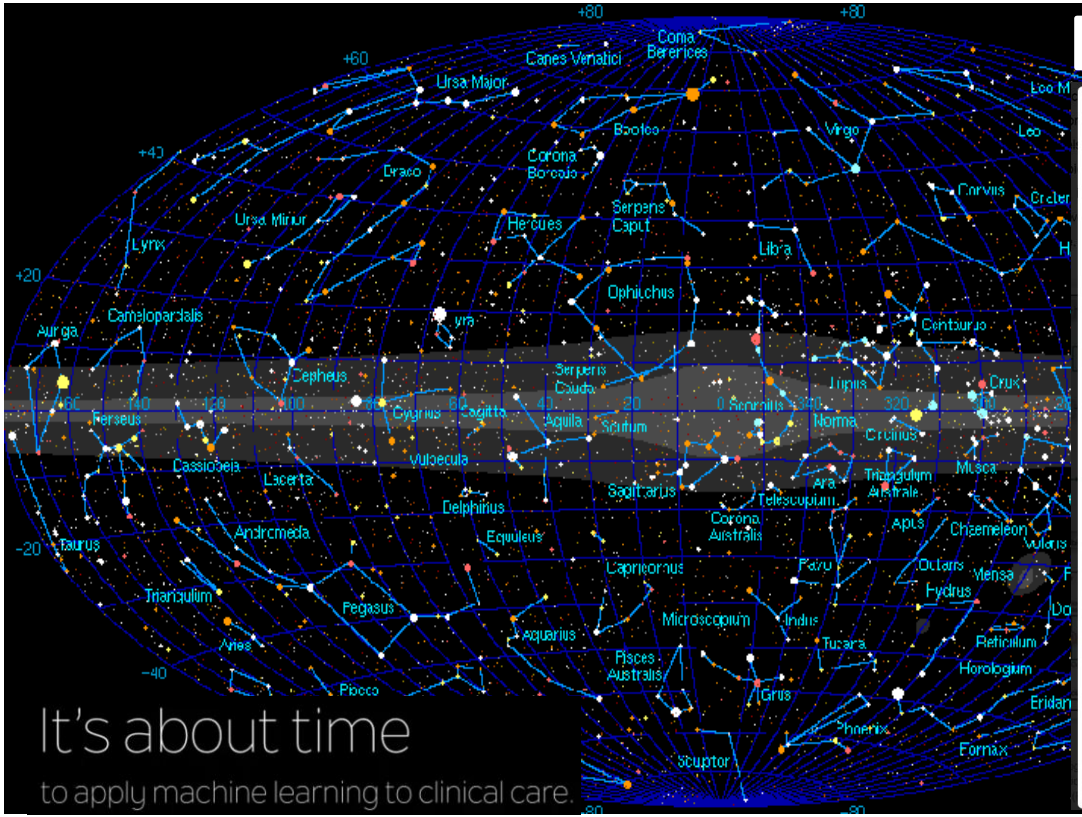
Stephens ZD, et al. (2015) Big Data: Astronomical or Genomical?
http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002195

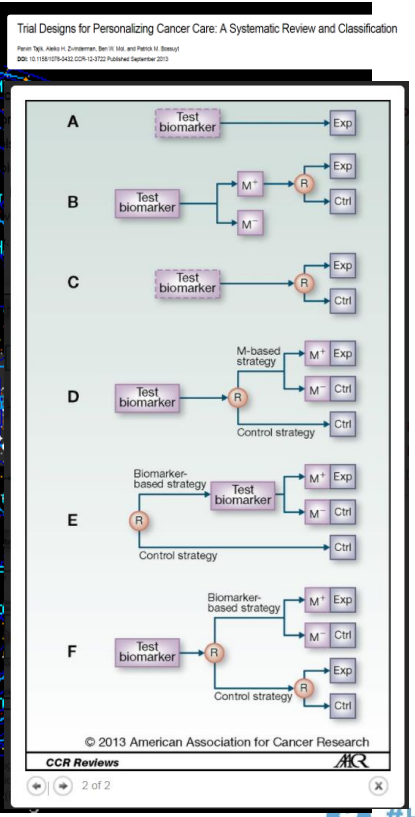
The interpretation of this data is a bottleneck



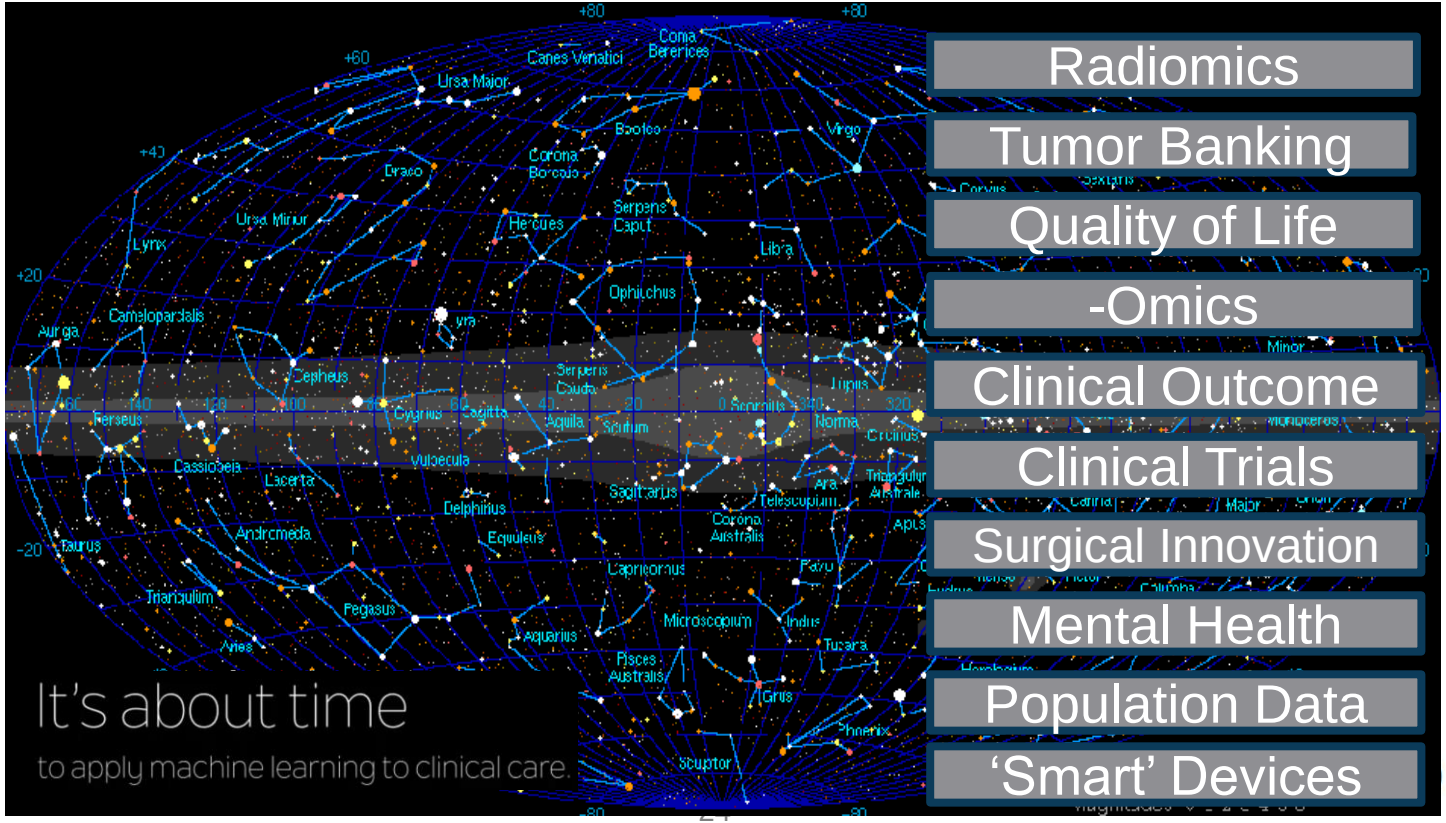
Good BM, Genome Biology 2014; **15**:438

We are modern day cartographers for the future of oncology…





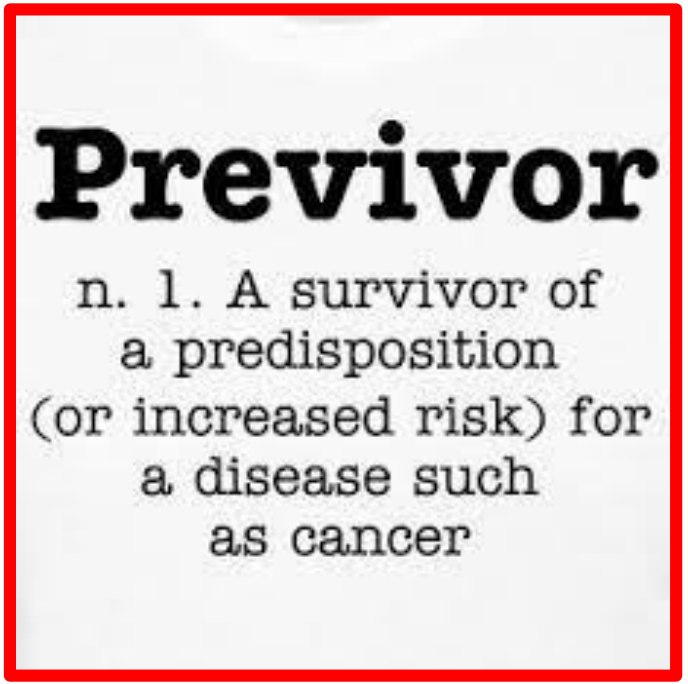
...identifying new constellations for investigation

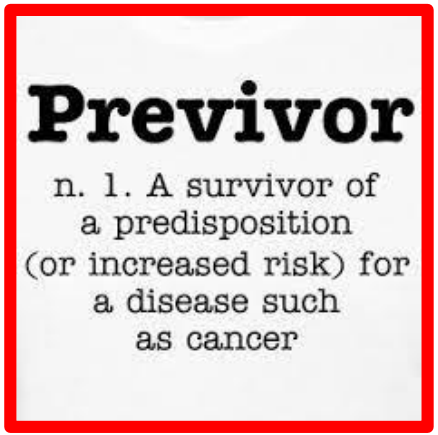


Using Big Data to Predict the Future: *Convergence of AI and Precision Medicine*

TheFutureOf.org and The Jacobs Institute

Using Big Data to Predict the Future: *Convergence of AI and Precision Medicine*





- **Artificial Intelligence** + **Precision Medicine** + **Machine Learning** means we may become "**previvors**"—identifying **which of 10,000 known human diseases are in our future long before symptoms**
- Soon, predictions will become more accurate and occur earlier—increasing the time we have to effect change and seek help
- *ONCE WE BECOME A PREVIVOR OF A PARTICULAR DISEASE,* ***WHAT CAN WE DO ABOUT IT?*** BAND TOGETHER INTO PREVIVOR COMMUNITIES—AND PUSH FOR CURES
- Impact already seen in BRCA1 and BRCA2 mutation previvors and among healthy individuals carrying HIV → groups coalesced into large consumer-activist organizations advocating for novel treatments and compelling regulatory agencies to speed adoption of promising drugs and interventions
- Unfortunately, ability to forecast disease outpaces breakthroughs for effective interventions. Facilitated by social media, connected groups of previvors will band together to share peer-to-peer information—some junk science, but some valuable and potential curative innovations as well

Henry Ford Health System
Henry Ford Cancer Institute

Previvor

n. 1. A survivor of a predisposition (or increased risk) for a disease such as cancer

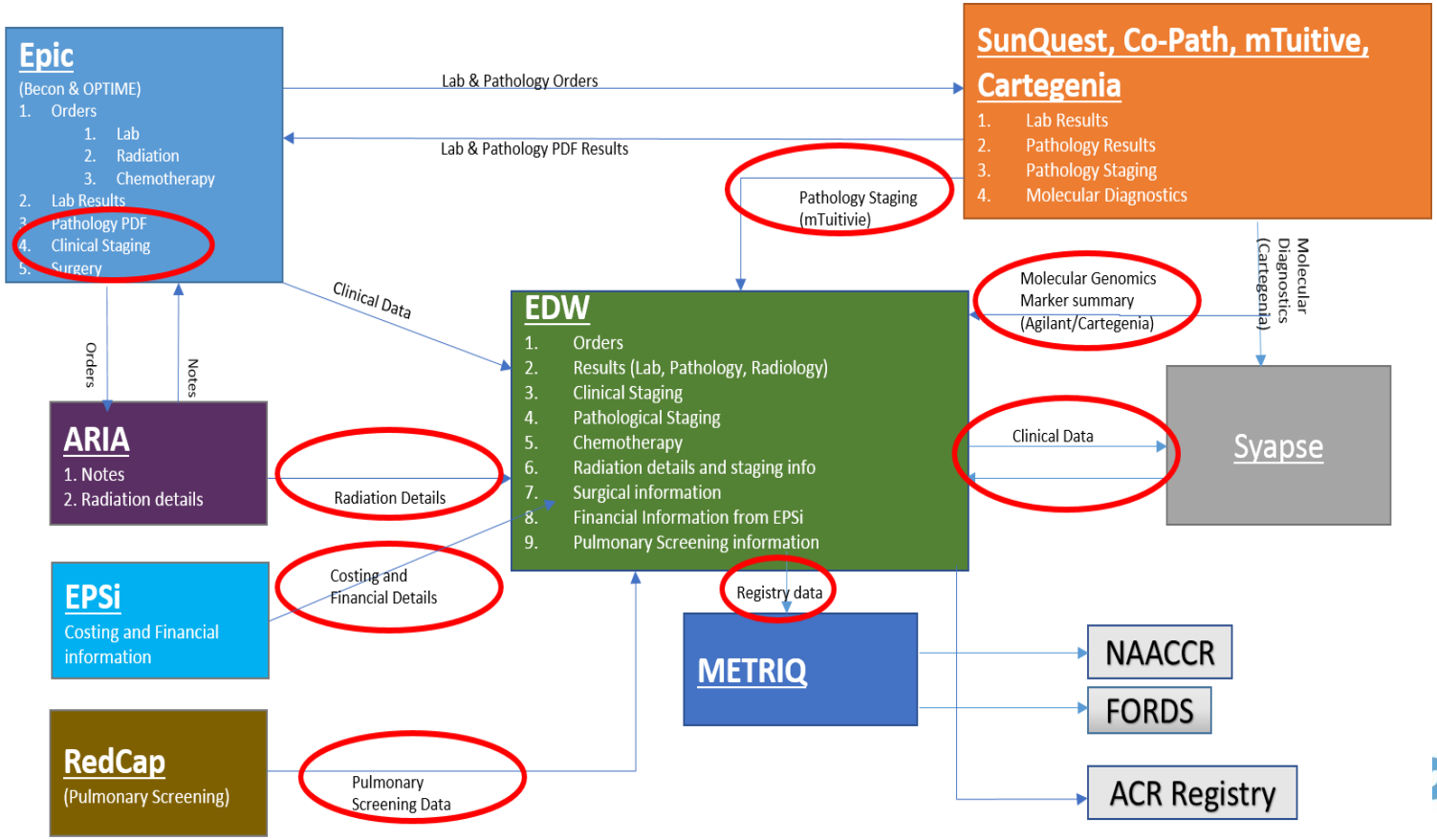
CONDITION	CURRENT DIAGNOSIS AND TREATMENT	KEY PREVIVORS FUTURE MOMENTS	POSSIBLE PREVIVORS PREVENTATIVE TREATMENTS
Breast cancer	BRCA1 and BRCA2 mutation. Breast removal.	AI algorithms will allow women to know with more certainty when or if breast removal is necessary.	Gene therapy using CRISPR will remove health threats encoded in BRCA genes and keep them from being passed to future generations.
Parkinson's disease	Disease diagnosed at onset of symptoms. Family history increases likelihood.	Our interactions with touch screens will pick up early signs of the condition.	Early deep-brain stimulation—either through wearable or implantable devices—will be employed at earliest signs of the condition.
Alzheimer's disease	No specific test exists to diagnose Alzheimer's. Family history increases likelihood. Low efficacy drug treatments.	AI algorithms analyzing polygenic risks and brain imaging will predict the disease in early adulthood.	Optogenetic stimulation of interneurons through implantable devices may decrease amyloid-beta production before symptoms appear.
Celiac disease	A blood test and intestinal biopsy can provide a diagnosis. Dietary changes.	Sensors in toothbrushes and toilets will monitor and predict all gut-related conditions.	A sensor and drug delivery device placed into the digestive tract meters out pneumococcal vaccine for ongoing treatment.
Type 2 diabetes	Prediabetes blood testing can give type 2 previvors a decade to make behavior changes.	Lifestyle, diet and blood monitoring through sensors and the internet of things will provide new data for doctors and patients.	Personalized diet designed for individual genome. Constant blood and metabolism monitoring.
Cardiovascular disease	Diagnosis is attained through blood tests, X-rays and electrocardiograms—often after a dramatic heart event.	Implanted vascular flow bots and heart rhythm monitors warn of coming danger.	Patients check into hospitals before life-threatening cardiovascular events.

How do we achieve this?

Previvor

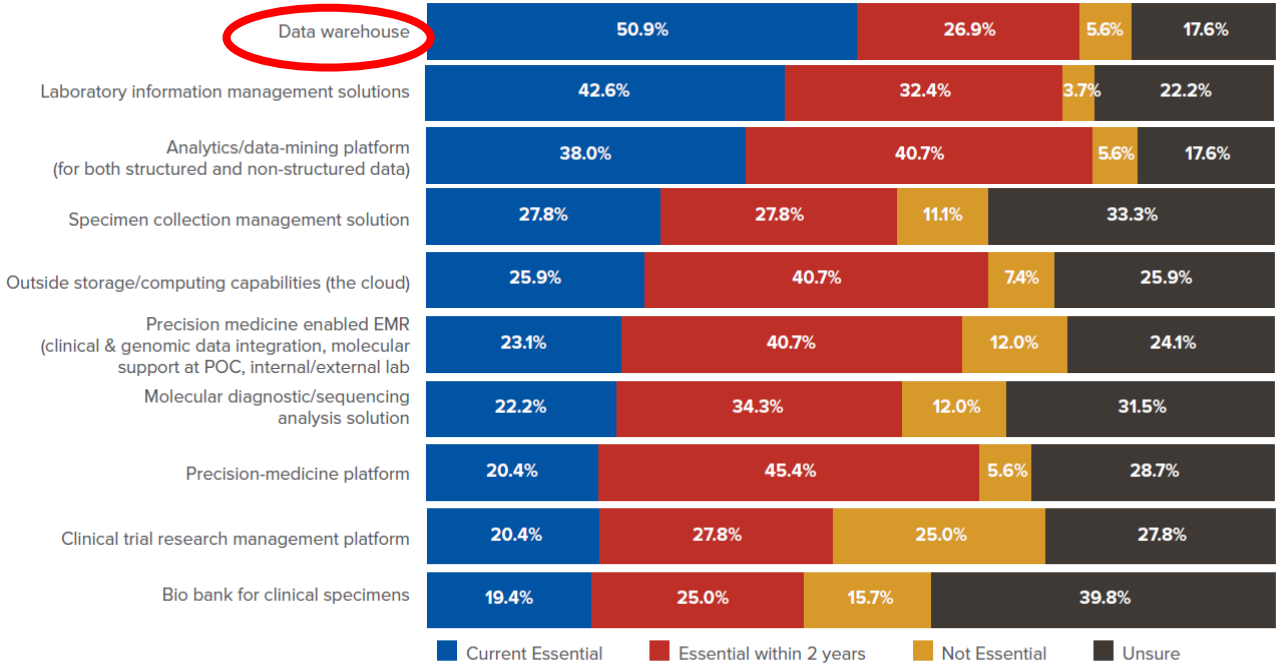
n. 1. A survivor of a predisposition (or increased risk) for a disease such as cancer

Setting the Foundation – Data interoperability



Key capabilities needed for precision medicine

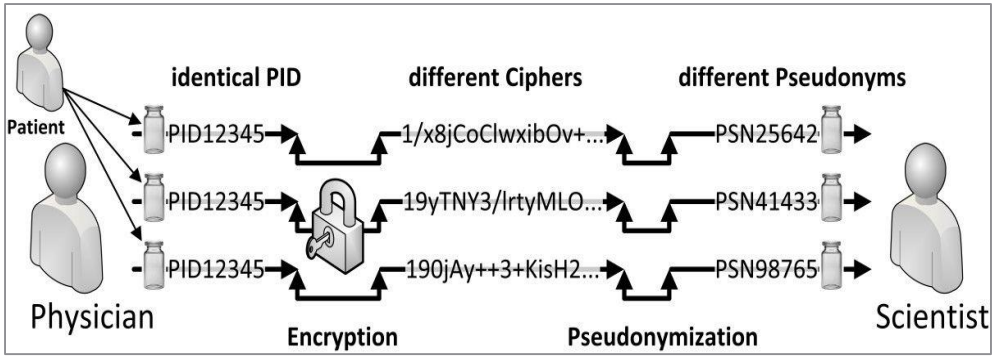
Figure 2. When it comes to supporting precision medicine with technology, respondents feel data warehouses are essential.
Which technologies does your organization consider essential in the development of a precision medicine program? Select all that apply.



HIMSS 2017 Precision Medicine survey of Healthcare organizations

Data Protection

- Pseudonymization: Informational Separation of Powers
  - The larger the data set the more likely to identify the patient
  - nonspeaking pseudonym: replace patients' identifying data (eg, name, date of birth) with an identifier that conveys no meaning by itself
- Record Linkage
  - motivation to delegate pseudonymization
- Intellectual property protection

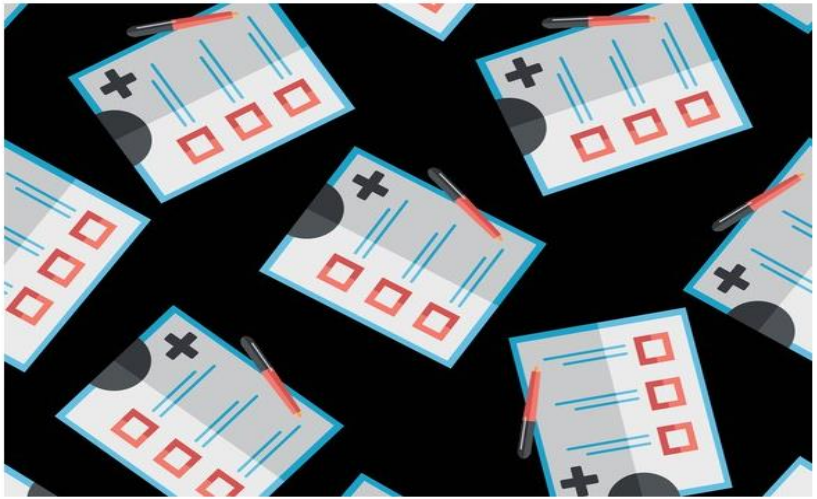


BMC Medical Informatics and Decision Making 2015 15:2 | https://doi.org/10.1186/s12911-014-0123-5

Will Blockchain help us?

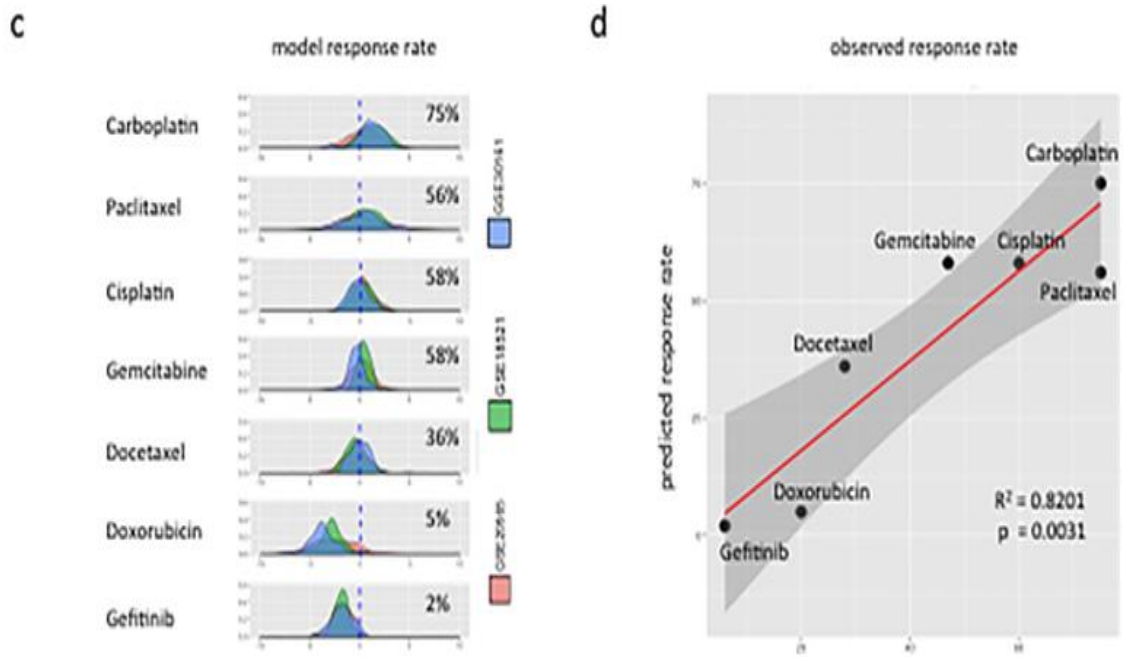
MEGAN MOLTENI SCIENCE 02.01.17 07:00 AM

MOVING PATIENT DATA IS MESSY, BUT BLOCKCHAIN IS HERE TO HELP



GETTY IMAGES

https://www.wired.com/2017/02/moving-patient-data-messy-blockchain-help/



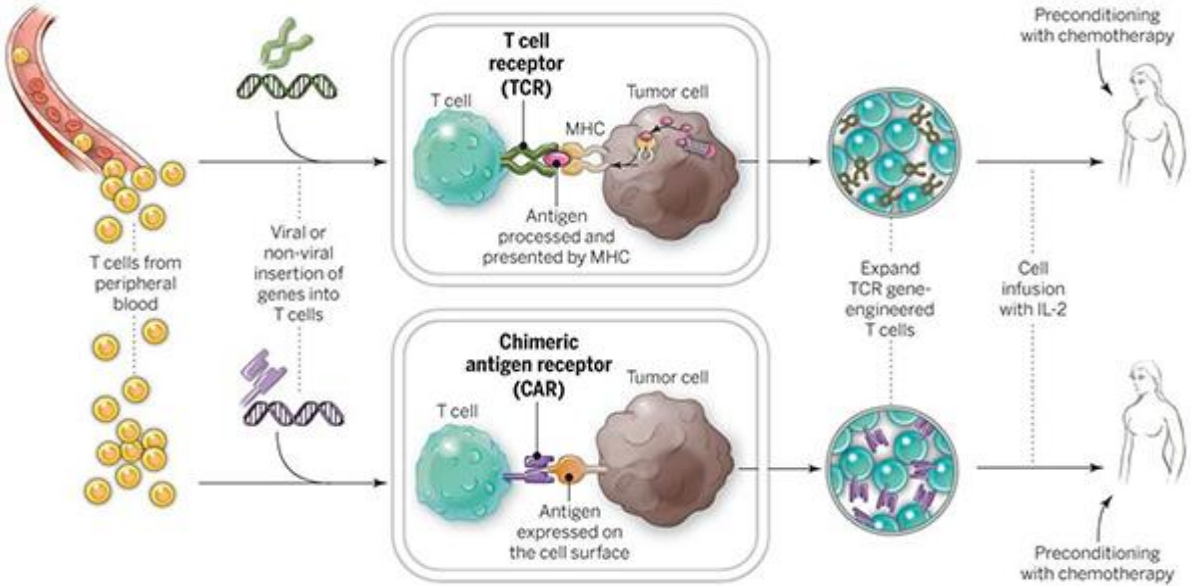
Huang C. PLoS ONE 12 (10): e0186906

Convergence of Research and Routine Clinical Care: *Precision Medicine 2025?*

Wearable devices

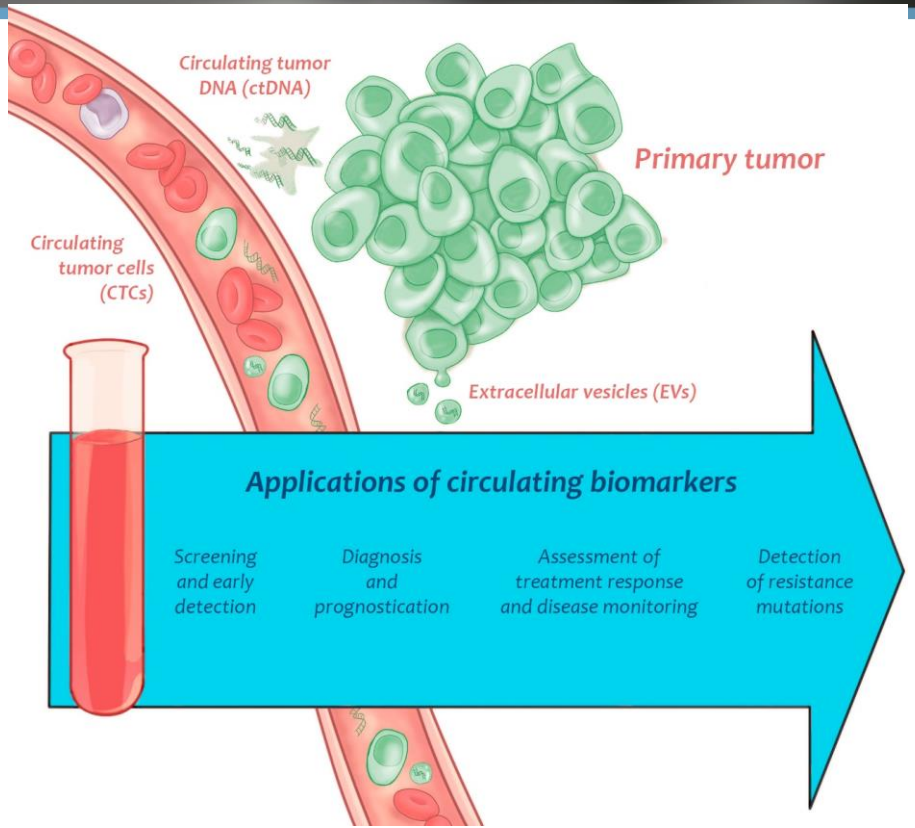
www.optune.com

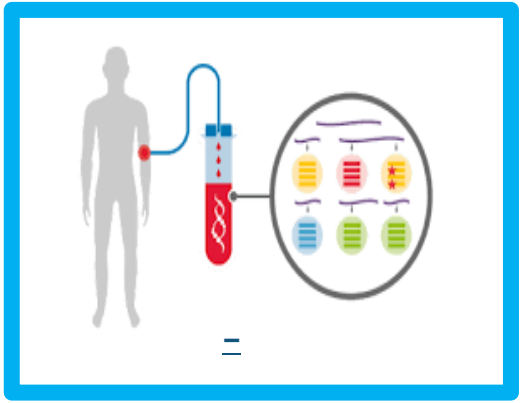
CAR-T Therapy



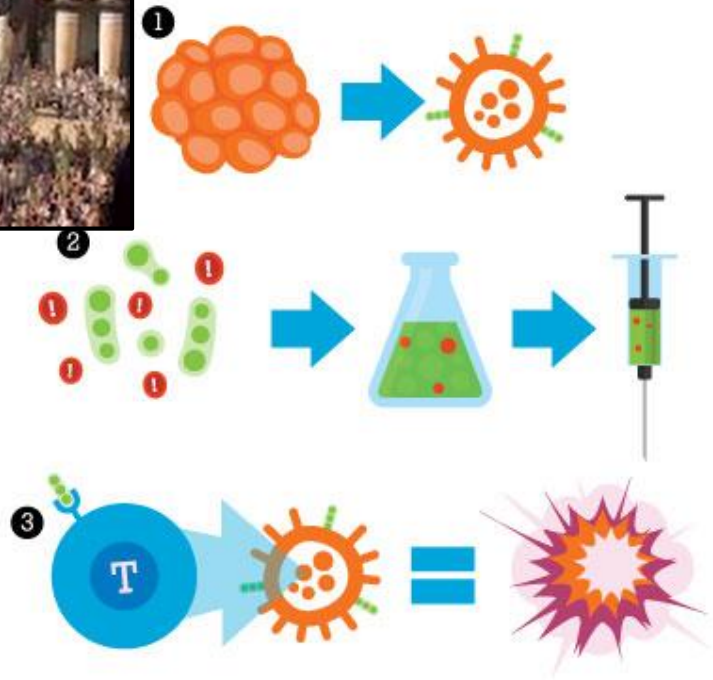
National Cancer Institute

Circulating tumor DNA (ctDNA)





Retroviral Gene Therapy and Cancer Vaccines



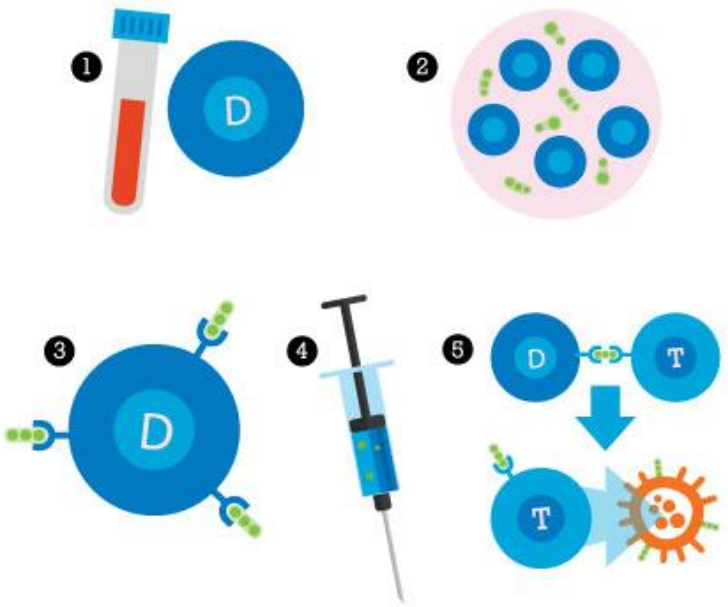
Cancer Vaccine Treatments:

Antigen Vaccines

1. Cancer cells are removed from a patient's tumour.
2. Specific markers on the cancer cells (antigens) are isolated and mixed with a "danger signal" called an adjuvant to create the vaccine.
3. Vaccine is given to the patient. These cancer markers teach the immune system (T cells) to recognize cancer cells and to attack and destroy them.

http://www.cancer.ca/en/research-horizons/e/c/9/immunotherapy-promising-new-field-treatment/?region=on

Dendritic Cell Vaccines



Cancer Vaccine Treatments:

Dendritic cell vaccines

1. Dendritic cells, a type of immune cell that plays an important role in starting an immune response, are isolated from a patient's blood.
2. They are mixed with a cancer marker (antigen) in a dish, in the lab.
3. Dendritic cells take in the antigen and post them like flags on their surface.
4. The vaccine is created from the dendritic cells and is injected back into the body.
5. The vaccine triggers another type of immune cell (T cells) to destroy cancer cells.

http://www.cancer.ca/en/research-horizons/e/c/9/immunotherapy-promising-new-field-treatment/?region=on

ONCONNECT

27 female

kps 70

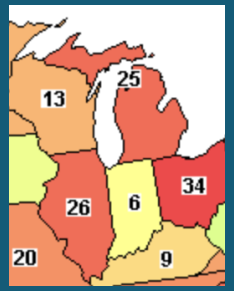
GLIOBLASTOMA

WHO IV

MGMT methylated
IDH-1 mutated
ATRX mutated
EGFRviii mutated
P53 mutated

Immune-environment

Clinical Trial Opportunities in the Region

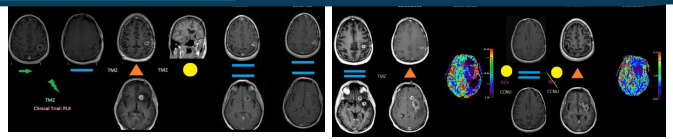


16 Henry Ford Hospital

7 University Of Michigan

2 Spectrum Health

11 Cleveland Clinic



- Guidelines
- Tumor Board Review
- New Approaches
- Clinical Trials
- Decision Support Tool
- Imaging Support Tool
- Patient's Care Team
- Generate Note
- Patient Resources
- Predictive Analytics

ONCONNECT

27 femal

kps 70

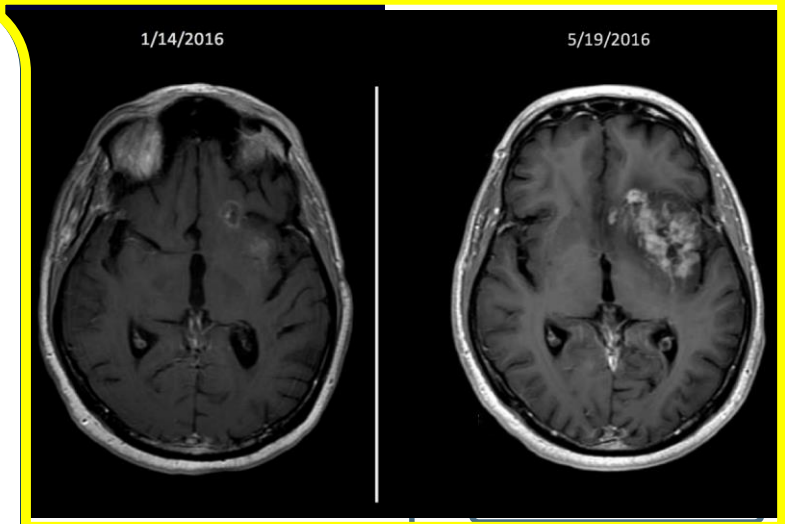
GLIOBLASTO
A

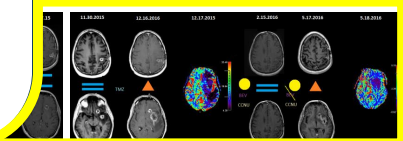
WHO IV

MGMT methylat
IDH-1 mutated
ATRX mutated
EGFRviii mutat
P53 mutated

Immune-
environment

08.14.14: presentation
seizure
08.22.14: Surgery- 80% GBM
09.22.14: EBRT+Temodar
11.03.14: Temodar started
04.14.15: MRI progression
05.02.15: CCNU
09.10.15: MRI progression
09.11.15: ABTC surgical trial
09.14.15: Surgery 2
09.23.15: Study drug day 9
05.19.16: MRI progression

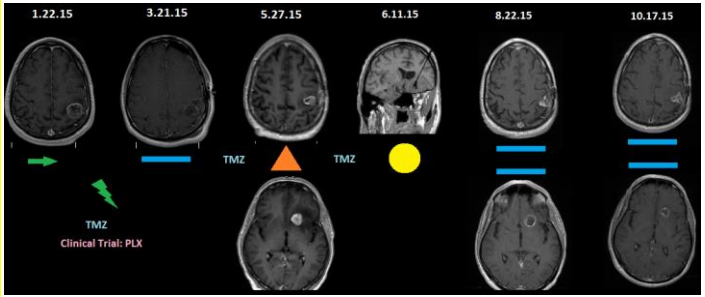


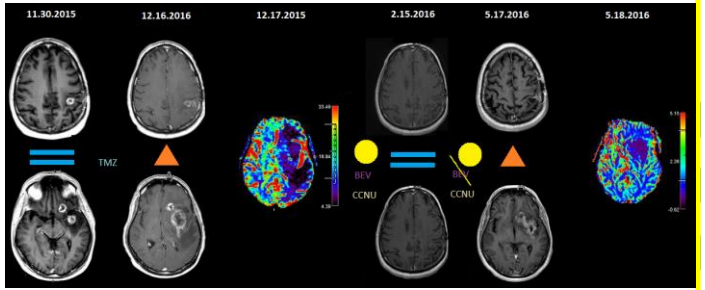


Patient Resources

Predictive Analytics

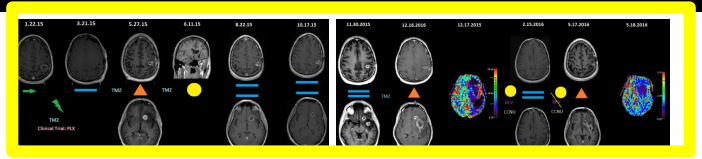
ONCONNECT





IDH-1 mutated
ATRX mutated
EGFRviii mutated
P53 mutated

Immune-environment



Patient's Care Team

Generate Note

Patient Resources

Predictive Analytics

ONCONNECT

27 female

kps 70

GLIOBLASTOMA

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Immune-environment

Select Reference Institution

Henry Ford Hospital

- 72% of patients with this molecular profile and diagnosis treated at Henry Ford are treated with Surgery using
  - intra-operative imaging 65%
  - tractography 42%
- 52% of those are followed with clinical trial
- 32% are treated with Bevacizumab
- 28% non-surgical patients are treated with next line cytotoxic chemotherapy

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Henry Ford Cancer Institute

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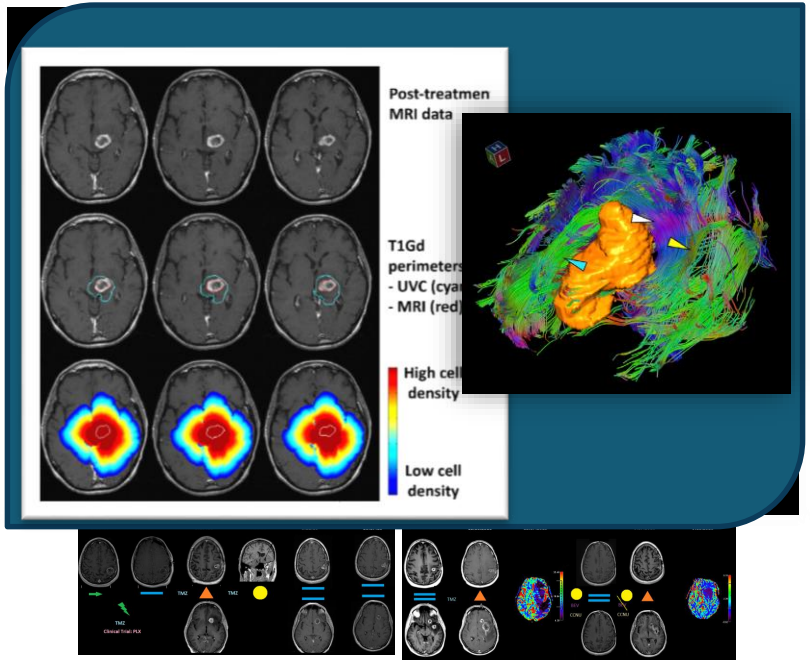

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Generating Real World Evidence vs. RCTs

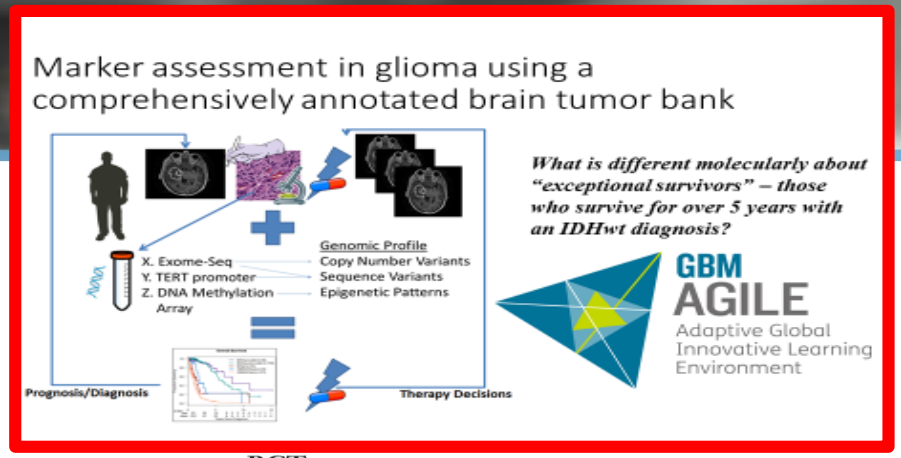


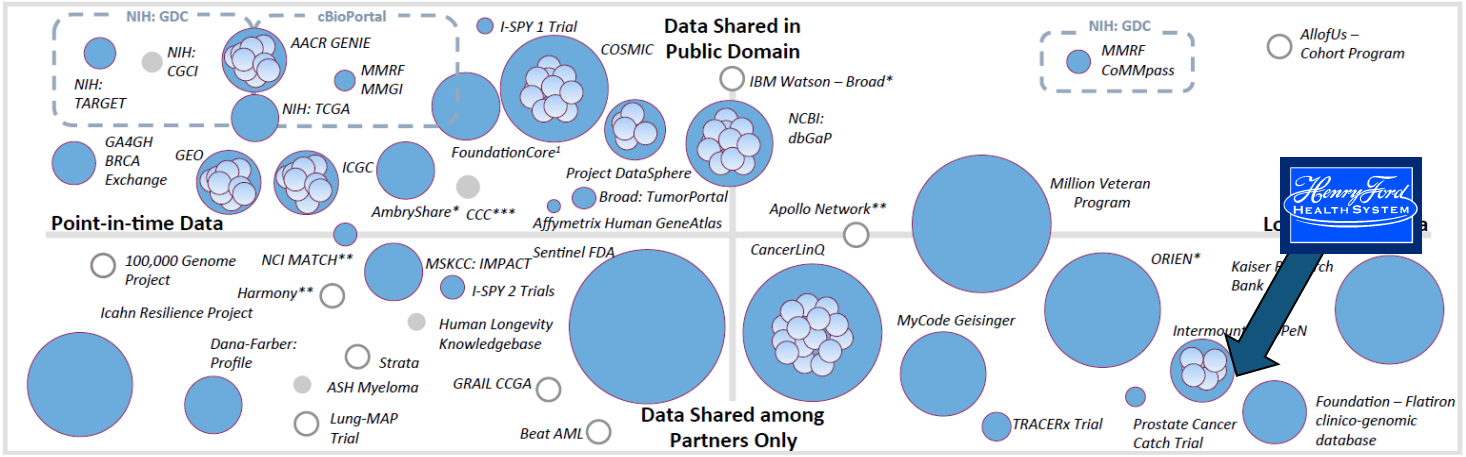
Table 1. Strengths and Weaknesses of RWE and RCTs

Characteristic	RWE	RCTs
Standard of evidence	Complementary to RCT	Gold standard
Cost	Less costly	Costly to develop and conduct
Patient population	Promotes evaluation of patient populations not typically studied in clinical trials; helps verify evidence in real-world patient population	Patient population is well defined within the constraints of specific eligibility criteria; results reflect outcomes in limited population
	Patient data derived from atypical sources, such as insurance claims and disease databases	Requires substantial number of patients to identify differences between treatments
Sample size	Enormous sample size possible (big data)	Limited sample size; prior knowledge required for sample-size calculation
Efficacy	More chances for data bias and residual confounding because true randomization and blinding not possible	Minimizes the risk for data bias and confounding because randomization and blinding possible
Toxicity	Helps uncover important toxicity signals that require long follow-up	Only acute and common toxicities are revealed
Approval of new therapies	Not suitable for approving interventions but helpful to validate RCT findings	Considered the gold standard necessary for new drug approval
Role in precision oncology	Can reveal some important target-drug combinations for later testing in an RCT	Helpful to definitively test the target-drug combinations identified through RWE
	Can encourage drug-repurposing efforts in precision oncology[25]	

Bishal Gyawali, Sandeep Parsad, Bruce A. Feinberg, and Chadi Nabhan
JCO Precision Oncology 2017:1, 1-5

Data Sharing

Oncology Precision Medicine Data Landscape



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

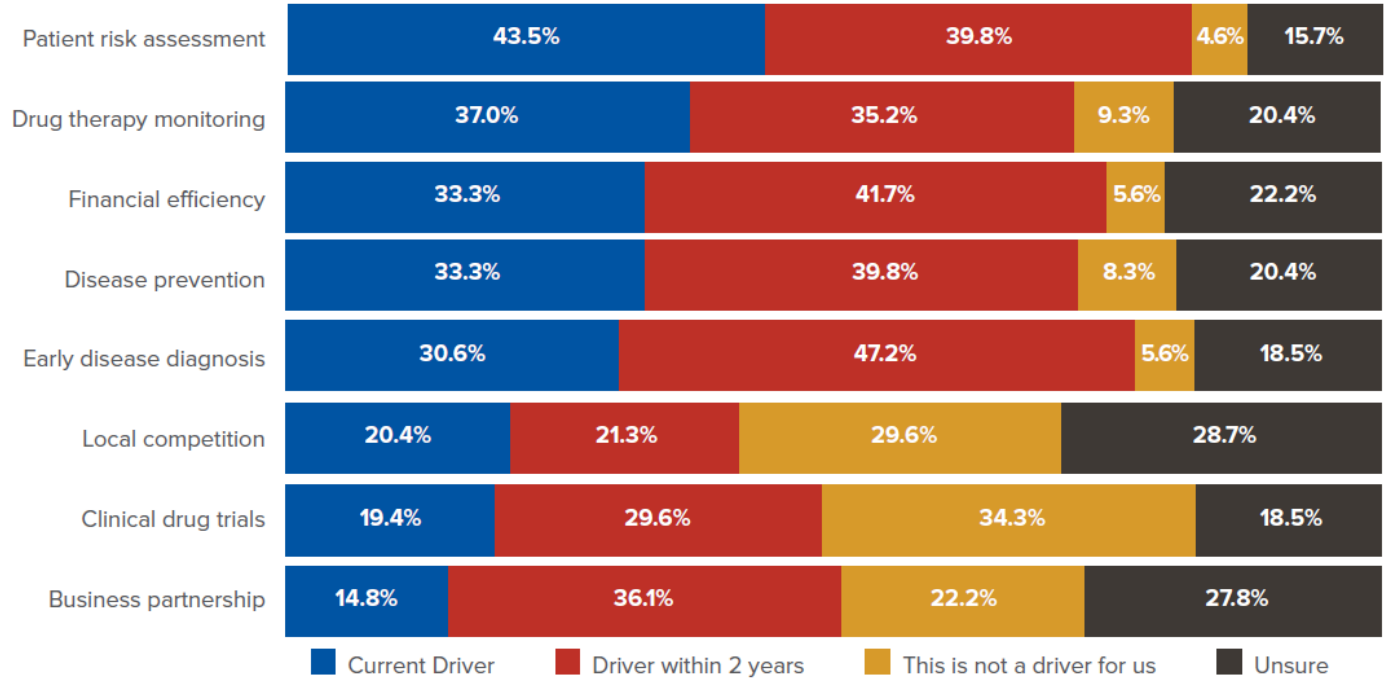
1. FoundationCore's pediatric cancer data has been made public

Henry Ford Health System
Henry Ford Cancer Institute

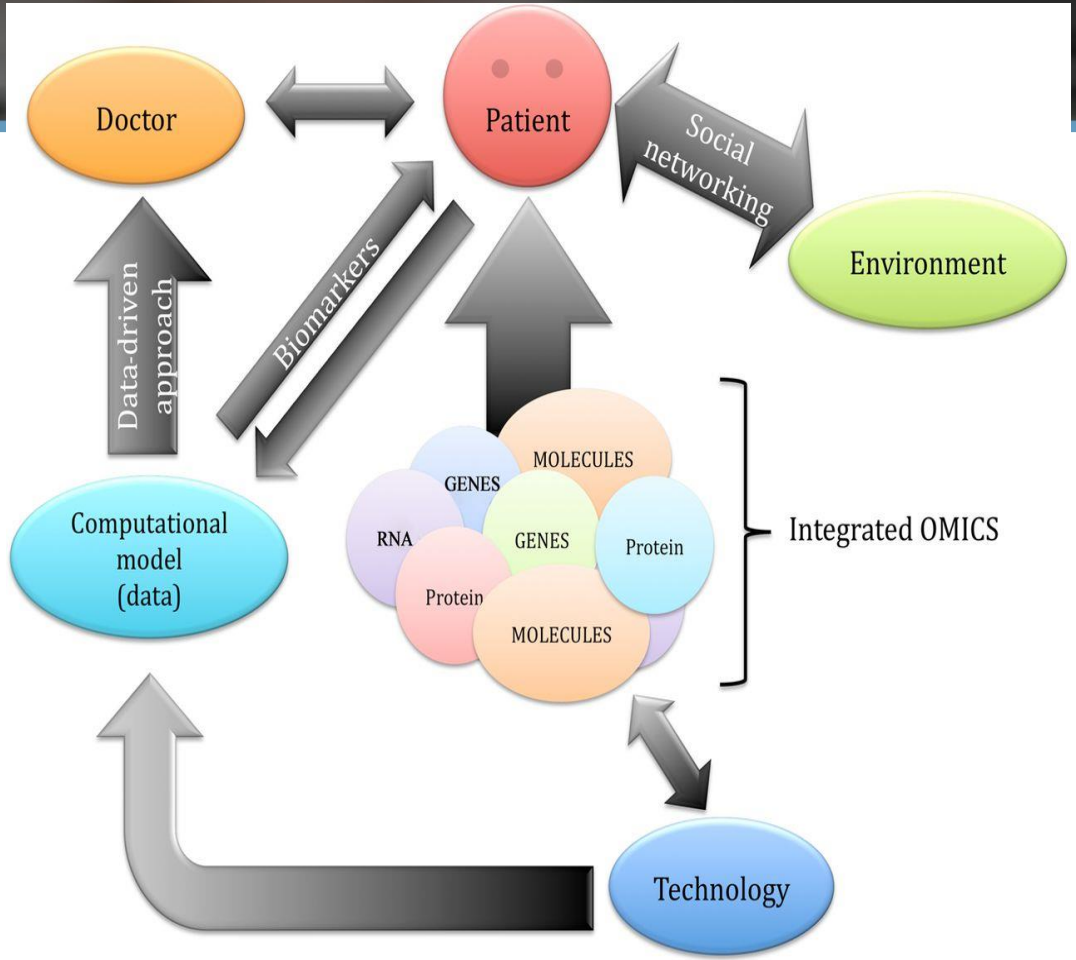
Harvard Business School
Kraft Precision Medicine Accelerator

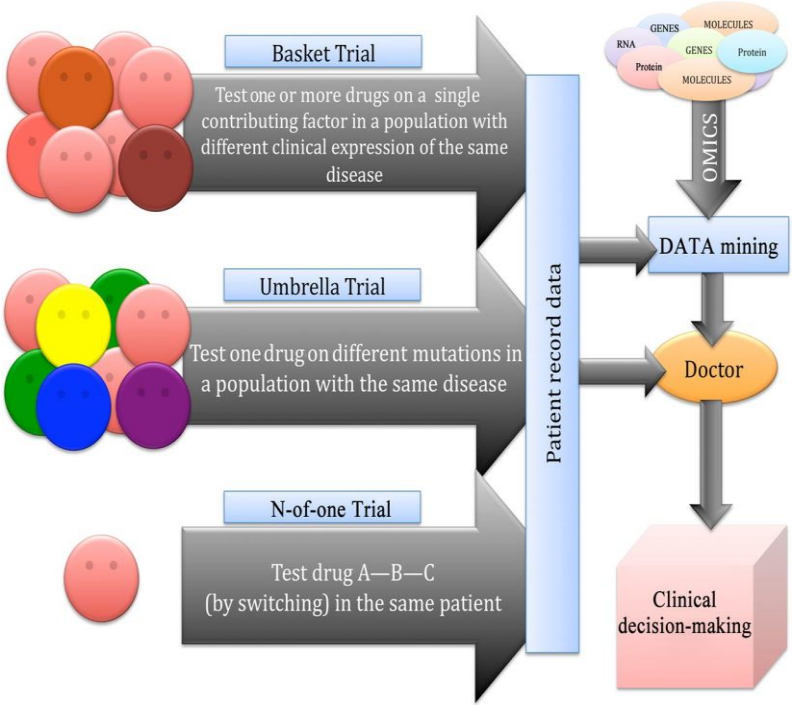
http://www.hbs.edu/healthcare/Documents/KPMA/Precision%20Medicine%20Data%20Landscape_011617_Web.pdf

Drivers for Precision Medicine



Source- HIMSS 2017 Precision Medicine survey of Healthcare organizations





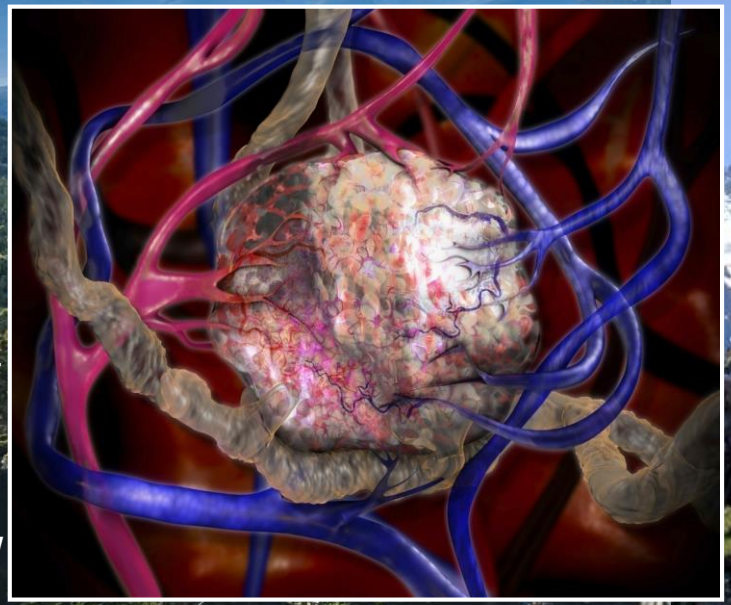
Carmine Savoia et al. Clin. Sci. 2017;131:2671-2685

What have we learned from genomic profiling?

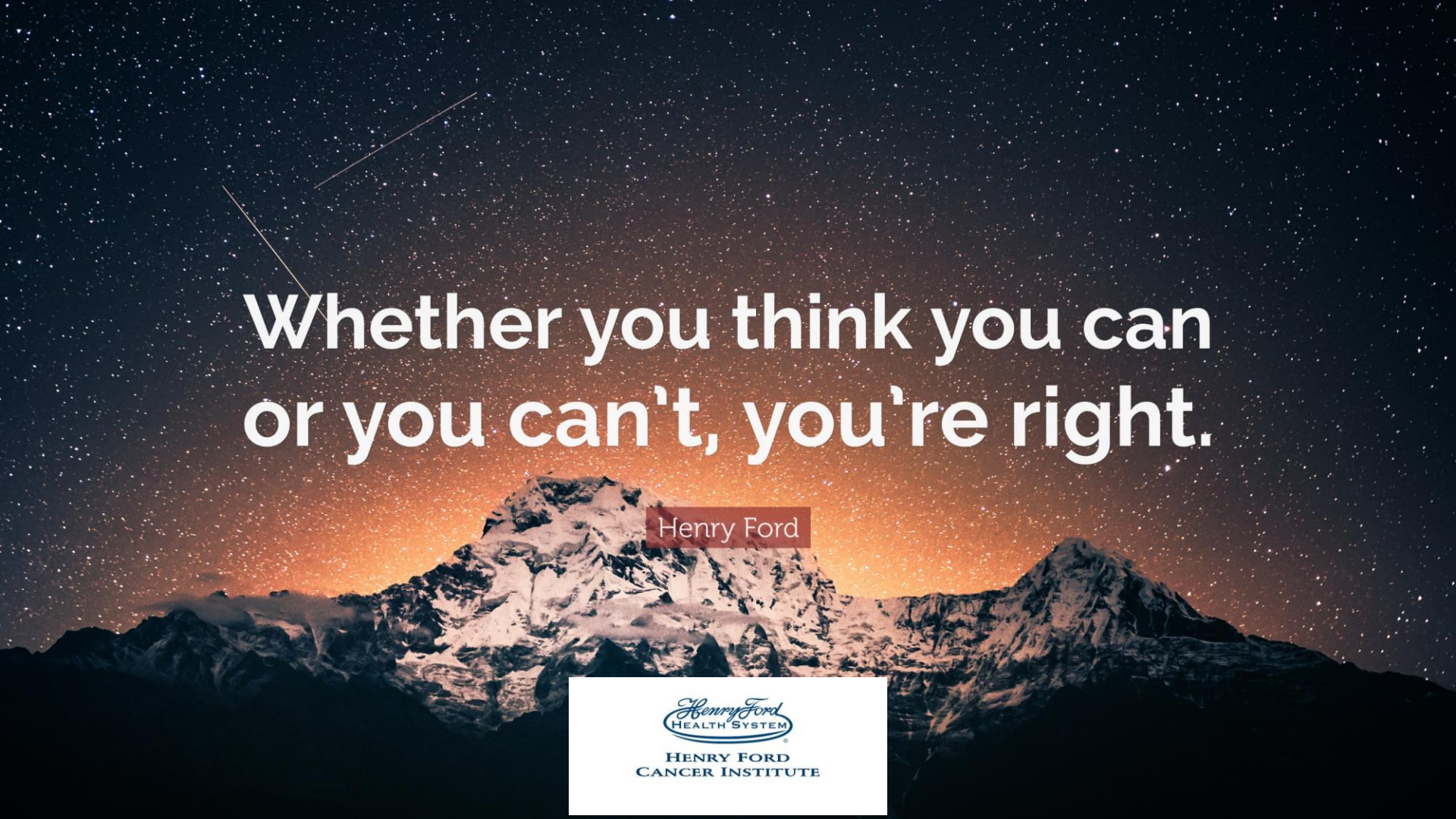
- We are 99.9% identical at DNA level
- But… every one of us is unique.
- If we print DNA sequence … that is 3 billion bases in a haploid genome of your entire genetic code
  - would occupy some 262,000 pages, or 175 large books!
  - ***only about 500 pages would be unique to us***

Going From the Trail to the Summit in Precision Medicine

- Massive Data Storage
- Unprecedented data analytics
- Point of care data interpretation via global bioinformatic crowdsourcing
- Explosion in new targeted drugs



What you think is the summit is only the next step up…



Henry Ford Health System

Henry Ford Cancer Institute

Questions

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