Precision Medicine in an Era of Value Based Medicine

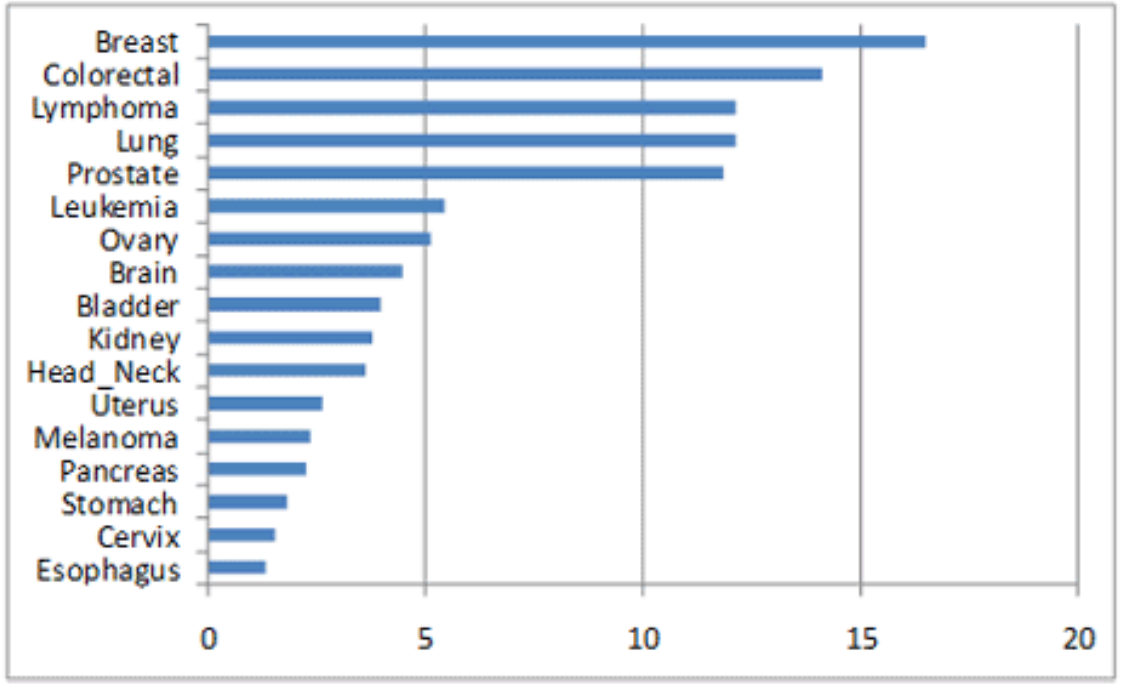

Vincent Chung, MD, FACP
City of Hope
August 12, 2018

Objectives

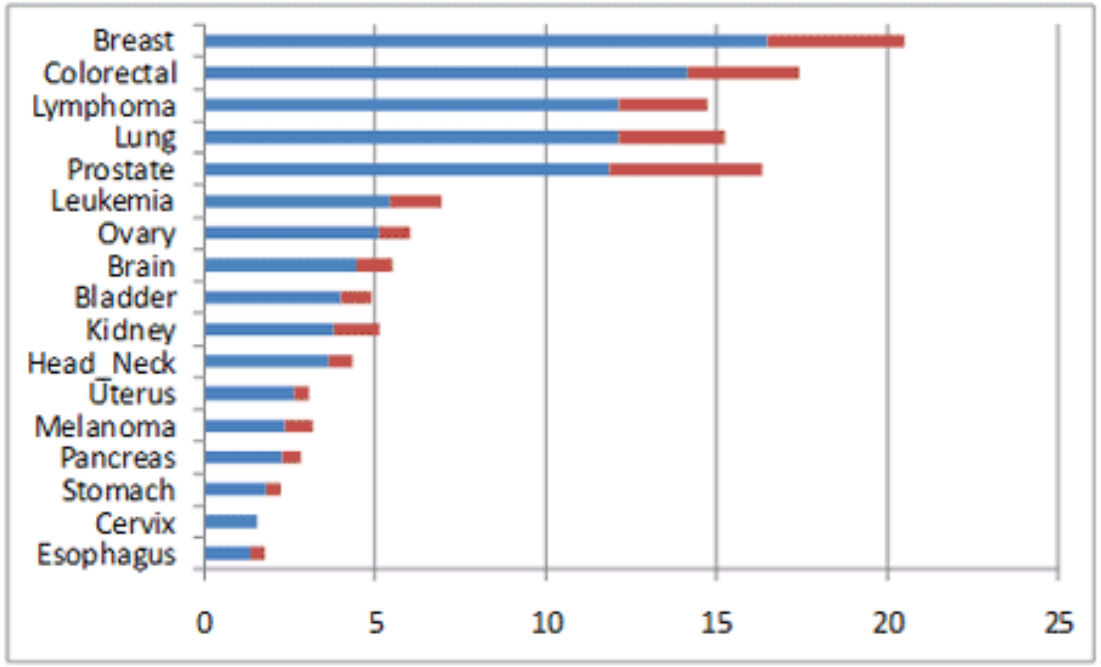
- Promise of precision medicine
- Challenges
- On-going precision medicine projects
- Innovations

National Expenditures for Cancer Care Projected to Increase by at Least 27% Between 2010 to 2020 Because of Aging and Growing Population

Total Cancer Expenditure in 2010: $124.57 Billion



Total Cancer Expenditure in 2020: $157.77 Billion

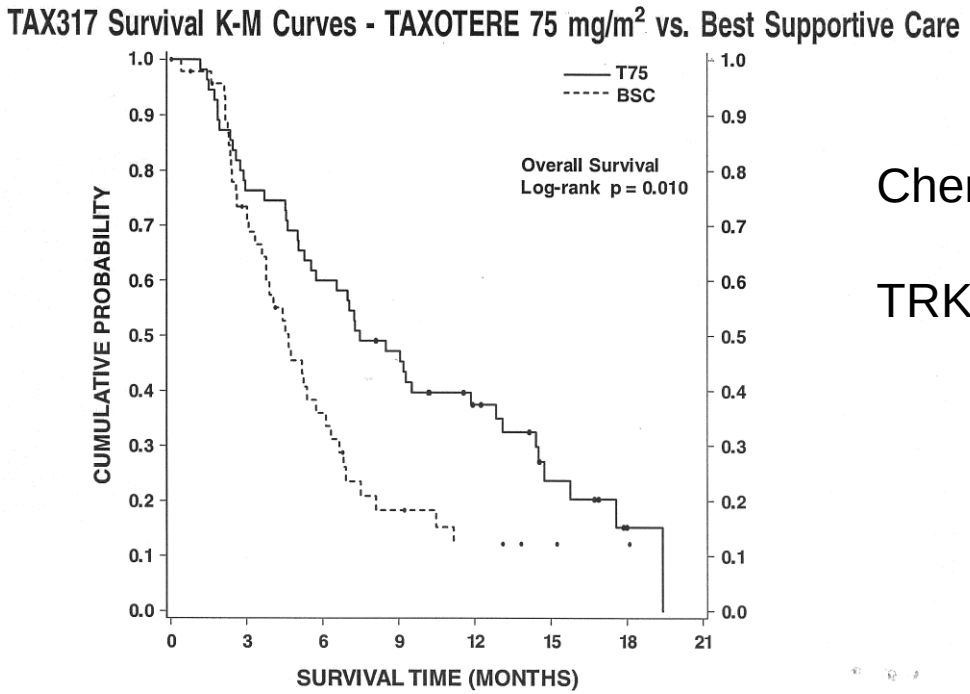


The Promise of Precision Medicine

- With limited health care dollars, we need to improve response rates and survival with our treatments

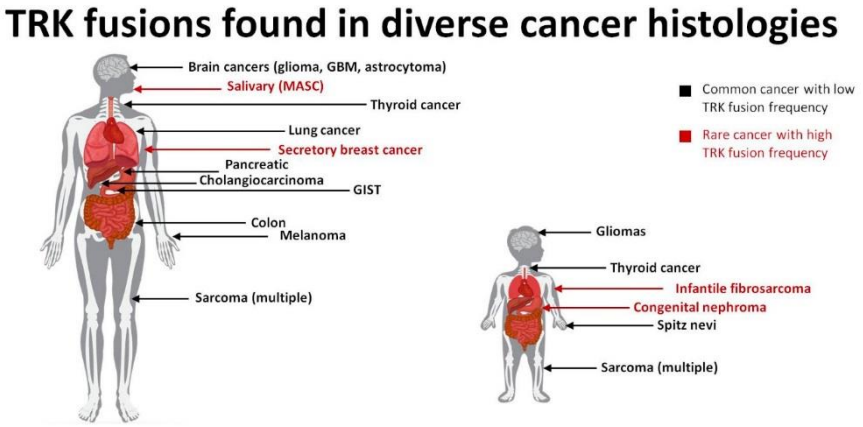
- Tailoring therapy for patients based upon molecular characteristics of the tumor can lead to impressive responses

Shifting treatment paradigms

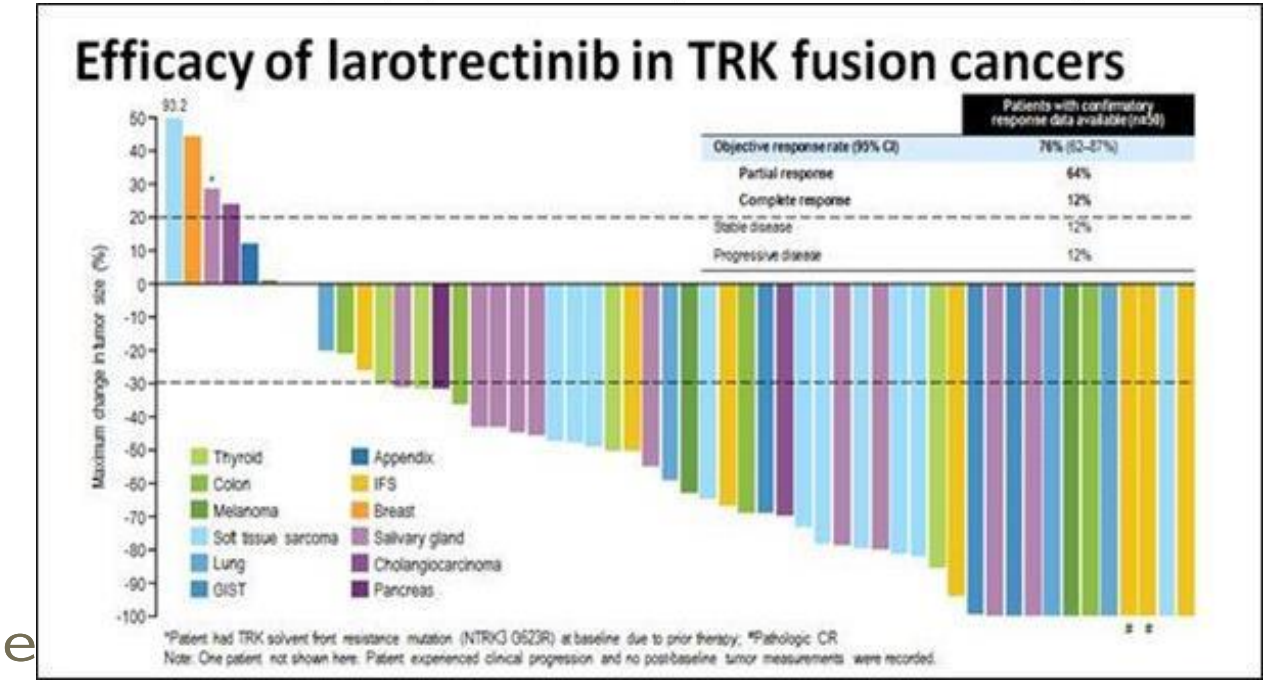


Chemo RR 5%

TRK fusion - RR 78%

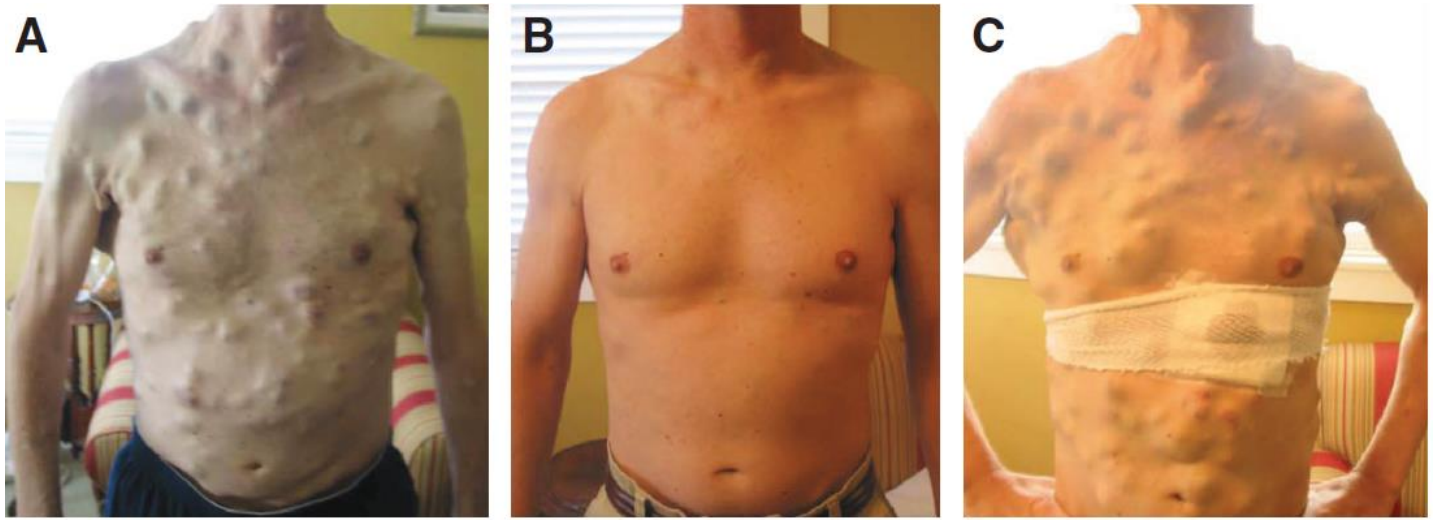


Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

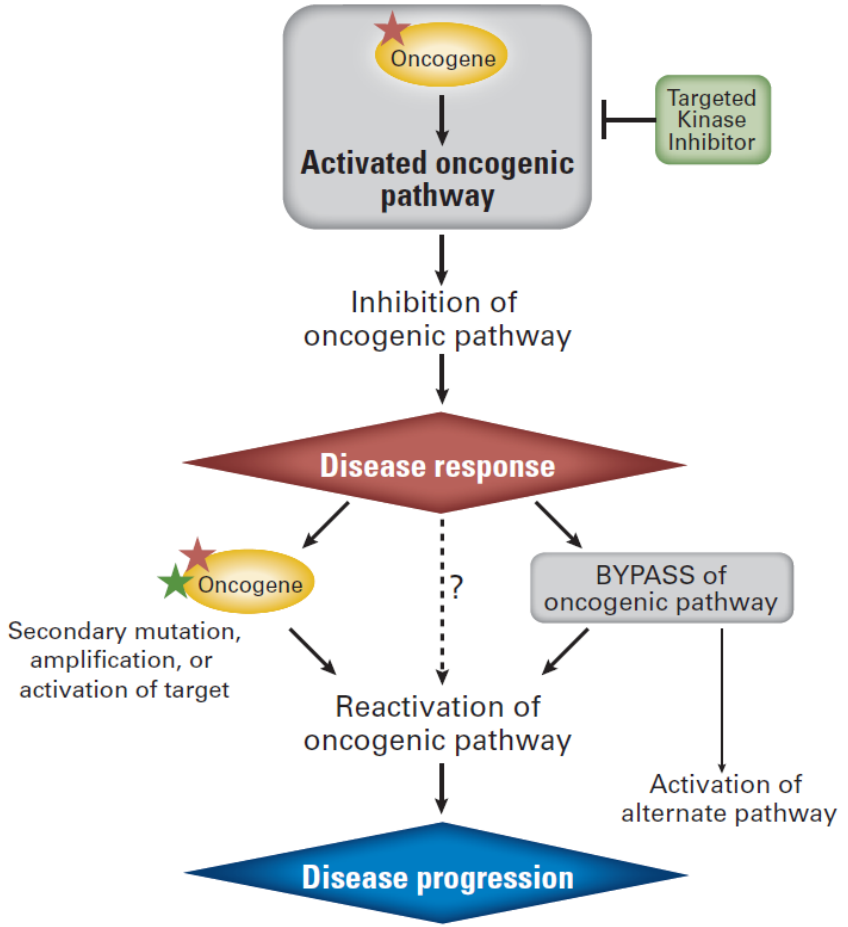


Shepherd FA, et al. JCO 2000
Drilon A, et al. NEJM 2018

Genomic driven therapy can have dramatic results



A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken
(A) before initiation of vemurafenib
(B) after 15 weeks of therapy with vemurafenib
(C) after 23 weeks of therapy.



Wagle, *JCO* (2011), Chapman, *NEJM* (2011)

The Shifting Focus of Clinical Trial Design Towards Precision Medicine

Editorial

Payer View of High-Quality Clinical Pathways for Cancer

Lee N. Newcomer and Jennifer L. Malin

From a payer perspective, the most surprising gap in the ASCO recommendations is the ***failure to recommend adoption of a pathway program by every oncology practice in the United States****. The policy statement is clear: pathways reduce costs while maintaining or improving quality. JOP, 2017*

ASCO Special Article

American Society of Clinical Oncology Criteria for High-Quality Clinical Pathways in Oncology

Robin T. Zon, Stephen B. Edge, Ray D. Page, James N. Frame, Gary H. Lyman, James L. Omel, Dana S. Wollins, Sybil R. Green, and Linda D. Bosserman

Well-designed and effectively implemented ***clinical pathways*** *can be an important tool for improving adherence to evidence-based medicine and reducing* ***unwarranted variation in care****. Clinical pathways also can enhance communication and patient education, serving as a way for oncology providers to share* ***evidence-based information*** *with patients about the complex details of treatment options.*
JOP, 2017

POLICY FORUM

BIOMEDICAL INNOVATION

How economics can shape precision medicines

By **A. D. Stern,[1,2] B. M. Alexander,[3,4] A. Chandra[1,5,6]**

Despite the potential link between the high price of precision medicines and lower access to them, ***establishment of genomic databases and validated biomarkers*** *is expected to* ***decrease the cost of trials and time-to-market*** *by allowing smaller, more focused clinical studies, particularly in the more expensive, later phases of development.*
Science, 2017

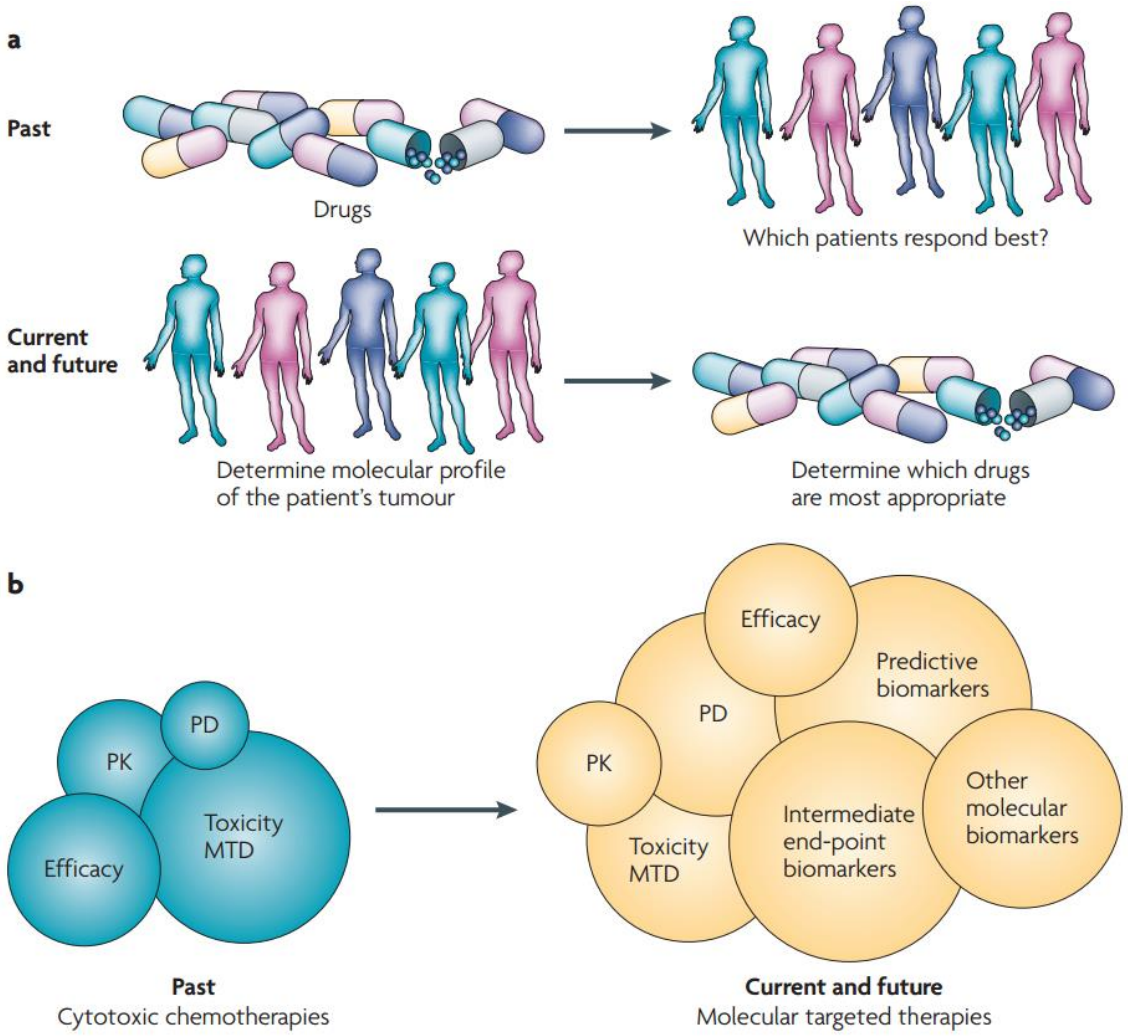
ASCO UNIVERSITY

Value-Based Medicine and Integration of Tumor Biology

Gabriel A. Brooks, MD, MPH; Linda D. Bosserman, MD; Isa Mambetsariev and Ravi Salgia, MD, PhD

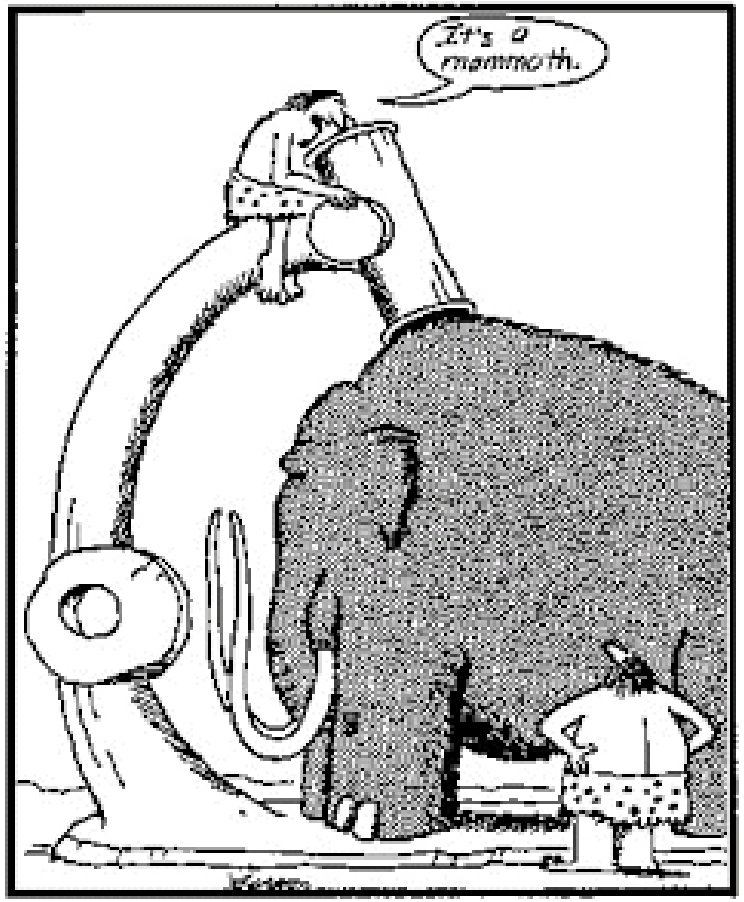
ASCO Ed Book, 2017

If oncologists expect to fully integrate these numerous data points to help guide the best care for each patient, ***clinical systems*** *are needed to prompt for* ***order and collection of discrete data*** *to offer real-time decision support and extractable data for outcome reporting. These systems will need rapid updatability…*



Yap, et al, "Envisioning the future of early anticancer drug development"

What are the challenges of genomic medicine?



Early microscope

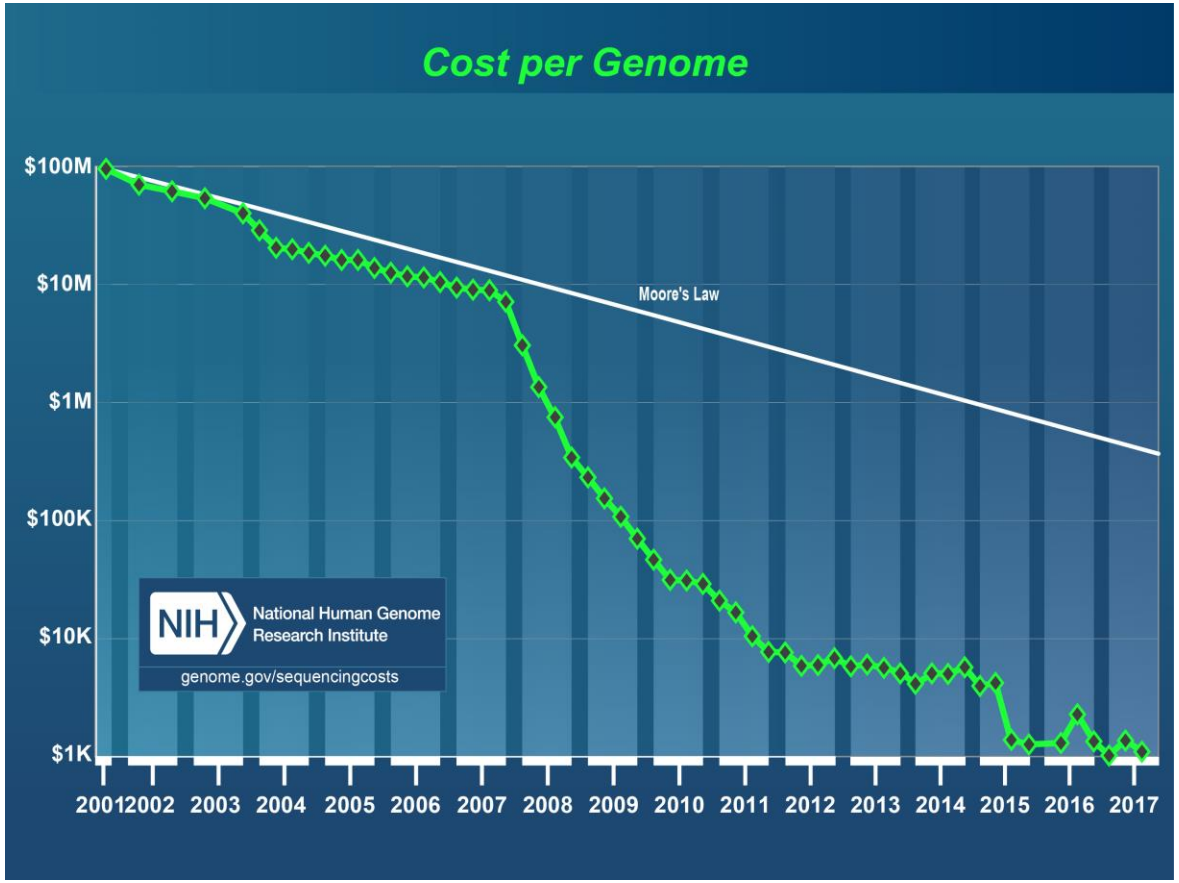
Value of Genomic Testing has to be critically evaluated

Table 2 Costs and Clinical Roles of Tests

Test	Clinical Role	Predictive or Prognostic?	Tumor-Specific or Host-Specific?	Cost	Source
DPD	Predicts 5-FU metabolism	Predictive	Host-specific	$82[a]	CPT code: 81400 http://www.palmettogba.com/Palmetto/Providers.Nsf/files/MoPath_Claims_Submission_Guidelines.pdf/$File/MoPath_Claims_Submission_Guidelines.pdf
UGT1A1*28 polymorphism	Predicts irinotecan metabolism	Predictive	Host-specific	$108	CPT code: 81350 Laboratory and Economics Newsletter http://www.thestreetsweeper.org/ckfinder/userfiles/files/GenPathRateSlashed.pdf
UGT1A1 sequencing	Predicts irinotecan metabolism	Predictive	Host-specific	$875	University of Chicago genetic services
KRAS	Predicts benefit from EGFR-targeted therapies	Predictive	Tumor-specific	$197	CPT code: 81275 Medicare laboratory fee schedule
BRAF	Detection of a *BRAF* mutation indicates sporadic rather than hereditary disease in patients with MSI	Prognostic	Tumor-specific	$179	CPT code: 81210 Medicare laboratory fee schedule
MSI/IHC	Indicates possibility of Lynch syndrome and risk of recurrence	Predictive and prognostic	Tumor-specific	$475	CPT code: 88342 x 4 = $118.79 x 4 (estimated from fairhealthconsumer.org)
MSI/PCR	Indicates possibility of Lynch syndrome and risk of recurrence	Predictive and prognostic	Tumor-specific	$395	CPT code: 81301 Medicare laboratory fee schedule
Oncotype DX	In stage II disease, helps guide decision making regarding adjuvant therapy	Prognostic	Tumor-specific	$3,640	Alberts et al. 2014[73]
ColoPrint	In stage II disease, helps guide decision making regarding adjuvant therapy	Prognostic	Tumor-specific	$4,000	Personal communication with Agendia
FoundationOne	Identifies targetable mutations via NGS	Predictive	Tumor-specific	$5,800	Personal communication with Foundation Medicine
Molecular Intelligence Profile	Identifies targetable mutations via NGS	Predictive	Tumor-specific	$5,500	Personal communication with Caris Life Sciences

[a]For DPD test that assesses for mutations in the *DPYD* gene: IVS14 + 1G > A

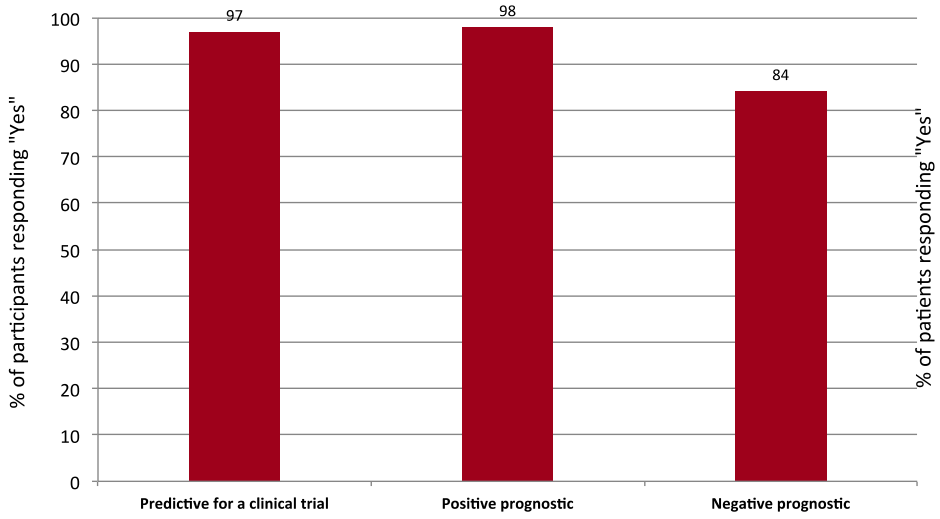
5-FU = fluorouracil; DPD = dihydropyrimidine dehydrogenase; EGFR = epidermal growth factor receptor; IHC = immunohistochemistry; MSI = microsatellite instability; NGS = next-generation sequencing; PCR = polymerase chain reaction; UGT1A1 = 5'-diphospho-glucuronosyltransferase.



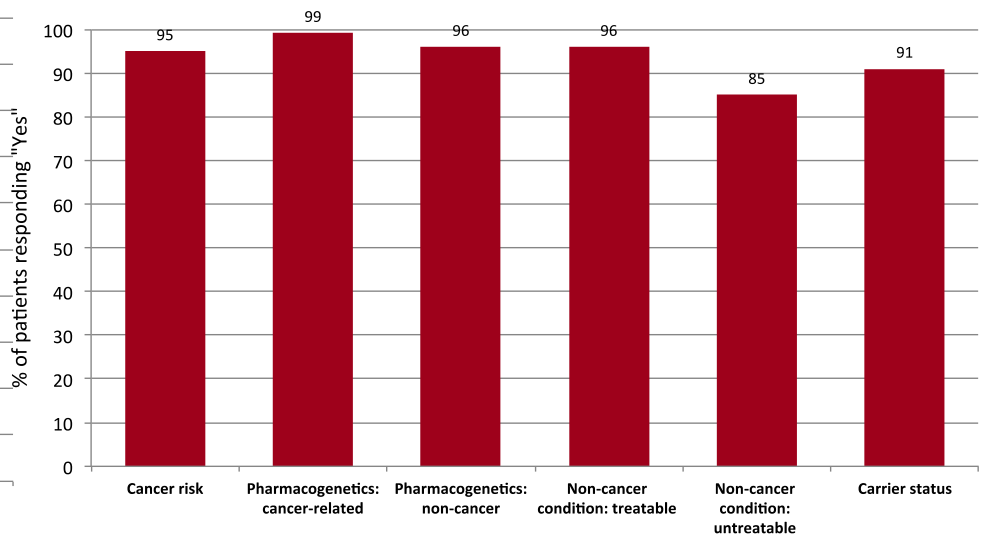
Goldstein, et al, Oncology, 2015

Most patients want their genomic information

Somatic Results



Germline Results



Dana-Farber, MD Anderson and Memorial Sloan Kettering studies:

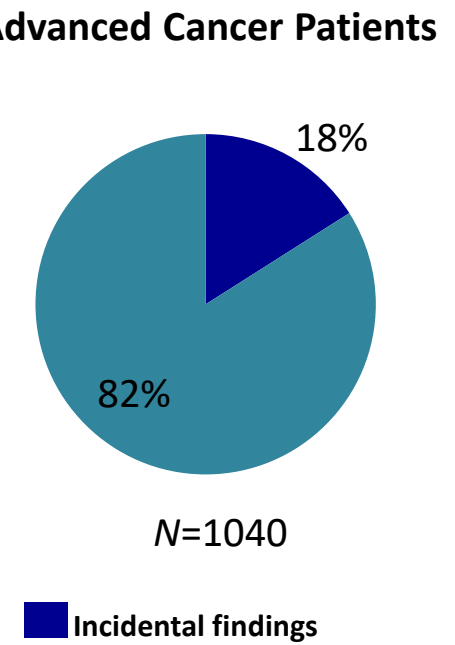
- Most patients want genomic results 57%-99%

Gray, *Genet Med* (2016); Meric-Bernstam, ASCO 2015 (Abstract 1510)
Hamilton, *JOP* (2017)

Incidental findings are common in cancer patients

Somatic panels can reveal unexpected germline results

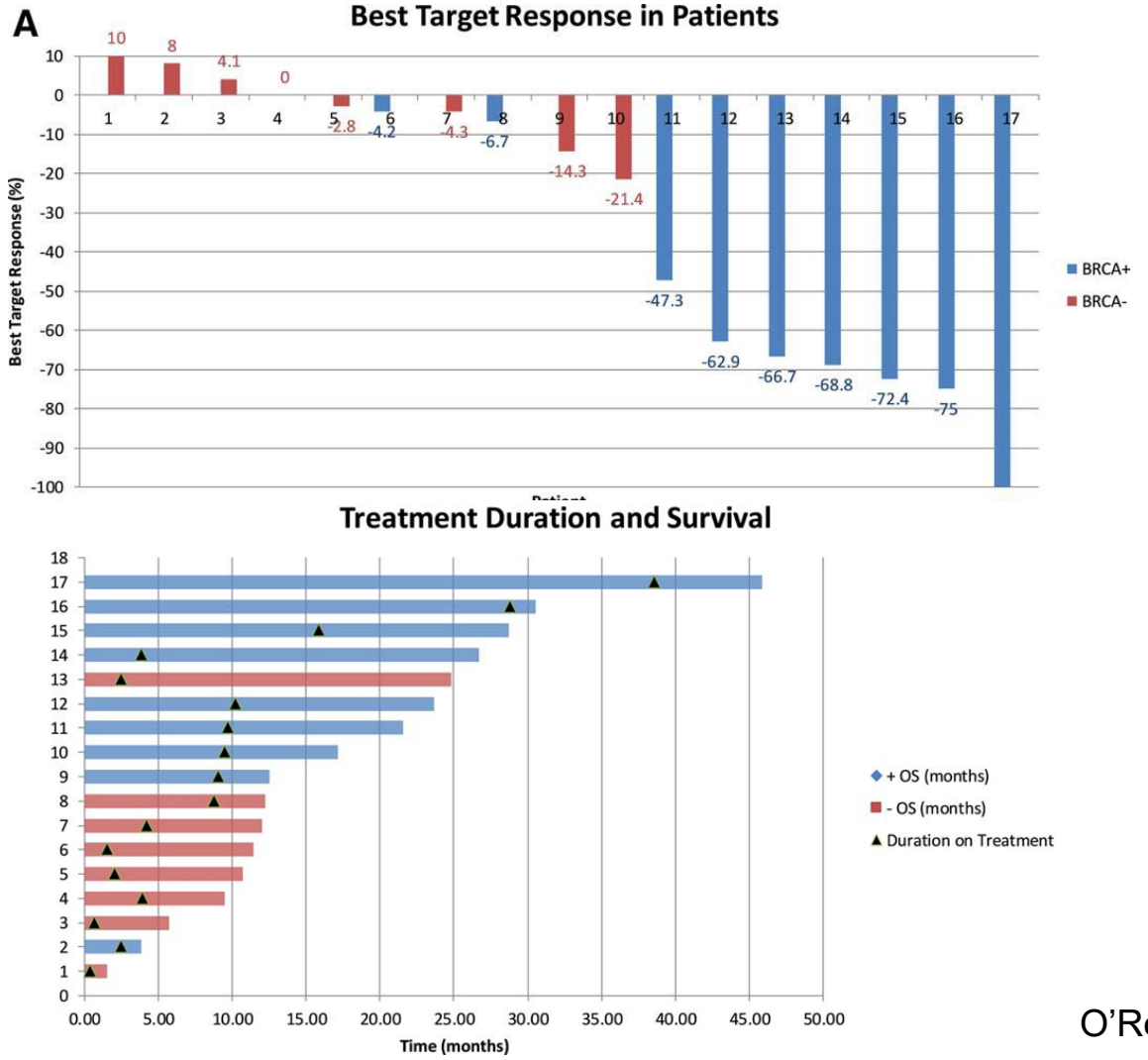
APC	NF2	SDHC
BRCA 1	NTRK 1	SDHD
BRCA 2	PMS 2	STK11
MEN 1	PTEN	TP53
MLH 1	RB1	TSC1
MSH 2	RET	TSC2
MSH 6	SDHAF2	VHL
MUTYH	SDHB	WT1



- Approximately 1.7 million cases of cancer each year therefore
  - Up to 269,000 cancer patients with incidental findings each year

Amendola *et al*.,(2015, *Genome Res*); Parsons et al. 2016 (*JAMA Onc*)
Zhang *et al*., *NEJM* (2015); Schrader *et al*., 2016 (*JAMA Onc*);
Mandelker et al, JAMA (2017); Gray ASCO 2015 (Abstract 1510)

Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma



Gemcitabine 600 mg/m^2 and cisplatin 25 mg/m^2 on days 3 and 10 of a 21-day cycle

Veliparib given orally twice daily on days 1 to 12

Continuous dosing of veliparib resulted in grade 4 neutropenia and thrombocytopenia (DLT's)

O'Reilly EM, et al. Cancer. 2018 Apr 1;124(7):1374-1382.

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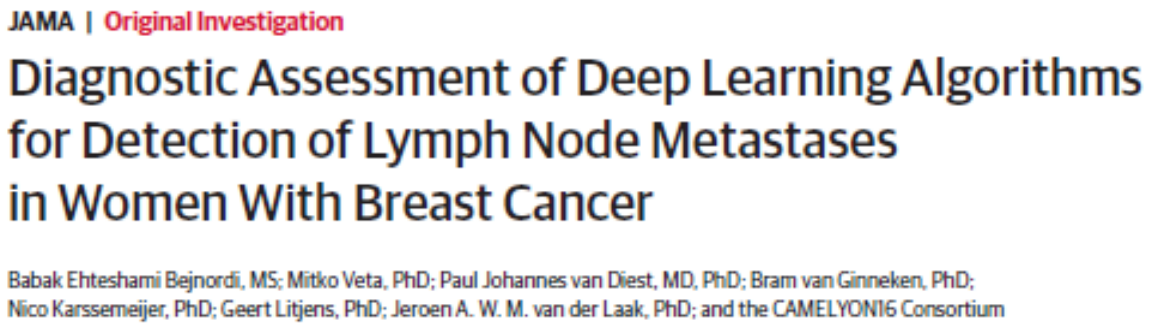
Challenges of genomic medicine

- Most patients don't have actionable mutations
- Limitations in knowledge/ insufficient evidence
- Flaws in interpretation
  - Both providers and patients
  - Lack of understanding about how to advance new knowledge into general care
- Need for molecular tumor boards

- Future of artificial intelligence in medicine


JAMA | Original Investigation

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS; Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssemeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium

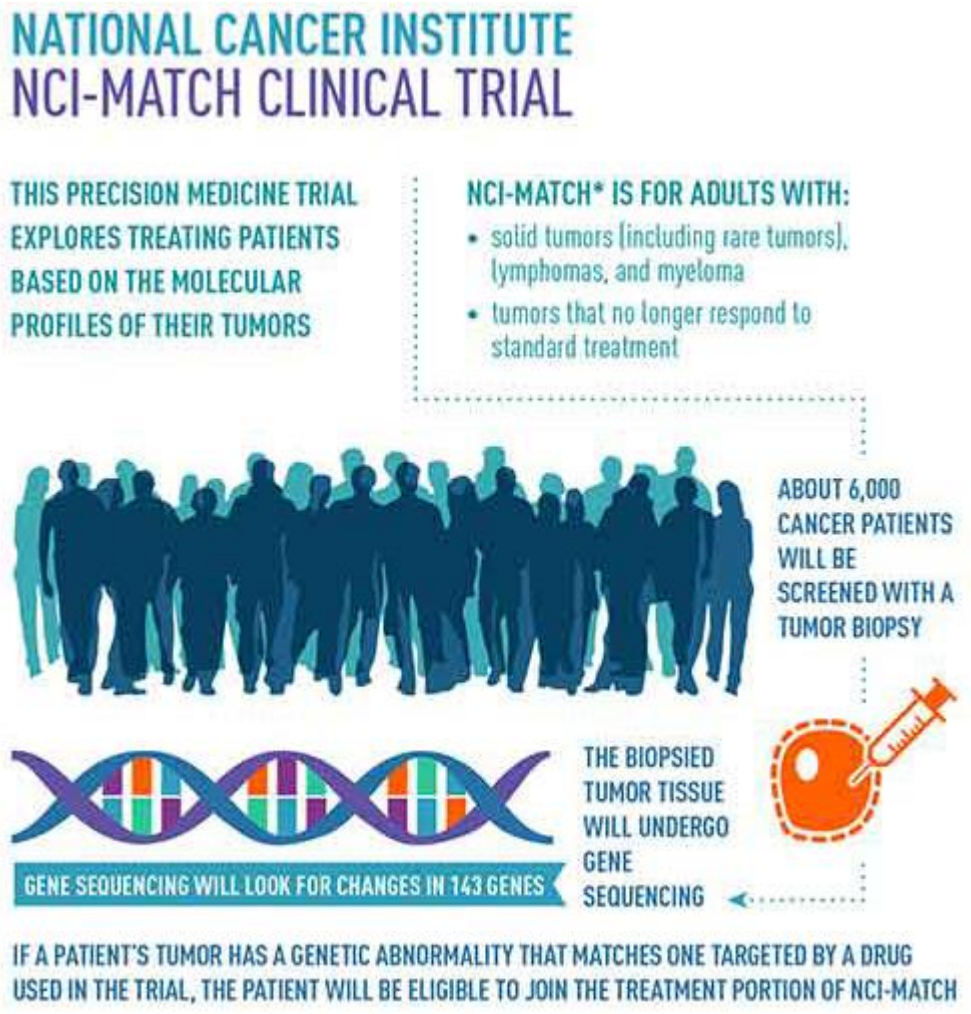
- Caution
  - Programming the algorithms may also inherit our biases
  - Training sets lack diversity.

Institute of Medicine (2001), McNiff *JOP* (2014), Abernethy, *JCO*, 2010

How do we achieve success with precision medicine?

- Mutations are rare
- Need available trials to accrue patients
- Robust biomarker analysis

Precision Medicine Trials



- Afatinib - EGFR
- Crizotinib - MET amp, MET ex 14 sk, ALK, ROS1
- AZD9291 - EGFR T790M
- Trastuzumab and Pertuzumab - HER2 amp
- TAK-228 - mTOR
- TAK-228 - TSC1 or TSC2
- Trametinib - GNAQ/GNA11
- Vismodegib - SMO/PTCH1
- Sunitinib - cKIT mut
- Larotrectinib - NTRK fusions
- AZD1775 - BRCA1 or BRCA2

TAPUR
American Society of Clinical Oncology
Targeted Agent and Profiling Utilization Registry Study

- Axitinib - VEGFR
- Bosutinib – Bcr-abl, SRC, LYN, LCK
- Crizotinib – ALK, ROS1, MET
- Palbociclib – CDKN2A, CDK4, CDK6
- Sunitinib – CSF1R, PDGFR, VEGFR
- Temsirolimus – mTOR, TSC
- Trastuzumab and Pertuzumab – ERBB2
- Vemurafenib and Cobimetinib – BRAF V600E
- Cetuximab – KRAS, NRAS, BRAF
- Dasatinib - Bcr-abl, SRC, KIT, PDGFRB, EPHA2, FYN, LCK, YES1
- Regorafenib – RET, VEGF1/2/3, KIT, PDGFRB, RAF-1, BRAF
- Olaparib – BRCA1/2, ATM
- Pembrolizumab – POLE/POLD1, high TMB
- Nivolumab and Ipilimumab – MSI high, high TMB

Industry Sponsored Precision Medicine Trials

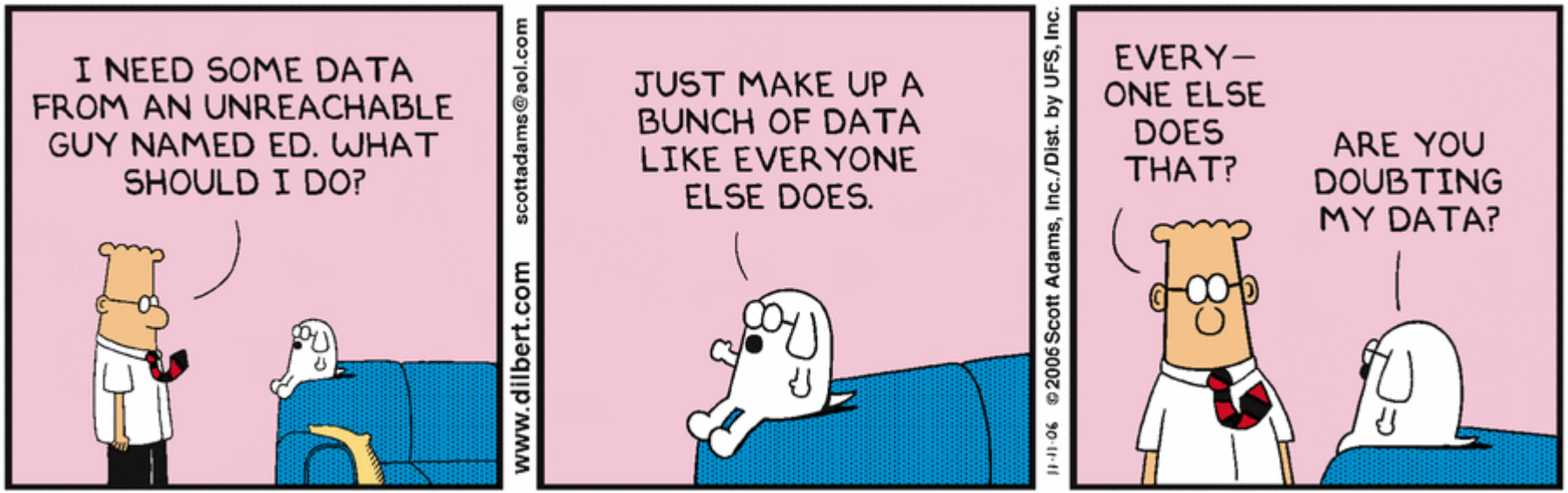
- My Pathway (NCT02091141) – Genentech
  - HER2 overexpression or amplification
  - EGFR-activating mutations
  - BRAF V600 mutations
  - Activating mutation of smoothened [SMO] or loss-of-function mutation of protein patched homolog-1 [PTCH-1]
  - ALK gene rearrangements, ALK mutations, ALK copy number gain
  - PD-L1 copy number gain/amplification, deficiency in mismatch repair enzymes (dMMR), high levels of microsatellite instability (MSI-H) or elevated tumor mutational burden (TMB >=10 mutations/ MB).

- Signature Trial – Novartis
  - Trial is opened when a patient is identified

“Phenotype to Genotype” trial

- The “Exceptional Responders” study
  - NCI will collect up to 300 samples to successfully analyze 100 cases
  - As of November 21, 2017, the Exceptional Responders study accrual goals have been met, and the study is now closed to accrual
  - Discover molecular features in the tumors that may predict benefit to a particular drug or type of drug
  - The molecular and clinical information (de-identified) will be placed into a large database and shared with other approved researchers so that they can help determine why the patient(s) had such an exceptional response

Building for the future



ORIEN

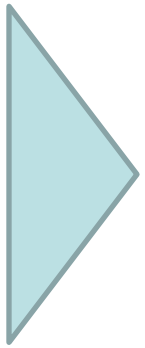
ONCOLOGY RESEARCH INFORMATION EXCHANGE NETWORK℠

Mission: Accelerating cancer discovery and delivering hope through collaborative learning and partnerships.

Meeting the Challenges of Therapy Development and Clinical Trials

Challenges:

- Trials are too slow and costly
- Individual patients identified for trial at time of need
- High ratio of screening to actual enrollment
- Costs of bringing a drug to market estimated to be $2.6 billion[1] and take 10 – 15 years[2]
- Patients with aggressive disease often have narrow “trial matching window”, making enrollment especially challenging



ORIEN Solution:

- Enroll ***high volume of patients*** in Total Cancer Care (TCC) Protocol through ORIEN
- ***Anticipate need*** of patients enrolled in TCC by understanding patients clinical and molecular properties
- Follow TCC consented patients over time and ***track disease progression/recurrence***
- ***Proactively Identify patients*** that are appropriate for target-based trial
- ***Rapid accrual, less cost, meeting patient need***

(1) Tufts Center for the Study of Drug Development
(2) PhRMA

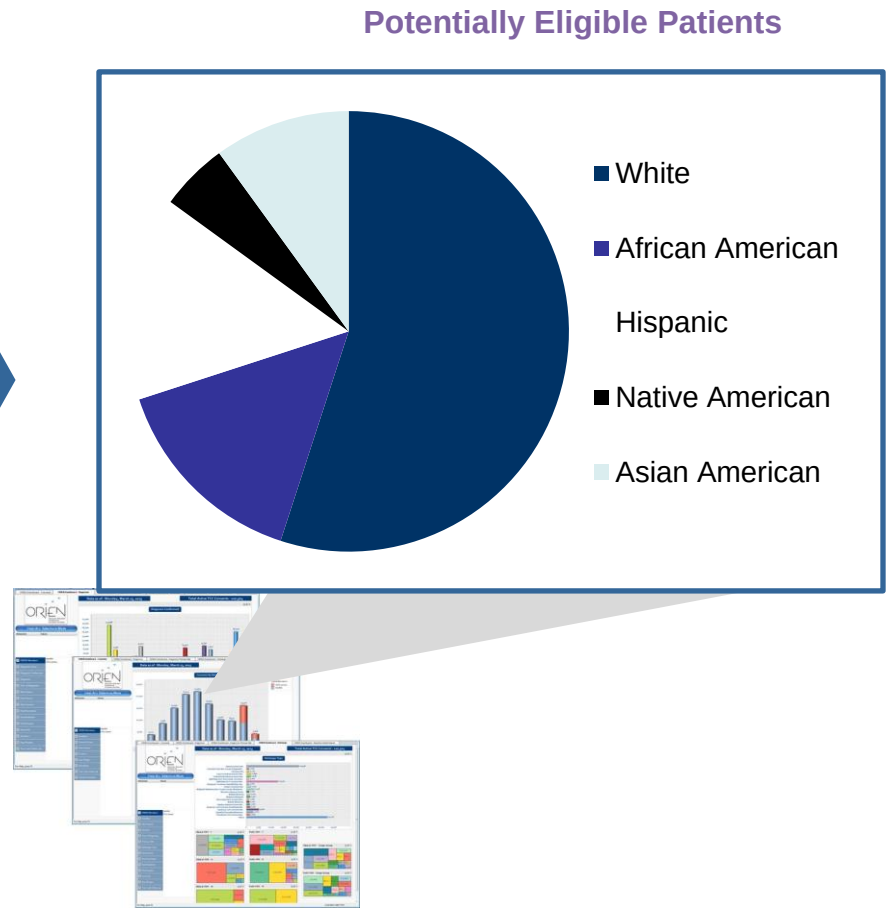
NCI-MATCH: In Silico Identification of Patients

Using ORIEN Avatar, your team can query the database for patients meeting inclusion/exclusion criteria for the trial…

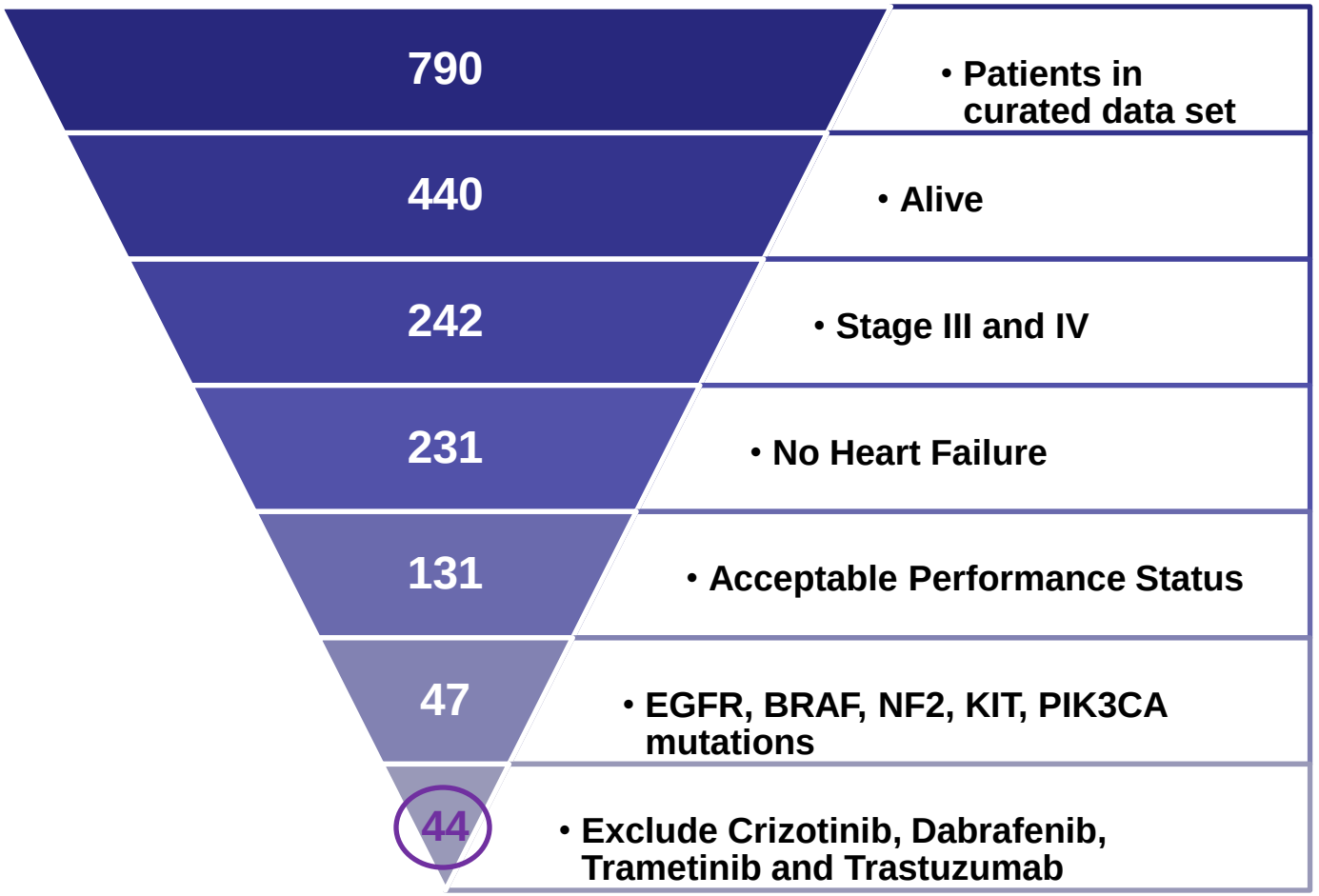
Clinical Criteria
▪ Histologic or cytologic confirmation of advanced, unresectable or metastatic solid tumors ▪ ECOG ≤ 1 ▪ **NO** Heart Failure

Molecular Criteria
▪ EGFR, BRAF, NF2, KIT, or PIK3CA mutation

…in order to identify potentially eligible patients.



NCI-MATCH: Summary of Query Results



AACR
American Association for Cancer Research®

FINDING CURES TOGETHER®

PROJECT GENIE®

Genomics **E**vidence **N**eoplasia **I**nformation **E**xchange

- Dana-Farber Cancer Institute
- Institut Gustave Roussy, France
- Memorial Sloan Kettering Cancer Center
- The Netherlands Cancer Institute on behalf of the Center for Personalized Cancer Treatment, The Netherlands
- Princess Margaret Cancer Centre, Canada
- Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland
- University of Texas MD Anderson Cancer Center
- Vanderbilt-Ingram Cancer Center

To confirm or refute that mutation X or mutations X, Y, and Z predict patient response to drug A or that the patient's disease is likely to do better or worse over time.

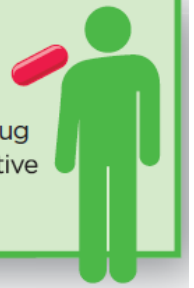
Drug B is approved for patients with mutation Y1. The GENIE registry indicates that patients with mutation Y2 can also be successfully treated with drug B.

Drug C is approved for lung cancer patients with mutation W. The GENIE registry indicates that many blood cancers, colorectal cancers, and stomach cancers also have mutation W.

- Novel disease-causing proteins could be identified and become new drug targets.
- Novel mutation signatures could be uncovered that predict drug sensitivity or patient outcomes.

New clinical trial(s) are opened to test drug C in blood, colorectal, and stomach cancers.

Enough blood, colorectal, or stomach cancer patients in the GENIE data set have already been treated with drug C, showing that it is an effective treatment for these patients.

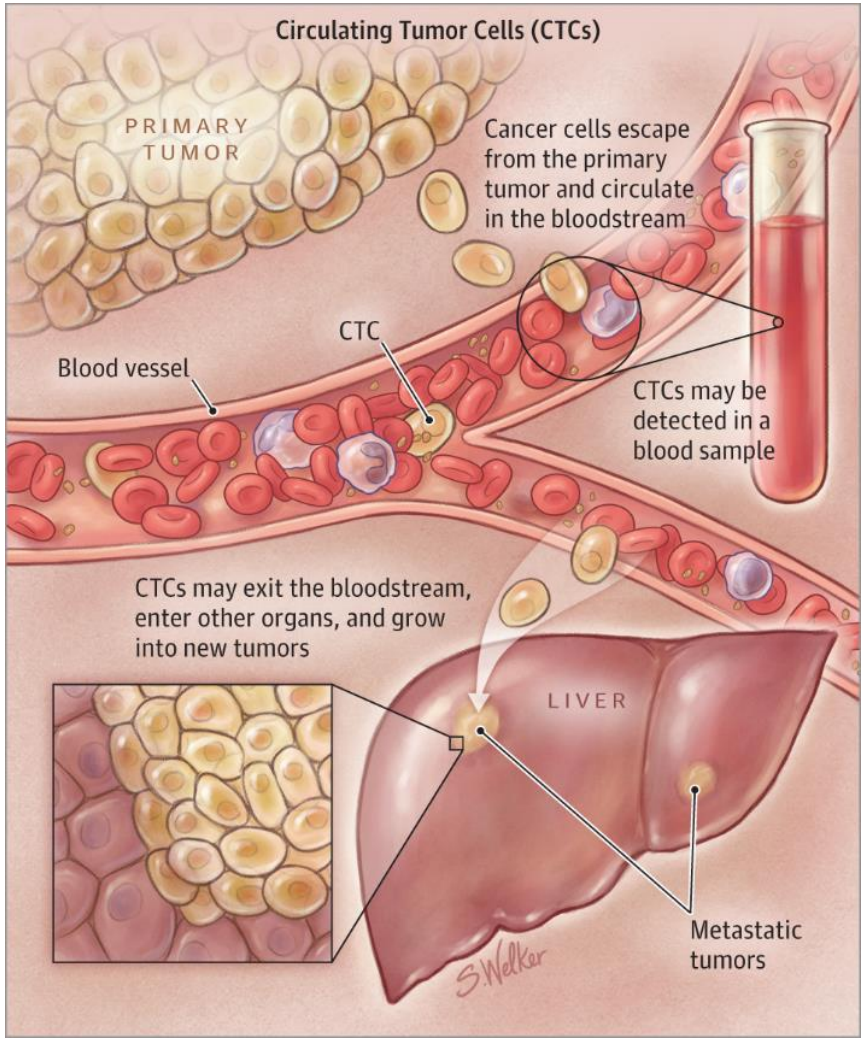


The GENIE registry could provide the evidence necessary to support reimbursement for next-generation sequencing by payers, opening this technology to all patients.

Lessons learned from the assembly and operation of GENIE could benefit other global consortia and vice versa.

the MIRACLE

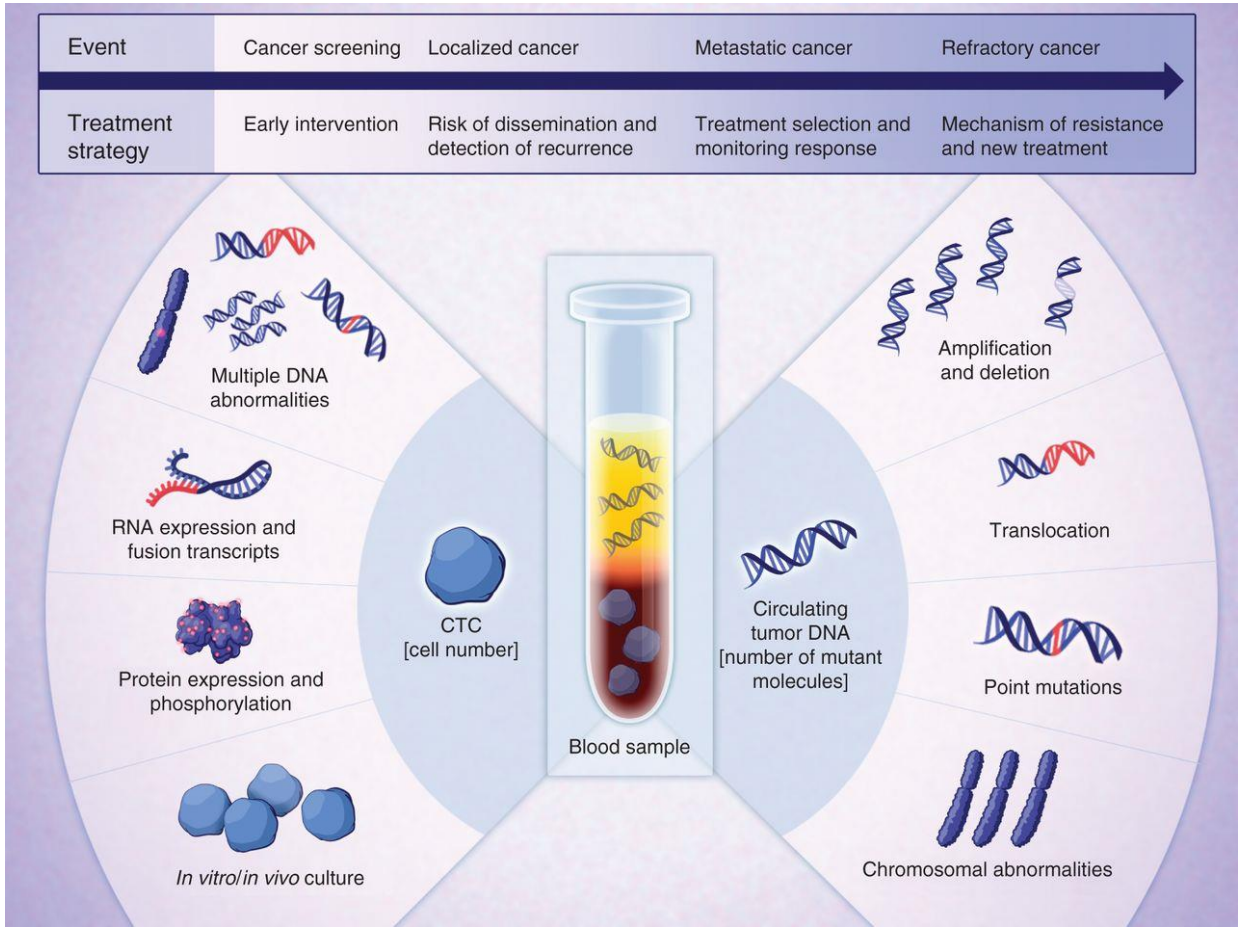
Liquid Biopsies



- EGFR-mutated lung cancer - monitoring treatment response through liquid or tumor biopsies is considered standard of care
  - Appearance of the EGFR T790M mutation prompts the switching of therapies to osimertinib

West H, Jin JO. Circulating Tumor Cells. JAMA Oncol. 2015;1(3):394.

Liquid Biopsies

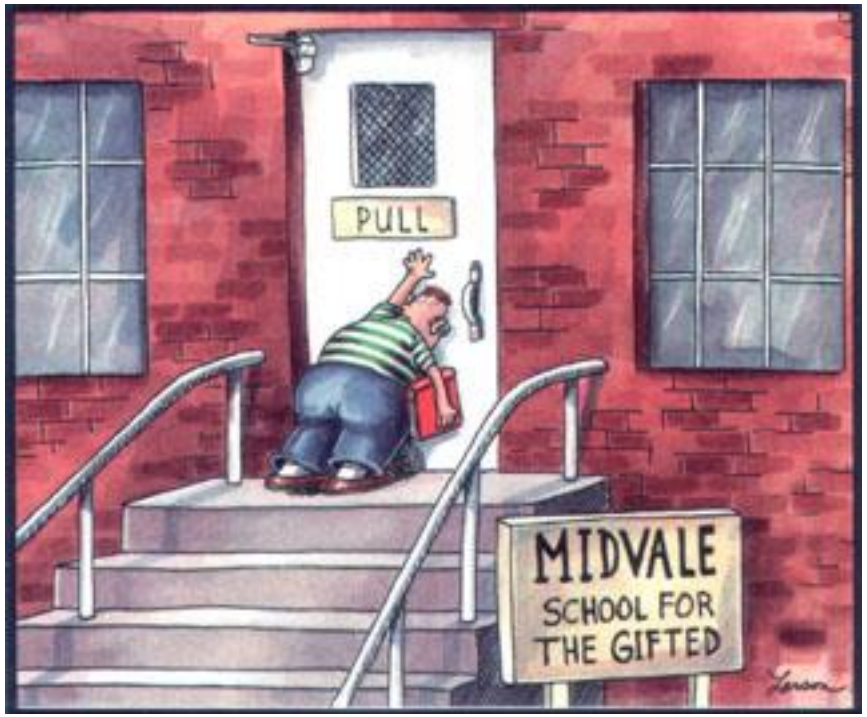


- Serial samples can be obtained
  - Safe
  - Non-invasive
- Profile tumor landscape as tumor is shed into the bloodstream
- A negative liquid biopsy is not considered actionable – need to obtain tumor tissue

Haber DA and Velculescu VE, (2014) Cancer Discov 4:650-661

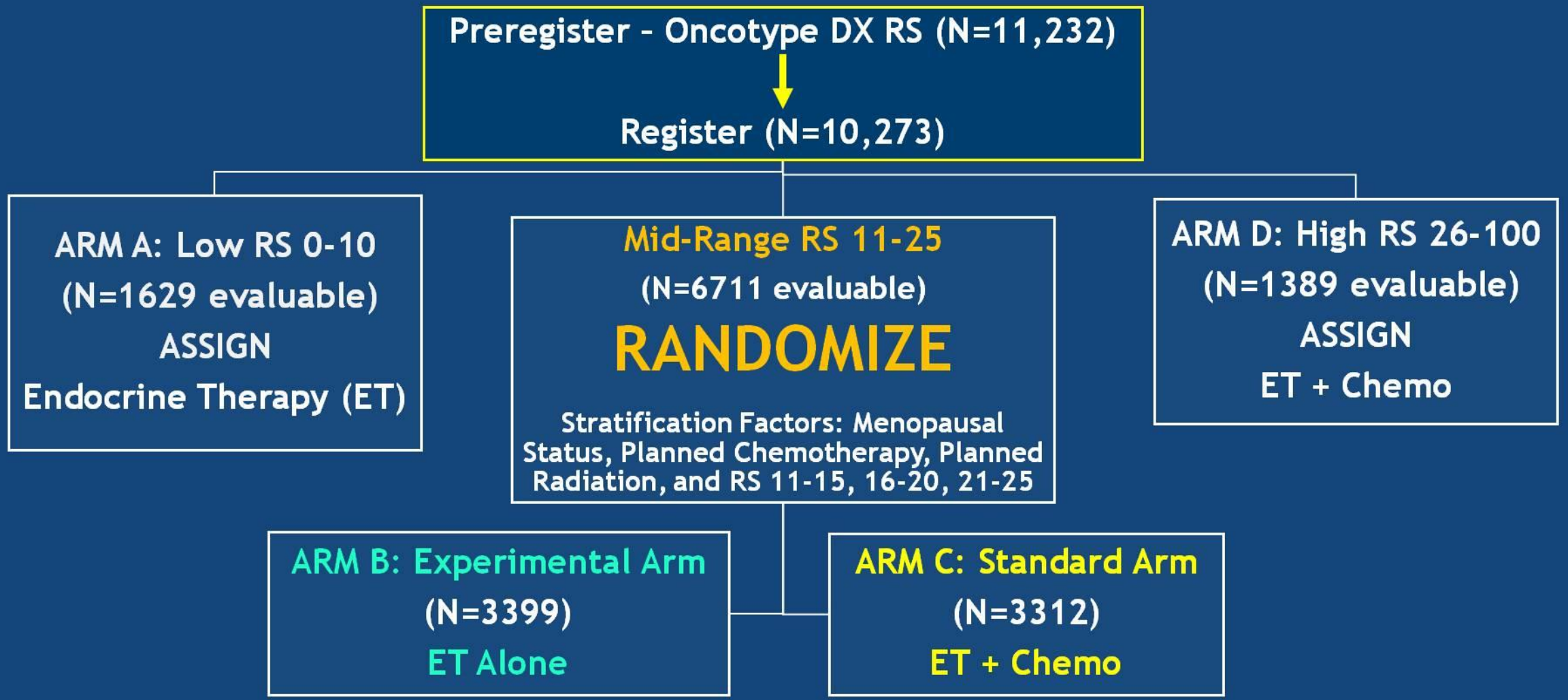
We continue to make progress

- Actionable mutations
- Gene expression signatures
- Biomarkers for immunotherapy



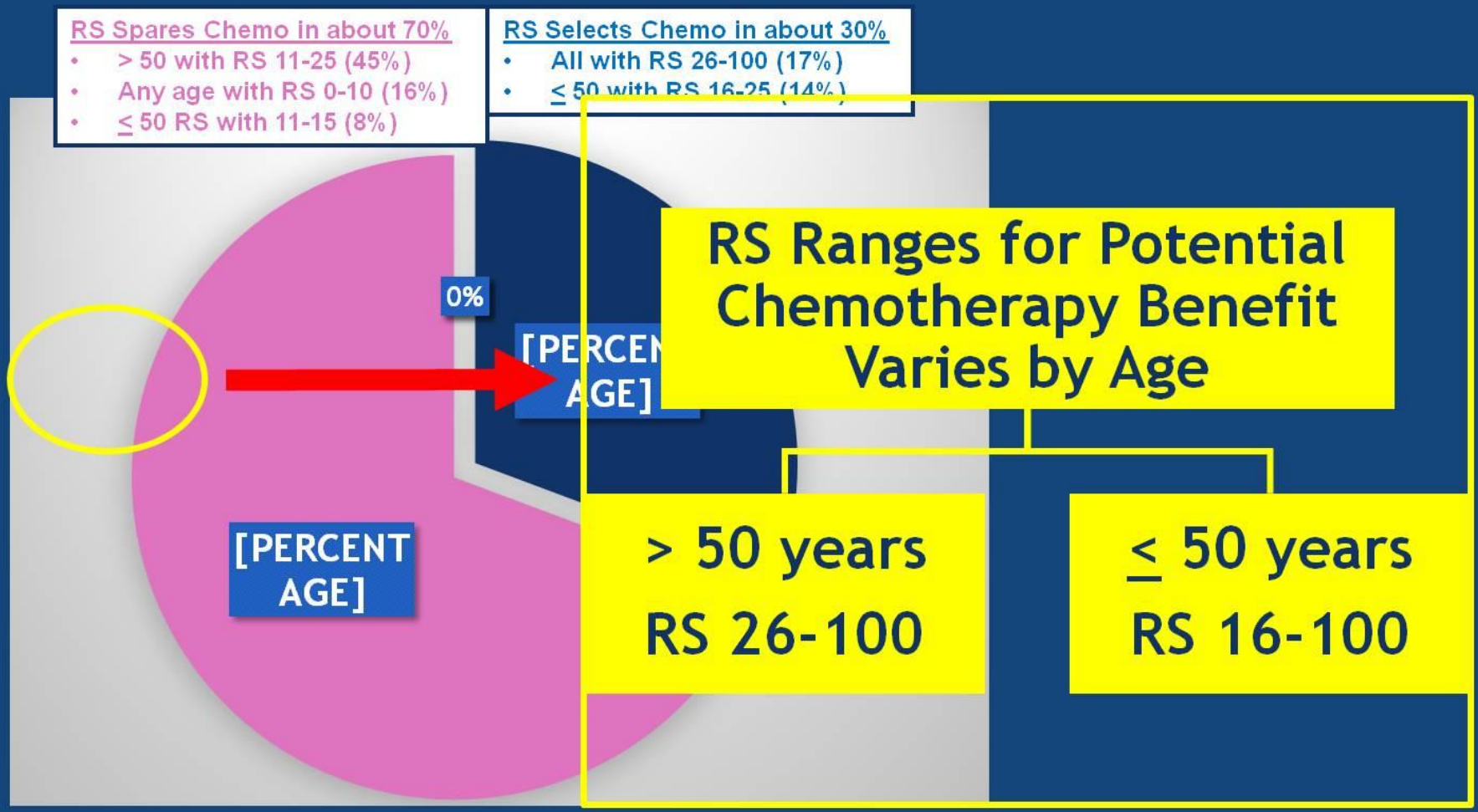
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



Presented By Joseph Sparano at 2018 ASCO Annual Meeting

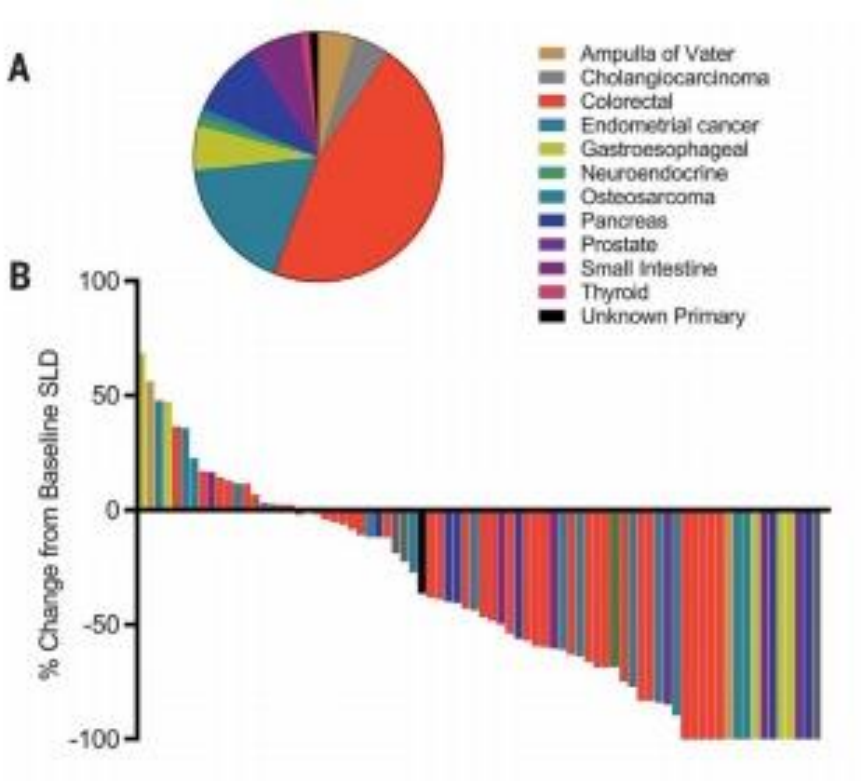
TAILORx Results: Impact on Care



Presented By Joseph Sparano at 2018 ASCO Annual Meeting

FDA Grants Accelerated Approved – May 2017

Pembrolizumab in MMR deficient cancers



- The objective response rate (ORR) with pembrolizumab was 39.6% (95% CI, 31.7-47.9), including 11 (7.4%) complete responses (CRs) and 48 (32.2%) partial responses (PRs). The ORR was 36% in patients with CRC and 46% in patients with other tumor types.

- 1st drug to be approved based on a tumor's biomarker regardless of the tumor's original location

Le DT, et al. N Engl J Med 2015; 372:2509-2520

Promise of precision medicine

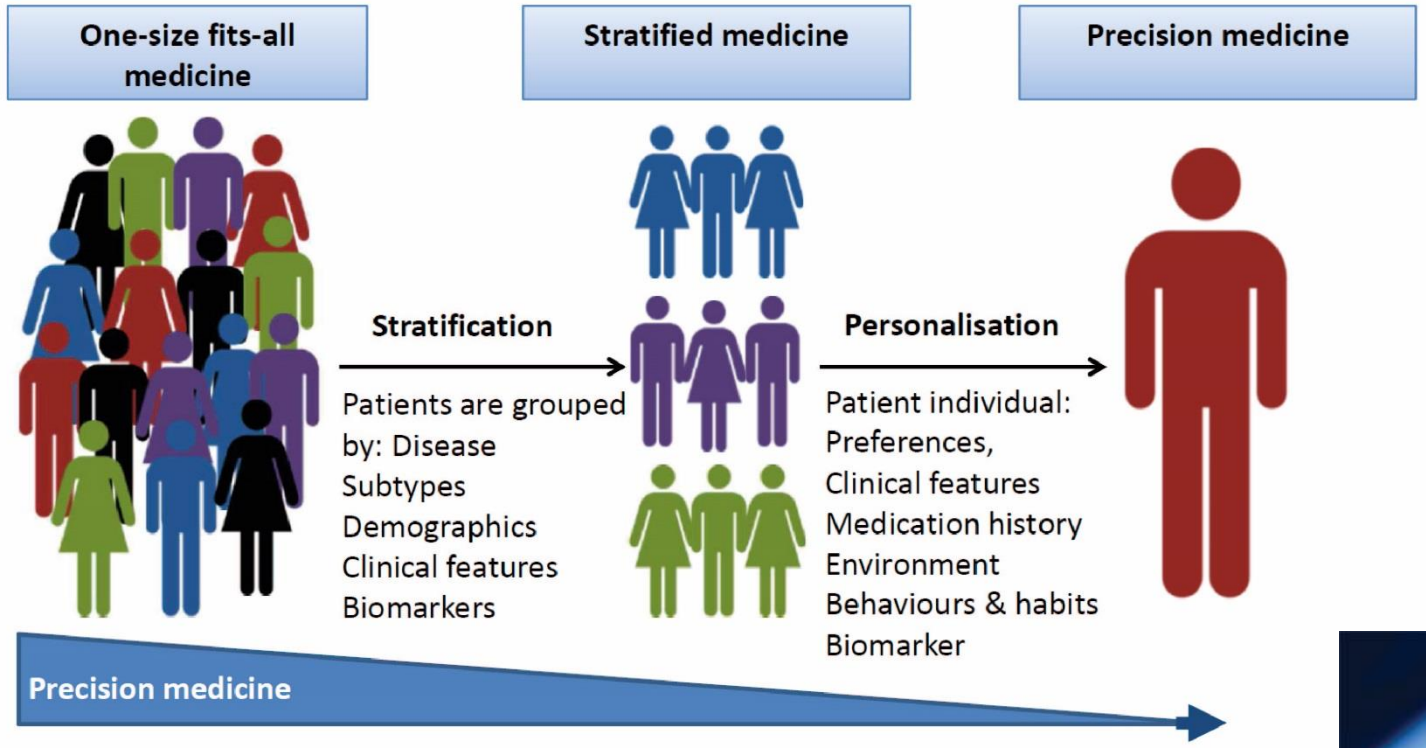
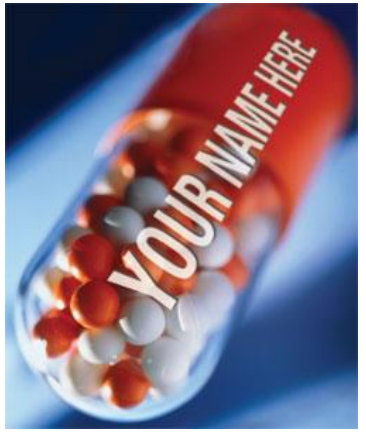


Figure from Manchester Precision Medicine Institute



Conclusions

- Precision medicine is powerful – potentially reduce toxicities while improving responses

- Collaborative effort is needed to advance precision medicine
  - Biomarker development
  - Molecular tumor boards
  - AI

- Data collection essential component

"After careful consideration of all 437 charts, graphs, and metrics, I've decided to throw up my hands, hit the liquor store, and get snockered. Who's with me?!"

Thank you for your attention

http://project-iasis.eu

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