Welcome to Oncology!

John L Marshall, MD
Director, The Ruesch Center for the Cure of GI Cancers
Frederick P. Smith Endowed Chair
Chief, Hematology and Oncology
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center

Disclosures

- Seagen
- Pfizer
- Daichii
- Bayer
- Taiho
- Takeda
- Arcus
- Merck
- Caris
- Indivumed
- OnDose
- 2Curex

What a difference a decade makes….

2010

- Cancer is clonal
- All cancer is the same
- Immune therapies will never work
- Gene testing for some
- Randomized phase 3 trials
- Microbiome is disgusting
- Cancer treatment is expensive
- We love our jobs

2020

- Cancer is polyclonal
- All cancer is different
- Immune therapies are miraculous
- Broad testing for many
- Small single arm trials
- Microbiome is beautiful
- Cancer treatment is more expensive
- Highest burnout and suicide in medicine

New FDA Approved Oncology Drugs 2021-22

- **FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU)** was approved for patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2–based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy. May 4, 2022.
- **ALPELISIB (VIJOICE)** was approved for adult and pediatric patients two years of age and older with severe manifestations of *PIK3CA*-related overgrowth spectrum who require systemic therapy.
- **AXICABTAGENE CILOLEUCEL (YESCARTA)** was approved for adult patients with large B-cell lymphoma who are refractory to first-line chemoimmunotherapy or who experienced relapse within 12 months of first-line chemoimmunotherapy. April 1, 2022.
- **LUTETIUM (LU-177) VIPIVOTIDE TETRAXETAN (PLUVICTO)** was approved for prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer after other therapies. March 23, 2022.
- **PEMBROLIZUMAB (KEYTRUDA)** was approved as a single agent for patients with advanced endometrial carcinoma that is microsatellite instability–high or mismatch repair–deficient. Eligible patients have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. March 21, 2022.
- **NIVOLUMAB AND RELATLIMAB-RMBW (OPDUALAG)** was approved for unresectable or metastatic melanoma. March 18, 2022.
- **OLAPARIB (LYNPARZA)** was approved for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib. March 11, 2022.
- **NIVOLUMAB (OPDIVO)** was approved in combination with platinum-doublet chemotherapy for the neoadjuvant treatment of early-stage non–small cell lung cancer (NSCLC). March 4, 2022.
- **PACRITINIB (VONJO)** was approved for adults with intermediate- or high-risk primary or secondary (post–polycythemia vera or post–essential thrombocythemia) myelofibrosis with a platelet count below 50×10^9/L. February 28, 2022.
- **CILTACABTAGENE AUTOLEUCEL (CARVYKTI)** was approved for the treatment of adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- **TEBENTAFUSP-TEBN (KIMMTRAK)** was approved for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. January 25, 2022.
- **PEMBROLIZUMAB (KEYTRUDA)** was approved for the adjuvant treatment of adult and pediatric (≥ 12 years of age) patients with stage IIB or IIC melanoma following complete resection. December 3, 2021.
- **RITUXIMAB (RITUXAN)** was approved in combination with chemotherapy for pediatric patients with previously untreated, advanced-stage, CD20-positive diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia. December 2, 2021.
- **DARATUMUMAB PLUS HYALURONIDASE-FIHJ (DARZALEX FASPRO)** was approved for adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. December 1, 2021.
- **CARFILZOMIB (KYPROLIS)** was approved combined with dexamethasone for adult patients with relapsed/refractory multiple myeloma who have received one to three prior lines of therapy. December 1, 2021.
- **PAFOLACIANINE (CYTALUX)**, an imaging drug, received approval for use in adult patients with ovarian cancer to help identify cancerous lesions during surgery. November 29, 2021.
- **SIROLIMUS PROTEIN-BOUND PARTICLES FOR INJECTABLE SUSPENSION (FYARRO)** was approved for treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor. November 22, 2021.
- **PEMBROLIZUMAB (KEYTRUDA)** was approved for the adjuvant treatment of patients with renal cell carcinoma at intermediate-high or high risk of disease recurrence following nephrectomy or nephrectomy and resection of metastatic lesions. November 17, 2021.

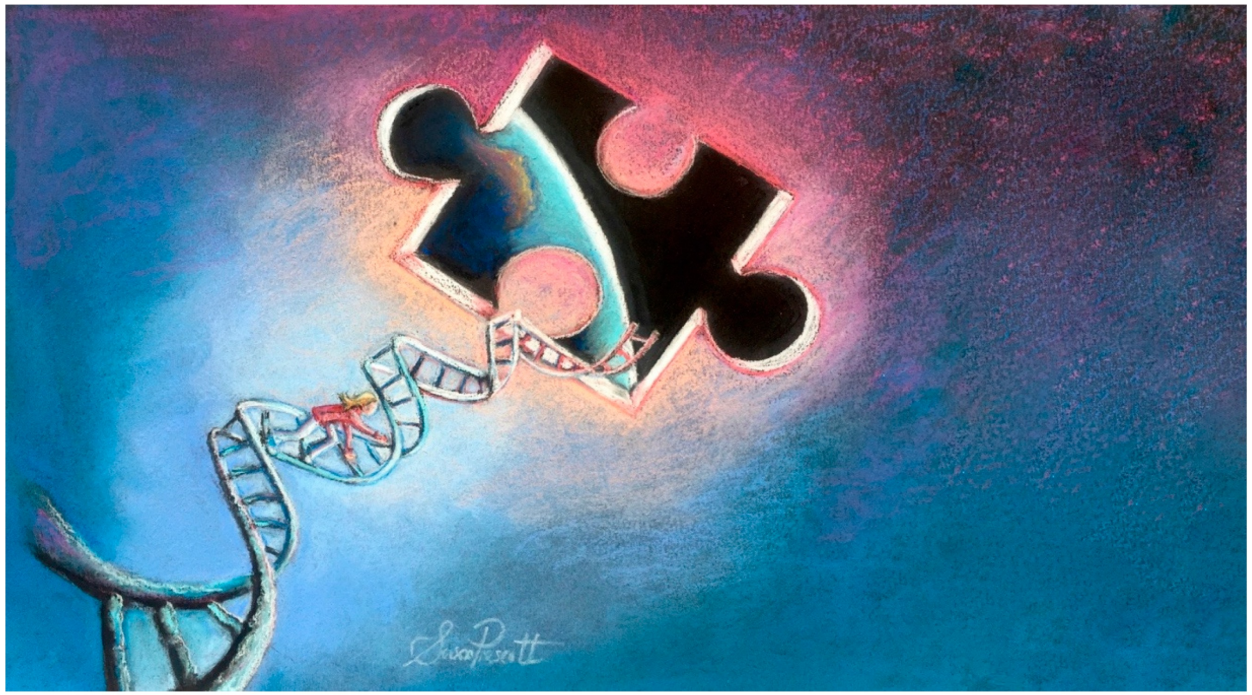
New FDA Approved Oncology Drugs 2021-22

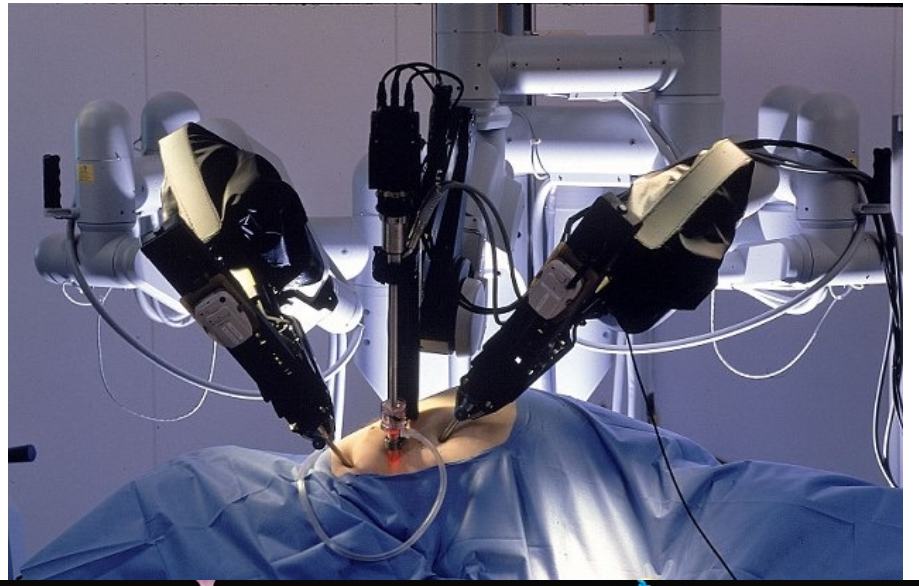
- **ASCIMINIB (SCEMBLIX)** received accelerated approval for Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, previously treated with two or more tyrosine kinase inhibitors, and was approved for adult patients with Ph+ CML in chronic phase with the T315I mutation. October 29, 2021.
- **ATEZOLIZUMAB (TECENTRIQ)** was approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells. October 15, 2021.
- **PEMBROLIZUMAB (KEYTRUDA)** combined with chemotherapy, with or without bevacizumab (Avastin), was approved for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (combined positive score ≥ 1). October 13, 2021.
- **ABEMACICLIB (VERZENIO)** combined with endocrine therapy was approved for adjuvant treatment of patients with hormone receptor–positive, HER2-negative, node-positive early breast cancer who are at high risk of disease recurrence and who have a Ki67 score ≥ 20%. October 12, 2021.
- **BREXUCABTAGENE AUTOLEUCEL** (TECARTUS) received approval for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). October 1, 2021.
- **CETUXIMAB (ERBITUX)** was approved combined with encorafenib (Braftovi) for the treatment of adults with metastatic colorectal cancer and a *BRAF* V600E mutation after prior therapy. September 28, 2021.
- **RUXOLITINIB (JAKAFI)** was approved for the treatment of chronic graft-vs-host disease (GVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients aged 12 years and older. September 22, 2021.
- **TISOTUMAB VEDOTIN-TFTV (TIVDAK)** was approved to treat adult patients with recurrent or metastatic cervical cancer who experienced disease progression on or after chemotherapy. September 20, 2021.
- **CABOZANTINIB (CABOMETYX)** was approved to treat adult and pediatric patients aged 12 years and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine–refractory or ineligible. September 17, 2021.
- **MOBOCERTINIB (EXKIVITY)** was granted accelerated approval to treat adults with locally advanced or metastatic NSCLC and epidermal growth factor receptor exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. September 15, 2021.
- **ZANUBRUTINIB (BRUKINSA)** received accelerated approval for the treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received at least one anti–CD20-based regimen. September 15, 2021.
- **ZANUBRUTINIB (BRUKINSA)** was approved for the treatment of adult patients with Waldenström's macroglobulinemia. August 31, 2021.
- **IVOSIDENIB (TIBSOVO)** was granted approval for previously treated locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 *(IDH1)* mutation. August 25, 2021.
- **NIVOLUMAB (OPDIVO)** was approved for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of disease recurrence after undergoing radical resection. August 19, 2021.

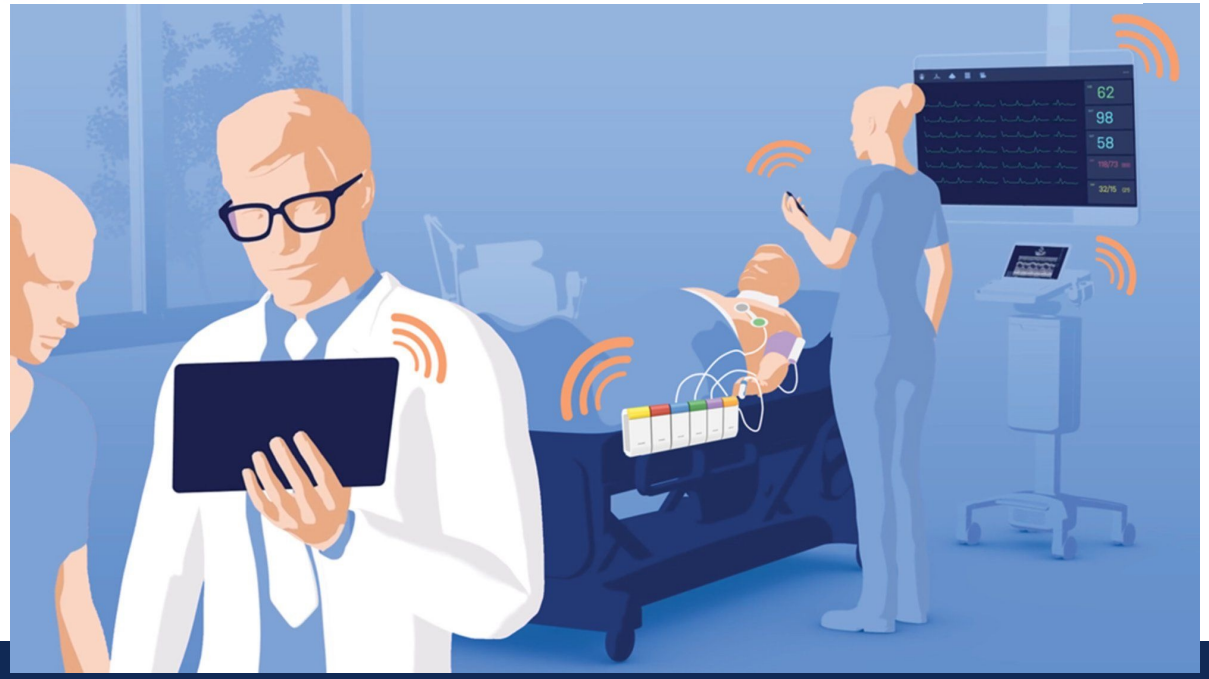
New FDA Approved Oncology Drugs 2021-22

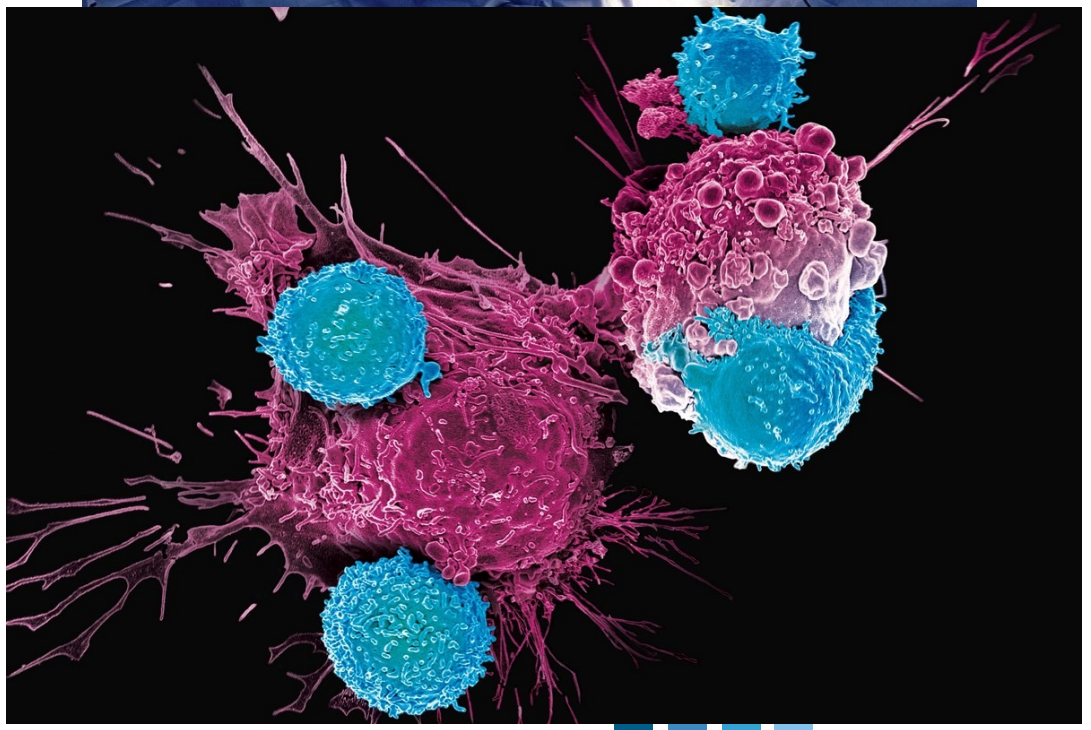
- **DOSTARLIMAB-GXLY (JEMPERLI)**, an anti–PD-1 antibody, received accelerated approval for adult patients with mismatch repair–deficient (dMMR) recurrent or advanced solid tumors who have had disease progression on or following prior treatment and who have no satisfactory alternative treatment options. August 17, 2021.
- **LENVATINIB (LENVIMA) PLUS PEMBROLIZUMAB (KEYTRUDA)** received approval for the first-line treatment of adult patients with advanced renal cell carcinoma. August 10, 2021.
- **PEMBROLIZUMAB (KEYTRUDA)** was approved for high-risk, early-stage triple-negative breast cancer in combination with chemotherapy as a neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery. July 26, 2021.
- **PEMBROLIZUMAB (KEYTRUDA) PLUS LENVATINIB (LENVIMA)** was granted approval for treatment of patients with advanced endometrial carcinoma that is not microsatellite instability–high or dMMR. July 21, 2021.
- **BELUMOSUDIL (REZUROCK)** was approved for adult and pediatric patients aged 12 years and older with chronic GVHD after failure of at least two prior lines of systemic therapy. July 16, 2021.
- **ENFORTUMAB VEDOTIN-EJFV (PADCEV)** was approved for adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy. It also was approved for patients who are ineligible for cisplatin-containing chemotherapy and have received one or more prior lines of therapy. July 9, 2021.
- **DARATUMUMAB AND HYALURONIDASE-FIHJ (DARZALEX FASPRO)** combined with pomalidomide and dexamethasone was approved to treat adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor. July 9, 2021.
- **ASPARAGINASE ERWINIA -CHRYSANTHEMI (RECOMBINANT)-RYWN (RYLAZE)** was approved for ALL and lymphoblastic lymphoma in patients allergic to *Escherichi coli*–derived asparaginase products, as a component of a chemotherapy regimen. June 30, 2021.
- **AVAPRITINIB (AYVAKIT)** was approved to treat adult patients with advanced systemic mastocytosis, including those with aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia. June 16, 2021.
- **INFIGRATINIB (TRUSELTIQ)** received accelerated approval for adults with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or other rearrangement. May 28, 2021.
- **SOTORASIB (LUMAKRAS)** was approved as the first treatment for adult patients with NSCLC whose tumors have a *KRAS* G12C genetic mutation and who have received at least one prior systemic therapy. May 28, 2021.
- **PIFLUFOLASTAT F-18 INJECTION (PYLARIFY)** was approved for the identification of suspected metastasis or recurrence of prostate cancer. May 27, 2021.
- **AMIVANTAMAB-VMJW (RYBREVANT)** received accelerated approval for adult patients with locally advanced or metastatic NSCLC and *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. May 21, 2021.
- **NIVOLUMAB (OPDIVO)** was approved for patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy. May 20, 2021.

Drug Shortages?
How could this be!






62
98
58



21st Century Oncology

- Remote/telemedicine + robots
- Fewer docs and RNs, more apps
- Shortage of trained professionals
- Baseline molecular profiling + real time metabolomics
- Expansion of IO (Immune Oncology)
- Cell therapies
- Mo AB with “payloads”
- Total Loss of control over research

Unequal Access, Unequal Standards

The World of Oncology in the US

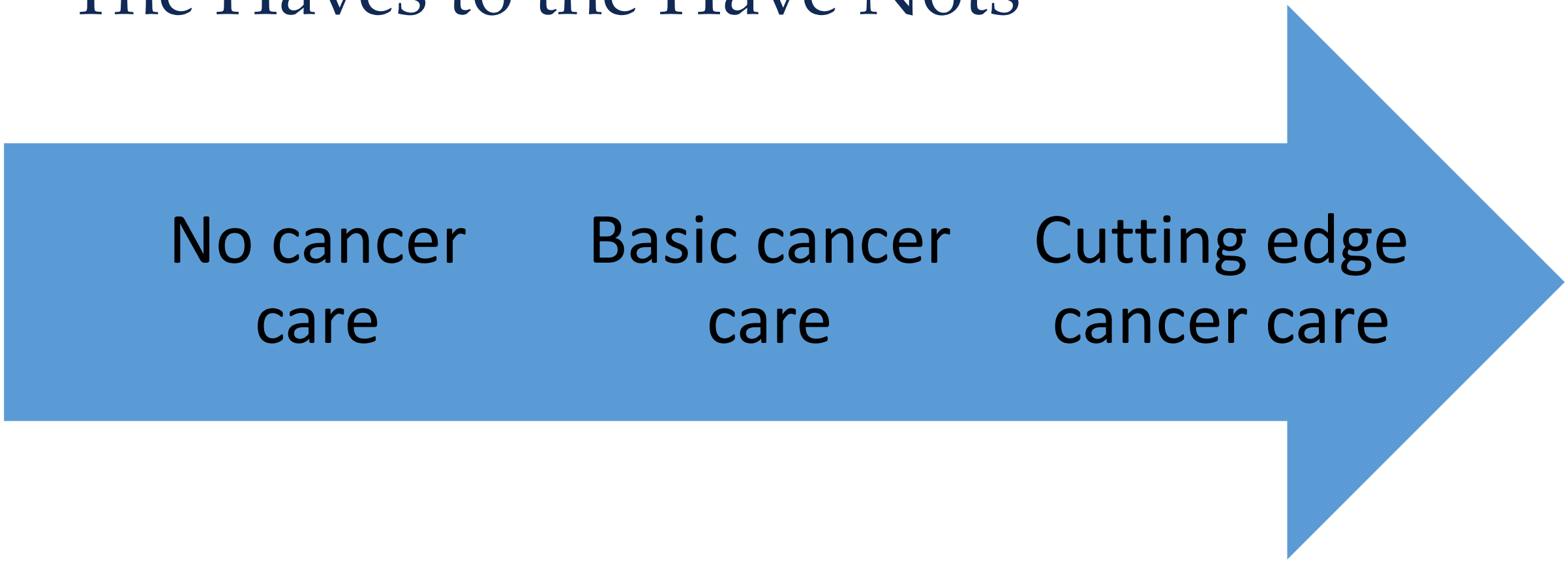
- We have EVERYTHING and more
- We pay a lot for everything
- Cancer care teams are in cities, limited access in rural areas
- Our patients treat us like employees
- By law, we cannot judge value
- Everything we do is monitored by insurance companies
- Our entire economy is dependent on this system
- If you don’t have insurance, we pay for you anyway

Inconvenient Truths

- There is dramatic global imbalance of access, costs, and outcomes
- Cancer care costs are rising rapidly without proportional gains in outcomes.
- Healthcare providers are incentivized by amount consumed, not outcomes.
- Empirical cancer drug therapy is ineffective- adjuvant therapy fails most of the time, many patients with met cancer do not “respond”, with benefit being measured by small gains in survival.
- Over 95% of cancer patients receive today’s “standard of care” guideline based therapy resulting in no scientific progress.
- Current drug approvals require an average of 17 years from concept to approval, in large part due to slow clinical trial accrual.
- Current regulatory, privacy, and intellectual property laws do not support the needs of the government, patient, and private industry in the collective goal of curing cancer.
- We are clearly making progress
- It cannot go on like this

How to Get Better Value Cancer Care,
Oxford Press, 2013. David J Kerr, Muir Gray
Modified by J Marshall

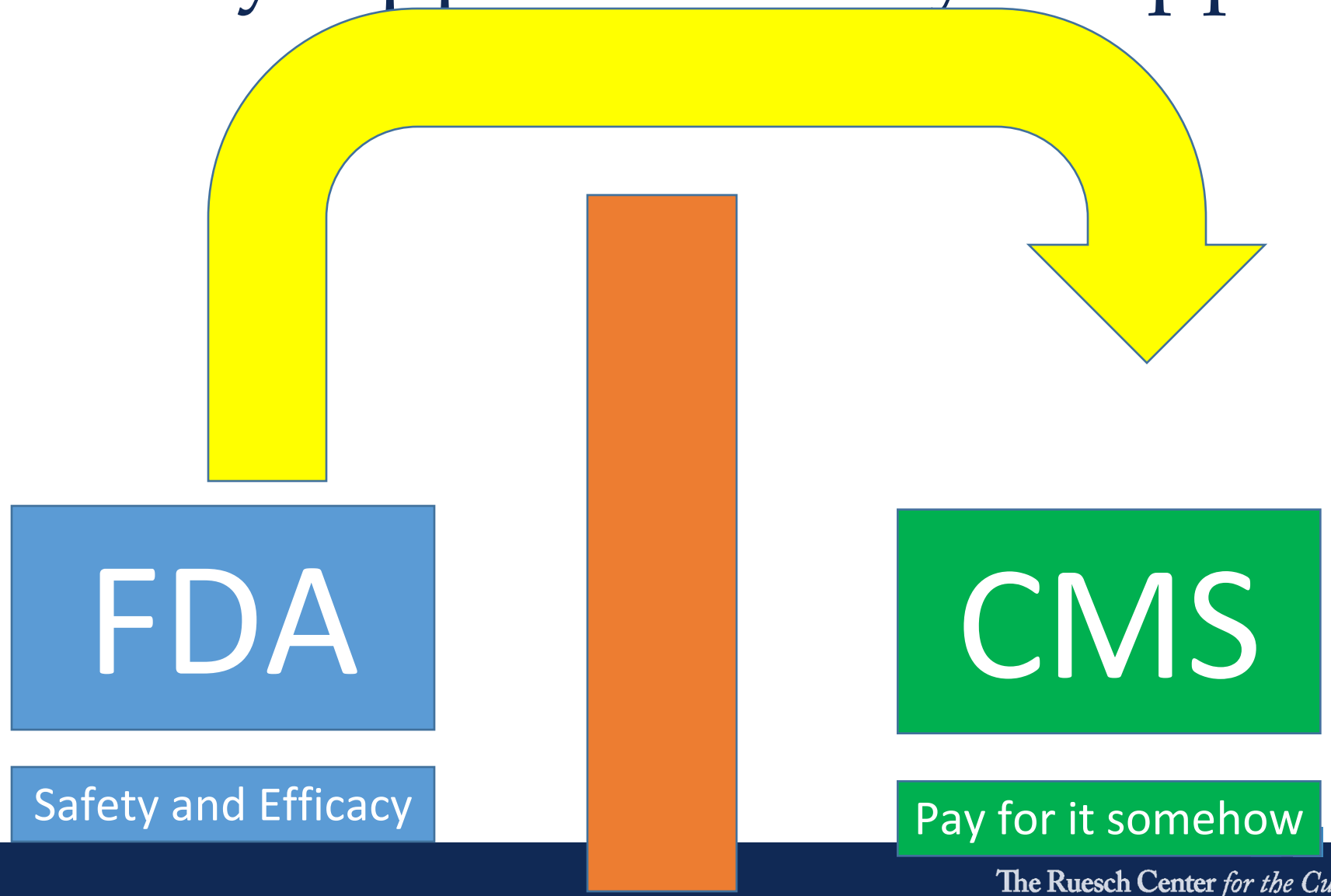
Health Care Access:
The Haves to the Have Nots



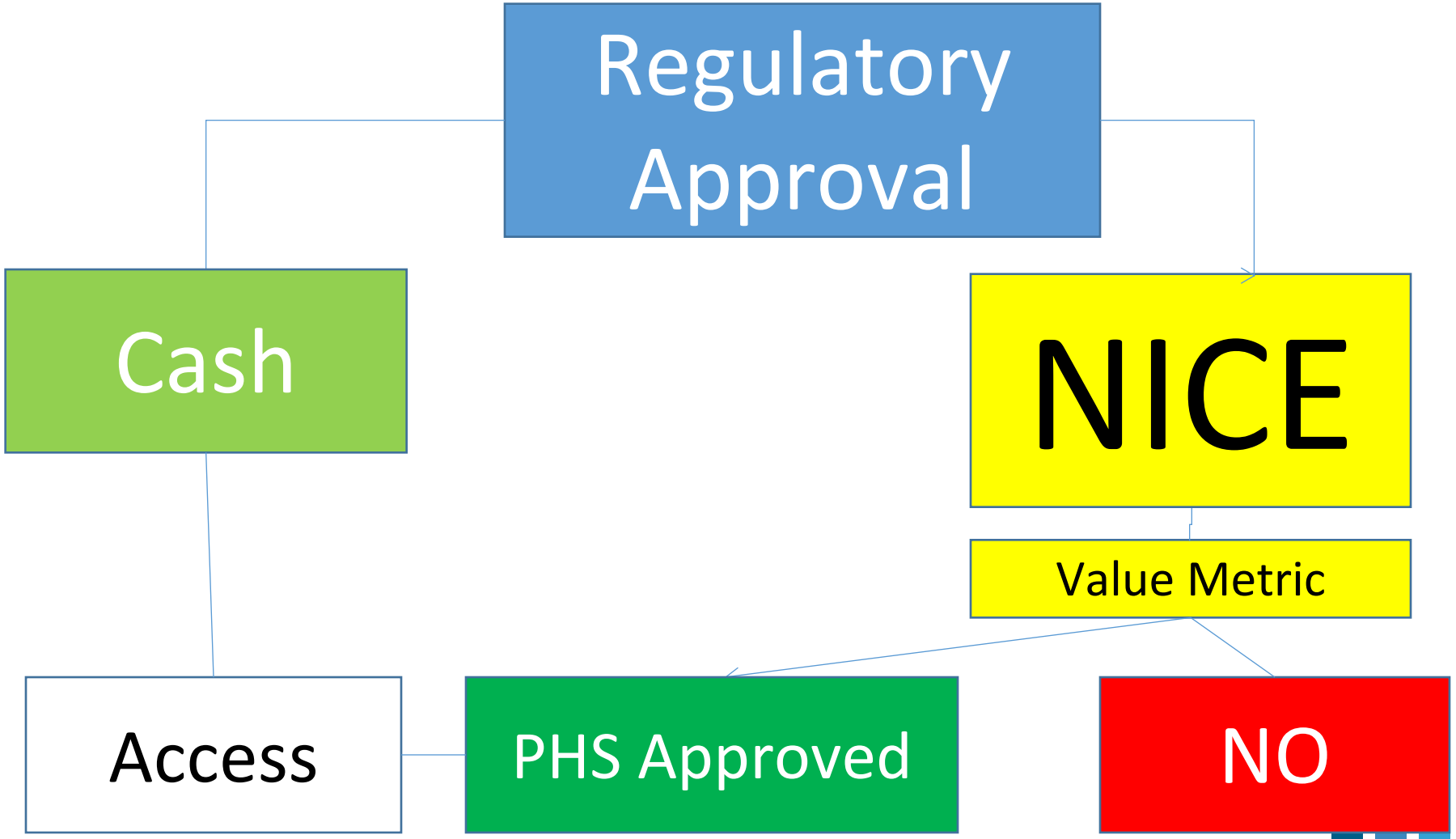
The Value of One Life

- -$160. for the chemical elements
- -Is it $50-200,000/QALY? (USA)
- -Is it £13-20,000/QALY? (NICE)
- -Does it depend on where you live?
- -Does it vary by education and resources?
- -Is it priceless?
- -Can we agree on an amount?
- -Balance between personal and collective responsibility?

Regulatory Approval vs Payer Approval



Regulatory Approval vs Payer Approval Great Britain

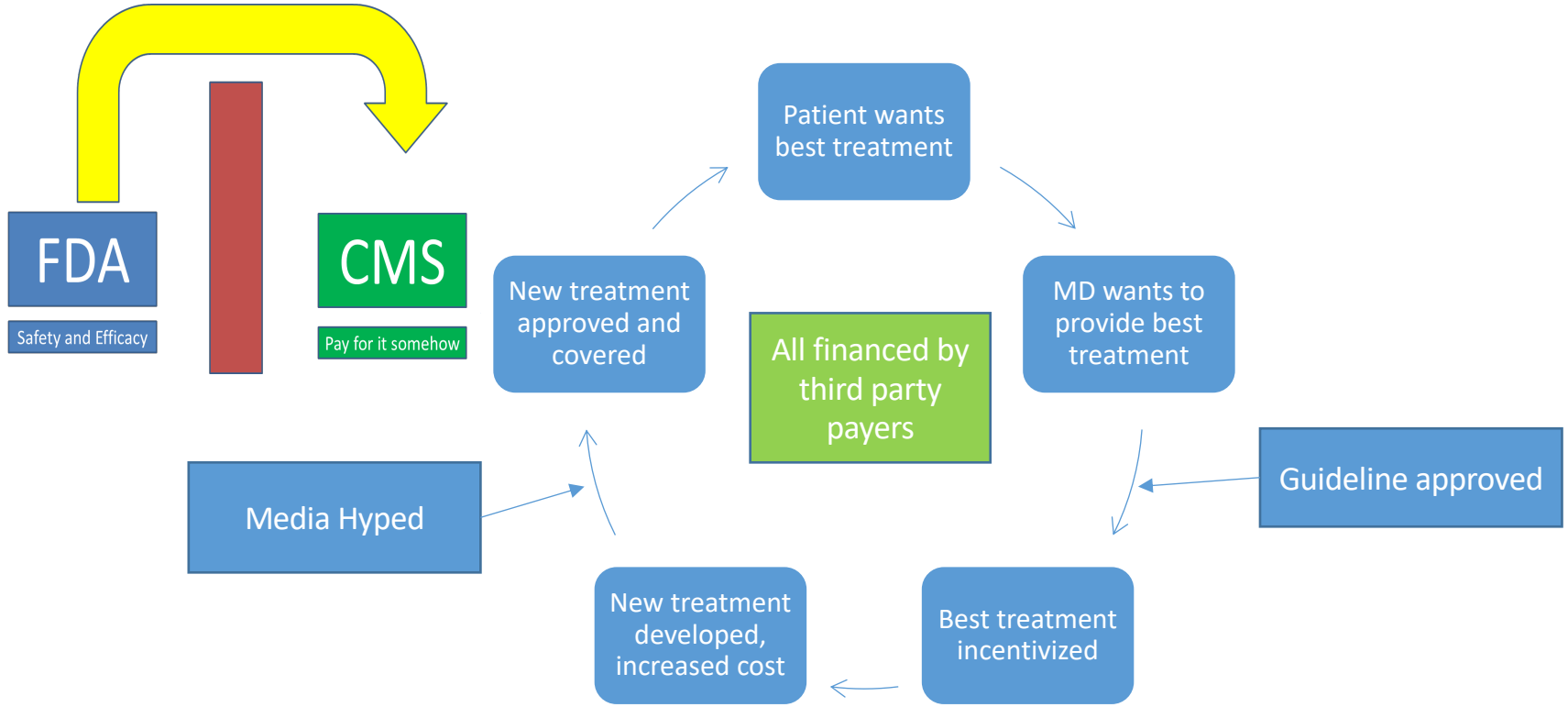


Poorer Countries

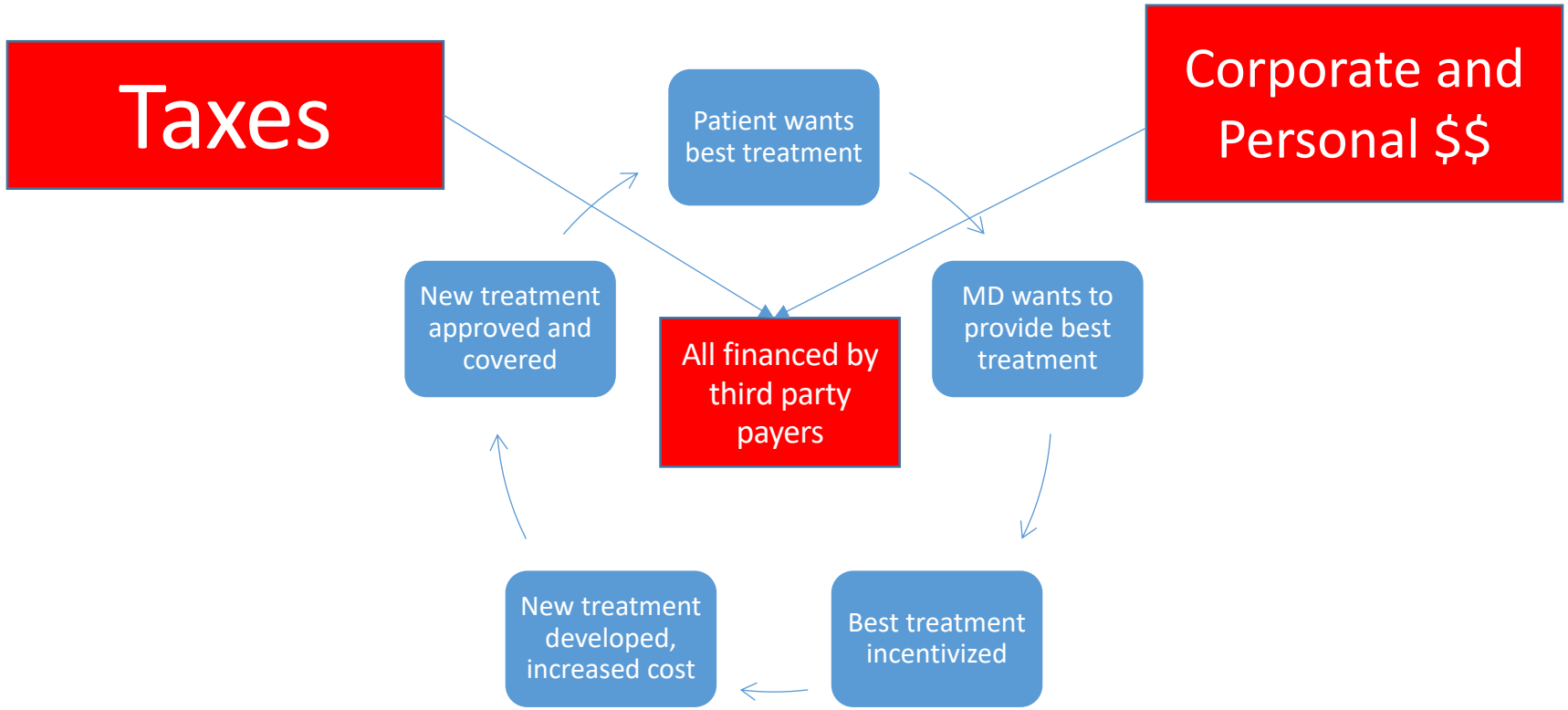
Their patients help do our trials

Limited access to the drugs they helped test

How we got here

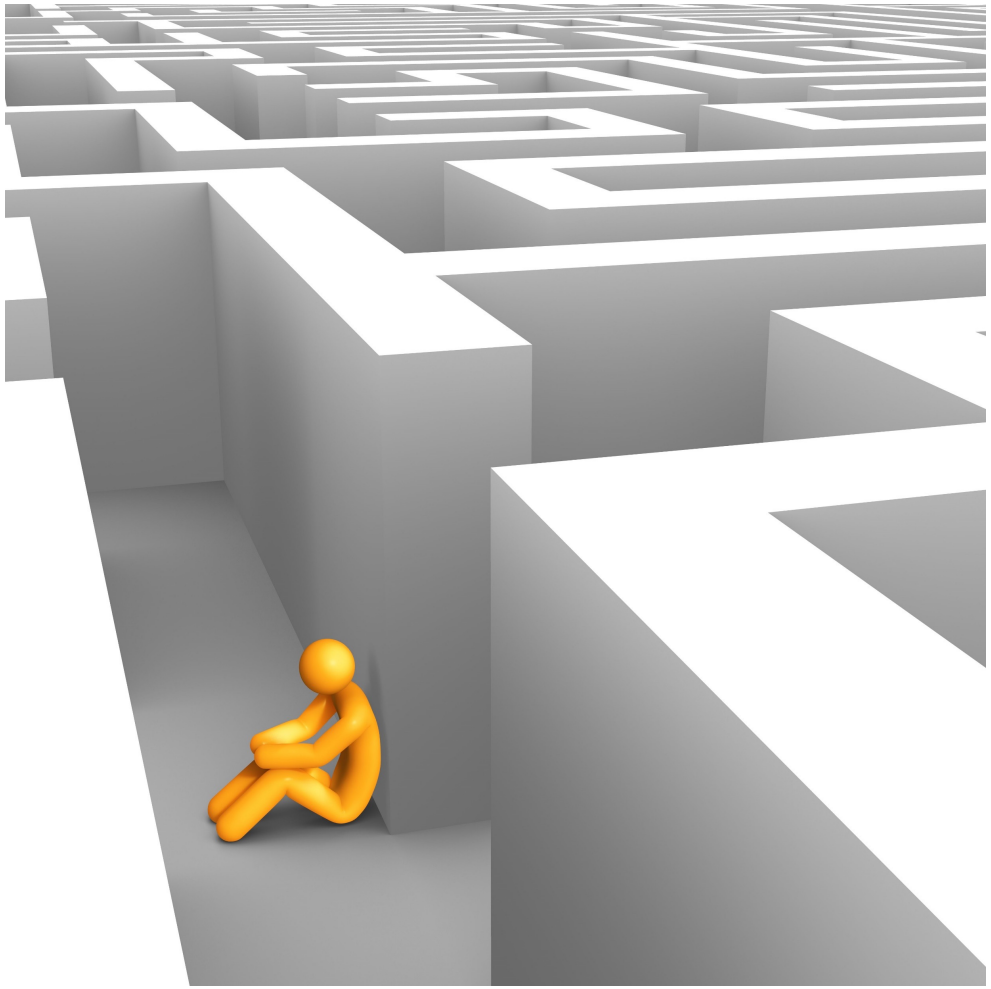


How we got here



Would you swipe your own credit card?

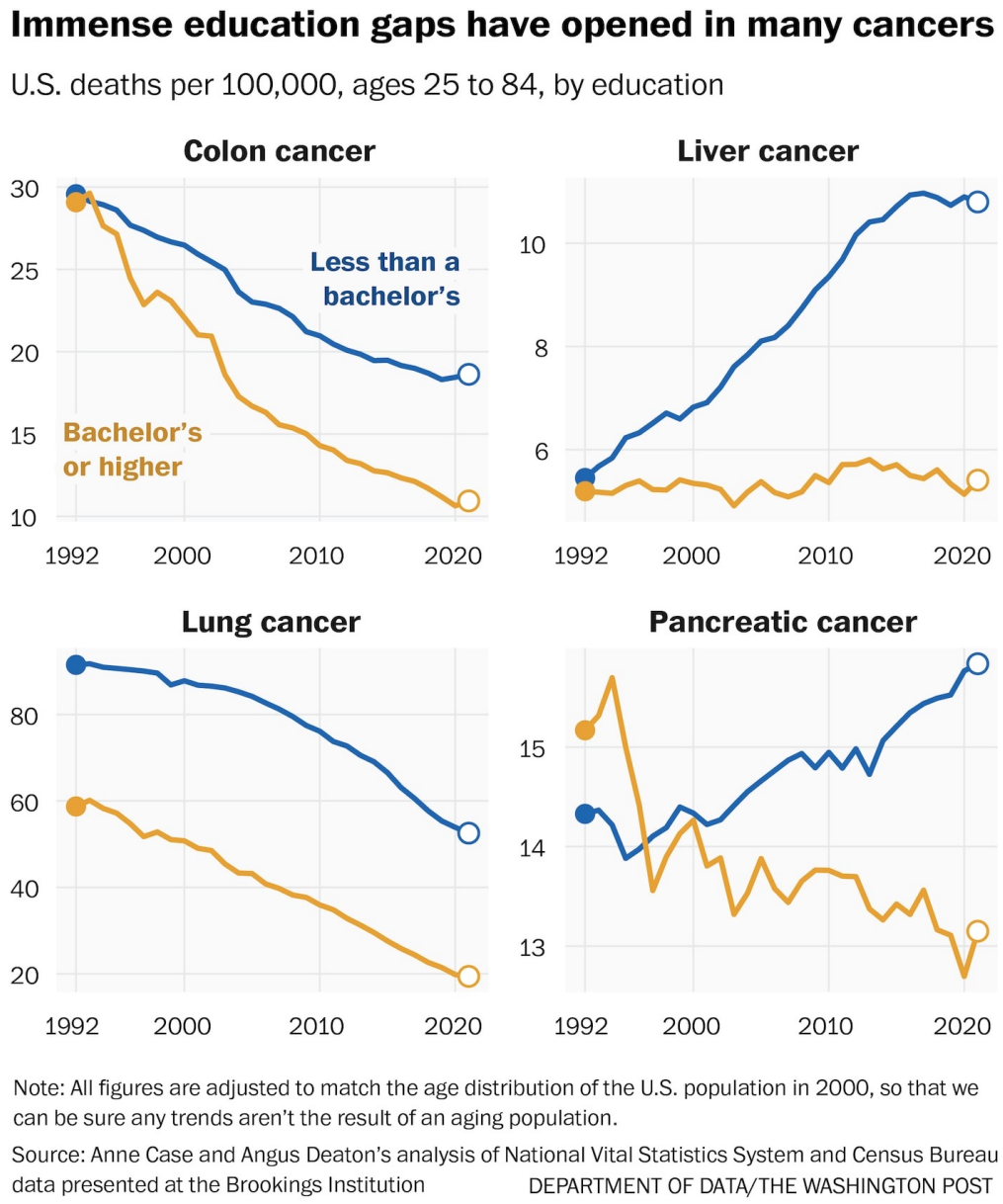
A cancer diagnosis and treatment is overwhelming



- Transforming emotional impact
- Steep learning curve
- Major time investment
- Major financial impact
- Cannot be done alone

The Washington Post

If you didn’t go to college, you’re more likely to struggle with everything from colon, liver and pancreatic cancer to low odds of marriage, more mental distress and even difficulty socializing.

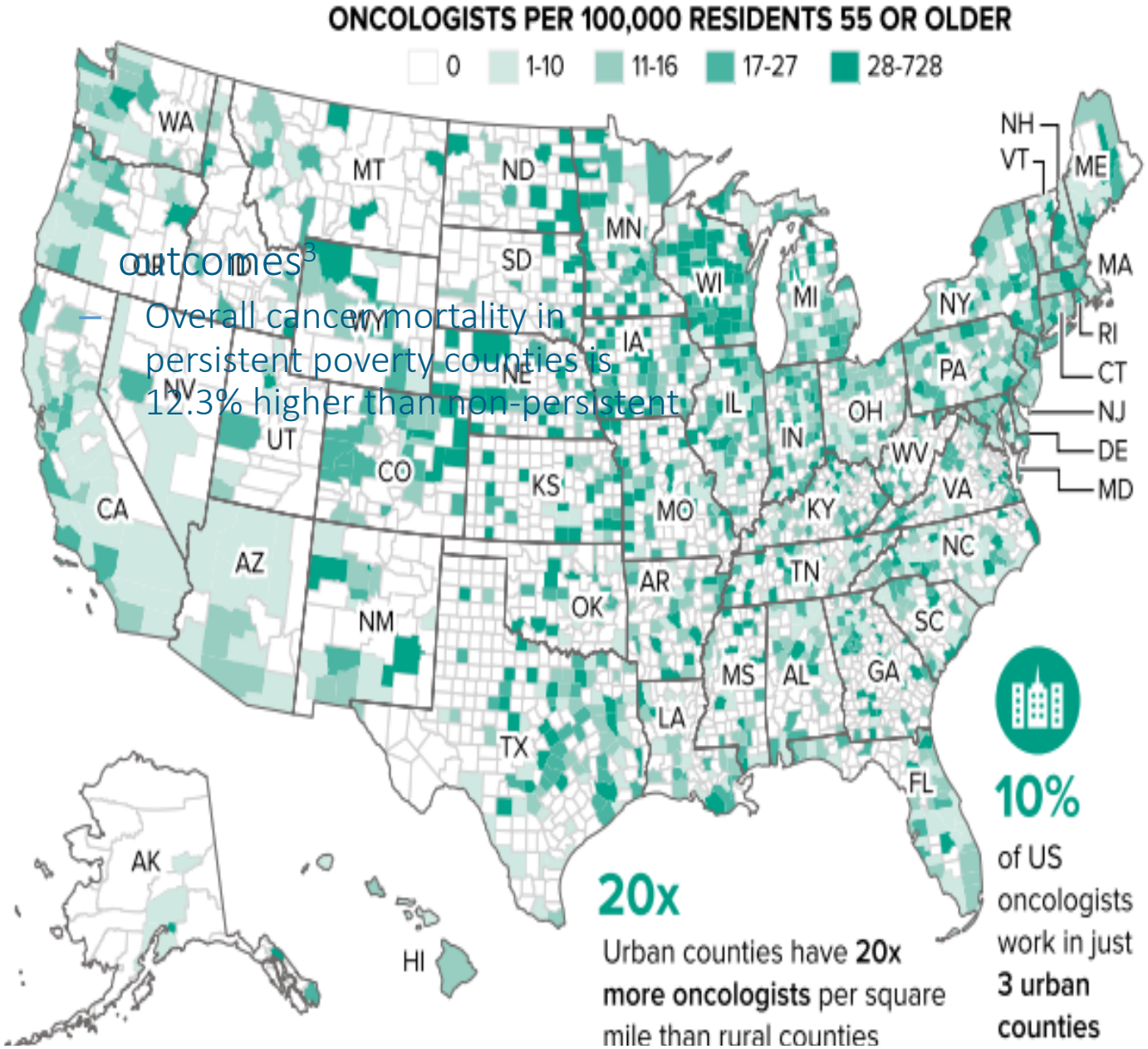


https://www.washingtonpost.com/business/2023/10/06/jobs-likely-to-overdose/

AmerisourceBergen

Factors Contributing to Disparities in Care

- Established risk factors for cancer are more prevalent among some minority groups, including Black and Hispanic populations and those from lower socioeconomic backgrounds[1]
  - Lack of preventive care
  - Environmental exposure to chemicals
  - Untreated chronic diseases such as diabetes
- Location matters[2]
  - 66% of rural counties have no oncologist
- Persistent poverty impacts outcomes[3]
  - Overall cancer mortality in persistent poverty counties is 12.3% higher than non-persistent



1. https://www.nature.com/articles/d41586-020-02678-7#ref-CR4
2. 2020 Snapshot: State of the Oncology Workforce in America JCO Oncology Practice 2021 17:1, 30-30
3. Moss JL, Pinto CN, Srinivasan S, Cronin KA, Croyle RT. Persistent Poverty and Cancer Mortality Rates: An Analysis of County-Level Poverty Designations. Cancer Epidemiol Biomarkers Prev. 2020 Oct;29(10):1949-1954.

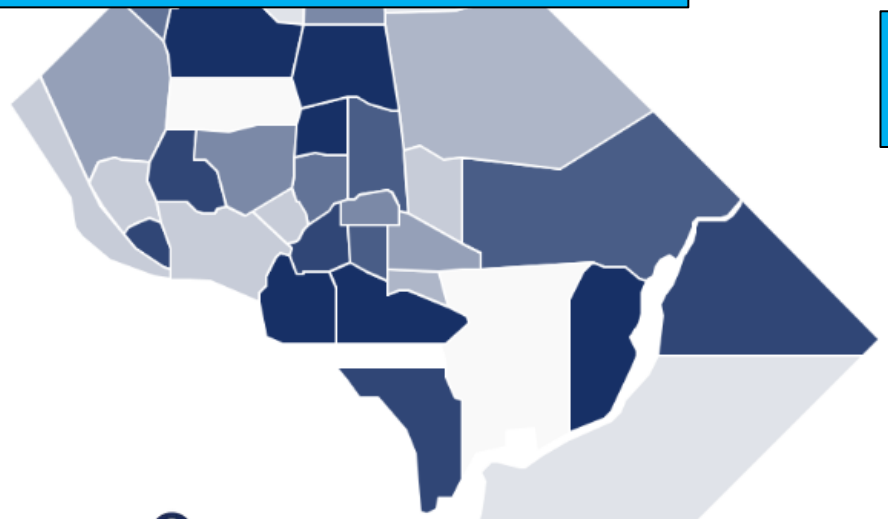
GI Cancers Equity Initiative Team

colorectal cancer alliance

Philanthropy partner, on line navigators, Blue HQ app, care model development

The Ruesch Center
for the Cure of Gastrointestinal Cancers

Oversight, patient management, clinical expertise, clinical research, philanthropy partners



MedStar Health

Sponsoring medical facilities, Clinic Coach, Multidisciplinary care

COTA

Data abstraction and analysis

GEORGETOWN UNIVERSITY
HEALTH JUSTICE ALLIANCE

Patient and caregiver legal support

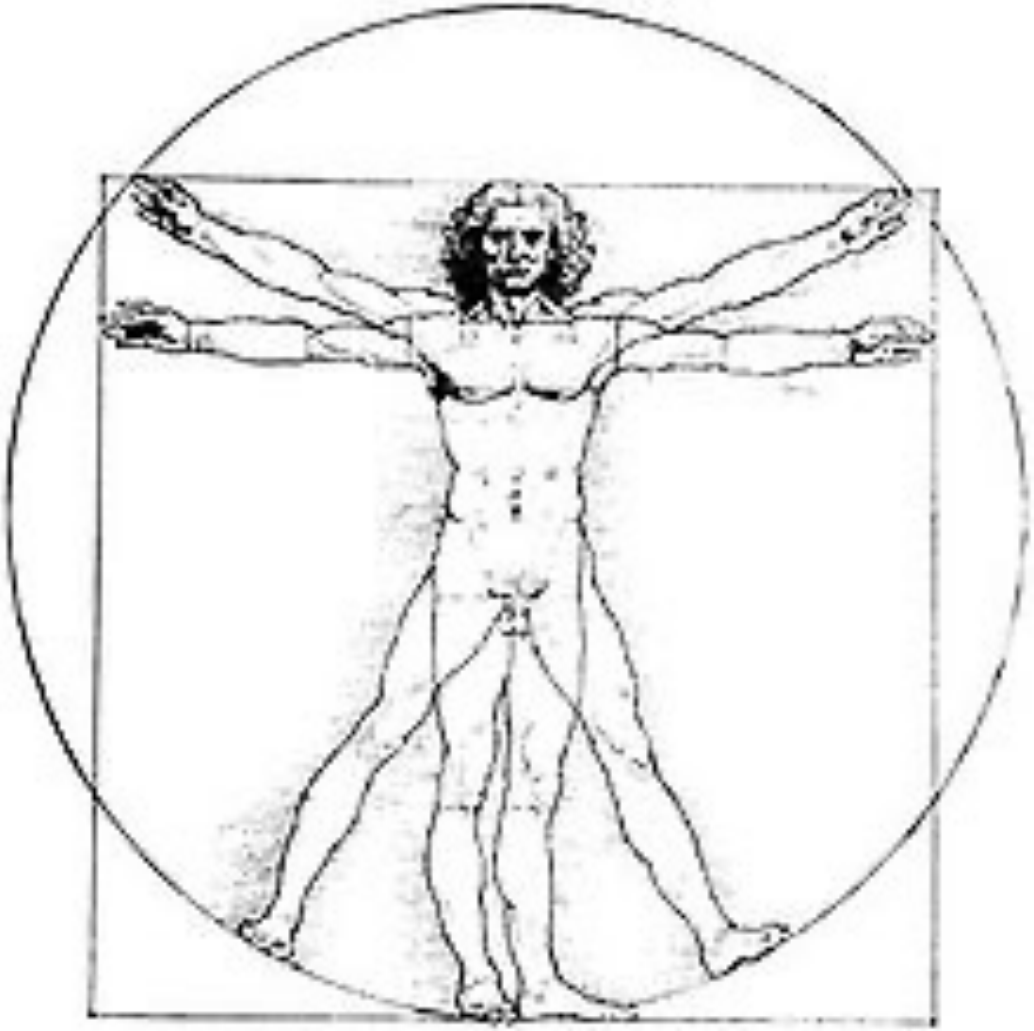
RALPH LAUREN CENTER
FOR CANCER CARE AND PREVENTION

Community connections, outcomes research

Precision Medicine

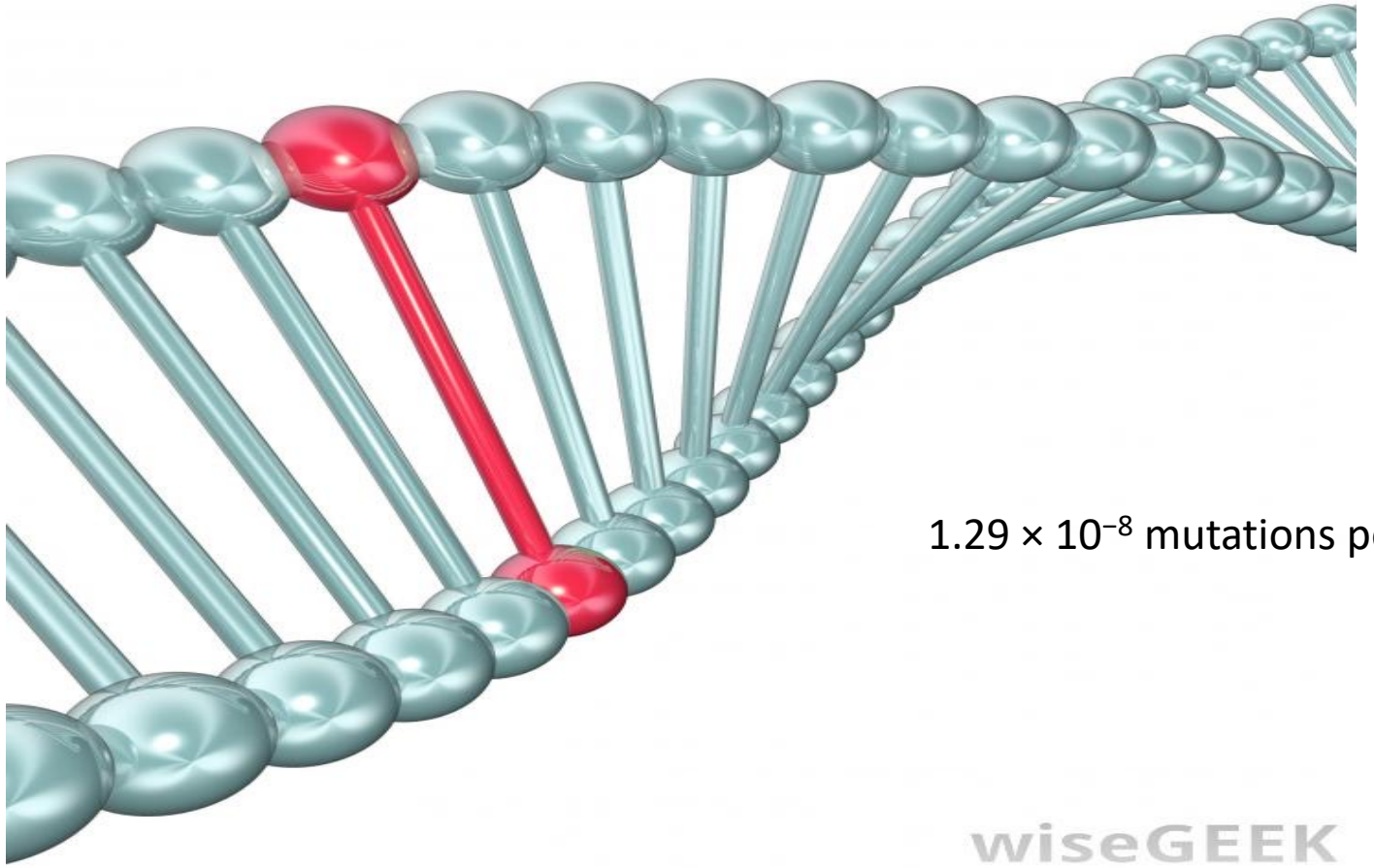
Prospective incorporation of molecular profiling will transform global cancer care

What is normal?



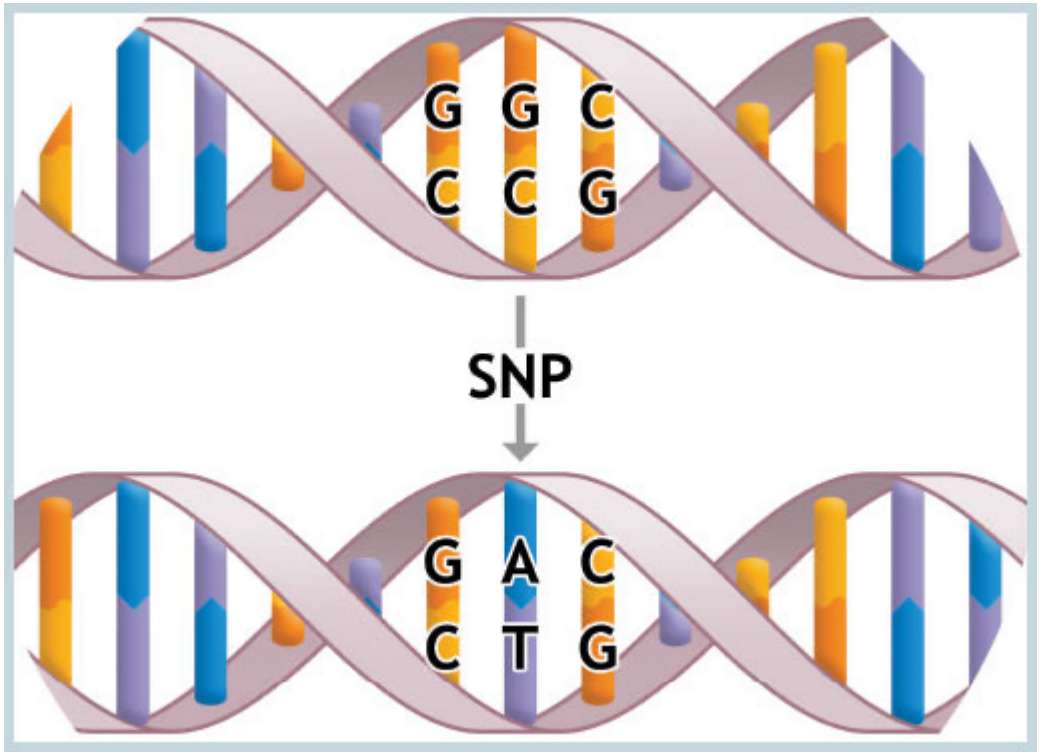
Maturation of Precision Medicine

A Mutation



1.29×10^{-8} mutations per base pair per meiosis

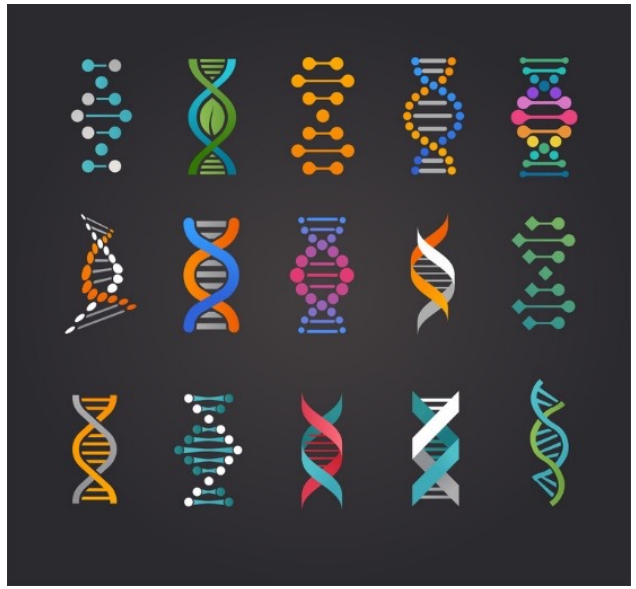
Single Nucleotide Polymorphism

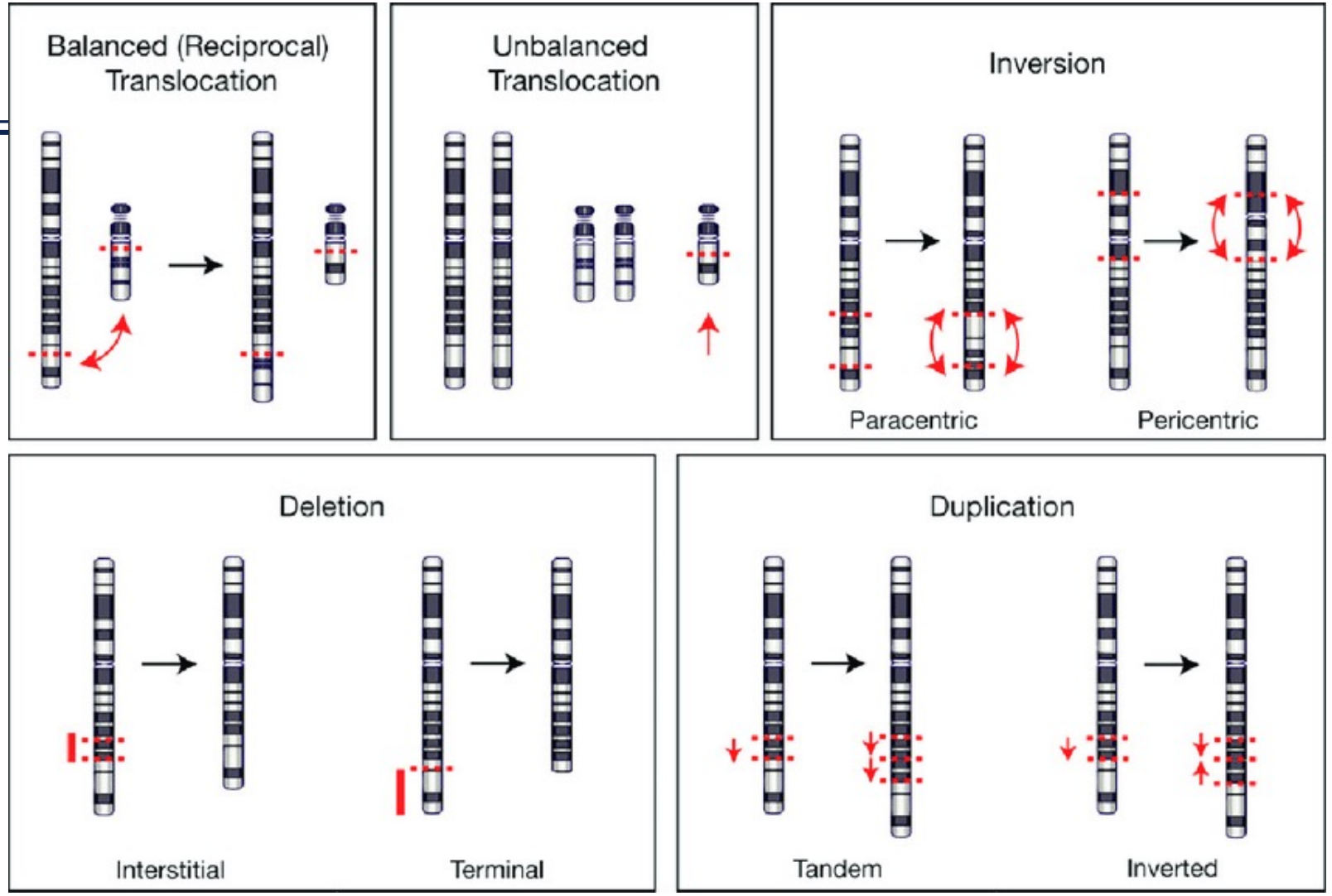


- A substitution of a single nucleotide that occurs at a specific position in the genome, where each variation is present at a level of 0.5% from person to person in the population
- Occur normally throughout a person's DNA
- The most common type of genetic variation among people
  - roughly 4 to 5 million SNPs in a person's genome

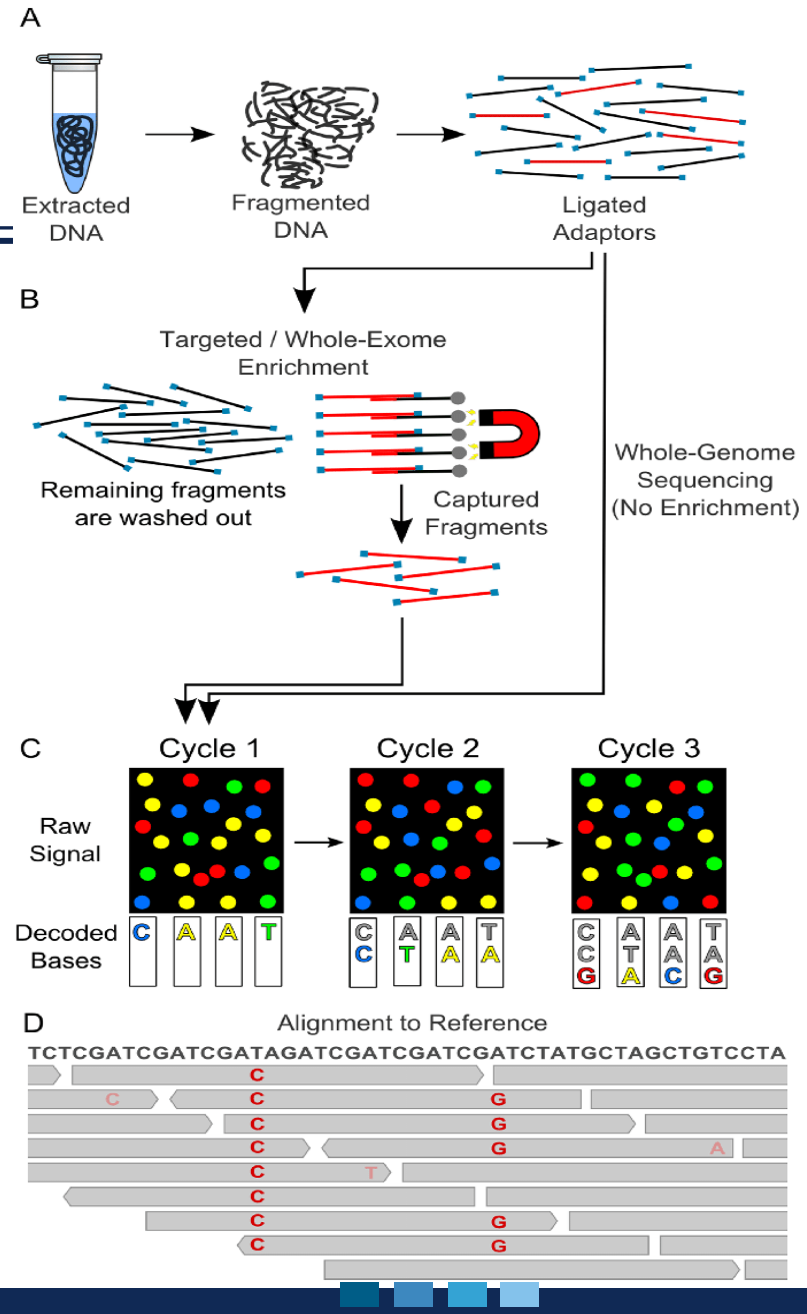
https://ghr.nlm.nih.gov/primer/genomicresearch/snp

Chromosomal Rearrangements

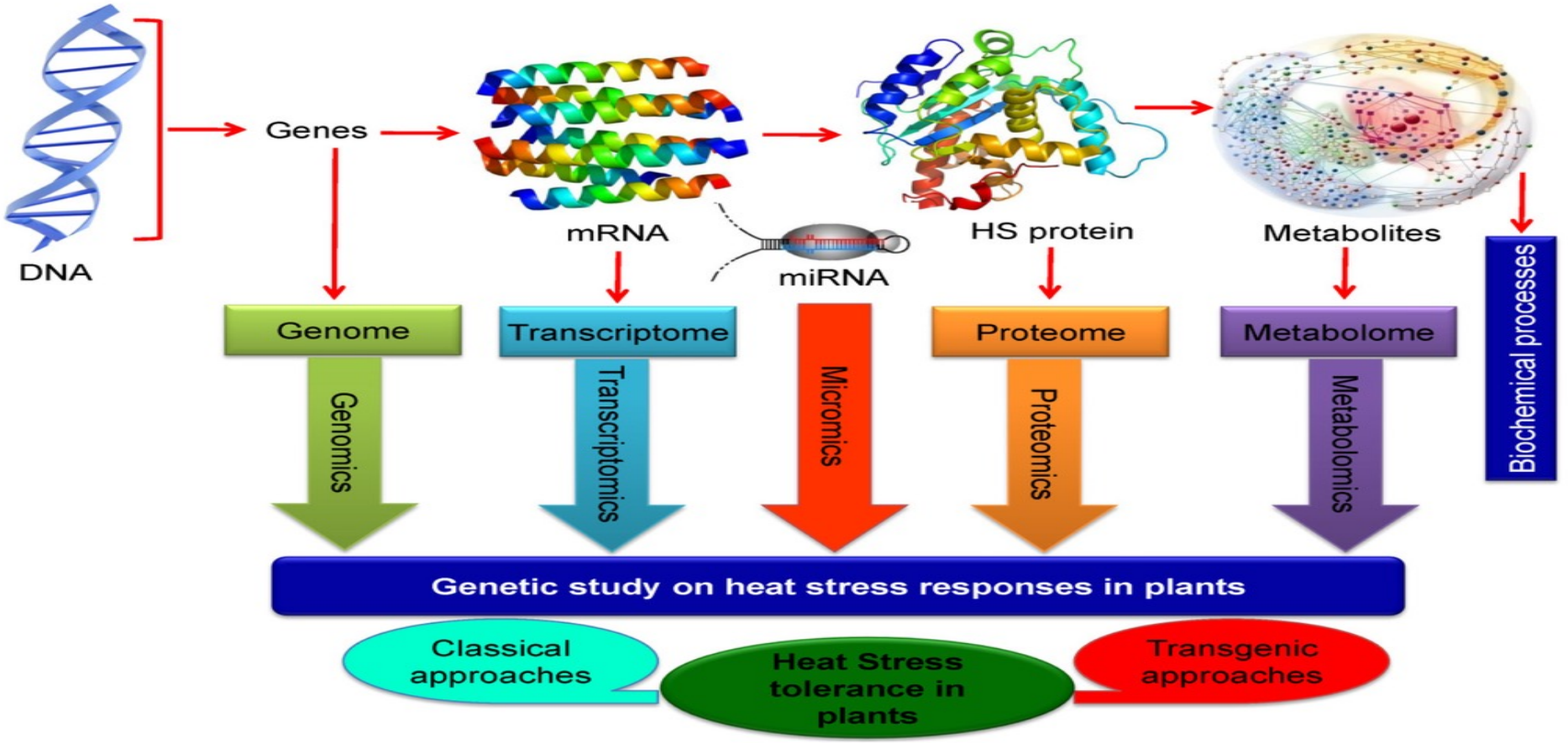




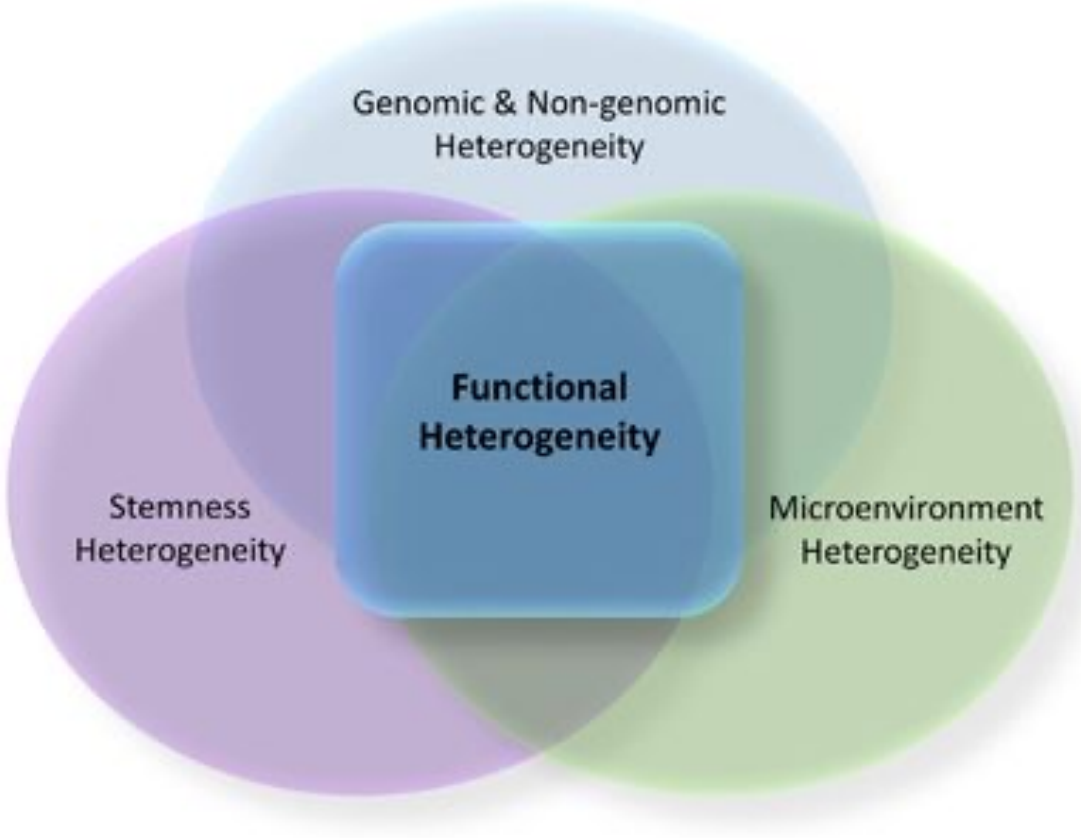
Gene Sequencing

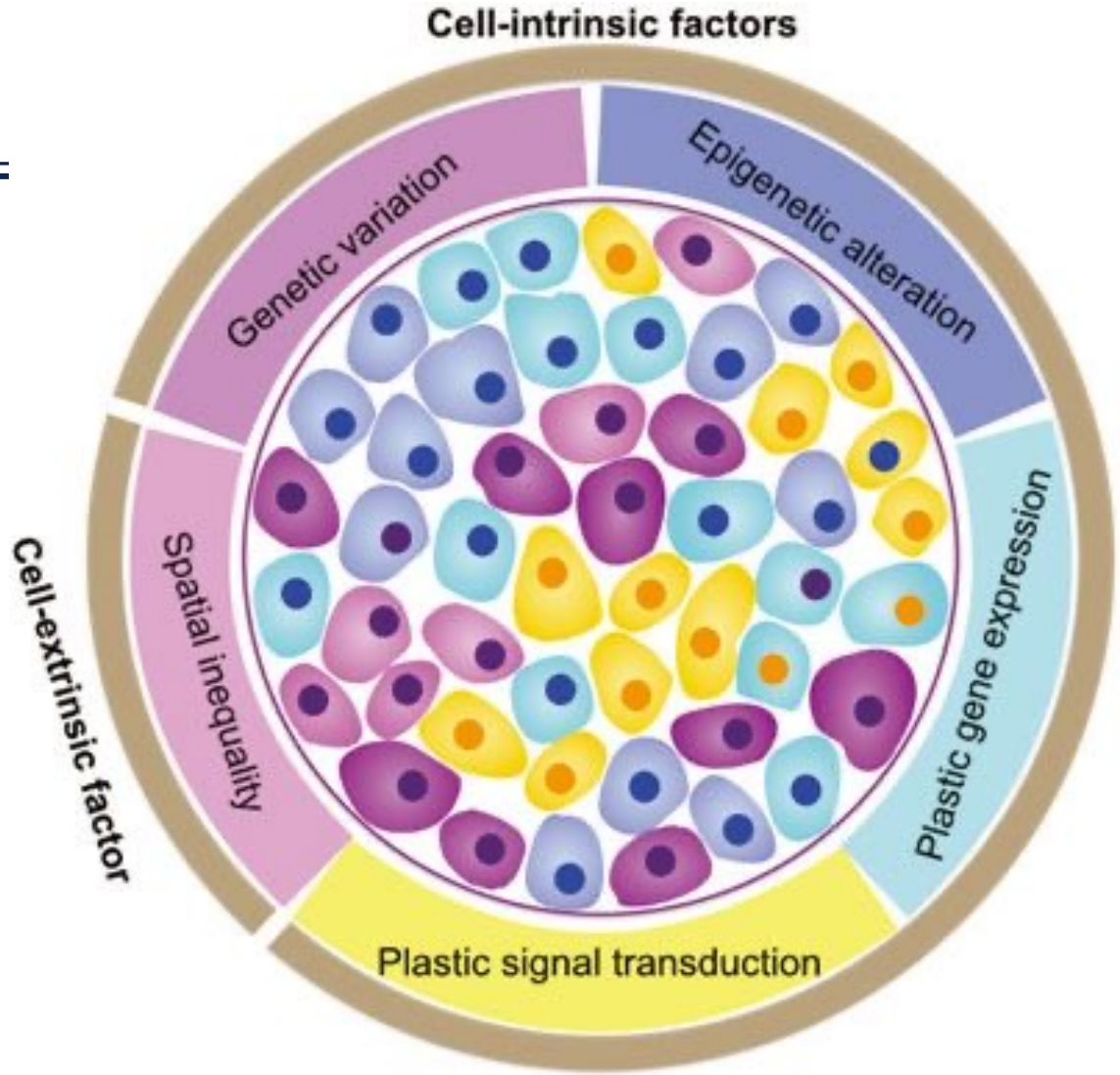


Multi-Omics

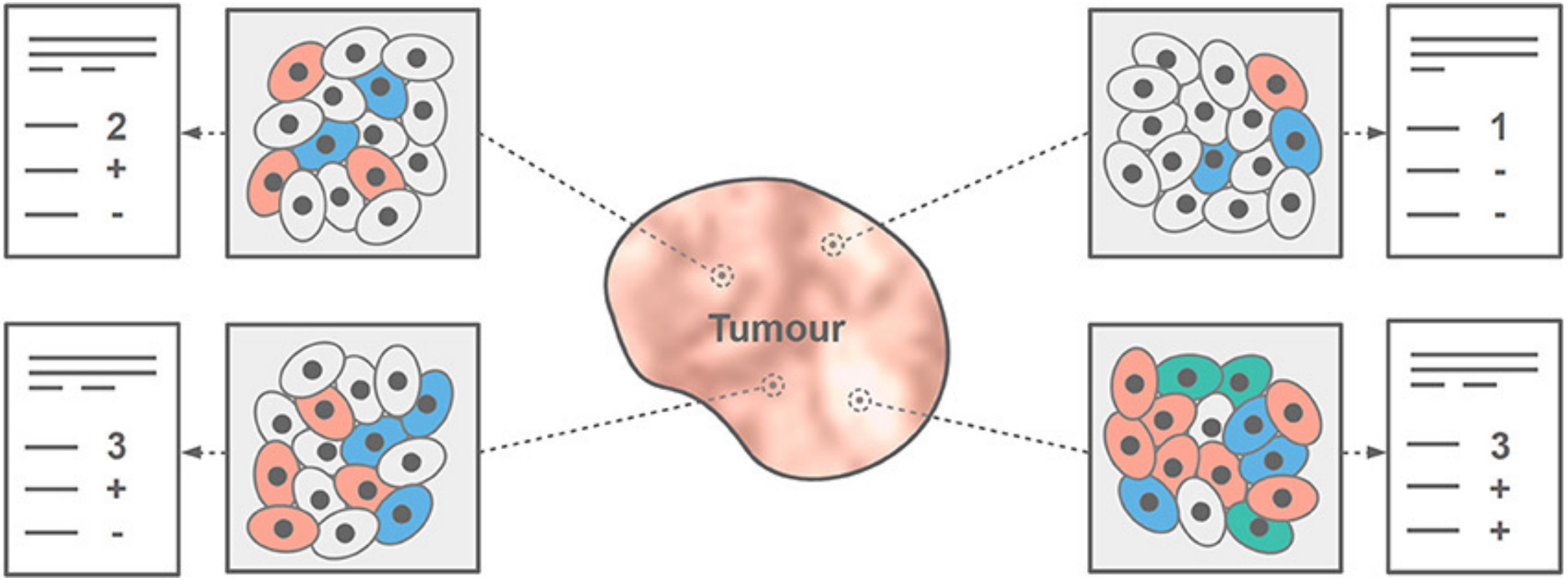

DNA
Genes
mRNA
miRNA
HS protein
Metabolites
Biochemical processes
Genome
Transcriptome
Proteome
Metabolome
Genomics
Transcriptomics
Micromics
Proteomics
Metabolomics
Genetic study on heat stress responses in plants
Classical approaches
Heat Stress tolerance in plants
Transgenic approaches

Heterogeneity

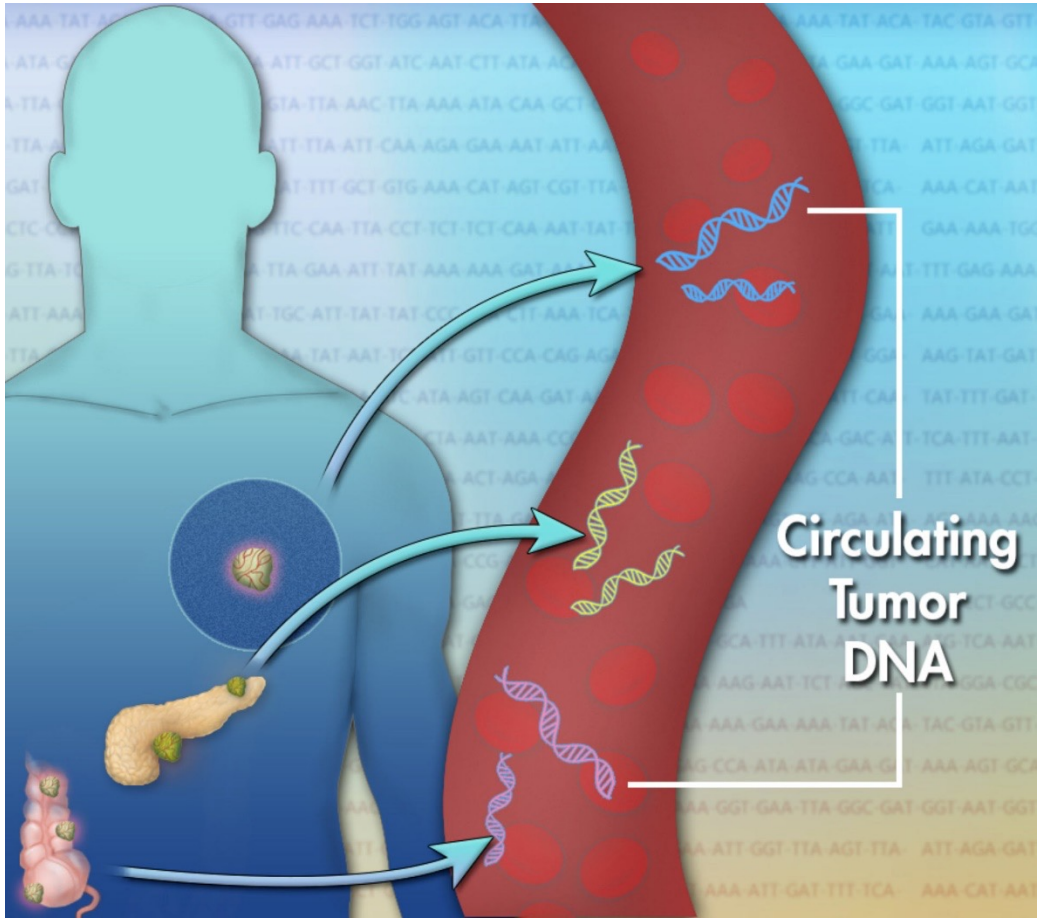




Tumor Heterogeneity



Circulating Profiling



Best Sample?

Advantages

- Biomarker identification in situ at primary site of interest
- Spatial resolution of tumor microenvironment

Challenges

- Invasive procedure
- Serial assessments very limited
- Tumor heterogeneity

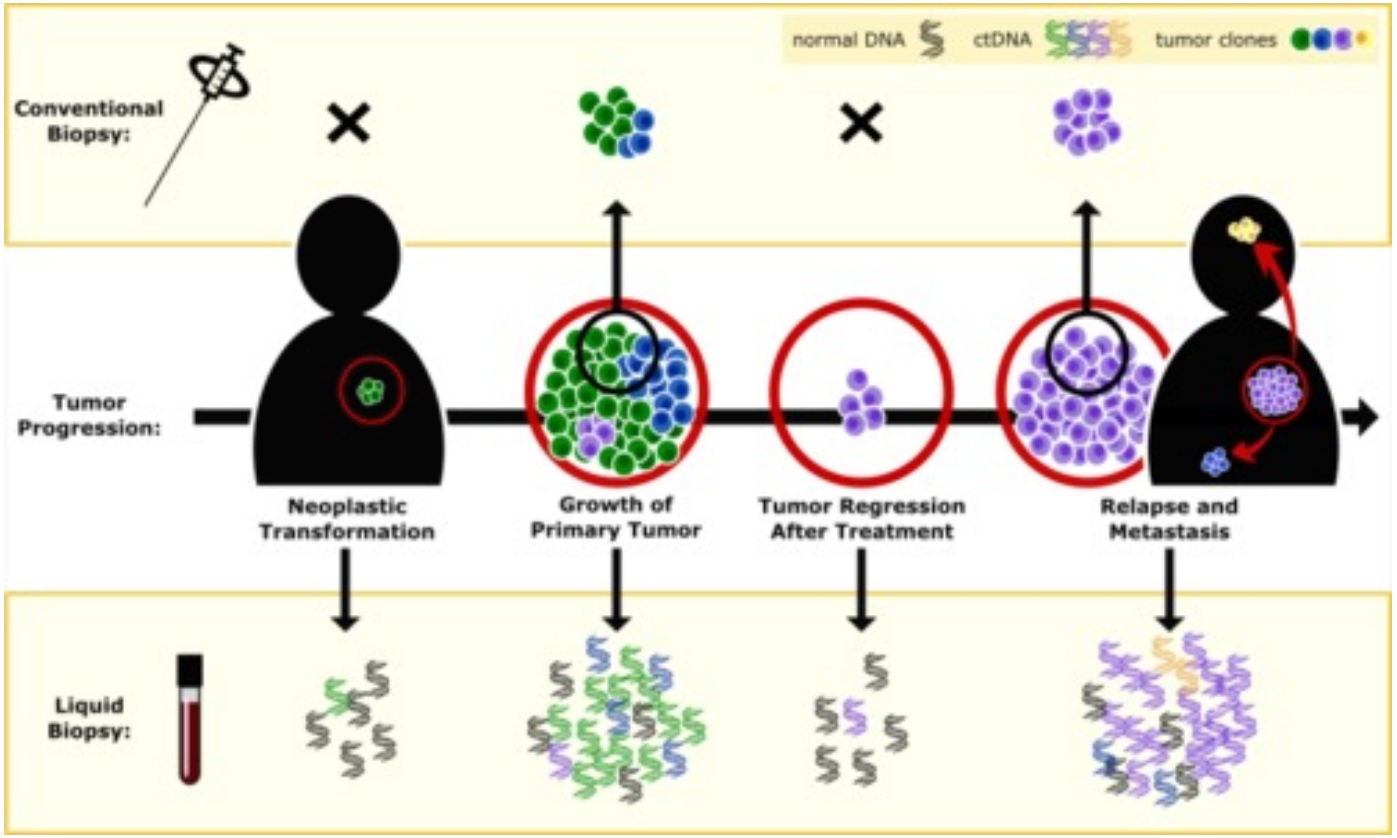
Advantages

- Minimal invasive
- Serial assessments
- Live monitoring
- Systemic (may compensate for intra-patient tumor heterogeneity)

Challenges

- No spatial resolution
- Real representative surrogate for tumor host interaction?
- Blood-derived biomarker represent true tumor heterogeneity?

Biopsies are not simple

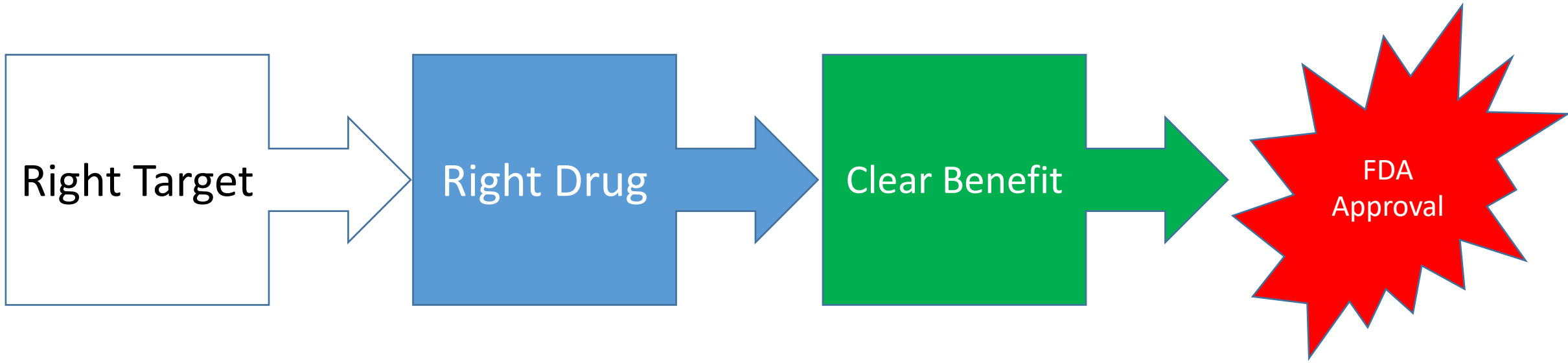


Every cancer patient should be profiled

- Rapidly evolving technology
- Costs falling
- The tests are NOT all the same
- We must prove better outcomes, improved “value”
- Early profiling requires lifetime tracking

The New Order of Clinical Research

- Phase 3 trials are less necessary
- Drugs are approved for biomarkers, not cancer types
- Guidelines may be just as important as regulatory approval



Precision Medicine in GI Cancers

Current State

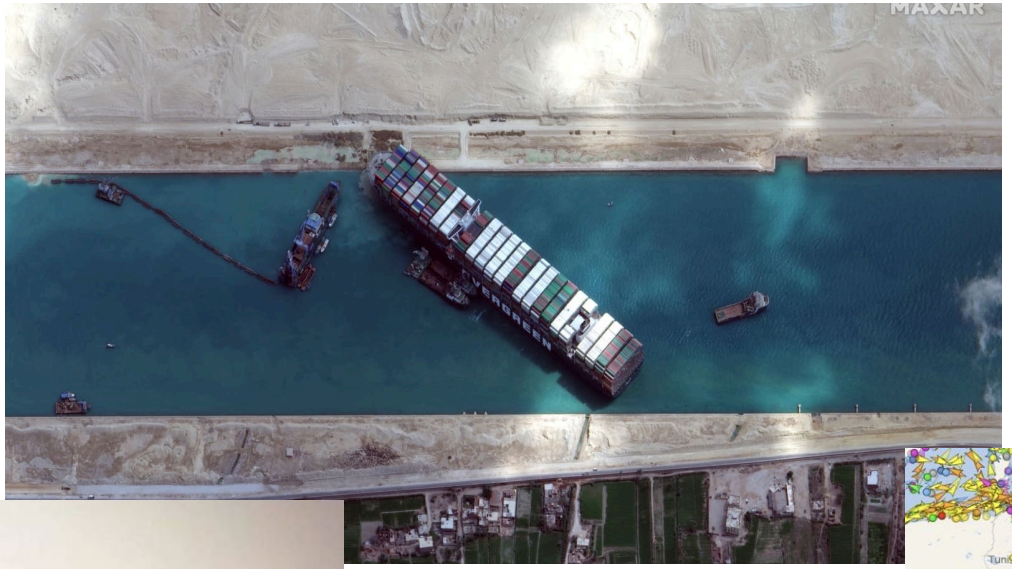
Essential Testing 2022

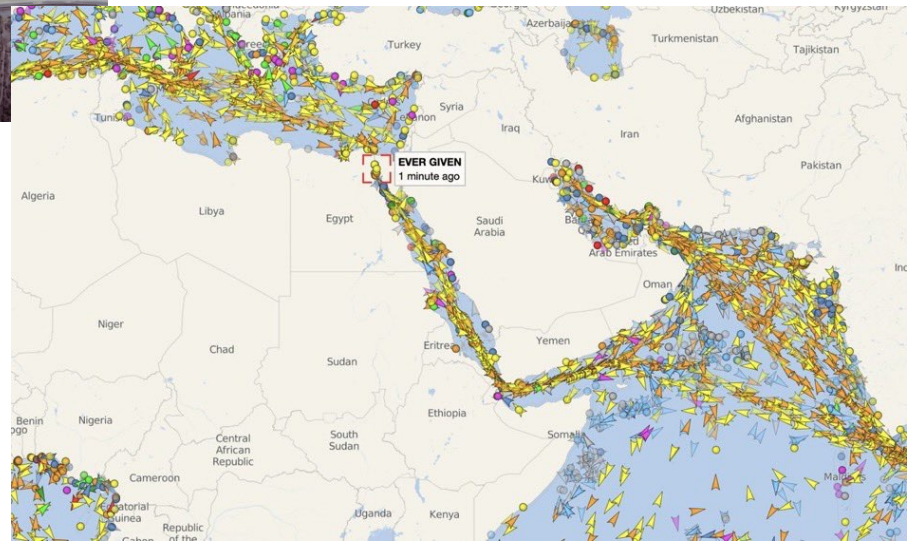
	Early Stages	Stage IV	All
Esophageal/Stomach	?None	Her2, PDL1, MSS/I	MSS/I TMB NTRK Germ Line?
Pancreas	BRCA	BRCA	
Bile Duct	None	FGF, IDH, BRAF, HER2	
Liver	None	None	
CRC	MSS/I	MSS/I, RAS, RAF, HER2	

Why is GI Cancer so Different

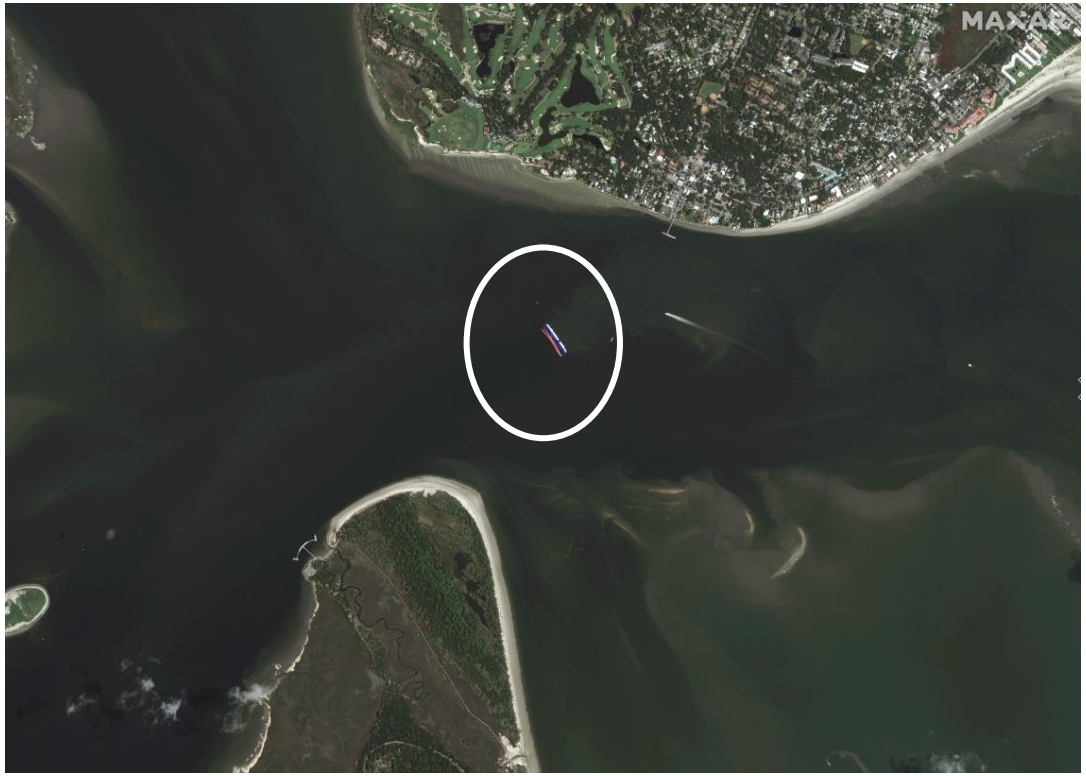
- Metastatic Disease ≠ Local Disease
- Are neo-adjuvant strategies Met or local biology?
- Esophageal ≠ EGJ ≠ Gastric
- Squamous ≠ Adenocarcinoma

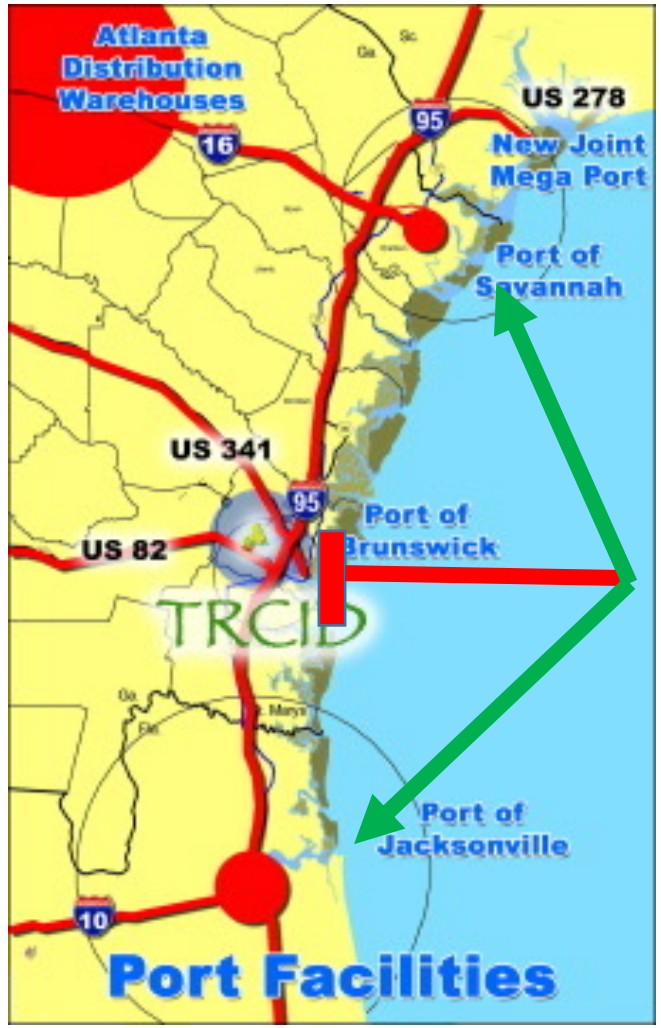
A Powerful Driver





A GI Cancer Driver

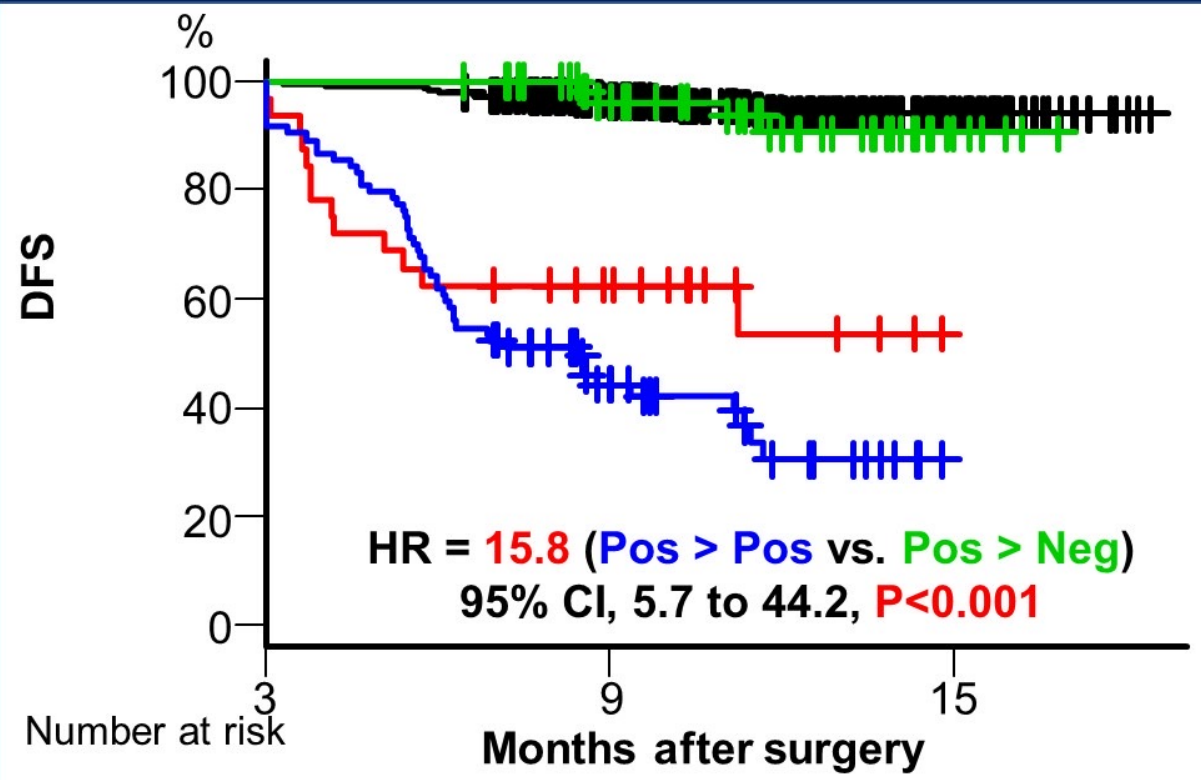




Stage 2/3 Colon CA: Need A Sorting Hat

- Cured by Surgery
- Not cured by surgery but 5FU will cure you
- Not cured by surgery but 5FU and Oxali will cure you
- Not cured by surgery and chemo will not cure you

DFS by ctDNA dynamics from post-op-4w to 12w

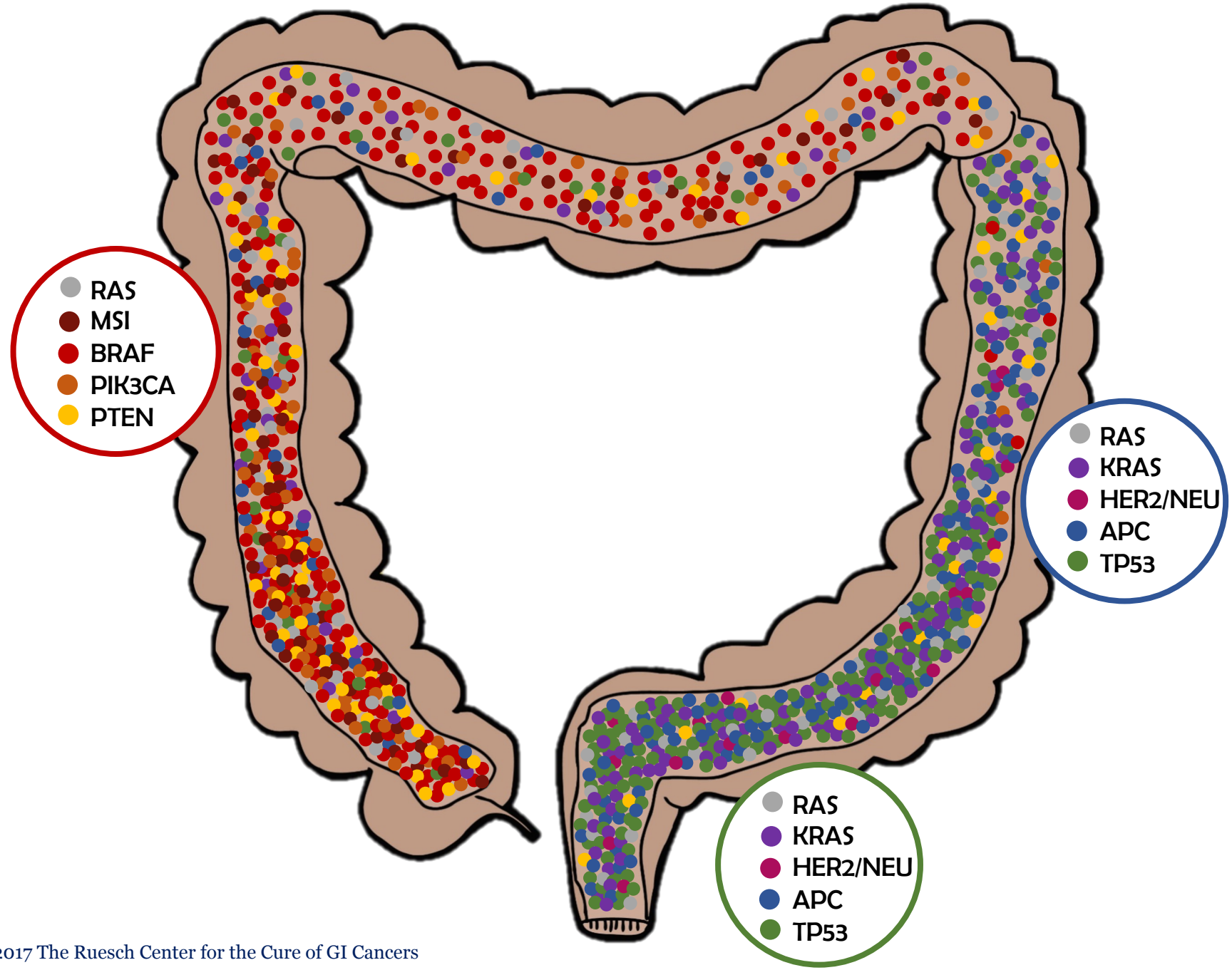


ctDNA dynamics — Neg > Neg — Neg > Pos — Pos > Neg — Pos > Pos

dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27–2.15	3.0–28.4	-	5.7-44.2
P	0.60	<0.001	-	<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Landmark analysis at the post-op-12w was performed.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.



Research Now **Requires** Collaboration

Caris POA Members: University / Academic

CARIS | PRECISION ONCOLOGY ALLIANCE

CARIS
PRECISION ONCOLOGY ALLIANCE
57 SITES

Brown
Columbia University
Cleveland Clinic
Duke University
Emory Winship Cancer Institute
Fox Chase Cancer Center, Temple Health
Georgia Cancer Center, Augusta University
MedStar Health
Indiana University Melvin and Bren Simon Comprehensive Cancer Center
Karmanos Cancer Institute
Loma Linda University
Medical College of Wisconsin
Memorial Sloan Kettering Cancer Center
Montefiore
NYU Langone Health
Northwestern Medicine
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
The Ohio State University Comprehensive Cancer Center
OU Health Stephenson Cancer Center
PennState Cancer Institute
Rutgers Cancer Institute of New Jersey
Sidney Kimmel Cancer Center, Jefferson Health
Siteman Cancer Center
TGH Tampa General Hospital Cancer Institute
Tulane University, Tulane Cancer Center
UAB Comprehensive Cancer Center, The University of Alabama at Birmingham
Cancer Center
UCI
UC San Diego Moores Cancer Center
At the Forefront UChicagoMedicine Comprehensive Cancer Center
University of Cincinnati Cancer Center
Cancer Center
University Hospitals
University of Iowa Holden Comprehensive Cancer Center
The University of Kansas Cancer Center
HealthCare Markey Cancer Center
University of Maryland
Sylvester Comprehensive Cancer Center, University of Miami Health System
Masonic Cancer Center, University of Minnesota
Penn Medicine Abramson Cancer Center
UPMC Hillman Cancer Center
UPR Universidad de Puerto Rico
USA Health Mitchell Cancer Institute
USC Norris Comprehensive Cancer Center, Keck Medicine of USC
The University of Tennessee Medical Center Cancer Institute
UT Health San Antonio
UTSouthwestern Harold C. Simmons Comprehensive Cancer Center
University of Utah Huntsman Cancer Institute
Massey Cancer Center, VCU
WVU
Weill Cornell Medicine
Yale

Caris POA Members: Community / Hybrid

CARIS PRECISION ONCOLOGY ALLIANCE

23 SITES

AdventHealth Orlando
Atrium Health Levine Cancer Institute
Barrow Neurological Institute
CARTI
Highlands Oncology
hoag.
HonorHealth
Maryland Oncology Hematology
Memorial Healthcare System
Miami Cancer Institute
Nebraska Cancer Specialists
New England Cancer Specialists
New York Cancer & Blood Specialists
Northside Hospital Cancer Institute
Piedmont Healthcare
Saint John's Cancer Institute
Saint John's Health Center
Providence
St. Joseph Health
St. Jude Medical Center
St. Joseph Health
St. Joseph Hospital
St Luke's University Health Network
Sarah Cannon
Fighting Cancer Together
Sutter Health CPMC
Virginia Cancer Specialists
West Cancer Center

Caris POA Members: Cooperative Groups & Research Consortiums

CARIS | PRECISION ONCOLOGY ALLIANCE

JOINED

SWOG CANCER RESEARCH NETWORK

NRG ONCOLOGY

Advancing Research. Improving Lives.™

IN DISCUSSIONS

ECOG-ACRIN cancer research group

Caris POA Members: International

CARIS PRECISION ONCOLOGY ALLIANCE

CURIE ONCOLOGY
SPRING WILL COME

国立研究開発法人
国立がん研究センター
National Cancer Center Japan

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

SARAH CANNON
Fighting Cancer Together™

tirol kliniken

VHIO
VALL D'HEBRON
Institute
of Oncology

Overall Actionability Estimates For Individual Pipelines

Single agent actionability across individual GI cancer cohorts

	ALL GI (5377)	CRC (2961)	PAAD (935)	ESCA (397)	STAD (384)	CHOL (234)	HCC (133)	NET (113)
PD-1/PD-L1 mAb	7%	9%	4%	5%	10%	6%	5%	4%
PARP inh	15%	14%	14%	17%	24%	27%	14%	13%
ATM/ATR inh	10%	10%	7%	12%	15%	15%	7%	10%
CHEK1 inh	19%	20%	15%	23%	20%	14%	14%	21%
WEE1 inh	4%	4%	5%	4%	5%	1%		2%
NTRK inh	<1%	<1%						
ALK/ROS1/MET inh	<1%	<1%	<1%	3%	3%	3%	2%	4%
PDGFR/KIT/ABL1 inh	2%	<1%	<1%	<1%	2%	3%	2%	<1%
VEGF/VEGFR inh	2%	3%	<1%		<1%	<1%		
FGFR inh	2%	2%	2%	3%	3%	2%	<1%	<1%
EGFR inh	1%	<1%	<1%	5%	5%		<1%	
PI3K/AKT/mTOR inh	24%	31%	11%	20%	22%	23%	11%	14%
BRAF inh	5%	8%	2%	2%	2%	3%		4%
pan-RAF inh	8%	9%	2%	2%	2%	5%		4%
MEK/ERK inh	13%	18%	4%	5%	9%	13%	4%	7%
CDK4/6 inh	5%	4%	4%	16%	6%	2%	10%	3%
BET inh	3%	2%	2%	5%	4%	3%	5%	4%
SMO inh	1%	2%	<1%	<1%	2%	<1%		
Wnt inh	8%	9%	5%	3%	9%	3%	33%	2%
epigenetic modulator	1%	1%	1%	3%	3%	<1%	<1%	2%

Abbreviations: colorectal (CRC), pancreatic (PAAD), esophageal (ESCA), stomach (STAD), bile duct (CHOL), hepatocellular (HCC) cancers and GI neuroendocrine tumors (NET). Patient cohort sizes are shown in parentheses

MI FOLFOXai™ - Now Published

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Clinical Validation of a Machine-learning–derived Signature Predictive of Outcomes from First-line Oxaliplatin-based Chemotherapy in Advanced Colorectal Cancer

Jim P. Abraham[1], Daniel Magee[1], Chiara Cremolini[2], Carlotta Antoniotti[2], David D. Halbert[1], Joanne Xiu[1], Phillip Stafford[1], Donald A. Berry[3], Matthew J. Oberley[1], Anthony F. Shields[4], John L. Marshall[5], Mohamed E. Salem[6], Alfredo Falcone[2], Axel Grothey[7], Michael J. Hall[8], Alan P. Venook[9], Heinz-Josef Lenz[10], Anthony Helmstetter[1], W. Michael Korn[1], and David B. Spetzler[1]

ABSTRACT

Purpose: FOLFOX, FOLFIRI, or FOLFOXIRI chemotherapy with bevacizumab is considered standard first-line treatment option for patients with metastatic colorectal cancer (mCRC). We developed and validated a molecular signature predictive of efficacy of oxaliplatin-based chemotherapy combined with bevacizumab in patients with mCRC.

Experimental Design: A machine-learning approach was applied and tested on clinical and next-generation sequencing data from a real-world evidence (RWE) dataset and samples from the prospective TRIBE2 study resulting in identification of a molecular signature, FOLFOX*ai*. Algorithm training considered time-to-next treatment (TTNT). Validation studies used TTNT, progression-free survival, and overall survival (OS) as the primary endpoints.

Results: A 67-gene signature was cross-validated in a training cohort ($N = 105$) which demonstrated the ability of FOLFOX*ai* to distinguish FOLFOX-treated patients with mCRC with increased benefit from those with decreased benefit. The signature was predictive of TTNT and OS in an independent RWE dataset of 412 patients who had received FOLFOX/bevacizumab in first line and inversely predictive of survival in RWE data from 55 patients who had received first-line FOLFIRI. Blinded analysis of TRIBE2 samples confirmed that FOLFOX*ai* was predictive of OS in both oxaliplatin-containing arms (FOLFOX HR, 0.629; $P = 0.04$ and FOLFOXIRI HR, 0.483; $P = 0.02$). FOLFOX*ai* was also predictive of treatment benefit from oxaliplatin-containing regimens in advanced esophageal/gastro-esophageal junction cancers, as well as pancreatic ductal adenocarcinoma.

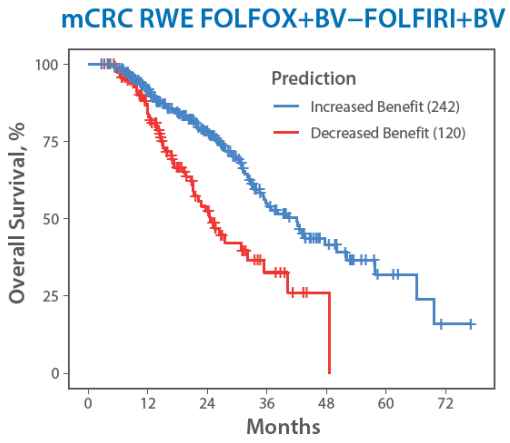
Conclusions: Application of FOLFOX*ai* could lead to improvements of treatment outcomes for patients with mCRC and other cancers because patients predicted to have less benefit from oxaliplatin-containing regimens might benefit from alternative regimens.

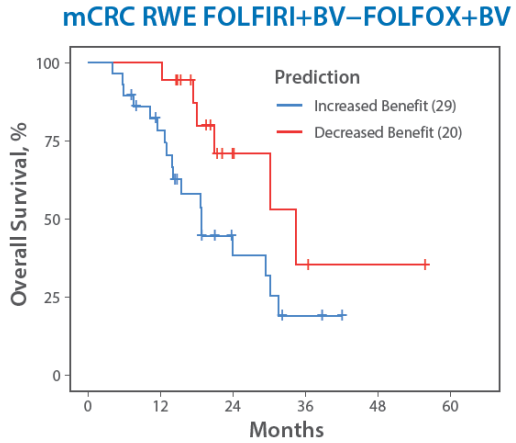
Introduction

Over the last 2 decades, conventional chemotherapies (e.g., oxali-

MI FOLFOXai™: 1st Clinically Validated AI-Driven Frontline Chemotherapy Predictor

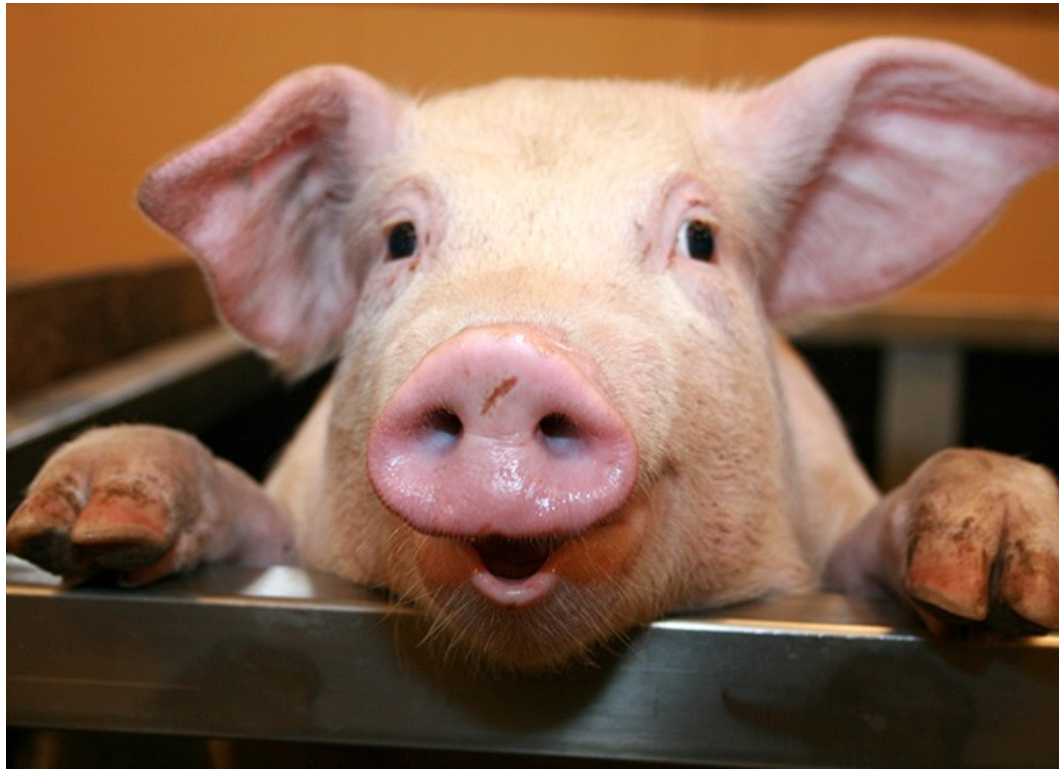
- 17.5 month increase in Median OS in patients treated in manner consistent with MI FOLFOXai predictor than patients treated counter to the prediction.
- Demonstrated ~71% difference in median OS for patients in the FOLFOX 1st arm compared to the FOLFIRI 1st arm.
- MI FOLFOXai demonstrates the impact of how FOLFOX and FOLFIRI are sequenced in patient treatment.
- Two independent data sets:
  - 412 manually curated cases with RWE
  - 149 cases analyzed retrospectively from the randomized, prospective Phase III TRIBE2 study





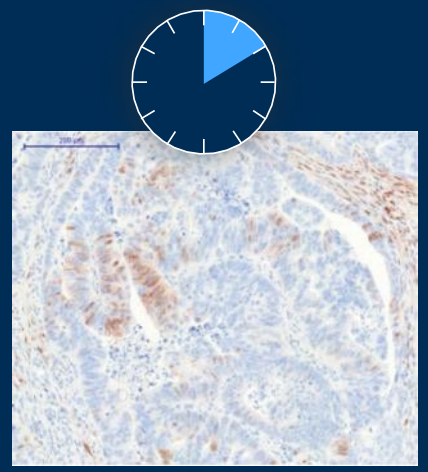
Median Overall Survival	MI FOLFOXai™ Indicates:	
	FOLFOX+BV 1st → FOLFIRI+BV 2nd (FOLFOX/BV RWE cohort)	FOLFIRI+BV 1st → 2nd FOLFOX+BV (FOLFIRI/BV RWE cohort)
OS When Patient Received: FOLFOX/BV 1st → FOLFIRI+BV 2nd	**42.0 months**	18.7 months
OS When Patient Received: FOLFIRI+BV 1st → FOLFOX 2nd	24.5 months	**34.4 months**

Why DNA Mutations Only Tell Part of the Story

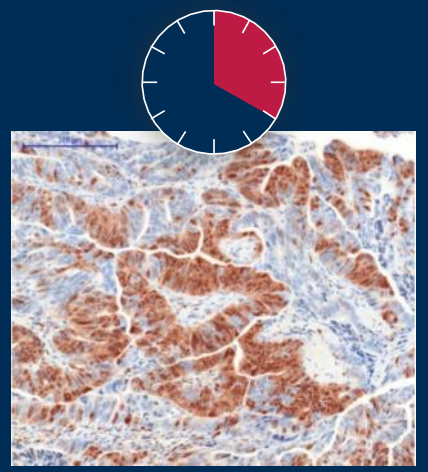


TISSUE IS THE ISSUE

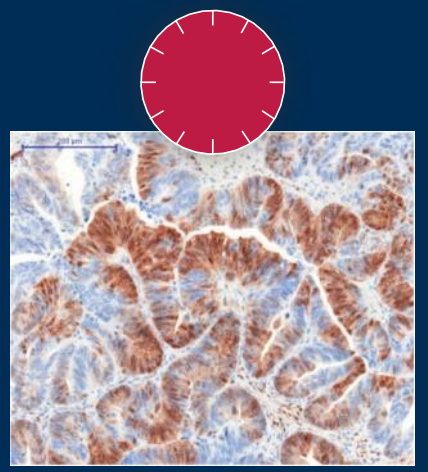
The thought on which all of Indivumed is based



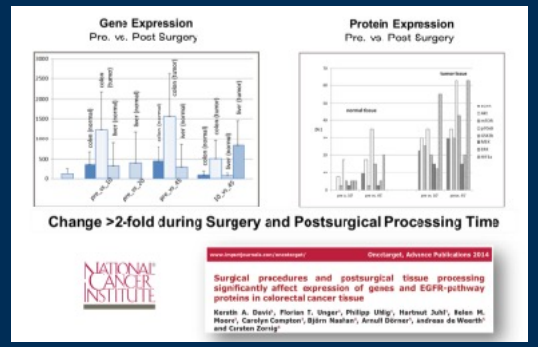
10 min



20 min



60 min



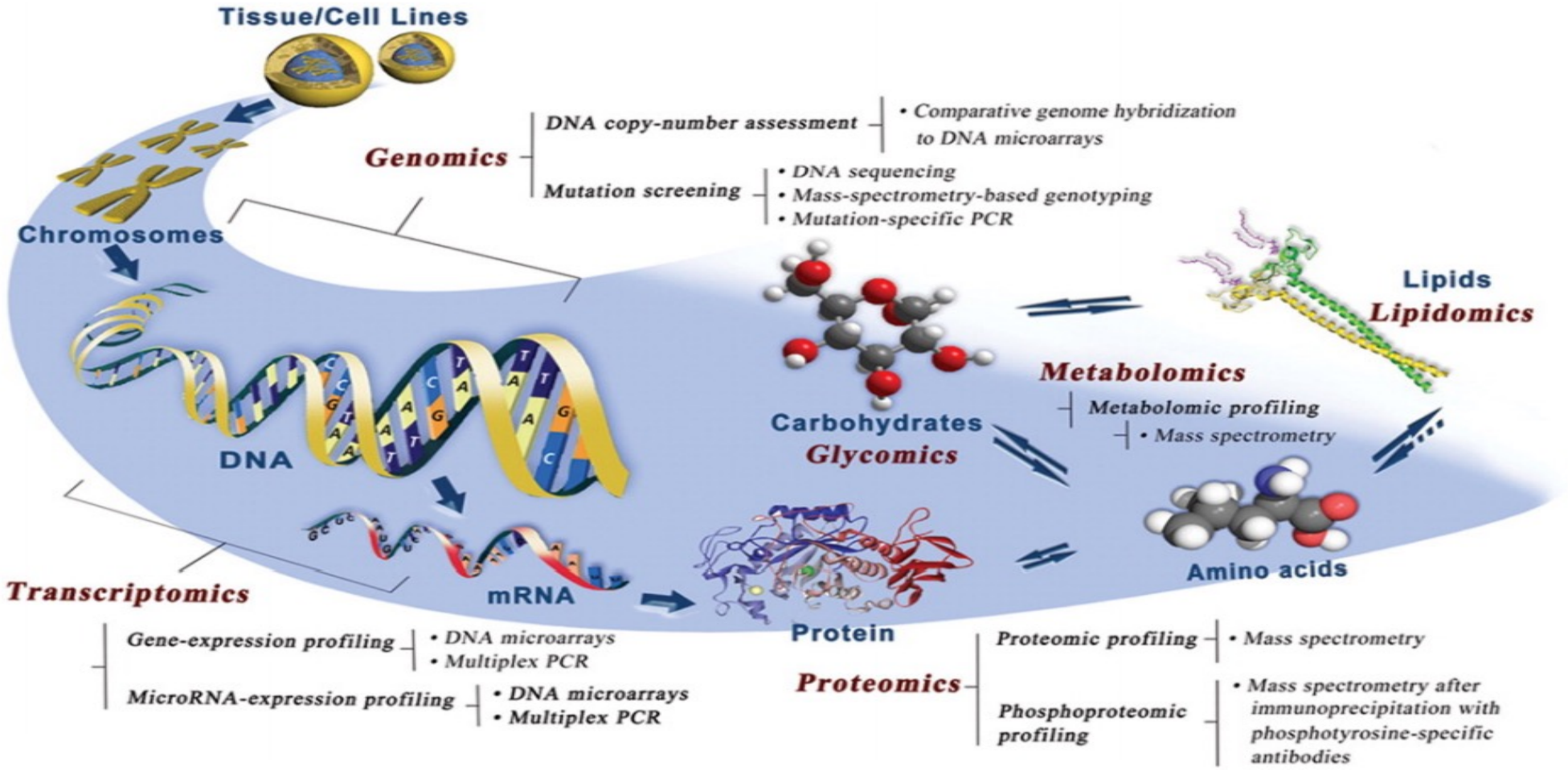
** David et all, Oncotarget, 2014*

Change of biological tissue composition within minutes after surgical tissue removal

>20% of expressed molecules are affected within 20 min ischemia time*

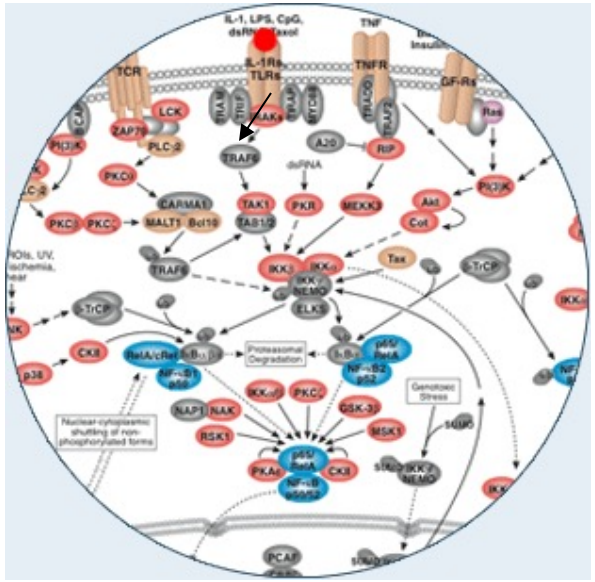
Indivumed Therapeutics

Multi-omics

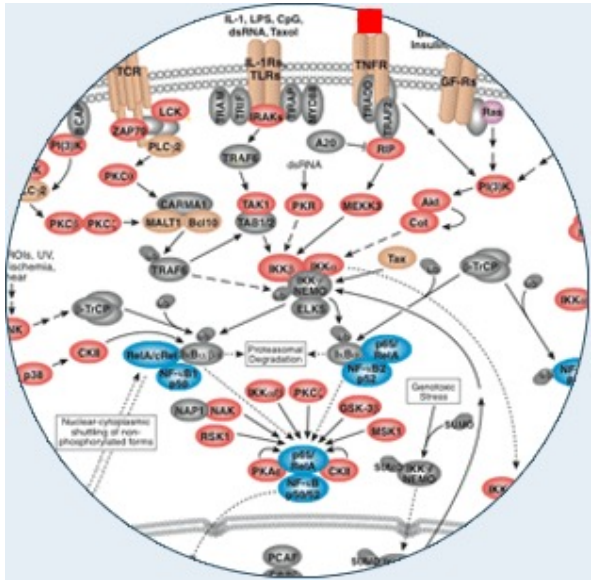

Tissue/Cell Lines
Chromosomes
DNA
mRNA
Protein
Carbohydrates
Glycomics
Lipids
Lipidomics
Metabolomics
Metabolomic profiling
• Mass spectrometry
Amino acids
Genomics
DNA copy-number assessment
• Comparative genome hybridization to DNA microarrays
Mutation screening
• DNA sequencing
• Mass-spectrometry-based genotyping
• Mutation-specific PCR
Transcriptomics
Gene-expression profiling
• DNA microarrays
• Multiplex PCR
MicroRNA-expression profiling
• DNA microarrays
• Multiplex PCR
Proteomics
Proteomic profiling
• Mass spectrometry
Phosphoproteomic profiling
• Mass spectrometry after immunoprecipitation with phosphotyrosine-specific antibodies

Cancer is driven by hyperactive or defective protein circuits

The components of these circuits contain the drug targets of the future.

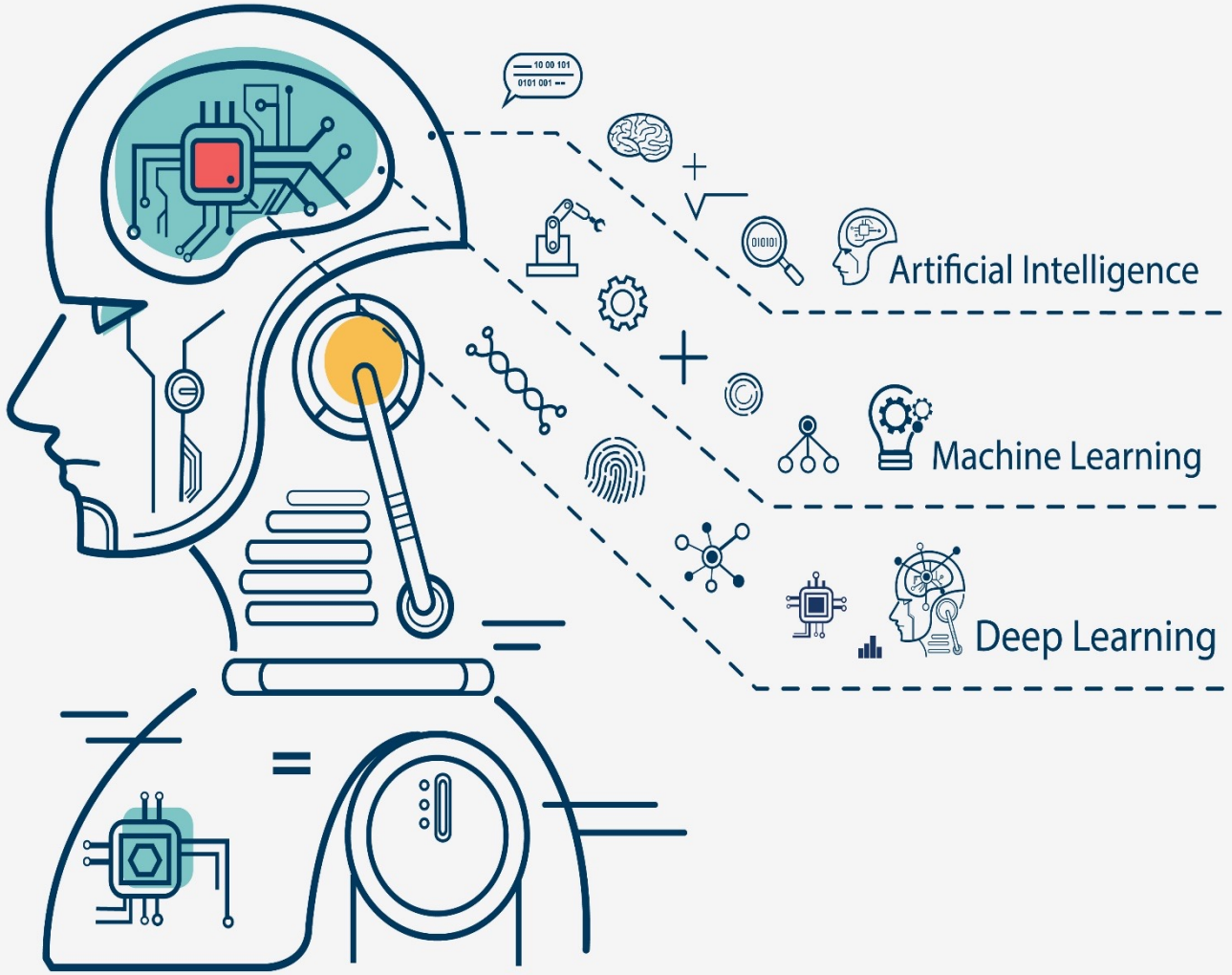


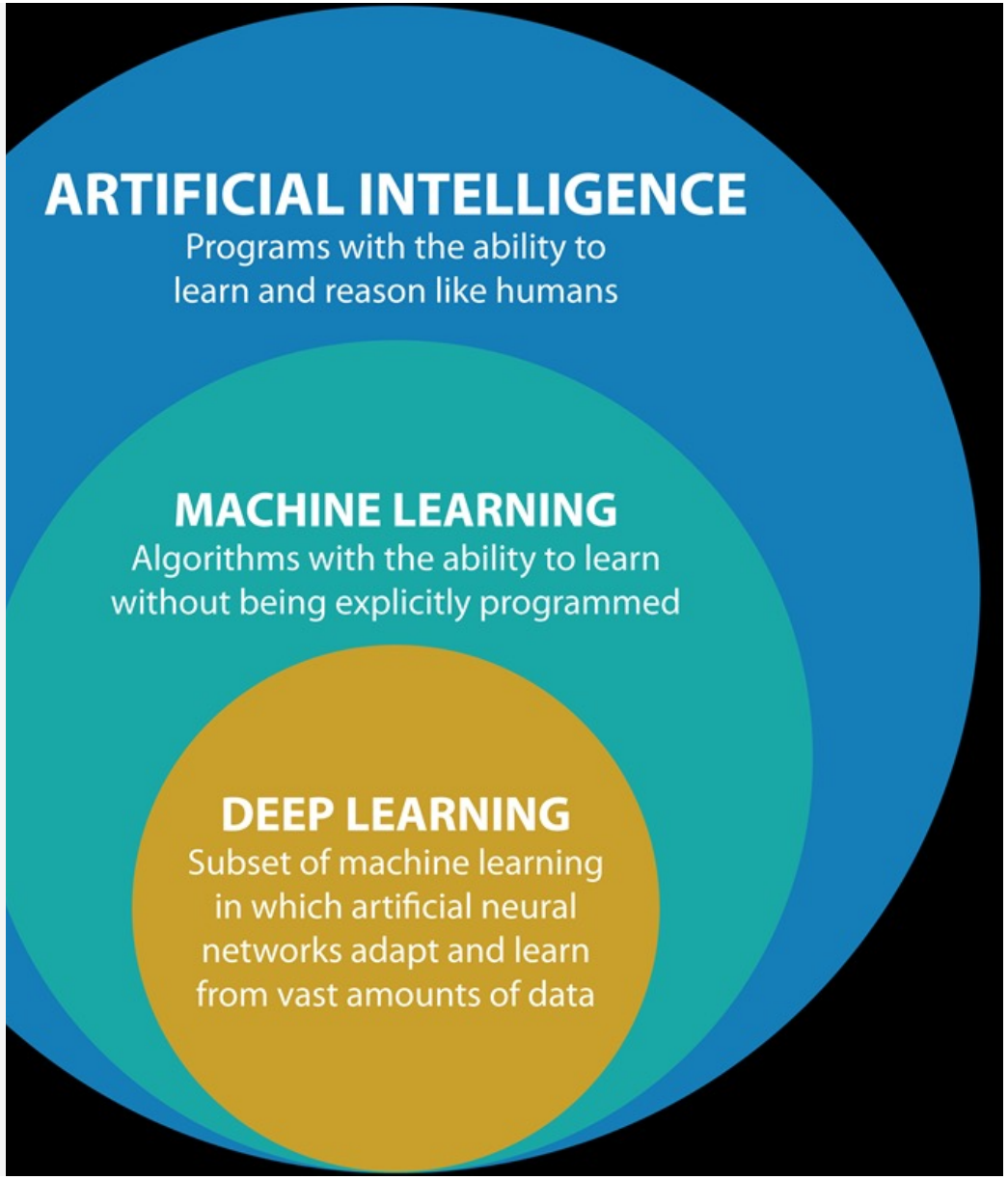
Patient A



Patient B

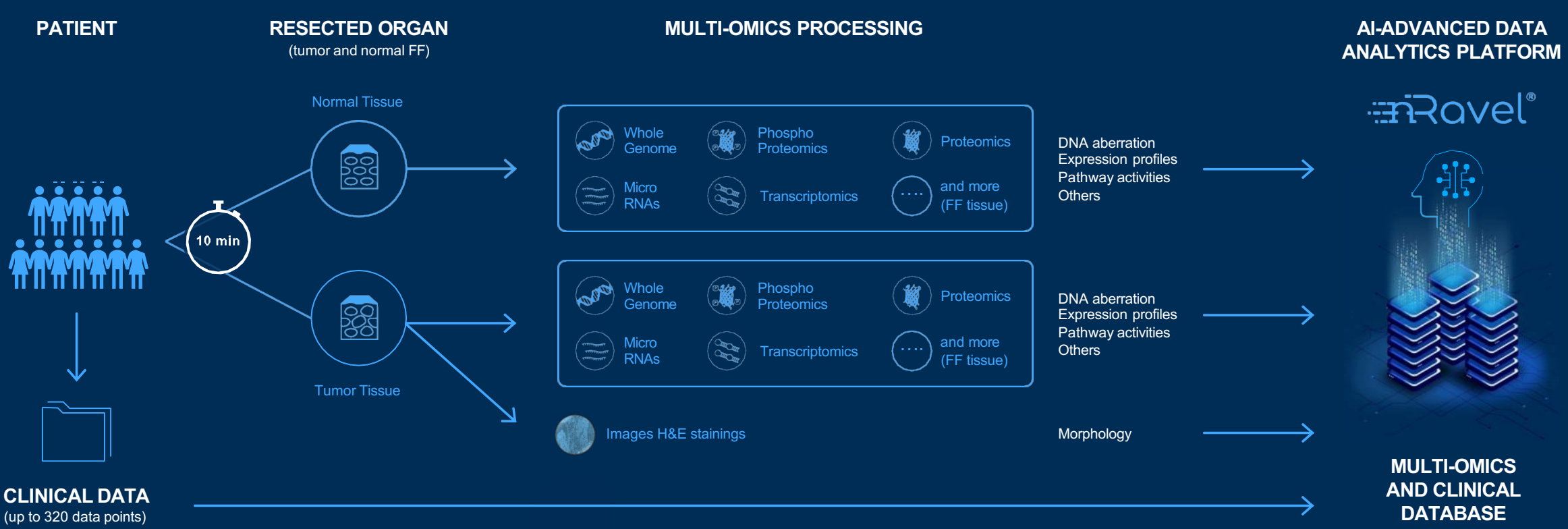
Each patient's cancer is different. A drug that works for one patient may not work for another patient with the same cancer.


Artificial Intelligence
Machine Learning
Deep Learning


ARTIFICIAL INTELLIGENCE
Programs with the ability to learn and reason like humans
MACHINE LEARNING
Algorithms with the ability to learn without being explicitly programmed
DEEP LEARNING
Subset of machine learning in which artificial neural networks adapt and learn from vast amounts of data

FROM PATIENT TO DISCOVERY

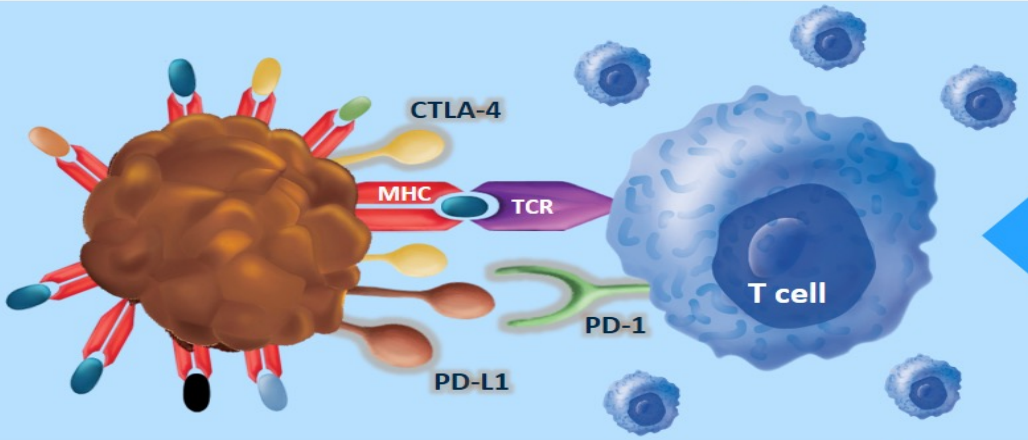
Complete data from every individual patient



Immune Therapy

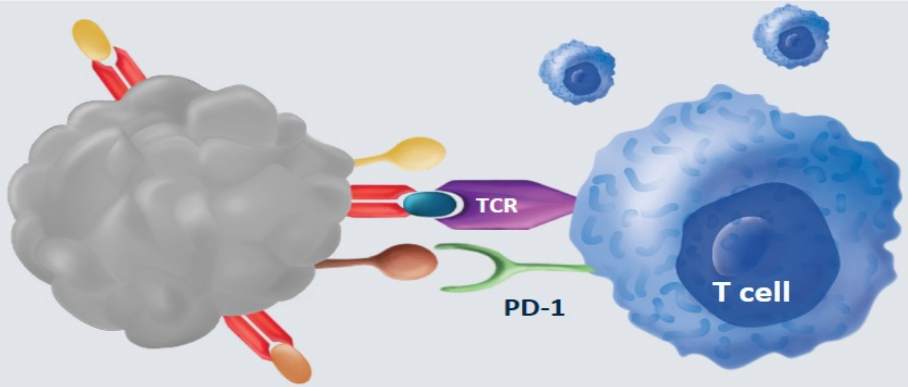
Immune Checkpoint (PD-1) Blockade Can Be a Therapeutic Target in MSI-H/dMMR Tumors

MSI-H/dMMR Tumors Have High Expression of Immune Checkpoint Molecules[1,2]



MSI-H/dMMR tumor

MSI-H/dMMR tumors are characterized by high expression of checkpoint molecules such as PD-1, PD-L1, CTLA-4, LAG-3, and IDO[1]



MSS tumor

CTLA-4 = cytotoxic T lymphocyte antigen-4; dMMR = mismatch repair deficient; IDO = indolamine 2′3′-dioxygenase; LAG-3 = lymphocyte-activation gene 3; MHC = major histocompatibility complex; MSI-H = microsatellite instability high; MSS = microsatellite stable; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand-1; TCR = T-cell receptor.

1. Llosa NJ, et al. *Cancer Discov.* 2015;5(1):43–51. **2.** Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264.

Immune Oncology

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

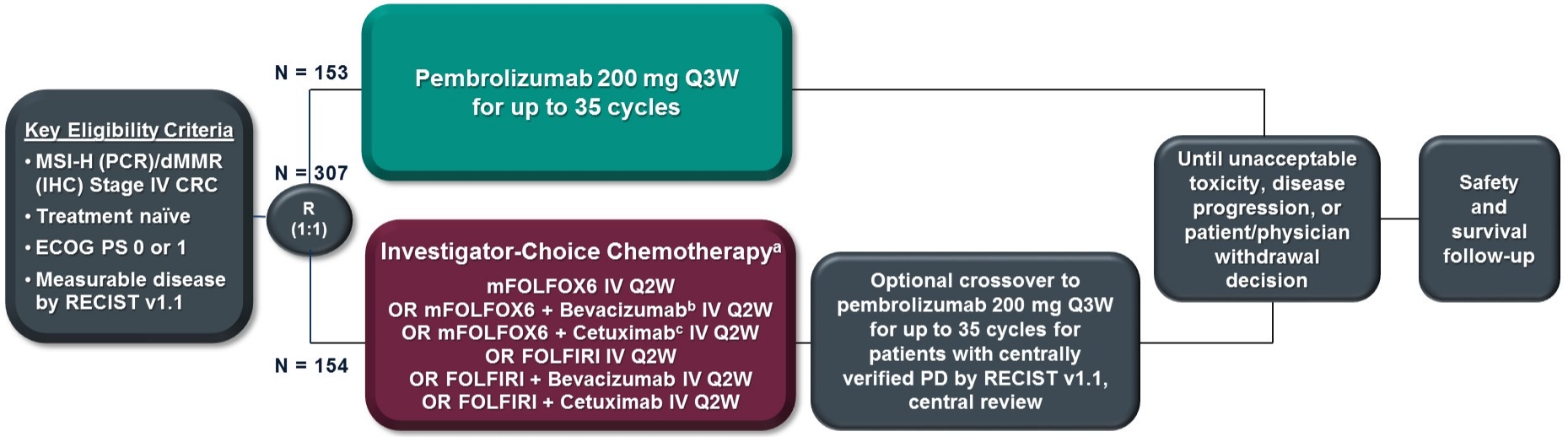
Thierry André,[1] Kai-Keen Shiu,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis Punt,[6] Denis Smith,[7] Rocio Garcia-Carbonero,[8] Manuel Benavides,[9] Peter Gibbs,[10] Christelle de la Fouchardiere,[11] Fernando Rivera,[12] Elena Elez,[13] Johanna Bendell,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Ping Yang,[17] Mohammed Farooqui,[18] Patricia Marinello,[18] and Luis A. Diaz Jr[19]

[1]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [2]University College Hospital, NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Thierry Andre, MD

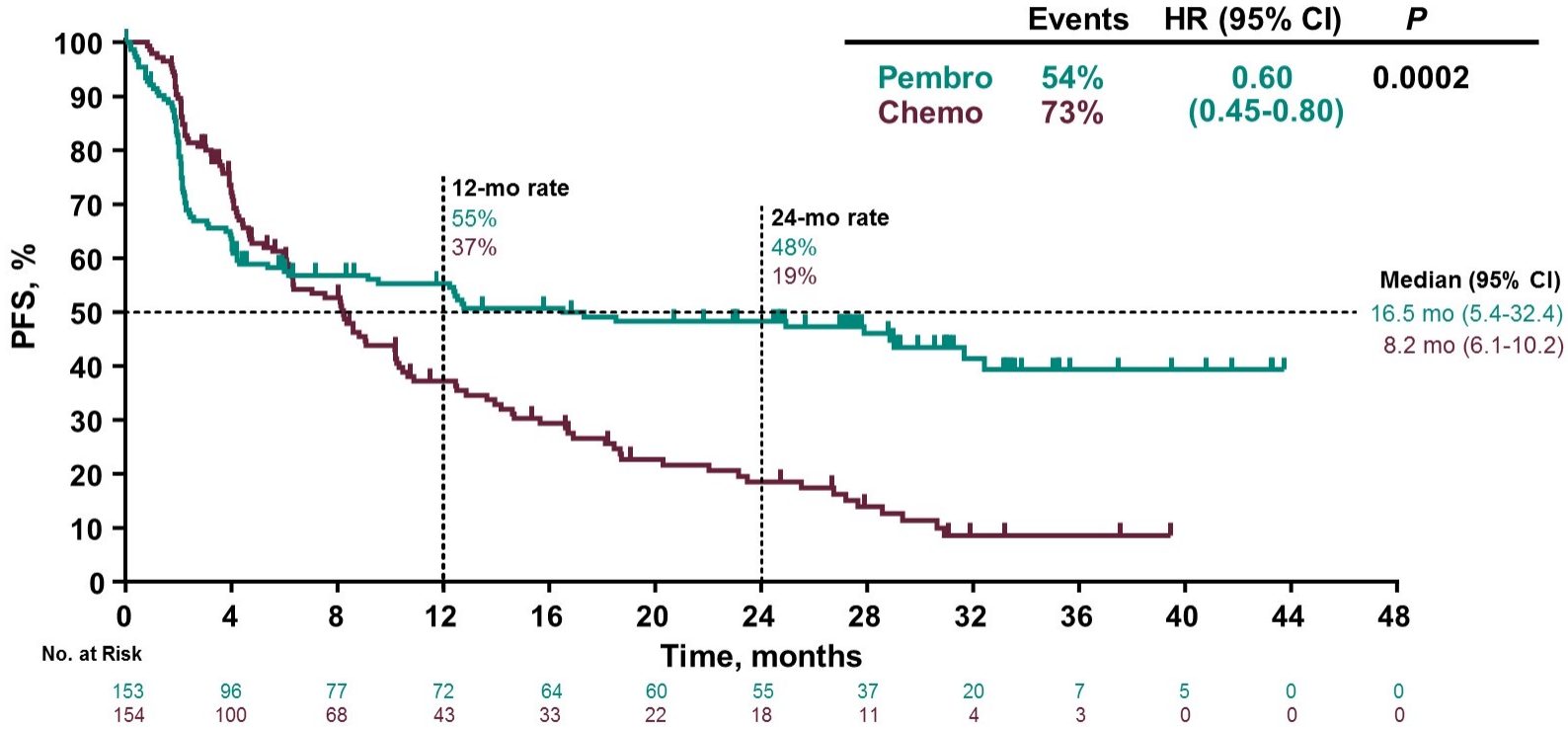
KEYNOTE-177 Study Design (NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

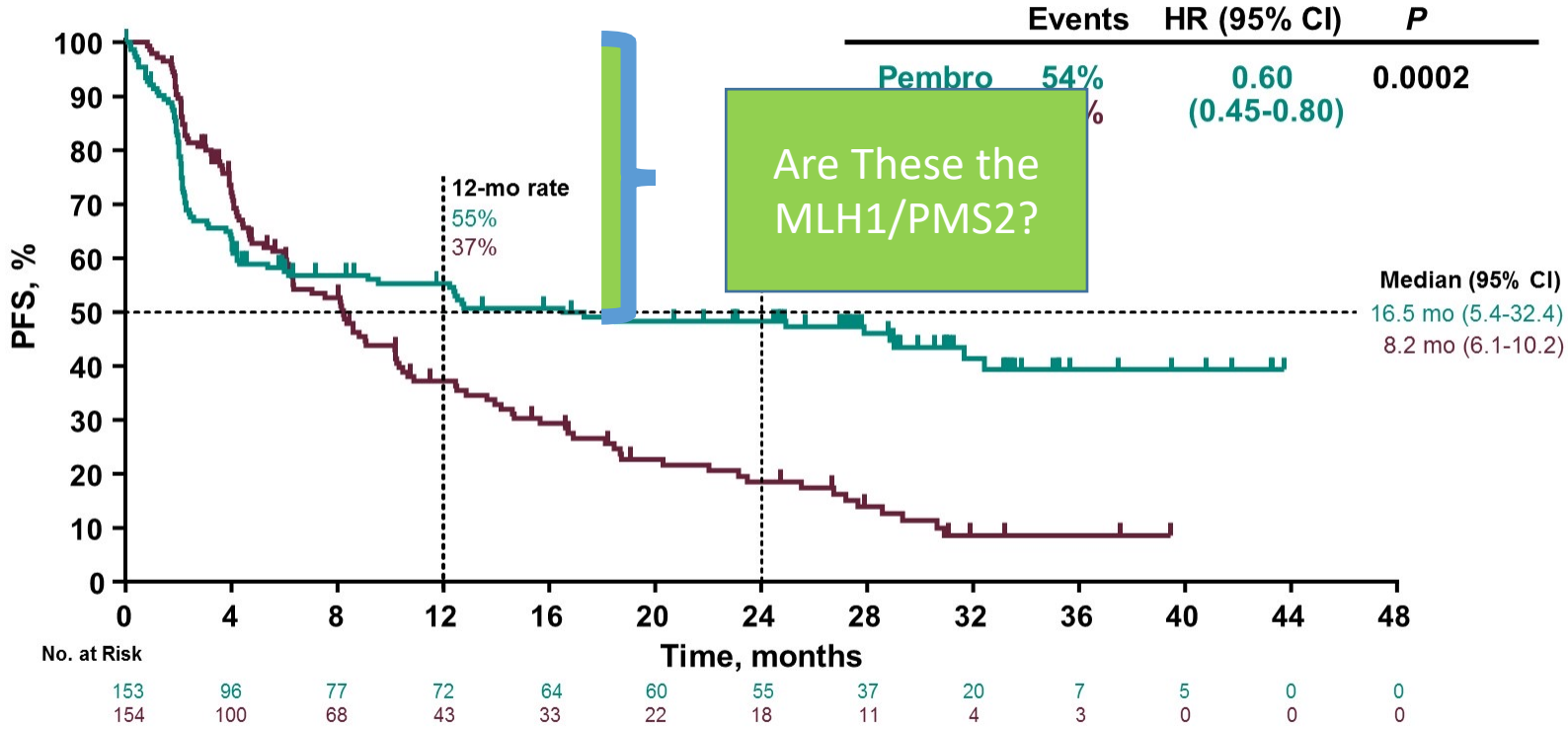
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Progression-Free Survival



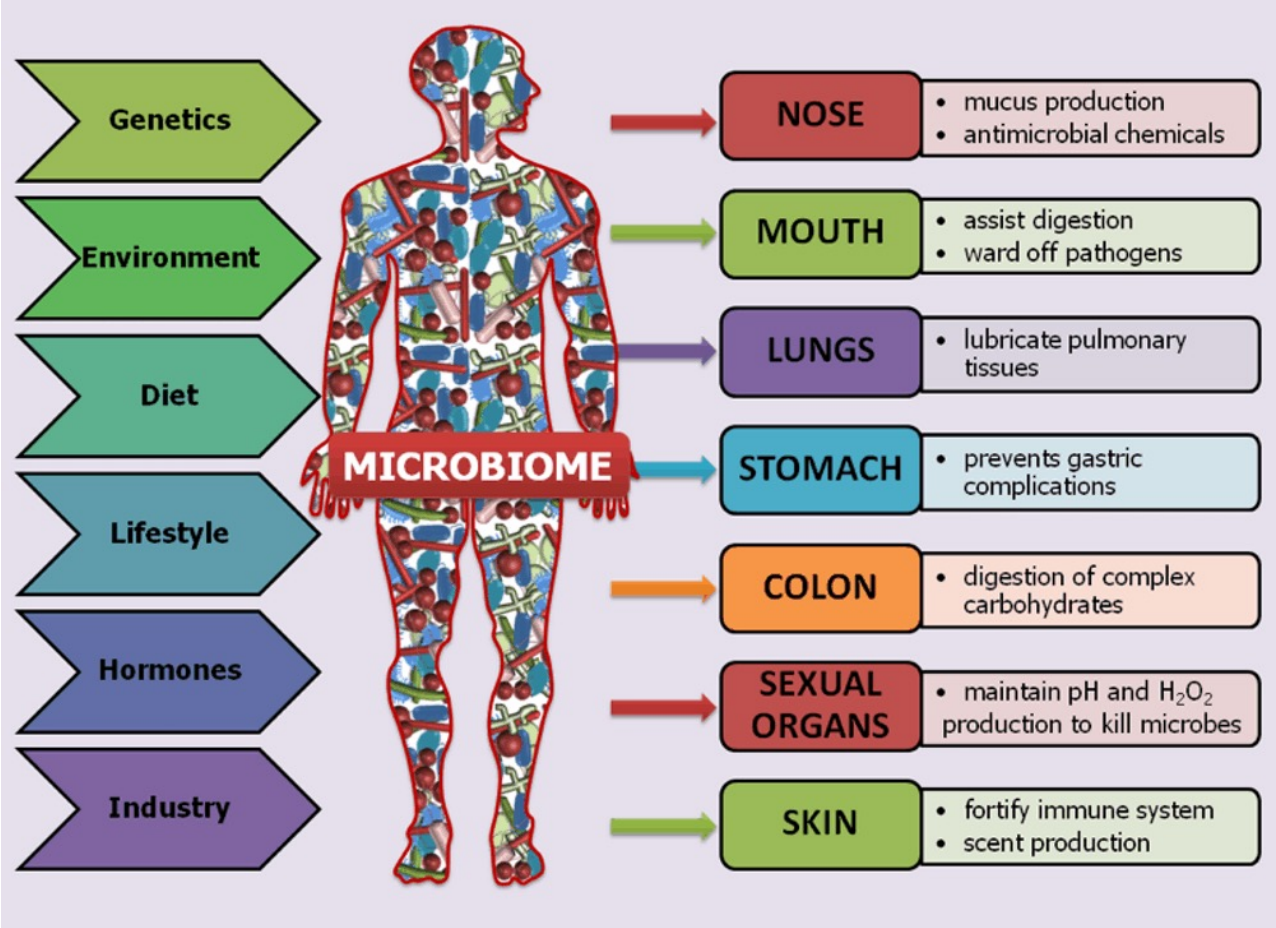
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

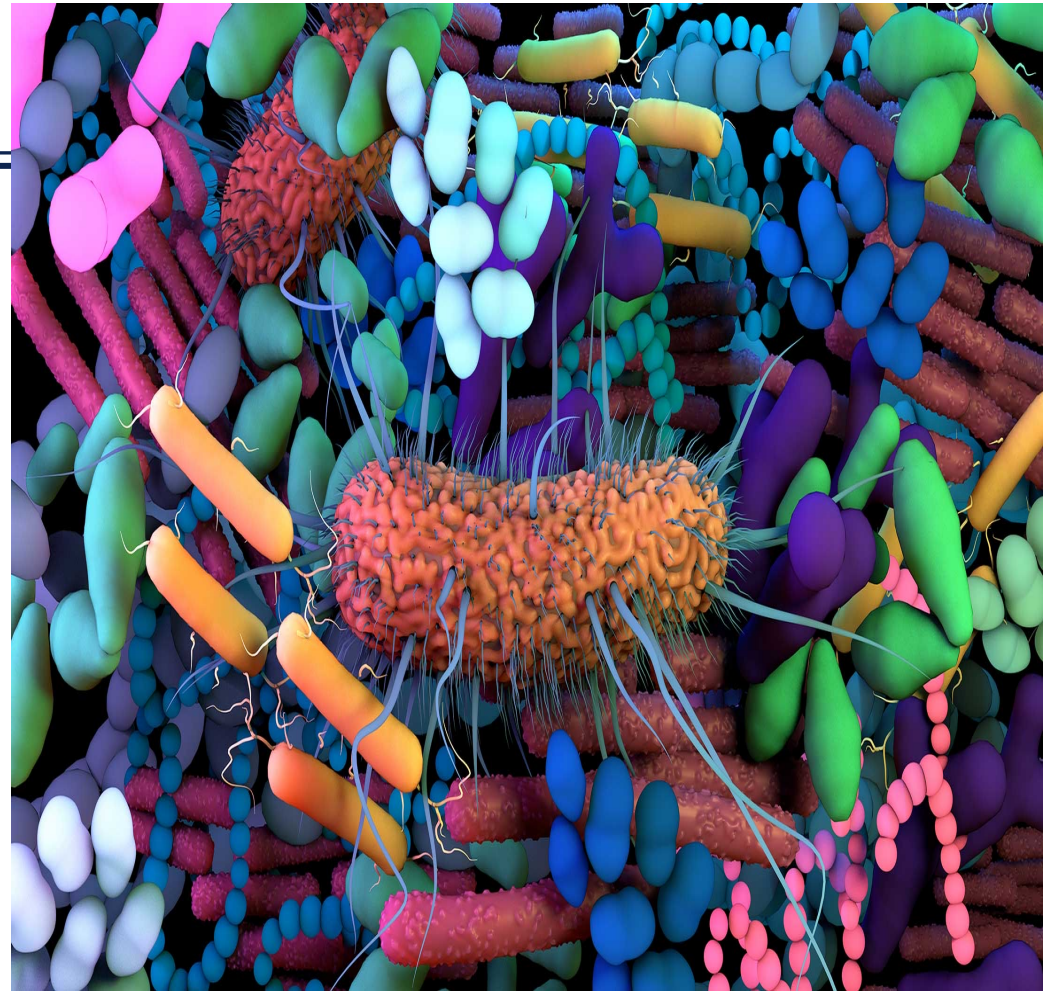
Progression-Free Survival



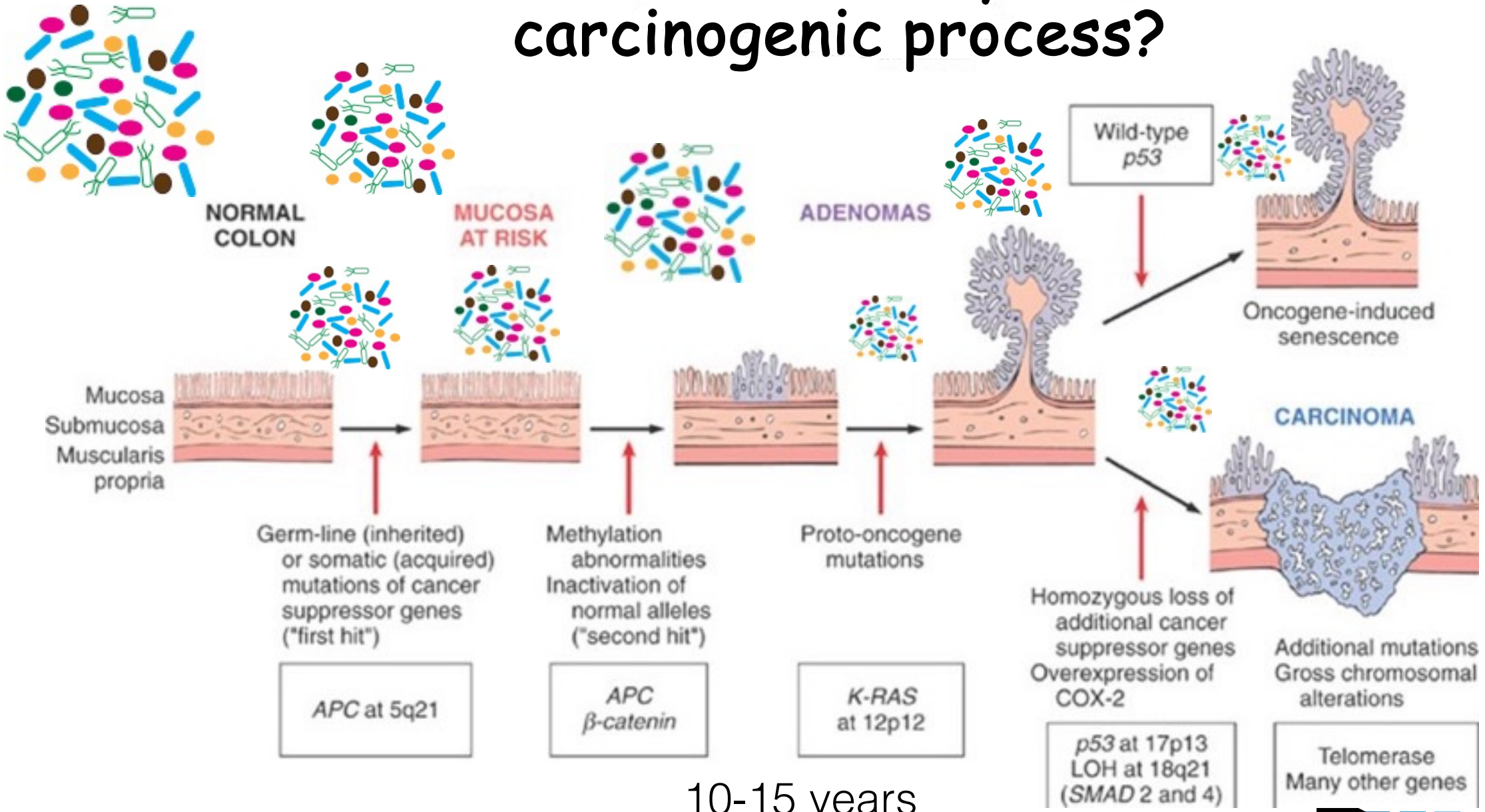
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

So what is next?



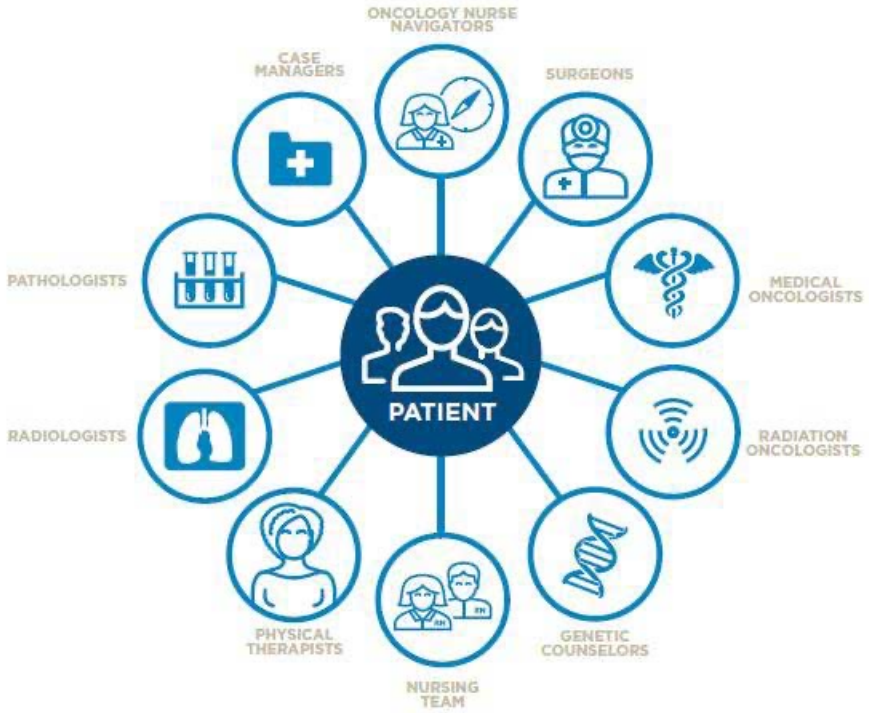


Are intestinal bacteria bystander to the carcinogenic process?



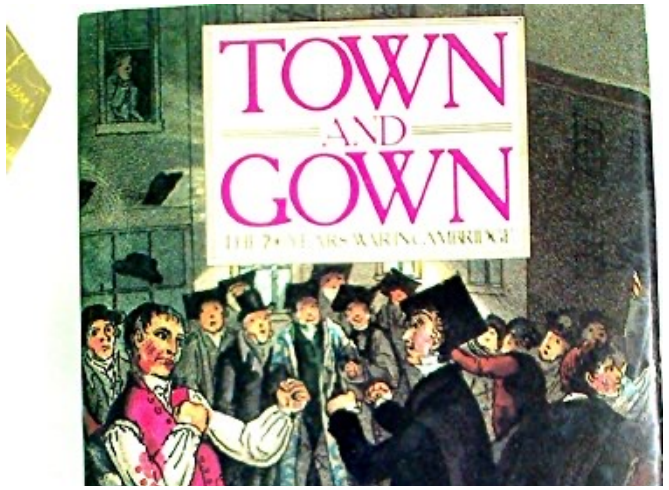
10-15 years

Our Central Role



Academic vs Community Medicine

- Academics
  - Lower pay, lower RVU
  - More focused
  - Teaching
  - Research
  - Protected time
  - Employed
  - Your KOLs



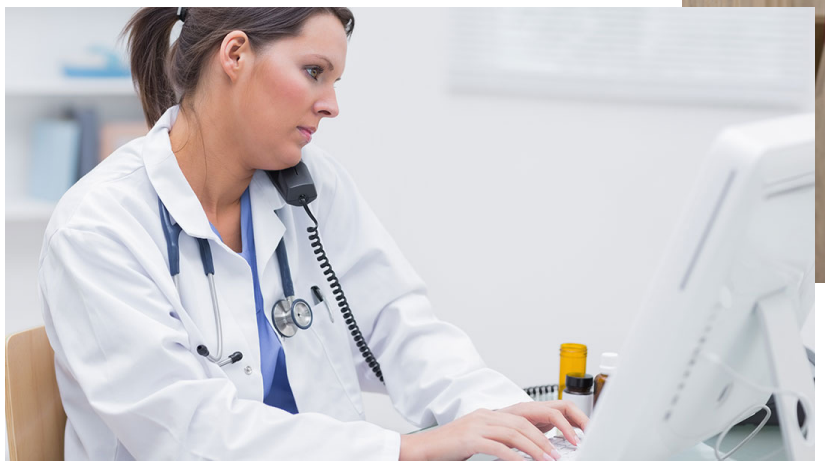
- Community
  - Higher pay, higher RVU
  - See everything
  - Full time clinician
  - Increasingly employed
  - Business management
  - Independent or not?

What keeps us awake at night

- Details of patient care, did we miss anything
- RVUs
- Staffing
- Margin
- Reimbursement
- Competition

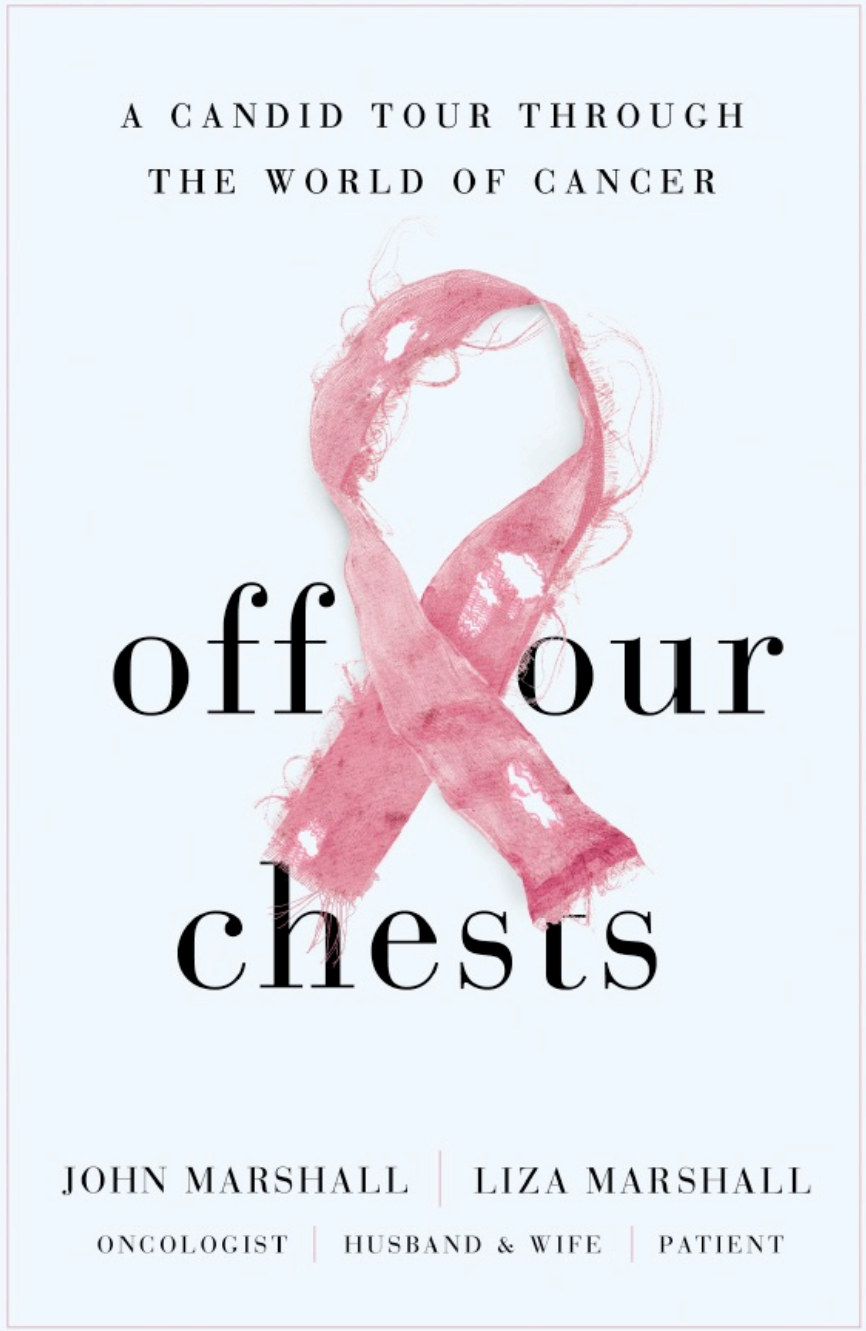
Electronic Medical Records

- OMG
- It is constant
- It is never done
- Patients can see it
- It is a blessing
- It is a curse



The Future of Cancer Care

- Continues to mature
- More cures, longer survival
- More subgroups
- More AI
- Less trial and error
- Will the business model change?



This is a wonderful and engaging book - part memoir, and in equal part an “autopsy” of the cancer establishment in this country. Written with immense care and kindness, it reminds us of how much we’ve achieved, and how much remains to be done.
Dr. Siddhartha Mukherjee 2011 Pulitzer Prize for The Emperor of All Maladies

"Off Our Chests offers an unusually intimate and revealing glimpse into the reality of dealing with a cancer diagnosis. At once deeply personal and bracingly universal, this book can offer cancer patients and healthcare workers alike the chance to meet one of life's most devastating situations with a rare sense of mastery and, yes, even hope."
Katie Couric

The incredible journey of what happens when the accomplished spouse of an eminent oncologist develops an oft-fatal cancer.
I laughed, I cried, I identified.
Together they teach us the way forward.
Daniel D. Von Hoff, M.D., F.A.C.P.
Medical Oncologist, Translational Genomics Research Institute/City of Hope

Available Spring 2021
Pre-orders on amazon.com