USF HEALTH
COLLEGE OF PUBLIC HEALTH
UNIVERSITY OF SOUTH FLORIDA

# Precision Genetic Testing in Cancer Treatment and Prognosis

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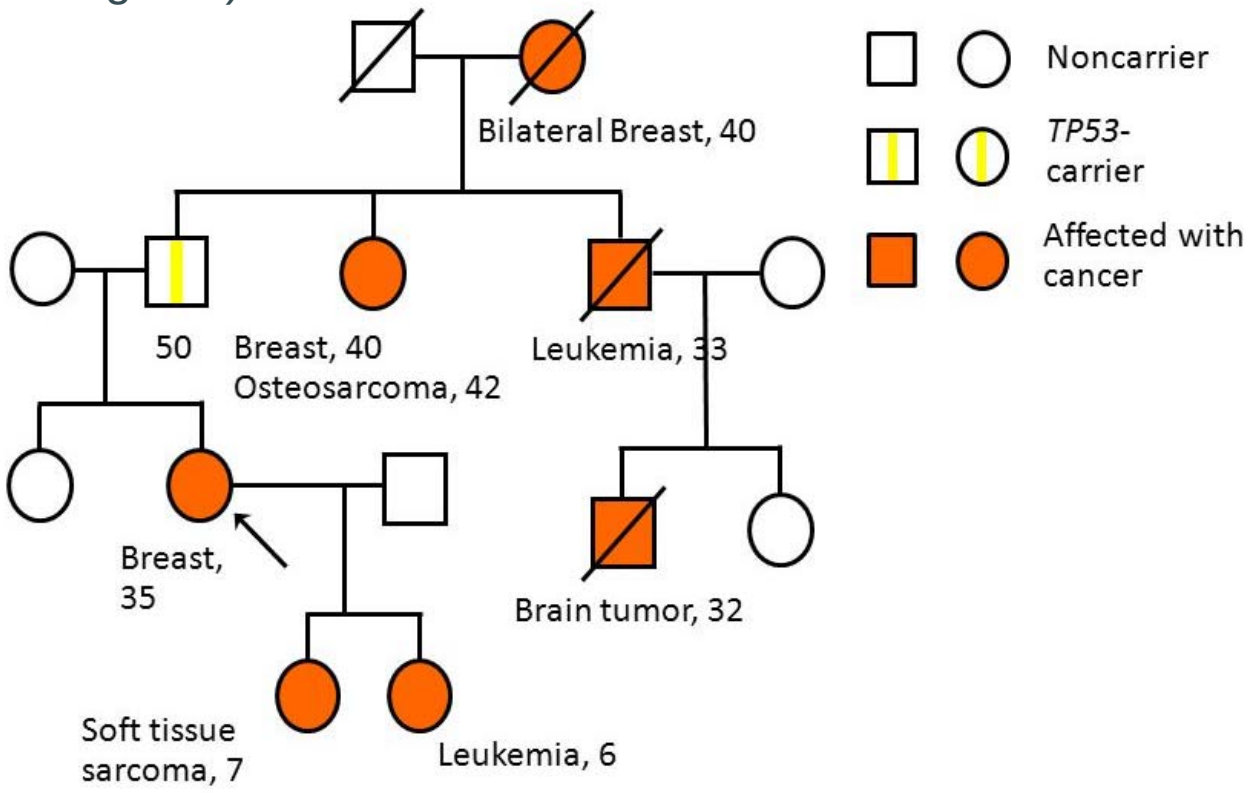
# Case #1


- Diana is a 47 year old cancer patient
- Tumor testing - *TP53* mutation
- She looked up *TP53* mutation online
- Became worried about Li- Fraumeni syndrome
- Wondered what it meant for her & her daughter

# Li-Fraumeni syndrome (LFS)

- Caused by an inherited mutation in the p53 gene
- ~90% lifetime risk of any type of cancer
  (half occur before age 30)

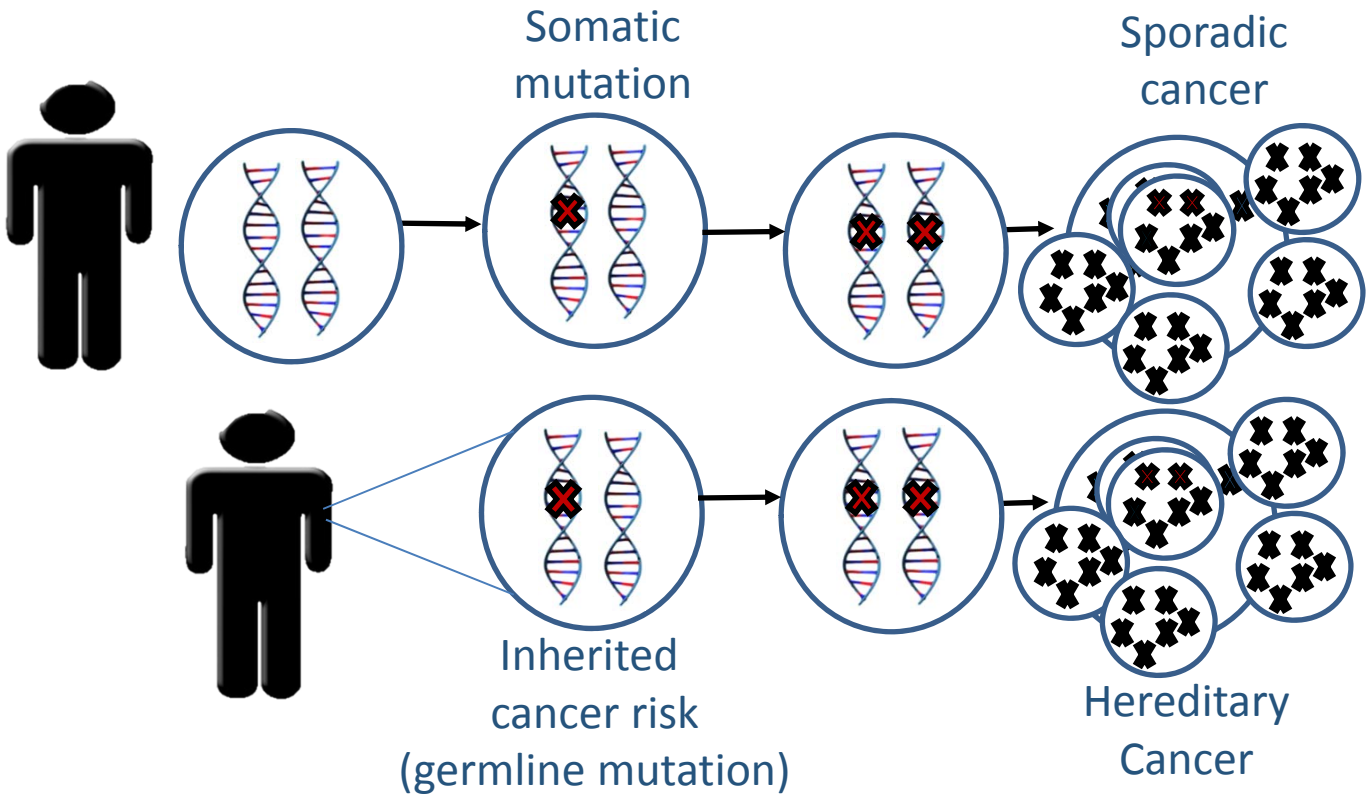


# Chance to Inherit Cancer Risk Gene

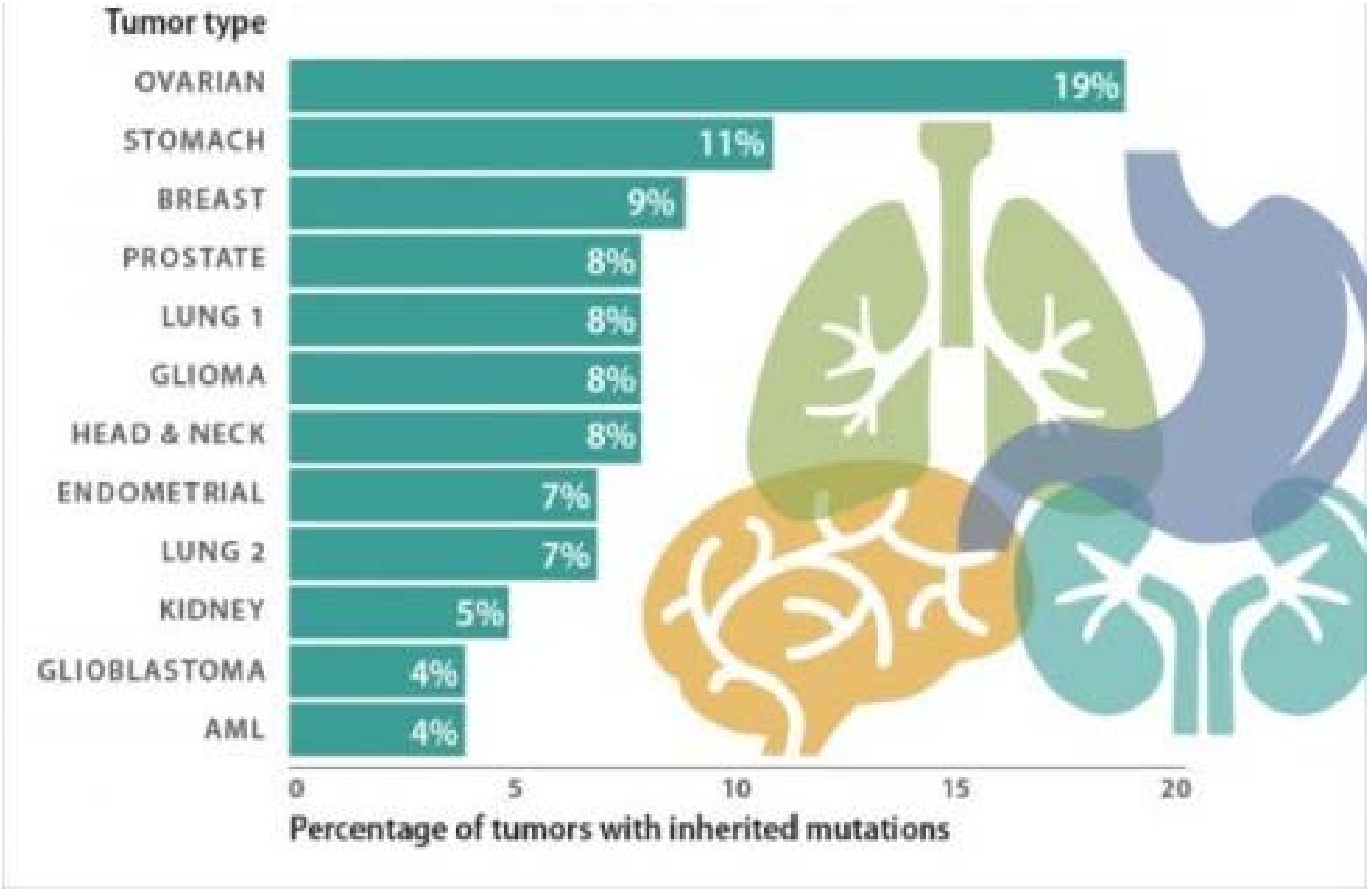
Non-functional copy
(increases cancer risk)


Functional copy
(helps prevent cancer)

# How Gene Mutations Cause Cancer



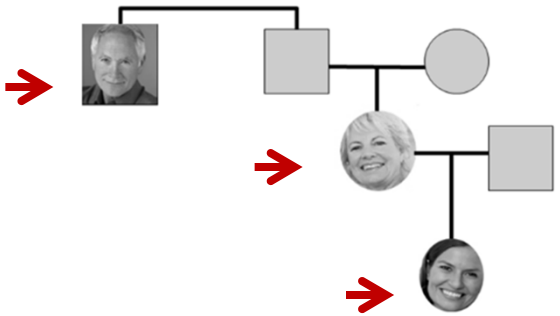
# Cancers caused by inherited mutation

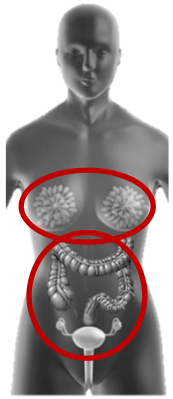


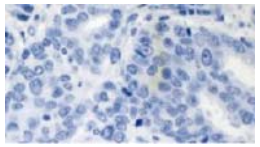

https://www.sciencedaily.com/releases/2015/12/151222084730.htm

# Signs of Inherited Cancer Risk

- Cancer diagnosed young
- Cancer in multiple family members across generations
- A person with multiple cancers
  - Paired organs
  - Different organs
- Certain ethnic backgrounds
- Some tumor study results



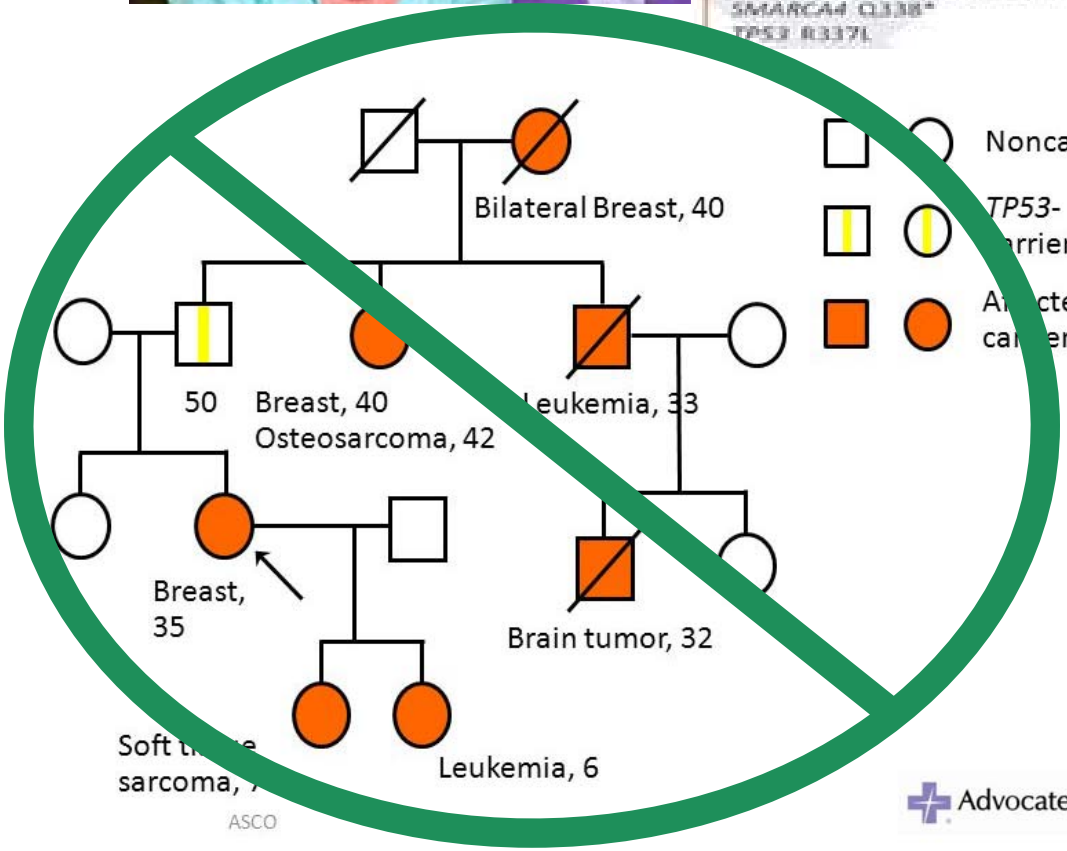




# Case #1

**Genomic Alterations Identified†**

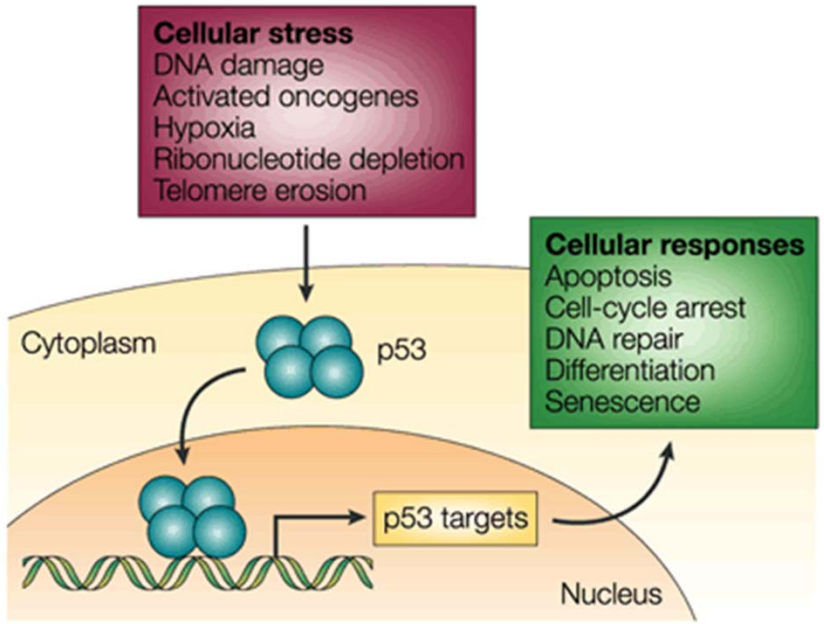
*EGFR* amplification
*LRP1B* splice site 1553-2A>T, splice site 2887+1G>T
*NOTCH2* H1300fs*15
*RBM10* K653fs*51
*SETD2* splice site 6061-1G>T
*SMARCA4* Q338*
*TP53* R337L




ASCO

# *TP53*

- Most commonly mutated gene in tumors (>50%)
- Most *TP53* mutations are acquired (not inherited)



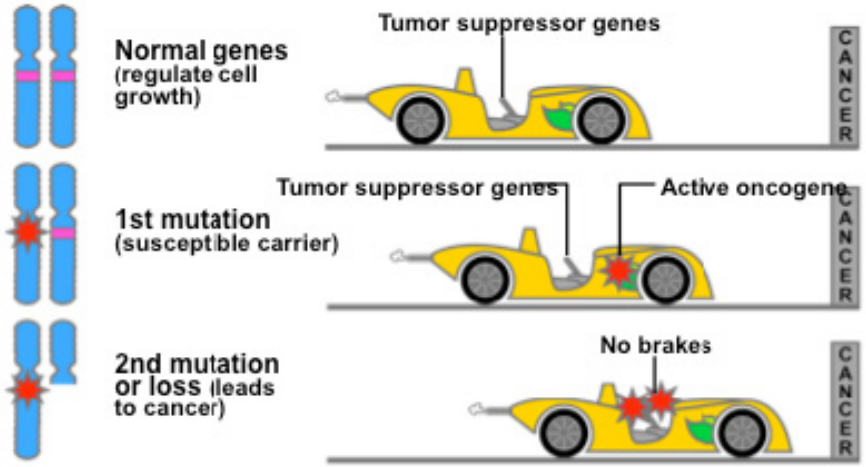

Nature Reviews | Cancer

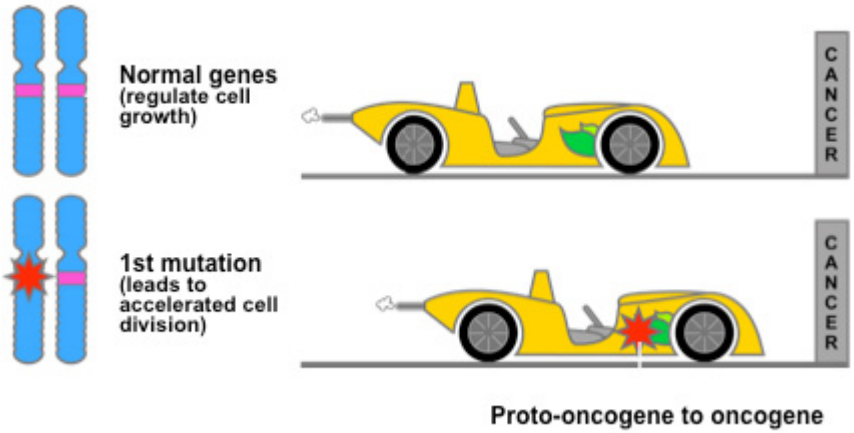
# Tumor Gene Mutations

- Driver mutations
  - Provide selective growth advantage
- Passenger Mutations
  - Do not cause or propel cancer growth


# Types of Driver Mutations

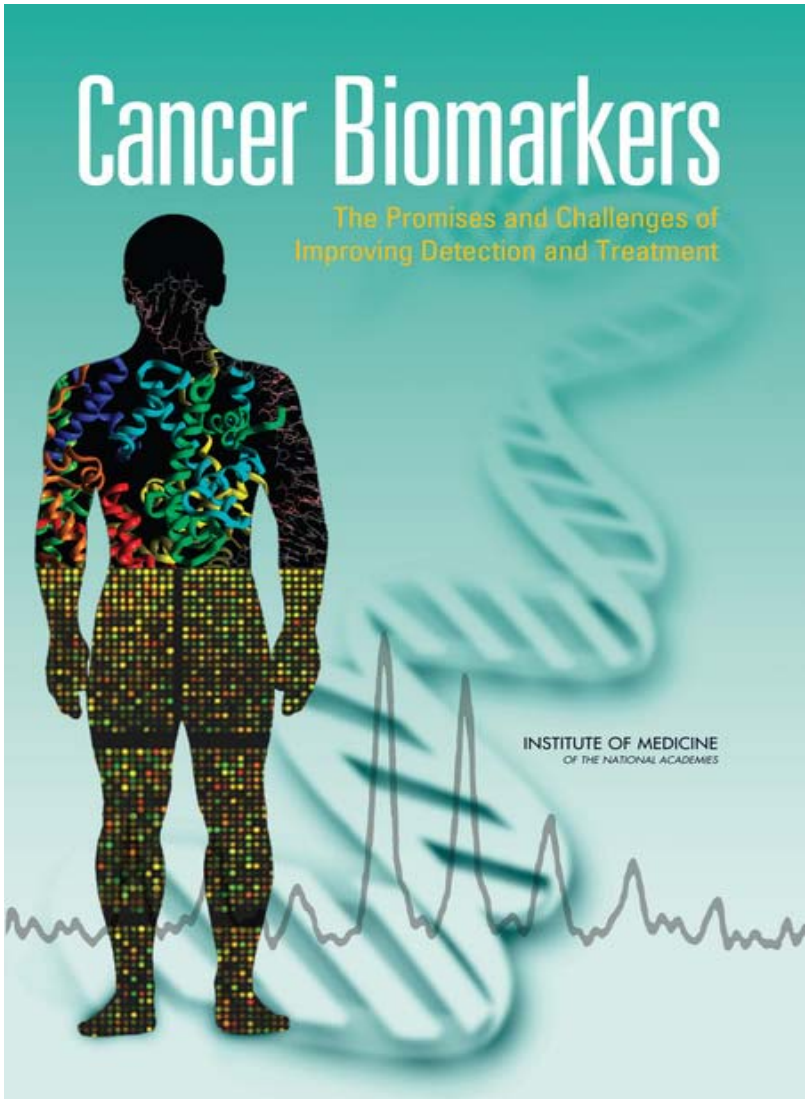
- Tumor suppressor genes become inactivated
- Proto-oncogenes become activated to form oncogenes



# Objectives

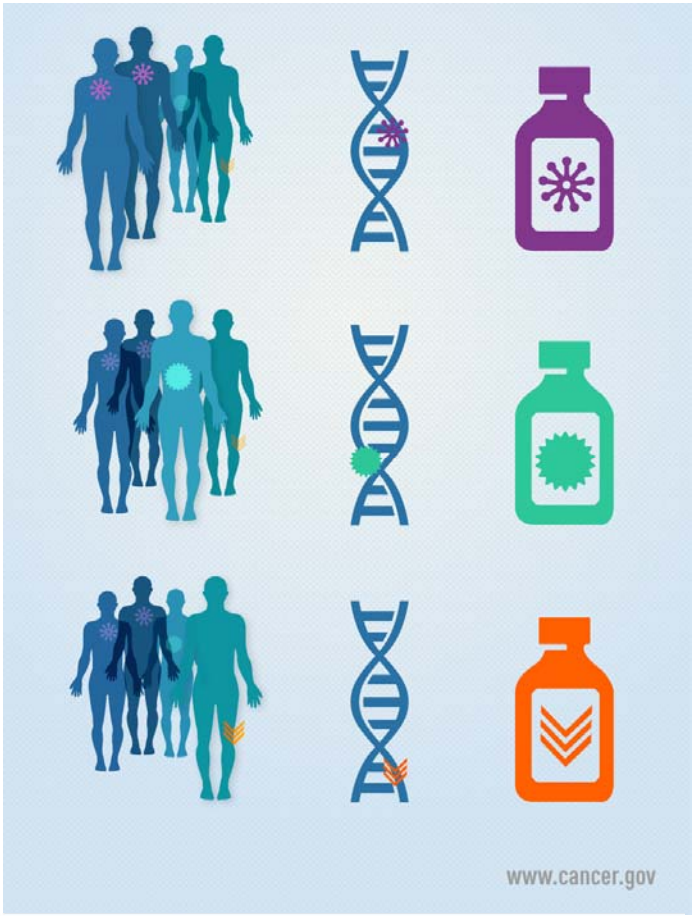
1. Review the current use of tumor genomic testing in cancer treatment



# Targeted Cancer Therapies

- Goal: Target cancer cells with more precision

- How: Interfere with unique molecular changes that promote tumor growth and progression




https://www.mycancergenome.org

MY CANCER GENOME®
GENETICALLY INFORMED CANCER MEDICINE

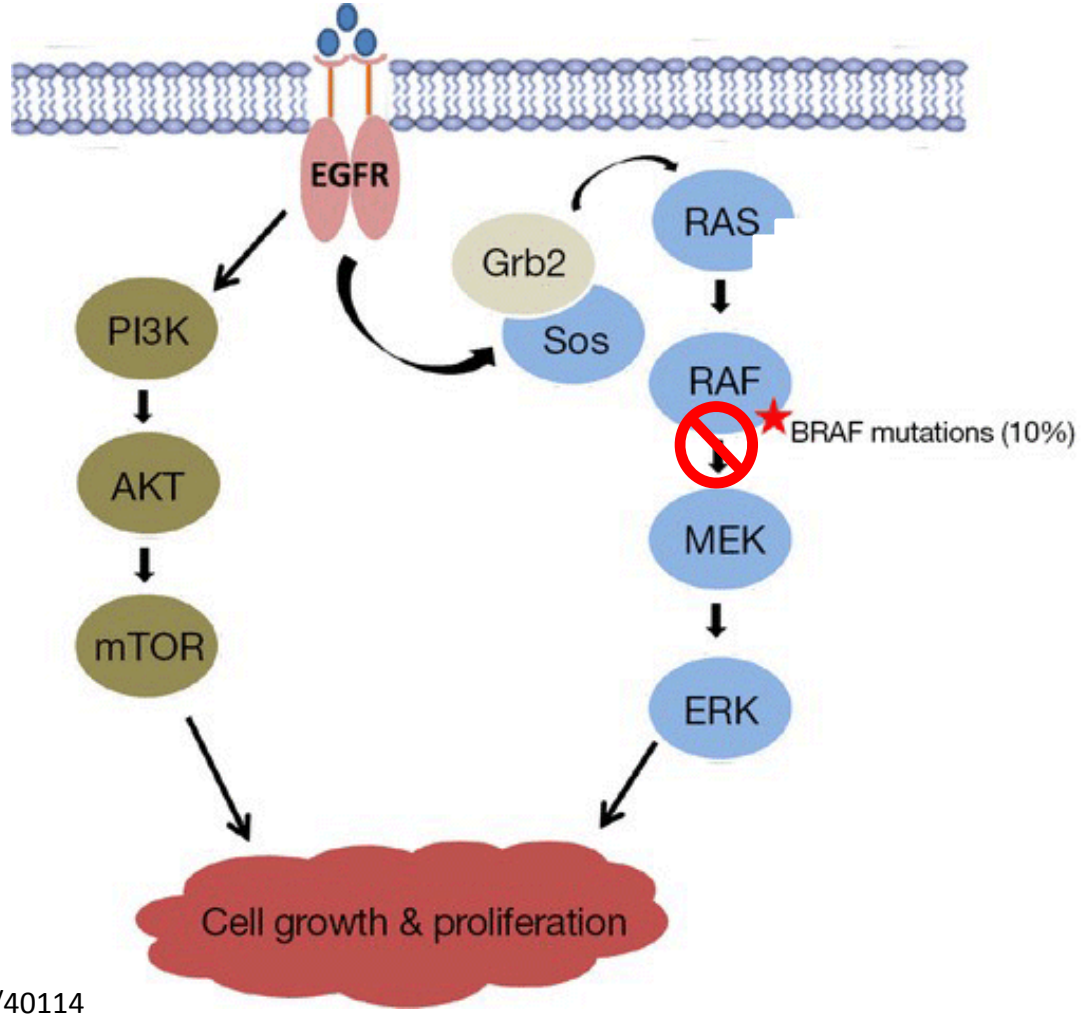
# Examples of Driver Genes

| GENE | MECHANISM | TARGETED THERAPY |
|---|---|---|
| **EGFR** | • **Activating point mutations**<br>• **Gene Amplification**<br>• **Overexpression** | Cetuximab, panitumumab erlotinib, gefitinib, afatinib |
| **KRAS** | **Activating point mutations** | Tipifarnib, lonafarnib |
| **BRAF** | **Activating point mutations** | Dabrafenib, sorafenib,vemurafenib |
| **NRAS** | **Activating point mutations** | MEK162 |

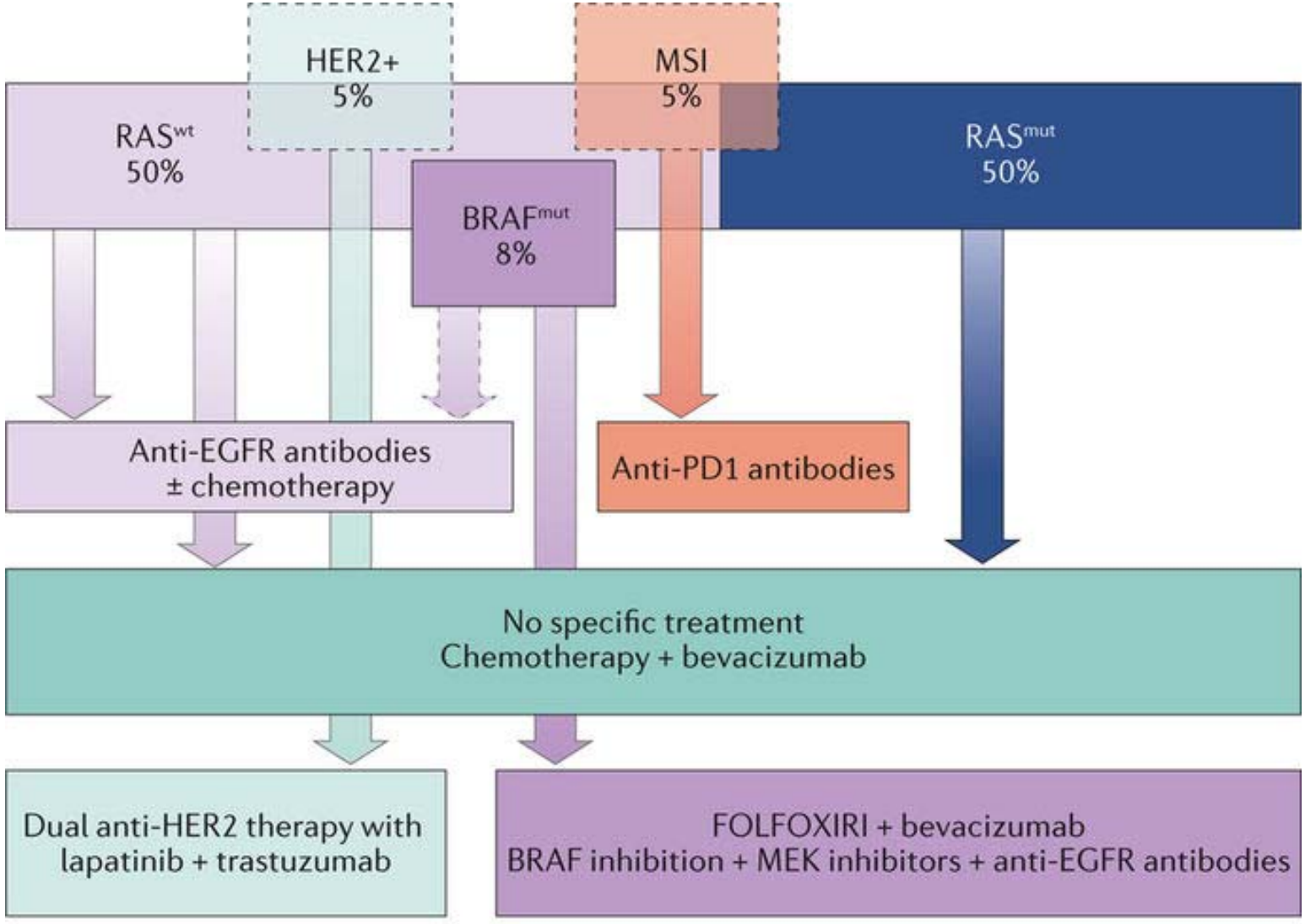
# Activating BRAF mutations

- Occur in ~50% of advanced Melanoma patients
  - 50-60% respond to BRAF inhibitors
- Occur in only 8-10% of colorectal cancers
  - NOT responsive to BRAF inhibitors alone *(due to feedback activation of EGFR)*

# Signaling Pathways



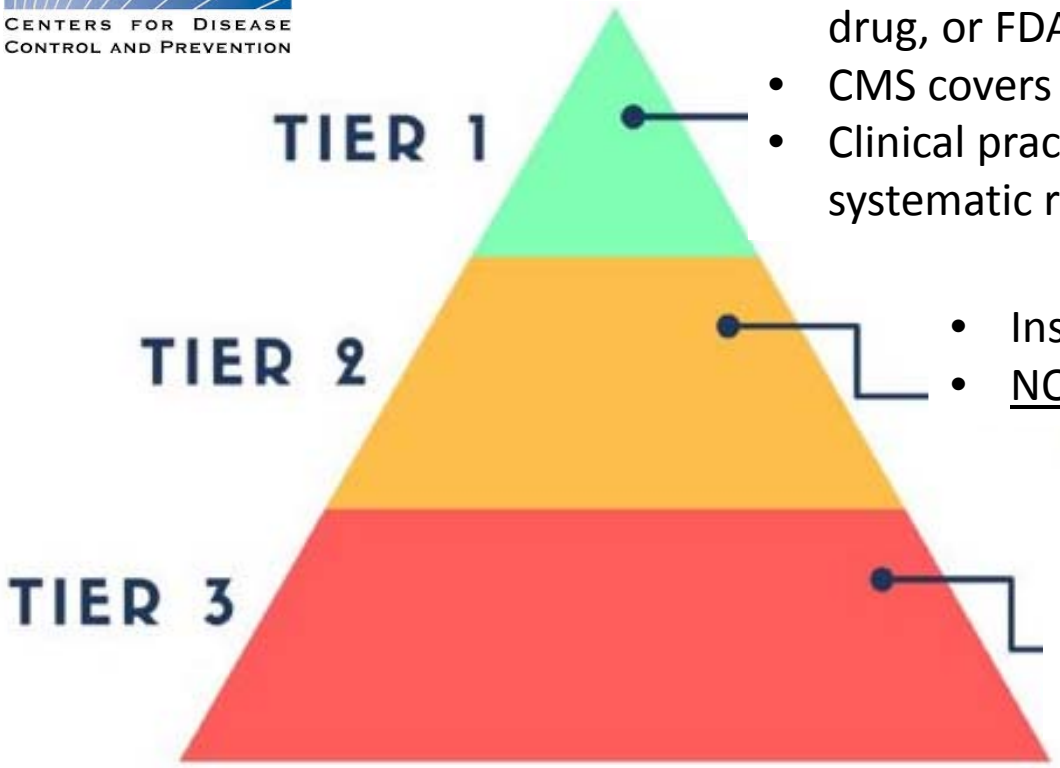

http://jgo.amegroups.com/article/viewFile/4881/html/40114




**Nature Reviews** | Clinical Oncology

# Tier system for classifying genomic tests

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION




- FDA label requires use of test prior to using drug, or FDA approved companion diagnostic
- CMS covers testing
- Clinical practice guidelines based on systematic review support testing

- Insufficient evidence
- NOT discourage use of test

- FDA label cautions against use
- Clinical guidelines or systematic reviews discourage testing

https://phgkb.cdc.gov/PHGKB/topicStartPage.action

| Table 1. Examples of Successful Biomarkers, Specific Therapies, and the Relevant Cancer Diagnoses[a] | | | |
|---|---|---|---|
| Biomarkers | Matched Targeted Therapies | Cancer Diagnoses | Approximate Response Rates |
| *ALK* | Alectinib<br>Ceritinib<br>Crizotinib | Non–small cell lung cancer | 60%–70% |
| *BCR/ABL* | Bosutinib<br>Dasatinib<br>Nilotinib<br>Ponatinib<br>Imatinib | Chronic myelogenous leukemia (newly diagnosed) | 100% |
| *BRAF* V600 | Cobimetinib<br>Dabrafenib<br>Trametinib<br>Vemurafenib | Melanoma | 50%–60% |
| *BRAF* V600 | Vemurafenib | * Non–small cell lung cancer<br>Erdheim-Chester disease | 40% |

*Not yet FDA approved

For a more comprehensive list and updates visit:
https://www.mycancergenome.org/content/molecular-medicine/overview-of-targeted-therapies-for-cancer/
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

| | | | |
|---|---|---|---|
| *BRCA* | Olaparib<br>Rucaparib | Ovarian cancer | 50% |
| *BRCA* | Olaparib | * Prostate cancer | 86% |
| *EGFR* | Erlotinib<br>Osimertinib (T790M) | Non–small cell lung cancer | 70% |
| HER2 | Lapatinib<br>Pertuzumab<br>Trastuzumab | Breast cancer | 50%–70% (combination with chemotherapy) |
| *KIT* | Imatinib | Gastrointestinal stromal tumors | 50%–80% |
| *PDGFRA/KIT* | Imatinib | Hypereosinophilic syndrome | 40% |
| *PDGFRB* | Imatinib | Dermatofibrosarcoma protuberans | 80% |
| PD-L1/PD-L2 amplification | Nivolumab<br>Pembrolizumab | Classical Hodgkin lymphoma | 65%–87% |
| *ROS1* | Crizotinib | Non–small cell lung cancer | 70% |
| Microsatellite instability | Atezolizumab<br>Nivolumab<br>Pembrolizumab | Any solid tumor, including colorectal cancer | 70%–80% |

*Not yet FDA approved

# Generic naming formula

Name = prefix + substem(s) + stem

variable

| | |
|---|---|
| -mab | monoclonal antibody |
| -ib | small molecule with inhibitory properties |

**Monoclonal antibodies**

| *Target* | *Source of antibodies* |
|---|---|
| -ci(r)- circulatory system | -ximab chimeric human-mouse |
| -li(m)- immune system | -zumab humanized mouse |
| -t(u)- tumor | -mumab fully human |

**Small molecules**

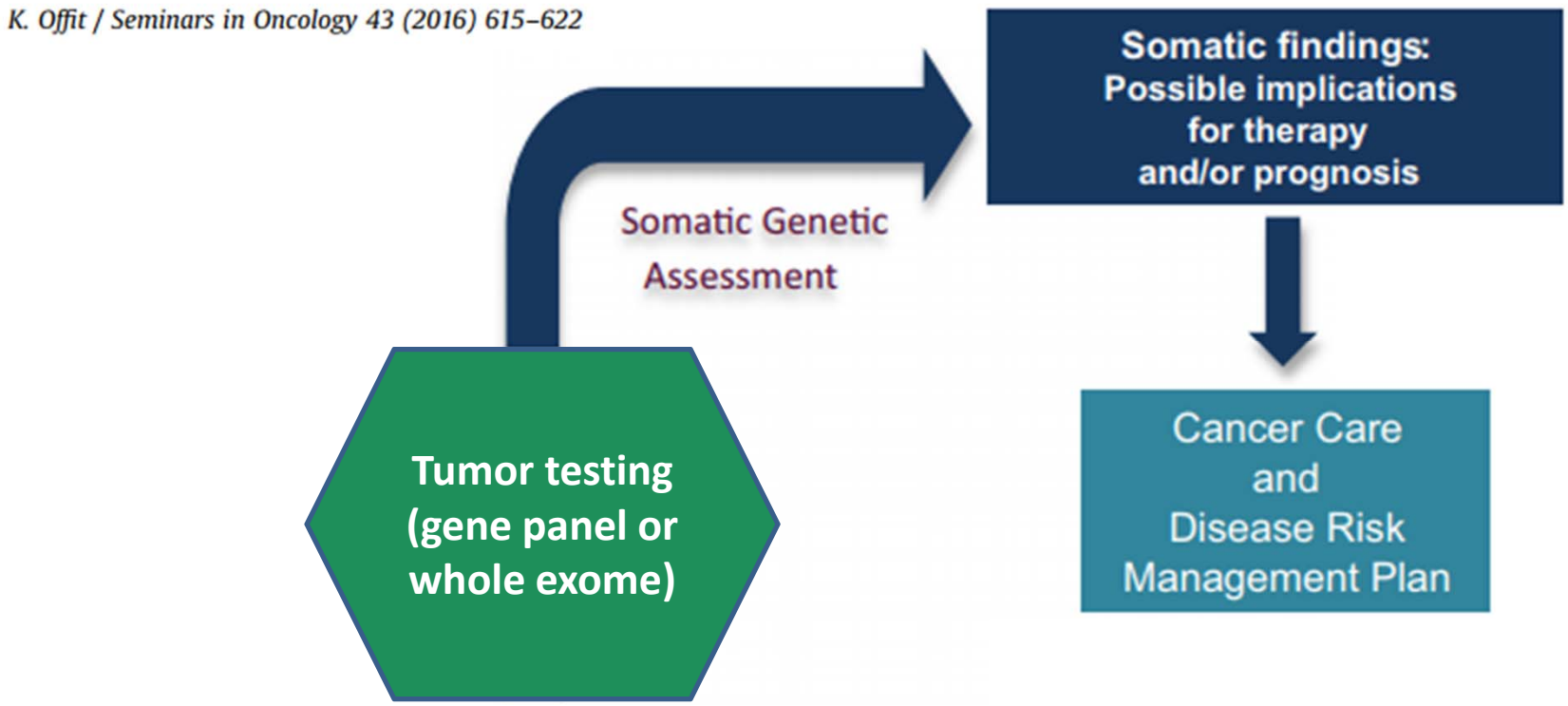
-tinib tyrosine kinase inhibitor
-zomib proteasome inhibitor
-ciclib cyclin-dependent kinase inhibitor
-parib poly ADP-ribose polymerase inhibitor

# Objectives

1. Review the current use of tumor genetic testing in cancer treatment

2. **Discuss the impact of both germline and tumor genetic-based treatments on mortality**

# Tumor Testing



Preliminary Communication

September 5, 2017

# Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing

Diana Mandelker, MD, PhD[1]; Liying Zhang, MD, PhD[1]; Yelena Kemel, MS, ScM[1,2]; et al

» Author Affiliations

*JAMA*. 2017;318(9):825-835. doi:10.1001/jama.2017.11137

**1040 patients with advanced cancers**

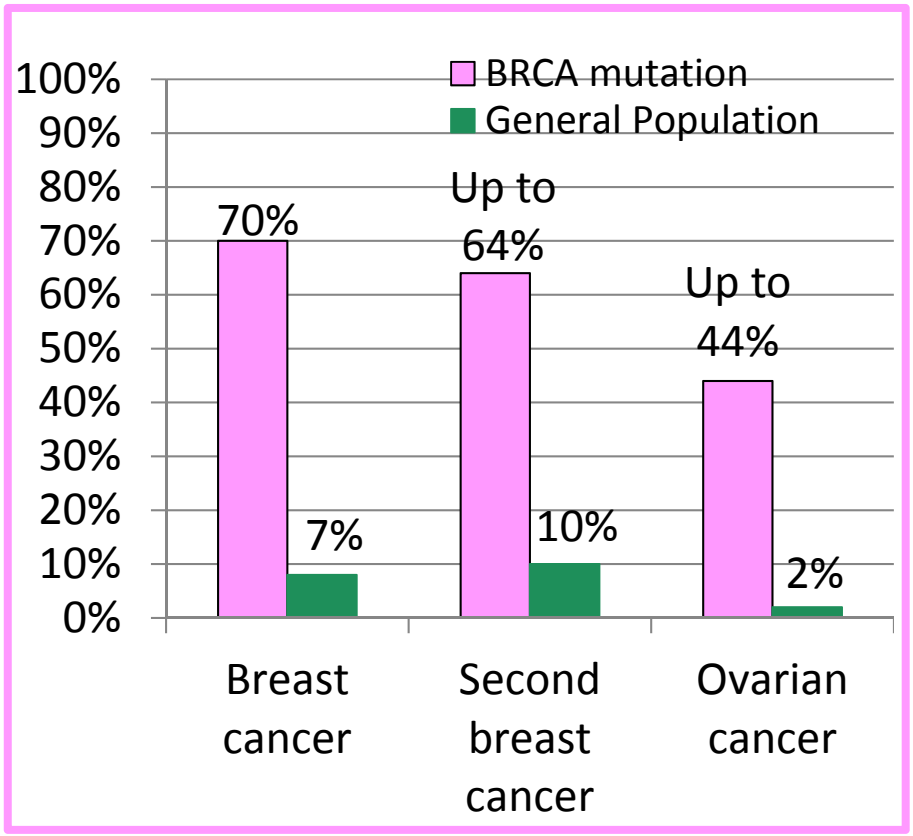
***(76 gene panel test)***

**182 (17.5%) had germline mutations**

# Hereditary Breast and Ovarian Cancer

(*BRCA1* or *BRCA2* germline mutation)

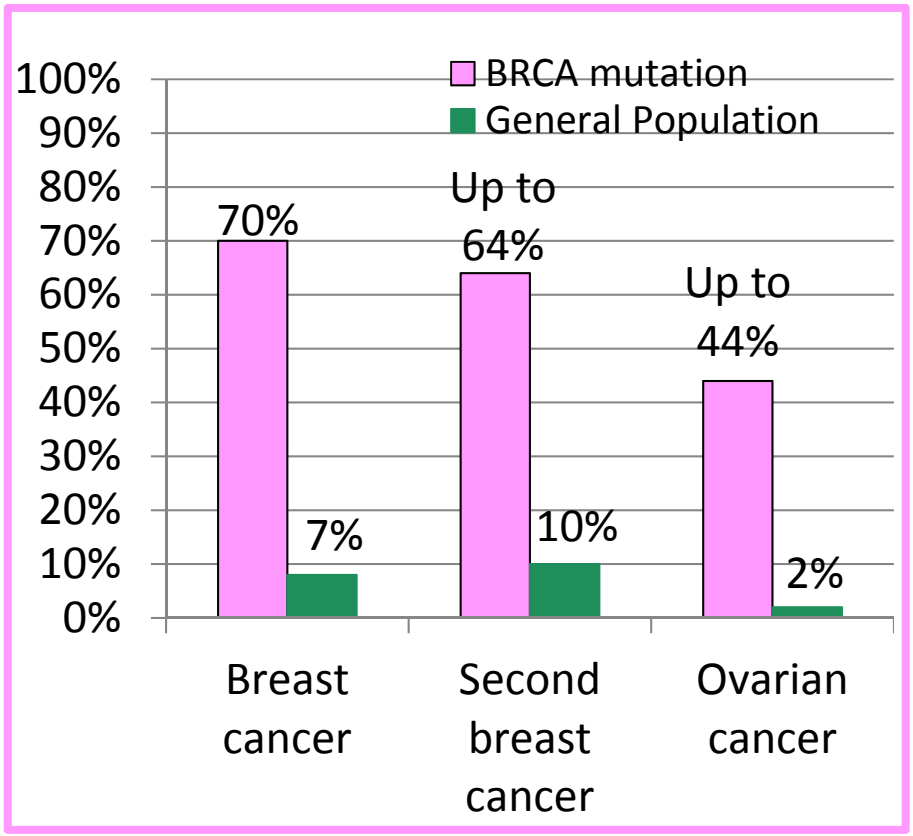
## Cancer Risks



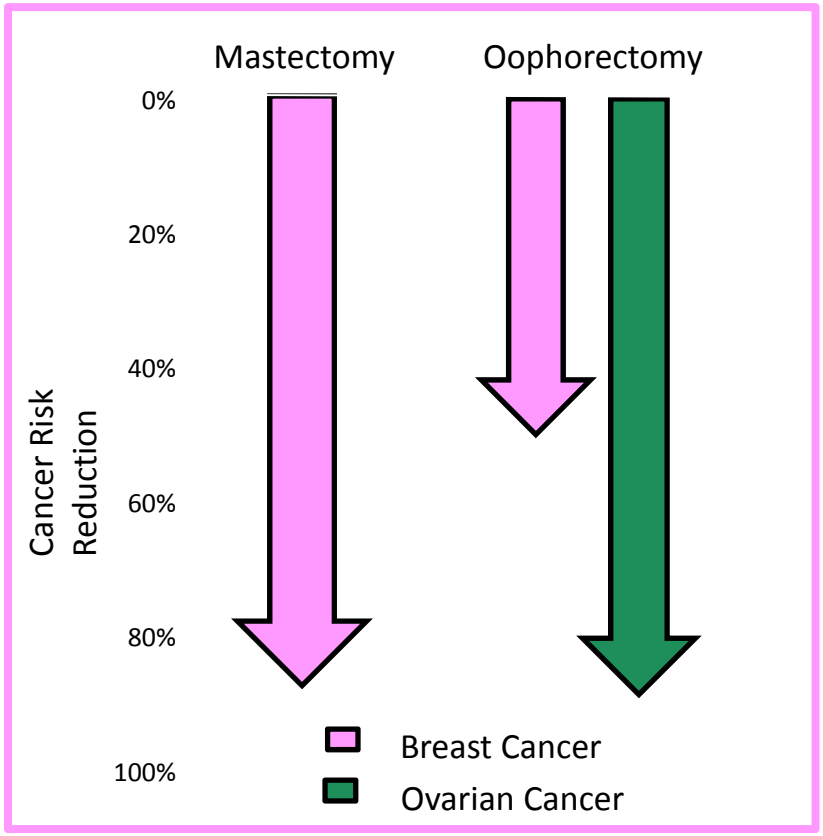
# Hereditary Breast and Ovarian Cancer

(*BRCA1* or *BRCA2* germline mutation)

## Cancer Risks




## Risk Management



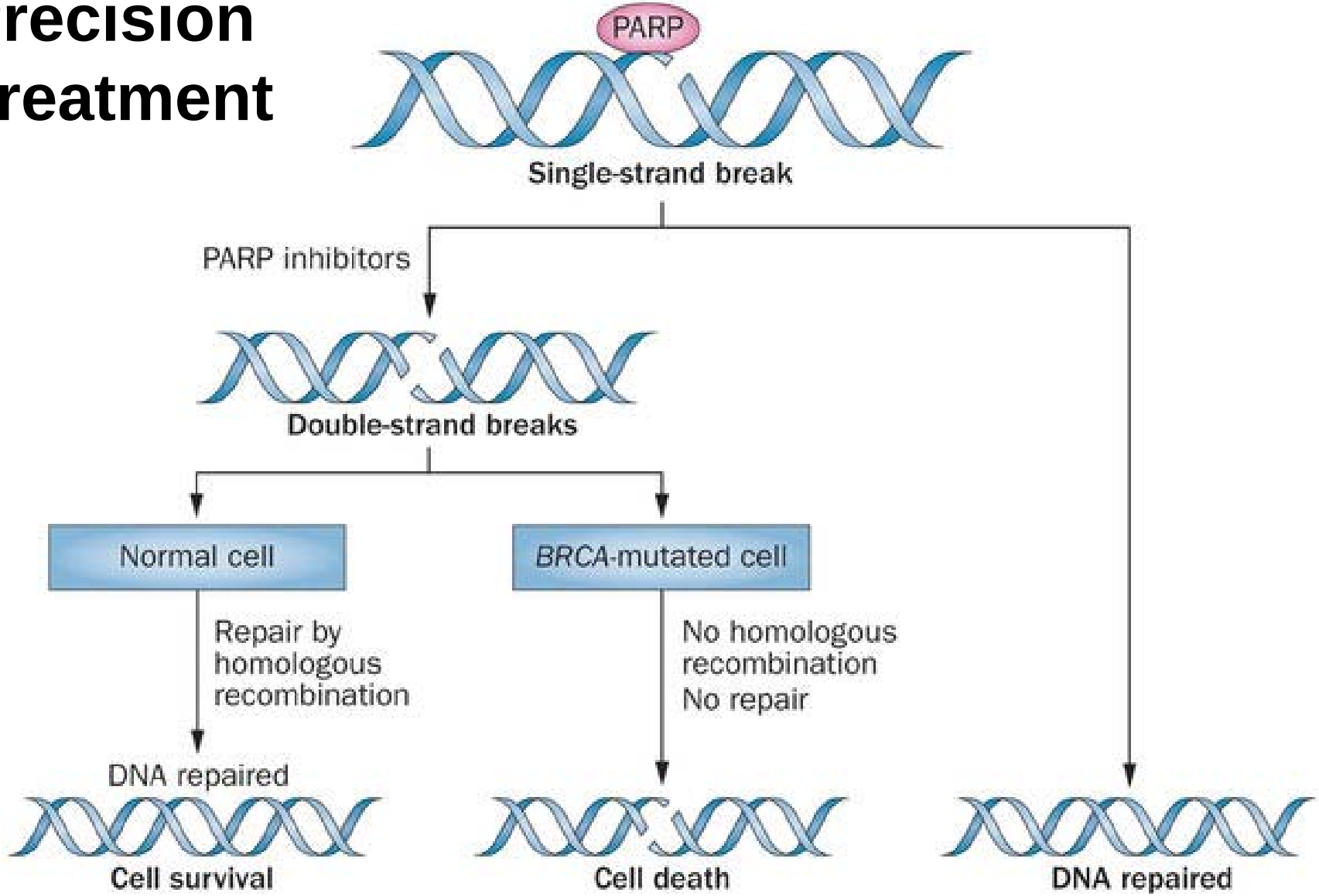
# PARP Inhibitor and breast cancer

- 2018 FDA approved **olaparib** for metastatic breast cancer with germline *BRCA* mutations

- Advantage of olaparib (PARP inhibitor) over standard-of-care chemotherapy:
  - Progression free survival (8.6 vs. 5.6 months)
  - Prolongation to second progression
  - Improved health-related quality of life

Robson et al., NEJM 2017, 377:523-533.

# Precision Treatment



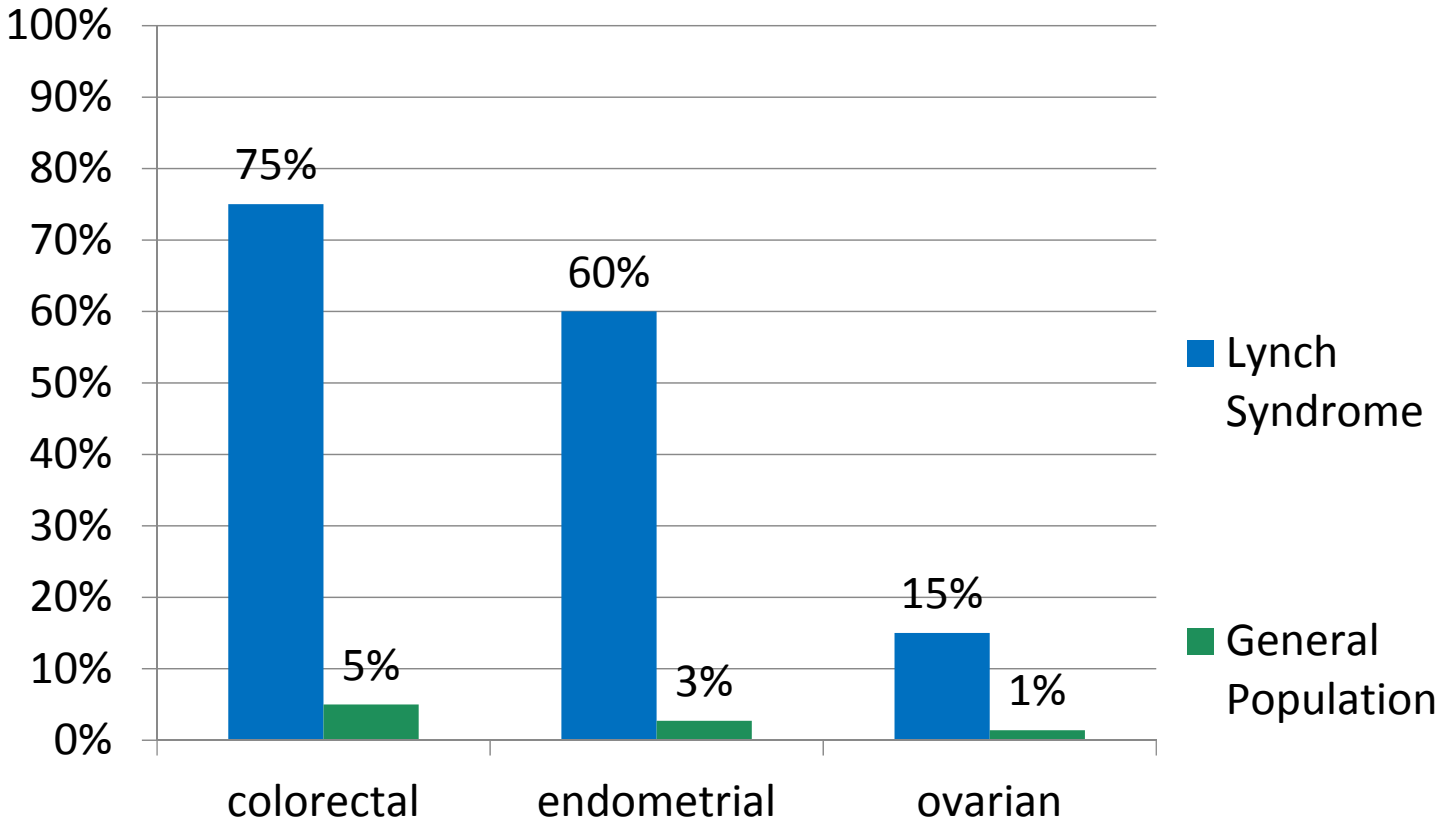
# Median Progression-free survival (PFS) –

- BRCA-mutated ovarian tumors (germline or somatic)
  - 11.2 months olaparib
  - 4.3 months placebo, HR=0.18, P<0.0001
- Regardless of BRCA status
  - 8.4 months with olaparib
  - 4.8 months with placebo (HR=0.35, P<0.001)

(NEJM 2012, 366:1382–92).

# Lynch syndrome

(*MLH1, MSH2, MSH6, PMS2 germline mutation*)



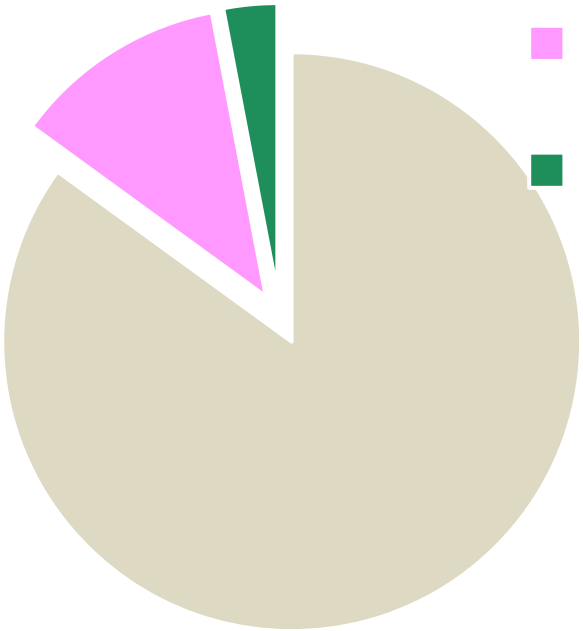
# MSI-high (MMR deficient) tumors

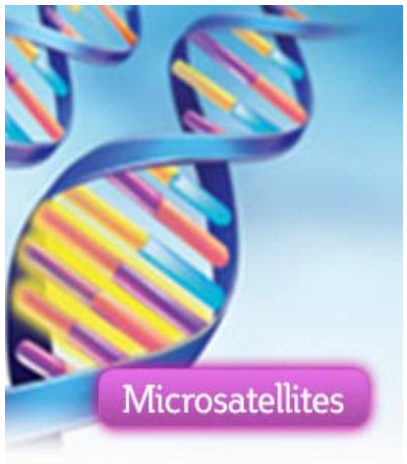
Microsatellite instability (MSI-high) is the result of an absent or nonfunctional MMR protein in the tumor

Characteristic of Lynch syndrome tumors

# Colorectal Cancers

~15% MSI-high



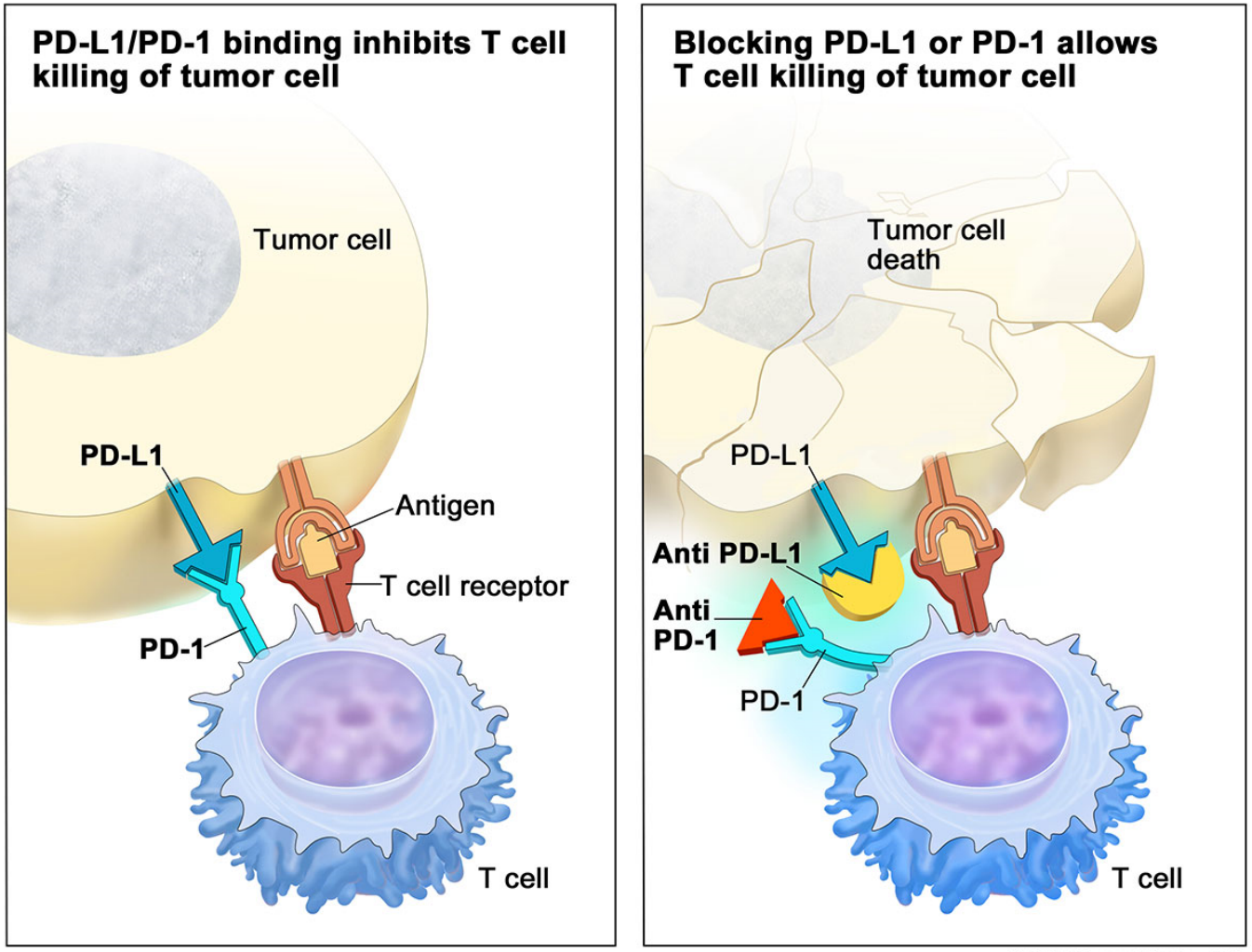



# Case #2

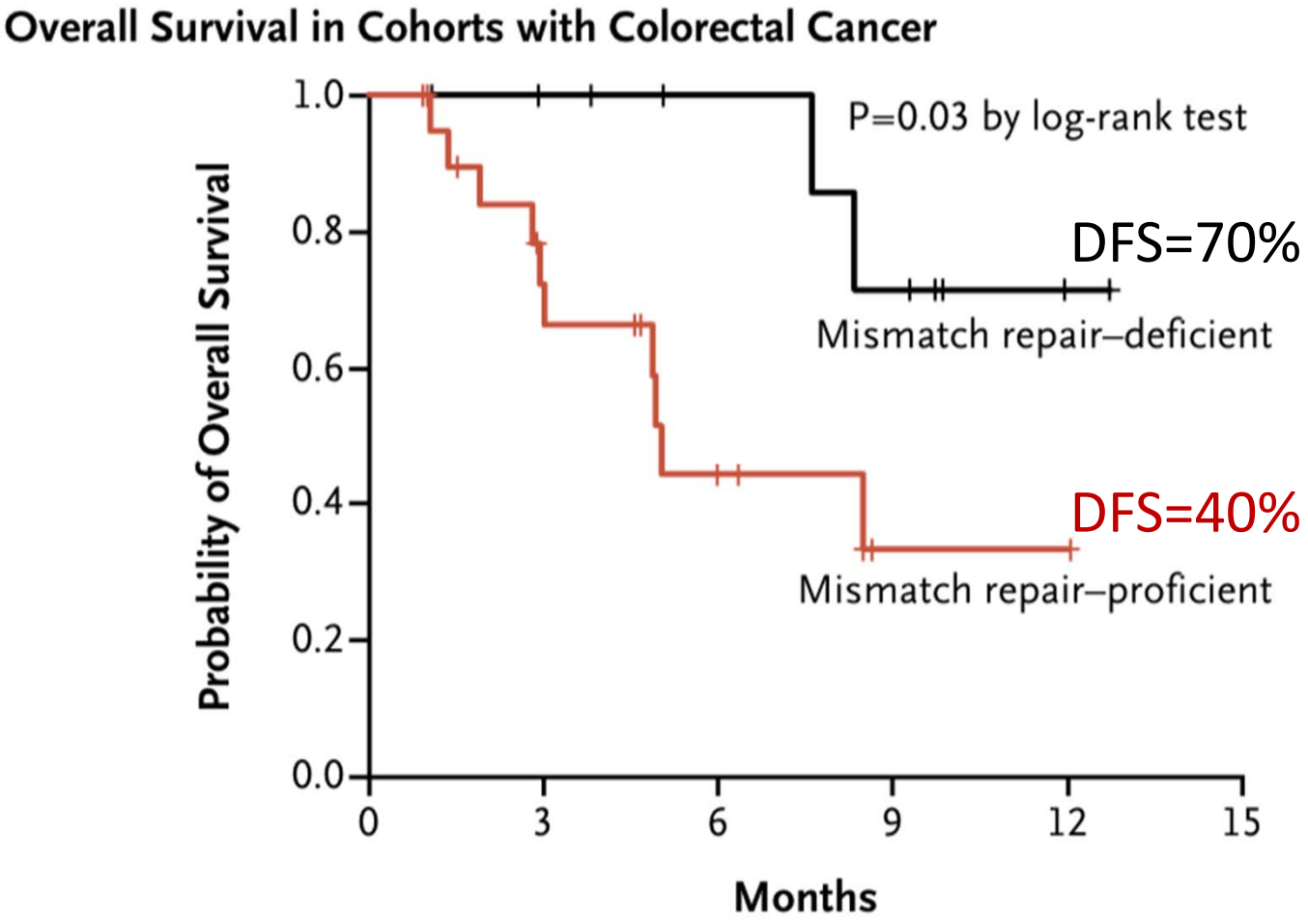
- Patient with stage IV CRC
- Tumor showed microsatellite instability (MSI-high)

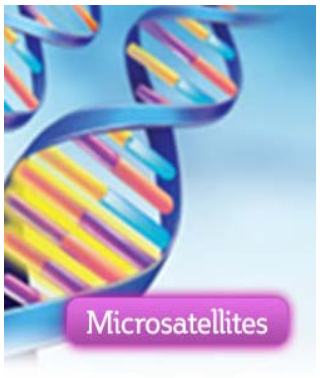
- **Determining if he has Lynch syndrome beneficial - cancer prevention for family**
- **MSI-high alters treatment of his metastatic CRC**

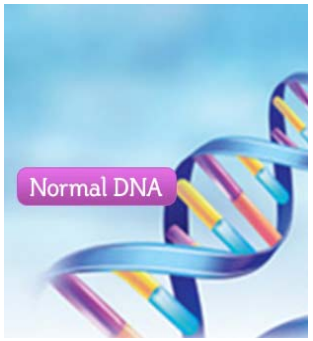
# Immunotherapy with Pembrolizumab for Colorectal cancer



# Pembrolizumab Effectiveness




N Engl J Med. 2015 Jun 25;372(26):2509-20. PD-1 Blockade in Tumors with Mismatch Repair

# May 23, 2017


FDA
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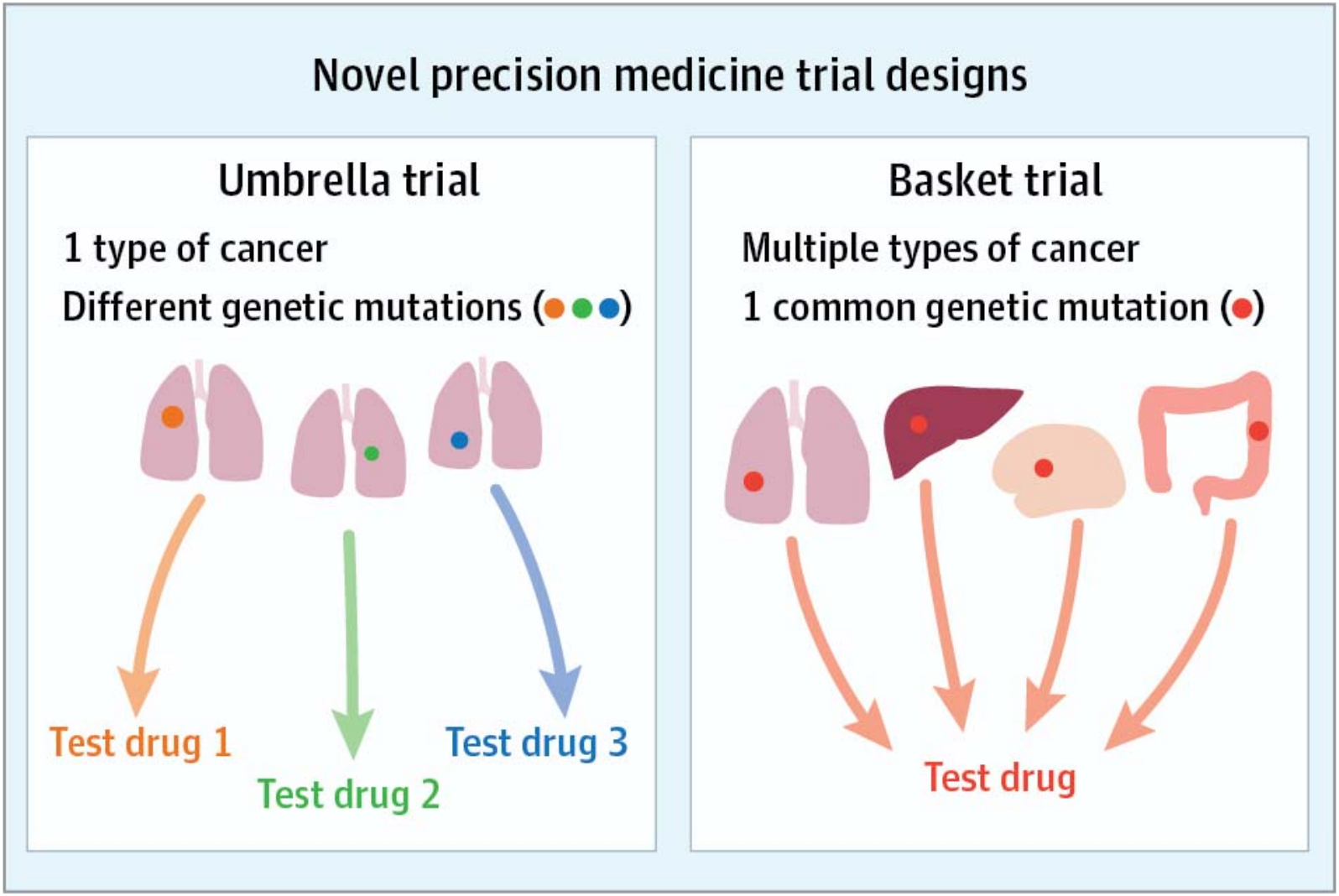
Drugs
Home > Drugs > Drug Approvals and Databases > Approved Drugs
Approved Drugs
Hematology/Oncology (Cancer) Approvals & Safety Notifications
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

# Objectives

1. Review the current use of tumor genetic testing in cancer treatment

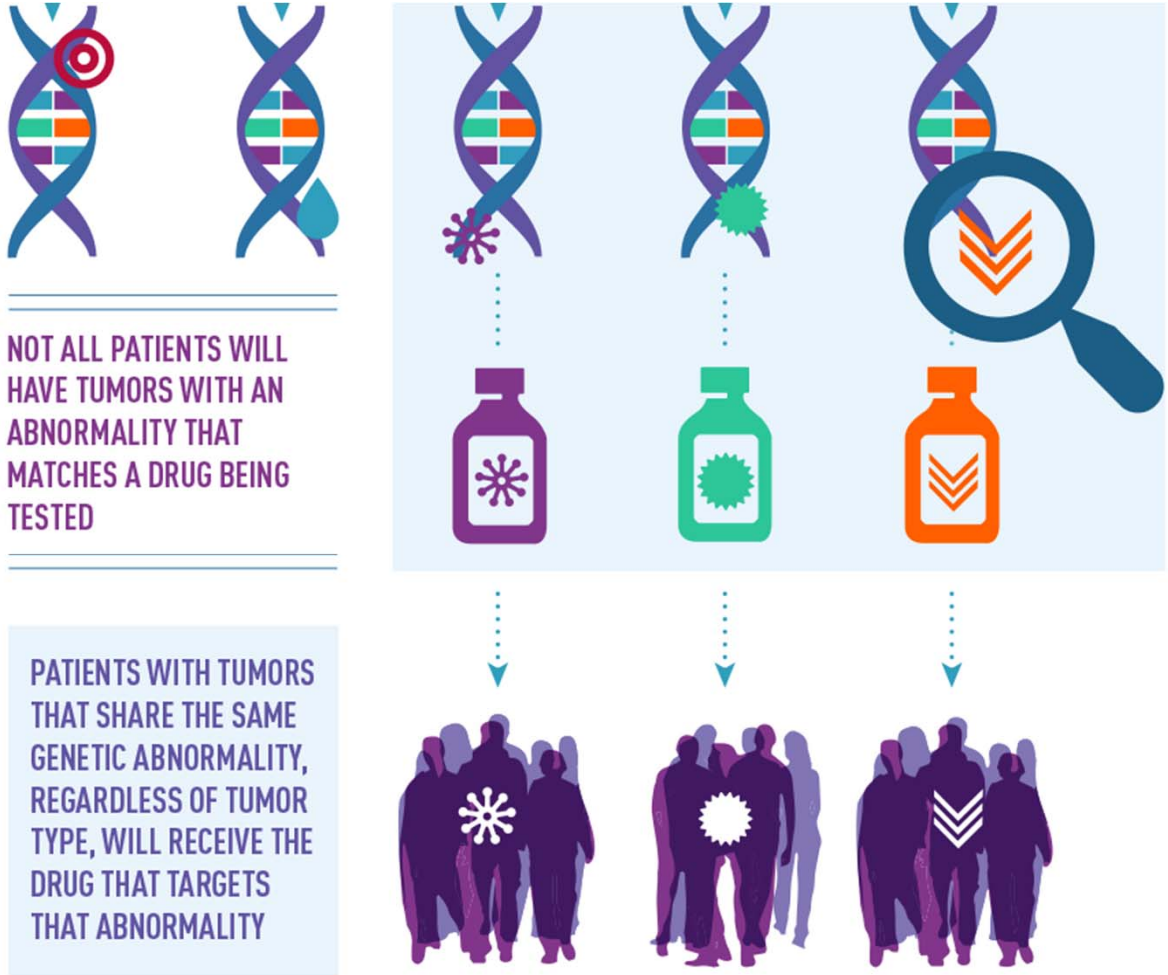
2. Discuss the impact of both tumor and germline genetic-based treatments on mortality

3. **Outline the focus of current research related to precision medicine and cancer treatments**




JAMA Oncology: doi:10.1001/jamaoncol.2016.5299

# NCI-MATCH (Molecular Analysis for Therapy Choice)




*NCI-Molecular Analysis for Therapy Choice

www.cancer.gov/nci-match

# Multi-center trial in France (SHIVA)

- Randomized basket trial of adult patients with metastatic solid tumors (refractory to standard care)

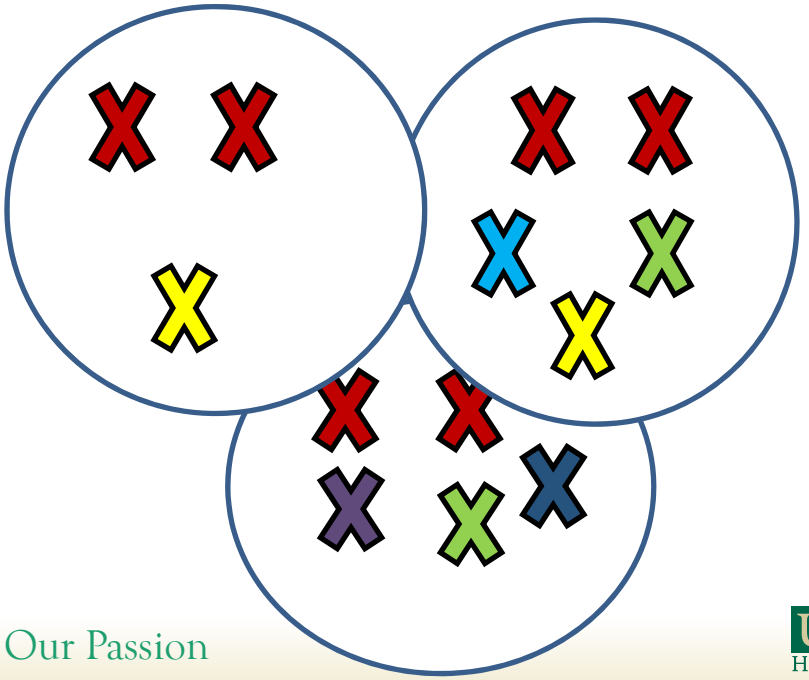
- Endpoint progression free survival (PFS)
  - 99 used genomically guided targeted agents
  - 96 physician's choice

- After 11.3 months **PFS 2.3 vs. 2.0 months**

Le Tourneau, C. *et al*. *Lancet Oncol*. **16**, 1324–1334 (2015).

# Challenges in Targeted Treatment

- Differences in response based on tumor histology
- Many mutations (complex & unique)
- Tumor heterogeneity & evolution
- Drug resistance

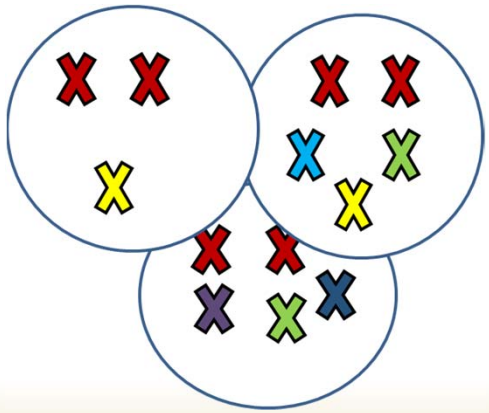


# Overcoming Challenges

1) Customized drug combinations?

2) Administer earlier in the disease?

3) Use immunotherapy for patients with more genetic alterations (checkpoint inhibitors)?



# Revamping Clinical Trials

- Add drugs at multiple specified time points – (evaluate the contribution of each drug)
- Single arm trials - (approval of most recent oncology therapies)
- Adaptive trials - (changes respond to unexpected events)
- Real-world evidence - (enhance safety & efficacy data)
- Surrogate endpoints (shorten trials)

# Objectives

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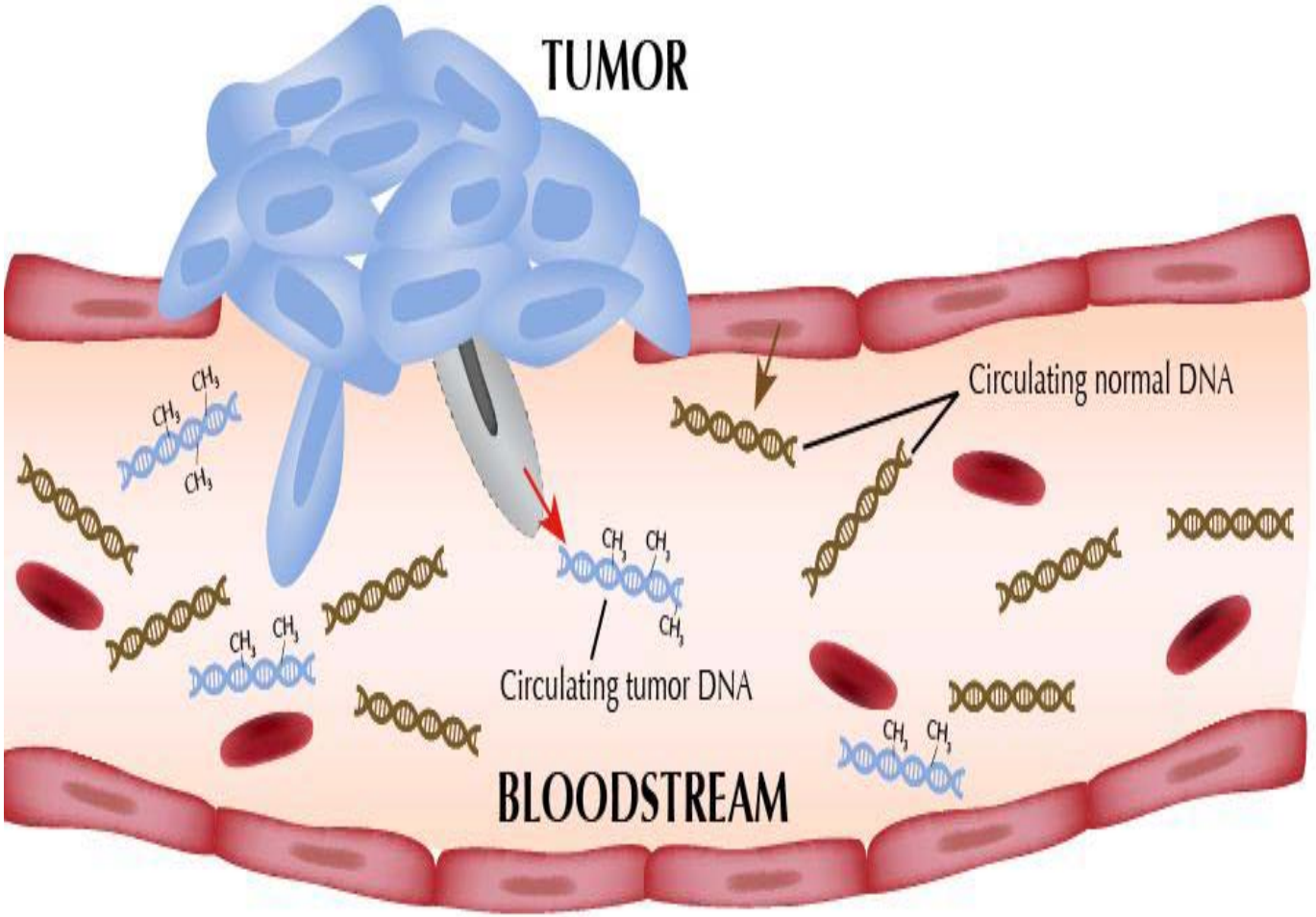
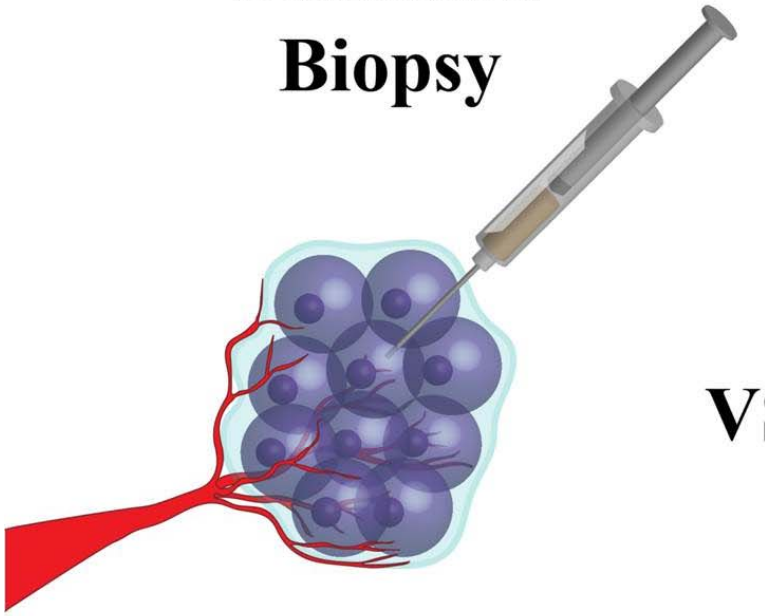
3. Outline the focus of current research related to precision medicine and cancer treatments
4. **Discuss the potential role of the liquid biopsy in identifying tumor genetic biomarkers for directed treatments and for cancer screening**

# Circulating tumor DNA (ctDNA)

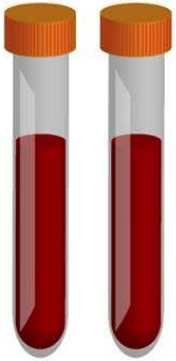


## Standard Biopsy



VS.

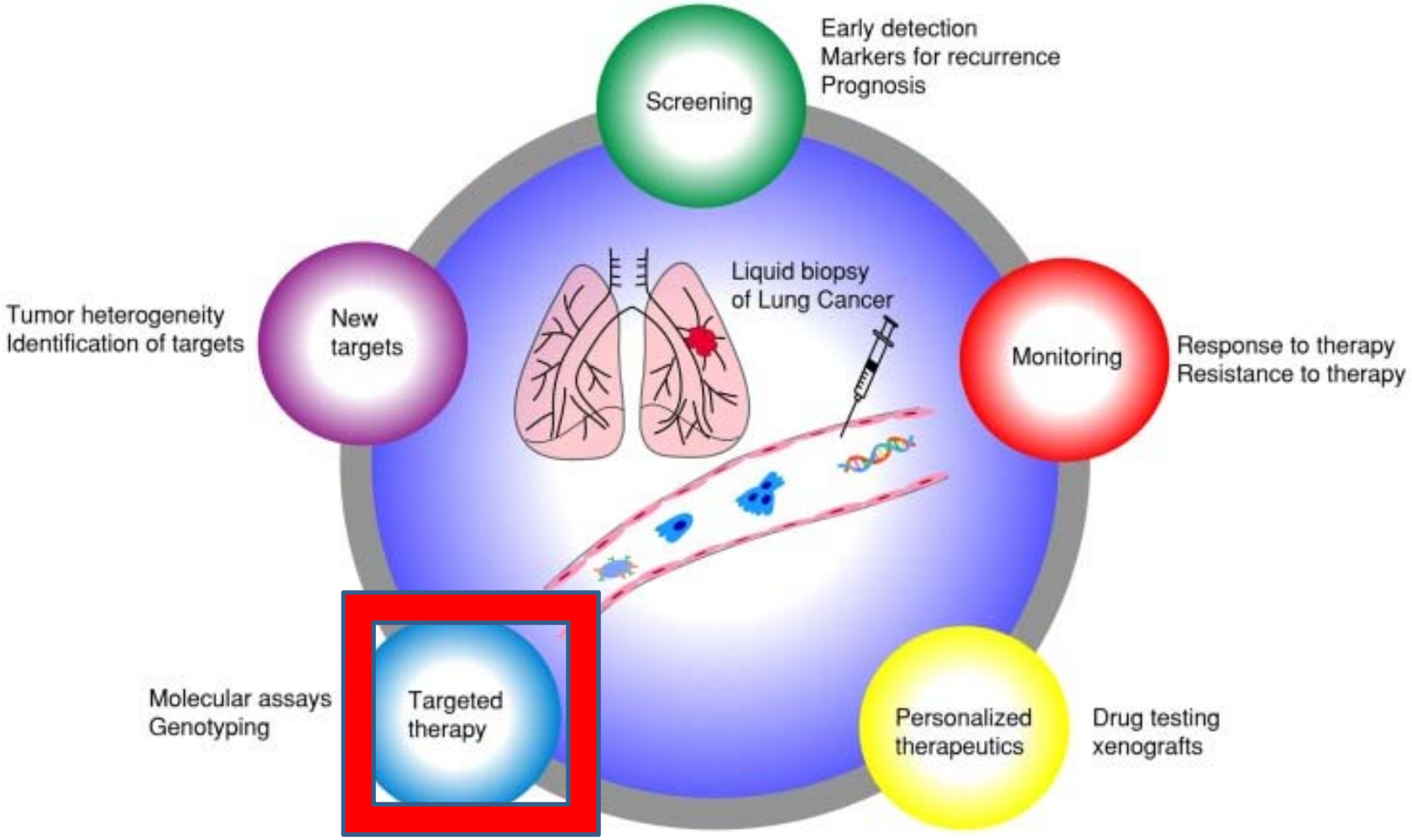
## Liquid Biopsy



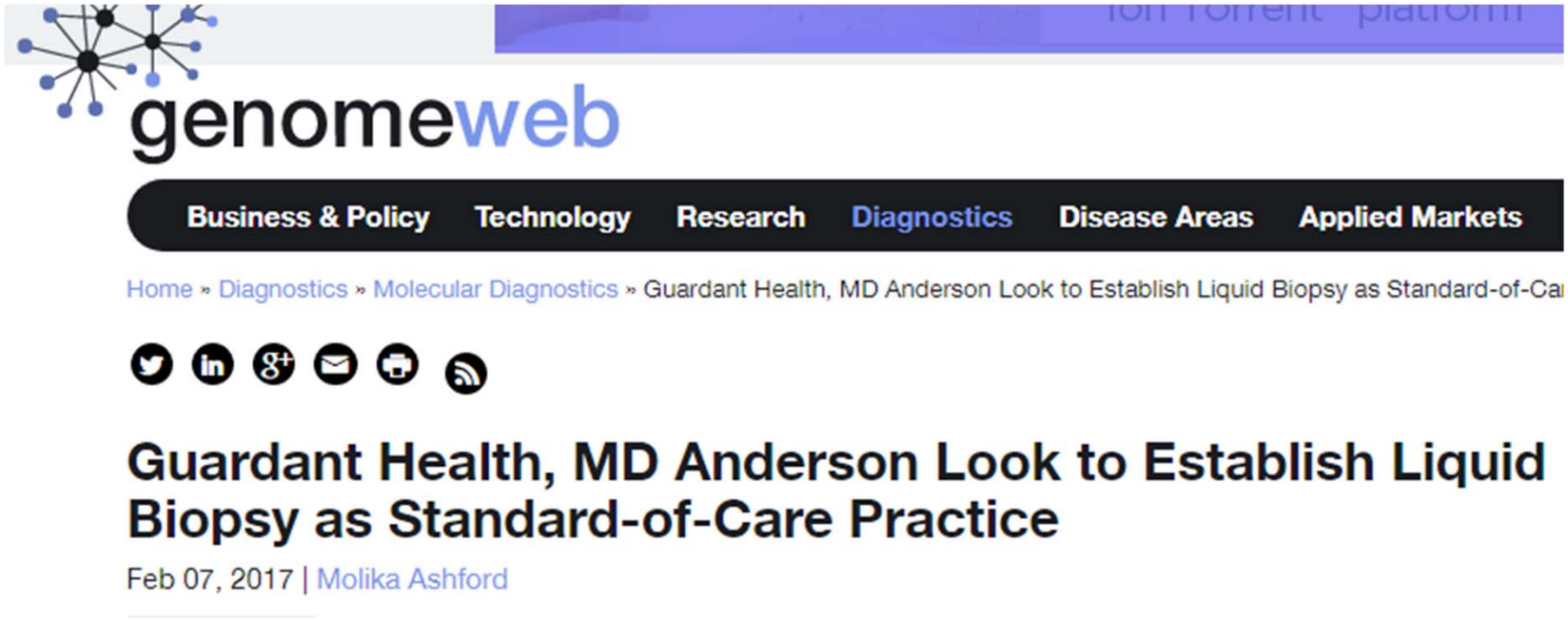
Time-Intensive Procedure
Localized Sampling of Tissue
Not Easily Obtained
Some Pain/Risk
Invasive

Quick
Comprehensive Tissue Profile
Easily Obtained
Minimal Pain/Risk
Minimally Invasive

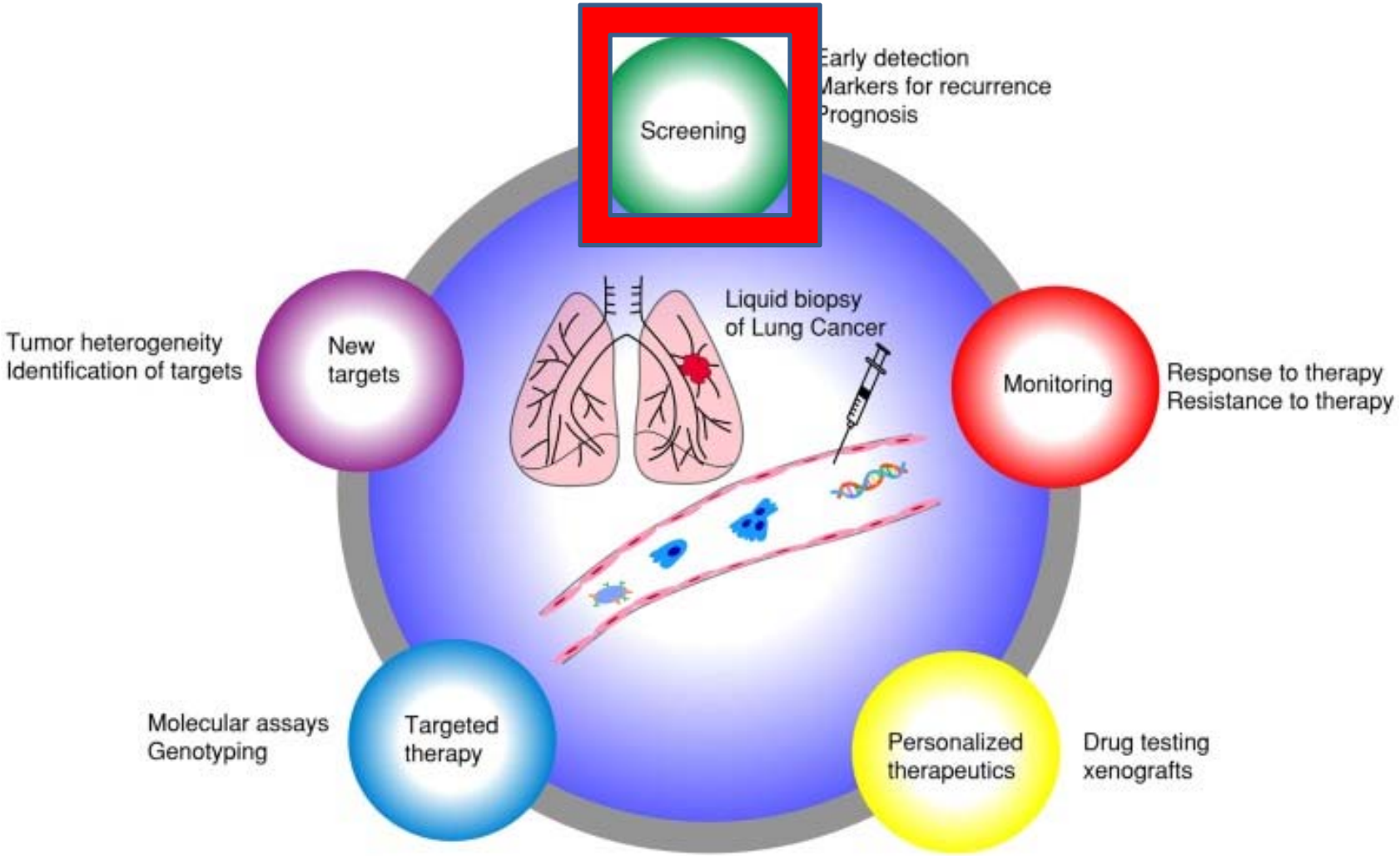
http://liquid-biopsy.gene-quantification.info/


Screening
Early detection
Markers for recurrence
Prognosis
Tumor heterogeneity
Identification of targets
New targets
Liquid biopsy of Lung Cancer
Monitoring
Response to therapy
Resistance to therapy
Molecular assays
Genotyping
Targeted therapy
Personalized therapeutics
Drug testing xenografts

# June 1, 2016 test for EGFR mutations



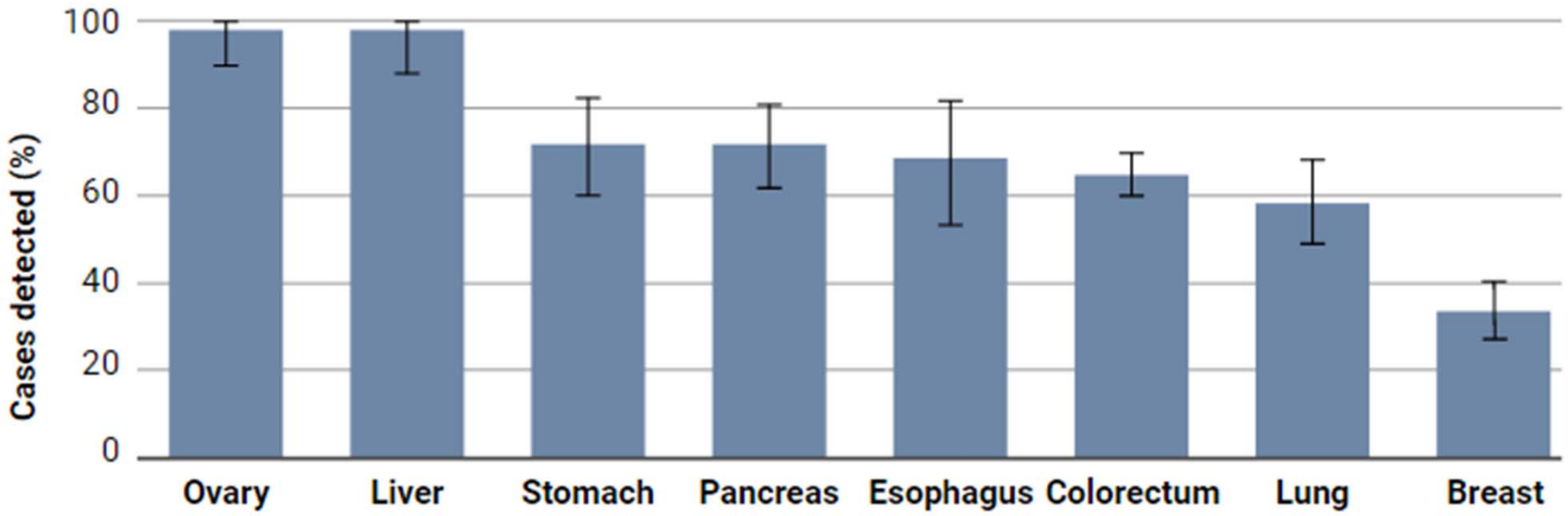

https://www.genomeweb.com/molecular-diagnostics/guardant-health-md-anderson-look-establish-liquid-biopsy-standard-care


Screening
Early detection
Markers for recurrence
Prognosis
Liquid biopsy
of Lung Cancer
Tumor heterogeneity
Identification of targets
New
targets
Monitoring
Response to therapy
Resistance to therapy
Molecular assays
Genotyping
Targeted
therapy
Personalized
therapeutics
Drug testing
xenografts

# Detection Rates

## mutations in 16 Genes & protein markers

A new cancer blood test worked better for some types than others, and caught only 43% of stage 1 cancers. (Error bars represent 95% confidence intervals.)




J. COHEN *ET AL.*, *SCIENCE* 10.1126/SCIENCE.AAR3247, 2018, ADAPTED BY A. CUADRA/*SCIENCE*

http://science.sciencemag.org/content/359/6373/259

Cancer screening

Early intervention

Localized cancer

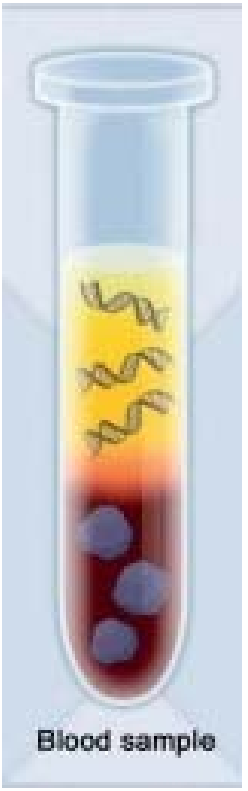
Risk of dissemination and detection of recurrence

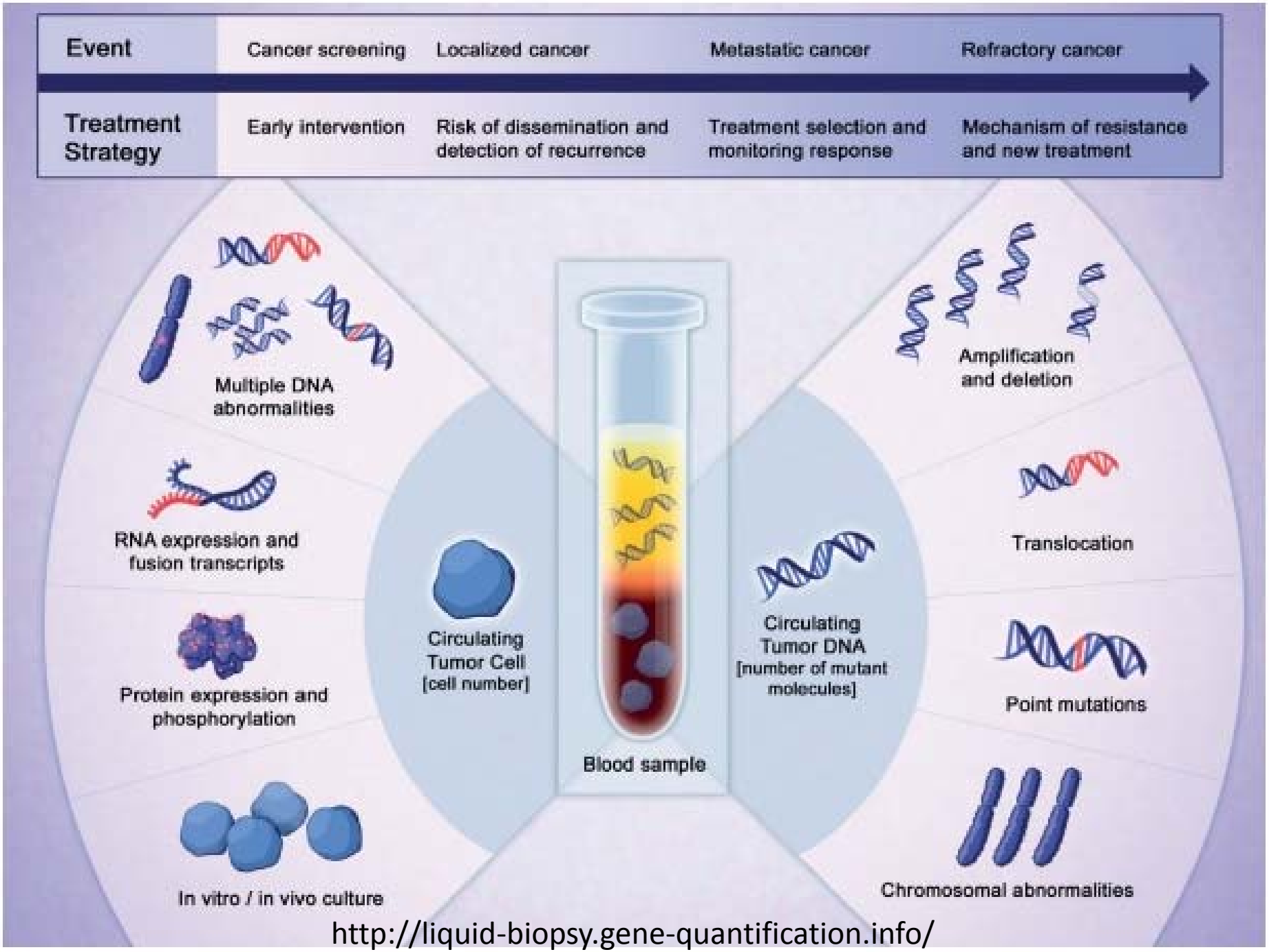
Metastatic cancer

Treatment selection and monitoring response

Refractory cancer

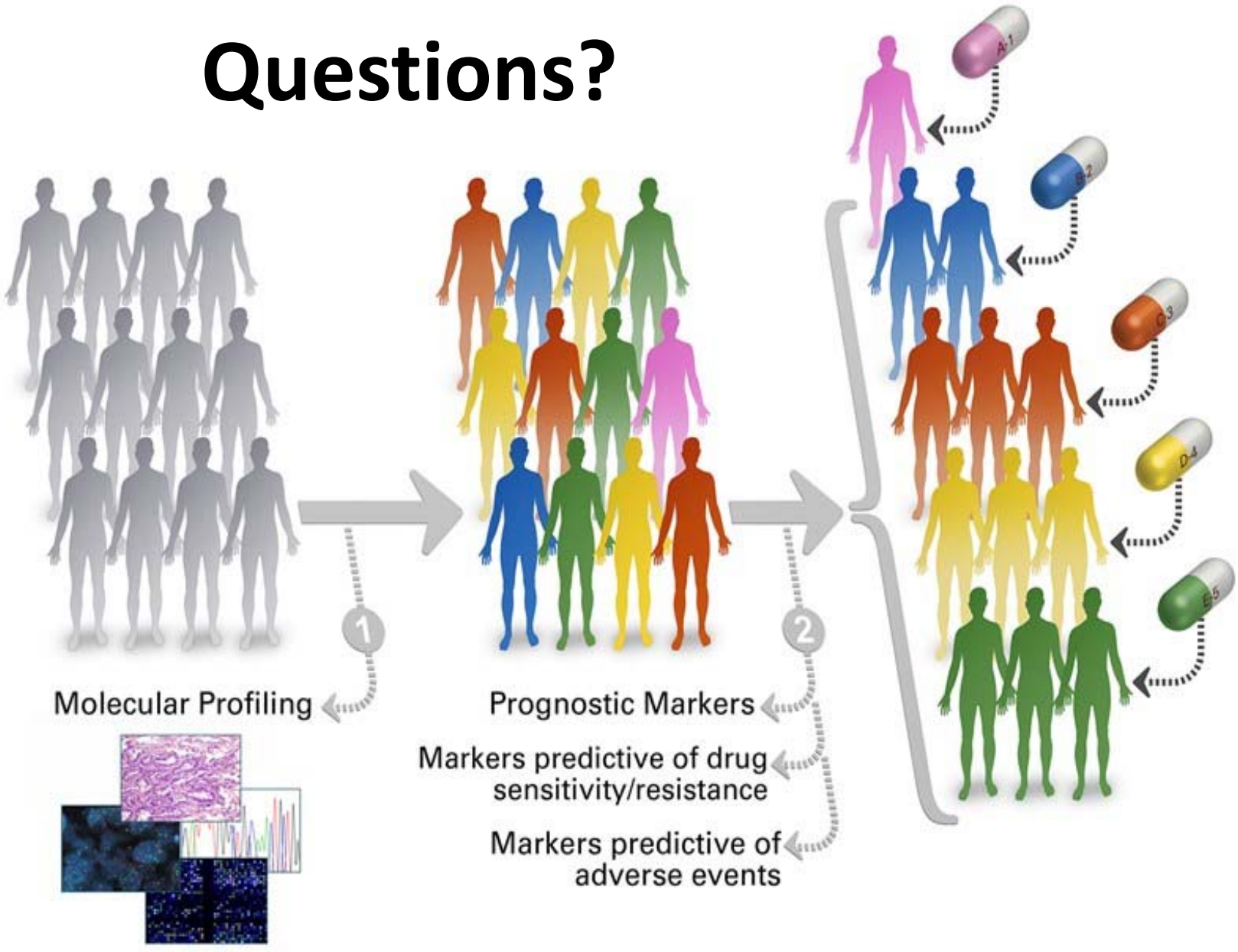
Mechanism of resistance and new treatment






http://liquid-biopsy.gene-quantification.info/

# Questions?


Molecular Profiling
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events