BIOTECH 101

Session 3: cancer

Dr. Neil Lamb, Vice President for Educational Outreach

Cancer
Key Objectives

- All cancer is genetic, but only a small fraction is heritable
- Cancer arises from a stepwise combination of mutations in genes responsible for cell growth & DNA damage repair (+ environmental risks).
- Genomic technologies allow us to classify cancers at the molecular level - valuable for prognosis and therapeutics
- Cancer is at the forefront of personalized medicine

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Cancer is more than rapid cell growth

Neoplasm: an abnormal growth of cells that usually grows more rapidly than normal cells & will continue to grow if not treated

Benign: a non-cancerous neoplasm that tends to grow slowly, remains localized and does not spread to other parts of the body - on its own, it is not dangerous, although the location may pose a threat

Malignant: when neoplastic cells invade neighboring tissues, enter blood vessels or lymph and metastasize to other sites

Tumor: *common, nonspecific term for a mass of tissue - can refer to a neoplasm, but also to a swelling or fluid-filled sac*

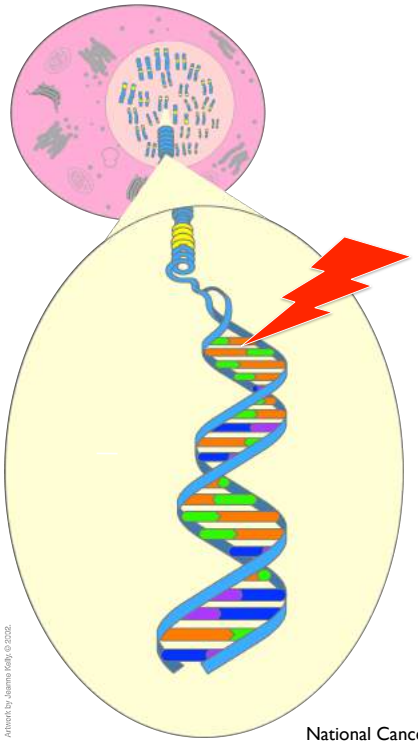
Cancer: *another word for a malignant neoplasm*

Precancer: *abnormal cells that may develop into cancer*

all cancer is genetic

- it arises from mutations in DNA

  - during replication
  - due to environmental agents (UV rays, carcinogens)



Artwork by Jeanne Kelly, © 2002.

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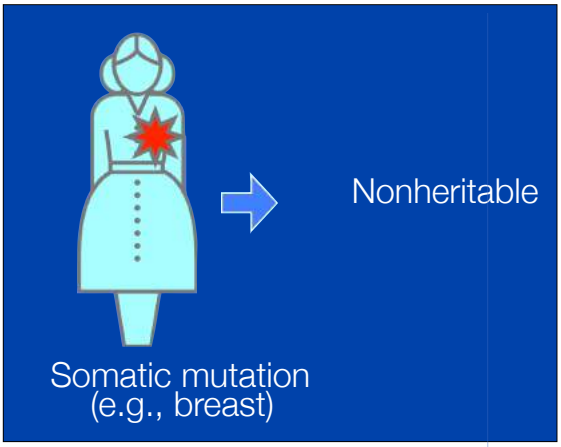
Most cancer is NOT inherited

Most forms of cancer

Somatic mutations

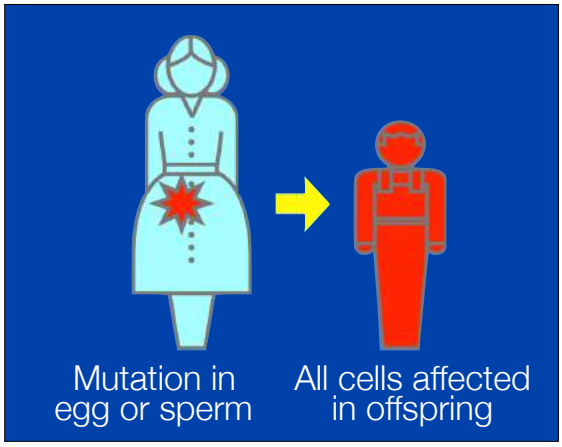
- Occur in nongermline tissues
- Are nonheritable



Rare inherited forms

Germline mutations

- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes



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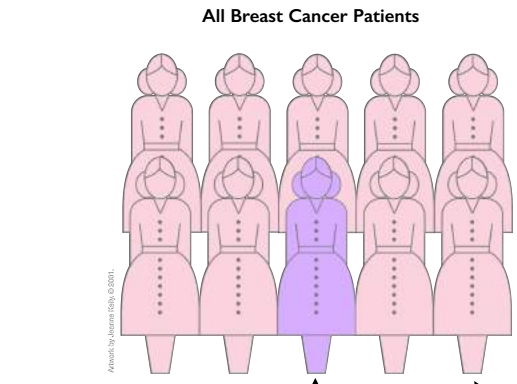
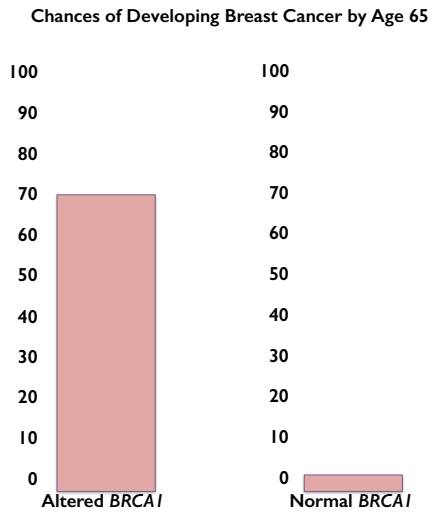
As an example.....breast cancer





caused by a known Inherited Factor (*BRCA1/2* mutation)
1 in 10 of breast cancers

caused by multiple acquired mutations
9 in 10 of breast cancers

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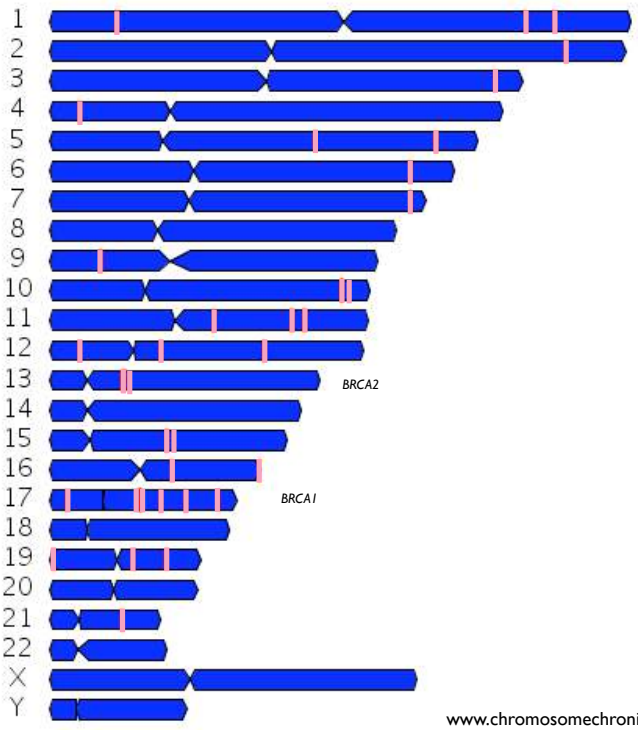
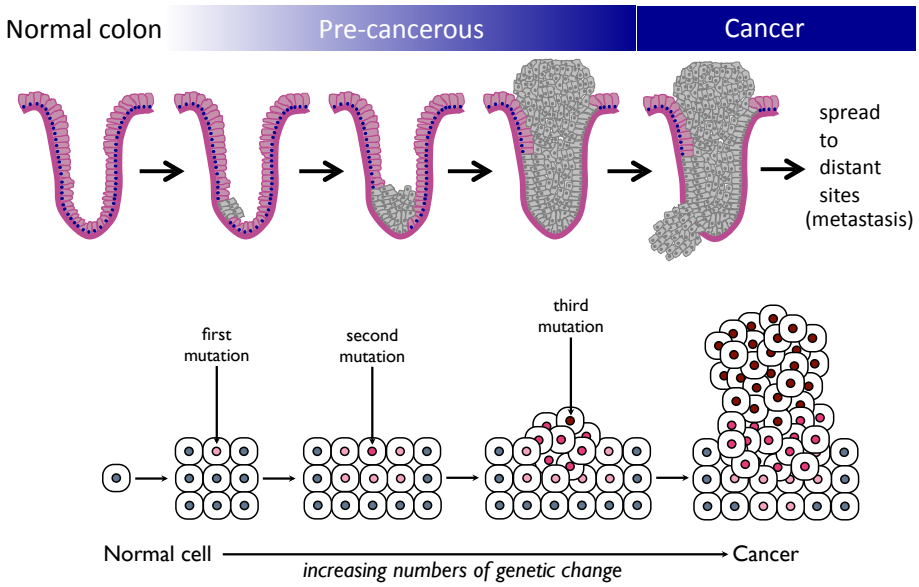


www.chromosomechronicles.com

Each pink line is a place where one letter change in DNA has been associated with an increased risk for breast cancer.
(There are >30.)

Cancer occurs by a stepwise process, caused by mutations in key "driver" genes



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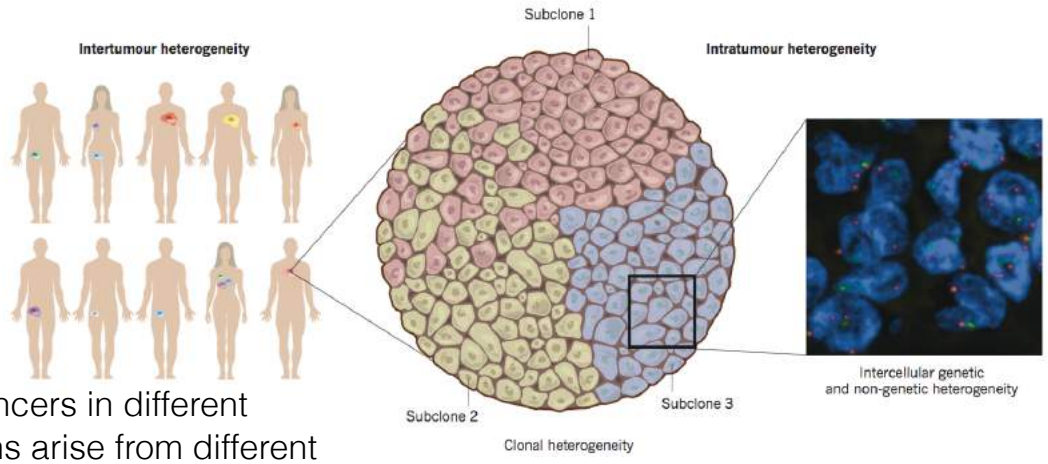
cancer exhibits heterogeneity

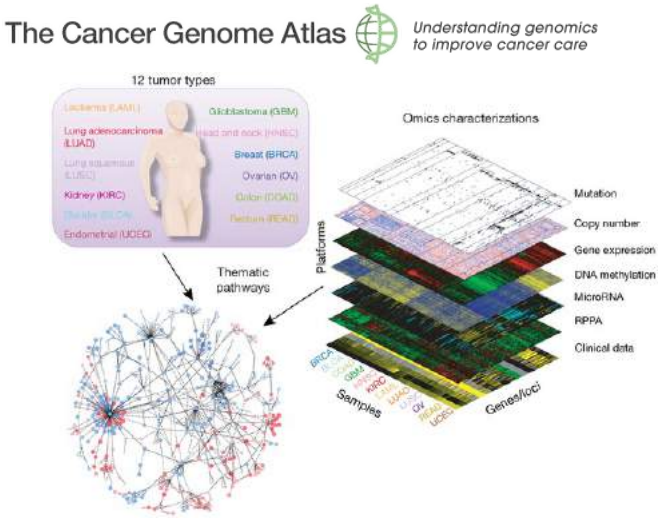


cancers in different locations arise from different mutations

cancers in the same location can also arise from different mutations

within a single cancerous tumor, there may be mixed populations of cells with different combinations of mutation

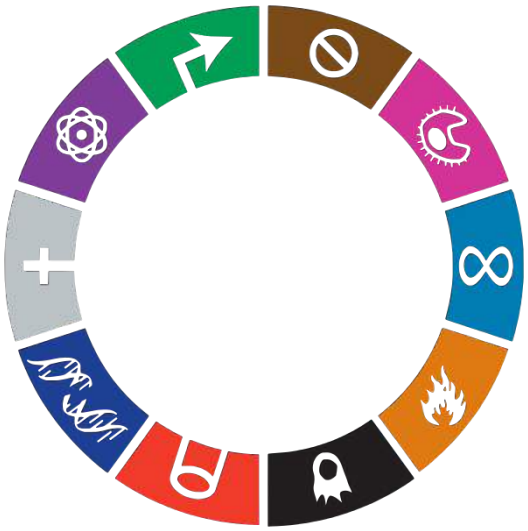
genomic technologies have **revolutionized** our understanding of cancer



The Hallmarks of Cancer

underlying biological principles common to cancers

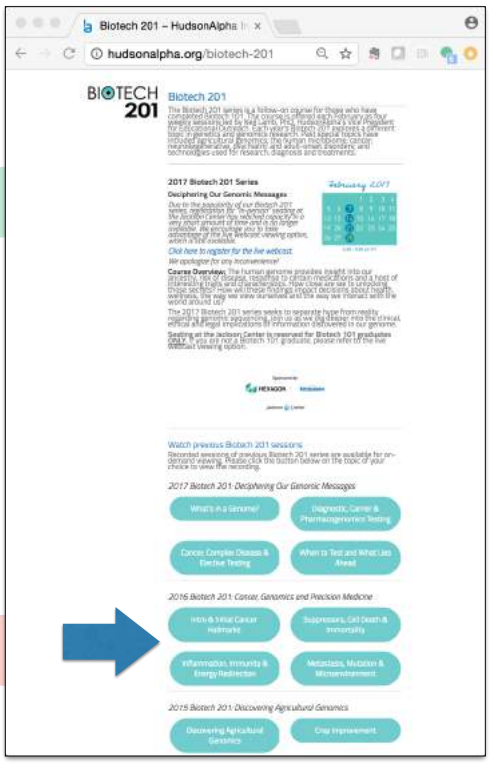
present a simplified way to think about the complexities of cancer



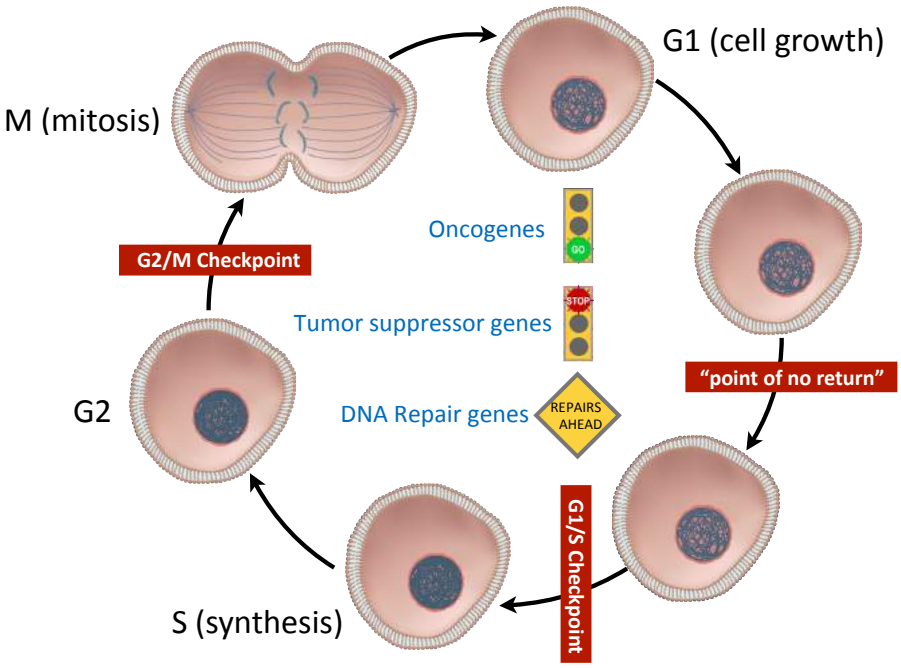
Hanahan and Weinberg Cell 144:646 (2011)

The Hallmarks of Cancer

- Sustaining proliferative signaling
- Inducing angiogenesis
- Evading growth suppressors
- Resisting cell death
- Enabling replicative immortality
- Avoiding immune destruction
- Tumor promoting inflammation
- Reprogramming energy metabolism
- Activating invasion & metastasis
- Genome instability & mutation



The Cell Cycle: normal cell growth



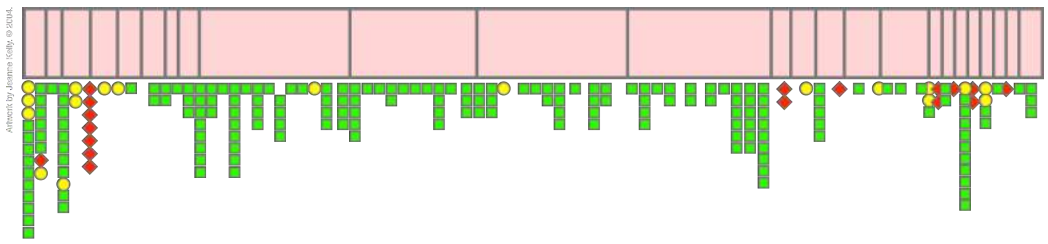
key regulatory points where the cell decides to move ahead or stop

mutations in checkpoint genes influence cancer formation

Digging a little deeper - BRCA1 & 2

Two tumor suppressor genes that contribute much greater risk of developing breast & ovarian cancer

BRCA1



~500 different mutations reported

- Nonsense/Frameshift
- Missense
- Splice-site

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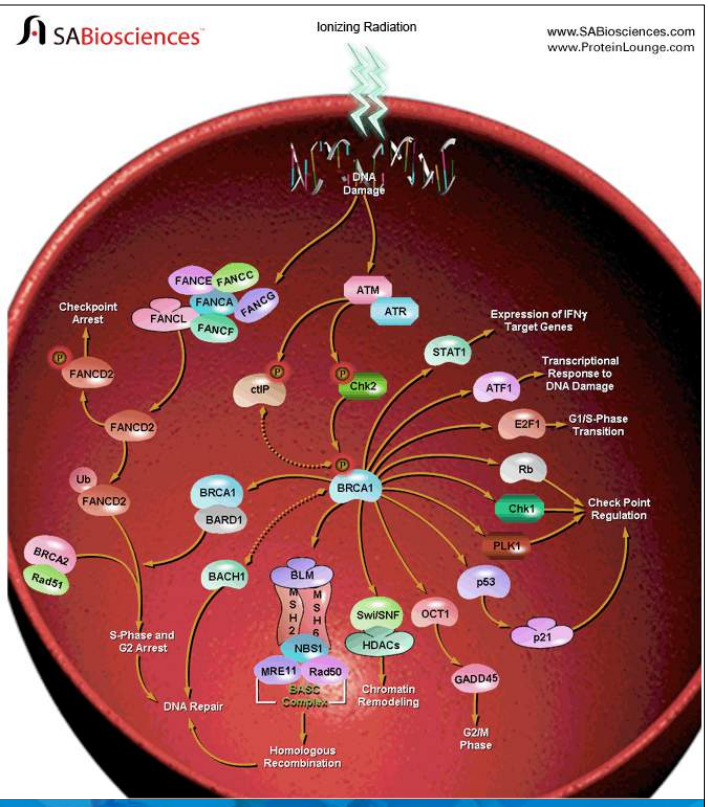
BRCA1/2

The proteins produced by the BRCA1/2 genes interacts with many other proteins in cells

- involved in DNA repair and cell cycle checkpoints
- mutations in these genes have wide ranging consequences



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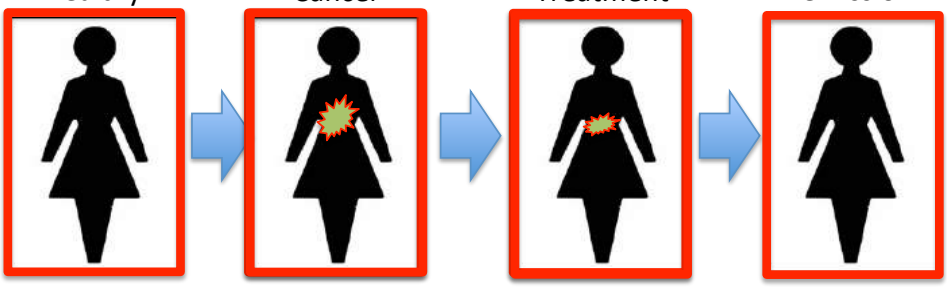
cancer research at HudsonAlpha



Early Diagnosis
Non-invasive test for cancer-specific molecular defects

Prognosis & Treatment
Molecular defects that predict survival and indicate appropriate personalized treatment

Treatment Efficacy
Monitor molecular signatures of the tumor's response or resistance to treatment

- **Glioblastoma**
- **Ovarian**
- **Lung**
- **Breast**
- **Prostate**
- **Kidney**

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Collaboration is key

Work with other groups to characterize the genomes of more cancers, and translate these findings into the clinic.

International Cancer Genome Consortium

Ontario Institute for Cancer Research
science → discoveries → solutions

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

St. Jude Children's Research Hospital

CCI CLEARVIEW CANCER INSTITUTE

Applying Discoveries at HudsonAlpha

Associate companies actively working in the cancer arena

conversant bio
Go Further. Faster.

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Focus of cancer studies

Identifying the changes in DNA that:

- make people more susceptible to cancer,
  so we can enable earlier diagnosis and lifestyle changes

- determine which treatment will be most effective,
  so we can enable development of targeted therapeutics

- allow for prediction of prognosis,
  so we can enable individualized medicine and patient choice.

Studying Cancer Formation

whole genome sequencing to compare cancer and normal cells

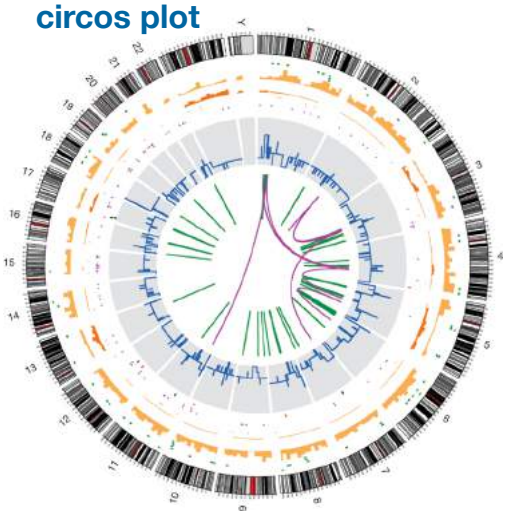
2010 - 22,910 mutations identified in small cell lung cancer

challenge is distinguishing the “drivers” from the “passengers”

most mutations carried the signature of chemicals found in tobacco smoke

scientists estimate that every 15 cigarettes smoked results in a DNA mutation

circos plot



Pleasance et al., Nature 463, 191-196 (2010)

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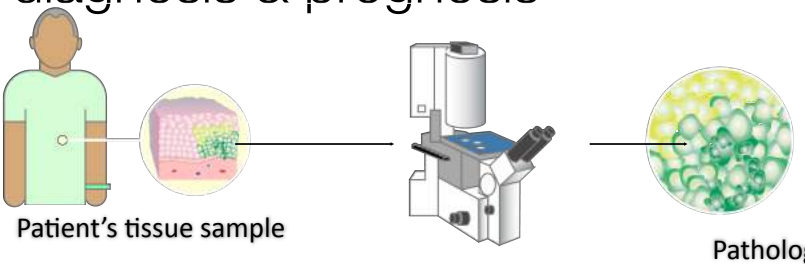
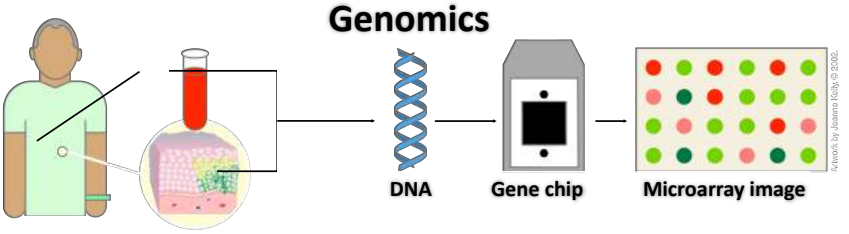
Genomics in diagnosis & prognosis

Old Way



New Way



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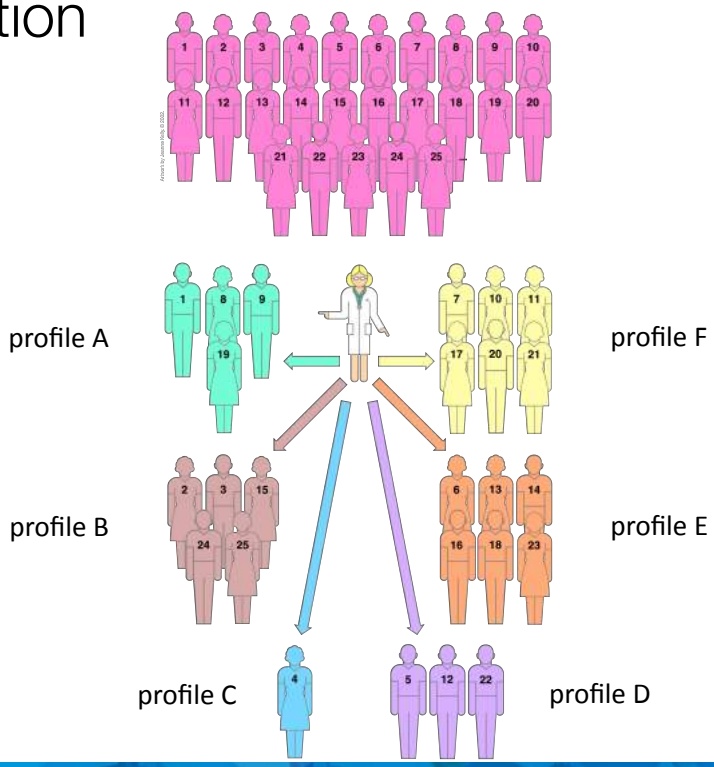
Typing genetic variation in cancers

The value of individual genetic profiles



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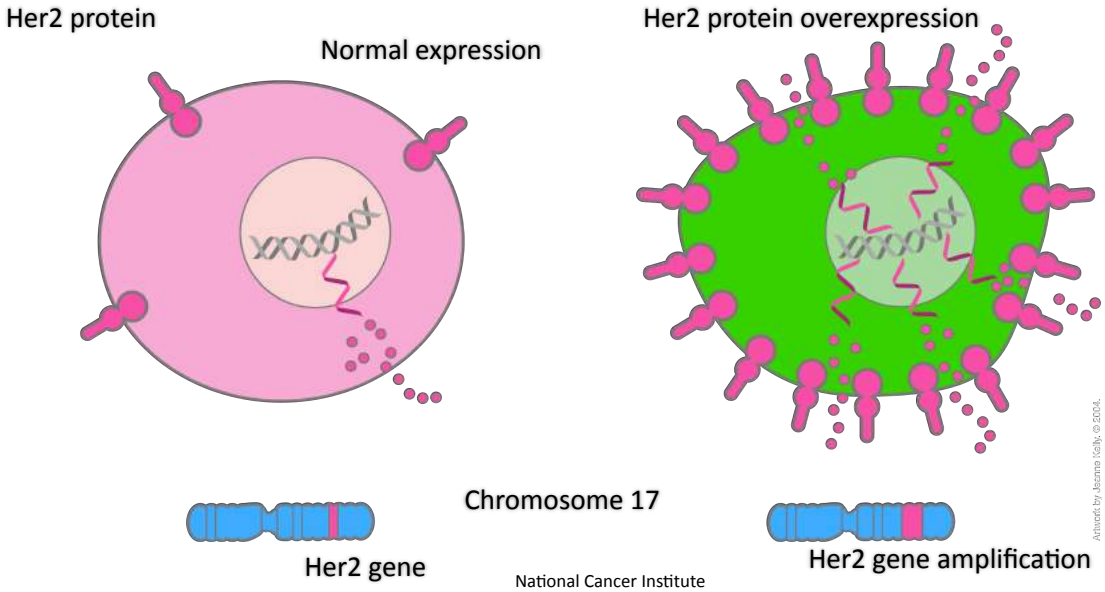
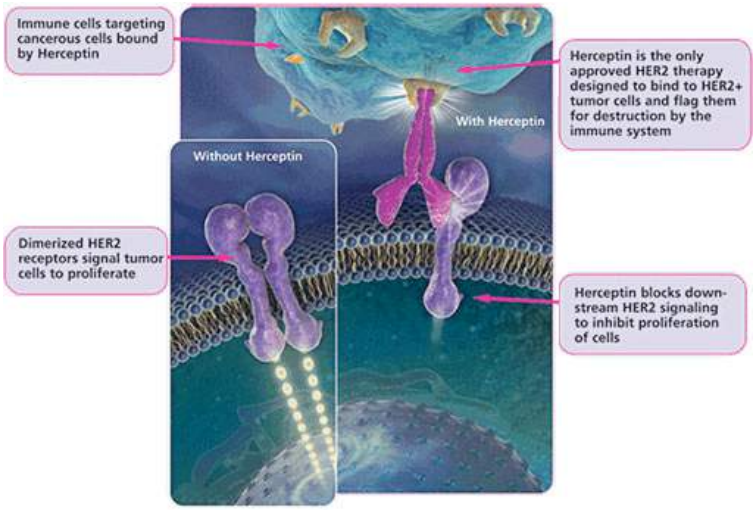
Using genetic information to guide treatment

Mutations in the gene HER2 affect ~ 25% of breast cancer patients



Knowing HER2 status informs treatment

Herceptin is an antibody that specifically targets HER2+ cancer cells



1998: first approval in breast cancer

2006: expanded FDA approval for earlier stages of breast cancer; discovery that ~25% of breast cancers are eligible for this therapy

2009: filing for use in gastric cancer based on limited clinical trial

Aug 2010: about 20% of gastric cancers eligible; survival time increased by 5 mos.

Examples of similar cancer-causing mutations and corresponding targeted drugs

Drug	Drug target	Cancer type (or types)	Somatic markers
Cetuximab	EGFR	Colorectal, head and neck	*EGFR* and *KRAS*
Erlotinib	EGFR	Lung, pancreatic	*EGFR*
Exemestane	Aromatase	Breast	*ESR1*, *ESR2* and *PGR*
Gefitinib	EGFR	Lung	*EGFR*
Imatinib	BCR–ABL, KIT and PDGFRα tyrosine kinases	Chronic myeloid leukaemia, gastrointestinal	Philadelphia chromosome, *KIT* and *PDGFRA*
Lapatinib	ERBB2 receptor	Breast	*ERBB2*
Letrozole	Aromatase	Breast	*ESR1*, *ESR2* and *PGR*
Panitumumab	EGFR	Colorectal	*EGFR* and *KRAS*
Tamoxifen	Oestrogen receptor	Breast	*ESR1*, *ESR2* and *PGR*
Trastuzumab	ERBB2 receptor	Breast, stomach	*ERBB2*

Wheeler, H.E. et al. Nature Reviews Genetics. 14:23-34 (2013)

hereditary cancer testing panels

- 5-10% of all cancers are driven by **inherited** risk factors
- historically researchers/physicians examined 1 gene at a time
- ~2013, new technology allowed simultaneous testing of several genes

Cancer panels help identify **predisposition** risks

Integrated GENETICS LabCorp Specialty Testing Group

myriad WHEN DECISIONS MATTER

INVITAE

Ambry Genetics

PATHWAY GENOMICS®

KAILOS GENETICS

GeneDx DNA DIAGNOSTIC EXPERTS

Information is POWER

free genetic testing for cancer risk

http://hudsonalpha.org/information-is-power

$0

30 year old women
& men in Madison, Limestone, Morgan, Jackson & Marshall County, Alabama

$129

19+ year old men and women in these 5 Alabama counties

$225

everyone else

initiative concludes October 28, 2017

HudsonAlpha Institute for Biotechnology

Redstone Federal Credit Union

Kailos Genetics

Information is POWER

free genetic testing for cancer risk

The Details

ATM	NBN
BARD1	PALB2
BRCA1	PMS2
BRCA2	PTEN
BRIP1	RAD50
CDH1	RAD51C
CHEK2	RAD51D
EPCAM	RINT1
MLH1	STK11
MRE11A	TP53
MSH2	XRCC2
MSH6	

- gene panel test — Kailos Genetics
- Genetic changes in all selected genes have been associated with increased breast *or* ovarian cancer risk (plus other cancers as well)

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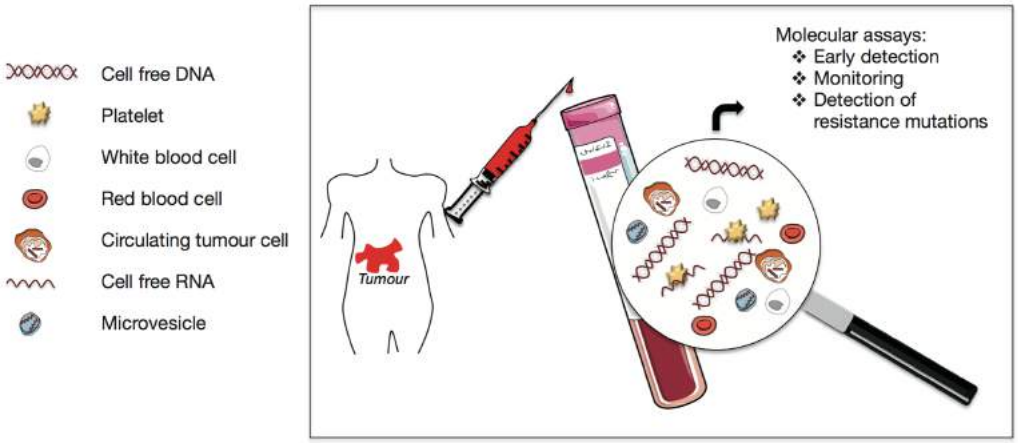
on the horizon

liquid biopsies

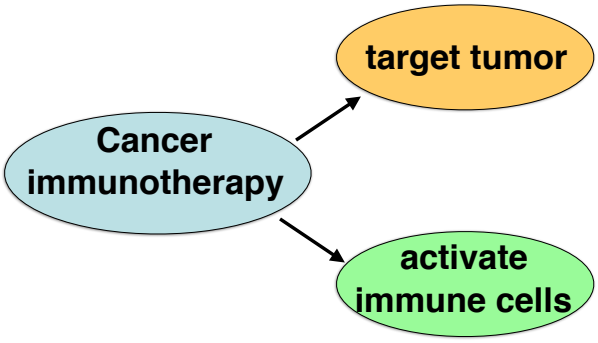
using a liquid sample - blood, urine, spinal fluid - to **non-invasively** test for the presence of cancer



on the horizon

Immunotherapy

treatment that uses part of the body's immune system to fight cancer



The goal of cancer immunotherapy is to initiate or reinitiate the immune system to attack cancer cells, **without** generating unrestrained autoimmune inflammatory responses

More than 50% of current US cancer clinical trials include some form of immunotherapy

Sathyanarayanan V. and Neelapu S. Molecular Oncology 9:2043-53 (2015)

on the horizon

only a fraction of patients appear to respond when immunotherapy is used as the sole form of treatment

early results suggest that combination strategies are likely to significantly improve responses

immunotherapy may also be combined with traditional therapies (chemo and radiation)

http://www.wsj.com/articles/cancers-super-survivors-how-immunotherapy-is-transforming-oncology-1417714379

putting it all together

What causes cancer? genetic mutation

How do the mutations cause cancer?

by impacting the various hallmark pathways

certain mutations confer a **selective advantage** on cells, enabling their outgrowth and eventual dominance

multistep tumor progression can be portrayed as a succession of cell expansions, each triggered by the chance acquisition of a hallmark mutation

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putting it all together

What causes cancer? genetic mutation

What causes the mutations?

3 main sources

- random mutations in stem cells that give rise to body cells (bad luck)
- inherited mutations
- environmental mutations

putting it all together

A similar analogy *What determines the likelihood of an auto accident?*

the length of the journey

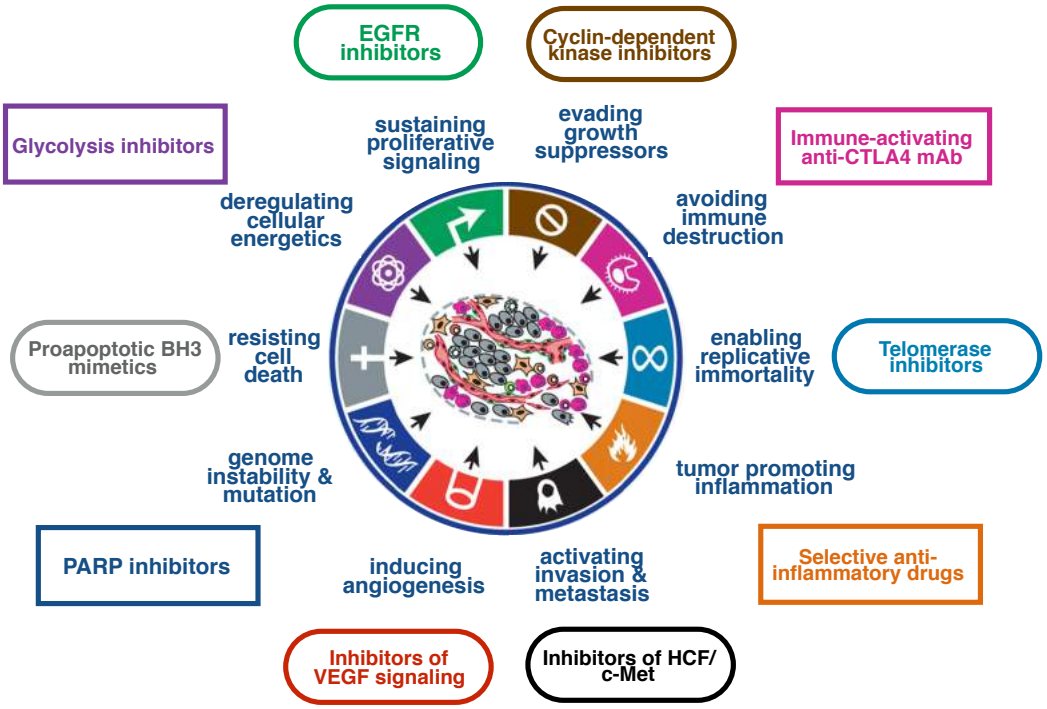
the shape of the car

the condition of the road

putting it all together

How does knowing mutation benefit treatment?

knowing the biology of the mutations allows us to design treatments that strike back at the abnormal results



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