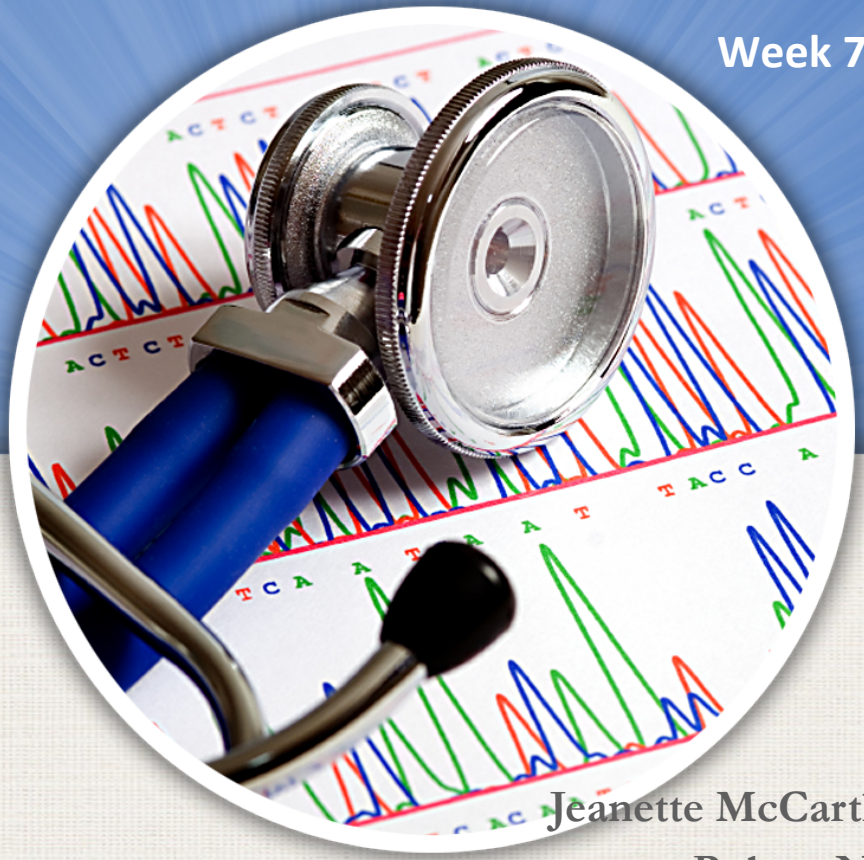
Genomic and Precision Medicine



Week 7: Clinical application of genomics – cancer management

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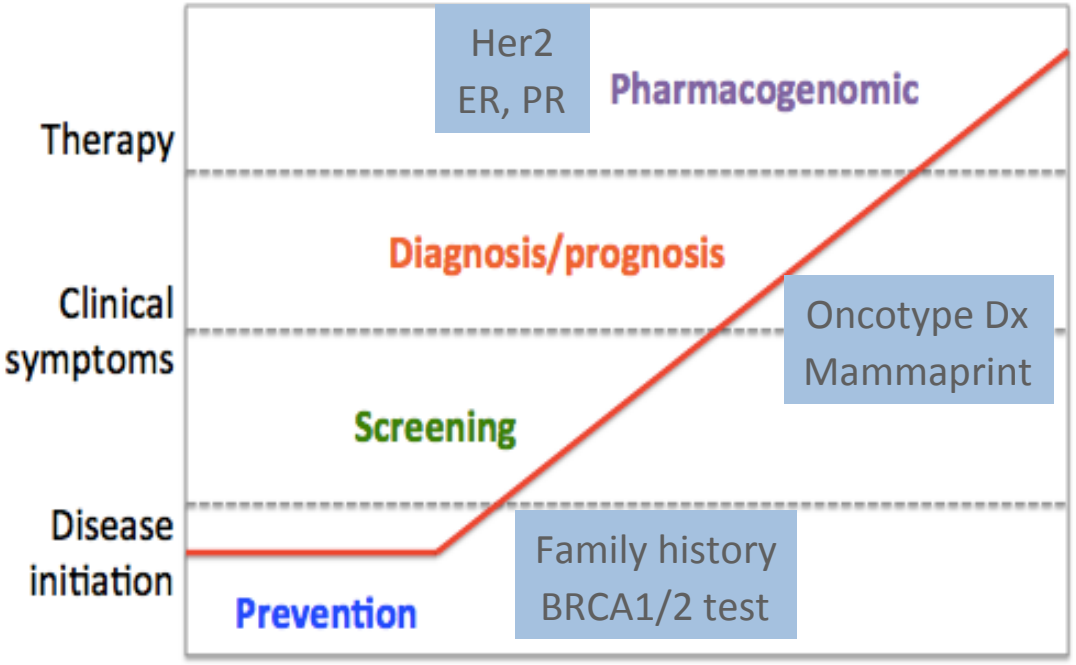
What's so special about cancer?

- Second leading cause of death
  - Incidence decreasing
  - 1 in 3 affected
  - Mortality ~50%
- Accessible tissue
- Cancer is a genetic disease



What happens in personalized medicine usually happens in cancer first

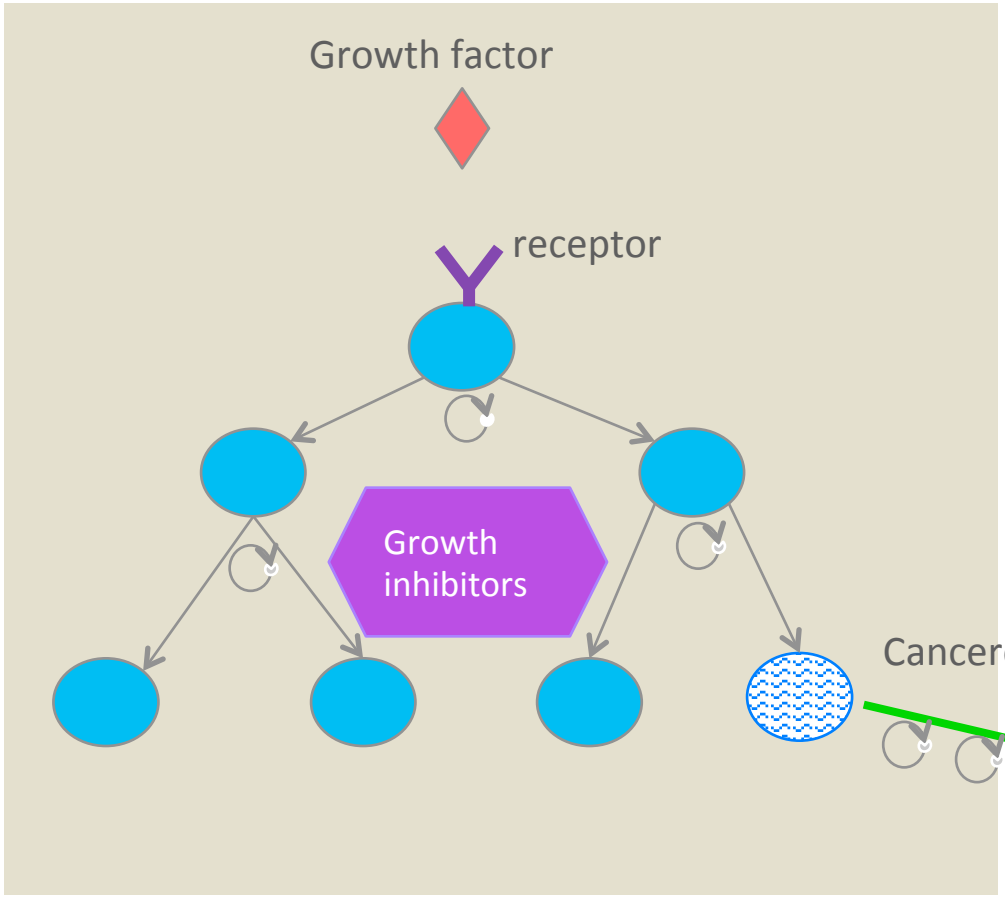
Lecture overview

- Cancer biology
- Hereditary cancers
- Tumor genetics
- Clinical applications

Cancer biology

Normal cellular proliferation and cancer

Cell division (mitosis) is regulated by cell-cycle controllers, growth factors and their receptors that induce or inhibit proliferation

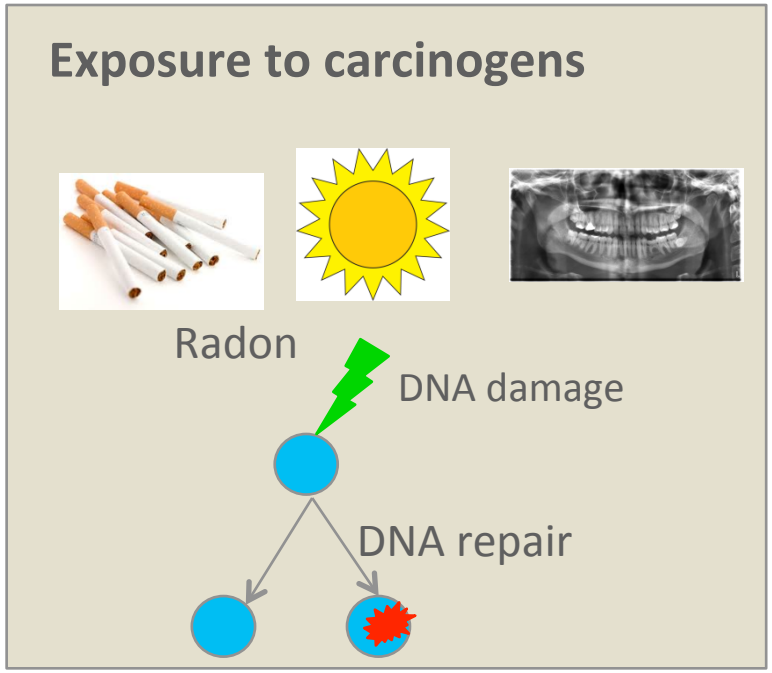


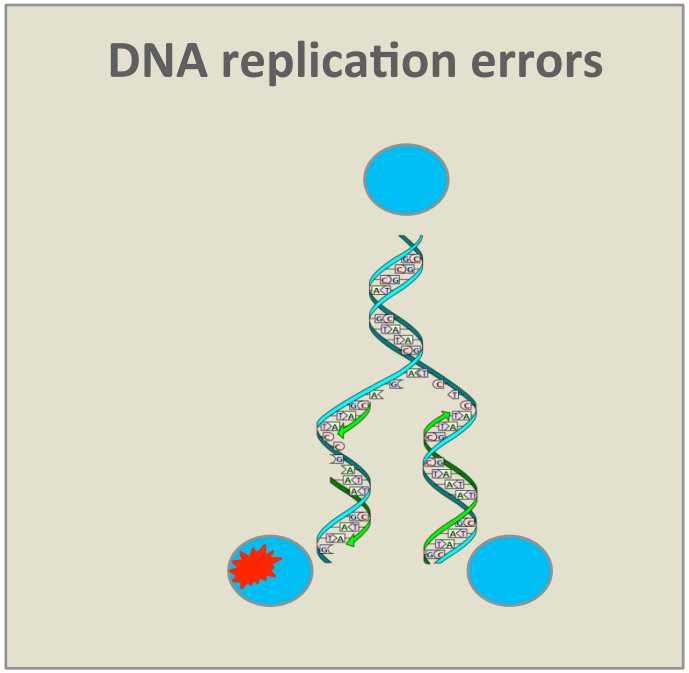
Cancer cells have acquired ability to bypass growth signalling and lose growth control

Cancer invades and metastasizes

Cancer is a genetic disease

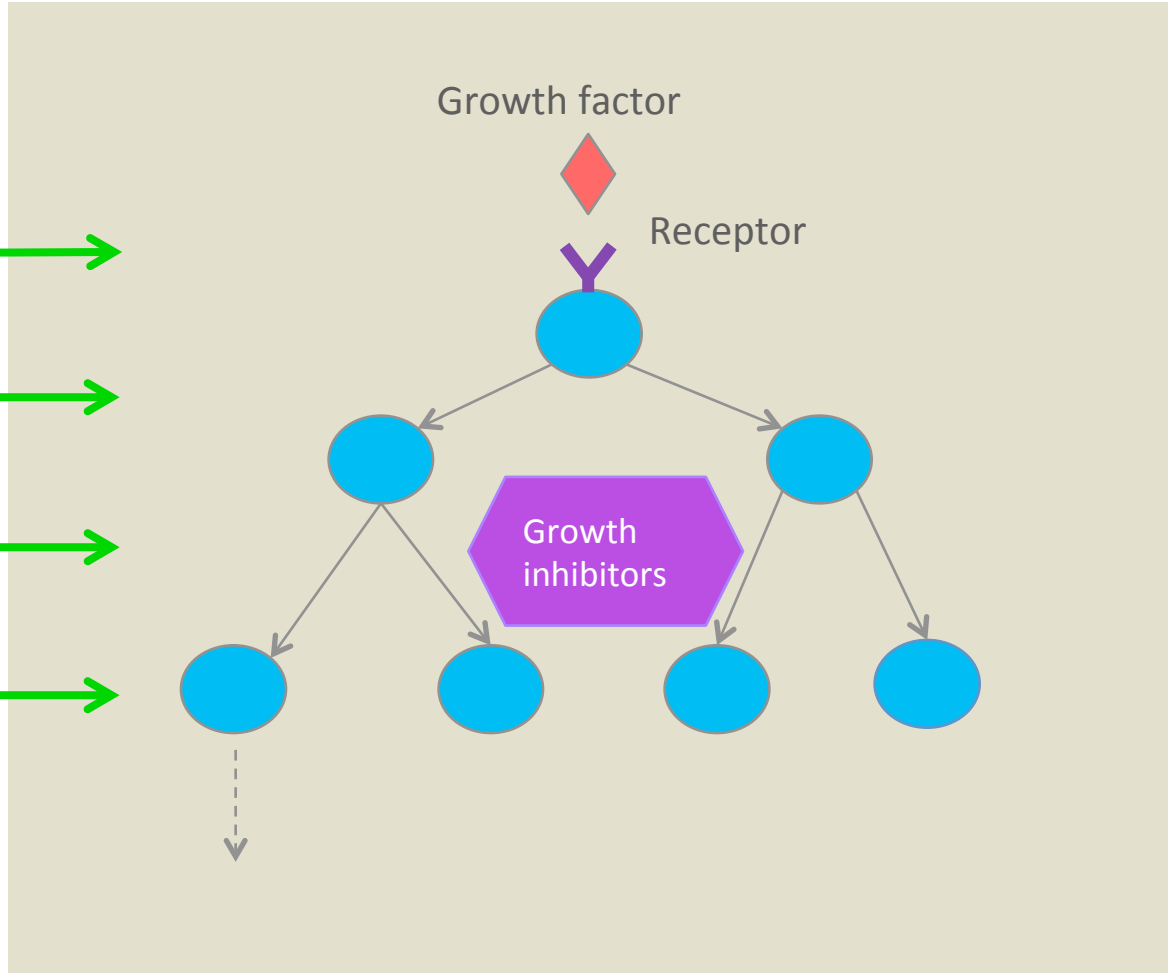
- Loss of growth control is acquired through mutations in the DNA
- Mutations are acquired through faulty DNA damage repair or during normal replication





What kinds of mutated genes are involved in cancer?

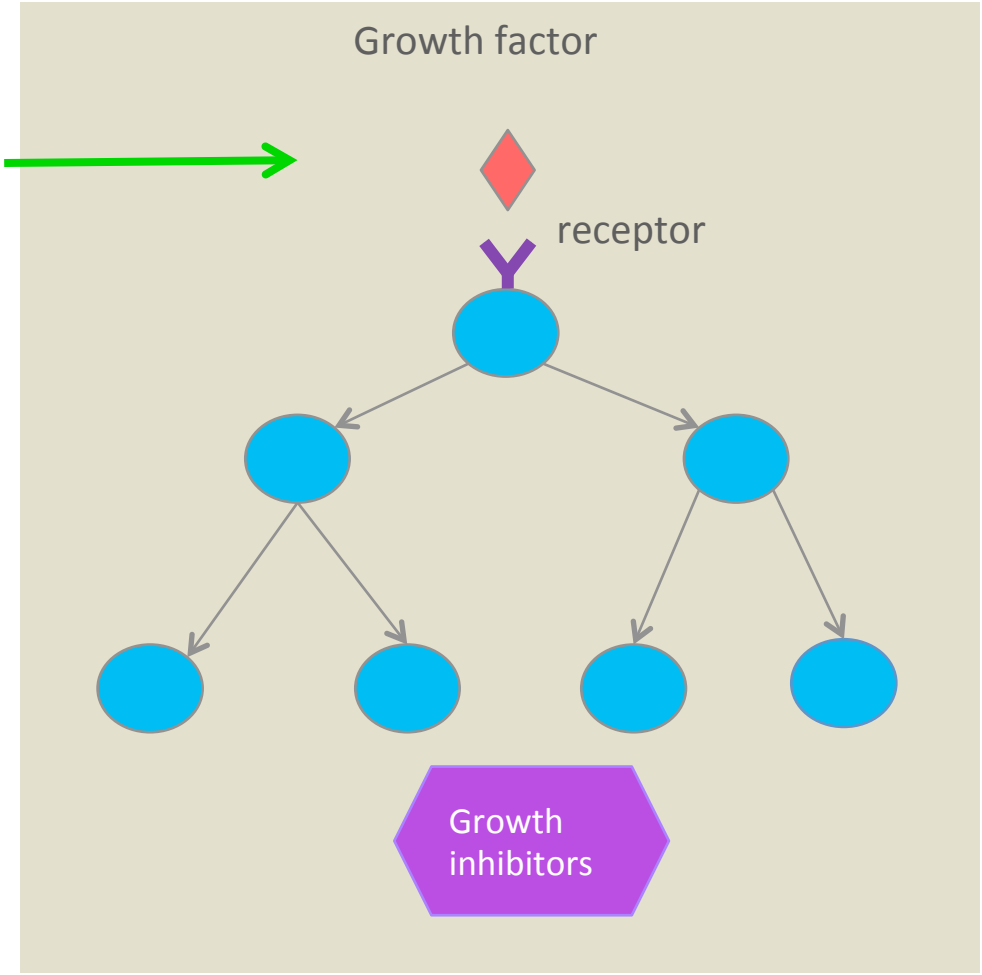
- Oncogenes
- DNA repair enzymes
- Tumor suppressors
- Chromatin modifiers



Oncogenes

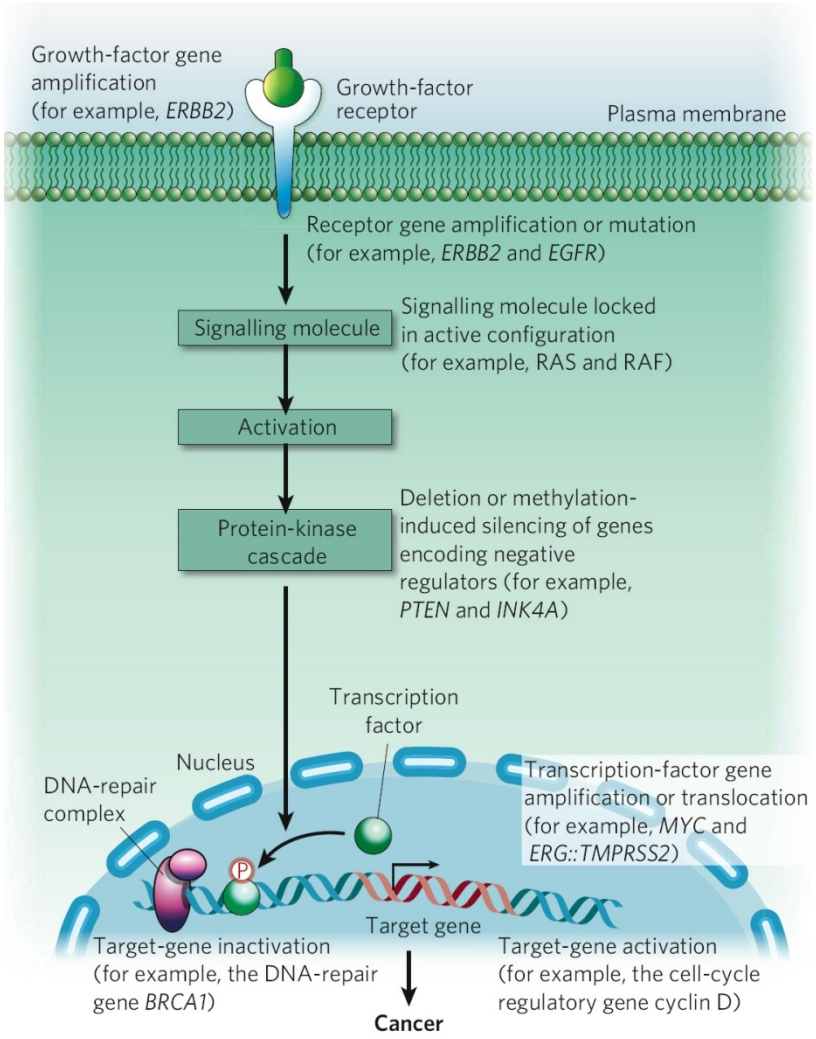
Proto-oncogenes

- Normally involved in cell cycle and growth signalling
- 'On' switch
- When mutated become ONCOGENES
- Gain of function
- Promote proliferation



Known oncogenes disrupting growth signaling in cancer

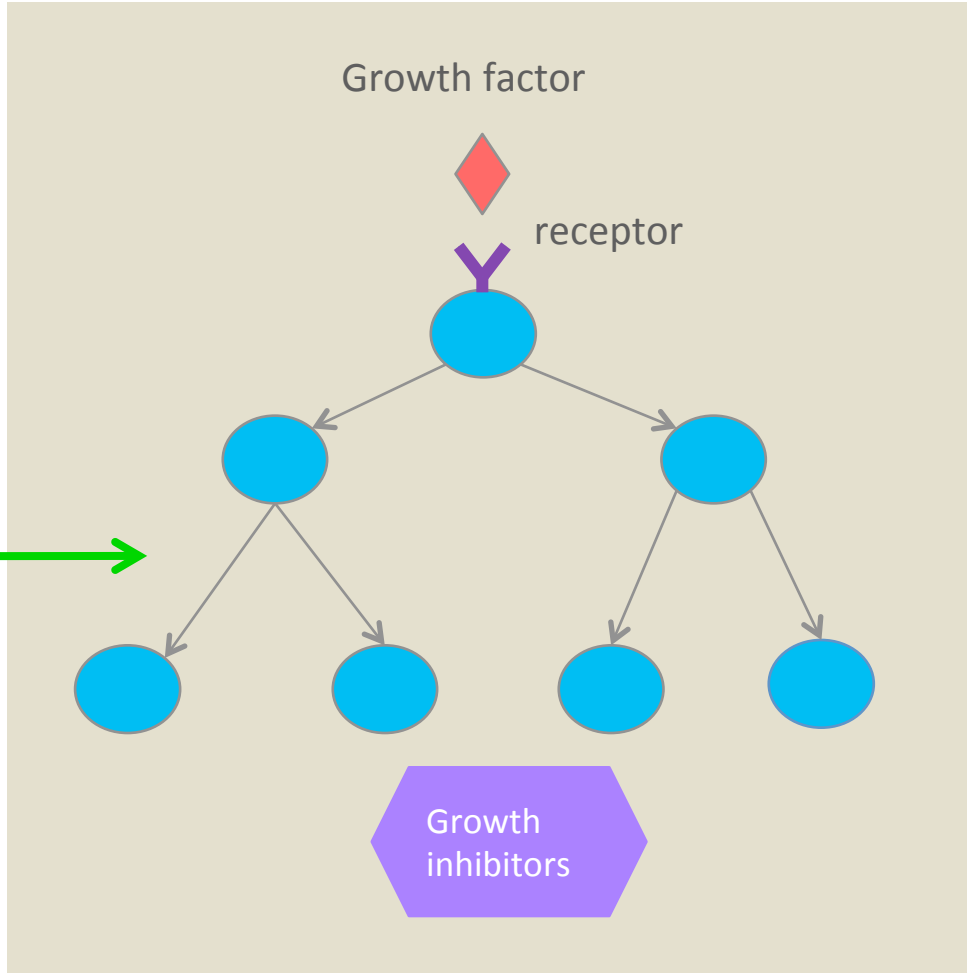
- Growth factors and receptors
- Intracellular transducers, receptors
- transcription factors



Chin, L. & Gray, J.. Insight Nature 452, 559 (2008).

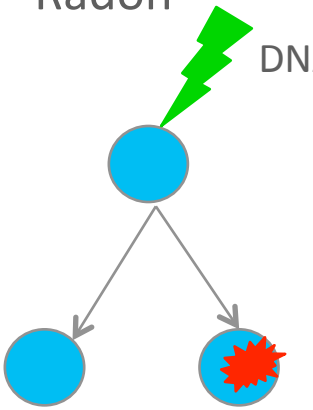
DNA repair

- DNA repair



DNA repair during replication and exposure to carcinogens

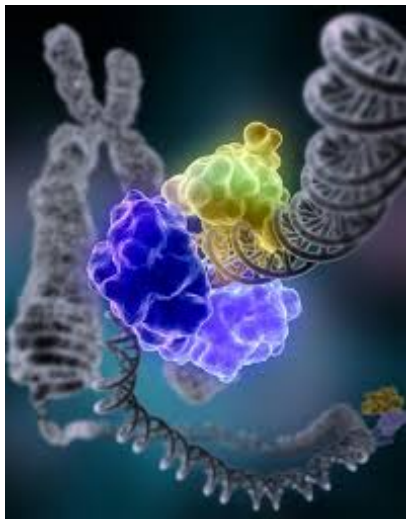
Radon



DNA damage

Repair enzymes

- Excision repair
- Recombinational repair
- Mismatch repair



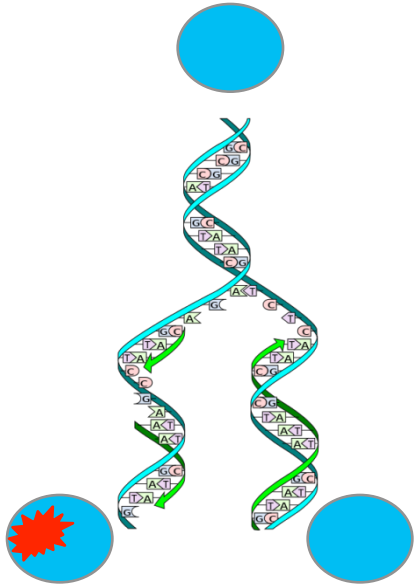
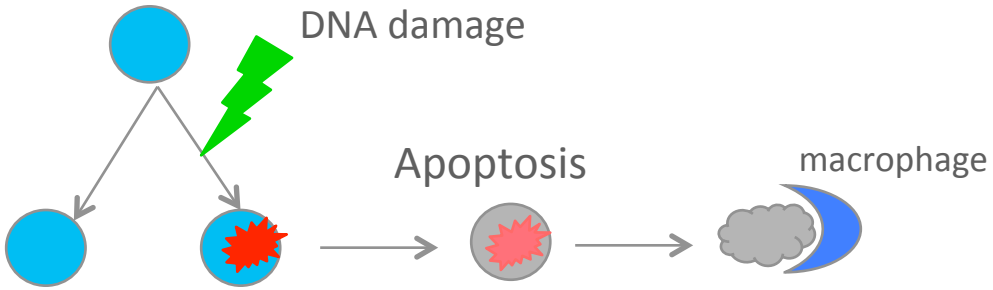


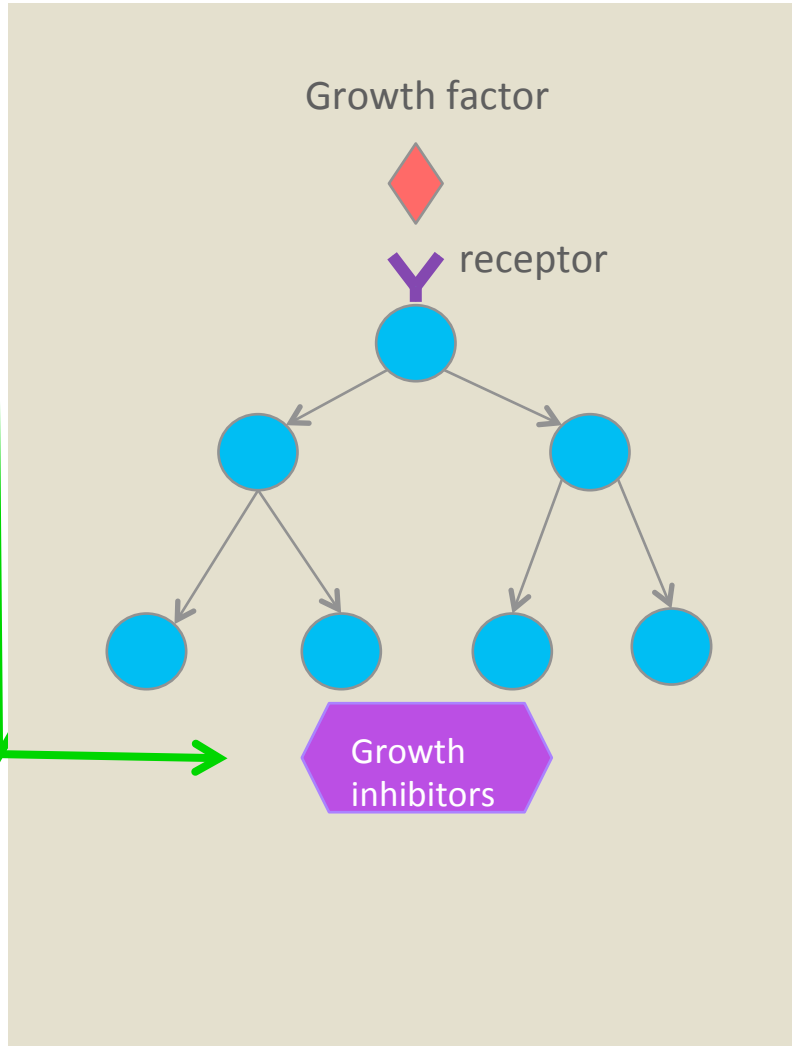
Image of DNA ligase repairing broken strand of DNA: Courtesy of Tom Ellenberger, Washington University School of Medicine

Tumor suppressors

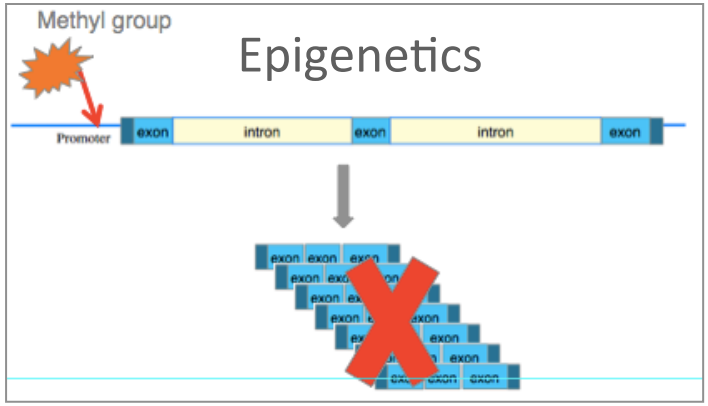
Tumor suppressors

- Slow cell growth
- 'Off' switch
- Signal apoptosis of damaged cells
- Mutated – loss of function



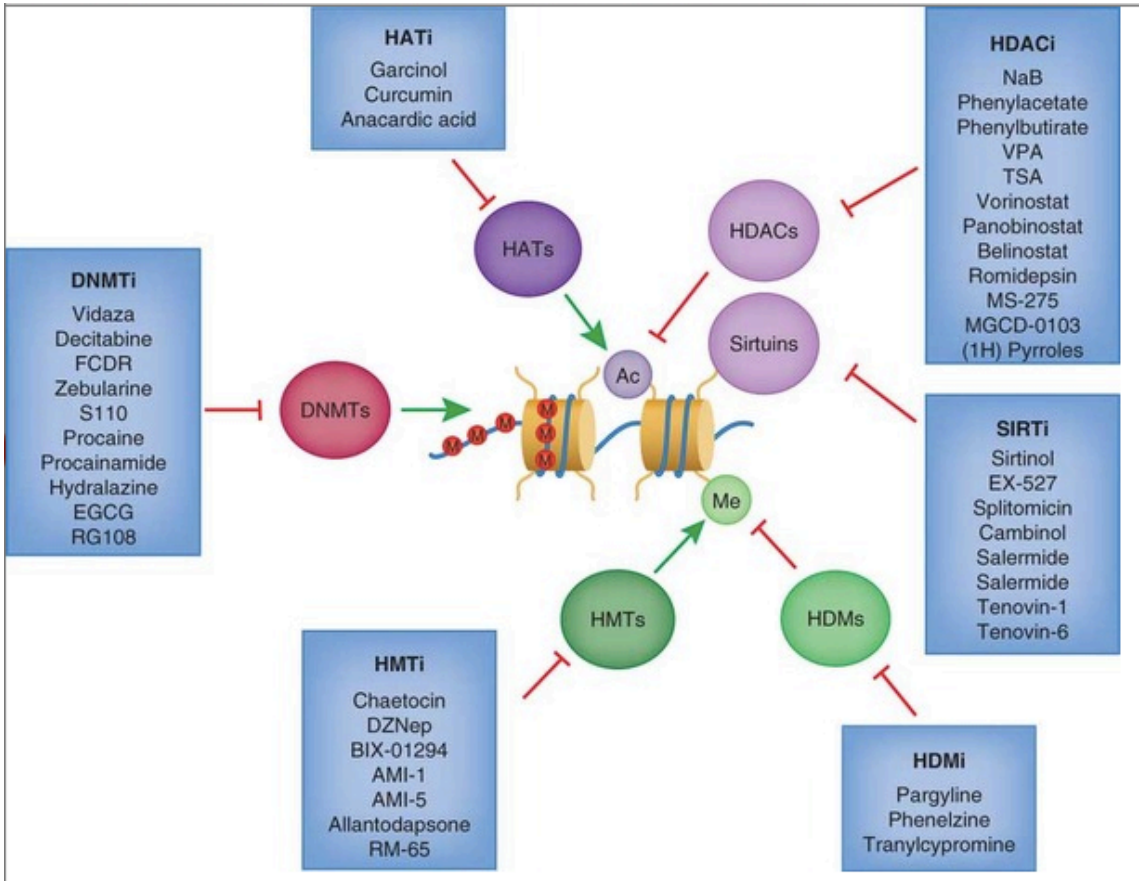


Chromatin modifiers - epigenetics



Cancer genomes are characterized by:

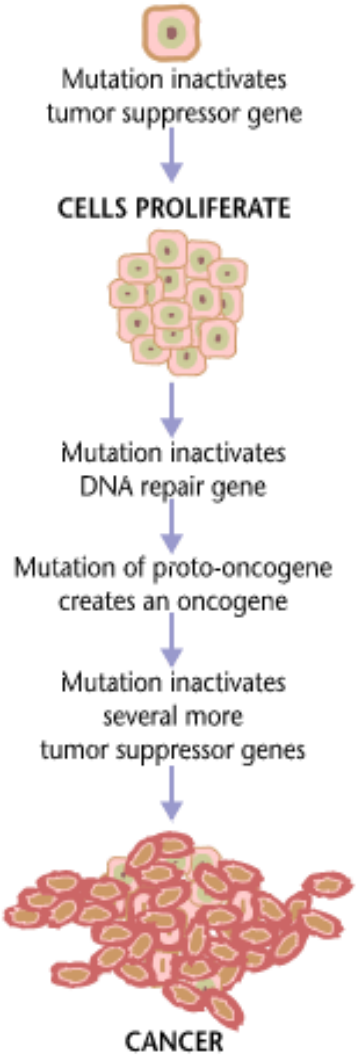
- Mutations in epigenetic machinery
- Global hypomethylation
- Promoter-specific hypermethylation



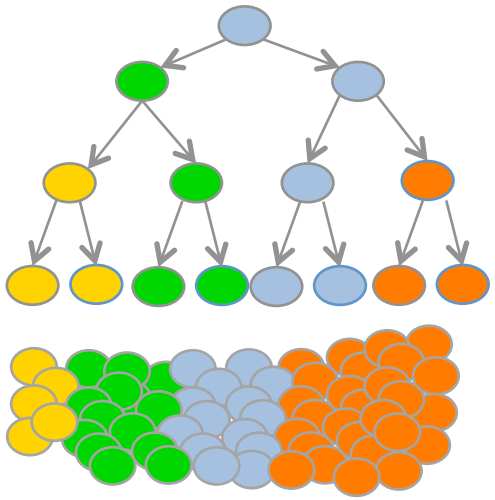
Rodriguez-Paredes M and Esteller M. Nat Med. 2011 Mar;17(3):330-9.

Model of carcinogenesis

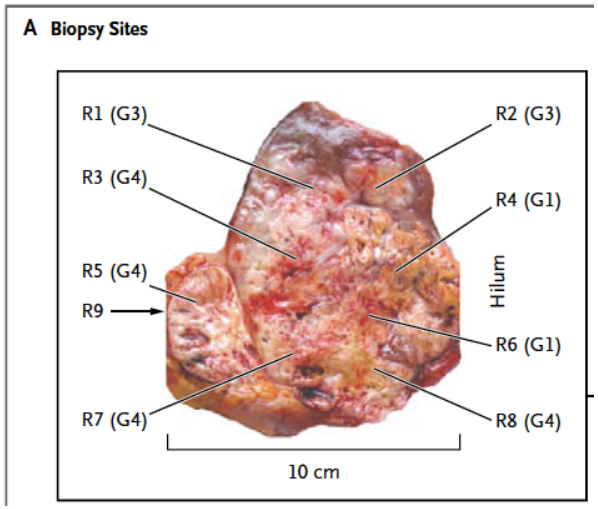
- Proposed by Fearson and Vogelstein in 1990 – colorectal cancer
- Multi-stage process – up to 12 or more independent mutational events ("driver mutations") depending on tumor type
- Cascade effect
- Multi-year process – cancer usually develops over decades

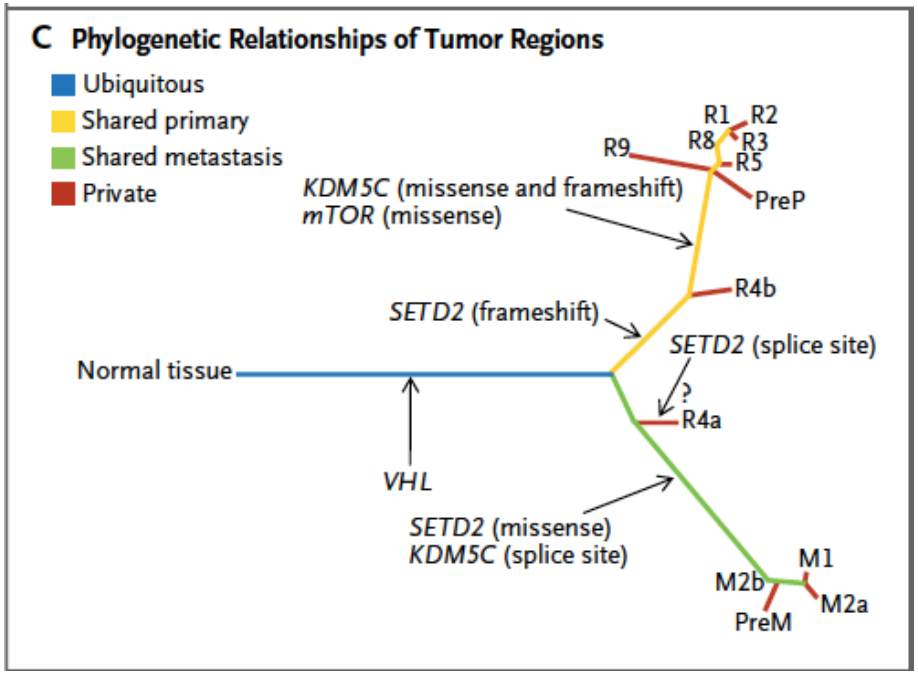


Tumor heterogeneity



- Rapid genetic diversification and selective pressures





Gerlinger M et al. N Engl J Med 2012; 366:883-892

Question

Oncogenes and tumor suppressor genes are mutated in cancers. Which is characterized by 'loss of function' and which by 'gain of function'?

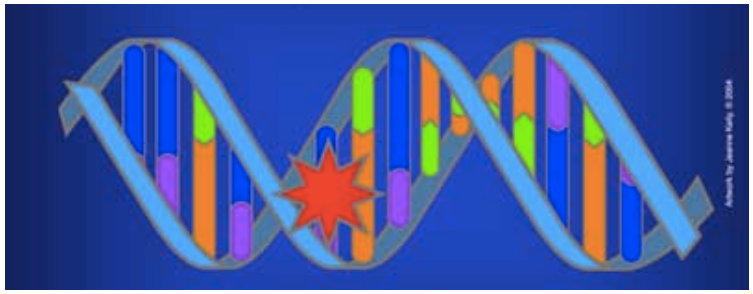
Answer

Oncogenic mutations are ‘gain of function’ and tumor suppressor mutations are ‘loss of function’

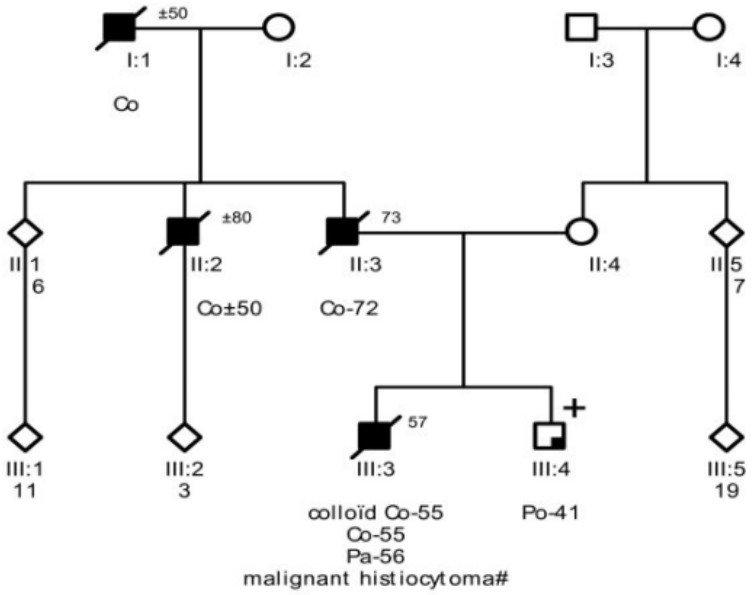
Hereditary cancer

Hereditary vs acquired changes

- Cancer is always a genetic disease
  - Somatic mutations acquired

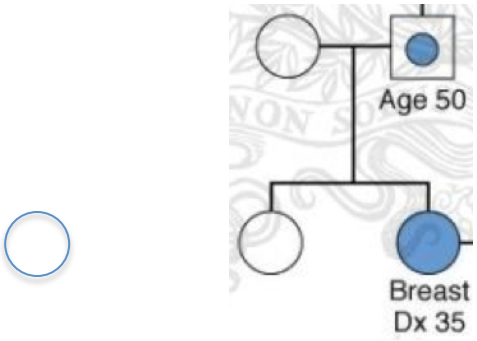


- Cancer mutations are sometimes inherited
  - Germline

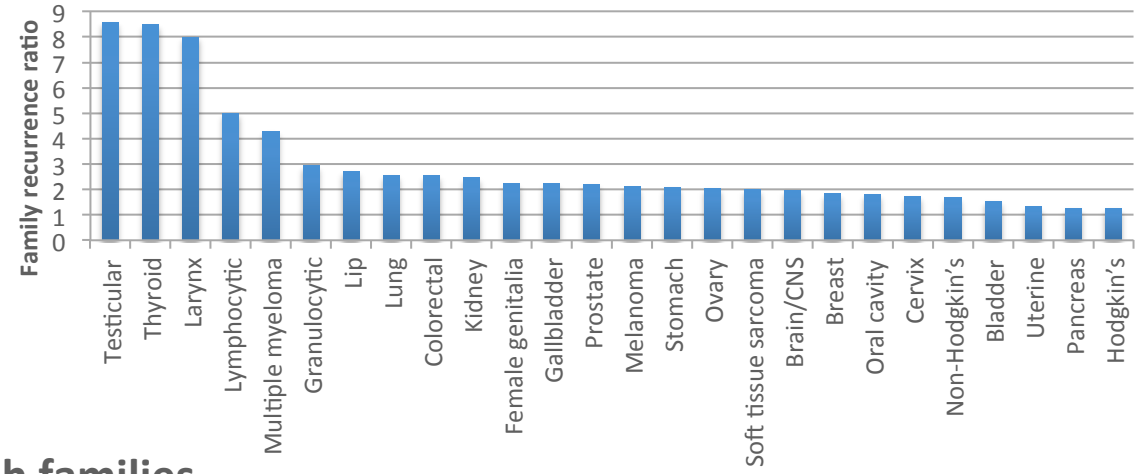


Heritability of cancers

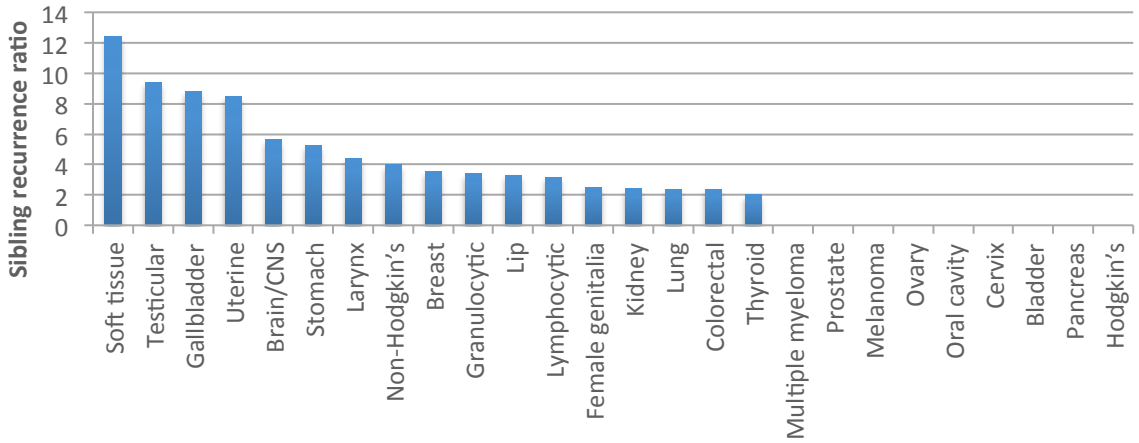
Familial Recurrence Risk



FRR (total) from Utah families



FRR (sibling) from Swedish families



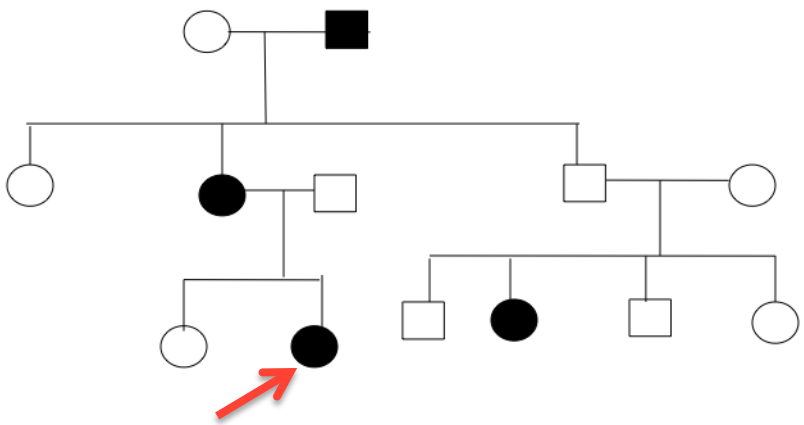
Testicular cancer

Risk to sibling of affected individual is 8-9 times higher than risk in the general population

Risch N. Cancer Epidemiol Biomarkers Prev July 2001 10; 733

Minimum elements for adequate family history of cancer

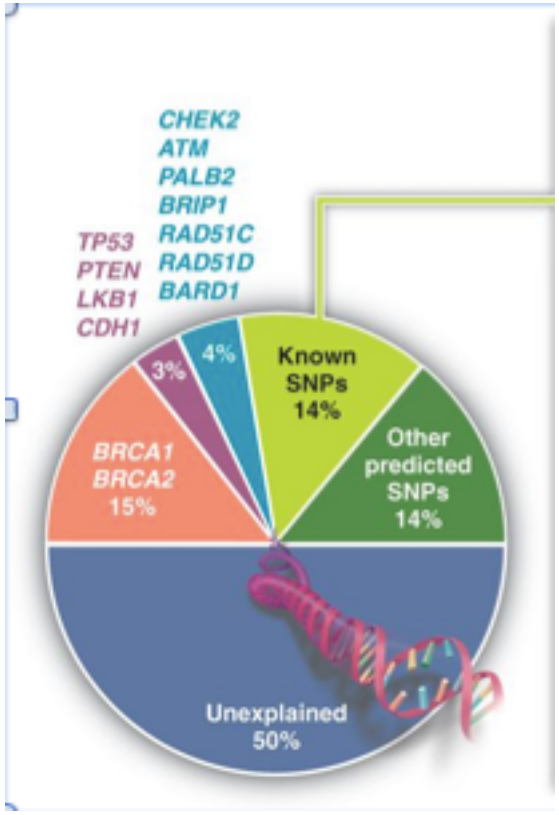
- Taken at diagnosis and updated regularly
- 1st and 2nd degree relatives
- Ask the following questions about each member of the family who has cancer:
  - Type of primary cancer
  - Age at diagnosis of primary
  - Lineage (maternal or paternal)
  - Ethnicity
  - Results of any genetic testing



Features of hereditary cancers

- In the individual patient:
  - Multiple primary tumors in the same organ or different organs
  - Bilateral primary tumors in paired organs or multifocality within a single
  - Younger-than-usual age at tumor diagnosis
  - Tumors with rare histology
  - Tumors occurring in the sex not usually affected
- In the patient's family:
  - First-degree relatives with same tumor history

Genetic basis of hereditary breast cancer

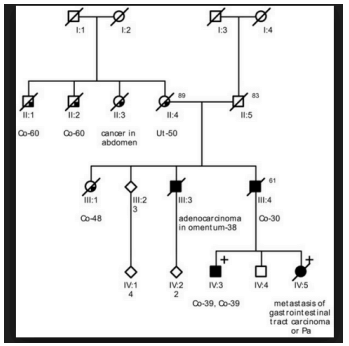


- First degree family history increases risk 2-fold
- Only 5-10% of breast cancer is hereditary
- Inheritance is complex at the disease level, but some individual genes behave in Mendelian fashion
- BRCA1/2 – Hereditary Breast and Ovarian Cancer

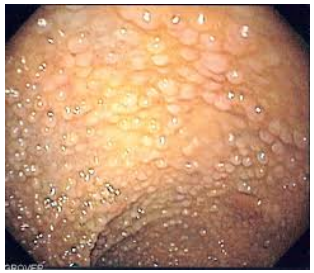
Couch FJ. et al. Science (2014); 343: 1466-70.

Genetic basis of hereditary colon cancer

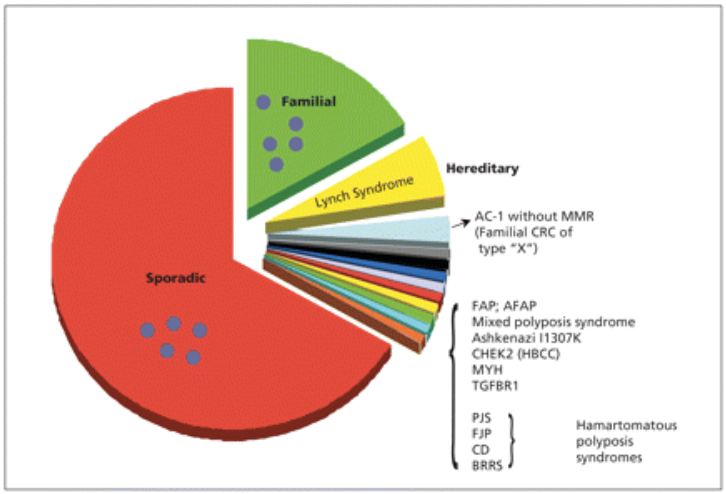
- Family history increases risk 2-4 fold



- Familial adenomatous polyposis (FAP)
  - Mutations in APC gene

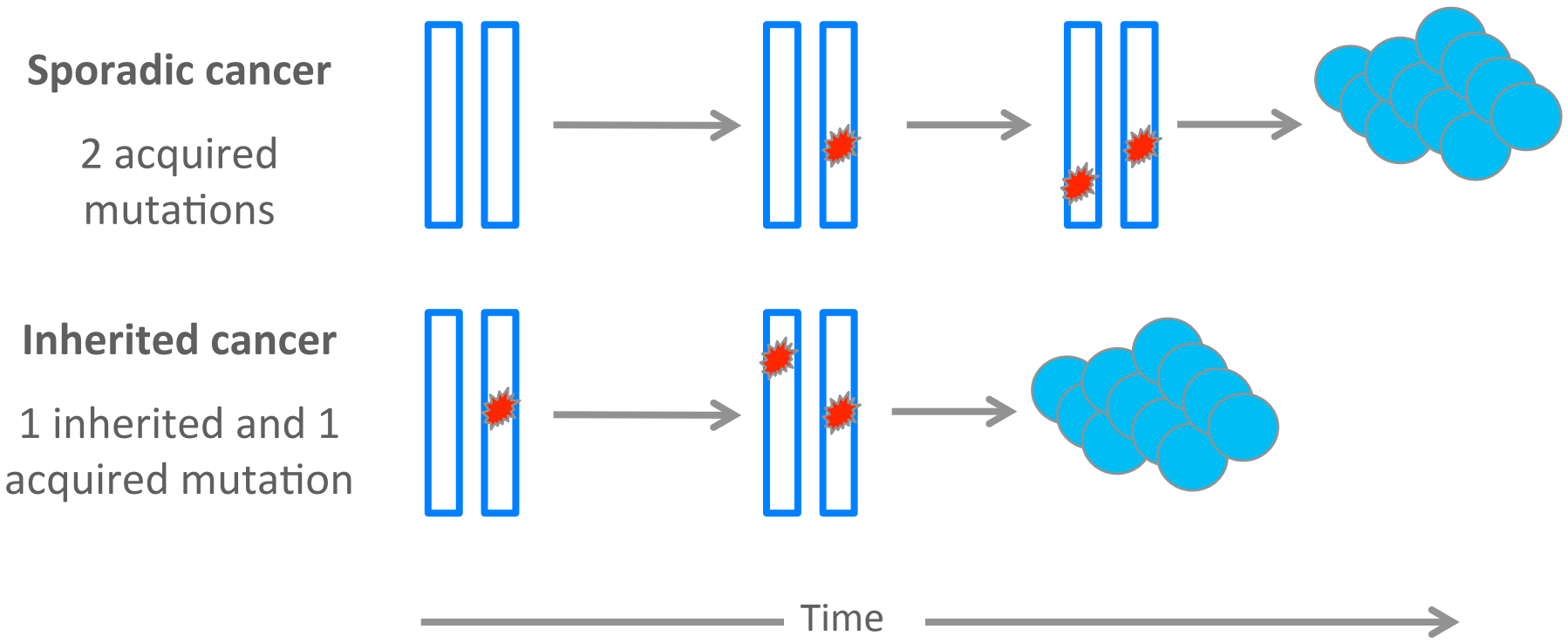


- HNPCC – Lynch Syndrome
  - Mutations in DNA repair enzyme genes MLH1, MSH2, MSH6, PMS1, or PMS2
  - accounts for 2%–5% of the total burden of colorectal cancer



Knudson's 2 Hit hypothesis for tumor suppressor genes

- Tumor suppressors are recessive at cellular level
- Inherited cancers behave as dominant trait

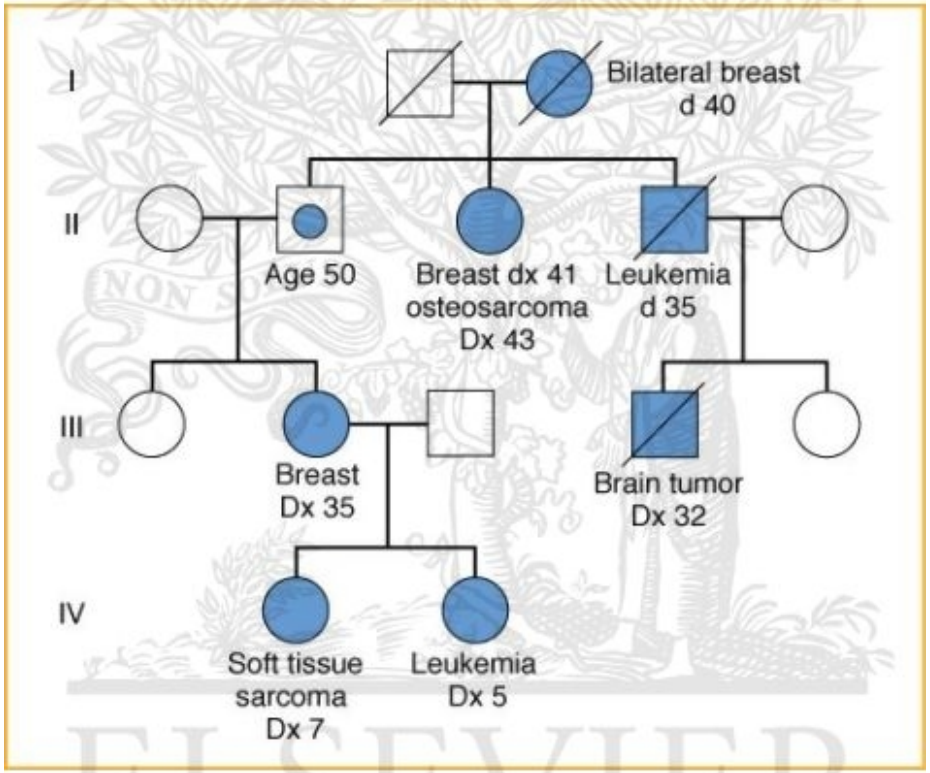


Familial cancer syndromes

Cancer	Syndrome	Associated Gene
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid and endometrial cancers	Cowden syndrome	*PTEN*
Colorectal cancer	Familial adenomatous polyposis (FAP)	*APC*
Melanoma	Familial atypical multiple mole–melanoma syndrome (FAMM)	*CDKN2A*
Retinal cancer	Familial retinoblastoma	*RB1*
Leukemia	Fanconi's anemia	*FACC, FACA*
Colorectal cancer	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	*PRSS1, SPINK1*
Leukemias, breast, brain and soft tissue cancers	Li-Fraumeni	*TP53*
Pancreatic cancers, pituitary adenomas, benign skin and fat tumors	Multiple endocrine neoplasia 1	*MEN1*
Thyroid cancer, pheochromacytoma	Multiple endocrine neoplasia 2	*RET, NTRK1*
Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers	Peutz–Jeghers syndrome	*STK11/LKB1*
Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys	von Hippel-Lindau syndrome	*VHL*
Kidney cancer	Wilms' tumor	*WT1*
Skin cancer	Xeroderma pigmentosum	*XPD, XPB, XPA*

http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

Li Fraumeni pedigree



When to seek genetic counseling

Table 2. Cancers for Which Genetic Counseling and Testing Should Be Considered, Even in Absence of Family History*

Tumor Diagnosis	Genetic Loci
Common adult cancers	
Triple-negative (ER/PR/HER2-neu negative) breast cancer, particularly if diagnosed at age < 60 years[20]	*BRCA1/BRCA2*
Epithelial ovarian, fallopian tube, or primary peritoneal cancer (most commonly, high-grade serous histology)[21]	*BRCA1/BRCA2*
Colorectal cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of *MLH1* promoter and somatic *BRAF* mutation)[22,23]	*MLH1/MSH2/MSH6/PMS2/EPCAM*
Endometrial cancer demonstrating mismatch repair deficiency (via tumor studies including microsatellite instability analysis and/or immunohistochemistry, excluding known somatic causes including hypermethylation of *MLH1* promoter[24]	*MLH1/MSH2/MSH6/PMS2*
Rare tumors	
Adrenocortical carcinoma,[25] choroid plexus carcinoma[26]	*TP53*
Pheochromocytoma, paraganglioma[27]	*VHL*, *RET*, multiple *SDH* loci
Retinal or cerebellar hemangioblastoma, endolymphatic sac tumor[28]	*VHL*
Medullary thyroid cancer[29]	*RET*
Pediatric cancers	
Retinoblastoma[28,30]	*RB1*
Optic pathway tumor, malignant peripheral nerve sheath tumor, juvenile myelomonocytic leukemia[28]	*NF1*
Atypical teratoid/rhabdoid tumor[28]	*INI1/SMARCB1*
Acoustic or vestibular schwannomas[28]	*NF2*
Pulmonary pleuroblastoma[31]	*DICER1*
Multiple gastrointestinal polyps[32]	*BMPR1A, SMAD4, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, APC, STK11, MYH*

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
*The cancer types included here are examples of those more commonly encountered by the oncology provider. This list is not intended to be exhaustive and should not be interpreted as guidance to limit the consideration of additional counseling or testing to only those identified. Furthermore, as an increasing number of genes become discovered, this list is likely to change with time.

UCSF

Lu, KH, et al. J Clin Oncol. 2014 Mar 10;32(8):833-40.

Should my patient undergo genetic testing?

Table 3. Risk Assessment Tools to Guide Referral for Comprehensive Genetic Evaluation

Disease	Gene	Models/Criteria
Lynch syndrome[33,34]	*MLH1, MSH2, MSH6*	PREMM model: http://premm.dfci.harvard.edu MMRPRO model: http://bcb.dfci.harvard.edu/bayesmendel/mmrproqa.html
Breast and ovarian cancer syndrome[35]	*BRCA1, BRCA2*	BRCAPRO model: http://bcb.dfci.harvard.edu/bayesmendel/brcapro.php PENN2 model: http://www.afcri.upenn.edu/itacc/penn2 MYRIAD risk calculator and prevalence tables: http://www.myriadtests.com/provider/brca-mutation-prevalence.htm BOADICEA Cambridge University Web site: http://ccge.medschl.cam.ac.uk/boadicea/web-application/
Melanoma[36]	*CDKN2A* (p16)	MELAPRO model: http://bcb.dfci.harvard.edu/bayesmendel/melapro.php
Pancreatic cancer[37]		PANCPRO model: http://bcb.dfci.harvard.edu/bayesmendel/pancpro.php
Li-Fraumeni syndrome[38]	*TP53*	CHOMPRET criteria: http://jco.ascopubs.org/content/27/26/e108.full.pdf
Cowden syndrome[39]	*PTEN*	PTEN risk model: http://www.lerner.ccf.org/gmi/ccscore/

Lu, KH, et al. J Clin Oncol. 2014 Mar 10;32(8):833-40.

Resources for locating cancer genetics specialists

Table A1. Resources for Locating Cancer Genetics Specialists

Resource	Web Site
National Society of Genetic Counselors	http://www.nsgc.org/tabid/68/Default.aspx
National Cancer Institute Cancer Genetic Services Directory	http://www.cancer.gov/cancertopics/genetics/directory
American College of Medical Genetics Provider Directory	http://www.acmg.net/GIS/Disclaimer.aspx
American Board of Medical Genetics	http://www.abmg.org/pages/searchmem.shtml
American Board of Genetic Counselors	https://abgcmember.goamp.com/Net/ABGCWcm/Find_Counselor/ABGCWcm/PublicDir.aspx?hkey=0ad511c0-d9e9-4714-bd4b-0d73a59ee175

Lu, KH, et al. J Clin Oncol. 2014 Mar 10;32(8):833-40.

Genetic testing for known cancer susceptibility genes

- A negative test result is no guarantee that cancer WILL NOT develop
- A positive test result is no guarantee that cancer WILL develop
- Risk management strategies for a positive test (e.g. BRCA1 – breast cancer)
  - Surveillance
  - Hormone therapy
  - Lifestyle changes
  - Prophylactic surgery

Question

- Cancer is primarily due to which type of mutations, somatic or germline?

Answer

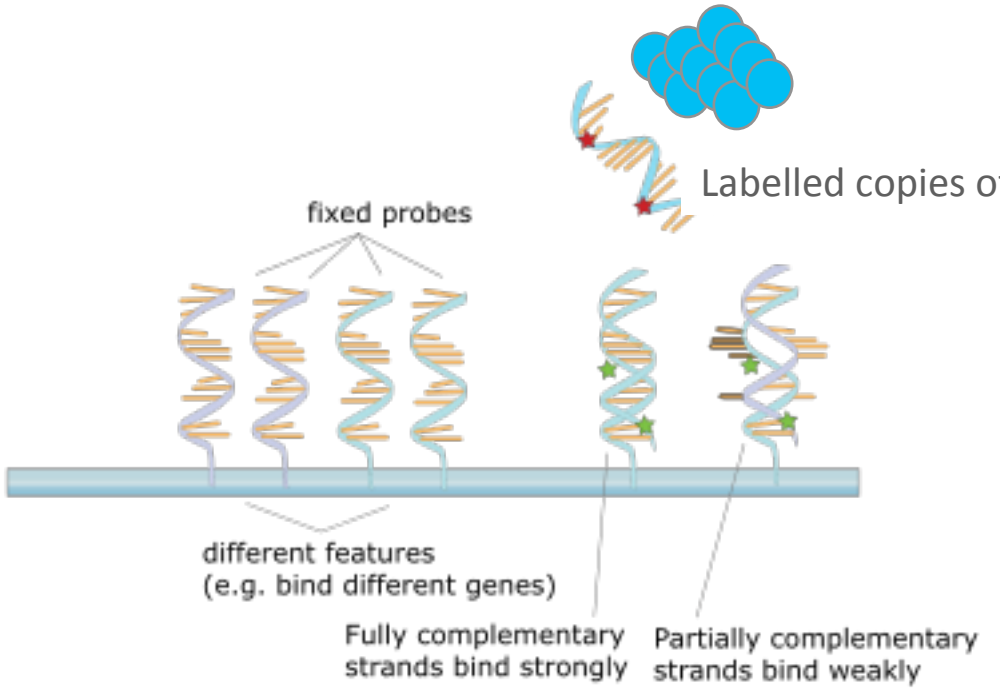
- Cancer is always a somatic disease; only 5-10% of cancers are inherited.

Tumor genetic landscape

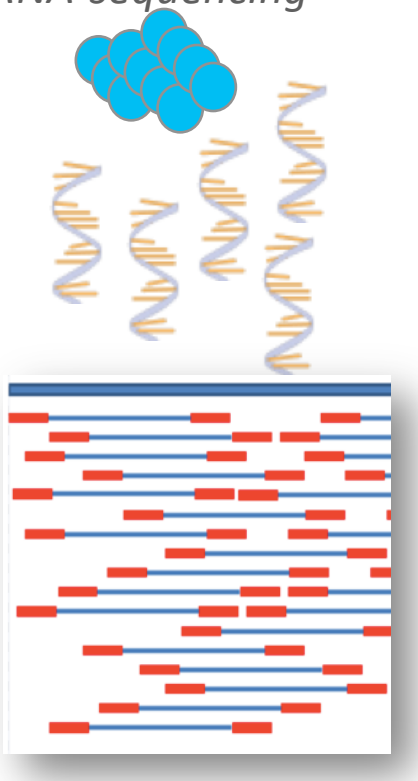
Measuring tumor gene expression

- One or a few genes at a time: e.g. HER2, ER, PR
- Genome-wide measures (Expression microarrays, RNA-seq)

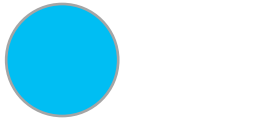
Expression Microarrays



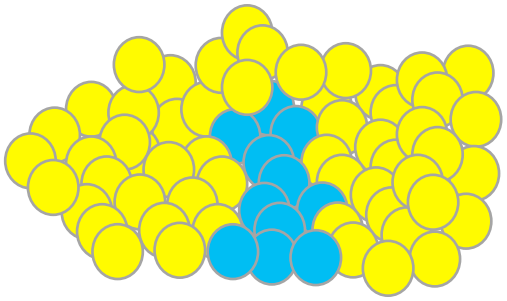
RNA-sequencing

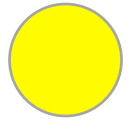


Measuring somatic mutations in tumors

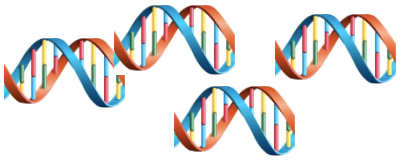


Tumor DNA

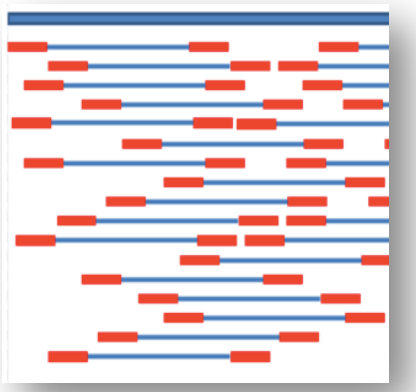




Normal DNA

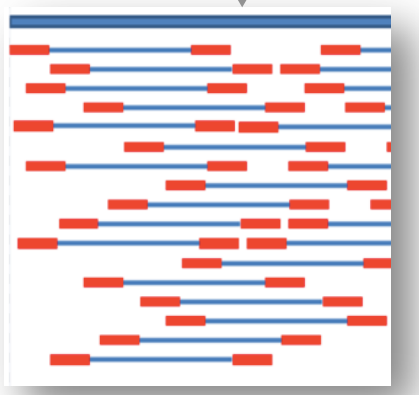


- Sequencing DNA from tumor-normal pairs



Germline variants and somatic changes

Germline variants



Large-scale efforts to characterize tumors at the molecular level

http://cancergenome.nih.gov/

International Cancer Genome Consortium

COSMIC database

http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/

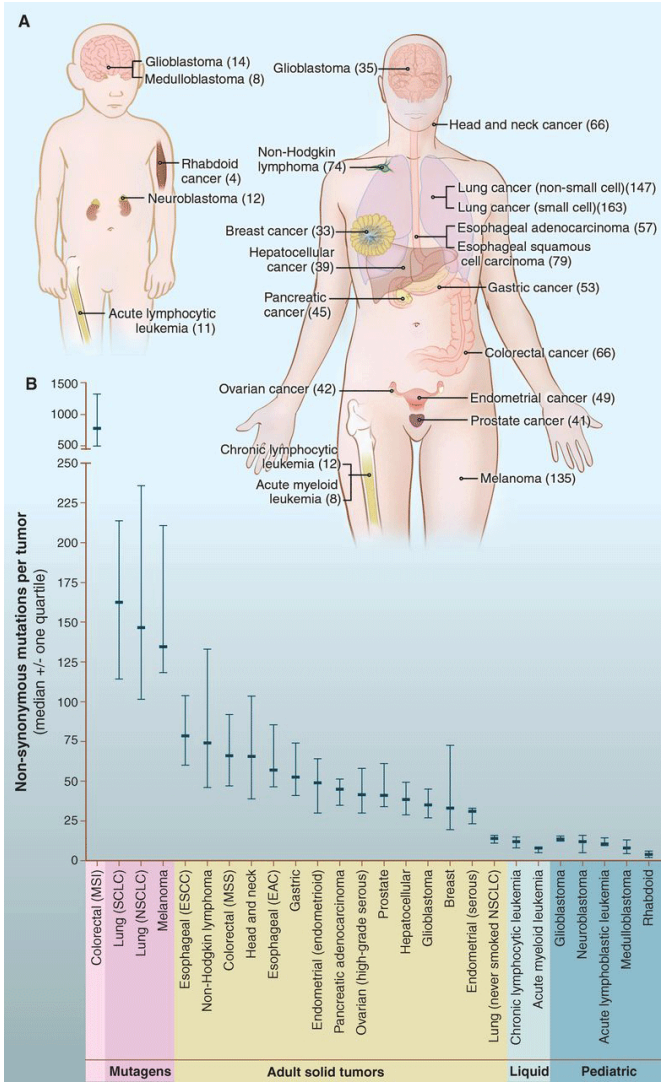
How many genes are mutated in the average solid tumor?

33-66 genes in an average solid tumor

Mostly SNVs

Variable by cancer type

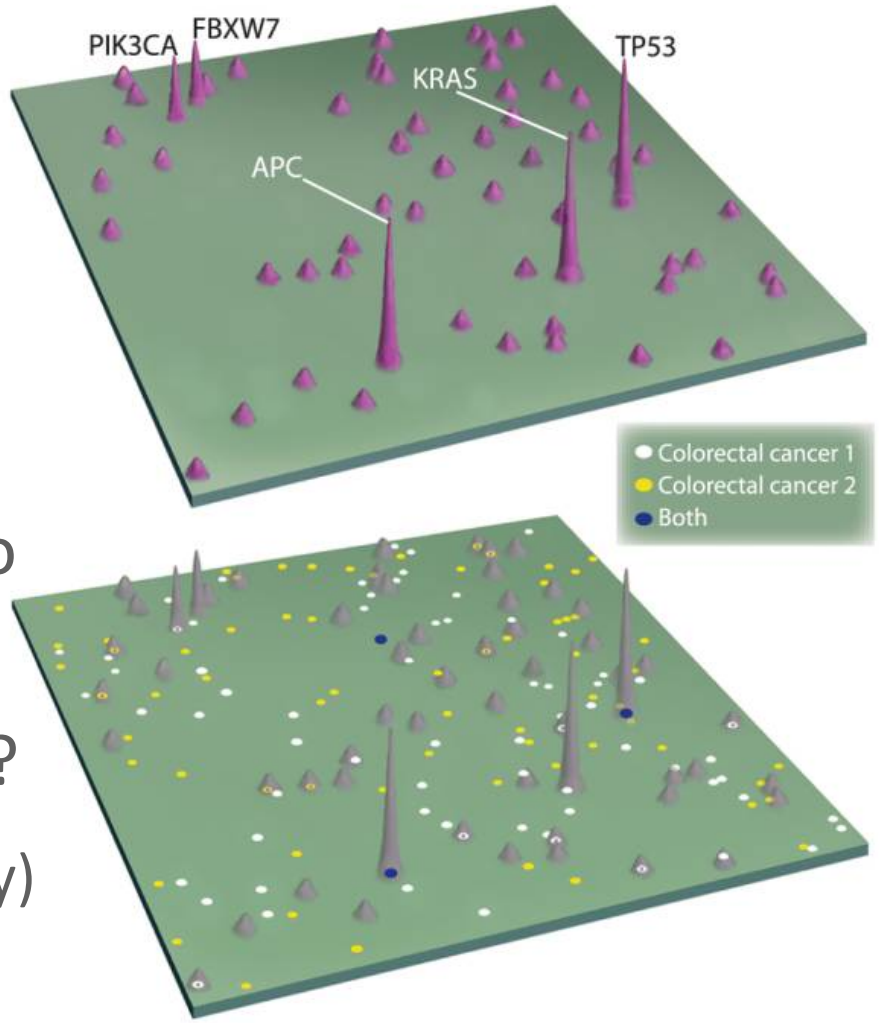
Why?



Vogelstein B et al. Science (2013); 339: 1546-58.

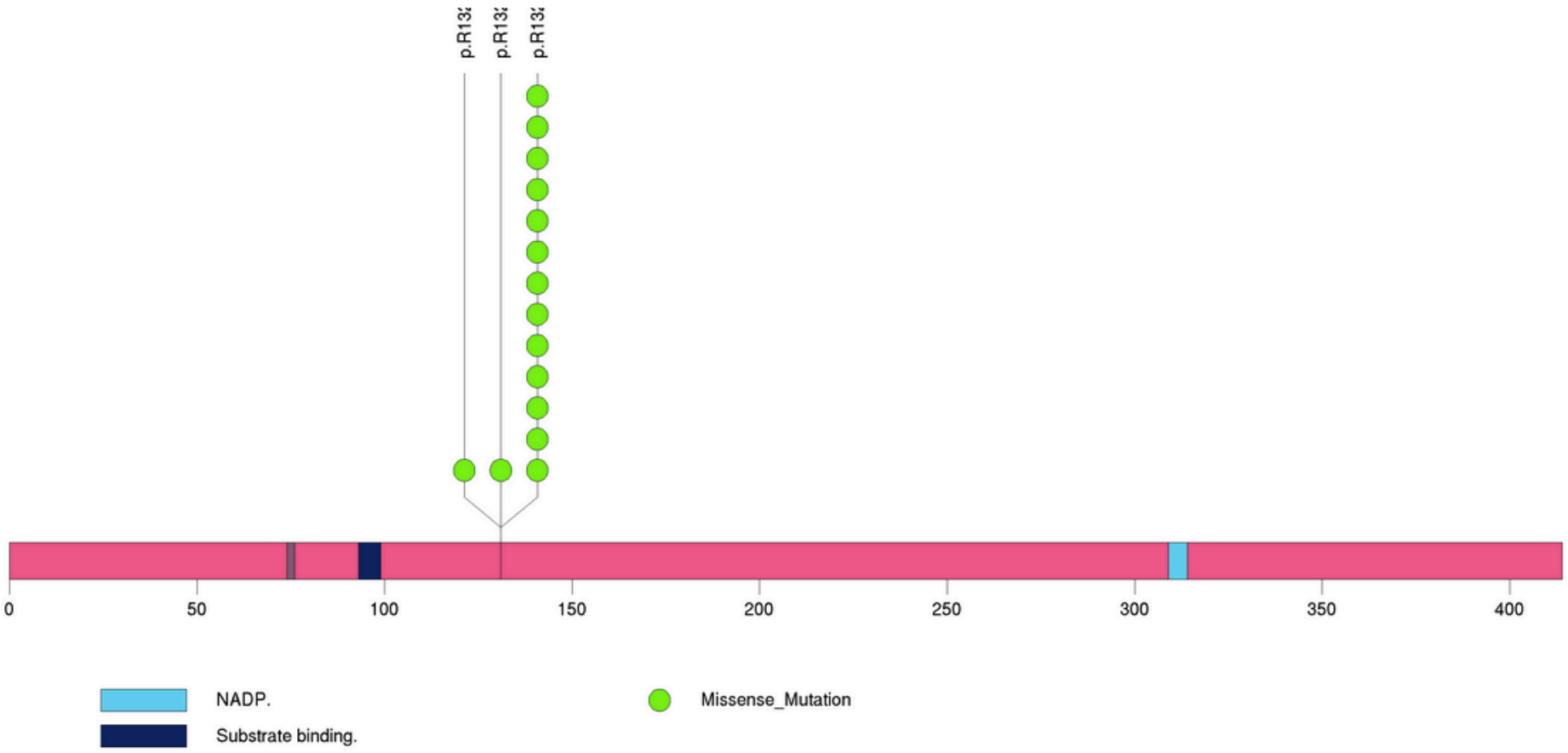
Drivers and passengers

- Driver mutations provide a selective growth advantage
- Passenger mutations have no effect on neoplastic growth
- How to identify driver genes?
  - Mountains and hills (frequency)
  - Patterns



Wood LD. Science 2007: 318 (5853);1108-1113

Distribution of mutations and mutation types across IDH1 in brain tumors



UCSF

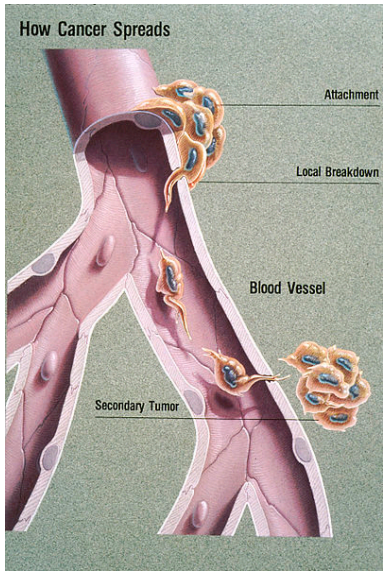
http://gdac.broadinstitute.org/runs/analyses__2013_01_16/reports/cancer/SKCM-TM/mutsignozzlereports2n/nozzle.html

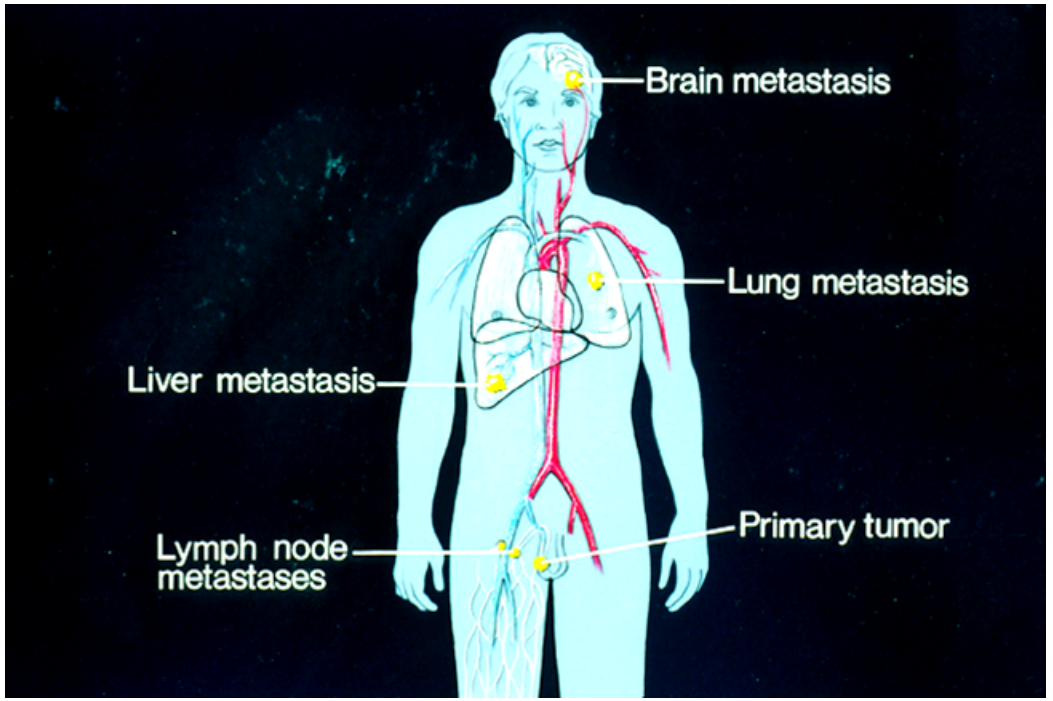
How many driver genes exist?

- 3284 tumors sequenced
- 294,881 mutations reported
- 125 mutation driver genes identified
  - 71 tumor suppressor genes
  - 54 oncogenes

Vogelstein B, et al. Science 2013; 339(6127):1546-58

Basis of metastatic disease





- Specific mutated genes that lead to metastasis?
- Stochastic process more likely
- Metastatic disease accounts for >90 percent of cancer deaths

Images courtesy of US National Cancer Institute

Clinical applications: prognosis and treatment response

Histological classification of breast cancer

Histological classification

Infiltrating Ductal

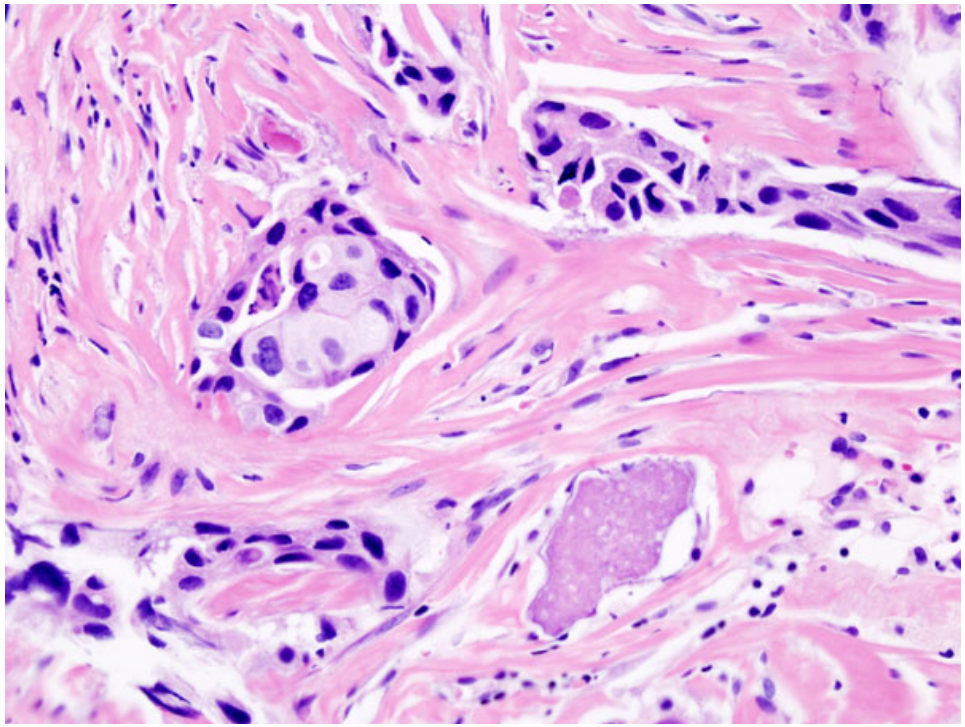
Infiltrating Lobular

Other

Mixed

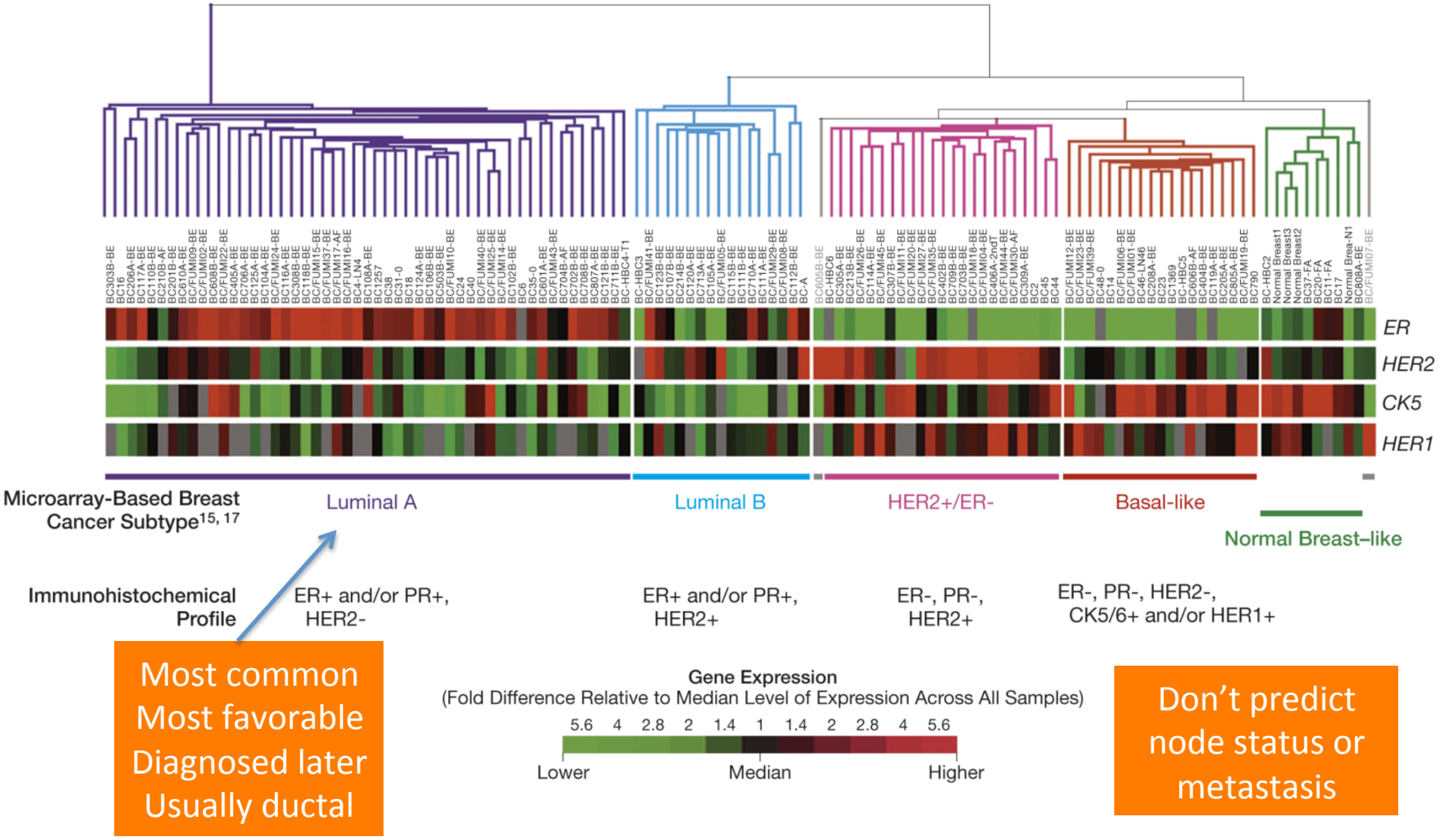
Mucinous

Medullary



- Morphology-based
- Similar morphology can exhibit different clinical presentations, disease aggressiveness and treatment responsiveness

Immunohistochemical classification



Most common
Most favorable
Diagnosed later
Usually ductal

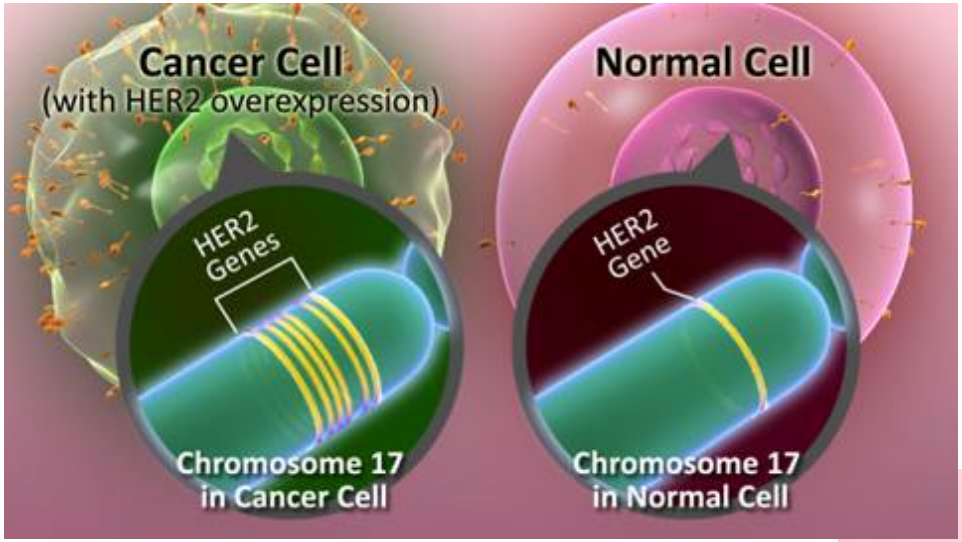
Don't predict node status or metastasis

Carey LA. JAMA. 2006;295(21):2492-2502.

Breast cancer prognostic markers

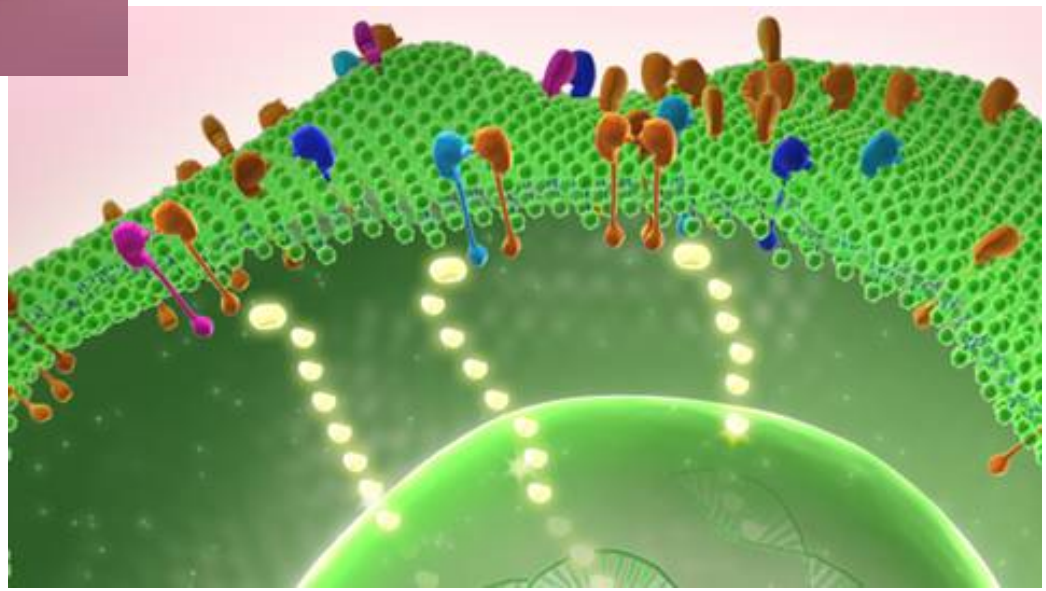
- Oncotype DX® (Genomic Health)
  - A 21-gene expression score (16 prognostic genes and 5 housekeeping)
  - Scale of 0-100, strata of low, intermediate or high risk
  - Ppredicts 10-year risk of distant recurrence in Estrogen Receptor (ER) positive breast cancers (may beneift from adding chemo to their hormone treatment)
  - Predicts responsiveness to CMF (Cyclophosphamide, Methotrexate and 5-Fluorouracil) chemotherapy
- MammaPrint® (Avendia)
  - A 70-gene expression profile
  - Regardless of estrogen receptor (ER) status, with tumors of less than 5 cm
  - Distinguishes those predicted to have good prognosis (no relapse within 5 years) from poor prognosis (relapse within 5 years)

HER2-positive breast cancer



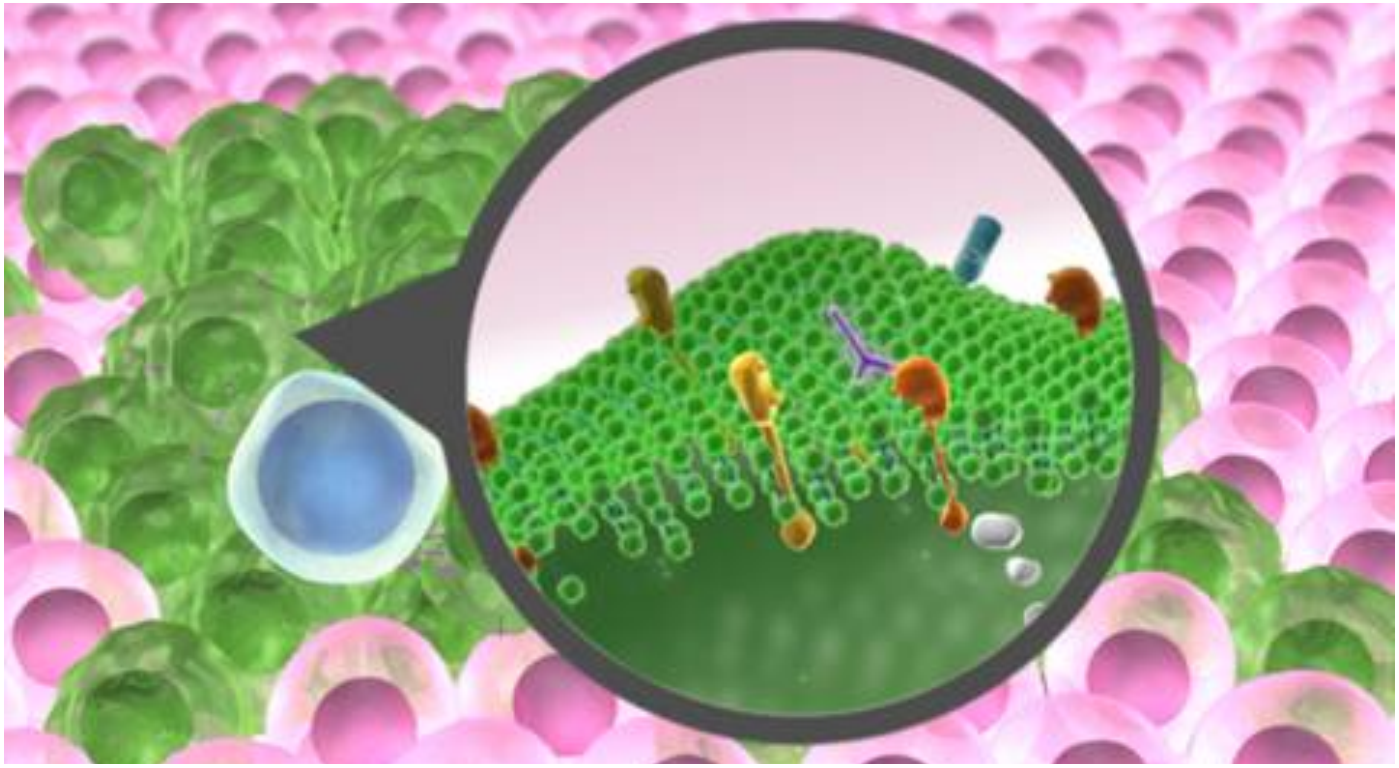
- The HER2 gene is amplified in 20% of breast cancers
- Referred to as HER2-positive cancers
- Make more HER2 protein than HER2-negative cancers

The extra HER2 protein causes increased signal pathway activation, which contributes to the uncontrolled growth and survival of these cancers.



HER2- Herceptin

Herceptin® (trastuzumab) is a monoclonal antibody that binds to HER2. This prevents the receptor from activating the pathways that promote the proliferation and survival of breast cancer cells.



Chronic myelogenous leukemia (CML)

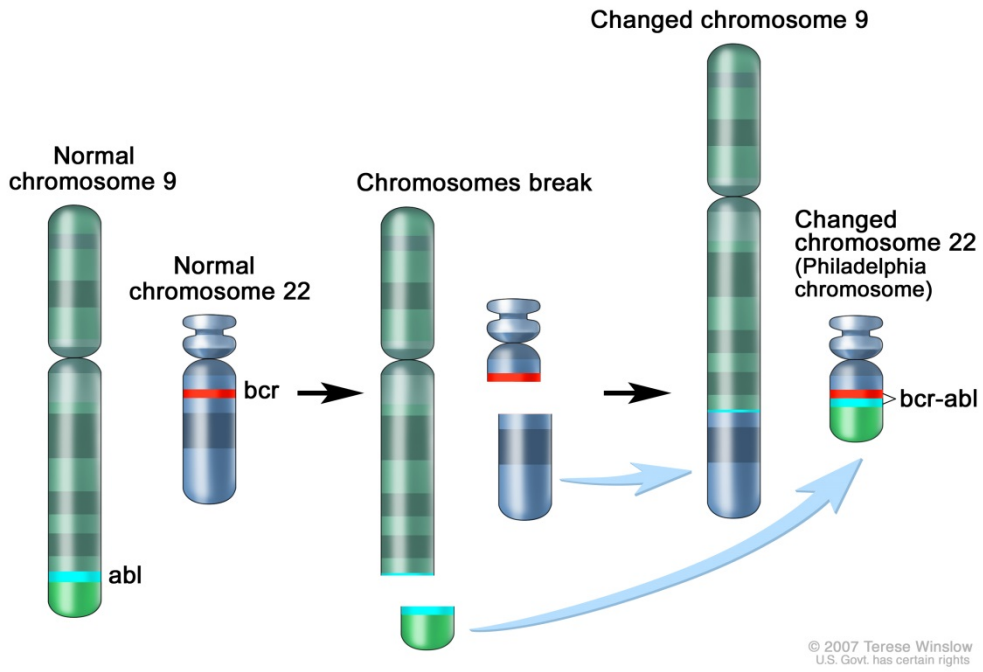
Blood cancer caused by reciprocal translocation (Philadelphia Chromosome), resulting in oncogenic BCR-ABL gene fusion

BCR-ABL found in 95% of CML

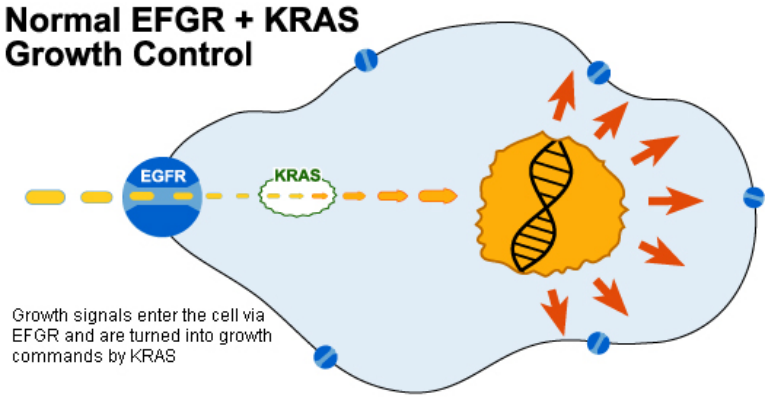
Multiple targeted medications have been created which specifically inhibit this oncogene (imatinib, dasatinib, nilotinib)

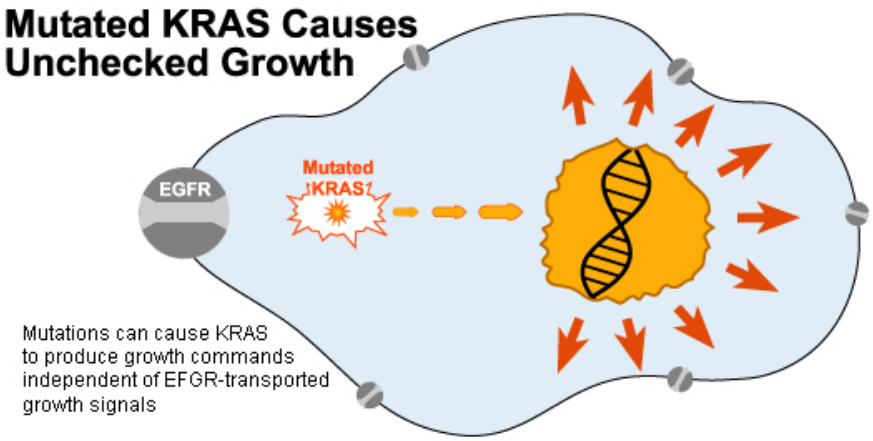
Previously – median survival 4 years

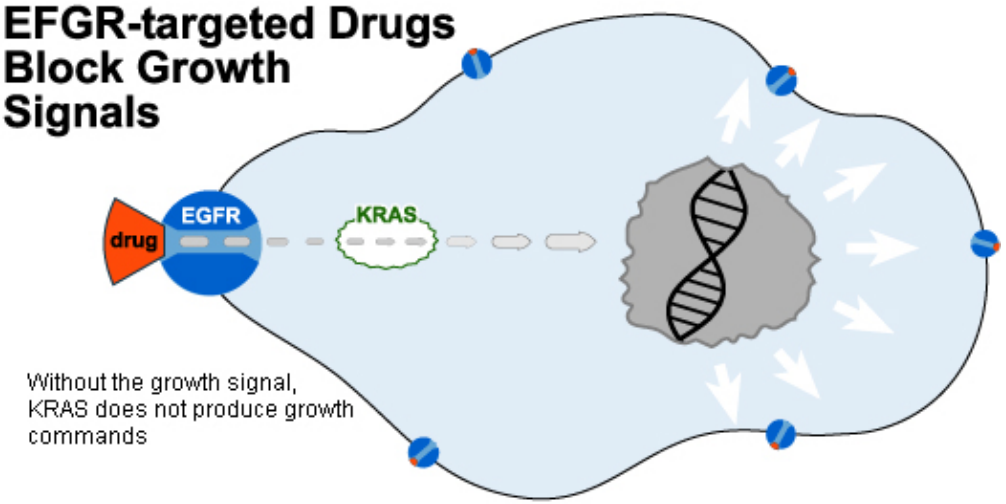
Survival now 20-25 years



KRAS mutations in colorectal cancer

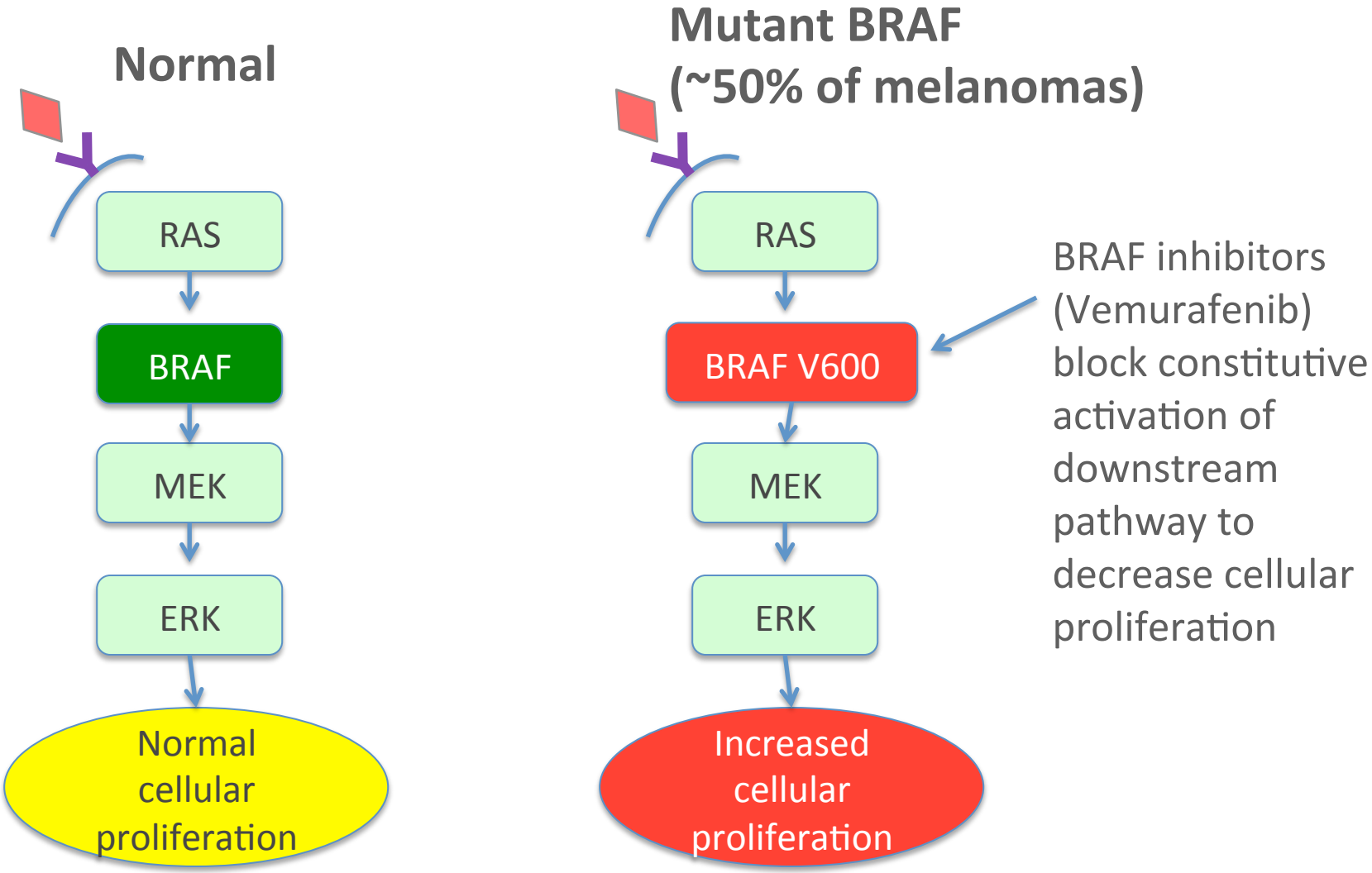




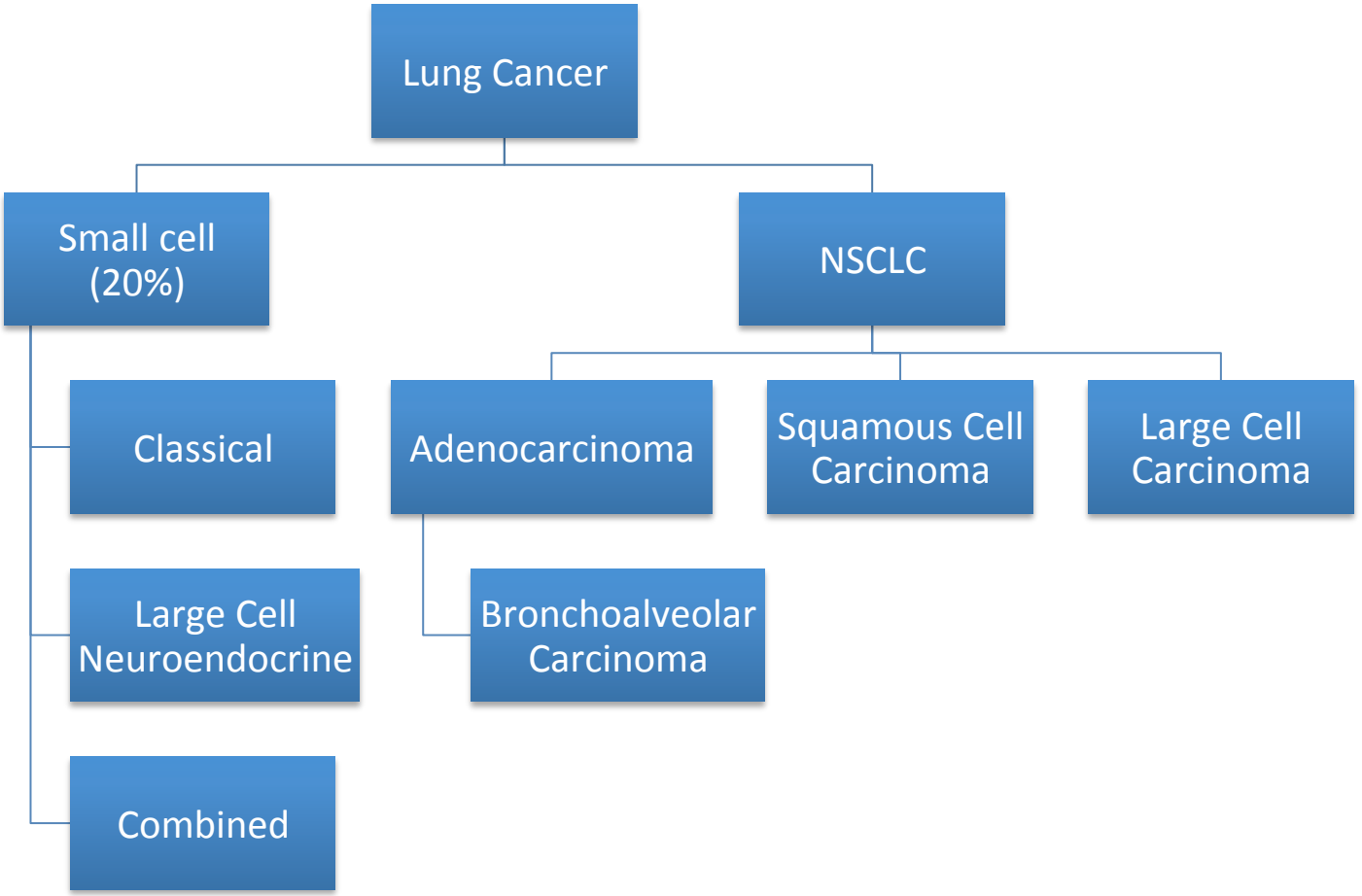


Anti-EGFR therapies (anti-EGFR therapies cetuximab (Erbitux) and panitumumab (Vectibix) don't work in KRAS-mutated cancers

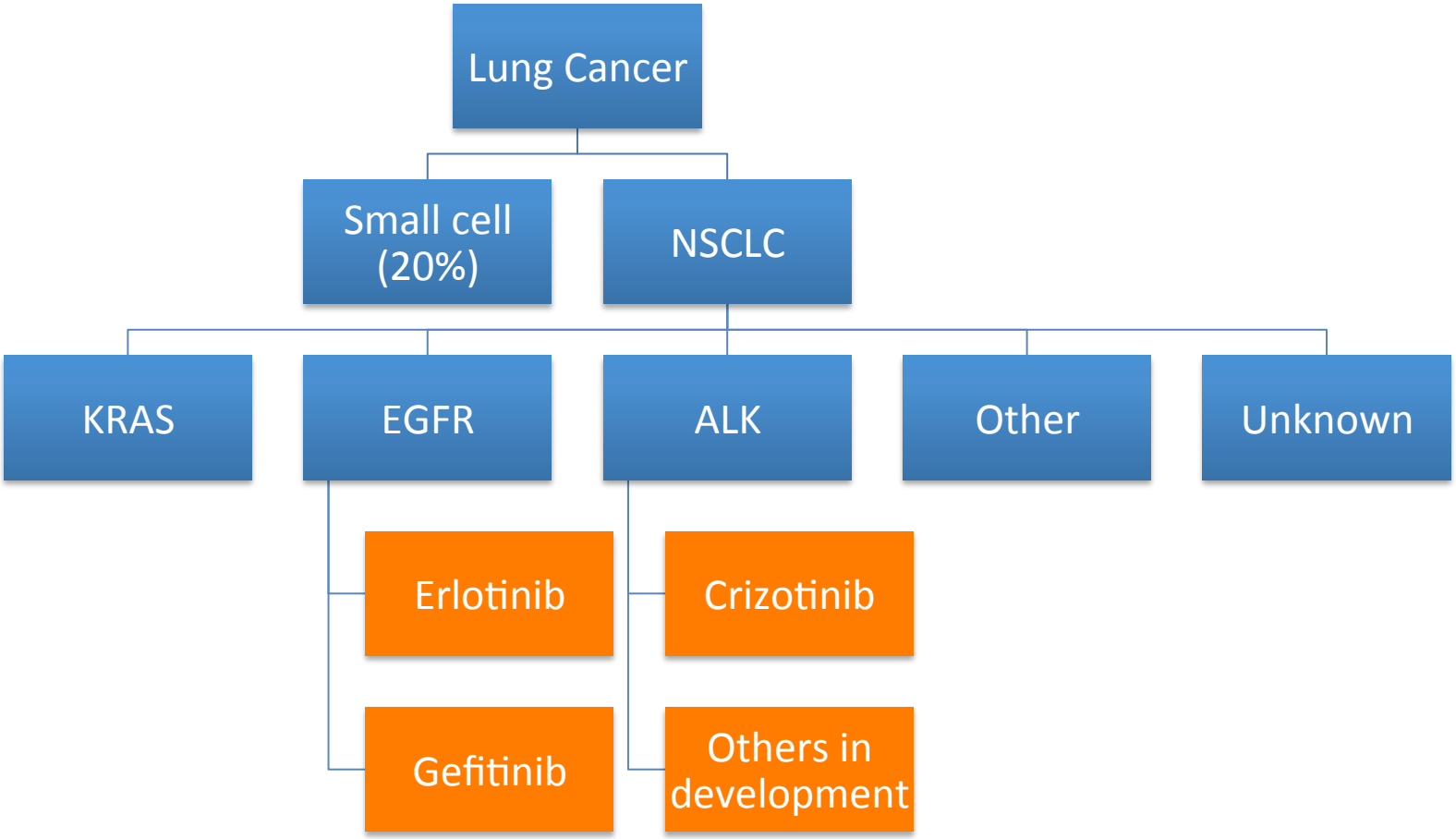
Vemurafenib and malignant melanoma



Lung cancer – histological classification



Lung cancer molecular classification and targeted therapy



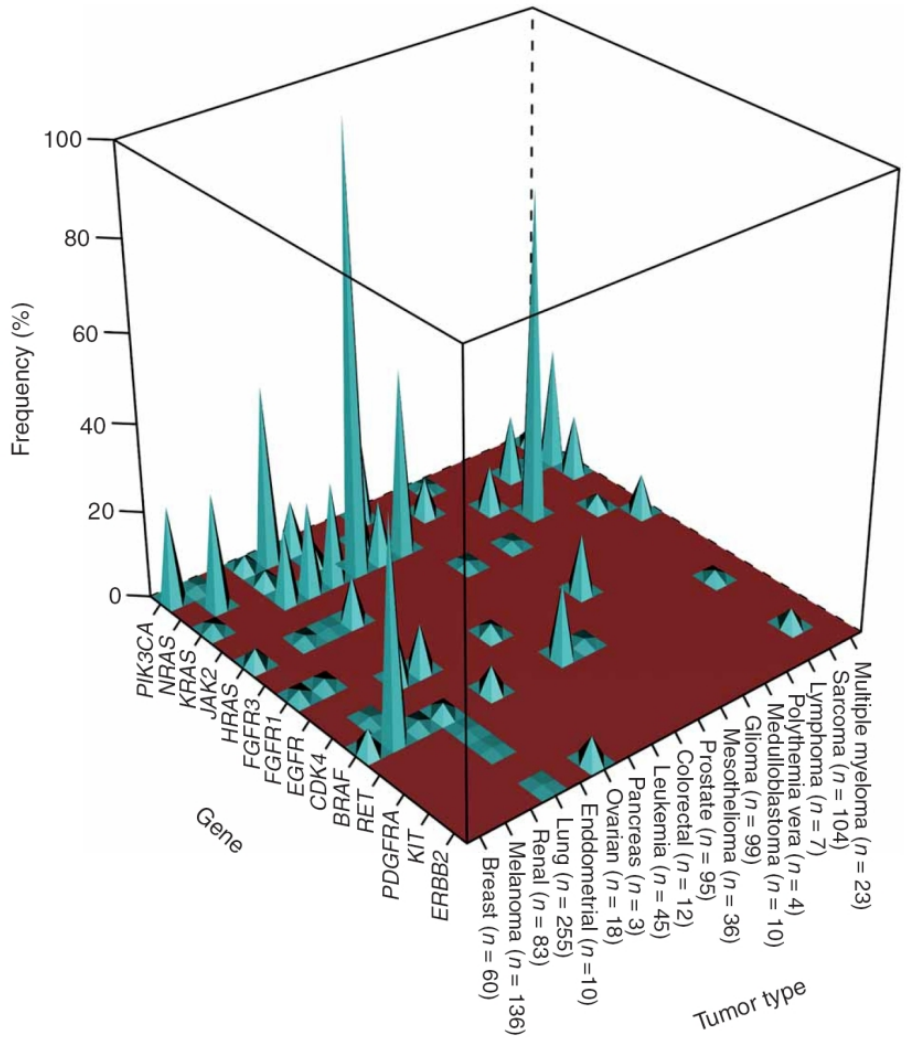
Different cancers may share common genetic alterations

BRAF

60% of melanomas
Respond to the *BRAF* inhibitor vemurafenib

100% of hairy cell (HC) leukemias
Response to BRAF inhibitor

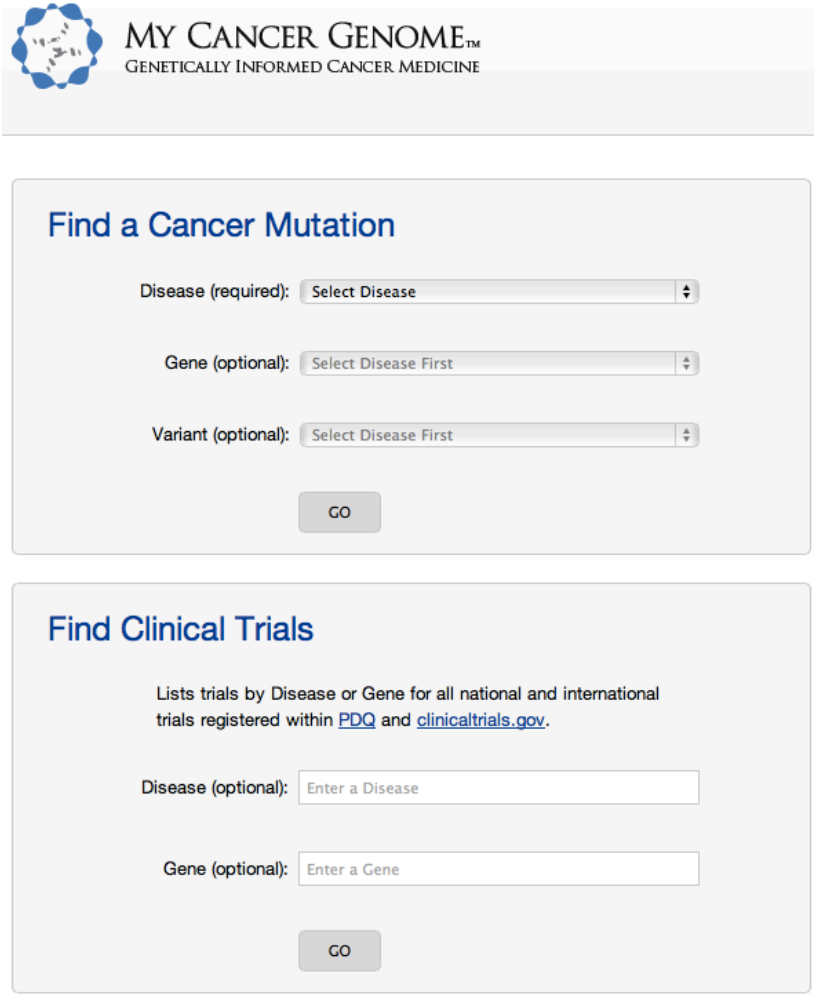
5-10% colorectal cancers
No response to BRAF inhibitor



Thomas, R. K. et al. Nature Genetics 2007; 39, 348.

Tumor profiling in the clinic

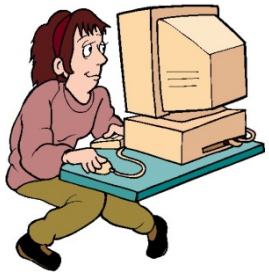
- Many academic medical centers beginning to offer testing
- Commercial options
  - FoundationOne
  - Caris Target Now
  - SNaPshot
- Only activated oncogenes are targetable; tumor suppressor genes (loss of function) are not
- Most useful – link to treatment OR clinical trials



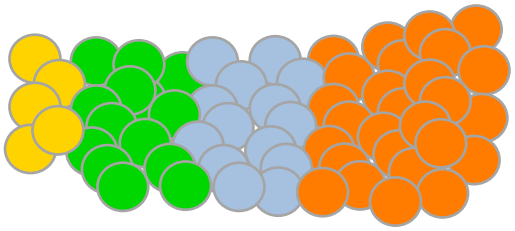
Vanderbilt-Ingram Cancer Center

Challenges in Molecular Profiling for Targeted Treatment

- Bioinformatics



- What does it mean when a mutation normally associated with an inherited cancer is found in a tumor sample?
- Tumor heterogeneity



- Tumor targets identified but therapy not approved or reimbursed for that indication

Advances in cancer genomics

- Continued development of targeted treatments
- New treatment paradigms – immunotherapy
- Improved diagnosis - liquid biopsies