CANCER GENOMICS

Lecture 1: Introduction to Cancer Genome Analysis

GENOME 541

Spring 2020

FRED HUTCH
CURES START HERE®

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Overview of Cancer Genomics Module

1. Introduction to Cancer Genome Analysis
2. Probabilistic Methods for Mutation Detection
3. Probabilistic Methods for Profiling Copy Number Alteration
4. Additional Topics: Tumor Heterogeneity, Mutation Detection Power, Structural Variation

Homework Assignments and Office Hours

TA for Module: Anna-Lisa Doebley (adoebley@uw.edu)

Homework #5

Due: May 8th

Office Hours

- Monday, May 4, 2-3pm
- Wednesday, May 6, 2-3pm

Homework #6

Due: May 15th

Office Hours

- Monday, May 11, 2-3pm
- Wednesday, May 13, 2-3pm

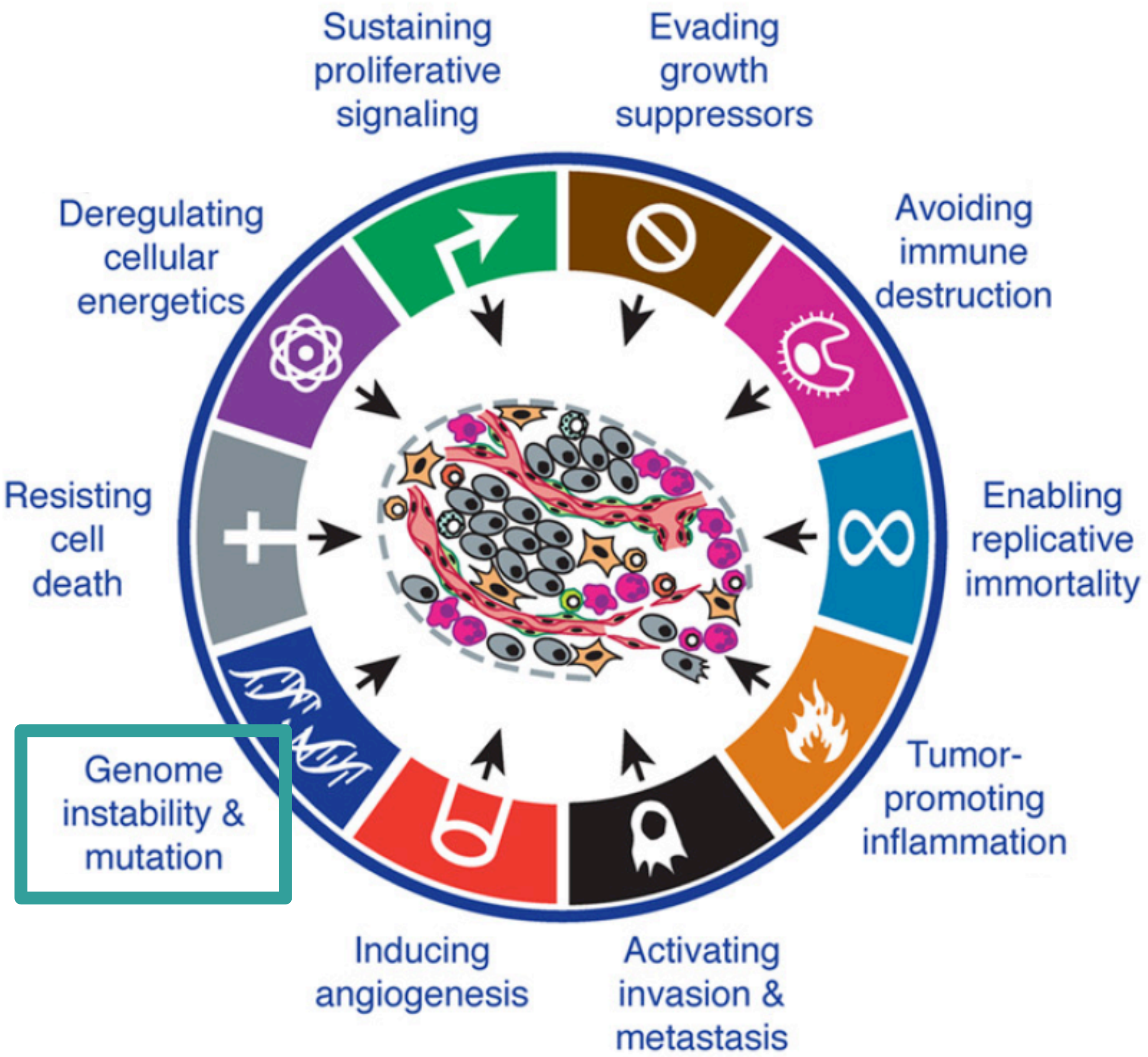
Outline: Introduction to Cancer Genome Analysis

1. **Intro to Cancer Genome Alterations**
   - Genomic alterations in cancer: drivers vs passengers, somatic vs germline
   - Tumor evolution and heterogeneity
2. **Overview of Cancer Genome Analysis**
   - Computational strategy and workflow
   - Tumor DNA Sequencing
   - Types of genomic alterations predicted from tumor sequencing
   - Methods/tools/algorithms in following lectures
3. **Primer on statistical modeling**
   - Binomial probability distribution, Bayesian statistics, parameter learning

The hallmarks of cancer

- All cancers exhibit many of these hallmarks that lead to tumor growth

- **Genome instability** & **mutation** is an enabling characteristic that can result in multiple hallmarks

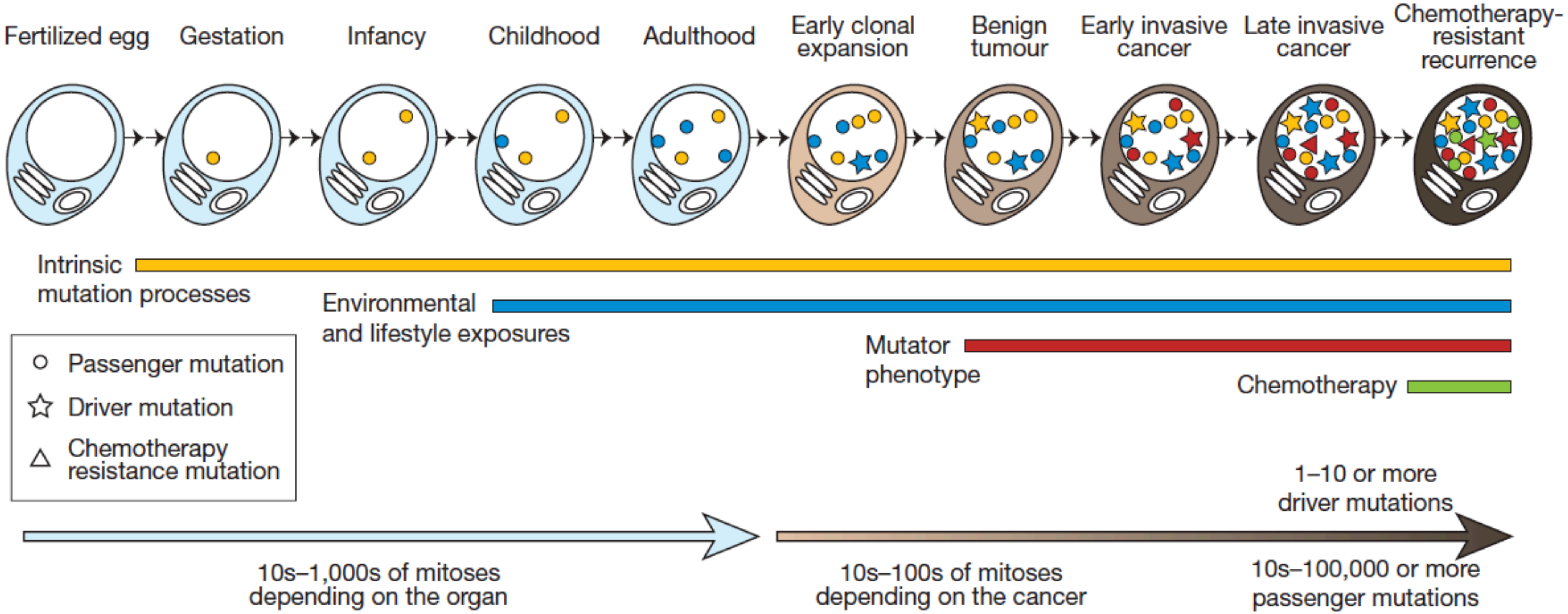

Sustaining proliferative signaling
Evading growth suppressors
Avoiding immune destruction
Enabling replicative immortality
Tumor-promoting inflammation
Activating invasion & metastasis
Inducing angiogenesis
Genome instability & mutation
Resisting cell death
Deregulating cellular energetics

Hannahan & Weinberg. *Cell* **144**:646-74 (2011)

Cancer is a disease of the genome

Cancer progression results from **mutations** acquired throughout lifetime

- Few **driver** mutations, many **passenger** mutations
- Mutational process can be intrinsic and from environmental mutagens


Fertilized egg
Gestation
Infancy
Childhood
Adulthood
Early clonal expansion
Benign tumour
Early invasive cancer
Late invasive cancer
Chemotherapy-resistant recurrence
Intrinsic mutation processes
Environmental and lifestyle exposures
Mutator phenotype
Chemotherapy
○ Passenger mutation
☆ Driver mutation
△ Chemotherapy resistance mutation
10s–1,000s of mitoses depending on the organ
10s–100s of mitoses depending on the cancer
1–10 or more driver mutations
10s–100,000 or more passenger mutations

Stratton, Campbell & Futreal. *Nature* **458**:719-24 (2009)

Genomic Variation: Somatic and Germline

Variant or Mutation or Alteration or Polymorphism

- Changes in the genome sequence of a sample compared to a reference sequence

Germline Variant

- Chromosomes: 22 autosomal pairs + 1 sex pair
  - Each set inherited from maternal and paternal germline cells
- Variant inherited from one or both parental chromosomes
- Source of genetic differences between ancestral populations and individuals
- Polymorphism: >1% frequency in a population

Somatic Variant

- Mutation acquired during individual’s lifetime
- Important to identify in sporadic cancers and other non-familial diseases

Types of Genomic Variation: Small/Short mutations

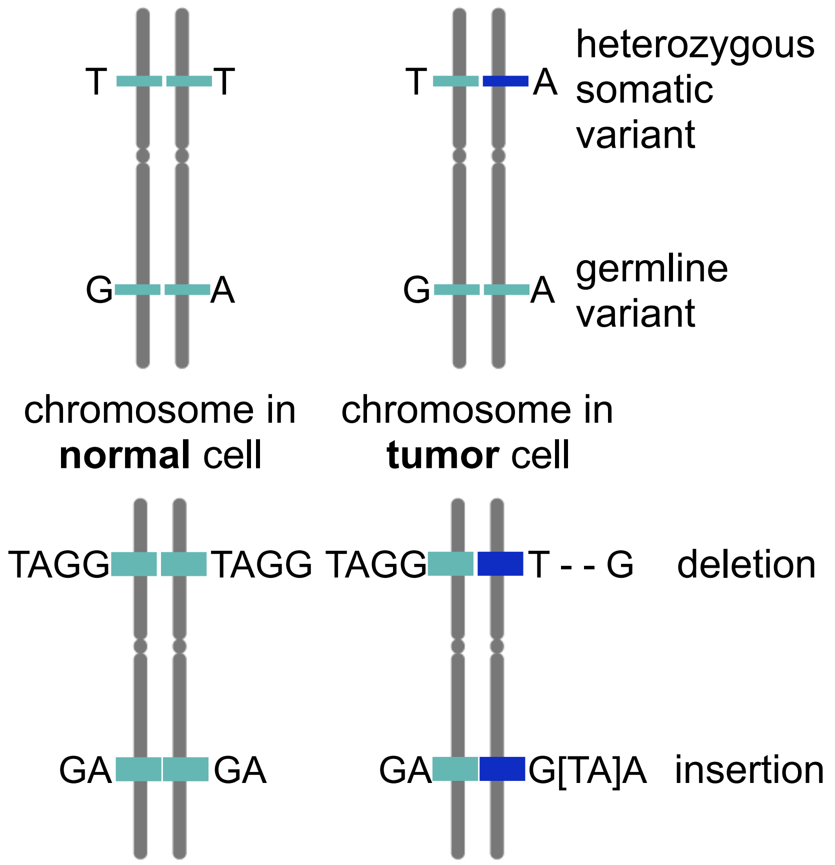
1. Single nucleotide base substitutions

- Germline single nucleotide polymorphism (SNP)
- Somatic single nucleotide variant (SNV)

2. Small insertions or deletions

- Germline or somatic insertion or deletion (INDEL)
- Small indels: 1 bp - 20 bps
- Large indels: 20 - 10,000 bps

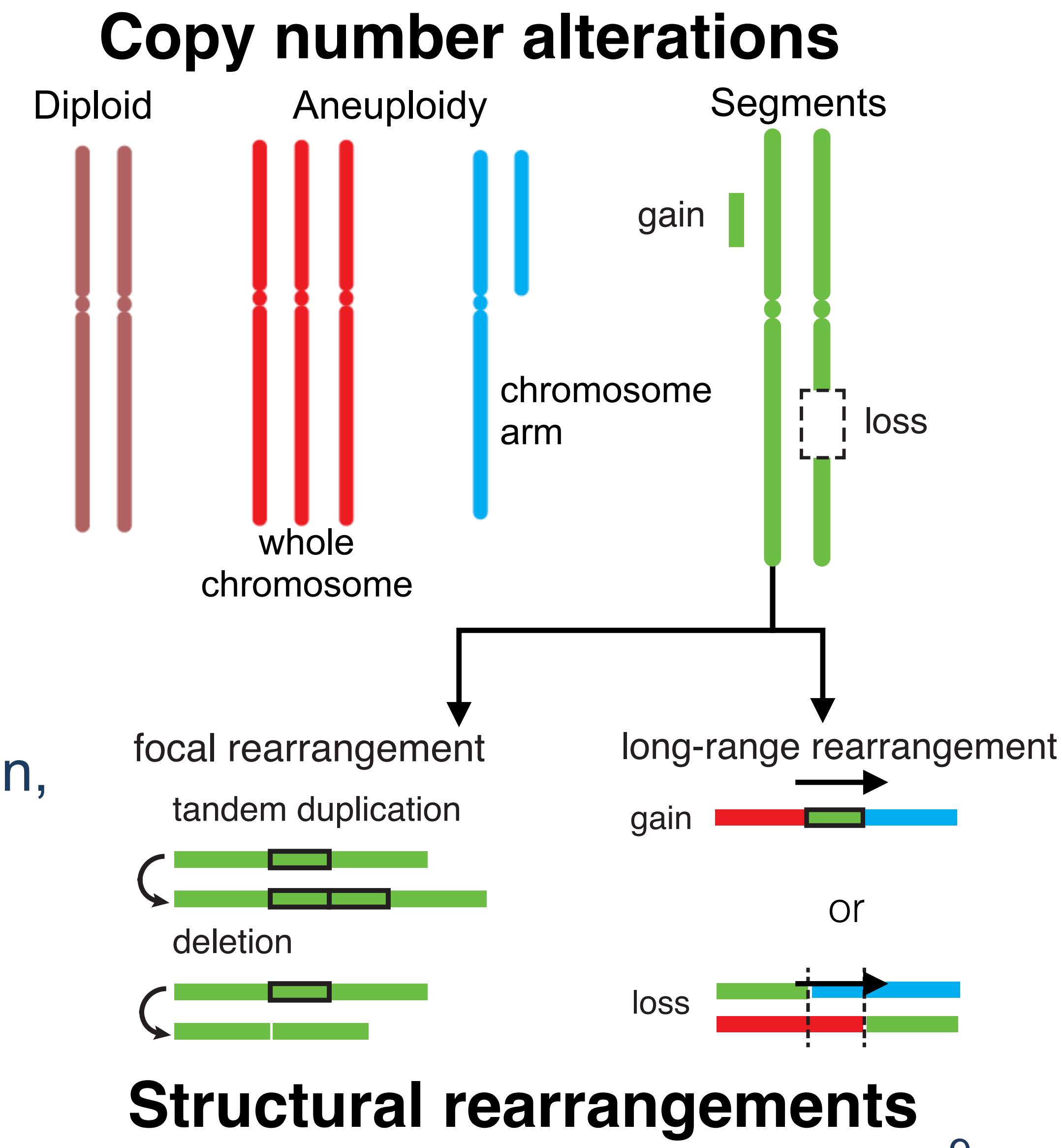
Single nucleotide variant


T
T
G
A
T
A
heterozygous somatic variant
G
A
germline variant
chromosome in **normal** cell
chromosome in **tumor** cell
TAGG
TAGG
TAGG
T - - G
deletion
GA
GA
GA
G[TA]A
insertion

Insertion-Deletion (INDEL)

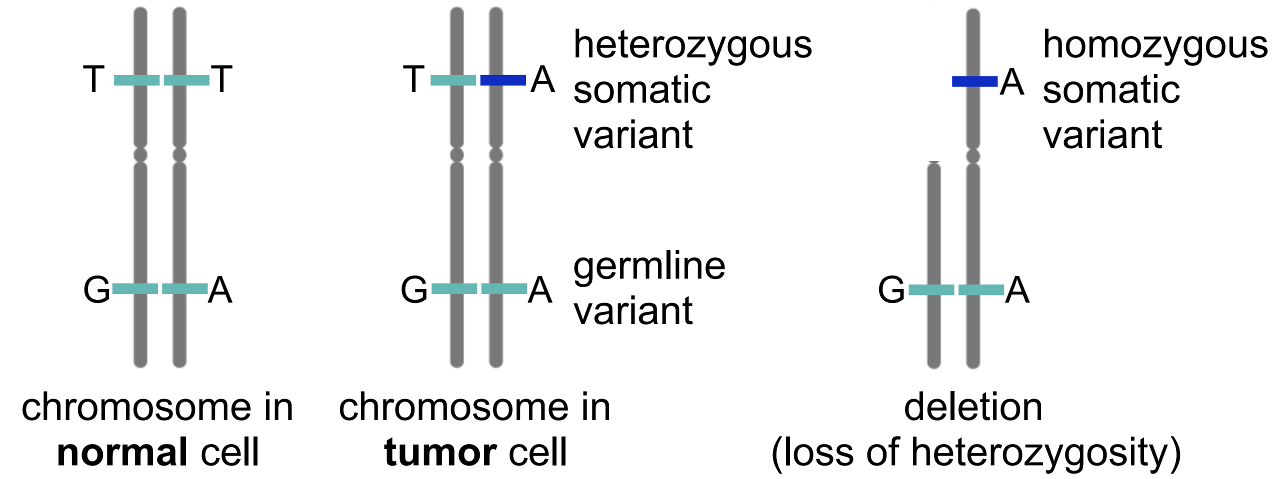
Types of Genomic Variation: Large alterations

3. **Copy number changes**
   - Germline copy number variant (CNV) or polymorphism (CNP)
   - Somatic copy number variant (CNV) or alterations (CNA)
   - Size > 1 kbps, typically mega-bases (depending on resolution)
4. **Structural rearrangements**
   - Germline or Somatic structural variant (SV)
   - Simple events: deletion, duplication, inversion, translocation
   - Single nucleotide resolution for breakpoints
   - Size > 20 bps, typically kilo-bases to mega-bases



Types of Genomic Variation in Cancer

Single nucleotide variant



T T

G A

chromosome in **normal** cell

T A

heterozygous somatic variant

G A

germline variant

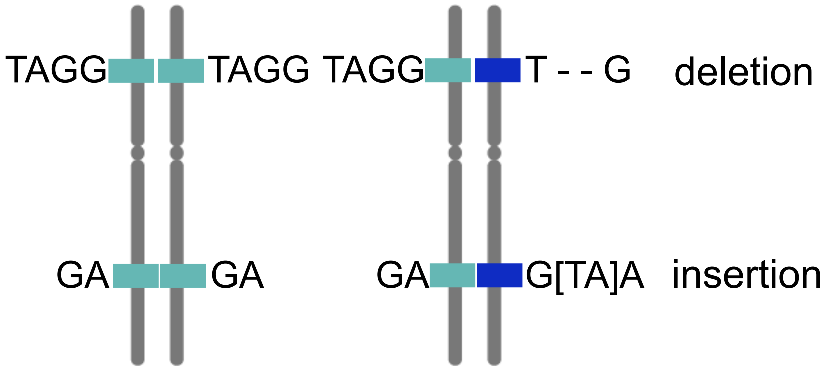
chromosome in **tumor** cell

A

homozygous somatic variant

G A

deletion
(loss of heterozygosity)



TAGG TAGG

GA GA

TAGG T - - G

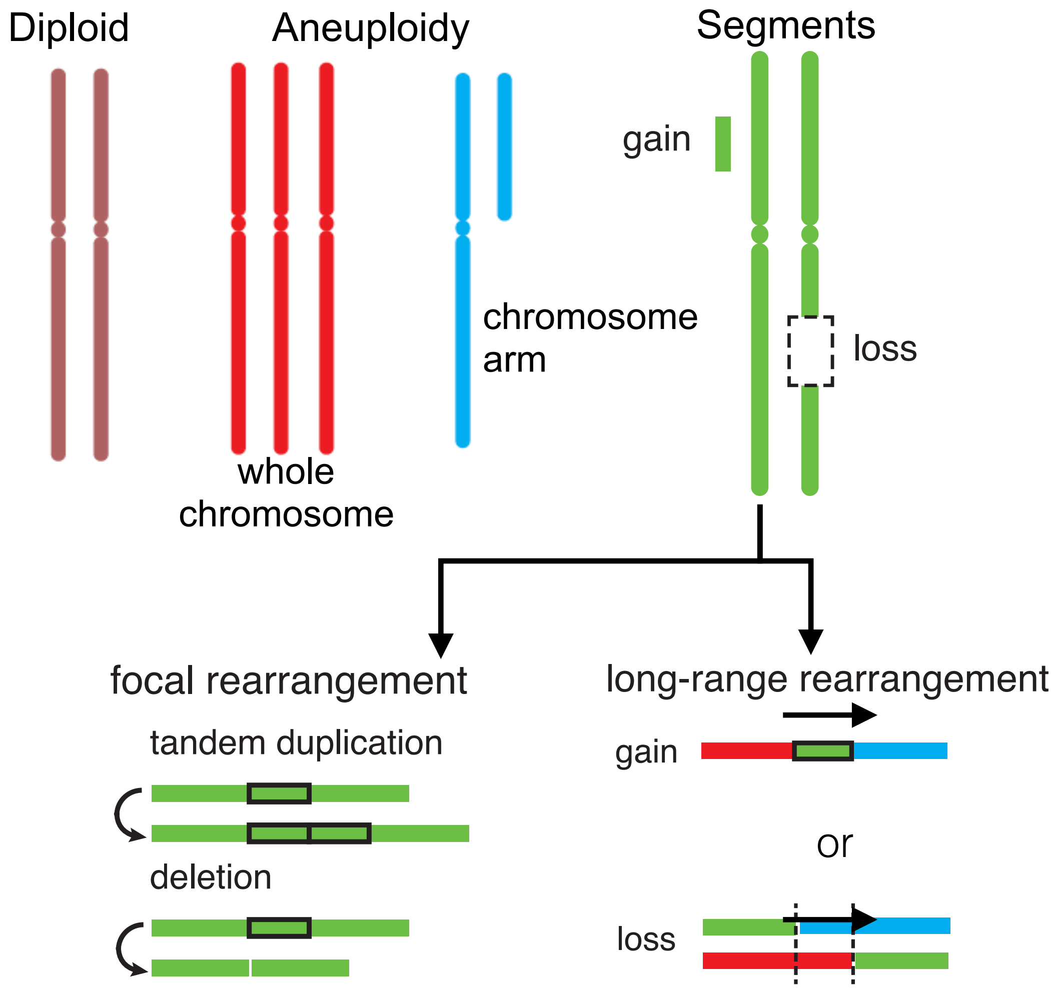
deletion

GA G[TA]A

insertion

Insertion-Deletion (INDEL)

Copy number alterations



Diploid

Aneuploidy

whole chromosome

chromosome arm

Segments

gain

loss

focal rearrangement

tandem duplication

deletion

long-range rearrangement

gain

or

loss

Structural rearrangements

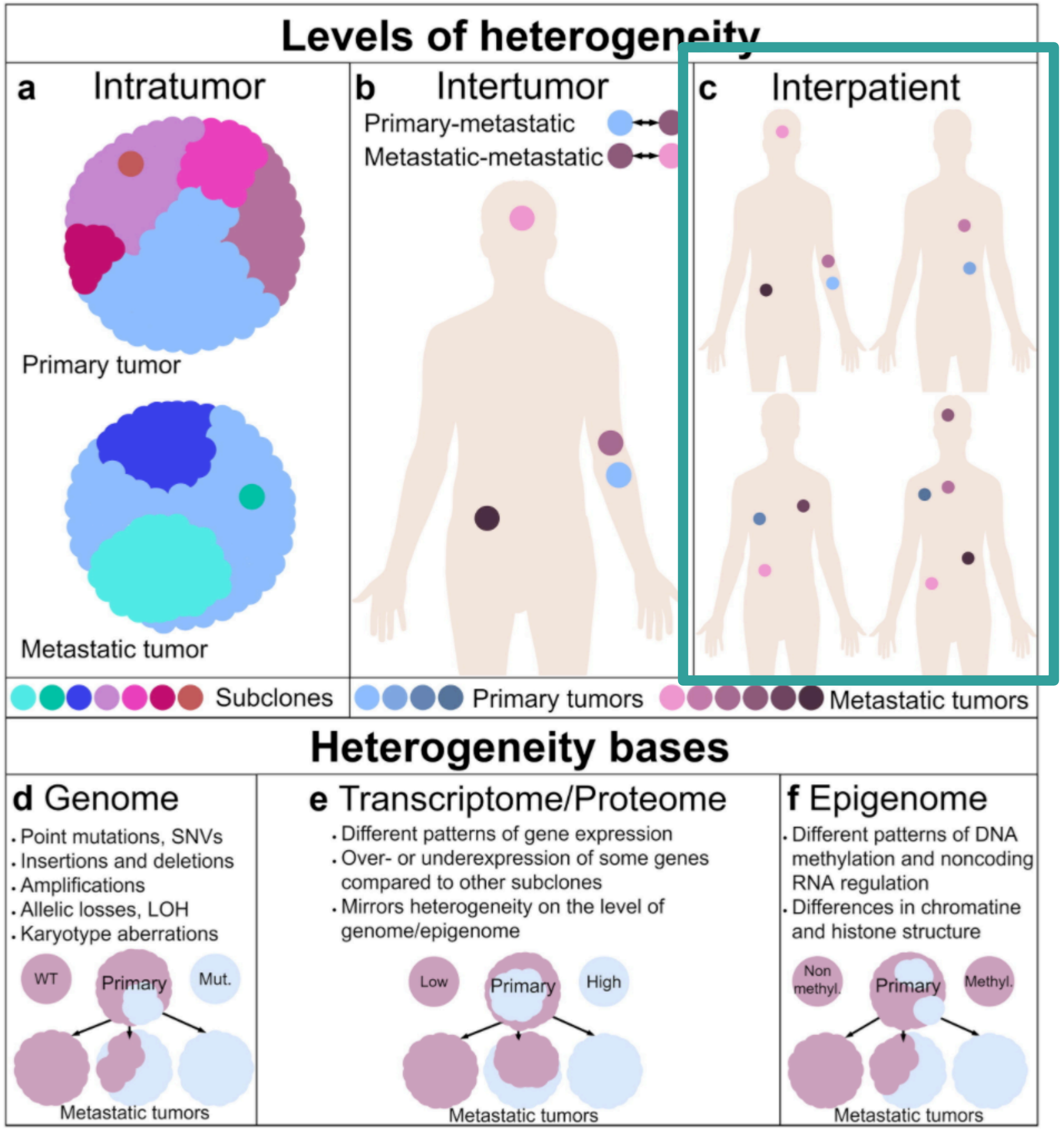
Tumors exhibit different levels of heterogeneity

Across patient populations:

1. **Cancer types**: between primary tumors of different organs or tissue-of-origin (eg. Breast and lung cancers)
2. **Same-subtype**: between tumors from different patients
3. **Tumor subtypes**: between subset of patients with tumors having similar molecular features (e.g. ER+ and ER- breast cancers)

Within an individual patient:

4. **Inter-tumor**: between tumors within a patient
5. **Intra-tumor heterogeneity**: between cells within a tumor lesion (e.g. tumor clones, stromal cells, infiltrating lymphocytes)



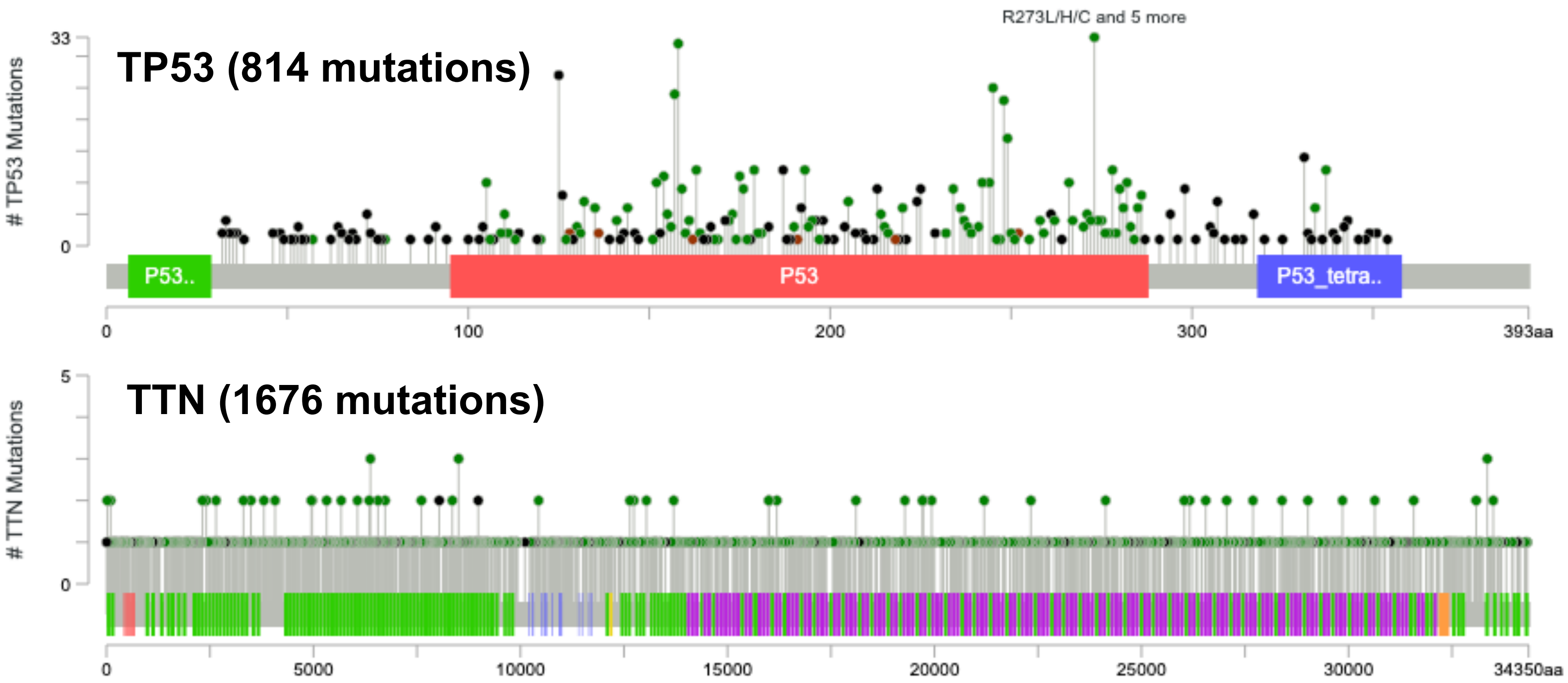
Grzywa et al. *Transl Oncol.* **10**:956-75 (2017)

Cancer Genes: Driver vs Passenger Genomic Alterations

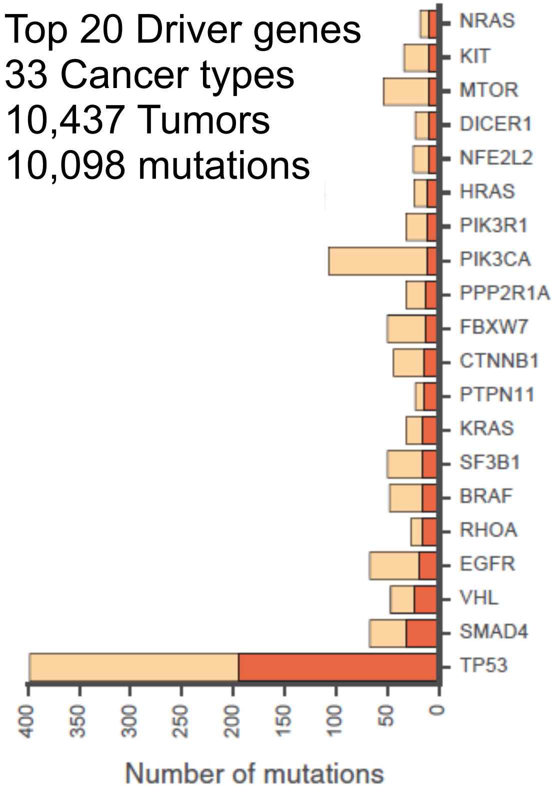
How do we find the mutated genes that ***drive*** cancer?

- **Significantly Mutated Genes:** recurrently mutated genes in patient cohorts
- Account for covariates (e.g. gene length, expression, replication timing)

1144 Lung Cancers



Top 20 Driver genes
33 Cancer types
10,437 Tumors
10,098 mutations



https://www.cbioportal.org/

Bailey et al. *Cell* **173**:371-85 (2018)

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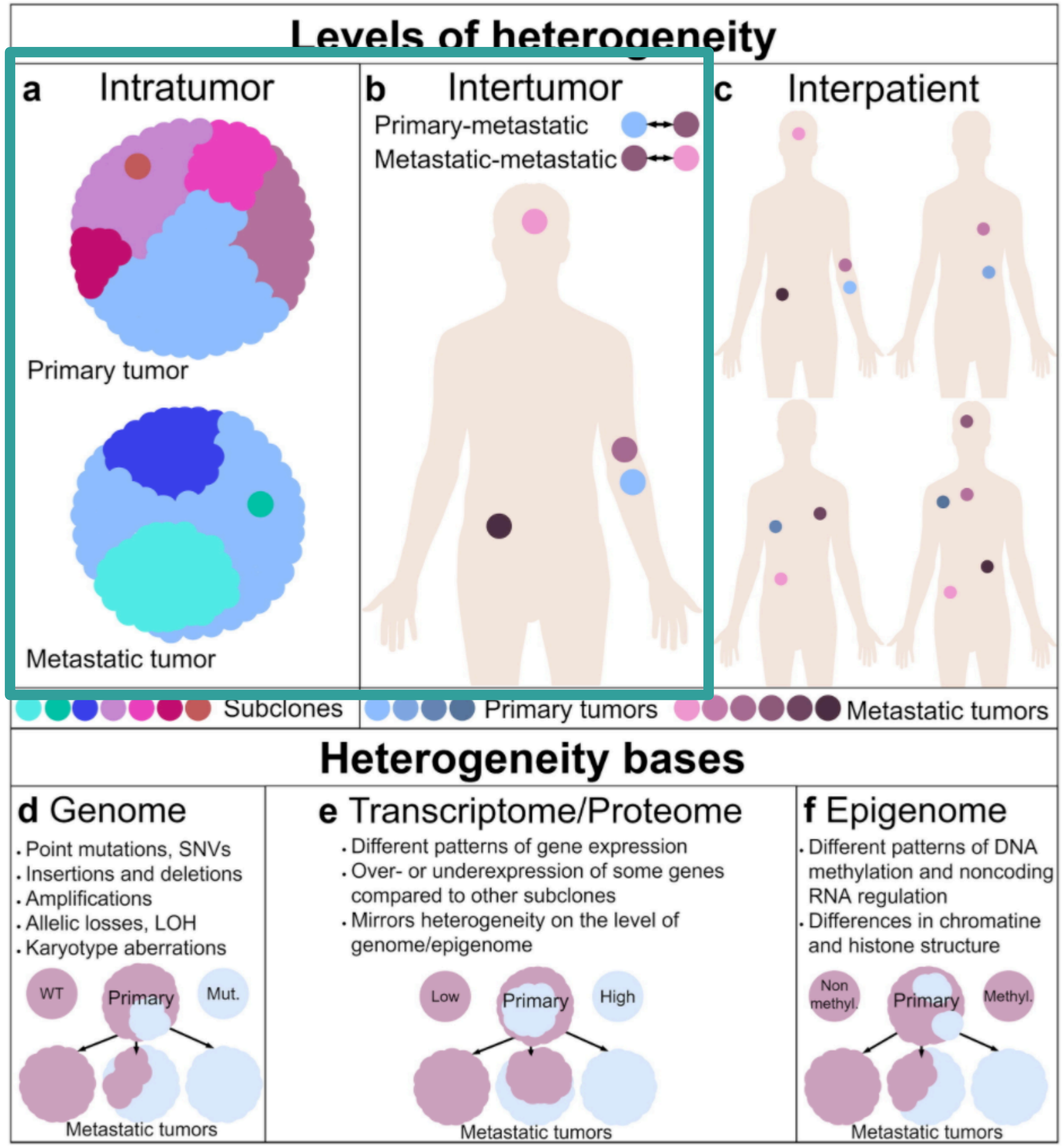
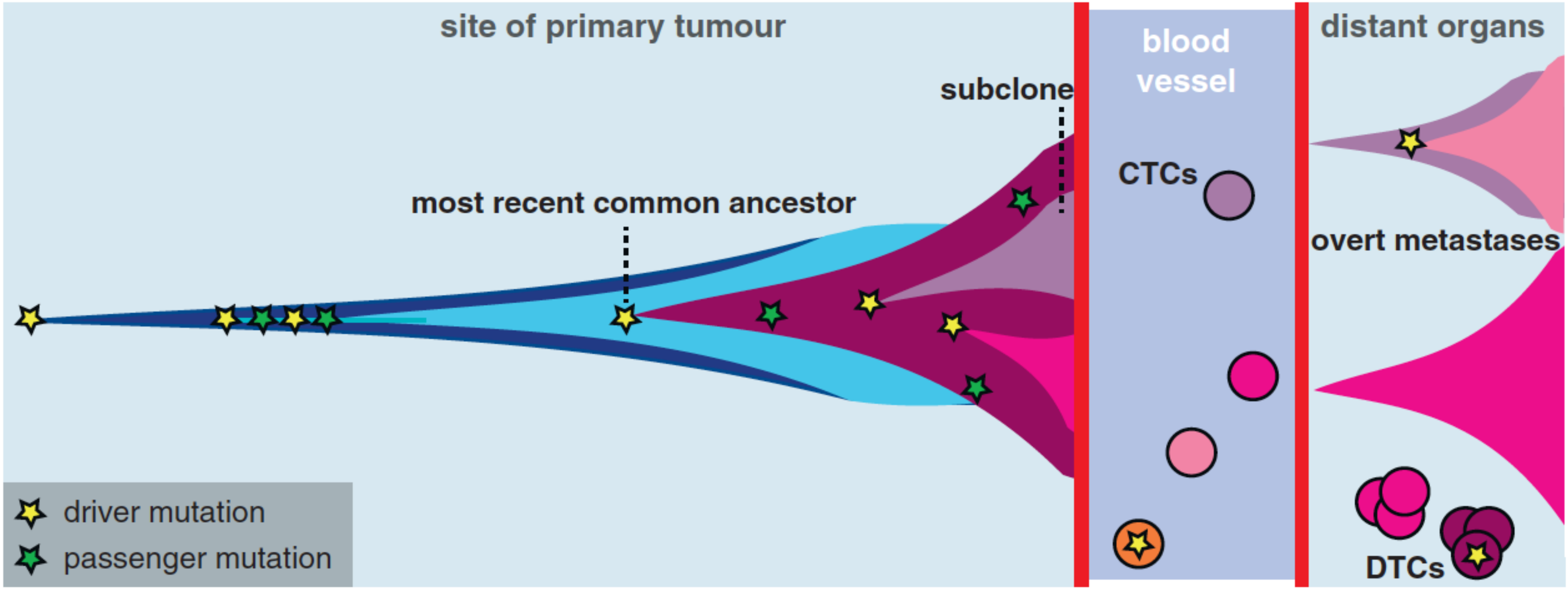


Grzywa et al. *Transl Oncol.* **10**:956-75 (2017)

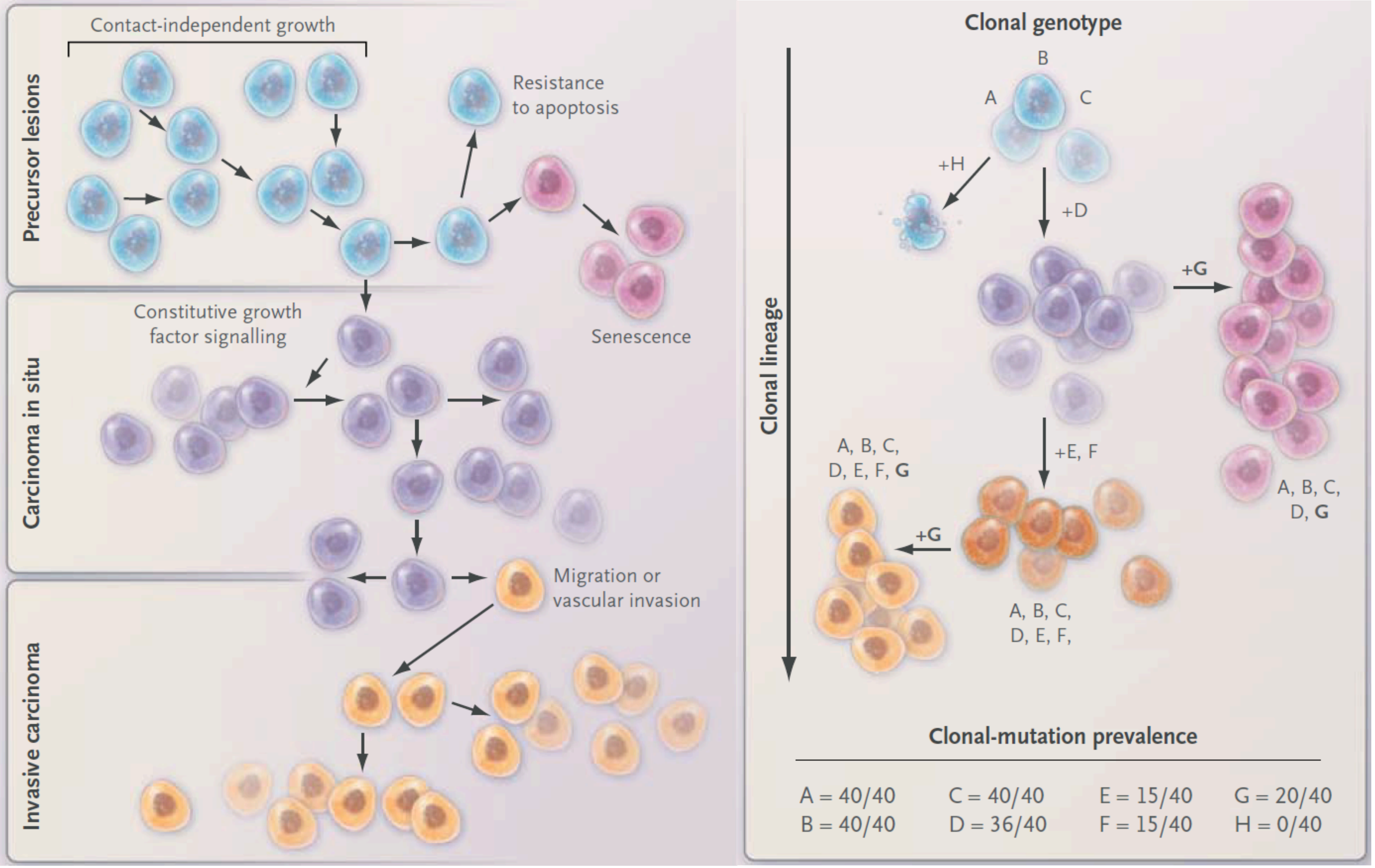
Tumors undergo genome evolution and clonal expansion

- Clonal diversity may have implications for treatment resistance
- Dynamics of clones can change in the blood and metastases



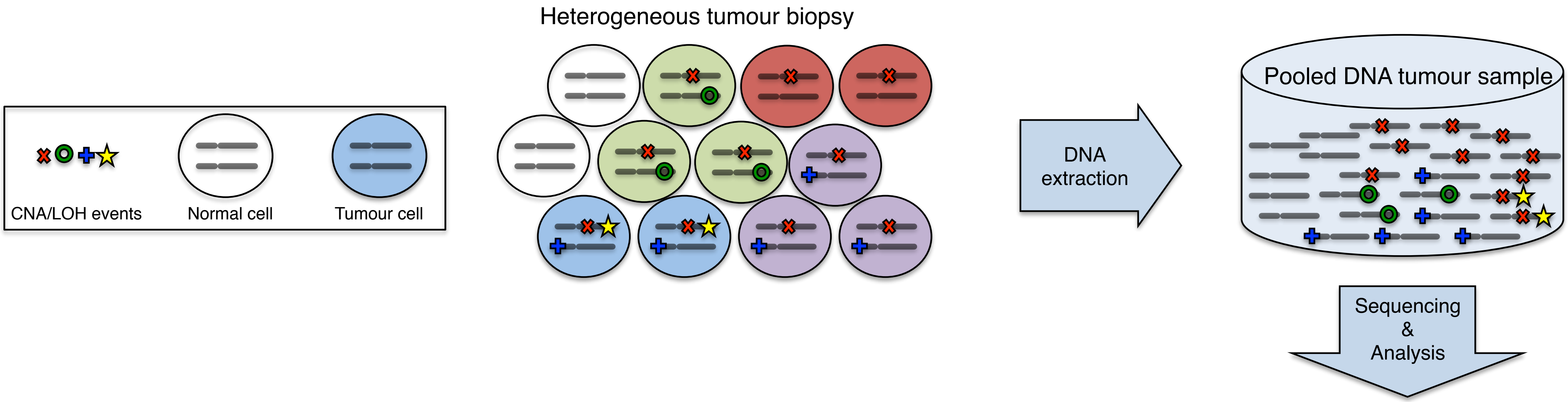
Van Loo and Voet. *Curr Opin Genet Dev* (2014)

Tumor genome evolution selects for cellular phenotypes



Aparicio & Caldas. *NEJM*. **368**:842-51 (2013)

Inferring intra-tumor genomic heterogeneity from sequencing



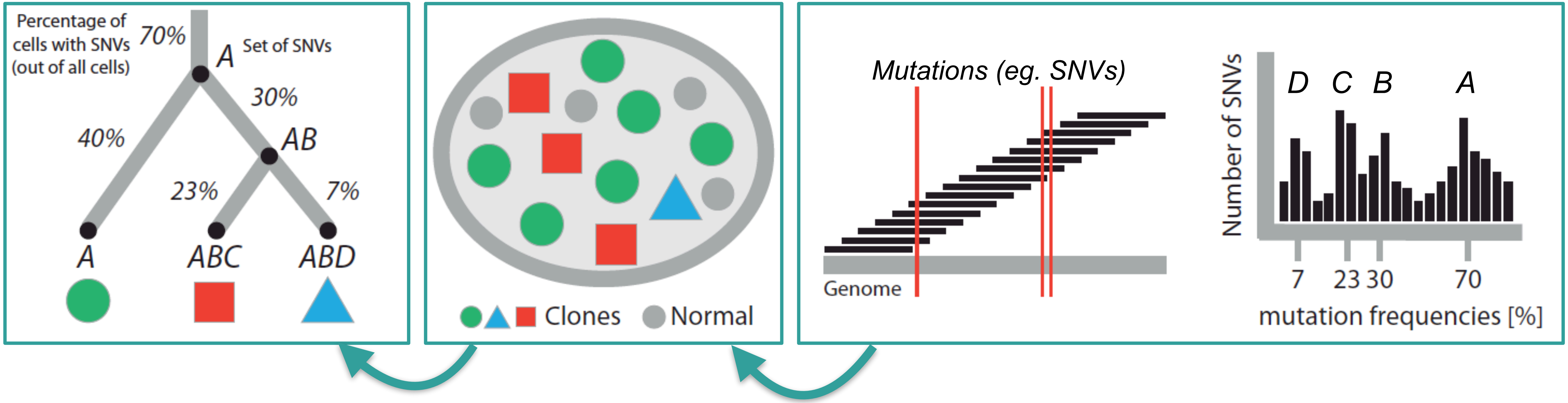
Subclonal events
Cellular prevalence

✖ 100%
✚ 50%
○ 30%
☆ 20%

- Combined signals from normal and multiple populations of tumor cells.
- Cellular prevalence: proportion of tumor cells harboring event
- Discuss further in Lecture 4…

Inferring evolutionary history of a tumor from sequencing

Evolutionary History | **Clonal Cell Populations** | **Sequencing Data**



3. Infer evolutionary (phylogenetic) tree

2. Infer clonal prevalence

1. Mutation Calling & Analysis

Adapted from Beerenwinkel et al. *Syst. Biol.* **64**:e1-25 (2015)

2. Overview of Cancer Genome Analysis

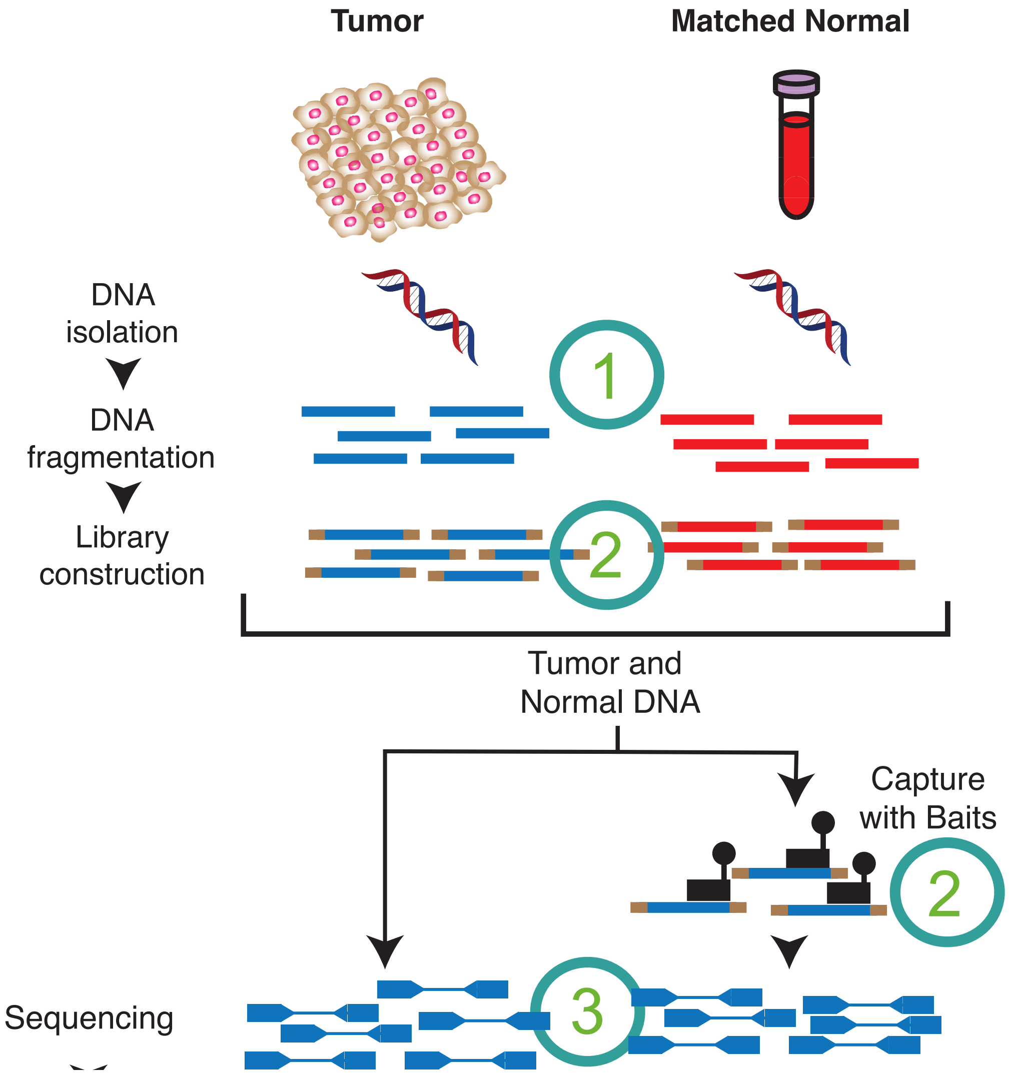
- Computational strategy and workflow
- Tumor DNA sequencing
- Whole genome vs whole exome vs targeted sequencing
- Types of genomic alterations predicted from tumor sequencing
- Methods/tools/algorithms in following lectures

General Workflow of Tumor Genome Sequencing (1)

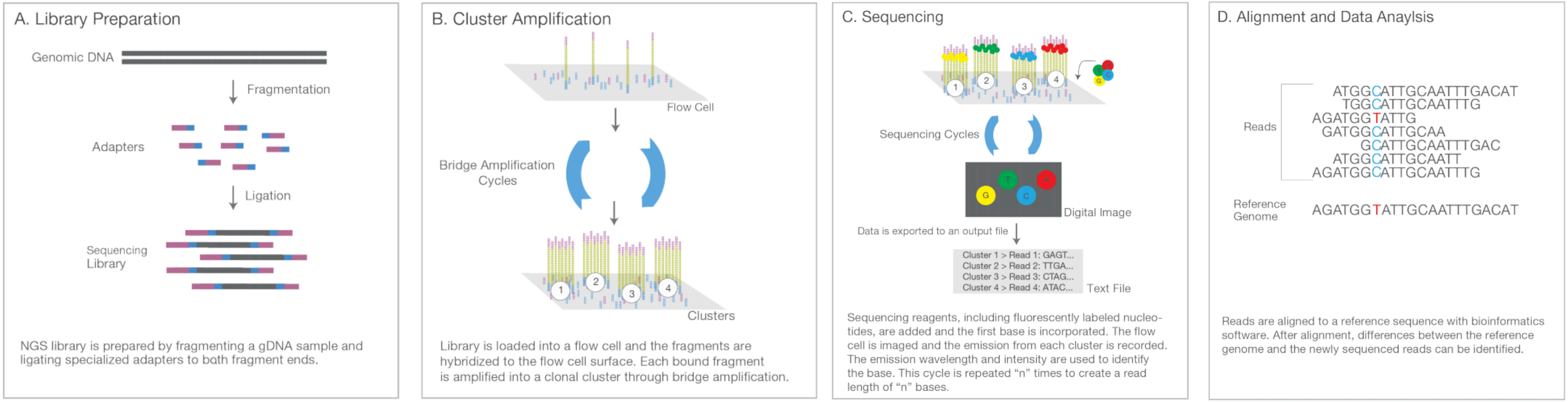
- Tumor and Normal pairing
  - Distinguish somatic and germline alterations

- Capture baits can be used to select regions
  - e.g. whole exome or targeted gene panels

- Potential sources of error can arise
  1. 8-oxoG transversions (C>A/G>T)
  2. PCR errors and GC content bias
  3. Sequencing errors



Genome Sequencing: Massively Parallel Sequencing

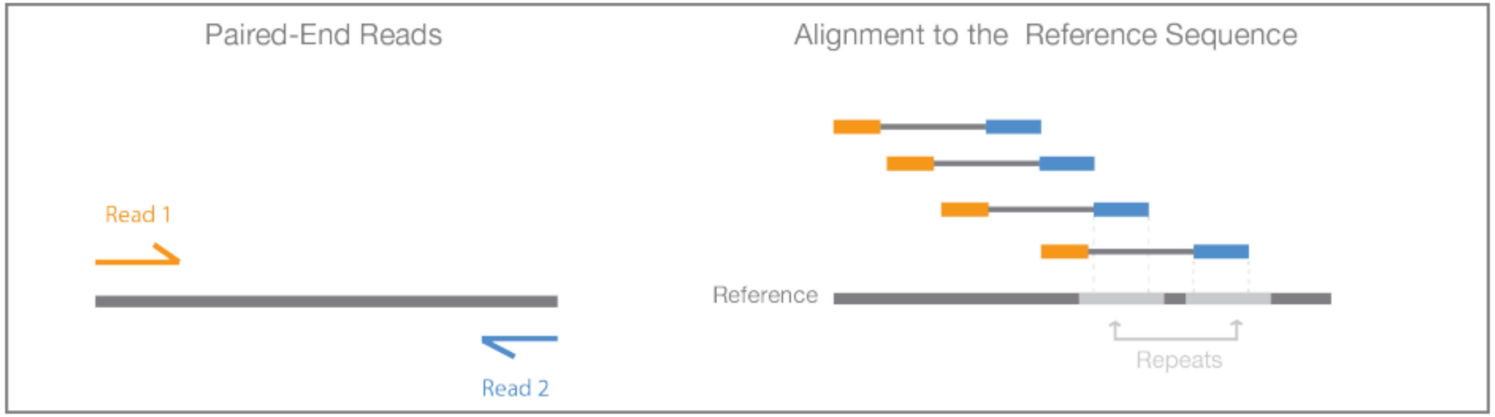


NGS library is prepared by fragmenting a gDNA sample and ligating specialized adapters to both fragment ends.

Library is loaded into a flow cell and the fragments are hybridized to the flow cell surface. Each bound fragment is amplified into a clonal cluster through bridge amplification.

Sequencing reagents, including fluorescently labeled nucleotides, are added and the first base is incorporated. The flow cell is imaged and the emission from each cluster is recorded. The emission wavelength and intensity are used to identify the base. This cycle is repeated "n" times to create a read length of "n" bases.

Reads are aligned to a reference sequence with bioinformatics software. After alignment, differences between the reference genome and the newly sequenced reads can be identified.



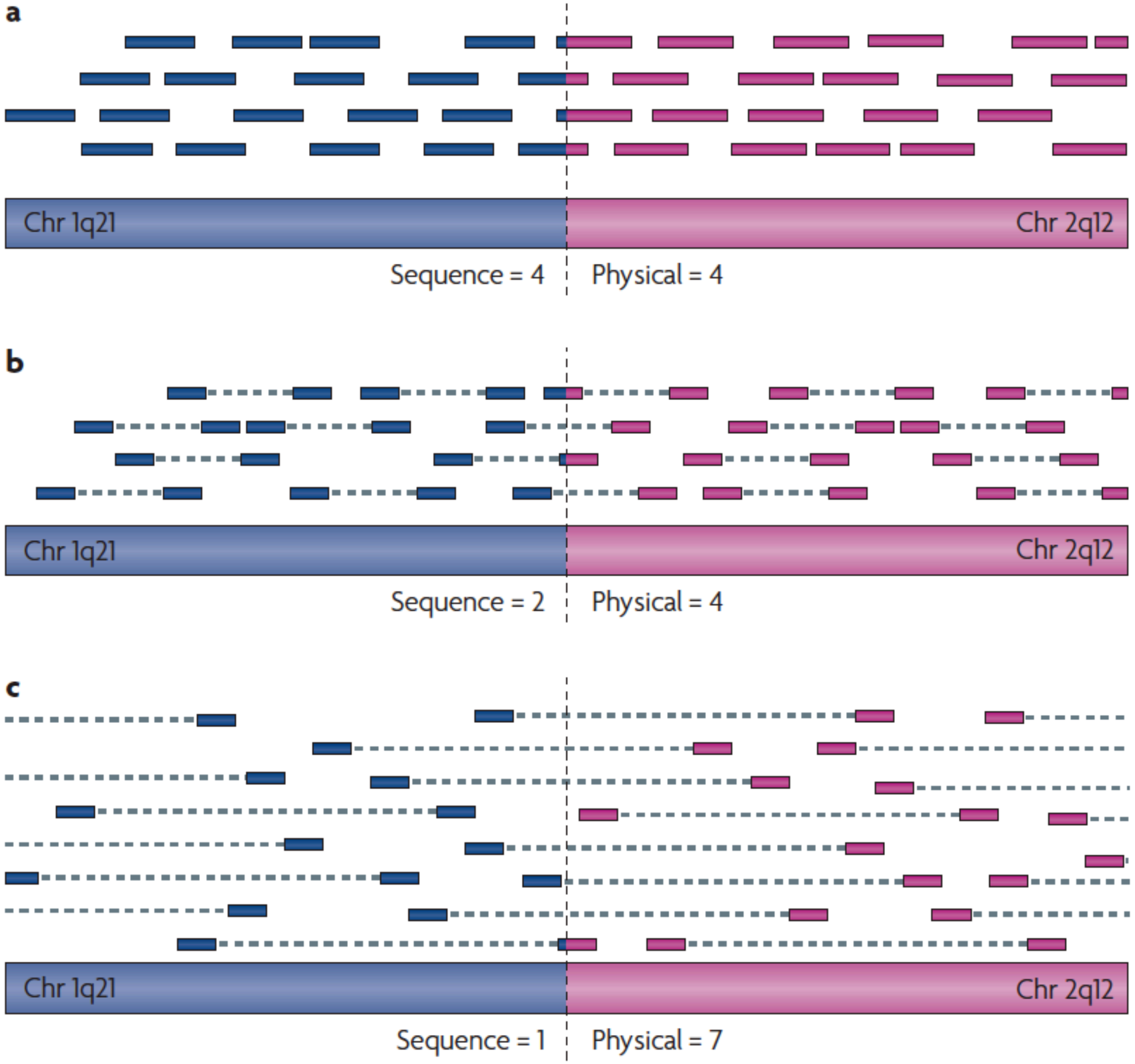
https://www.illumina.com/content/dam/illumina-marketing/documents/products/illumina_sequencing_introduction.pdf

Genome Sequencing: Sequence vs Physical Coverage

Single End

Paired End

Paired End



Sequence Coverage = number of sequenced reads spanning locus

Physical Coverage = number of DNA fragments spanning locus

- Mutation detection rely on sequence coverage
- Rearrangement detection rely on both

Meyerson, Gabriel & Getz. *Nature Review Genetics* **11**:685-96 (2010)

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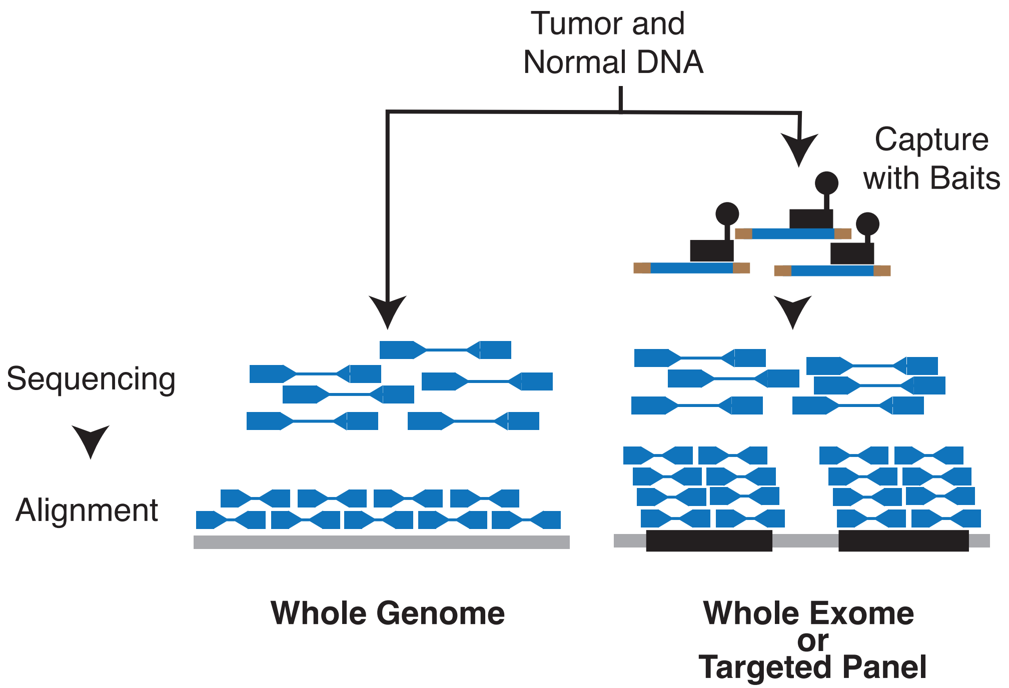
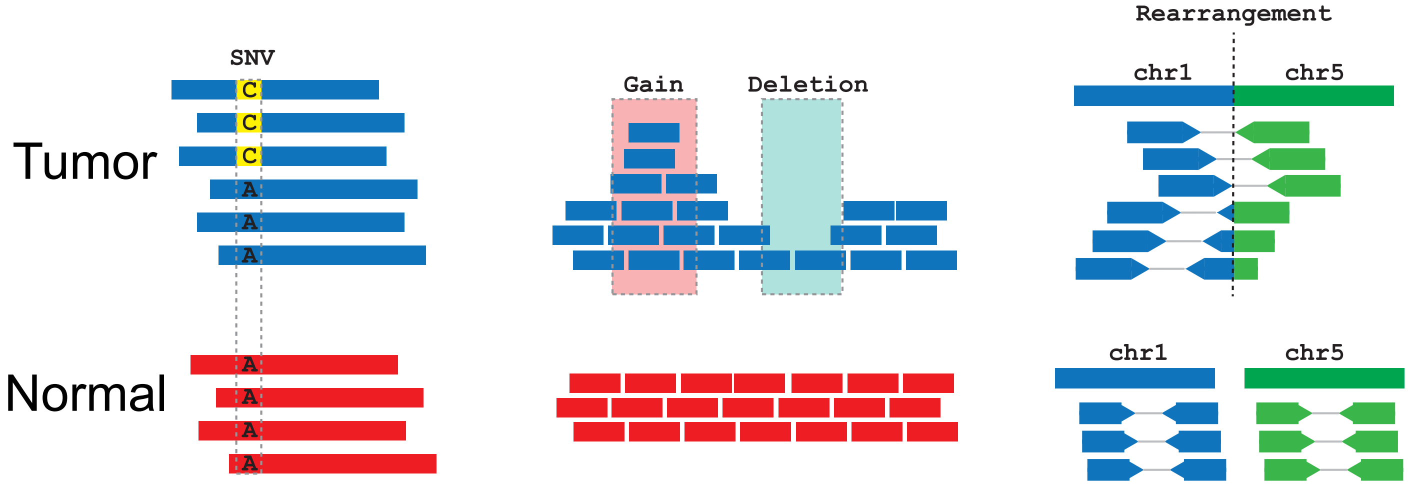
General Workflow of Tumor Genome Sequencing (2)



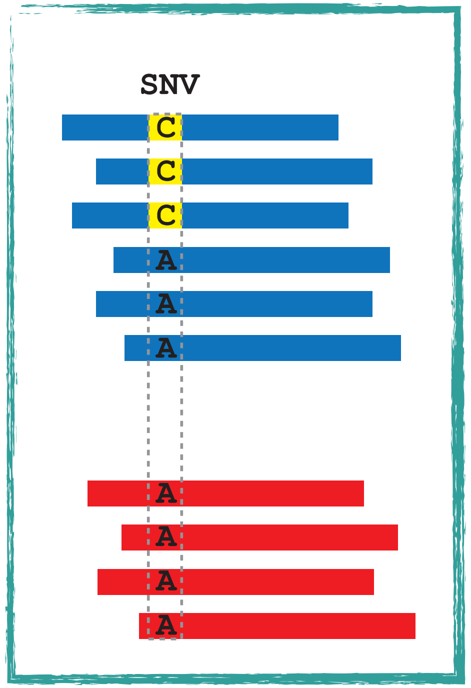
Mutations (SNV, INDEL) **Copy Number Alterations** **Structural Variants**



Whole Genome Sequencing	Whole Exome Sequencing	Targeted Gene Sequencing
• Genome-wide (unbiased) • 0.1-100x genome coverage	• Exons (2% of genome) • 50-500x target coverage	• Target regions (1-5Mb) • 100-25000x target coverage
• More sequencing required • Expensive	• Less sequencing required • Cost-effective	• Least sequencing required • Panel design costs
• Coding/Non-coding mutations • Copy number alterations • Structural variation	• Coding mutations (all genes) • Copy number alterations • Gene fusions rearrangements	• Coding mutations (selected) • Targeted rearrangements

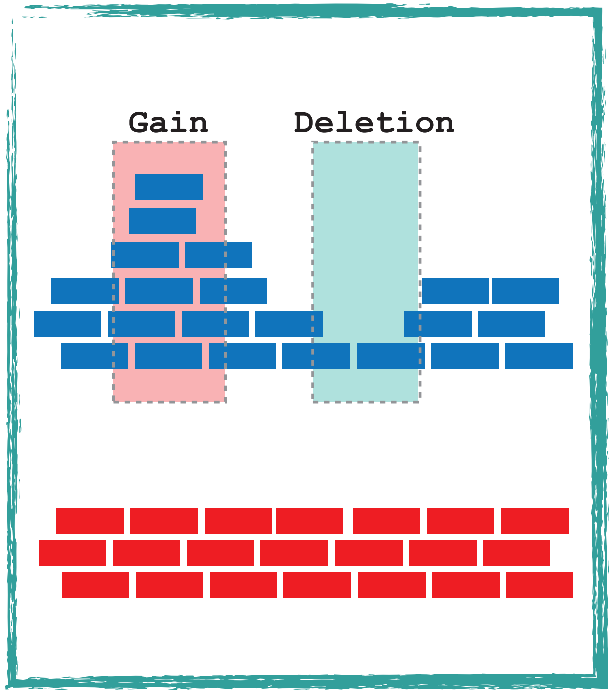
Types of Genomic Alterations Predicted from Sequencing

Mutations (SNV, INDEL)



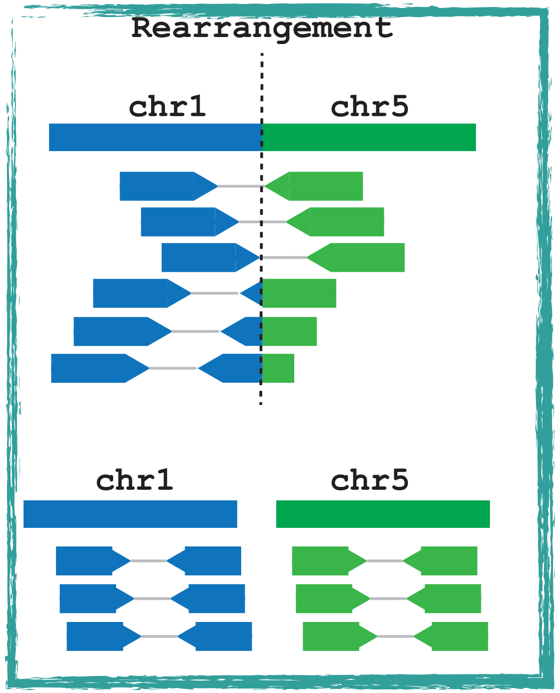
Lecture 2

Copy Number Alterations



Lecture 3

Structural Variants



Lecture 4?

Genome Sequencing: International Consortia & Projects

1000 Genomes Project (https://www.internationalgenome.org/)

UK10K (https://www.uk10k.org/)

The 100,000 Genomes Project (https://www.genomicsengland.co.uk/)

- Rare disease, cancer, infectious disease

Genome 10K Project (https://genome10k.soe.ucsc.edu/)

- Genomic “zoo” of 16,000 vertebrate species

Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/)

Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/)

The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov/)

International Cancer Genome Consortium (ICGC) (https://icgc.org/)

IGSR: The International Genome Sample Resource

Providing ongoing support for the 1000 Genomes Project data

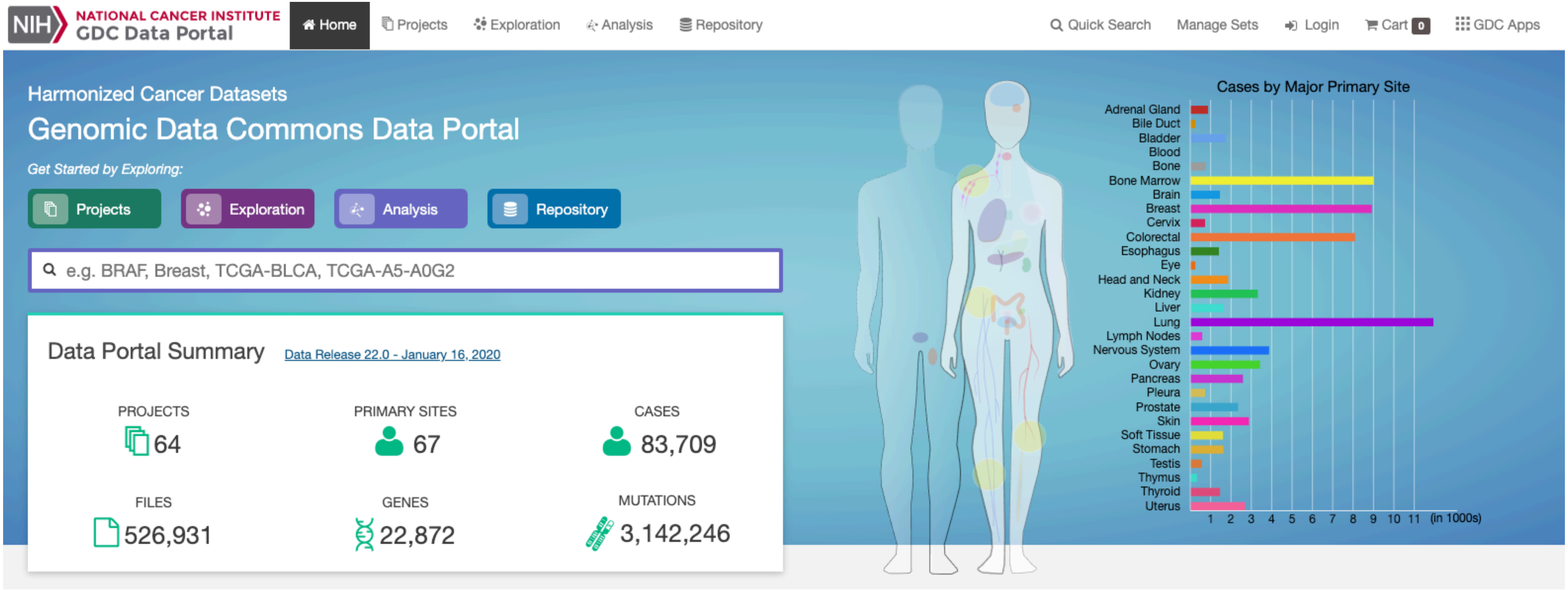
UK10K

Rare Genetic Variants in Health and Disease

Genomics england

#100kThankYous

Cancer Genome Sequence Data: Databases & Online Resources



Harmonized Cancer Datasets

Genomic Data Commons Data Portal

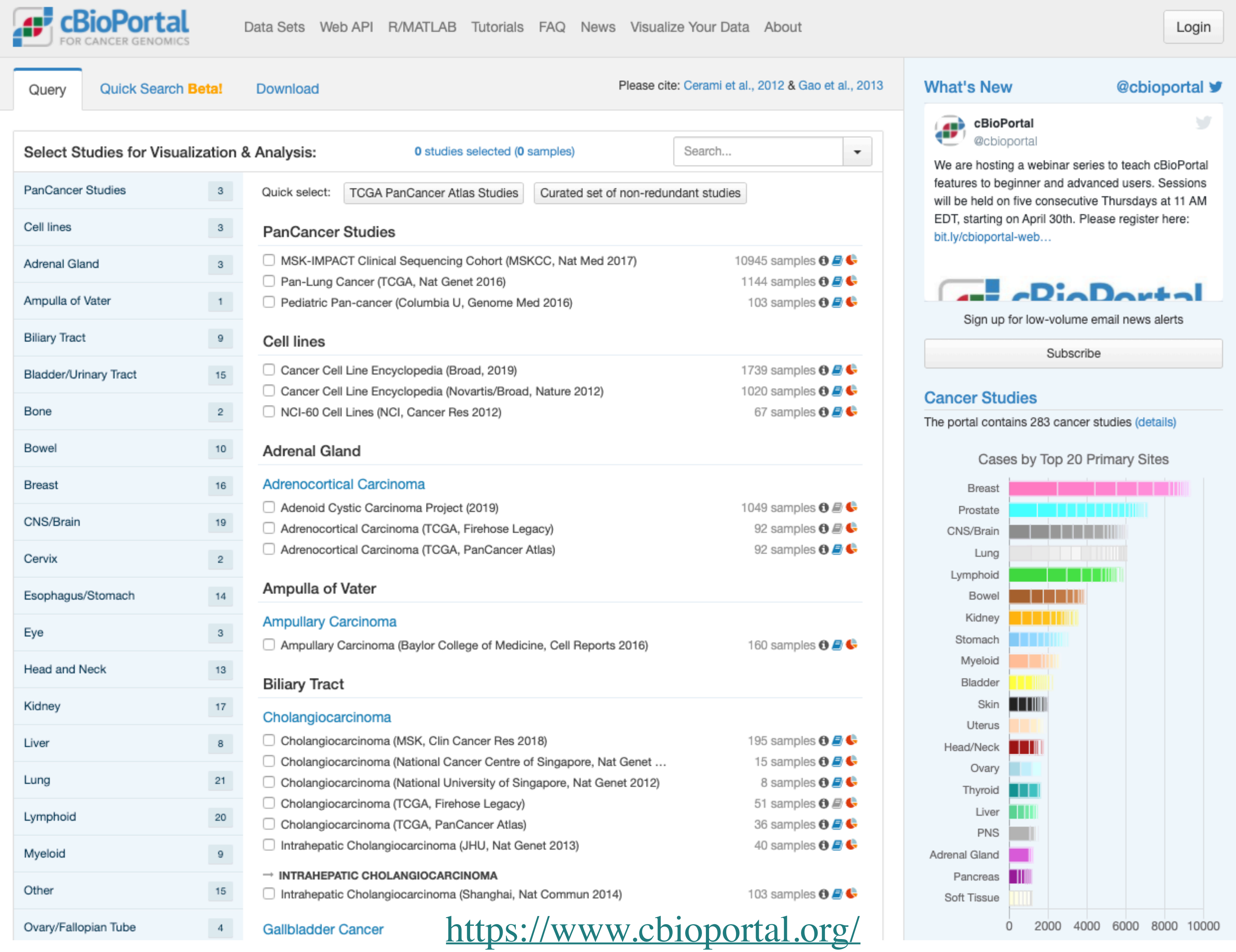
Get Started by Exploring:

Data Portal Summary [Data Release 22.0 - January 16, 2020]

PROJECTS	PRIMARY SITES	CASES
64	67	83,709
FILES	**GENES**	**MUTATIONS**
526,931	22,872	3,142,246

https://portal.gdc.cancer.gov/

Cancer Genome Sequence Data: Databases & Online Resources



Please cite: Cerami et al., 2012 & Gao et al., 2013

Select Studies for Visualization & Analysis: 0 studies selected (0 samples) Search...

PanCancer Studies	3
Cell lines	3
Adrenal Gland	3
Ampulla of Vater	1
Biliary Tract	9
Bladder/Urinary Tract	15
Bone	2
Bowel	10
Breast	16
CNS/Brain	19
Cervix	2
Esophagus/Stomach	14
Eye	3
Head and Neck	13
Kidney	17
Liver	8
Lung	21
Lymphoid	20
Myeloid	9
Other	15
Ovary/Fallopian Tube	4

Quick select: TCGA PanCancer Atlas Studies | Curated set of non-redundant studies

PanCancer Studies

- □ MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017) — 10945 samples
- □ Pan-Lung Cancer (TCGA, Nat Genet 2016) — 1144 samples
- □ Pediatric Pan-cancer (Columbia U, Genome Med 2016) — 103 samples

Cell lines

- □ Cancer Cell Line Encyclopedia (Broad, 2019) — 1739 samples
- □ Cancer Cell Line Encyclopedia (Novartis/Broad, Nature 2012) — 1020 samples
- □ NCI-60 Cell Lines (NCI, Cancer Res 2012) — 67 samples

Adrenal Gland

Adrenocortical Carcinoma

- □ Adenoid Cystic Carcinoma Project (2019) — 1049 samples
- □ Adrenocortical Carcinoma (TCGA, Firehose Legacy) — 92 samples
- □ Adrenocortical Carcinoma (TCGA, PanCancer Atlas) — 92 samples

Ampulla of Vater

Ampullary Carcinoma

- □ Ampullary Carcinoma (Baylor College of Medicine, Cell Reports 2016) — 160 samples

Biliary Tract

Cholangiocarcinoma

- □ Cholangiocarcinoma (MSK, Clin Cancer Res 2018) — 195 samples
- □ Cholangiocarcinoma (National Cancer Centre of Singapore, Nat Genet ... — 15 samples
- □ Cholangiocarcinoma (National University of Singapore, Nat Genet 2012) — 8 samples
- □ Cholangiocarcinoma (TCGA, Firehose Legacy) — 51 samples
- □ Cholangiocarcinoma (TCGA, PanCancer Atlas) — 36 samples
- □ Intrahepatic Cholangiocarcinoma (JHU, Nat Genet 2013) — 40 samples

→ INTRAHEPATIC CHOLANGIOCARCINOMA

- □ Intrahepatic Cholangiocarcinoma (Shanghai, Nat Commun 2014) — 103 samples

Gallbladder Cancer

What's New @cbioportal

cBioPortal
@cbioportal

We are hosting a webinar series to teach cBioPortal features to beginner and advanced users. Sessions will be held on five consecutive Thursdays at 11 AM EDT, starting on April 30th. Please register here: bit.ly/cbioportal-web…

Sign up for low-volume email news alerts

Subscribe

Cancer Studies

The portal contains 283 cancer studies (details)

Cases by Top 20 Primary Sites

https://www.cbioportal.org/

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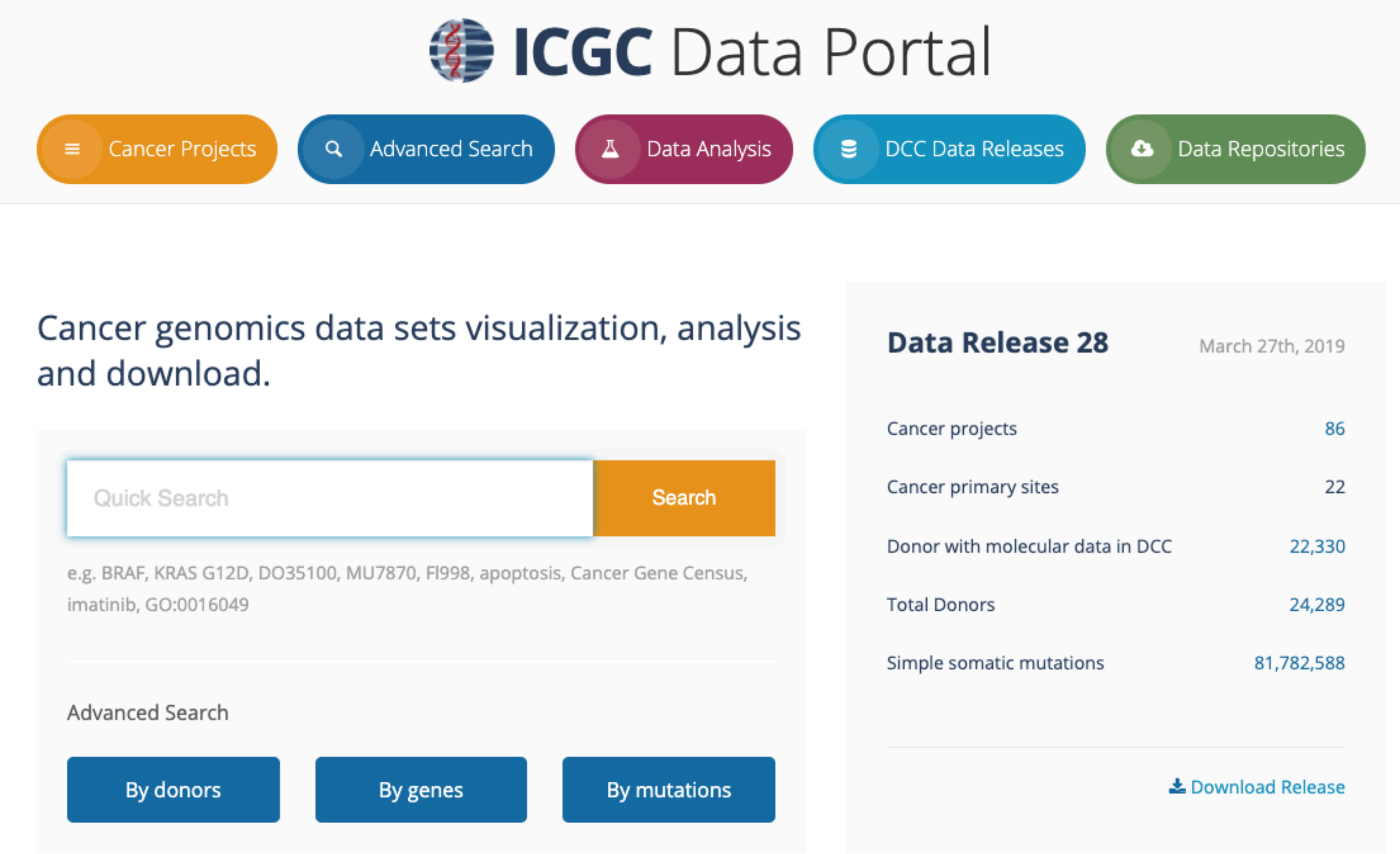
Cancer Genome Sequence Data: Databases & Online Resources



ICGC Data Portal

Cancer genomics data sets visualization, analysis and download.

e.g. BRAF, KRAS G12D, DO35100, MU7870, FI998, apoptosis, Cancer Gene Census, imatinib, GO:0016049

Advanced Search

Data Release 28 March 27th, 2019

Cancer projects	86
Cancer primary sites	22
Donor with molecular data in DCC	22,330
Total Donors	24,289
Simple somatic mutations	81,782,588

3. Primer on statistical modeling

- Probability
  - Unsupervised learning, probability rules & Bayes’ theorem
  - Binomial distribution, Bayesian statistics
  - Beta-binomial model example
- Mixture models, EM inference
- References:
  - Murphy, K. (2012). Machine Learning: A Probabilistic Perspective. MIT Press. ISBN: 9780262018029
  - Bishop, C. M. (2006). Pattern Recognition and Machine Learning (Information Science and Statistics). Springer. ISBN: 0387310738
  - https://www.cs.ubc.ca/~murphyk/Teaching/CS340-Fall06/reading/bernoulli.pdf

Sequencing Data Analysis Requires Probabilistic Models

- Sequencing data contain uncertainty due to
  - Technical noise from imperfect measurements & errors
  - Biological features in the signal measurements
- How do we predict genomic alterations accounting for these features and noise?
  - Need approaches to learn the patterns of these features from the data…

Types of machine learning:

- Supervised: output data y, input data $\boldsymbol{x}$, and *training set* $D = \{(\boldsymbol{x}, y)\}$
  - Classification (y are labels), Regression (y is continuous)
- Unsupervised: Only given input data $D = \{\boldsymbol{x}\}$, *learn the patterns of the data*
  - E.g. clustering input data $\boldsymbol{x}$ into K clusters by estimating their assignments z

Primer: Probability Theory

Let X be a random variable. The probability for the event $X = x$ for some value x is $p(X = x)$ or $p(x)$ for short. Let Y be another random variable.

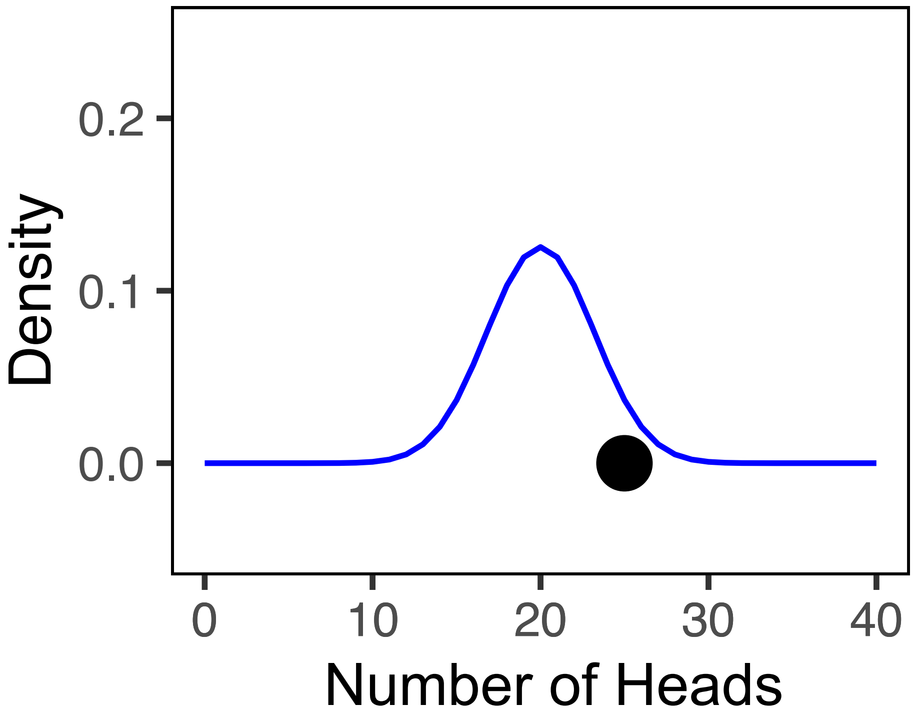
Probability Rules

- **Sum rule:** $p(X) = \sum_Y p(X, Y)$
- **Product rule:** $p(X, Y) = p(Y|X)p(X)$ and $p(Y, X) = p(X|Y)p(Y)$
- Conditional Probabilities: $p(Y|X) = \frac{p(X, Y)}{p(X)}$
- Marginal Probabilities: $p(X) = \sum_Y p(Y, X) = \sum_Y p(X|Y)p(Y)$
- **Bayes' Theorem (rule):** $p(Y|X) = \dfrac{p(X, Y)}{p(X)} = \dfrac{p(X|Y)p(Y)}{\sum_{Y'} p(X|Y')p(Y')}$

Probability distribution: Binomial

Binomial Distribution: Referee Coin Toss Example

- A referee has a coin that he uses to decide which team gets first possession. She tossed the coin N times last season, once per game. We assume this coin was fair and had a probability $\mu = 0.5$ for showing a head. We kept track of the number of heads x that appeared.
- What is the probability of seeing a specific number of heads? e.g. $x = 25$ out of $N = 40$ tosses



Probability distribution: Binomial

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Probability mass function

- Let X be the random variable representing the number of heads. If the probability of heads is μ, then X has a binomial distribution, $X \sim Bin(N, \mu)$ or $p(X = x \,|\, N, \mu) = Bin(x \,|\, N, \mu)$ where

$$Bin(x \,|\, N, \mu) = \binom{N}{x} \mu^x (1 - \mu)^{N-x}$$

$$\binom{N}{k}$$

number of ways the 25 heads is observed among the sequence of 40 tosses.

- Our coin-toss example: for $x = 25$ out of $N = 40$ and a fair coin $\mu = 0.5$

$$p(X = 25 \,|\, N = 40, \mu = 0.5) = Bin(25 \,|\, 40, 0.5) = \binom{40}{25} 0.5^{25} (1 - 0.5)^{40-25}$$

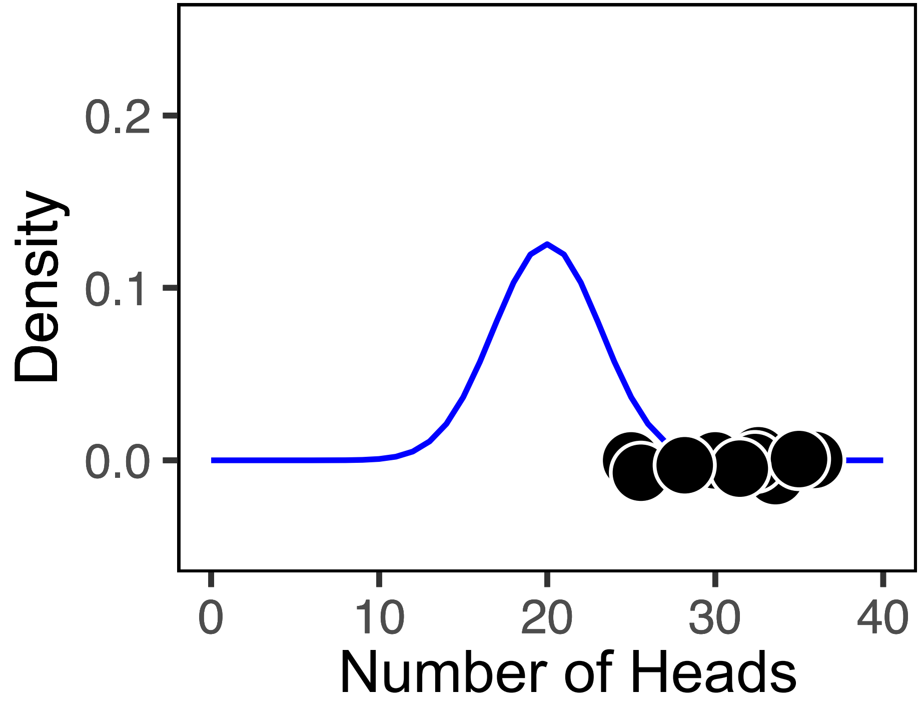
Binomial likelihood model

- Suppose there are T different referees who toss the *same* coin $N = \{1, \ldots, N_T\}$ times and come up with head counts $\boldsymbol{x} = \{1, \ldots, x_T\}$.
- Assuming the referees' tosses are *independent* and *identically distributed* (**iid**), what is the probability of observing the head counts given the coin (e.g. $\mu = 0.5$)?

$$p(x_{1:T} | N_{1:T}, \mu) = \prod_{i=1}^{T} Bin(x_i | N_i, \mu)$$

Likelihood

- What if the coin wasn't fair and the probability of heads, μ, might not be 0.5?



	# of tosses (*N*)	# of heads (*x*)
Referee 1	40	25
Referee 2	42	35
Referee 3	39	27
Referee T	x_T	N_T

Maximum likelihood estimation (MLE)

- What is the probability of heads, μ, of this coin given the evidence?
- We can estimate this model *parameter* using

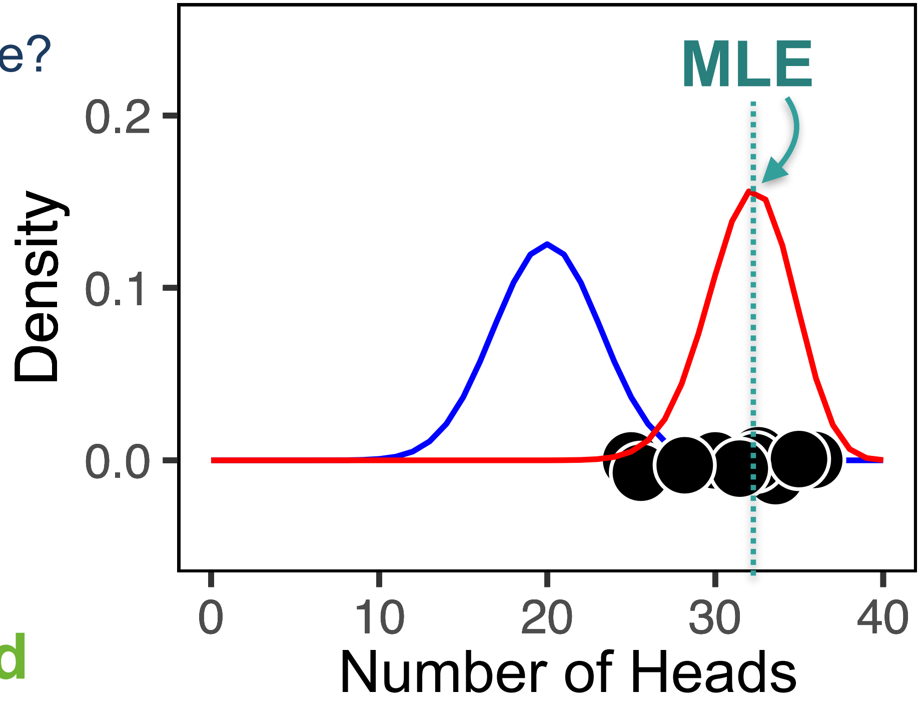
  maximum likelihood estimation

$$p(x_{1:T}|N_{1:T},\mu) = \prod_{i=1}^{T} Bin(x_i|N_i,\mu)$$ **Likelihood**

$$\log p(x_{1:T}|N_{1:T},\mu) = \sum_{i=1}^{T} \log Bin(x_i|N_i,\mu)$$ **Log-likelihood**

$$\hat{\mu} = \frac{\sum_{i=1}^{T} x_i}{\sum_{i=1}^{T} N_i}$$ **MLE**

1. Log of the likelihood
2. Take the derivative wrt to μ
3. Equate to 0
4. Solve for μ



https://www.cs.ubc.ca/~murphyk/Teaching/CS340-Fall06/reading/bernoulli.pdf

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Bayesian Statistics: Prior distribution for model parameters

	# of tosses (N)	# of heads (x)	Prop. of heads
Referee 1	40	25	0.63
Referee 2	42	35	0.83
Referee 3	39	27	0.69
Referee T	x_T	N_T	x_T/N_T

Likelihood for Binomial Model

$$p(x_{1:T}|N_{1:T},\mu) = \prod_{i=1}^{T} Bin(x_i|N_i,\mu)$$

Likelihood

- MLE uses the evidence to estimate parameter $\hat{\mu}$ but our sample size is small and MLE may **overfit**
- **Zero count or sparse data problem:** If you have a bad record keeper who only tallies coin tosses from referees who never tosses a tail, then does that mean the concept of tails on a coin does not exist at all?
- Can we capture a more natural expectation of how a coin might behave? Also, what if we have some knowledge that the coin might be biased?

Prior Distribution for binomial parameter, μ

- The proportion of heads is between 0 and 1 ($\mu \in [0,1]$) and can be sampled from a distribution itself
- μ can be drawn from a Beta distribution, which is in the interval $[0,1]$, with ***hyper-parameters*** α and β

$$\mu \sim Beta(\alpha,\beta)$$

$$p(\mu) = Beta(\mu|\alpha,\beta)$$

Prior

Bayesian statistics: Posterior for Beta-Binomial Model (1)

Binomial likelihood and Beta prior

- T different head counts $\boldsymbol{x} = \{1, \ldots, x_T\}$ for $\boldsymbol{N} = \{1, \ldots, N_T\}$ sets of tosses and a ***prior*** distribution on μ (prob. of heads)

$$p(x_{1:T} \mid N_{1:T}, \mu) = \prod_{i=1}^{T} Bin(x_i \mid N_i, \mu) \qquad \text{Likelihood}$$

$$p(\mu) = Beta(\mu \mid \alpha, \beta) \qquad \text{Prior}$$

- To estimate parameter μ in a Bayesian framework
  - We need the ***posterior***, $p(\mu \mid \boldsymbol{x})$, but only have $p(\boldsymbol{x} \mid \mu)$ and $p(\mu)$

- Recall Bayes' Theorem:

$$\underbrace{p(Y \mid X)}_{\text{Posterior}} = \frac{p(X \mid Y) p(Y)}{\sum_{Y'} p(X \mid Y') p(Y')} \propto \underbrace{p(X \mid Y)}_{\text{Likelihood}} \; \underbrace{p(Y)}_{\text{Prior}}$$

- The ***posterior*** is our **belief state** by combining evidence from observations and our prior beliefs.

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Bayesian statistics: Posterior for Beta-Binomial Model (2)

Beta-Binomial Model: Posterior distribution

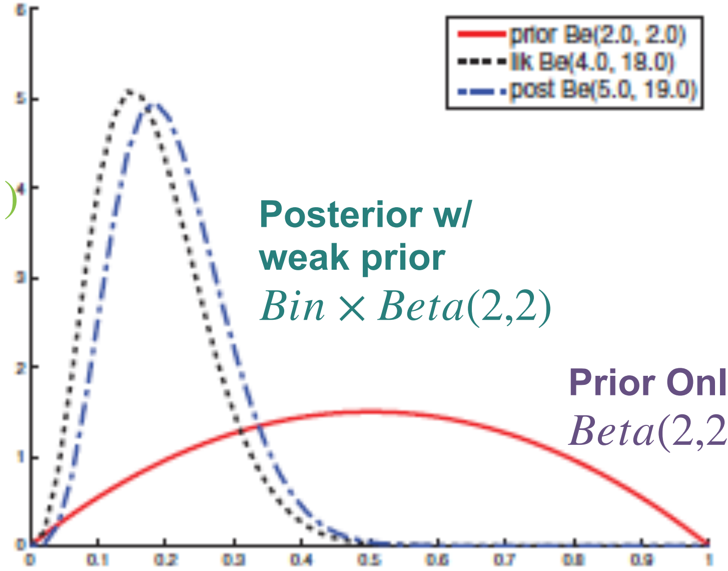
- To estimate the model parameter μ in a Bayesian framework, we compute the ***posterior***, $p(\mu\,|\,\boldsymbol{x})$

$$p(\mu\,|\,\boldsymbol{x}) \propto \prod_{i}^{T} Bin(x_i\,|\,N_i, \mu) \times Beta(\mu\,|\,\alpha, \beta)$$

- Beta is a ***conjugate prior*** for the binomial; *the product of binomial and Beta has the form of a Beta*

$$p(\mu\,|\,\boldsymbol{x}) \propto \prod_{i}^{T} \underbrace{Bin(x_i\,|\,N_i, \rho)}_{\text{Likelihood}} \times \underbrace{Beta(\mu\,|\,\alpha, \beta)}_{\text{Prior}} = \prod_{i}^{T} \underbrace{Beta(\mu\,|\,x_i + \alpha, N_i - x_i + \beta)}_{\text{Posterior}}$$

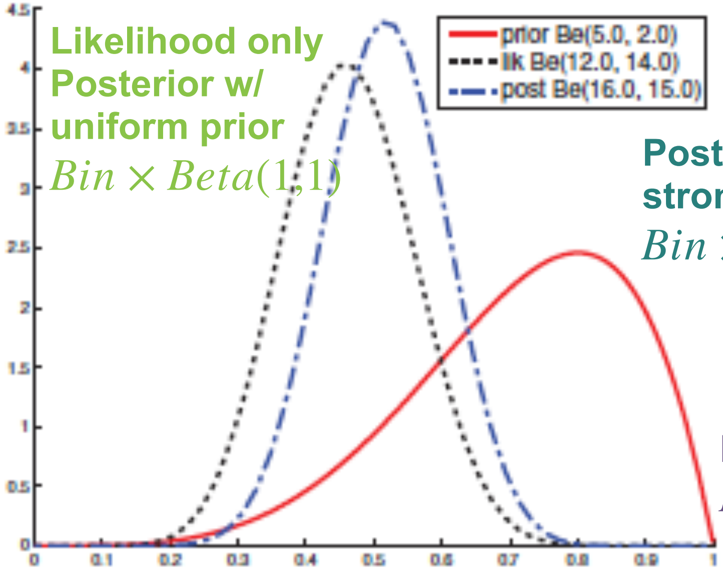
Figure 3.6 in Murphy, K. (2012). Machine Learning: A Probabilistic Perspective. MIT Press



Likelihood only
Posterior w/ uniform prior
$Bin \times Beta(1{,}1)$

Posterior w/ weak prior
$Bin \times Beta(2{,}2)$

Prior Only
$Beta(2{,}2)$



Likelihood only
Posterior w/ uniform prior
$Bin \times Beta(1{,}1)$

Posterior w/ strong prior
$Bin \times Beta(5{,}2)$

Prior Only
$Beta(5{,}2)$

Bayesian statistics: MAP estimate

Beta-Binomial Model: Posterior distribution

$$p(\mu \,|\, \boldsymbol{x}) \propto \prod_{i}^{T} Bin(x_i \,|\, N_i, \rho) \times Beta(\mu \,|\, \alpha, \beta) = \prod_{i}^{T} \underset{\textbf{Posterior}}{Beta(\mu \,|\, \overset{\alpha'}{x_i + \alpha}, \overset{\beta'}{N_i - x_i + \beta})}$$

- Then, what is the probability of heads, μ, of this coin given the **evidence** and the **prior**?

Maximum a posteriori (MAP) estimate

- From the posterior, we can estimate the parameter using the ***maximum a posteriori (MAP)***, $\hat{\mu}_{MAP}$
- MAP refers to the mode of the posterior distribution and the mode of a Beta is $\frac{\alpha - 1}{\alpha + \beta - 2}$
- Since the posterior has the form of a Beta distribution, then the MAP is $\frac{\alpha' - 1}{\alpha' + \beta' - 2}$

$$\alpha' = \sum_i^T x_i + \alpha$$

$$\beta' = \sum_i^T \left(N_i - x_i\right) + \beta$$

$$\hat{\mu}_{MAP} = \frac{\sum_i^T x_i + \alpha - 1}{\sum_i^T N_i + \alpha + \beta - 2}$$

MAP

1. Log of the posterior
2. Take the derivative wrt to μ
3. Equate to 0
4. Solve for μ

Section 3.3 in Murphy (2012). Machine Learning: A Probabilistic Perspective. MIT Press

Mapping the Referee Example to Mutation Calling

Referee Coin Toss Example

Data

Referees $1,\ldots,T$

For each Referee i

- Coin Tosses: N_i
- Count of heads: x_i
- Count of tails: $N_i - x_i$

Parameters

Probability to draw coins: $\pi_{fair}, \pi_{heads}, \pi_{tails}$

Probability of heads for 3 types of coins

$$\mu_{fair}, \mu_{heads}, \mu_{tails}$$

Responsibilities

Probability that Referee i used coin k: $\gamma(Z_i = k)$

Mutation Calling from Sequencing Data

Data

Genomic loci $1,\ldots,T$

For each locus i

- Depth (total reads): N_i
- Count of reference reads: x_i
- Count of variant reads: $N_i - x_i$

Parameters

Probability of genotypes: $\pi_{AA}, \pi_{AB}, \pi_{BB}$

Probability of reference base for 3 genotypes:

$$\mu_{AA}, \mu_{AB}, \mu_{BB}$$

Responsibilities

Probability that locus i has genotype k: $\gamma(Z_i = k)$

Mixture Models: Online Tutorial and Resource

fiveMinuteStats (https://stephens999.github.io/fiveMinuteStats/)

by **Dr. Matthew Stephens**, Professor in Statistics & Human Genetics at University of Chicago

1. Introduction to mixture models with probabilistic derivations and R code
   - Examples with Bernoulli and Gaussian models
   - https://stephens999.github.io/fiveMinuteStats/intro_to_mixture_models.html
2. Introduction to EM with Gaussian Mixture Model example and R code
   - https://stephens999.github.io/fiveMinuteStats/intro_to_em.html

Homework #5: Single-nucleotide Genotype Caller

Implement a standard binomial mixture model described in Lecture 2.

- Learn the parameters and infer the genotypes
- Annotate the mutation status for a set of genomic loci.
- Expected outputs for each question will be provided so that you can check your code.
- RStudio Markdown and Python Jupyter Notebook templates provided.

Due: May 8th

Office Hours with Anna-Lisa Doebley (adoebley@uw.edu)

- Monday, May 4, 2-3pm
- Wednesday, May 6, 2-3pm