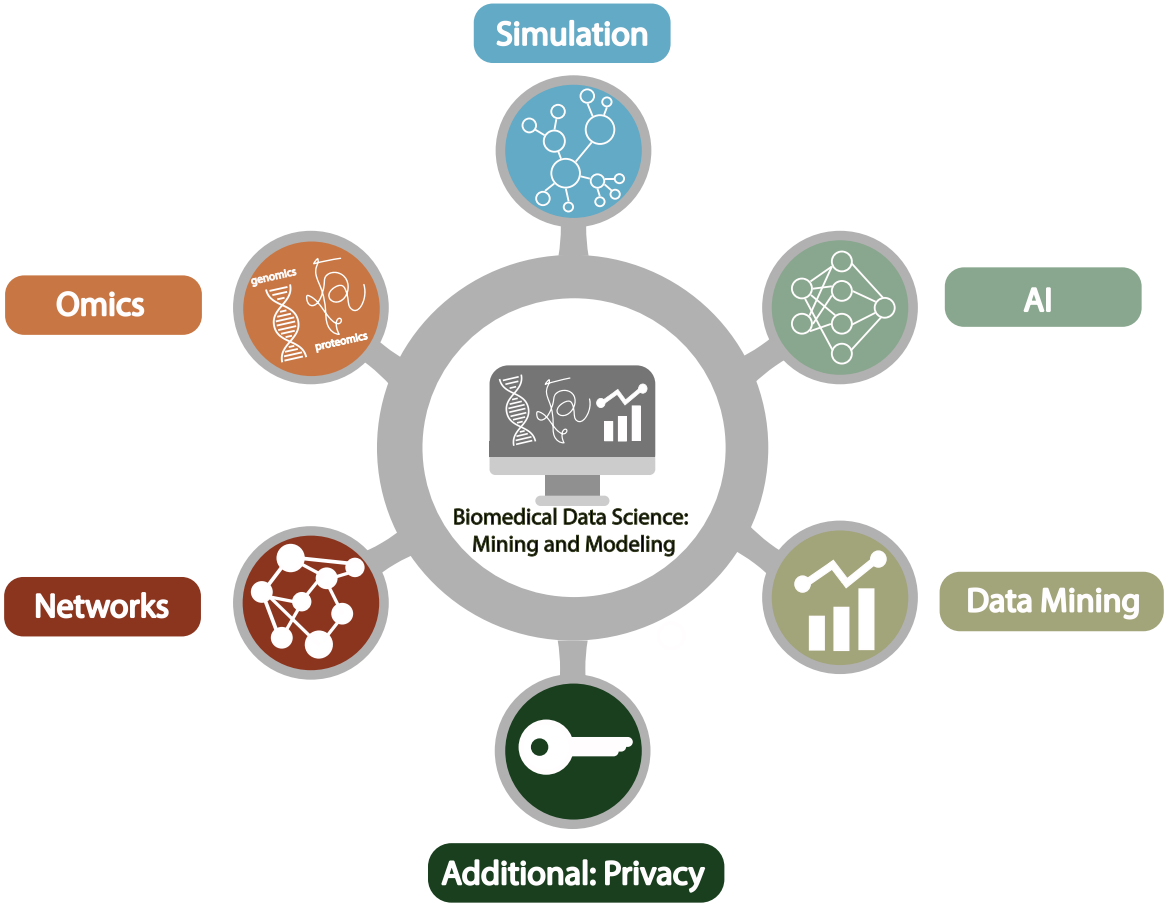
Biomedical Data Science (GersteinLab.org/courses/452)

Variant Identification, Focusing on SVs (23m6a)

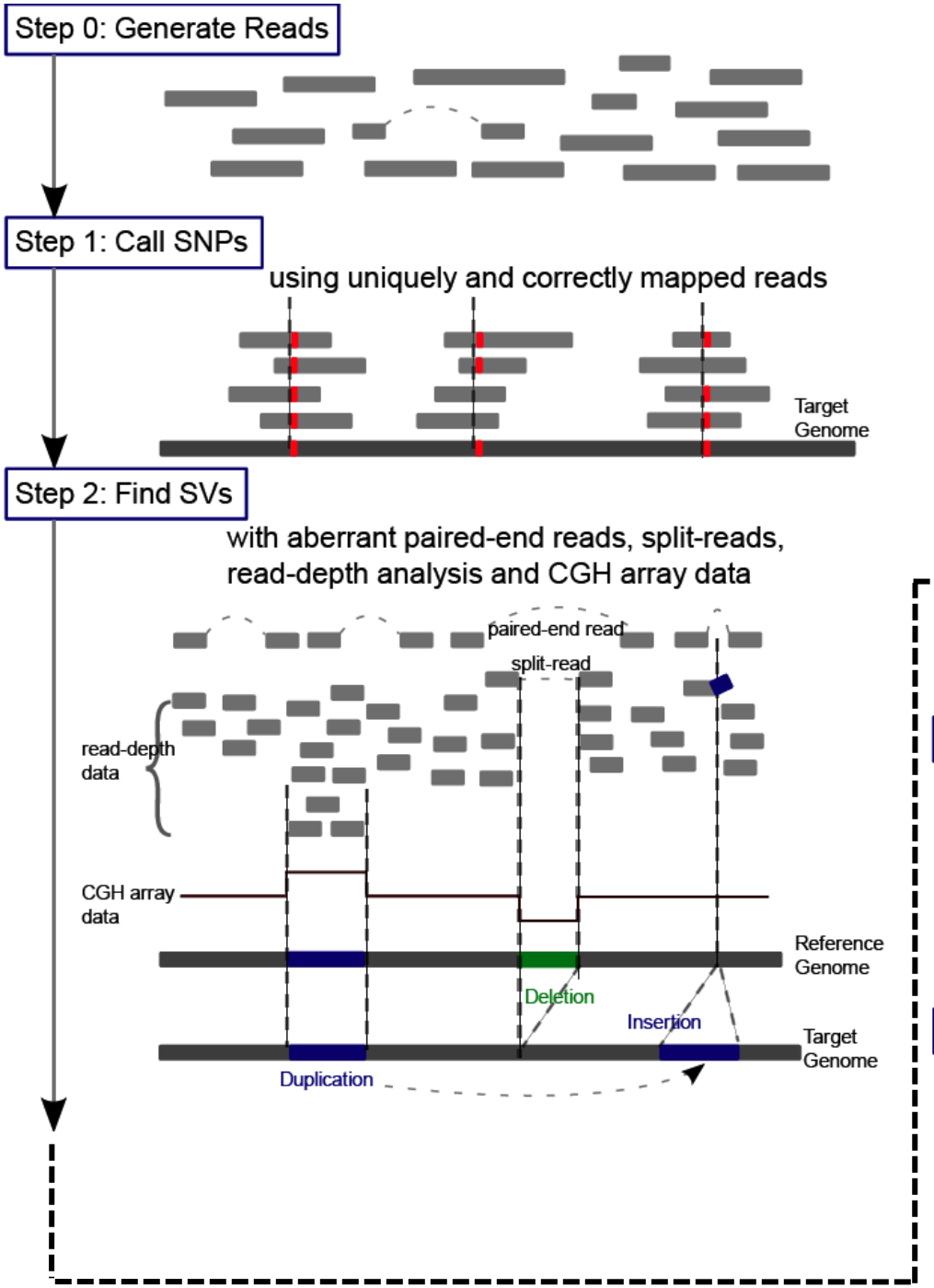


Mark Gerstein
Yale U.

Last edit in spring ’23. Unchanged (but with slight edits) from 22m6a & 2021’s M6a [which has a video].

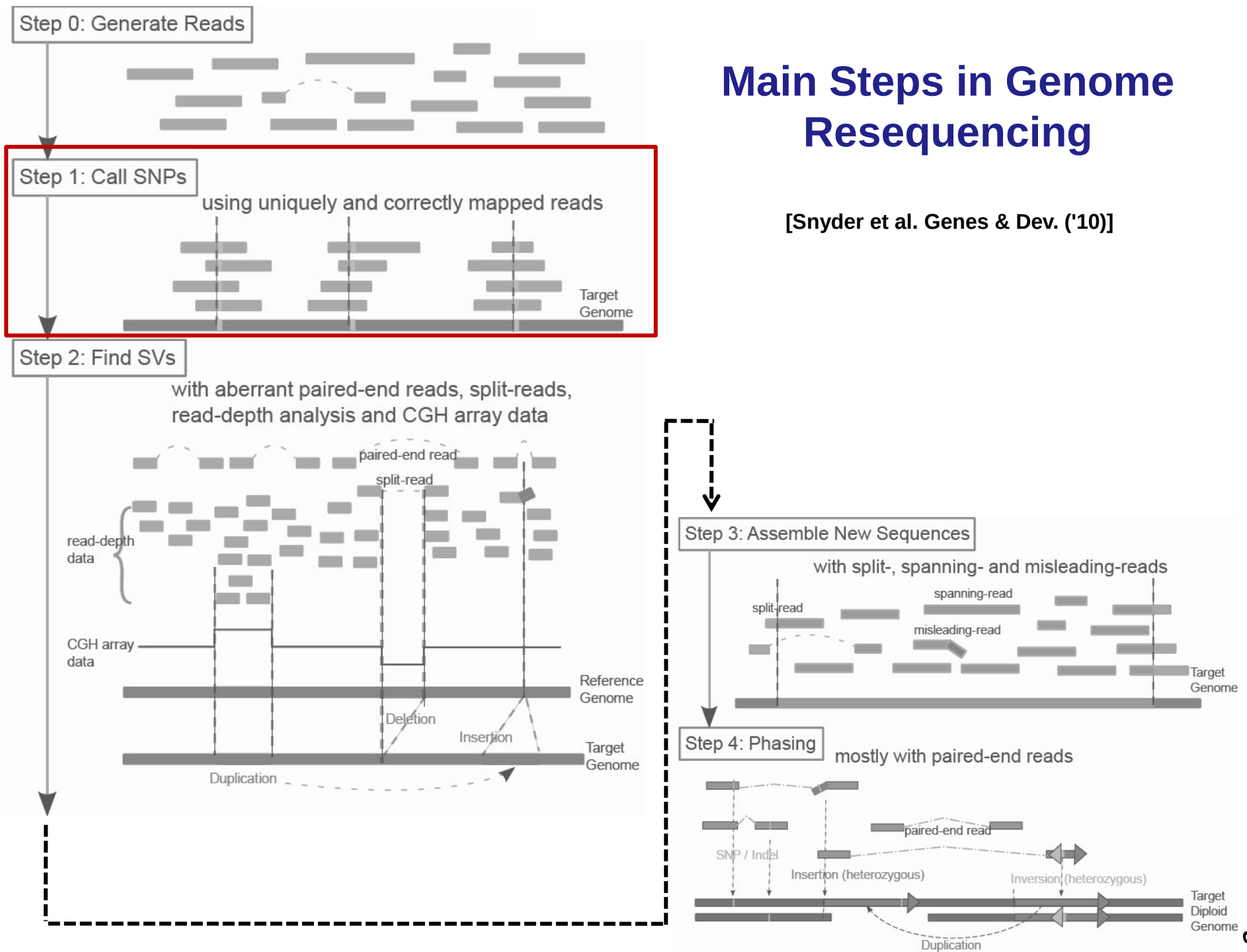
Main Steps in Genome Resequencing

[Snyder et al. Genes & Dev. ('10)]

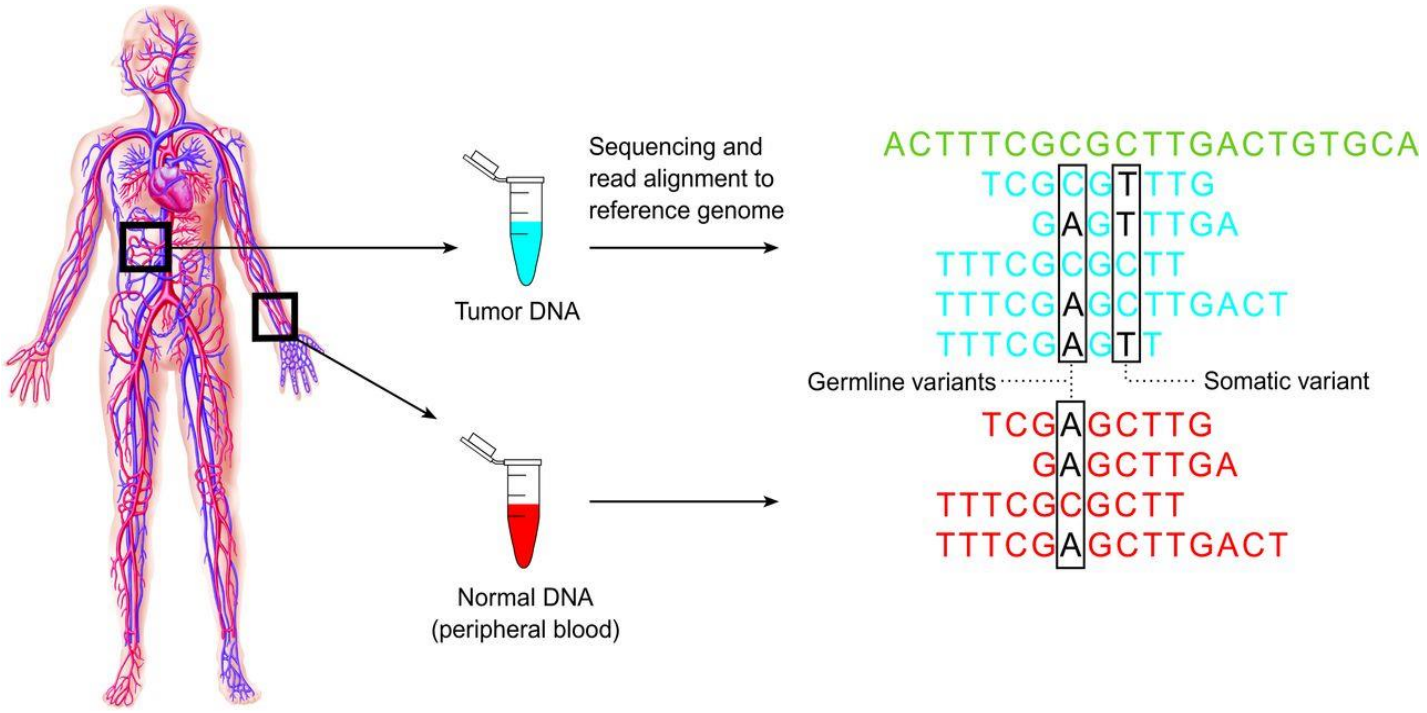


Main Steps in Genome Resequencing

[Snyder et al. Genes & Dev. ('10)]



Characterization of genomic variations: somatic vs germline



Sequencing tumor and normal samples from cancer patients provide insight into somatic and germline variation profile.

Samuel et al, Clinical chemistry, 2013

Bayes' Theorem to detect genomic variant

$$P(G|D) = \frac{P(D|G)P(G)}{P(D)}$$

$$= \frac{P(D|G)\,P(G)}{\sum_{i=1}^{n} P(D|G_i)\,P(G_i)}$$

In the above equation:

- D refers to the observed data
- G is the genotype whose probability is being calculated
- G_i refers to the ith possible genotype, out of n possibilities

[You et al. ('12) Bioinformatics 28: 643 doi: 10.1093/bioinformatics/bts001]

Calculating the conditional distribution $P(D|G)$:

Assuming an error free model, for each heterozygous SNP site of the diploid genome, covered by K reads, the number of reads i representing one of the two alleles follows binomial distribution.

$$\boldsymbol{P_{err\_free}(D|G) = f(i|k, 0.5) = \binom{k}{i} 0.5^k}$$

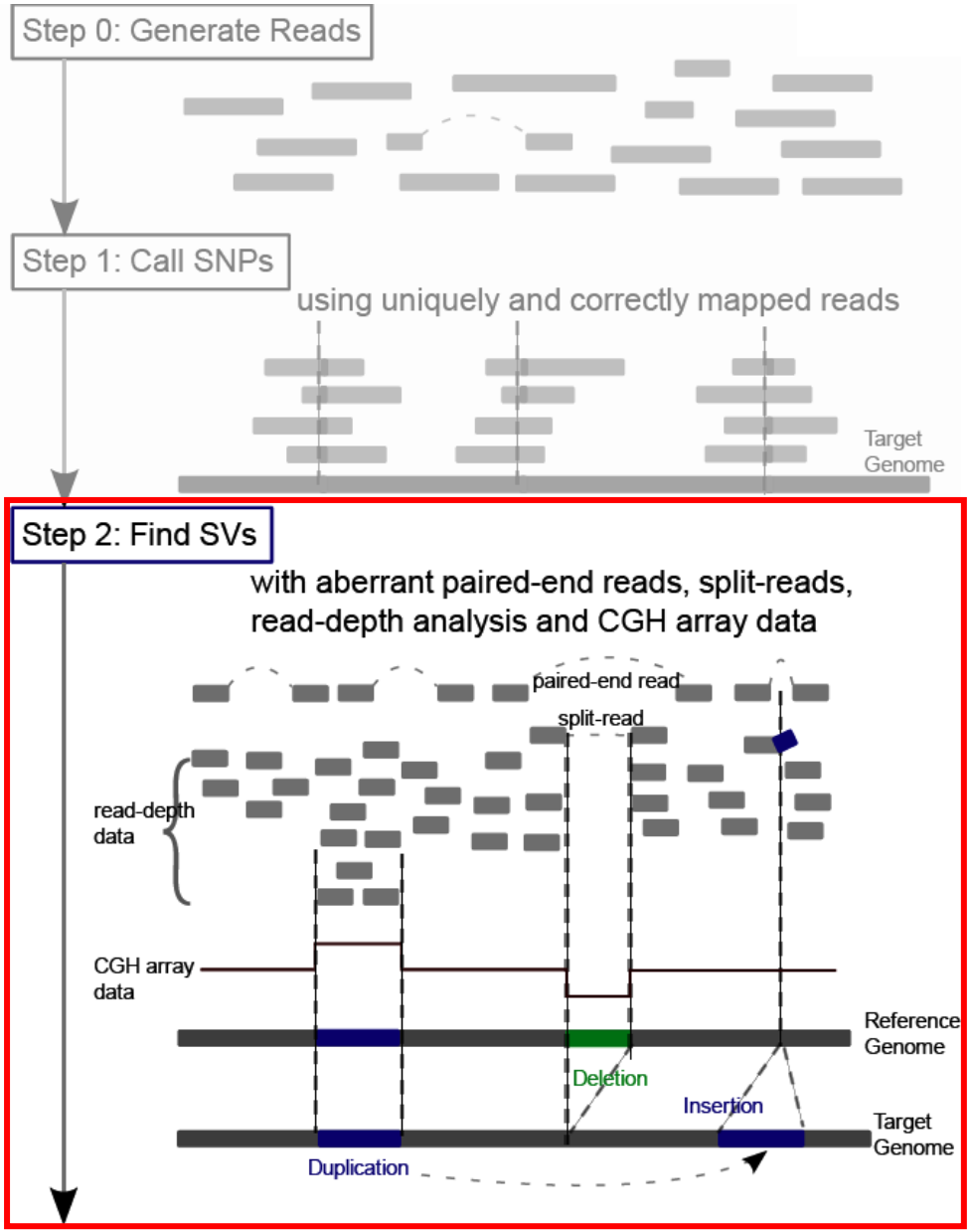
With errors, the calculation is more complicated. (However, the Bayesian formulation becomes more useful.) In general:

$$\boldsymbol{P(D|G) = P_{err\_free}(D|G) + P_{err}(D|G)}$$

[You et al. ('12) Bioinformatics 28: 643 doi: 10.1093/bioinformatics/bts001]

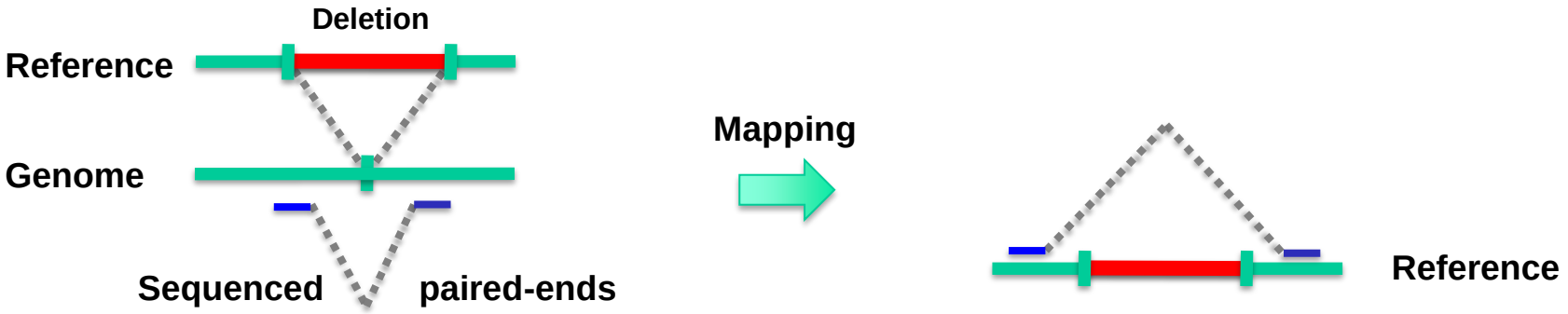
Main Steps in Genome Resequencing

[Snyder et al. Genes & Dev. ('10)]

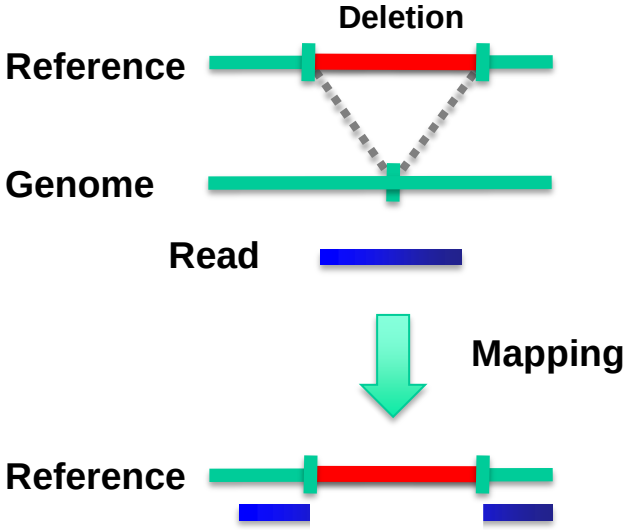


Methods to Find SVs

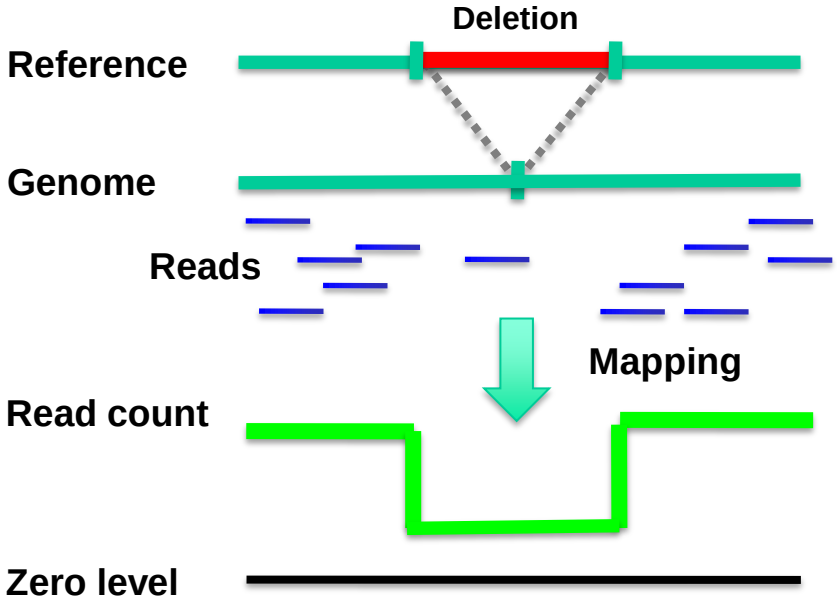
1. Paired ends



2. Split read



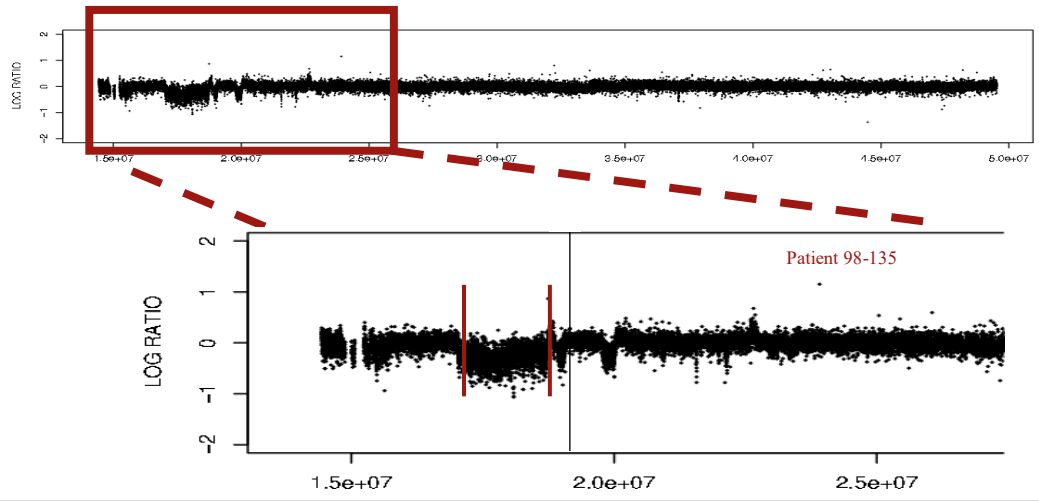
3. Read depth (or aCGH)



4. Local Reassembly

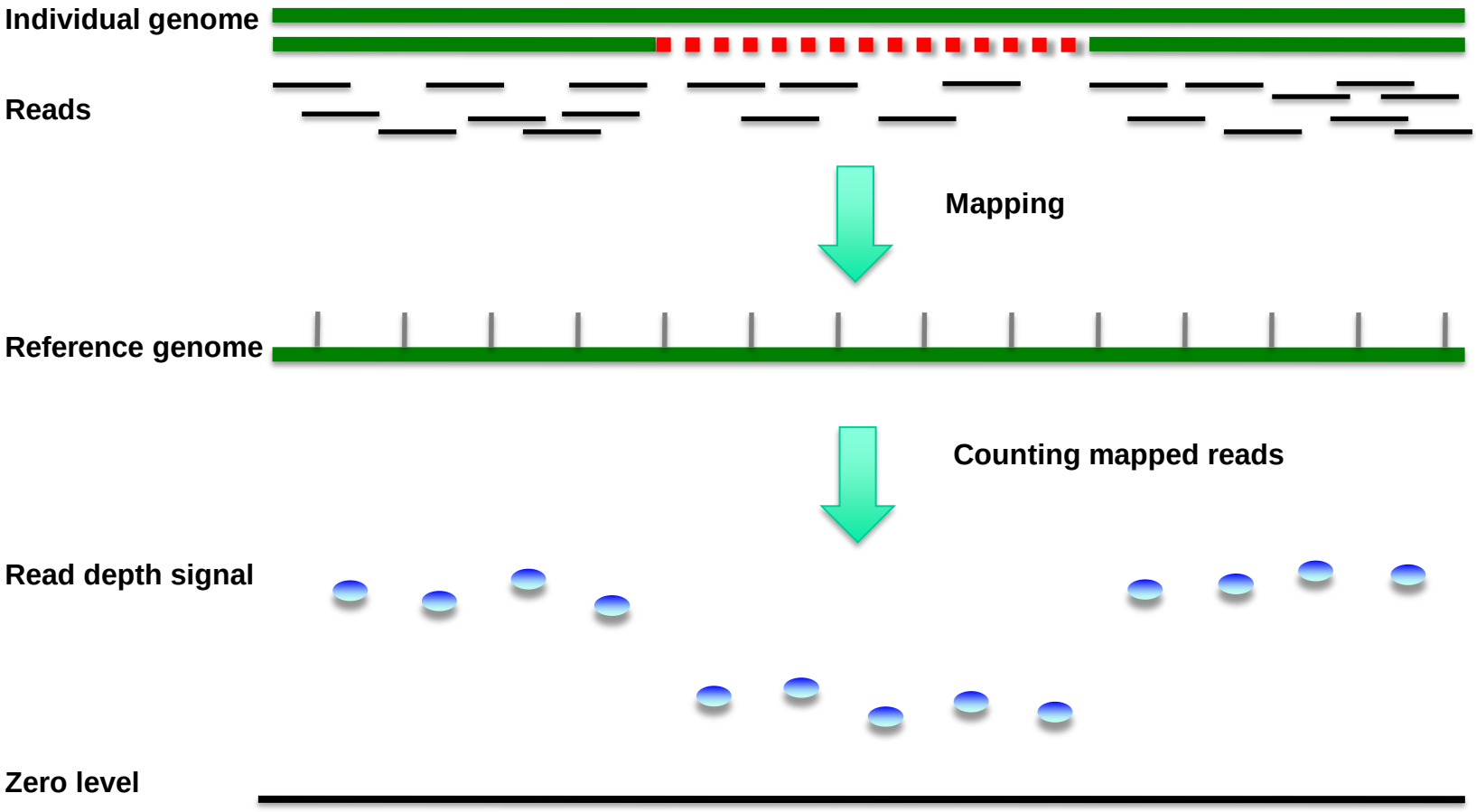
[Snyder et al. Genes & Dev. ('10)]

Read Depth



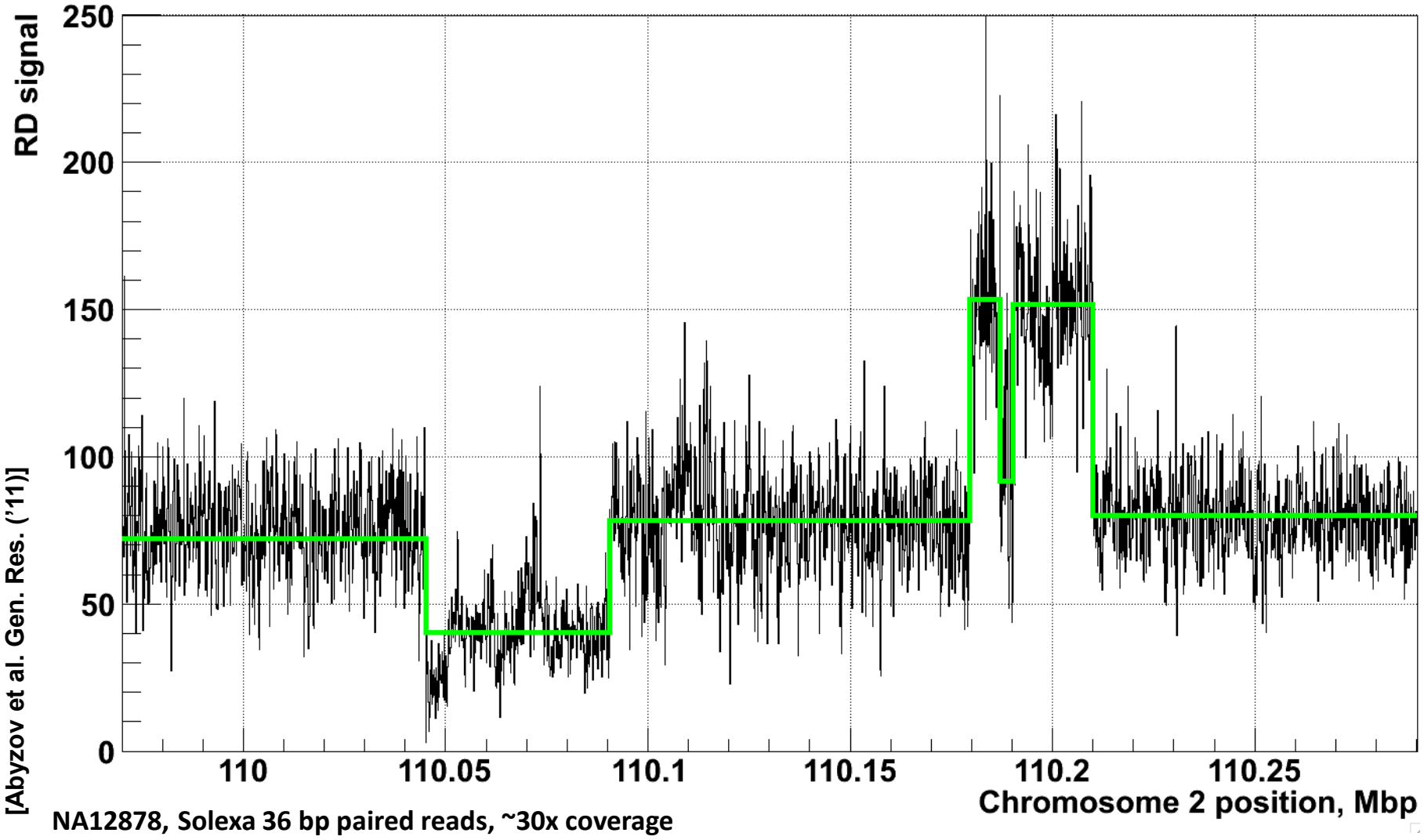
Array Signal

Read depth



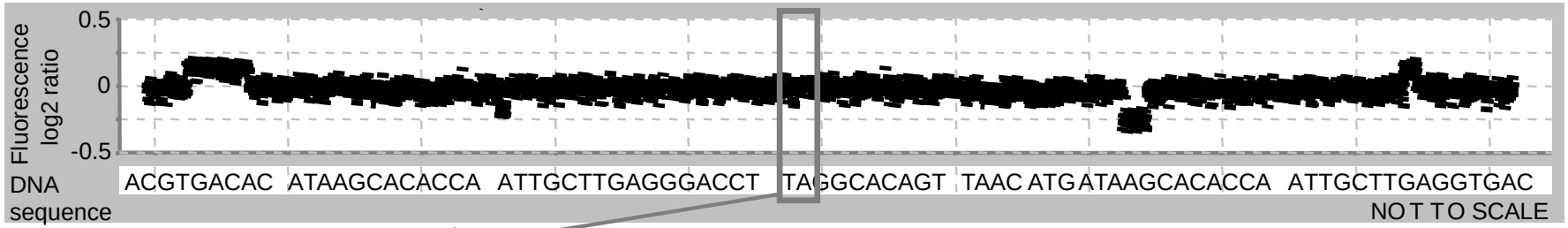
[Urban et al. ('06) PNAS; Wang et al. Gen. Res. ('09); Abyzov et al. Gen. Res. ('11)]

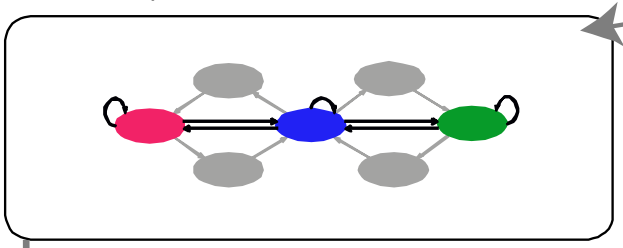
Example of Application to RD data

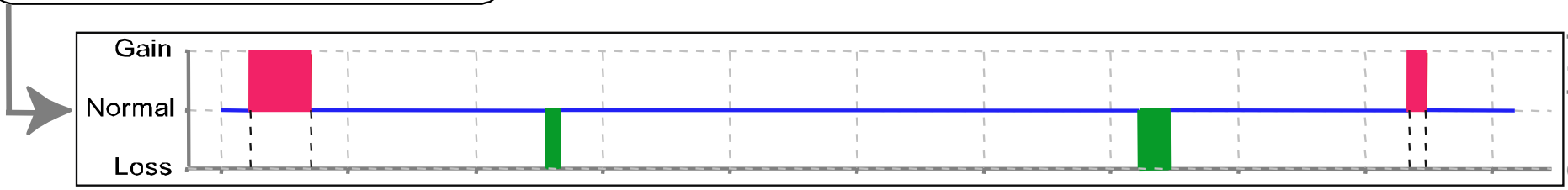


HMM

- To get highest resolution on breakpoints need to smooth & segment the signal
- BreakPtr: prediction of breakpoints, dosage and cross-hybridization using HMMs

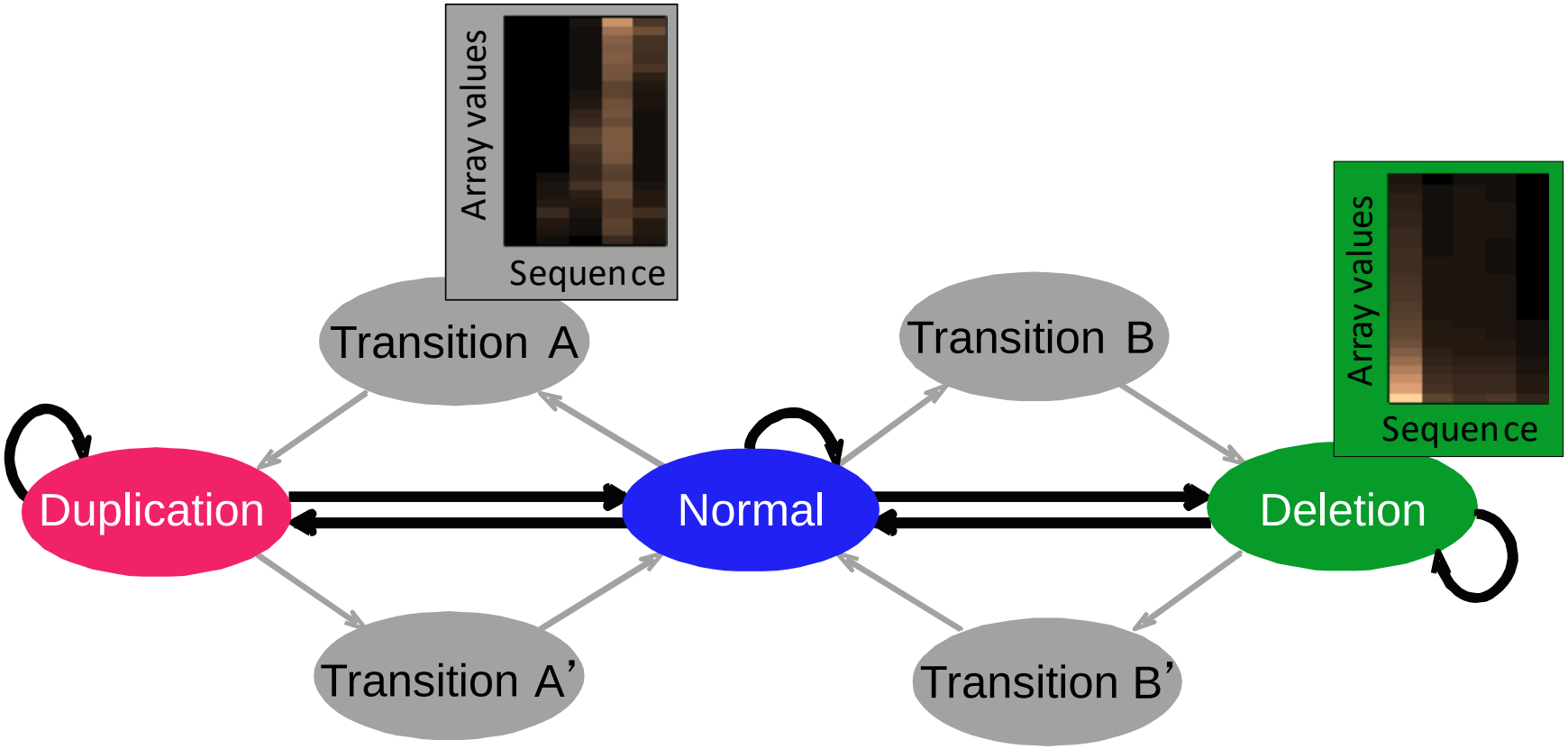






Korbel*, Urban* *et al.*, PNAS (2007)

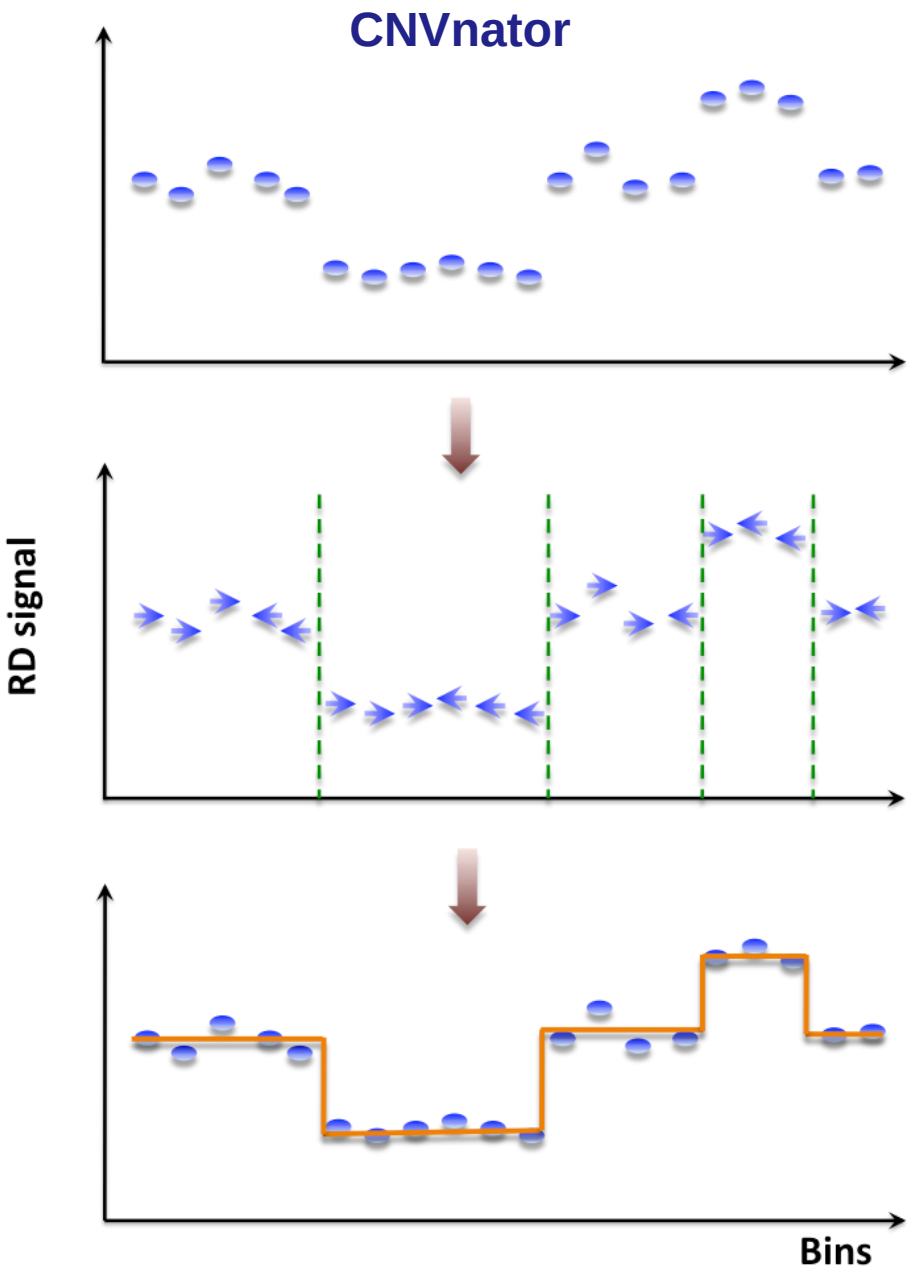
Statistically integrates array signal and DNA sequence signatures (using a discrete-valued bivariate HMM)



Korbel*, Urban* *et al.*, PNAS (2007)

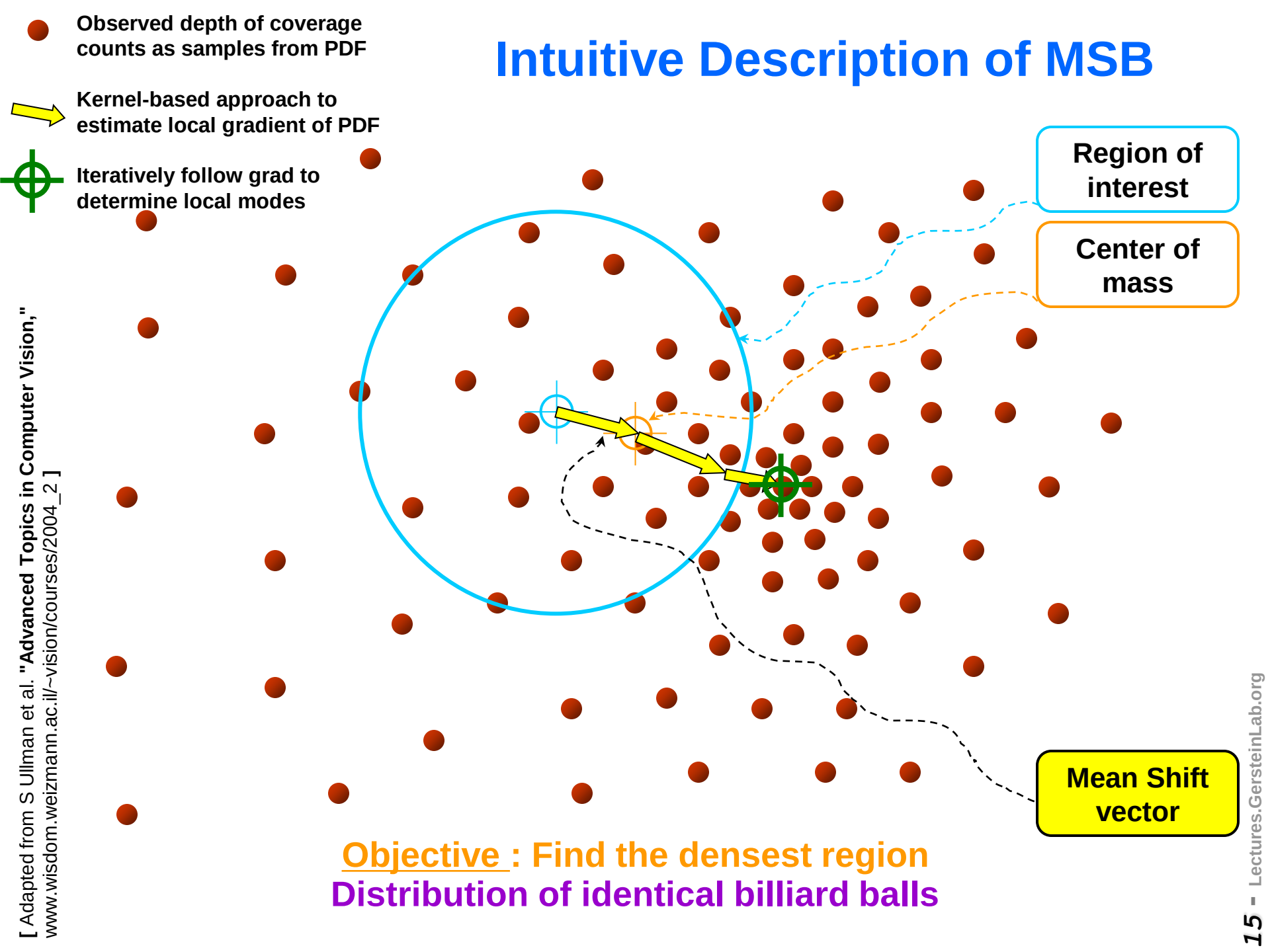
Mean-shift-based (MSB) segmentation: no explicit model

- For each bin attraction (mean-shift) vector points in the direction of bins with most similar RD signal
- No prior assumptions about number, sizes, haplotype, frequency and density of CNV regions
- Not Model-based (e.g. like HMM) with global optimization, distr. assumption & parms. (e.g. num. of segments).
- Achieves discontinuity-preserving smoothing
- Derived from image-processing applications



[Abyzov et al. Gen. Res. ('11)]

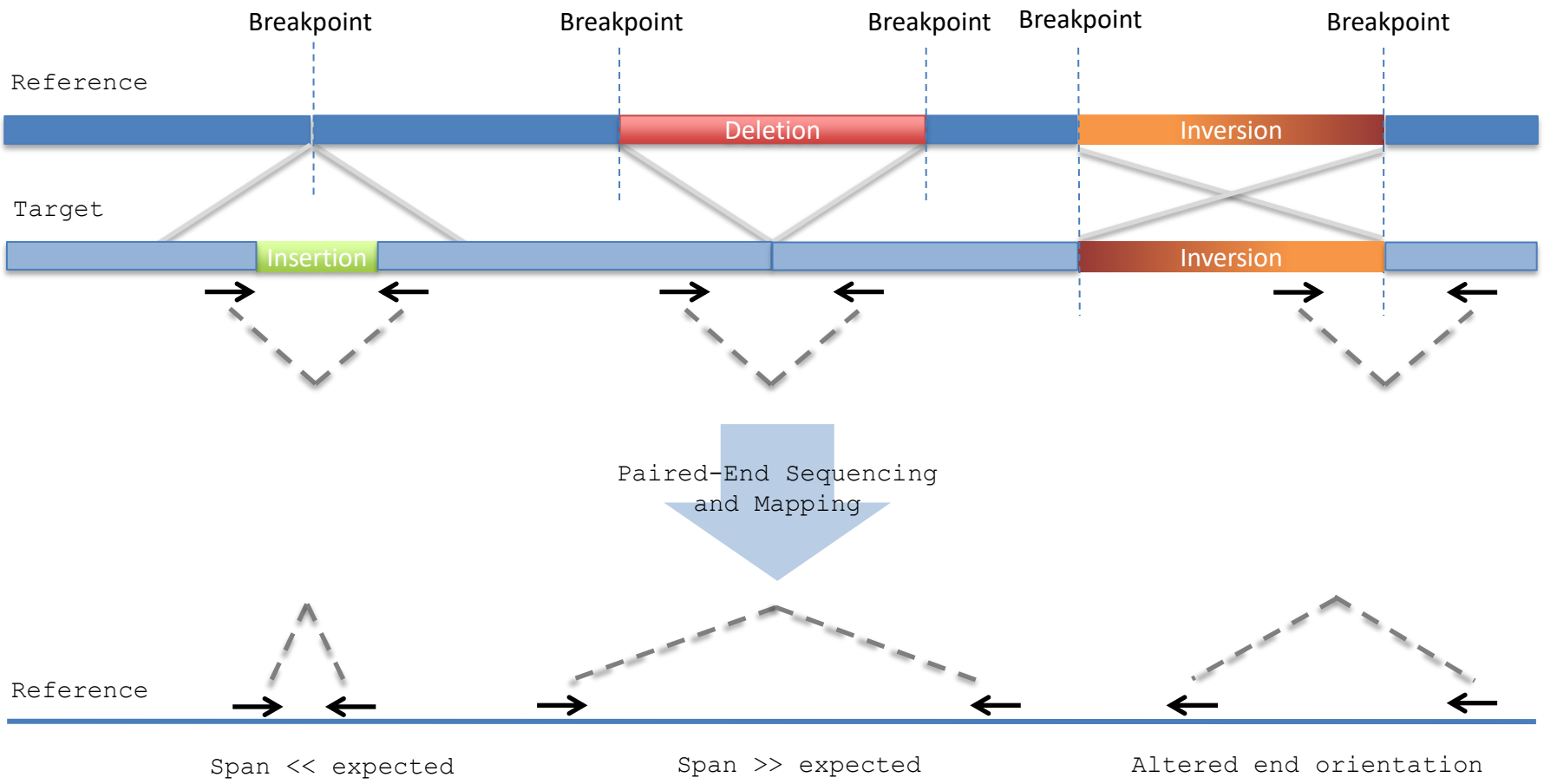
Intuitive Description of MSB



[Adapted from S Ullman et al. **"Advanced Topics in Computer Vision,"** www.wisdom.weizmann.ac.il/~vision/courses/2004_2]

Paired-End

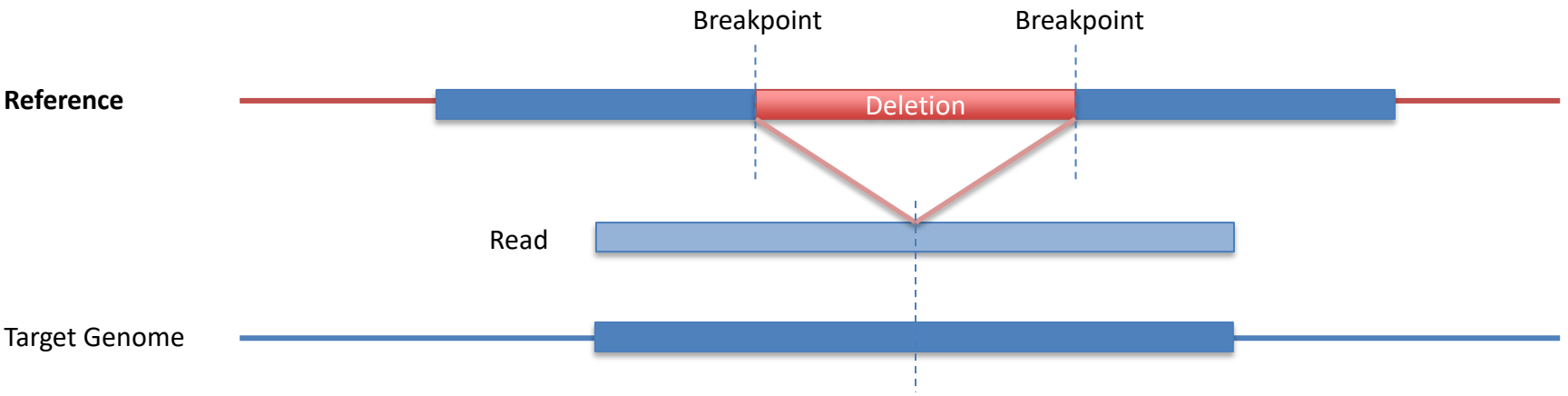
Paired-End Mapping

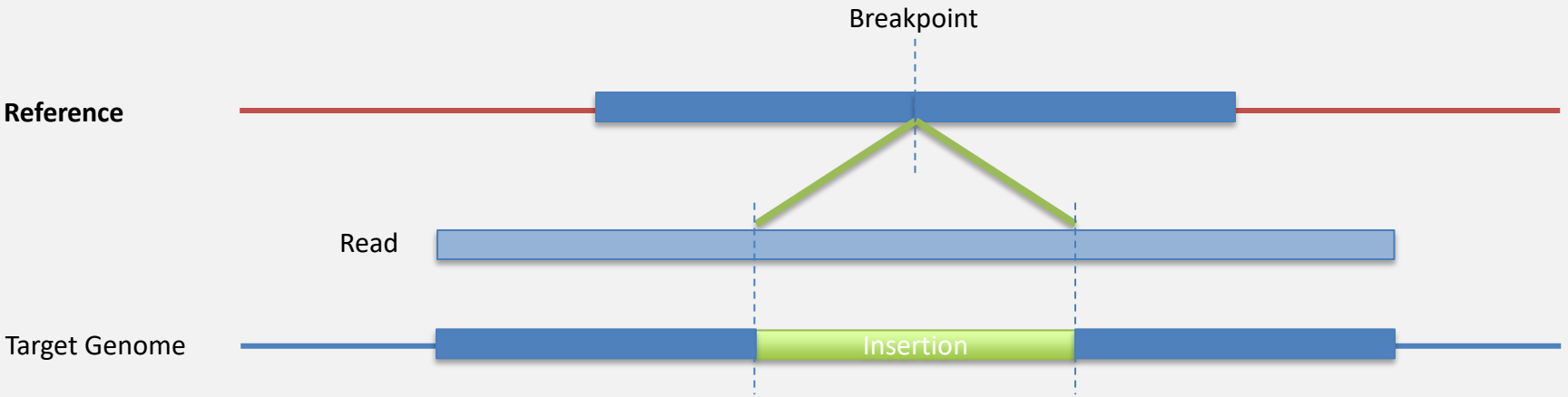


- Both paired-ends map within repeats.
- Limited the distance between pairs; therefore, neither large nor very small rearrangements can be detected

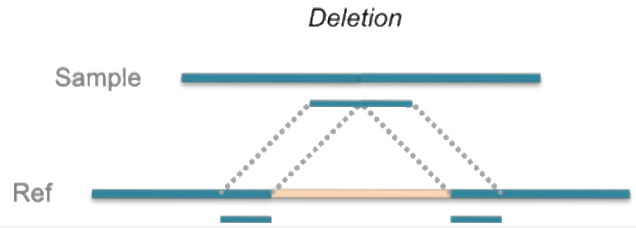
Split Read

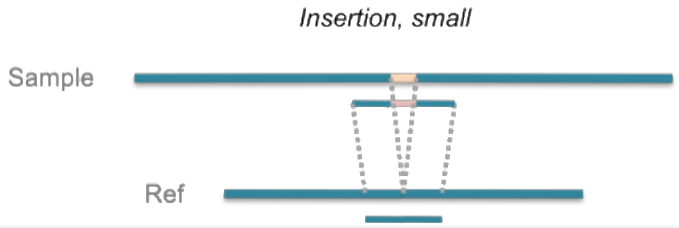
Split-read Analysis

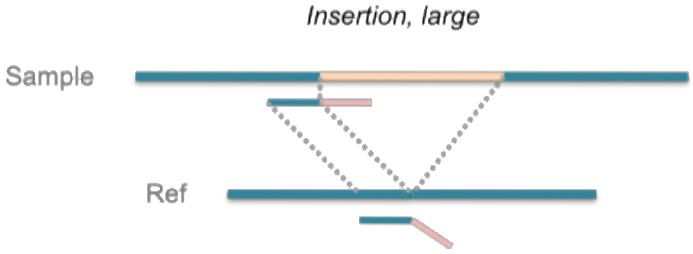




Simple SVs

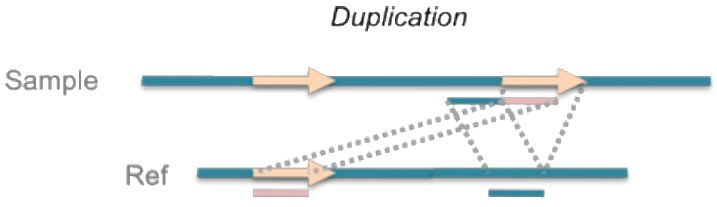


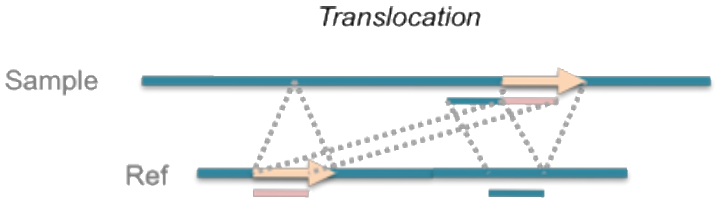


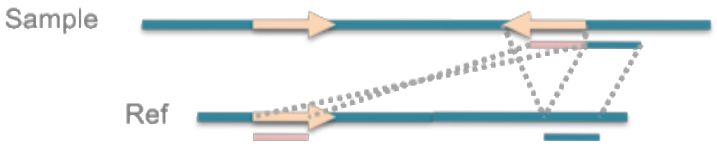


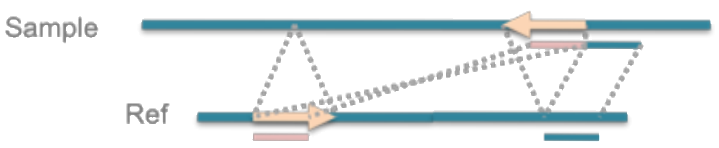
Deletions are the Easiest to Identify

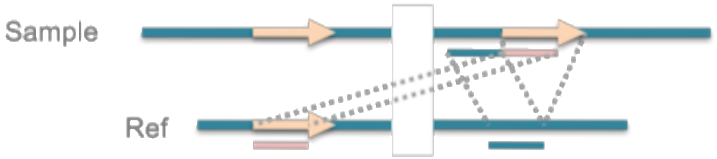
Complex SVs

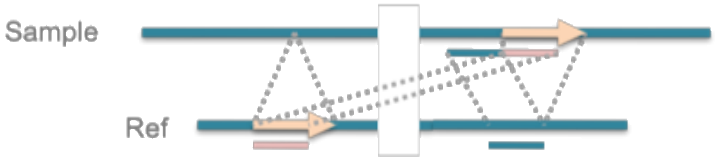








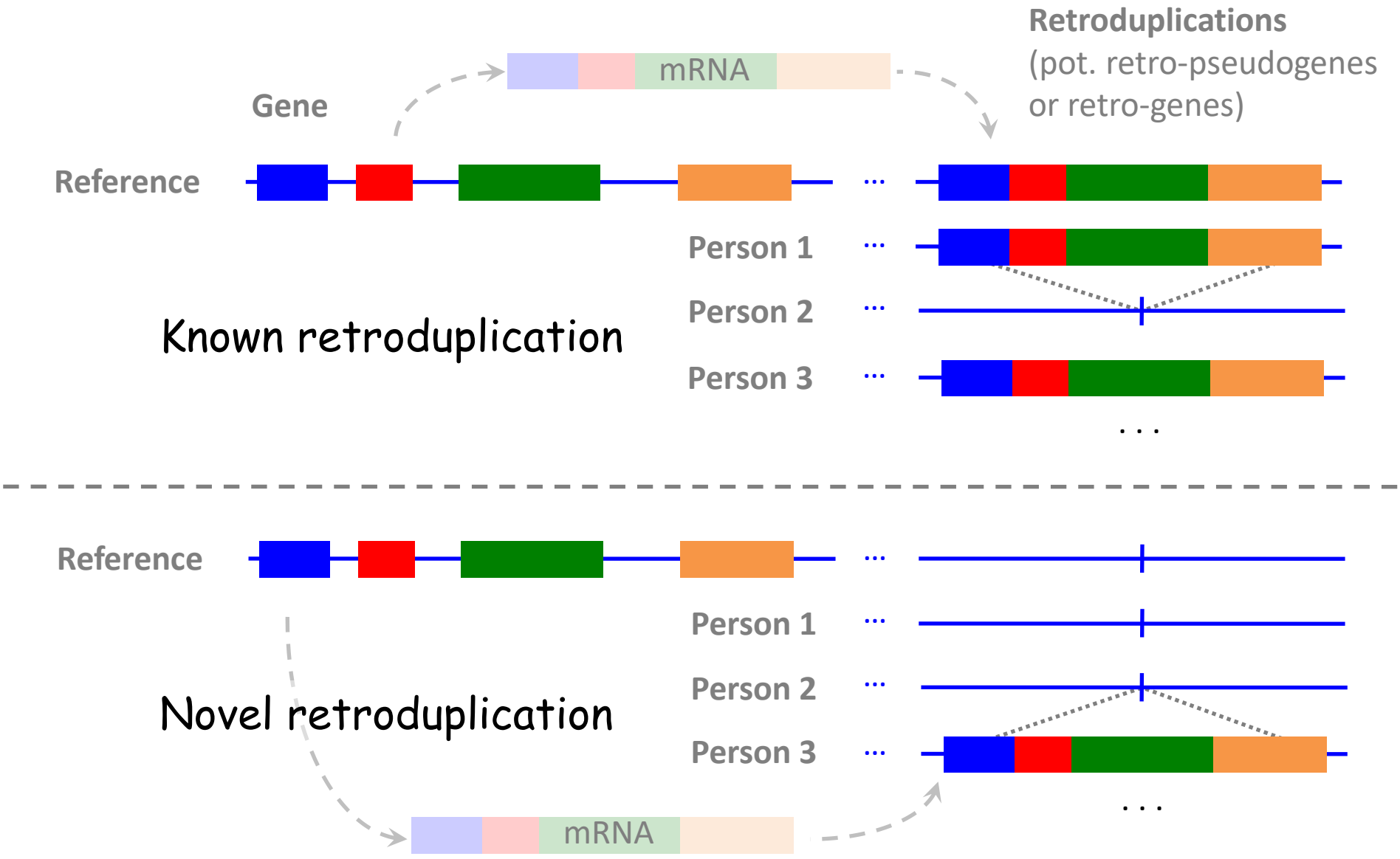




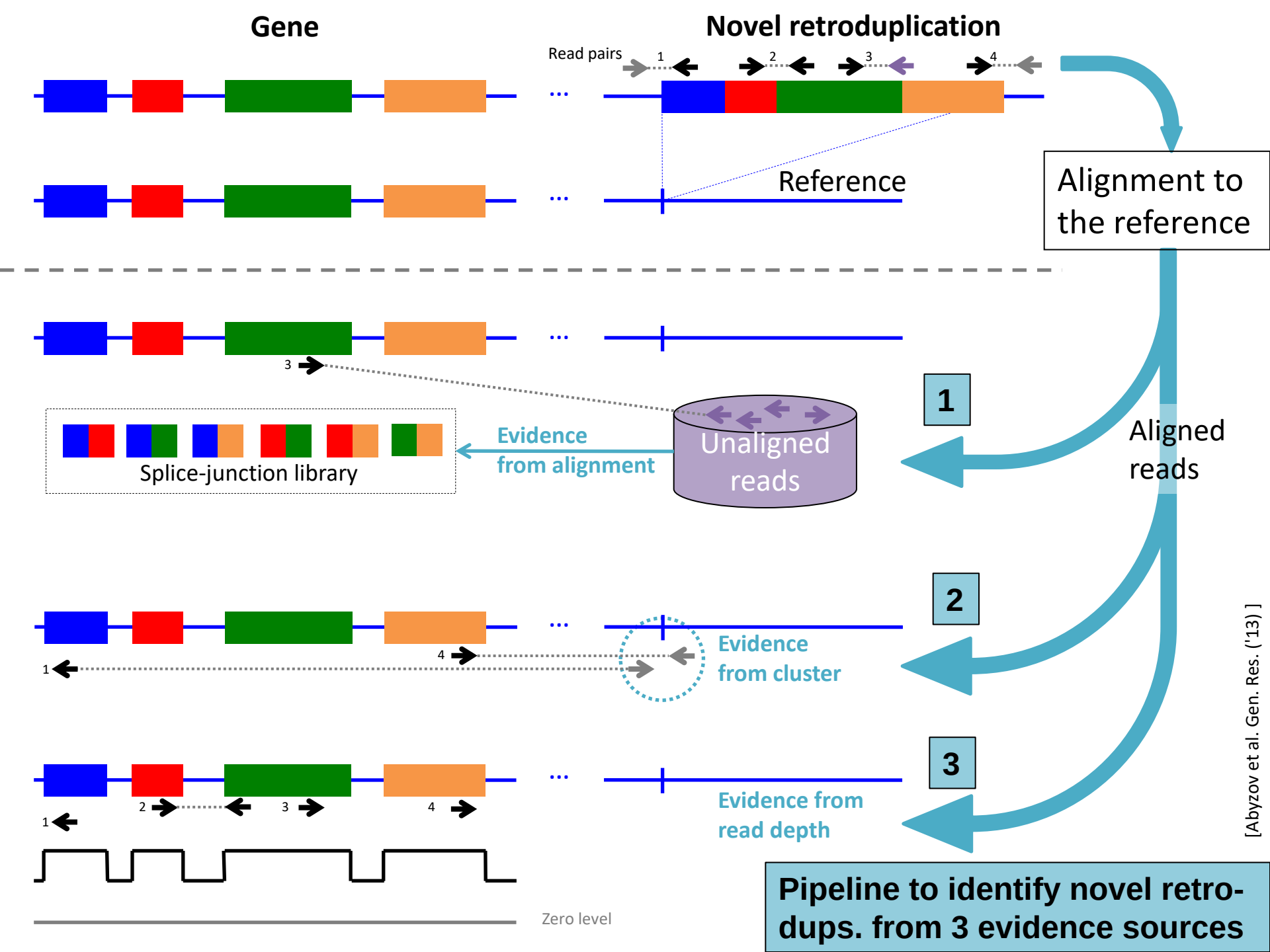
[Zhang et al. ('11) *BMC Genomics*]

RDV & Mobile Elements

Retroduplication variation (RDV)



[Abyzov et al. Gen. Res. ('13)]


Gene
Novel retroduplication
Read pairs
1
2
3
4
Reference
Alignment to the reference
Aligned reads
1
Unaligned reads
Evidence from alignment
Splice-junction library
2
Evidence from cluster
3
Evidence from read depth
Zero level
[Abyzov et al. Gen. Res. ('13)]
Pipeline to identify novel retro-dups. from 3 evidence sources