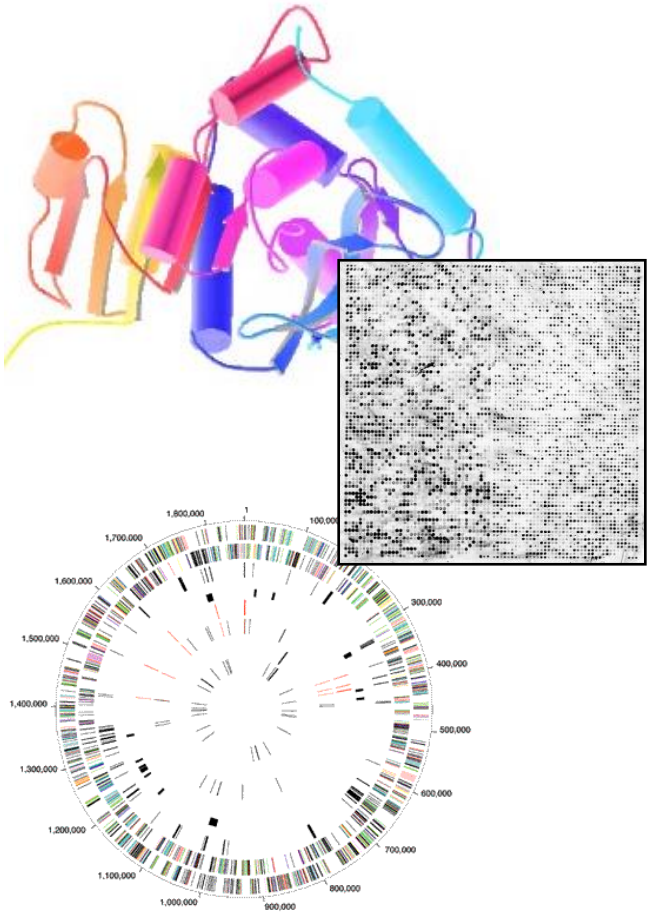
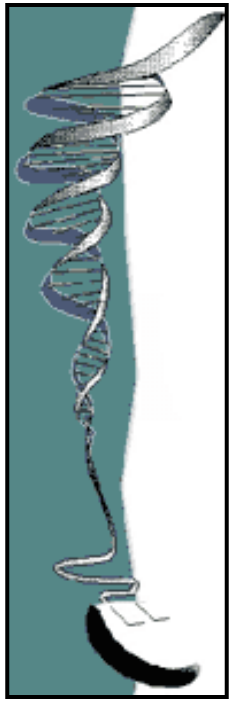
Biomed. Data Sci:

# Variant Identification, Focusing on SVs





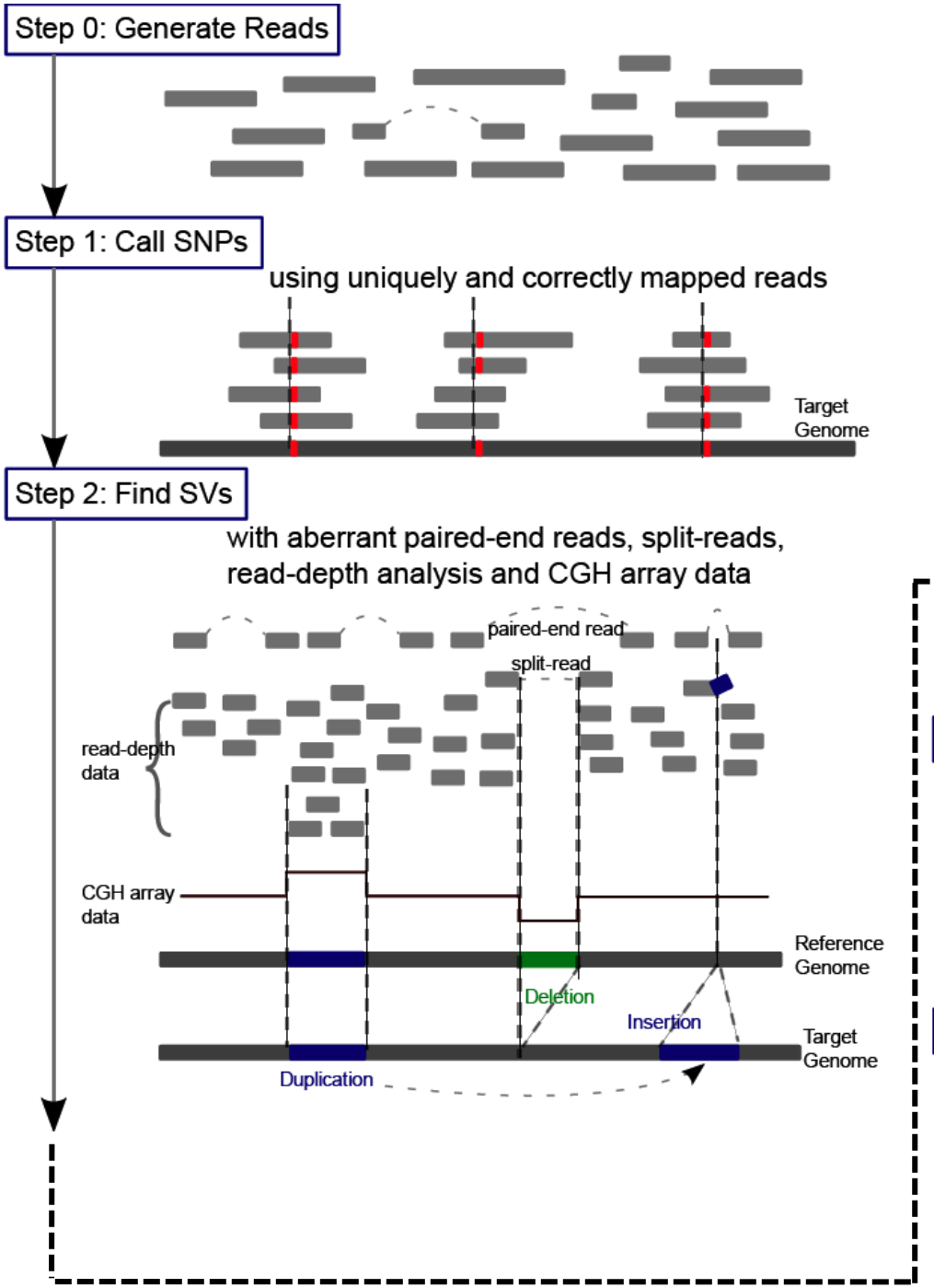
Mark Gerstein, Yale University

gersteinlab.org/courses/452

(Last edit in spring ’22; pack 22m6a has a slight edit on slide 6 relative to M6a)

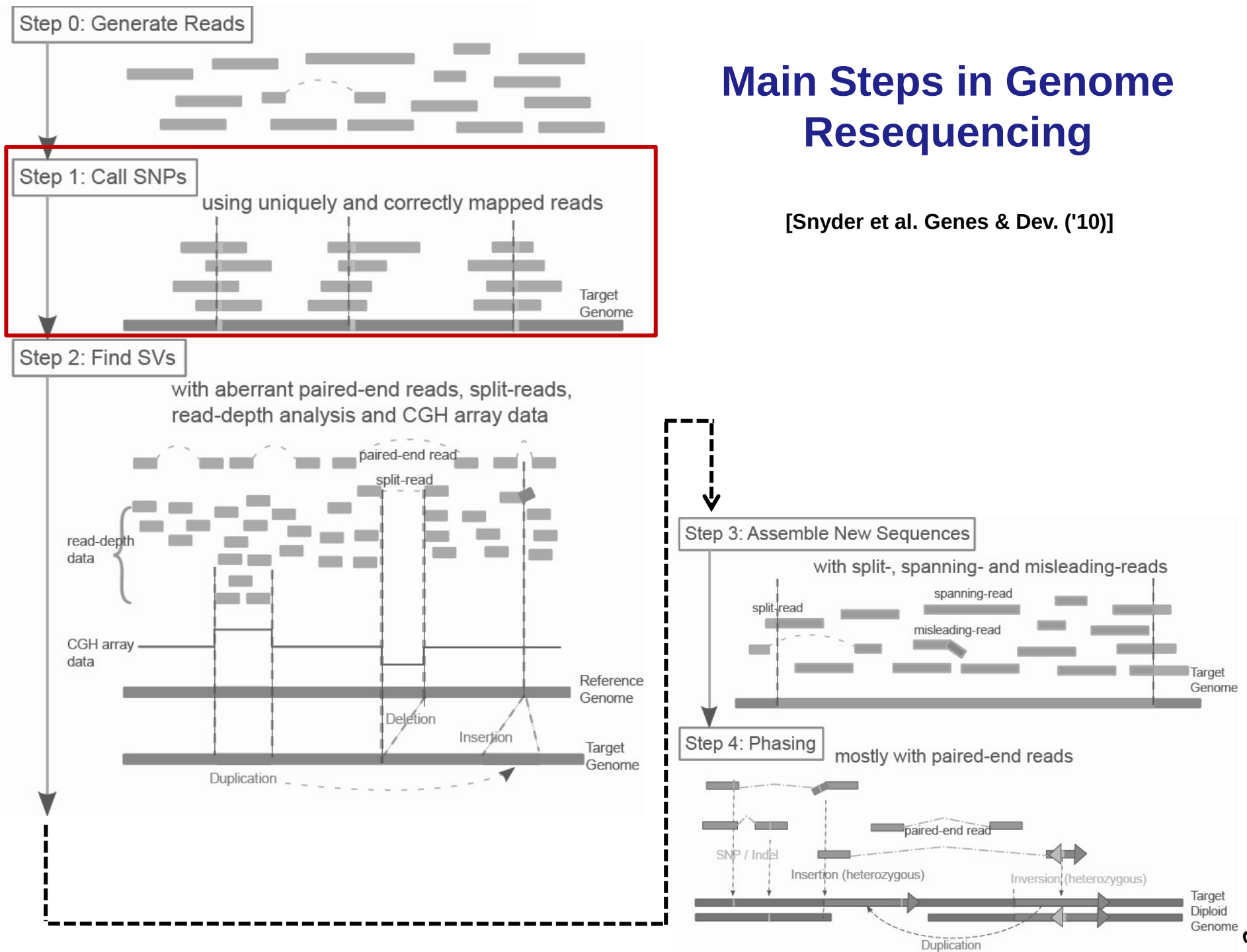
# Main Steps in Genome Resequencing

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

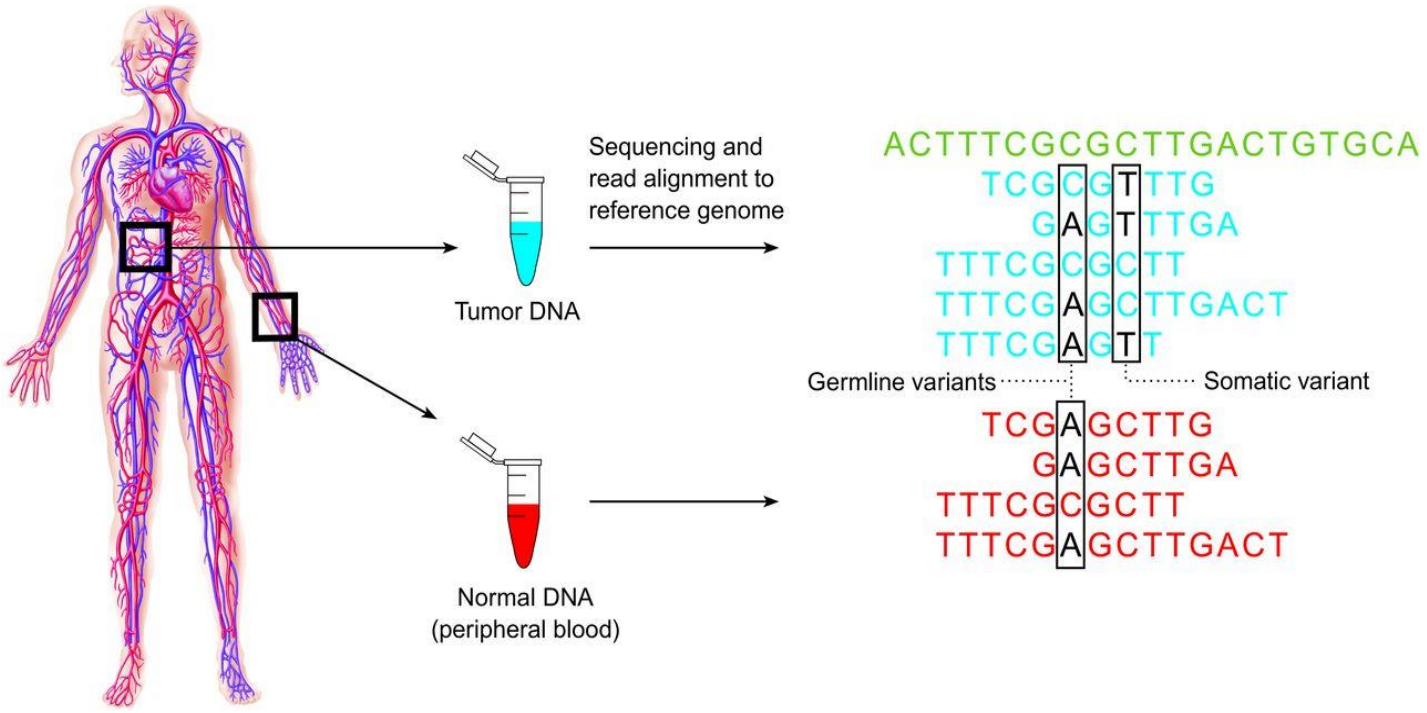


# Main Steps in Genome Resequencing

**[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 $i$th 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.

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

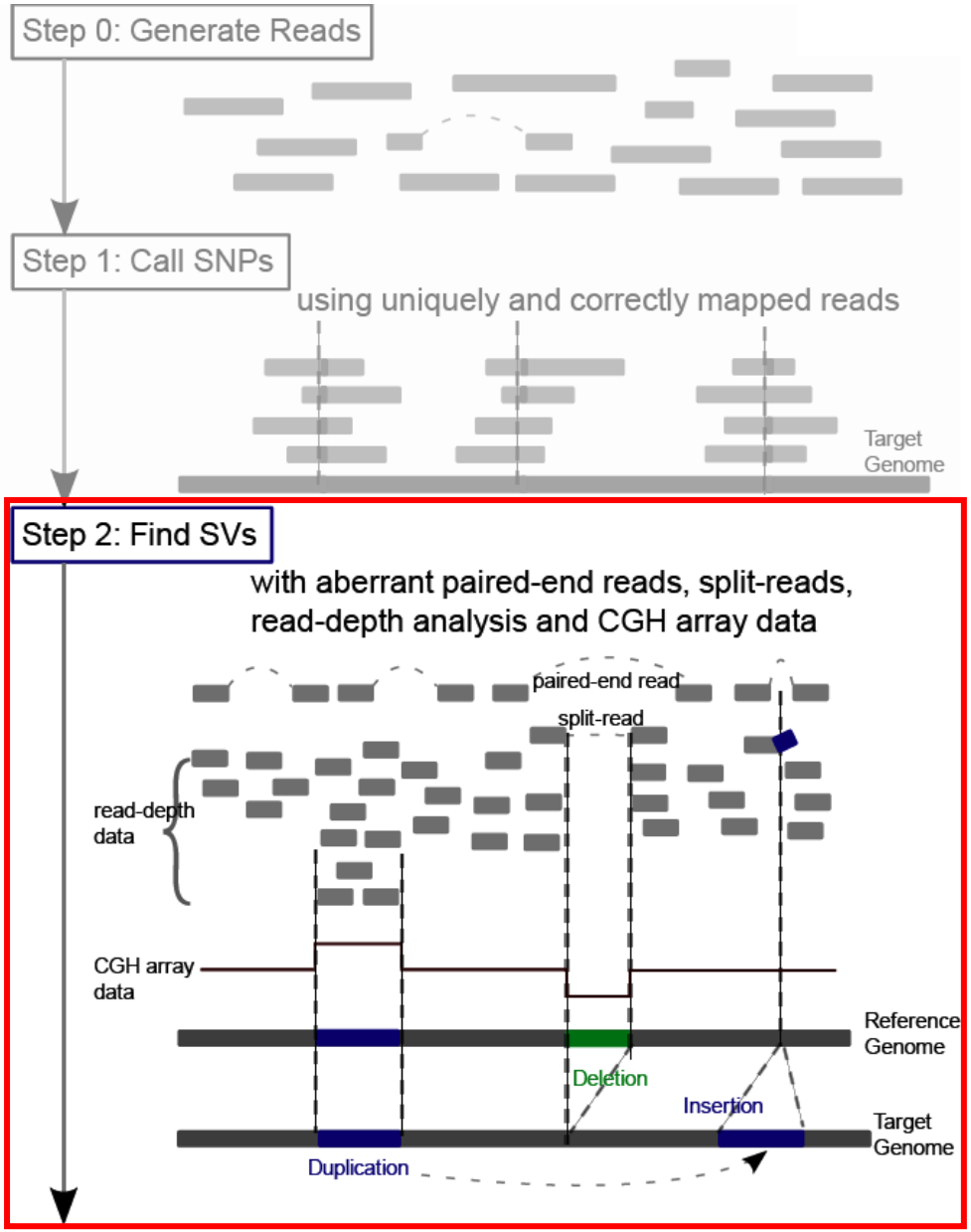
With errors, the calculation is more complicated. (However, the Bayesian formulation becomes more useful.) In general:

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

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

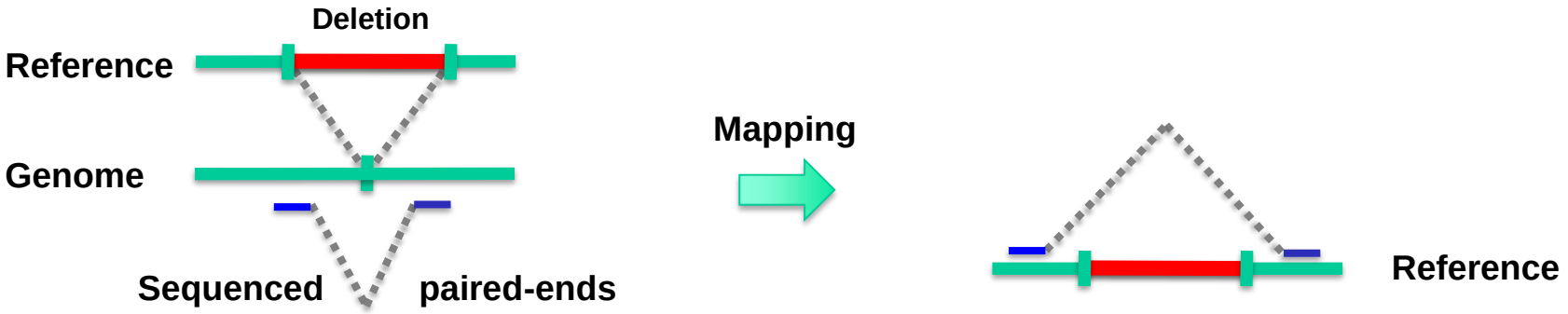
# Main Steps in Genome Resequencing

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

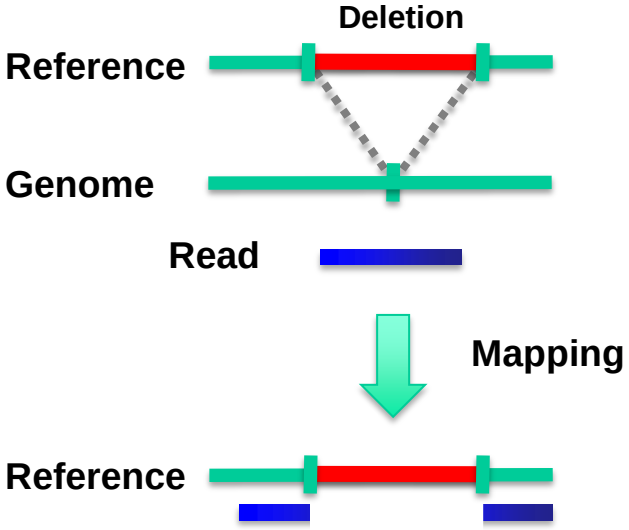


# Methods to Find SVs

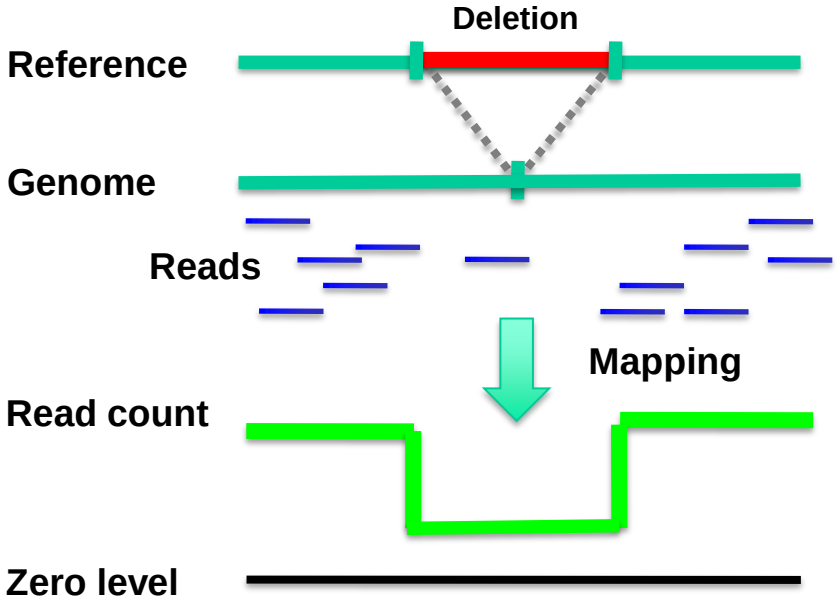
## 1. Paired ends




## 2. Split read



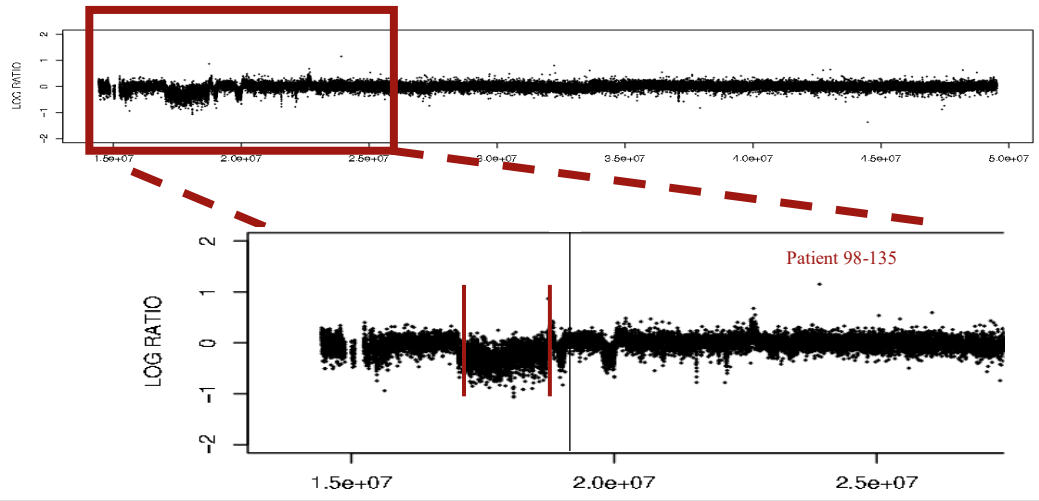

## 3. Read depth (or aCGH)




## 4. Local Reassembly

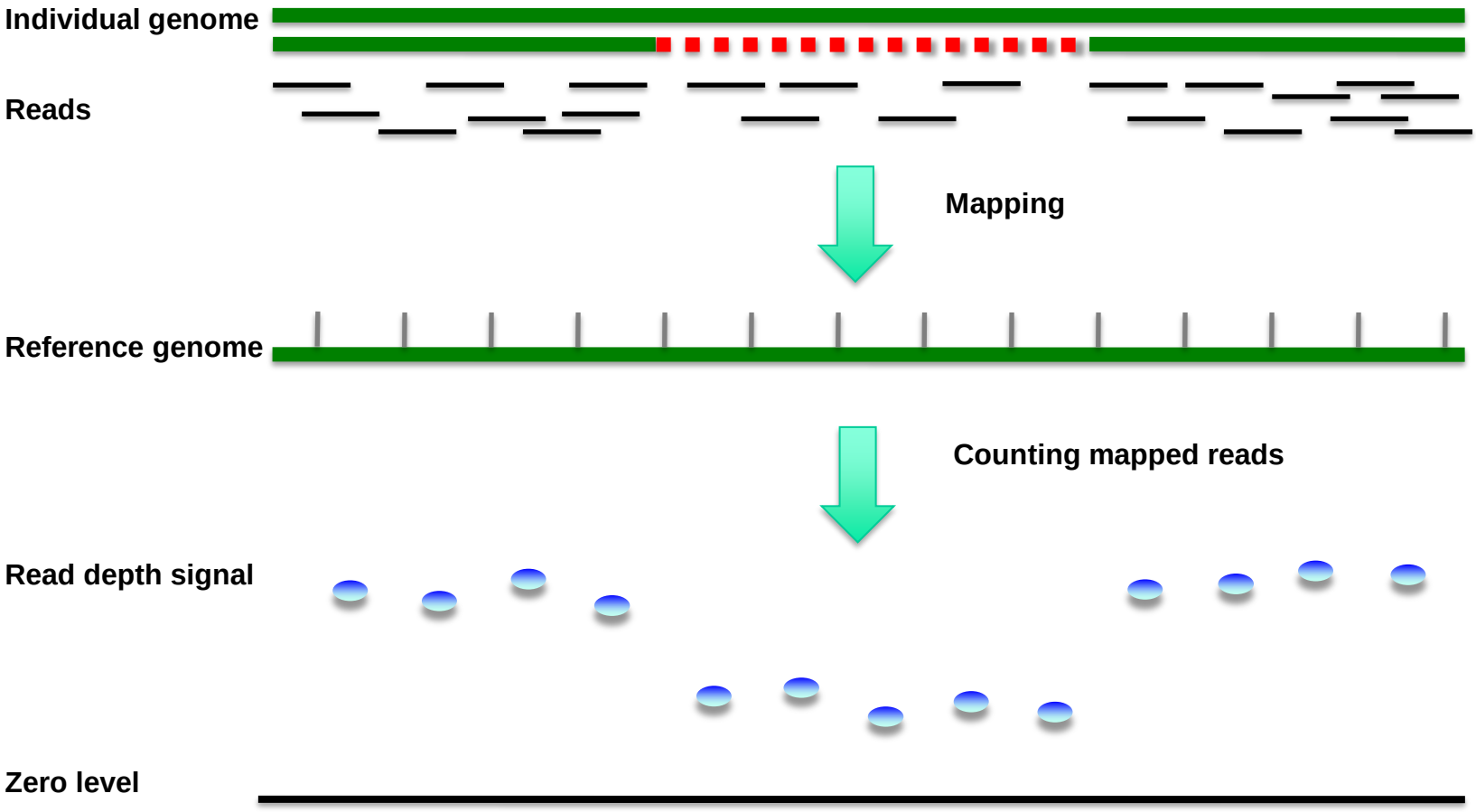
[Snyder et al. Genes & Dev. ('10)]

# Read Depth



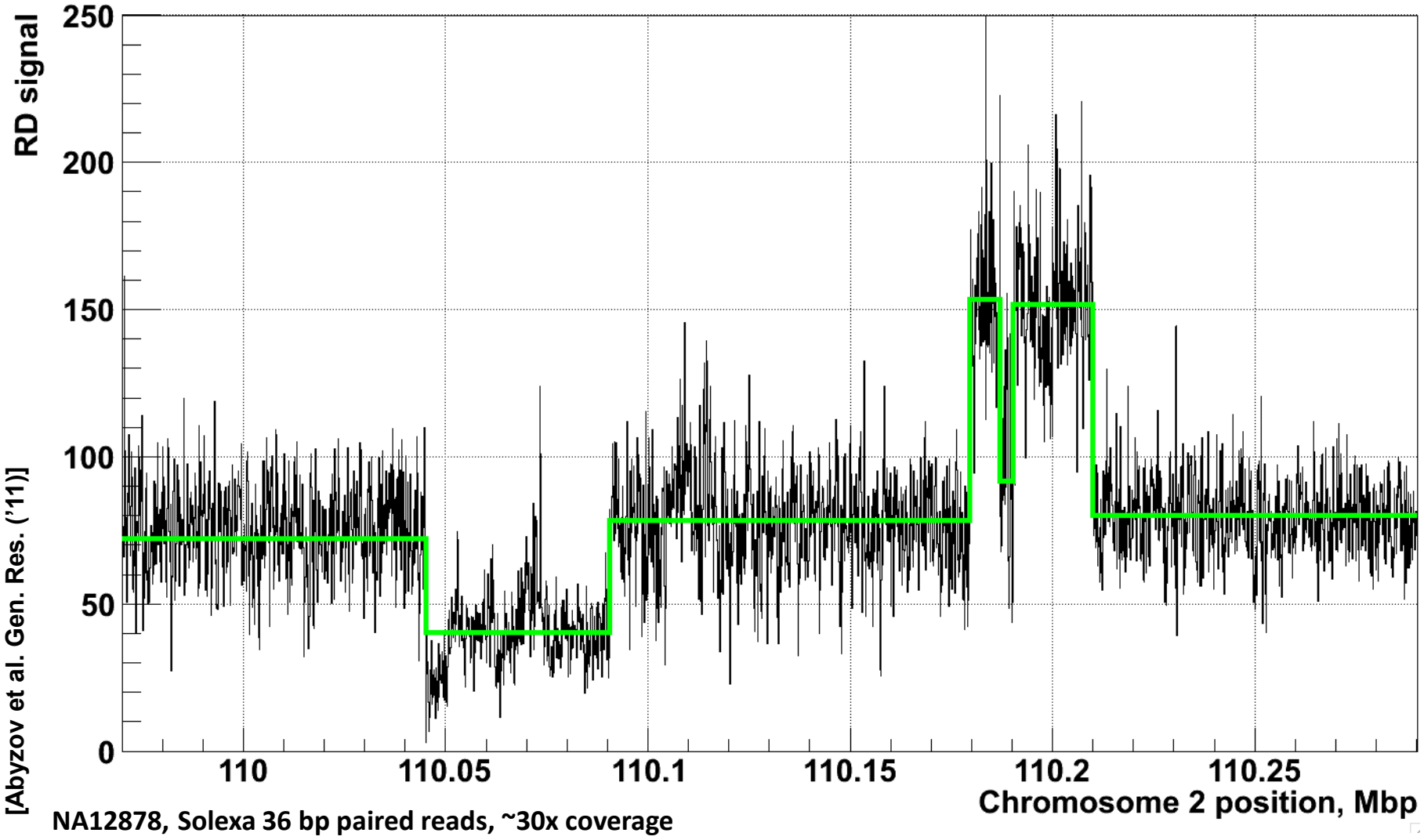

# Array Signal

# Read depth



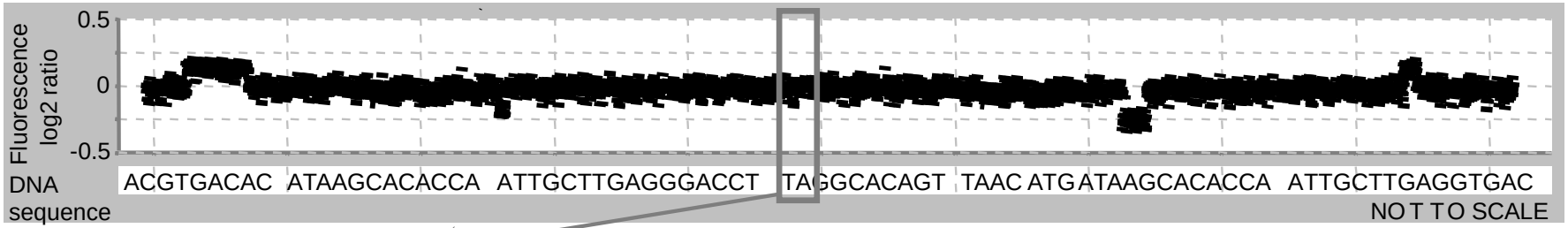

[Urban et al. ('06) PNAS; Wang et al. Gen. Res. ('09); Abyzov et al. Gen. Res. ('11)]

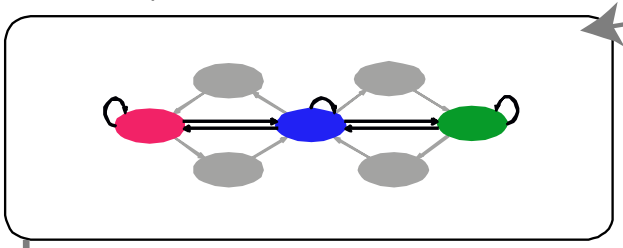
# Example of Application to RD data

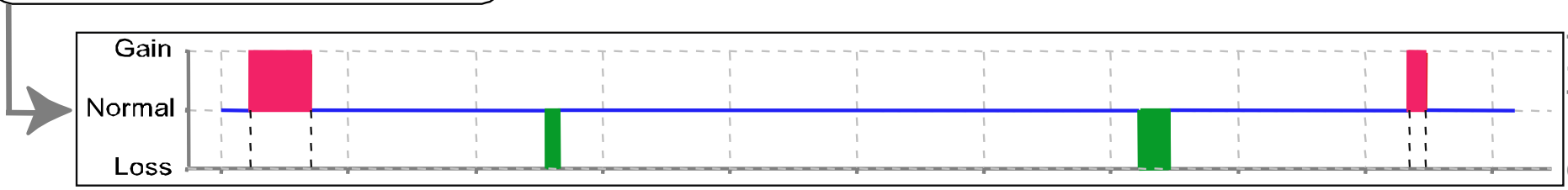


# HMM

- To get highest resolution on breakpoints need to smooth & segment the signal
- BreakPtr: prediction of breakpoints, dosage and cross-hybridization using a system based on Hidden Markov Models

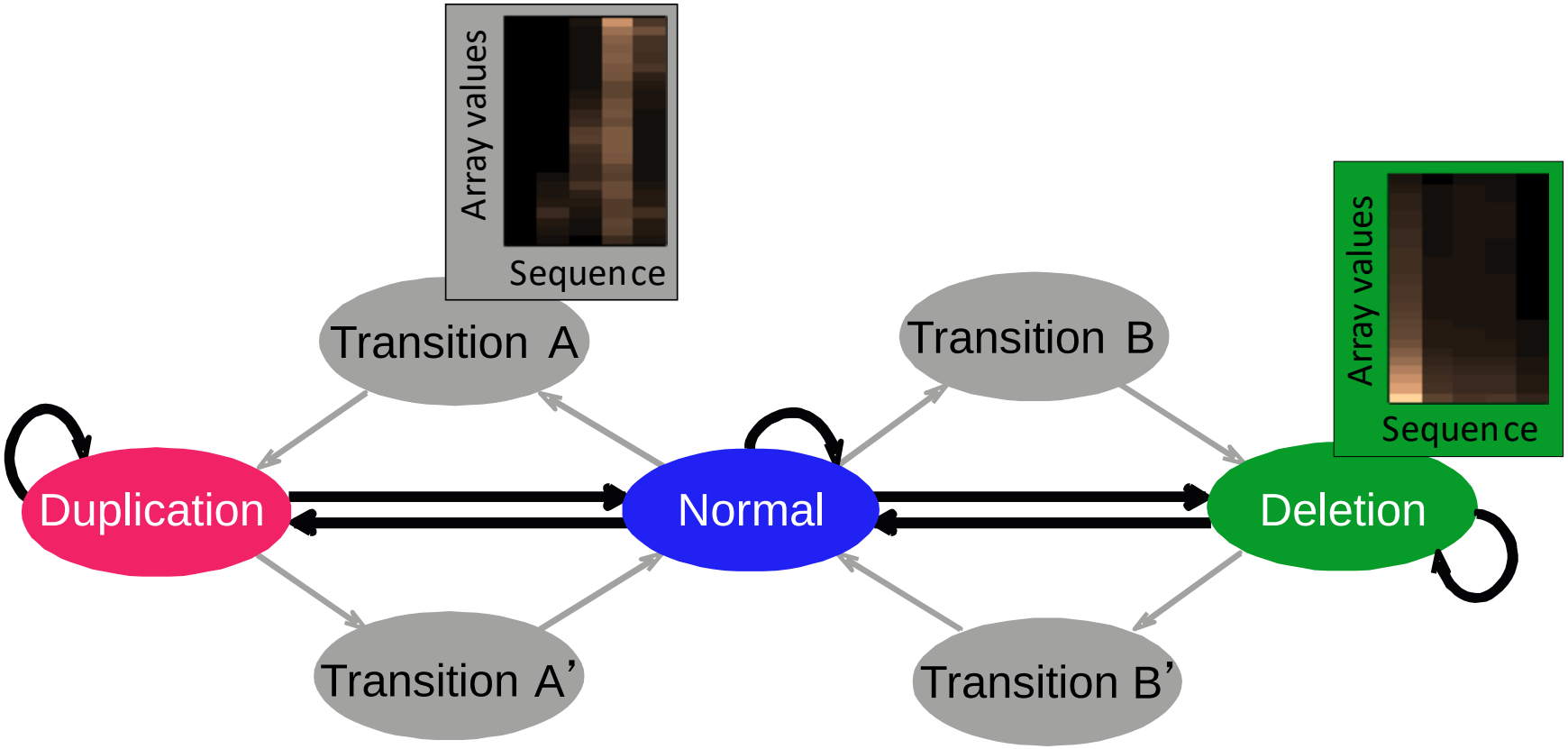





Korbel*, Urban* *et al.*, PNAS (2007)

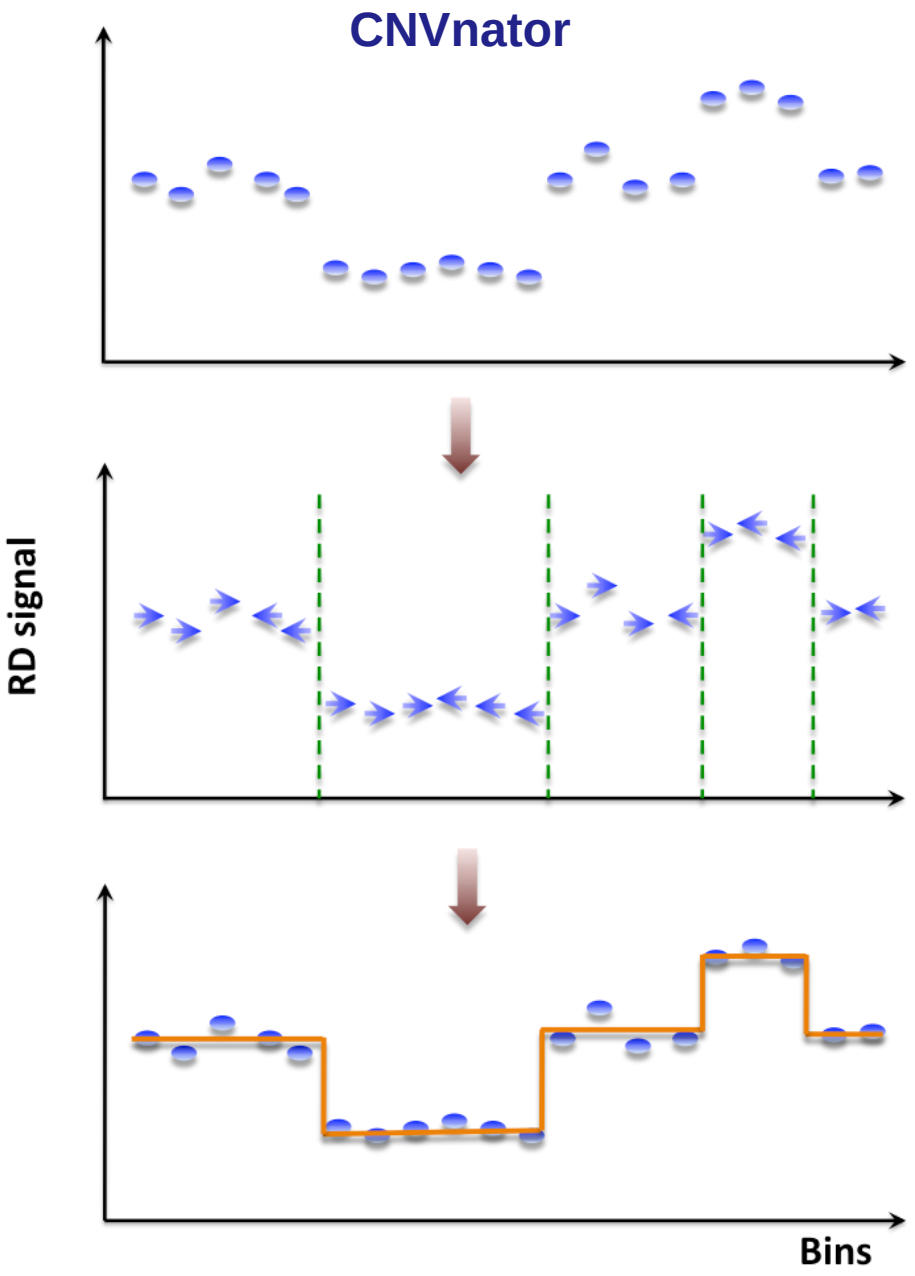
# Statistically integrates array signal and DNA sequence signatures (using a discrete-valued bivariate HMM)




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

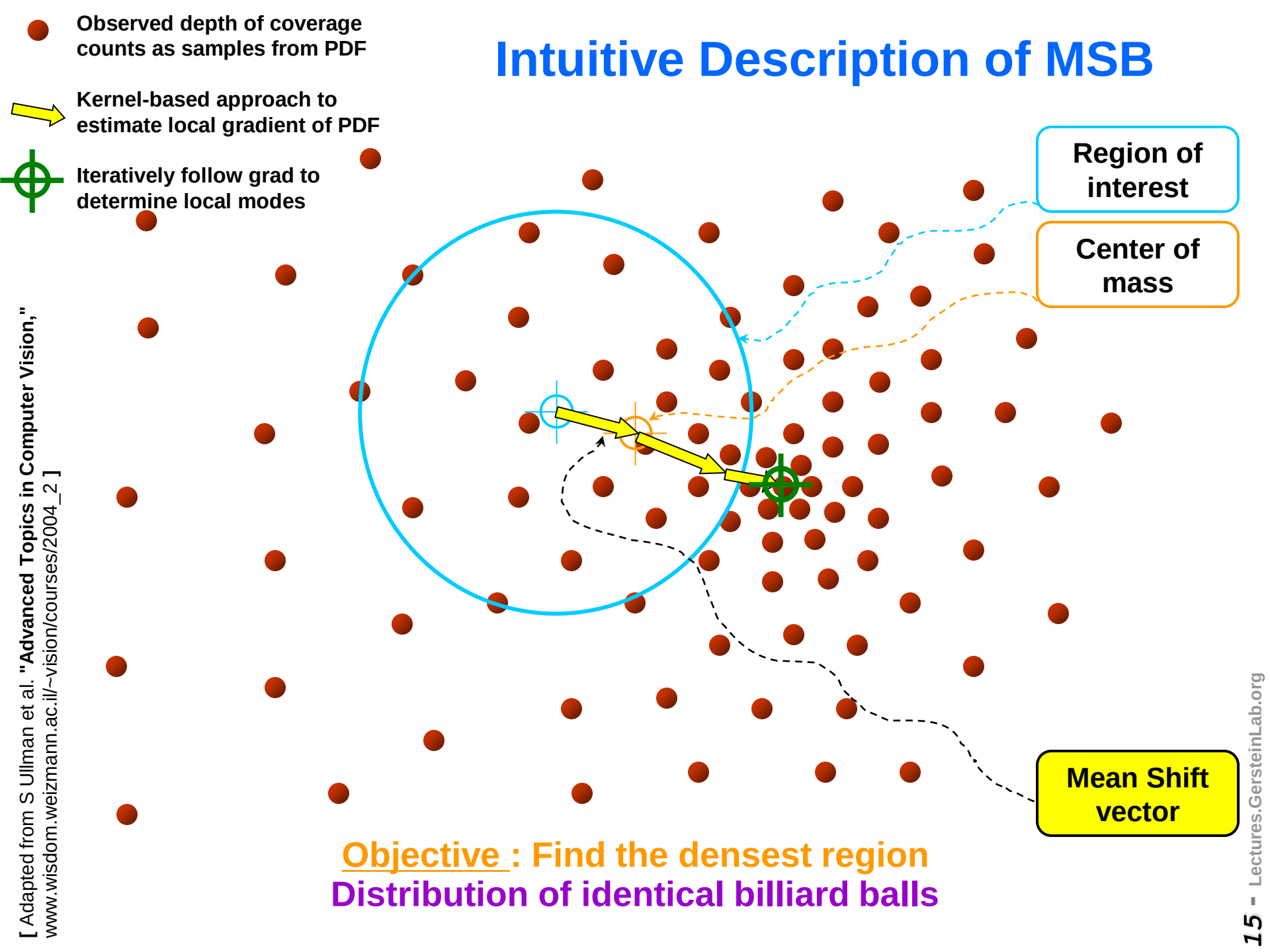
# Mean-shift-based (MSB) segmentation: no explicit model

- 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)]

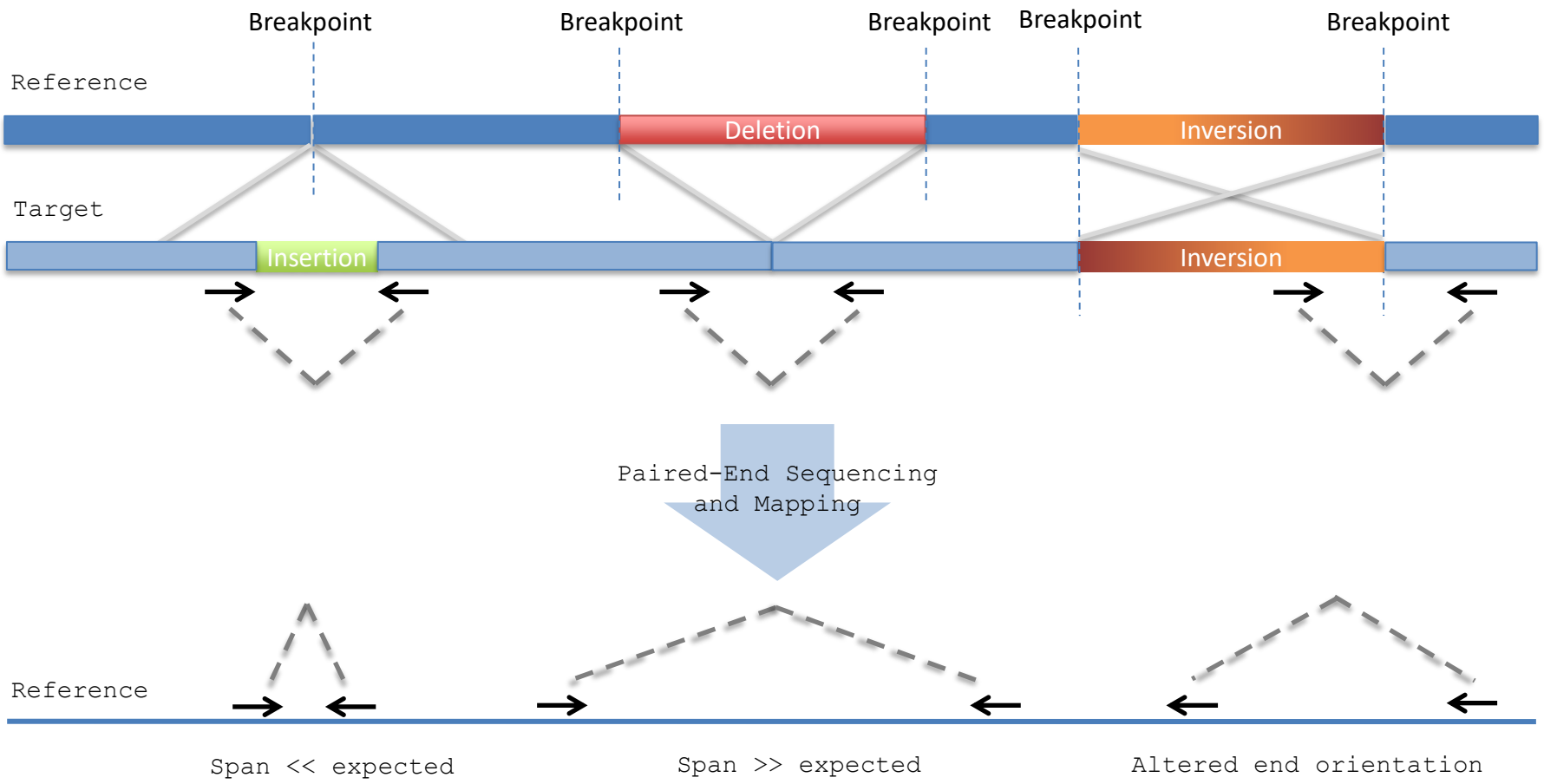
# Intuitive Description of MSB




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

# Paired-End

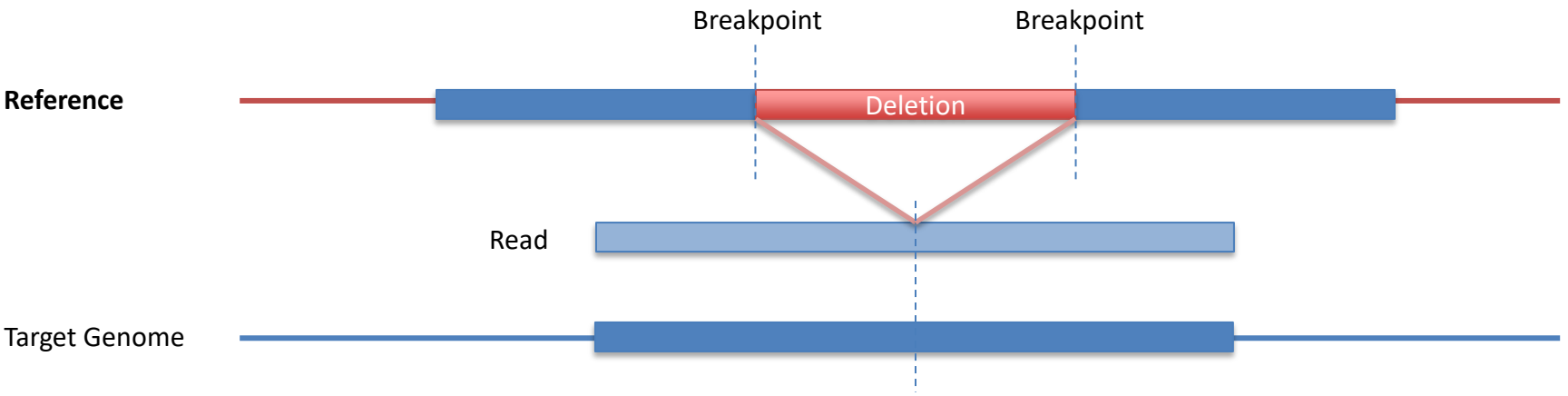
# Paired-End Mapping

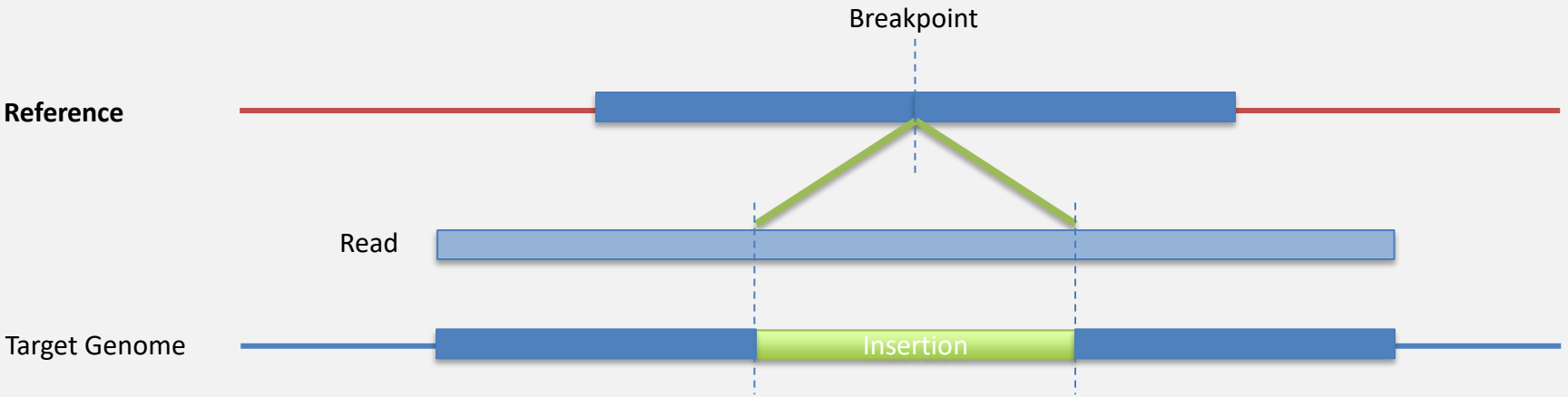



- Both paired-ends map within repeats.
- Limited the distance between pairs; therefore, neither large nor very small rearrangements can be detected

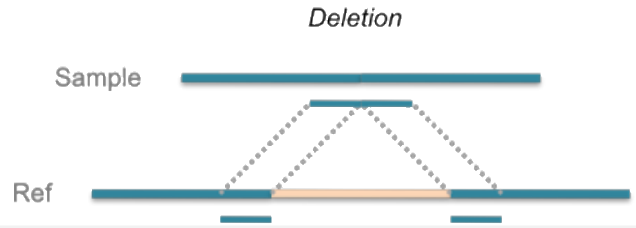
# Split Read

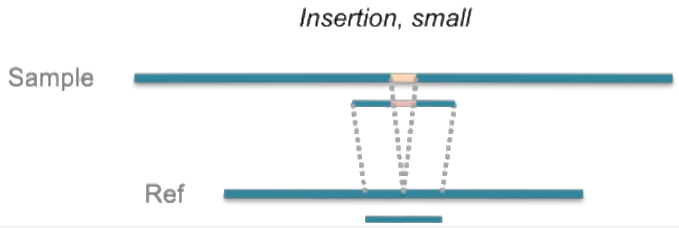
# Split-read Analysis

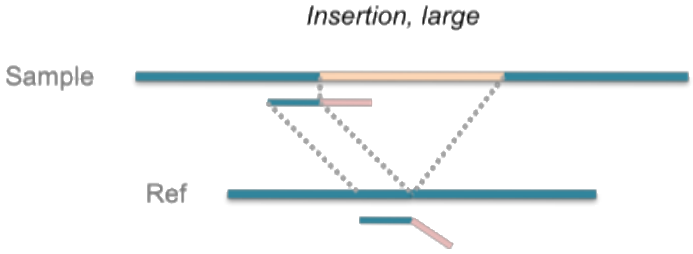


Simple SVs

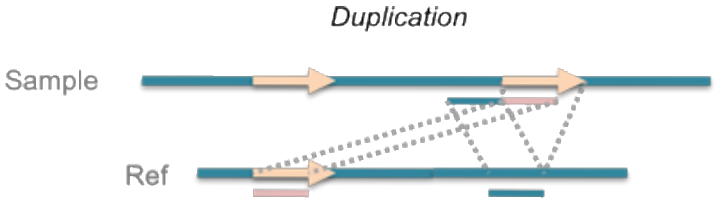


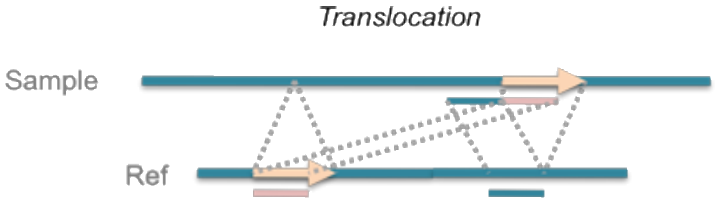



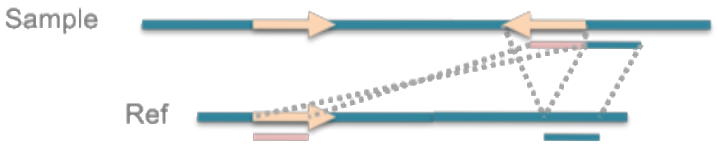



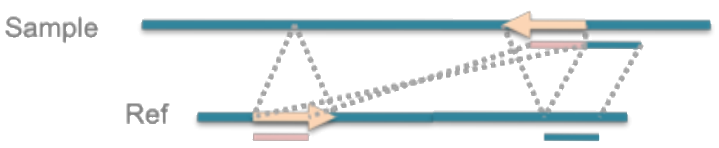

Deletions are the Easiest to Identify

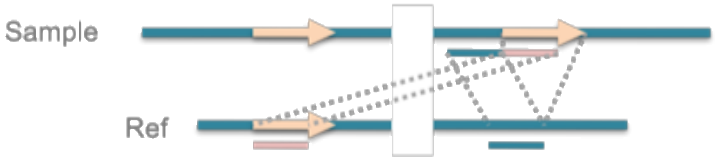
Complex SVs

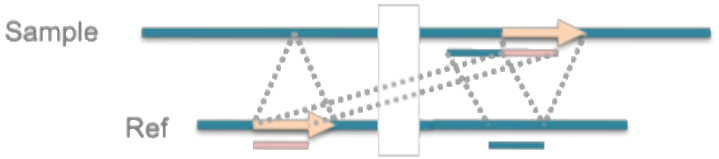


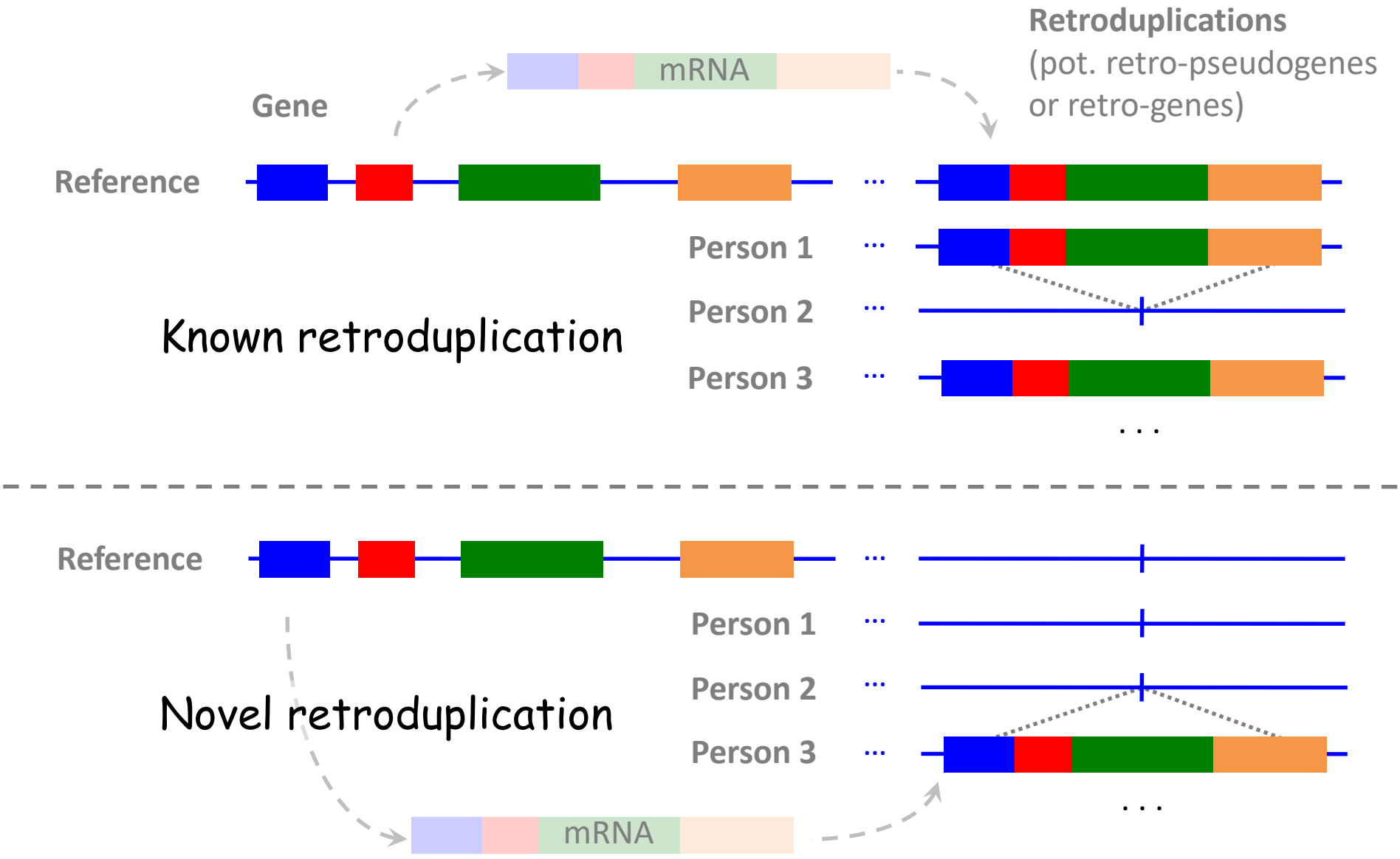




[Zhang et al. ('11) *BMC Genomics*]

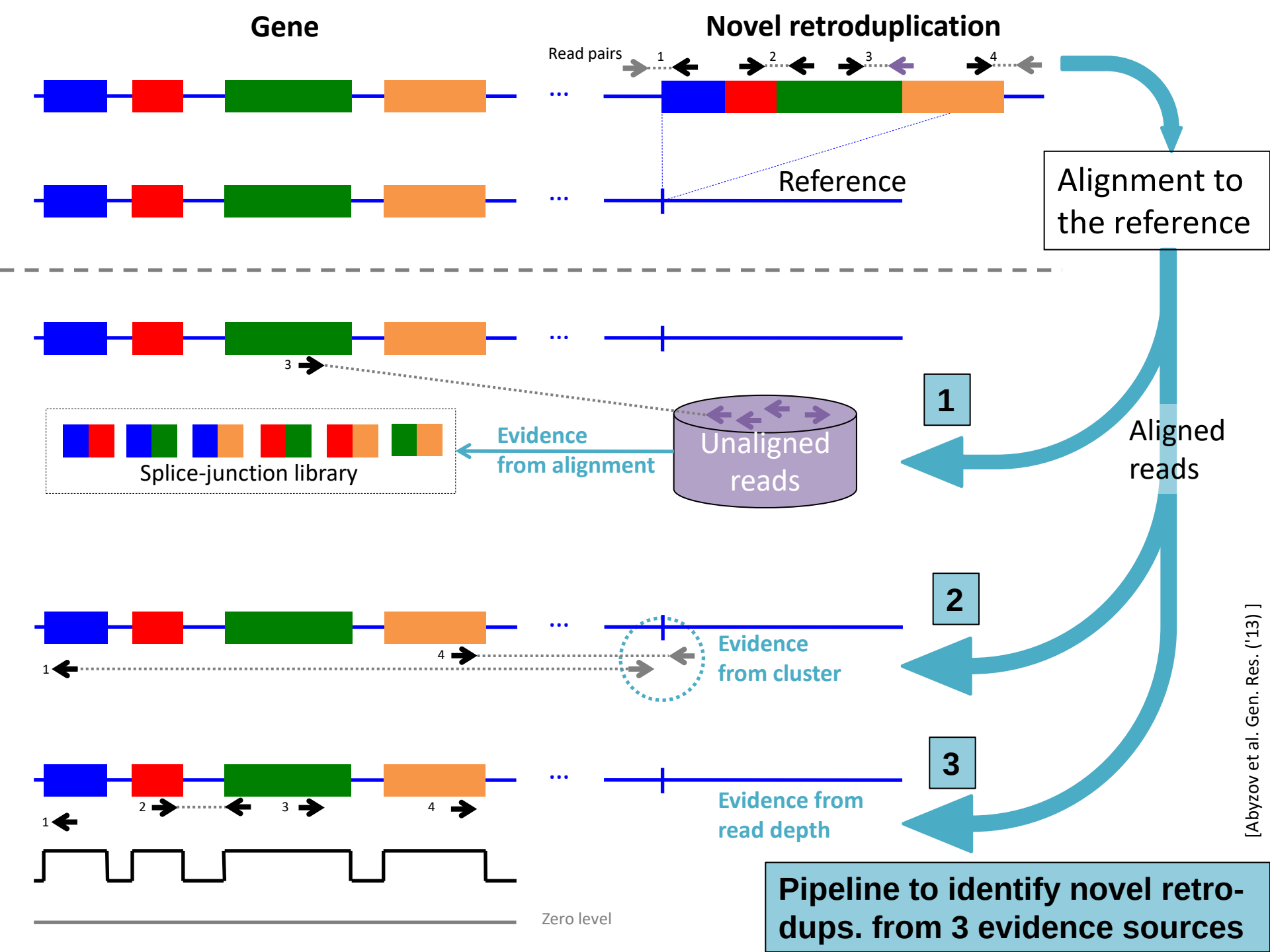
# RDV & Mobile Elements

# 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