Haplotype-based somatic mutation calling in heterogeneous cancer samples

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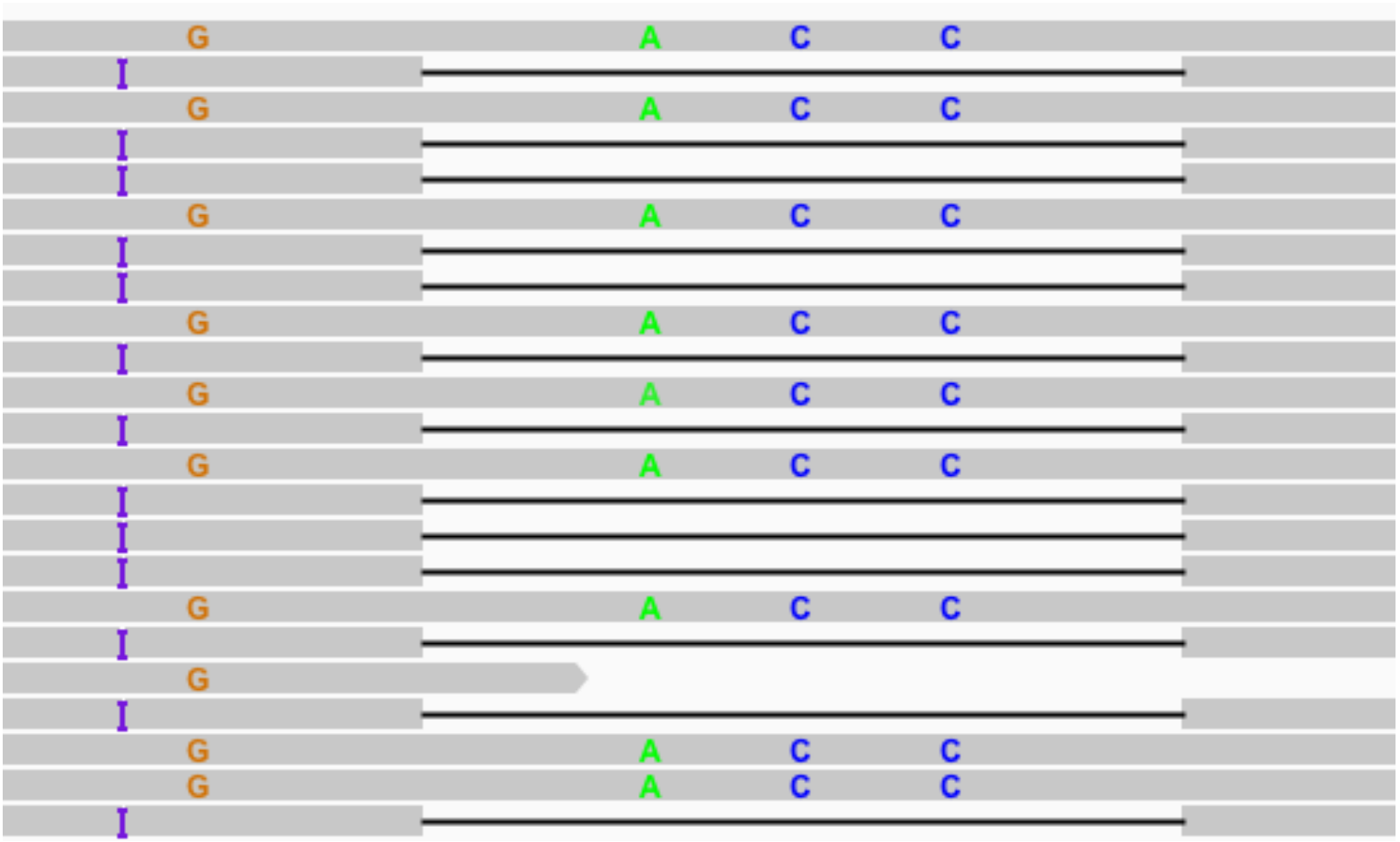
October 26, 2015

Haplotype-based variant calling

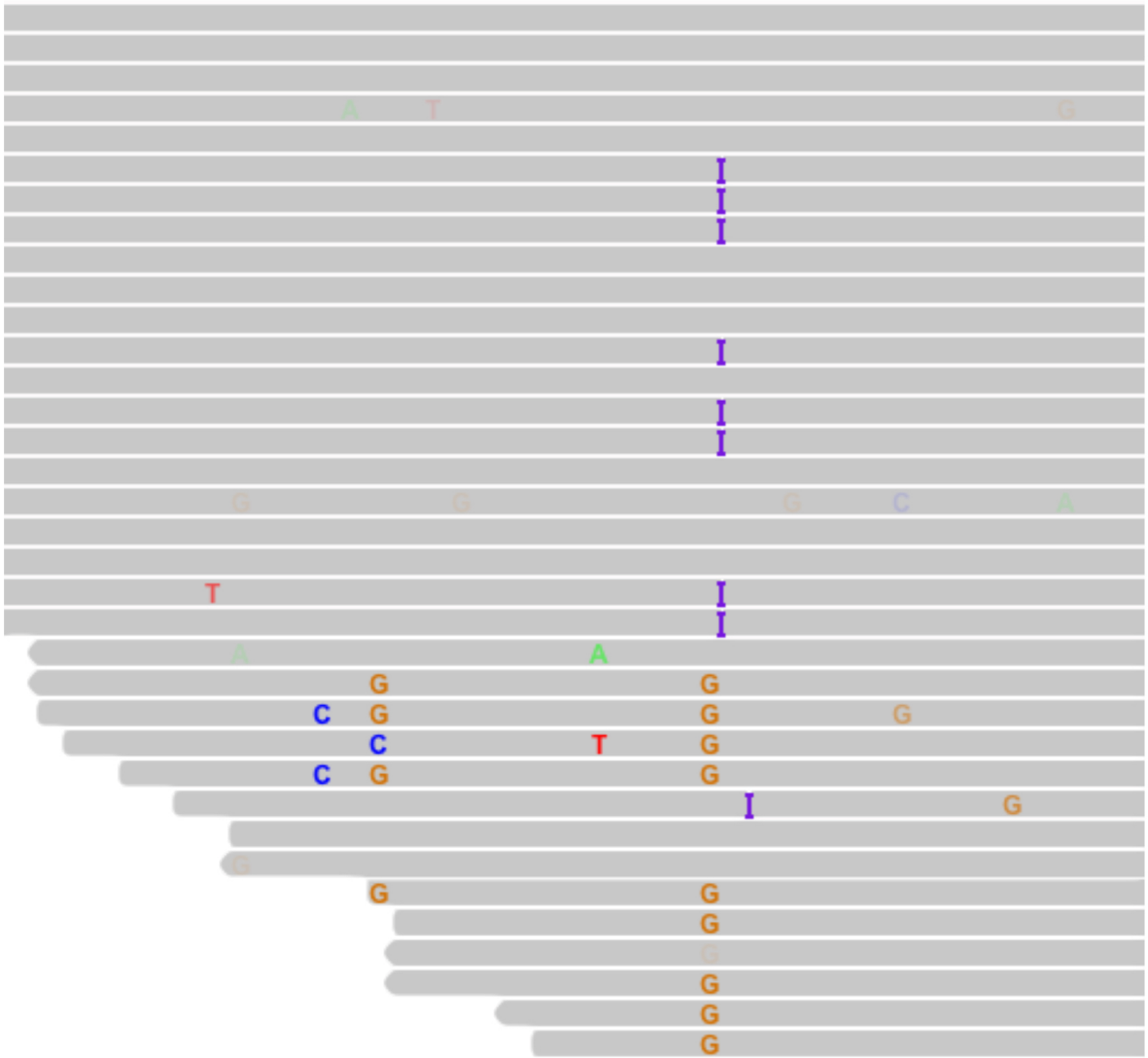
gatk

freebayes

Haplotype methods can resolve alignment errors



Haplotype methods can resolve alignment errors



Haplotype methods give local phasing

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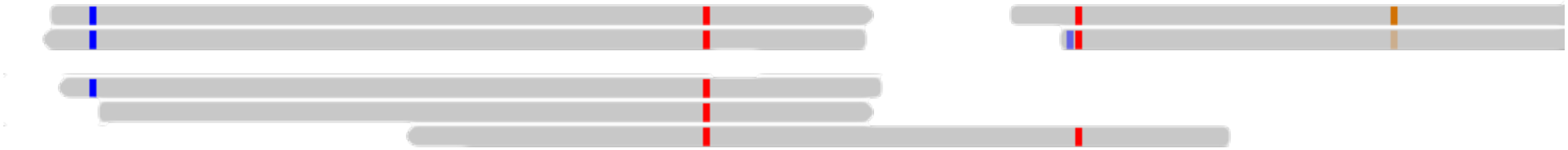
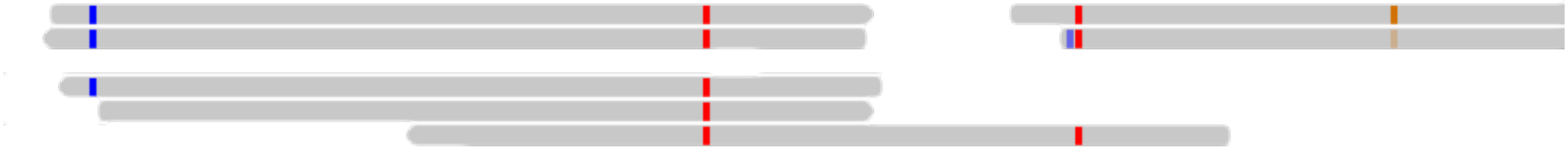
First haplotype



Haplotype methods give local phasing

First haplotype



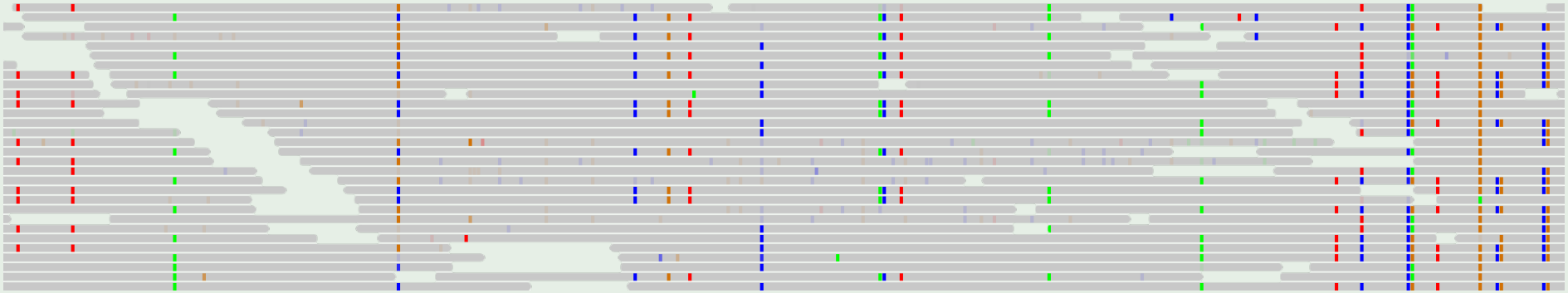
Second haplotype

Phasing is often intractable

$$\#\text{haplotypes} \approx 2^{\#\text{alleles}}$$

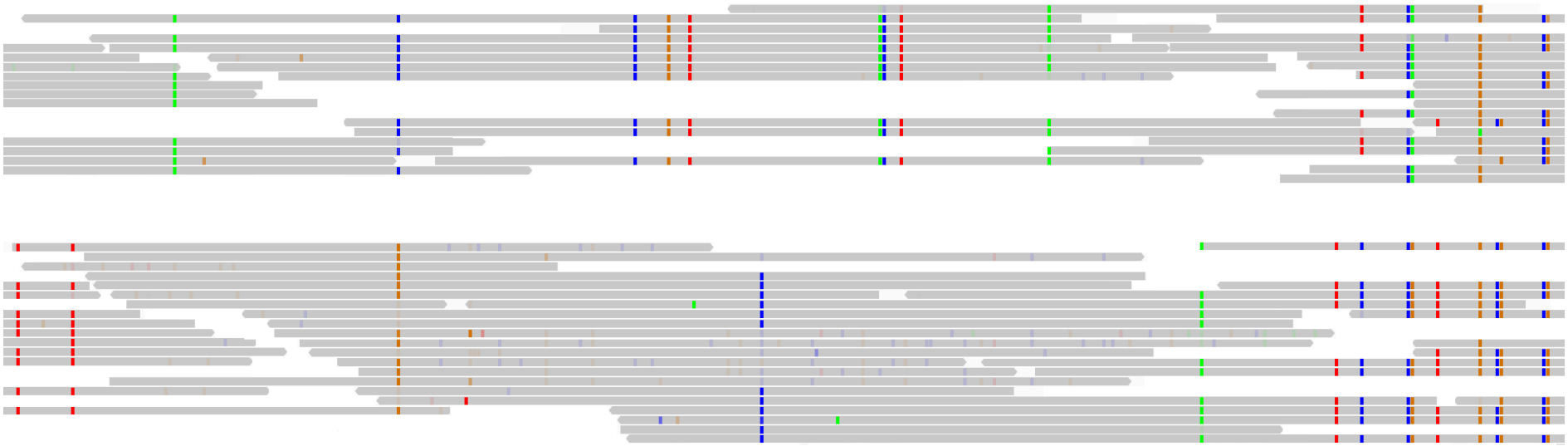
$$\#\text{genotypes} = \binom{\#\text{haplotypes} + \text{ploidy} - 1}{\#\text{haplotypes}}$$

Example: HLA loci

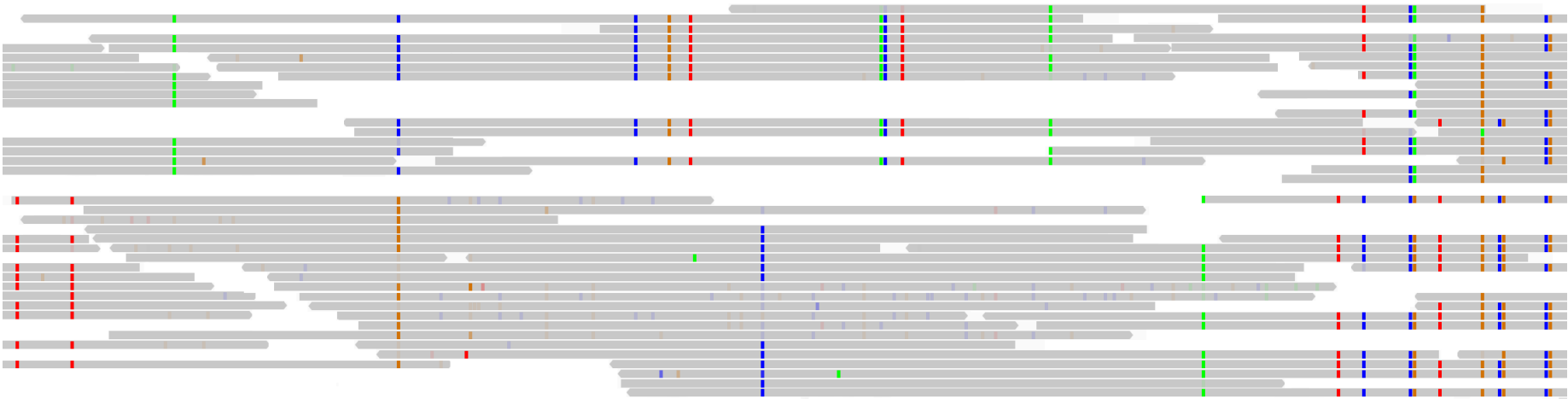


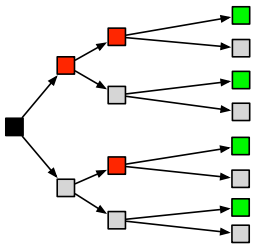
$$\#\text{alleles} \approx 70 \rightarrow \#\text{haplotypes} \approx 2^{70} \rightarrow \#\text{genotypes} \approx \text{lots}$$

Haplotype tree phasing

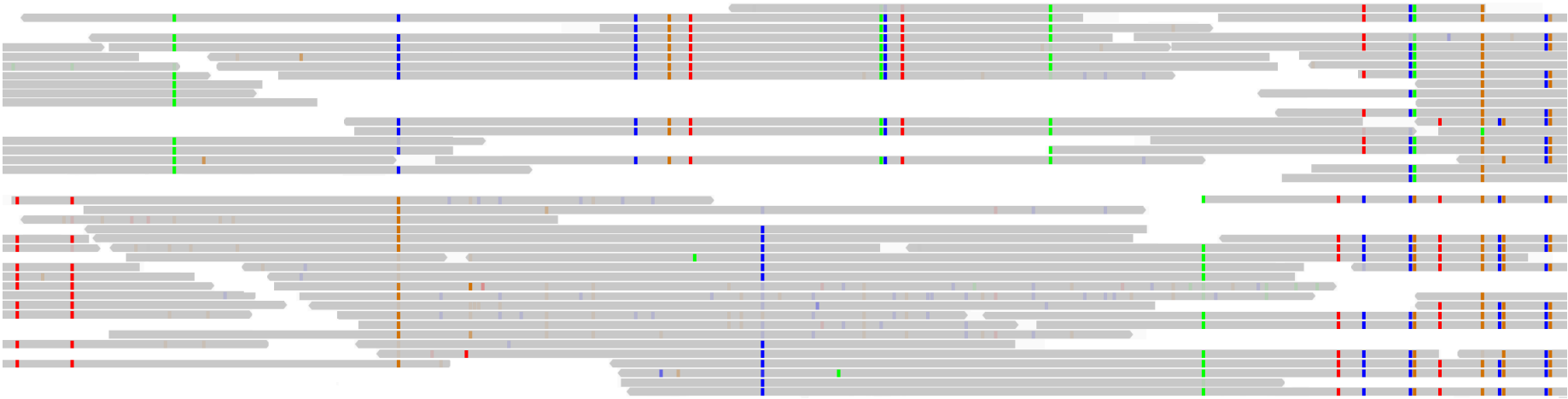


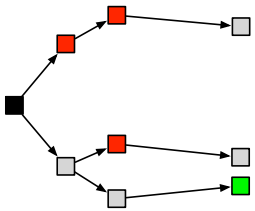
Haplotype tree phasing



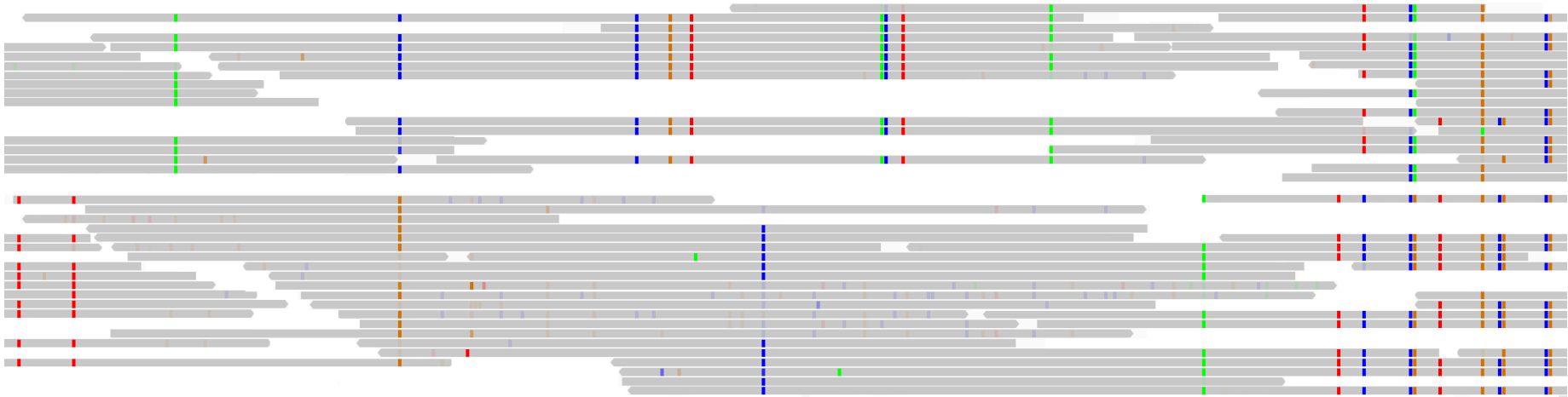


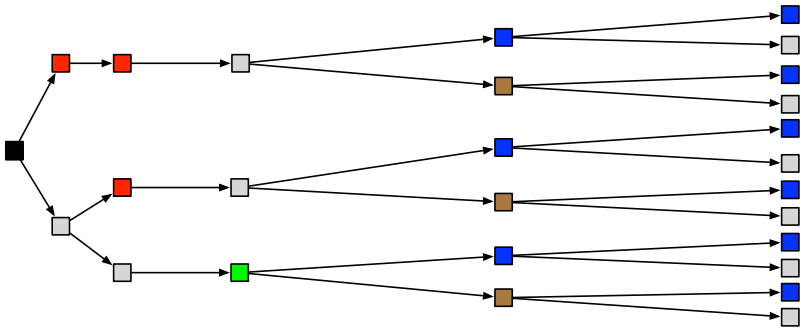
Haplotype tree phasing



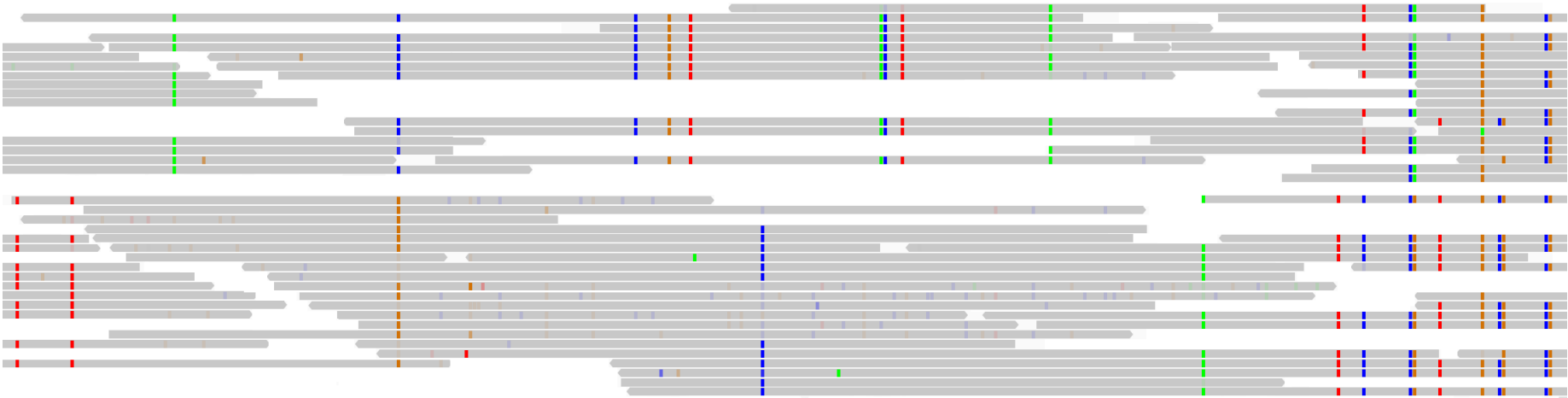


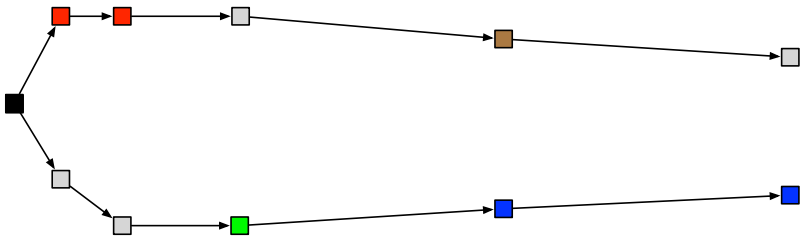
Haplotype tree phasing



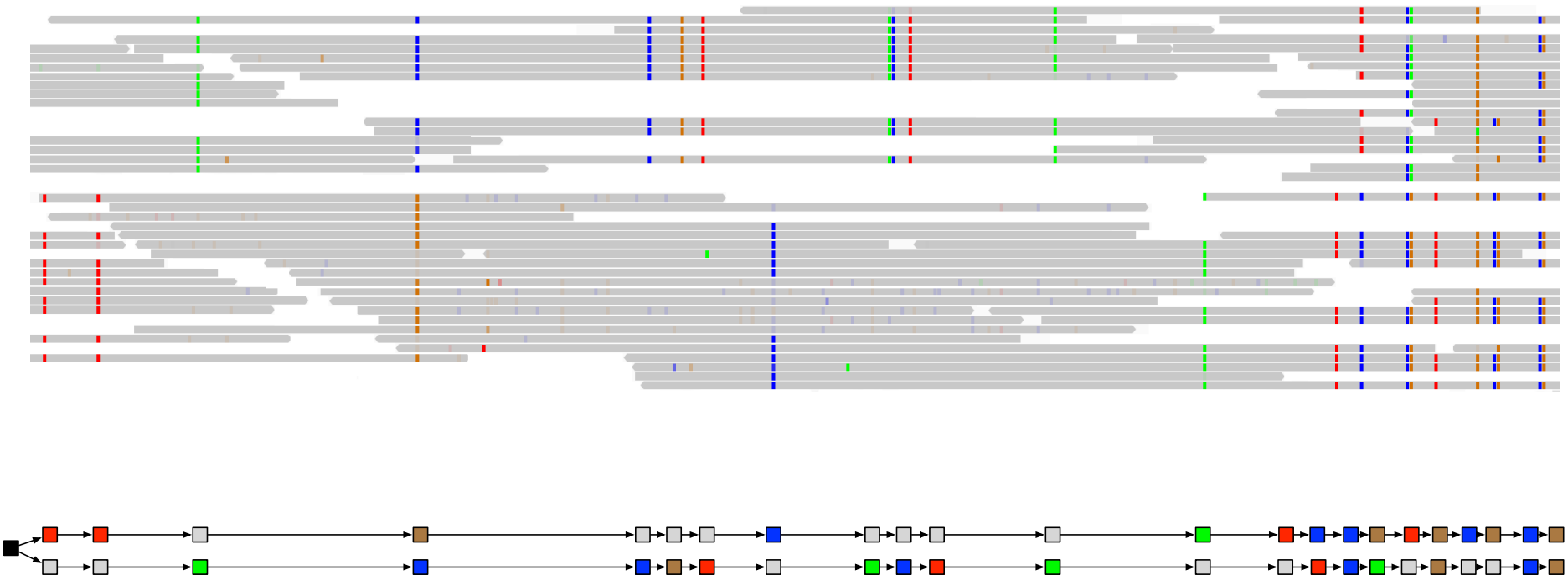


Haplotype tree phasing

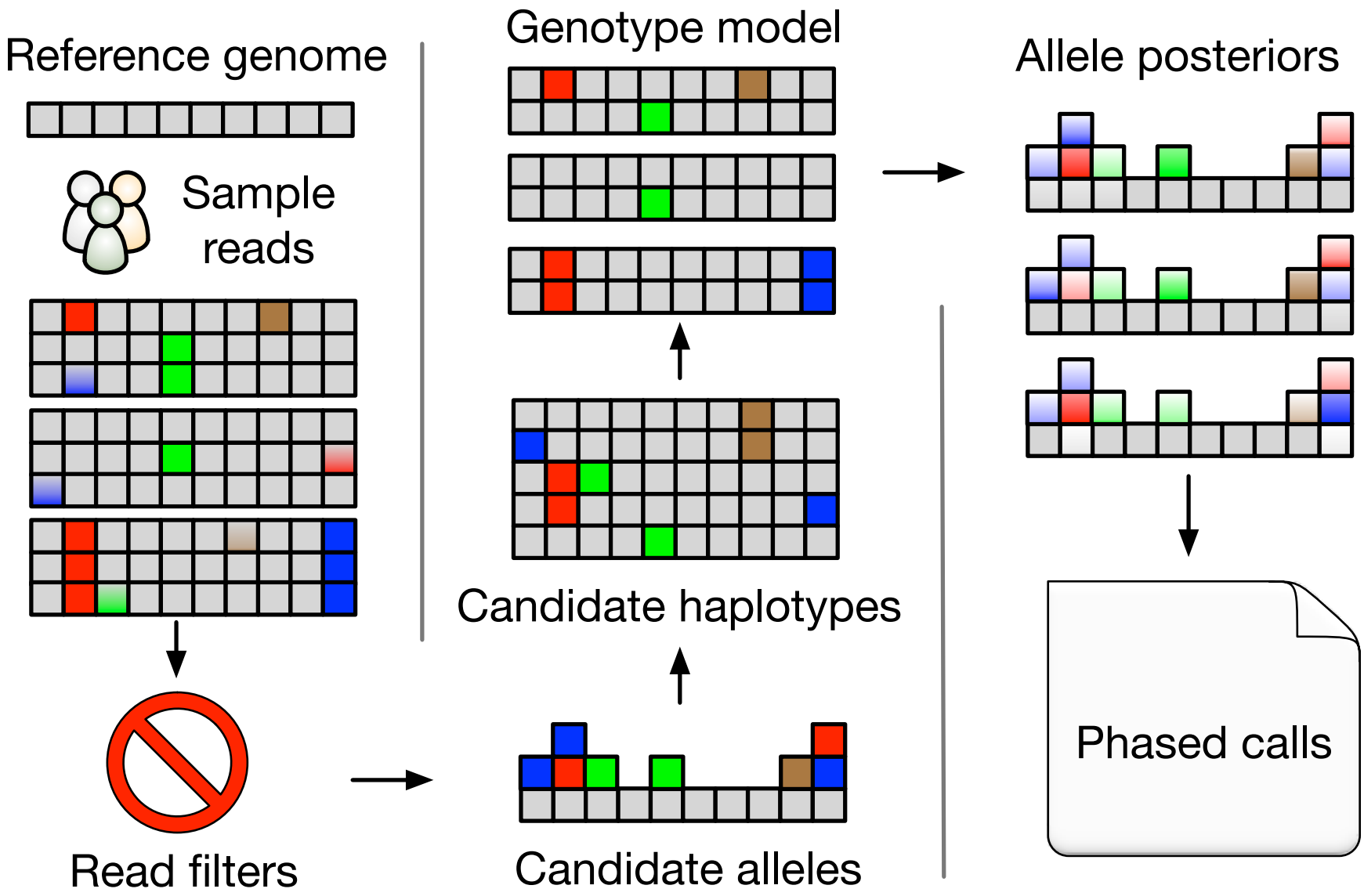




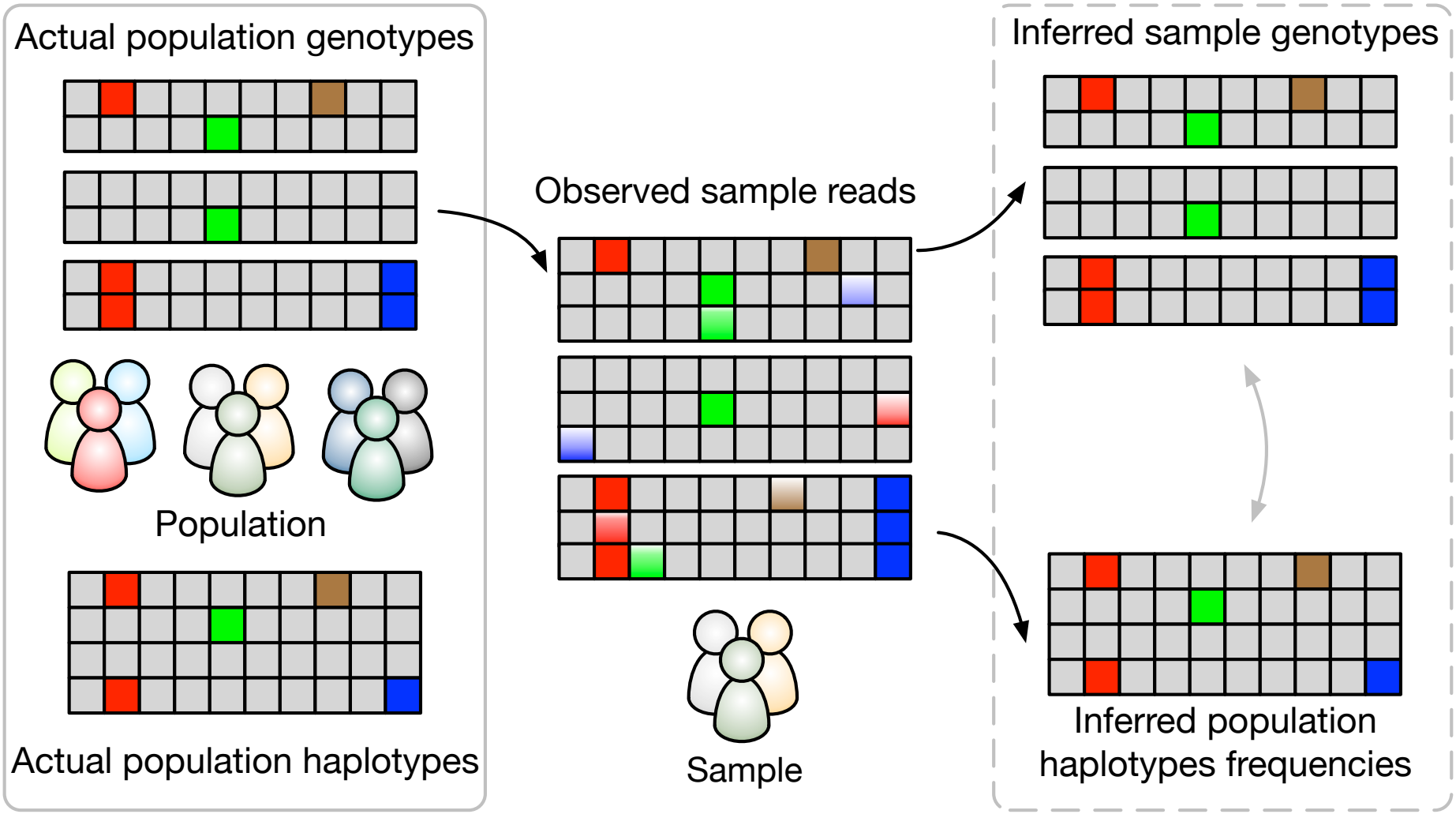
Haplotype tree phasing



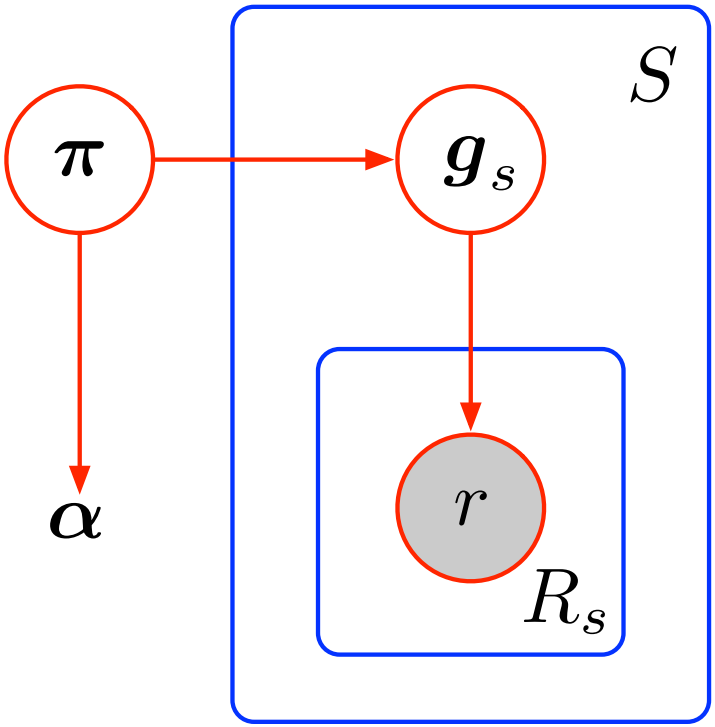
Algorithm overview



Population genotype model: overview



Population genotype model: maths

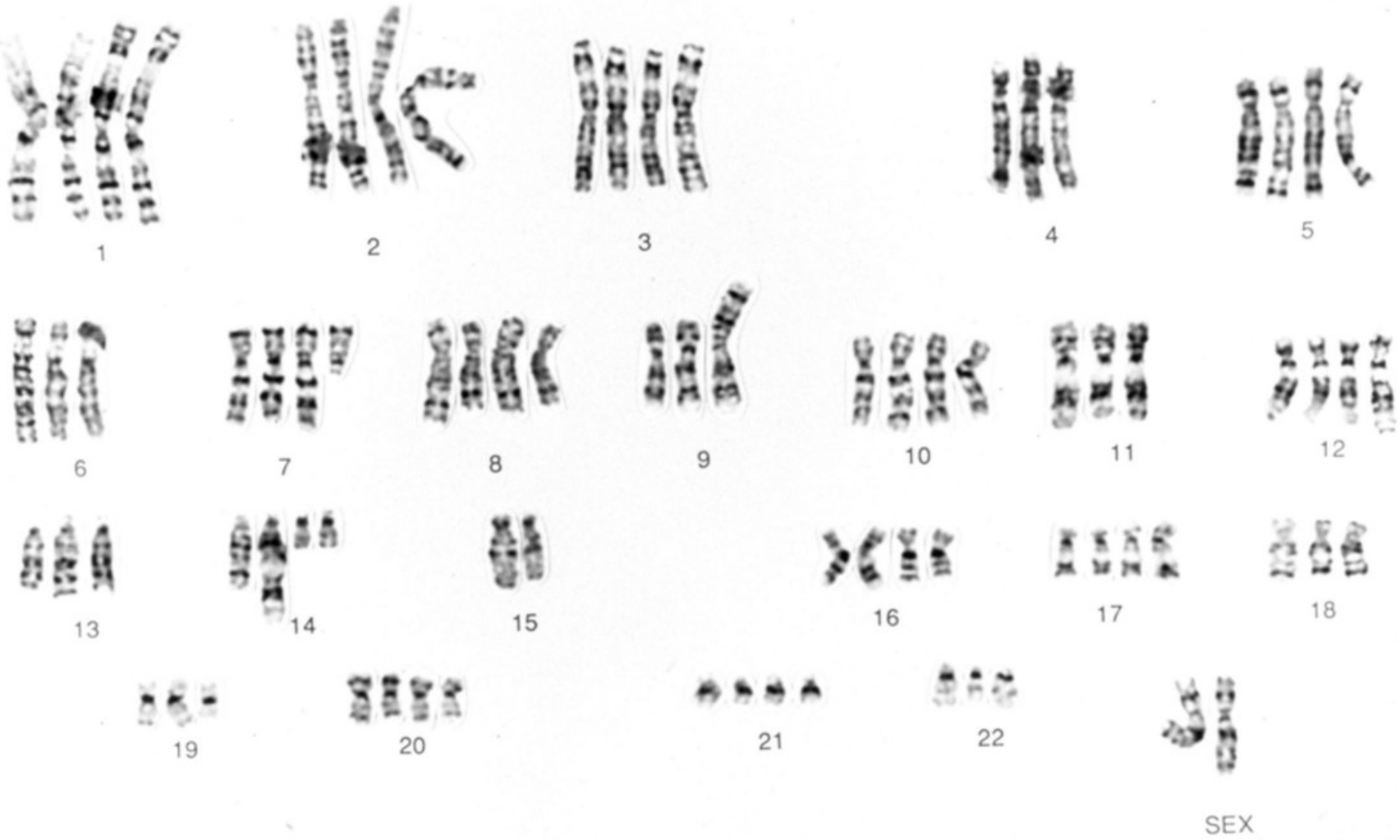


- Unknown population haplotype frequencies π
- Unknown sample genotypes $\boldsymbol{g}_s$
- Known sample ploidy

Marginal distribution: diploid case

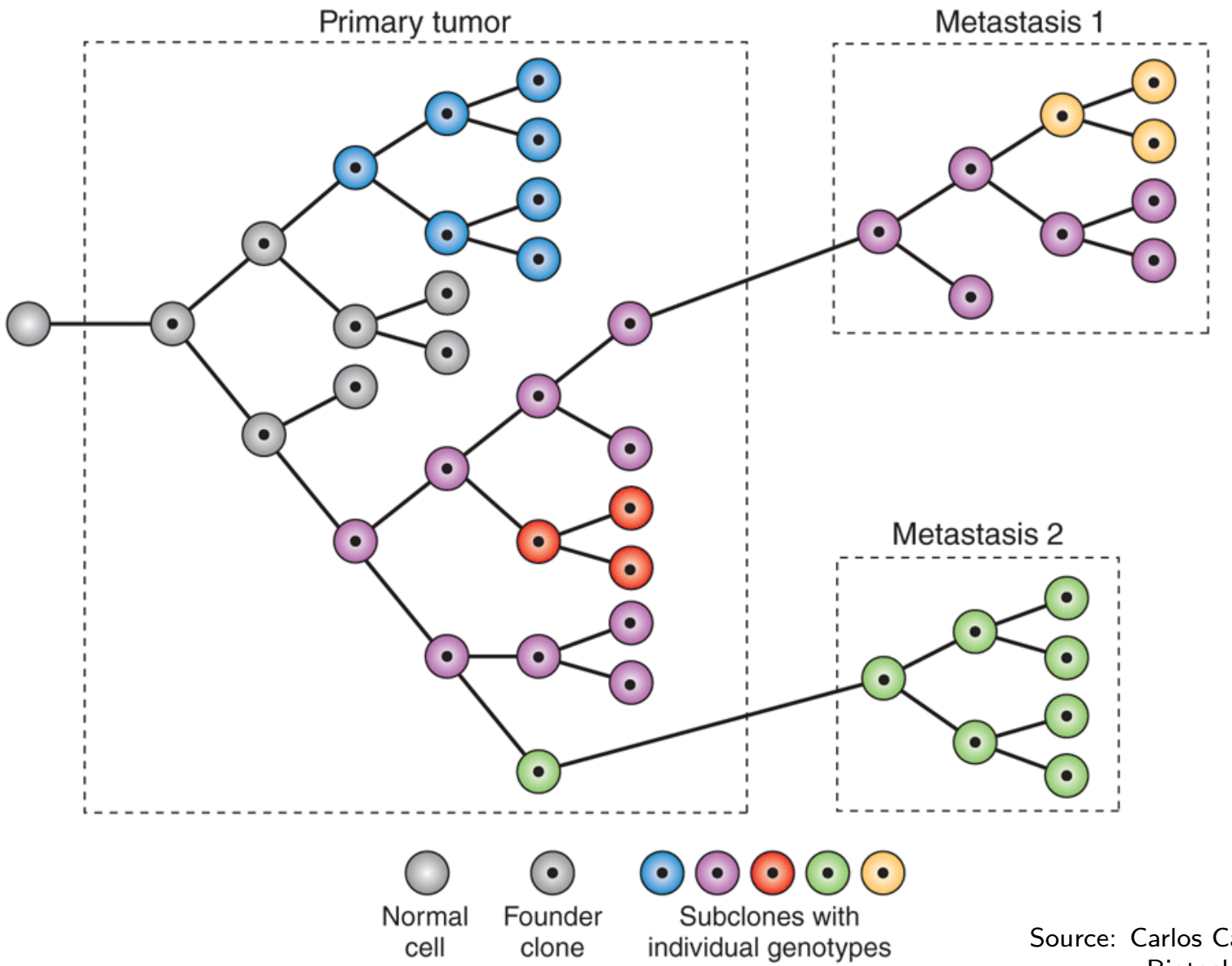
$$p(\boldsymbol{R}, \pi) = p(\pi|\alpha) \prod_{s=1}^{S} \sum_{\boldsymbol{g}} p(\boldsymbol{g}|\pi) \prod_{r \in R_s} \left\{ \frac{1}{2} p(r|\boldsymbol{g}_1) + \frac{1}{2} p(r|\boldsymbol{g}_2) \right\}$$

Challenges of cancer calling: messy karyotypes



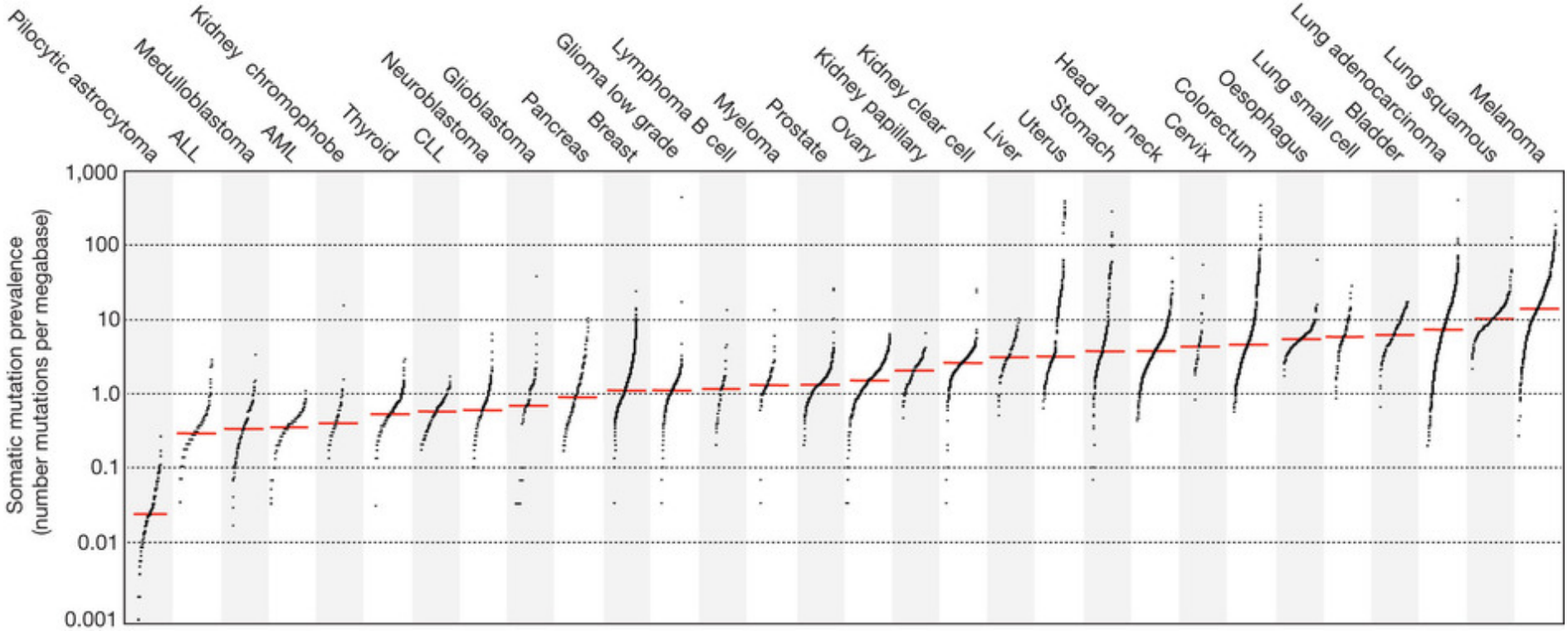
Source: Hillman et al. BMC Cancer 2007

Challenges of cancer calling: tumor heterogeneity



Source: Carlos Caldas Nature Biotechnology 2012

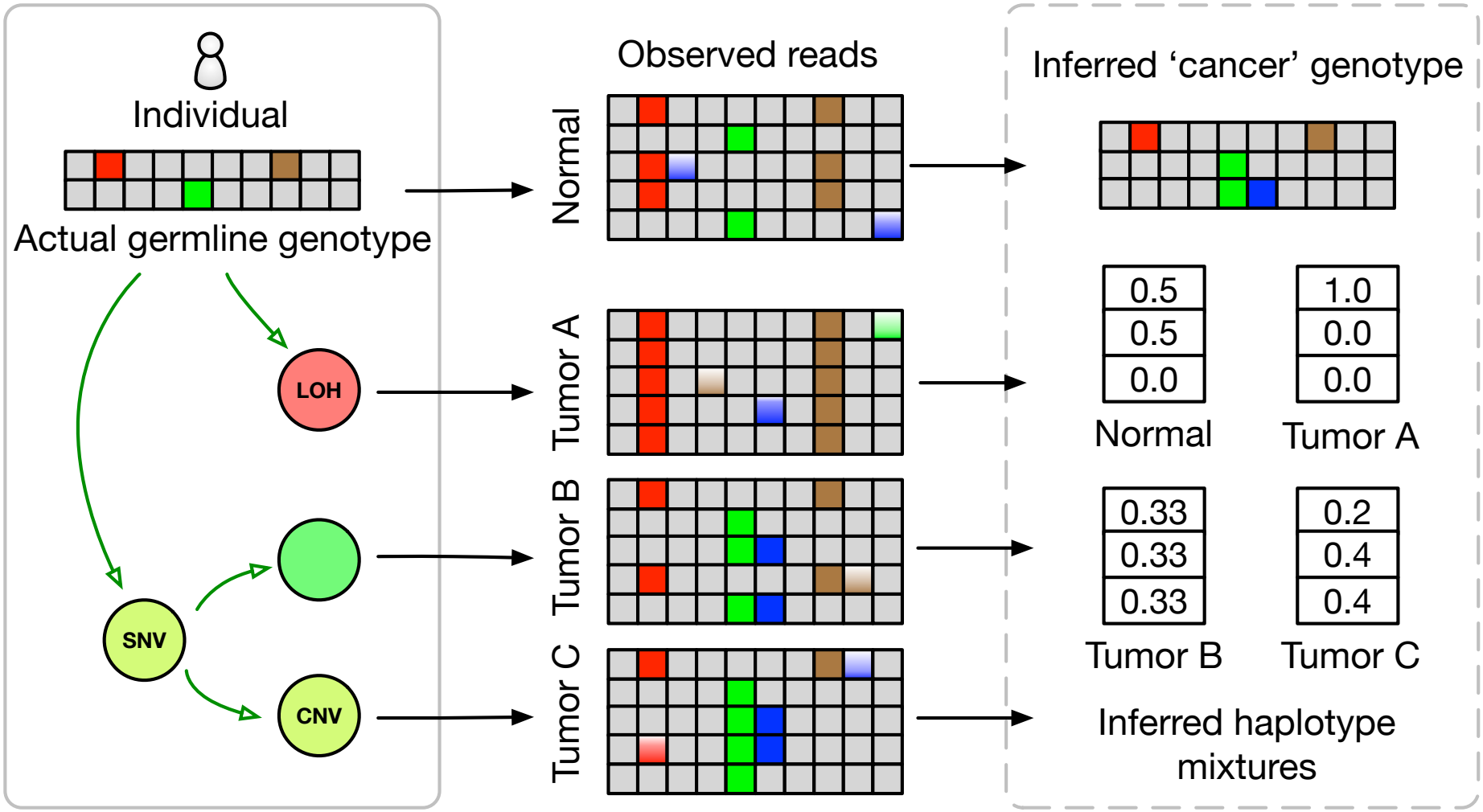
How many haplotypes do we need?



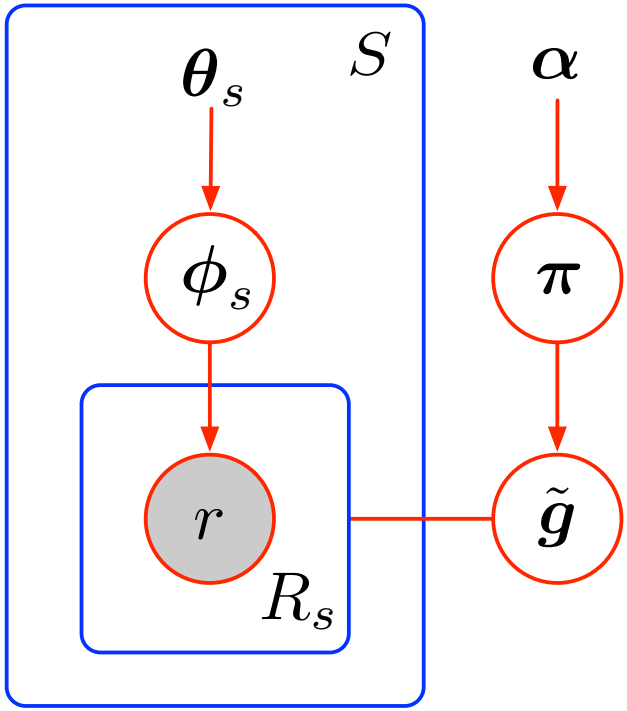
More than three local haplotypes are rare in most cancer types

Source: Alexandrov et al. Nature 2013

Cancer genotype model: overview



Cancer genotype model: maths

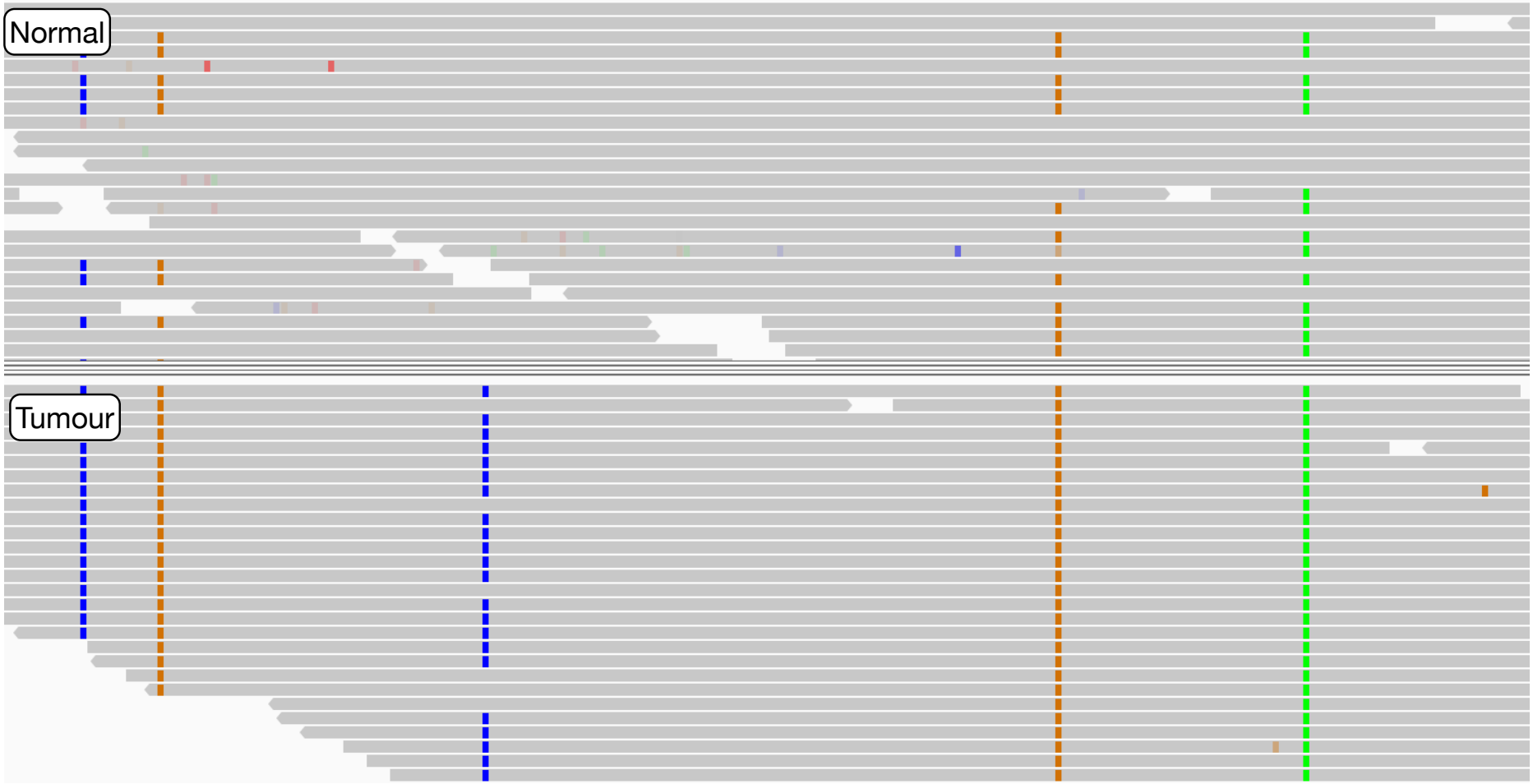


- One unknown 'cancer' genotype $\tilde{\boldsymbol{g}}$
- Unknown haplotype mixtures ϕ_s
- Mixture priors θ_s implicitly model 'normal'

Marginal distribution: diploid case

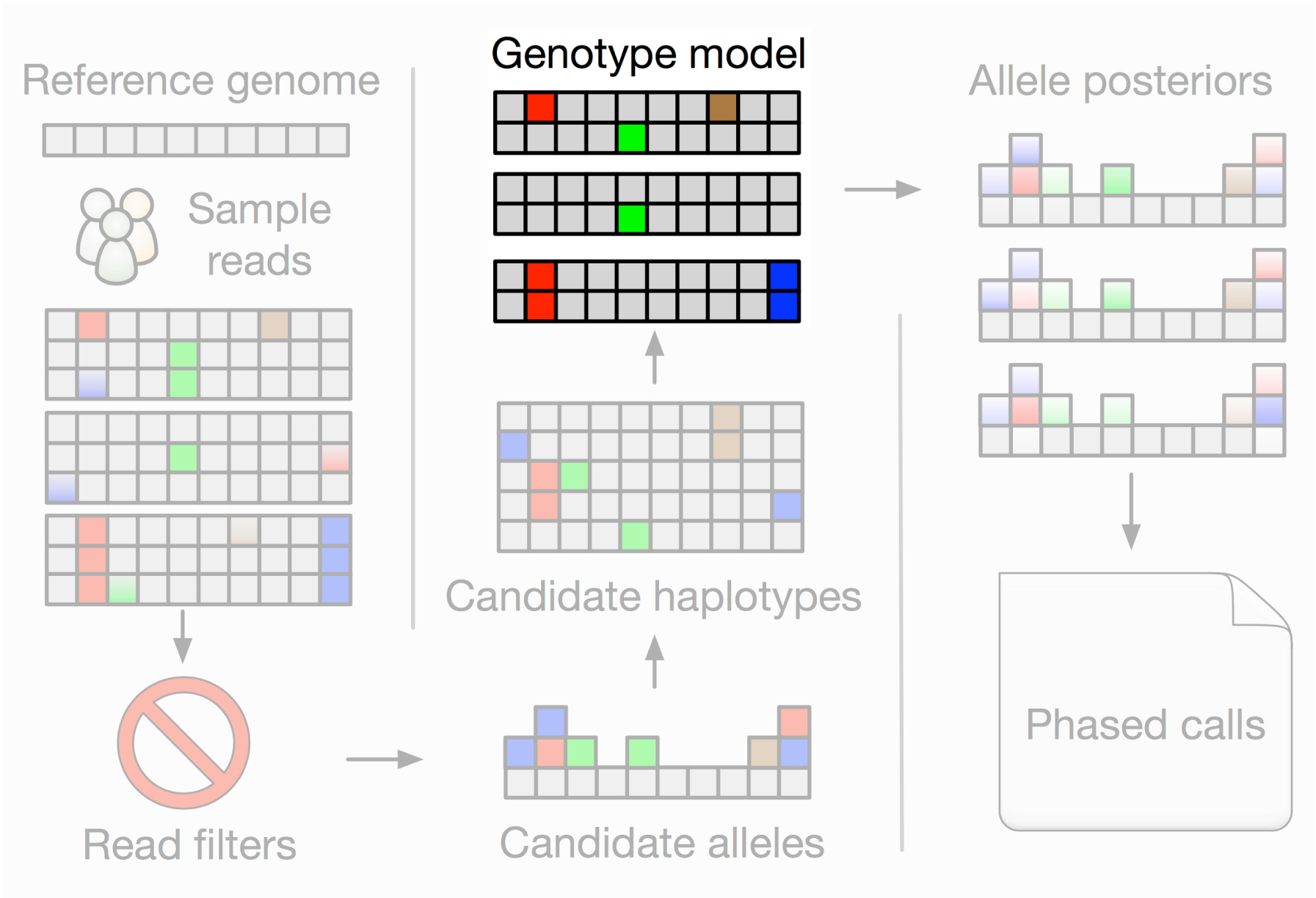
$$p(\boldsymbol{R}, \pi) = p(\pi|\alpha) \sum_{\tilde{\boldsymbol{g}}} p(\tilde{\boldsymbol{g}}|\pi) \prod_{s=1}^{S} \int d\phi_s p(\phi_s|\theta_s) \prod_{r \in R_s} \sum_{i=1}^{3} p(\tilde{\boldsymbol{g}}_i|\phi_{si}) p(r|\tilde{\boldsymbol{g}}_i)$$

Phased somatic mutation calls



Phased somatic mutation calls

Summary & future work



Acknowledgements

Supported by
wellcome trust

UNIVERSITY OF
OXFORD

Lunter group
with special thanks to Gerton Lunter