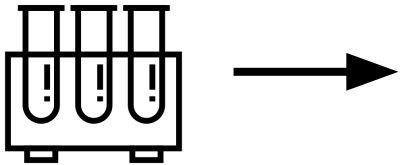
Variant calling, phasing, and imputation

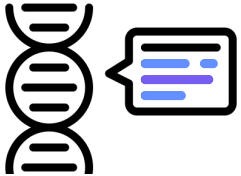
Nik Baya
Oxford Statistical Genomics Summer School
June 19 2023

Overview

Sequencing



Calling



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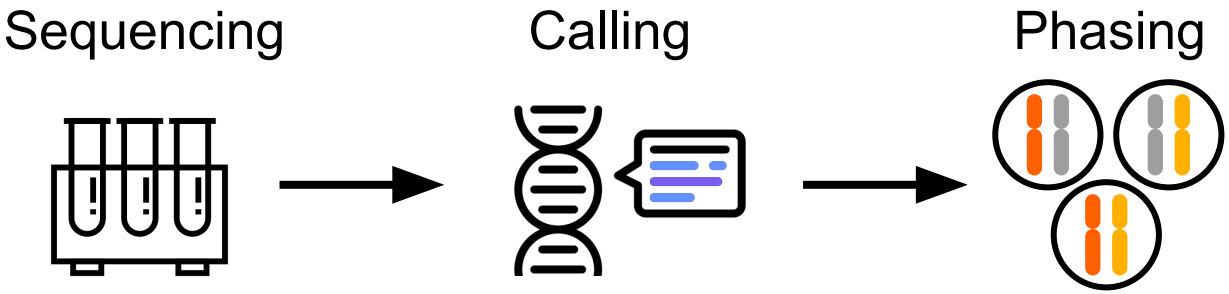

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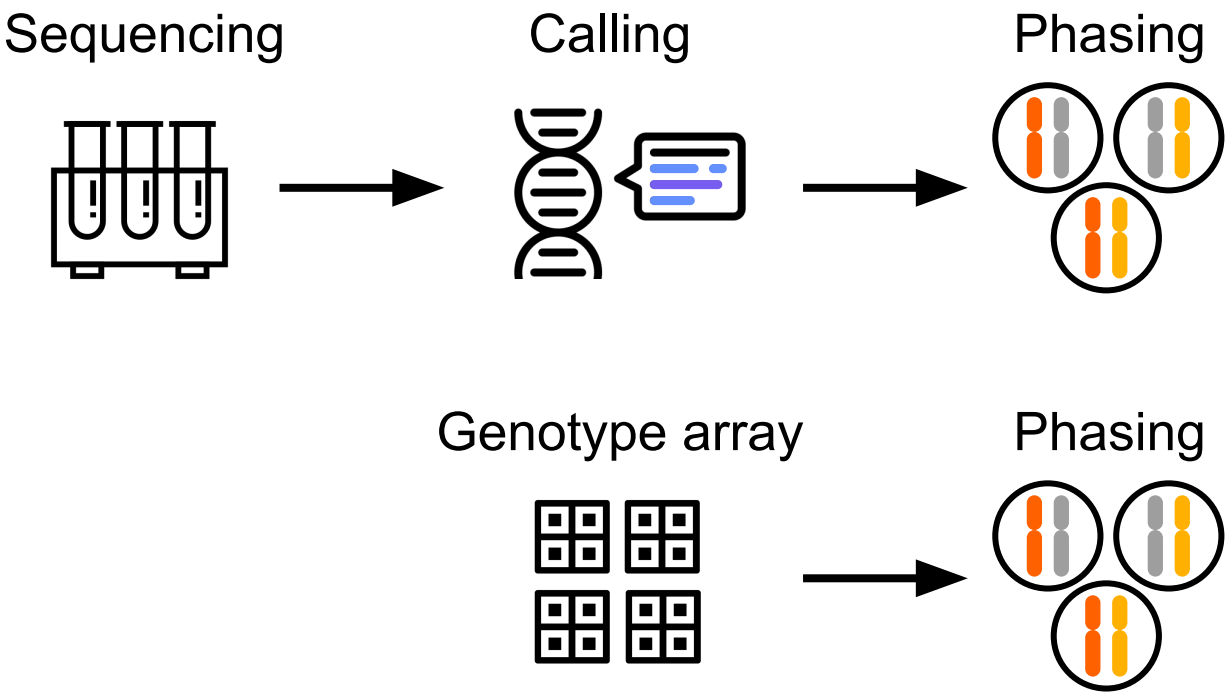

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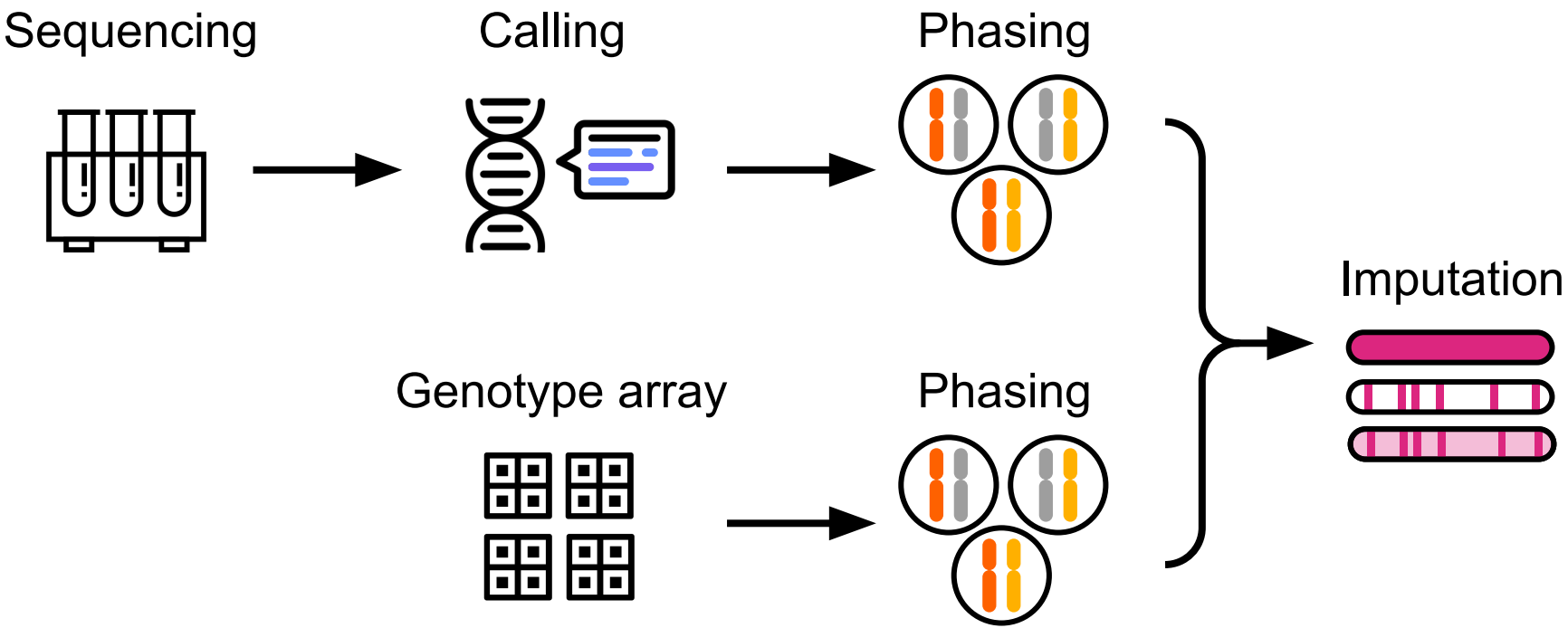
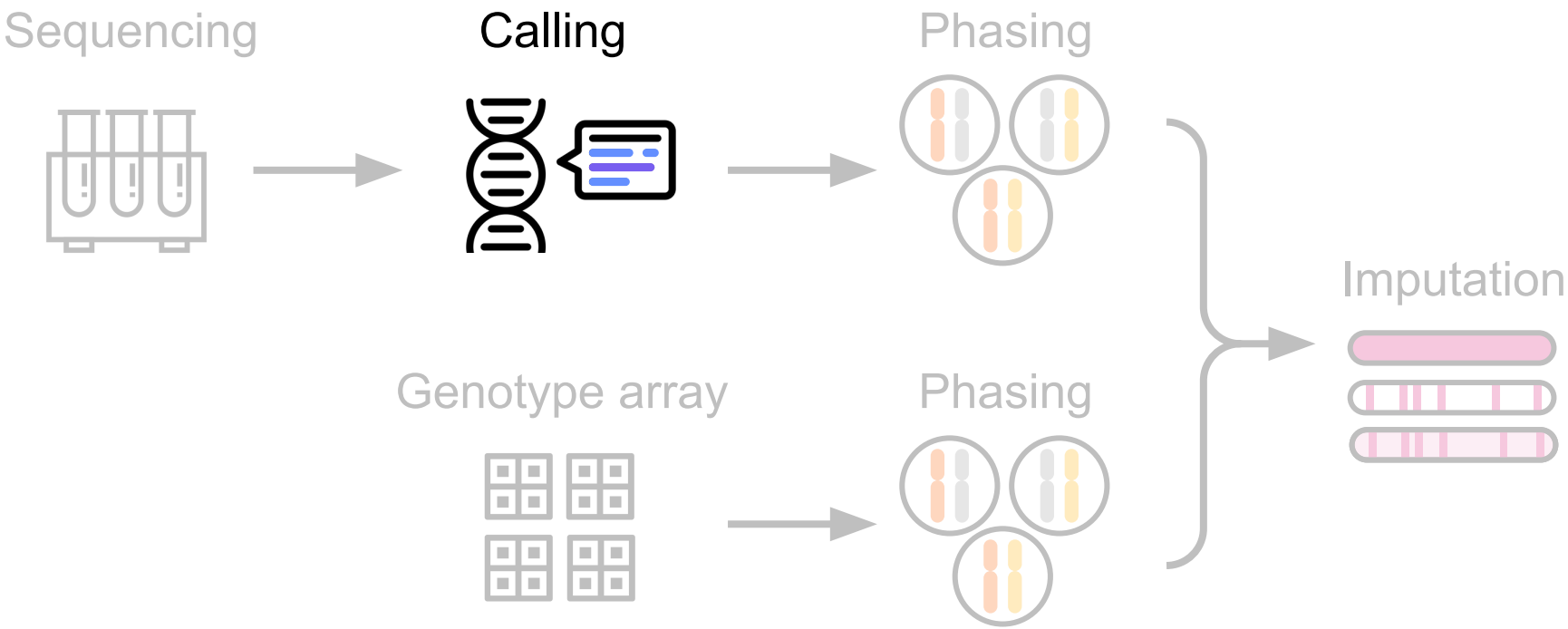

Sequencing
Calling
Phasing
Imputation
Genotype array
Phasing

Overview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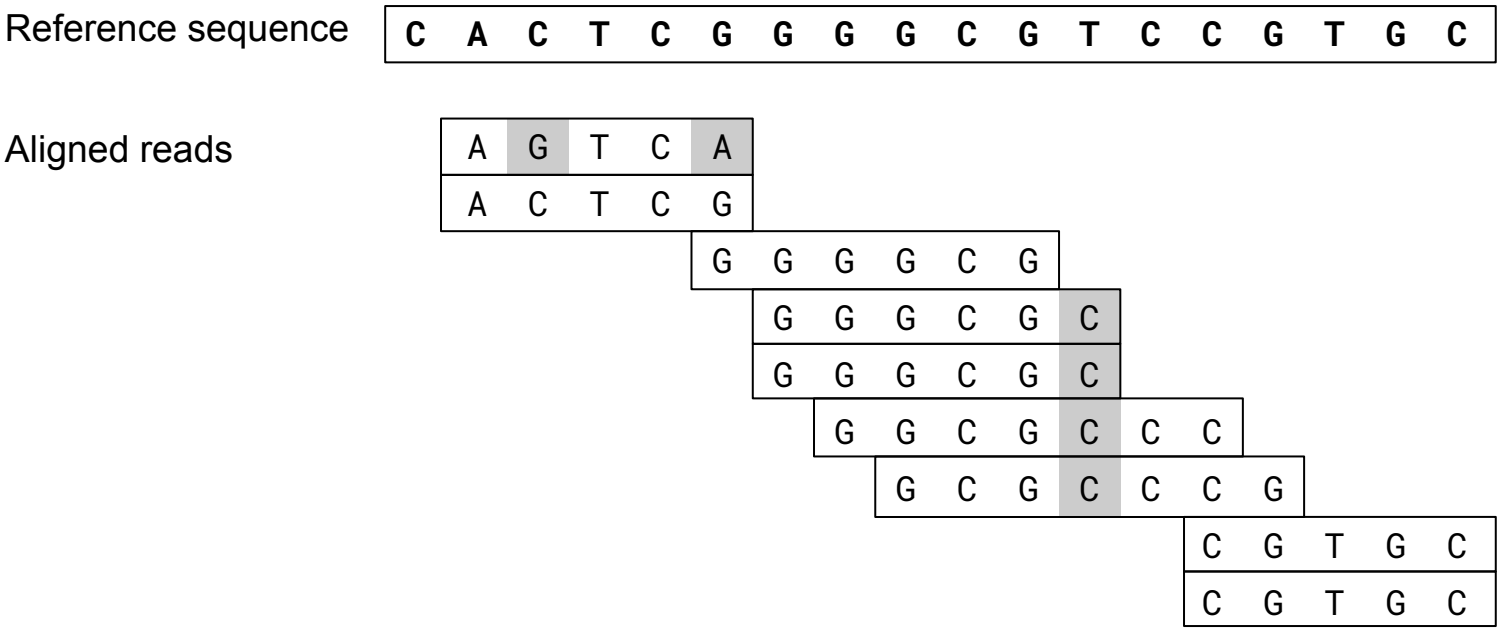
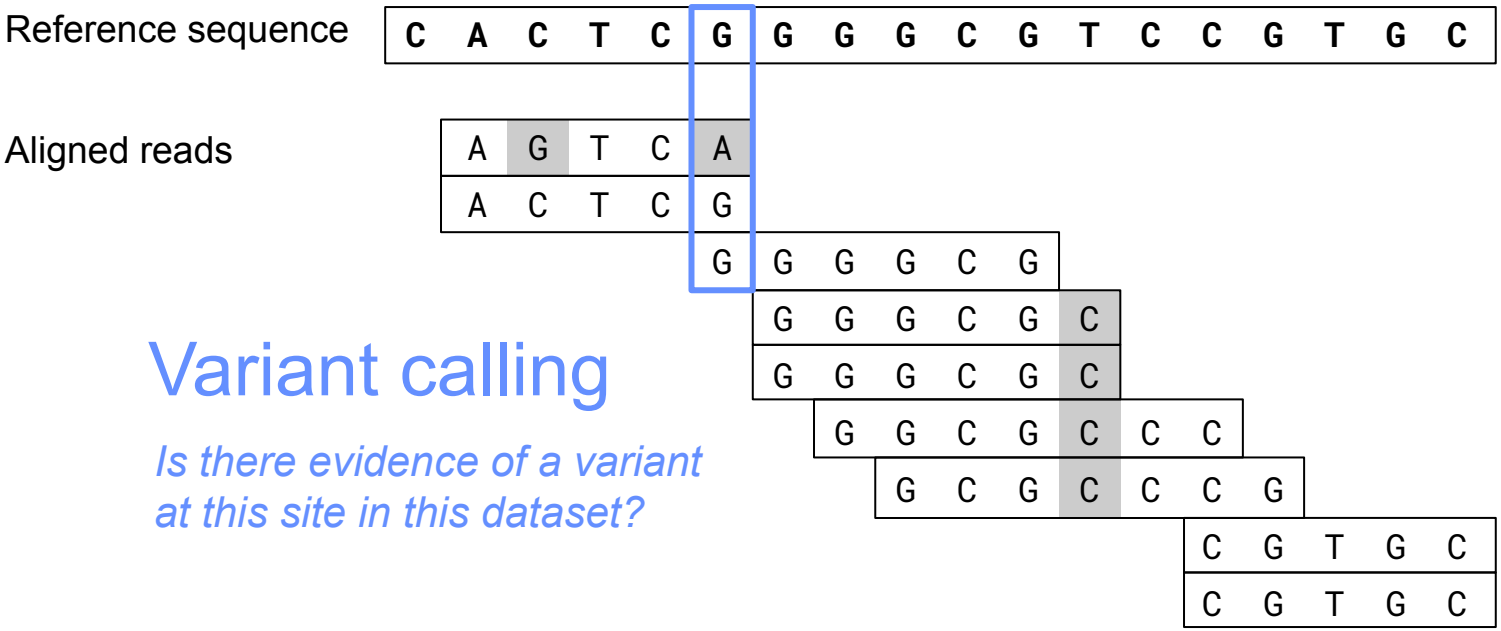

Reference sequence
C A C T C G G G G C G T C C G T G C
Aligned reads
A G T C A
A C T C G
G G G G C G
G G G C G C
G G G C G C
G G C G C C C
G C G C C C G
C G T G C
C G T G C



Variant calling

Is there evidence of a variant at this site in this dataset?

Variant calling

$$Pr(variable\ site|Data)$$

Probability that this site is variable, given the data

Slide adapted from Luke Jostins-Dean

Variant calling

Bayes' Theorem

$$Pr(A|B) = \frac{Pr(B|A)Pr(A)}{Pr(B)}$$

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$$Pr(variable\ site|Data) = \frac{Pr(Data|variable\ site)Pr(variable\ site)}{Pr(Data)}$$

Probability that this site is variable, given the data

$$= \frac{prior \prod_i L_x^i}{(1 - prior) \prod_i L_{ref}^i + prior \prod_i L_x^i}$$

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"is variable"

"is not variable"

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Prior probability that a site is variable (i.e. site is a variant)

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Prior probability of site being a variant

$$prior(N) = 4N_e\mu \sum_{k=1}^{2N-1} 1/k$$

N : Size of sequenced population

N_e : Effective population size

μ : Mutation rate

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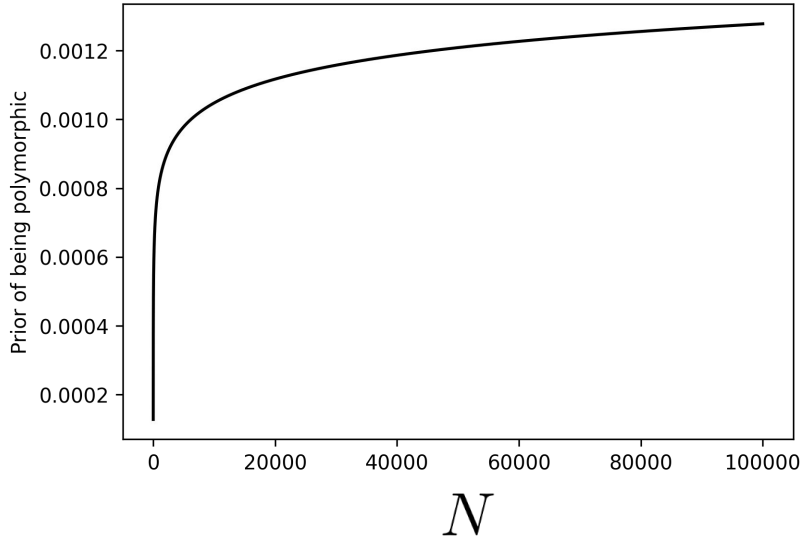
$$\approx 0.0001 * (1.270147 + \log(N))$$



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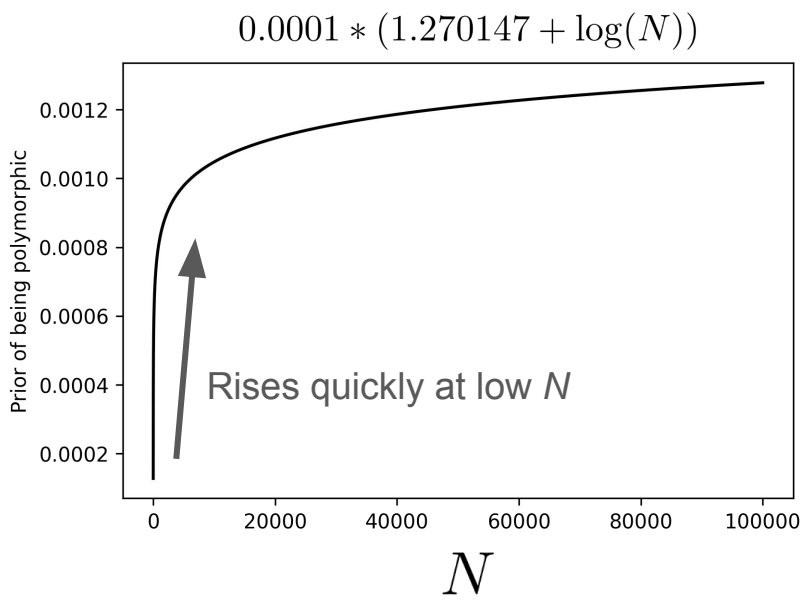

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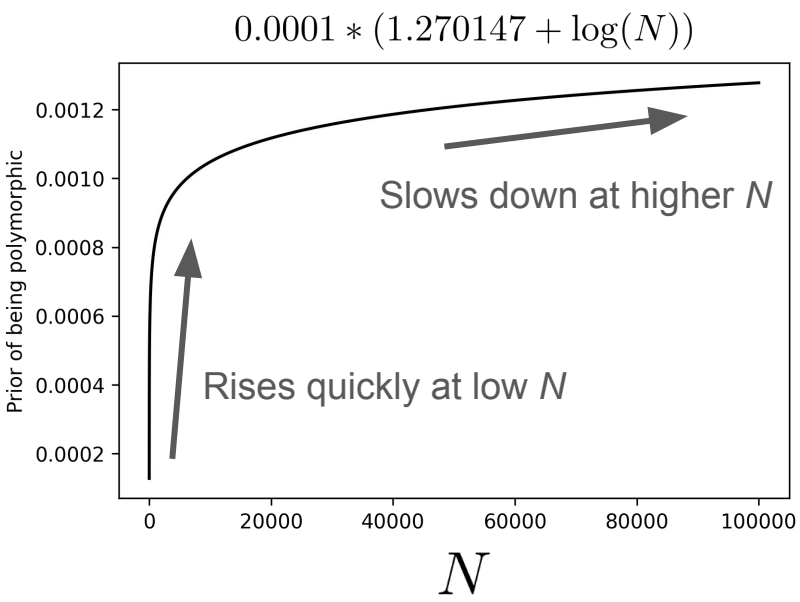

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Likelihood being variable

Likelihood of being invariant

Slide adapted from Luke Jostins-Dean

Allele likelihood

Likelihood of site being **variable**:

$$\mathcal{L}_x^i = 2 * [G_i(g=1)f_x(1-f_x)] + G_i(g=2)f_x^2$$

Likelihood of being **invariant**:

$$\mathcal{L}_{ref}^i = G_i(g=0)(1-f_x)^2$$

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Allele likelihood

f_x : Frequency of allele x

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Genotype likelihoods

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Genotype likelihood

$$\mathcal{L}(g) = \frac{1}{m^k} \prod_{j=1}^{l} \Big[(m-g)\epsilon_j + g(1-\epsilon_j) \Big] \prod_{j=l+1}^{k} \Big[(m-g)(1-\epsilon_j) + g\epsilon_j) \Big]$$

g : genotype expressed as number of ref alleles

Li 2011

Genotype likelihood

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E[# of true reference reads]

E[# of true alternate reads]

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Example: Varying proportion of reference reads

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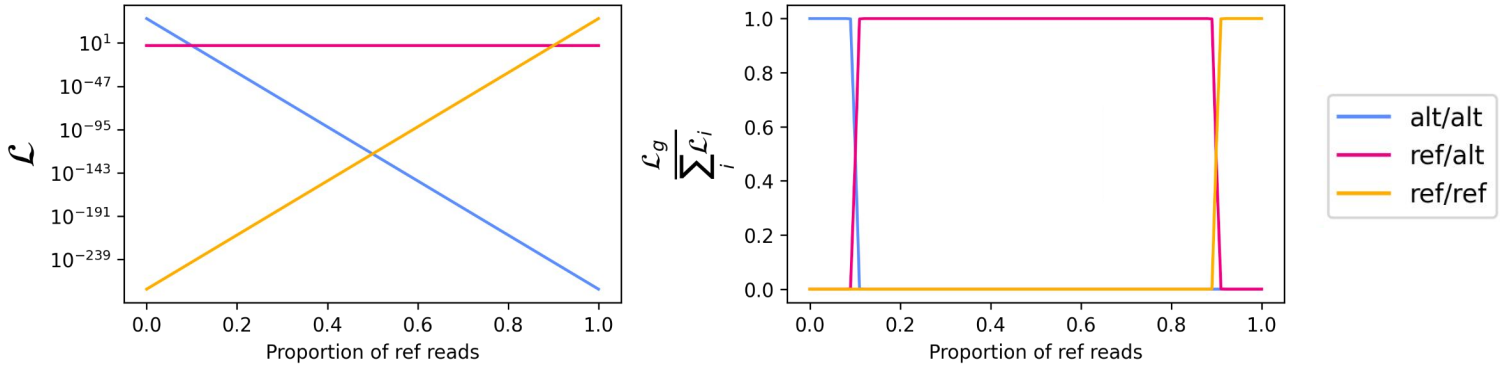

Total reads = 100, error=1e-3

Li 2011

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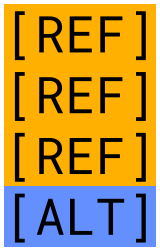
Example: Increasing error rate



3 ref reads, 1 alt read

Li 2011

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Example: Increasing error rate

[REF]
[REF]
[REF]
[ALT]

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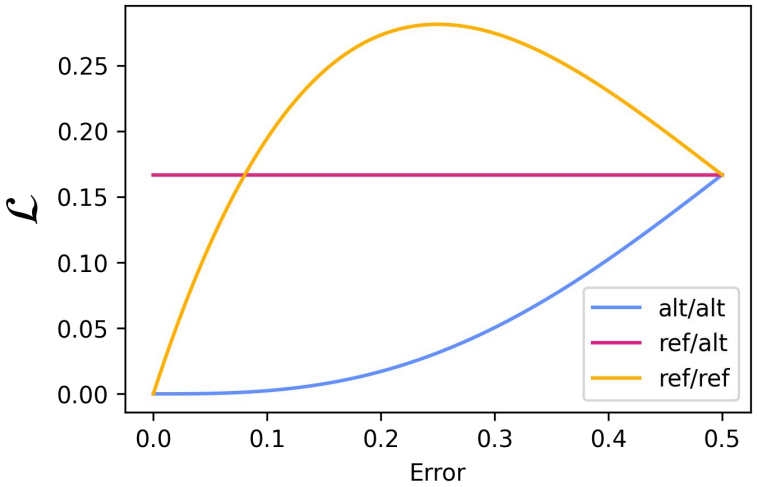

error rate constant across reads (Var(e_j)=0)

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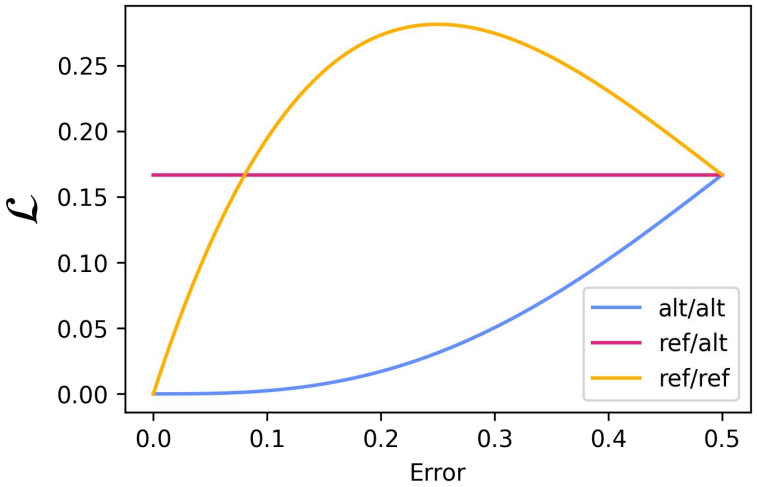

error → 0.5
(i.e. random)

all likelihoods converge

error rate constant across reads (Var(e_j)=0)

Li 2011

Summary: Variant calling

Slide adapted from Luke Jostins-Dean

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QUAL score

(or site quality score)

#CHROM	POS	ID	REF	ALT	QUAL
chr19	48693829	.	C	T	3357.45
chr19	48693956	.	A	G	6806.98
chr19	48693992	.	G	A	1802.53
chr19	48694122	.	C	G	125.986

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$$Q = -10 \cdot \log_{10}(\text{Probability of error})$$

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Error = 1	Error = 1/100	Error = 1/1000
Q = 0	Q = 20	Q = 30

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higher score = higher quality

QUAL score

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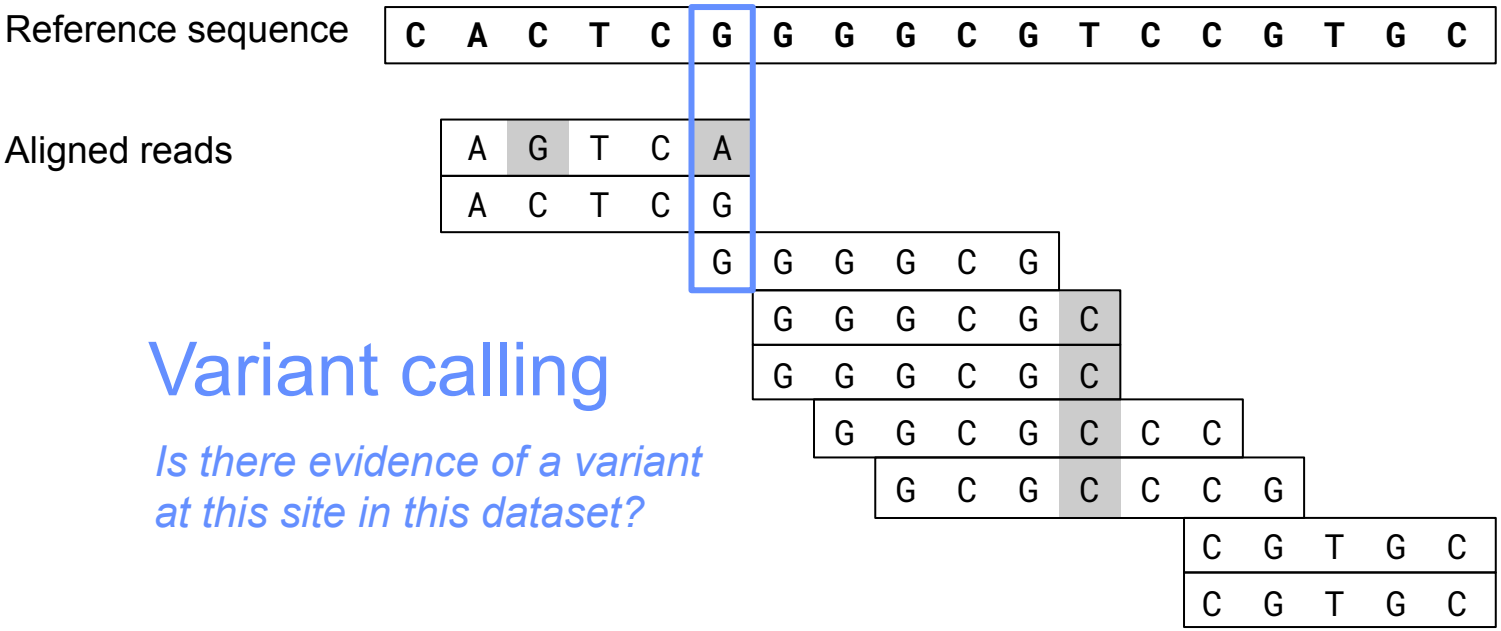


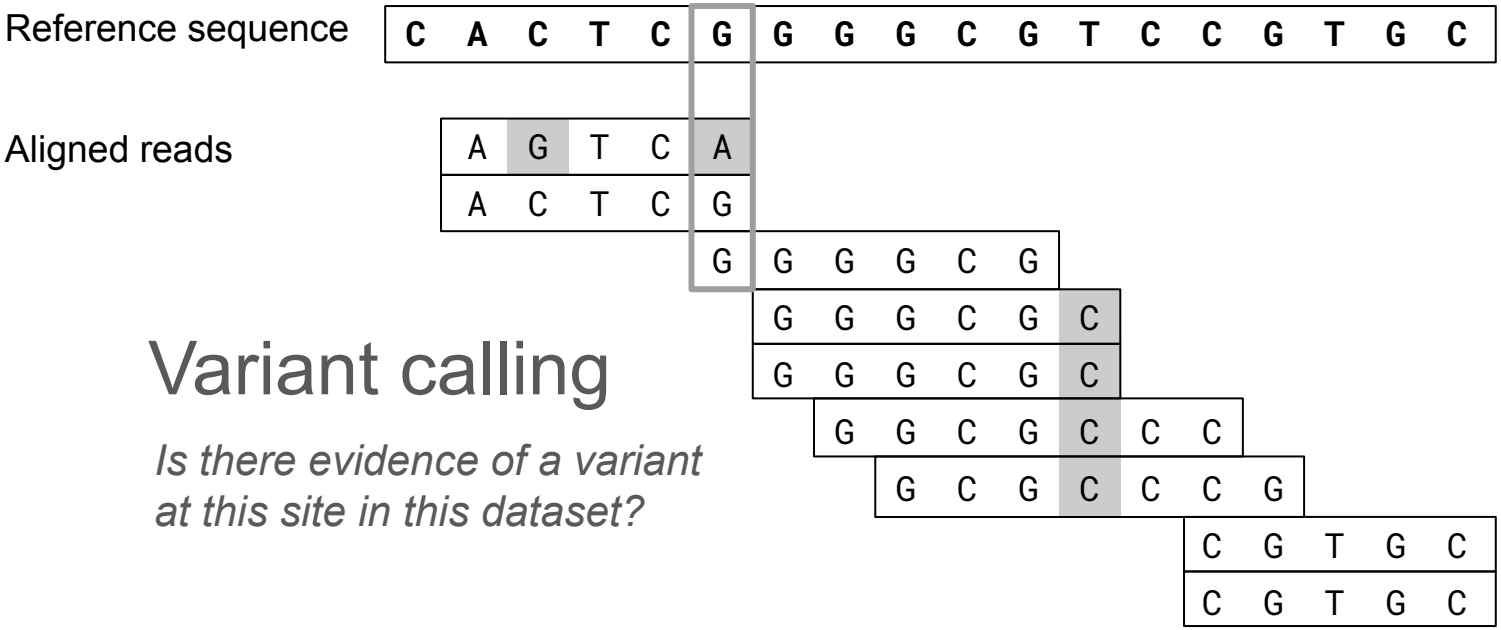
Variant calling

Is there evidence of a variant at this site in this dataset?

G/A?

Genotype calling

What are the genotypes for each individual?



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Genotype calling

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$$Pr(g|Data_i) = \frac{Pr(Data_i|g)Pr(g|f_x)}{Pr(Data_i)}$$

Probability of genotype g, given data for sample i

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Probability of genotype g, given data for sample i

$$= \frac{G_i(g)Pr(g|f_x)}{\sum_{g'} G_i(g')Pr(g'|f_x)}$$

Genotype calling

Genotype posterior (**GP**)

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Genotype priors

Genotype likelihoods
(**GL**, or **PL** if phred-scaled)

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#CHROM	POS	ID	REF	ALT	QUAL	FILTER	FORMAT	HG02461	HG02462
chr19	48693829	.	C	T	3357.45	.	GT:PL:GP	0/0:0,9,75:0.810234,0.189766,2.21701e-08	1/1:85,9,0:2.87613e-09,0.213018,0.786982
chr19	48693956	.	A	G	6806.98	.	GT:PL:GP	0/0:0,99,255:1,3.1458e-11,4.93632e-28	0/0:0,105,255:1,7.9019e-12,4.93632e-28
chr19	48693992	.	G	A	1802.53	.	GT:PL:GP	0/0:0,96,255:1,1.43086e-11,2.56527e-29	0/0:0,105,255:1,1.80134e-12,2.56527e-29

Genotype calling

Choose genotype with **highest probability**

Genotype posterior (**GP**)

$$Pr(g|Data_i) = \frac{Pr(Data_i|g)Pr(g|f_x)}{Pr(Data_i)}$$

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A few notes:

- Types of variants
- Single-sample vs. joint calling
- Types of errors

Variant types

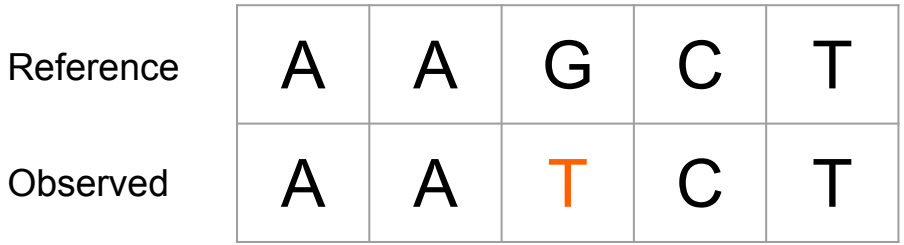
Variant types

Single-nucleotide polymorphism (SNP)

Insertion-deletion (indel)

Structural variant (SV)

Copy number variant (CNV)



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Copy number variant (CNV)

Insertion

A	A	G	C	T
A	A	TCGA	C	T

Deletion

A	A	GATT	C	T
A	A	T	C	T

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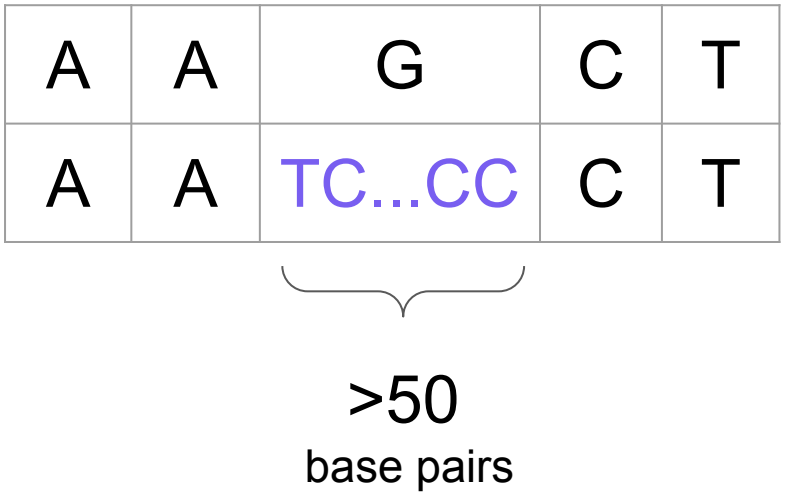

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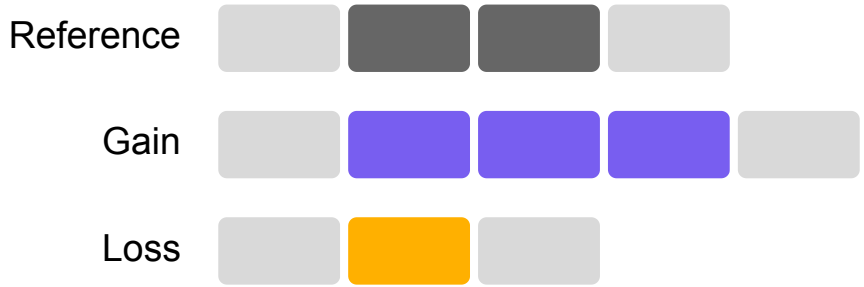

Calling types

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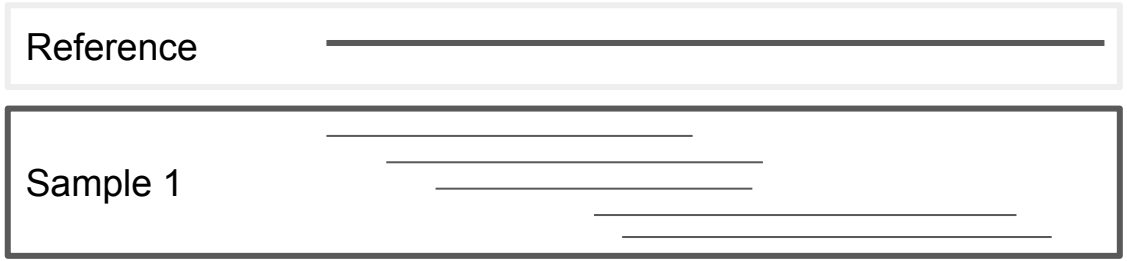
Single-sample calling

Joint calling

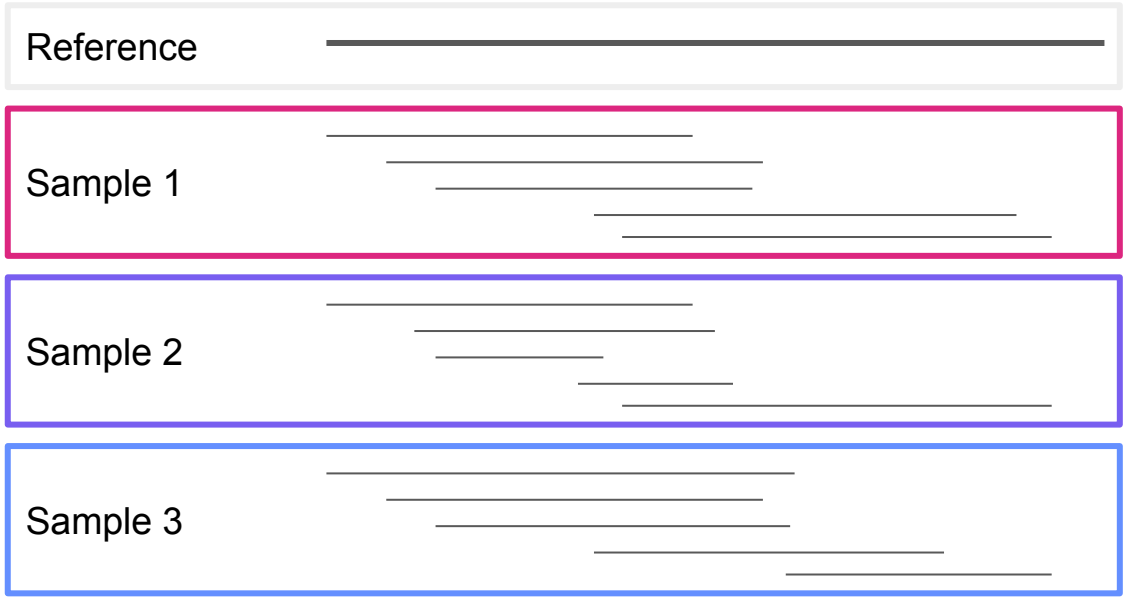


Calling types

Single-sample calling

Joint calling

Pros: Better at identifying rare variants
Cons: More computationally expensive



Error types

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Almost all variant callers rely on probabilistic models

(i.e. truly at random)

These models make assumptions – the biggest of which being that errors are **independent**

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Example: Independent errors

If there's a 0.01 chance of seeing G when truth is a C, the chance of seeing it 5 times is 0.01^5

Slide adapted from Luke Jostins-Dean

Error types

Almost all variant callers rely on probabilistic models

(i.e. truly at random)

These models make assumptions – the biggest of which being that errors are **independent**

> Example: Independent errors
>
> If there's a 0.01 chance of seeing G when truth is a C, the chance of seeing it 5 times is 0.01^5

But in practice, systematic (non-random) errors exist!

Slide adapted from Luke Jostins-Dean

Example: Context-specific errors

Truth	AGGGCAA
Sequencing	AGGGCAA
	AGGG**G**AA
	AGGGCAA
	AGGG**G**AA
	AGGG**G**AA

“GGG” motif

Slide adapted from Luke Jostins-Dean

Example: Context-specific errors

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Sequencing	AGGGCAA
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	AGGG**G**AA
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"GGG" motif

Solution: Strand bias test

Compare enrichment of alternate alleles in forward vs. reverse strands.

Slide adapted from Luke Jostins-Dean

Example: Context-specific errors

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Sequencing
AGGGCAA
AGGG**G**AA
AGGGCAA
AGGG**G**AA
AGGG**G**AA

"GGG" motif

Solution: Strand bias test

Compare enrichment of alternate alleles in forward vs. reverse strands.

Solution: Read position bias test

Correct for bias of sequencing errors typically occurring at the ends of reads.

Slide adapted from Luke Jostins-Dean

Example: Systematic mapping errors

Reference TCCACATGAACCACGTCTTGAAATC

Truth TCCACATGAACCACGT---GAAATC

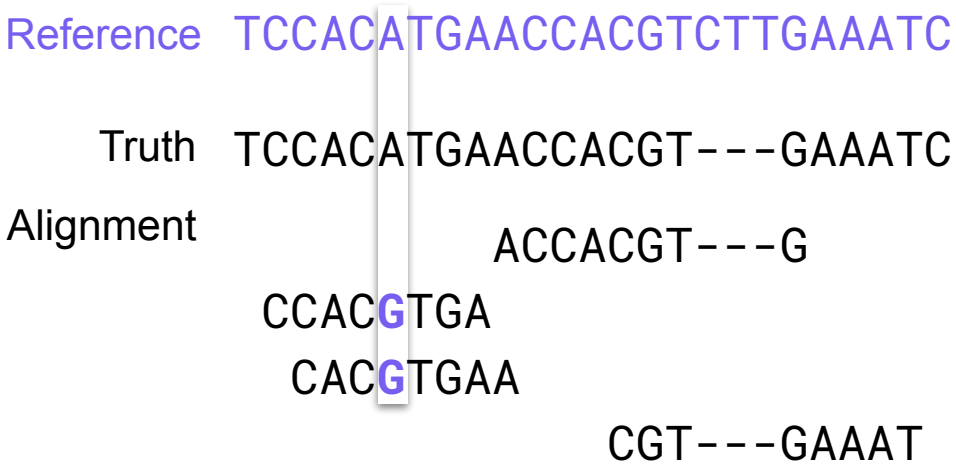
Alignment

```
ACCACGT---G
 CCACGT---GA
  CACGT---GAA
    CGT---GAAAT
```

This is the **true mapping**
(CTT deletion)

Slide adapted from Luke Jostins-Dean

Example: Systematic mapping errors

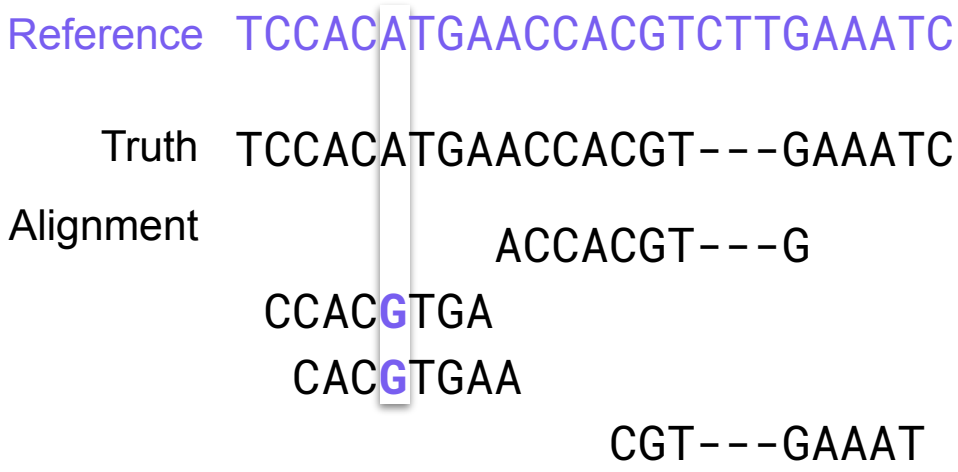


However, the alignment algorithm may lead to **incorrect mapping**.

This looks like a new SNP but the SNP doesn't exist!

Slide adapted from Luke Jostins-Dean

Example: Systematic mapping errors



Solution:
Mapping quality bias test

Test whether non-reference reads have lower quality.

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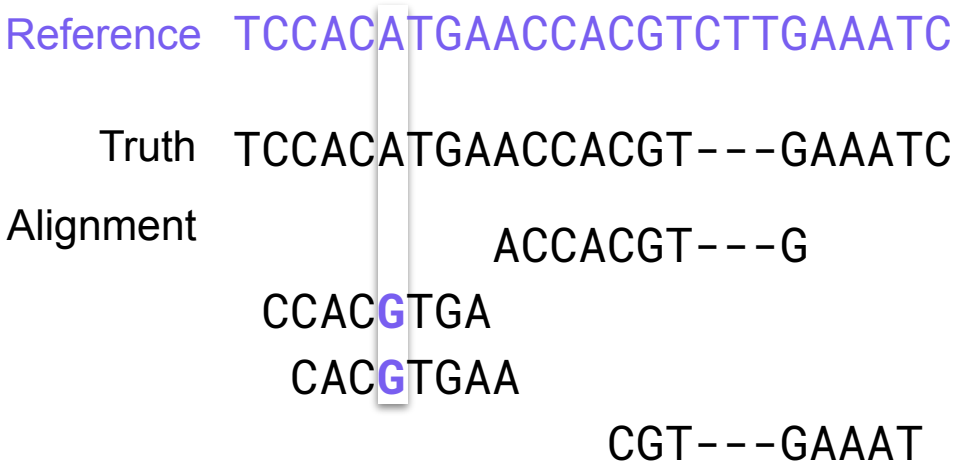
Slide adapted from Luke Jostins-Dean

Example: Systematic mapping errors



However, the alignment algorithm may lead to **incorrect mapping**.

This looks like a new SNP but the SNP doesn't exist!

Solution:
Mapping quality bias test

Test whether non-reference reads have lower quality.

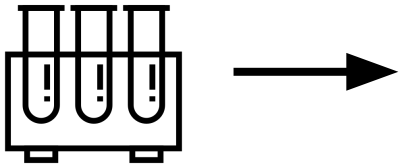
Solution: mapQ0

Remove variants with high counts of Q=0 reads

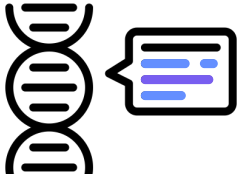
Slide adapted from Luke Jostins-Dean

Overview

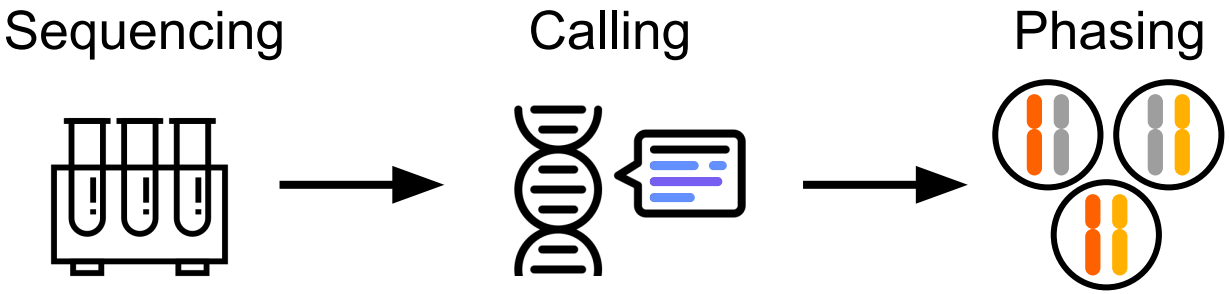
Sequencing



Calling

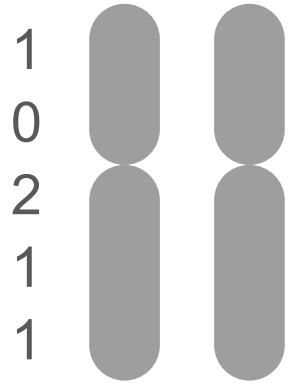


Overview

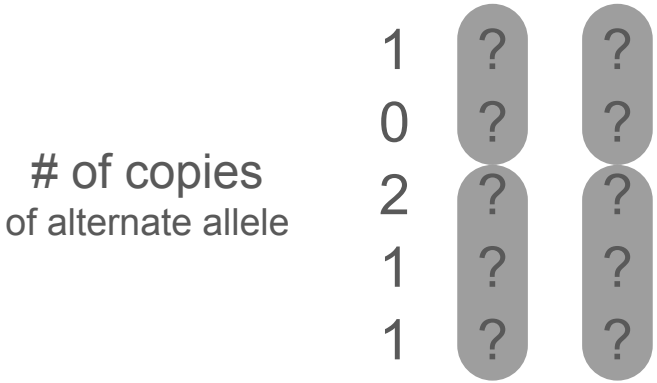



A/G
T/T
G/G
A/T
T/G

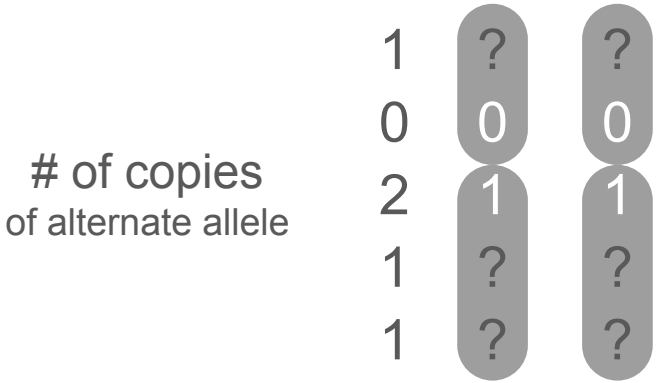
# of copies
of alternate allele



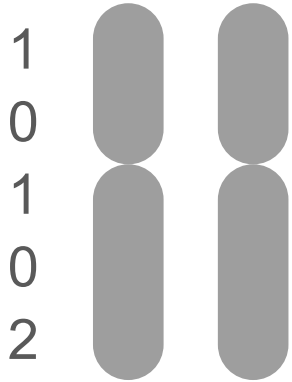
How to separate genotype into haplotypes?

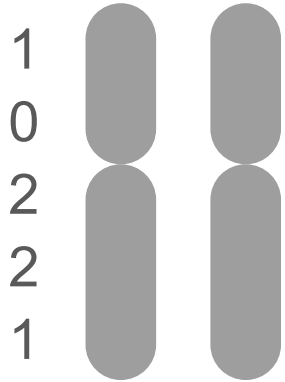


How to separate genotype into haplotypes?



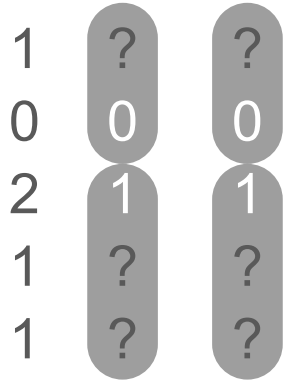
Mother



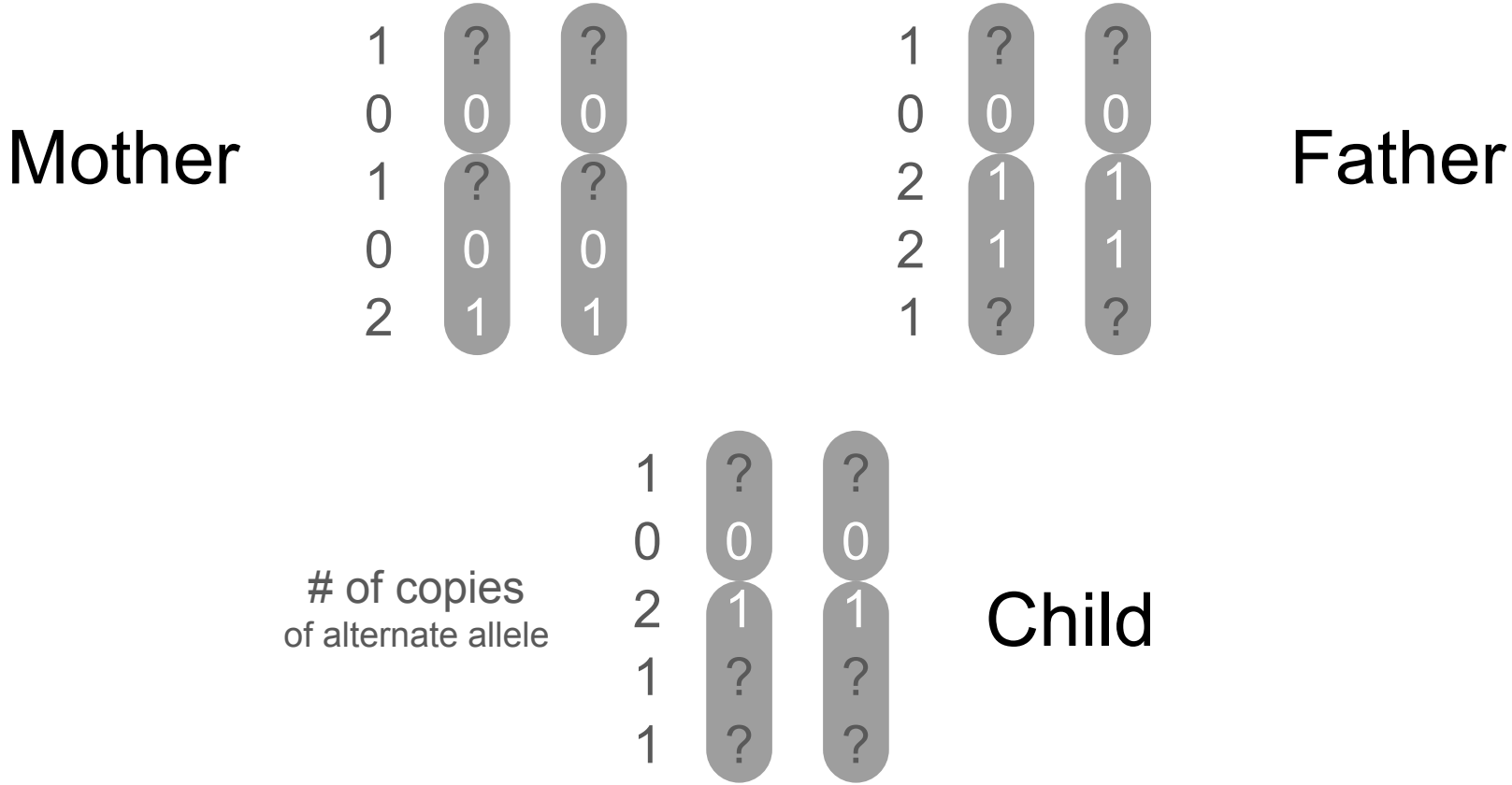


Father

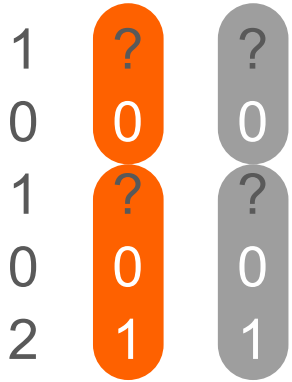
# of copies
of alternate allele

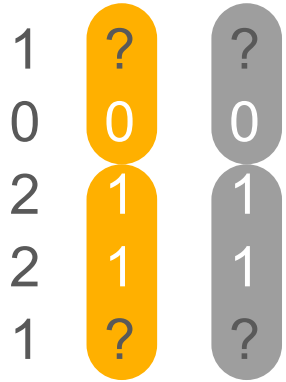


Child


Mother
1 ? ?
0 0 0
1 ? ?
0 0 0
2 1 1
1 ? ?
0 0 0
2 1 1
2 1 1
1 ? ?
Father
# of copies
of alternate allele
1 ? ?
0 0 0
2 1 1
1 ? ?
1 ? ?
Child

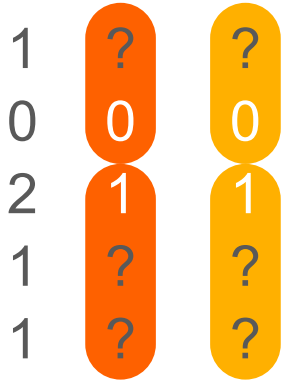
Mother





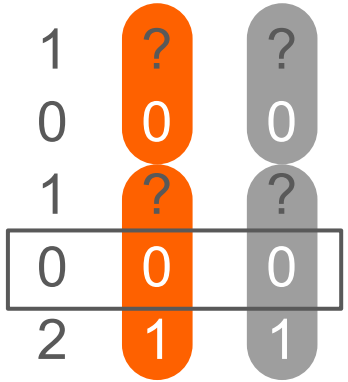
Father

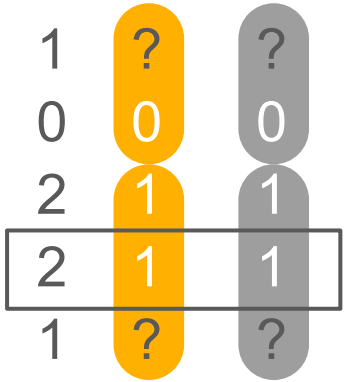
# of copies
of alternate allele



Child

Mother





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# of copies
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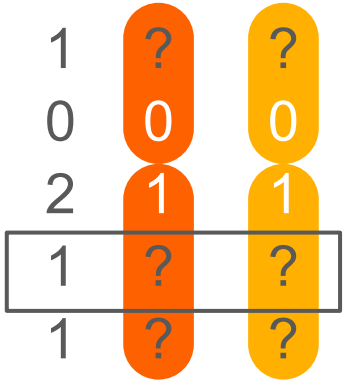
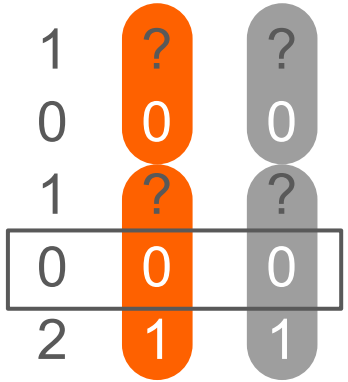
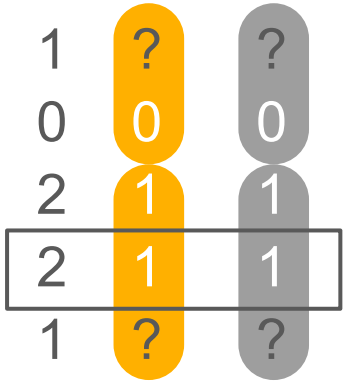


Child

Mother





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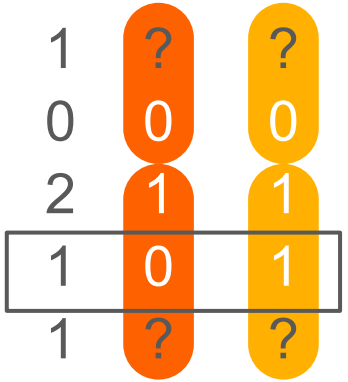
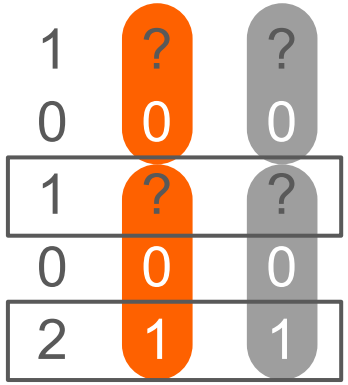
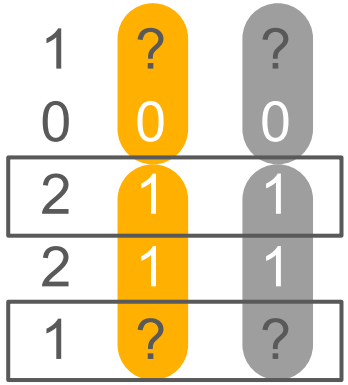


Child

Mother





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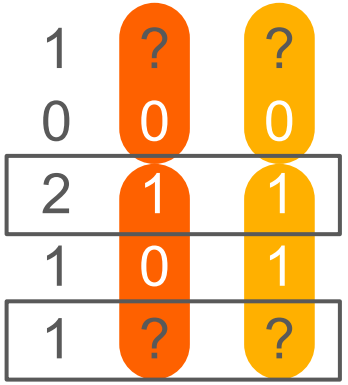
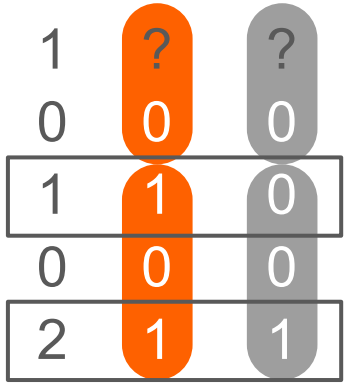
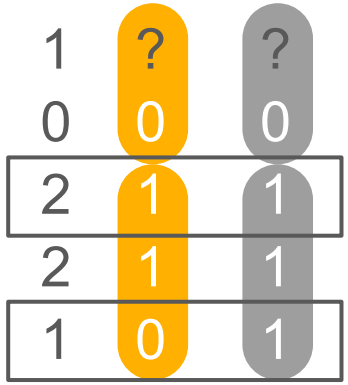


Child

Mother





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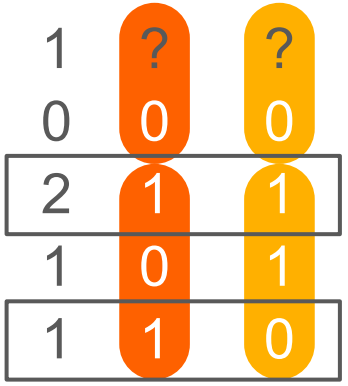
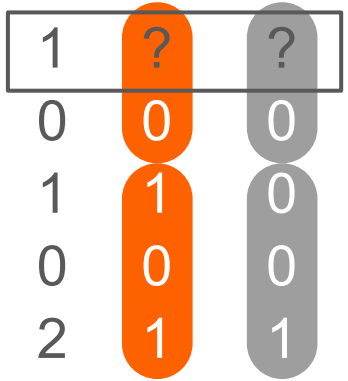
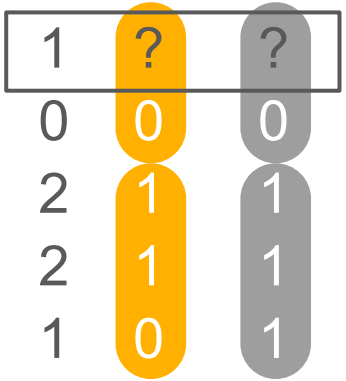
# of copies
of alternate allele



Child

Mother





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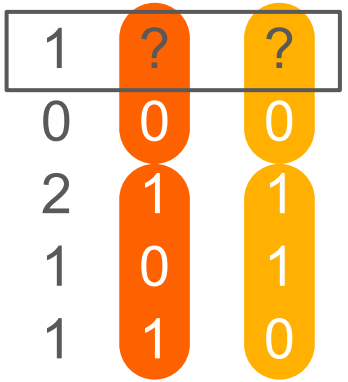
# of copies
of alternate allele



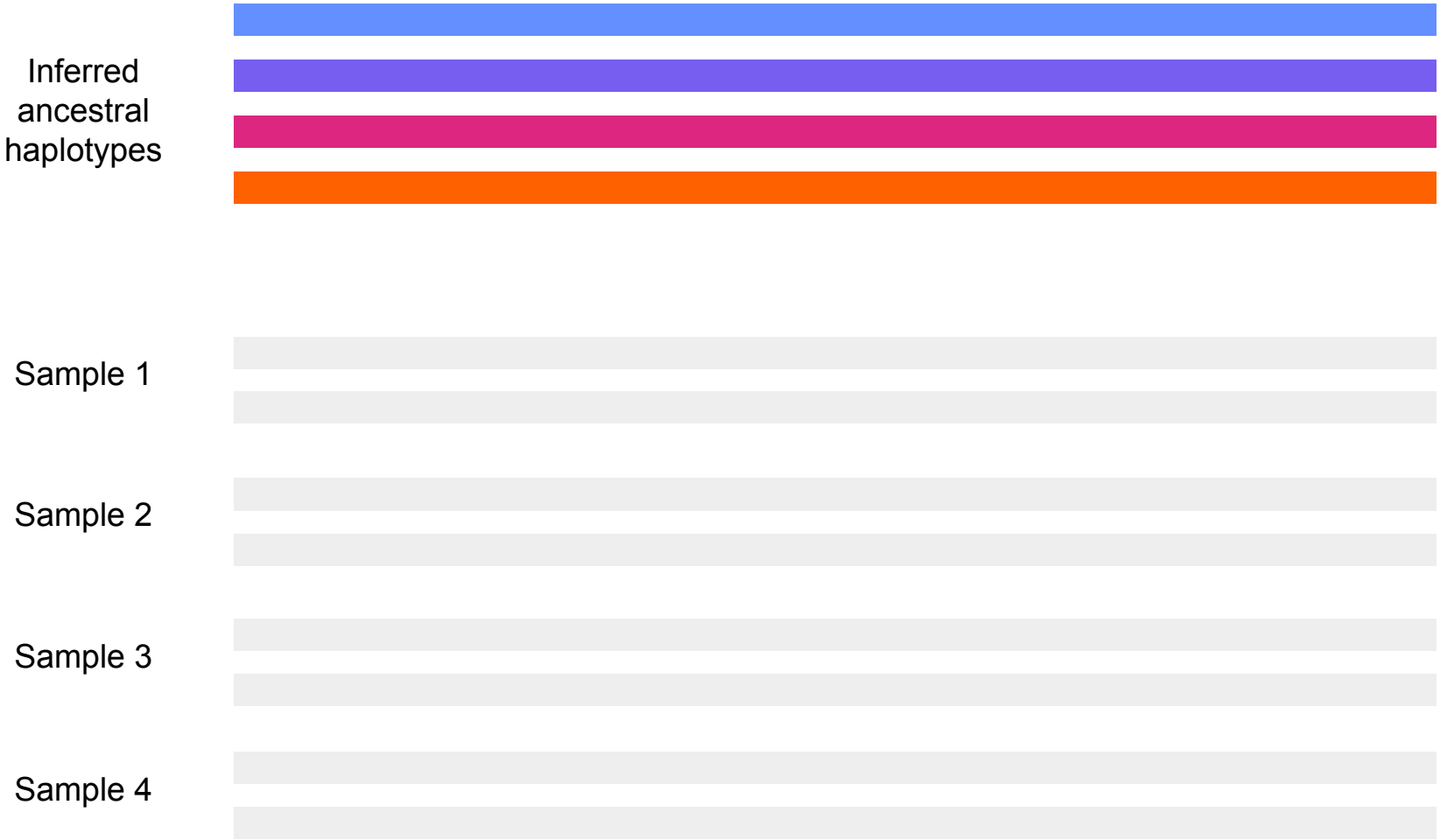
Child

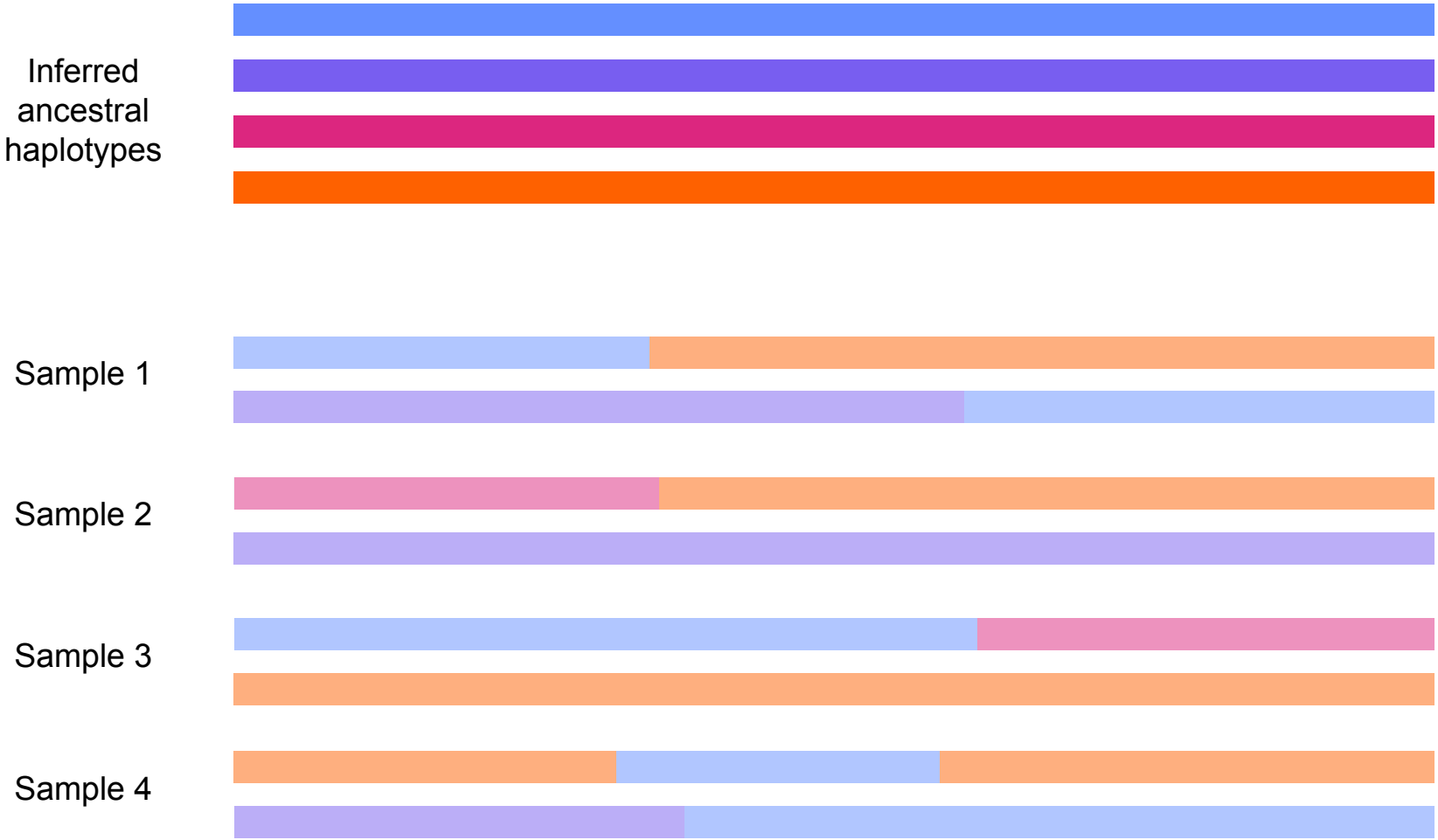
Sample 1

Sample 2

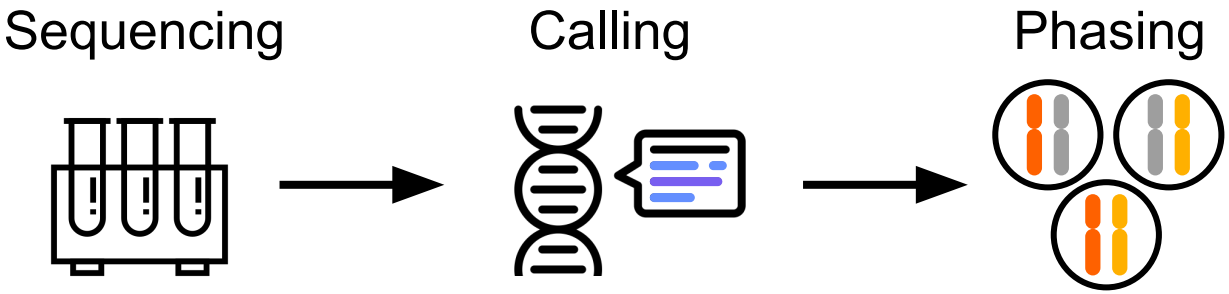
Sample 3

Sample 4

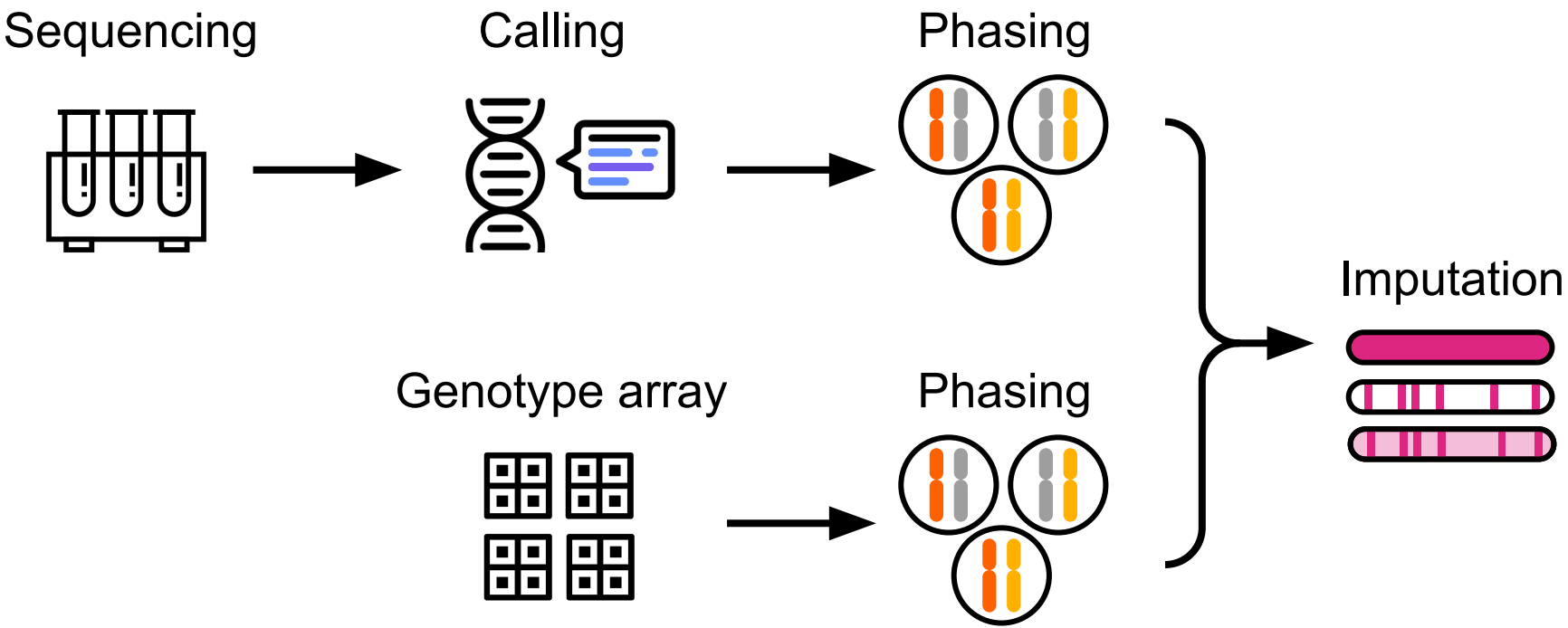

Inferred ancestral haplotypes
Sample 1
Sample 2
Sample 3
Sample 4


Inferred ancestral haplotypes
Sample 1
Sample 2
Sample 3
Sample 4

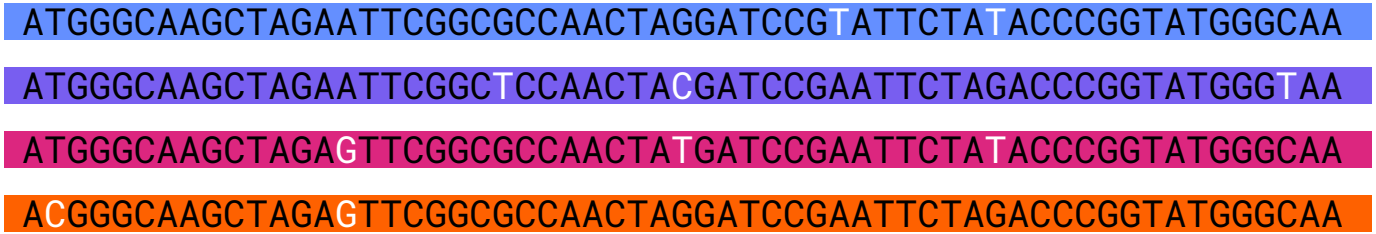
Overview



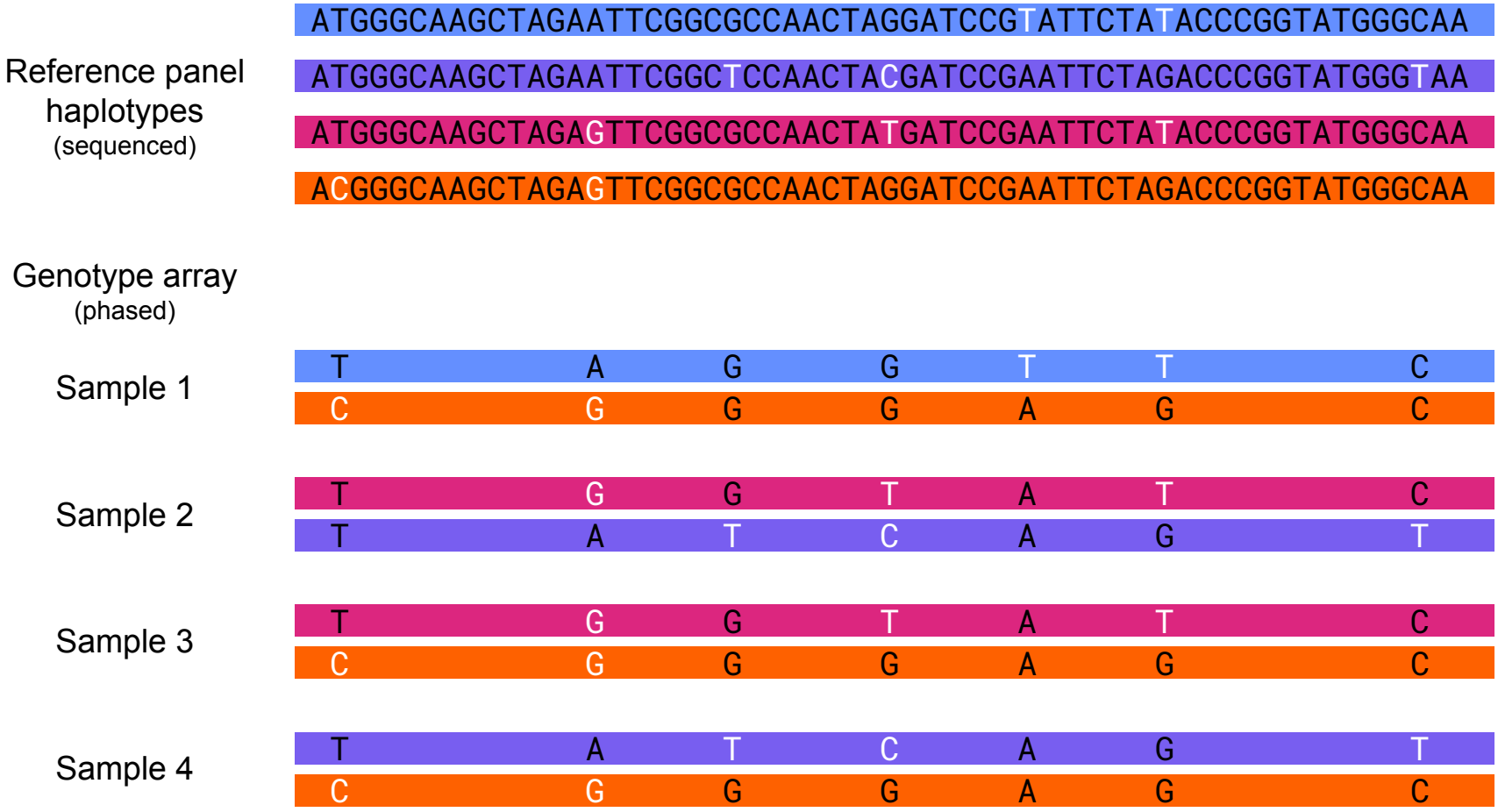
Overview


Sequencing
Calling
Phasing
Imputation
Genotype array
Phasing

Reference panel haplotypes
(sequenced)




Reference panel haplotypes
(sequenced)
ATGGGCAAGCTAGAATTCGGCGCCAACTAGGATCCGTATTCTATACCCGGTATGGGCAA
ATGGGCAAGCTAGAATTCGGCTCCAACTACGATCCGAATTCTAGACCCGGTATGGGTAA
ATGGGCAAGCTAGAGTTCGGCGCCAACTATGATCCGAATTCTATACCCGGTATGGGCAA
ACGGGCAAGCTAGAGTTCGGCGCCAACTAGGATCCGAATTCTAGACCCGGTATGGGCAA
Genotype array
(phased)
Sample 1
T A G G T T C
C G G G A G C
Sample 2
T G G T A T C
T A T C A G T
Sample 3
T G G T A T C
C G G G A G C
Sample 4
T A T C A G T
C G G G A G C


Reference panel haplotypes
(sequenced)
ATGGGCAAGCTAGAATTCGGCGCCAACTAGGATCCGTATTCTATACCCGGTATGGGCAA
ATGGGCAAGCTAGAATTCGGCTCCAACTACGATCCGAATTCTAGACCCGGTATGGGTAA
ATGGGCAAGCTAGAGTTCGGCGCCAACTATGATCCGAATTCTATACCCGGTATGGGCAA
ACGGGCAAGCTAGAGTTCGGCGCCAACTAGGATCCGAATTCTAGACCCGGTATGGGCAA
Genotype array
(phased)
Sample 1
T A G G T T C
C G G G A G C
Sample 2
T G G T A T C
T A T C A G T
Sample 3
T G G T A T C
C G G G A G C
Sample 4
T A T C A G T
C G G G A G C


Reference panel haplotypes (sequenced)
ATGGGCAAGCTAGAATTCGGCGCCAACTAGGATCCGTATTCTATACCCGGTATGGGCAA
ATGGGCAAGCTAGAATTCGGCTCCAACTACGATCCGAATTCTAGACCCGGTATGGGTAA
ATGGGCAAGCTAGAGTTCGGCGCCAACTATGATCCGAATTCTATACCCGGTATGGGCAA
ACGGGCAAGCTAGAGTTCGGCGCCAACTAGGATCCGAATTCTAGACCCGGTATGGGCAA
Genotype array (phased)
Sample 1
ATGGGCAAGCTAGAATTCGGCGCCAACTAGGATCCGTATTCTATACCCGGTATGGGCAA
ACGGGCAAGCTAGAGTTCGGCGCCAACTAGGATCCGAATTCTAGACCCGGTATGGGCAA
Sample 2
ATGGGCAAGCTAGAGTTCGGCGCCAACTATGATCCGAATTCTATACCCGGTATGGGCAA
ATGGGCAAGCTAGAATTCGGCTCCAACTACGATCCGAATTCTAGACCCGGTATGGGTAA
Sample 3
ATGGGCAAGCTAGAGTTCGGCGCCAACTATGATCCGAATTCTATACCCGGTATGGGCAA
ACGGGCAAGCTAGAGTTCGGCGCCAACTAGGATCCGAATTCTAGACCCGGTATGGGCAA
Sample 4
ATGGGCAAGCTAGAATTCGGCTCCAACTACGATCCGAATTCTAGACCCGGTATGGGTAA
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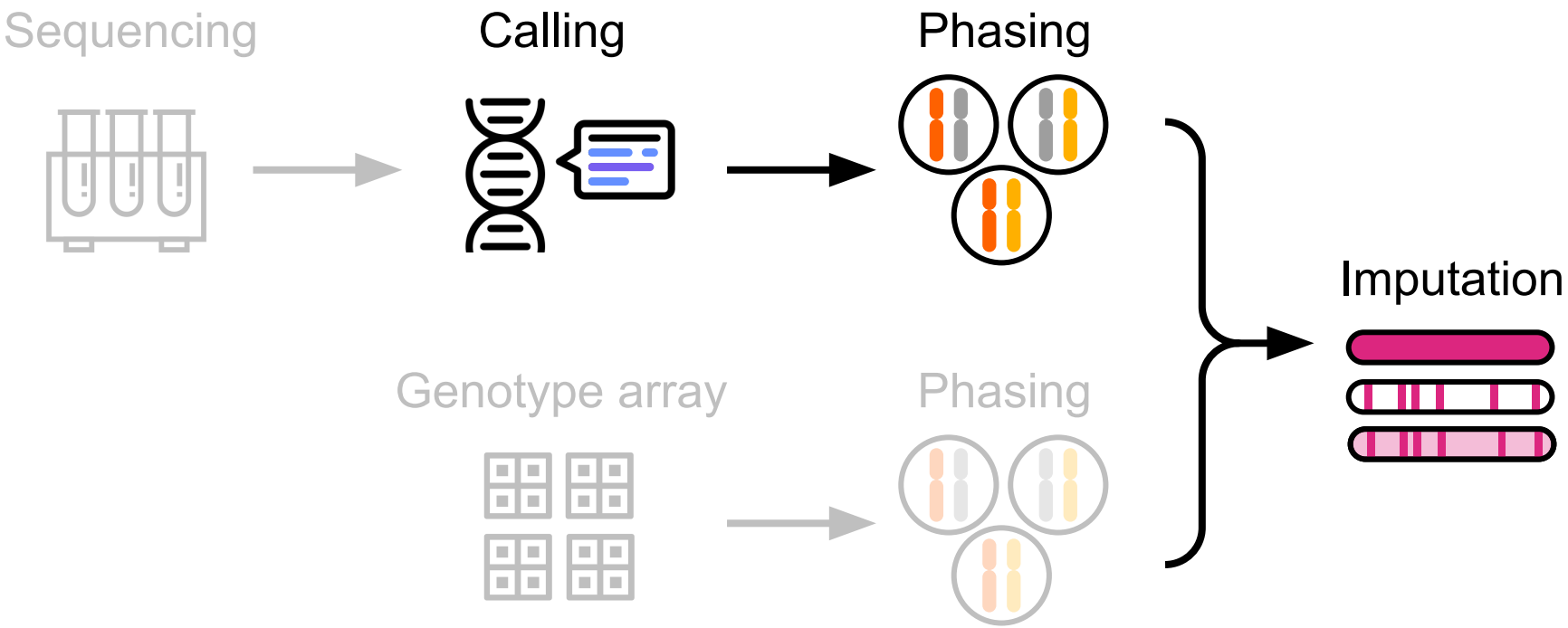
Practical


Sequencing
Calling
Phasing
Imputation
Genotype array
Phasing