

# Haplotype Phasing and Genotype Imputation

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# Outline

- Haplotype estimation
- Genotype imputation
- Refining genotype calls
- Imputation performance
- Reference panels for imputation
- Information on the practical

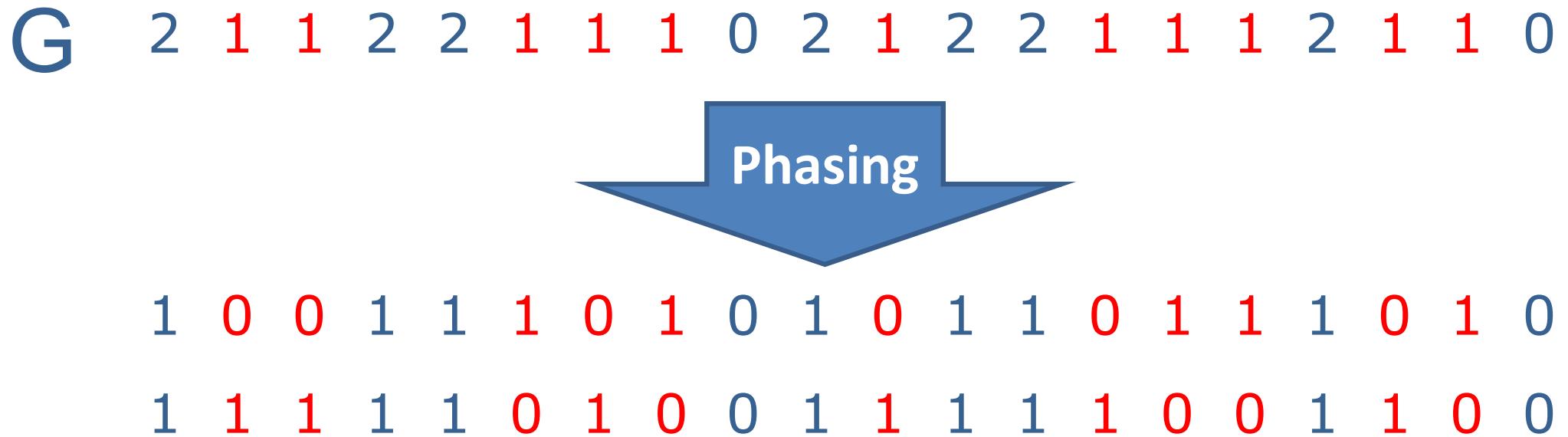
# Haplotype estimation

We observe genotypes for each individual

G 2 1 1 2 2 1 1 1 0 2 1 2 2 1 1 1 2 1 1 0

# Haplotype estimation

We observe genotypes for each individual



We want to recover the underlying haplotypes

Complex problem:

N heterozygotes  $\rightarrow 2^N$  haplotypes

N heterozygotes  $\rightarrow 2^{N-1}$  pairs of haplotypes

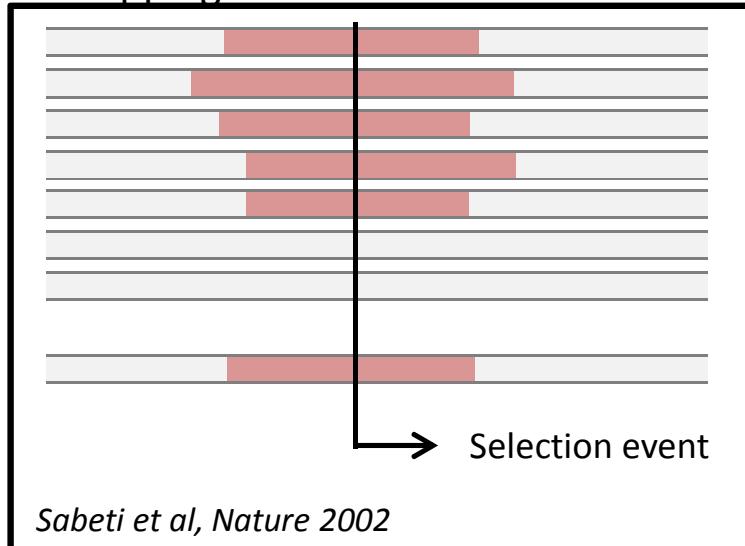
# Haplotypes in disease genetics

Estimation of haplotypes from array-based and sequencing studies is an important problem for multiple reasons:

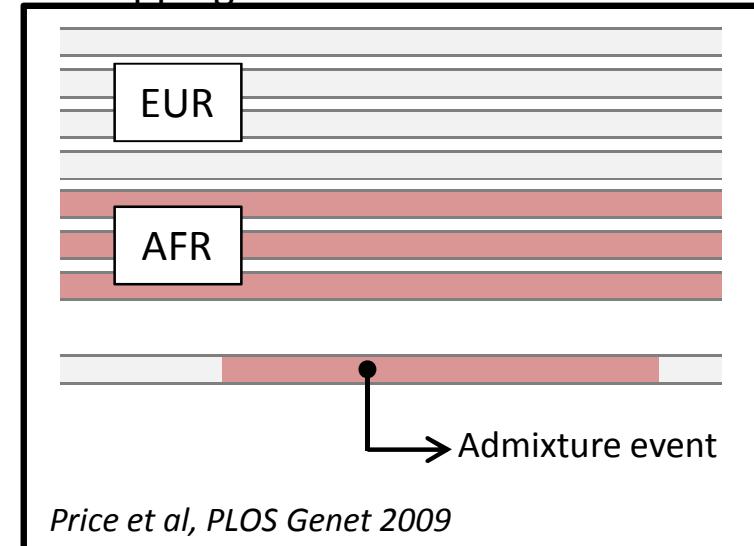
1. Construction of reference panels of haplotypes (HapMap, 1000 Genomes, UK10K, GoNL, etc...).
2. Imputation of Genome Wide Association Studies (i.e. GWAS).
3. Detection of novel associations in GWAS or fine-mapping of known effects e.g. compound heterozygotes.

# Haplotypes in population genetics

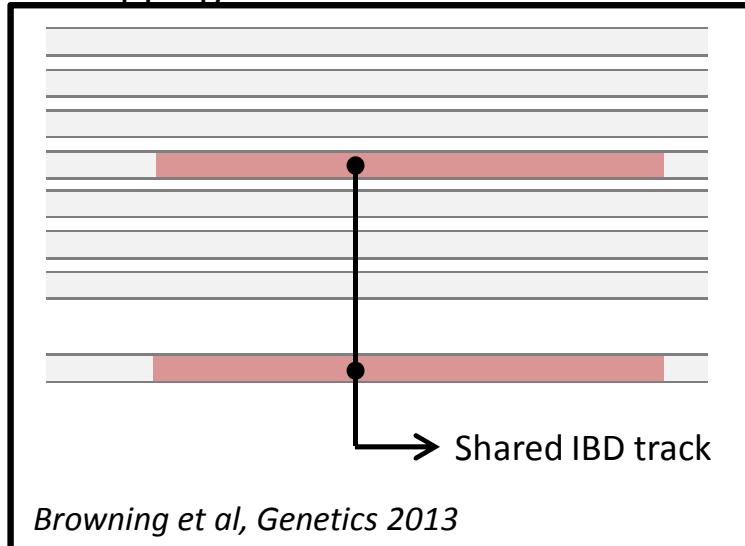
1. Mapping selection



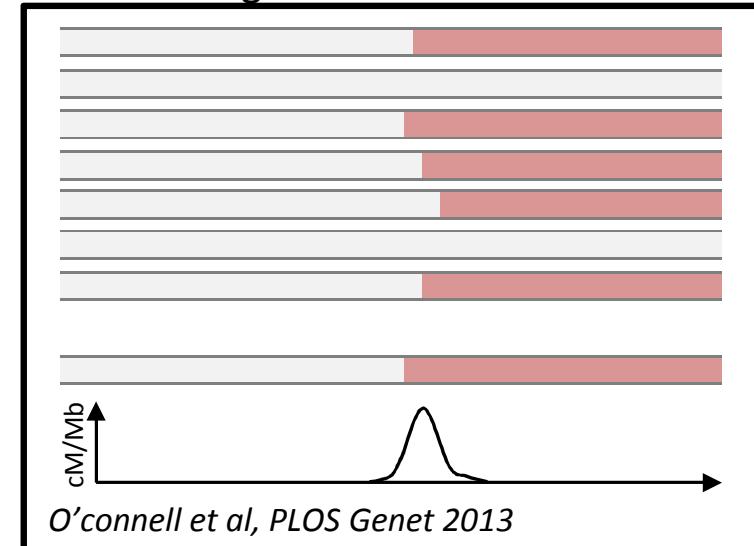
3. Mapping admixture



2. Mapping IBD



4. Estimating recombination rates



# Basic idea of phasing

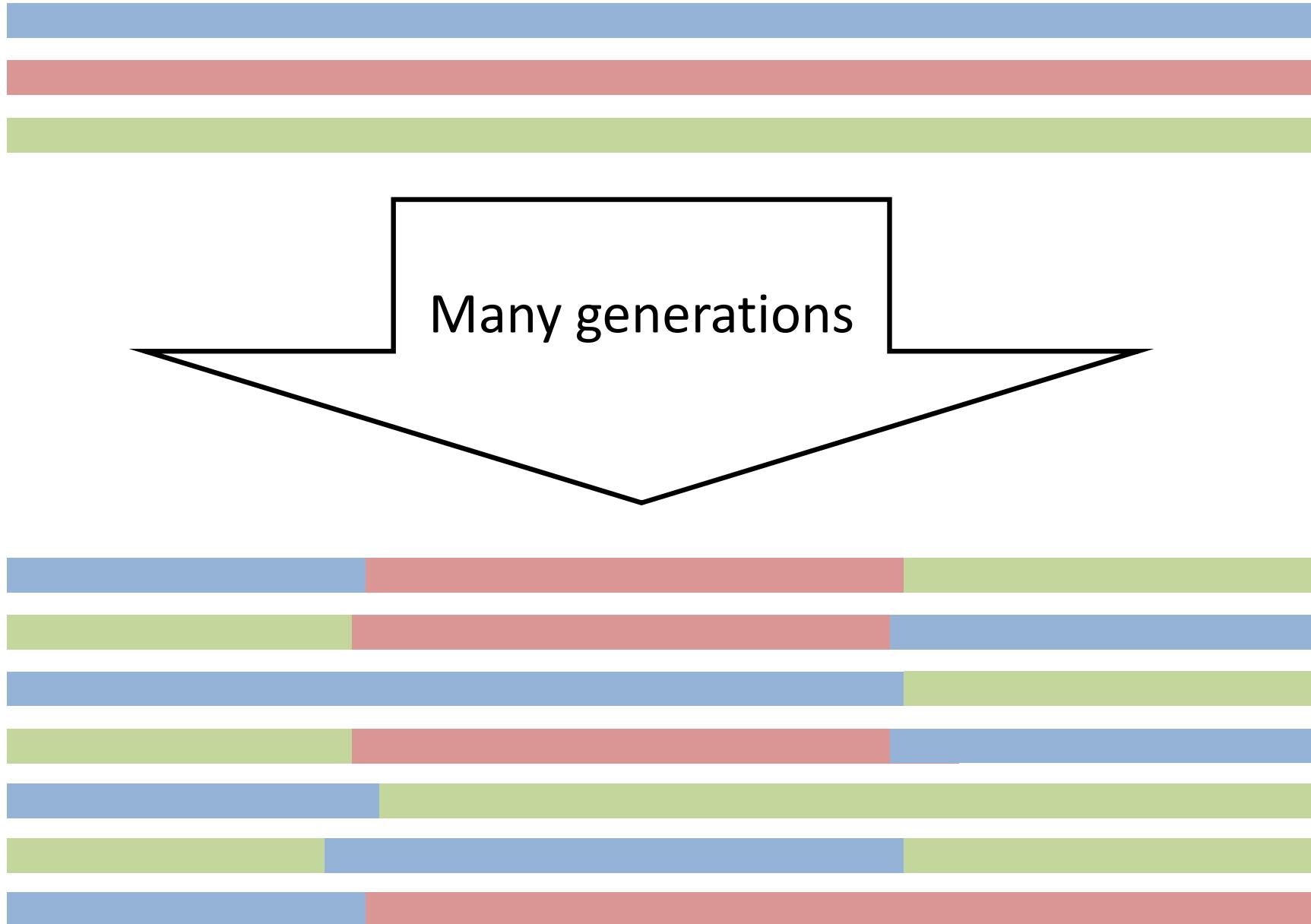
$H$  00110101 11001010 00110101 11101111 11101111 11001010 11000010 00010101 11101010 11000010 11101010 11101010 11101010 00111101 00111101 11101111 00110101 00110101 11000101 11000101 00010000

G 2 1 1 2 2 1 1 1 0 2 1 2 2 1 1 1 2 1 1 0

# Haplotype estimation works iteratively:

It takes each individuals genotype vector (**G**) in turn and estimates the underlying haplotypes using the current haplotype estimates of other individuals (**H**).

# Haplotype structure



Individuals share stretches of haplotypes inherited from common ancestors

# Basic idea of phasing

H	0	1	0	1	1	1	1	0	1	0	1	1	1	1	0	0	0	1	0	1	1	0
	0	1	0	1	1	1	1	0	1	0	1	1	1	1	0	0	0	1	1	0	1	0
	1	0	1	1	1	1	0	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0
	1	0	1	1	0	0	1	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1
	1	0	1	0	1	1	1	1	0	1	0	0	1	0	1	1	1	1	1	1	1	0
	0	1	0	1	1	1	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	0
	1	0	1	1	1	0	1	1	0	1	0	0	1	0	1	0	0	1	1	0	1	0
G	2	1	1	2	2	1	1	1	1	0	2	1	2	2	1	1	1	1	2	1	1	0
	1	0	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	1	1	1	0	0
	0	1	0	1	1	1	0	1	1	0	1	1	1	1	0	0	1	1	0	1	1	0

It uses Hidden Markov Models (*Li and Stephens, 2005*) that models the underlying haplotypes as mosaics of haplotypes of other individuals.

# Popular phasing methods

There are several popular methods for haplotype estimation from genotype data:

**MACH** - <http://www.sph.umich.edu/csg/abecasis/MACH/>

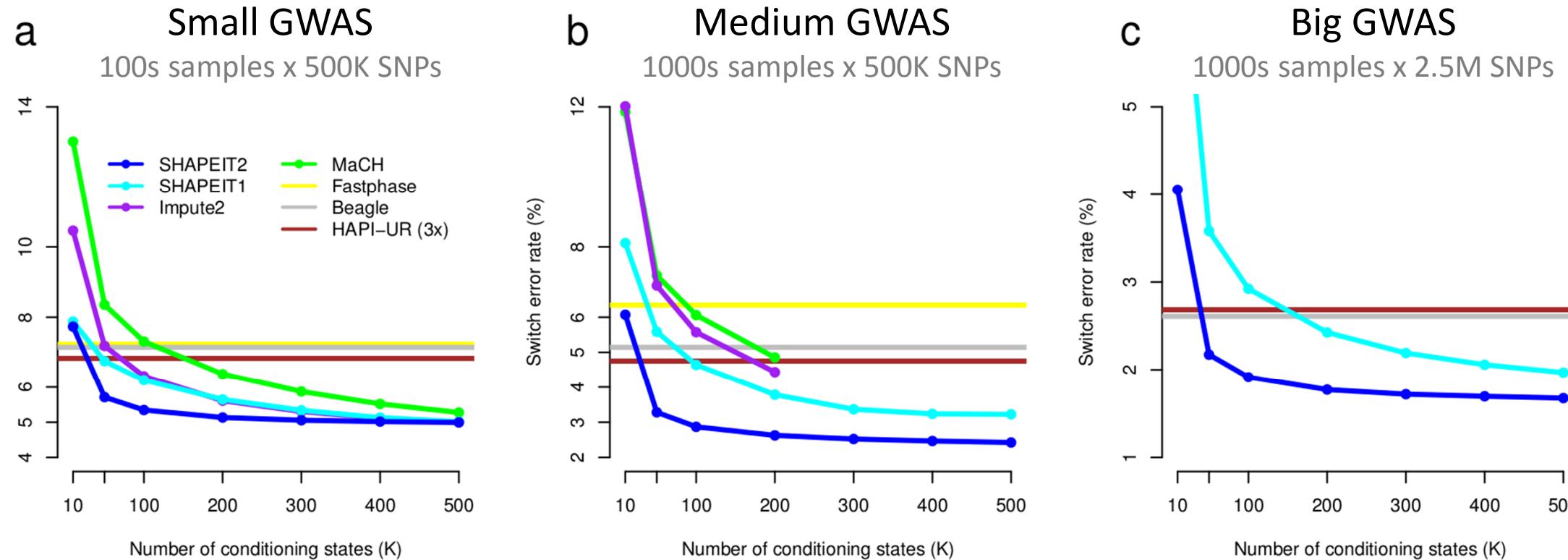
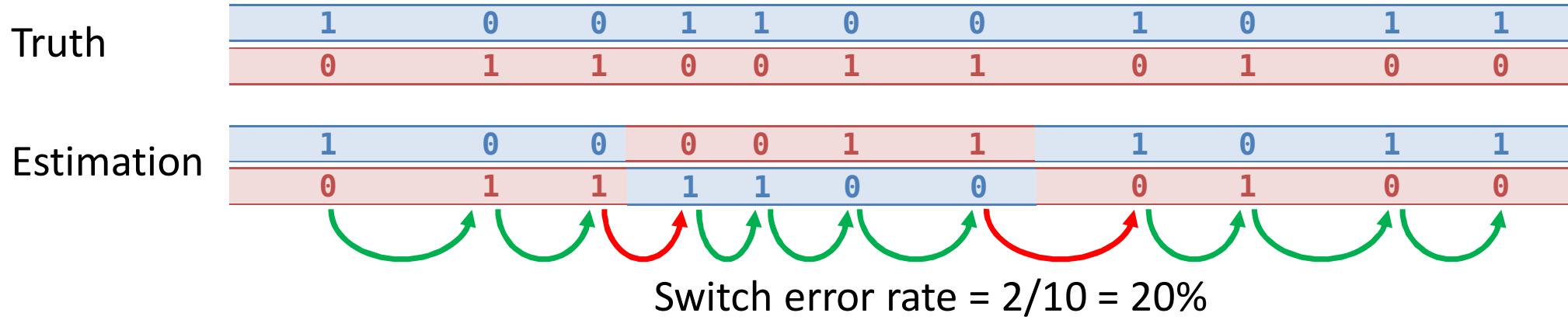
**BEAGLE** - <http://faculty.washington.edu/browning/beagle/beagle.html>

**SHAPEIT2** - [http://mathgen.stats.ox.ac.uk/genetics\\_software/shapeit/shapeit.html](http://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html)

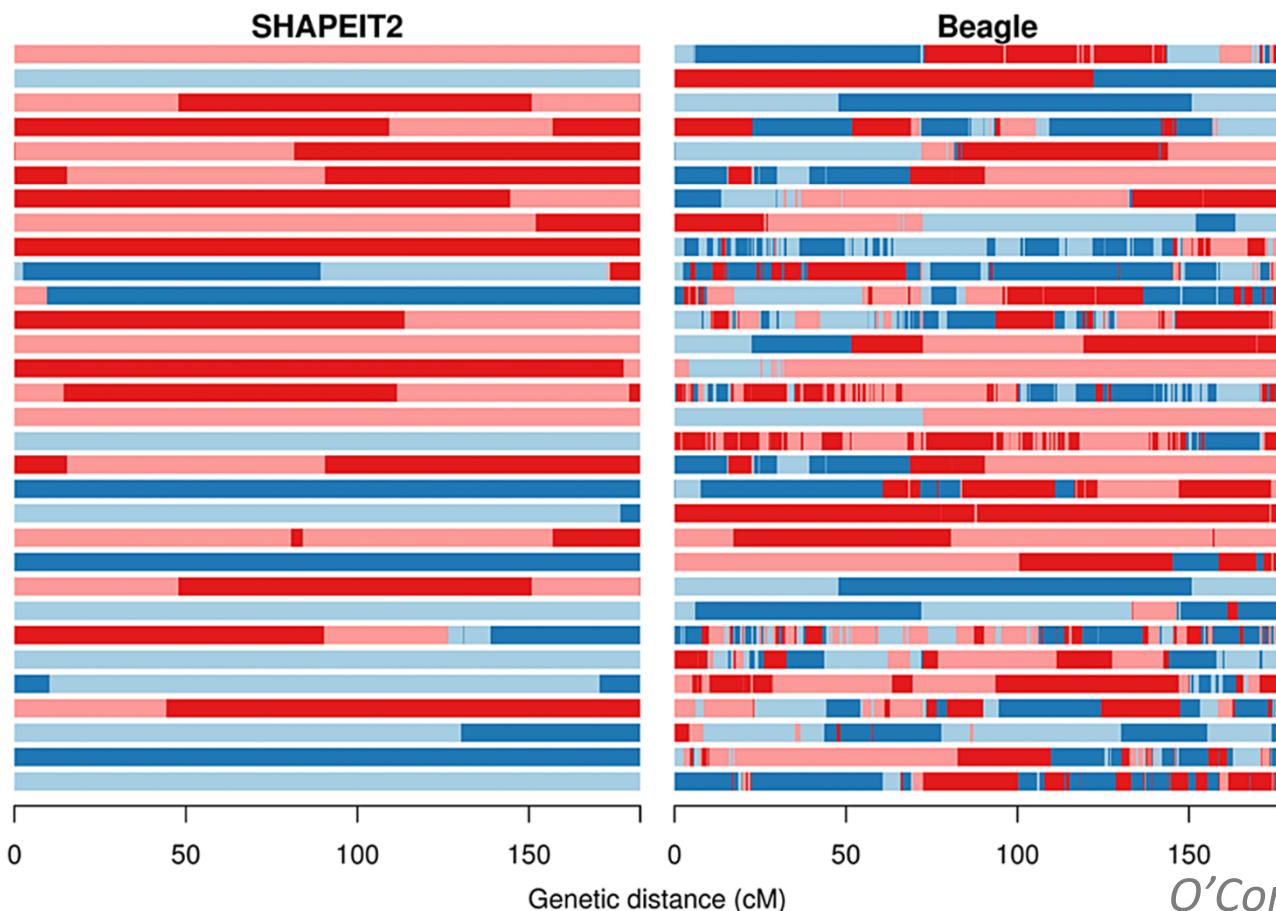
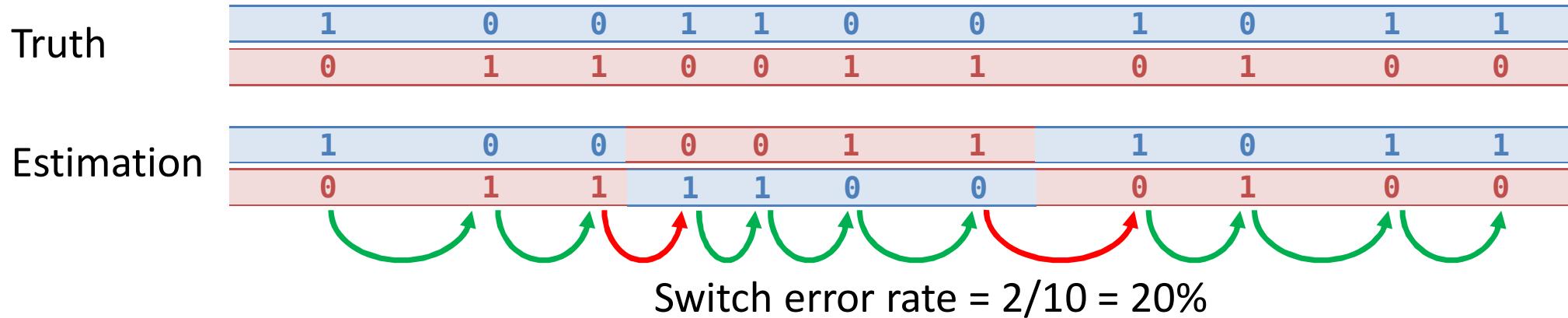
**EAGLE** - <https://data.broadinstitute.org/alkesgroup/Eagle/>

**SHAPEIT3** - [http://mathgen.stats.ox.ac.uk/genetics\\_software/shapeit/shapeit.html](http://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html)

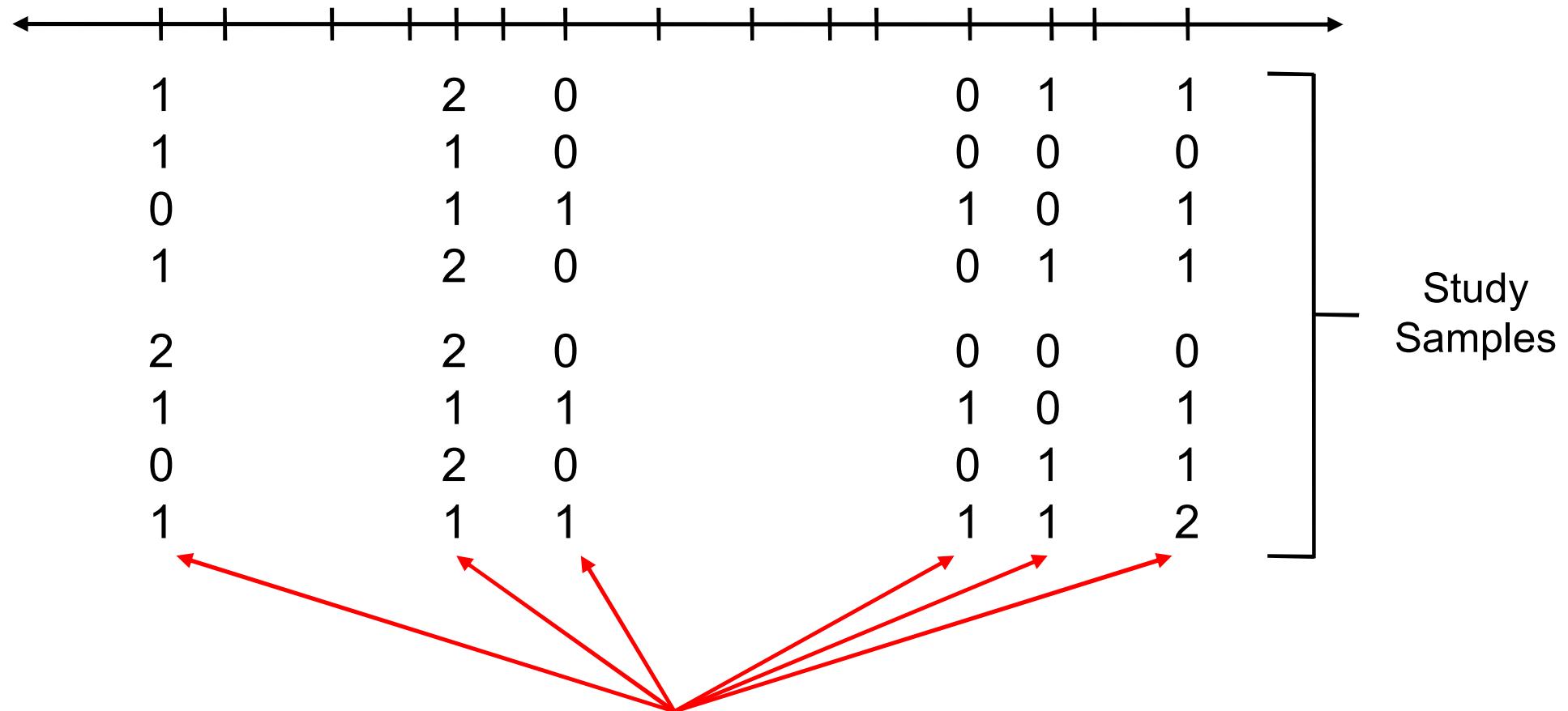
# Measuring performance



# Measuring performance

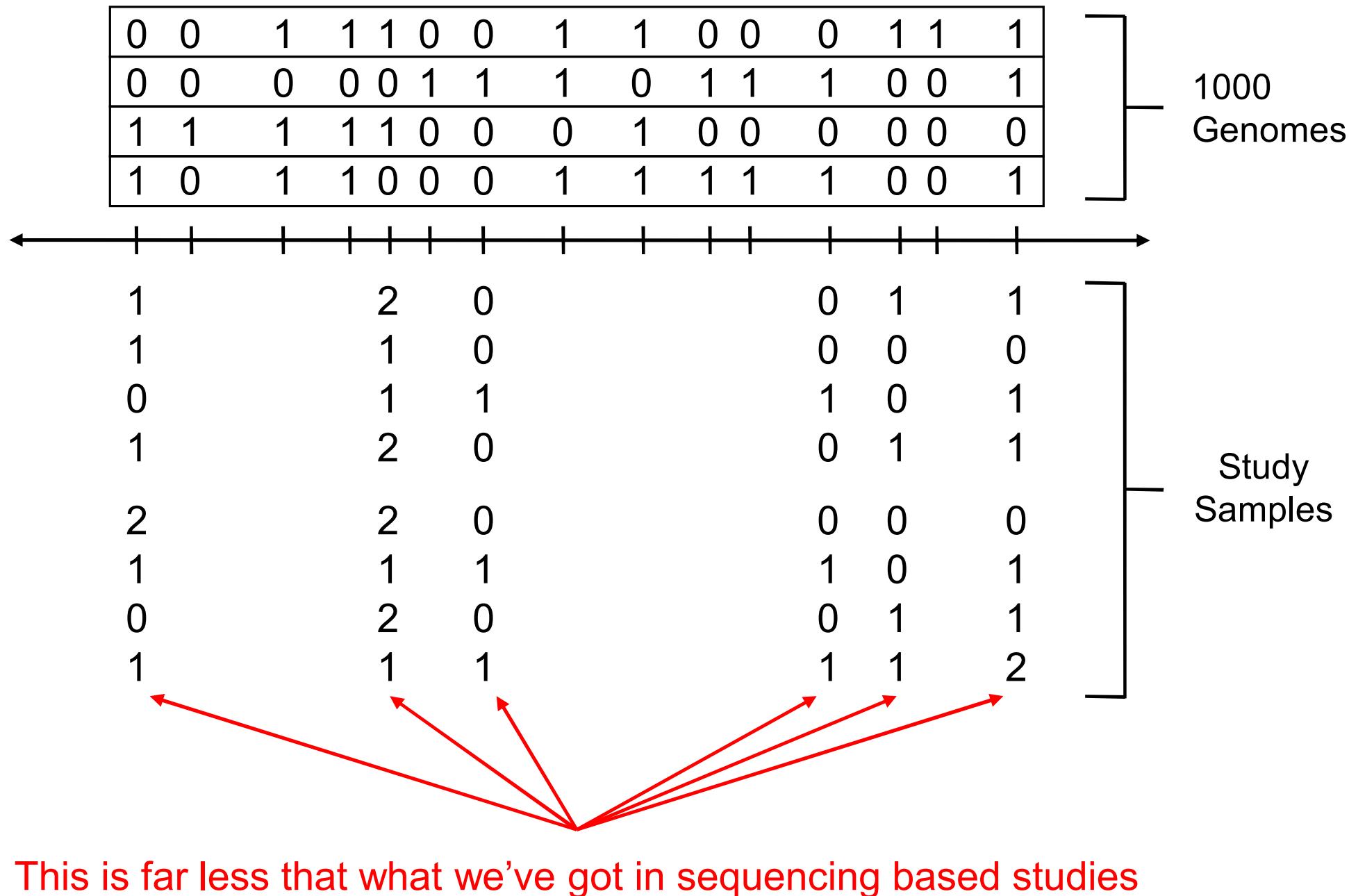


# Limitation of genotyping data

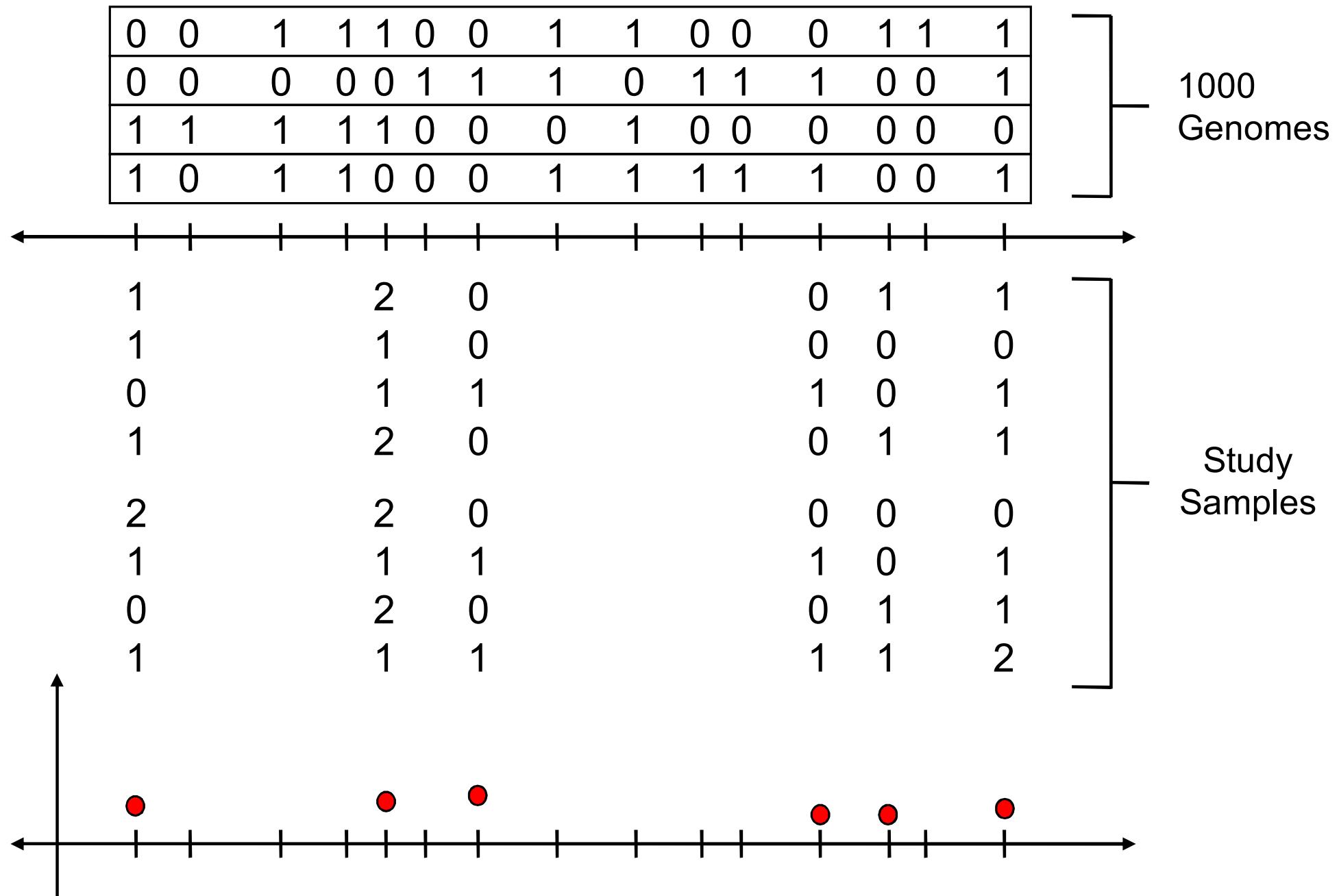


SNPs genotyped in a genomic study: 1 to 5M variants, 100s to 1000s of samples

# Limitation of genotyping data



# Limitation of genotyping data



# Solution: Imputation

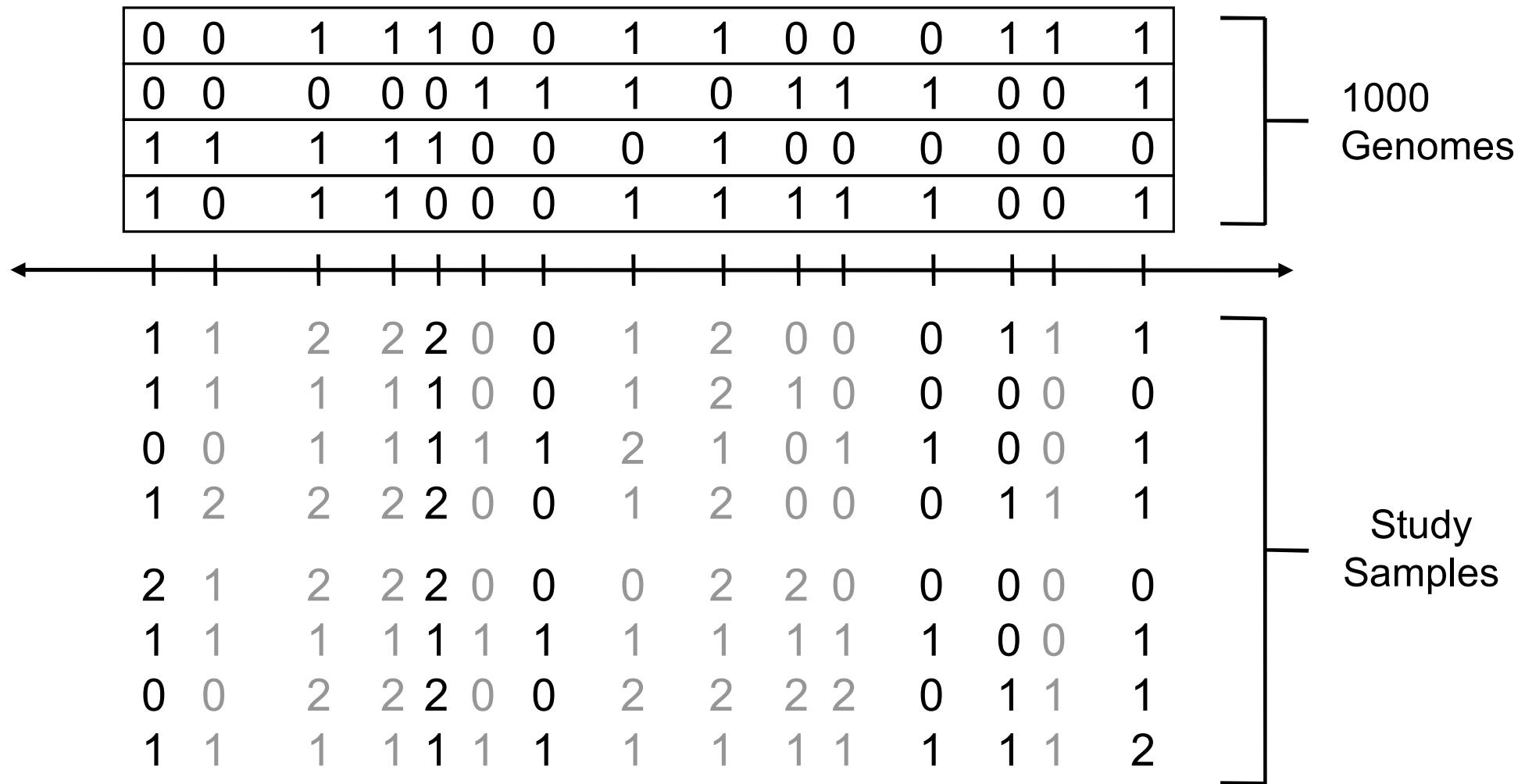
← →

1000 Genomes

Study Samples

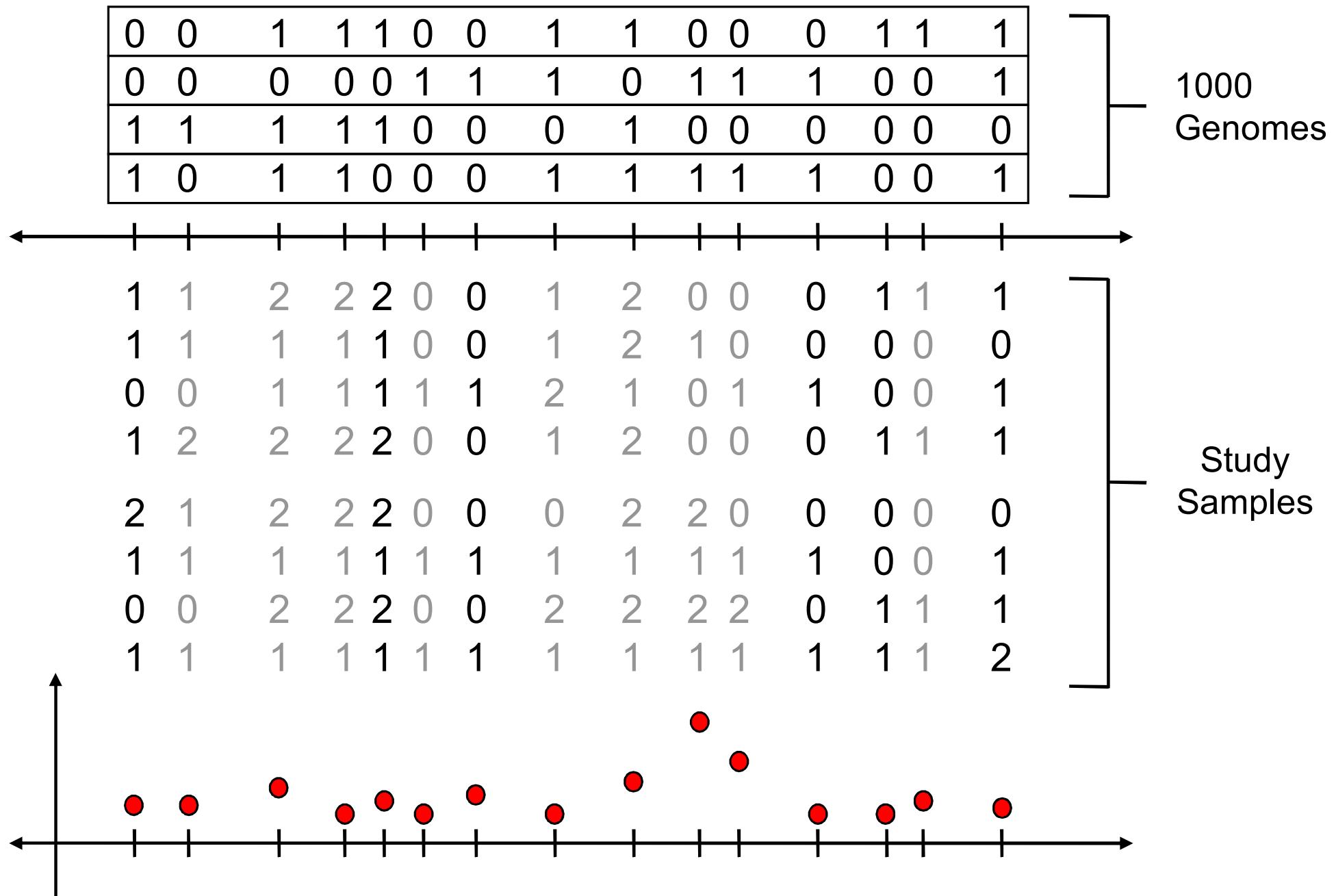
Un-typed variants are treated as missing data.

# Solution: Imputation

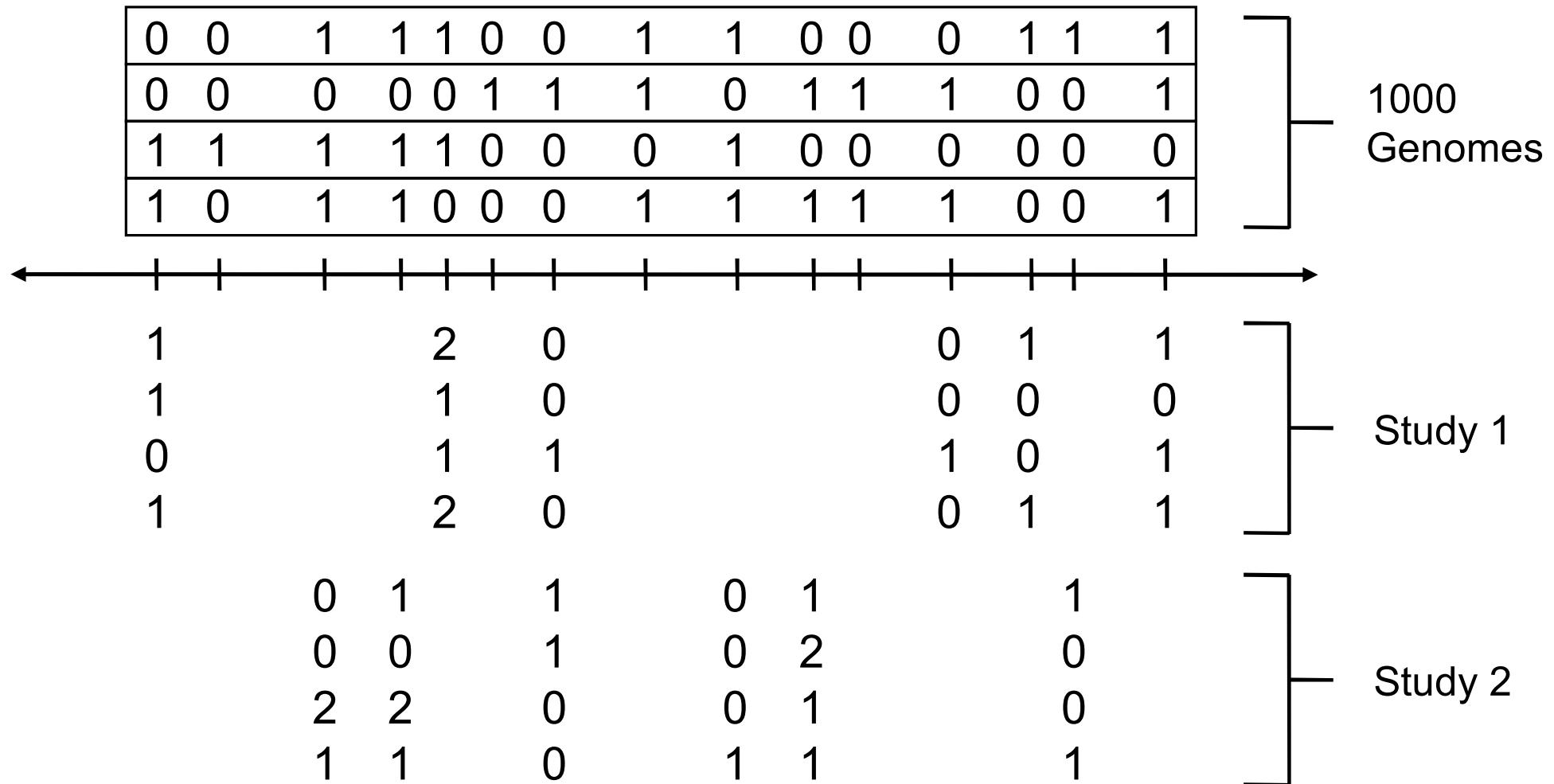


The goal of imputation is to estimate the missing genotypes at these variants

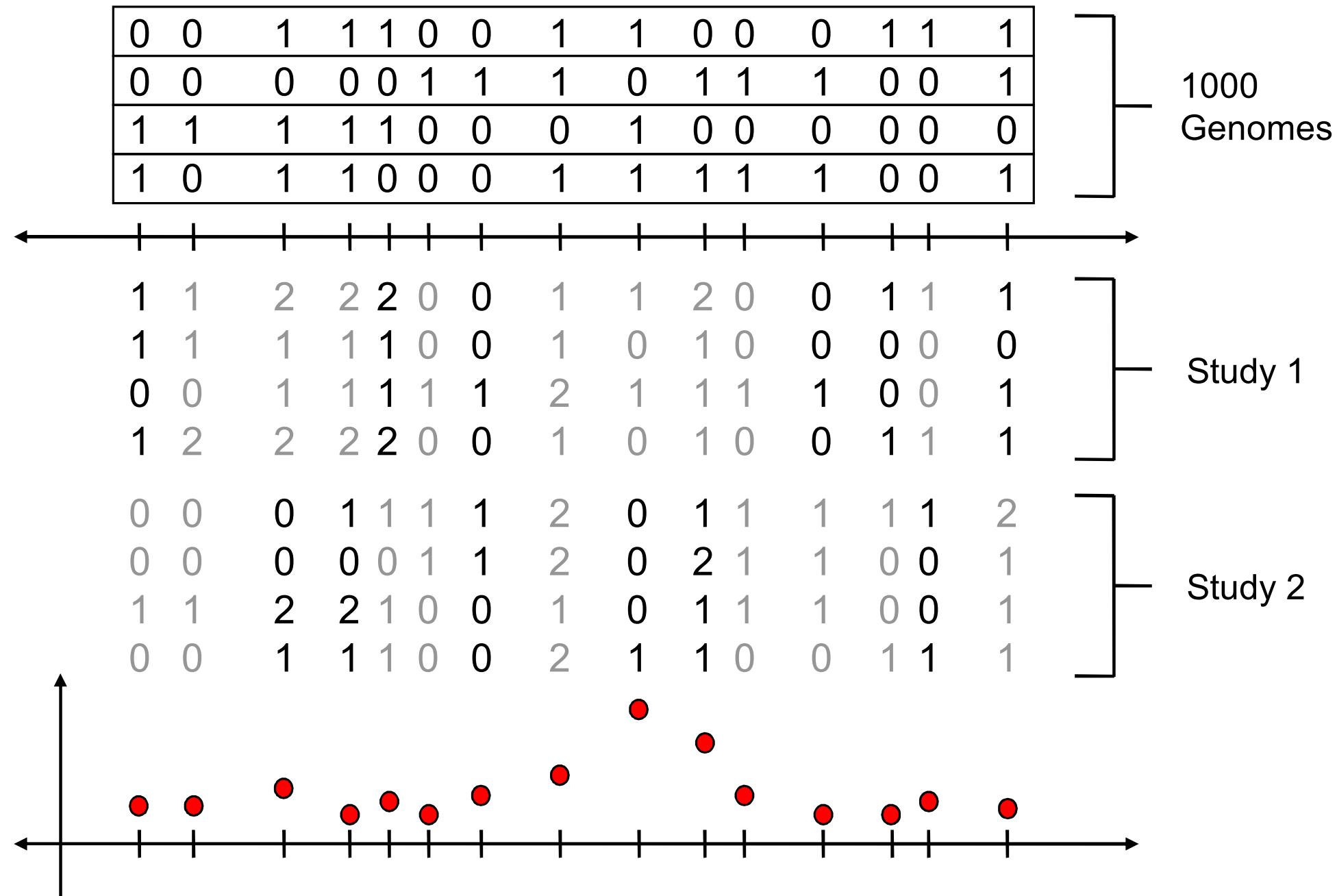
# Solution: Imputation



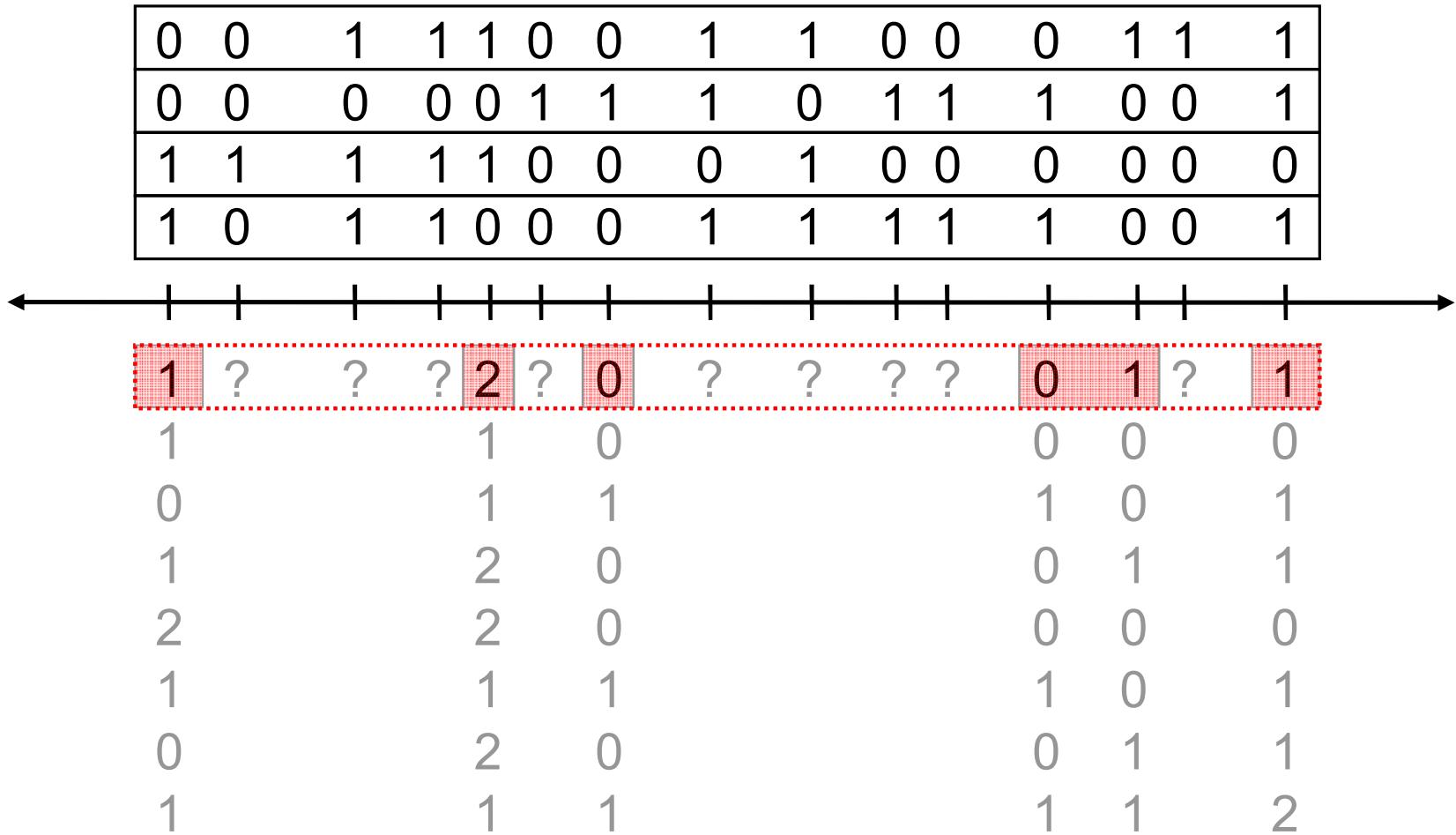
# Combining genotype data sets



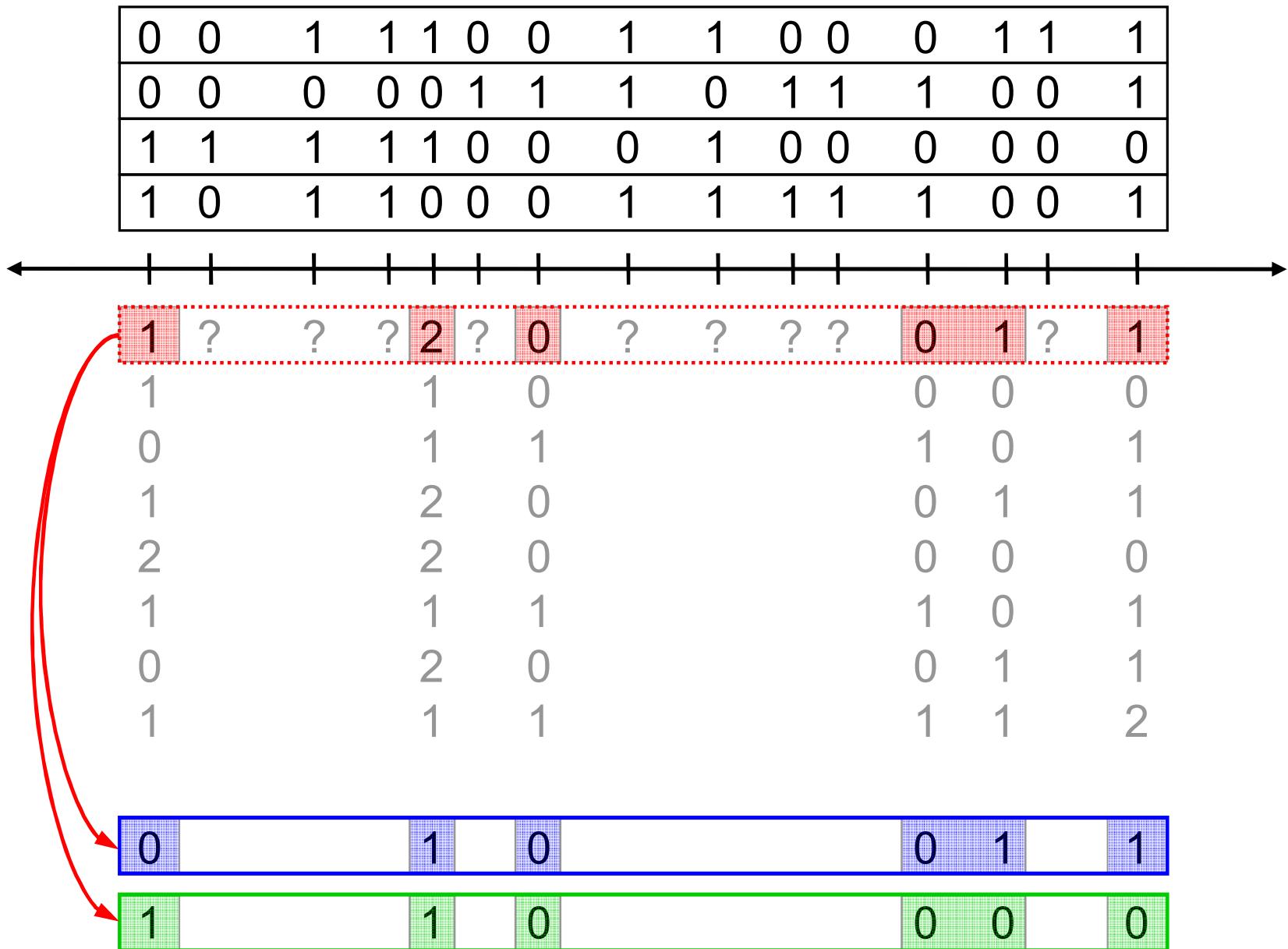
# Combining genotype data sets



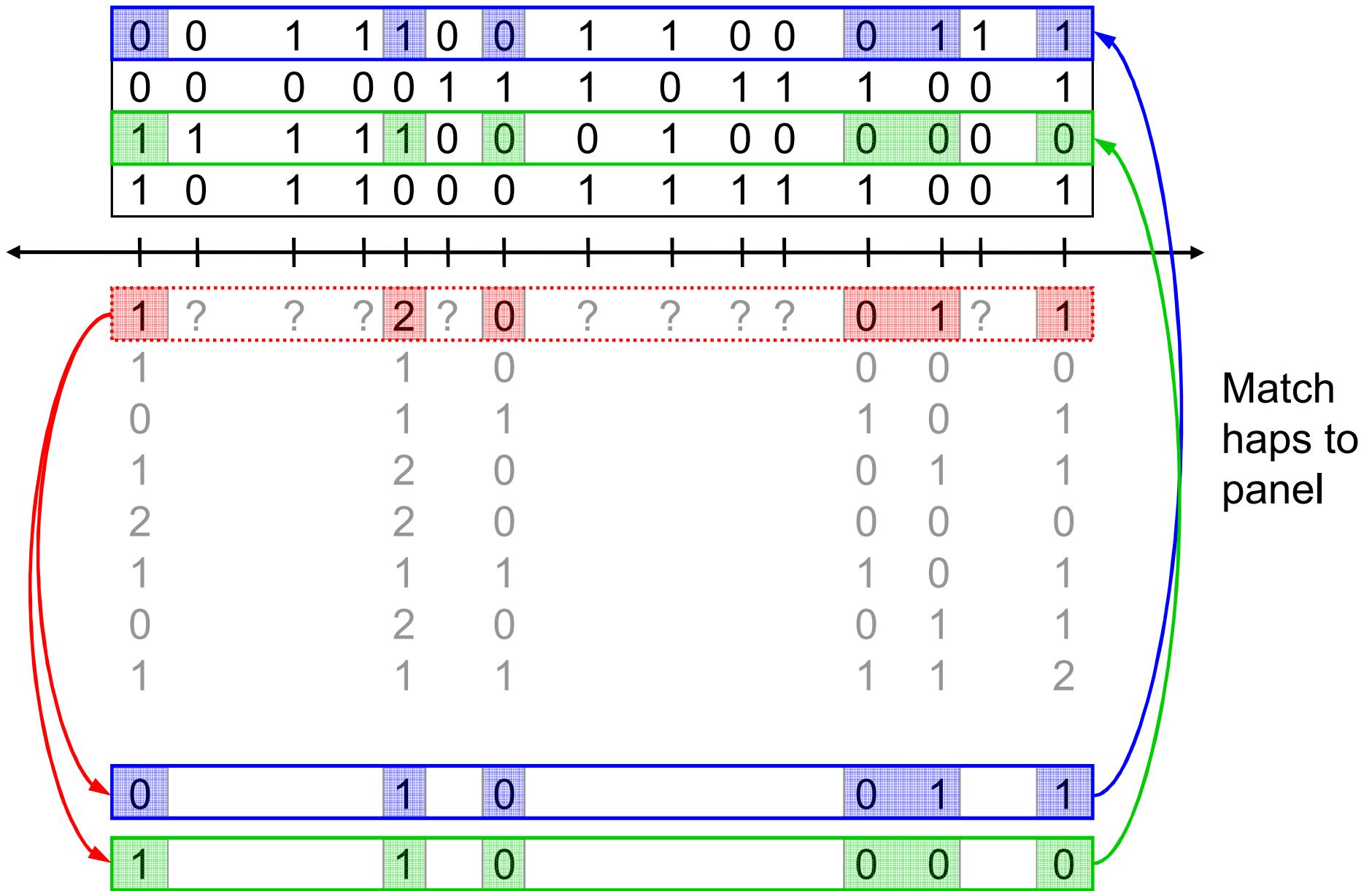
# How does it work?



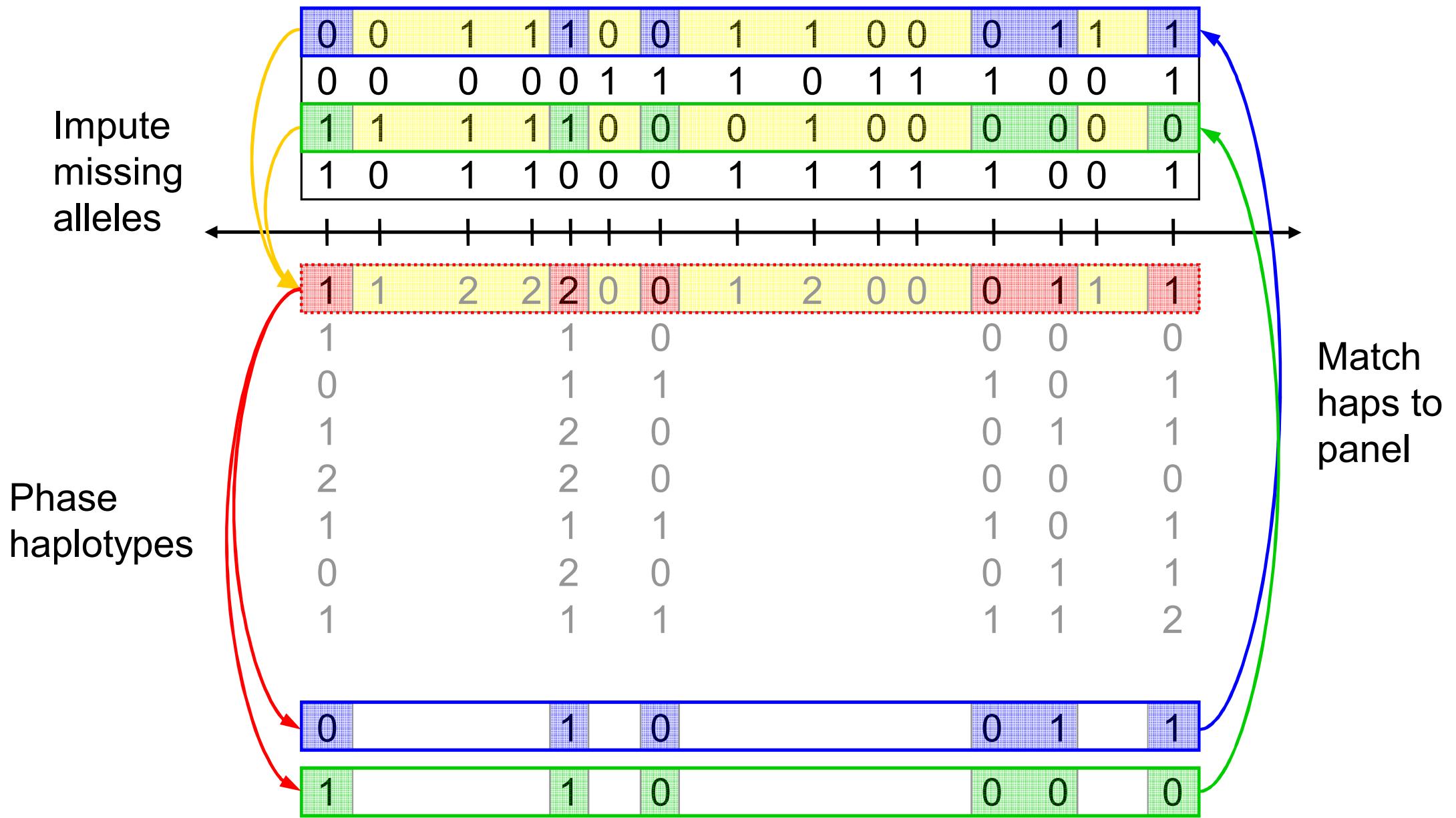
# How does it work?



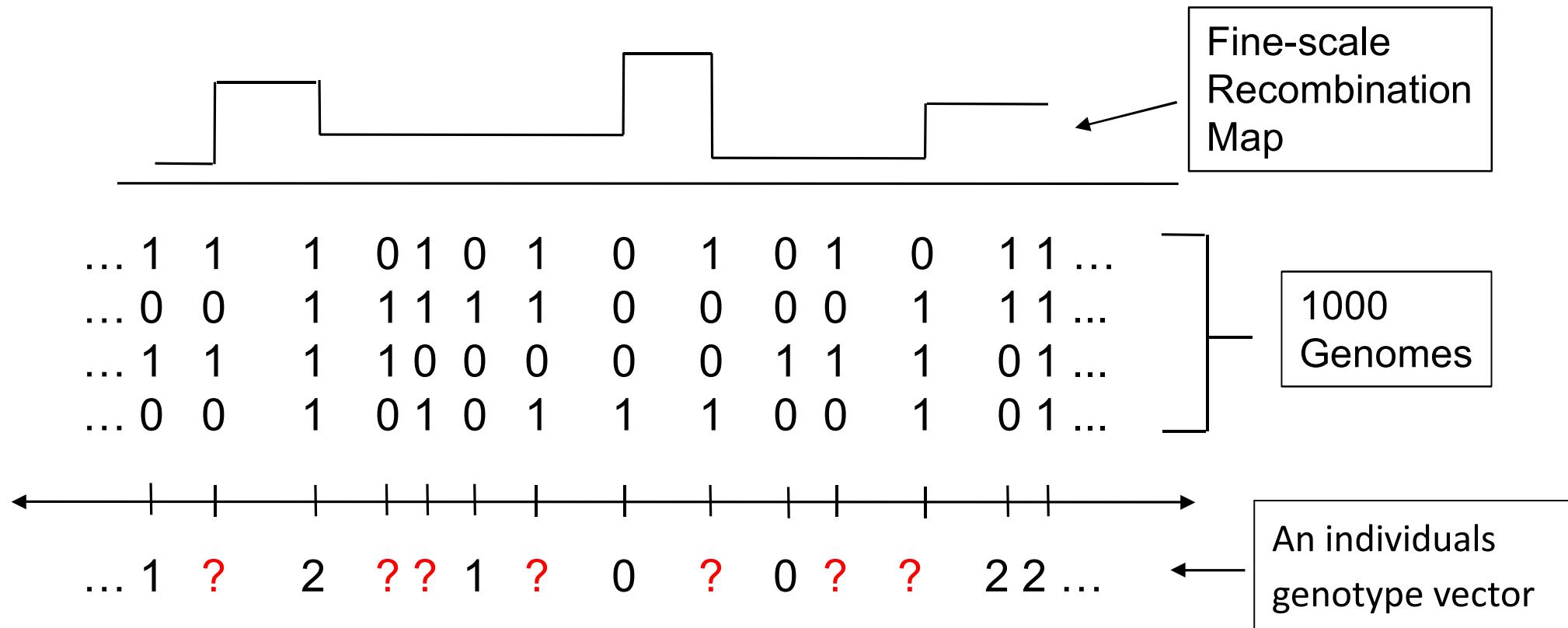
# How does it work?



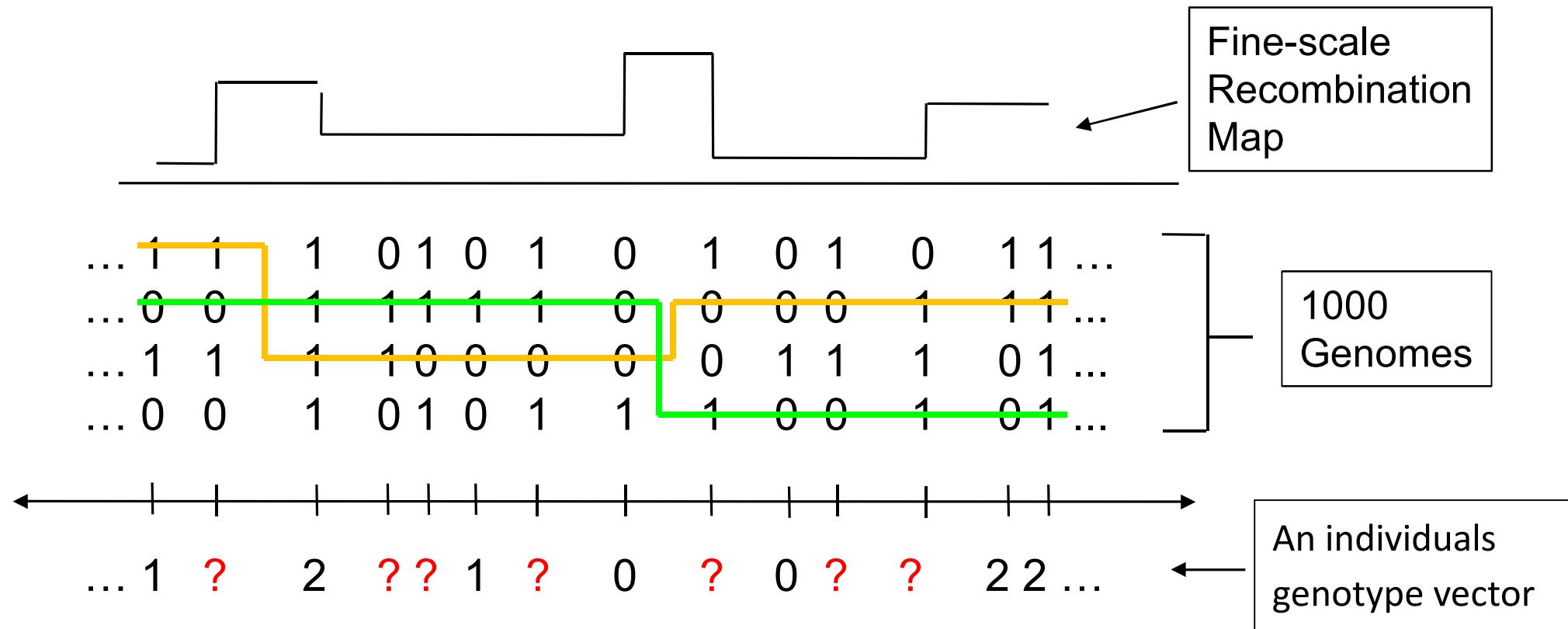
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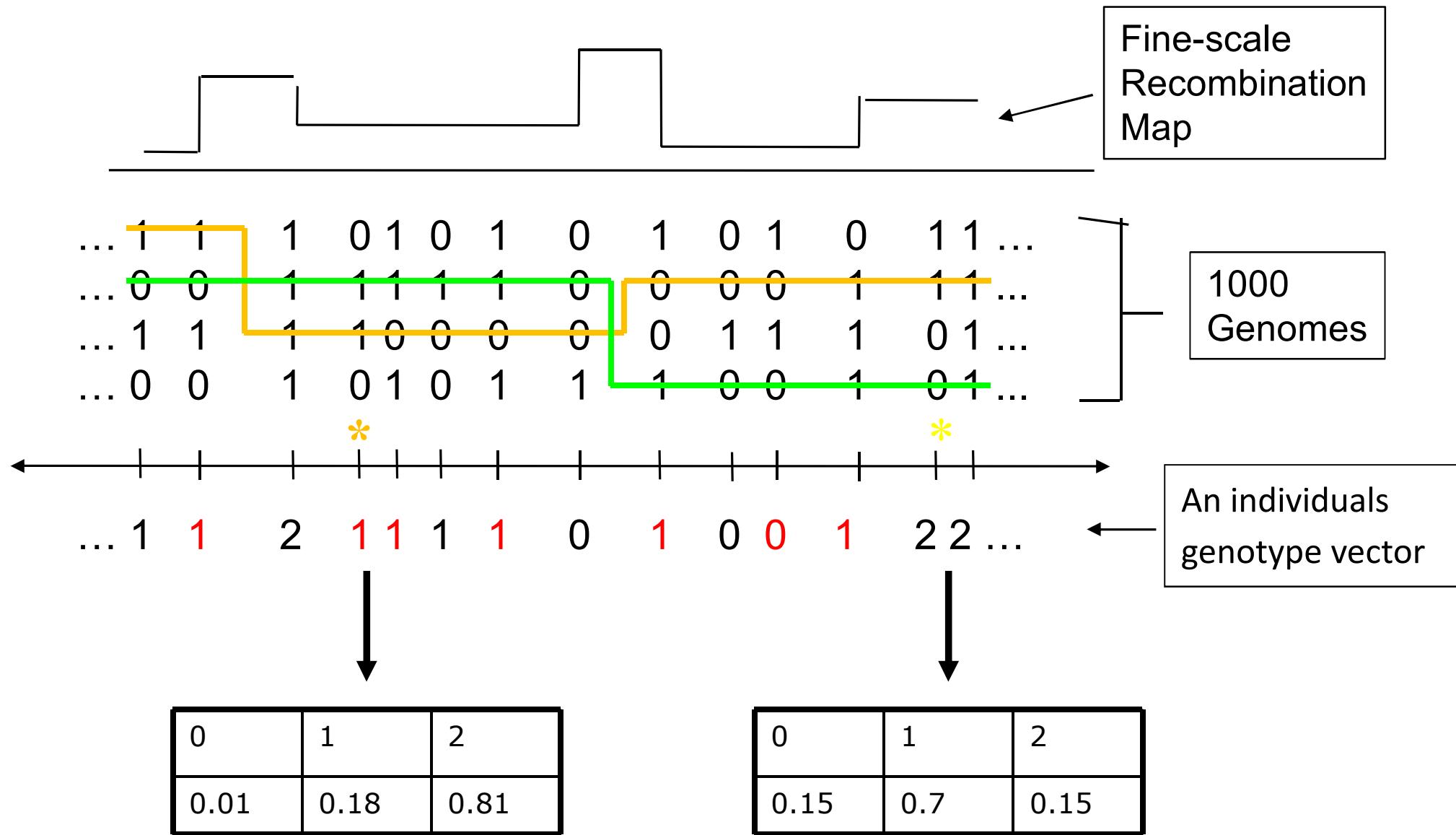


# How does it work?



The model says that an individuals genotype is constructed by copying alleles along two paths through the space of haplotypes. The switch rates of the paths are controlled by the recombination map. Mutation events are also allowed.

# How does it work?



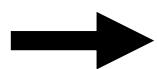
We produce estimates of genotype uncertainty at both untyped and typed genotypes

# Accounting for genotype uncertainty

There are several ways the imputed genotype probabilities can be used.

1. Threshold the probability distribution to give genotype calls
2. Use the expected allele counts

AA	AB	BB
0.01	0.18	0.81



$$0 \times 0.01 + 1 \times 0.18 + 2 \times 0.81 = 1.8$$

3. Average over uncertainty

- Can be done in both the Frequentist and Bayesian frameworks
- Very few implementations (SNPtest)

### **CD hit region, chromosome 1**

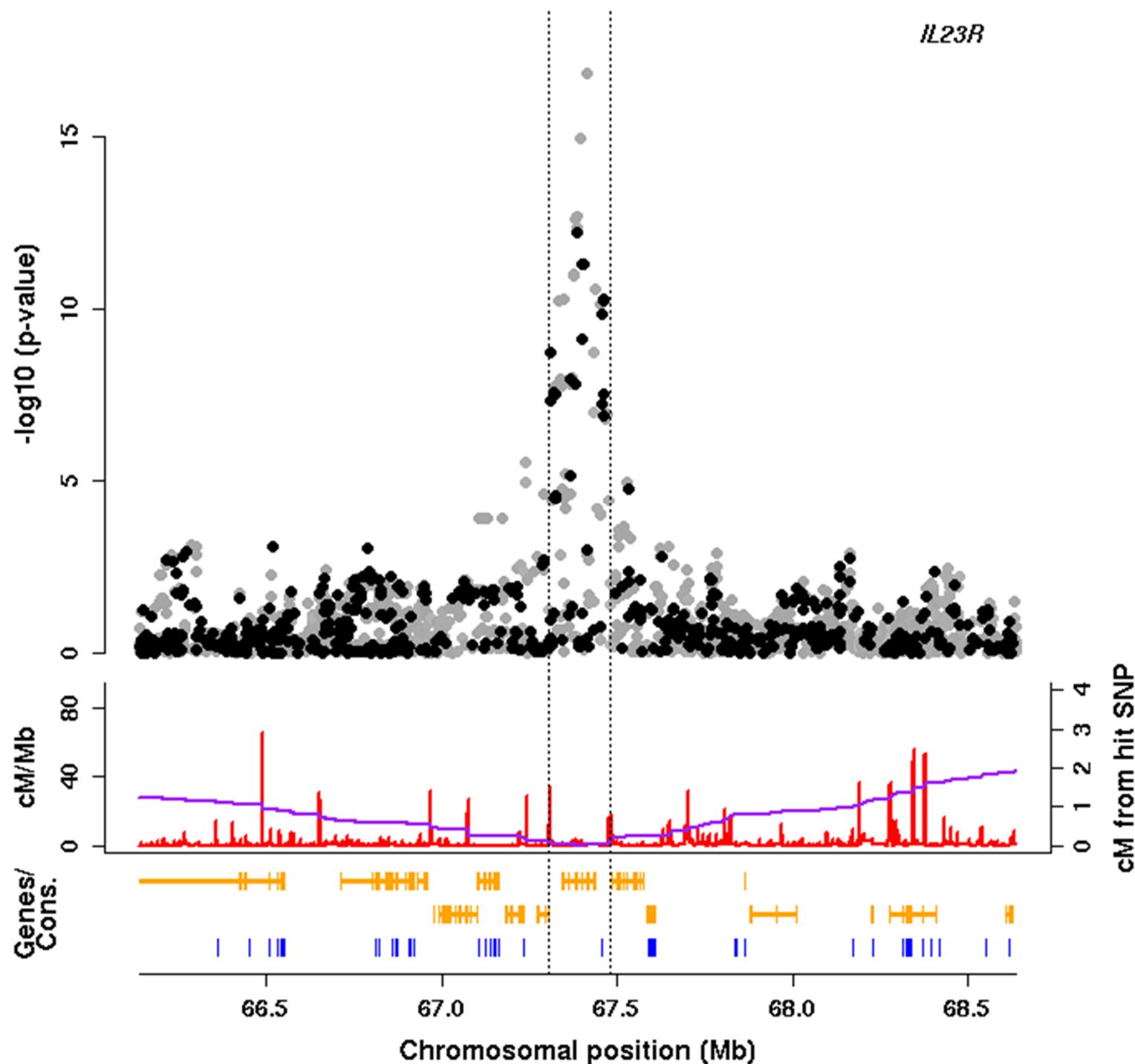


Image from The Wellcome Trust Case Control Consortium (2007) Genomewide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447;661-78. DOI: 10.1038/nature05911.

# Popular imputation methods

There are several popular methods for genotype imputation:

**IMPUTE2** - [https://mathgen.stats.ox.ac.uk/impute/impute\\_v2.html](https://mathgen.stats.ox.ac.uk/impute/impute_v2.html)

**MINIMACH** - <http://genome.sph.umich.edu/wiki/Minimac>

**BEAGLE** - <http://faculty.washington.edu/browning/beagle/beagle.html>

# Note1: Genome build

The Human Reference Sequence is updated periodically, each version is referred to a ‘genome build’.

Positions of SNPs can change between builds.

Almost all imputation programs align SNPs between the reference panels and the GWAS datasets using the position of SNPs.

So it is very important that the genotypes of your GWAS are mapped to the same genome build as the reference panel you are using.

Currently, all the most commonly used reference panels use build 37.

# Note2: Strand issue

Genotypes from SNP chips are called relative to either the + or – strand of the human reference genome.

Maternal chromosome	ACGTAGCTCTCTGATCGAT TGCATCGAGAGACTAGCTA	+ strand - strand
Paternal chromosome	ACATAGCTCTCTGAACGAT TGTATCGAGAGACTTGCTA	+ strand - strand
	 + strand GA - strand CT	 + strand TA - strand AT

Haplotype reference panels have alleles aligned to the + strand.

Genotype chips can have a mixture of genotypes from + and - strand

This needs to be fixed prior to imputation.

The strand info about all chips can be found here

<http://www.well.ox.ac.uk/~wrayner/strand/>

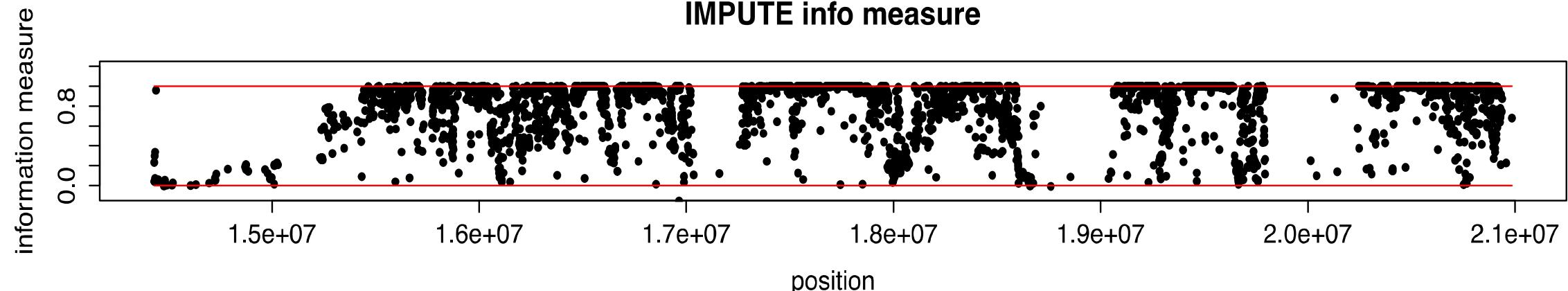
# Note3: Information metric

Once imputation has been carried out, it is a good idea to try and measure how well imputed the genotypes are at each SNP. IMPUTE produces an information measure for each SNP in the range [0,1]:

- 1 means there is no uncertainty at all in any of the imputed genotypes.
- 0 means there is complete uncertainty for all of the genotypes.

Approximately, an information measure of  $\alpha$  means the imputed genotypes contain as much information as  $\alpha N$  genotypes that are completely certain (where  $N$  is the total number of genotypes).

In recent published studies (especially those that have used imputation for meta-analysis), variants with  $\text{info} < 0.4$  have been excluded from the study.



# 1000 Genomes project

nature International weekly journal of science

2015

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Archive > Volume 526 > Issue 7571 > Articles > Article

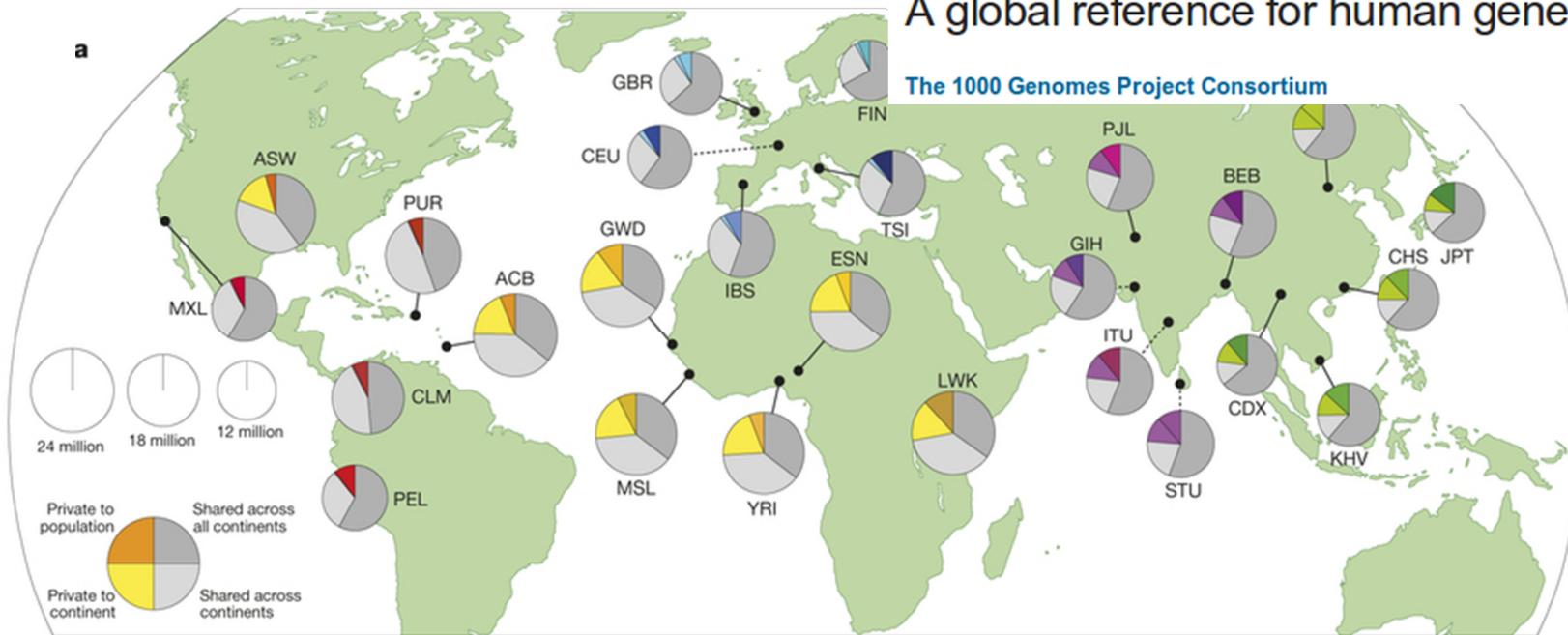
NATURE | ARTICLE OPEN

日本語要約



A global reference for human genetic variation

The 1000 Genomes Project Consortium



Population	Number of samples
African	661
Americas	347
Est Asian	504
European	503
South Asian	489
<b>Total</b>	<b>2,504</b>

Type of variants	Number of variants
Bi-allelic SNPs	81,102,777
Bi-allelic Indels	3,196,364
Multi-allelic SNPs	274,425
Multi-allelic Indels	169,601
Structural variants	58,713
<b>Total</b>	<b>84,801,880</b>

# Why did we phase 1000 Genomes?

1. To get fully resolved haplotypes, obviously,

ATGC**A**TCGAGCT**G**ACTGAGG**A**CTGGACTAG**C**GATCAG  
ATGC**T**TCGAGCT**T**ACTGAGG**C**CTGGACTAG**G**GATCAG

ATGC**A**TCGAGCT**G**ACTGAGG**A**CTGGACTAG**C**GATCAG  
ATGC**A**TCGAGCT**T**ACTGAGG**A**CTGGACTAG**G**GATCAG

# Why did we phase 1000 Genomes?

1. To get fully resolved haplotypes, obviously,
2. But also to refine the genotype calls.

ATGC**A**TCG

CGAGCT**G**A

ATGC**A**TCGAGCT**G**ACTGAGG**A**CTGGACTAG**C**GATCAG

ATGC**T**TCGAGCT**T**ACTGAGG**C**CTGGACTAG**G**GATCAG

ATGC**T**TCG CTTACTGA **G**CCTGGAC

**C**TTCGAGC

**G**C GATCAG

**GG**GATCAG

GC**A**TCGAG

CTGAGG**A**C

CTAG**C**GAT

GG**A**CTGGA

ATGC**A**TCGAGCT**G**ACTGAGG**A**CTGGACTAG**C**GATCAG

ATGC**A**TCGAGCT**T**ACTGAGG**A**CTGGACTAG**G**GATCAG

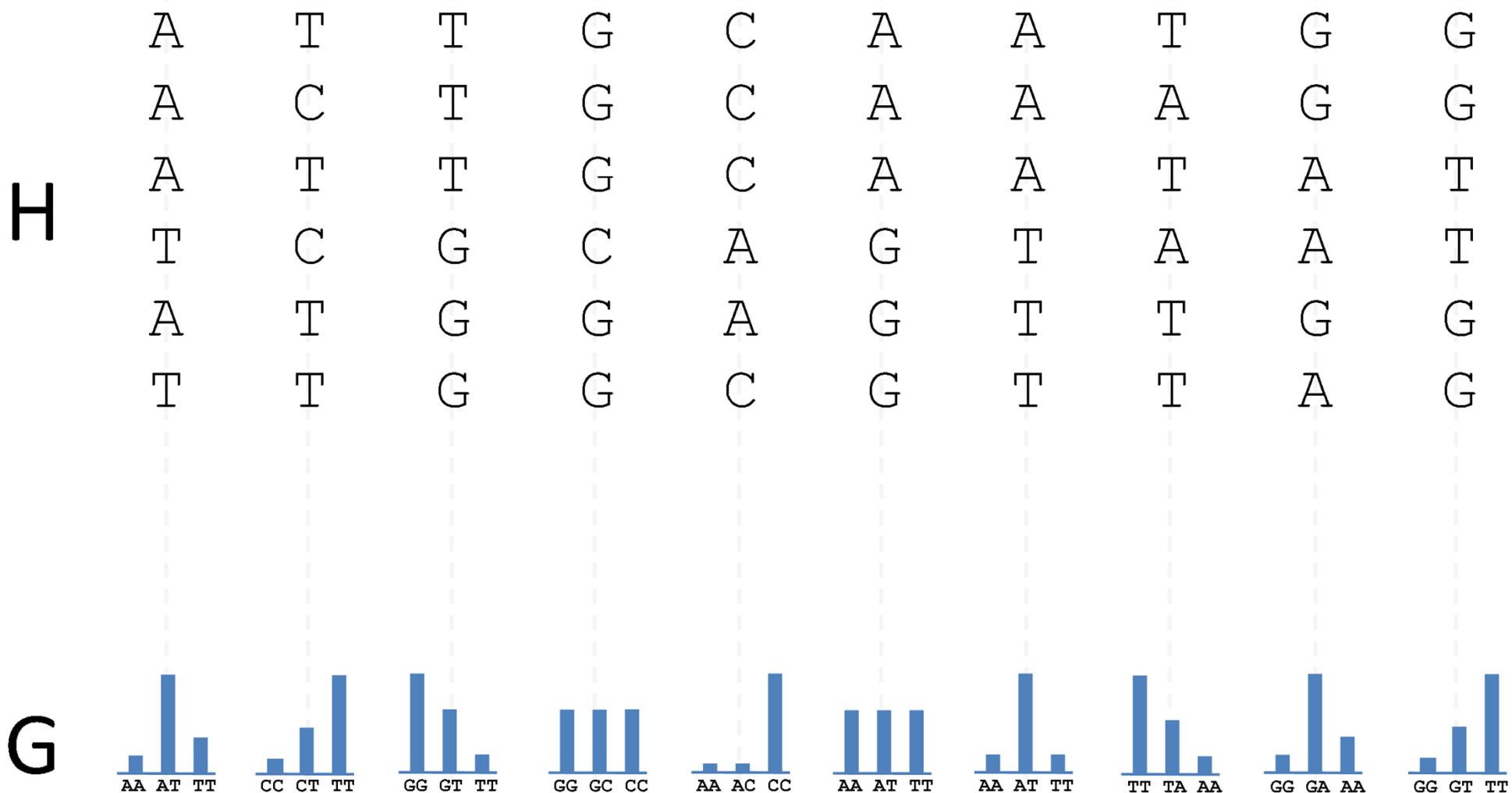
ATGC**A**TCG

AGG**A**CTGG

CGAGCT**T**A

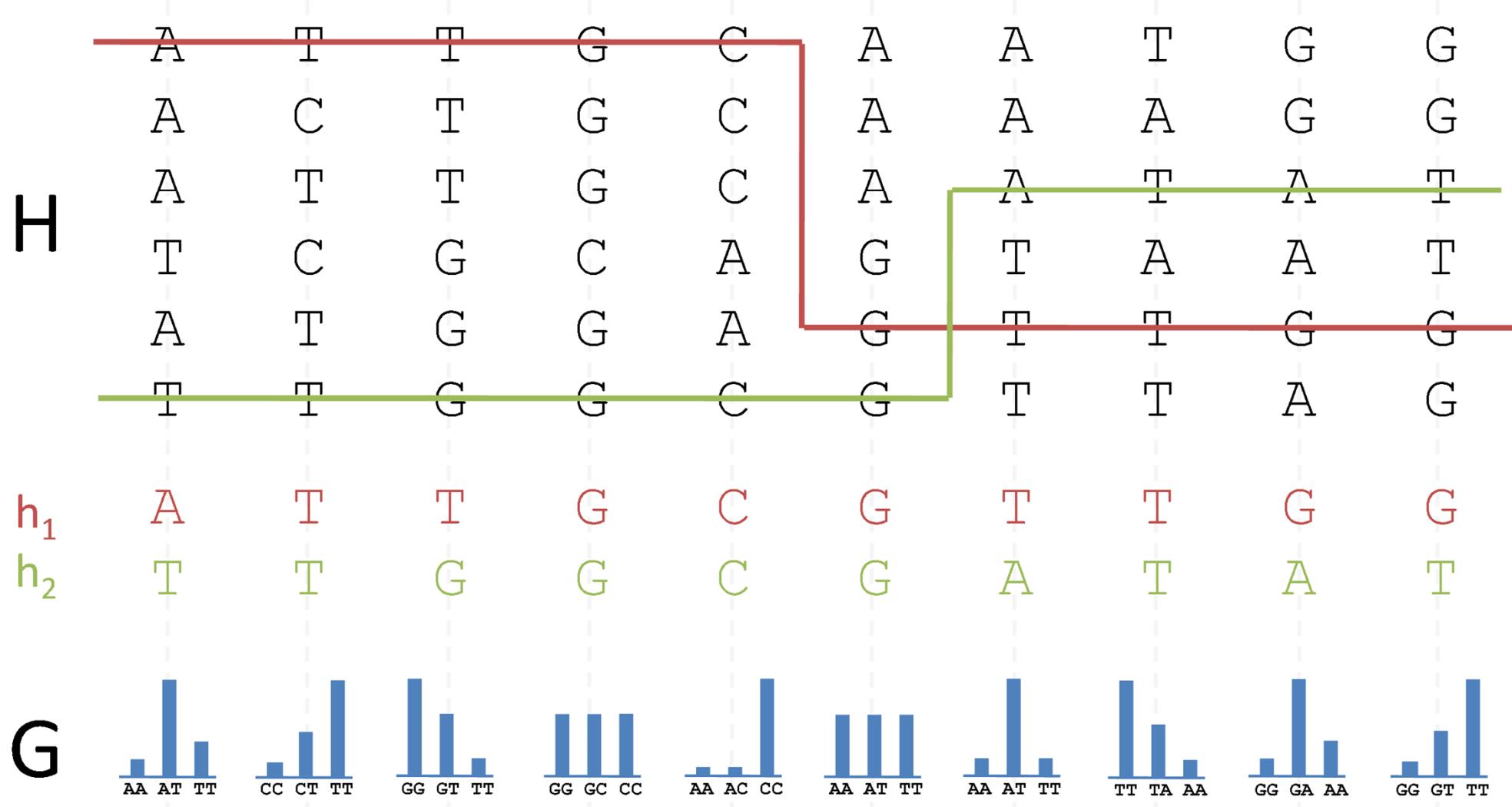
**GG**GATCAG

# How does it work?



Uncertainty in genotypes is modeled with genotype likelihoods (GLs)

# How does it work?



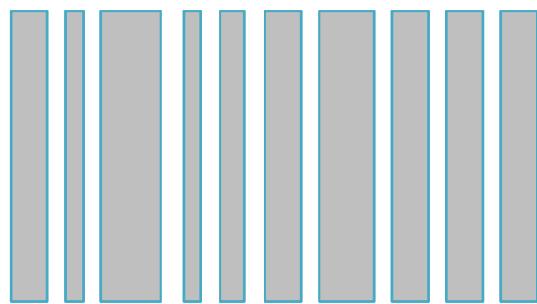
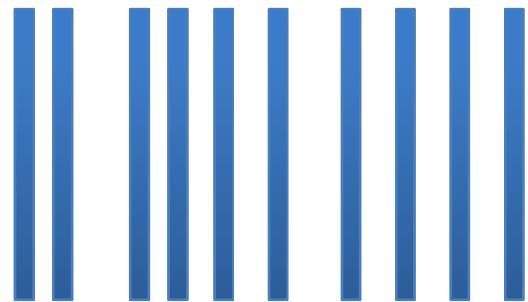
Estimating haplotypes produces genotype calls.

# Measuring imputation performance

Complete Genomics  
Genotypes

# Measuring imputation performance

Genotypes on Illumina 1M

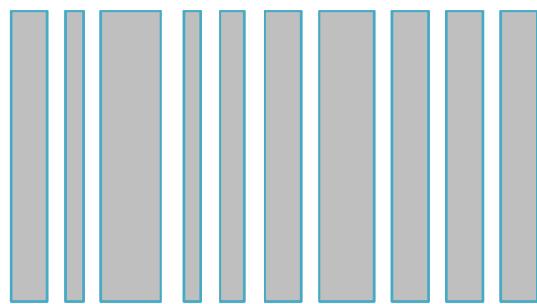
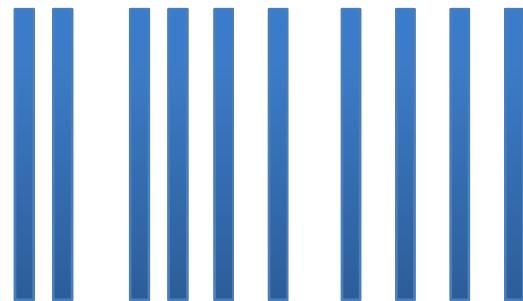


Genotypes NOT on Illumina 1M

# Measuring imputation performance

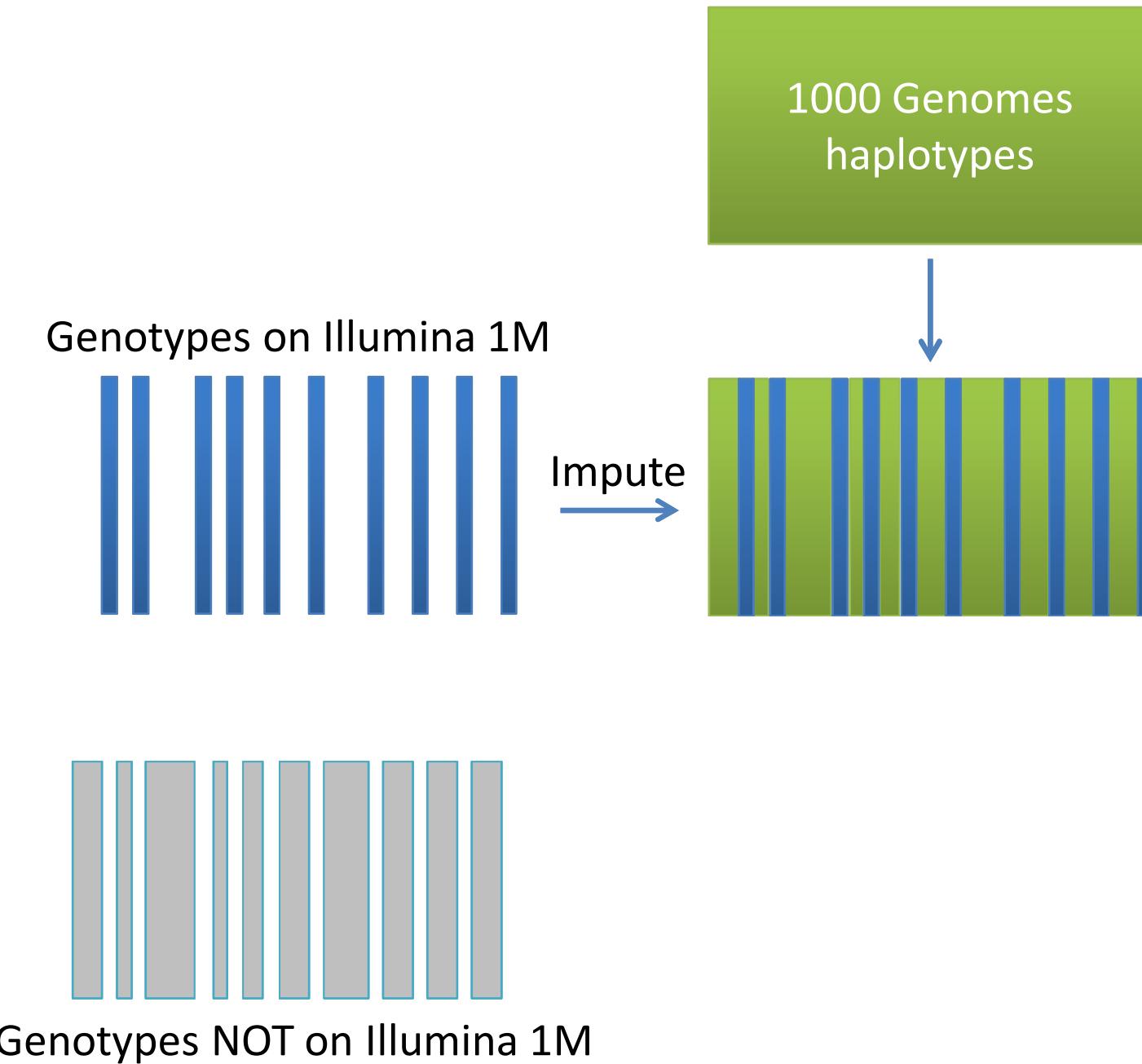
1000 Genomes  
haplotypes

Genotypes on Illumina 1M

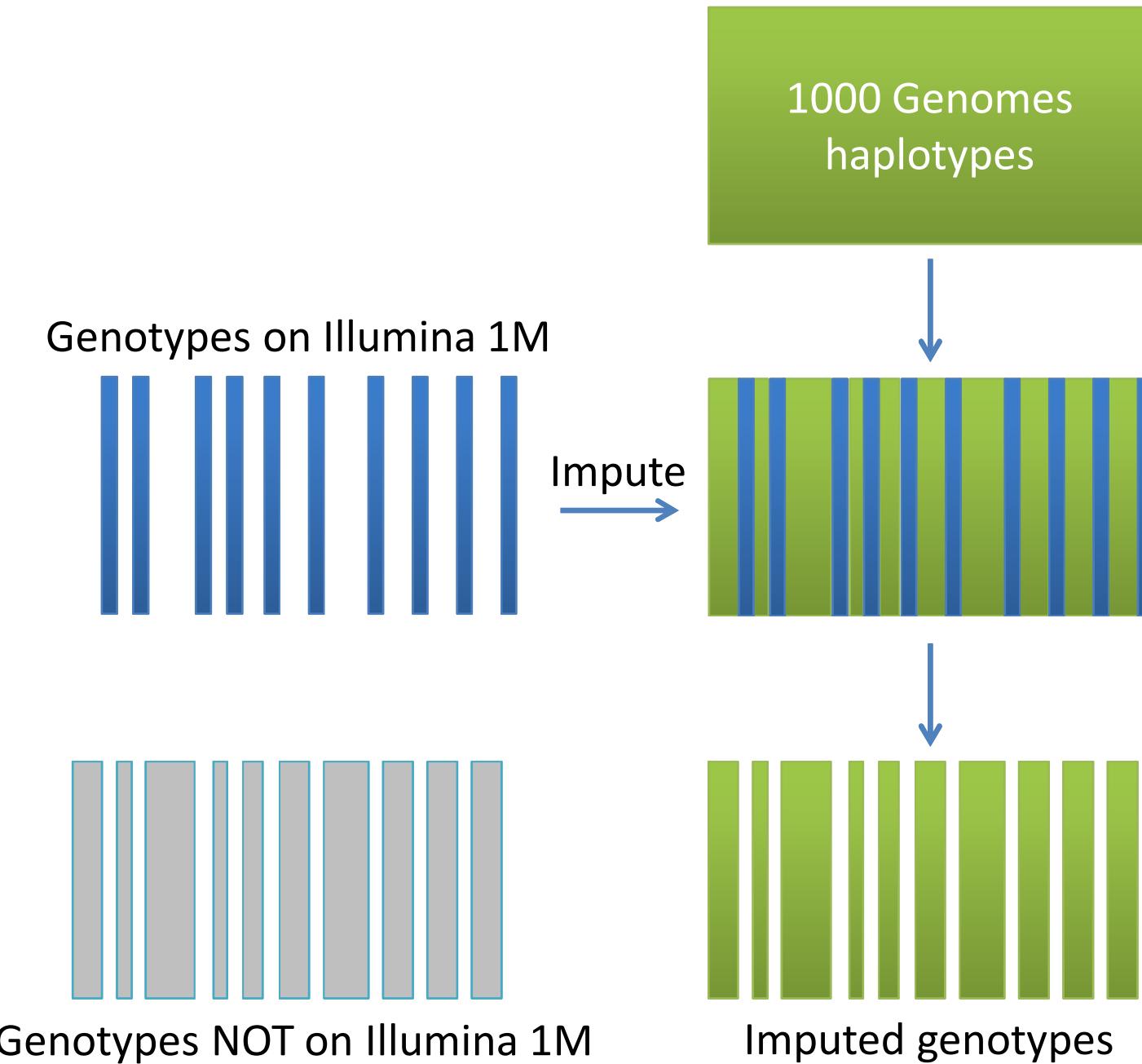


Genotypes NOT on Illumina 1M

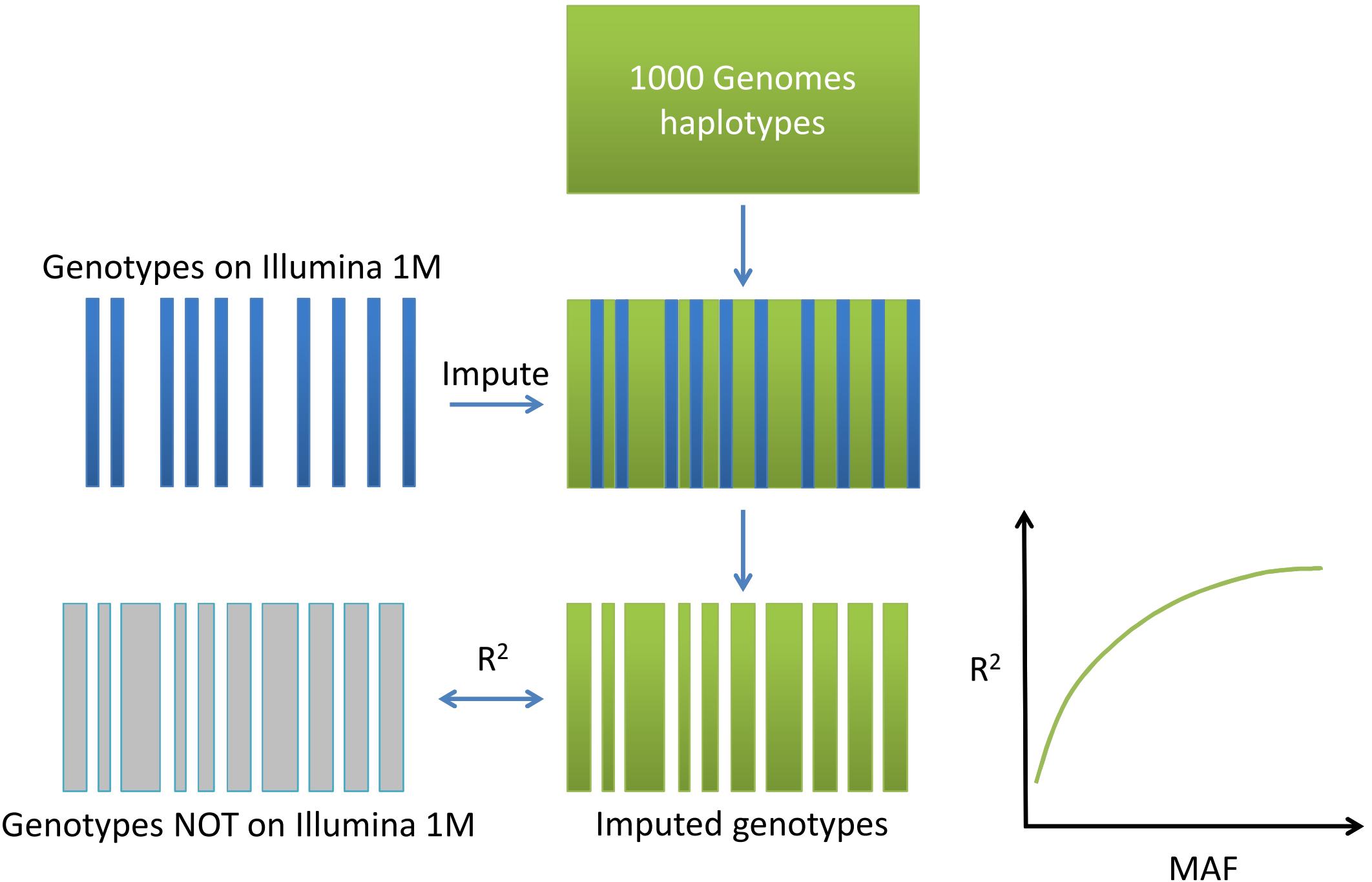
# Measuring imputation performance



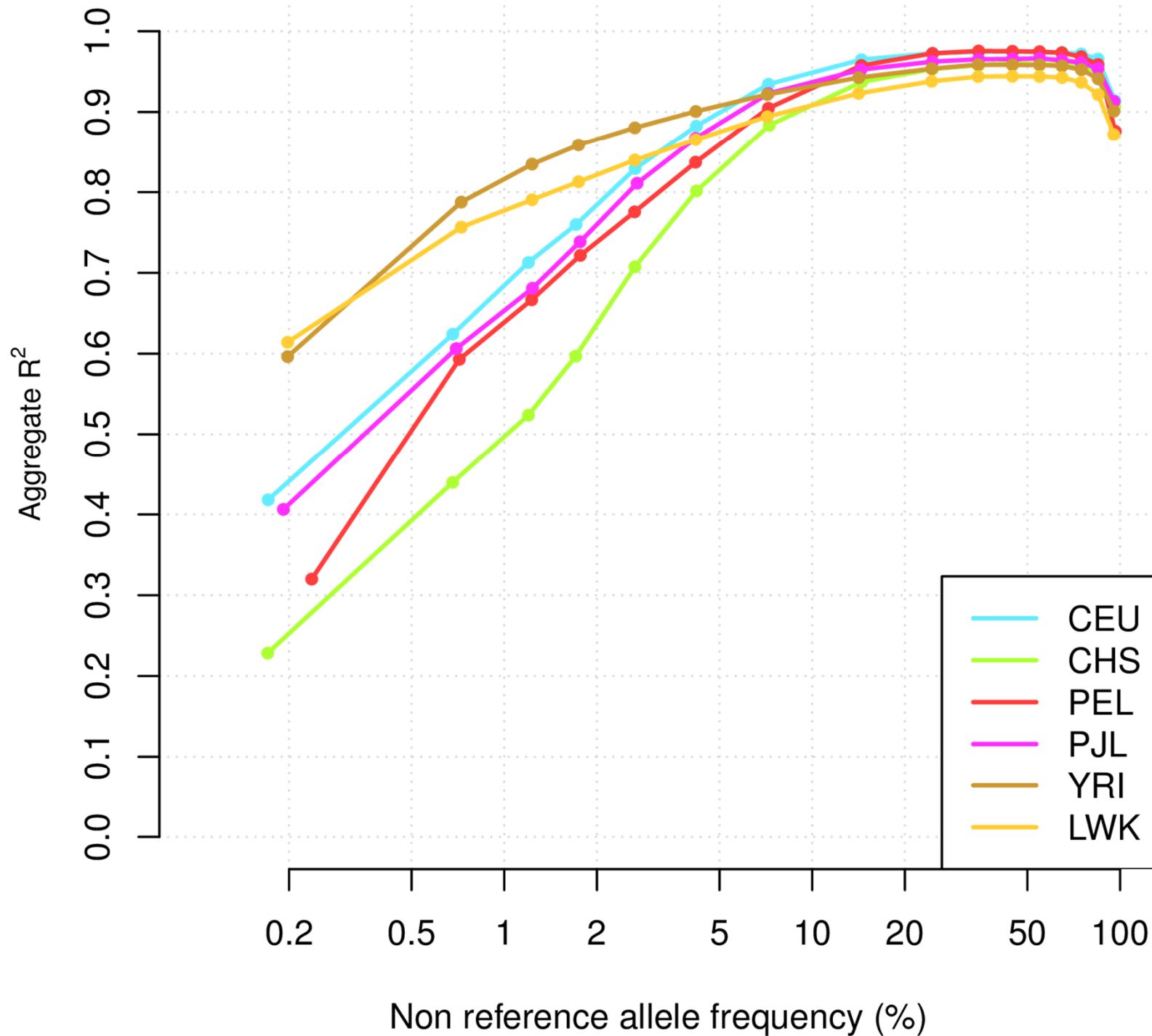
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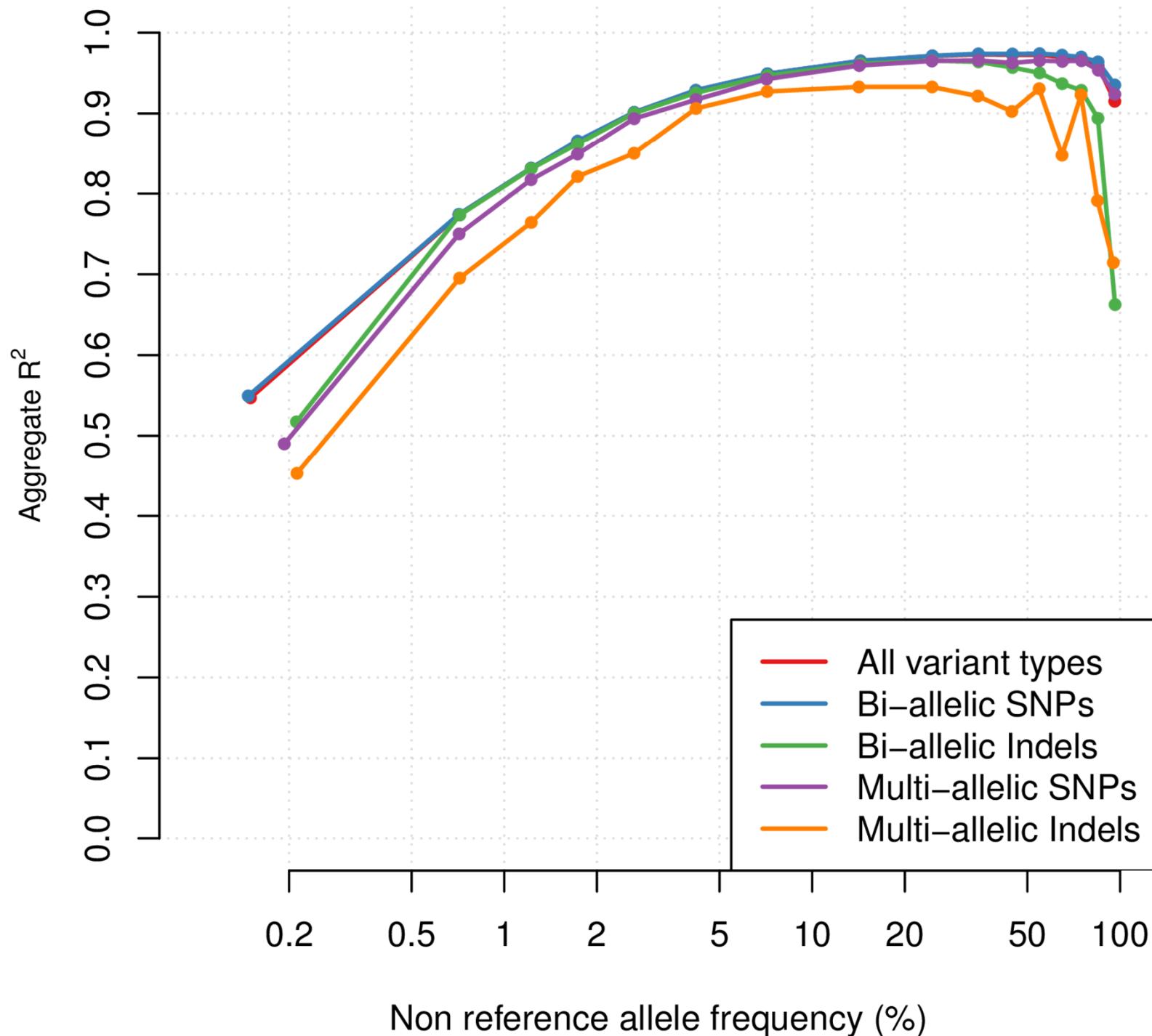
# Measuring imputation performance



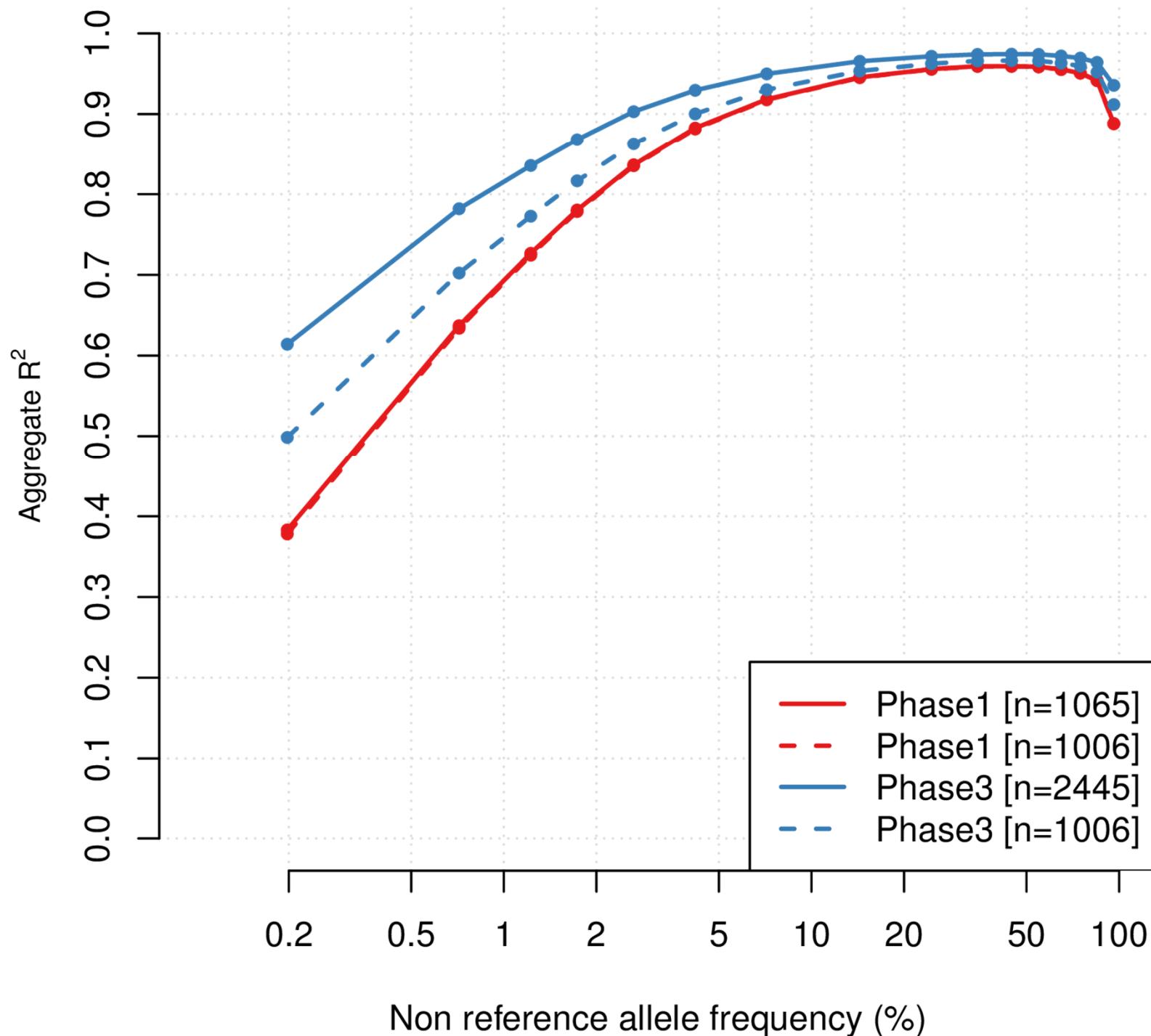
## Stratified by populations



## Stratified by variant types



## Phase1 versus Phase3



# Haplotype reference panels

Reference	Year	# haplotypes	# populations	# variants
HAPMAP 2	2006	420	3	2,139,483
HAPMAP 3	2009	2,368	11	1,440,616
1000GP Pilot	2010	358	3	14,894,361
1000GP 2010	2010	1,258	14	22,242,654
1000GP Interim	2011	2,186	14	38,558,931
1000GP Phase 1	2012	2,186	14	38,219,282

Reference	Year	# haplotypes	populations	# variants
1000GP Final	2014	~5,000	25	~80,000,000
UK10K	2013/14	~8,000	UK	~50,000,000
GoT2D	2013/14	~5,600	European	~27,000,000
GoNL	2013/14	1,000	NL	~20,000,000

Q Which reference panel to use for imputation into GWAS?

# The Haplotype Reference Consortium

<http://www.haplotype-reference-consortium.org/>

- The HRC data **is NOT publically available**, as HapMap and 1000GP haplotypes are, due to consent issues.
- Currently 2 imputation servers exist that allow users to upload genotypes from their GWAS samples, and have imputation carried out remotely and efficiently
  - <https://imputation.sanger.ac.uk/>
  - <https://imputationserver.sph.umich.edu>
- A phasing server for phasing high coverage sequenced samples is available at:
  - <https://phasingserver.stats.ox.ac.uk/>

# The Haplotype Reference Consortium

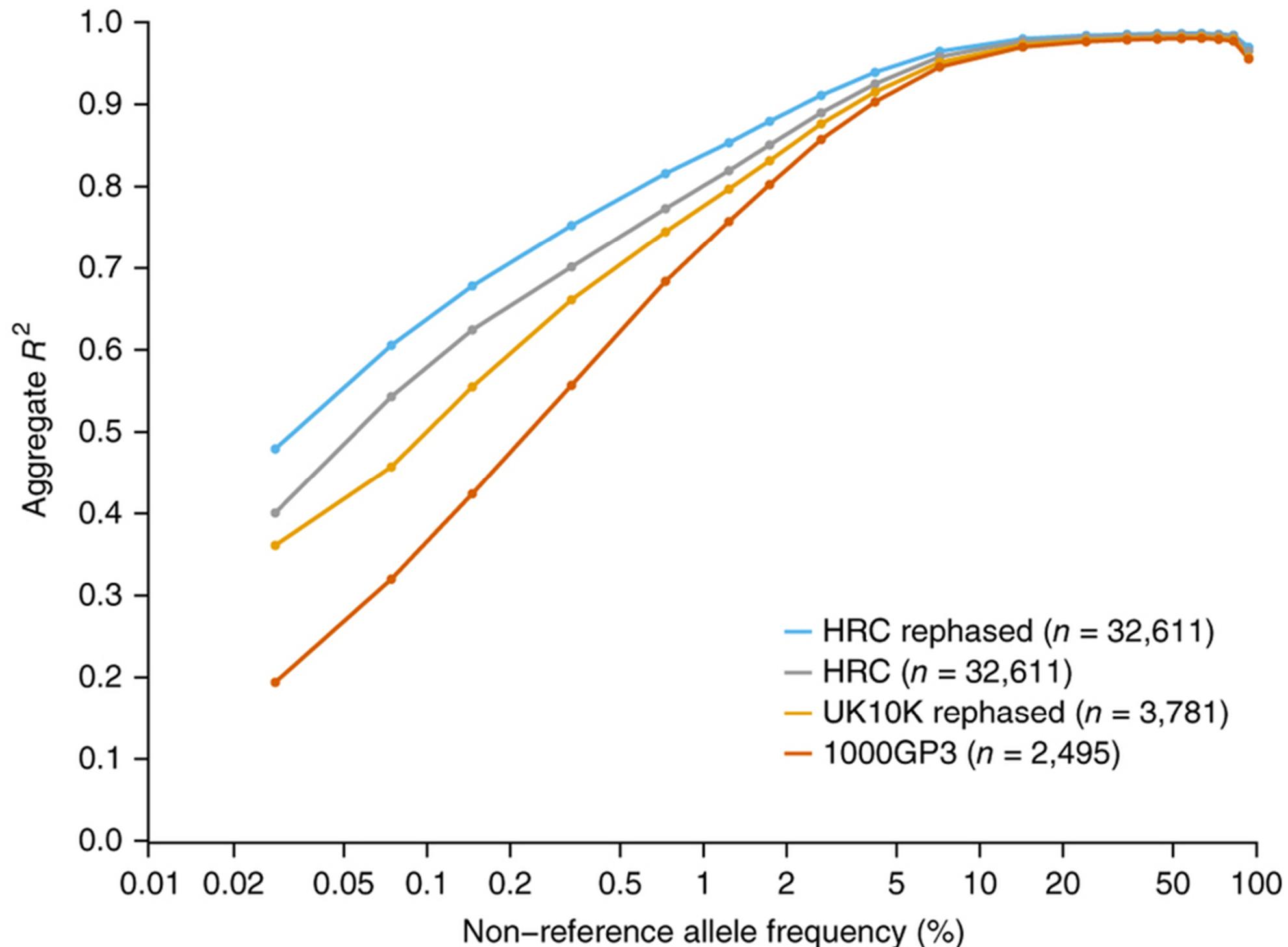
Dataset	Samples	Coverage
IBD	4514	2-4x
UK10K	3781	6.5x
Sardinia	3514	4x
GoT2D	2874	4x + Exome
1000GP Phase 3	2535	4x + Exome
BRIDGES	2489	6-8x
AMD	2099	4x
Finland	1941	4-6x
MCTFR	1339	10x
HUNT	1024	4x
GECCO	954	4-6x
Project MinE	943	45x
GPC	767	30x
GoNL	748	12x
inCHIANTI	680	7x
Orkney	399	4x
Neptune	253	4x
FVG	250	4-10x
MANOLIS	249	4x
Val Borbera	225	6x
	32,488	

**Goal** : create a European haplotype map of over 50,000+ haplotypes by combining together many low-coverage sequencing studies.

## Release 1

64,976 haplotypes  
39,235,157 SNPs  
estimated MAC  $\geq 5$

# The Haplotype Reference Consortium



# The practical

- The goal of the practical is to impute the data we QCed yesterday
- We will use multiple approaches for genotype imputation
- Look at */home/delaneau*, everything you need is there.