Bayesian Nonparametric Statistics for Fostering Innovation and Discovery in Biomedical Research

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Outline

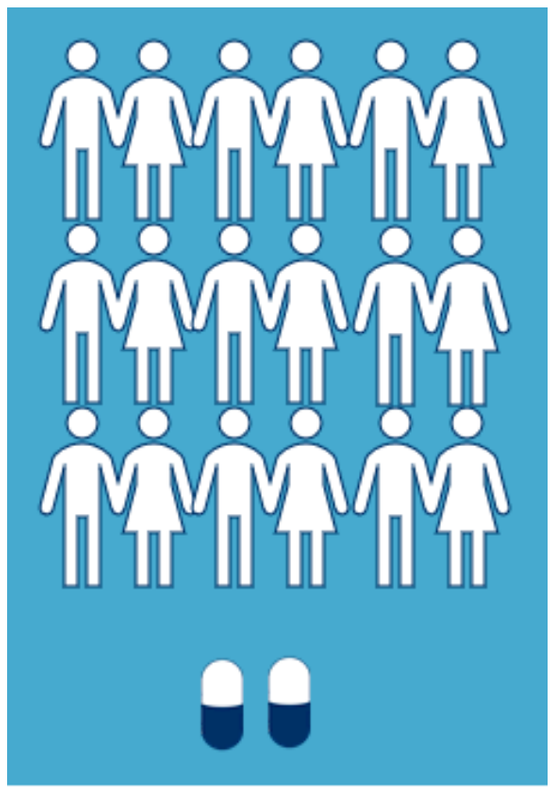
- **Part 1:** *Monday*
  - **Density estimation** for efficient clinical trial designs
  - **Regression** for precision dosing

- **Part 2:** *Wednesday*
  - **Clustering** for subgroup finding
  - **Latent feature models** for tumor heterogeneity

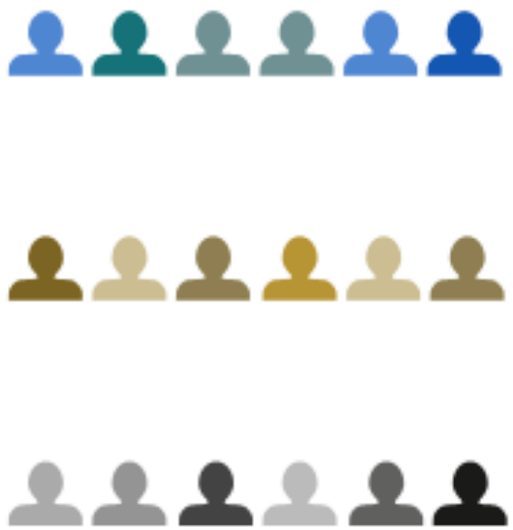
- **Part 3:** *Friday*
  - Estimating treatment effects from observational data

Treatment Effect

Clinical Trials



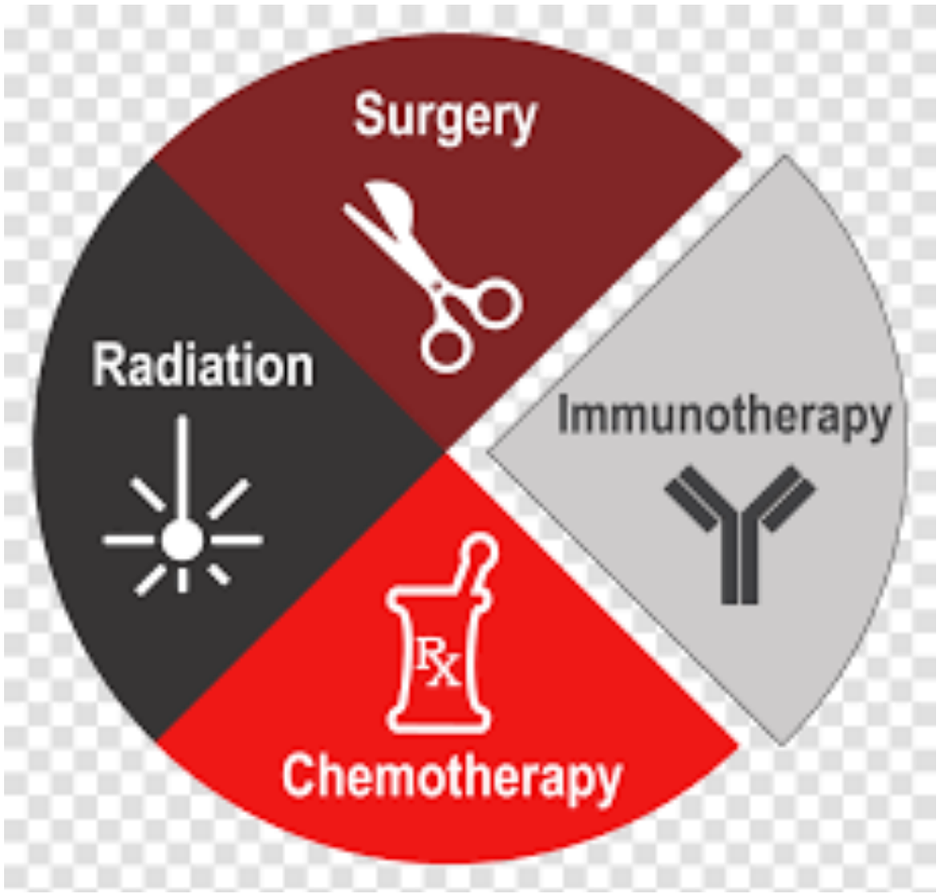
Biomarker-based Trials



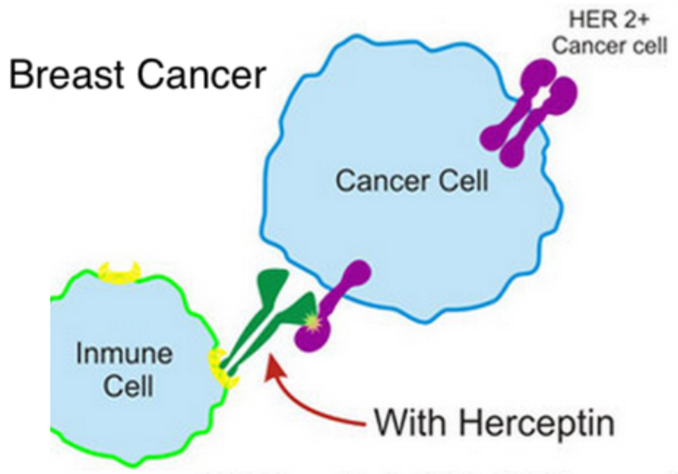
Observational Data

Population → Subgroup → Personalization

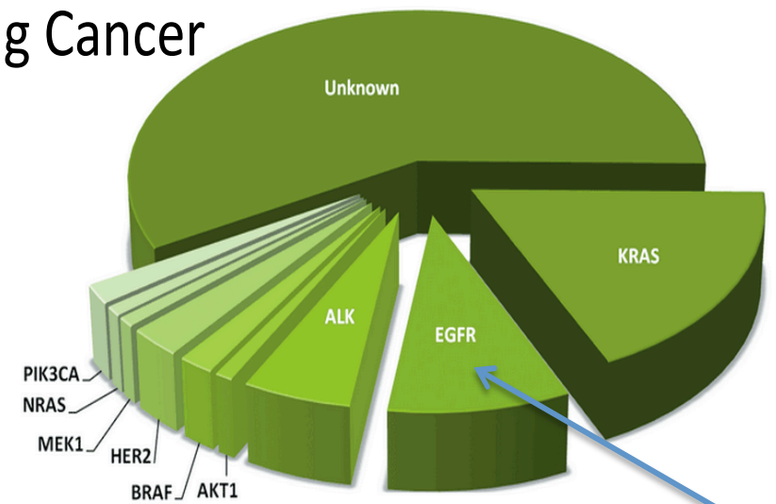
One-size Fits All Cancer Treatment



Targeted Therapy



Lung Cancer



Courtesy of Lung Cancer Foundation of America

Erlotinib

Genomic-driven Cancer Trials

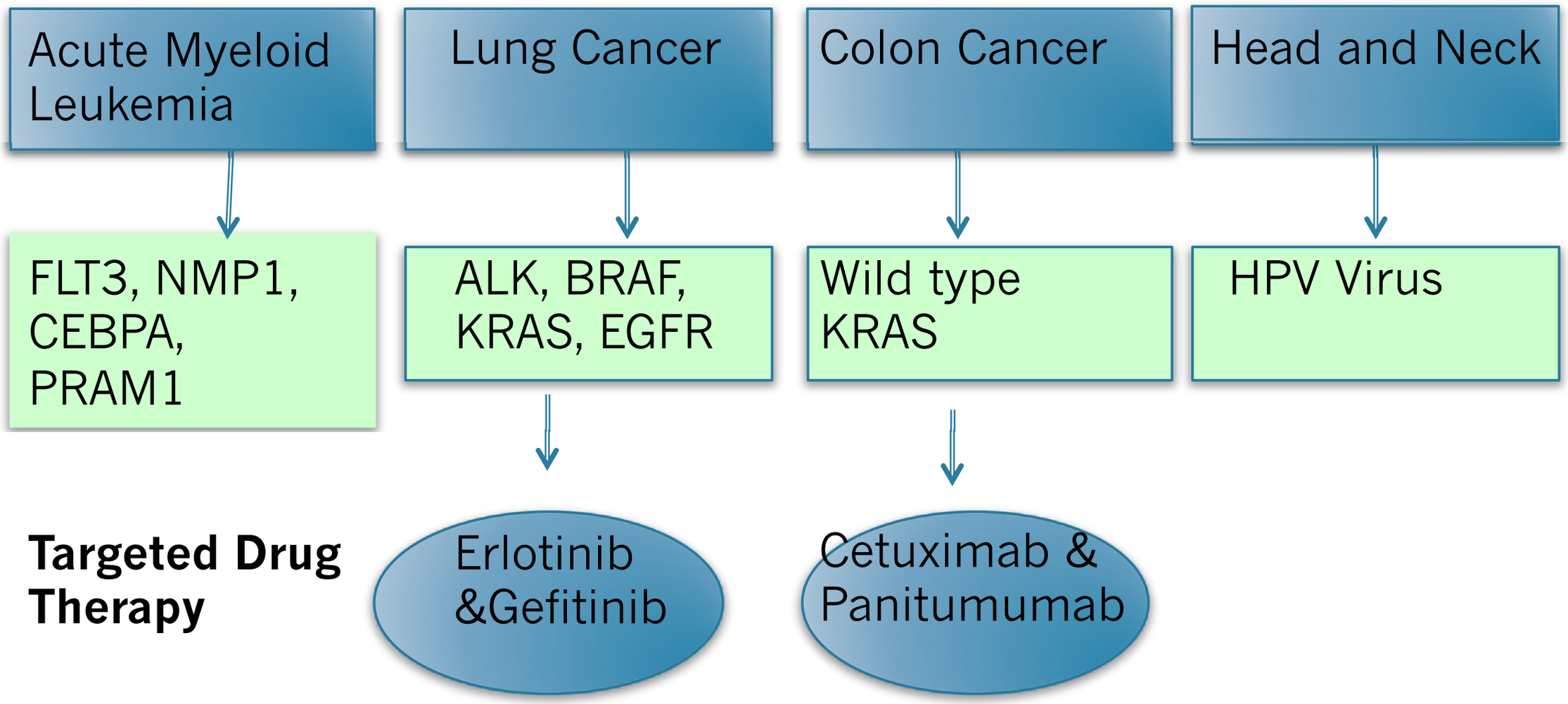
Umbrella Trials

in one **single** cancer type, test the effect of targeted agents on different alterations.

Basket Trials

across **multiple** cancer types, test the effect of targeted agents on the same genomic alternations.

Basket Trial



Motivation Trial: IMPACT II

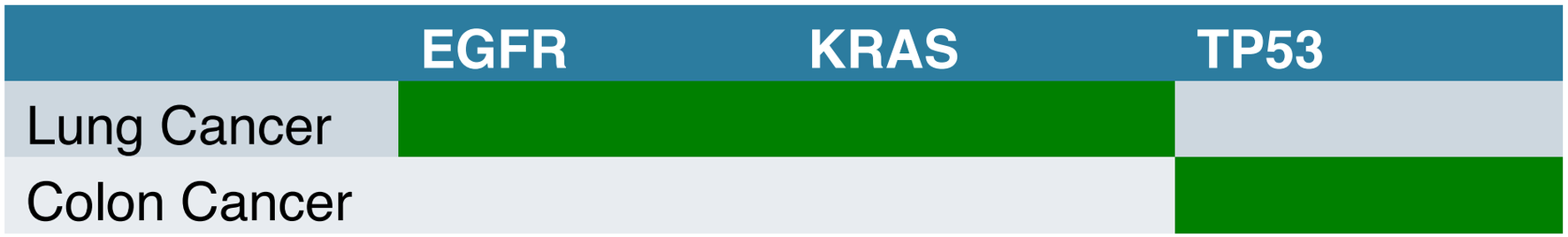
- **Clinical Trial**: study of targeted agents in metastatic cancers.
- **Patients:** with metastatic cancer (thyroid, ovarian, melanoma, lung, breast, CRC and other)
- **Treatments**: therapy that targets particular molecular aberrations (TT) vs. standard of care (S)
- **Population**: heterogeneous population; different mutations; different cancers; baseline covs . . . Treatment might be effective in a sub-population

Data:

TRT	TUMOR	PFS	CENS	MUTATIONS					
				m1	m2	m3	m4	m5	m6
TT	THYROID	2.6	0	NA	NA	NA	NA	NA	NA
TT	THYROID	3.6	0	NA	0	0	0	NA	0
S	OVARIAN	4.2	1	0	NA	0	0	0	0
S	MELANOMA	5.8	1	NA	0	0	0	NA	0
. . .	. . .	. . .	. . .						

Motivation Trial: IMPACT II

Objective: determine the subpopulation that achieves the maximum benefit from TT.



We will cast this goal as a **decision problem**.

Subpopulation Finding: Decision Problem

- Outcome: progression free survival (PFS) time, $y_i, i = 1,\ldots,n$
- Action: report a subgroup of patients who might benefit from the TT. A set of **mutation-tumor pairs**,

$$A = \{a : a = (j_a, c_a)\}$$

- $j_a = \{1,\ldots,q\}$: Molecular aberration
- $c_a \in \{1,\ldots,n_c\}$: tumor type

{(KRAS, Lung), (TP53, Breast)}

Subpopulation Finding: Decision Problem

- Action: report a subgroup of patients who might benefit from the TT. A set of **mutation-tumor pairs**,

$$A = \{a : a = (j_a, c_a)\}$$

Bayes Rule: $A^* = \text{argmax}_A \int u(A, \theta) p(\theta \mid y, X) d\theta$

Utility: we favor a subpopulation with difference in log hazards ratio (LR) and large size

Data from IMPACT

- Outcome: progression free survival times, y_i
- Covariates: $x_i = (c_i, m_i, b_i)$
  - Tumor type c_i (categorical)
  - Molecular aberrations $m_i = (m_{i1}, \ldots, m_{iM})$ (binary)
  - Other baseline covariates b_i (age, # prior therapies, etc)

Challenges

Probability model needs to allow for:

- interactions of covariates
- heterogeneous population
- missing data
- Extrapolation with small # observations

BNP!

Random Partition

- $s = (s_1, \ldots, s_n)$ be cluster membership indicators, $s_i \in \{1,\ldots,J\}$
- $S_j = \{i : s_i = j\}$

Product partition model: $p(s) \propto \prod_{j=1}^{J} c(S_j)$

For DP, $c(S_j) = \alpha(|S_j| - 1)!$

Random Partition

- $s = (s_1, \ldots, s_n)$ be cluster membership indicators, $s_i \in \{1,\ldots,J\}$
- $S_j = (i : s_i = j)$
- x_j^* by cluster

Product partition model with covariates (PPMx):

$$p(s \mid x) \propto \prod_{j=1}^{J} c(S_j) g(x_j^*)$$

Favors clusters homogeneous in x_i with $g(x_j^*)$ scoring similarity of $x_j^* = \{i : s_i = j\}$.

Mueller et al. (2011 JCGS), Quintana et al. (2015 StandJS)

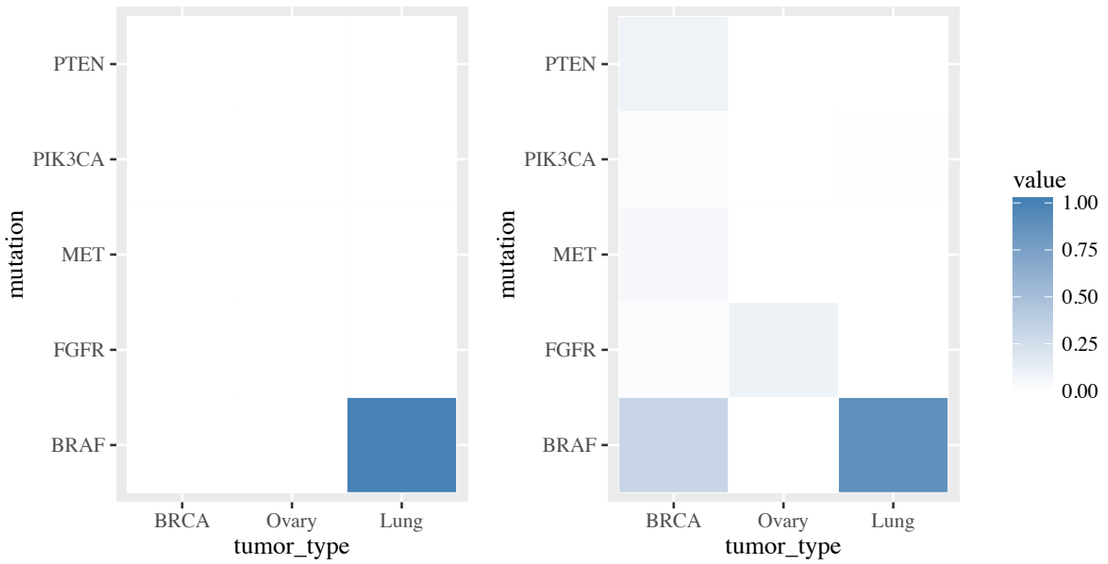
Similarity function: over observed covariates only

$$g(x_j^*) = \prod_{l=1}^{p} g_l(\{x_{il}, i \in S_j \text{ and } x_{il} \text{ observed}\}$$

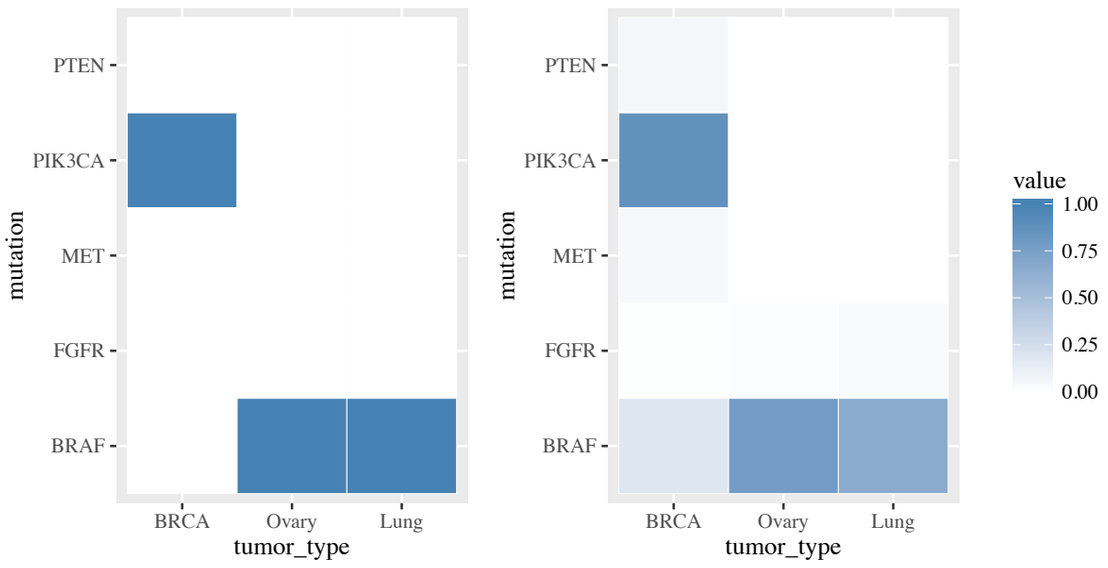
Sampling model: exchangeable within clusters (e.g., lognormal regression model)

$$p(y \mid s, x, \eta) = \prod_{j=1}^{J} \prod_{i \in S_j} p(y_i \mid \eta_j)$$

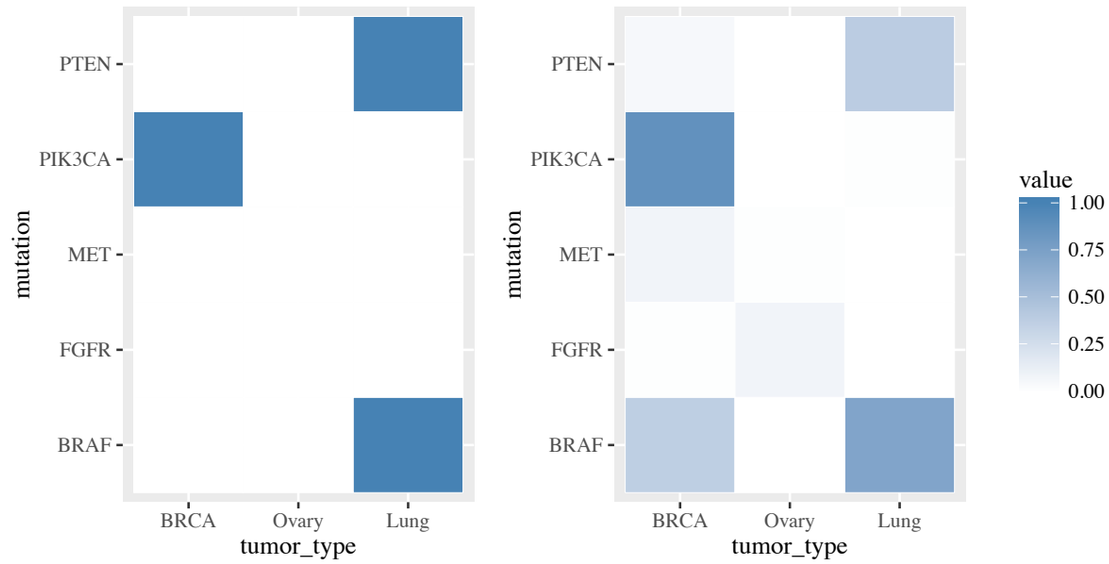
Results



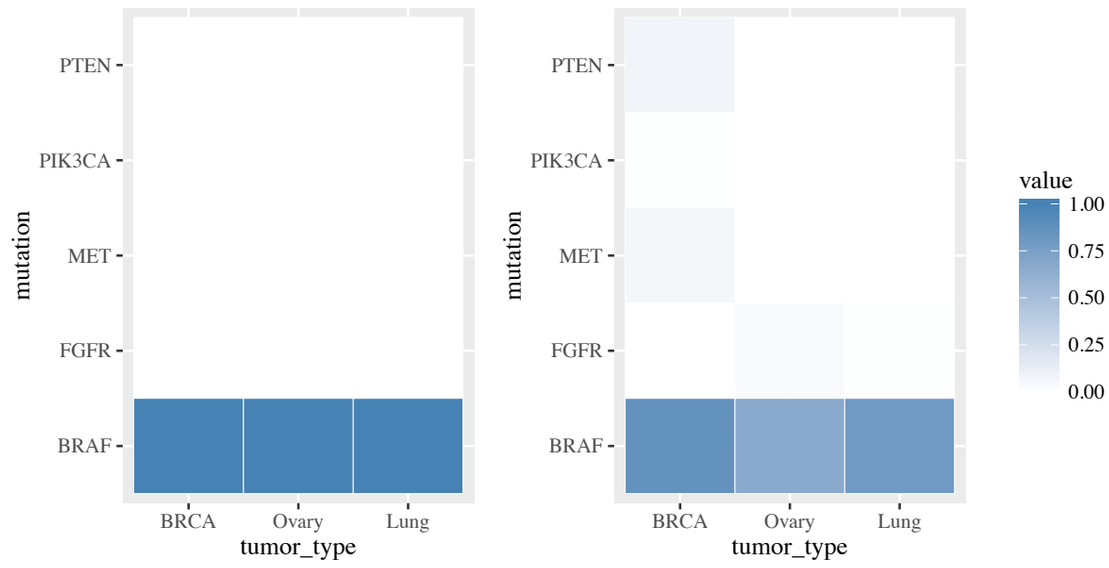
Scenario 3



Scenario 4



Scenario 5



Scenario 6

Take-home Messages

- A general class of probability models that allow for interactions and missing data
- Subgroup finding can be casted as a decision problem.
- Separate the decision problem with probability model
- Can be used in clinical trial designs to adaptively assign patients

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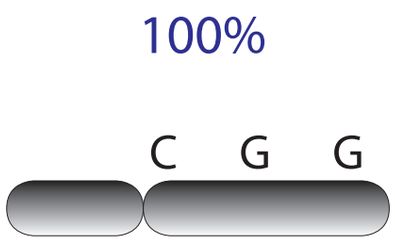
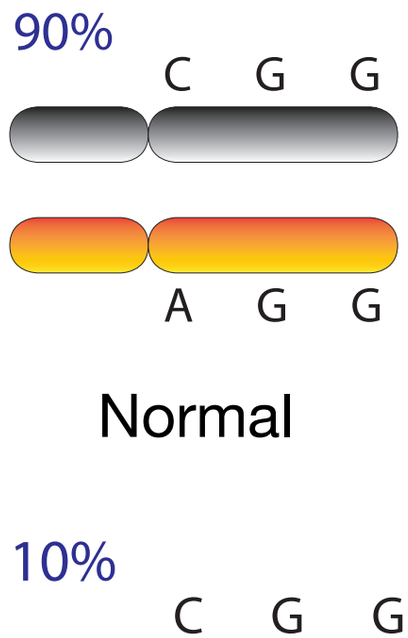
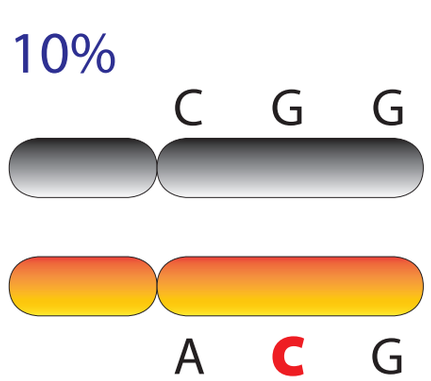
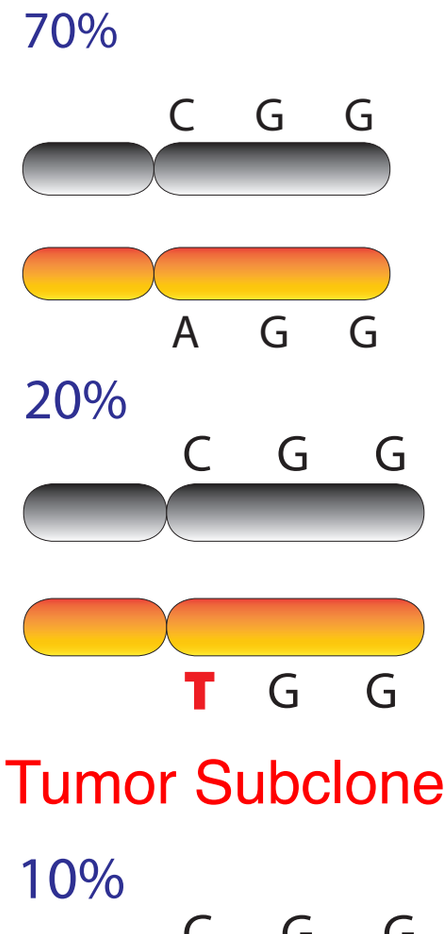
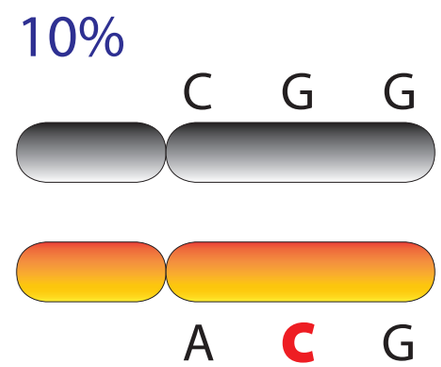
Tumor Heterogeneity (TH)

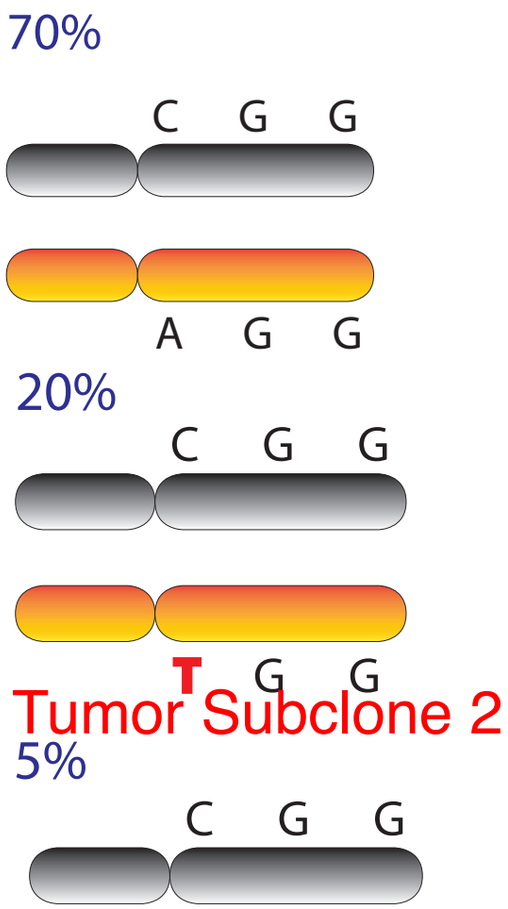


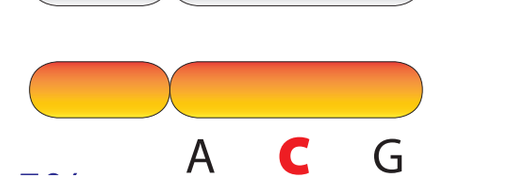






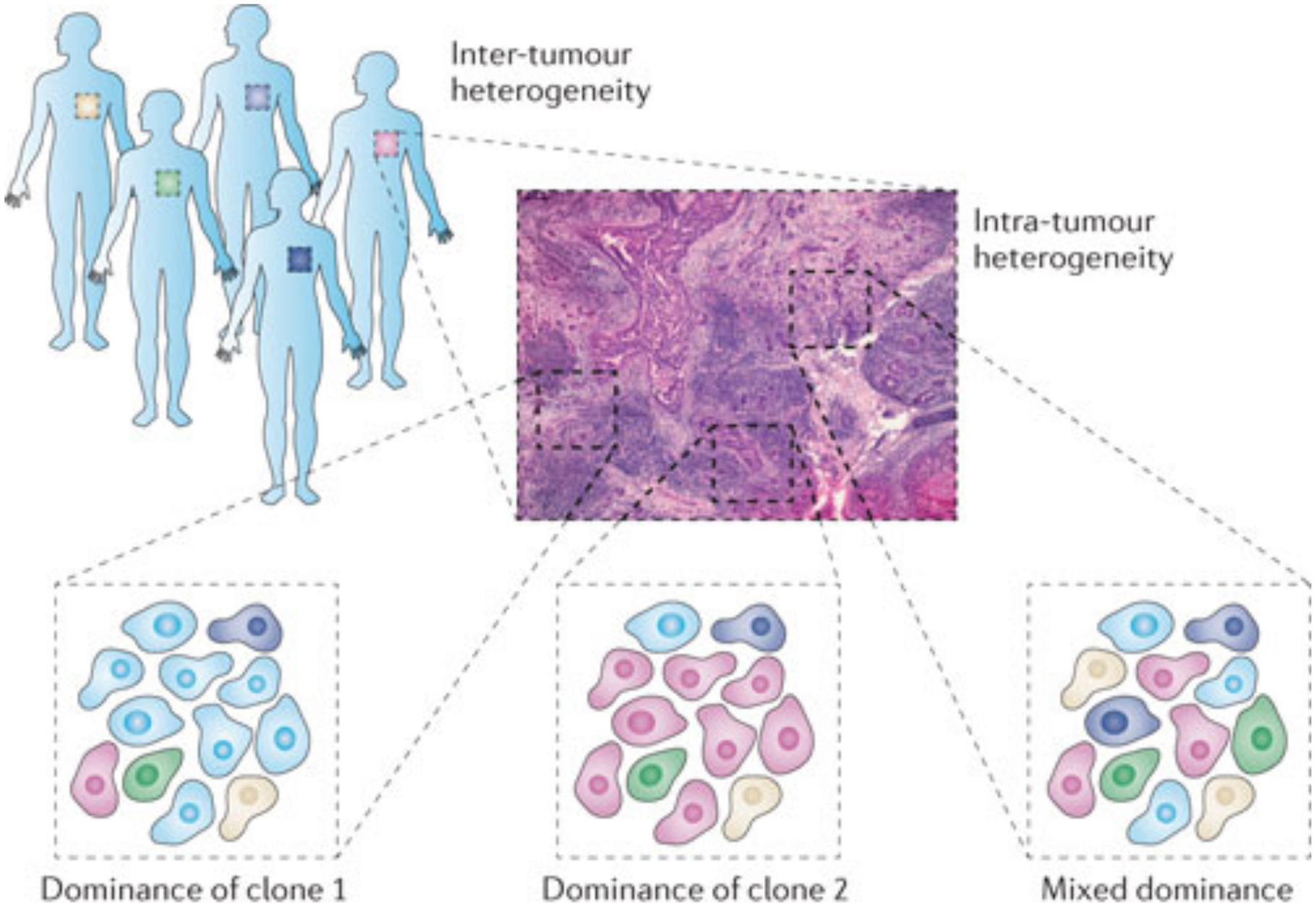






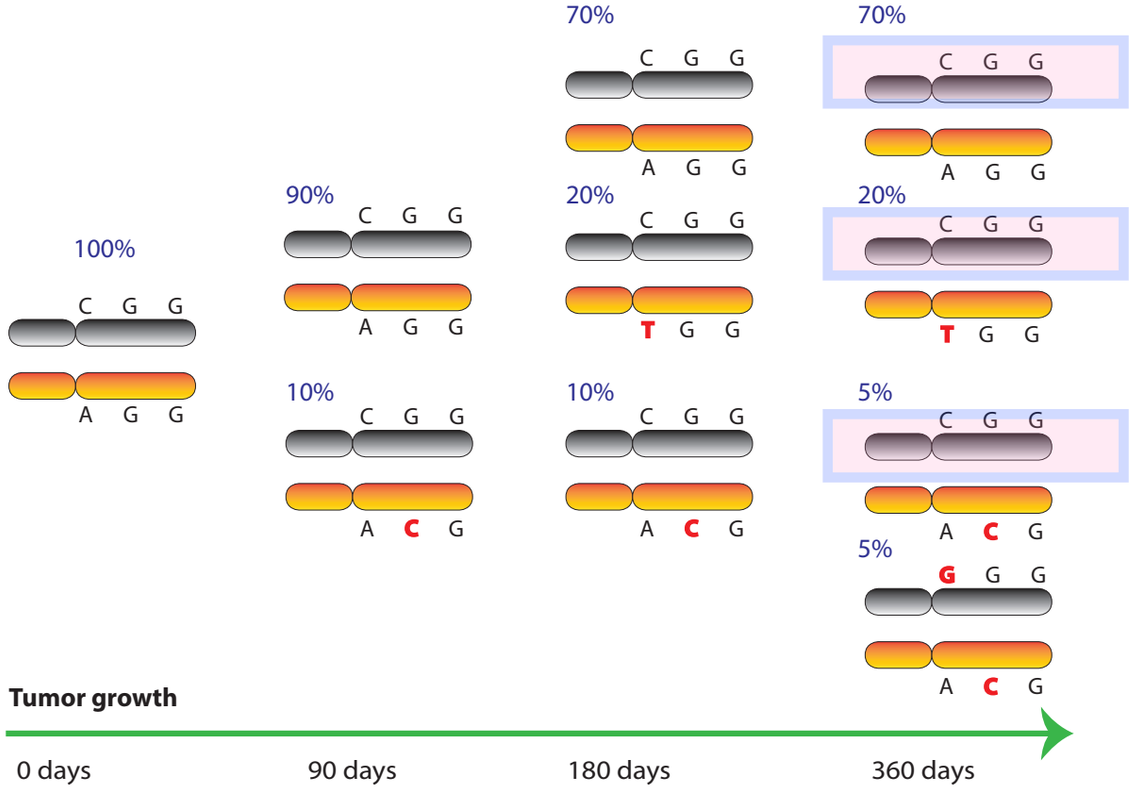
Life History of a Tumor

Clinical Utility of TH

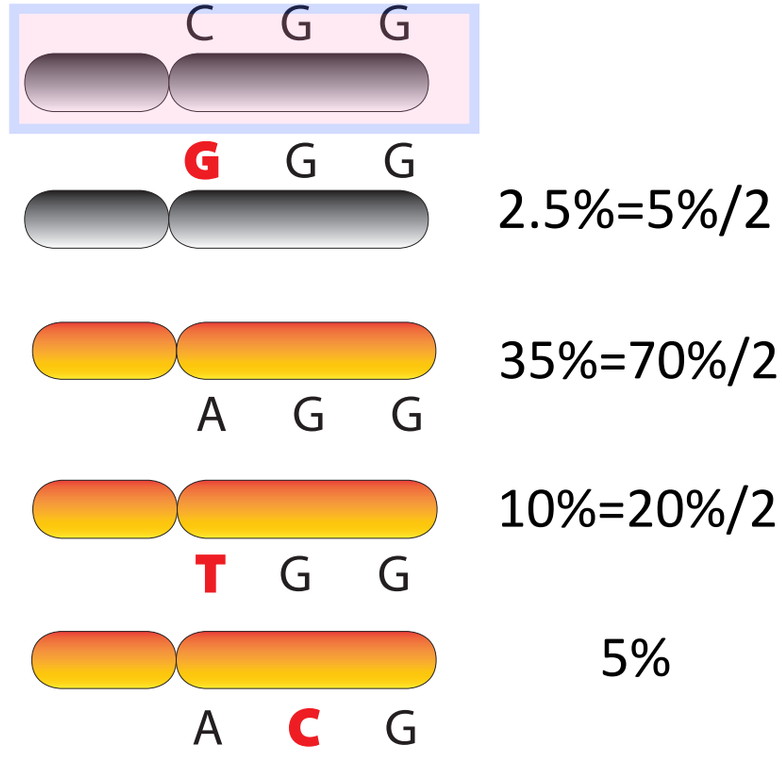


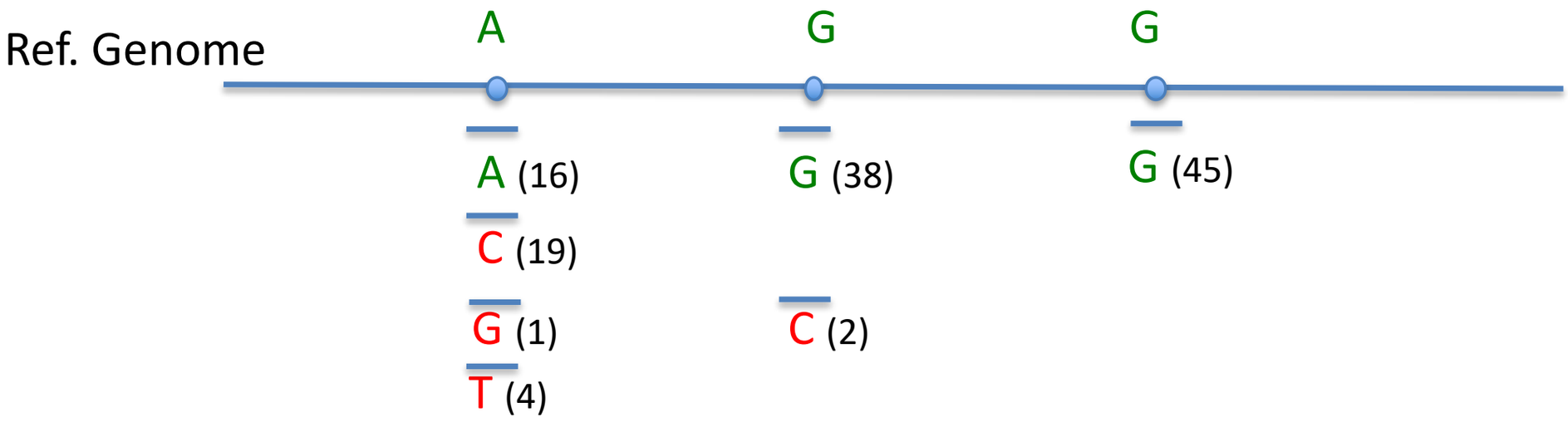
Nature Reviews | Cancer

Haplotype



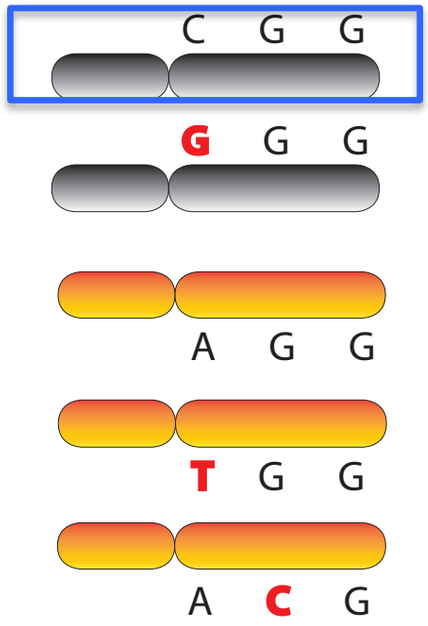
47.5%=(70%+20%+5%)/2





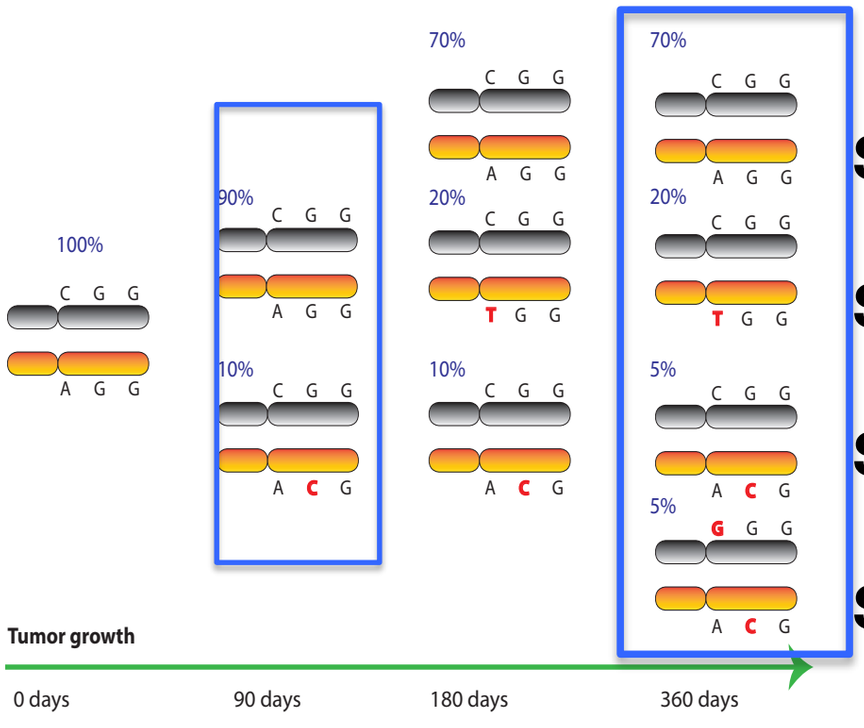
47.5% (CGG) + **2.5** (GGG) + **35%** (AGG) + **10%** (TGG) + **5%** (ACG)

Tumor Heterogeneity in Terms of Haplotype Genome (Z) and Cellular Fractions (W)



	Hap1	Hap2	Hap3	Hap4	Hap5
SNV1	1	1	0	1	0
SNV2	0	0		0	1
SNV3	0	0	0	0	0

The ***Z*** Matrix



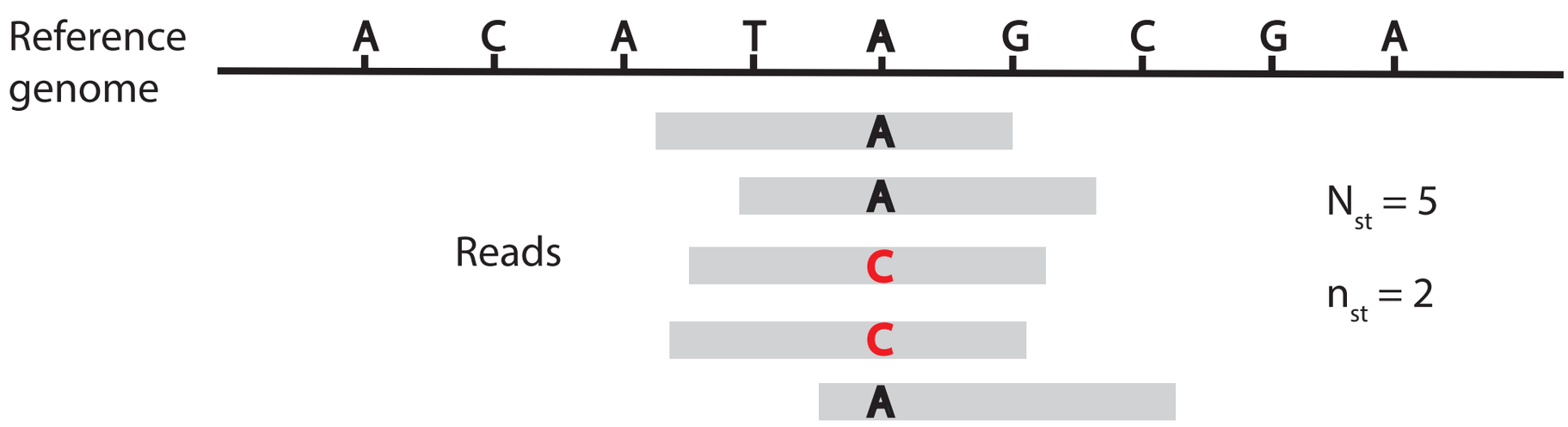
	Hap1	Hap2	Hap3	Hap4	Hap5
Sample 1	47.5%	2.5%		10%	5%
Sample 2	50%	0	35	10%	5%
Sample 3	50%	0	%	0	5%
Sample 4	50%	0	%	0	0

The ***W*** Matrix

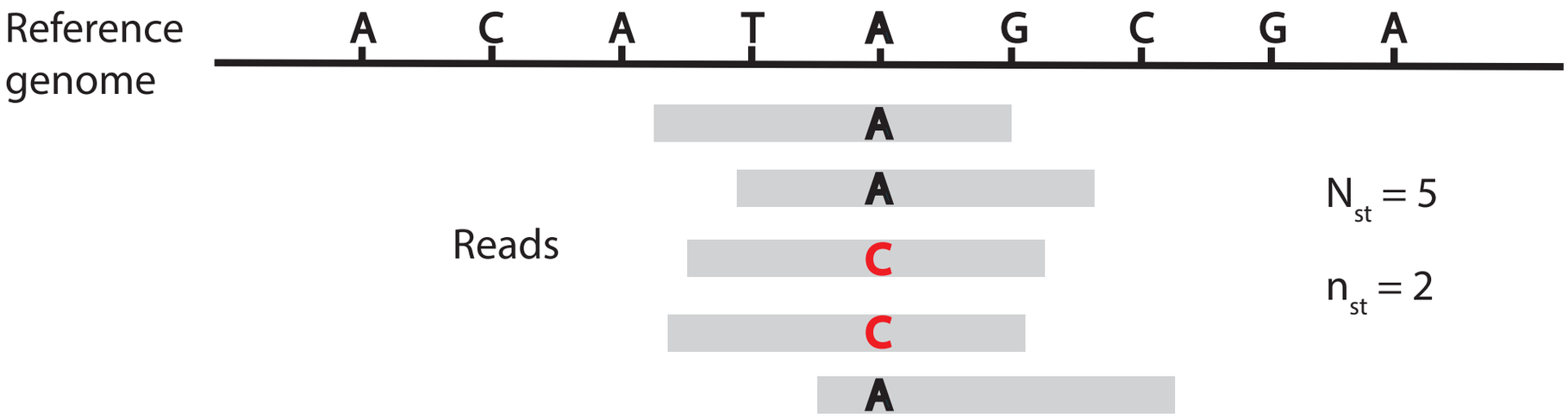
Notations

- SNV: point mutations, $s = 1,\ldots,S$
- Sample: $t = 1,\ldots,T$
- Data: N_{st} = # reads mapped to locus of SNV s in sample t

  n_{st} = # of them with SNV.



Sampling Model

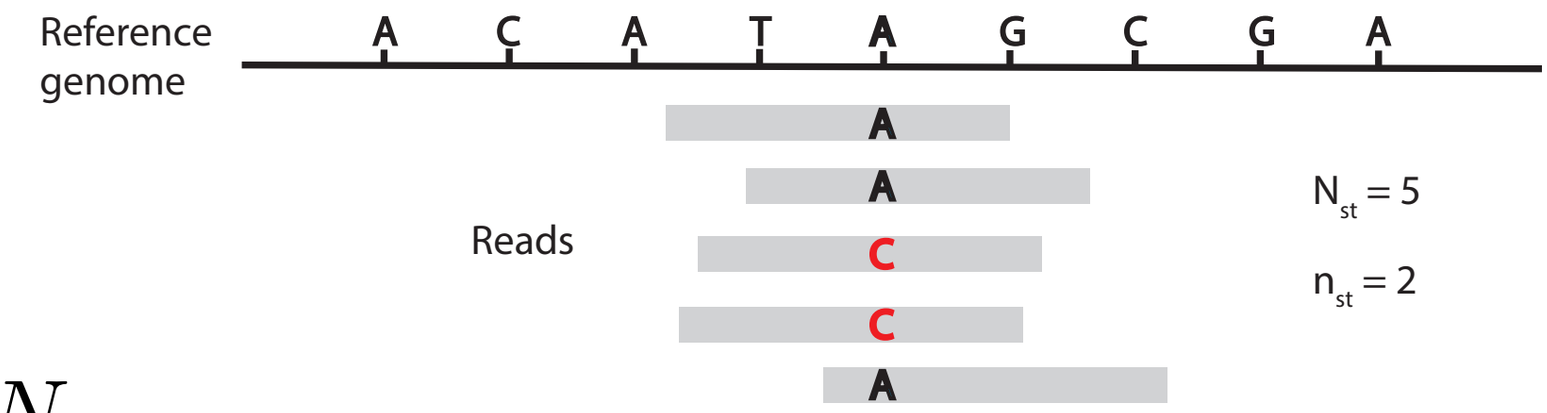


$$n_{st} \sim \text{Binomial}(N_{st}, p_{st})$$

VAF: variant allele fraction

$$\text{Observed VAF: } n_{st}/N_{st}$$
$$\text{Expected VAF: } p_{st} = E(n_{st}/N_{st})$$

Link VAFs with Haplotypes



Observed VAF: n_{st}/N_{st}

Expected VAF: $p_{st} = E(n_{st}/N_{st})$

Key Idea: A variant read must be from a haplotype with variant.

Link VAFs with Haplotypes

Key Idea: A variant read must be from a haplotype with variant.

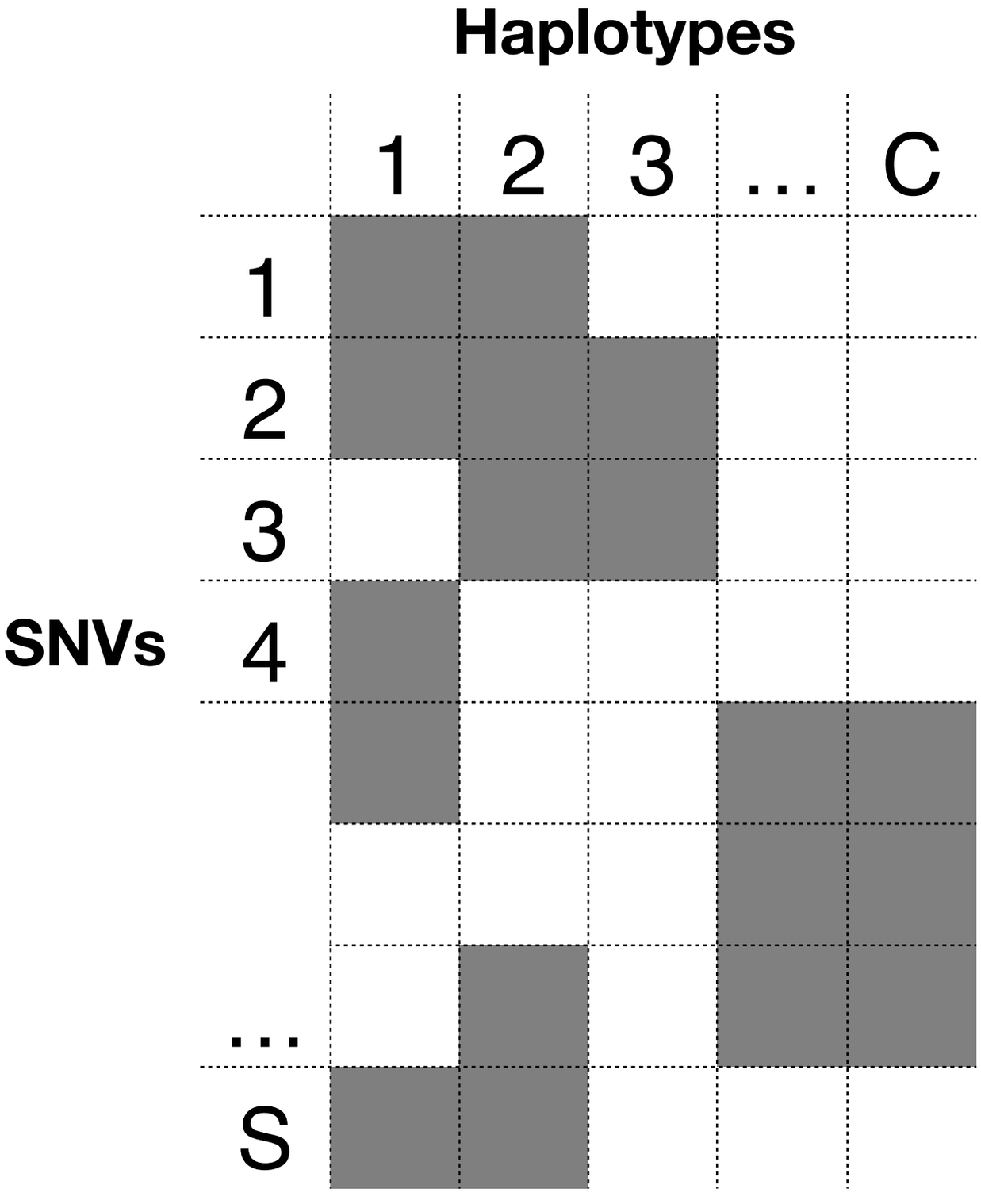
s: SNV; c: haplotype (latent); t: sample

$z_{sc} = 1$: haplotype c has a variant on SNV s.
$z_{sc} = 0$: haplotype c has no variant on SNV s.
w_{tc}: fraction of haplotype c in sample t.

Linking Equation:

$$p_{st} = \sum_c w_{tc} z_{sc}$$

Haplotype Genotype Z



$p(Z)$ on $(S \times C)$ binary matrix

Indian Buffet Process (IBP)

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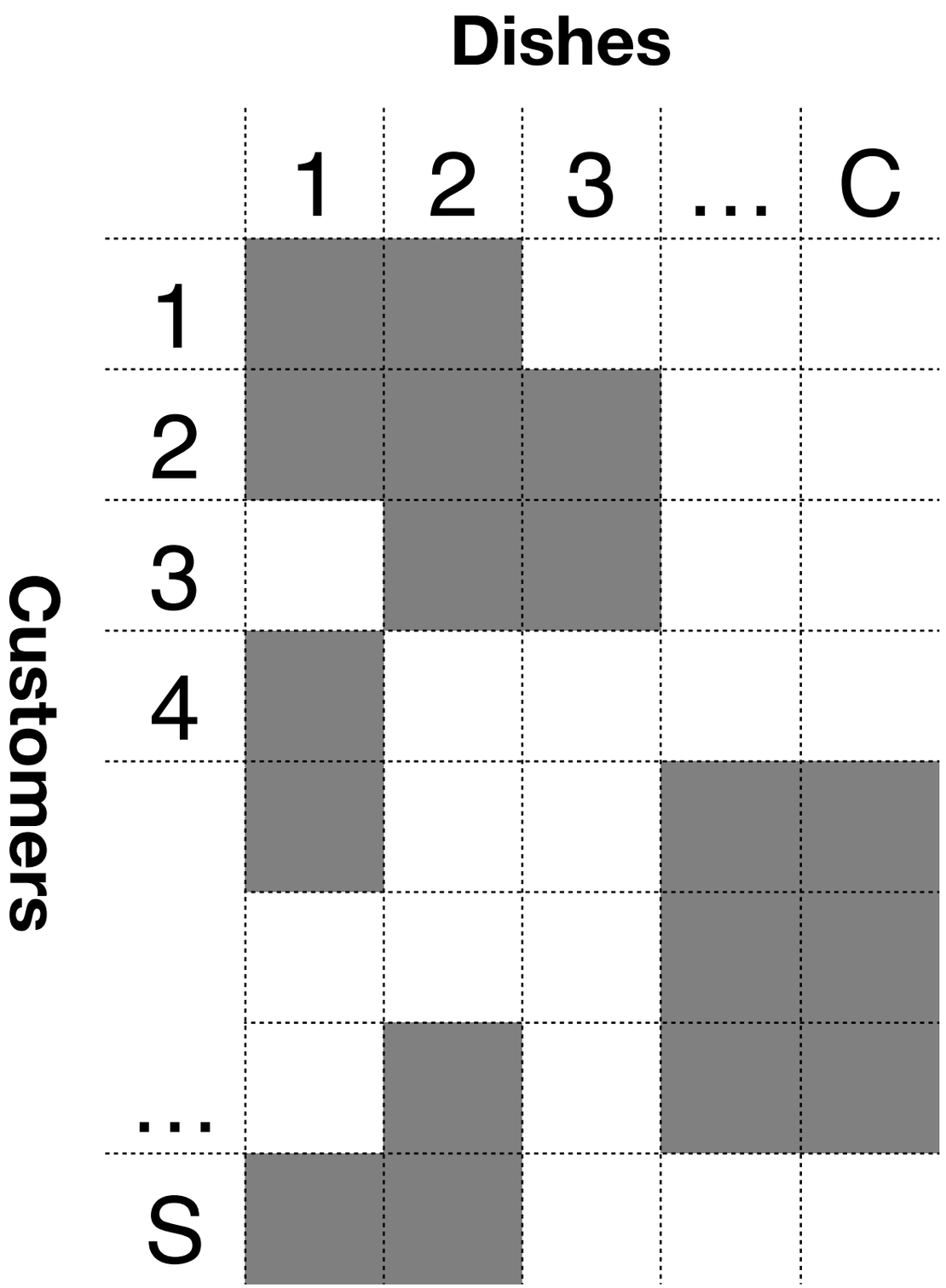
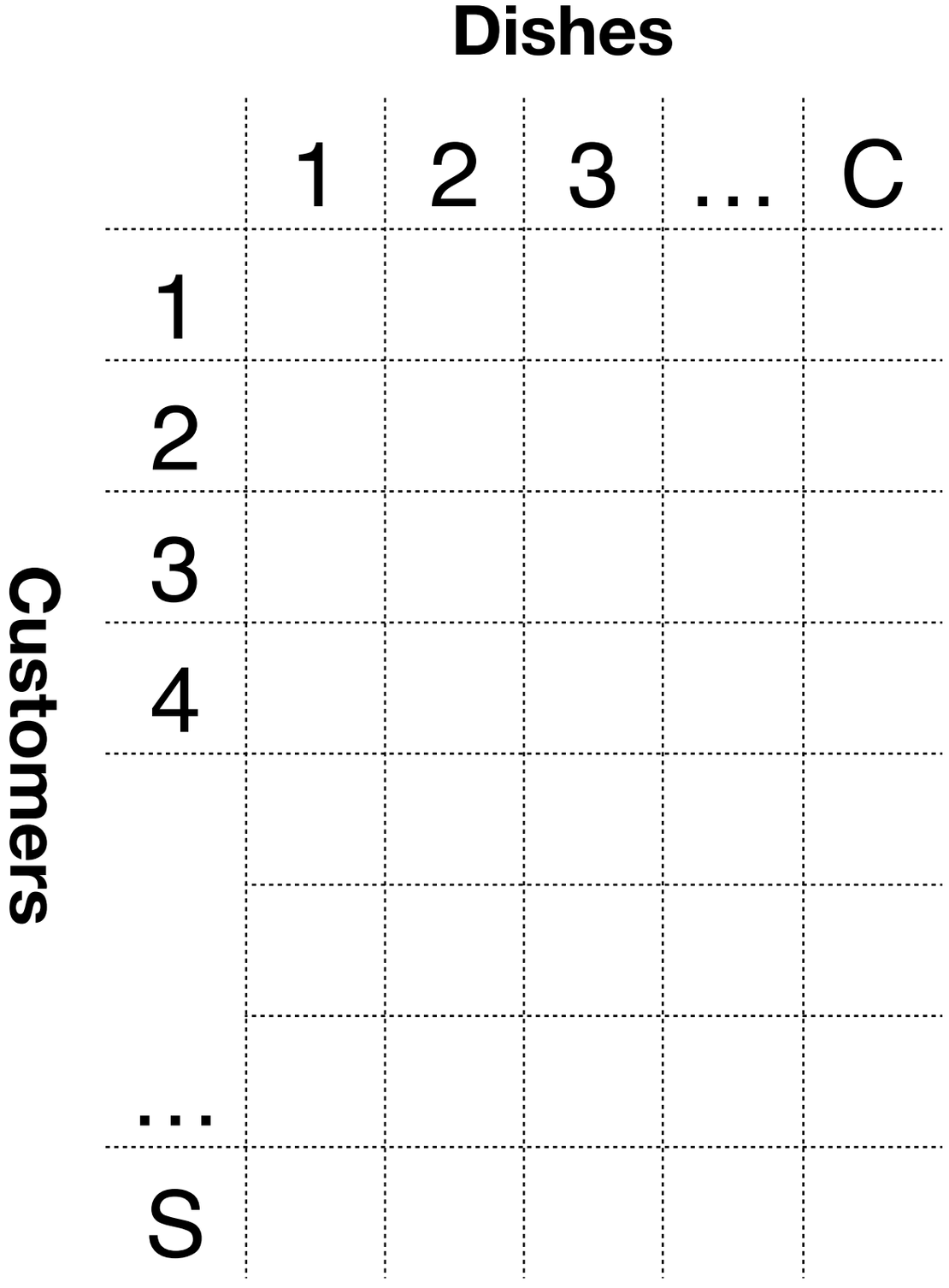


For $s = 1, \ldots, S$

- Customer s chose dish c that has been already chosen m_k time with probability m_k / s
- Number of new dishes: $K_s \sim \text{Poisson}(\gamma / \text{s})$

Indian Buffet Process (IBP)



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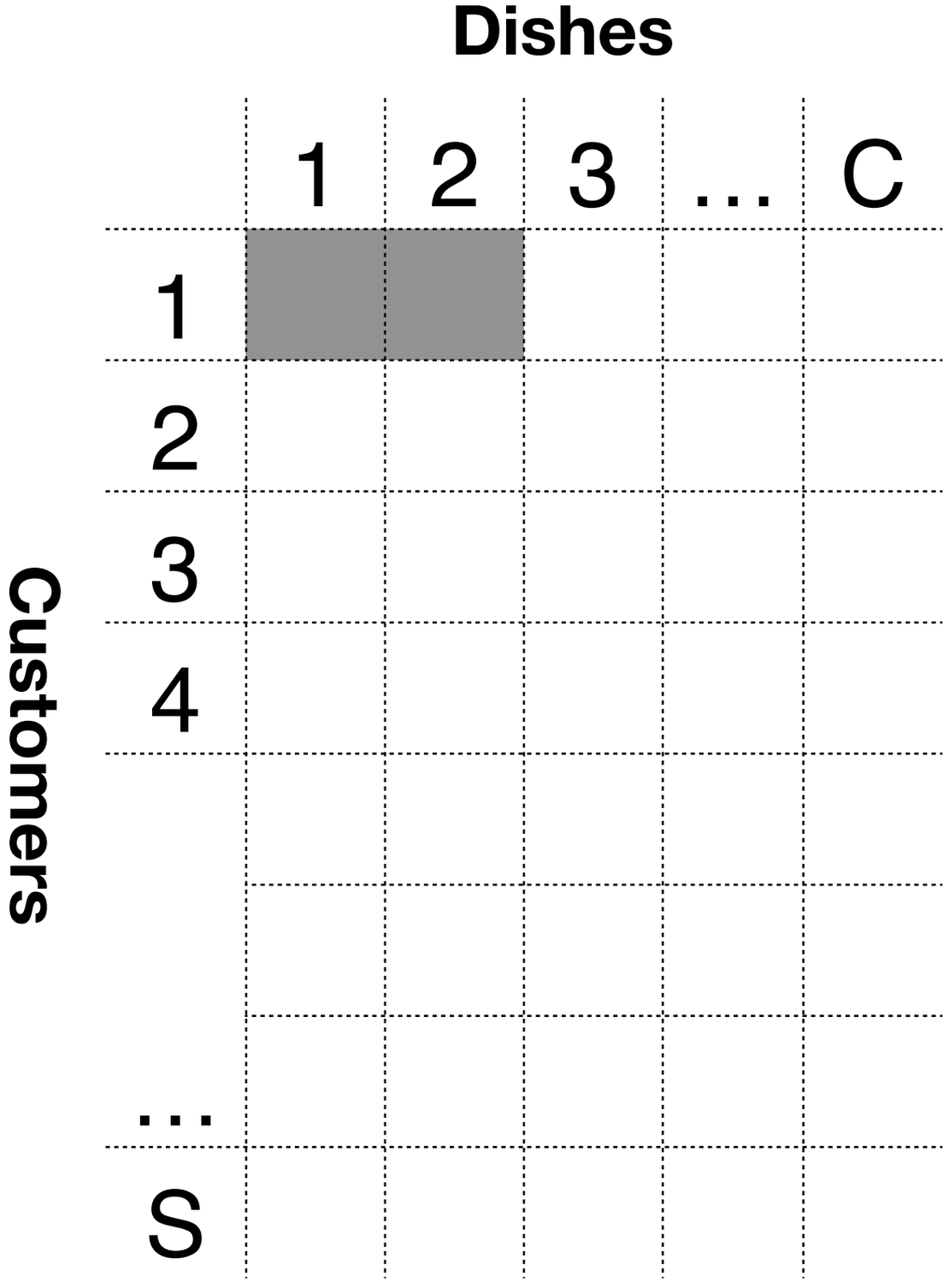

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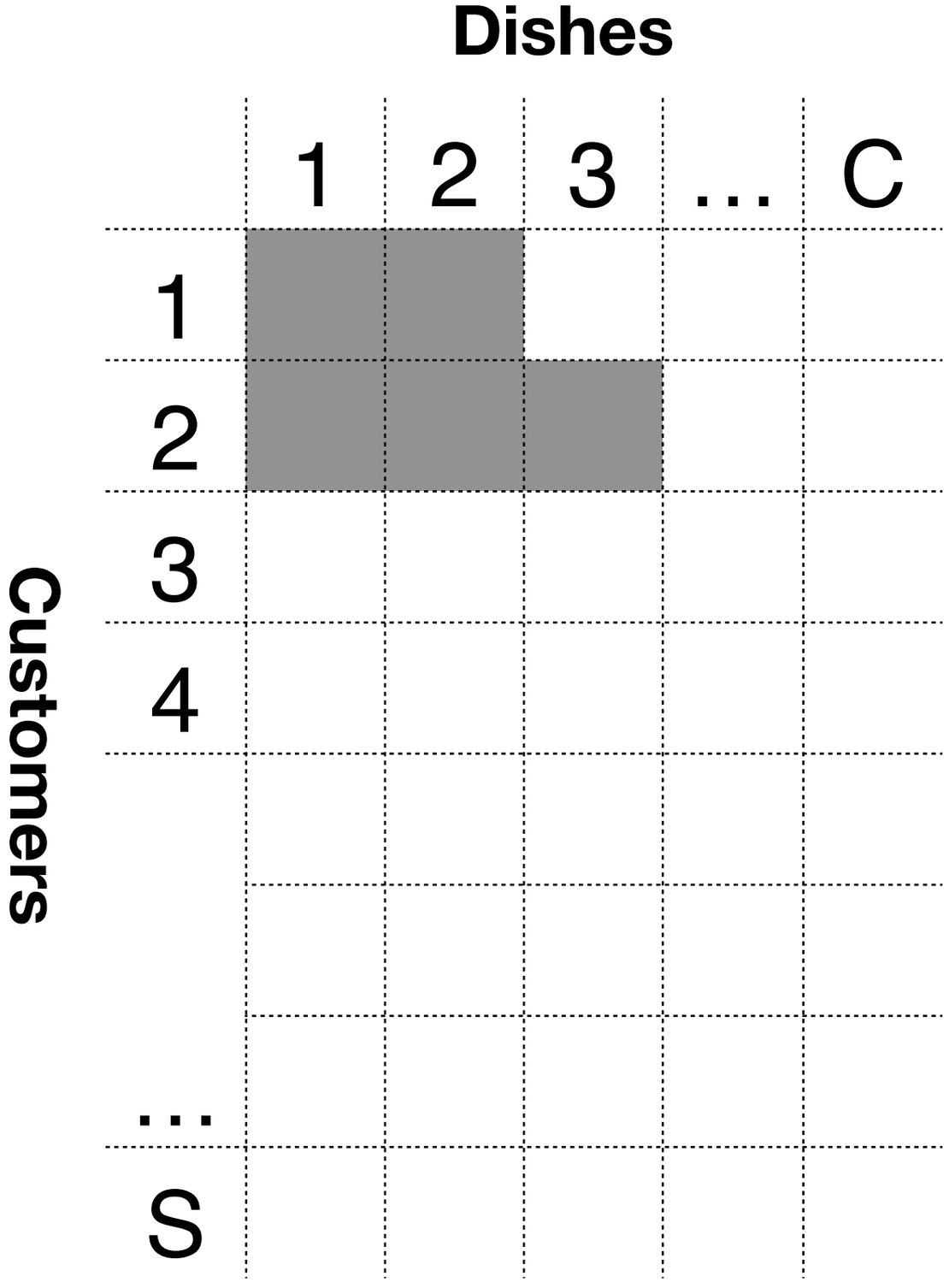

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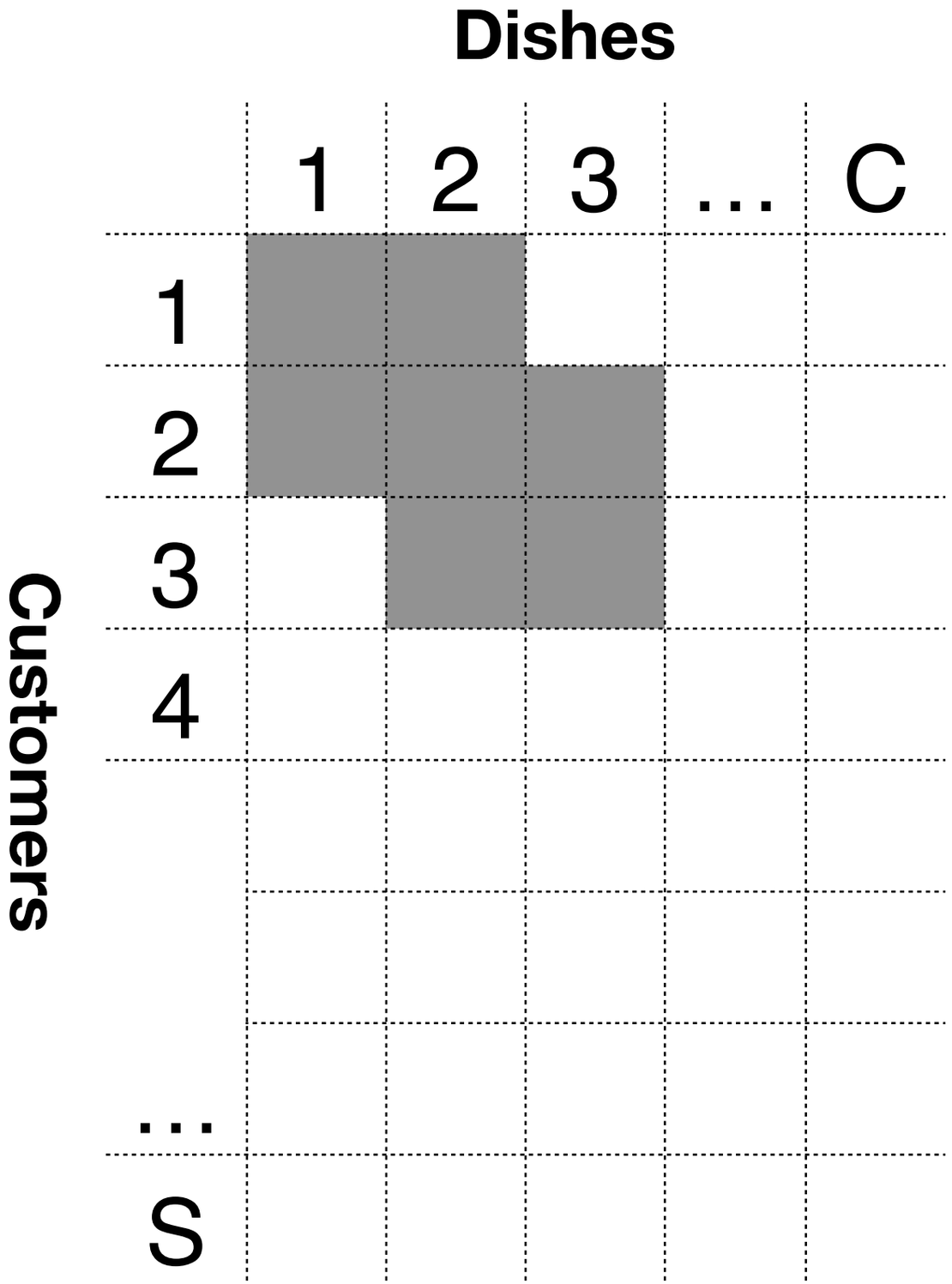

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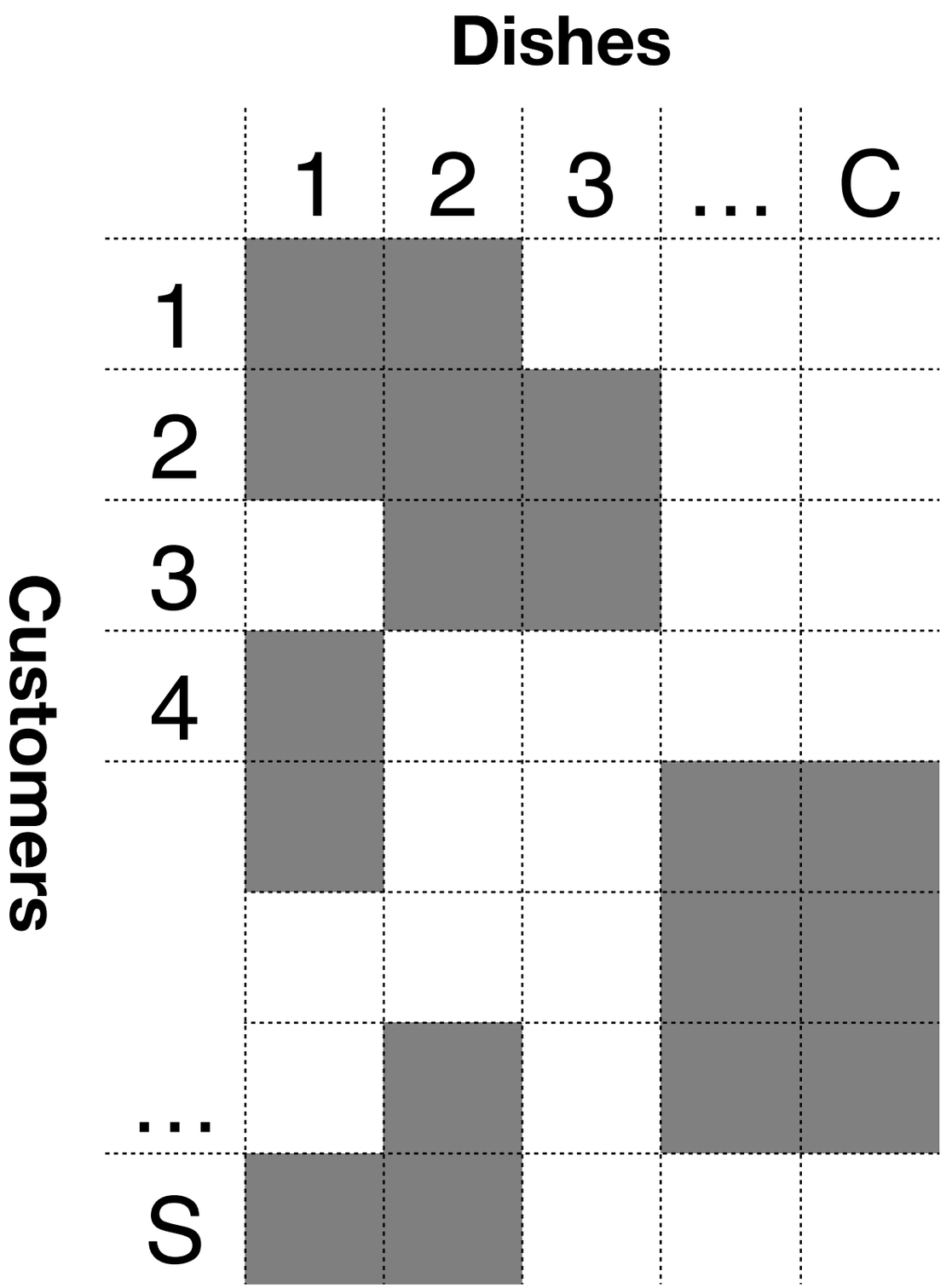

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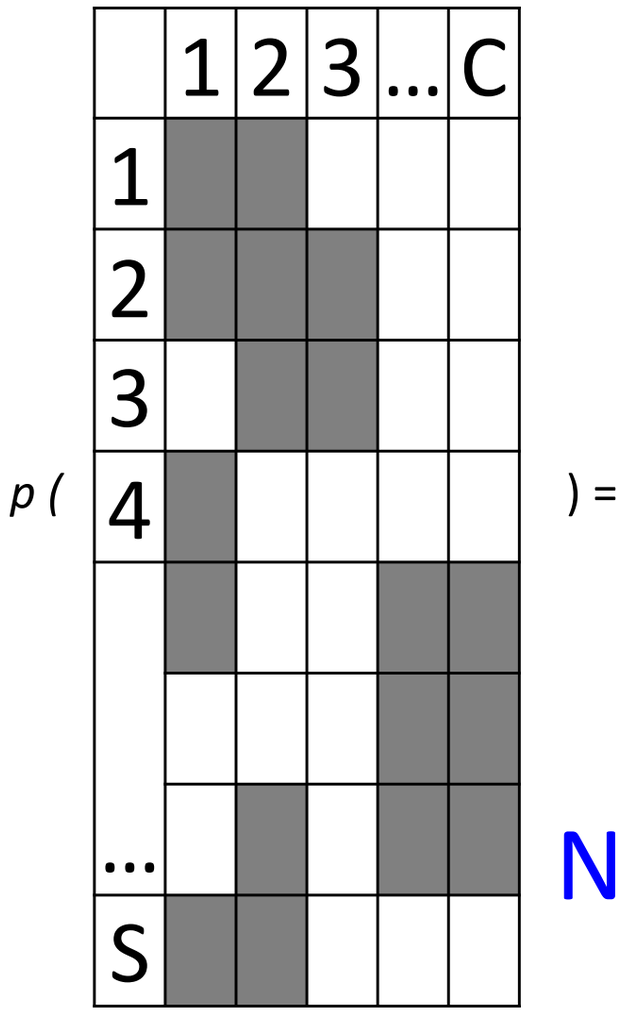
IBP Prior



$p($ $)=$

customers (SNVs) who chose dish c (haplotype)

Number of customers (SNVs)

Number of dishes (haplotypes)

$$p(\mathbf{Z} \mid \gamma) = \frac{\gamma^C \, e^{-\gamma H_S}}{C!} \prod_{c=1}^{C} \frac{(S - m_c)!(m_c - 1)!}{S!}$$

Model Summary

$$p(Z, w, n \mid N) = \underbrace{p(Z)}_{\text{IBP}}\, p(w \mid Z)\, \underbrace{p(n \mid Z, w, N)}_{\text{Binomial}}.$$

$$p_{st} = \sum_{c} w_{tc} z_{sc}$$

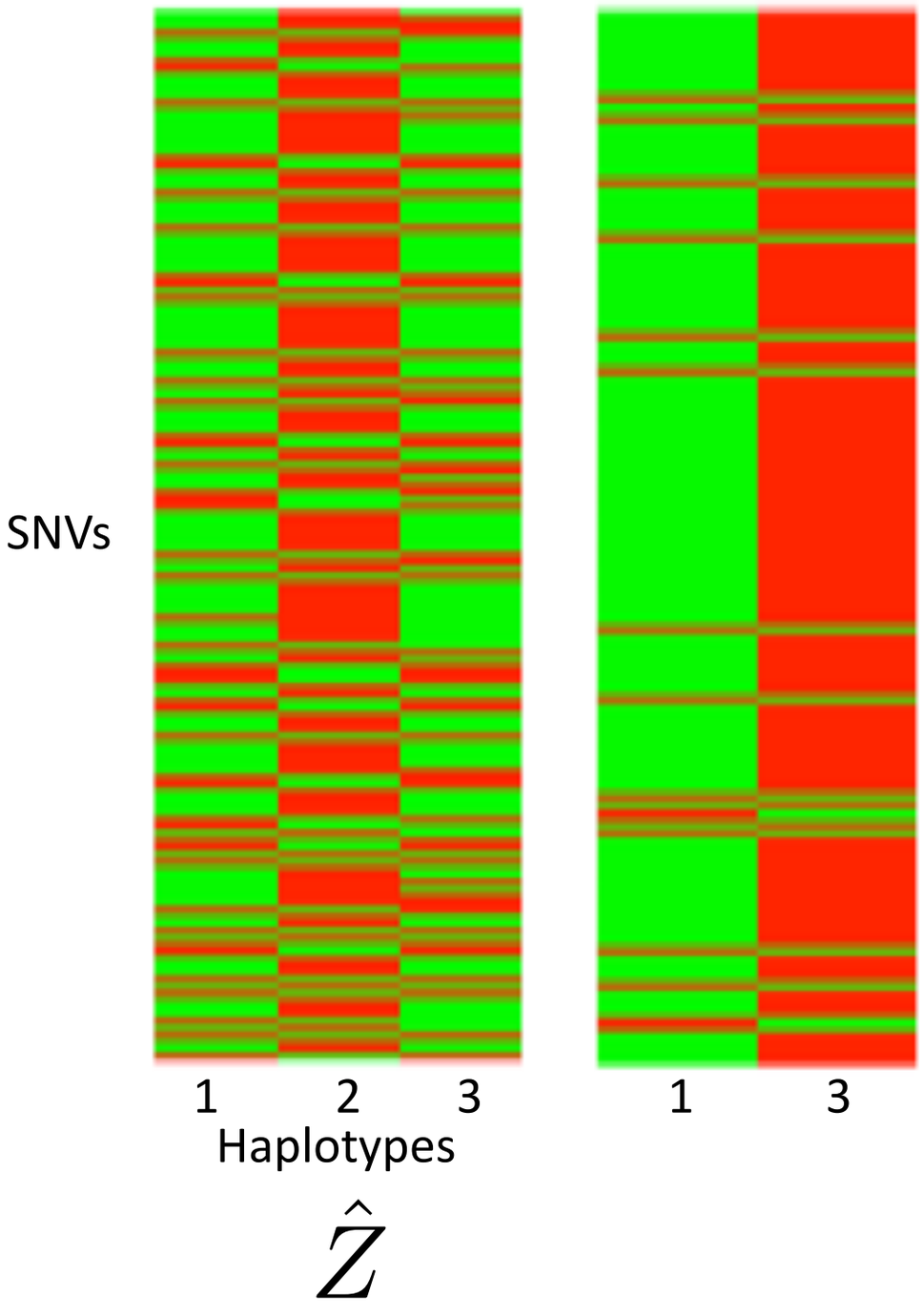
$$p(w_t) \sim \text{Dir}(a_1, \ldots, a_C),\ t = 1, \ldots, T.$$

$$p(Z, w \mid N, n)$$

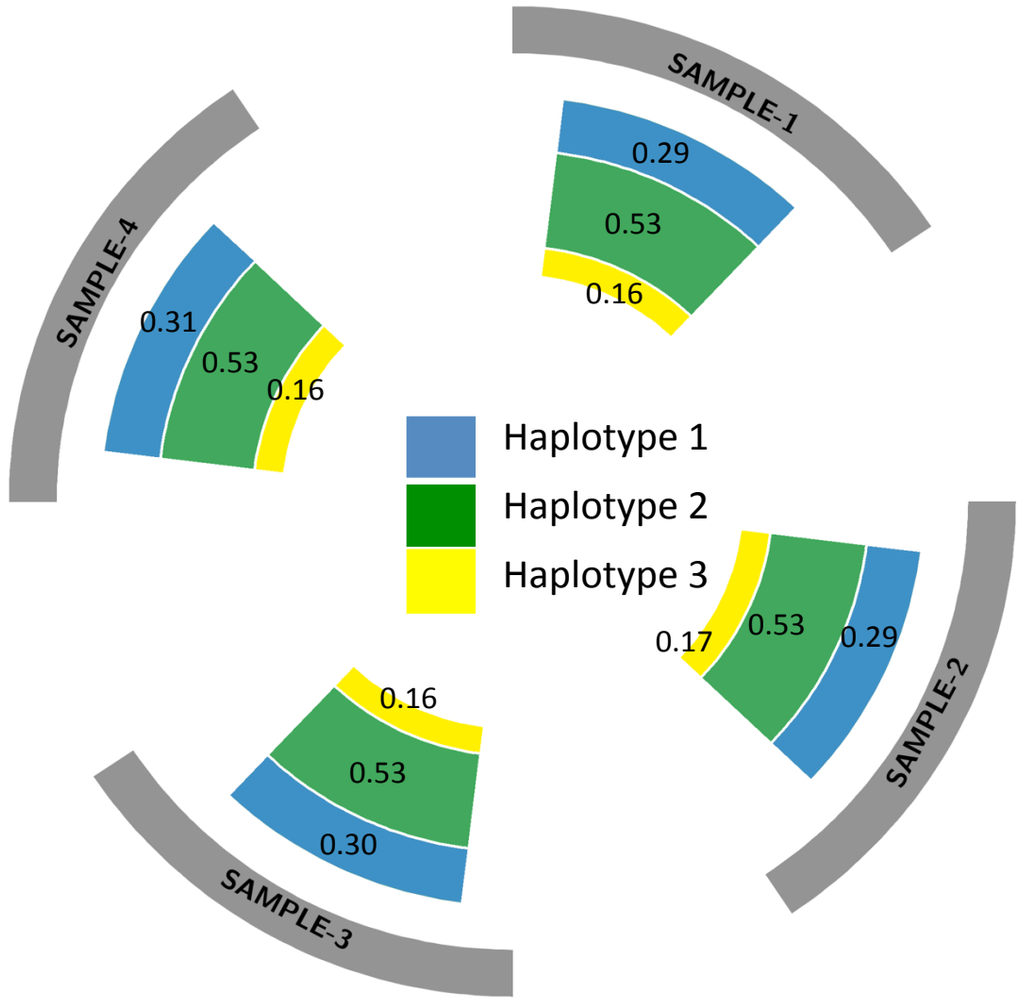
Application: Intra-Tumor Heterogeneity

- One tumor from lung cancer; 4 samples surgically dissected
- Each sample generates a whole-genome sequencing data set
- Bio-X pipeline (BWA, Samtools, GATK) for data preprocessing: coverage ~ 100X.
- Selected S=17,160 SNVs

Application: Intra-Tumor Heterogeneity



$\hat{Z}$

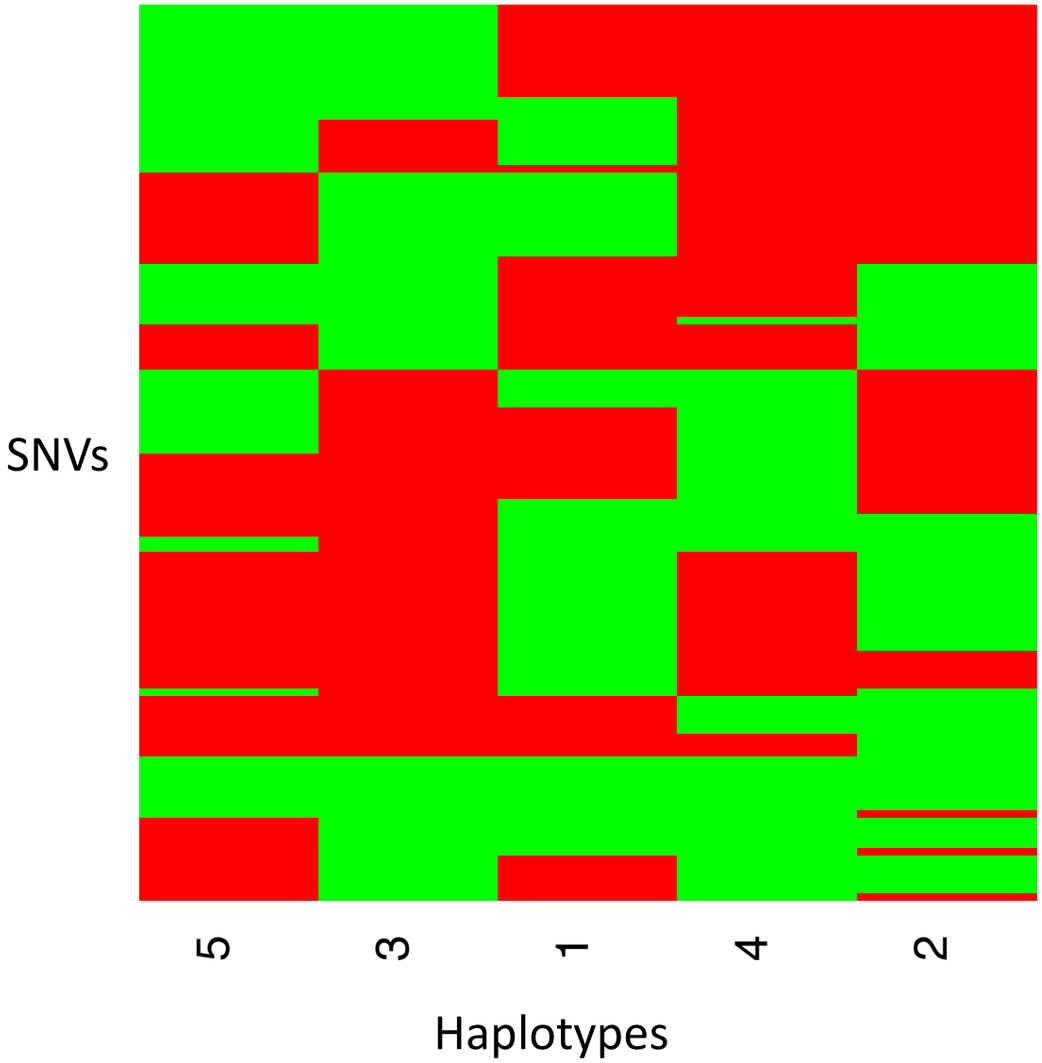


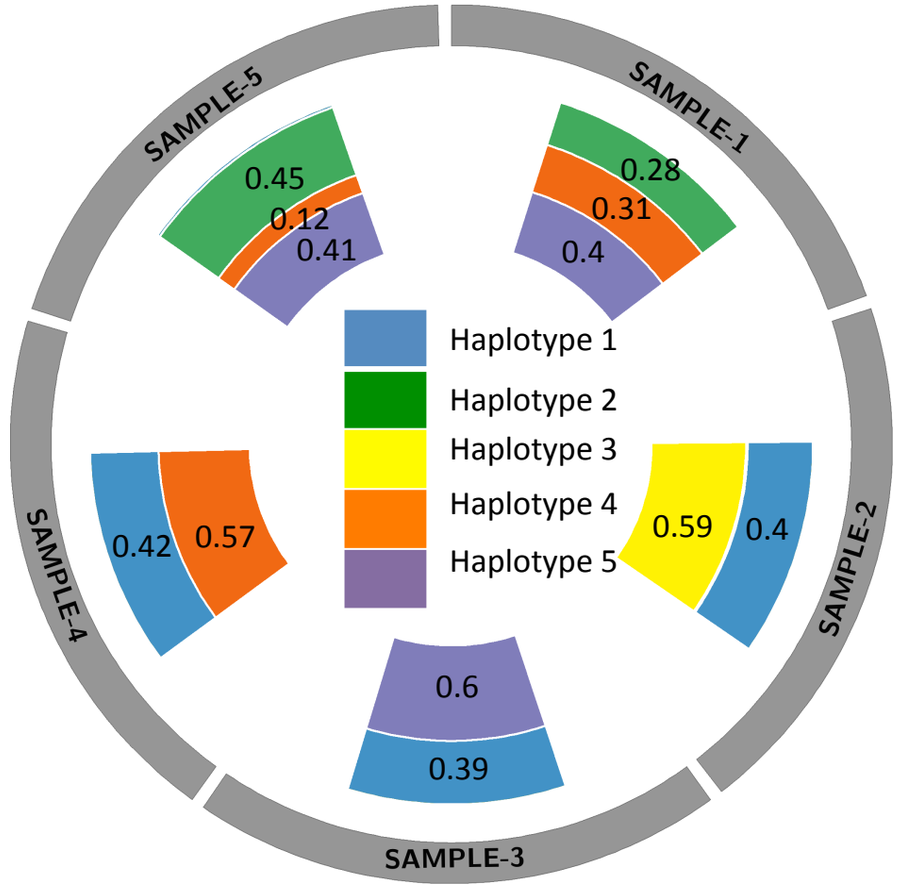
$\hat{w}$

Application: Inter-Tumor Heterogeneity

- Exome-sequencing data for five tumor samples from four different pancreatic ductal adenocarcinoma (PDAC) patients
- Bio-X pipeline (BWA, Samtools, GATK) for data preprocessing: coverage ~ 70X.
- Selected 118 SNVs: 1) significant coverage in all samples; 2) related to PDAC in the KEGG pathway database; 3) are nonsynonymous

Application: Inter-Tumor Heterogeneity





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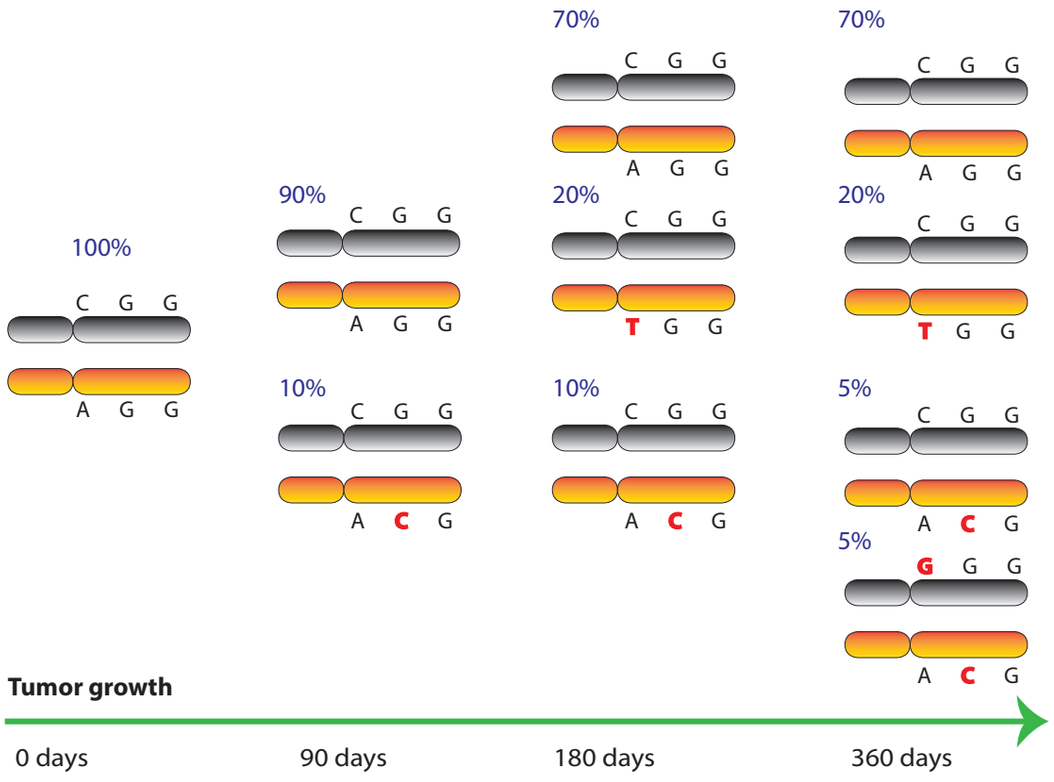
Extension: Categorial IBP



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Clinical Trial Based on TH

The PANGEA -IMBBP Trial

Personalized ANtibodies for Gastro-Esophageal Adenocarcinoma: A Pilot 1st Metastatic Trial of Biologics Beyond Progression

Historical Control (Arm A) → FOLFOX → PFS_1 6m → FOLFIRI 60% → PFS_2 4m → FOLTAX 30% → PFS_3 2m

Biomarker Evaluation in all samples to allow for treatment assignment

Diagnosis: metastatic cancer

i) Primary Endpoints:
Feasibility:
Time to treatment assignment
Safety: toxicity
ii) mOS (HR 0.67) in HER2+/MET+
Historic Arm A v Arm B
(Improve to 18 months from 12 months)
HR: 0.67 of combined HER2+ & MET+
{12 month survival rate ~63%}
N= 68 (80% power)

•Secondary Endpoints:
$PFS_{1,2,3}$, PFS_{1+2+3} for HER2+/MET+
mOS for all 5 groups
2nd/3rd line treatment rates, RR
-Arm A_1 v A_2/ B_1 v B_2
-Compared to Historic Controls
Tissue correlates
- primary tumor to metastatic lesion
- baseline v $PFS_{1,2,3}$

Anticipated Incidence

Primary mOS Endpoint (N=68)

15-20%	HER2 amplified	Arm B1	FOLFOX -Trastuzumab	PD →	FOLFIRI + T	PD → FOLTAX + T
30-50%	MET amplified/Hi	Arm B2	FOLFOX -METab	PD →	FOLFIRI + M	PD → FOLTAX + M
5-10%	FGFR2 amplified	Arm B3	FOLFOX -FGFR2ab	PD →	FOLFIRI + F	PD → FOLTAX + F
25%	EGFR amplified/Hi KRAS wild type NI HER2,FGFR2,RON,MET	Arm B4	FOLFOX -EGFRab	PD →	FOLFIRI + EGFRab	PD → FOLTAX + EGFRab
20-25%	KRAS/BRAF/ PIK3CA/AKT/PTENdel mt/amplified NI HER2,FGFR2,RON,MET	Arm B5	FOLFOX -VEGFR2ab	PD →	FOLFIRI + V	PD → FOLTAX + V

ARM B: Therapy based on molecular profile

Secondary mOS Endpoint (N~104)