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A Bayes Rule for Subgroup Reporting – Adaptive Enrichment Designs

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TRT	TUMOR	PFS	CENS	MUTATIONS								
				m1	m2	m3	m4	m5	m6	m7	m8	...
TT	THYROID	2.6	0	NA	NA	NA	NA	NA	NA	NA	NA	
TT	THYROID	3.6	0	NA	0	0	0	NA	0	NA	NA	
S	OVARIAN	4.2	1	0	NA	0	0	0	0	0	0	
S	MELANOMA	5.8	1	NA	0	0	0	NA	0	0	0	
...	...	...	...									

1 Example: A study for targeted therapy

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1. A Clinical Trial of Targeted Therapies

with Riten MITRA, U. Louisville, Don BERRY and A. TSIMBORIDOU, M.D. Anderson, Siji nWEN, U WVa.

Clinical trial: study of targeted agents in metastatic cancers.

Patients: with metastatic cancer (thyroid, ovarian, melano, lung, breast, CRC and other)

Treatments: therapy that targets particular molecular aberrations (TT) vs. standard of care (S)

Objective: determine whether TT leads to > progression free survival (PFS)

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Patient population: patients eligible for non-FDA approved targeted therapy
record mutations, all cancers

Population finding: heterogeneous pat population different mutations; different cancers; basline covs ... Treatment might be effective in a sub-population (subgroup analysis with a purpose)

Data: Can use data from similar *observational* study to design the trial and evaluate frequentist operating characteristics

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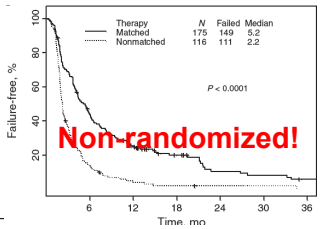
Data

Different PFS under TT vs. control,



PFS

- mutations are recorded only for small numbers n of patients,
- with varying fraction of observed mutation.

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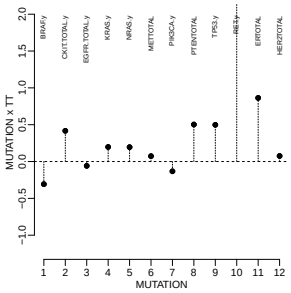
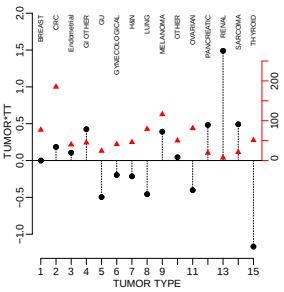
Data (ctd.)

TT effect varies substantially by mutation



TT effect by mutation



TT effect by tumor

and by tumor type.

2 Decision problem

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2. Decision Problem

Data: response y_i (PFS), covariates $x_i = (x_{i1}, \ldots, x_{ip})$.

Actions: Report a (i.e., *one*) subgroup of patients who might most benefit from the experimental therapy:

$$\mathbf{a} = (I, \mathbf{x}^\star),$$

Covariates: $I \subset \{1, \ldots, p\}$

Levels: $\mathbf{x}^\star = (x_j^\star,\ j \in I)$.

Population finding: recommend subpop $\{x_j = x_j^\star,\ j \in I\}$

use, e.g., in adaptive clinical trial with population finding.

Decision problem: separate inference (predicting PFS) vs. decision (report subpopulation).

- no need for multiplicity control
- arbitrary prob model
- disentagle stat significance vs. clinical relevance
- allow for variable # covs.

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Utility: we favor a subpopulation with difference (relative to the overall population) in log hazards ratio (LR), large size and parsimonious description with few covariates

$$u(a, \theta) = (\mathrm{LR}(a, \theta) - \beta) \cdot \frac{n(\mathbf{a})^\alpha}{(|I| + 1)^\gamma}$$

with $\beta > 0$ a fixed clinically decided threshold and $n(\mathbf{a})$ is the size of the subpopulation.
θ indexes the sampling model (*any* model for $p(y \mid x, \theta)$)

Alternative utility: Foster, Taylor & Ruberg (2011, StatMed) use

$$Q(A) = \text{enhanced treatment effect } - \text{average trt effect}$$

and sensitivity and specificity to evaluate a reported subpopulation A.

Model: Decicsion problem and solution remain meaningful for *any* model.
For example, we use the following.

3 Model

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3. Probability Model

Flexible nonparametric Bayesian model.

Variables: for each patient $i = 1, \ldots, n$

- Outcome y_i PFS;
- Covariates $x_i = (c_i, m_i, b_i)$
  - tumor type $c_i \in \{1, \ldots, C\}$ (categorical)
  - molecular aberrations $m_i = (m_{i1}, \ldots, m_{iM})$ with $m_{is} = 1$ for observed aberration, $m_{is} = -1$ for not observed (and 0 for n/a).
  - other baseline covariates b_i (age, # prior threrapies, etc.)

Challenges: prob model needs to allow for

- interacations of m_j
- many m_j are not recorded $\rightarrow$ var dimension covariate vector $x_i = (m_{ij}, c_i, b_i)$,
- extrapolation with small # obs.

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Random Partition

$s = (s_1, \ldots, s_n)$ = cluster membership indicators
$s_i \in \{1, \ldots, J\}$.
Let $y_j^\star$ and $x_j^\star$ variables by cluster and $S_j = \{i :\ s_i = j\}$.

Random partition: favor clusters homogeneous in x_i

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

with $g(x_j^\star)$ scoring "similarity" of $x_j^\star = (x_i;\ i \in S_j)$. over *observed* covariates only.

Sampling model: exchangeable within clusters

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

Prediction: future patient $i = n + 1$ is

- matched with one of the earlier clusters, on the basis of similar covariates $x_i = (c_i, m_i, b_i, z_i)$.
- predict similar PFS. That's all!

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Probability model with

Random partition: includes a regression on covariates, through $g(x_j^\star)$

Variable size regression: Cluster allocation is possible with available (subset of) covariates – no problem with variable size cov vector.

Extrapolation: restricted to matching with observed patients

4 Simulation

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4. Simulation

Scenarios: 7 scenarios, $p = 8$ covariates (7 mutations, 1 cancer type).
Siumlation truth is a log normal regression for $y_i \in \Re$.

True subgroups: Evaluation of (frequntist) error rates requires "true" subgroups.
Defined as a function of the assumed sampling model.

- Evaluate $u(a, \cdot)$ under the simulation truth using the true log hazards ratios for a subgroup a.
- Repeat for *all* poss subgroups.
- The top 10 subgroups are labeled as "truth"

Results: next slide.

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Operating Characteristics: Error Rates

TIE $= p(H_0^c \mid H_0)$ type-I error
TPR $= p(H_1 \mid H_1)$ true positive r.
TSR $= p(H_\mathbf{a} \mid H_\mathbf{a})$ true subgroup r.
FNR $= p(H_0 \mid H_0^c)$ false negative rate
FSR $= p(H_\mathbf{a} \mid H_\mathbf{a}^c)$ false subgroup r.
FPR $= p(H_1 \mid H_\mathbf{a})$ false positive r.

	Truth		
	Subgroup Effect		
Decision	H_0	M_{ih}	H_1
H_0	1-TIE		FNR
M_{ih}		TSR_{ih}	FSR
H_1		FPR_{ih}	TPR

- Choose c_0 to control TIE, and c_1 to control (average) FSR.
- All but the TIE require additional specification:
  - effect size for FNR, TPR and FSR.
  - TSR and FPR depend on i, h.

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Simulation results

Scenario	TIE	FNR	TPR	FSR	TSR	FPR
1		.00	-	.06	.92	.01
2		.00	-	.04	.95	.00
⋆3	.02	-	-	-	-	-
4		-.01	.94	.05	-	-
5		.03	-	.23	.75	.04
6		.01	-	.12	.87	.02

⋆ scenario 3 is true H_0
all others are true subgroup and overall effects

TIE $= p(H_0^c \mid H_0)$ type-I error
TPR $= p(H_1 \mid H_1)$ true positive r.
TSR $= p(H_\mathbf{a} \mid H_\mathbf{a})$ true subgroup r.
FNR $= p(H_0 \mid H_1)$ false negative rate
FSR $= p(H_\mathbf{a} \mid H_\mathbf{a}^c)$ false subgroup r.
FPR $= p(H_1 \mid H_\mathbf{a})$ false positive r.

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Treatment Allocation

Scenario	AP_{trt}	AP_{ctrl}	d
1	.92	.85	-.11
2	.91	.81	-.13
3	-	-	-
4	1	-	-
5	.83	.73	-.18

AP_t = prob of correct assignment to TT.
AP_c = prob of correct assignment to C.
$\bar{d}$ = bias in estimating succ probs.

5 Multiple Subgroups

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5. Multiple Subgroups

With Lurdes INOUE, U. Washington and Riten MITRA, U. Louisville.

Action set: generalize to a subgroup report with multiple subsets

$$\mathbf{a} = \{\mathbf{a}_d,\ d = 1, \ldots, D) \text{ with } \mathbf{a}_d = (I_d, \mathbf{x}_d^\star),$$

Covariates: $I_d \subset \{1, \ldots, p\}$

Levels: $\mathbf{x}_d^\star = (x_{dj}^\star,\ j \in I_d)$.

Utility function: favor subgroups with distinct prediction, large size and parsimonious description:

$$u(\mathbf{a}, \theta) = \prod_d \{\text{LR}(\mathbf{a}_d, \theta) - \beta\} \cdot \frac{n(\mathbf{a}_d)^\alpha}{(|I_d| + 1)^\gamma}$$

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Example: Large ICD study

Study: Large study of implantable cardioconverter defribrillators (ICD), to reduce the risk of sudden cardiac death.

Outcome: overall survival

Covariates:

- AGE, coded as age < 65 vs. ≥ 65
- ISCH, presence of ischemia

- EFCAT, ejection fraction, coded as < 30 versus ≥ 30
- QRS, coded as QRS < 120 vs. ≥ 120
- MALE
- NYHA, NY heart association class (III vs. IV)

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Results: The Bayes rule subgroup report

AGE	MALE	NYHA	EFCAT	MI	QRS	ISCH
-	1	-	1	-	-	-
-	-	-	-	-	0	1
-	-	-	1	-	0	-
-	-	0	1	-	-	-
-	-	-	1	-	-	1
-	-	-	-	-	-	1

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Computation

Single subset: with moderate p, use full enumeration and posterior MCMC to evaluate expected utilities.

Multiple covariates: use inhomogeneous MCMC (variation of simulated annealing).

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Summary

- A Bayesian approach to pre-planned subgroup analysis with a sensible strategy to detect subgroup effects.
- Bayes rule (approx)
- Coherent posterior probabilites for subgroup effects.
- Multiplicity control is achieved by
  - choice of priors,
  - by controlling frequentist error rate.
- Report ≥ 1 subgroup effects (under Bayes rule)

Design: use inference on subgroups for population finding or enrichment design.