Precision Oncology Trials: Big Hope, Big Challenges.

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The 3rd Stat4Onc Symposium

April 25, 2019
Peter’s First Trial and Design

Study MDACC 2017 0772 is based on subgroup-stratified randomization.

**Medically,** would like to test if $\theta_{N,i} > \theta_{C,i}$ for subgroup $i \in \{\text{Primary, Salvage}\}$. Suppose $m_i = 1$ means $\theta_{N,i} > \theta_{C,i}$.

**Statistically,** one could use a Bayesian hierarchical model to conduct inference:

- **Likelihood** $Y \mid \theta_{N,i}, \theta_{C,i} \sim f(\cdot; \theta_{N,i}, \theta_{C,i})$,
- **Prior for $\theta$**
  
  $$(\theta_{N,i}, \theta_{C,i}) \mid m_i = 1 \sim f_1(\cdot)$$
  $$(\theta_{N,i}, \theta_{C,i}) \mid m_i = 0 \sim f_0(\cdot)$$
- **Prior for $m_i$** $m_i \mid p \sim \text{Bern}(p)$
- **Hyper prior for $p$** $p \sim \text{Beta}(a, b)$
Reducing 6-dimension outcome to 1 utility value

Ordinal outcome $y$ – a Post Operative Morbidity (POM) score = \{0, 1, 2, 3, 4, 5\}

Prob. of POM $\theta = (\theta_0, \ldots, \theta_5)$ – a six dimensional probability vector

Utility $\bar{U} = \sum_{k=0}^{5} \theta_k \ast U(y=k)$ where $U(y=k)$ is an elicited utility score.

<table>
<thead>
<tr>
<th>Elicited POM score Probabilities for C= Standard of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Salvage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elicited numerical POM score Utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
</tr>
<tr>
<td>Utility</td>
</tr>
</tbody>
</table>

Subgroup-Specific interim and final $N$-versus-$C$ tests are based on $\text{Pr}\{\bar{U}(N, g, \theta) > \bar{U}(C, g, \theta)\}$ where $\bar{U}(N, g, \theta) =$ Mean Utility of $N$ in subgroup $g = P$ or $S$

$\bar{U}(C, g, \theta) =$ Mean Utility of $C$ in subgroup $g = P$ or $S$
The Bayesian models work – of course

BHM gives the right inference and good operating characteristics

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Pr Conclude N Superior to C</th>
<th>Pr Conclude N Inferior to C</th>
<th>Mean N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Null/Null)</td>
<td>.02</td>
<td>.02</td>
<td>199.2</td>
</tr>
<tr>
<td>2 (Alt/Null)</td>
<td>.78</td>
<td>.04</td>
<td>189.6</td>
</tr>
<tr>
<td>3 (Null/Alt)</td>
<td>.03</td>
<td>.80</td>
<td>187.0</td>
</tr>
<tr>
<td>4 (Alt/Alt)</td>
<td>.82</td>
<td>.84</td>
<td>172.4</td>
</tr>
</tbody>
</table>

If we ignore subgroups (Primary or Salvage), BHM still works but cannot (it’s impossible) differentiate subgroup by treatment interaction

<table>
<thead>
<tr>
<th>Scen(Prim/Salv)</th>
<th>Pr Conclude N Superior to C</th>
<th>Pr Conclude N Inferior to C</th>
<th>Mean N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Null/Null)</td>
<td>.02</td>
<td>.02</td>
<td>199.4</td>
</tr>
<tr>
<td>2 (Alt/Null)</td>
<td>.44</td>
<td>.44</td>
<td>193.0</td>
</tr>
<tr>
<td>3 (Null/Alt)</td>
<td>.56</td>
<td>.56</td>
<td>189.6</td>
</tr>
<tr>
<td>4 (Alt/Alt)</td>
<td>.98</td>
<td>.98</td>
<td>145.1</td>
</tr>
</tbody>
</table>
What did we learn?

When there is a subgroup by treatment interaction, model it!

When we do, big rewards!
Peter’s Second Trial and Design

It gets much more complicated

Subgroups Six (known) subgroups (three diseases by two tumor sizes)

Treatments Three doses of natural killer (NK) cells ($10^5$, $10^6$, and $10^7$ cells per kg) modified NK cells;

Outcomes Five co-primary time-to-event outcomes!

Goal: Subgroup Specific Dose Finding

Solution:

- Use a utility score to summarize the total health benefits from the five outcomes – the right way!

<table>
<thead>
<tr>
<th>$\delta_C$</th>
<th>$\delta_T$</th>
<th>$(\delta_P, \delta_R)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>(1,0)</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>(0,0)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>(0,1)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>(1,1)</td>
</tr>
</tbody>
</table>

$\Rightarrow$ Convert a 12-dimensional outcome into a ONE continuous score!

- Introduce patient-specific fraiity to account for additional variabilities and a regression model to induce parsimony

- A complex and smart design allows learning across subgroups
Subgroup-specific modeling and designs pay off

Simulation: Scenario 6

$\bar{U}^{TR}$ varies with $(d, Z, r)$, and the set of acceptable doses varies with $Z = (Z, r)$.

<table>
<thead>
<tr>
<th>Dose</th>
<th>$d = 1$</th>
<th>$d = 2$</th>
<th>$d = 3$</th>
<th>$\bar{\pi}_D$</th>
<th>$d = 1$</th>
<th>$d = 2$</th>
<th>$d = 3$</th>
<th>$\bar{\pi}_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{n}_D$</td>
<td>0.35</td>
<td>0.03</td>
<td>0.13</td>
<td>0.15</td>
<td>0.75</td>
<td>0.10</td>
<td>0.37</td>
<td>0.30</td>
</tr>
<tr>
<td>$\bar{U}^{TR}$</td>
<td>41.74</td>
<td>59.80</td>
<td>57.69</td>
<td></td>
<td>14.53</td>
<td>55.48</td>
<td>40.90</td>
<td></td>
</tr>
<tr>
<td>$P_{\text{stop}}$</td>
<td>0.76</td>
<td>0.00</td>
<td>0.09</td>
<td></td>
<td>0.99</td>
<td>0.00</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>$P_{\text{sel}}$</td>
<td>0.00</td>
<td>0.56</td>
<td>0.44</td>
<td></td>
<td>0.00</td>
<td>0.99</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

- The design picks the right dose for each subgroup with high probabilities
- The design stops the bad dose with high probabilities

But, only Juhee Lee and Peter Thall probably knows how to do it. 😊
What did we learn?

When there is a subgroup by treatment interaction, model it!

When we do, big rewards!

BUT, it is complicated to model!
Dan’s World – Welcome to the World of an Oncologist’s Precision Medicine

Oncologists do “precision oncology all the time and in a much more complex fashion!”

The PANGEA-2MBBP Trial
Personalized Antibodies for Gastro-Esophageal Adenocarcinoma:
Phase II Metastatic Biologic Beyond Progression Trial (R 2:1)

Diagnosis: metastatic cancer

Stratify:
1. Stage
2. PS
3. Biomarker
4. GEO x clinical response
5. Line of metastasis

Anticipated Incidence

ARM A: Standard Chemotherapy + Placebo
Arm A1: HER2 amplified
Arm A2: MET amplified
Arm A3: FGFR2 amplified
Arm A4: KRAS/PTEN wild type
Arm A5: KRAS/BRCA/PIK3CA mtamplified
Arm A6: NRAS, High TMB, EBV+, PD-L1+

FOLFOX + placebo
FOLFIRI + Ram
FOLFOX + Trastuzumab
FOLFOX + FOLFOX + Trastuzumab
FOLFOX + FOLFOX + Trastuzumab
FOLFOX + FOLFOX + Trastuzumab

Biomarker Evaluation in all samples prior to randomization

ARM B: Therapy based on molecular profile

18% HER2 amplified
7% MET amplified
7% FGFR2 amplified
7% EGFR/HER2 amplified
33% KRAS/BRAF/PIK3CA/PTEN/REItamtamplified
28% NRAS, High TMB, EBV+, PD-L1+

FOLFOX -Trastuzumab
FOLFOX -METab
FOLFOX -FGFR2ab
FOLFOX -EGFRab
FOLFOX -VEGFR2ab
FOLFOX -PD-1ab

Standard care: Control Arm

FOLFOX + placebo
FOLFIRI + Ram
FOLFOX + Trastuzumab
FOLFOX + E
FOLFOX + V
FOLFOX + PD1

PD
PD
PD
PD
PD
PD

Primary Endpoint: OS (HR 0.67)
1) Arm A + B (N=152, 128:R:64-A )
2) Arm A vs B

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Disc. Prec. Onc. C.T.
Precision Oncology is about **HETEROGENEITY**

- **Inter-patient heterogeneity**
- **Every patient is different**: no two patients have the same genome; mutations; phenotypes;
- **We can only model a small number of biomarkers using statistical models**: *Multiplicity almost kills validity*
- **Even if we can overcome multiplicity, we only have a small number of drugs!** – Patients are different, but we *only have so many drugs to treat.*
Precision Oncology is about HETEROGENEITY

Intra-patient heterogeneity

- Every cell is different: no two tumor cells have the same genome!
- How do we accommodate Multiplicity at cellular level?
- Even if we can overcome multiplicity, we only have a small number of drugs! – cells are different, but we only have so many drugs to treat.
- Drug combinations might provide some hope!
- Individualized therapeutics based on genomics profiling is coming!
How Can Statistics Help Oncology?

Many subgroup analysis methods and designs have been proposed!

2.1. Regression:
- shrinkage priors on the treatment and treatment × covariate interaction coefficients
- shrinkage priors on competing models

2.2. Model selection:
- shrinkage prior on model parameters

2.3. Potential outcome framework:
- priors for the mean outcomes in the leaves of the tree
- enhanced treatment effect

2.4. Decision problem:
- implicit in the underlying probability model
- optimal subgroup report (action)

2.5. Random Quantity:
- implicit in the underlying probability model
- a random subset \( B \), none in the covariate space

See review at Nugent et al. (2019, JCO Precision Oncology, In press)
How Can Statistics Help Oncology?

How many trials are based on subgroup enrichment designs?
To my knowledge, very few!


We need statistical tools that can work in real-world settings.
We need to start testing strategies rather than treatments
We need statisticians to work closely with physicians!
How Could Precision Oncology Look Like in 10 years?

- Biomarkers are based on a low-dimensional summary of the multi-omes (genome, transcriptomes, proteomes, etc)
- Real-world data continuous update a statistical (Bayesian) predictor to output optimal decision rules for treatment
- Enrichment platform trials based on a master protocol allows approval of new treatment strategies
- Patients survival and health benefits keep increasing although new diseases emerge as humans survive longer