Precision Oncology Trials: Big Hope, Big Challenges.

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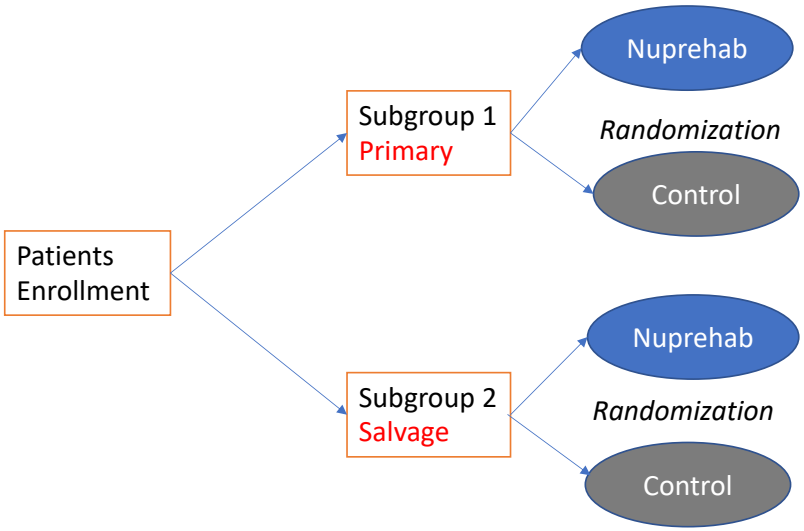
The 3rd Stat4Onc Symposium

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 $i \in \{Primary,\ Salvage\}$. 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 θ

$$\begin{aligned} (\theta_{N,i}, \theta_{C,i}) \mid m_i = 1 &\sim f_1(\cdot) \\ (\theta_{N,i}, \theta_{C,i}) \mid m_i = 0 &\sim f_0(\cdot) \end{aligned}$$

Prior for m_i $m_i \mid p \sim Bern(p)$
Hyper prior for p $p \sim Beta(a, b)$

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

Elicited prior POM score Probabilities
for C= Standard of Care

	0	1	2	3	4	5
Primary	.50	.20	.10	.10	.05	.05
Salvage	.30	.25	.10	.10	.10	.15

Elicited numerical POM score **Utilities**

Score	0	1	2	3	4	5
Utility	100	85	65	25	10	0

Subgroup-Specific interim and final N-versus-C tests are based on $\Pr\{\overline{U}(N, g, \theta) > \overline{U}(C, g, \theta)\}$ where

$\overline{U}(N, g, \theta)$ = Mean Utility of N in subgroup $g = P$ or S

$\overline{U}(C, g, \theta)$ = 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

	Pr Conclude N Superior to C		Pr Conclude N Inferior to C		Mean N
Scenario	Prim	Salv	Prim	Salv	
1 (Null/Null)	.02	.02	.03	.03	199.2
2 (**Alt**/Null)	**.78**	.04	**.00**	.02	189.6
3 (Null/**Alt**)	.03	**.80**	.02	**.00**	187.0
4 (**Alt**/**Alt**)	**.82**	**.84**	**.00**	**.00**	172.4

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

	Pr Conclude N Superior to C		Pr Conclude N Inferior to C		Mean N
Scen(Prim/Salv)	Prim	Salv	Prim	Salv	
1 (Null/Null)	.02	.02	.03	.03	199.4
2 (**Alt**/Null)	**.44**	.44	**.00**	.00	193.0
3 (Null/**Alt**)	.56	**.56**	.00	**.00**	189.6
4 (**Alt**/**Alt**)	**.98**	**.98**	**.00**	**.00**	145.1

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!

		(δ_P, δ_R)		
δ_C	δ_T	(1,0)	(0,0)	(0,1)
0	0	**20**	**50**	**90**
0	1	**10**	**30**	**70**
1	0	**10**	**30**	**70**
1	1	**5**	**20**	**50**

$\Longrightarrow$ Convert a 12-dimensional outcome into a ONE continous score!

- Introduce patient-specific fraity 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

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

prognostic subgroup (Z)	LBD	HBD
CLL	(0, 1)	(1, 1)
ALL	(0, 2)	(1, 2)
NHL	(0, 3)	(1, 3)

Dose	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
$\bar{U}^{\text{TR}}$	41.74	59.80	57.69		14.53	55.48	40.90	
P_{stop}	0.76	0.00	0.09		0.99	0.00	0.34	
P_{sel}	0.00	0.56	0.44		0.00	0.99	0.01	
π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
$\bar{U}^{\text{TR}}$	57.75	34.95	57.83		47.19	7.81	55.07	
P_{stop}	0.00	0.82	0.00		0.02	0.99	0.00	
P_{sel}	0.80	0.00	0.20		0.04	0.00	0.96	
π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
$\bar{U}^{\text{TR}}$	59.50	57.18	46.28		52.57	44.10	18.84	
P_{stop}	0.00	0.01	0.51		0.00	0.03	0.91	
P_{sel}	0.53	0.47	0.01		0.89	0.11	0.00	

- 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!

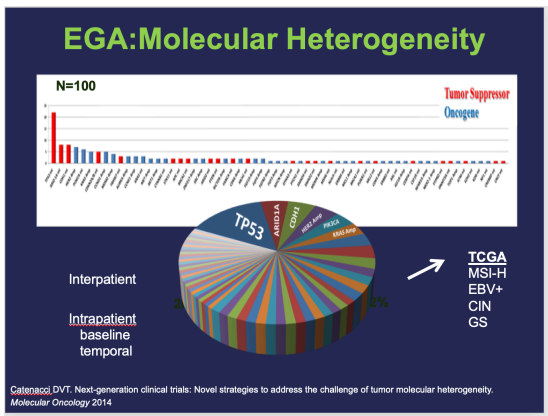
When we do, big rewards!

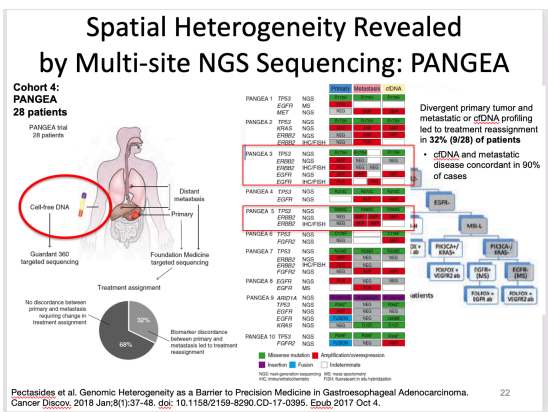
BUT, it is complicated to model!

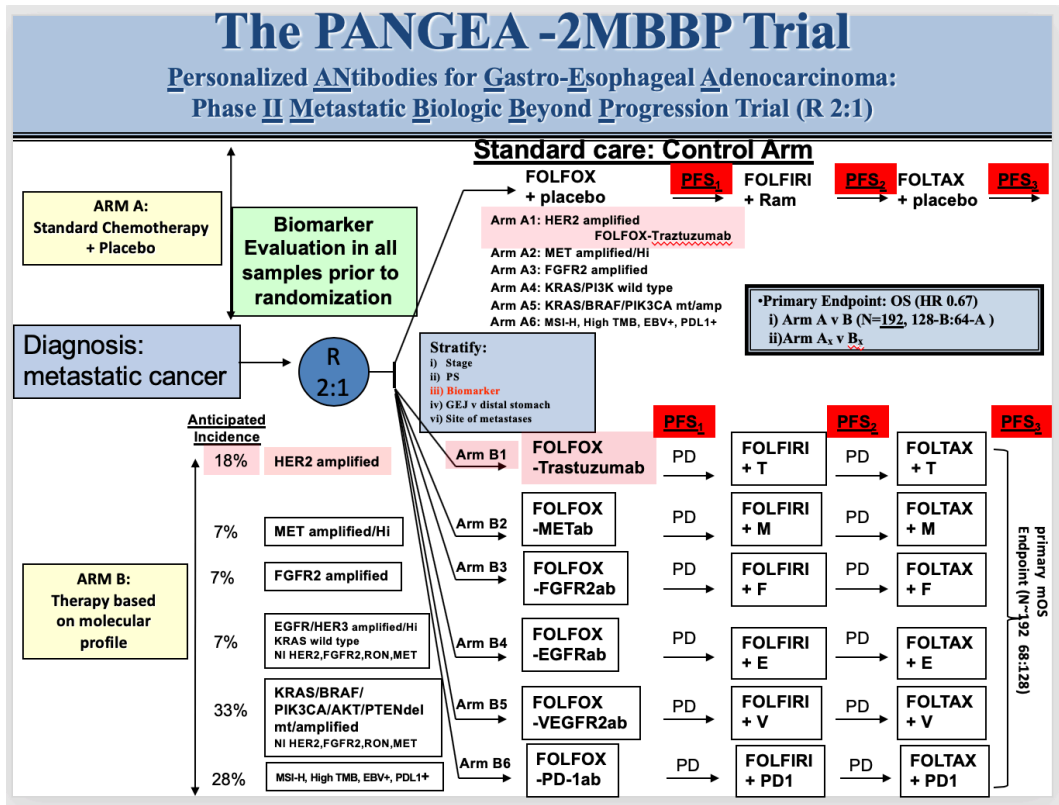
Dan's World – Welcome to the World of an Oncologist's

Precision Medicine

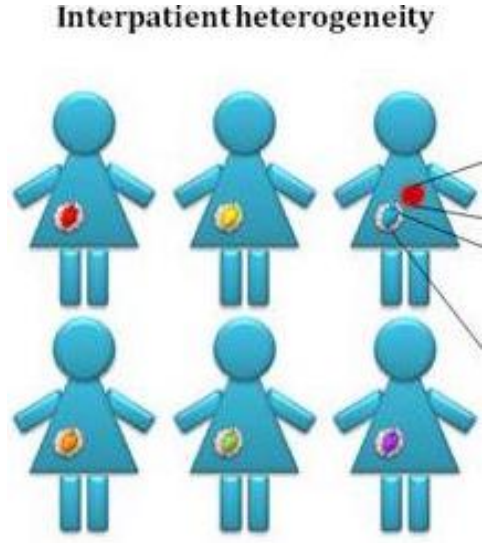
Oncologists do "precision oncology all the time and in a much more complex fashion!







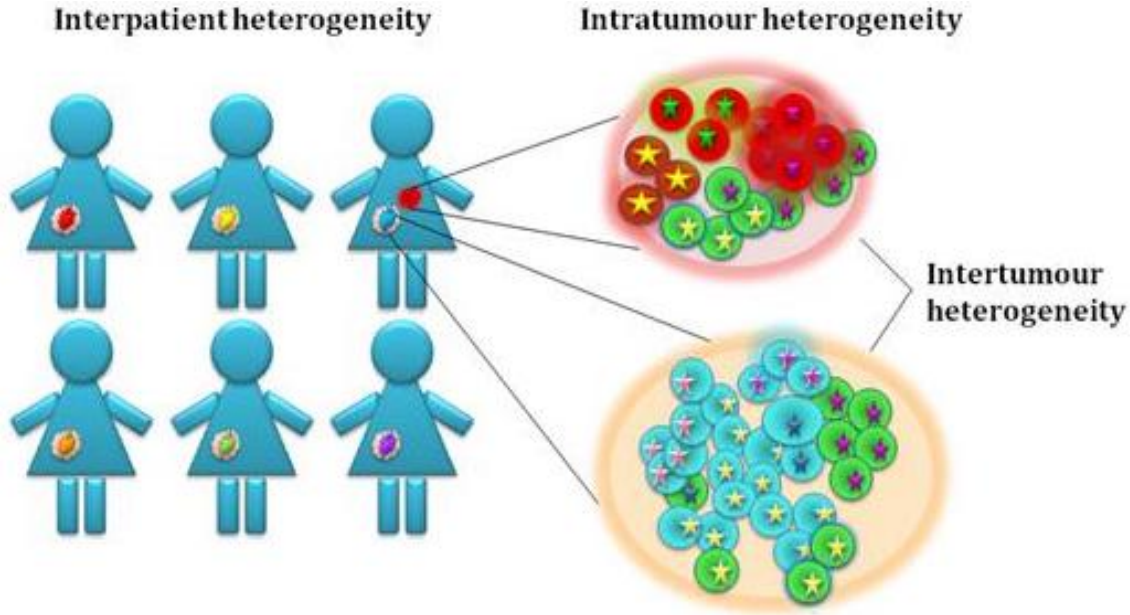
Precision Oncology is about HETEROGENEITY



Inter-patient heterogeneity Precision oncology is about 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 Precision oncology will be at the cellular level

- 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!

Shrinkage	Inference Target
2.1. Regression:	
priors on the treatment and treatment × covariate interaction coefficients	treatment × covariate interaction coefficients
2.2. Model selection:	
shrinkage prior on model parameters	competing models
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) in the covariate space

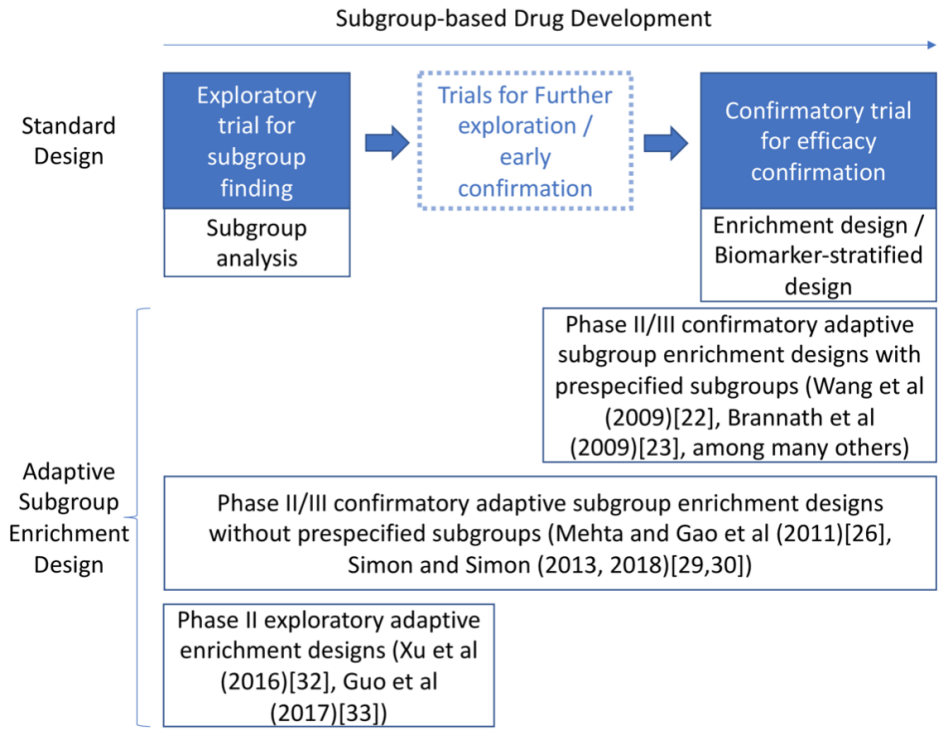


Figure 2: Overview of different subgroup-based designs.

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!

- Martin M, Chan A, Dirix L, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2–advanced breast cancer (BELLE-4). Annals of Oncology. 2016;28:313–320.
- Simon KC, Tideman S, Hillman L, et al. Design and implementation of pragmatic clinical trials using the electronic medical record and an adaptive design. JAMIA Open. 2018;1:99–106.

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