Global Cumulative Treatment Analysis

What Efficient Clinical Science Could Look Like

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Why is Cancer so Hard?

We are searching an extremely high dimensionality, low data density, problem space the same way that ants search for food!

BOE (Before the OMIC Era)
- ~1 Million patients/year
- ~100 cells
- ~10,000 patients/cell
- Plenty for Classical Clinical Trials

OE (Modern Times)
- ~1 Million patients/year
- \(~11^2\) cells
- ~0 patients/cell
- Need a new paradigm (and “big data” won’t cut it!)

O(10) Phenotypes: Lung, Breast, ...
O(10) Treatments: Chemo1, Chemo2, ...

Millions of features
Thousands of treatment parameters
Figure 1. AERO graph for studies investigating MGMT testing as a predictive diagnostic for first-line TMZ therapy in adult GBM patients. Solid arrows are all references to Hegi et al. (2005)—the landmark retrospective study.

Judging Quality and Coordination in Biomarker Diagnostic Development

Spencer Phillips Harvard
What Would Efficient Clinical Science Look Like?

- A Perpetual Global Prospective Experiment
Global Cumulative/Coordinated/Continuous Treatment Analysis

A Perpetual Global Prospective Experiment
What Would Efficient Clinical Science Look Like?

• A *Perpetual Global Prospective Experiment* in which every patient who wants to participate is welcomed.

• Every plausible action, including tests, INDs, novel cocktails, and even hospice are included.

• No one who wants to be included can be excluded or dropped...Ever!

• Overlapping ”arms” that inter-control one another are dynamically created, merged, split, or aborted. (If there is no arm/cohort for a patient, they become an n-of-1 arm, and patients in aborted arms are either re-assigned to another arm, or become an n-of-1 arm.)

• Equipoise sets are dynamically computed for each decision on each patient using all available information, and the offerings are ranked based upon patient preference, physician opinion, and global information gain (based upon real-time prospective simulations).

• Patients have complete autonomy; They can do anything they choose, and still remain in the study if they want to. We must dynamically recompute every subsequent decision with this patient’s choice in the mix. (The only thing we ask, aside from continued tracking, is for a *decision rationale.*)
Global Cumulative/Coordinated/Continuous Treatment Analysis

Presentation → Panomics and other patient information → Treatment hypotheses

No acceptable choices at all → Standard or clear best choice, and patient agrees?

No clear best choice or patient preference → Choose best choice for learning purposes

Yes → Treat and monitor

Response?

No response or recurrence

Yes

Precision oncology 3.0
Three Possible GCTA Settings

1. “Complete” Control
3. “Virtual” Tumor Boards (xCures with Cancer Commons)
Complete Control is **NOT** a fantasy!
Some Ethical Issues in GCTA

1. Can technical equipoise ever be achieved between expensive treatments and those that are covered (or cheap)?
2. Can psychological equipoise be achieved among these?
3. What are the priors on INDs?
4. The “Self-Driving Car Problem”: What if the most informative choice would not normally be in the equipoise set for a specific patient?
5. What if someone with no diagnosis at all offers the greatest information opportunity?