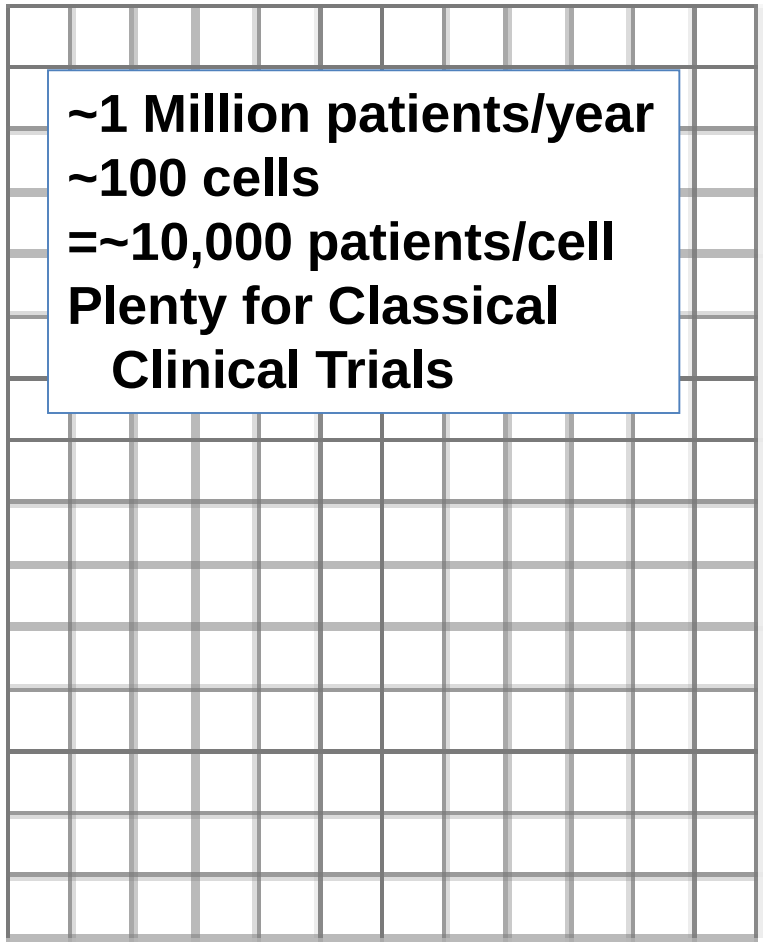
Global Cumulative Treatment Analysis

What Efficient Clinical Science Could Look Like

Jeff Shrager (jshrager@stanford.edu)
Presentation to the Harvard Clinical Trial Ethics Discussion Group
2018-10-26
Hosted by Spencer Hey

Why is Cancer so Hard?

BOE (Before the OMIC Era)

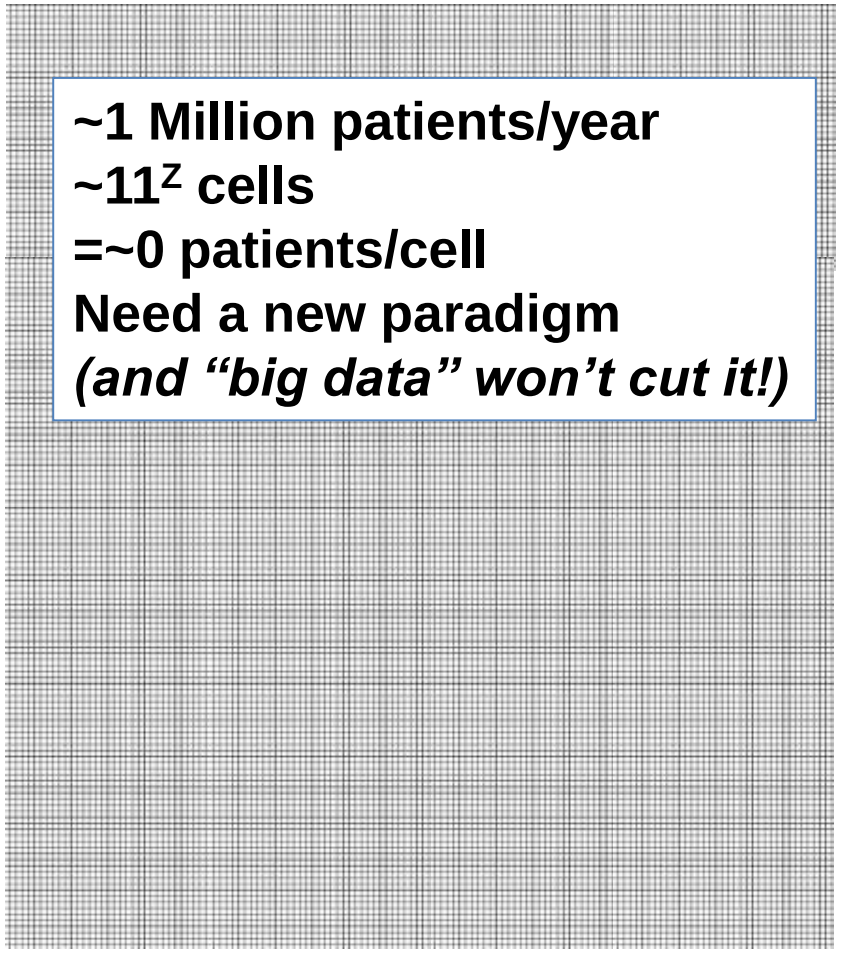


O(10) Treatments: Chemo1, Chemo2, ...

O(10) Phenotypes: Lung, Breast, ...

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

OE (Modern Times)



Thousands of treatment parameters

Millions of features

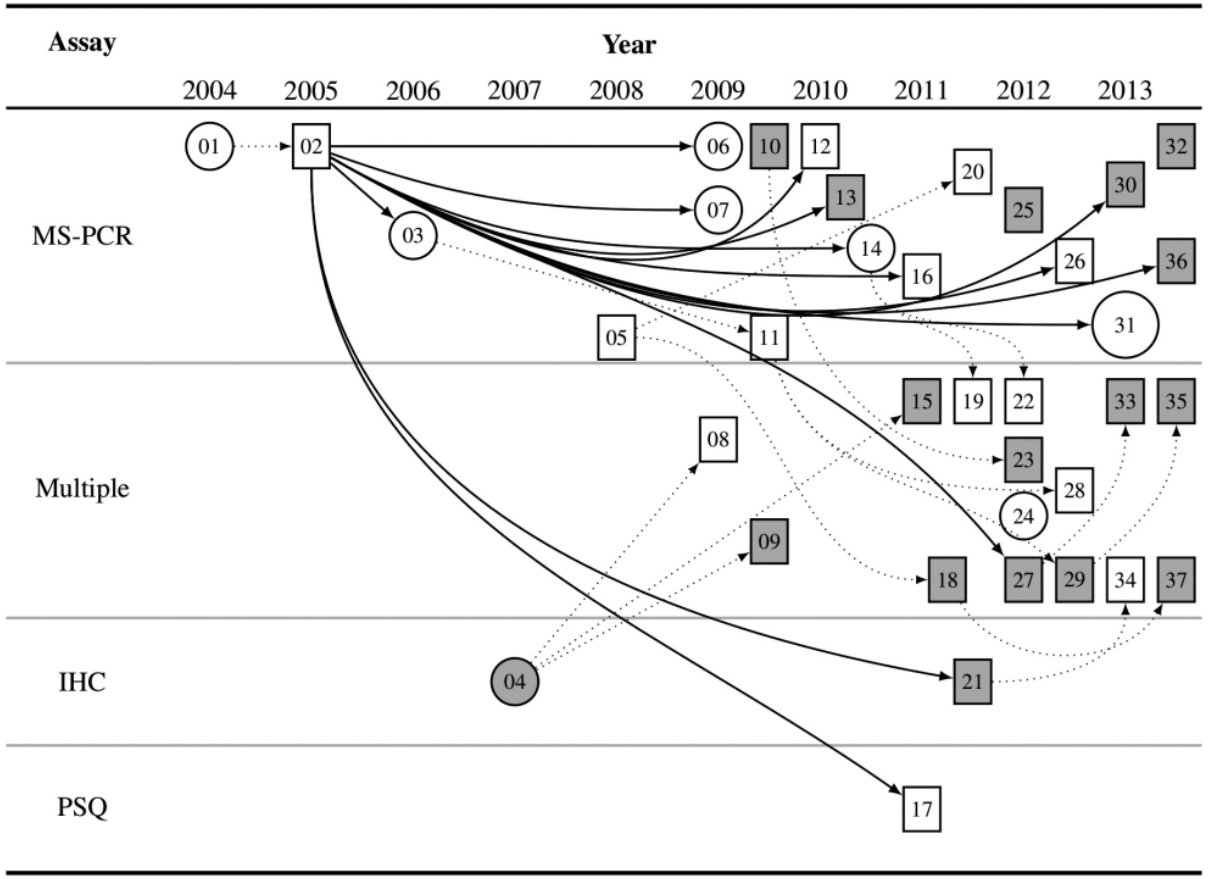
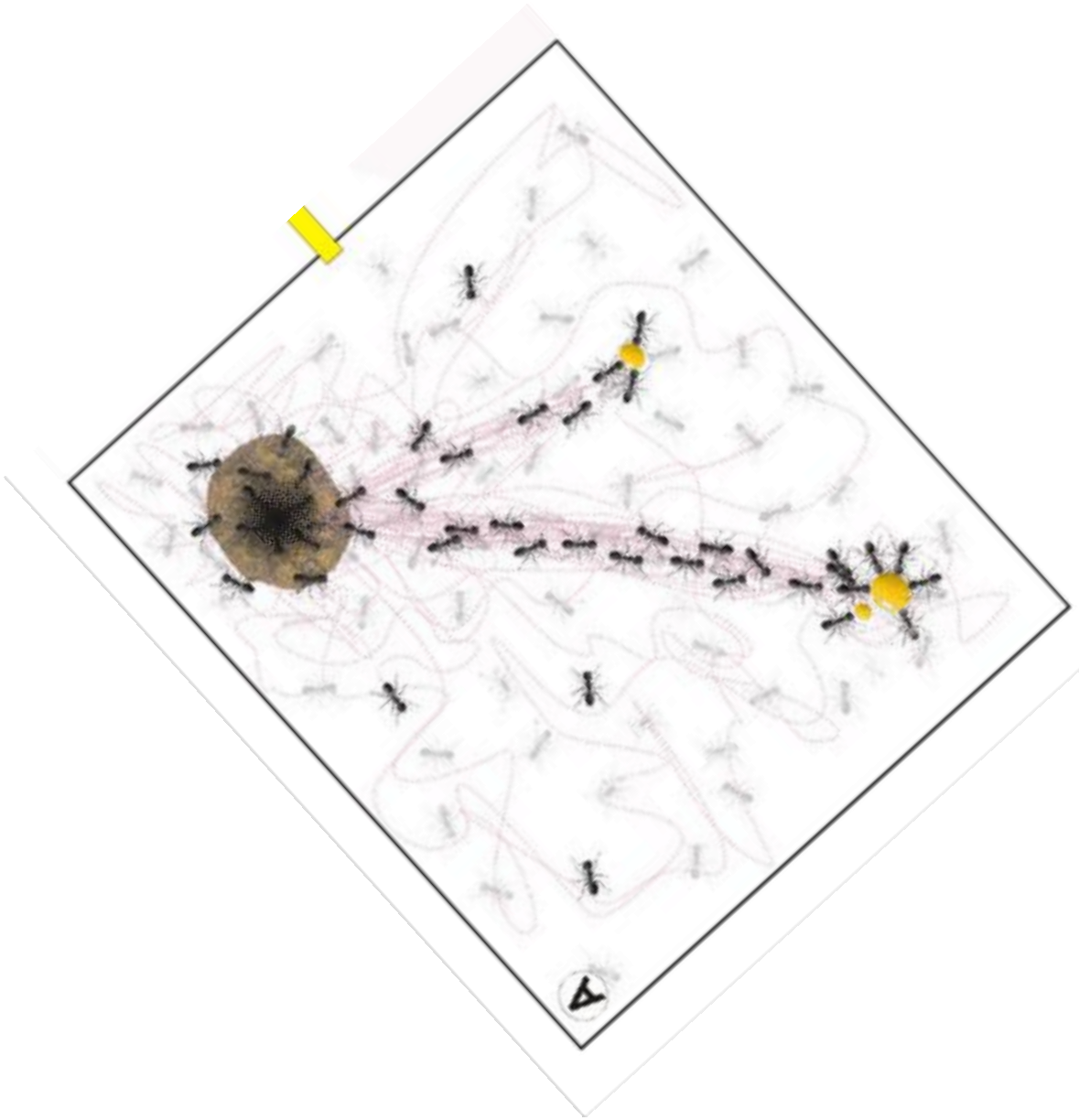


Figure 1. AERO graph for studies investigating MGMT testing as a predictive diagnostic for first-line TMZ therapy in adult GBM patients. Solid arrows are all references to Hegi et al. (2005)—the landmark retrospective study

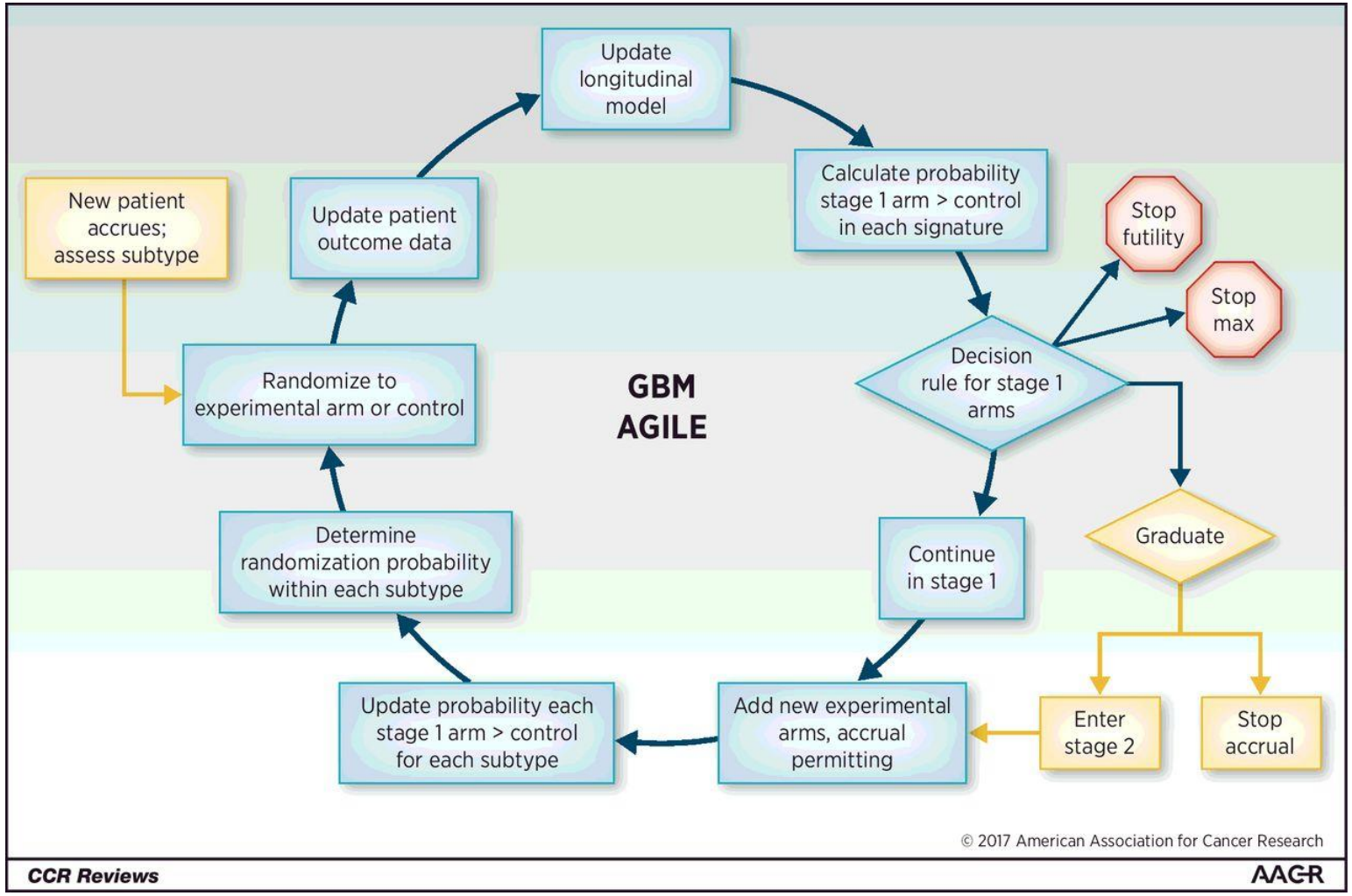


Judging Quality and Coordination in Biomarker Diagnostic Development*

Spencer Phillips Hey

What Would Efficient Clinical Science Look Like?

- A *Perpetual Global Prospective Experiment*



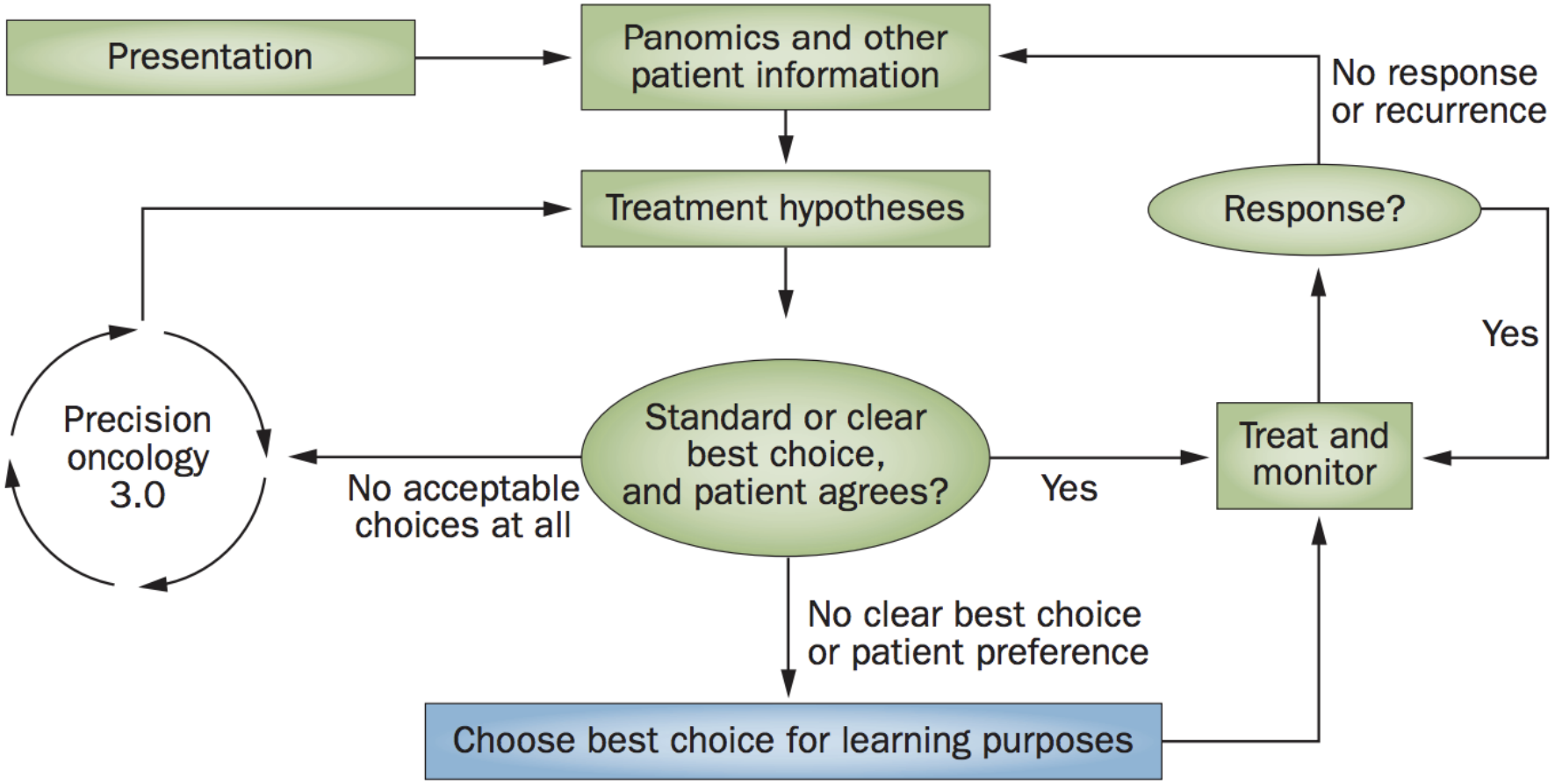
Global Cumulative/Coordinated/Continuous Treatment Analysis

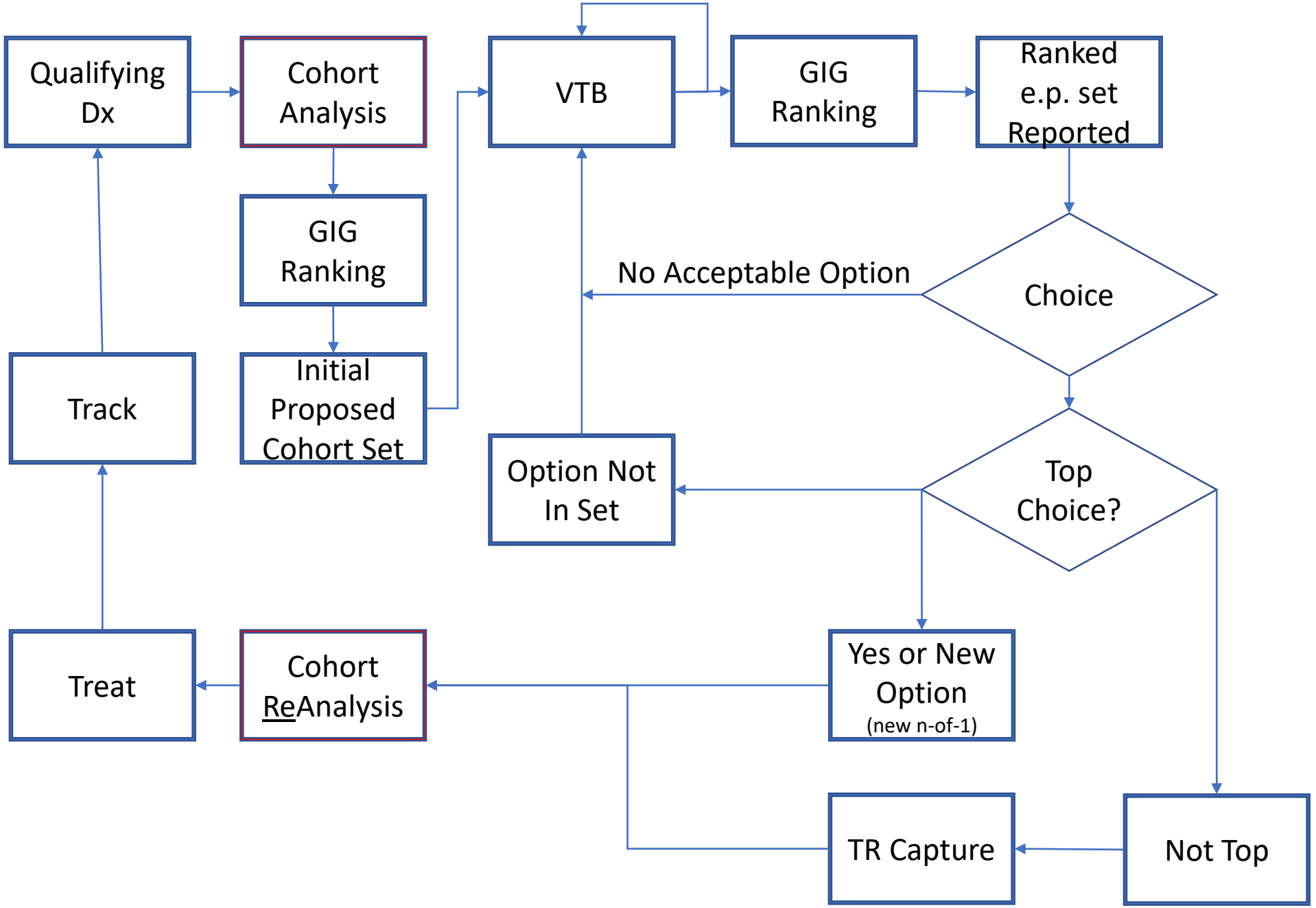
A *Perpetual Global Prospective Experiment*

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




Qualifying Dx
Cohort Analysis
VTB
GIG Ranking
Ranked e.p. set Reported
GIG Ranking
No Acceptable Option
Choice
Track
Initial Proposed Cohort Set
Option Not In Set
Top Choice?
Treat
Cohort ReAnalysis
Yes or New Option
(new n-of-1)
TR Capture
Not Top

Three Possible GCTA Settings

1. “Complete” Control
2. Tumor Board Network (proposed by Sweetnam et al. BMC Bioinformatics, Oct. 2018)
3. “Virtual” Tumor Boards (xCures with Cancer Commons)

Complete Control is *NOT* a fantasy!

Journal List › Biomark Cancer › v.8; 2016 › PMC4772906

Libertas Academica

Biomarkers in Cancer

www.la-press.com

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The VA Point-of-Care Precision Oncology Program: Balancing Access with Rapid Learning in Molecular Cancer Medicine

Louis D. Fiore,[1] Mary T. Brophy,[1] Sara Turek,[1] Valmeek Kudesia,[1] Nithya Ramnath,[2] Colleen Shannon,[1] Ryan Ferguson,[1] Saiju Pyarajan,[1] Melissa A. Fiore,[1] John Hornberger,[3,4,5] and Philip Lavori[6,7]

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Abstract

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The Department of Veterans Affairs (VA) recognized the need to balance patient-centered care with responsible creation of generalizable knowledge on the effectiveness of molecular medicine tools. Embracing the principles of the rapid learning health-care system, a new clinical program called the Precision Oncology Program (POP) was created in New England. The POP integrates generalized knowledge about molecular medicine in cancer with a database of observations from previously treated veterans. The program assures access to modern genomic oncology practice in the veterans affairs (VA), removes disparities of access across the VA network of clinical centers, disseminates the products of learning that are generalizable to non-VA settings, and systematically presents opportunities for patients to participate in clinical trials of targeted therapeutics.

Keywords: veterans, precision oncology, learning health-care system, lung cancer, Bayesian

Introduction

Go to:

Oncology clinical practice guidelines recommend more than 30 molecular tumor biomarkers across all cancers to aid treatment selection, a list of potential biomarkers that continues to grow.[1–3] In addition to reimbursable, standard-of-care assays, physicians can order biomarker panel tests that sequence large regions of the tumor genome. The proximate goal of biomarker panel testing is to identify potential, even unproven, therapeutic agents that may offer longer survival and improved quality of life than existing

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?