Basket and Umbrella Trial Designs in Oncology

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Background

- Historically, phase I conducted with mixture of solid tumors, then phase II and III oncology trials were histopathologic focused (*e.g.* lung cancer study, breast cancer study, etc.)
- Phase II studies ask the question: Does the treatment, with the selected dose and within the context (histology) improve the clinical outcome
- Improvements in molecular profiling of tumors has seen shift to biomarker driven clinical trials
- Refines definition of "context" to incorporate molecular context with histology

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Biomarkers

Observation

Many genomic aberrations are recurrent across multiple histologies

Question

Is presence of genomic aberration more predictive of drug sensitivity than histology of tumor?

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Biomarker Driven Clinical Trials

Basket Trials

Single treatment and single biomarker, different histologies placed in baskets

Umbrella Trials

Single histology, multiple biomarkers each matched to treatments

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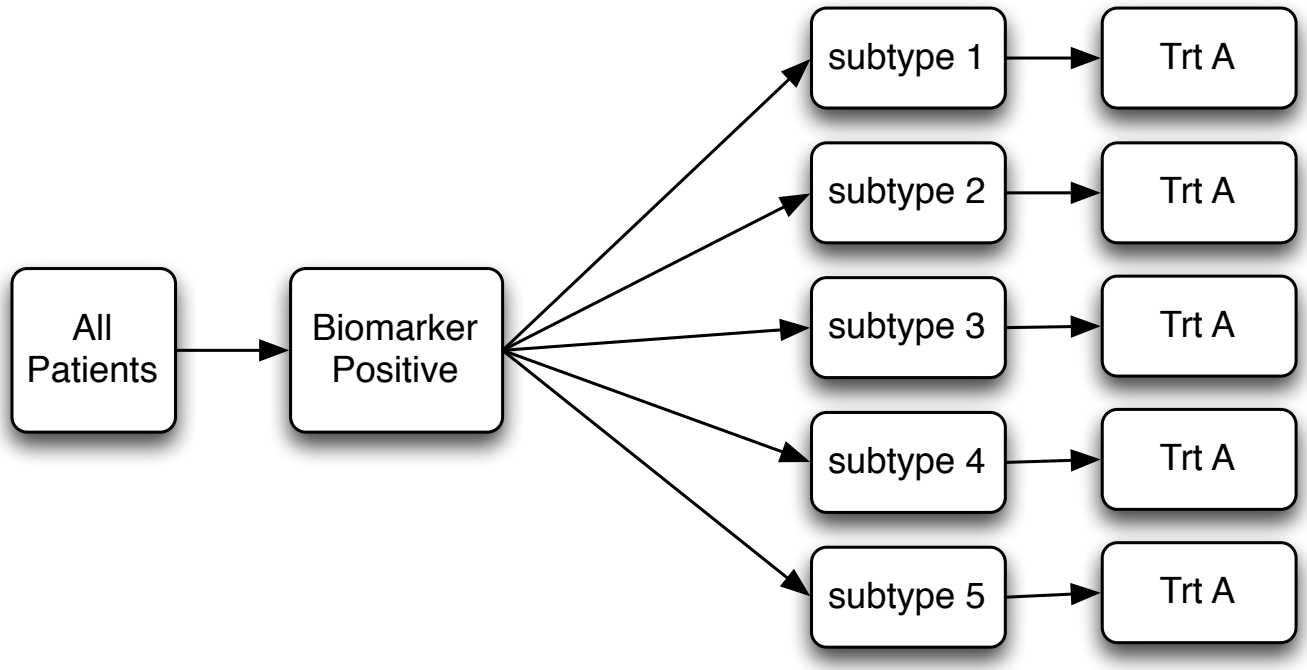
Basket Trials

If the interest is in the effect of a specific treatment within a biomarker positive subgroup, a basket (or bucket) trial is an option



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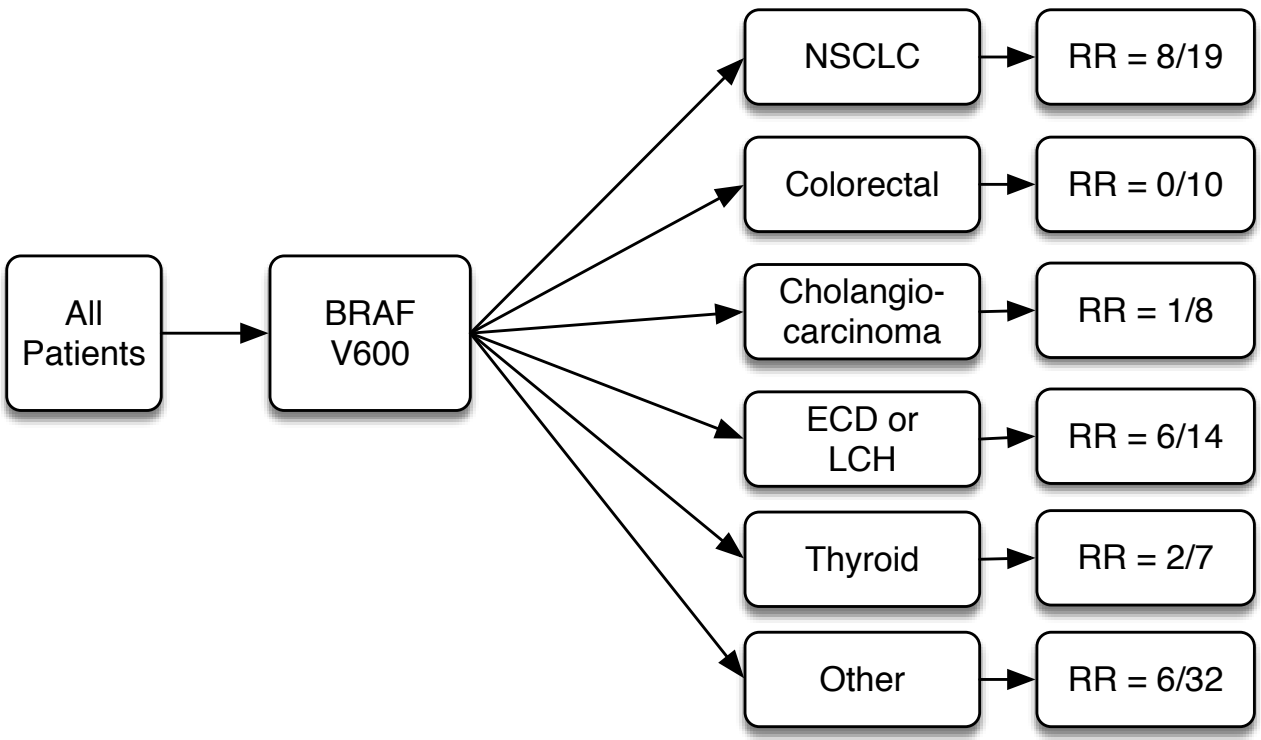
Basket Trials

An example basket trial is BRAF V600 Vemurafenib[1]. They enrolled 122 patients with BRAF V600 mutations from 5 pre-specified baskets, plus an "other" basket.



[1] Hyman *et al.* Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*, 2015, 373:726-36

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Basket Trials

- Can be designed with decision points for aggregating baskets [2]
- Hierarchical Bayesian model for sharing information [3]
- Exposure in multiple contexts can provide additional understanding of mechanism of sensitivity and resistance

[2] Cunanan, *et al.* An efficient basket trial design. *Statistics in Medicine* 2017, 1568-79.

[3] Thall *et al.* Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. *Statistics in Medicine* 2003, 763-780

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Basket Trials

- If biomarker prevalence is rare for some baskets, may delay study
- Analytic performance of assay for biomarker determination should be similar across baskets, some studies require a study specific assay for eligibility
- Can be extended to include a randomization step within each basket (different baskets may have different control treatments)
- Doesn't learn anything about biomarker negative patients, so requires good assay and biological knowledge of the treatment mechanism of action
- Can include adaptive rules for adding or dropping baskets

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Basket Trials

Strengths:

- Can be more efficient than multiple histology specific enrichment trials
- If treatment already approved in another disease, can quickly learn if efficacy translates to other indications
- Only need to develop one assay for the trial

Weaknesses:

- Disease subtype is often prognostic so choice of endpoints is limited
- Without a comparative arm, can't distinguish predictive from prognostic
- Some baskets may have small sample sizes if mutation is rare

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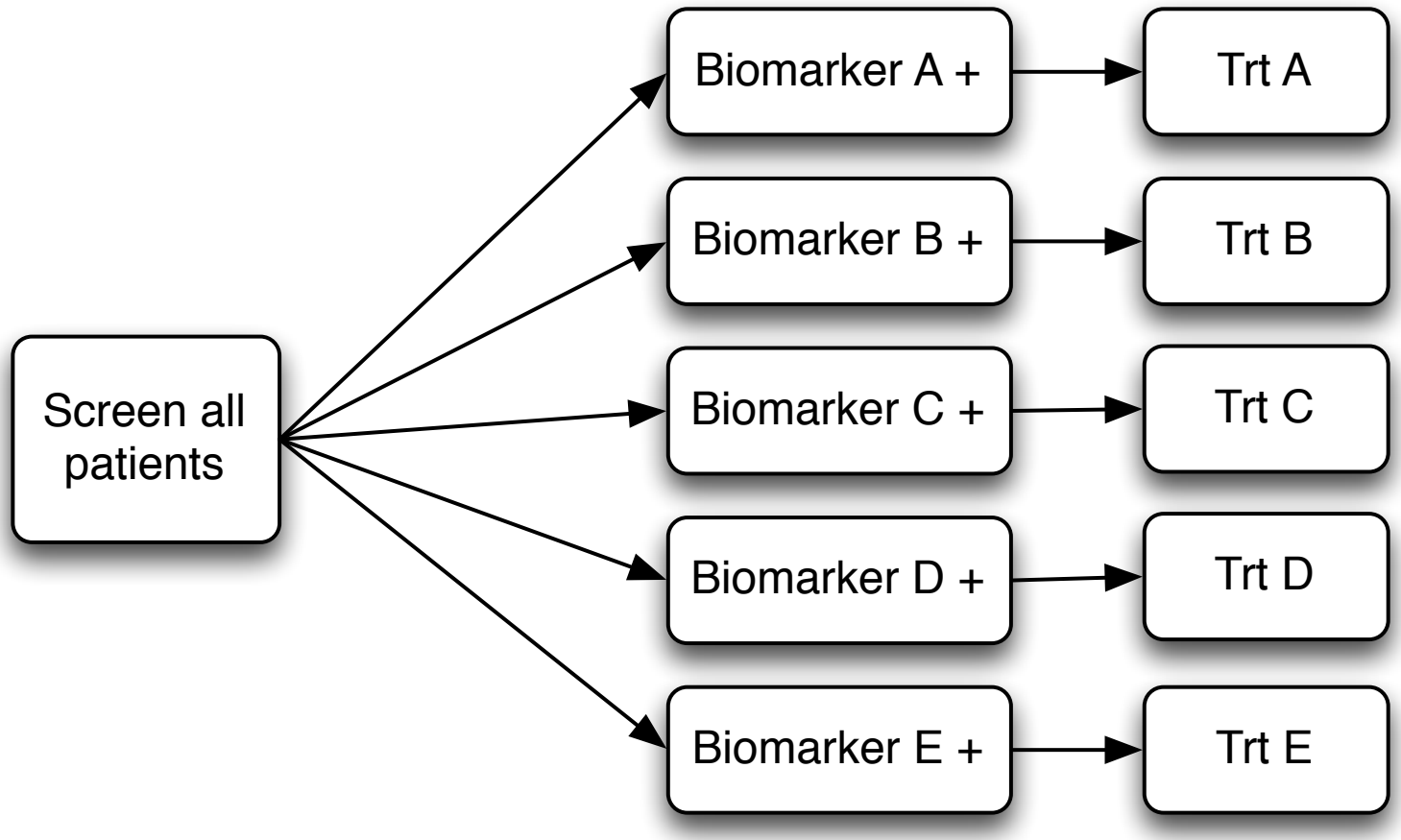
Umbrella Trials



In contrast to basket trials, the umbrella trial evaluates many treatments within a single histology. A multiplex assay is used for treatment arm eligibility. Each arm is a biomarker enrichment design.

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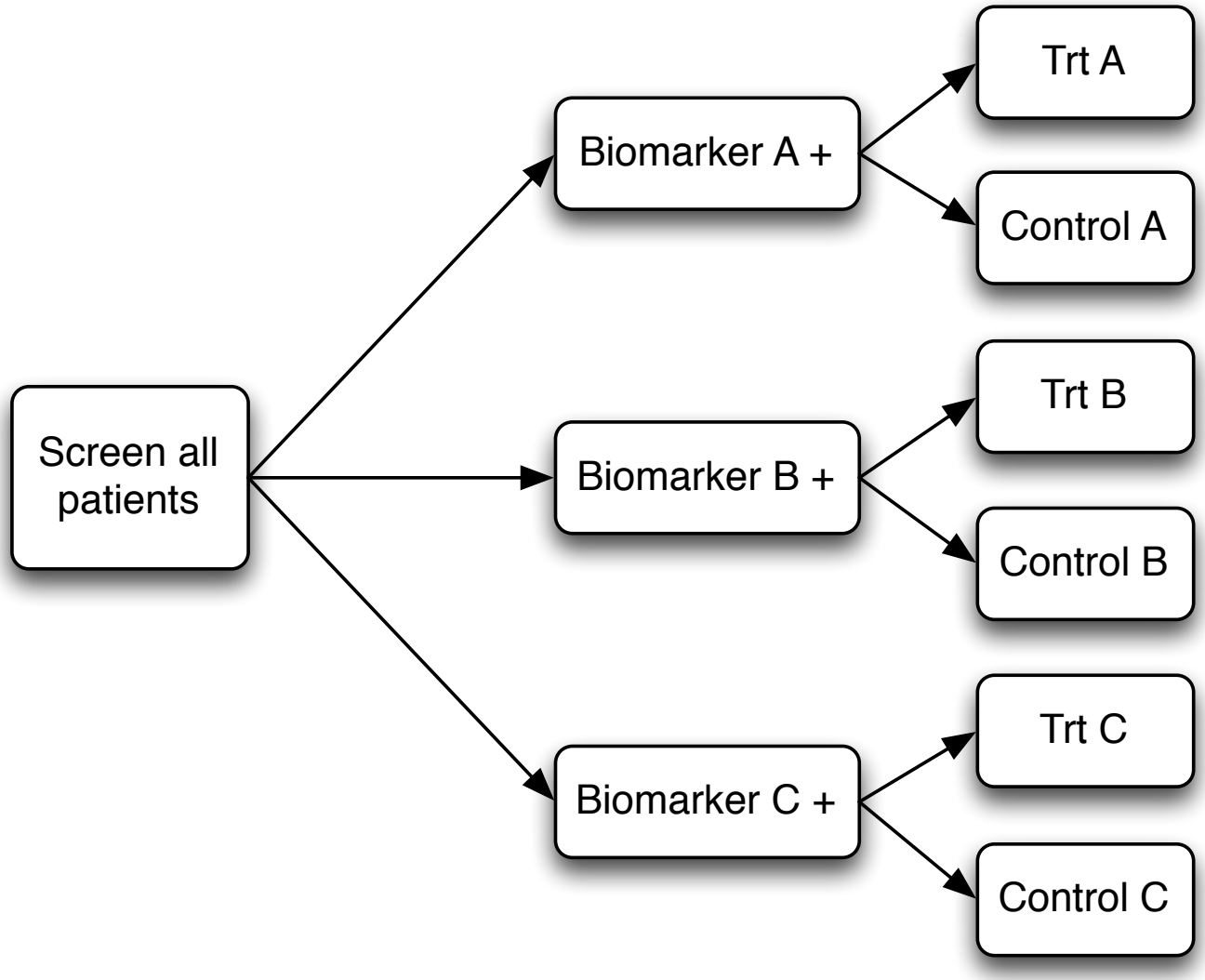
Umbrella Trials



Examples include Lung-MAP (SWOG) and FOCUS4 (UK)

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Umbrella Trials

One unique consideration with umbrella trials is that a patient could be eligible for multiple arms (e.g. the tumor contains multiple actionable aberrations). Inference and hypothesis testing should account for the overlap.

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Super Umbrella Trials

The combination of the bucket trials and the umbrella trials creates the "Super Umbrella Trials"

The design is the same as the Umbrella trials, but open to multiple histologies. Examples are the NCI-MATCH study and the CUSTOM study

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NCI-MATCH

- The NCI-MATCH study opened in Fall 2015 with 10 treatment options, now has 30 active [4]
- Co-developed by NCI and ECOG-ACRIN
- Open to solid tumor or lymphoma patients who progressed on standard therapy, with plan to screen 6000 patients
- Each treatment is an independent single arm Phase II study with objective response rate as the primary outcome
- The study incorporates a custom DNA sequencing assay performed by a network of labs. Each treatment option has a set of rules mapping the biomarker and clinical information into a list of eligible treatments

[4] https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match

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Umbrella Trials

Strengths:

- When biomarker prevalence is low, improves screen success rate with multiple arms
- Flexible design can easily add or drop arms

Weaknesses:

- May require large number of drugs and biomarkers
- Development of multiplex assay more complex than single biomarker
- Often requires regulatory review of both drugs and assay

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Trial Design

- A common feature for many of these studies is biomarker enrichment (only evaluate treatment in biomarker positive patients)
- Requires good preclinical models for the biological knowledge of the treatment mechanism of action in various tumor environments
- Requires an assay with strong analytic performance in a clinical setting
- Assay with low specificity will dilute the treatment effect in enrichment designs
- Assay with low sensitivity for resistance variants also dilutes treatment effect

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Summary

- Basket and Umbrella study designs allow incorporation of biomarkers and clinical information
- As these designs move early in clinical development, opportunity to incorporate dose selection
- Pharmacogenomic models using study data plus prior information could improve decisions for future studies (Does it work? How does it work? Who benefits?)
- Assay development just as critical as drug development

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Thanks

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