

# Key design considerations for basket and umbrella trials

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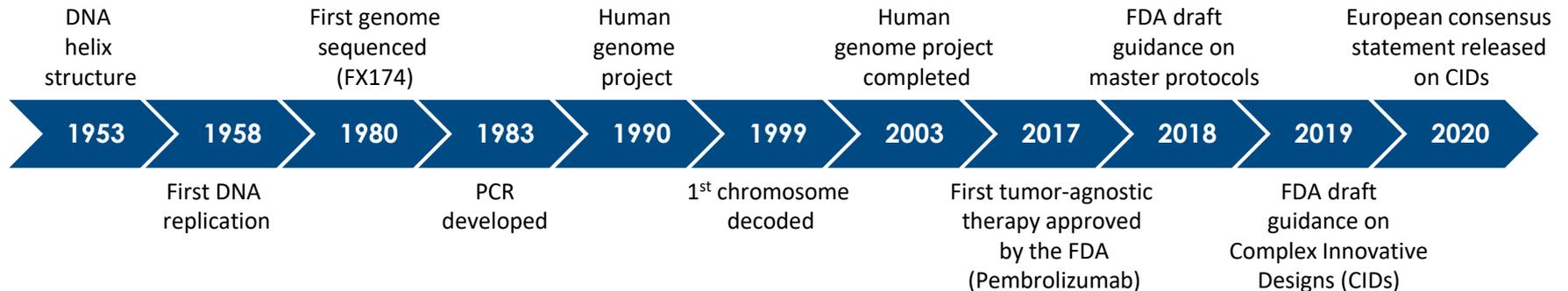
# Agenda

## To discuss:

1. The concept of master protocols and their sub-types – basket and umbrella trials
2. Important design considerations for these types of master protocols

# Background

- With increasing advancements in genomics, there have been increasing interests in biomarkers and how they can be used to improve biomedical interventions
- Biomarker-guided trials are becoming more popular to identify therapies that can specifically affect disease targets based on their genetic make-up – *known as ‘targeted therapies’*



Adapted from Baxter C. After the double helix. Nature Reviews Genetics. 2003 Apr 1;4(4):246-7.

# Changing landscape in oncology

- Increasing number of biomarker-targeted therapies now being investigated and approved in oncology
- We are shifting away from histology- and organ-specific cancer therapies towards molecularly defined sub-cancer and tumor-agnostic therapies
- With this changing therapeutic landscape, it is important to recognize the importance of biomarkers and how they are used to develop targeted therapies in clinical research



# Master protocols

- Generally refer to a single overarching protocol developed to evaluate multiple hypotheses with general goals of improving efficiency and uniformity through standardized procedures
- Often categorized as *basket trials*, *umbrella trials*, and *platform trials*
- Our landscape analysis has found 83 master protocols registered (July 8th, 2019)

## REVIEW ARTICLE

### THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,  
and Janet Woodcock, M.D., *Editors*

## Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

## Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry DRAFT GUIDANCE

REVIEW

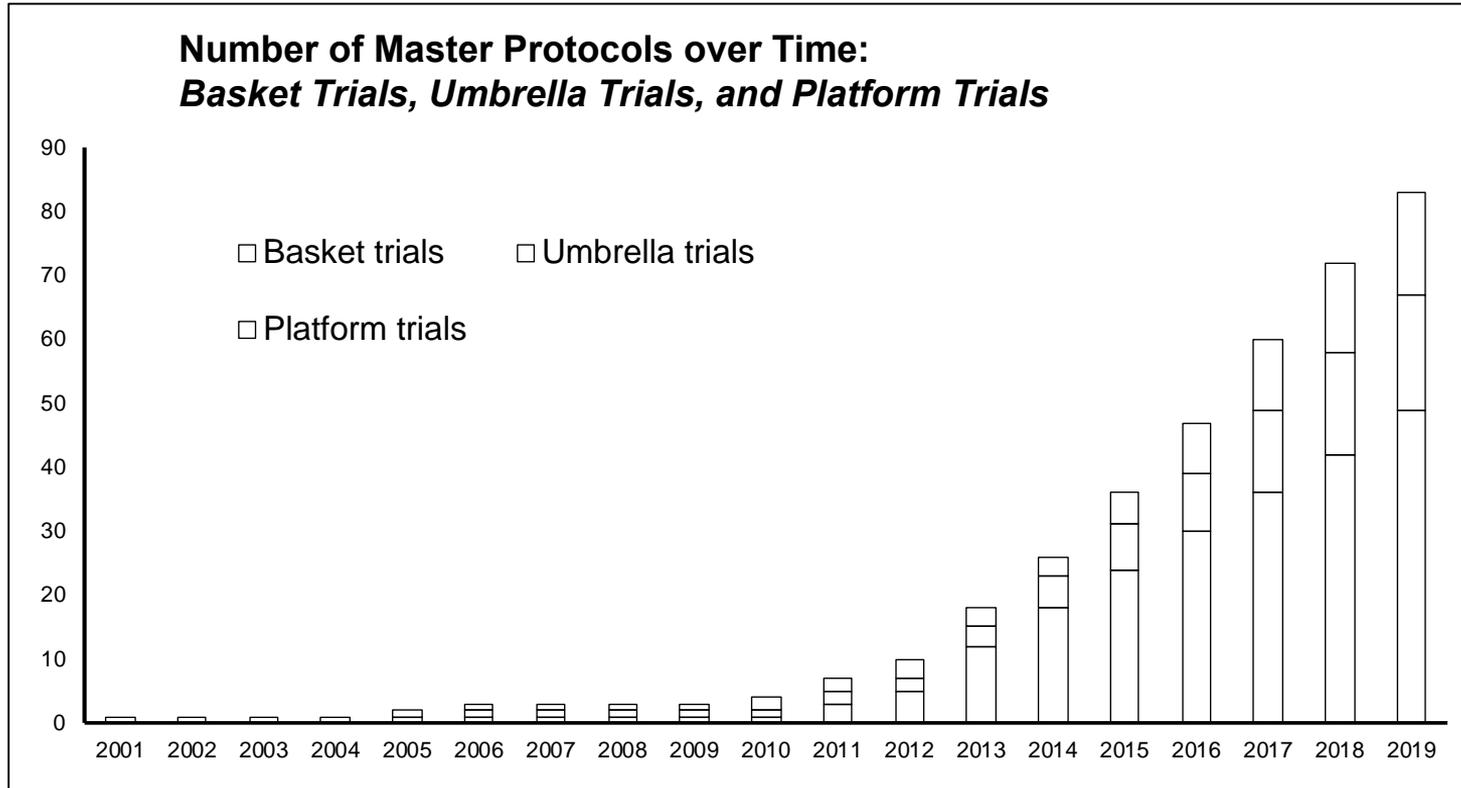
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Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols



Jay J. H Park<sup>1,2</sup>, Ellie Siden<sup>2</sup>, Michael J. Zoratti<sup>3</sup>, Louis Dron<sup>2</sup>, Ofir Harari<sup>2</sup>, Joel Singer<sup>4,5</sup>, Richard T. Lester<sup>1</sup>, Kristian Thorlund<sup>2,3,6</sup> and Edward J. Mills<sup>2,3,6</sup>

# Rising popularity of master protocols



# What is a basket trial?

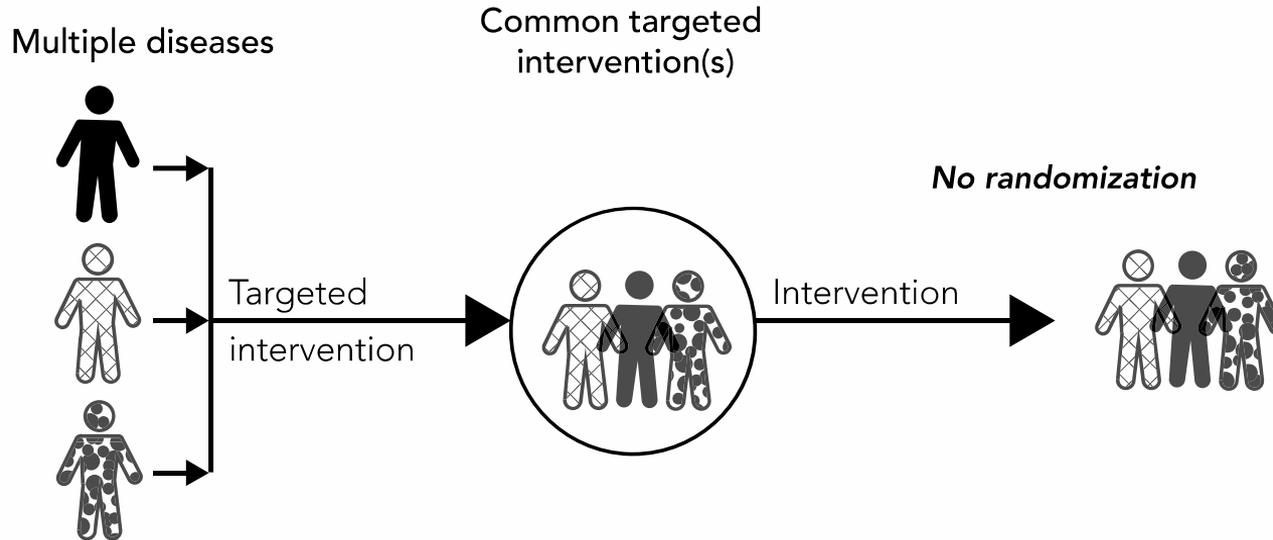
- A clinical trial that tests one or more targeted interventions across multiple types of diseases that share common molecular alterations and/or other risk factors
- There are unifying eligibility criteria usually based on predictive risk factors that combine patients with different diseases into a single “basket”
- Predictive risk factors are usually based on the intervention’s mechanism of action since it can help predict whether the patient will respond to a specific intervention

## A basket trial in cancer

- Multiple histological types of cancer
- Common targets as unifying eligibility criteria
- Interventions agnostic to tumor and histology

# An illustrate example of a single-arm basket trial

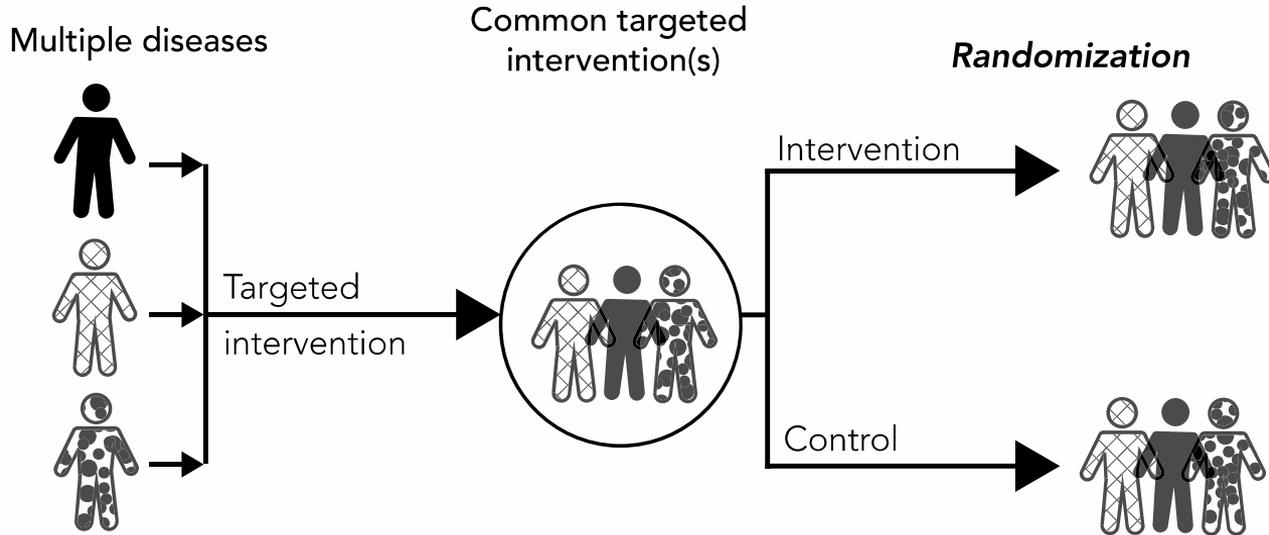
## A Basket trial - no control



# An illustrate example of a randomized basket trial

**B**

## Basket trial - with control



# What is an umbrella trial?

- A clinical trial that tests multiple targeted interventions for a single disease based on predictive biomarkers and/or other risk factors
- In an umbrella trial, a single disease (e.g. breast cancer) is stratified into multiple groups
  - For example, the eligibility for each group can be defined by the intervention's mechanism of action

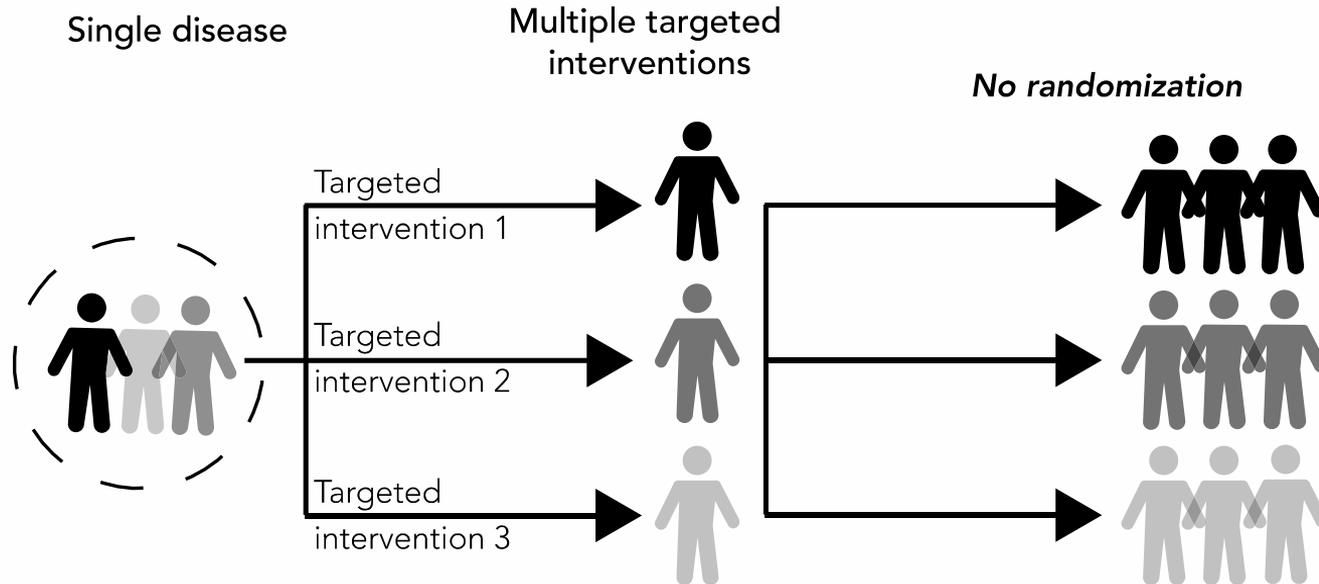
## An umbrella trial in cancer

- A single histological cancer type
- Multiple targets used to stratify patients
- Multiple interventions

# An illustrate example of a single-arm umbrella trial

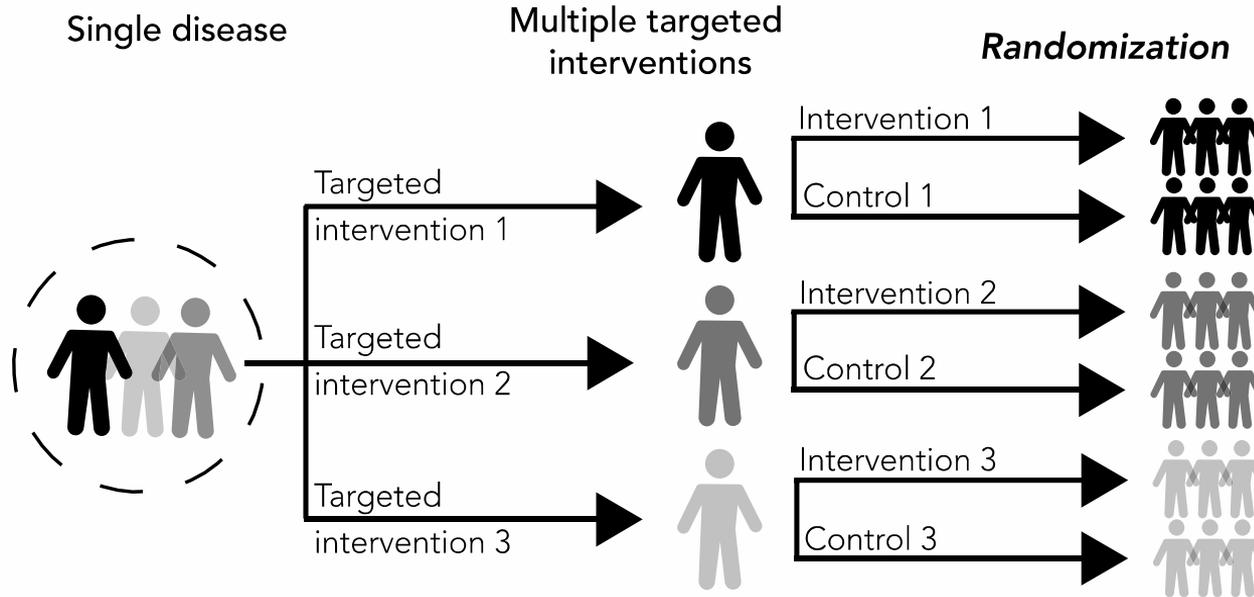
**A**

## Umbrella trial - no controls

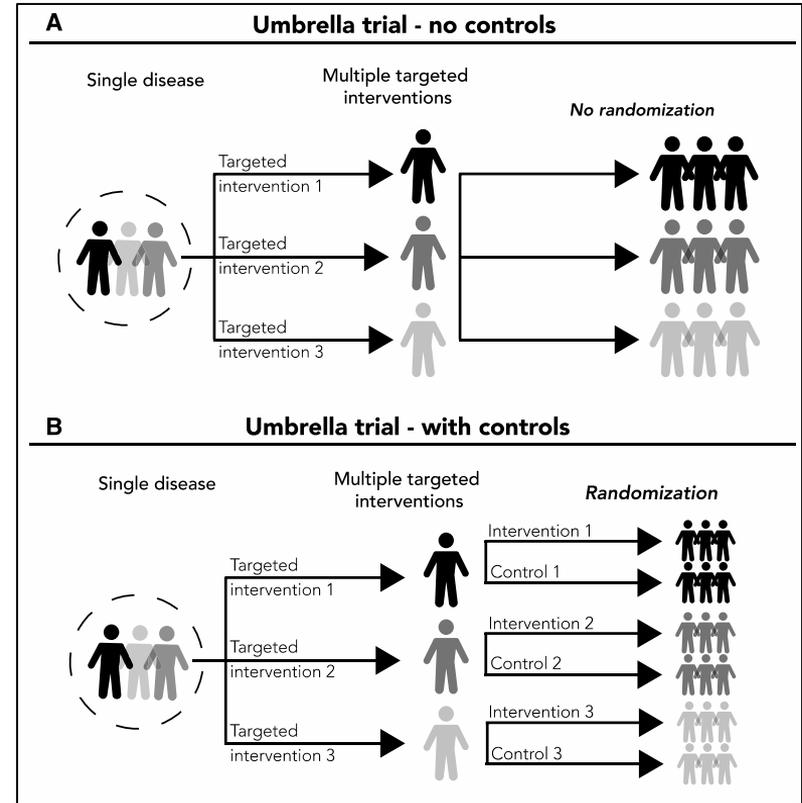
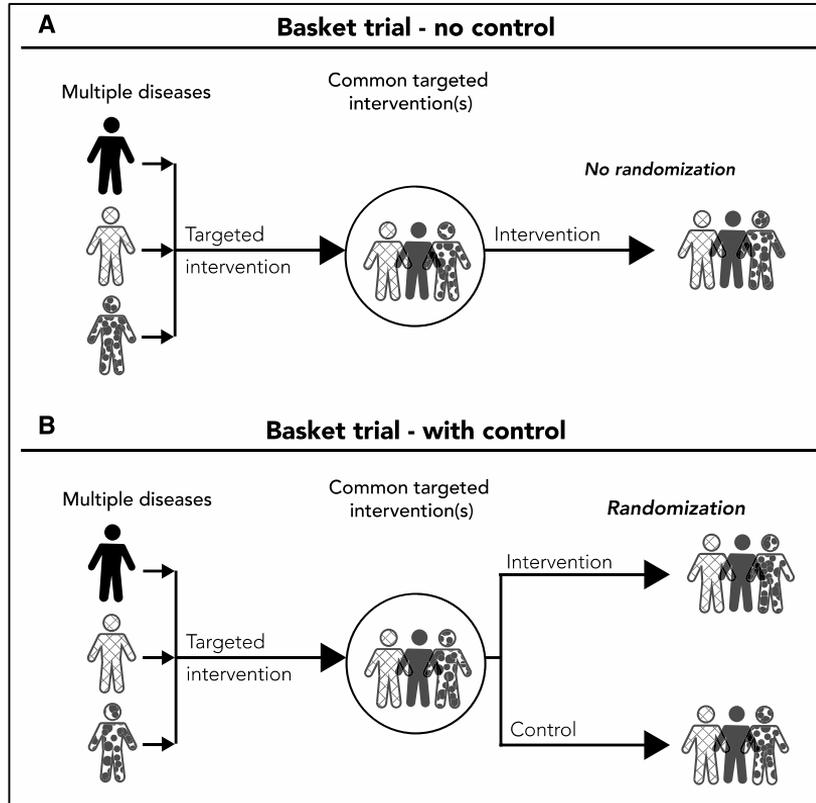


# An illustrate example of a randomized umbrella trial

## B Umbrella trial - with controls



# Illustrations of basket and umbrella trials



# Basket and umbrella trials

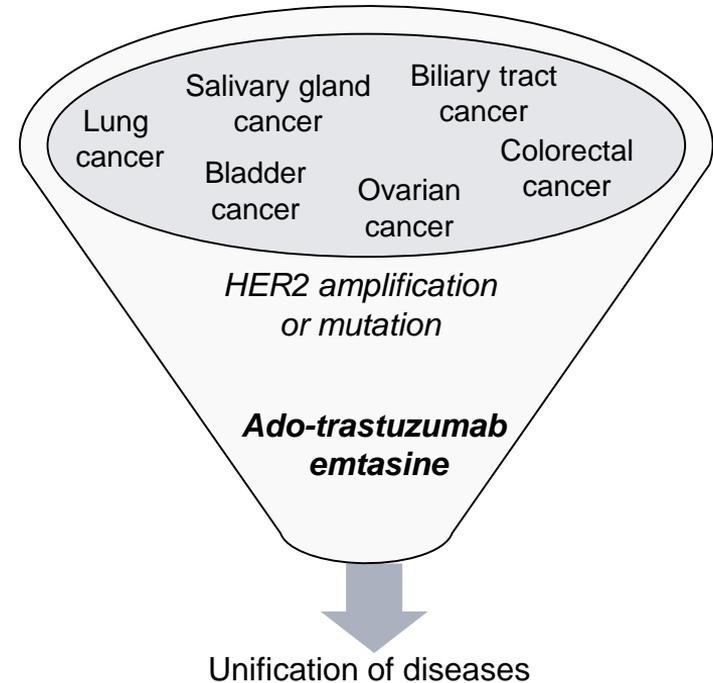
A basket trial in cancer	An umbrella trial in cancer
<ul style="list-style-type: none"><li>• Multiple histological types of cancer</li></ul>	<ul style="list-style-type: none"><li>• A single histological cancer type</li></ul>
<ul style="list-style-type: none"><li>• Common targets as unifying eligibility criteria</li></ul>	<ul style="list-style-type: none"><li>• Multiple targets used to stratify patients</li></ul>
<ul style="list-style-type: none"><li>• Interventions agnostic to tumor and histology</li></ul>	<ul style="list-style-type: none"><li>• Multiple sub-cancer interventions</li></ul>

# Are basket and umbrella trials similar in any way?

- In both trials, a common molecular screening protocol is used to determine eligibility
  - Standardized biomarker assays are used within the trial ecosystem – *features of master protocols*
- Intervention assignment may or may not be determined using randomization in these trials

# Basket trials

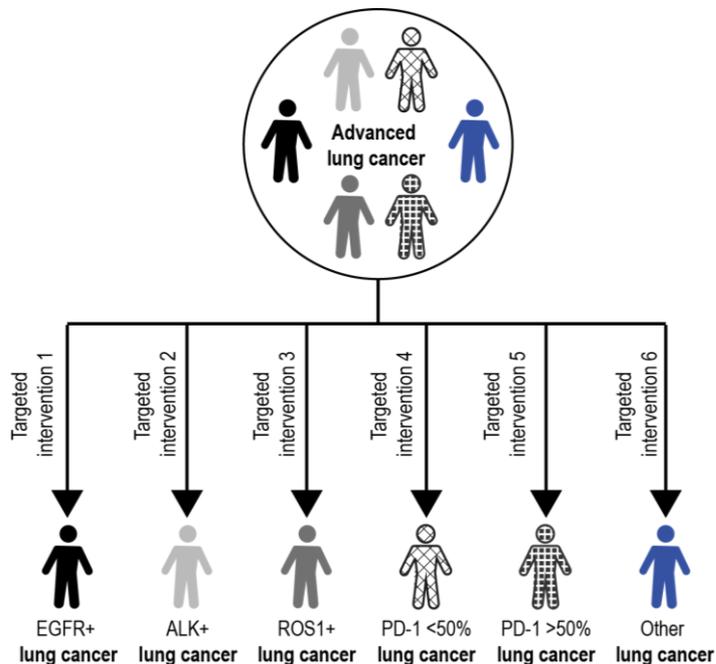
- The inherent nature of basket trials may be described as “*unification of diseases*”
- Patients in a basket trial will represent multiple diseases that share a common unifying predictive risk factor
- Given that the disease sub-type is often a prognostic factor, patient subgroups may be defined based on the disease sub-types, but they are usually not powered to detect subgroups



*Adapted from NCT02675829: “Trial of Ado-Trastuzumab Emtasine for Patients With HER2 Amplified or Mutant Cancers”*

# Umbrella trials

- Umbrella trials have an inherent feature of using multiple predictive risk factors to stratify single-disease patients into multiple groups (patient stratification)
- Each group is statistically powered as each sub-study of the master protocol



*Adapted from NICE's advanced non-squamous non-small cell lung cancer systematic anti-cancer therapy guideline*

# Basket and umbrella trials: Trial design characteristics

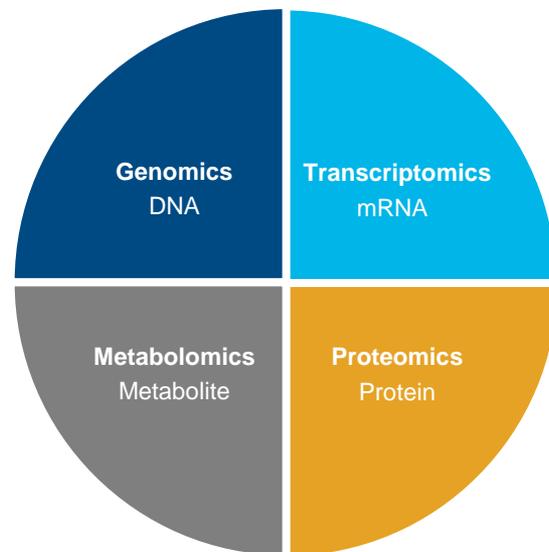
Trial design characteristics*	Basket trials (N = 49)	Umbrella trials (N = 18)
Exploratory (phase I or II)	96% (n = 47)	89% (n = 16)
Use of randomization	10% (n = 5)	44% (n = 8)
Number of interventions investigated	Median: 1 (IQR: 3-1 = 2)	Median: 5 (IQR: 6-4 = 2)

**Acronym:** Interquartile range - IQR (Q3 – Q1)

\*Park JJ et al. BMC Trials. 2019 Dec;20(1):1-0.  
Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols.

# Basket and umbrella trials vs. other biomarker-guided trials

- Similar to other biomarker-guided trials, basket and umbrella trials aim to use “omic” technologies to define disease and eligibility criteria for improved characterization and identification of predictive biomarkers and targeted therapies
- Basket trials aim to identify histology-agnostic therapies
- Traditionally, it is not uncommon for phase I trials to recruit multiple tumors to test for the existence of signal, but basket trials’ histology-agnostic approaches are now being considered for phase 2 and 3 evaluations



# Basket and umbrella trials vs. other biomarker-guided trials - continued

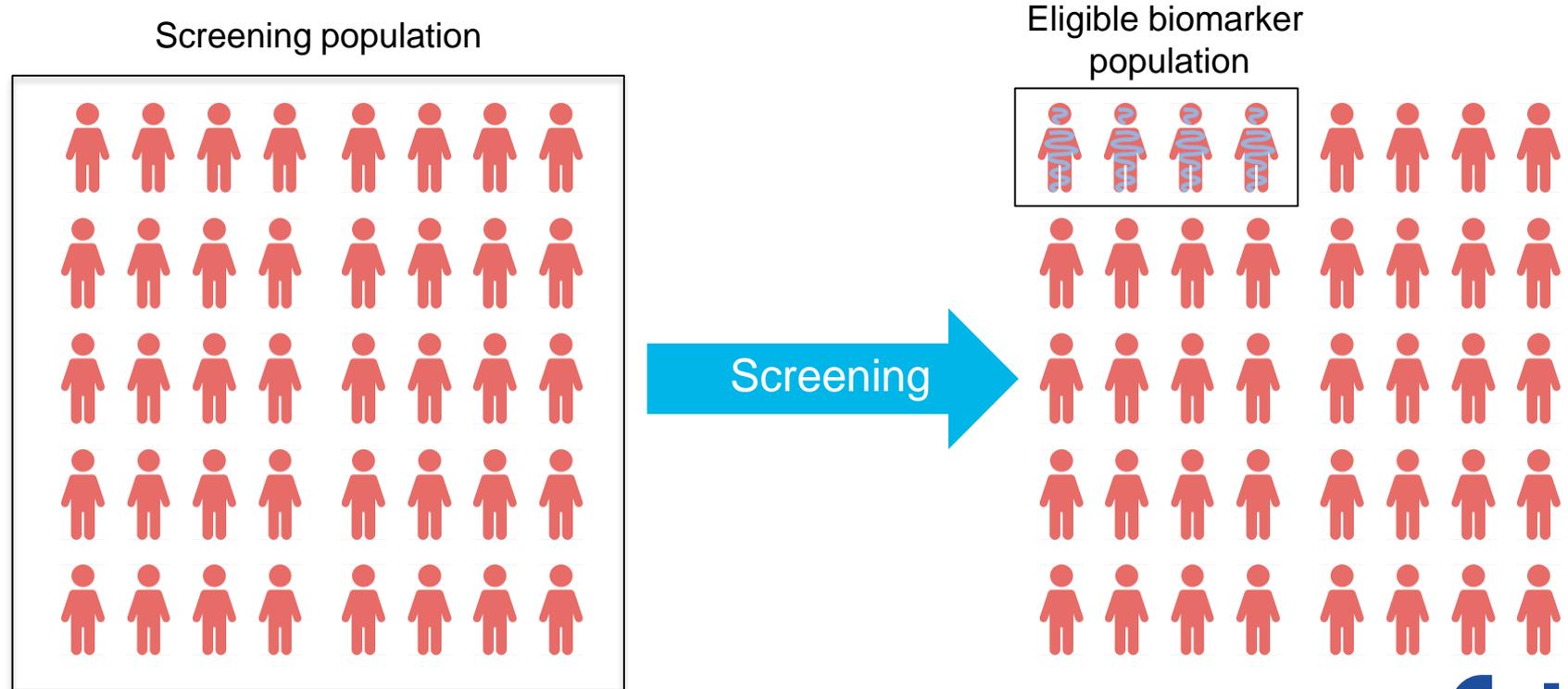
- The use of a single master protocol with standardized operating procedures is a key difference!
- In umbrella trials, multiple histology-dependent targeted therapies are evaluated as different sub-studies that are molecularly differentiated
- Use of a master protocol in an umbrella trial allows for **screening efficiency**

## Basket and umbrella trials vs. other biomarker-guided trials - continued

- For example, if we assume that 10% of breast cancer patients will have the biomarker of interest, an expected 1000 cancer patients will need to be screening to reach the recruitment target of 100 patients

$$\frac{\textit{Sample size target}}{\textit{Biomarker prevalence (\%)}} = \textit{Expected screening number}$$

# Screening for eligible biomarker-positive population



# Basket and umbrella trials vs. other biomarker-guided trials - continued

- For example, if we assume that 10% of breast cancer patients will have the biomarker of interest, an expected 1000 cancer patients will need to be screening to reach the recruitment target of 100 patients

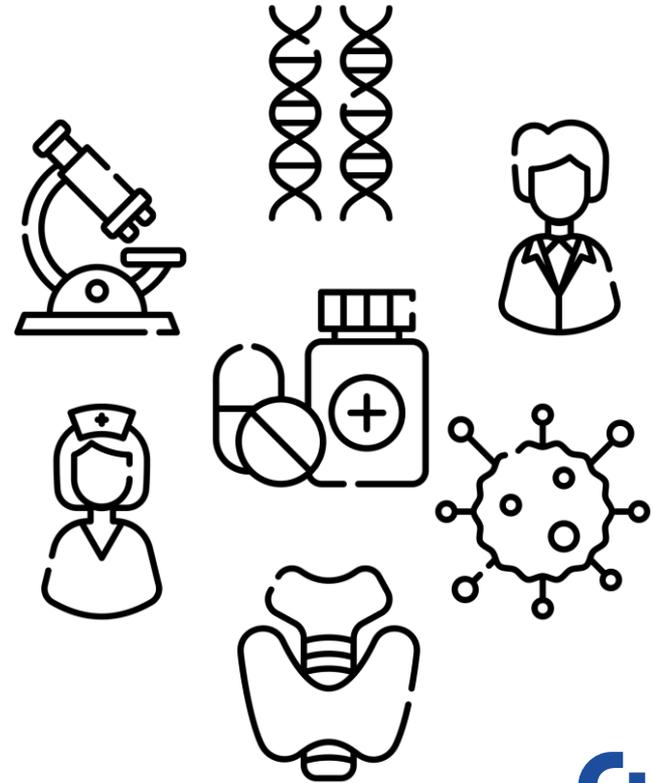
$$\frac{\text{Sample size target}}{\text{Biomarker prevalence (\%)}} = \text{Expected screening number}$$

- **In principle**, each sub-study of an umbrella trial can be conducted separately as a non-master protocol, but conducting them independently would require a much larger number of patients that would need to be screened!

# Key design considerations for basket and umbrella trials

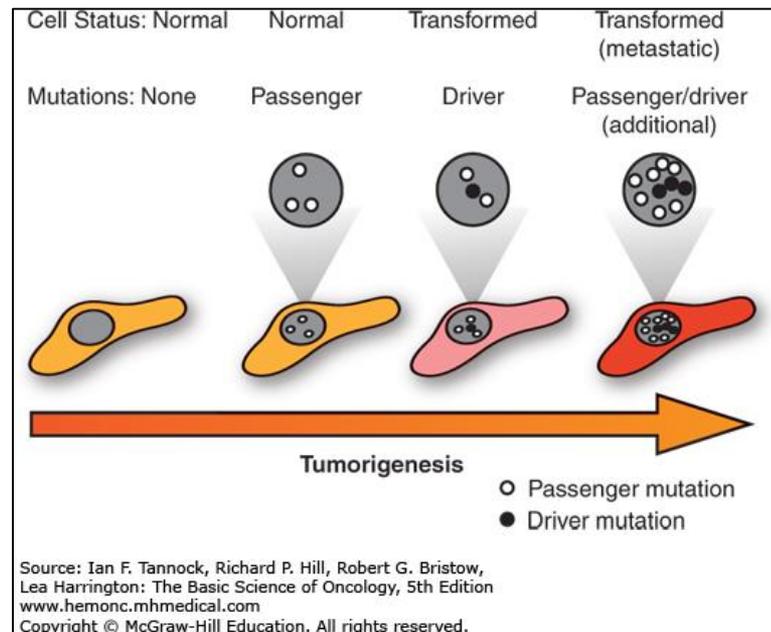
# Key design considerations for basket and umbrella trials

- Biological plausibility
- Accuracy of biomarker assays
- Biospecimen collection
- Biomarker prevalence
- Sample size calculations
- Use of randomization



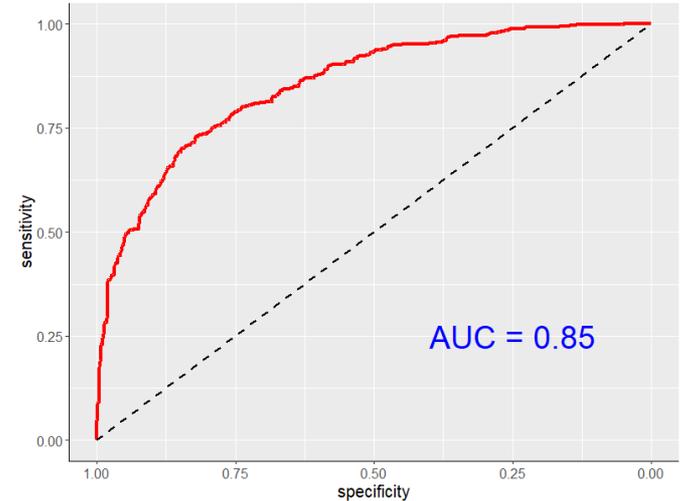
# Biological plausibility

- Most important to consider the biological plausibility of the targeted intervention strategies being evaluated
- It is common for cancers to have multiple genetic mutations, but most mutations are **passenger mutations** that do not affect the underlying carcinogenic process.
- Intervention strategies should be targeting **driver mutations**, but it can be difficult to separate driver mutations from passenger mutations



# Accuracy of biomarker assays

- Conceptually, a targeted intervention should be more efficacious against the disease with the biomarker target versus the disease without the target
- Given that all medical tests have some degree of diagnostic inaccuracy, a proportion of false positive patients are expected in basket and umbrella trials
- In exploratory biomarker-guided trials, it has been shown that increasing false positive rates of biomarker tests will reduce statistical power



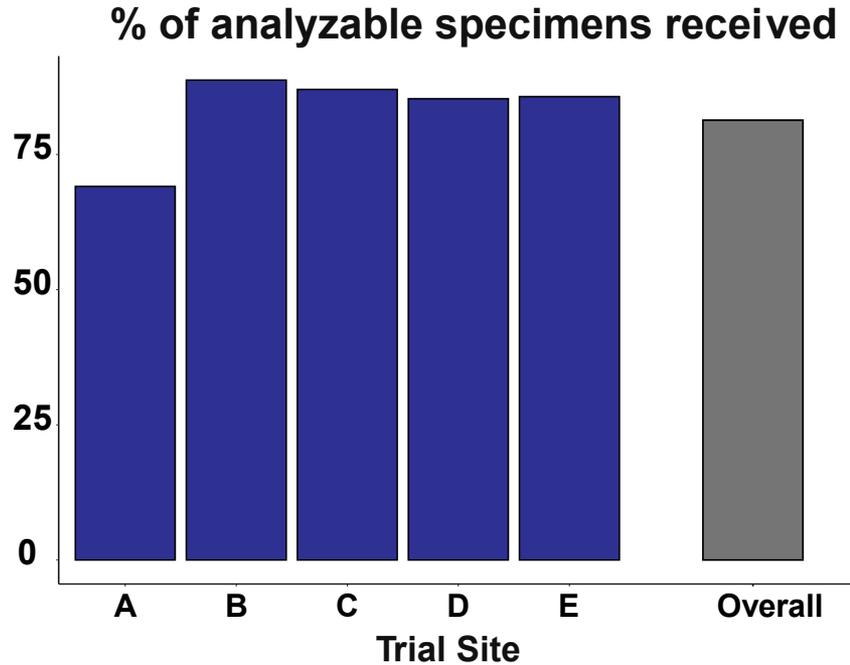
# Biospecimen collection

- Ensuring adequate biospecimen collection procedures and standards across multiple trial institutions are important
- Centralized biospecimen processing and molecular analyses established through a master protocol can help
- Ease of biospecimen collection, biospecimen quality, and biospecimen yield should be similar between different tumors

# Biomarker prevalence

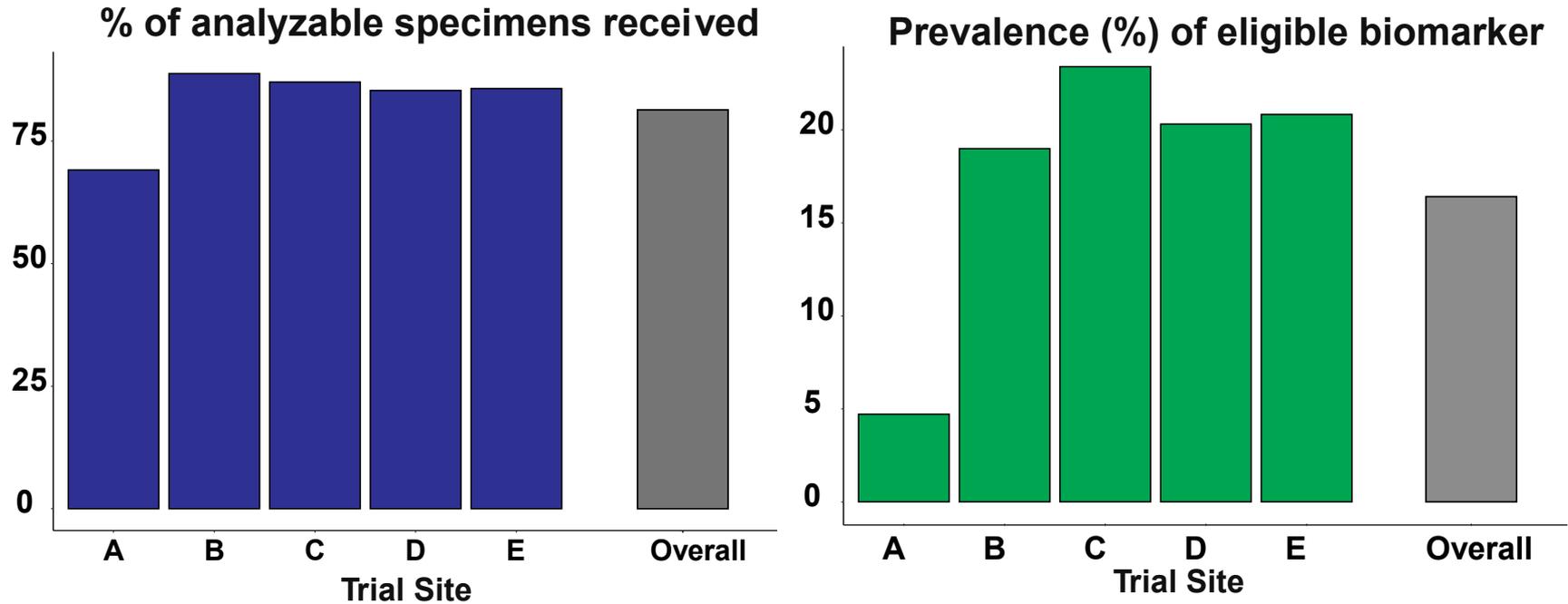
- Patient recruitment is a key determinant for any clinical trials
- Biomarker prevalence will affect the size of eligible patient pool. If the target biomarker has a low prevalence, recruitment challenges can be amplified
- Planning for comprehensive recruitment strategies to reach the target sample size within the desired trial duration will be essential

# Biospecimen collection and biomarker prevalence - continued



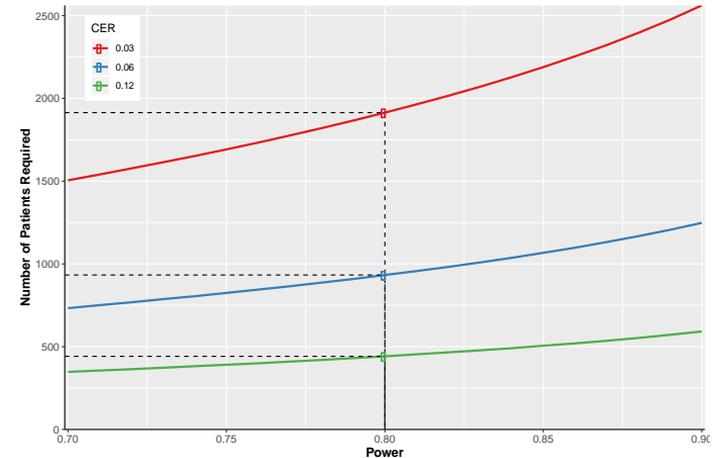
*Fewer analyzable samples submitted from Site A*

# Biospecimen collection and biomarker prevalence - continued



# Sample size calculations

- For basket trials, sample size calculations may be done for the overall cohort.
  - It can be difficult to differentiate 'responders' and 'non-responders' between different disease sub-types
- For umbrella trials, sample size calculations may be done for each of the sub-studies given that multiple targeted interventions are being evaluated



# Use of randomization

- Randomization is generally preferable, as it can help determine whether the risk factors being used as part of the targeted intervention strategies are indeed predictive
- In single-arm basket and umbrella trials, it can be difficult to differentiate between predictive and prognostic factors
- Statistical adjustments may be made on disease sub-types and/or other prognostic risk factors, but adjustments are difficult in smaller data sets

# Use of randomization - continued

## *Choice in control arm:*

- If there are multiple standard-of-care across different tumors, it might be difficult to pick a single control in a basket trial
- In an umbrella trial, each sub-study can have its own control and powered accordingly

# Summary

- Methodological advancements in master protocol framework and basket and umbrella trials now bring opportunity for precision medicine into becoming a reality
- There are several important considerations that need to be made for these clinical trials
- For further details, please refer to our recently published article on basket and umbrella trials on CA - A Cancer Journal for Clinicians
  - *Park et al., 2020 “An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians”*

# An Overview of Precision Oncology Basket and Umbrella Trials for Clinicians

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**DISCLOSURES:** The authors report no conflicts of interest.

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**Abstract:** With advancements in biomarkers and momentum in precision medicine, biomarker-guided trials such as basket trials and umbrella trials have been developed under the master protocol framework. A master protocol refers to a single, overarching design developed to evaluate multiple hypotheses with the general goal of improving the efficiency of trial evaluation. One type of master protocol is the basket trial, in which a targeted therapy is evaluated for multiple diseases that share common molecular alterations or risk factors that may help predict whether the patients will respond to the given therapy. Another variant of a master protocol is the umbrella trial, in which multiple targeted therapies are evaluated for a single disease that is stratified into multiple subgroups based on different molecular or other predictive risk factors. Both designs follow the core principle of precision medicine—to tailor intervention strategies based on the patient’s risk factor(s) that can help predict whether they will respond to a specific treatment. There have been increasing numbers of basket and umbrella trials, but they are still poorly understood. This article reviews common characteristics of basket and umbrella trials, key trials and recent US Food and Drug Administration approvals for precision oncology, and important considerations for clinical readers when critically evaluating future publications on basket trials and umbrella trials and for researchers when designing these clinical trials. CA Cancer J Clin 2020;0:1-13. © 2020 The Authors. CA: A Cancer Journal for Clinicians published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**Keywords:** basket trials, master protocols, precision medicine, precision oncology, umbrella trials

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