

Clinical Utility of Molecular Tests for CUP

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Disclaimer

- Views expressed are my own and not necessarily those of the National Cancer Institute, NIH, or DHHS.
- No Conflicts of Interest



Promise of Molecularly Guided Treatment of Cancer

- “Get it right the first time”
- Avoid unnecessary toxicity
- Better survival
- Better quality of life
- Cancer as another chronic disease



Cancer of unknown Primary site

- 3-5% of adult malignancies – reasonably common
- Metastatic on presentation
- Median survival 2-12 months
- No reliable correlation of genetic characteristics with response, survival



Histology

- 60% Adenocarcinoma
- 30-35% PD adenocarcinoma, carcinoma, undifferentiated
- 5% squamous
- 2% neuroendocrine



Open Questions

- Given that carcinomas of unknown primary present with metastatic disease – is the biology/prognosis different compared to carcinomas where the primary is evident?
- Can we expect CUP to do the same, better or worse if we knew the tissue of origin?



Cancer of Unknown Primary Site

Favorable (20%)

- Women – papillary peritoneal carcinoma
- Women – axillary
- Men – blastic bone mets; elevated PSA
- Poorly differentiated –midline nodal
- Poorly diff neuroendocrine
- SCC – cervical LN
- AdenoCa with colon cancer profile
- Isolated inguinal squamous
- Potentially resectable
- Merkel cell adenopathy

Unfavorable (80%)

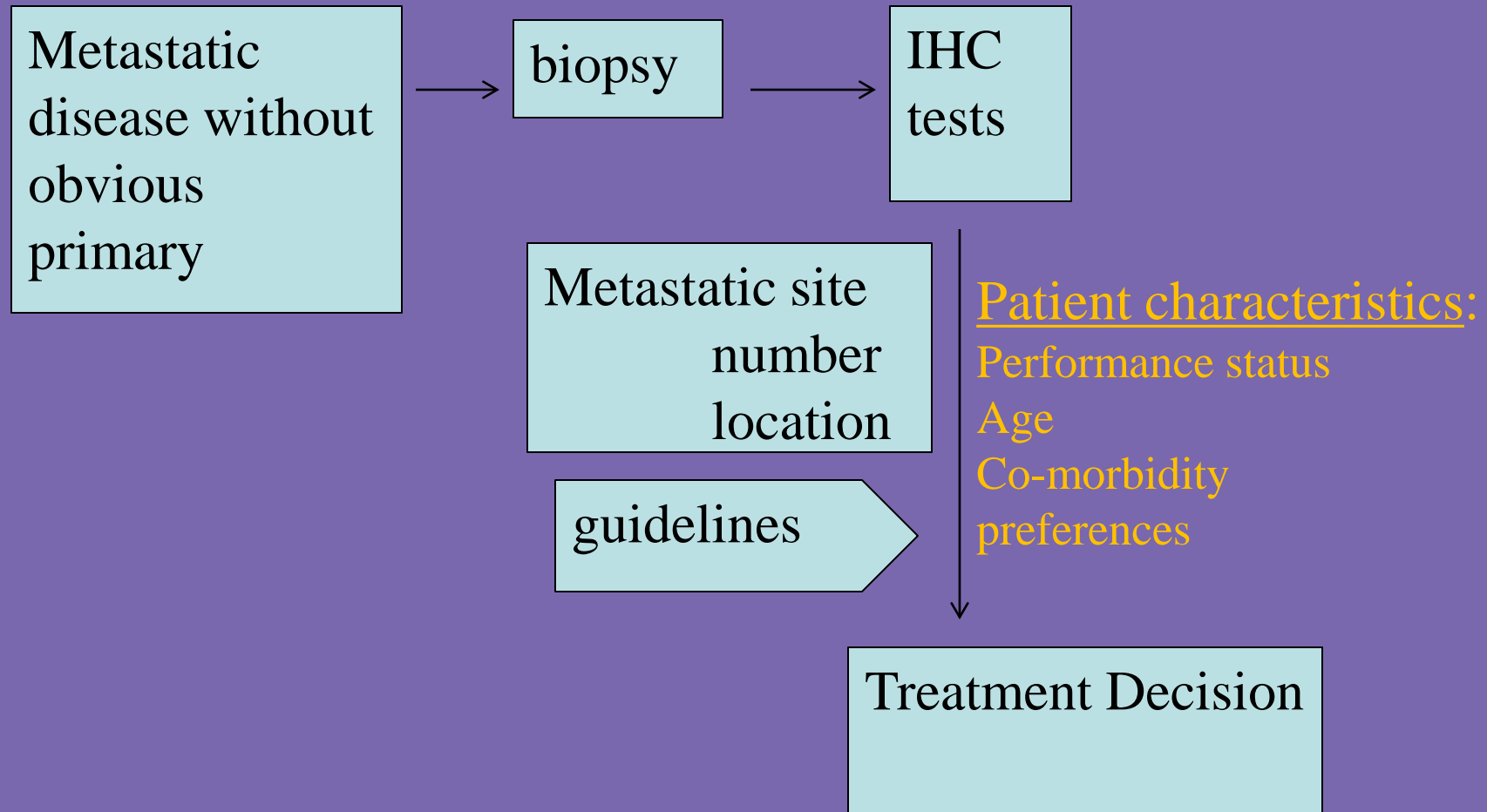
- AdenoCa met to liver or other organs
- Multiple brain mets
- Multiple lung or pleural mets
- Multiple lytic bone disease (non-PSA)
- SCC abdom/pelvic area



What is clinical utility

- Gold standard - Results in *better outcomes* than what is currently available.
 - Survival is improved – by how much?
 - Toxicity is lessened – by how much?

Current situation





What we want to know

- Will using molecular tissue of origin tests result in better outcome for patients?




CUP: Assumptions in the clinic

- *If a primary site can be suggested, beneficial treatment can be given*
 - No studies show definite improved outcomes even with current procedures
 - Validation of procedures across sites: not done
 - Most current treatments give little if any benefit for most CUP (or most solid tumors)
- *Molecular profiling can give guidance when other studies are not optimally informative*



Clinical utility: Molecular CUP Test

- *Guides treatment better than current IHC based tests (survival at least equivalent; potentially conservative of resources)*
- *Adds benefit to current diagnostic (imaging, clinical, histologic) procedures: better survival and/or less toxicity*
- *? Allows patients with CUP to be eligible for clinical trials with patients with known primaries*



Validation: Clinical Utility of prognostic/predictive markers

- Define: Setting and desired utility of the marker/assay
- Magnitude of the outcome or treatment effects for a “positive” assay must be sufficiently different from “negative” assay so that clinician or patient would accept different treatment strategies for the two groups
- Estimates of that magnitude must be reliable

Adapted from Simon R, Paik S, Hayes DF, JNCI
101(21): 1446, 2009



How can we get the information?

- Randomized clinical trial (prospective)
 - Stratify? (poor/good prognosis groups)
 - Will standard care change during trial?
- Prospective-Retrospective study
 - Do enough trials exist?
- Registry



Types of Clinical Studies

Retrospective Analyses Designs

- Hypothesis generation studies
 - Retrospective analyses based on convenience samples
- Prospective/retrospective designs

Prospective Designs

- Marker by treatment interaction designs (biomarker stratified design)
- Adaptive analysis designs
- Biomarker-strategy designs
- Sequential testing strategy designs
- Hybrid designs



Improving survival: requirements

- There must be an efficacious treatment.
- Best to use the most efficacious treatment first – might not be able to give 2nd line treatment
- Patient must be fit for treatment (but some targeted treatments benefit even those with poor performance status)



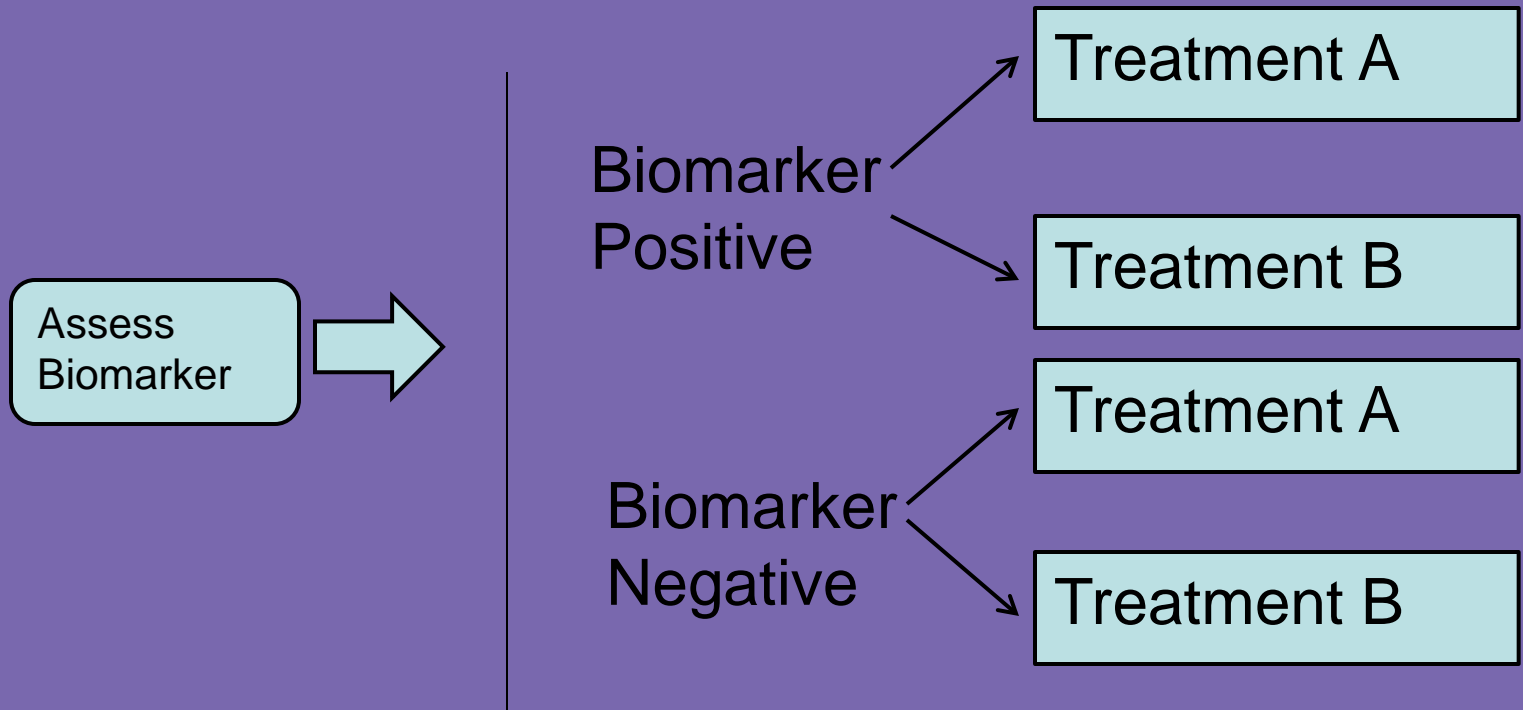
RCT: “Gold Standard with CHALLENGES

- CUP is uncommon
- CUP is heterogeneous
 - Randomization difficult
- Patient characteristics are heterogeneous
- Define magnitude of benefit that would justify use of a new test in this group -

Prospective versus Retrospective Analysis

	Advantages	Disadvantages
Prospective	<ul style="list-style-type: none">• Fewest patients• Guaranteed to have sufficient power to show treatment effect	<ul style="list-style-type: none">• Must know marker to select patients• Rapid turnaround essential
Retrospective	<ul style="list-style-type: none">• Maximize accrual• Need not know marker• Refine marker/assay while trial ongoing• Allows assessment in marker +/- groups	<ul style="list-style-type: none">• Risk of insufficient numbers within marker group(s)• Collection of samples compromised• Results may not be generalizable due to bias sampling

Biomarker Stratified



Unbiased benefit: risk

Can we lump all
TOO?



Biomarker stratified design

- Allows assessment of new therapy in biomarker positive AND biomarker negative patients.
- May not be practical to use with > 2 evaluated therapies
- Some treatments may not be appropriate for all biomarker groups
 - Limit choices for certain biomarker status
 - Equipoise necessary



Enrichment Designs

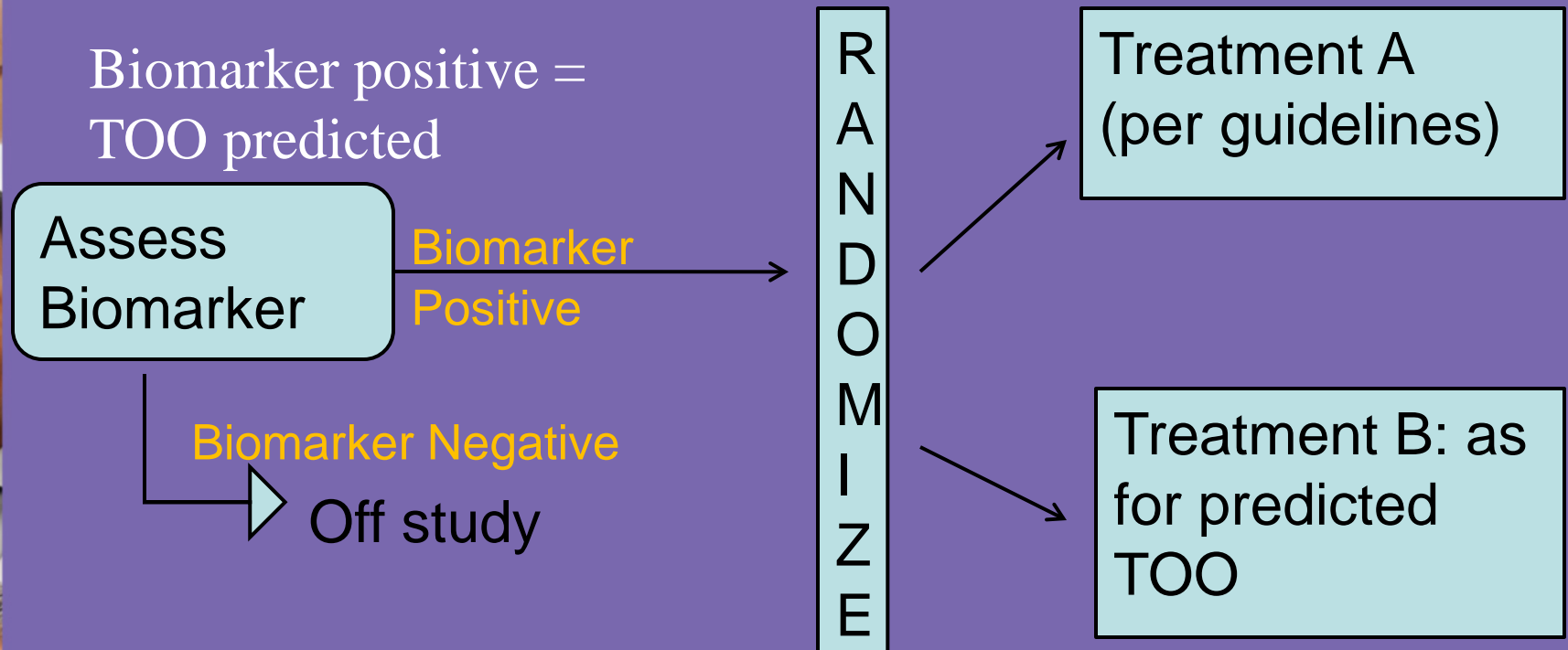
- Convincing clinical evidence that treatment benefit is limited to one biomarker-defined subgroup
- Biomarker stratified design not preferred – ethical
- Measure biomarker on all, but randomization is restricted to a certain biomarker result



Biomarker enrichment design

- Need to be sure that biomarker can identify patients who will benefit from treatment with reasonable accuracy
 - Cannot answer whether treatment is better in biomarker negative group
 - Cannot answer if biomarker is prognostic, predictive

Enrichment Design



Assess Std treatment vs. targeted treatment in biomarker

Positive patients; will not know effect of treatment in Biomarker negative patients

Would you need one trial for each tissue of origin?



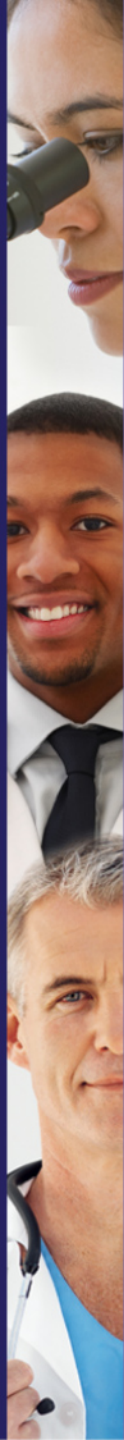
Philosophical question

- Is it better to find the TOO and treat according to guidelines for metastatic disease from a known primary cancer?
- Or, should we concentrate on predictive tests for all tumors: known or CUP?



Conclusions

- Evidence of clinical utility of tissue of origin tests may be difficult to obtain with RCT or with prospective-retrospective study (but trying is good)
- Registry may provide some advantages
 - Concurrent controls and experimental group
 - Wide participation
 - Enroll only good performance status patients



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