Biomarkers in Cancer Clinical Trials: Optimizing Questions, Tools, and Trials for High Impact Results

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Definition of a Biomarker

- "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

Biomarkers Definitions Working Group: Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin pharmacol ther 2001;69:89-95.

- FDA Pharmacogenomics Guidance further defines possible, probable and known valid biomarker categories depending on available scientific information on the marker

- *May be a tissue, plasma, urine, or imaging measure*

Biomarkers in Oncology

- A “biomarker” may be used:
  - For diagnosis/early detection
  - As a prognostic test to identify which patients do better/worse independent of specific treatment
  - To assess delivery of drug to tumour
  - To assess impact of drug on target
  - To assess impact of drug on tumour
  - To assess impact of drug on patient
  - As a predictive test to identify who to treat with a specific drug
  - As a surrogate endpoint for efficacy

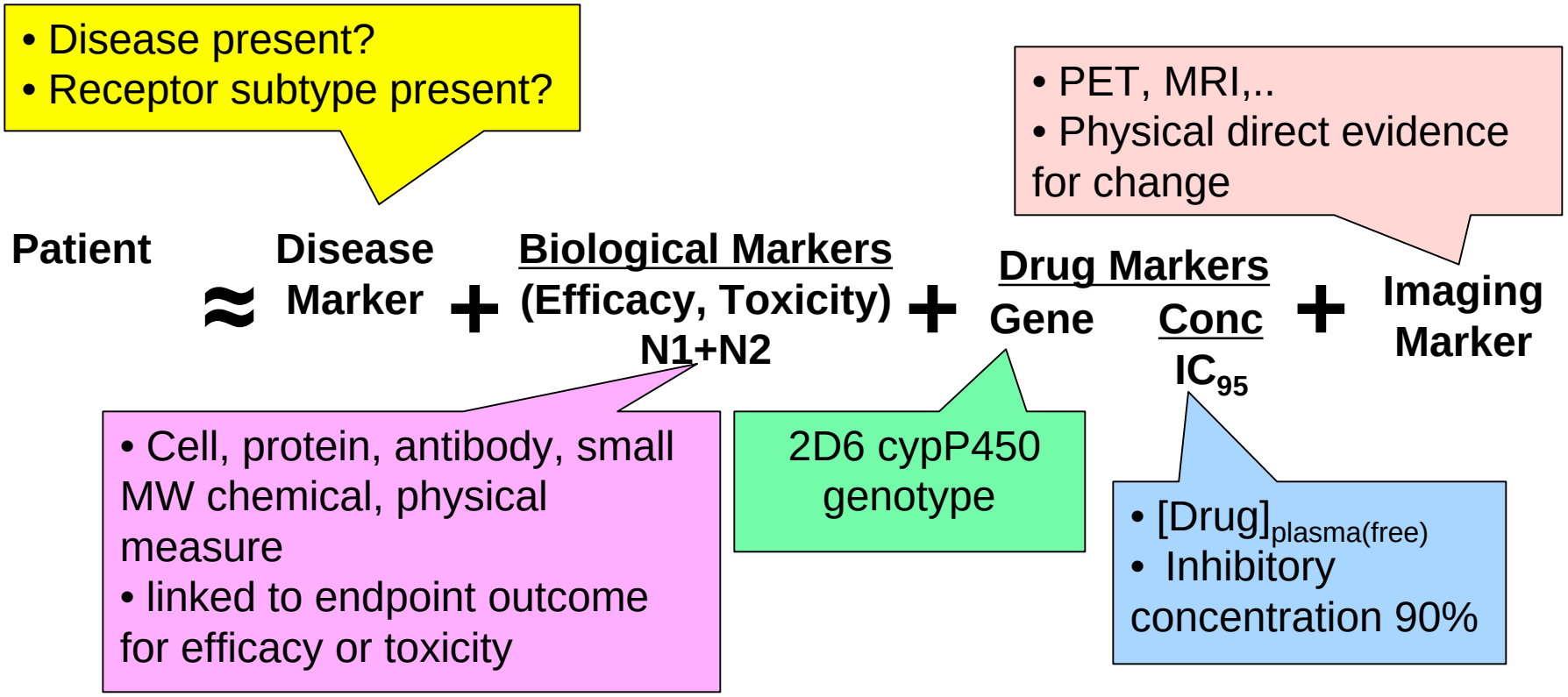
Why are Biomarkers for Cancer Therapeutics Important?

- Risk/benefit: Since benefit is survival, high risks (i.e. toxicity) are tolerated
- Most agents provide marginal benefit
- Patient selection for trials (and treatment) should minimize risk and maximize potential benefit
- Biomarkers are may assist efficient medical product development
- Fundamental to evidence-based clinical medicine: who should be treated, how and with what

"If new refrigerators hurt 7% of customers and failed to work for another one-third of them, customers would expect refunds."

BJ Evans, DA Flockhart, EM Meslin Nature Med 10:1289, 2004

Biomarkers in Future Clinical Practice: The Ultimate in Personalized Medicine



Or is this a development & therapeutic nightmare?

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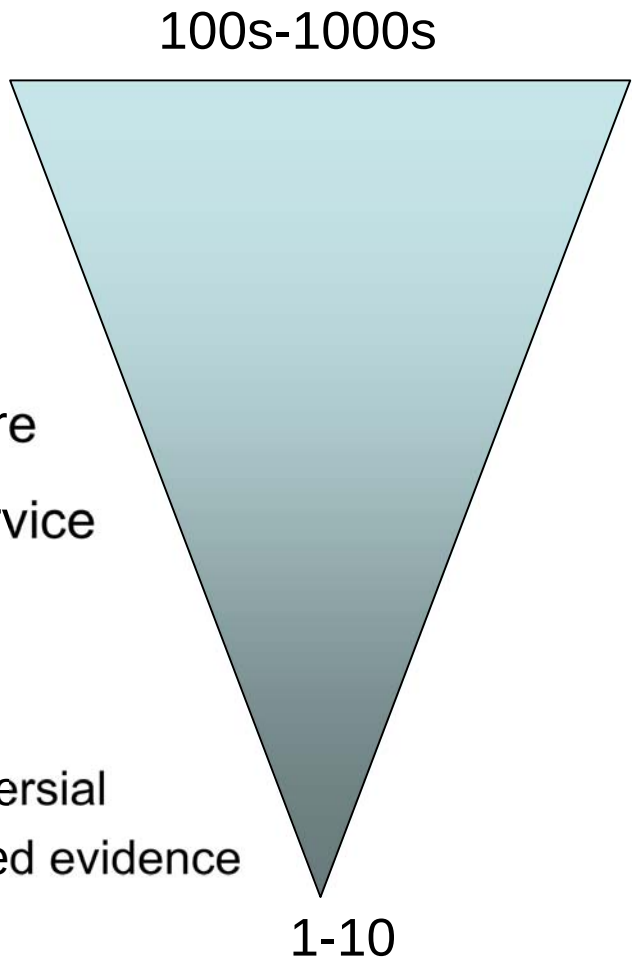
Modified from J Woodcock, FDA 2006

Fate of Most Candidate Biomarkers

- Discovered in academic laboratory
- Clinical series published (if positive)
- Further small series published
- Some uptake in academic centers in clinical care
- Some assays commercialized as laboratory service
- Small number developed into laboratory tests
- Few integrated into clinical care
  - Evidence base for use often remains slim/controversial
  - Not adopted for use because of absence of needed evidence



Biomarker Development: Challenges

- Potential biomarker discovery outpaces validation studies.

  BUT (have) rarely led to clinical use.

  WHY? validating cancer biomarkers can be hard.

- Multidisciplinary collaboration between clinicians, laboratory scientists, pathologists, imagers, and statisticians and industry over a period of years.
- Different cultures/goals/priorities.
- Buy-in from collaborators is essential.

Barriers to successful inclusion of biomarker studies

- Often: add-on studies that aren't necessary for achieving the (primary) objectives of the clinical trial
  - Clinical trials are hard to do well
  - If something is not a primary or secondary objective it is even harder to do it well
- Biomarker studies tend to use assays that are not well established
  - It is almost impossible to learn to do an assay while studying a novel treatment
  - Too many variables

Considerations for Biomarkers

- Biomarker(s)
- Assay
- Specimen
- Study/Trial Design
- Study Execution
- Study Outcome
- Likely Impact

Integrating Biomarkers into Clinical Research: Biomarker

- Why this/these biomarker(s)?
  - What is the question/purpose?
    - (Is there one?)
    - (Is it an important one?)
  - Determining potential “value-added”
- Rationale and supporting data
  - Laboratory experimentation
    - relevance to disease and/or therapy
  - Clinical evaluation
    - prevalence and significance in normal and cancer patients

Integrating Biomarkers into Clinical Research: Assay

- Why this technology?
- Analytical/Laboratory Validation (Laboratory performance)
  - How well are you measuring the measurand?
    - Precision / Reproducibility
    - Method Comparison
    - LoB, LoD, LoQ
    - Linearity
    - Stability
      - Clinical Laboratory Standards Institute (CLSI) http://www.nccls.org/
  - Is it fit for proposed purpose i.e. on the proposed samples/patients?
- Clinical Validation ("Qualification")
  - Does the test have clinical utility?
  - Does it have added value over standard tests?
    - FDA guidance : "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests" issued in final form in March, 2007, http://www.fda.gov/cdrh/osb/guidance/1620.html

Integrating Biomarkers into Clinical Research: Samples

- Will the Samples Be Adequate?

  Consider:

  Type, Number, Timing, handling, shipping, storage

  Demands on patients/clinic/laboratory staff

  Technical requirements of the proposed analysis

  Likely impact/plan for handling missing/inadequate specimens

- Can the question still be answered?

Is the proposed clinical trial and analysis optimal/adequate?

- Phase 1 – Determine dose/schedule for further testing
  - Few patients
  - Heterogenous
  - ***Pharmacodynamic markers to support dose selection***
- Phase 2 – Screen for antitumour activity
  - Relatively few patients for subset analysis
  - May not have a control arm (cannot distinguish prognostic vs predictive)
  - Drug may not be active
  - ***Predictive markers present at baseline***
  - ***Pharmacodynamic surrogates for anti-tumour effects***
- Phase 3 – biomarkers related to clinical benefit
  - Relatively few patients for subset analysis
  - Specimen collection may be suboptimal
  - Drug may be inactive
  - ***Predictive markers; prognostic markers***
  - ***Surrogate markers for clinical benefit***

Phase 1 Trials: Considerations

- Primary goal: To identify an appropriate dose/schedule for further evaluation
- Secondary goals:
  - Description of the nature, severity, reversibility, and dose dependence of the toxic effects of the new agent
  - Determination of the pharmacokinetic (PK) behaviour of the drug.
  - Description of any observed objective anti-tumour effects
  - Assessment of dose-related (or PK-related) pharmacodynamic (PD) effects in normal tissue and tumour by a number of measures.
- Design principles:
  - Maximize safety
  - Minimize patients treated at biologically inactive doses
  - Optimize efficiency

Biomarkers in Phase 1 Trials: Utility

- Proof of mechanism (drug hits proposed target)
- When toxicity may be insufficient to determine active dose/schedule
  - Unlikely to occur at dose/exposure that affects the target
  - Due to off target effects and effects on target are uncertain
  - To target a specific degree of target inhibition to avoid significant toxicity
- When pharmacokinetics may be insufficient to determine active dose/schedule
  - Assay lacking
  - Pharmacokinetics in plasma does not match effect in tissues

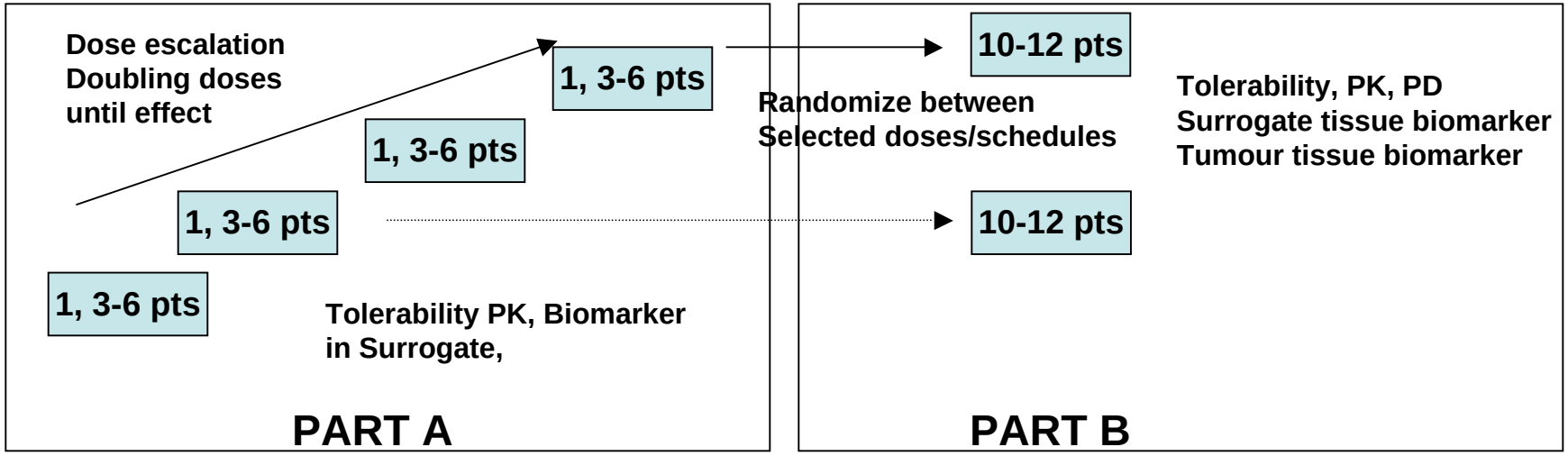
Phase 1 Trial Assessment of Target Effects - Requirements

- Agent with acceptable preclinical activity, toxicology, pharmacology
- Known association of target effect and tumour activity
- Well-characterized assay
  - % change in target or target level associated with efficacy
  - Concentration/exposure required for target effect
  - Time course for effect on target, duration, recovery
  - Threshold of detection and CV of target measurements
  - Target effect on tumour vs other tissues (eg PBMC, Skin, Buccal)
  - Collection, processing, shipping, storage effects known/optimized
- Usual target values and variability in human tissue known
- Patients' tumours have relevant target
- Commitment from investigators/patients
  - mandatory requirement (just like PK)

Phase I FIH Study to Assess Safety, PK and PD of Targeted Agent.

- Considerations

Toxicity anticipated? Target or non-Target related?
PK from preclinical models to determine target concentration?
PD marker in surrogate tissue?
PD in marker tumour tissue?



- Phase 1A Dose escalation phase to define dosing range
  - Can use traditional designs/dose escalations
  - Incorporate Toxicity, PK and PD into decisions to expand cohorts, & dose escalate
- Phase 1B Expanded cohorts to refine dose/schedule
  - Doses/schedules and cohort based on PART A biomarker assays, PK, toxicity

Biomarker Studies in Phase 1 Trials

- MGMT activity after O^6-benzylguanine
  - Developed assay to measure enzyme activity
  - Depletion of in tumour cells required higher O^6BG dose than PBMC
    - Friedman H et al J Clin Oncol 16:3570-5, 1998; Spiro et al. Cancer Res 59:2402-10 1999; Dolan et al Clin Cancer Res 8:2519-23, 2002
- 20S proteosome inhibition after bortezomib
  - Lightcap E et al. Clin Chem 46:673-683, 2000; Adams J, Oncologist 1: 9-16, 2002;
- DCE-MRI after PTK787/valatanib
  - Galbraith S et al NMR in Biomed 15:132-142, 2002; Morgan, B. et al. J Clin Oncol; 21:3955-3964 2003;
- S6K inhibition after everolimus
  - Tanaka C et al J Clin Oncol 26:1596-1602, 2008
- PARP Inhibition after ABT-888

Phase 1 Trials: Summary

- Biomarkers that assist in dose/schedule selection
- Small patient numbers and heterogeneity and limited likelihood of clinical benefit limit the types of questions that can be addressed
- Small patient numbers require MORE robust assays to yield interpretable results

Phase 2 Trials: Considerations

- Goal: estimate level of anti-tumour activity
- Four aspects of phase 2 clinical trial designs:
  - Defining the patient population for evaluation
    - Patient and disease related eligibility criteria
  - Defining the agent/intervention
    - Single agent, combination with active treatment
  - Selecting endpoint(s) of interest
    - Tumour shrinkage versus delayed progression
  - Determining a level of activity that supports further development
  - Estimating sample sizes
    - Endpoint and magnitude of effect of interest
    - Level of certainty that the result is “true”
      - alpha and beta

Biomarkers for Phase 2/3: Predictive markers

- Goal: identification of patients likely to benefit (or elimination of those least likely to benefit)
- Considerations:
  - Drug activity
  - Treatment effect across patient subsets.
  - Prevalence of the subset(s) of patients with “sensitive” disease or at risk for toxicity.
  - Assay performance i.e sensitivity/specificity/predictive value.
  - Samples requirements
  - Trial design to distinguish treatment and prognostic effects

Caveats for Assessing Treatment Effects in Biomarker Defined Groups

- Biomarker defines a subgroup with a different prognosis from historical outcome data from trials done in an unselected group

  E.g. ER+ is both prognostic and predictive

  If the outcome with standard treatment is not well defined and/or the outcome of interest is PFS/OS consider a randomized controlled phase 2 design

- If a trial is designed to assess treatment effects in Marker+ and/or Marker- groups

  False positives will dilute effect in marker+ group

  False negatives will dilute the apparent differences in treatment effect between marker defined groups.

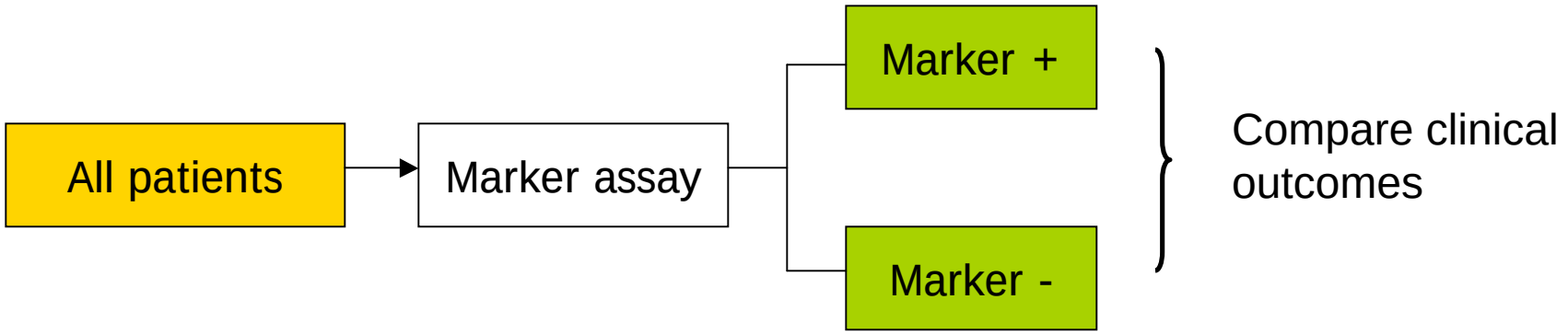
  Specimen loss or assay failure will increase the sample size

  Trial may be 2-4x size of a conventional study

Clinical Trials To Assess Effects in Biomarker Defined Patient Groups

- Rationale:
  - Treatment benefit is limited to a defined group of patients
- Biomarker issues
  - Marker positive group has a large benefit of treatment
  - Marker assessment is robust
    - Reliable,
    - Low false positive/negative rates
    - Low assay failure rate (inability to assess sample and yield a result)
    - Turnaround time is short (delay is clinically acceptable)
  - Marker positive group prevalence is reasonable for screening and accrual
- Design Issues
  - The benefit of treatment has/has not been defined for the unselected group
- Sample Size Conditions:
  - Prevalence of the marker defined group
  - Assay failure rate, sensitivity, specificity, predict value
  - Magnitude of benefit
  - Frequency of events

Prognostic Marker Study Design

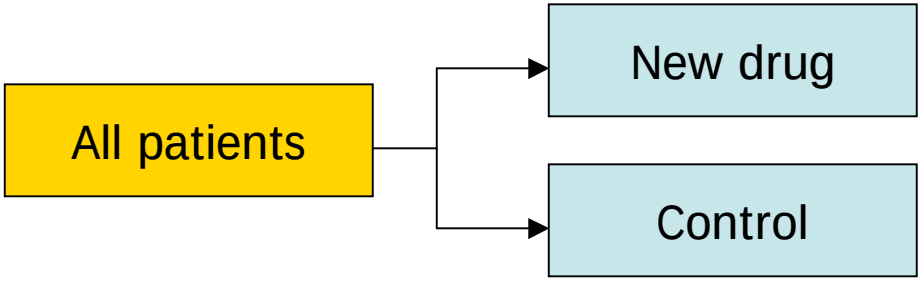


- Standard statistical methods such as log rank test or Cox PH regression assume that study subjects constitute a random sample.
- If sampling is stratified or based on outcome, prognostic effect estimates can be biased.
- Dichotomization of marker is often artificial and inefficient. Markers should be considered as continuous variables when appropriate.

Predictive Marker Study Design

Completely Randomized Design

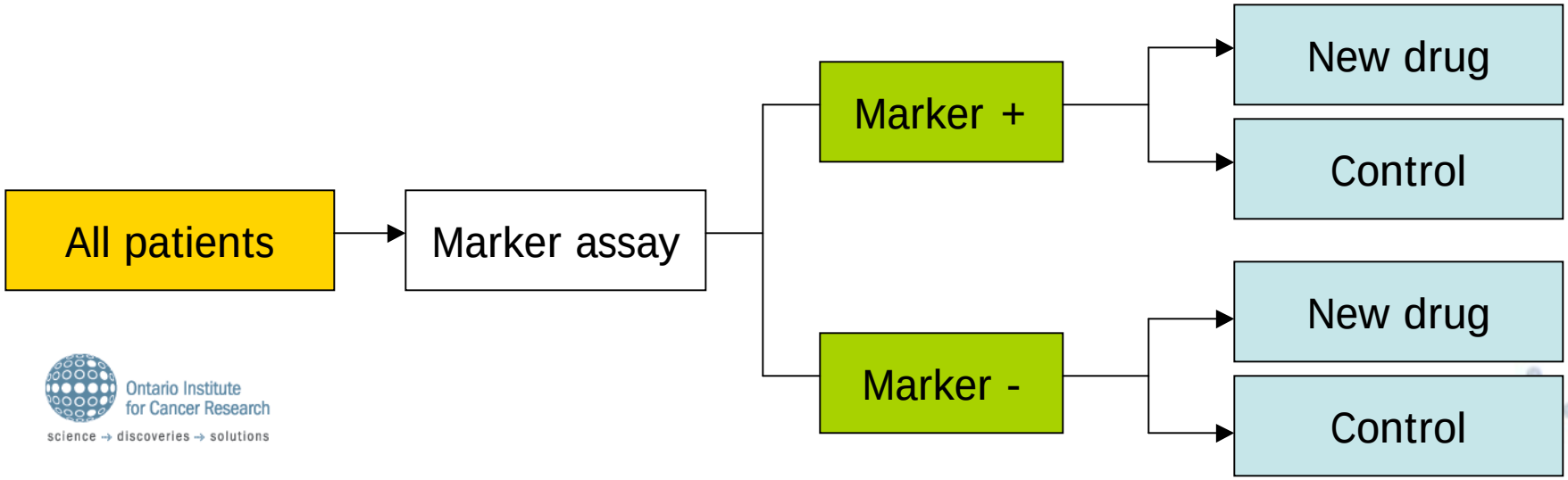
Marker tested on all patients, but result not used for randomization



Analysis: Marker x Treatment

Randomized Block Design

Marker tested pre-randomization, stratification by marker



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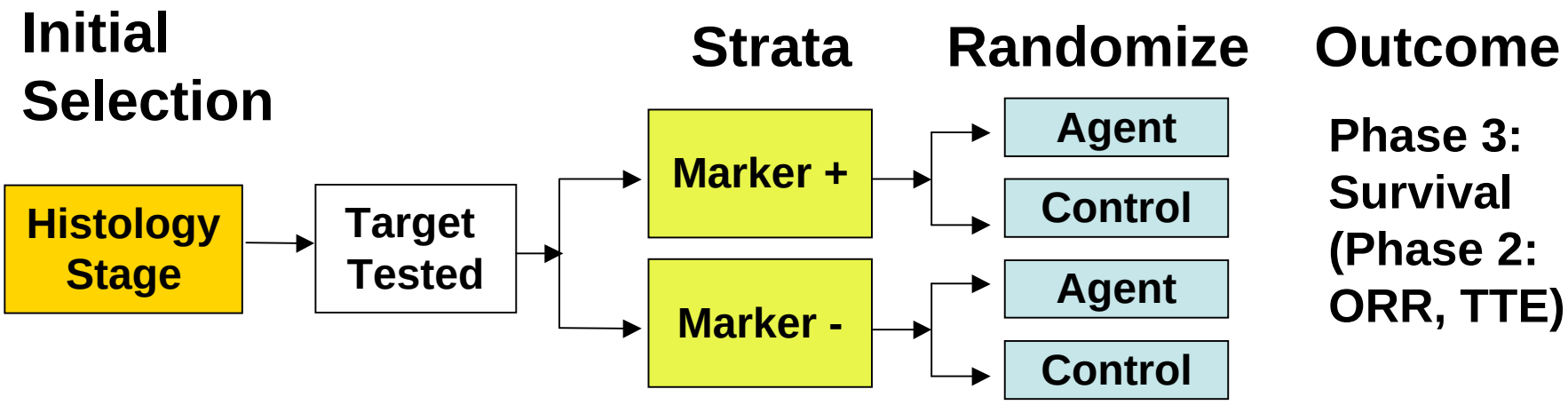
Phase 2 or 3 Trial – Histologically Defined and Biomarker Defined Patient Populations

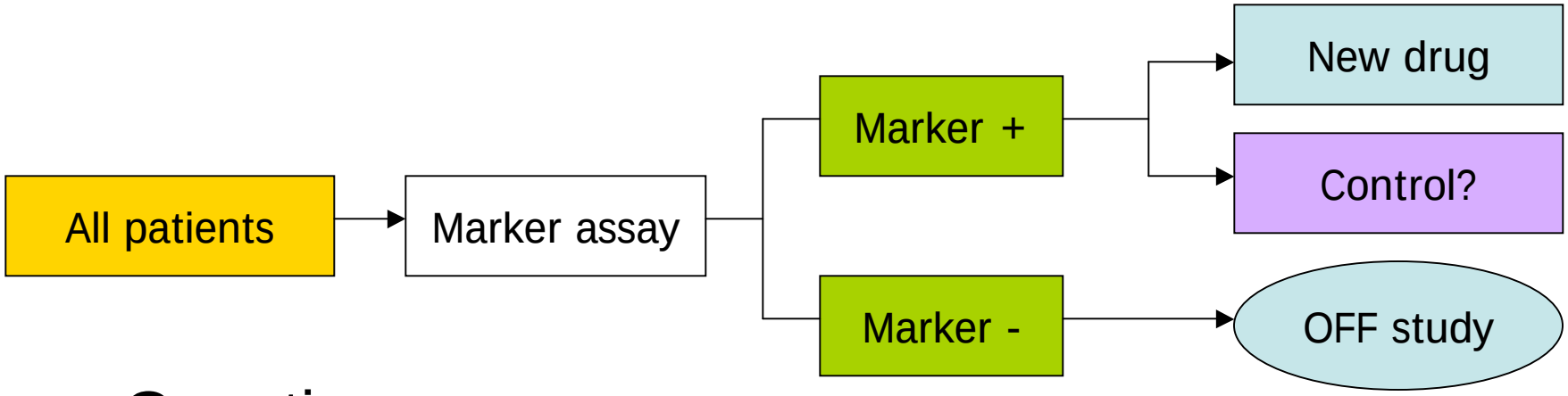


- Trial is designed to assess treatment effects in Marker+ and Marker- groups
  - NB: need not be prospective stratification
- Marker assessment
  - Assay failure increases number of patients screened
  - False positives will dilute effect
  - False negatives will increase the number of patients screened
- If negative within marker groups, analyze between treatment groups

Predictive Marker Study Design

Enrichment Design

Only marker+ patients are randomized and/or treated



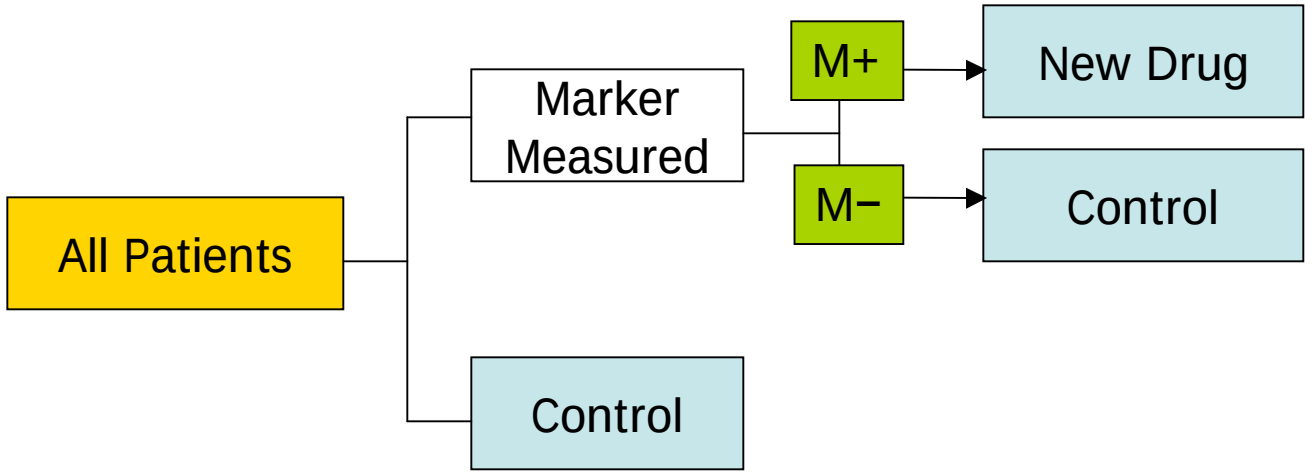
Questions:

- Does new drug benefit marker negative patients also?
- If no control arm
  - Is good outcome due to better prognosis?
  - Is good outcome due to new drug?

Predictive Marker Study Design

Marker-guided Vs. Control Design

Randomize To Use Of Marker Versus No Marker Evaluation

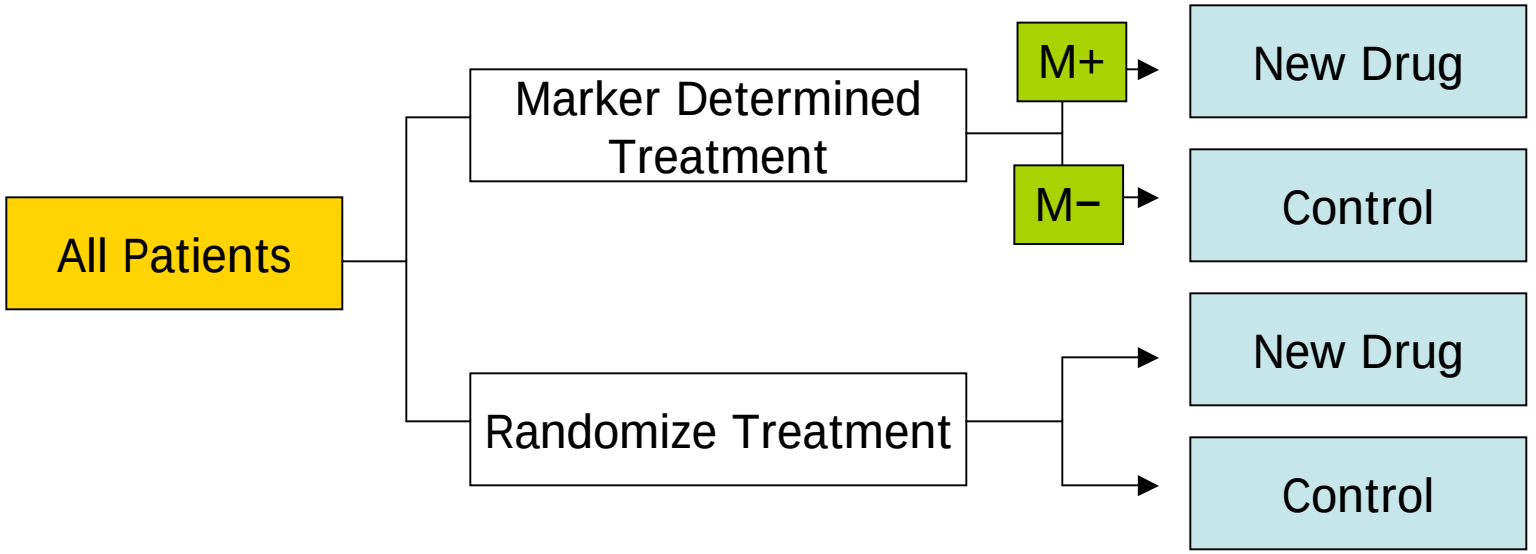


- Cannot Compare New Drug And Control In Marker Negative Patients
- What If New Drug Benefits Marker Negative Patients Too?
- May consider if ≥ 2 or more standard therapies equivalent in unselected patients

Predictive Marker Study Design

Marker-guided Vs. Randomized Design

Randomize To Use Of Marker Versus No Marker Evaluation



- Provides direct measure of patient willingness to follow marker-assigned therapy
- Marker guided treatment may be attractive to patients or clinicians
- Inefficient compared to completely randomized or randomized block design

Predictive Marker Study Design

- The completely randomized or randomized block designs offer the greatest flexibility to examine multiple markers
- Require no *a priori* assumptions, and are more efficient than marker-guided designs.
- Larger studies compared to enrichment studies or studies in unselected patients

Sample Size Considerations for Prognostic Marker Studies

- Often a two-group comparison between marker+ and marker- groups
- Power depends on

  Number of EVENTS (NOT sample size)

  Magnitude of effect (e.g., hazard ratio or survival difference)

  Distribution of marker (e.g., prevalence)

  Testing significance level (e.g., usually 0.05)

Sample Size Considerations for Predictive Marker Studies

- Testing for an interaction between marker status and treatment
- Power depends on

  Number of EVENTS and their distribution into marker-by-treatment categories

  Magnitude of effect (e.g., ratio of hazard ratios or difference of survival differences)

  significance level (e.g., usually 0.05)

- Test of interaction typically requires 2-4 times as many events as test for treatment main effect

Power Problems

- Embedding prognostic and predictive questions in "large" treatment trials
  - Events sufficient for answering treatment question, may be insufficient for prognostic or predictive questions in marker defined subgroups
  - Specimen retrieval and assay failures exacerbate sample size problem
- If initial trial does not provide definitive answer, may not be able to prospectively test marker question

Overcoming Sample Size Limitations

- Combine over multiple small studies
  - Patients and assays comparable?
  - Identify relevant studies?
    - Publication bias
    - Description limited
    - REMARK reporting guidelines (McShane et al, 2005: BJC, EJC, JCO, JNCI, NCPO) might help facilitate pooled analyses
- Some large prospective marker trials will be needed
  - MINDACT
  - TAILORx
  - N0723
- Reduce noise in marker measurements to lessen attenuation of marker effects
  - Assay improvements

Phase 2/3 Biomarker Summary

- Biomarkers focus on predicting benefit
  - Identifying patients more/less likely to benefit
  - Identifying evidence of anti-tumour activity
    - (surrogate marker)
- Randomized designs (experiment versus control) are best
  - Determine prognostic versus predictive
  - Assess and refine assay/biomarker
- Identifying predictive markers is most useful if the agent has evidence of activity

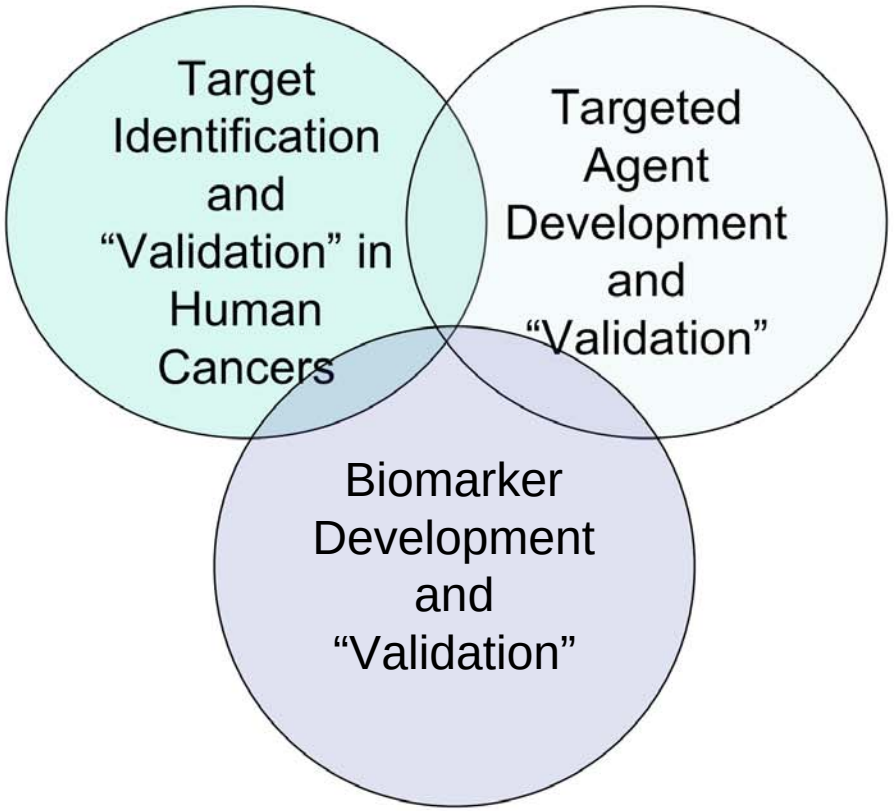
Biomarkers in Clinical Research: Implications

- Compelling rationale BUT
- Increased burden on patients/clinical staff
- Significant coordination effort required
- Significant increased cost over ‘traditional’ treatment trials
  - Numbers of patients may be increased and cost/patient will increase
- Qualification, standardization and QA takes time, energy and money

Biomarkers in Clinical Research: Efficiencies

- Phase I – proof of target inhibition after reaching biologically active dose/concentration
- Phase II – predictive marker assessment after identifying promising level of activity; studies should be larger and randomized
- Phase III – prospective testing of biomarker and treatment
- Phase IV – prospective testing of biomarker and treatment

Challenges/Opportunities



- Coordination of these processes is critical

Biomarkers in Clinical Trials: Summary

- Effective inclusion of biomarker studies in oncology clinical trials requires:
  - Clear and compelling hypothesis
    - Strong rationale based on experimentation and investigation
  - Well defined assay
    - Laboratory validation
    - Fit for use on clinical study
  - Well defined collection, storage, analysis
  - Well designed and executed clinical trial

HICT Program Vision Statement

To support clinical trials that will change how we prevent, diagnosis, monitor and treat cancer

Goal and Objectives

- To support high priority hypothesis-testing biomarker evaluations through well-designed and conducted clinical trials
  - To facilitate multi-disciplinary collaborations
  - To ensure reliable assays and imaging technologies
  - To ensure quantity and quality of biospecimens or imaging in trials
  - To ensure study population and trial design
  - To ensure efficient and effective execution of the trial
  - Promote research and identification of “best-practices” in biomarker clinical trials.

HICT Program

To assure that:

- The most promising concepts enter the developmental pathways that lead to clinical testing
- Concepts that do enter advance to the clinic testing or to productive failure
- Progress is as rapid, efficient, and effective as possible

OICR-HICT – Key Elements

- **Strategic Partnerships**
- **Coordinated Management**
- **Transparent Prioritization Process**
- **Tailored Funding**
- **Operational Effectiveness**
- **Training Programs and Career incentives**

Strategic Partnerships

- **OICR Programs, Platforms and Activities**
- **Ontario-Based Clinical Trial Organizations**
- **Laboratory and Imaging Researchers**
- **Bio-repositories and Pathologists**
- **Industry**
- **Cancer Care Ontario**
- **Government**
- **Foundations**

Coordinated Management

- OICR-Programs, Projects, Platforms, Activities
- CCO-OICR Experimental Therapeutics Network
  - Early trials of experimental therapeutics, diagnostics, imaging
  - Hub for information exchange, to encourage and facilitate multi-disciplinary, multi-institutional collaborations testing innovative technologies, therapeutics, trial designs.
  - Catalyst to initiate projects and needed collaborations.
- Academic-Industry

HICT will support translation of discoveries to and from OICR Innovative Programs and Platforms

- Innovation Projects
  - Ontario Cancer Cohort
    - Prevention, screening trials
  - Cancer Stem Cells: The GENESIS Project
    - Prognosis, treatment trials
  - Vulnerabilities in Cancer Genomes
    - Prognosis, prediction trials
  - Targeted agents and Bio/Immuno-therapy
    - Treatment, prediction trials

- Innovation Platforms
  - Imaging and Interventions
    - Evaluation,
    - Prognosis, prediction
  - Bio-repositories and Pathology
    - Evaluation, SOPs, assay,
    - Prognosis, prediction,
  - Genomics and High-Throughput Screening
    - Prognosis, prediction, therapeutic trials
  - Chemical Biology
  - Informatics and Bio-computing
    - Modeling, design
    - Prognosis, prediction

OICR Programs and Funded Activities that can support HICT

- OICR Clinical Trials Program
  SOPs, Education, Patient Recruitment, Coordination
- Ontario Cancer Research Ethics Board (OCREB)
- Cancer Research Fund (CRF)
- Ontario Tumour Bank (OTB)
- Ontario Cancer Biomarker Network (OTBN)
- Ontario Translational Research Network (OTRN)

Transparent Prioritization Process

- Scientific validity
- Feasibility
- Clinical need and Opportunity for impact on health/wellbeing of cancer patients
- Multi-disciplinary collaboration
- Priority for OICR and Partners
- Availability of resources/funding from collaborators
- Ontario-Based Investigator(s)/Activities
  - Includes national and international collaborations

HICT Tailored Funding

- **Support** evaluation, laboratory validation, and clinical qualification of diagnostic, prognostic, predictive tissue, blood, imaging markers in high priority clinical trials

  - **Personnel**: pathologists, pharmacologists, imagers, CRAs, laboratory staff, biostatisticians, trial operations staff, regulatory staff for imaging/diagnostics, project managers

  - **Resources**: equipment, GMP/GLP up grades and other preclinical services, sops, education for next generation of research trials.

  - **Specimen** collection, processing, storage, and analysis

Operational Effectiveness

- Project management
- Core services coordination
- Enhance biorepositories
- Improve contract negotiations
- Enhance collaborations
- SOP development/implementation

Career Incentives and Training programs

- OICR-HICT Clinician Scientists
  3 positions
- CCO Experimental Therapeutics Chairs
  5-6 positions
- Workshops on state of science and technology in priority areas
  Eg. Circulating Tumour cells Workshop, March 28, 2008
- Fellowship funding
  Eg. ECCO-NCI-AACR Workshop on Clinical Trials Methods (Flims 2009)

High Impact Clinical Trials

- **Implementation**
  - Explore interests/opportunities with strategic partners
  - Define structure/governance
    - Scientific Advisory Board
    - Review/approval of projects
  - Identify resource needs of strategic partners
  - Identify translational research/trial opportunities of mutual interest
  - Select projects
    - Proposals, timelines, milestones, resources

High Impact Clinical Trials

- Best questions
- Best interventions
- Best trial designs
- Best result