Breakout sessions 2A & 2B – Disease Classifiers & Prognostic Assays

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Charge to Breakout Group #2

- Define criteria for clinical utility for prognostic and classifier assays.
- Flavors of clinical utility
- Issues other than test performance
- What evidence is necessary to confirm clinical validity?
- Role of NCI and other groups?

Continuum of Cancer Testing

- Susceptibility and risk of getting disease (germ line)
- Prognosis
- Diagnosis / Classifier
- Prediction of response to therapy
- Monitoring disease response / recurrence

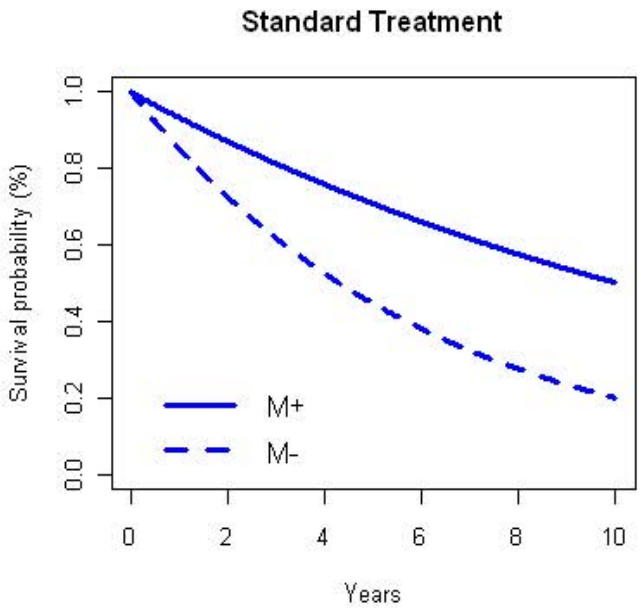
Clinical Utility

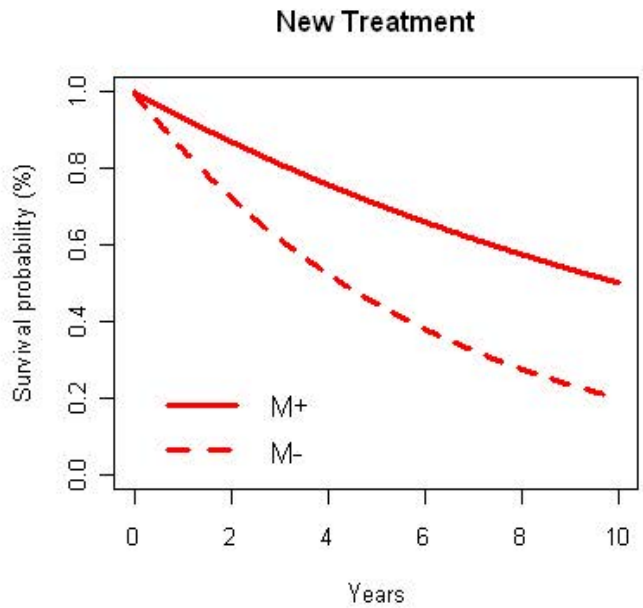
A. Classificaton / Diagnosis only without further prognostic, management, or predictive (therapeutic) implications
B. Purely prognostic (no treatment -- surgery only)
C. Prognostic within homogeneous (standard) therapy
D. Diagnostic classifier with prognostic or predictive implications
E. Predictive markers which identify optimal therapy or targeted therapy
F. Markers of tumor recurrence which indicate further diagnostic or treatment steps

(III)

prognostic

~~predictive~~

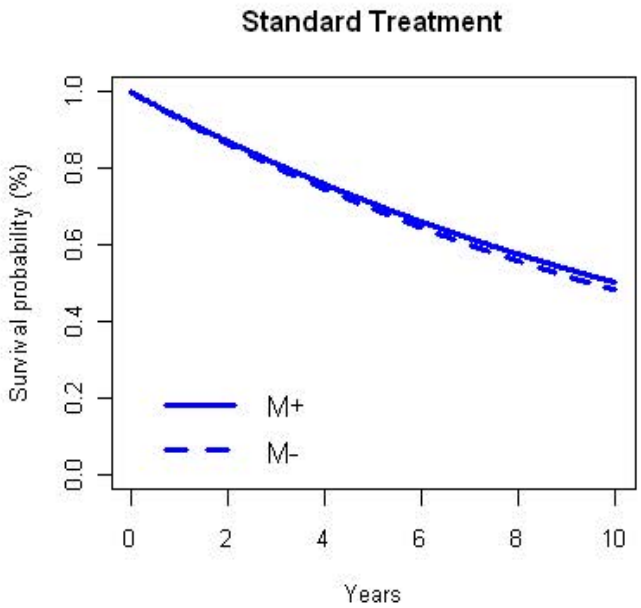


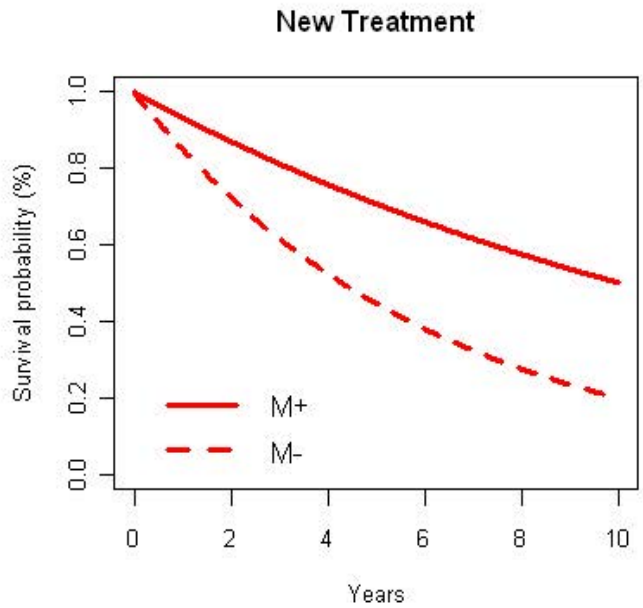


(IV)

~~prognostic~~

predictive





Statistical Principles for Developing Prognostic Signatures

1. Patient selection should be based on intended use of the prognostic signature.
2. The signature must be validated on at least one independent dataset.
3. The new signature should show better performance than other standard variables.
4. Hazard ratios and regression coefficients are measures of association, not of predictive power.

The definition of clinical utility – When is a test useful?

- It is actionable. Drives a treatment/management decision.
- Assists in difficult clinical decision re treatment (yes or no, which one)
- Current clinical and laboratory indicators are not sufficient to make management decision
- New test is better: performance (sensitivity and specificity), less invasive (blood test vs. biopsy), less costly (more available)

Why do we care about clinical utility?

- Provide the best clinical care to each cancer patient. Standards of medical care.
- Prioritization of resources for research and clinical care
- Payor reimbursements are based on guidelines and outcomes
- Affordable Care Act will drive testing towards clinical utility through health economics

When is a classifier or prognostic assay clinically useful?

- Is a purely prognostic assay ever clinically useful, even if it does not affect clinical management directly? (Patient need? Who pays?)
- **Tumor staging: AJCC staging is beginning to include tumor markers for some tumor types, moving beyond anatomical TNM staging only.**
- Decision to treat or not to treat
- Choice of therapy (how aggressive, gene targeted)
- Assay result indicates next steps in diagnosis or treatment
- Is qualification for a clinical trial in and of itself sufficient clinical utility to release a test to the community?

What other factors may be in play?

- Drug efficacy, toxicity, cost, QOL issues
- Assay cost
- Assay portability
- Guidelines for use
- Other assays available currently in use for same clinical indication (none or many?)
- Size of the market (rare disease or common tumor type)?

What do we need to know about a test to determine its utility?

- Performance characteristics
- Clinical validity vs. clinical utility
  - Clinical Validity = sensitivity, specificity, pos/neg predictive value
  - Clinical Utility = effect on clinical management and outcome
  - Requirement for clinical effectiveness may vary with context (companion vs. LDT)
  - Evidence of clinical utility may vary over time (may strengthen or weaken, like therapeutics.) Need for post-marketing review?

What do we need to know about a test to determine its utility?

- Test performance in the context in which it will be used (tumor type, stage, …)
  - Does is work with the specimens of choice?
  - Does it define the population of interest (e.g. prevalence of HepB in Asia vs. US)
  - Outcome: has it been demonstrated that the identified population benefits from one treatment vs another

What do we need to know about a test to determine its utility?

- Quantitation of Clinical Utility – how much difference between groups is needed to establish clinical utility?
- There is no single answer
  - Each tumor type different
  - Depends on treatment efficacy and toxicity
  - Patient context may drive “degree” of utility
  - Economic impact

Companion Diagnostics

- Approval of Companion Diagnostic establishes clinical utility (prediction).
- How to establish acceptability of equivalent platforms?
  - Examples: Sequencing vs. PCR, NGS vs. Sanger, even equivalent PCR assays
  - Test trial samples using new platform?
  - Show analytic equivalence?

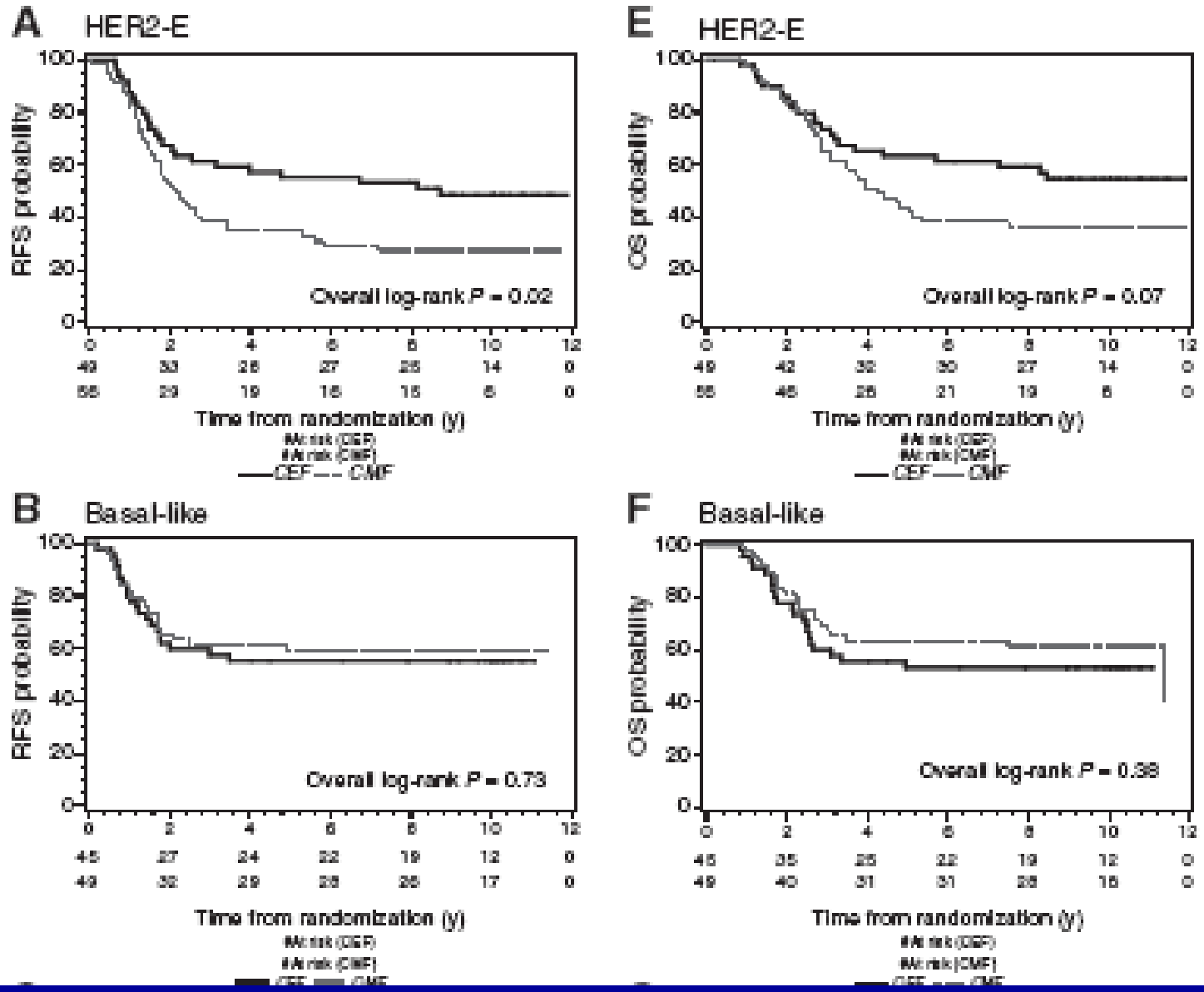
Companion diagnostics versus disease classifier-based decision aids

Companion diagnostic

- New agents in development needs enrichment strategy
- Successful examples are mostly single gene traits and single agents (ALK, RAF, EGFR, BCR-ABL, cKIT)
- Pharma funds development hand in hard with agent development
- No real savings to the health care system as new drugs are expensive
- Regulatory pathway is FDA

Genomic Clinical Decision Aid

- Focused on generic agents with marginal risk-benefit ratio (multi-agent chemotherapy, radiotherapy)
- Multi-gene assays requiring complex diagnostics and computational biology and LDT route
- Successful examples limited (Oncotype) and rely on describing known biology better than qualitative pathology
- Best models incorporate known prognostic factors (stage)
- Funding model more limited, no Pharma, development needs public private -partnerships
- Rather than retrospective trials, NCI could fund more discovery efforts that are aimed to develop genomic decision-aids in a concerted fashion using next generation discovery tools
- Better decision aids may not improve cancer survival but can improve risk benefit ration, quality of life and these should be measured


A
HER2-E
RFS probability
Overall log-rank P = 0.02
Time from randomization (y)
CEF
CMF
E
HER2-E
OS probability
Overall log-rank P = 0.07
Time from randomization (y)
CEF
CMF
B
Basal-like
RFS probability
Overall log-rank P = 0.73
Time from randomization (y)
F
Basal-like
OS probability
Overall log-rank P = 0.38
Time from randomization (y)

NCI Role

- Support generation of TCGA-like omics data for cooperative group trials. Piggy back efforts in subset of Trial patients will allow clinical utility to be investigated.
- Promote **rapid** reporting of marker analyses from cooperative group trials.
- Support cooperative group and other banking efforts for tumor DNA, RNA, blood, etc.

NCI and other Orgs

- Facilitate linkage of data between the community and diagnostic industry to leverage depth of data available in each
- Foundations and advocacy groups to support marker studies in association with clinical trials.
- Professional societies to coordinate activities for guidelines, standards, etc. Identify gaps.
- Tumor staging guidelines to evolve to combined anatomic and molecular systems

Recommendations to NCI

- Continue to improve cooperative group tissue banking and clinical trials activities.
- Apply TCGA-like approach to establish clinical utility using cooperative group trials and specimens.
- Emphasize clinical utility in reviews of translational science / tumor marker proposals.

Thanks