“Negative” RCTs: Enriching and Improving

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GSK,
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Enriching and Improving

- Enrichment strategies for efficient testing of new treatments
  - Prognostic enrichment
  - Predictive enrichment

- Examples
  - ARDS
  - Pediatric sepsis
  - Trauma
Enrichment is defined as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.
Enrichment Strategies

• Decrease heterogeneity (noise) of enrolled subjects – common to nearly all efficacy studies
  • Fashion entry criteria to assure patients within a syndrome have the targeted biologic process
  • Exclude patients likely to die prior to exposure
  • Exclude concomitant medications with similar effects
  • Eliminate placebo responders with run-in
  • Exclude patients with unstable baseline
  • Etc. etc. etc.
Enrichment Strategies

• Prognostic enrichment
  • Choosing patients with a greater likelihood of having a disease-related endpoint (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints)
  • Increase the absolute effect difference between groups but will not alter relative effect
• An excellent example of prognostic enrichment
• FDA approved 70-gene microarray (MammaPrint®) for clinical detection of high risk women with breast cancer in 2014
Preoperative PSA Velocity and the Risk of Death from Prostate Cancer after Radical Prostatectomy

Anthony V. D'Amico, M.D., Ph.D., Ming-Hui Chen, Ph.D., Kimberly A. Roehl, M.P.H., and William J. Catalona, M.D.
Enrichment Strategies

• Predictive enrichment
  • Choosing patients more likely to respond to the drug treatment.
    • Increases both absolute and relative effects and reduces sample size
  • Selection of patients could be based on:
    • A patient’s physiology or a disease characteristic related to the study drug’s mechanism
    • Empiric (e.g., the patient has previously appeared to respond to a drug in the same class)
Table 1. Response rate of successful targeted therapies in molecularly-selected populations evaluated in early clinical trials

<table>
<thead>
<tr>
<th>Marker/population</th>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 overexpressed/amplified breast cancer</td>
<td>Trastuzumab</td>
<td>anti-HER2 antibody</td>
<td>12%</td>
<td>[6]</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab-DM1</td>
<td>anti-HER2 antibody + drug conjugate</td>
<td>44%</td>
<td>[12]</td>
</tr>
<tr>
<td>CD117 overexpressed GIST</td>
<td>Imatinib</td>
<td>c-KIT, PDGFR inhibitor</td>
<td>54%</td>
<td>[13]</td>
</tr>
<tr>
<td>BRCA1/2 mutant breast, ovarian and prostate cancer</td>
<td>Olaparib</td>
<td>PARP inhibitor</td>
<td>47%</td>
<td>[7]</td>
</tr>
<tr>
<td>BRAF V600E mutant melanoma</td>
<td>Vemurafenib</td>
<td>BRAF inhibitor</td>
<td>75%</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>Dabrafenib</td>
<td>BRAF inhibitor</td>
<td>60%</td>
<td>[14]</td>
</tr>
<tr>
<td>Basal cell carcinomas (majority have inactivating mutations in PTC1 or activation of SMO)</td>
<td>Vismodegib</td>
<td>SMO inhibitor (Hh pathway)</td>
<td>58%</td>
<td>[15]</td>
</tr>
<tr>
<td>ALK rearranged NSCLC</td>
<td>Crizotinib</td>
<td>ALK, MET inhibitor</td>
<td>57%</td>
<td>[9]</td>
</tr>
<tr>
<td>Medullary thyroid cancer (known to have RET mutations, MET expression and VEGF activation)</td>
<td>Cabozantinib</td>
<td>MET, VEGFR2, RET inhibitor</td>
<td>29%</td>
<td>[16]</td>
</tr>
<tr>
<td>PIK3CA mutant breast cancer</td>
<td>BYL719</td>
<td>selective PI3K alpha inhibitor</td>
<td>44%</td>
<td>[10]</td>
</tr>
<tr>
<td>FGFR1 or FGFR amplified breast cancer</td>
<td>E-3810</td>
<td>FGFR, VEGFR inhibitor</td>
<td>70%</td>
<td>[11]</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; GIST, gastrointestinal stromal tumor; Hh, hedgehog; MET, mesenchymal epithelial transition; NSCLC, nonsmall cell lung cancer; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; SMO, smoothered; VEGF, vascular endothelial growth factor.

* Tumor shrinkage > 20%.
Additional examples of predictive enrichment

- High-rennin status and response to ACEI and ARBs
- Cystic fibrosis genotype
  - Ivacaftor (4% with G551D)
  - Lumacaftor/Ivacaftor (48% with F508del/F508del)
- Atopic Asthma Endotype
  - Omalizumab (αIgE), Mepolizumab (αIL-5), Dupilumab (α IL-4), Lebrikizumab (α IL-13)
• Double-blind RCT
• 104 patients with moderate/severe persistent asthma
• Atopic endotype = elevated serum eosinophil counts

A Exacerbations — Primary End Point

87% reduction
p<0.001

NEJM 2013
Biomarker enrichment strategies: matching trial design to biomarker credentials

Boris Freidlin and Edward L. Korn

NATURE REVIEWS 2014

Diagram:

a) Evaluate biomarker
   - Biomarker positive
     - Randomize
       - New treatment
       - Standard treatment
   - Biomarker negative
     - Off study

b) Evaluate biomarker
   - Biomarker positive
     - Randomize
   - Biomarker negative
     - Randomize
Prognostic and/or Predictive Enrichment in Critical Care?
Prognostic Enrichment with the Berlin Definition

ARDS
N=3670

Mild
27%*

Moderate
32%

Severe
45%

*Mortality

Rubenfeld, Ranieri, Thompson, et al  JAMA 2012
• Enrolled ARDS patients with P/F < 150
• High event rate and +/- significant effect size
✓ Prognostic enrichment
Enrolled patient with P/F < 150 (mean ~100) and found both a high event rate and a large effect

- Prognostic enrichment
- Predictive enrichment
Is the Severe ARDS classification a form of predictive enrichment?

Rubenfeld JAMA 2012, Gattinoni NEJM 2006
Mortality Probability Depends on P/F response to PEEP

Potential for Predictive enrichment

Goligher AJRCCM 2012
Predictive Enrichment in ARDS

- Enrichment by P/F (or change in P/F) or mortality risk (APACHE or MODS) are sensible approaches.

- As for sepsis, pharmacologic therapy will likely require enrichment strategies targeting the underlying disease mechanisms.
Low Vt beneficial for all subsets

Eisner et al.  AJRCCM 2001
Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

- Latent class analysis (LCA) on two separate cohorts of patients with ARDS enrolled in clinical trials
- Conducted using baseline data only (clinical + biomarker data) and NOT clinical outcomes
- Agnostic to prior beliefs and biases
- Does class assignment predict response to treatment?
ARDSnet 01 Cohort, Continuous Variables

Nearly identical findings in ALVEOLI
Response to PEEP Differs By Endotype

- Significant interaction for mortality ($p=0.049$)

<table>
<thead>
<tr>
<th></th>
<th>Mortality in Class 1 (n=404)</th>
<th>Mortality in Class 2 (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low PEEP</td>
<td>16%</td>
<td>51%</td>
</tr>
<tr>
<td>High PEEP</td>
<td>24%</td>
<td>40%</td>
</tr>
</tbody>
</table>

✓ Prognostic and Predictive Enrichment

Calfee CS et al, Lancet Resp Med 2014
Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong¹,², Natalie Z. Cvijanovich³, Nick Anas⁴, Geoffrey L. Allen⁵, Neal J. Thomas⁶, Michael T. Bigham⁷,

• **Goal:** Develop a clinical test that meets the time sensitive demands of the critically ill patient
• Reduced the subclass-defining gene signature to the top 100 class-predictor genes
• Express the 100 genes using the “gene expression dynamics inspector”
Pediatric Septic Shock Endotypes

- The genes that enable sub classification correspond to adaptive immunity and the glucocorticoid receptor signaling pathway (repressed in high mortality subclass A).
- The use of corticosteroids is independently associated with 4 times the risk of dying in the subclass A patients.

✓ Prognostic and Predictive Enrichment
A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set

13 May 2015

Timothy E. Sweeney,¹,²* Aaditya Shidham,² Hector R. Wong,³,⁴ Purvesh Khatri²,⁵*

![Graph showing PCA analysis of SIRS/trauma and Sepsis data.](attachment:image.png)
Prognostic and Predictive Enrichment: Summary

- Requires a better understanding of underlying disease mechanisms
- Advances in bedside (companion) diagnostics will enable enrichment strategies
- Potential to reduce both population and treatment heterogeneity
- May improve efficiency of clinical trials
Thank you