Leveraging AI in multi-omics oncology

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- Evanthia Roussos-Torres
- Karam Ashouri
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- Joshua Millstein

#### mCRC clinical trials with molecular data

<table>
<thead>
<tr>
<th>Clinical trial/Study name (phase) [country]</th>
<th>Treatment</th>
<th>Clinical Outcome</th>
<th>Oncoarray (GWAS)</th>
<th>Gene expression</th>
<th>Mutation panel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRE-3 (III) [Germany]</strong></td>
<td>FOLFIRI/CET (N=260)</td>
<td>PFS, OS, TR</td>
<td>✓</td>
<td>✓ (hTG)</td>
<td>KRAS wildtype</td>
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<tr>
<td></td>
<td>FOLFIRI/BEV (N=260)</td>
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<tr>
<td><strong>TRIBE (III) [Italy]</strong></td>
<td>FOLFOXIRI/BEV (N=230)</td>
<td>PFS, OS, TR</td>
<td>✓</td>
<td>✓</td>
<td>KRAS, NRAS, BRAF</td>
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<tr>
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<td>FOLFIRI/BEV (N=230)</td>
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<td><strong>MAVERICC (II) [USA]</strong></td>
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<td>✓ (Nano)</td>
<td>NGS</td>
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<td>KRAS, NRAS, BRAF</td>
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<tr>
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<td><strong>VALENTINO (II) [Italy]</strong></td>
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<td>RAS, BRAF wildtype</td>
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<td><strong>MSI-H CRC (retrospective) [Italy]</strong></td>
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<td>MSI, KRAS, NRAS, BRAF</td>
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<td><strong>JACCRO-CC05/06 (II) [Japan]</strong></td>
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<td>RAS mutant</td>
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<td><strong>PANAMA (II) [Germany]</strong></td>
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<td>PFS, OS, TR</td>
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<td>RAS wildtype</td>
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<tr>
<td><strong>CALGB/SWOG080405 Alliance (III) [USA]</strong></td>
<td>CHEMO/BEV (N=315)</td>
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<td>CHEMO/CET (N=321)</td>
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<td>OS, ToT</td>
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<td>WES</td>
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</table>
Objectives for the high-dimensional molecular data

• **Biomarker development**
  - Predictive (predicts response to treatment)
  - Prognostic (predicts outcome)

• **New target identification**
Leveraging computational algorithms to identify patterns in molecular data

**Conventional approach:**

1. Hypothesis
2. Model
3. Experimental design
4. Data collection
5. Hypothesis testing

**Data-driven paradigm:**

1. Data resource
2. Training
3. Testing
4. Objectives
5. Computational algorithms
6. Predictive models
Gene expression networks to predict response to FOLFIRI vs FOLFOX

Step 1. Overall survival ~ coexpression treatment

Step 2. Network components

Step 3. Elastic net (or other ML algorithm)

Step 4. Biomarker score for FOLFOX – FOLFIRI
Prognostic gene expression signature for overall survival

• **Biomarker development**
  – Predictive (predicts response to treatment)
  – Prognostic (predicts outcome)

• **Machine learning approaches to predict 2 yr and 5 yr OS**
  – Backward stepwise regression after filtering
  – Elastic net
  – Survival random forests
  – Gradient boosting


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Prognostic gene expression signature for overall survival

- 276 of 513 genes replicated with FDR < 0.05 for OS

FP


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