Biomarkers in Practice: A Review of Outcomes & Reimbursement Issues

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Disclosures

• Nothing to Disclose
Objectives

1. Summarize The Role of Biomarkers in Cancer Treatments
2. Review Outcomes with Biomarkers and Chemotherapy Treatment
3. Examine issues with Biomarker Reimbursement
Phase Two: Interpretation

I think I found a corner piece.
Human Genome
Changes in Sequencing
The Genome is Who We Are on the inside!

- Chromosomes consist of DNA
  - molecular strings of A, C, G, & T
  - base pairs, A-T, C-G

- Genes
  - DNA sequences that encode proteins
  - less than 3% of human genome
Beyond the genome

Same genome
Different proteome
Biomarker Development
Tumor Biomarkers

• Produced by the tumor cells and enters the circulation
• Present at low levels in the serum of healthy individuals and those with benign disease but increases substantially in cancer (preferably in one cancer type only)
• Easily quantifiable with an inexpensive assay
• Present in detectable (or higher than normal) quantities at early or preclinical stages
• Quantitative levels of the tumor marker reflect the tumor burden
• High diagnostic sensitivity (few false negatives) and specificity (few false positives)
Biomarker Definitions

• Genomic
  – DNA based analysis (i.e., SNP’s)
• Transcriptome
  – RNA expression profiles
• Proteomic
  – Protein Profiles
• Metabolomic
  – Metabolite profiles
Developing Candidate Biomarkers

- Identification of candidate markers: cDNA microarray
- Verification of sequence: Clone sequence
- Corroboration at mRNA expression level: Oligonucleotide arrays (Affymetrix)
- Corroboration at level of protein expression: Reverse-phase protein lysate array
- Prospective validation by screening of clinical tumours: Tissue microarray
Biomarkers in Development

![Graph showing the number of cancer-related biomarker publications and approved plasma-protein markers from 1994 to 2003. The graph indicates an increasing trend in both categories over the years.](image-url)
Translation of Biomarkers in Cancer

![Diagram showing the translation of biomarkers in cancer](image)

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**Example: Breast Cancer**

- **Clinical methods**:
  - Family history
  - Mammography, breast examination
  - Physical examination, imaging, biopsy, nodal status, histological grade

- **Biomarker**:
  - **BRCA1, BRCA2**: None
  - **ER, PR, HER2/NEU (IHC or FISH)**: Molecular subclassification, PET scanning
  - **CA15-3**: Physical examination, imaging
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
<th>Source</th>
<th>Cancer type</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Fetoprotein</td>
<td>Glycoprotein</td>
<td>Serum</td>
<td>Nonseminomatous testicular</td>
<td>Staging</td>
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<tr>
<td>Human chorionic gonadotropin-β</td>
<td>Glycoprotein</td>
<td>Serum</td>
<td>Testicular</td>
<td>Staging</td>
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<tr>
<td>CA19-9</td>
<td>Carbohydrate</td>
<td>Serum</td>
<td>Pancreatic</td>
<td>Monitoring</td>
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<td>CA125</td>
<td>Glycoprotein</td>
<td>Serum</td>
<td>Ovarian</td>
<td>Monitoring</td>
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<td>Pap smear</td>
<td>Cervical smear</td>
<td>Cervix</td>
<td>Cervical</td>
<td>Screening</td>
</tr>
<tr>
<td>CEA</td>
<td>Protein</td>
<td>Serum</td>
<td>Colon</td>
<td>Monitoring</td>
</tr>
<tr>
<td>Epidermal growth factor receptor</td>
<td>Protein</td>
<td>Colon</td>
<td>Colon</td>
<td>Selection of therapy</td>
</tr>
<tr>
<td>KIT</td>
<td>Protein (IHC)</td>
<td>Gastrointestinal tumour</td>
<td>GIST</td>
<td>Diagnosis and selection of therapy</td>
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<tr>
<td>Thyroglobulin</td>
<td>Protein</td>
<td>Serum</td>
<td>Thyroid</td>
<td>Monitoring</td>
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<tr>
<td>PSA (total)</td>
<td>Protein</td>
<td>Serum</td>
<td>Prostate</td>
<td>Screening and monitoring</td>
</tr>
<tr>
<td>PSA (complex)</td>
<td>Protein</td>
<td>Serum</td>
<td>Prostate</td>
<td>Screening and monitoring</td>
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<tr>
<td>PSA (free PSA %)</td>
<td>Protein</td>
<td>Serum</td>
<td>Prostate</td>
<td>Benign prostatic hyperplasia versus cancer diagnosis</td>
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<tr>
<td>CA15-3</td>
<td>Glycoprotein</td>
<td>Serum</td>
<td>Breast</td>
<td>Monitoring</td>
</tr>
<tr>
<td>CA27-29</td>
<td>Glycoprotein</td>
<td>Serum</td>
<td>Breast</td>
<td>Monitoring</td>
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<tr>
<td>Cytokeratins</td>
<td>Protein (IHC)</td>
<td>Breast tumour</td>
<td>Breast</td>
<td>Prognosis</td>
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<td>Oestrogen receptor and progesterone receptor</td>
<td>Protein (IHC)</td>
<td>Breast tumour</td>
<td>Breast</td>
<td>Selection for hormonal therapy</td>
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<td>HER2/NEU</td>
<td>Protein (IHC)</td>
<td>Breast tumour</td>
<td>Breast</td>
<td>Prognosis and selection of therapy</td>
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<td>HER2/NEU</td>
<td>Protein</td>
<td>Serum</td>
<td>Breast</td>
<td>Monitoring</td>
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<tr>
<td>HER2/NEU</td>
<td>DNA (FISH)</td>
<td>Breast tumour</td>
<td>Breast</td>
<td>Prognosis and selection of therapy</td>
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<tr>
<td>Chromosomes 3, 7, 9 and 17</td>
<td>DNA (FISH)</td>
<td>Urine</td>
<td>Bladder</td>
<td>Screening and monitoring</td>
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<td>NMP22</td>
<td>Protein</td>
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<td>Bladder</td>
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<td>Fibrin/FDP</td>
<td>Protein</td>
<td>Urine</td>
<td>Bladder</td>
<td>Monitoring</td>
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<tr>
<td>BTA</td>
<td>Protein</td>
<td>Urine</td>
<td>Bladder</td>
<td>Monitoring</td>
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<tr>
<td>High molecular weight CEA and mucin</td>
<td>Protein (Immunofluorescence)</td>
<td>Urine</td>
<td>Bladder</td>
<td>Monitoring</td>
</tr>
</tbody>
</table>

BTA, bladder tumour-associated antigen; CA, cancer antigen; CEA, carcinoembryonic antigen; FDP, fibrin degradation protein; FISH, fluorescent in-situ hybridization; GIST, gastrointestinal stromal tumour; IHC, immunohistochemistry; NMP22, nuclear matrix protein 22; PSA, prostate-specific antigen.
Current applications of tumor markers and their limitations

<table>
<thead>
<tr>
<th>Application</th>
<th>Current usefulness</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population screening</td>
<td>Limited</td>
<td>A screening test should have very high sensitivity and exceptional specificity, to avoid too many false positives in populations with a low cancer prevalence. The test must demonstrate a benefit in terms of clinical outcome. Current biomarkers suffer from too low diagnostic sensitivity and specificity to serve as screening markers. Except for PSA, current tumor markers are more frequently elevated at late stages of disease.</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Limited</td>
<td>Current biomarkers suffer from too low diagnostic sensitivity and specificity to serve as diagnostic markers.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Limited</td>
<td>Most cancer markers have some prognostic value. Specific therapeutic interventions cannot be determined because the accuracy of prediction of current markers is rather poor.</td>
</tr>
<tr>
<td>Prediction of therapeutic response</td>
<td>High</td>
<td>Very few markers have predictive power (exceptions include steroid hormone receptors and HER2 amplification for breast cancer), but the information they provide aids therapy selection.</td>
</tr>
<tr>
<td>Tumor staging</td>
<td>Limited</td>
<td>Besides AFP and HCG, the accuracy of the markers in determining tumor stage is poor.</td>
</tr>
<tr>
<td>Detecting early tumor recurrence</td>
<td>Controversial</td>
<td>Lead time is short and does not considerably affect outcome. Clinical relapses could occur without biomarker elevation. Biomarker elevation can be nonspecific.</td>
</tr>
<tr>
<td>Monitoring effectiveness of cancer therapy</td>
<td>High</td>
<td>Current biomarkers provide information on therapeutic response (effective or noneffective) that is readily interpretable and more economical than imaging modalities.</td>
</tr>
</tbody>
</table>

70 prognosis genes are involved in all aspects of tumor cell biology.
70 Gene Prognosis Profile

van ‘t Veer et al., Nature 415, p. 530-536, 2002

Threshold set with 10% false negatives
91 % sensitivity, 73% specificity
Proteins as biomarkers

The protein composition may be associated with disease processes in the organism and thus have potential utility as diagnostic markers.

1. Proteins are closer to the actual disease process, in most cases, than parent genes
2. Proteins are ultimate regulators of cellular function
3. Most cancer markers are proteins
4. The vast majority of drug targets are proteins

Biomarker discovery

• Markers can be easily found by comparing protein maps.
• SELDI is faster and more reproducible than 2D PAGE.
• Has been being used to discover protein biomarkers of diseases such as ovarian cancer, breast cancer, prostate and bladder cancers.

Non-coding RNA: the NA formerly known as “junk”

RNA Transcripts

Protein-coding mRNA

Non-coding RNA Transcripts

Regulatory RNA
- miRNA
- siRNA
- piRNA
- Anti-sense RNA

snoRNAs

Housekeeping RNAs
- tRNA
- rRNA
- snRNA
- tmRNA
- Rnase P RNA
- vRNAs
- gRNAs
- MRP RNA
- SRP RNAs
- Telomerase RNA

• Transcription/chromatin structure regulators
• Translational regulators
• Protein function modulators
• RNA/Protein localization regulators

NC-RNAs compose majority of transcription in complex genomes
Unique MicroRNA Profile in Lung Cancer Diagnosis and Prognosis

- miRNAs are small non-coding RNAs which play key roles in regulating the translation and degradation of mRNAs

- Genetic and epigenetic alteration may affect miRNA expression, thereby leading to aberrant target gene(s) expression in cancers

- Yanaihara et al, Cancer Cell, 2006:
  - miRNA profiles of 104 pairs of primary lung cancers and corresponding non-cancerous lung tissues were analyzed by miRNA microarrays
  - 43 miRNAs showed statistical differences
Unique MicroRNA Profile in Lung Cancer Diagnosis and Prognosis

- A univariate Cox proportional hazard regression model with a global permutation test indicated that expression of the miRNAs hsa-mir-155 and hsa-let-7a-2 was related to adenocarcinoma patient outcome.

- Lung adenocarcinoma patients with either high hsa-mir-155 or reduced hsa-let-7a-2 expression had poor survival.

<table>
<thead>
<tr>
<th>microRNAs</th>
<th>Tumorigenesis</th>
<th>Diagnosis</th>
<th>Prognosis</th>
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</thead>
<tbody>
<tr>
<td>miR-9</td>
<td>Neuroblastoma</td>
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<tr>
<td>miR-10b</td>
<td>Breast cancer</td>
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<tr>
<td>miR-15, miR-15a</td>
<td>Leukemia, pituitary adenoma</td>
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<td>miR-16, miR-16-1</td>
<td>Leukemia, pituitary adenoma</td>
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<tr>
<td>miR-17-5p, miR-17-92</td>
<td>Lung cancer, lymphoma</td>
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<tr>
<td>miR-20a</td>
<td>Lymphoma, lung cancer</td>
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<tr>
<td>miR-21</td>
<td>Breast cancer, cholangiocarcinoma, head &amp; neck cancer, leukemia</td>
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<td>Pancreatic cancer</td>
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<tr>
<td>miR-29, miR-29b</td>
<td>Leukemia, cholangiocarcinoma</td>
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<td>miR-31</td>
<td>Colorectal cancer</td>
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<td>miR-34a</td>
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<td>miR-96</td>
<td>Colorectal cancer</td>
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<td>Neuroblastoma</td>
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<tr>
<td>miR-98</td>
<td>Head &amp; neck cancer</td>
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<td>miR-103</td>
<td>Pancreatic cancer</td>
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<td>miR-107</td>
<td>Leukemia, pancreatic cancer</td>
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<td>miR-125a, miR-125b</td>
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<td>miR-128</td>
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<td>miR-133b</td>
<td>Colorectal cancer</td>
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<td></td>
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<td>Colorectal cancer</td>
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<td>miR-143</td>
<td>Colon cancer</td>
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<td>miR-145</td>
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<td>miR-146</td>
<td>Thyroid carcinoma</td>
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<tr>
<td>microRNAs</td>
<td>Tumorigenesis</td>
<td>Diagnosis</td>
<td>Prognosis</td>
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<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------</td>
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<td>miR-155, has-miR-155</td>
<td>Breast cancer, leukemia, pancreatic cancer</td>
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<td>Lung cancer</td>
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<tr>
<td>miR-181, imR-181a, imR-181b, imR-181c</td>
<td>Leukemia, glioblastoma, thyroid carcinoma</td>
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<td>miR-183</td>
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<td>miR-184</td>
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<td>miR-193</td>
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<td>miR-196a-2</td>
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<tr>
<td>miR-221</td>
<td>Glioblastoma, thyroid carcinoma</td>
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<td>Pancreatic cancer</td>
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<tr>
<td>miR-222</td>
<td>Thyroid carcinoma</td>
<td></td>
<td></td>
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<tr>
<td>miR-223</td>
<td>Leukemia</td>
<td></td>
<td></td>
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<td>miR-301</td>
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<td>Pancreatic cancer</td>
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<tr>
<td>miR-376</td>
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<td>Pancreatic cancer</td>
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<tr>
<td>let-7, let-7a, let-7a-1, has-let-7a-2, let-7a-3</td>
<td>Lung cancer, colon cancer</td>
<td></td>
<td>Lung cancer</td>
</tr>
</tbody>
</table>
Outcomes with Biomarkers

“90% of the game is half-mental”-Yogi Berra
Outcomes & Biomarkers

- CML
  - T315I
- Melanoma
  - BRAFV600E
- Colorectal Cancer
  - Kras mutation
- Many others to follow
Targets of Cancer Therapy

- Growth factors
- Growth factor receptors
- Adaptor proteins
- Docking proteins/binding proteins
- Guanine nucleotide exchange factors
- Phosphatases and phospholipases
- Signaling kinases
- Ribosomes
- Transcription factors
- Histones
- DNA
- Transcription
gene expression
- RNA translation
- Microtubule dynamics
- Nuclear membrane
- Plasma membrane
- DNA replication and repair
- Expression factors
- Transcription factors
- Histones
- DNA
- Plasmids
- Microtubules
- Cell growth
- Motility
- Survival
- Proliferation
- Angiogenesis
Conventional cancer treatment:

Diagnosis
- Stage, Grade, IHC

Rx
- Treatment
  - Chemotherapy

Personalized cancer treatment:

Diagnosis:
- Molecular diagnostics
  - Which pathways are active?

Rx
- Treatment:
  - Pathway targeted therapy
Epidermal Growth Factor Receptor (EGFR)

- Transmembrane growth factor receptor with tyrosine kinase activity
  - HER1 (ERBB1), belongs to HER/ErbB family
  - Selectively binds 10 different ligands
  - After binding, forms dimers that causes autotransphosphorylation through intrinsic tyrosine kinase on cytoplasmic domain
EGFR

- EGFR is overexpressed in more than 85% of tumors from patients with metastatic CRC.
- Only a subset of patients with mCRC achieve a clinical benefit from treatment with EGFR inhibitors.
- Why?
**RAS**

- *RAS* genes are the most common targets for somatic *gain-of-function* mutations in human cancers
- Activating *RAS* mutations occur in 30% of human cancers
  - Specific *RAS* genes are mutated in different cancers
- *KRAS* prevalent in pancreatic, colorectal, endometrial, lung, and cervical cancers
Colon Cancer Has Many Biologic Subsets That Differ in Response to EGFR-Targeted Agents

Low expression of EGFR ligands → decreased response to EGFR targeted agents

Mutant BRAF → decreased response to EGFR-targeted agents

PTEN loss of expression → decreased response to EGFR-targeted agents

Signaling to the nucleus
Frequency of Significant *KRAS* Mutations

<table>
<thead>
<tr>
<th>Codon</th>
<th>Amino Acid Substitution</th>
<th>Amino Acid Change</th>
<th>Incidence, %</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>Gly12Asp</td>
<td>Aspartate</td>
<td>32.5</td>
</tr>
<tr>
<td>12</td>
<td>Gly12Val</td>
<td>Valine</td>
<td>22.5</td>
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<tr>
<td>12</td>
<td>Gly12Cys</td>
<td>Cysteine</td>
<td>8.8</td>
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<td>Gly12Ser</td>
<td>Serine</td>
<td>7.6</td>
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<td>Gly12Ala</td>
<td>Alanine</td>
<td>6.4</td>
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<tr>
<td>12</td>
<td>Gly12Arg</td>
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<tr>
<td>13</td>
<td>Gly13Asp</td>
<td>Aspartate</td>
<td>19.5</td>
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<tr>
<td>Others</td>
<td></td>
<td></td>
<td>1.8</td>
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</table>
## Results of the NCIC CTG CO.17 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Therapy</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best Supportive</td>
<td>Cetuximab</td>
<td></td>
</tr>
<tr>
<td><strong>Mutant KRAS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>0</td>
<td>1.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Median PFS</td>
<td>1.8 months</td>
<td>1.8 months</td>
<td>0.99 (0.73-1.35)</td>
</tr>
<tr>
<td>Median OS</td>
<td>4.6 months</td>
<td>4.5 months</td>
<td>0.98 (0.70-1.37)</td>
</tr>
<tr>
<td><strong>Wild-type KRAS</strong></td>
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</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>0</td>
<td>13%</td>
<td>NA</td>
</tr>
<tr>
<td>Median PFS</td>
<td>1.9 months</td>
<td>3.7 months</td>
<td>0.40 (0.34-0.59)</td>
</tr>
<tr>
<td>Median OS</td>
<td>4.8 months</td>
<td>9.5 months</td>
<td>0.55 (0.41-0.74)</td>
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</tbody>
</table>

# Results of the OPUS Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Therapy</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td></td>
<td>FOLFOX alone</td>
<td>FOLFOX + cetuximab</td>
</tr>
<tr>
<td><strong>Unselected Patients</strong></td>
<td></td>
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</tr>
<tr>
<td>ORR</td>
<td>36%</td>
<td>46%</td>
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<tr>
<td>mPFS</td>
<td>7.2 months</td>
<td>7.2 months</td>
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<tr>
<td><strong>Mutant KRAS</strong></td>
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<tr>
<td>ORR</td>
<td>49%</td>
<td>33%</td>
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<tr>
<td>mPFS</td>
<td>8.6 months</td>
<td>5.5 months</td>
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<tr>
<td><strong>Wild-type KRAS</strong></td>
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<tr>
<td>ORR</td>
<td>37%</td>
<td>61%</td>
</tr>
<tr>
<td>mPFS</td>
<td>7.2 months</td>
<td>7.7 months</td>
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</table>
CRYSTAL Trial: Study Design and Treatment Arms

- Stratification factors
  - Regions
  - ECOG PS
- Populations
  - Randomized patients: n = 1217
  - Safety population: n = 1202
  - ITT population: n = 1198

Cetuximab + FOLFIRI
Cetuximab IV 400 mg/m² on Day 1, then 250 mg/m² wkly + irinotecan 180 mg/m² + 5-FU 400 mg/m² bolus + 2400 mg/m² as 46-hr CI + FA q2w

FOLFIRI
Irinotecan 180 mg/m² + 5-FU 400 mg/m² bolus + 2400 mg/m² as 46-hr CI + FA q2w
CRYSTAL Trial: Progression-Free Survival (ITT Population)

ITT Population Independent Review

HR: 0.851 (95% CI: 0.726-0.998; stratified log-rank \( P = .0479 \))

1-yr PFS rate: 23% vs 34%

PFS Estimate

Patients at Risk, n

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI alone</th>
<th>Cetuximab + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI alone</td>
<td>599</td>
<td>499</td>
</tr>
<tr>
<td>Cetuximab + FOLFIRI</td>
<td>599</td>
<td>499</td>
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Results of the CRYSTAL Trial

<table>
<thead>
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<th>Outcome</th>
<th>Therapy</th>
<th>Hazard ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>FOLFIRI alone</td>
<td>FOLFIRI+cetuximab</td>
<td></td>
</tr>
<tr>
<td>Unselected patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>39%</td>
<td>47%</td>
<td>1.40 (1.12-1.77)</td>
</tr>
<tr>
<td>mPFS</td>
<td>8.0 months</td>
<td>8.9 months</td>
<td>0.85 (0.72-0.99)</td>
</tr>
<tr>
<td>mOS</td>
<td>18.6 months</td>
<td>19.9 months</td>
<td>0.93 (0.81-1.07)</td>
</tr>
<tr>
<td>Mutant KRAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>36%</td>
<td>40%</td>
<td>0.80 (0.44-1.45)</td>
</tr>
<tr>
<td>mPFS</td>
<td>8.1 months</td>
<td>7.6 months</td>
<td>1.07 (0.75-1.40)</td>
</tr>
<tr>
<td>mOS</td>
<td>17.7 months</td>
<td>17.5 months</td>
<td>1.03 (0.74-1.44)</td>
</tr>
<tr>
<td>Wild-type KRAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>43%</td>
<td>59%</td>
<td>1.91 (1.24-2.93)</td>
</tr>
<tr>
<td>mPFS</td>
<td>8.7 months</td>
<td>9.9 months</td>
<td>0.68 (0.50-0.93)</td>
</tr>
<tr>
<td>mOS</td>
<td>21.0 months</td>
<td>24.9 months</td>
<td>0.84 (0.64-1.11)</td>
</tr>
</tbody>
</table>

**KRAS as a Biomarker for Pmab Response in mCRC**

- Patients with mutant KRAS receiving panitumumab had 0% RR and SD similar to BSC alone (12% vs 8%)
- PFS log HR significantly different depending on KRAS status ($P < .0001$)
- Percentage decrease in target lesion greater in patients with wild-type KRAS receiving Pmab

![Graphs showing event-free proportion and hazard ratios](image_url)

**KRAS Mutation and CRC**

- Improved *progression-free* and *overall survival*
  - ~12-20 weeks PFS, 8-12 weeks OS
- Both drugs are *ineffective* when the patient's tumor has a *KRAS* mutation.
- NCCN and ASCO recommend that *KRAS* mutation testing be part of the evaluation of patients with *metastatic* CRC.
KRAS Mutation and CRC

- Improved progression-free and overall survival
  - ~12-20 weeks PFS, 8-12 weeks OS
- Both drugs are ineffective when the patient's tumor has a KRAS mutation.
- NCCN and ASCO recommend that KRAS mutation testing be part of the evaluation of patients with metastatic CRC.
Colon Cancer Has Many Biologic Subsets That Differ in Response to EGFR-Targeted Agents

- Low expression of EGFR ligands (EREG or AREG) → decreased response to EGFR targeted agents
- Mutant BRAF → decreased response to EGFR-targeted agents
- Mutant KRAS → decreased response to EGFR-targeted agents
- PTEN loss of expression → decreased response to EGFR-targeted agents

Signaling to the nucleus
Colon Cancer Is More Than 1 Disease

KRAS wild type
Positive EGFR agents

KRAS mutant
Negative EGFR agents

MSI-H
15% to 20%\[^{2,3}\]
? No 5-FU

MSS
80% to 85%\[^{3}\]

\[^{1}\]

Am J Gastroenterol. 2006;101:2818-2825.
Eternal Question

- Identify patients who are most likely to respond to a drug or treatment
- Identify patients at risk for adverse reactions
- Monitor response to treatment to adjust dosing
- Identify patients matching the population that was studied in the pivotal therapeutic trial
Biomarkers and Reimbursement

• Less risk for payers
  – Prevents use of ineffective therapies
  – Decreased variation in patient outcomes
  – Adverse outcomes will decrease overall costs for healthcare systems

• Regulatory Consequences
  – Development of tests not validated
    • But noted literature
  – Socioeconomic barriers

• Clinical Trial Development

• Reimbursement
  – Questions on payment bundles
Use and potential economic value of cancer biomarkers in patient care.

<table>
<thead>
<tr>
<th>Biomarker use</th>
<th>Clinical objective</th>
<th>Economic considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Detect and treat early-stage cancers among the asymptomatic</td>
<td>Potential savings if total costs of treatment for patients diagnosed with early-stage cancer are less than costs for those diagnosed in later stages</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Accurately and quickly establish the presence of cancer</td>
<td>Potential savings from optimizing treatment approach(^\d) and timing</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Determine whether treatment is having the intended effect; enable timely detection of post-treatment recurrence</td>
<td>Potential savings from optimizing treatment approach(^\d) and facilitating timely second-line treatment</td>
</tr>
<tr>
<td>Treatment optimization</td>
<td>Predict outcomes; determine aggressiveness of treatment; predict response to particular treatments ('stratified' medicine(^\d))</td>
<td>Potential savings from optimizing treatment approach(^\d) leading to improved outcomes, and minimizing costs of adverse events</td>
</tr>
</tbody>
</table>

Optimize treatment approach\(^\d\) refers to selecting the most appropriate treatment and treatment venue with the best possible outcome given a patient's biomarker levels and other relevant characteristics.
Biomarkers and Drug Labeling

• The FDA expects that companion tests will usually be lab tests that are co-developed with the medication and approved at the same time as the medication.

• The drug will be reviewed by the FDA’s Center for Drug Evaluation and Research and the test will be reviewed by the Center for Devices and Radiological Health (CDRH) under its separate procedures for medical devices.

• The widely reported price of the companion diagnostic test kit for crizotinib, developed by Abbott Molecular, is less than $200, while established reimbursement is $400–$500. The reported price of crizotinib is $9,600 per month.
Biomarker Coverage

- The coverage and reimbursement issues facing cancer biomarker testing may be more problematic than those facing new oncology products.
- If the oncology product label specifies that biomarker testing is required to identify appropriate patients for therapy then it must be ensured that the label reads broad enough to accommodate all current and future methods of testing for the respective biomarker.
- For example, the initial Herceptin label specified HER2 testing using the Dako HercepTest.
- Early on, some patients had insurance benefits coverage denied because the laboratories contracted by their health benefits either did not have access to or utilize HercepTest, or the laboratory used different IHC methods for HER2 testing.
Biomarker Conundrums

• Individually, commercial insurers decide whether biomarker testing will be required before they cover the targeted therapy

• As such, some insurers will likely require evidence for biomarker testing (and submission of the testing results) prior to coverage and reimbursement of the targeted therapy

• Other insurers may require patients to sign a waiver of acknowledgement that they are not candidates for a certain therapy if the insurer approves coverage and reimbursement for biomarker testing, and the testing comes back negative
Biomarker Decisions

- Test is required in the FDA label for a specific drug: 12% 16% 66% (Mean: 6.3)
- Test is recommended in NCCN guidelines: 4% 6% 4% 30% 28% 28% (Mean: 5.4)
- Test is recommended in ASCO guidelines: 4% 8% 10% 28% 30% 18% (Mean: 5.2)
- Cost of diagnostic: 10% 12% 10% 22% 22% 22% (Mean: 4.9)
- Number of patients required to test before finding an eligible patient: 12% 6% 8% 22% 20% 18% 14% (Mean: 4.4)
Biomarker Companion Tests

• The FDA expects that companion tests will usually be lab tests that are co-developed with the medication and approved at the same time as the medication.

• The drug will be reviewed by the FDA’s Center for Drug Evaluation and Research and the test will be reviewed by the Center for Devices and Radiological Health (CDRH) under its separate procedures for medical devices.

• If both pass muster, the drug label will say that the approved use of the medication requires testing.

• The widely reported price of the companion diagnostic test kit for crizotinib, developed by Abbott Molecular, is less than $200, while established reimbursement is $400–$500. The reported price of crizotinib is $9,600 per month.
Biomarker Coverage

• Obtaining coverage and reimbursement is perhaps the primary obstacle to commercial adoption of new cancer biomarker tests.

• If the test is not reimbursed by the Centers for Medicare and Medicaid (CMS) and commercial insurers, then market adoption of the new therapy will be impacted. Genentech/Dako worked with Medicare in advance of the FDA approval for HercepTest to ensure national coverage policy.

• Later, ImClone/BMS advocated Medicare coverage for EGRF testing in advance of Erbitux® (cetuximab) approval.

• National coverage policy ensued.
CMS Reimbursement

• The Centers for Medicare & Medicaid Services the final national payment limits for 65 genetic tests described by Tier code

• Tier 1 lists CPT codes for commonly performed tests described by the specific analyzes they gauge
  – BRCA mutations associated with hereditary breast
  – Ovarian cancer and KRAS mutations linked to outcomes

• Tier 2 lists codes for less commonly performed tests and groups them based on their complexity
  – Diagnostics for coagulation factor VIII for hemophilia and von Willebrand factor for inherited coagulation defects
    • CMS hasn't finalized reimbursement levels for any Tier 2 codes
    • Medicare contractors will continue to establish pricing for tests that fall in this coding category
Biomarker Testing Reimbursement

• For example, KRAS mutation testing to personalize cancer treatment, performed by companies like Qiagen and Roche, received an average final gapfill price of around $200 from CMS

• Final price is a 2 percent increase from previously proposed pricing but a 74 percent decrease from what labs received from CMS with old stacked codes

• Meanwhile, Medicare contractor final pricing for such testing was still 23 percent below previously proposed payment levels
Biomarker Testing Reimbursement

• Qiagen, which markets an FDA-approved KRAS test as a companion diagnostic in colorectal cancer

• Negotiated a higher rate from its contractor for its test compared to other non-FDA cleared lab tests gauging KRAS mutations

• Compared to a median payment level of around $200 for non-FDA approved KRAS tests
  – Qiagen HAD reimbursement rate of $385 per test for its FDA-approved kit
Summary

• Biomarkers have become a mainstay in the diagnosis and treatment of patients
• Companion tests during clinical studies is now common practice
• Continued issues with reimbursement will be problematic as more molecular tests come to light
Questions