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Disclosures

• **UpToDate** - Editor, head and neck cancer section - Royalties

• **Merck** - Advisory board in last 2 years - honorarium

• **Blueprint Medicines** - Advisory board in last 2 years - honorarium
Overview

1. Rationale for testing
2. Terminology
3. Cases/questions
4. Specific Tests
5. Specifics uses- tumor sites etc
Rationale- Why test

- Prognostication
- Prediction of response to therapeutics- specific tumor type
- Pathways to cancer converge- can’t exclude an alteration just based on site of origin- Non-specific to tumor type/site
- Sometimes diagnostic
- Learn of individual or family member’s predisposition to cancer
Terminology and examples

• Germline vs somatic

• **Genetics** – inheritance/ behavior /properties /structures of genes- often applies to specific genes

• **Genomics**- study of organism’s genes/sequences- health or disease, using sequence data/ bioinformatics, etc
• **Hereditary**
  
  Germline predisposition panel - e.g. Invitae Multi-Cancer panel.

• **Tumor/Somatic**
  
  – IHC - immunohistochemistry
  
  – Single gene tests – e.g. EGFR mutation (pcr/ pyrosequencing)
  
  – NGS/ Next Generation Sequencing/ Genomics panels – e.g. our 50 gene hot spot panel or broad panel “Foundation One”
  
  – Cancer of unknown Primary Panels - e.g. Caris-
  
  – Gene expression profiling tests/ Panels - e.g. Oncotype Dx breast /Decision Dx melanoma. Thyroseq v.3 d for thyroid cancer dx
  
  – Translocation panels - again may be diagnostic/prognostic or predictive
Cancer Panels available at NorthShore

- Individual genes- pcr/pyrosequencing/Sanger sequencing- selective reporting of 50 gene panel
- 50 gene “hot spot” panel
- Hematologic malignancy panel
- Translocation panel

- New expanded panel (441 genes, 170 reported, along with “TMB”)
Case 1

- 58 y.o. woman with breast cancer - (node negative, 1.5 cm, Her-2 negative, ER positive tumor) = intermediate risk for need for chemo added to hormone therapy
- She *will* benefit from at least 5 years of hormonal therapy
- Will she benefit from chemotherapy also?
- What test/s might you run?
- What is the category of this test?
Case 1

- 58 y.o. woman with intermediate risk for chemo added to hormone therapy (node negative, 1.5 cm, Her-2 negative, ER positive tumor)
- She will benefit from at least 5 years of hormonal therapy
- Will she benefit from chemotherapy also? MAYBE
- What test/s might you run? ONCOTYPE DX, MAMMOPRINT
- What is the category of this test? GENE EXPRESSION PROFILE- PREDICTIVE AND PROGNOSTIC
ONCOTYPE DX- "TAILORx" Trial

**Trial Assigning Individualized Options for Treatment (TAILORx):**

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score


on behalf of the TAILORx Investigators
Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer


N Engl J Med
Volume 379(2):111-121
July 12, 2018
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)

RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo
## Role of chemotherapy in women \(\leq 50\) for recurrence free survival

<table>
<thead>
<tr>
<th>End Point and Treatment Group</th>
<th>Rate at 5 Yr</th>
<th>Rate at 9 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive disease–free survival†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score of (\leq 10), endocrine therapy</td>
<td>95.1±1.1</td>
<td>87.4±2.0</td>
</tr>
<tr>
<td>Score of 11–15, endocrine therapy</td>
<td>95.1±1.1</td>
<td>85.7±2.2</td>
</tr>
<tr>
<td>Score of 11–15, chemoendocrine therapy</td>
<td>94.3±1.3</td>
<td>89.2±1.9</td>
</tr>
<tr>
<td>Score of 16–20, endocrine therapy</td>
<td>92.0±1.3</td>
<td>80.6±2.5</td>
</tr>
<tr>
<td>Score of 16–20, chemoendocrine therapy</td>
<td>94.7±1.1</td>
<td>89.6±1.7</td>
</tr>
<tr>
<td>Score of 21–25, endocrine therapy</td>
<td>86.3±2.3</td>
<td>79.2±3.3</td>
</tr>
<tr>
<td>Score of 21–25, chemoendocrine therapy</td>
<td>92.1±1.8</td>
<td>85.5±3.0</td>
</tr>
<tr>
<td>Score of (\geq 26), chemoendocrine therapy</td>
<td>86.4±1.9</td>
<td>80.3±2.9</td>
</tr>
</tbody>
</table>
Case 2

- 66 y.o. non-smoking Asian woman found to have an adenocarcinoma of the lung metastatic to the bone

- Is she likely to have a mutated tumor gene?
- Which one?
- How likely
- How will she be tested?
Case 2

- 66 y.o. non-smoking Asian woman found to have an adenocarcinoma of the lung metastatic to the bone
- Is she likely to have a mutated tumor gene?- **YES**
- Which one? **EGFR**
- How likely **60%**
- How will she be tested?-
  - **Single Gene**
  - “Lung Cancer Panel”
    - 50 gene panel plus translocation panel
- **Prognostic/predictive/diagnostic**
- **Turnaround time 1-7 days**
Advanced Lung Cancer—What information do we need to Guide Treatment Selection?

- Test for predictive biomarkers

**Lung Adenocarcinoma**

<table>
<thead>
<tr>
<th>EGFR</th>
<th>ALK</th>
</tr>
</thead>
</table>


# Prevalence of Molecular Targets in Lung Adenocarcinoma – LCMC\(^1\) Experience

<table>
<thead>
<tr>
<th>Molecular Target</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>25</td>
</tr>
<tr>
<td>EGFR (Sensitive) – exon 19 del, L858R, L861Q, G719X</td>
<td>17</td>
</tr>
<tr>
<td>ALK rearrangement</td>
<td>8</td>
</tr>
<tr>
<td>EGFR (not sensitive) – exon 20 insertion, de novo T790M</td>
<td>4</td>
</tr>
<tr>
<td>HER2 (exon 20 insertions)</td>
<td>3</td>
</tr>
<tr>
<td>BRAF</td>
<td>2</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1</td>
</tr>
<tr>
<td>NRAS</td>
<td>1</td>
</tr>
<tr>
<td>MEK1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>MET amplification</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\(^1\)LCMC = Lung Cancer Mutation Consortium

- Oncogenic driver found in 64% of patients with full genotyping
- Overall, results used to select targeted therapy in 28% of patients.

Lung Cancer Genomic directed therapy

- Driven by Genomic alteration in 30% of NSCLCa, (adenocarcinoma)
- Most others will get immunotherapy first or second line

- Immunotherapy predictive markers are
  - PD-L1 score
  - Tumor mutation burden
Case 3

• 74 y.o. man treated for advanced gastric cancer received “FOLFOX” chemotherapy, Taxol plus ramicurimab, and then Pembrolizumab anti-PD-1 checkpoint inhibitor immunotherapy.

• He asks if his physician can search for an abnormal gene we can treat.

• What type of panel might be used?
74 y.o. man treated for advanced gastric cancer received “FOLFOX” chemotherapy, Taxol plus ramicurimab, and then Pembrolizumab anti-PD-1 checkpoint inhibitor immunotherapy.

He asks if his physician can search for an abnormal gene we can treat.

What type of panel might be used? **Multi-gene next generation sequencing (NGS) panel**

- E.g. Foundation Once
- Our internal 50 or 441 gene panel
NGS- Multi gene Panel – Foundation One

**Patient Information**
- Patient Name: Katherine McDonald
- Date of Birth: 11/14/1962
- Gender: Female
- Physician: Dr. Smith
- Additional Physician: Dr. Jones
- Pathologist: Dr. Jones

**Specimen**
- Specimen Received: 05/15/2012
- Specimen Site: Core biopsy
- Collection Method: Colon
- Specimen Date: 02/19/2011
- Specimen Type: Block

**Diagnosis**
- Colorectal Cancer

**About the Test**
FoundationOne is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

**Patient Results**

<table>
<thead>
<tr>
<th>Genomic alterations</th>
<th>pp1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 genetic alterations</td>
<td></td>
</tr>
<tr>
<td>2 therapies associated with clinical benefit</td>
<td>pp3-4</td>
</tr>
<tr>
<td>2 therapies with lack of response</td>
<td>pp3-4</td>
</tr>
<tr>
<td>50+ clinicopathologic</td>
<td></td>
</tr>
</tbody>
</table>

**Tumor Type: Colorectal Cancer**

- Genomic alterations identified:
  - PTEN Loss
  - KRAS G12D
  - APC E941*, E1552

- Additional disease-relevant genes with no reportable alterations detected:
  - BRAF

**Therapeutic Implications**

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN Loss</td>
<td>None</td>
<td>Temsirolimus, Everolimus</td>
<td>Yes. See Clinical Trials section.</td>
</tr>
<tr>
<td>KRAS G12D</td>
<td>None</td>
<td>None</td>
<td>Yes. See Clinical Trials section.</td>
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<tr>
<td>APC E941*, E1552*</td>
<td>None</td>
<td>None</td>
<td>Yes. See Clinical Trials section.</td>
</tr>
<tr>
<td>BRAF</td>
<td>No alteration detected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient may be resistant by therapy.

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient’s tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for the patient, nor are they based on randomized controlled trials for the patient’s diagnosis.
# NGS - Multi gene Panel – Foundation One

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>11/14/1962</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>FMI Case #</td>
<td>1062100092</td>
</tr>
<tr>
<td>Medical Record #</td>
<td>12345</td>
</tr>
<tr>
<td>Block ID</td>
<td>JH32145</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Katherine McDonald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report Date</td>
<td>05.29.2012</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Colorectal Cancer</td>
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**Client**
- Mercy Hospital
- Dr. Smith
- N/A
- FMIO0001
- Dr. Jones

**Specimen Received**
- 05/15/2012
- Colon
- Core biopsy
- 10/31/2011
- Block

About the Test:
FoundationOne is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

**Patient Results**
- 3 genomic alterations: pp1-2
- 2 therapies associated with clinical benefit: pp3-4
- 2 therapies with lack of response: pp3-4
- 50+ clinical markers: pp5-6

**Tumor Type: Colorectal Cancer**

- Genomic alterations identified:
  - PTEN Loss
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<td>Yes. See Clinical Trials section.</td>
</tr>
<tr>
<td><strong>KRAS G12D</strong></td>
<td>(-) Panitumumab†</td>
<td>None</td>
<td>Yes. See Clinical Trials section.</td>
</tr>
<tr>
<td></td>
<td>(-) Cetuximab†</td>
<td></td>
<td>Yes. See Clinical Trials section.</td>
</tr>
<tr>
<td><strong>APC E914, E1552</strong></td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>BRAF</strong> No alteration detected</td>
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Case 4

- A 22 y.o. woman has pleuritic chest pain and a PE protocol CT scan shows a 6 cm posterolateral chest wall mass.
- Biopsy shows a small round blue cell tumor
- There is concern for Ewing’s/PNET vs embryonal rhabdomyosarcoma.
- What category of test/s can be done to assess for a specific diagnosis?
Case 4

• A 22 y.o. woman has pleuritic chest pain and a PE protocol CT scan shows a 6 cm posterolateral chest wall mass.
• Biopsy shows a small round blue cell tumor
• There is concern for Ewing’s/PNET vs embryonal rhabdomyosarcoma.
• What category of test/s can be done to assess for a specific diagnosis? **TESTS FOR TRANSLOCATION**

• **Findings: EFS– PNET- A diagnostic test**
• TESTS FOR TRANSLOCATION
  – Cytogenetics
  – PCR
  – FISH t(11;22)(q24;q12)
  – Microarray/sequencing
44 y.o. man has a CT of the neck after an MVA and trauma. No fracture, but he has an 11 mm thyroid nodule.

A guideline driven biopsy is indeterminate (FLUS/AUS or follicular neoplasm- cancer risk 10-40%)

In addition to observation, is there a diagnostic test to determine if he has cancer?
• 44 y.o. man has a CT of the neck after an MVA and trauma. No fracture, but he has an 11 mm thyroid nodule.
• A guideline driven biopsy is indeterminate (FLUS/AUS or follicular neoplasm- cancer risk 10-40%)
• In addition to observation, is there a diagnostic test to determine if he has cancer? – YES
  – Thyroseq v.3- (mutations, insertions/deletions, fusions, cnv, in 112 genes. Sensitivity/specificity 94/89% range
Conclusions

• Molecular diagnostics currently play a major role in cancer
  – Diagnostic
  – Prognostic
  – Predictive

• Becoming more widely available
• Becoming quicker and cheaper
• NorthShore is a leader in this field
Thank you!