Successfully Navigating Diagnosis And Treatment In The Age Of Targeted Cancer Therapy

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November 15, 2013

Vision

At Foundation Medicine, we are leading a transformation in cancer care, where each patient's treatment is informed by a deep understanding of the molecular changes that contribute to their disease
Learning Objectives

- Explain the paradigm shift toward thinking about cancer as a disease of the genome
- Discuss the increased number of diagnostic and therapeutic options available to personalize treatment
- Describe the various challenges in using traditional technologies to characterize cancer in guiding treatment
- Introduce how next-generation sequencing can address these challenges
- Recognize the role next-generation sequencing plays in personalized medicine

The Evolution In Our Understanding Of Solid Tumors And Their Treatment
Our Earlier Understanding Of Cancer Was Incomplete

Factors linked to causation

Environment

Lifestyle

Genetics and Family History

Exposure to Carcinogens

Malignant Tumor

– Mass of abnormal cells that divide uncontrollably
– May be able to invade other tissues

Traditional Treatment Paradigm

Diagnosis

– Biopsy
– Pathology

Treatment

– Surgery
– Radiation
– Traditional Chemotherapy

Outcome

– Potential for significant side effects
– Highly effective in some but less effective in others
Cancer Is A Disease Of The Genome

- DNA is exposed to carcinogenic events every day; this causes gene alterations to occur
- Exposure to cancer risk factors increases the chances of gene alterations

The Genome

- Chromosome
- Cell
- Gene
- DNA
- T
- C
- A
- G
The Role Of Genes In Normal Cells

GENES
Instructions for protein synthesis

PROTEINS
Structure, function and regulations for tissues and organs

PATHWAYS
Complex networks that regulate cell growth, division and survival

How Gene Alterations Can Cause Cancer

ALTERED GENES
Code for

ALTERED PROTEINS
Resulting in

ALTERED PATHWAYS
CANCER
Cancer Related Genes

Of the ~20,000 genes in the genome, only a subset of a few hundred are unambiguously associated with cancer.

<table>
<thead>
<tr>
<th>Gene names</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL</td>
</tr>
<tr>
<td>ERBB2 (HER-2)</td>
</tr>
<tr>
<td>BRAF</td>
</tr>
<tr>
<td>KRAS</td>
</tr>
<tr>
<td>EGFR</td>
</tr>
<tr>
<td>KIT</td>
</tr>
</tbody>
</table>

Types Of Alterations In Cancer Genes

- Normal
- Copy number alterations
- Substitutions
- Insertions and deletions
- Rearrangements
Each Cancer Is Unique

- Even among patients with breast cancer, there are many different types of disease and each has characteristic types of alterations

Our Understanding Of Cancer Is Increasing In Complexity

Lung Adenocarcinoma

- Known mutations: KRAS, EGFR, ALK, PIK3CA, BRAF, NRAS
- Unknown mutations: MAP3K1, AKT1, PIK3CA, MAP2K1, AKT1, PIK3CA, MAP2K1
- ALK fusions
- ERBB2

The Shift Toward Targeted Therapy

**Chemotherapy**
- Anticancer drugs may be highly effective in some, but less effective in others
- Patients encounter side effects which are often significant

**Targeted Therapy**
- In personalized medicine, clinicians use biomarkers to predict a patient’s response to therapy
- Patients are more likely to get therapies with the greatest impact which often have fewer side effects

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Time Between Target Discovery And Development Of Effective New Cancer Treatments Is Narrowing

<table>
<thead>
<tr>
<th>Year</th>
<th>Target</th>
<th>Years between target discovery and therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>BCR-ABL</td>
<td>41</td>
</tr>
<tr>
<td>1970</td>
<td>EGFR</td>
<td>26</td>
</tr>
<tr>
<td>1980</td>
<td>HER2</td>
<td>16</td>
</tr>
<tr>
<td>1990</td>
<td>KIT</td>
<td>4</td>
</tr>
<tr>
<td>2000</td>
<td>BRAF</td>
<td>8</td>
</tr>
<tr>
<td>2010</td>
<td>ALK</td>
<td>3</td>
</tr>
</tbody>
</table>
The Number Of Targeted Therapies Will Continue To Grow

Coming Soon
～500 compounds evaluated
～400 targets in development


Cancer Diagnostics And Treatment: A New Frontier

• Enhanced understanding of cancer biology has led to a rapid expansion in the field of cancer diagnostics and treatment
  – Accelerating pace of discovery
  – New markers
  – New drugs
Diagnosing And Characterizing Cancer

Pathological Examination

Pathological examination of a tumor specimen is a cornerstone of cancer diagnostics

- Chemical stains can accentuate features pathologists look for
## Immunohistochemistry: IHC

**Immunohistochemistry (IHC)**
- Uses specially designed chemical stains to "tag" certain features of normal and cancer cells
- Slide-based test can evaluate alterations at the protein level

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relatively low cost</td>
<td>• Must know alterations ahead of time to detect potential mutations</td>
</tr>
<tr>
<td>• Designed to tag one target</td>
<td>• Variations on the results based on how sample was handled and how the stain was applied</td>
</tr>
<tr>
<td>• Can evaluate expression of key proteins in tumor</td>
<td>• Subjectivity in interpreting the results</td>
</tr>
<tr>
<td></td>
<td>• Can only evaluate protein expression of one or few targets at a time</td>
</tr>
</tbody>
</table>

## Fluorescence in situ Hybridization: FISH

**Fluorescence in situ hybridization (FISH)**
- Uses special dyes attached to DNA to find changes on a chromosome
- Slide-based test can assess alterations in DNA

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highly accurate</td>
<td>• Must know which alterations to test for ahead of time</td>
</tr>
<tr>
<td>• Objective</td>
<td>• High cost</td>
</tr>
<tr>
<td>• Can detect copy number alterations and rearrangements</td>
<td>• Sample cannot be stored for review</td>
</tr>
<tr>
<td></td>
<td>• Does not detect several major classes of DNA alterations</td>
</tr>
</tbody>
</table>
Hot Spot Panels

- Use a variety of molecular techniques
- Examine defined sections of a limited number of genes

Advantages
- Simultaneously examine multiple genes for alterations

Disadvantages
- Can only examine a limited number of genes
- Only examines segments of each gene and can miss alterations that lie outside of the hot spot
- May miss some alterations (copy number, small indels, rearrangements)

Traditional Testing

Limitations
- Only a limited number of alterations screened at once
- Misses some types of alterations
- May deplete tissue sample
- Results are specific for the test used; need to know ahead of time what questions to ask

DNA Alterations Detected or Missed by Traditional Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Detects</th>
<th>Can Miss</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC</td>
<td>Protein expression</td>
<td>Any alteration not known of ahead of time</td>
</tr>
<tr>
<td>FISH</td>
<td>Copy number alterations, rearrangements, substitutions</td>
<td>Indels</td>
</tr>
<tr>
<td>Hot Spot Panels</td>
<td>Substitutions</td>
<td>Indels, copy number alterations, rearrangements</td>
</tr>
</tbody>
</table>
Next-Generation Sequencing (NGS)

- Newer technology which allows for the simultaneous sequencing of hundreds of millions of DNA molecules.
NGS: Various Approaches

• Whole Genome Sequencing (WGS)
  – Determines the complete DNA sequence of an organism’s genome at a single time

• Whole Exome Sequencing (WES)
  – Selectively sequences only the coding areas of the genome

• Targeted Sequencing (e.g. FoundationOne)
  – Sequences a defined subset of genes of interest in their entirety

• Targeted Sequencing (Hot spot)
  – Sequences only the hot spots of a subset of genes of interest

Hot Spot vs. Targeted Sequencing

Chromosome

Gene 1 Gene 2 Gene 3 Gene 4

Hot spot approach
Only sequences select regions of a gene

Targeted approach*
Sequences genes in their entirety

* As implemented by Foundation Medicine
Sequencing: WGS Versus WES Versus Targeted Sequencing

<table>
<thead>
<tr>
<th></th>
<th>Whole Genome Sequencing</th>
<th>Whole Exome Sequencing</th>
<th>Targeted Sequencing - FoundationOne approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well suited for clinical use</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Turn-around time</td>
<td>Months</td>
<td>Months</td>
<td>Avg 14 days</td>
</tr>
<tr>
<td># of genomic alterations</td>
<td>10,000+</td>
<td>1000+</td>
<td>Average 1 to 3 &quot;actionable&quot;</td>
</tr>
<tr>
<td>detected</td>
<td>Many not known to be</td>
<td>Cannot detect gene</td>
<td>Of 200+ known cancer genes</td>
</tr>
<tr>
<td></td>
<td>drivers of cancer</td>
<td>fusions (ie ROS1, ALK, RET)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinical utility and</td>
<td>• Clinical utility and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>actionability?</td>
<td>actionability?</td>
<td></td>
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Targeted sequencing - hot spot approach is not comprehensive
- Can only examine a limited number of genes
- Only examines segments of each gene and can miss alterations that lie outside of the hot spot
- May miss some alterations (copy number, small indels, rearrangements)

Advantages Of Targeted Sequencing Versus Traditional Testing

**Hot Spot or Single-Marker Testing**
- Misses some types of mutations (rearrangements, copy number alterations)
- Limited number of alterations screened at once
- Results are specific for the test used: need to know ahead of time what questions to ask
- Exhusts tissue

**Targeted Sequencing**
- Covers all types of DNA alterations
- Able to identify hundreds of clinically relevant mutations at once
- Allows the opportunity to identify all alterations
- Tissue sparing

* As implemented by Foundation Medicine
FoundationOne Assay Workflow

1. Sample preparation
   • DNA is extracted from a biopsy

2. DNA optimization and sequencing
   • Raw sequencing data is overwhelming
   • 1000+ alterations can be identified

3. Computational biology analysis
   • Extensive and complex analysis narrows the large amount of data to provide meaningful and relevant results
   • 1000+ alterations are narrowed down to an average of 1-3

4. Clinical report
   • The analysis is interpreted and a clinical report is curated

NGS Can Be Used In Cancer To Identify Gene Targets To Personalize Therapy

<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>
</tr>
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<tbody>
<tr>
<td>EGFR L858R</td>
<td>Erlotinib</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Afatinib</td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crizotinib</td>
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<th>FDA Approved Therapies (in another tumor type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK EML4-ALK fusion TSC2</td>
<td>Crizotinib</td>
<td>None</td>
</tr>
<tr>
<td>splice site 3285-1 G&gt;A</td>
<td></td>
<td>Everolimus Temozolomol</td>
</tr>
</tbody>
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</thead>
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<tr>
<td>BRAF V600E</td>
<td>None</td>
<td>Vemurafenib Transient Dobrotienib</td>
</tr>
</tbody>
</table>
Case Study: Patient With Inflammatory Breast Cancer (IBC)

**Background/ Medical History**
- 53 yo woman presents with peau d’orange
- Right breast biopsied
- Diagnosis of IBC
- Inexorable cancer progression

Case Study: A Novel ERBB2 Mutation In IBC

- Targeted sequencing of patient tumor sample revealed novel ERBB2 (HER2) mutation in inflammatory breast cancer (IBC)
- Identified personal therapeutic options based off previously approved treatments for targeting ERBB2 in breast cancer:
  - Trastuzumab (Herceptin®)
  - Pertuzumab (Perjeta®)
  - Lapatinib (Tykerb®)
**Summary**

- Cancer is a disease of the genome
- The era of a "One Treatment Fits All" approach to cancer is ending
- The utility of traditional tests is limited
  - The current model of testing is unsustainable
- Targeted NGS* meets clinical needs today and in the future

* As implemented by Foundation Medicine

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**Comprehensive Genomic Analysis Can Optimize Patient Care**