Comprehensive Genomic Profiling with FMI – bringing value to patients

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Region Europe
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Why should physicians consider profiling?

CGP from Foundation Medicine – *understanding the difference*

Foundation Medicine’s experience – *translating into clinical benefit*
Cancer is a disease of the genome

Our understanding of cancer has been evolving
Many genetically driven characteristics—many therapeutic options
Lung Adenocarcinoma:

Moving from one disease to multiple disease types by molecular alterations that require distinct tx plans

**Biomarker Drugs**
- EGFR mutations: erlotinib, gefitinib, afatinib
- ALK rearrangements: crizotinib
- BRAF V600E: vemurafenib*, dafradenib*
- MET amplifications: crizotinib
- ROS1 rearrangements: crizotinib
- HER2 mutations: trastuzumab*, afatinib
- RET rearrangements: cabozantinib*

* Drugs not approved for lung cancer

**2015 NSCLC NCCN guidelines** recommend broad molecular profiling for the following biomarker/drug associations:
Treating Lung Cancer patients based on their tumour profiling results improves outcomes

Kris MG et al (2014); JAMA 311 (19)
Barlesi R et al (2016); Lancet 3140-6736
Meta-analysis of Phase II studies – 32 149 patients

Meta-analysis of 570 Phase II, single-agent studies (including total of 32,149 patients) studying the impact of personalized and targeted treatment strategies in diverse cancer types

**RR, PFS and OS from pooled meta-analyses**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (pooled)</th>
<th>PFS (meta-analysis)</th>
<th>OS (meta-analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized</td>
<td>30.16% (95% CI: 25.93% - 34.90%)</td>
<td>6.5 months (95% CI: 5.9 - 7.1)</td>
<td>20 months (95% CI: 18.5 - 21.5)</td>
</tr>
<tr>
<td>Not personalized</td>
<td>20.00% (95% CI: 15.87% - 24.13%)</td>
<td>4.3 months (95% CI: 3.7 - 4.9)</td>
<td>14 months (95% CI: 12.5 - 15.5)</td>
</tr>
</tbody>
</table>

Personalized treatment strategies, across malignancies, were independent predictors of better outcomes and fewer deaths from treatment toxicity than non-personalized therapies.

“Matched therapy using genomic markers offers better outcomes than using protein biomarkers”


“Matched therapies are associated with better outcomes than non-matched therapies”

OS: Overall survival; PFS: Progression-free survival; RR: Response rate; CI: Confidence interval
Profiling guidelines

NCCN Guidelines® now recommend “broad molecular profiling” for advanced NSCLC patients

<table>
<thead>
<tr>
<th>Genomic Alterations (i.e. driver event)</th>
<th>Available targeted agents with activity against driver event in lung cancer</th>
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<tr>
<td>EGFR mutations</td>
<td>erlotinib, gefitinib, afatinib</td>
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<tr>
<td>ALK rearrangements</td>
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NCCN Guidelines® Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed March 13, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. now recommends “broad molecular profiling” for advanced NSCLC patients
Profiling initiatives

Investigating the potential to match treatments to genomic alterations across tumor types

And more…

CAPTUR  Canadian Profiling and targeted Utilization trial

DRUP  The Drug Rediscovery Protocol

TAPUR  Targeted Agent and Profiling Utilization Registry Study

Initiatives to decipher which patients respond to which therapies, irrespective of in which tumor type the therapies are approved in

http://www.nature.com/nm/journal/v22/n5/fig_tab/nm.4089_T1.html
Why should physicians consider profiling?

Comprehensive genomic profiling from Foundation Medicine

How to benefit from Foundation Medicine’s experience
Foundation Medicine
Pioneer and leader in molecular information

- Founded 2010 in Cambridge, MA, USA
- Proprietary molecular information platform
- First to market comprehensive genomic profiling solutions for cancer
- 90,000+ clinical cases profiled
- 30+ pharmaceutical clinical trial partners
- Roche collaboration for R&D and commercialization outside USA
Foundation Medicine offers two solutions

*FoundationOne®* and *FoundationOne® Heme*

Comprehensive: Detect all classes of genomic alterations

- **FOUNDATION ONE**
  - Coding regions of 315 genes
  - Introns of 28 genes
  - Known as drivers of solid tumors

- **FOUNDATION ONE Heme**
  - DNA sequences of 405 genes
  - RNA sequences (cDNA) of 265 genes
  - Commonly altered in hematologic malignancies (leukemia, lymphoma and myeloma) and


*Jie H et al. Blood 2016*
How does FoundationOne work?

A process that follows standard operating processes

Pre-Analytic Process (Pre-Sequencing)

1) DNA/RNA extraction
   Extensive optimization

2) LC, Hybrid Capture
   Extensive optimization

Sequencing

Genomic DNA

Sequencing Library  Biotinylated DNA Baits

Hybridization Capture

Analysis & Interpretation

3) Analysis pipeline
   Advanced computational biology

Post-Analytic Process (Post-Sequencing)

4) Clinical report
   Resource intensive

Powered by 20+ bioinformaticians and genomic scientists who optimize state-of-the-art algorithms to report the most clinically relevant information for a patient.
Why should physicians consider profiling?

CGP from Foundation Medicine – understanding the difference

How to benefit from Foundation Medicine’s experience
Types of genomic alterations driving tumor growth

Limitations of traditional and hotspot testing

<table>
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<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</td>
<td>Insertions &amp; deletions, Substitutions</td>
</tr>
<tr>
<td>Hot Spot NGS*</td>
<td>Substitutions</td>
<td>Insertions &amp; deletions, Copy number alterations, Rearrangements</td>
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Foundation Medicine finds more targets

Completely sequenced genes enables detection of novel alterations missed by hot spot testing

Example: EGFR gene

Hot spot tests detect selective alterations in selective parts of the EGFR gene*

....When there is an insertion/deletion or rearrangement that removes one of the primer sites, hot spot tests will not amplify the region or detect the alteration

FoundationOne detects all genomic alterations across the entire EGFR gene

Foundation Medicine finds more targets

While hot spot tests can miss alterations...

MULTI-GENE “hot spot” TEST

Missed

Missed

Missed

Missed
Foundation Medicine finds more targets

...Comprehensive Genomic Profiling identifies all four classes of alterations with validated performance

**COMPREHENSIVE GENOMIC PROFILING**

- **MET exon 14 splice**
  - ALK inhibitor

- **EGFR L858R**
  - EGFR inhibitor

- **ROS1 fusion**
  - ALK inhibitor

- **MET amplification**
  - ALK inhibitor

- **EGFR exon 19 deletion**
  - EGFR inhibitor

**Base substitutions:**
- Sensitivity: >99%
- PPV: >99%

**Rearrangements:**
- Sensitivity: ≥90%
- PPV: >99%

**Copy number alterations:**
- Sensitivity: >95%
- PPV: >99%

**Insertions/deletions:**
- Sensitivity: >97%
- PPV: >99%

Validated performance published in peer-reviewed journal*

* Frampton G et al. (2013) Nature Biotech 31, 1023-34
Why should physicians consider profiling?

Comprehensive genomic profiling from Foundation Medicine

How to benefit from Foundation Medicine’s experience
Improve profiling of NSCLC patients

**FoundationOne finds more alterations associated with NCCN guidelines than single gene or hot spot NGS**

**SINGLE GENE TESTING**
misses up to 35% of ALK rearrangements by FISH\(^1\) and 17% of EGFR alterations by hot spot test\(^2\)

**Hot spot NGS**
Up to 50% of targetable alterations can be missed without supplemental FISH\(^3\)

detects all four classes of NSCLC clinically relevant alterations\(^3\) and genetic biomarkers\(^4\) included in the NCCN Guidelines\(^\circledR\)

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4. NCCN Guidelines® Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung
Clinical utility of finding more alterations with FoundationOne
NSCLC patients can benefit from targeted therapies

- 17% of EGFR exon 19 deletions missed by hotspot tests¹
- 75% of NSCLC patients with EGFR exon 19 deletions can respond to EGFR tyrosine kinase inhibitors, with median OS > 1 year²
- 35% of ALK-rearranged cases missed by FISH³
- 80% of ALK-rearranged patients identified by FoundationOne respond to ALK inhibitor crizotinib³

Patient case: EGFR/ALK negative

Identification of complex fusion led to treatment/response

### Patient Information

- **43-year-old male**
- **Never-smoker**

### At Presentation
- **Pericardial tamponade**
- **No detection of EGFR mutation; atypical FISH staining for ALK**

### Diagnosis
- **Metastatic NSCLC** with a pericardial tamponade

### Treatment status
- **Disease progression** despite 4 cycles of cisplatin/pemetrexed

### FoundationOne® analysis and subsequent treatment

- **Identification of complex EML4-ALK fusion separated by genomic shards**
- **Initiation of treatment with crizotinib**

Patient had a rapid response to crizotinib treatment; **75% shrinkage** of primary lesion (RECIST) after 4 months of treatment

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FoundationOne may lead to improved outcomes

Studies show potential in other tumor types, ability to impact physician decisions

3. Reinbolt RE et al. (2016) Ohio State University, ASCO poster

- **Triple-negative breast cancers**
  - Targeted therapy based on tumor genomic alterations
  - Improved response (33% vs. 8%, p=0.018) & longer progression-free survival\(^1\) (6.4 vs. 1.9 months; p=0.001)

- **Rare/refractory gynecological cancers**
  - Targeted therapy based on tumor genomic alterations
  - Radiologic response or stability in 64% of patients\(^2\)

- **Breast cancer**
  - Targeted therapy based on tumor genomic alterations
  - 41% of treatment decisions influenced by FoundationOne\(^3\)

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3. Reinbolt RE et al. (2016) Ohio State University, ASCO poster
Targeting ERBB2 Mutations in Metastatic Breast Cancer

- Responses reported with both antibody therapeutics and kinase inhibitors
- 38% response rate in ERBB2 mutated BC to kinase inhibitor at SABCS
- High frequency (> 30%) of ERBB2 mutations in CDH1 mutated relapsed ILC

RESEARCH ARTICLE

Activating HER2 Mutations in HER2 Gene Amplification Negative Breast Cancer

Non-Amplification ERBB2 Genomic Alterations in 5,605 Cases of Refractory and Metastatic Breast Cancer: an Emerging Opportunity for anti-HER2 Targeted Therapies


Foundation Medicine, Inc., Cambridge, MA; Albany Medical College Albany, NY; Washington University School of Medicine
Response of a HER2 FISH/IHC Negative Cutaneous Adnexal Carcinoma with an ERBB2 S310f Mutation to anti-HER2 Targeted Therapy
Why consider profiling with Foundation Medicine?

• Profiling has been shown to **improve outcomes for patients** with lung cancer or considering clinical trials, while evidence is evolving in additional indications¹-³

• Foundation Medicine’s profiling services are designed to **capture all four types of genomic alterations** which single gene and hotspot NGS testing can miss

• Proprietary **bioinformatics** have been optimized over 90,000 cases to call alterations

• These alterations are delivered in a **comprehensive report** which describes potential therapies, trials, and the latest clinical literature to inform physician’s decisions

• Evidence has shown **FoundationOne detects alterations in patients that are pan-negative with single gene panels**⁴-⁶, and in some indications can improve outcomes⁸-⁴, ⁷-

Profiling with FoundationOne finds more clinically-relevant alterations and can lead to better patient outcomes

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Doing now what patients need next