Clinical Evidence for Genomic Medicine Sustainability: State of Science and Gaps – Molecular Profiling in Cancer

August 30, 2016
Roger D. Klein, MD JD
Medical Director, Molecular Pathology
Precision Medicine

‘The right drug, for the right patient, at the right dose, at the right time’
Traditional Analysis

• Tumor type and marker specific
• IHC, ISH, PCR
• Single or small number of markers
• Highly specific, limited information

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HER2 (ERBB2)
The resistance mutation arising as a result of the threonine to arginine amino acid substitution at position 858 within exon 21 of the EGFR gene, which encodes part of the tyrosine kinase domain, results in increased receptor activation after ligand binding. Patients harboring these mutations have increased sensitivity to TKIs over patients with wild-type EGFR. Analysis of the crystal structures of L858R/EGFR mutants has demonstrated that the kinase is activated through disruption of autocatalytic interactions, resulting in receptors with 50-fold more activity compared to wild-type EGFR receptors. (Reference: 12)
Changes affect pathways involved in regulation of cellular growth, differentiation, senescence, and cell death (apoptosis).
Next Generation Sequencing
How to Read the FoundationOne™ Report

THE FIRST PAGE OF THE REPORT SHOWS
the patient and ordering physicians information...

The genomic alterations identified in the hundreds of genes assayed...
The targeted therapies that may be relevant based on those genomic alterations both in the patient’s tumor type and in other tumor types...
and whether there are relevant clinical trials.

<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>EGFR N771_P772&gt;KKP</td>
<td>Erlotinib</td>
<td>Cetuximab</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>CCND1 amplification</td>
<td>Gefitinib</td>
<td>Panitumumab</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>ARID1A Q633</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
**Ion AmpliSeq Cancer Hotspot Panel v2**

Just one tube. Just 10ng of DNA. Just one day.

The Ion AmpliSeq™ Cancer Hotspot Panel v2 allows translational and disease researchers to fast-track oncology research by surveying hotspot regions of 50 oncogenes and tumor suppressor genes, with wide coverage of the KRAS, BRAF and EGFR genes.

This research panel, with improved primer design, contains 207 primer pairs in a single tube and requires as little as 10ng of DNA, enabling researchers to sequence challenging samples such as formalin-fixed, paraffin-embedded (FFPE) tissue. The convenient predesigned panel allows researchers to focus on data generation and analysis, not on the labor-intensive primer design and target selection steps. While hybridization-based target selection methods require 7 to 72 hours to complete both target selection and library preparation, Ion AmpliSeq™ technology makes it possible to complete the entire process in about 3.5 hours using simple PCR reactions. Additionally, Ion AmpliSeq™ library construction steps are automated using standard 96-well plate-based protocols, further simplifying the workflow and allowing large projects to be rapidly completed without additional sample transfer steps.

“Sequencing gene panels with Ion Torrent™ technology is complete. You have the Ion AmpliSeq™ gene selection technology, the Ion PGM™ sequencing system and also the Ion Reporter™ analysis software.

For me, it is important to have a whole integrated solution so researchers can advance from the tumor to results.”

Pierre Laurent-Puig, M.D., Ph.D.
Paris-Descartes University Medical School, Paris, France
NGS in Oncology Practice

• Diagnosis
  - help identify tumor vs. benign
  - tumor subtypes

• Appropriate targeted therapy

• Identification of resistance mutations
  - primary
  - secondary

• Off-label use and clinical trial selection
Use of NGS in cancer

• Use of NGS has resulted in discovery of large numbers of mutations with potential prognostic and therapeutic relevance
  - many genes overlap different cancer types
  - germline variants must be distinguished
• Translation into useful clinical test requires ability to
  - accurately and reproducibly detect variations
  - meaningfully interpret results
  - effectively communicate results

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Questions in Interpretation

• Is the mutated gene potentially relevant to the patient’s management?
  - if so, in what way?
• Is the particular variant potentially relevant to the patient’s management?
  - If so in what way?
• Is it of the type that appears to respond to therapy, impact prognosis, or aid in diagnosis?
MOLECULAR PROFILING TO GUIDE CANCER TREATMENT

Coverage Rationale

Molecular profiling using multiplex or next generation sequencing (NGS) technology is proven and medically necessary for guiding systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when the following criteria are met:

- Molecular profiling using multiplex or NGS technology to test for epidermal growth factor receptor (EGFR) mutations, human epidermal growth factor receptor 2 (HER2) mutations, RET rearrangements, and anaplastic lymphoma kinase (ALK) gene rearrangements.

Molecular Profiling to Guide Cancer Treatment

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Note: See the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Non-Small Cell Lung Cancer, available at: www.nccn.org, for updates regarding oncogenes used in molecular profile testing for NSCLC. (Accessed April 21, 2016)

- The laboratory providing molecular profiling testing services must be approved by the New York State Department of Health for performing the molecular profile test.

Note: See the following website for clinical laboratories holding a New York State Department of Health permit in the category of oncology molecular and cellular tumor markers:

Molecular profiling using multiplex or NGS technology is unproven and not medically necessary for ALL other indications.

There is insufficient evidence in the clinical literature demonstrating that molecular profiling has a role in clinical decision-making or has a beneficial effect on health outcomes for other indications. Further studies are needed to determine the analytic validity, clinical validity and/or clinical utility of molecular profiling using multiplex or NGS technology for other indications.
Fig. 4 An illustration of new clinical trial designs. Basket and umbrella trials both incorporate genomic data into the basic construction of the trial. Basket trials are designed around specific mutations, regardless of the primary tumor site. Umbrella trials are first separated by primary tumor site and then split into conventional therapy and precision medicine arms.
NCI launches trial to assess the utility of genetic sequencing to improve patient outcomes

Posted: January 30, 2014

A pilot trial to assess whether assigning treatment based on specific gene mutations can provide benefit to patients with metastatic solid tumors is being launched this month by the National Cancer Institute (NCI), part of the National Institutes of Health. The Molecular Profiling based Assignment of Cancer Therapeutics, or M-PACT, trial is one of the first to use a randomized trial design to assess if assigning treatment based on genetic screening can improve the rate and duration of response in patients with advanced solid tumors. A trial in which patients are randomly assigned to various treatment options is the gold-standard method for determining which treatment option is best.

Researchers hope that in addition to the knowledge gained from the trial about assigning therapy based on results of genetic sequencing of tumors, this trial could identify patient sub-groups that are likely to benefit from certain treatments and result in new treatments being developed quickly for some cancers. This could ultimately lead to smaller, more definitive clinical trials, which would be helpful to clinicians and patients in terms of cost and time.
### M-PACT
**4 Treatment Regimens, 3 Pathways, and 20 Targeted Genes**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gain of Function</th>
<th>Loss of Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAS pathway:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK 1120212</td>
<td>BRAF, KRAS</td>
<td>NF1</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>NRAS, HRAS</td>
<td></td>
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<tr>
<td><strong>PI3K pathway:</strong></td>
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<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>AKT1, PIK3CA,</td>
<td>PTEN</td>
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<tr>
<td>mTOR inhibitor</td>
<td>MTOR</td>
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<td><strong>DNA repair pathways:</strong></td>
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<tr>
<td>Veliparib (PARP inhibitor)</td>
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<td>ATM, ATR, ERCC1,</td>
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<tr>
<td>+ TMZ</td>
<td></td>
<td>MLH1, MSH2, NBN,</td>
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<tr>
<td>MK1775 (Wee1 inhibitor)</td>
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<td>PARP1, PARP2,</td>
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<tr>
<td>+ carboplatin</td>
<td></td>
<td>TP53</td>
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**391 aMOIs (with COSMIC ID) selected**

*National Cancer Institute*
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About the TAPUR Study

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a non-randomized clinical trial that aims to describe the performance (both safety and efficacy) of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic variant. The study provides approved targeted therapies that are contributed to the program by collaborating pharmaceutical companies, catalogues the choice of genomic profiling test by clinical oncologists and aims to learn about the utility of registry data to develop hypotheses for additional clinical trials.

To find responses to commonly asked questions, please visit our FAQ page and review our patient brochure.
Find a Cancer Mutation

Disease (required): Select Disease
Gene (optional): Select Disease First
Variant (optional): Select Disease First

Due to changes in how the National Cancer Institute provides information about clinical trials, the My Cancer Genome clinical trials search and filters will not be available until further notice. For information about cancer clinical trials, please visit the following resources:

- For all cancer-related clinical trials, both open for enrollment and closed, see ClinicalTrials.gov and search for cancer or other relevant search terms.
- For open and enrolling NCI-funded cancer clinical trials, see Cancer.gov.

Learn About My Cancer Genome

Support My Cancer Genome

Molecular Medicine
- Pathways
- Immunotherapy in Cancer
- Overview of Targeted Therapies for Cancer
- List of Anticancer Agents
- Types of Molecular Tumor Testing

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- Newsletter Sign-Up
- MCG Mobile App
- Take Our Survey

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N-of-One is a molecular decision support company providing clinicians with the most concise, accurate and clinically meaningful interpretation of molecular test results.
Showing **Interventional** and **Enrolling** trials and drugs specific to **PIK3CA**.

### MATCHING DRUGS | FDA 23

<table>
<thead>
<tr>
<th>TEMsiROLimus</th>
<th>FDA</th>
<th>EVERsiROLimus</th>
<th>FDA</th>
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<td><strong>Brand/Trade</strong></td>
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### MATCHING TRIALS | 168

**NCCT0343335** - CANCER: A Study Of Tafasib + Fulvestrant Versus Placebo + Fulvestrant In Patients With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Anastrozol Inhibitor Therapy

- **Phase**: 1 2 3 4 6
- **Notes**: Report a problem

**NCCT0353002** - A Phase II Study Of BKM120 With Fulvestrant In Patients With HR+/HER2- AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed or on After inTORTI

- **Phase**: 1 2 3 4 6
- **Notes**: Report a problem

**NCCT0344680** - Lung-AIP: ST1400 Biomarker-Targeted Second Line Therapy In Treating Patients With Recurrent Stage IIB/IV Squamous Cell Lung Cancer

- **Phase**: 1 2 3 4 6
- **Notes**: Report a problem

**NCCT0365555** - Phosphatidylinositol 3-Kinase (PI3K) Alpha Inhibition In Advanced Breast Cancer

- **Phase**: 1 2 3 4 6
- **Notes**: Report a problem

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Cleveland Clinic

Every life deserves world class care.