Oncology pre-profiling: Using genetic biomarkers to pre-identify oncology patients for clinical trials

Jennifer Cubino, MA, CCRA, Senior Director, Compound Lead, Oncology Project Leadership
Winfred Shaw, MBA, Senior Director and Head, Precision Medicine Center of Excellence
Terry Murdock, MS, Vice President and Head, Oncology Center of Excellence

Background
Cancer genomics is moving into practice, driven by improved understanding of molecular heterogeneity within cancers and increasing availability of drugs that target genomic alterations. Evaluating biomarker-targeted cancer therapies with companion diagnostics is essential to contemporary oncology drug development strategies.¹
**Table of contents**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Current status</td>
<td>3</td>
</tr>
<tr>
<td>Future potential</td>
<td>4</td>
</tr>
<tr>
<td>Pilot study: Impact of genomic profiling on clinical trial participation</td>
<td>4</td>
</tr>
<tr>
<td>References</td>
<td>6</td>
</tr>
<tr>
<td>About the authors</td>
<td>7</td>
</tr>
</tbody>
</table>
Unfortunately, prevailing methods for clinical study subject selection using predictive biomarkers create unnecessary barriers for patient participation. In trials that employ genomic biomarker selection, screening patients for only a single biomarker is common. Further, typical prevalence for the biomarkers being studied in clinical trials is less than 10% within a given patient population. From a patient’s perspective, this means that from the point of diagnosis or recurrence, he or she will provide a tissue sample from a limited supply and then more than 90% of the time, absence of the required biomarker will lead to a screen failure for the clinical trial. As an industry, we are asking too much of very sick patients in terms of time and precious tissue while offering them insufficient expected value in return.

Pre-profiling – prospectively stratifying patients through genomic screening – was developed to provide value to patients via access to rapid, broad-based genomic testing of their cancer and to drive value to clinical study sponsors through faster recruitment of niche patient populations. Pre-profiling is a core component of Quintiles Precision Enrollment, which connects the right patient to the right trial quickly.

**Current status**

The number of targeted agents in oncology is increasing; five out of eight new oncology molecules approved by the U.S. FDA in 2014 were indicated for biomarker-selected populations. Concurrently, the recent technical development of genomic testing platforms and the adoption of Next-Generation Sequencing (NGS) is enabling rapid and broad genomic pre-profiling and allowing matching of patients with approved or investigational therapies.

As illustrated in Figure 1, genomic pre-profiling involves two steps. First, tumors are biopsied and the tissue samples are used to detect and identify genomic alterations. Second, patients with specific genomic alterations are matched to approved therapies or potential clinical trial protocols.

**Figure 1: Genomic pre-profiling: What is it?**

1. **Step 1**
   - Genomic alterations are identified in tumor samples and reported back to patient/research site
   - Cancer patients in pre-profiling network → Genomic analysis of tumors → Cancer patients in pre-profiling network with alterations identified

2. **Step 2**
   - Patients with specific genomic alterations are matched to potential protocols
   - Cancer patients in pre-profiling network with alterations identified → Protocols with specific genomic alteration entry criteria → Pre-profiled cancer patients matched to right protocol

5 out of 8 new oncology molecules are indicated for biomarker-selected populations
Future potential

This personalized approach is focused on the patient, potentially helping to achieve better patient outcomes. Testing with a broad panel of biomarkers provides more information from each limited biopsy sample, helping to support physicians’ rapid decision-making and identification of appropriate next steps, including possible clinical trials for each patient.

Our approach lays the groundwork for alternative development pathways in which a new therapy would initially be approved for a subset of appropriate responders, and then more data would be gathered in observational studies to ensure safety and bolster efficacy before broadening authorization. By targeting biomarker-selected patient populations who are more likely to respond appropriately to a particular therapy, smaller resulting trials may yield strong efficacy signals along with practical evidence of safety.

A small-scale pilot study targeting 50 metastatic colorectal cancer (mCRC) patients, sponsored by Quintiles, suggests that genomic profiling may increase clinical trial participation among cancer patients from the current level of 3% to 35% (see details below).³ Importantly, the patients were not selected for clinical trial eligibility based on ECOG scores (used for measuring performance status, and developed by the Eastern Cooperative Oncology Group), life expectancy or organ function. Enrollment into the genomic sequencing pilot was completed in less than three months, demonstrating both patient and clinician value in receiving broad-based genomic data. This suggests that there is potential to increase screening rates and shorten timelines for clinical trials by providing a broad genomic panel rather than using a single biomarker – more patients may be willing to be screened due to the value of the results; rapid turnaround time for sample testing; and ability to gain maximum insight into their disease using a limited sample amount.

Pilot study: Impact of genomic profiling on clinical trial participation

Goals
A genomic sequencing registry study was carried out to explore the feasibility and potential clinical benefits of a prospective, centralized and rapid cycle time approach to the genomic profiling of tumors from mCRC patients. The study sought to determine the number of drug targetable genomic changes in mCRC patients, including a comparison of patients who progress early versus late, split between progression at less than or greater than a one year timeframe.

Methods
The study targeted enrollment of 50 mCRC patients within the US Oncology Network, followed by collection of archival formalin-fixed paraffin embedded (FFPE) samples and genomic testing. Sample collection and pathology assessment was performed at Quintiles Central Laboratories followed by NGS and bioinformatic analysis at the Quintiles EA Genomics Laboratory (both laboratories are now branded and known as Q² Solutions, a Quintiles Quest joint venture). Genomic profiling was performed on the Ion Torrent PGM following enrichment of tumor DNA via the AmpliSeq Cancer Hotspot Panel v2 assay, enriching for hotspots within 50 cancer-related genes. Clinical annotation and reporting to treating oncologists was provided by N-of-One. Basic demographic and clinical information was collected but formal disease monitoring and follow-up were not performed. Clinicians were asked to report the impact of the genomic test report on recommendations for the next step in patients’ disease care.

- **Test/profiling feasibility and performance:** High-quality genomic data and a clinical report, developed by N-of-One, were delivered to doctors in an average of 15 days from sample submission to report, demonstrating that rapid turnaround time from centralized sample testing is feasible. Rapid patient enrollment into the pilot was achieved, indicating clinician and patient enthusiasm for access to genomic information.

By targeting biomarker-selected patient populations who are more likely to respond appropriately to a particular therapy, smaller resulting trials may yield strong efficacy signals and practical evidence of safety.

A small-scale pilot study targeting 50 mCRC patients suggests that genomic profiling may increase clinical trial participation from 3% to 35%.
Results
Interestingly, genomic pre-profiling and the genomic report influenced the treating physician to recommend a clinical trial in more than one-third (35%) of cases that reported actionable mutations (15/43) vs 3-5% of oncology patients that currently participate in clinical trials. The study enrolled and profiled 51 stage IV mCRC patients from July 2013 to October 2013 from 14 sites in the United States; one additional patient was enrolled over the targeted number. Subjects were stratified by time to progression prior to entering the study. The study population was evenly distributed across early (< 1 yr) and late progressors (> 1 yr) with a median age of 62. Turnaround time from sample submission to results reported averaged 15 days. Some 98% of the bases sequenced in the genomic analysis reached the target coverage necessary to identify 5% variant frequency in the sample. Genomic variants associated with approved therapies in mCRC were observed in 7.8% of patients while 64.7% of patients had variants associated with approved therapies in other indications. A total of 84.3% of patients had variants linked with open clinical trials. Of these 43 patients, 32 had multiple biomarkers with associated trials. Overall, more than 100 mutations were identified, including alterations in KRAS, BRAF, EGFR, PIK3CA, GNAS, TP53, APC and other genes. The number of actionable mutations was not associated with progressor status.

- Profiling results: Overall, 100 mutations were observed, encompassing all three categories of actionability – which is defined as there being an FDA-approved medication for that indication, FDA-approved medication for a different indication or clinical trials currently available using a molecule targeting that biomarker. Sixty distinctly different actionable alterations were observed in 43 out of the 51 total patients (84%). The most frequent actionable mutations had associated clinical trials, followed by therapeutics approved in other indications and therapeutics approved in CRC. The number of actionable mutations did not statistically correlate with patient demographics or progression status. In addition, progression status did not statistically correlate with specific alterations, although further investigation may be warranted.

Discussion
Patient pre-profiling may rapidly identify potential patients for biomarker-driven oncology drug development. Pre-profiling may improve trial timelines by increasing patient and clinician engagement with clinical trials using such highly informative screening procedures. By effectively utilizing limited tissue, providing rapid results and reporting on a broad panel of biomarkers, patients are encouraged to participate in the screening process. Implementation of pre-profiling will require collaboration between stakeholders including sponsors, clinical research organizations (CROs), clinicians, patients and payers.

Conclusions
The outcome of this observational study demonstrates the feasibility of rapid screening and reporting of NGS genomic results targeting actionable mutations in mCRC. The lack of an association between early and late progressors suggests that a greater sample size will be required for future studies. The reported impact on clinician recommendations indicates the value of the results to inform treatment and clinical trial decisions.
References


2. Quintiles analysis based upon data compiled by the Personalized Medicine Coalition. Available at: http://www.personalizedmedicinecoalition.org/News/Press_Releases/PMC_Analysis_More_Than_20_Percent_of_FDAs_2014_Novel_New_Drug_Approvals_are_Personalized_Medicines

Jennifer Cubino, MA, CCRA  
Senior Director, Compound Lead, Oncology Project Leadership  
Jennifer Cubino has 13 years’ experience in clinical research, with the last five years developing innovations to drive change in how we conduct clinical trials. She has worked in a variety of roles on oncology studies for 12 years, including creating operational strategies for using biomarker selection in clinical trials; combining companion diagnostics and molecule strategies within protocol conduct; designing IT solutions to improve start-up efficiency and patient recruitment; and advising on strategies to reduce patient burden for participating in clinical trials. Jennifer was a seven-year appointed member on the Tufts Institutional Review Board and was the recipient of the Louis Lasagna, MD award for dedication to medical ethics.

Jennifer has a Master’s Degree in Clinical Investigation from Boston University School of Medicine and an undergraduate degree from Cornell.

Winfred Shaw  
Senior Director and Head, Precision Medicine Center of Excellence  
Winfred Shaw is senior director and head of the Precision Medicine Center of Excellence at Quintiles. He joined Quintiles in 2010 as part of corporate strategic services and held numerous leadership positions focused on global healthcare industry evolution, scientific strategy and corporate growth before assuming his present role in 2014. Win’s current responsibilities include development and implementation of precision medicine strategy; integration of Quintiles’ scientific expertise and cross-functional capabilities into precision medicine solutions; and oversight of operational coordination for precision medicine services.

Prior to joining Quintiles, Win held consulting positions within AVOS Life Sciences and Resonant Life Science Partners, both boutique strategy firms serving corporate and capital clients within the biopharmaceutical and medical device sectors. Before pursuing a graduate management degree and directing his career into healthcare in 2003, he enjoyed eight years of progressive engineering and global product management experience within the semiconductor capital equipment industry.

Win earned an M.B.A from the University of North Carolina Kenan-Flagler Business School with dual academic concentrations in Corporate Finance and Entrepreneurship and also holds an A.B. Physics degree from the University of North Carolina at Chapel Hill.
Terry Murdock, MS
Vice President and Head, Oncology Center of Excellence

Terry L. Murdock is vice president and head of the Oncology Center of Excellence at Quintiles. He focuses on developing insights and innovations that help improve the probability of success of Quintiles’ oncology customer development projects and programs. As part of a team, he provides customers with alternative and innovative design aimed to improve the efficiency of development of oncology assets.

Terry has 20 years of work experience as a successful senior executive in the medical research industry, specializing in oncology, multiple sclerosis and other autoimmune diseases. He is experienced at establishing operational excellence within culturally diverse environments with a track record executing operational, clinical and commercial plans. Prior to joining Quintiles, Terry held senior positions focused on clinical drug development at Ergomed, Genzyme/Sanofi, ILEX Oncology and US Oncology.

Terry earned his M.S. in biology and a B.S. in science in microbiology from the University of Texas at Arlington. He is a registered microbiologist for the American Society of Clinical Pathology and a registered medical technologist for American Medical Technologists.