Precision medicine: Shifting from one drug for all patients to personalized genomics-based therapeutic options

Victor Weigman, Ph.D., Associate Director, Translational Genomics, Q² Solutions, a Quintiles Quest Joint Venture
Patrice Hugo, Ph.D., Chief Scientific Officer, Q² Solutions, a Quintiles Quest Joint Venture

With advancements in clinical informatics and genomics, there has been a paradigm shift from “one drug fits all” toward precision medicine – taking account of individual variability in genes, environment and lifestyle across therapeutic areas. Precision medicine allows identification of patients who would likely benefit the most from a treatment and suffer the least side effects. For instance, such screening can reveal genetic make-up likely aligned with the molecular mechanisms of action of a drug, increasing the probability of a patient’s response to the therapy. This helps find better matches for existing and novel drugs, with the goal of ensuring that the right drug is used in the right patient at the right time.

Industry challenges

Precision medicine is now a reality for biomarker assessments that are predictive, prognostic and pharmacodynamic (PD) to be routinely used in development of most drugs across indications. Currently, some 56 percent of the 189 oncology therapies under development had an associated biomarker. Some 20 of the 34 oncology drugs expected to launch by 2017 will be targeted to biomarkers. In addition, of the more than 800 cancer drugs currently in clinical trials, almost all are targeted at particular gene products. These trends reflect the increased need for earlier go/no-go decision-making based on biomarker-driven PD and safety/efficacy signals. There is a shift away from protein or single-analyte assessments to biomarker “signatures” with R&D and clinical applications. These signatures may include pathway analysis (such as PDs/target engagement, resistance mechanisms); immune gene signature and/or analysis of immune T-cell receptor and immunoglobulin repertoire, which is predictive for immuno-oncology therapies; and prognostic panels for oncology indications.

Greater adoption of testing for these signatures in the clinical space necessitates incorporation of genomics in drug and diagnostics development. A focus on translational research and biomarker-driven drug development has led to increased demand for assays incorporating higher sensitivity such as:

- Challenging/limiting input material, including “liquid biopsies,” minimal residual disease (MRD) and neoantigen identification
- Multiple gene-based biomarkers targeting cancer “hotspots” and disease risk portfolios
- Multiple genome identification, such as microbiome assessments.

These approaches are especially valuable in the clinical trial space, due to the push for biopharma companies to “do more with less,” and demanding less invasive and multi-parameter solutions tempered with efficiency, reduced sample input and faster turnaround times.

Biomarkers changing the way drugs are delivered

The use of biomarkers to provide information on whether a patient will respond appropriately to treatment, both in terms of efficacy and safety, is changing the way drugs are delivered (Figure 1).
Rather than a “one-size-fits-all” paradigm, precision medicine takes a personalized approach, giving a particular therapy only to a pre-screened population with a biomarker that predicts a response along with a lack of adverse events.

Genomics powering the immuno-oncology landscape

Advances in oncology therapy are increasingly showing promise of turning a fatal disease into a chronic, treatable disorder. However, the complexity of cancer as group of diverse diseases remains a major challenge, despite improvements in understanding of cell signaling pathways and host immune responses. Genetic alterations play a pivotal role in the growth of all types of cancer, and researchers have found that individual tumors have unique genetic profiles due to somatic mutations, which have been shown to evolve during the course of the disease.5

Analyzing these genetic profiles with next generation sequencing (NGS) aids in understanding the relationship between biomarkers and patient responses. Using genomic technologies provides a broader lens that can be leveraged to understand mechanisms of action and/or resistance pathways to better design clinical trials. Given the appropriate laboratory collaboration, this can be leveraged for custom Laboratory Developed Tests (LDTs) to power clinical trials where the tumor genetic profiles can be used to identify the best therapeutic options.

Fundamental challenges in cancer treatment include the fact that cancers are rarely detected early, and rapidly develop resistance to targeted therapies and chemotherapies due to the aforementioned heterogeneity and clonal evolution of the disease. In addition, while immunotherapies are changing the paradigm by targeting the immune system rather than the cancer, not all patients respond. Typical response rates, toxicities and survival rates for various classes of therapy are shown below (Table 1 and Figure 2).

Table 1: Response rates, toxicity and long-term survival with various oncology therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response rate</th>
<th>Toxicity</th>
<th>Long-term survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy/radiation</td>
<td>Low</td>
<td>High</td>
<td>Poor</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Mid</td>
<td>Low</td>
<td>Good</td>
</tr>
</tbody>
</table>

Figure 2: Survival rates for various cancer therapies6

Products are in development for a wide range of targets; a greater understanding of patient genomics and susceptibility would enable more to be matched to appropriate trials and therapies.
Pre-profiling to accelerate study recruitment

Genomic pre-profiling (Figure 3, 4) offers a way to identify and enroll biomarker-defined oncology patients, potentially enabling cost-effective and timely development of drugs with anticipated high screen failure rates. With “just-in-time” (JIT) start-up, this approach offers:

- Reduction in set-up costs by avoiding sites that are not able to deliver on expected number of patient enrollments
- Faster study enrollment due to improved access to patients with the appropriate genomic signature, and quick start-up when potential patients are identified
- More rapid development decisions, based on faster enrollment and reduced time to key decision points, leading to a reduction in overall R&D spend
- Increased opportunities to develop drugs in niche settings, since protocols with high screen failure rates become feasible, opening up new commercial opportunities.

Genomic panels that are matched to the clinical trial design allow for increased biomarker information, enabling researchers to find the right patients and bring the trial to them (Table 2).

Figure 3: Genomic pre-profiling to identify and enroll biomarker-defined oncology patients

Figure 4: Patient pre-profiling based on prospective genomic testing

Patient pre-profiling

Matching patients to studies based on prospective genomic testing

Table 2: Matching the genomic panel to the clinical trial design

Matching panel to trial design

Solutions for identifying and enrolling biomarker defined oncology patients

<table>
<thead>
<tr>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Operational design</td>
<td>Identify sites where genomic sequencing is occurring for oncology pts in indication</td>
<td>Longitudinal registry umbrella followed by treatment (Tx) trial enrollment of variant patients</td>
<td>Pre-profiling limited scope registry followed by Tx trial enrollment of variant patients</td>
<td>Pre-screening/ genomic testing within one protocol</td>
<td>Pre-screening/ genomic testing within one protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test patients – newly Dx, newly recurred</td>
<td>Test patients at stable disease</td>
<td>Pre-profiling limited scope registry and JIT for investigator sites</td>
</tr>
</tbody>
</table>
Potential for comprehensive cancer panels

Genomic tests – including comprehensive cancer panels, human leukocyte antigen (HLA) typing, Exome sequencing and pan-cancer immune-profiling – can supplement many endpoints for complex clinical trials. These assays can be used singly or in combination to:

• Detect the most common actionable somatic alterations currently reported in cancer, including point mutations, insertions, deletions and structural rearrangements;

• Build comprehensive molecular information on genes involved in the most well understood pathways, creating a data source that can be used to identify new patient populations likely to benefit from targeted therapies; and

• Do more with less material, for reduction in testing turnaround time and overall cost.

A comprehensive cancer panel has been successfully used to leverage understanding of drug/gene interactions for FDA-approved drugs, and for mining clinical trial databases to highlight biomarkers that can be used to help increase clinical trial enrollment (Figure 5). This panel also has been used to identify value for drugs across indications based on knowledge of biomarkers.

Due to the risk involved in searching for low-frequency genetic variants and complex changes, accuracy is critical. Shifting from single- to multi-analyte assays increases risk; each variant is associated with its own level of error, and this is compounded when as many as 1.34 million positions are interrogated. Validation has shown variants in up to 10 percent of cells, and variant reporting needs to account for risks with sequencer error. In addition, high sequencing depth is needed, which increases noise.

One panel can power many protocols

A single panel can power multiple protocols across the world (Figure 6), opening the door to multiple protocol delivery options. Using a central laboratory avoids the need to use multiple local laboratories, with their risk of inconsistencies between testing sites. The rapidly growing range of biomarkers also can be stored and mined for indications data across global network.

Figure 5: A comprehensive cancer panel linking mutations and drug responses

Q2 Solutions Comprehensive Cancer Panel

Focusing on pairing patient to treatment

• Leveraged relationships between mutation and drug response/resistance
• Pan-cancer biomarker approach identifying novel associations to indications
• Can help segment price-value comparisons for drug pricing
Increasing the adoption of genomic pre-profiling has positive impacts for both patients and biopharma companies. These include:

- **High ‘actionability,’** which increases patient and physician interest.
  - One test and/or one biopsy with quick turnaround times (2-3 weeks)
  - General oncology assay can identify many pan-cancer biomarkers
  - Increases chance for rare positive biomarkers in the population to be found for various trials
  - Patients can be matched with approved drug as first line therapy

- **Enhanced trial enrollment,** with a large sample study finding that 11 percent of 2,000 patients went onto genotype-matched trials. Many groups facilitate this matching, including Molecular Match, Caris, and IBM’s Watson platform.

New protocols are leveraging this power, such as the American Society of Clinical Oncology’s Targeted Agent and Profiling Utilization Registry (TAPUR), the National Cancer Institute’s Molecular Profiling-Based Assignment of Cancer Therapy for Patients with Advanced Solid Tumors (NCI-MPACT), the Lung Cancer Master Protocol Trial (Lung-MAP), the Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer (IMPACT-2), and molecular selection of therapy in colorectal cancer: a molecularly stratified randomized controlled trial program (FOCUS-4, UK).

There remain opportunities for molecular characterization, including approaches such as immunosuppression, development of cancer-specific vaccines or stimulation of a T-cell response. Immuno-oncology offers potential to gain a deeper understanding of drug safety and pharmacokinetics/pharmacodynamics (PK/PD), coupled with more precise tumor characterization (Figure 7).
Data value from genomic panels

These types of genomic panels have great value to power precision medicine for a given patient, helping find targets to help boost treatment options and trial enrollment. However, the data generated also have immense longer-term value. This is due to the ability to compare biomarker information across panels, enabling future matching of profiled patients with new trials or discovery efforts. Collection of hundreds to thousands of biomarker results per patient can be leveraged to:

- Find patients for new trials
- Mine biomarker and indication interactions to identify new associations in disease development and drug responses\(^\text{15}\)
- Provide information on valuable variant and wild type responses for different genes, reducing the need for re-testing

Developing an assay

For biopharma companies, engaging laboratory resources and expertise to complement therapeutic efforts can provide access to a diverse network of clinicians and scientists from the earliest point in product development. This network may include bioinformaticists, geneticists, flow cytometrists, mass spectrometrists, microbiologists, virologists, immunologists, anatomic pathologists, cytopathologists, hematopathologists, regulatory experts, bioanalytical/medical writers and physicians. This expertise can help determine appropriate approaches to gaining informed consent from patients and develop data organization analysis strategies for future studies. Taken together, these approaches can offer insights to optimize protocol design and execution. The development pathway for biomarkers and companion diagnostics (CDx) is illustrated below (Figure 8).

Many of the materials required to start developing a genomic assay are already available from typical specimen collection (Figure 9).

The outputs that can be obtained from integrated bioinformatics capabilities – including assay validation, custom panel design, computer system validation, data mining and biomarker development – are shown below (Figure 10).

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**Figure 8: The development pathway for CDx**

**Q2 Solutions**

Laboratory partner of choice for CDx development from biomarker ID to CDx launch

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1. Biomarker R&D services and CDx strategic consulting
2. Assay development expertise and Dx partnerships
3. Assay optimization/Bridging study/CLIA laboratory testing
4. Global study execution for pivotal CDx trials
5. Regulatory support, including BIMO/FDA inspection support
6. Commercial, diagnostic and late-phase expertise
Figure 9: Input needs for genomic assays

Assay input needs

<table>
<thead>
<tr>
<th>Assay</th>
<th>Blood</th>
<th>FFPE</th>
<th>Solid Tissue</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA allele calling</td>
<td></td>
<td>500</td>
<td></td>
<td>1000</td>
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<tr>
<td>qPCR</td>
<td>30</td>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR-enriched (NGS)</td>
<td>40</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole exome (NGS)</td>
<td>375</td>
<td>1250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted (NGS) panel</td>
<td>375</td>
<td>1250</td>
<td></td>
<td></td>
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<tr>
<td>IGVH testing</td>
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<td></td>
<td></td>
</tr>
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<td>Genotyping risk alleles</td>
<td>500</td>
<td>1000</td>
<td></td>
<td></td>
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<tr>
<td>HLA allele calling</td>
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<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA-Seq</td>
<td>500</td>
<td>1000</td>
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</tbody>
</table>

Figure 10: Outputs from integrated bioinformatics capabilities

Integrated bioinformatics capabilities

Performance, scalability, flexibility

- 10,000s of samples per year
- Pipeline execution/QC
- Customized delivery (HDs/Cloud)
- Software creation/maintenance
- Pipeline efficiencies
- High-performance computing
- Preclinical biomarker development
- Pipeline creation/algorithm dev.
- Assay CLIA/GxP compliance
- NGS delivery to FDA
- HL7 formats
- Formal validation procedures
Conclusion

Taken together, earlier adoption of genomic panels into testing of trial patients can provide a mechanism to identify targeted therapy, along with ability to predict the toxicity of therapies. Building broad genomic datasets across indications has high long-term potential for data mining payoff. Trends in using genomics to power trials include:

- The shift from single-analyte to multi-use panels
- Genomic pre-profiling as a successful model
- Bringing trials to the patient
- Immuno-oncology applications of genomics
- Custom assay design and specimen collection needs

Multi-analyte genomic assays provide a mechanism for enhancing trial design for precision medicine, with many successful examples of genomics-based laboratory-developed tests (LDTs) pairing patient to the best treatment option, and biomarker identification helping in trial enrollment.

Existing trials are already collecting specimens that can be used for genomic assays to power targeted therapy and immuno-oncology applications. For biopharma companies, working with laboratory service providers from the earliest stage can help with trial design and, in partnership with a diagnostics manufacturer, with companion diagnostic applications. The long-term payoff of genomic panels is to provide a wellspring of information for identifying novel biomarkers via data mining.
About the authors

**Victor Weigman, Ph.D.**

Associate Director, Translational Genomics, Q² Solutions, a Quintiles Quest Joint Venture

Dr. Victor Weigman has been doing biomarker discovery research with genomics for more than 10 years, with seven of those being with Expression Analysis (EA), a Q² Solutions Company. He obtained his Ph.D. at the University of North Carolina in Biology and Bioinformatics within the Lineberger Comprehensive Cancer Center. He has published 14 papers on biomarker identification and assay development and has contributed to the development and launch of several genomic CLIA Assays. Dr. Weigman currently directs the Translational Genomics Unit of Q² Solutions, whose goal is the continued facilitation of preclinical drug development through biomarker identification. Ongoing research revolves around the genomic profiling of solid tumors from both DNA and RNA approaches including the development of robust assays that can be leveraged as laboratory developed tests.

**Patrice Hugo, Ph.D.**

Chief Scientific Officer, Q² Solutions, a Quintiles Quest Joint Venture

Dr. Patrice Hugo is Chief Scientific Officer at Q² Solutions, a Quintiles Quest joint venture. He currently leads global scientific strategy and is responsible for the medical affairs and scientific activities in the central laboratories, genomic and BioAnalytical/ADME facilities worldwide. Dr. Hugo has more than 25 years of senior scientific leadership experience with extensive management expertise laboratory operations; biomarker discovery and validation applied to diagnostics; therapeutic targets and clinical trials. He obtained his Ph.D. at McGill University and completed five years of post-doctoral fellowship at the Walter Elisa Hall Institute in Australia, and Howard Hughes Medical Institute in Denver, Colorado. Dr. Hugo was Associated Vice President Chief Scientist, Scientific Affairs, at Laboratory Corporation of America (LabCorp)/Covance, and has held several other senior leadership positions at Clearstone Central Laboratories, Caprion and PROCREA BioSciences. A noted industry expert, Dr. Hugo has more than 75 scientific publications in internationally renowned journals. He also played an active role in a number of industry organizations, including being a member of the Board of Directors for the non-for-profit Personalized Medicine Partnership for Cancer in Quebec and the Steering Committee for the Biomarker Factory.
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Contact us

Toll free:  1 855.277.9929
Direct:  +1 919.998.7000
International:  +44 (0) 1506 814000
Website:  www.Q2LabSolutions.com

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