**Integration of Molecular Biomarkers into Clinical Development**

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In the first of this two-part series, strategic drug developers Eric Groves, Jason Hill and Christopher Ung explain why biopharma cannot afford to ignore the growing surge of interest in biomarkers in oncology and discuss their critical role in the modern-day clinical development process.

**Introduction**

The availability of targeted compounds aimed at the molecular pathways involved in oncogenesis has created major opportunities that have led to the development of highly specific cancer treatments, with the potential for greater efficacy and lower toxicity than conventional cytotoxic agents. Imatinib (Gleevec®/Glivec®) displays the full potential for these new approaches and has revolutionized the treatment of chronic myeloid leukemia (CML), while treatments such as trastuzumab (Herceptin®) have transformed the futures of many patients with HER2+ breast cancer.

Yet despite these advances, drug development in oncology remains painfully slow. It is a costly and often wasteful process; just 8% of new molecular entities in oncology make it through to market, less than in almost any other area.¹ Moreover, late-stage failures are common, with approximately six out of ten oncology drugs tested failing in Phase III.²
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The Reasons for Drug Failure

Drug development failures in oncology often originate from a lack of understanding regarding the biology of the drug, its mechanism(s) of action (MOA), the complexity of patient physiology, and inadequate characterization of patient tumors. Poor understanding of the criteria required for patient selection for the drug may lead to misapprehensions of the drug’s potential for safety and efficacy. It is these misapprehensions that can persist through to late development until the clinical program crashes in a late and costly failure.

Clearly, there is an urgent need for detailed information on new anticancer drugs to help make critical development decisions at the earliest possible point, speeding up the development process and enabling valuable time and resources to be placed where they can do the most good.

The Role of Biomarkers

Molecular biomarkers are widely recognized as being integral to this solution. They provide a set of tools which can provide invaluable information to support two major development concerns.

1. Does the drug perform according to the expected mechanism of action?
2. Which patients will experience benefit in disease management utilizing the drug?

Thus, appropriately selected biomarkers can be used to confirm the MOA while patient selection biomarkers can be used to guide the selection of the most appropriate patients for therapies. Correct use of biomarkers for patient selection can enrich the treatment population by identifying those most likely to benefit from the treatment. This reduces the risk to the non-responder population and, by allowing earlier assessment of therapeutic efficacy, substantially shrinks the costs of development.

Over the past two decades, molecular biomarkers have become established components of clinical research in a way few could have foreseen. Today, approximately 50% of new molecular entities are estimated to have a biomarker element also in development.1
**Biomarkers are key in both clinical development and patient care**

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Biomarkers’ role in optimizing likely therapeutic effects and outcomes is seen as critical to improving success rates in the oncology development pipeline, yet biomarkers come with their own set of challenges to be overcome, notably:

> the need to understand precisely what the biomarker can measure and the role it can play in the development or clinical management process
> the need for a reliable test or assay which can reproducibly demonstrate the required results
> the constant evolution of testing technology which reshapes the boundaries of detection and clinical applicability
> the possibility of a novel biomarker emerging, forcing a re-evaluation of the planned development strategy.

All are factors that need to be considered with due care.

**Timing is Key**

Many of these issues are shaped by timing of the biomarker utilization in the development process.

> Biomarkers used to confirm the MOA ideally need to be available at the initiation of clinical development (Phase I) in order to be most useful.
> Biomarkers for patient selection can be developed prospectively with drug and biomarker development occurring in parallel, or they can be developed by effectively playing “catch-up” at a later stage.
The approach to patient selection biomarker development will naturally affect the choices and the decisions that have to be made.

There is no hard and fast ruling on which option is best; biomarkers can be introduced as patient selection criteria at any point in the course of development (including post-registration). While regulators might prefer their early introduction – and many pharma R&D groups have a similar preference – circumstances are not always cooperative.

As examples, the development of Herceptin was guided from its earliest stages by the use of the selection biomarker – HER2 – as an integral part of the original development plan for the product. However, in the cases of Erbitux® (cetuximab) and Vectibix® (panitumumab) in colorectal cancer (CRC), the original hypothesis that the level of epidermal growth factor receptor (EGFR) expression was critical for success of the antibody turned out to be non-helpful. Only recently has the crucial role of KRAS wild type (or non-KRAS mutant carrying) tumor cells been found to be a necessary element for Erbitux functioning and thus has been introduced into the drug’s label. Thus in this latter case, early attempts at identifying a patient selection biomarker proved unsuccessful.

It is an interesting speculation, however, that had the initial indication for Erbitux been for head and neck cancer – where 95% of tumors are KRAS wild type – this particular dependence upon KRAS wild type may have gone unnoticed. Thus, the expression and distribution of a particular parameter are important considerations too. Care must be taken when extrapolating from one tumor type to another.

**Biomarkers are not Just Facilitating Improved Patient Therapy; Biomarkers are Forcing Changes in the Definitions of Potential Target Patient Populations**

The advent of biomarkers has permanently changed the clinical development process.

One of the most far reaching impacts has been on diagnostic pathology. Now a particular tumor type is no longer classified by its histological properties alone; biomarkers are increasingly being used to segment particular tumor types by molecular profile so, for example, breast cancer is now recognized as containing luminal A, luminal B, basal type, erbB2, and triple negative sub-populations, each of which have a different management strategy, and vary in patient prognoses and therapy response characteristics. Similar changes are occurring in leukemias and lymphomas, as well as other tumor types.
Defining these patient groups and their likely prognostic outcomes is of key importance to defining clinical trial populations and thereby potential market indications. These definitions translate into defining the relative patient numbers, which are such a critical part of the development strategy.

**Evolving Biomarker Knowledge is Producing Further Change in Therapeutic Choices**

As previously described, subjects with KRAS-mutated tumors are now being largely excluded from clinical trials of EGFR inhibitors in CRC. Many investigators are now taking this approach further by examining BRAF variants in determining outcomes and also looking at biomarkers for microsatellite instability.5

In non-small cell lung cancer (NSCLC) also, the characterization of molecular alterations that serve as biomarkers is changing the way we look at the disease. Biomarker detection has played a key role in defining the clinical development and use of the EGFR tyrosine kinase inhibitors (TKIs), including Iressa® (gefitinib) and Tarceva® (erlotinib). Biomarkers are now involved in the development of a range of new therapies, including those inhibiting anaplastic lymphoma kinase (ALK)-fusion proteins that have been associated with various cancers such as NSCLC.6,7

Marketed products now live in an environment where the market’s size (target population) is continually being affected by evolving patient selection biomarkers, and these effects on the potential use and sales of a drug can be large.

**Biomarker-Facilitated Patient Selection Approaches are Evolving**

Up until a few years ago, biomarker-informed patient selection depended upon the outcome of just a few biomarker assays. This process is changing and is having a profound effect on the level of complexity of clinical development.

For therapies with well-defined pathways, there is now an evolution towards more sophisticated collections of biomarkers to identify patients who are appropriate for therapy. Components of the collections might include patient-genetic, tumor-genetic and drug mechanism biomarkers. Even among therapies with less well-defined pathways, efforts to develop multi-parameter scoring systems to select patients appropriate for treatment are underway (examples are the systems used for guiding breast cancer adjuvant therapy).
Three major approaches have been pioneered.

1. A **prospective enrichment strategy** is possible where an assay has been defined in advance. The enrichment design is planned with the goal of understanding the clinical value of a treatment based around subpopulations defined by a specific predefined marker. Patients are randomized first, according to the presence or absence of biomarkers, before undergoing further stratification into drug or placebo groups. This approach is still comparatively rare. It is also possible that patients who are positive for the biomarker of interest and patients who are negative for the biomarker are randomized into the same treatment arms to ascertain whether patients negative for the biomarker do not benefit from treatment. Finally, patients found to be negative for the selection biomarker may be excluded from study entry. The choice of approach should be governed by science and regulatory considerations.

2. A **post-hoc statistical analysis** occurs when patients are randomized to either drug or placebo and biomarkers are used, not to define inclusion criteria, but to stratify patients as they are being enrolled. In this way, analysis can be performed – either in parallel, or at program completion – to determine which, if any, of the stratified groups are correlating with response. Either single or multiple analytes can be used to build up a detailed picture, and an algorithm can be created to provide a score that correlates with patient outcome. This has the advantage of developing and validating both assay and scoring system in parallel.

3. A completely **retrospective analysis** is one in which biomarker samples are collected from an unselected patient population but assay results are not correlated with response until trial end. Indeed with this approach, the sets of analytes to be used in future trials are not known until the analysis is complete.

The choice between Phase II trial designs has major implications for patient accrual, sample size, study complexity, and risk. It might also have consequences for the subsequent labelling of the assay, for the drug label and for later reimbursement. Herceptin was developed using a single-arm Phase II study but with HER2-patient selection as an entry criterion. Subsequently, development was restricted to the HER2+ population, and this restriction was carried into the label indication and presumably into reimbursement practices.

Biomarkers as Part of the Clinical Development Process

Biomarkers are proving to be of immense value during the drug development process, but a variety of factors are involved in decision making at each stage. Careful consideration and planning are beneficial in achieving success.

Currently, such multi-analyte assays most often appear during the late stage of development because relatively large outcome-based datasets are needed for their refinement and validation. But the expectation is that this approach will evolve to become part of the overall development plan for many drugs. As noted, such scoring systems can be expanded to include the patient genetic information that governs drug clearance and metabolism. These latter data have been shown to potentially impact tamoxifen therapy.

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**Biomarkers as part of the preclinical development process**

- **Basic research**
  - Target ID and validation
  - Compound and safety profiles
  - Trial optimization: patient enrichment/stratification

- **Preclinical development**
  - Biomarker and drug development
  - Characterize tumor and compound biology

- **Approval and launch**
  - Clinical utility and validation
  - Post-approval

- **Expansion of indications**
  - Credible plan

- **Compound and safety profiles**
  - Credible drug

- **Trial optimization**
  - Credible plan

- **Target ID and validation**
  - Credible target

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Preclinical Development

Investment decisions around biomarker development at the preclinical stages are very much a judgment call. However, there are some considerations that should be strong factors in decision making. If a new molecular or biological entity (NME/NBE) is thought to affect a unique pathway, then a reliable means of measuring its effects is essential to establish MOA and confirm that the drug does indeed modulate its intended target. Conversely, a product that is non-specific in action will provide less of an incentive for up-front investment.

The most important factors relate to the proposed MOA. There have been many instances of drugs demonstrating early success as a result of off-target activities with misleading effects for later development. For example, agents with a previously unappreciated alkylating function often score very strongly in preclinical tests and can be a source of misinformation relative to the effects being measured.

Some agents have multiple parallel activities. In the case of Nexavar® (sorafenib), the key issue was in identifying the primary pathway of interest because its original role as a RAF kinase inhibitor was subsequently found to be subordinate to the stronger VEGFR TKI activity, which eventually led to its adoption as a therapy for renal cell cancer – several other anti-angiogenic RTKs have followed a similar course. Validation of a drug against its intended target or pathway should be a priority from the earliest stages.

Validation of a drug against its intended target or pathway should be a priority from the earliest stages

A range of assay technology exists to measure particular biomarkers, including immuno-histochemistry (IHC), enzyme-linked immunosorbent assays (ELISA), fluorescent in situ hybridization (FISH), and real-time polymerase chain reaction (RT-PCR). Early validation of the selected process to rigorous standards is key to the development of a test which can be taken forward with confidence and will provide robust data. Validation of the purpose of the assay is critical at this stage to assess the reproducibility and reliability of the assay. As the assay matures and is used in clinical practice, then the way it is to be used and by whom will also play a greater part.
Phase I Drug Development

As previously described, biomarkers are now playing an essential role in the Phase I process. Phase I trials are the prime opportunity to demonstrate not only the postulated MOA in patients for the first time but also to begin to explore a biomarker’s predictive value for the selection of patients. Through the use of robust pharmacodynamic (PD) biomarkers (for example, phospho-biomarkers), it may be possible to correlate target and/or pathway inhibition with drug activity and possibly clinical outcome. This would be an early indicator that a drug produces a desired outcome through modulation of the intended target or pathway. Conversely, if correlation is poor, it might be worthwhile at this stage to seek out alternative assay methodologies or to re-examine translational studies to further confirm the drug’s intended MOA.

Although clinical responses might be infrequent in Phase I trials and statistically significant correlations difficult to achieve, it may be possible to observe trends in correlating a biomarker or tumor sub-type with patient response. Phase I is a time for exploration. Whereas Phase I trials used to be traditionally about determining toxicity issues, there are now many more development strategies that can be tried. For example, studies can determine the practicality of collecting samples in a reliable way. Pharmacodynamic biomarkers also provide valuable information on how frequently a drug hits its target in patients’ tumors. The type and timing of sample collection are key here, as well as the use of techniques such as phospho-biomarkers to enhance marker detection.

One of the key stumbling blocks at Phase I is that the lack of tumor tissue and heterogeneous character of the populations can often lead to inconclusive results. Increasingly, good practice determines that you spend time deciding how best your chosen assay can be used to separate one population from another, which in itself helps to define patient numbers for the trials (and may suggest that the Phase I trial be conducted in a specific target population, although this can be a risky business if the postulated MOA is not yet fully validated).

Many companies are now using Phase Ib trials among early responders to selectively use predictive biomarkers to explore the concept of a particular subpopulation that may be relevant for that drug. In instances of well-established pathways (for example, for erbB inhibitors) patient selection is moving into the Phase I setting so that only defined EGFR+ and HER2+ patients are included.

Case Study
Biomarker Assay Validation – PI3 Kinase Pathway

The PI3 kinase (PI3K) pathway is key for many targeted therapies, and a true understanding of the mechanisms involved is critical to the design and successful development of assay technology across a range of potential therapeutics.

The PI3K pathway is a central axis in cell signalling, and alterations in this pathway are found in many different types of cancers. Biomarker interrogation of the pathway is therefore critical to maximize the value of dozens of assets currently in biopharma pipelines.

The major alterations in this pathway are found in two major molecules: PI3KCA and PTEN. PI3KCA is an oncogene and drives tumor progression through mutation or amplification. Analyzing alterations in PI3KCA is relatively straightforward with current technologies. In contrast, PTEN acts downstream as a tumor suppressor and counteracts the actions of PI3KCA.

PTEN seems to be the key factor in determining activity of the PI3K pathway, in both translational and clinical studies. Because there are many aberrations that can result in a loss of PTEN function – mutation, deletion or truncation and promoter methylation – measuring PTEN is a complicated affair and developing the right analytical method is critical.

Any assay for PTEN needs to be clinically feasible, meaning that it can be performed in a routine laboratory setting and in an expedient timeframe, since PTEN appears to be a biomarker that could be used to select patients for treatment. Thus, a deep understanding of the biology of complex biomarkers like PTEN must be married to an equally deep expertise in assay development to ensure that the right biological questions are answered as a result of confidence in the analytical method.

Assays that are useful to interrogate the PI3K-AKT pathway include the following:

> PI3KCA mutation by RT-PCR
  * Constitutive activation of the PI3K pathway can occur through mutations in the PI3KCA gene. In some breast cancer studies, PI3KCA mutations have been associated with poor prognosis.

> PTEN loss by IHC
  * The assessment of PTEN within a patient’s tumor is a complex endeavour as there are many aberrations that can result in loss of PTEN function. Loss of PTEN function plays a large role in determining how a patient’s tumor will respond to PI3K pathway modulation.

> PI3KCA amplification by FISH
  * Constitutive activation of the PI3K pathway can also occur because of multiple copies of the PI3KCA gene. This occurs with high frequency in squamous NSCLC.
These biomarker assays, together with other downstream biomarkers (such as p-AKT, p-4EBP1, p-S6, etc.) provide a pathway profile of a patient’s tumor. Armed with this information, a clinical development team is better able to design clinical trials and target patient populations who may benefit from treatment with the therapeutic agent.

The images below illustrate a process engaged in by Quintiles to develop a validated assay for PTEN using the IHC methodology.*

An initial step of screening commercially-available PTEN biomarkers against cell lines that are negative, wild-type and mutated for PTEN was used as a selection tool for the most specific reagent. This was then followed by assessment of the selected reagent on formalin-fixed, paraffin-embedded cell lines. Finally, the reagent was “translated” to tissue where the final reaction conditions are optimized.

PTEN IHC offers additional benefits since assessments of normal against tumor PTEN levels can be made within the same specimen. The levels of PTEN on both normal and tumor tissue can further be obtained in numerical values using image analysis measurements.*

Quintiles process for PTEN IHC assay validation

MWW, MCF-7, T47D, ZR75-1, DU145, PC3, LNCaP

T47D (wild-type PTEN)

Du145 (one wild-type allele, one mutant allele)

PC3 (PTEN homozygous deletion)

No tumor PTEN staining, high stromal cell staining

Moderate tumor PTEN staining, high stromal cell staining

*Patent pending.
Developing the Prototype Assay
A key question at this stage is whether to develop the prototype assay in-house or outsource to a central laboratory. A number of issues can play a part here.

> **Access to proprietary assay platforms**
> **The need to engage early at a translational level — an essential part of the process to link the biomarker successfully to its proposed target and to help in the elucidation of molecular pathways affected by a drug**
> **The ability to objectively analyze and validate existing exploratory assays that may have played a part in early development**
> **The capability to take any selected assay through to full stage development**
> **Access to a global skill set capable of supporting a multi-trial program — especially if the assay is to be used throughout the clinical development stages**
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Phase II Drug Development

Phase II is where biomarkers can make or break a development program, steering it to success or leading it to a cost-contained, early conclusion. Continued verification that the MOA holds for the treated trial population is required. But here the importance of biomarkers for patient selection grows substantially.

As noted previously, patient selection biomarkers can be developed in parallel with Phase II and confirmed in Phase III, or biomarker selection development can be delayed until after registration.

To address the latter strategy first: the delayed approach is increasing in risk because regulators would prefer better definition of treatment populations (thus potentially demanding such markers at a late development stage). Also once approved, introduction of biomarker patient selection can reduce the size of the treatment population bringing on significant pricing issues. At a minimum, appropriate patient samples should be collected during the registration trial process.

For the former strategy, trials at this stage should collect clinical biomarker data that can potentially be used to guide future development or patient management. Biomarker data could lead to identification of a relevant molecular patient selection profile that predicts for response to the drug in a clearly identified patient population. When identified in an unrelated tumor type, this profile might anticipate the potential for drug benefit. The same may hold true for identifying a molecular profile of drug resistance.

This approach can also guide future clinical development by indicating a disease type that might have been part of the original clinical plan, but for which biomarker data would suggest is not a good candidate disease.

Randomized Phase II designs which incorporate biomarkers are increasingly being used to provide more sophisticated results and to establish the predictive utility of a biomarker.9,10
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1. A **prospective enrichment strategy** is possible where an assay has been defined in advance. The enrichment design is planned with the goal of understanding the clinical value of a treatment based around subpopulations defined by a specific predefined marker. Patients are randomized first, according to the presence or absence of biomarkers, before undergoing further stratification into drug or placebo groups. This approach is still comparatively rare.

   It is also possible that patients who are positive for the biomarker of interest and patients who are negative for the biomarker are randomized into the same treatment arms to ascertain whether patients negative for the biomarker do not benefit from treatment. Finally, patients found to be negative for the selection biomarker may be excluded from study entry. The choice of approach should be governed by science and regulatory considerations.

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There are also challenges to resolve to ensure clear interpretation of the results. For example, whether the biomarker is also correlated with prognosis can complicate the correlation with predictive efficacy for the drug. There is also the question of whether the biomarker has a clear binary output – allowing easy stratification into groups of those patients who will respond and those who will not (for example, as occurs in patients whose tumors harbor KRAS mutations). In many cases (for example, PTEN) expression of the biomarker is a more continuous variable and interpreting the results may be more subjective and make it difficult to establish clear thresholds.
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In NSCLC and CRC, the characterization of molecular alterations that serve as biomarkers is changing the way we look at these diseases.

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**Phase III Drug Development**

By the time of the conduct of the registration study(s), a development program's focus will have shifted to the practical aspects of biomarker research and should include discussions with the regulatory bodies about the roles that have been selected for the biomarkers.

Aspects to be considered include: how will the biomarker and accompanying test be used to support real-life clinical management; is the clinical trial assay (CTA) appropriate to go through to commercial development or will a new companion diagnostic be required? If so, how should the diagnostics partner be selected, and what concordance measures will be required to ensure consistency? Will the assay be available in all geographies at the same time as the new drug enters the market? These issues will be returned to in more detail in part 2 of this series.

**Summary**

Increasingly, biomarkers are being incorporated into all stages of oncology drug development to provide a strong rationale and guidance for the design and use of targeted therapies. More and more, regulators are pressing for accumulated data showing a clear relationship between targeted activity and outcome, as well as a good explanation of how the marker assessment was chosen and the assay and trials designed.

What has become apparent over the past few years is that segmented patient populations and highly targeted treatments are driving a surge of interest in biomarker research and the technology and infrastructure needed to support it. Much time and effort can be wasted in repeating trials when biomarker assumptions were made at too early a stage or when decisions could not be backed with data and robust analysis. Crucially, some mistakes can be hard to put right – for example, prices fixed at the time of launch are not easy to renegotiate if subsequent biomarker research has the effect of reducing the size of the target population. There are strong reasons, therefore, for drug developers to put biomarker research at the center of their clinical development program and not at the periphery.

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**Plan well, for some mistakes can be hard to put right**
The approach to patient selection biomarker development will naturally affect the choices and the decisions that have to be made. There is no hard and fast ruling on which option is best; biomarkers can be introduced as patient selection criteria at any point in the course of development (including post-registration). While regulators might prefer their early introduction – and many pharma R&D groups have a similar preference – circumstances are not always cooperative.

As examples, the development of Herceptin was guided from its earliest stages by the use of the selection biomarker – HER2 – as an integral part of the original development plan for the product. However, in the cases of Erbitux® (cetuximab) and Vectibix® (panitumumab) in colorectal cancer (CRC), the original hypothesis that the level of epidermal growth factor receptor (EGFR) expression was critical for success of the antibody turned out to be non-helpful. Only recently has the crucial role of KRAS wild type (or non-KRAS mutant carrying) tumor cells been found to be a necessary element for Erbitux functioning and thus has been introduced into the drug’s label. Thus in this latter case, early attempts at identifying a patient selection biomarker proved unsuccessful. It is an interesting speculation, however, that had the initial indication for Erbitux been for head and neck cancer – where 95% of tumors are KRAS wild type – this particular dependence upon KRAS wild type may have gone unnoticed. Thus, the expression and distribution of a particular parameter are important considerations too. Care must be taken when extrapolating from one tumor type to another.

Biomarkers are Not Just Facilitating Improved Patient Therapy; Biomarkers Are Forcing Changes in the Definitions of Potential Target Patient Populations

The advent of biomarkers has permanently changed the clinical development process. One of the most far reaching impacts has been on diagnostic pathology. Now a particular tumor type is no longer classified by its histological properties alone; biomarkers are increasingly being used to segment particular tumor types by molecular profile so, for example, breast cancer is now recognized as containing luminal A, luminal B, basal type, erbB2, and triple negative sub-populations, each of which have a different management strategy, and vary in patient prognoses and therapy response characteristics. Similar changes are occurring in leukemias and lymphomas, as well as other tumor types.
Biomarkers are key in both clinical development and patient care.

- In drug development:
  - Mechanism of action
  - Pharmacokinetics
  - Pharmacodynamics

- In patient care:
  - Diagnostic
  - Prognostic
  - Predictive markers for selection of therapies likely to show patient benefit

For registration program:
- Predictive markers as surrogates of response
  - Surrogate marker for patient benefit (response or toxicity)

For overall characteristics of the treatment population:
- Prognostic and diagnostic markers

Biomarkers' role in optimizing likely therapeutic effects and outcomes is seen as critical to improving success rates in the oncology development pipeline, yet biomarkers come with their own set of challenges to be overcome, notably:

- The need to understand precisely what the biomarker can measure and the role it can play in the development or clinical management process
- The need for a reliable test or assay which can reproducibly demonstrate the required results
- The constant evolution of testing technology which reshapes the boundaries of detection and clinical applicability
- The possibility of a novel biomarker emerging, forcing a re-evaluation of the planned development strategy.

All are factors that need to be considered with due care.

Timing is Key

Many of these issues are shaped by timing of the biomarker utilization in the development process.

- Biomarkers used to confirm the MOA ideally need to be available at the initiation of clinical development (Phase I) in order to be most useful.
- Biomarkers for patient selection can be developed prospectively with drug and biomarker development occurring in parallel, or they can be developed by effectively playing “catch-up” at a later stage.

About the Authors

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Board certified in oncology and internal medicine, Dr. Groves has more than 20 years’ experience in drug development as corporate officer/senior manager, clinician and researcher. Prior to joining Quintiles in August of 2007, Dr. Groves was at Ligand Pharmaceuticals Inc., starting in August 1999 as Vice President, Project Management and corporate officer. From 1994 until joining Ligand, Dr. Groves held a number of positions at Sanofi Pharmaceuticals, most recently as Vice President, Project Direction, where he was responsible for the worldwide strategy of and project direction for late-stage Sanofi oncology projects. From May 1991 through October 1994, Dr. Groves served as Senior Project Director for the research division of Sterling Winthrop Corporation, and served as acting Vice President, Discovery and Clinical Research, Immunoconjugate Division. He was Director of Clinical Research and Development at CETUS Corporation from 1989 through 1991.

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Dr. Jason Hill works with Quintiles’ Central Laboratories, using his experience in tissue-based biomarkers to engage clinical and translational scientists in biopharma. Dr. Hill was formerly Director of Molecular Biology at Targeted Molecular Diagnostics (TMD), a company specializing in the development and deployment of tissue-based biomarker assays for oncology clinical trials. Quintiles acquired TMD in 2008. Dr. Hill received his PhD in molecular genetics from the University of Illinois at Chicago and completed his post-doctoral studies at the Cleveland Clinic Foundation in 2004. He developed model systems for screening of chemical libraries to identify p53-modulating compounds. A p53-activating compound that he helped characterize is currently in clinical studies.

**Christopher Ung**
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Christopher Ung directs anatomic pathology services and leads the implementation of digital pathology and tissue imaging services into Quintiles' central laboratories globally. Mr. Ung also focuses on business and strategic development efforts for Quintiles’ oncology customers and partners. Prior to joining Quintiles, Mr. Ung was Chief Operating Officer for Targeted Molecular Diagnostics and previously served as Chairman of the Pathology Business Group at Dako. He has engaged in numerous initiatives for personalized medicine and managed the development and commercialization of both the HercepTest™ and pharmDx EGFR assays, the industry standards used to identify patients for treatment with Herceptin and Erbitux. Mr. Ung has lectured internationally to business, medical and drug development leaders on topics relating to biomarker development, digital pathology and personalized diagnostics. He has authored several research articles and made television appearances to discuss issues relating to personalized medicine and diagnostics.

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Introduction

The availability of targeted compounds aimed at the molecular pathways involved in oncogenesis has created major opportunities that have led to the development of highly specific cancer treatments, with the potential for greater efficacy and lower toxicity than conventional cytotoxic agents. Imatinib (Gleevec®/Glivec®) displays the full potential for these new approaches and has revolutionized the treatment of chronic myeloid leukemia (CML), while treatments such as trastuzumab (Herceptin®) have transformed the futures of many patients with HER2+ breast cancer.

Yet despite these advances, drug development in oncology remains painfully slow. It is a costly and often wasteful process; just 8% of new molecular entities in oncology make it through to market, less than in almost any other area.1 Moreover, late-stage failures are common, with approximately six out of ten oncology drugs tested failing in Phase III.2

In the first of this two-part series, strategic drug developers Eric Groves, Jason Hill and Christopher Ung explain why biopharma cannot afford to ignore the growing surge of interest in biomarkers in oncology and discuss their critical role in the modern-day clinical development process.