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The cancer biomarker problem

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Genomic technologies offer the promise of a comprehensive understanding of cancer. These technologies are being used to characterize tumours at the molecular level, and several clinical successes have shown that such information can guide the design of drugs targeted to a relevant molecule. One of the main barriers to further progress is identifying the biological indicators, or biomarkers, of cancer that predict who will benefit from a particular targeted therapy.

In the past decade, there have been considerable improvements in the way that human tumours are characterized. Knowledge of cancer at the molecular level has therefore increased greatly, and this has catalysed a shift towards using targeted therapies for cancer. However, there has been much less progress in the development of clinical tools to determine which patients are most likely to benefit from particular targeted therapies. The articles that follow in this Insight summarize the tremendous advances that have been made in the molecular characterization of tumours, and this overview outlines the considerable challenges that remain before these advances can have the maximum clinical impact.

Much progress has recently been made in defining tumour cells in terms of two important features: DNA copy number (that is, the number of copies of each genetic region or chromosome, a property that is commonly aberrant in cancer cells), as discussed by Lynda Chin and Joe Gray (see page 553); and patterns of gene expression, as reviewed by Laura van 't Veer and René Bernards (see page 564). Advances in DNA-microarray technology have made it possible to define almost completely the chromosomal gains and losses in individual tumours and the resultant changes in gene expression, at very high resolution in a robust and reproducible manner (Box 1). When coupled with focused resequencing of specific genes to look for point mutations that are not detectable by DNA-microarray analysis, it is now possible to characterize individual human cancers in unprecedented molecular detail.

Box 1 | Technologies for characterizing tumours

Molecular alterations in tumours can be uncovered by using technologies that assess changes in the content or sequence of DNA, its transcription into messenger RNA or microRNA, the production of proteins or the synthesis of various metabolic products. Below is a partial list of the various types of information that can be obtained about tumours and some of the technologies that are used to make those assessments.

DNA copy-number assessment
- Comparative genome hybridization to DNA microarrays

Mutation screening
- DNA sequencing
- Mass-spectrometry-based genotyping
- Mutation-specific PCR

Gene-expression profiling
- DNA microarrays
- Multiplex PCR

MicroRNA-expression profiling
- DNA microarrays
- Multiplex PCR

Proteomic profiling
- Mass spectrometry

Phosphoproteomic profiling
- Mass spectrometry after immunoprecipitation with phosphotyrosine-specific antibodies

Metabolomic profiling
- Mass spectrometry

The impact of this improvement in characterization, initially on the conduct of clinical trials and subsequently on clinical practice, is potentially enormous. Consider, for example, the sudden interest of doctors and the general public in single-nucleotide-polymorphism-based genotyping to find alleles associated with an increased risk of developing certain diseases; this occurred on the heels of a remarkable series of discoveries of 'risk alleles' for cancer, diabetes and other diseases over the past year[1]. The uptake of molecular tools in oncology practice is similarly promising. It is more difficult logistically, however, because tumour tissue, which can be difficult to gain access to, is required rather than germline DNA, which can be obtained from any cell. Therefore, it is important to be able to assess tumours non-invasively. Several technologies offer the promise of analysing tumours comprehensively at the molecular level, both quantitatively and qualitatively, without subjecting patients to multiple clinical interventions to obtain tissue (Box 2). In particular, the use of proteomic technologies to analyse cancer-associated changes in serum proteins is discussed by Samir Hanash, Sharon Pitteri and Vitor Faca (see page 571), and the molecular imaging of tumours *in situ* is reviewed by Ralph Weissleder and Mikael Pittet (see page 580).

Collectively, the fields of genomics, proteomics and molecular imaging have matured to a level at which they are ripe for clinical exploitation. But there are considerable barriers to broad implementation of these technologies in the clinic. The challenge is discovering cancer biomarkers. Although there have been clinical successes in targeting molecularly defined subsets of several tumour types — such as chronic myeloid leukaemia, gastrointestinal stromal tumour, lung cancer and glioblastoma multiforme —using molecularly targeted agents, the ability to apply such successes in a broader context is severely limited by the lack of an efficient strategy to evaluate targeted agents in patients. The problem mainly lies in the inability to select patients with molecularly defined cancers for clinical trials to evaluate these exciting new drugs. The solution requires biomarkers that reliably identify those patients who are most likely to benefit from a particular agent. In this overview, I consider the complex set of barriers — logistical, scientific and commercial — that impede progress, and I argue for a public–private consortium approach to cancer biomarker discovery.

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Types of cancer biomarker

The topic of cancer biomarkers is broad, encompassing multiple disciplines, and it has been the focus of several recent reviews, workshops and planning committees[2]. Although most people agree on the scope of the problem, there is no consensus on a strategy to move forward and even scepticism about the ultimate usefulness of cancer biomarkers[3,4]. Here, I discuss three types of cancer biomarker — prognostic, predictive and pharmacodynamic — each of which can aid in the rational development of anticancer drugs (Fig. 1). Prognostic biomarkers allow the natural course of an individual cancer to be predicted, distinguishing 'good outcome' tumours from 'poor outcome' tumours, and they guide the decision of whom to treat (or how aggressively to treat). Notable recent examples include breast-cancer gene-expression signatures — marketed for clinical use as Oncotype DX (Genomic Health), MammaPrint (Agendia) and the H/I test (AviaraDx) — that estimate the probability of the original breast cancer recurring after it has been resected (that is, surgically removed). These multigene-expression tests can now be used to decide who should receive systemic therapy to eliminate any remaining tumour cells (that is, adjuvant therapy) after surgery, to reduce the risk of relapse.

Predictive (or response) biomarkers differ in that they are used to assess the probability that a patient will benefit from a particular treatment. Patients with breast cancer in which the gene *ERBB2* (also known as *HER2* or *NEU*) is amplified (that is, extra copies are present) benefit from treatment with trastuzumab (Herceptin), whereas when the gene encoding the oestrogen receptor is expressed by the tumour, the patients respond to treatment with tamoxifen instead. Similarly, patients who have leukaemia with the *PML–RARA* translocation respond to all-*trans* retinoic acid, and those with the Philadelphia chromosome (which contains the *BCR–ABL* fusion gene) respond to imatinib mesylate (Gleevec or Glivec). Biomarkers for leukaemia have traditionally been assessed by using routine cytogenetic analysis, but additional predictive information can be gained by using genotype-based analysis. For example, in patients with chronic myeloid leukaemia who develop resistance to imatinib mesylate, distinct mutations in the genetic region encoding the kinase domain of BCR–ABL predict differential sensitivity to the newer ABL inhibitors dasatinib and nilotinib[5]. In addition, mutations in the genetic region encoding the kinase domain of the epidermal growth-factor receptor (EGFR) predict the sensitivity of lung tumours to erlotinib or gefitinib[6]. Conversely, distinct mutations in *KRAS* predict that patients with lung cancer will fail to respond to these inhibitors and that patients with colon cancer will fail to respond to therapy with EGFR-specific antibody[7,8]. And, in glioblastoma multiforme, distinct mutations in the genetic region encoding the extracellular domain of EGFR predict sensitivity to EGFR inhibitors but only in cases in which the tumour-suppressor protein PTEN is also intact[9].

Pharmacodynamic biomarkers measure the near-term treatment effects of a drug on the tumour (or on the host) and can, in theory, be used to guide dose selection in the early stages of clinical development of a new anticancer drug. In cytotoxic chemotherapy, the dose that is used to determine antitumour activity in phase II clinical trials is usually the maximum tolerated dose, discovered in a phase I dose-escalation study. But this might be a less relevant end point for drugs that have been optimized to bind to a specific molecular target. An alternative way to determine an appropriate dose is to measure the impact of the drug on its target across a range of doses (known as a target engagement study) and then to select a dose for phase II clinical trials on the basis of the magnitude of target modulation. For example, imatinib mesylate has been shown to block the protein-kinase activity of BCR–ABL in the tumour cells of patients with chronic myeloid leukaemia at the same doses that induce clinical remission, which are well below those associated with toxicity. The utility of pharmacodynamic biomarkers might also extend beyond the clinical trial phase of drug development. Recently, the magnitude of BCR–ABL kinase activity inhibition was found to correlate with clinical outcome, possibly justifying the personalized selection of drug dose based on the results of target engagement assays[10].

Box 2 | Non-invasive strategies for the molecular profiling of cancer

Several technologies offer the promise of detecting cancer without the need for carrying out a biopsy or a surgical procedure and (when cancer is present) of allowing certain molecular studies of tumour cells. The examples listed are discussed here, in the accompanying Insight articles or in the cited references.

- Analysing circulating tumour cells[15,17] (see page 580)
- Carrying out mutation-specific PCR on circulating DNA[26]
- Using proteomic approaches to study serum or plasma (see page 571)
- Imaging tumours *in situ* at the molecular level (see page 580)
- Assessing autoantibodies specific for tumour cells[27]

Studying biomarkers in patients with solid tumours

Predictive and pharmacodynamic biomarkers are increasingly being used in clinical trials of leukaemia drugs. But there has been much less uptake in clinical trials for treating solid tumours, because it is challenging to gain access to tumour tissue so that biomarkers can be measured. Unlike leukaemia, in which large numbers of tumour cells are present in the peripheral blood, the only time at which access to solid tumour tissue is guaranteed is at diagnosis, when the tumour is biopsied or resected. Although this approach might be sufficient to study prognostic biomarkers, it severely limits the application of predictive and pharmacodynamic biomarkers, because these measurements are ideally carried out concurrently with treatment. In addition, experimental drugs are typically evaluated in patients with late-stage disease, who do not routinely undergo additional tumour biopsies.

Despite much discussion on this topic, most clinical trials in patients with solid tumours do not include provisions to obtain additional tissue samples. The reasons for this include concerns about slower patient enrolment in trials and insufficient research infrastructure to obtain and process tumour samples for molecular analysis. The reluctance of the clinical trial community to force the issue by designing studies that require additional tissues may be short-sighted. Successful 're-biopsy' studies have been carried out and have resulted, for example, in the discovery that patients with lung cancer who relapse during treatment with EGFR inhibitors have acquired mutations in the genetic region encoding the kinase domain of EGFR since the initial biopsy[11].

An alternative to the re-biopsy approach is to evaluate the experimental drug in patients who are already scheduled to undergo a surgical procedure as part of their treatment regimen. In this case, the treatment is administered for a brief period (days to weeks) before surgery, and the effect of the intervention on the tumour is assessed by comparing the surgically removed sample with the diagnostic biopsy sample (obtained before treatment). In one example of this approach, the proportion of proliferating tumour cells (as determined by staining cells with an antibody specific for the antigen Ki-67) was measured in patients with breast cancer who were undergoing resection after 2 weeks of neo-adjuvant

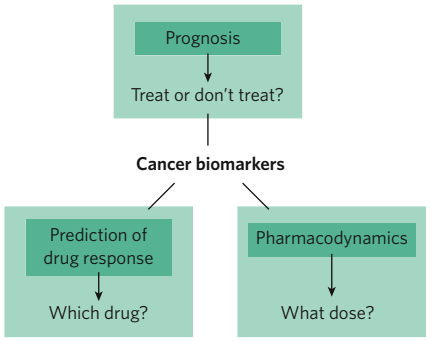

Figure 1 | Types of biomarker. Cancer biomarkers can be used for prognosis: to predict the natural course of a tumour, indicating whether the outcome for the patient is likely to be good or poor (prognosis). They can also help doctors to decide which patients are likely to respond to a given drug (prediction) and at what dose it might be most effective (pharmacodynamics).

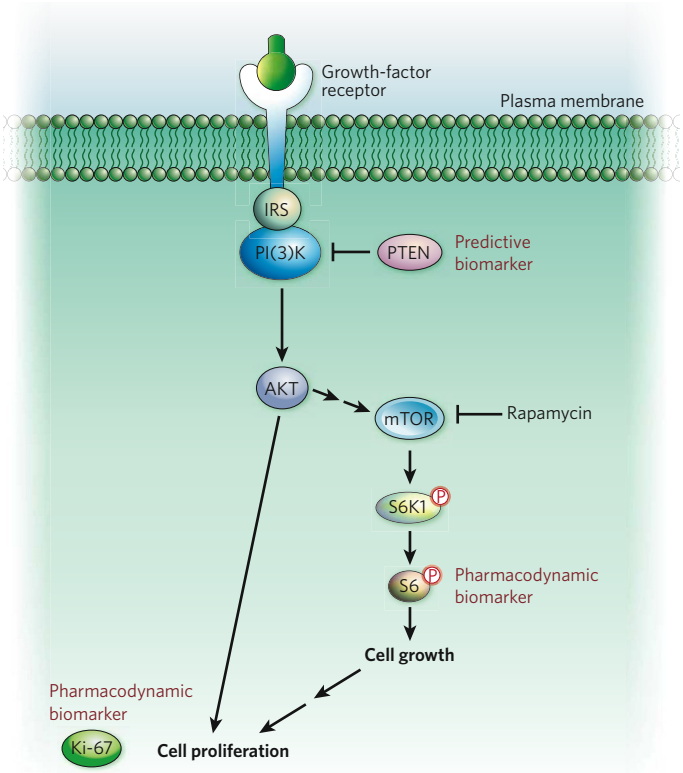

Figure 2 | Biomarkers in the PI(3)K–PTEN–mTOR pathway. The phosphatidylinositol-3-OH kinase (PI(3)K)–PTEN–mTOR signalling pathway is aberrantly activated in many tumours, leading to dysregulation of cell growth and proliferation. Activation of the pathway can be assessed by biomarkers such as loss of PTEN mRNA or protein production in tumour tissue. Biochemical inhibition of mTOR by rapamycin can be assessed by biomarkers such as the abundance of the phosphorylated form of the ribosomal protein S6, and its therapeutic effects on tumour cells can be assessed by the proliferation marker Ki-67. IRS, insulin-receptor substrate; S6K1, ribosomal protein S6 kinase, 70-kDa, polypeptide 1.

(that is, presurgical) hormonal therapy. In most patients, the proportion of tumour cells that were Ki-67$^+$ was smaller than in the pretreatment biopsy sample, and the magnitude of this reduction correlated with progression-free survival (that is, the length of time in which the individual's disease did not worsen)[12]. In another example, patients with glioblastoma multiforme received the mTOR inhibitor rapamycin (Fig. 2) for 1 week before a salvage resection (which is often carried out to reduce symptoms associated with tumour recurrence after initial surgery) and then postoperatively until evidence of tumour progression was obtained by magnetic resonance imaging[13]. On the basis of preclinical studies showing that loss of *PTEN* expression made tumours more sensitive to rapamycin[14], eligibility for the study was restricted to patients whose tumours showed loss of PTEN production, as determined by analysing the tissue from the initial surgery. The proportion of Ki-67$^+$ cells was substantially reduced in the tumours of half of the patients, and this reduction was correlated with the extent to which mTOR's kinase activity was inhibited, as measured by staining for the phosphorylated form of the ribosomal protein S6 (which is downstream of mTOR in the intracellular signalling pathway) (Fig. 2). Therefore, analysing tumour tissues for two biomarkers — Ki-67 and phosphorylated S6 — showed the importance of documenting target inhibition for guiding patient-specific dose selection.

Because the neo-adjuvant trial design and the re-biopsy trial design are challenging, there is great interest in developing tools that can gain access to tumour cells non-invasively, namely by a blood test. This process would help to gather the molecular information that is required to make informed decisions during clinical development of a new drug and, after regulatory approval, to identify those patients who are most likely to benefit from the drug. Much effort is focused on whether this information can be gained by studying the very small proportion of tumour cells that circulate in the blood or the cancer-associated proteins that are secreted or shed into the blood.

Recently, it has become clear that these rare circulating tumour cells (CTCs) are present in the blood of many patients with cancer and can be recovered by immunoaffinity purification, using antibodies specific for cell-surface proteins restricted to epithelial cells. For patients with breast cancer, the number of CTCs per 7.5 ml of blood is a prognostic biomarker[15], and there is great interest in determining whether a decrease in CTC number concomitant with treatment predicts long-term benefit. In prostate cancer, CTCs have been shown to contain the same genetic alterations as the primary cancer (such as amplification of the gene encoding the androgen receptor), indicating that CTCs could provide a window onto the tumour genome[16]. Despite these promising reports, CTCs can be detected reliably only in patients with advanced metastatic disease, and the number of CTCs is extremely small — often only 5–10 cells per 7.5 ml of blood. But evidence obtained by using microfluidic technologies indicates that CTCs might be present in a much larger proportion of patients (including those at earlier stages of disease) and in about 10–100-fold greater quantity[17].

Instead of studying the tumour cells themselves, it might be possible to characterize the molecular composition of a tumour indirectly, by sampling the blood and searching for alterations in the serum proteins. The idea of using blood to track cancer growth is well established in terms of measuring changes in the abundance of proteins that are secreted by the tumour (for example, prostate-specific antigen for prostate cancer, carcinoembryonic antigen for multiple cancers, CA125 for ovarian cancer and α-fetoprotein for liver cancer and testicular cancer). But this technique is not broadly applicable because of the paucity of known biomarkers and because most of the markers are organ specific rather than tumour specific. Mass-spectrometry-based proteomic technologies offer the promise of a genome-scale search for tumour-specific serum biomarkers and could transform the early detection and molecular characterization of cancers through non-invasive means. The initial enthusiasm for cancer-specific serum proteomics was tempered by problems with reproducibility. But progress in overcoming limitations in the sensitivity of detection, in the ability to make quantitative measurements and in the standardization of sample collection has led to increased confidence in data collection, and several large-scale, collaborative serum proteomic programmes are now underway (see page 571).

Discovering predictive biomarkers

Moving beyond the technical considerations of collecting tumour tissue, there is considerable debate about precisely which measurements will be most informative for predicting how a patient will respond to treatment. It is clear that gene-expression signatures have value as prognostic biomarkers (see page 564), but their value for predicting responses to particular treatments is less convincing. One reason is that the tissue collection associated with most treatment studies is incomplete, so the number of samples available is often too small to allow a formal evaluation of the hypothesis. As mentioned earlier, prognostic biomarker studies analyse tissue obtained at diagnosis, whereas studies assessing treatments (in which predictive or pharmacodynamic biomarkers could be measured) are typically carried out in patients with advanced disease, who do not routinely undergo surgery for additional tissue samples to be collected. Therefore, the 'data-driven' (unbiased) approach to prognostic biomarker discovery that is advocated by van 't Veer and Bernards (that is, surveying the entire genome rather that working from a hypothesis about a candidate biomarker) cannot be implemented for predicting treatment responses without overcoming enormous logistical challenges. An alternative strategy might be to search for candidate predictive gene-expression signatures in preclinical models (such as cell-line and animal models) and then to validate these in the clinic, thereby reducing the number of patients required for tissue collection[18]. But early reports of success using this approach have been challenged[19].

By contrast, the genotyping of tumour DNA has been found to be more useful for predicting responses to treatment, but the path to broader

clinical application of this technique remains unclear. The lung cancer, glioblastoma multiforme and chronic myeloid leukaemia examples discussed earlier show the value of knowing the 'mutation status' of the genes encoding the targets of protein-kinase inhibitors, but these studies also reveal the complex role of secondary mutations in predicting responses to treatment. For example, amplification of the gene encoding the drug target (in the absence of mutation) might be associated with sensitivity to treatment[6]. Therefore, predictive biomarkers must incorporate DNA copy-number assessment together with mutation detection. For most protein-kinase inhibitors, resistance is associated with secondary mutations in the gene encoding the drug target, so these mutations must be considered as an explanation for treatment failure. Tests that focus exclusively on the common oncogenic mutations in the gene encoding the drug target are therefore unlikely to detect drug-resistant variants that contain these secondary mutations. Furthermore, these drug-resistant alleles might be present in only a small proportion of the tumour cells initially and would be not be detected unless highly sensitive techniques, such as single-molecule sequencing, were used[20]. Also, mutations in additional genes such as *RAS* or *PTEN* can dampen sensitivity to inhibitors of the drug target that has mutated (as was the case in the lung cancer and glioblastoma multiforme examples discussed earlier). Therefore, a predictive biomarker test must incorporate these additional variables. Finally, patients who do not carry alterations in the gene encoding the drug target can have clinical responses, as in the case of treating lung cancer with EGFR inhibitors. Such tumours might be sensitive to EGFR inhibitors as a result of mutations in genes (either known or unknown) that regulate the EGFR pathway, but this association can be discovered only by more extensive sequencing.

The value of tumour-DNA genotyping is clear, but the challenge now is to decide how broadly and deeply to genotype. All of the measurements described here can be made with available technologies, but costs escalate quickly depending on the scale: that is, on the number of genes analysed by sequencing and the level of sensitivity required to carry out a thorough analysis. The data-driven (unbiased) approach analogous to that used for gene-expression profiling would require complete (or at least exon-focused) resequencing of the entire cancer genome. Such proposals cannot be considered today because of the prohibitive cost, but this barrier might soon disappear with the advent of improved sequencing technologies. Even then, the computational infrastructure required for data analysis and comparisons across tumour populations will be formidable. In the interim, it seems logical to use a more hypothesis-driven approach, such as genotyping patients for known cancer-associated mutations by using platforms that can easily be expanded to accommodate new discoveries. For example, the presence or absence of 238 cancer-associated mutations in 1,000 tumour-derived cell lines and archived tumour tissue samples has been determined using mass-spectrometry-based genotyping[21]. The value of such assessments in a clinical setting remains to be determined.

Because most of the anticancer agents in development inhibit targets in specific molecular pathways, another option would be to focus on pathway-specific biomarkers. The activation state of many pathways can be assessed by using antibodies that recognize downstream substrates in the pathway only when they are in their 'activated' form. The most common examples are phospho-specific antibodies, which recognize the substrates of various protein kinases after the kinases have phosphorylated them. Some of these antibodies have been used to document the inhibition of protein-kinase activity in clinical trials[13]. So far, pathway activation has been studied with only a few antibodies in the context of a known genetic lesion. But more global approaches such as those based on mass spectrometry could be used as an initial screening step to find tumours that are appropriate for focused sequencing, which could then identify the causative genetic lesion. Indeed, in global surveys of the phosphotyrosine-containing proteome in lung cancer, previously unidentified protein-tyrosine-kinase fusion proteins were found[22]. Extending this approach to other post-translational modifications, such as the acetylated or ubiquitylated proteome, is feasible as soon as robust antibodies that recognize the modifications of interest are available. Although these approaches rely on the direct assessment of pathway substrates to measure pathway activation, more indirect approaches might be possible using gene-expression signatures. The underlying concept — that pathway activation is associated with a specific gene-expression signature — has been shown for cell lines engineered to express specific oncogenes and for tumours with specific pathway-activating alterations such as loss of PTEN production[23–25].

Commercializing cancer biomarkers

Even if the logistical and scientific issues in cancer biomarker discovery can be overcome, there is concern that the commercial incentives to develop these complex assays for broad clinical use might not be in place. The process is expensive and lengthy because the biomarker must be identified, an assay that measures the biomarker reliably in clinical samples must be developed (validation) and the capacity of the biomarker to make a clinical distinction must be demonstrated (qualification). One strategy is to pair the diagnostic test with the therapeutic agent, an idea that is best illustrated by the development of a standardized immunohistochemical assay for ERBB2 protein (HercepTest; DAKO). This test identifies which patients with breast cancer are most likely to benefit from treatment with the ERBB2-specific antibody trastuzumab. In this model (sometimes referred to as the Dx/Rx model), the incentive for identification, validation and qualification of a predictive biomarker (all of which are essential to obtain drug approval) lies with the drug manufacturer, who therefore drives its commercial development, often in collaboration with a molecular diagnostics company. One huge challenge is that discovery of the biomarker and clinical testing of the drug are interdependent and move forward in parallel. Therefore, crucial decisions about biomarker-driven selection of patients for the phase III registration trial (which is required for drug approval) must often be made before the utility of the biomarker has been shown.

An alternative to the Dx/Rx model is to use pathway-based biomarkers to classify cancers into categories that are more appropriately matched to the many pathway-focused inhibitors in development. In this model, tumours would be categorized at diagnosis into distinct molecular subtypes, similarly to the current practice of karyotyping for chromosomal alterations cancer cells from all patients who are diagnosed with leukaemia. The challenge lies in discovering the biomarkers that will provide the best classification. As is the case for the Dx/Rx model, the incentive to discover and validate these biomarkers seems to lie with the companies developing pathway-specific drugs. But the scale of the research effort required to discover and commercialize pathway-based biomarkers is enormous and is probably beyond the capacity of most companies. Furthermore, the first company to succeed in defining predictive pathway biomarkers will make the process much simpler for its competitors, because the method of pathway classification used to gain approval will be in the public domain.

Another consideration is the question of biomarker ownership. The discovery of predictive biomarkers is likely to be a gradual process, building on the collection of large data sets from preclinical studies and clinical trials carried out by pharmaceutical companies in collaboration with academic partners. Furthermore, the biomarkers that ultimately prove most useful in the clinic are likely to include a suite of measurements that are modified over time as further clinical evaluation improves their predictive power. In this case, when (if ever) is it appropriate for any party to claim ownership of the biomarker? Will the filing of patents on various components of a multi-parameter biomarker impede commercial development? And is patent protection even essential for molecular diagnostic companies to enter the cancer biomarker arena? If patent protection is required, then one option to avoid the patenting of biomarkers themselves is to patent the tools that were developed to measure the biomarkers.

Regulatory authorities, although generally focused on approval of anticancer drugs, also have a crucial role in biomarker development, because validation and qualification of the predictive biomarker is required for drug approval in the Dx/Rx model. This level of regulatory endorsement provides the evidence, often demanded by health-care

payers (such as insurance companies and government agencies), to justify the reimbursement of patients and hospitals for the biomarker test, and it is a powerful commercial incentive for molecular diagnostic companies to enter the biomarker arena. But if the drug-development community moves away from the Dx/Rx model, the role of regulatory endorsement is less clear. In the United States, a biomarker test can be marketed without a formal demonstration of its clinical value if the technical aspects of the biomarker measurement are certified under Clinical Laboratory Improvement Amendments (CLIA). CLIA certification has encouraged the development of numerous highly innovative molecular assays, but few are put to the more rigorous test of prospective clinical qualification because of the time and expense required. At present, the price charged for these tests is often reimbursed by health-care payers, but growing pressure to reduce health-care costs will lead to greater scrutiny. With the move to more expensive assays that survey tumours for mutations or pathway activation, it will be crucial that the regulatory strategy used to approve these assays inspires health-care payers to be confident about reimbursement so that an overly burdensome initial proof of clinical value is not required. Similar to the current process of provisional drug approval, a strategy of provisional biomarker approval that encourages small, innovative molecular diagnostic companies to enter the marketplace can be envisaged.

A public–private biomarker consortium

The 'omic' technologies reviewed in this Insight are poised to launch a comprehensive approach to cancer biomarker discovery. The scale of this endeavour, which includes preclinical studies and large clinical trials, is considerable, making it expensive. Collaboration with the pharmaceutical industry is essential because experimental anticancer drugs are an essential reagent for biomarker discovery experiments. Many cancer biomarkers will be broadly applicable (for example, they will not be restricted to predicting the response to a single drug), so a collaborative, precompetitive partnership with industry is warranted. Similar to government-sponsored projects such as the Human Genome Project and The Cancer Genome Atlas, early results from collaborative biomarker discovery projects should be released into the public domain to encourage further study and to avoid downstream intellectual-property disputes that could delay commercialization efforts. It is time to establish a consortium approach using a public–private partnership model to solve the cancer biomarker problem. All the stakeholders — patients, doctors, pharmaceutical and molecular diagnostic companies, regulatory agencies and heath-care payers — stand to benefit. ■

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