Challenges of Cancer Biomarker Profiling

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Abstract

Objectives: New biomarkers are being developed to identify individuals at risk for cancer, detect disease earlier, determine prognosis, detect recurrence, predict response to particular agents, and monitor response to treatment. This article attempts to address some of the challenges facing the research and medical communities in the delivery of new biomarkers for individualized medicine.

Methods: A variety of issues and barriers can affect the transfer of clinical tests from research to clinical practice. Differences in sample collection, handling or storage, and profiling techniques may influence the protein profile obtained by any method.

Results: Standard procedures and quality check schemes are necessary because there is a lack of definition to guarantee reproducibility of new procedures. From technical and economic viewpoints, the assay has to be sufficiently robust to be completed in community-based hospitals. Although traditionally cancer patients were treated with drugs of low toxicity or of high tolerance regardless of their efficacy in a given patient if the benefits of that drug are proven in both experimental and clinical conditions, recent advances have provided opportunities to adapt “tailored” treatment modalities. The evolving trend is the usage of patterns of markers instead of a single marker. Further challenges in biomarker development are in finding the relevant markers that have the right degree of specificity and sensitivity and a reliable test to measure the outcome.

Conclusions: Discovery, testing, and validation of clinically appropriate and commercially useful tumor markers should permit individualization of therapy.

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1. **Introduction**

Cancer is a major public health problem in the United States and other developed countries. Currently, one in four deaths in the United States is due to cancer [1]. The disparity in the evolution of diseases with identical clinical and pathologic presentation is certainly related to molecular differences that we are still unable to detect. The development of biomarkers by genomic and proteomic means holds promise for the future.

### Table 1 – Challenges to and advances that may facilitate the development of clinically useful tissue biomarkers

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>FACTORS TO SUPPORT ADVANCES</th>
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<tr>
<td>Biologic factors</td>
<td>Defining the biology of prostate cancer and its processes with precision</td>
</tr>
<tr>
<td>- Progressive biologic heterogeneity with transient expression of certain features is a characteristic of tumor cells. Biologic heterogeneity is present both among cells within the tumor at a given time and in cells during the development of the tumor from earlier to later points in time. In addition, biomarkers may be affected by therapy and as yet uncharacterized, host factors. Biologic heterogeneity includes multiple pathways to the same end points and the variable metabolism of biomarkers, including posttranslational trans-modifications.</td>
<td>- Enhanced interaction among investigators of different disciplines and institutions. - Greater appreciation of the biokinetics of both cancer and its biomarkers permitting more dynamic views of how cancers evolve.</td>
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<td>- Age and the presence of other diseases also introduce variation in biomarker levels among individuals. Other physiologic or pathologic processes may generate biomarker profiles similar to those found in patients with tumor disease states.</td>
<td>- Defining host biology: pharmacogenomics and pharmacoproteomics</td>
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<td>- Exogenous substances that affect biomarker presence and concentration. Foods, drugs, and natural alternative therapies are well-known interferences.</td>
<td>- Biologic profiling does have the prospect of individualizing therapy, maximizing efficacy, and minimizing toxicity. Ideal markers would reflect both cancer activity and individual sensitivity to therapy.</td>
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<td>Clinical pathologic factors</td>
<td>Defining biomarkers and surrogate end points</td>
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<td>- Requirement to define and standardize more precisely concepts of the biologic events against which biomarkers are to be measured (eg, normal variation, different disease states). New tools for accurate detection of preneoplastic neoplasia, micrometastatic spread, and states of early or aggressive cancer recurrence need to be developed.</td>
<td>- Need for developing a consensus about definitions that are widely accepted and applied.</td>
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<td>Analytical sensitivity and detection limit</td>
<td>Creating guidelines for appropriate clinical use of each biomarker</td>
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<td>- Assay sensitivity needs to be sufficiently high to allow biomarker quantitation at concentrations that have biologic relevance. Clinical detection and measurement of biomarkers of this type, at worst, could lead to unnecessary investigation and therapy or, at best, unnecessary chronic anxiety for the patient.</td>
<td>- Plan a series of national multidisciplinary initiatives aimed at (1) surveying the quality control programs, (2) coordinating from a scientific viewpoint the activities in this area and producing guidelines for the clinical use of cancer biomarkers, (3) standardizing the procedures, and (4) developing laboratory quality control programs for the analysis of cancer biomarkers of validated clinical relevance in multicenter clinical protocols.</td>
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<td>- There is a lack of definition of standard procedures, standard reference materials, and quality control schemes necessary to ensure accuracy and reproducibility.</td>
<td>Standardization and stringency of analytical technology</td>
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<td>- There is a lack of clear guidelines for good manufacturing/laboratory practice and quality control requirements for all phases of biomarker development.</td>
<td>- Further standardize preanalytical, analytical, postanalytical methodology. However, standardization of biomarker assay technology involves considerations beyond analytical sensitivity and specificity. For example, advancing toward standardized technology, the advantages of comparability between various studies must be weighted against the desire and need for innovation and conditions that require protocol flexibility.</td>
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<tr>
<td>Intellectual property</td>
<td>High-quality specimen and clinical data repository</td>
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<td>- Ownership of a biomarker is a key element of its commercialization. Considering the cost of developing and validating a biomarker, no company will invest in a biomarker for which it cannot be assured a reasonable return on investment by means of protection of intellectual property. Only a very small fraction of candidate biomarkers demonstrate real clinical utility, such that the demand for return on investment is similar to the drug development models. These issues are well appreciated by bio-industry and demonstrated by their lack of interest in commercialization of the plethora of candidate biomarkers reported in the literature.</td>
<td>- Need for specimen and data repositories that address in a bioethical manner patient consent, confidentiality, specimen provenance, technical preparation, and storage.</td>
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the promise of “individualized medicine,” bringing a new dimension to disease diagnosis, classification, intervention, and therapeutics.

The recent mapping of the human genome together with advances in DNA microarray technology have led to an explosion of genomic information and the identification of a plethora of candidate molecular biomarkers and therapeutic targets. Yet for these candidate markers to be translated to the clinic, gene expression or copy-number alterations need to be evaluated at the protein level. In the “post-genomic era,” proteomics might be the key to understanding systems biology, that is, how the organism works. Proteomics have the ability to directly assess protein expression profiles, which gene expression can do only indirectly. Because the proteome changes constantly with the state of the organism, biologic variations that occur over time can easily be addressed. Proteomics are therefore expected to discover new oncologic biomarkers that could help diagnose cancer at an early stage or establish tumor-specific profiles that could predict tumor aggressiveness [2]. High-throughput platforms for analysis of protein expression and functionality in clinical samples and protein microarrays have been developed. These array platforms provide a quantitative or semiquantitative means for measuring protein expression and also provide the ability to identify posttranslational modifications, such as phosphorylation. Their increasing use in health research will significantly help the rapid validation and therefore translation of the massive amounts of data generated by modern genomic technologies, thereby fostering a new synergy between bench and bedside.

A variety of issues and barriers can affect the movement of clinical tests from research to clinical practice (Table 1). This article addresses some of the challenges facing the research and medical communities in the delivery of new biomarkers for individualized medicine [3,4].

2. **What is exactly a biomarker? Refining the definition**

According to the National Institutes of Health, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [5]. Though historically often a physical trait or physiological metric, the term biomarker is now typically shorthand for a molecular biomarker. There is a wide range of variations in the complexity of biomarkers going from the simplest (hair color, blood pressure, or cholesterol levels) to more complicated examples, such as mRNA profiles of tumors [6,7] and, more recently, combinations of proteins [8,9]. Cancer biomarkers are either produced by the tumor or by the body in response to the tumor. Six different types of biomarker can be differentiated in cancer:

1. **Early detection**: this biomarker is used for screening patients to discover cancer at an early stage.
2. **Diagnostic**: this biomarker can help identify classical histopathologic characteristics in assessing presence or absence of cancer. Prostate-specific antigen (PSA) [4], CA125, and nuclear matrix protein 22 (NMP22) are examples of such biomarkers currently used in clinical practice. Others are being investigated, such as carbonic anhydrase IX (CAIX), which expression on fine-needle aspiration biopsies could be useful to determine malignancy of small solid renal masses thereby assisting with therapeutic decision [10].
3. **Prognostic**: this biomarker is used to dissect the outcome of patients into different prognostic risk groups thereby allowing individualized management. It can foretell the course of a disease. It helps in our understanding of tumor behavior thereby identifying aggressive phenotype through methods such as survival probabilities. These markers provide information about the likely clinical course of a disease thereby guiding therapeutic decisions [11]. Classical prognostic markers are hormone receptors in breast cancer and PSA in prostate cancer. More recently, low levels of CAIX expression were found to be associated with a worse prognosis in patients with localized and metastatic renal cell cancer [12] and current phase 3 adjuvant clinical trials of specific CAIX antibodies in high-risk patients without metastases are ongoing [13].
4. **Predictive**: this biomarker is used to predict whether the treatment (drug or other therapy) will be effective or to monitor the effectiveness of the treatment. It can help identify the best treatment modality.
5. **Therapeutic target**: this biomarker can help identify patients who will benefit from a particular treatment regimen. It identifies the molecular targets of novel therapies and is affected by therapy. For example, breast tumors expressing estrogen receptors (ERs) are best treated with an antiestrogen such as tamoxifen or an aromatase inhibitor [7].
Surrogate end point: this biomarker is used to substitute for a clinical end point or to measure clinical benefit, harm, or lack of benefit or harm. Surrogates could replace traditional end points, such as mortality due to disease or the recurrence or relapse of disease. Biomarkers can reduce time factors and costs for phase 1 and 2 clinical trials by replacing clinical end points. An example for such a surrogate end point is posttherapy PSA changes to evaluate drugs in the clinical trial setting or in clinical practice. Criteria were proposed to screen for treatment effects in prostate cancer clinical trials on the basis of the hypothesis that PSA declines reflect significant cell kill in response to agents that cause reduction in overall tumor burden [14]. However, in clinical practice, the meaning of a biomarker used as a surrogate end point should be interpreted with caution. PSA has long been used to monitor patients after prostate cancer treatment because it is assumed that it provides an accurate measure of treatment efficacy. Nevertheless, the correlation between biochemical failure, clinical failure, and survival has been questioned [15]. For example, salvage radiation therapy after radical prostatectomy can provide short-term PSA control, but the eventual improvement in survival remains uncertain [16,17].

3. The impact of biomarkers on drug development and the debate around intellectual property

Currently, the development of new therapeutic agents outstrips the development of cognate biomarkers. This mismatch results in clinical trials in which only a minority of patients benefit from these targeted therapies, hurting drug development and potentially reducing the introduction of novel agents that may benefit well-selected patients. Drug development in all therapeutic areas, including oncology, has entered a critical period driven by the economic need of pharmaceutical companies to reduce time and expense to launch a new drug. Therefore, there is a clear need for pharmaceutical firms to develop robust, efficacious, and safe biomarkers that can be used in the development of new drugs to help in making decisions to withdraw suboptimal compounds at the earliest stage possible and to maintain promising drugs in development. These biomarkers can be in the form of disease markers, toxicity markers, or markers that segregate a population into responders and non-responders.

In that setting, the rationale for intellectual property is to facilitate and encourage the pursuit of innovation and the disclosure of knowledge into the public domain for the common good, by granting authors and inventors exclusive rights to exploit their works and invention for a limited period. Similarly to drug development, there are many potential discovered biomarkers but only a small minority will finally be useful in clinical practice. Patents over novel biomarkers can provide the biomedical industry the opportunity to recoup research and development costs and to garner a profit by exploiting exclusive rights. But unlike drugs where there are many means to capture the intellectual property (the compound itself, method for synthesis of the compound, the utility and final formulation of the drug), patent of a biomarker is usually more problematic. A common example is immunohistochemistry. Unless an investigator develops his own antibody, he rarely owns the antibody. It is more common that the investigator purchases the antibody from a company, who may or may not have protected the intellectual property of the antibody. If multiple antibodies for the same target are present on the market, the model becomes more complex. It is possible that only one antibody has the diagnostic utility or, the converse is also possible, that multiple antibodies may have the same utility depending on the epitopes, affinity, and other properties. Because of these issues, excellent candidate biomarkers never enter the phase of development and validation.

Nevertheless, biomedical industry’s claim for intellectual property can produce potential negative effects on ethical and social policy concerns that have to be kept in mind [18]. For example, there is a great concern regarding patents held by an American company giving exclusive rights to test for alterations of the BCRA1 gene, which are believed to account for approximately half of the inherited breast cancer cases [19]. Although the company may have invested large sums of money, this monopoly may preclude further optimization of the genetic testing of BCRA1 and increase costs.

4. Bringing the ideal marker to clinical practice: “easier, better, faster, cheaper”

Open any journal today and you will find multiple articles on the “next” biomarker. However, the market is not invaded by new biomarkers. This is because many of biomarkers lack clinical utility. For a new biomarker to be clinically useful, it has to answer a clinically relevant question and provide
information that is not available in a more simple and cost-effective way. However, too often, the newly described biomarker does not have any repercussion in clinical practice despite scientific value or validity. For example, many biomarkers are correlated with tumor stage or grade. Although this interesting finding may help us understand molecular pathways of the disease, it does not influence clinical management. A representative example is the ER status of women with breast cancer. It is now well established that these women have a greater benefit from adjuvant chemotherapy when their tumor does not express ER [7]. Nevertheless, ER status is only moderately useful in decision-making, considering adjuvant treatment, because both women with ER-positive and ER-negative breast cancer can benefit from adjuvant systemic therapy, although to a different extent. Furthermore, if ER status may indicate general sensitivity to chemotherapy, it does not help in selecting one regimen over another. However, we should not reject these biomarkers because it is possible that future progress in tumor biology or therapeutics could show a clinically relevant role. Thus, any newly discovered biomarker needs to provide a benefit over these standard criteria or at least improve their accuracy. Before a biomarker assay can be implemented in the community setting, it needs to address four concepts: “easier, better, faster, and cheaper”.

4.1. Easier

Easier refers to the assay’s analytical performance and robustness. For an assay to be clinically applicable, it should be able to be performed easily and promptly in a clinical environment. Specimen volumes are limited, specialized equipment must be economically justified, and training of technical staff for performance of the assay must be considered. For example, fluorescence in situ hybridization is not a routine, robust clinical assay. Although it is commonly performed in many hospitals, screening large numbers of samples in routine clinical environments is impractical and expensive. Therefore, assay characteristics such as simplicity, robustness, and accuracy, are necessary. Toward this end, biomarkers introduced in clinical laboratories should be able to be assessed on automated platforms that can perform multiple assays thereby limiting training of staff. Obviously, the assay should also be valid and reproducible. Moreover, for the marker to be evaluated in a simple and efficient way, the specimen has to be reliable. Most of the methods in use to manipulate tissues for macroscopic evaluation were developed in the first quarter of the 20th century and few changes have occurred since then [20]. Characterization of molecular changes requires delicate tissue morphology and RNA preservation. Because traditional fixatives usually result in fragmented DNA, recovery of DNA and RNA is often done on frozen tissues. Moreover, many factors such as time between removal and processing, as well as anoxic changes when there has been a clamping of the blood supply may influence the molecular profile of the tissue. Changes in the molecular profile can also occur during the processing itself [21]. Finally, frozen specimens must be preserved at −80 °C in storing facilities, which makes the routine storage of large numbers of samples expensive and impractical. Therefore, moving toward a more individualized characterization of the disease will imply major changes in the organization of clinical practice. Manipulations will have to be standardized, technical staff will have to be trained, and technology platforms will have to be adapted, which will undoubtedly raise economic concerns. Before we reach that point, current studies of potential markers should pay attention to the collected tissue and think of the way it could be managed in a clinical care environment.

4.2. Better

Better is by the far the most important challenge that has to be addressed. Demonstrating information equal to current clinically available variables is not enough. Any newly discovered biomarker should provide additional information that is helpful to the clinician for the management of the disease. The primary question is therefore: “Does the new biomarker significantly improve our ability to predict X, given all the other known clinical parameters?” The answer to this question requires more than conventional univariable and multivariable analyses with associated hazard rates and p values. The performance of predictive models, including or excluding any new putative biomarker, needs to show clinically significant improvement of performance to claim any real benefit. This is a tough task and only few biomarkers have passed this test. Kattan et al, for example, developed and internally validated a prognostic model that adds plasma transforming-growth factor-β1 and interleukin-6 soluble receptor to standard clinical predictors [22]. They found that addition of these molecular parameters to a standard clinical nomogram improved the prediction of disease recurrence after radical prostatectomy by a statistically and prognostically substantial margin (increase in predictive accuracy
from 75% to 84%). In a recent article, Raaijmakers et al. showed that the combination of human glandular kallicrein-2 and percentage of free PSA was a powerful prognostic tool to predict minimal prostate cancer within the PSA range of 4–10 ng/ml [23].

4.3. Faster

Faster means that the new biomarker should be able to make the information available in an efficient and timely manner. Even if the marker has been proven to offer valuable information regarding the disease, an unreasonable period of time for its delivery would considerably decrease its interest, particularly when therapeutic decisions have to be made promptly for the patient’s safety and well-being.

4.4. Cheaper

Cheaper is essential for a biomarker to be cost effective. With health care expenditures reaching record levels, medical decision-making is increasingly affected by economic concerns. Many parameters must be considered when assessing economic impact of a biomarker: cost of the assay, potential benefits of the assay (avoidance of ineffective therapy, benefit from targeted therapy), and positive/negative predictive values of the assay. Potential savings of new biomarker can be tremendous, particularly when dealing with newly released drugs that are very costly and might take several cycles of administration before any objective response.

5. Validation in a clinically relevant environment

In many cases, specimens used for the development of novel biomarkers correspond to patients operated a long time ago and they might no longer represent challenges encountered in daily clinical practice. Tissues are crucial for the development of biomarkers, but constant clinical practice evolution makes the face of the disease change by the time the biomarker is mature. For example, in the 1970s, 10% of renal tumors were discovered incidentally compared to 61% in 1998 [24]. Since those incidental tumors have been proven to have a better outcome than symptomatic tumors, samples used to develop biomarkers may not be applicable to current patients. Breast cancer is also a good paradigm of this problem. Biomarkers that predict response to therapy for tumors of average size of 6 cm have little utility in a care environment where the average breast cancer is <2 cm [25]. Even the historic data on estrogen and progesterone receptor expression and correlation with response to estrogen blockade and long-term disease-free survival are of questionable accuracy when compared to the disease as it is currently diagnosed.

Another limitation is that any information brought by a novel biomarker must be interpreted along with established markers of the disease. As such, even if the finding is of significant statistical value, the overall added information regarding clinical importance is often small if nonexistent. Furthermore, reproducibility is a main issue because a growing number of biomarkers are investigated by numerous teams with inherent differences regarding population size, demographics, techniques used, and interpretation of results. For example, p53 expression was originally proven to predict the outcome in patients with bladder cancer undergoing cystectomy [26]. However, a recent meta-analysis of the data of 117 studies showed that there was only a frail association between p53 and bladder cancer recurrence, progression, or mortality [27]. Finally, many negative results are not published either because of the lack of enthusiasm of authors for claiming negative findings or because of the reluctance of scientific journals to publish negative reports. This leads to publication biases because many experiences will not reach the scientific community.

6. The discovery-validation-implementation paradigm: a schema for biomarker development

The utility and importance of biomarkers has been recognized and biomarker discovery efforts are now common in both academic and industrial settings. Yet despite intensified interest and investment, few novel biomarkers are used in clinical practice, and their rate of introduction is falling [28]. The reasons for this disjunction are manifold and reflect the long and difficult pathway from candidate biomarker discovery to clinical assay, and the lack of coherent and comprehensive processes (pipelines) for biomarker development.

The development of various emerging biomarkers might be considered as a process that is conceptually similar to therapeutic drug evaluation. Drug development is a highly regulated process, especially from the point where it enters human testing. As a result we have the Food and Drug Administration (FDA) schema of phases. However, unlike a clinical trial design in which there are three phases, research on biomarkers has
largely been guided by intuition and experience. In 2002, the National Cancer Institute’s Early Detection Research Network developed a five-phase approach to systematic discovery and evaluation of biomarkers. Below is a modification of these structured phases:

**Preclinical testing**: biomarkers are developed in vitro or in animal models. It may not occur for every biomarker because an appropriate model may be lacking. This phase is essentially a hypothesis-generating step.

**Phase 0**: development of preliminary assays on patient samples. This phase does not take into account the potential benefit of the biomarker.

**Phase 1**: biomarker is tested on a small group of patients to determine its ability to discriminate between health or disease (or similar appropriate question). This stage includes discovery and marker optimization processes: define the marker, establish the prediction rules, and determine the assay cut-off points in a well-defined population. At this point, the assay may not be the final assay for patient care.

**Phase 2**: independent validation of the accuracy of the assay. The performance of the presumed biomarker is measured on independent cases. The reproducibility and robustness of the assay are appraised and reference ranges are determined. The assay should demonstrate an adequate dynamic range and show that the biomarker has a relationship to drug exposure or the grade or stage of the biologic process. Once proven to be analytically robust, the assay must be measured in a relevant, representative target population to determine normal or background variation between individuals and within individuals over time.

**Phase 3**: the efficacy is determined in large patient populations other than the discovery population (typically multi-institutional collaboration). The objective is to yield the sensitivity (ability to detect true positives) and specificity (ability to reject false positives) of the biomarker. Ideally, this phase would consist of randomized trial to show that the use of assay results generates better clinical decision-making than current standards.

**Phase 4**: post-approval reporting and testing for other disease processes or disease stages.

This proposed schema is not only an intellectual process but also provides a clear scale by which researchers and patients can apprehend the state of advancement of the development of a biomarker. The expected failure rate of biomarkers in development can be expected to be similar to the one of drugs. Biomarker development must not be considered to be any easier than drug development. It is crucial that researchers be aware of the complexity and poor success rate of potential biomarkers trying to enter the clinical arena.

### 7. Biomarkers in drug development

The major challenges in cancer drug development are discriminate responses, efficacy, and toxic side effects. The pharmaceutical industry, drug policy makers, and administrators are constantly looking for novel pharmacogenomic or pharmcoproteomic studies that might identify potential biomarkers to help solve these problems. Indeed, the molecular target of most therapeutic agents remains unknown. This has led to expensive development and production of cancer drugs because of a lack of information on targets, which can be used to test the efficacy of therapeutics. Novel methodologies are intended to identify individualized patient benefits of therapies, minimize the risk of toxicity, and reduce the cost of treatment. The primary challenge is which type of biomarker to use across the wide spectrum of disease processes. Phenotypic expression markers (RNA/protein) vary among cell types and change over time and show different posttranscriptional or posttranslational modifications. However, proteins are abundant, easily accessible, and show promise for measuring outcomes and studying changes in disease state. Another challenge in characterizing biomarkers is the complexity of the expression profile of potential markers in benign conditions close to the disease phenotypes.

### 8. Improved performance through combination

No single biomarker is likely to have perfect predictive accuracy for a specific neoplasm or disease stage. Instead, panels of biomarkers seem to be a promising alternative for the use in clinical laboratories. The performance advantages of panels have been confirmed in several recent publications [29–33]. One factor that should be considered when designing a panel of biomarkers is to choose biomarkers that reflect changes in independent pathways. If two biomarkers come from the same or associated pathways, factors contributing to their increase or decrease in cancer are likely to be the
same and, thus, their combined usage is unlikely to be more informative than when they are used individually.

9. Perspectives

Biomarkers have the potential to be used clinically to screen for, diagnose, or monitor the activity of diseases and to guide molecular targeted therapy or assess therapeutic response. However, discovery experiments have often overemphasized the significance of novel candidates, and efforts to further credential such candidates have been rare. This has been due in large part to a lack of effective and efficient strategies to determine which biomarker candidates justify the great investment of time and money required for assay development, optimization, and demonstration of analytical robustness. Demonstration of clinical utility and compliance with regulatory requirements remain formidable, uncertain, and costly steps toward the commercialization of novel biomarkers. The high costs of developing new diagnostics have combined with relatively low profit margins compared with drugs to foster a very conservative approach on the part of the diagnostics industry, marked by avoidance of newer and potentially riskier approaches. To date, there are no clear success stories in which discovery proteomics has led to a deployed biomarker. A large concerted effort is required to advance the field of biomarkers through systematic discovery, verification, and validation. Discovery and development of biomarkers must shift toward a more organized and industrialized setting similar to that of drug development framework. When these changes occur, we can expect improvements in both screening and development of biomarkers, although we should stay aware that very few molecules will make it to the routine clinical practice. In fact, it is most unlikely that a single biomarker will have the single decision as to a diagnosis or a prognosis of a particular pathology. It may rather be that a constellation of markers will have more predictive power. There is no doubt that progress will continue based on the collaboration of basic researchers, clinicians, and biomedical firms.

Conflicts of interest

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References


