Stratified Medicine: Maximizing Clinical Benefit by Biomarker-Driven Health Care

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Abstract
Stratified medicine involves the use of biomarkers to differentiate patient populations into subsets that provide more detailed information about the specific causes of conditions, and predict how patients will respond to a given drug or combination of drugs. Biomarker-driven patient stratification can empower clinicians by providing accurate assessments of patient status (diagnostic and prognostic utility) in order to strategize treatment planning and delivery (predictive and monitoring utility) based on information extracted from biomarker profiles. This approach may also help presymptomatic individuals by delaying the onset of disease, minimize the severity of the disease, or possibly prevent disease occurrence. Patients and clinicians may benefit from this approach as it may allow for the transformation of current empirical ‘medical practice’ to efficient data-driven ‘individualized therapeutic strategies’ with a low risk of medical error. The health care industry may also benefit from this approach by designing clinical trials based on appropriate patient stratification. Here, recent advances in the field of stratified medicine are highlighted in the context of our efforts to integrate this rapidly evolving concept into our research, and to ultimately develop potential diagnostic/prognostic/predictive products and nutritional solutions for individual patients and consumers.

Redefining the Use of Diagnostics in Medicine

Medical practice has always relied upon ‘individualizing’ treatment strategies based on an individual patient’s clinical history and the physician’s experience. Traditionally, diagnostic utilities have been used to ‘confirm’ decisions made by
clinicians based on observable symptoms. However, the role of biomarkers in the clinic and in drug development is rapidly expanding due to the advancement of both analytical technologies and our understanding of the molecular basis of diseases. Indeed, recent advances in biomarker-based diagnostics are redefining how diseases should be categorized and/or differentiated.

Diagnostic tools can provide valuable information that is critical to: (1) identifying the cause of a disease, (2) determining the disease course, (3) selecting the most effective treatment option(s) to maximize clinical outcome while minimizing adverse effects, and/or (4) monitoring efficacy during the course of treatment (fig. 1). Accurate assessment of the disease, its natural course of progression along with potential drug targets can influence the physician’s engagement strategy.

Fig. 1. The use of biomarkers may impact subsequent clinical strategies.
What Is a Biomarker?

A biomarker is a molecular, anatomical, physiological, histological, or biochemical factor with observable biological characteristics. In order to be effectively utilized in the clinic, biomarkers need to be objectively measurable. Good biomarkers can function as surrogates for the underlying cause(s) of disease as they act as biological indicators of disruption of homeostasis caused by pathological processes. The significance of diagnostics in the health care industry is rapidly increasing due to the accumulation of a repertoire of biomarkers with clear associations to diseases and observable phenotypes.

We are already familiar with the effective use of biomarkers in the context of infectious diseases, where it is critical to identify the pathogenic agent(s) responsible for an infection (e.g. detection of HIV-associated RNA). Often these biomarkers are used to monitor the efficacy of treatment strategies (e.g. viral load in the case of HIV). While it is relatively simple to use biomarkers for infectious diseases, it is often difficult to use them in the clinic for other diseases due to intrinsic complexities associated with pathophysiology. Biomarkers are used to identify the susceptibility of patients for certain diseases such as BRCA-1 for breast cancer. However, due to its incomplete penetrance (68% in breast cancer and 60% in ovarian cancer by age 70), the utility of BRCA-1 in the clinical setting is quite controversial, and the status of this biomarker should be evaluated in the context of each individual [1].

The role of biomarkers in predicting the likelihood of achieving a desired treatment outcome while minimizing adverse effects increasingly resonates with health care providers and other stakeholders, including payers and regulators. Some biomarkers function as surrogates for monitoring the efficacy of given treatments, thereby assisting clinicians in evaluating their clinical strategies. As diseases are reclassified based on their underlying molecular/cellular causes rather than on symptoms or organ-associated phenotypic display, better clinical strategies can be utilized to help prevent or delay disease onset, or minimize disease severity.

Prognostic Use of Biomarkers

Cardiovascular Disease
Statin therapy is effective at reducing cardiovascular (CV) incidents among patients with prior myocardial infarction, stroke, diabetes, or overt hyperlipidemia. It is strongly recommended that lipid-lowering therapies such as statins should be considered in these patients as an adjunct to aggressive lifestyle interventions. However, over 50% of heart attacks and strokes occur among...
apparently healthy individuals with average or low levels of cholesterol. Hence, there is an unmet need for novel screening of biomarkers to identify individuals at high risk of CV incidents despite the absence of hyperlipidemia in the primary care setting. A prospective study (JUPITER: Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) that enrolled 17,802 healthy individuals with elevated levels of high-sensitivity C-reactive protein (hsCRP) reported a dramatic reduction in CV events with 20 mg/day rosuvastatin compared with placebo \cite{2}. In this study, elevated hsCRP levels were a predictive marker for CV events among apparently healthy persons without hyperlipidemia. Therefore, as a biomarker, hsCRP is prognostic for CV incidents and predictive of response to rosvastatin, and its value can be used to screen/monitor apparently healthy individuals at risk of CV events \cite{2}.

\textbf{Cancer}

While a single biomarker may provide sufficient information for a certain condition such as the likelihood for CV incidents among individuals with high levels of hsCRP, it often takes a number of biomarkers to be an effective diagnostic tool. Multiple diagnostic applications that rely on panels of biomarkers to determine the severity of a disease as well as the likelihood of response to chemotherapy (e.g. Oncotype DX or MammaPrint for breast cancer) have been utilized in the oncology clinic. Based on current treatment guidelines, estrogen receptor-positive breast cancer patients are treated with hormonal therapy along with chemotherapy. In the TAILORx trial, profiling of 21 gene-based biomarkers was integrated into clinical decision making to facilitate maximal efficacy while minimizing unnecessary adverse effects by limiting chemotherapy to patients who are at higher risk of disease recurrence \cite{3}. The avoidance of unnecessary chemotherapy based on biomarkers also results in cost reductions associated with patient management.

\textbf{Inflammatory Bowel Disease}

There is an incomplete understanding of the pathogenesis of inflammatory bowel disease (IBD), but an algorithm of a combination of serological, genetic, and inflammatory (SGI) biomarkers has been effectively utilized to better differentiate IBD from overlapping symptomatic manifestations. Differentiating IBD into either Crohn’s disease or ulcerative colitis impacts treatment strategies caused by underlying differences in immunopathophysiology. Biomarker profiling based on noninvasive testing is preferred, particularly in the pediatric setting, as this allows clinicians to avoid colonoscopy in young patients. One of the most important applications of SGI in patients with established IBD is to determine the severity of disease, and moreover the risk of having complications or rapid disease progression. The conventional approach to managing IBD is to
induce/maintain clinical remission by the progressive intensification of aminosalicylates followed by corticosteroids. However, biologics are used as a last resort in patients with severe disease.

‘PROSPECT’, a prospective clinical study, utilizes the SGI algorithm to identify high-risk Crohn’s disease patients and maximize the clinical response to anti-TNF-α biologics, thereby preventing/slowing disease progression and preventing complications (fig. 2) [4]. Despite an increased number of therapeutic options for IBD, approximately one third of IBD patients require intestinal resection, as the primary focus in the clinic remains the control of symptoms. Hence, there is a critical unmet need for the prognostic identification of individuals at the preclinical stage, when there may be opportunities to alter the natural course of the disease.

Fig. 2. Principles behind the PROSPECT study: Crohn’s disease prognostics (top) and risk of complications (bottom). DX = Diagnosis; IM = immunomodulators.
Predictive Use of Biomarkers

Prognostic markers provide information regarding the outcome of a disease irrespective of therapy. For example, breast cancer patients with overexpression of human epidermal growth factor receptor 2 (HER2) have a poor clinical outcome. However, with the appropriate therapeutic agent specifically targeting HER2, a status which was once considered only as a prognostic biomarker, its use as a predictive biomarker for HER2-targeting therapies has begun.

Patients with activating epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) showed dramatic improvement in progression-free survival (PFS) when treated with EGFR-targeting erlotinib versus gemcitabine plus carboplatin in the OPTIMAL study (fig. 3) [5]. This result has strengthened the value of predictive biomarkers, and was further demonstrated in advanced NSCLC patients treated with gefitinib (IPASS: Iressa Pan-Asia Study) [6]. While INTACT (Iressa NSCLC Trial Assessing Combination Treatment) appeared to be unsuccessful when the clinical responses of all enrolled patients were evaluated without stratification, separating patients based on EGFR mutation status demonstrated a significant PFS benefit among patients with EGFR mutation [7, 8]. Furthermore, EGFR-mutant patients showed worse PFS when treated with conventional chemotherapy regimens containing carboplatin plus paclitaxel in IPASS [6]. This outcome confirmed the EGFR mutation as a predictive biomarker for a positive response to EGFR-targeting inhibitors and negative response to conventional chemotherapy. Similarly, in the BRIM-3 (BRAF Inhibitor in Melanoma-3) study, melanoma patients with the BRAF mutation also responded dramatically when treated with the BRAF inhibitor vemurafenib (response rate 48%) versus conventional treatment with dacarbazine (5%; fig. 3). The BRAF mutation is a highly predictive biomarker providing information critical for determining clinical strategies for melanoma patients [9]. This is an example of a number of positive predictive biomarkers in routine clinical use today (table 1).

Most current biomarkers are based on mutations or gene fusion, but only minor subsets of cancers are treated based on these predictive biomarkers. The vast majority of cancers require technologies that are able to decipher the complex pathophysiology responsible for disease occurrence, as well as disease reoccurrence without clear dominant driver mutations. Furthermore, most cancer patients with advanced disease, even those with favorable biomarker profiles, ultimately relapse with recurrent disease, in which the initial targeting agent is no longer effective as the tumor evolves using alternate pathways. Hence, there is an urgent need for methods to identify functional predictive biomarkers to alter treatment strategies in order to maintain control over dynamically evolving disease.
A proximity-mediated immunomicroarray technology (CEER: collaborative enzyme enhanced reactive immunoassay) developed by Prometheus/Nestlé Health Science has the capacity to evaluate small amounts of biological specimens (fig. 4). This technology is able to evaluate the functional status of multiple proteins in several pathways that have the potential to drive tumor proliferation with extreme sensitivity. CEER is based on signal amplification between two detector antibodies with enhanced specificity due to the requirement for three independent epitope-binding events. Rather than evaluating a single biomarker at a time, comprehensive evaluation of pathway physiology using CEER has opened clinical opportunities to keep up with evolving diseases. When NSCLC patients...
were evaluated for EGFR as well as other signaling proteins, cMET emerged as an important biomarker in predicting whether an NSCLC patient would respond to EGFR inhibitors with a high level of confidence. In the context of cMET, patients with higher EGFR/cMET index (EGFR-driven tumor) had a better response to EGFR-targeting agents, while patients with lower EGFR/cMET index (cMET-driven tumor) did not benefit from EGFR inhibitor monotherapy. Patients with activated cMET and with activating EGFR mutation would benefit from a combination of EGFR and cMET inhibitors (fig. 4). Patients with high EGFR/cMET index who initially responded well to EGFR inhibitors often developed resistance to the treatment. Upon analyzing tumor cells obtained from pleural effusion, we identified insurgence pathway signaling often triggered by activation of cMET and other receptor tyrosine kinases [10]. CEER could be a model platform to identify ‘functional predictive biomarkers’ for keeping up with evolving disease as tumors develop resistance. Similarly, 434 gastric cancer patients were profiled for the activation status of multiple receptor tyrosine kinases (RTKs, HER1, HER2, p95HER2, HER3, cMET, IGF1R, and PI3K). The results revealed that the combined RTK activity index was a good prognostic composite biomarker for predicting disease-free survival [11]. Furthermore, treatment monitoring by evaluating circulating tumor cells, as well as tumor cells from ascitic fluids, demonstrated a clinical potential for the rapid adaption of combinatorial treatments for patients with advanced gastric cancer.

Predictive biomarkers are often accurate for single disease indications. While BRAF mutation status works well as a predictive biomarker for BRAF inhibitor treatment in melanoma patients, the same mutation found in colorectal cancer is not predictive for clinical response when treated with BRAF inhibitor. Based on a multiplexed pathway analysis approach, several competing/redundant pathway drivers were identified in colorectal cancer patients. Multiplexed bio-

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CML = Chronic myeloid leukemia; GIST = gastrointestinal stromal tumor.
Advantages of Biomarker-Driven Health Care

Marker analysis delivered more accurate and comprehensive pathway status information to better select patients who would respond to a specific targeting agent and further provided the additional strategy for combining multiple agents. Tumors that have metastasized to the brain are often driven by different proliferative mechanisms compared with primary brain tumors; therefore, systemic treatments are often not effective in controlling metastatic brain tumors.

Fig. 4. CEER and its multiplexed biomarker analysis in NSCLC.
The sensitivity and specificity of CEER allows treatment options to be selected based on the predictive biomarker profile determined from small numbers of tumor cells isolated from cerebral spinal fluid, with dramatic clinical responses [12]. This study, along with others that evaluated tumor cells isolated from the circulation, ascitic fluids, and pleural effusions, demonstrated the value of clinical strategies based on predictive biomarkers.

Dealing with evolving disease is not limited to the field of oncology, but is also critical in chronic diseases such as IBD. Patients with advanced IBD are treated with monoclonal antibodies targeting TNF-α such as infliximab, which is often highly effective in the management of refractory IBD. However, more than one third of patients do not respond to induction therapy (primary nonresponse), and even among initial responders, the response wanes over time in 20–60% of patients (secondary nonresponse) [13]. Current hypotheses for the causes of nonresponse include: (1) inadequate serum levels or rapid consumption of the drug due to high inflammatory disease burden and (2) development of immunogenicity against biologics or activation of a non-TNF-α pathway [13].

The homogeneous mobility shift assay was developed by Prometheus/Nestlé Health Science to overcome the clinical challenges of determining the level of therapeutic biologic in the presence of antibodies to a drug. Recent studies using this test have demonstrated clinical advantages over other assays and have shown how monitoring can improve patient outcomes in various settings (e.g. loss of response or drug holiday) [14]. The development of antibodies against biologics (antibodies to infliximab) increases the probability of active disease even at low concentrations, and hence evaluating the level of antibodies to infliximab is critical to identifying alternative clinical strategies [15]. Patients with no antibody against biologic and with sufficient amount of biologic in the serum who still have active disease need further evaluation. Of note, some patients have active disease despite seemingly adequate anti-TNF-α levels in the serum; this is possibly due to high TNF-α levels in locally inflamed tissue resulting in a neutralizing effect on the anti-TNF-α drug [16].

It is not practical to subject patients with active disease to endoscopic evaluation; therefore, the need to identify biomarkers that function as surrogates for determining the severity of damaged mucosa, monitor the effectiveness of treatments, and provide an achievable therapeutic target for ‘mucosal healing’ is urgent. The pilot use of multipurpose biomarker panels was recently reported where biomarkers associated with the wound healing process were indicative of sustained mucosal healing [17]. The expanded second-generation panel is currently being validated, and will provide evidence-driven induction and proactive monitoring.
Conclusions

The value of diagnostics compared to therapeutics has been historically under-appreciated by the health care system. However, the stratification of patients for specific diseases has gained tremendous momentum in the postgenomic era. Using therapeutics in patient groups with minimal benefit, and often with severe adverse events, taxes the entire health care system. In order to provide highly effective health care solutions, patients should be stratified for specific diseases:

- Disease stratification is essential to better understand disease diversity/subtypes.
- Patient stratification is critical to strategize the best treatment options for each individual.
- Stratified health care will reduce the number of adverse drug reactions.
- Treatment of complex diseases requires comprehensive biomarker panels that can keep up with evolving disease.
- In order to become a leader in ‘emerging’ markets, we must utilize technologies and informatics to translate ‘research/clinical findings and learnings’ into practical products that address unmet needs in the clinic.
- Stratified medicine will reduce ineffective prescriptions and patient management leading to cost reductions for the health care system.
- Prognostic biomarkers may identify individuals at risk even in the presymptomatic stage, providing opportunities for nutritional therapeutics to prevent further disease progression.
- Stratification is desirable for every entity in the health care system: patients, care providers, payers, and pharmaceutical and diagnostic companies.
- While stratification may narrow the pool of eligible patients for a given indication, it can improve market share and should enhance efficacy with minimal side effects.
- Biomarker-based treatment monitoring will maximize clinical benefit and will lead to better patient compliance.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.
References


