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BIOMARKERS: HOPES AND CHALLENGES IN THE PATH FROM DISCOVERY TO CLINICAL PRACTICE

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Abstract

Biomarkers are objectively measured indicators of normal or pathological processes that may be helpful in diagnosis, staging, monitoring treatment, or prognostic evaluation of a disease. Although development of genomic, metabolomic and proteomic technologies has contributed to an explosion in identification of candidate analytes, validation remains expensive and challenging, and successful introduction of new biomarkers to clinical practice occurs at a very slow pace. The goal of this introductory overview is to provide the context for a series of review manuscripts published in the special issue on biomarkers. The promises and challenges of biomarker discovery are highlighted. Discovery and implementation of transformative new biomarkers in clinical practice requires close collaborations between scientists, clinicians and industry. High throughput technologies can identify a myriad of promising candidates but cannot predict their clinical value. In addition to rapid effective and systematic approaches for clinical validation, there is a need to study and establish links between the purported biomarker and the pathophysiologic basis of the disease of interest. Biomarkers are most informative when they provide insights into activation of specific pathways, thus serving as windows into the molecular basis of the disease.

Introduction

Biomarkers are measurable indicators of normal or abnormal biological processes that may be used to screen for, or diagnose disease, monitor its activity, predict its course, or assess response to treatment (1), (2). An NIH working group defined a biomarker as a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” (2). Although under this broad definition, physical traits, physiologic measurements, or quantifiable endpoints of imaging studies can be also considered biomarkers (3), nowadays the term most often refers to molecular or biochemical markers (1).

Depending on the type of information they provide, biomarkers have been classified (3) as: a) antecedent biomarkers that assess the risk of developing a disease, b) screening

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biomarkers that identify individuals with subclinical disease, c) diagnostic biomarkers that aid in diagnosis of overt disease, d) staging biomarkers that estimate disease severity and e) prognostic biomarkers that provide information on the course of a disease, predict response to therapy, or monitor efficacy of a therapeutic strategy.

Considering the wide range of their potential applications in clinical practice, the growing interest of the academic and industrial community in biomarkers is not surprising. In both inpatient and outpatient care settings, clinicians make extensive use of traditional biomarkers to screen their patients for early detection of serious conditions, to diagnose and assess the severity of disease, to derive prognostic information and to guide therapy. For example, plasma troponins are routinely used to diagnose patients presenting with chest pain, alpha-fetoprotein levels can assist in the diagnosis of hepatoma, while assessment of the plasma lipoprotein profile provides important prognostic information and is used to make therapeutic decisions in patients with metabolic and cardiovascular disease. In clinical research, the use of biomarkers as endpoints in early phase clinical trials may improve their predictive value reducing the expense and waste in phase III trials (4). In recent years advances in molecular biology and biochemistry and the rapid growth in genomic, proteomic and metabolomic approaches raised hopes for the development of new and more effective biomarkers (5). Thus, biomarker studies have become a cornerstone in translationally-oriented research.

The current special issue of Translational Research provides a collection of twelve state-of-the-art manuscripts discussing the current use of biomarkers in the clinical environment and the development of promising new markers for diagnosis and management of various diseases. The current overview provides the context necessary for introducing the series of detailed manuscripts, presenting the major challenges in discovery, validation and clinical implementation of new biomarkers, while discussing the transformative potential of biomarker-guided approaches in clinical practice.

Introduction of new biomarkers: a slow and challenging process

Despite the promises fueled by the “-omics” revolution and the extensive investment in biomarker development by both the academic and industrial communities, the pace of introduction of new biomarkers in clinical practice appears to be falling (1), (6). The slow progress is not due to lack of candidates as many new and promising biomarkers are continuously proposed. However, the explosion in the number of proposed biomarkers has not yet translated into the implementation of new clinically useful indicators as most clinical decisions continue to rely on more conventional forms of testing, such as routine laboratory measurements and imaging studies.

The disappointingly slow progress in development of clinically useful biomarkers is due to the multiple challenges associated with their discovery, verification, validation and clinical evaluation. Although advanced high-throughput technologies and hypothesis-driven approaches continue to provide clinicians and researchers with an expanding list of candidate markers, very few are likely to survive the test as useful clinical tools (7).

The path to successful introduction of a new biomarker

Biomarker discovery—The initial phase in the biomarker development pipeline (Figure 1) (8) is to identify suitable candidates. Two general approaches can be employed (3): the first strategy uses a deductive reasoning to identify candidates based on existing knowledge of the pathophysiology of disease. The second strategy is “unbiased”, employing proteomic or molecular techniques to identify candidate biomarkers on the basis of their differential expression between normal and diseased states (1). For example, mass spectrometry-based proteomic technologies may be used to compare protein expression between tissue samples obtained from normal and diseased subjects (9), resulting in compilation of a long list of candidate proteins, while avoiding “contamination” by other confounding pathologic conditions (1). Because this strategy surveys hundreds of analytes in a relatively small number of samples, many “candidate biomarkers” may simply represent “false discoveries”; in these cases the difference in protein abundance likely reflects interindividual variation and is not due to the underlying disease process (9).

Qualification—When using an “unbiased” strategy, identification of candidate biomarkers is followed by qualification. This phase serves to confirm the differential expression of the candidate using alternative methods and to examine whether the biomarker is differentially expressed in plasma from diseased patients, if the discovery phase was not performed in plasma samples. In both the discovery and qualification phases, the goal is to identify candidate biomarkers with high sensitivity. Thus, the emphasis is on documentation of a consistent association between the indicator and the disease of interest.

Verification—The goal of biomarker verification is to determine whether the candidate has sufficient potential for success to warrant investment in time-consuming (and expensive) clinical validation studies. Analysis is typically extended to a large number of human plasma samples attempting to include a broad range of patients and controls. Although confirmation of the high sensitivity of the candidate remains important, verification begins to assess the specificity of the biomarker by attempting to capture the variation of the population to be tested (1).

Prioritization of the candidates—Considering the daunting costs of clinical validation of biomarkers and the limited resources available, prioritization of candidate markers is crucial in order to identify the most promising indicators (8). Prioritization is based on knowledge: insights into the biology of the protein of interest and understanding of the pathophysiology of the disease can greatly contribute to selection of analytes with the highest potential usefulness in clinical practice.

Validation—Pilot studies performed during the verification phase and careful prioritization usually eliminate most candidate biomarkers from further consideration. The few surviving indicators are validated in a realistic clinical practice environment. In the early phases of the biomarker pipeline, samples from diseased individuals are compared with control samples obtained from healthy subjects; this typically results in overestimation of the sensitivity and specificity of the marker (10). The process of clinical validation requires systematic study of the impact of other clinical covariates and of pathophysiologically related conditions on the

association between the putative biomarker and the disease state. Thus, biomarker validation is a lengthy and expensive process that is dependent on enrollment of large numbers of patients with varied characteristics and outcomes (11). Robust clinical evidence derived from several large independent studies, demonstrating the incremental value of the purported biomarker, is crucial for successful implementation in clinical practice. Ioannidis and Panagiotou found that, in most cases, highly cited biomarker studies that appear in major journals report false-positive or exaggerated associations between biomarkers and disease (12). Premature adoption in clinical practice of findings from single studies with inflated results, in the absence of robust supporting clinical evidence, would be expected to increase healthcare costs with limited or no benefit. Careful interpretation of the literature and healthy skepticism about the clinical usefulness of a biomarker are recommended (12).

What makes a good biomarker?

Out of the myriad of promising markers entering the biomarker pipeline very few ultimately stand the test of time and transform clinical practice. Regardless of the intended use of a biomarker several important properties determine its clinical usefulness. First, the clinical value of a biomarker is dependent on the strength and consistency of the association between the marker and the outcome, or disease of interest (7), (3). This association needs to be confirmed in multiple studies to establish high sensitivity and specificity within a wide range of patient populations. Second, a transformative biomarker provides important new information that adds or improves upon existing tests (7). Third, accessibility of the assay, ease of analysis, simple interpretation and a reasonable cost greatly increase the value of the biomarker. Fourth, a biomarker is useful only when it helps the clinician to manage patients. Thus, evidence that a biomarker-guided approach translates into improved patient outcome greatly strengthens the clinical value of the marker; this implies that medical interventions are available to modify the course or outcome of the disease. Biomarkers that do not guide medical interventions may also be useful in some cases by providing psychological benefits to patients (such as reassurance from negative testing for a serious illness).

The requirements for success are of course dependent on the intended use of a biomarker. Biomarkers used to screen serious illnesses (such as cancer) in large healthy populations need to have extremely high specificity and low cost to be useful; moreover, an effective medical intervention needs to be available to treat the disease of interest (8). In contrast, for biomarkers used to monitor disease progression or response to treatment, a very high sensitivity and specificity may not be essential as serial measurements are performed in the same patient. Moreover, cost may be less important because only diseased individuals are tested.

Biomarkers in various conditions

Ultimately, optimal use of biomarkers in clinical practice requires understanding of the pathophysiology, clinical course and outcome of the disease of interest. The current special issue provides a series of outstanding reviews summarizing the current role of biomarkers in important clinical conditions.

Biomarkers in cardiovascular disease

Considering the significant limitations of traditional clinical evaluation, new tools are needed for early and accurate diagnosis, risk assessment and treatment monitoring in patients with cardiovascular disease. Introduction of biomarkers in cardiovascular practice has been typically based on hypothesis-driven approaches. For example, cardiomyocyte-specific proteins, such as troponins I and T, have been successful as indicators of acute cardiac injury. On the other hand, measurement of B-type natriuretic peptide (BNP) has become a valuable tool for diagnosis of heart failure in patients presenting with dyspnea (13), is useful in risk-stratification of heart failure patients (14) and may be used to tailor therapy in a biomarker-guided approach (15). The introduction of high-throughput approaches and the rapid development of genomic, proteomic and metabolomic strategies in the cardiovascular field are expected to revolutionize the field contributing promising new indicators of heart disease (9), (16), (17).

In the current special issue three manuscripts deal with the use of biomarkers in heart disease. The role of biomarkers in acute myocardial injury is reviewed by Kehl and co-workers (18). The authors summarize the current status of biomarkers available for rapid diagnosis of acute coronary syndromes (ACS) and discuss emerging evidence on promising new markers. The quest for development of markers detecting cardiomyocyte death is an excellent example of how new biomarkers can transform clinical practice. Aspartate aminotransferase and lactate dehydrogenase were the earliest markers used to diagnose myocardial infarction (19); due to their poor specificity their use is no longer recommended (20). Development of CK-MB assays resulted in improved specificity and represented an important advance in diagnosis of acute cardiomyocyte injury. Due to their high myocardial tissue specificity, their sensitivity and established usefulness in therapeutic decision-making (21), cardiac troponins are currently the gold standard biochemical markers for the diagnosis of acute coronary syndromes (22). However, conventional troponin assays are not sensitive in detection of the slight rise in troponin levels observed within the first 2 hours after myocardial infarction (21). The recent development of high-sensitivity troponin assays detecting pg/ml of circulating troponin (as opposed to ng/ml) greatly increases the sensitivity of the assay in detection of cardiomyocyte necrosis and may allow earlier diagnosis of acute myocardial infarction (23). Successful incorporation of these assays into clinical practice will require extensive research and adjustment of clinician's beliefs and attitudes. The use of high-sensitivity assays will result in detection of many more individuals with troponin elevations due to etiologies unrelated to ACS. Moreover, the notion that troponin elevation reflects permanent cardiomyocyte injury may need to be revised as transient stress-induced ischemia in patients undergoing exercise stress testing was associated with release of troponin I detected with an ultrasensitive assay (24). Several other biomarkers have shown promise in diagnosis and evaluation of patients with ACS. Beyond their established role in the diagnosis of dyspnea and in evaluation of patients with heart failure, natriuretic peptides may have predictive value in ACS patients. Newer biomarkers, such as copeptin, Growth-Differentiation Factor (GDF)-15, ischemia-modified albumin and heart-type fatty acid binding protein are currently under intense investigation and may provide important clinical information.

In the second cardiovascular manuscript of this special issue, Dadu and co-workers (25) review the role of biomarkers in identifying patients at risk for cardiovascular disease. The authors briefly discuss strategies for identification and development of new cardiovascular markers then focus on selected biomarkers of outstanding interest in cardiovascular risk prediction. Inflammation has been recognized as a central process in initiation and progression of atherosclerosis and also plays a crucial role in development of its complications (such as plaque rupture) (26). Although a myriad of inflammatory mediators have been identified as independent predictors of cardiovascular events, C-Reactive Protein (CRP), a member of the pentraxin family, remains the best-documented inflammatory indicator in cardiovascular risk prediction. The development of high-sensitivity CRP (hs-CRP) assays has greatly enhanced its usefulness as a prognostic indicator. Not only is CRP an independent predictor of cardiovascular events, but also identifies patients who benefit the most from risk reduction therapies. The highly-publicized “Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin” (JUPITER) study demonstrated that in a population without cardiovascular disease, statin treatment of individuals without overt hyperlipidemia (LDL cholesterol levels <130 mg/dl), but with elevated CRP levels (hs-CRP >2mg/dl), significantly reduced the incidence of major cardiovascular events (27). The JUPITER results were enthusiastically received and were described by various sources as a breakthrough that may expand the use of statins to millions of healthy individuals. However, it should be pointed out that, due to the low event rate in the asymptomatic low-risk population studied in JUPITER, the impressive relative risk reduction translates into a very small reduction in absolute risk (28). One of the most useful measures of the effectiveness of a therapeutic intervention is the number of patients needed to treat in order to prevent one additional adverse outcome. On the basis of the JUPITER data, 500 healthy individuals with high CRP levels need to be treated with a statin for one year to prevent one major coronary event (29). The modest effect on absolute risk raises concerns regarding the cost and safety of implementing a CRP-guided strategy for statin-induced risk reduction in healthy individuals.

Other inflammatory markers of plaque instability may also be useful in cardiovascular risk prediction. Lipoprotein-associated phospholipase A2 (Lp-PLA2), and myeloperoxidase, both products of inflammatory myeloid cells, have been associated with cardiovascular events and are under investigation as targets for biomarker-guided therapy.

The use of biomarkers in cardiac transplantation is reviewed by Labarrere and Jaeger (30). Although transplantation has become an established and effective treatment strategy for patients with end-stage heart failure, its success is limited by serious complications, such as acute cellular rejection, antibody-mediated rejection and cardiac allograft vasculopathy (CAV). Development of accessible, effective and inexpensive biomarkers to predict the occurrence of these complications would represent a major advance in the field. Despite intense investigation, the role of biomarkers in heart transplant patients remains limited. Endomyocardial biopsy remains the gold standard in the diagnosis of acute cellular rejection. Whole blood genomic biomarkers are currently under investigation as part of a surveillance strategy that may reduce the need for biopsies. In the IMAGE study use of a gene-based panel in patients at low risk for rejection, late after heart transplantation was non-inferior to a biopsy-based strategy (31). Tools predicting the development of CAV, the

most important cause of late deaths in cardiac transplant patients, are also of limited usefulness. Because the pathogenesis of CAV involves activation of immunoinflammatory pathways and prothrombotic signals resulting in intimal thickening of the microvasculature, inflammatory markers may hold promise (32).

The challenges of biomarker development in cancer

Because of the unique association between genomic changes in malignant cells and the development of neoplasia, there is great potential for development of biomarkers for early detection, diagnosis, disease subtyping, prognostic evaluation, assessment of the response to therapy and screening for recurrence in patients with cancer (33). Unfortunately, despite heavy investment in the field and great promise suggested by early investigations, introduction of new cancer biomarkers to clinical practice remains extremely slow. Wagner and Srivastava (34) provide their perspective on the factors responsible for the slow pace of biomarker translation in neoplastic disease. The manuscript highlights the inherent difficulties in development of effective screening biomarkers due to the very small size of the early tumor that may not be associated with measurable increases in biomarker levels in the blood, urine or stool. Moreover, the authors emphasize the importance of multidisciplinary and multi-skilled teams to integrate diverse data types in order to develop effective biomarker-based strategies. Unfortunately, in the current research environment early promising data are often based on work by a single laboratory with limited means to accomplish the objectives. To address these pitfalls the manuscript provides a systematic approach for discovery, verification and validation of biomarkers, applicable not only in cancer but in many other conditions.

Biomarkers and renal disease

There is an urgent need for introduction of new biomarkers to address the diagnostic and therapeutic challenges in acute and chronic renal disease. Slocum and co-workers (35) discuss the intense efforts for development of new markers for early diagnosis, prognostic evaluation and treatment guidance in acute kidney injury (AKI). Although serum creatinine has been the gold standard for evaluation of acute renal failure for over a century, its value as a marker of AKI has significant limitations. First, serum creatinine levels do not increase until 2–3 days after AKI. Because early detection of renal injury is important for effective treatment the low sensitivity of serum creatinine is a major problem. Second, serum creatinine is a relatively non-specific indicator of kidney damage and provides no information on the etiology and pathophysiologic basis of the disease. Third, its ability to predict response to treatment is limited. There is currently an intense effort to develop new plasma and urine biomarkers that may provide incremental information over the use of clinical evaluation and routine laboratory testing. Small clinical studies have suggested that Neutrophil Gelatinase-Associated Lipocalin (NGAL), an indicator of proximal tubule dysfunction, the pro-inflammatory cytokine Interleukin-18, proteins expressed by renal tubular epithelial cells, such as Kidney Injury Molecule (KIM)-1 and liver type Fatty Acid Binding Protein (L-FABP), and cystatin C, a protein fully catabolized by the renal epithelium, may hold promise as early and clinically useful markers of AKI. However, large

studies in heterogeneous populations are needed to assess the potential role of these biomarkers in clinical practice.

The great potential of genomic biomarkers in evaluation and treatment of patients with chronic renal disease is discussed by Ju and co-workers (36). Genomic markers are measurements of the expression, function or regulation of genes and may consist of one or more DNA characteristics (such as single nucleotide polymorphisms, DNA modifications, haplotypes or cytogenetic rearrangements) or RNA characteristics (such as RNA sequences and expression levels). Genomic biomarkers are of particular interest because they may provide direct links between pathophysiologic mechanisms and outcome. Although interest on genomic biomarkers assessed in tissues, biological fluids or cells is growing, none of these strategies is ready for application in kidney disease.

Biomarkers in pulmonary disease

In this special issue three manuscripts cover the evolving knowledge on the current use and future potential of biomarkers in pulmonary disease. Bhargava and Wendt (37) discuss the role of biomarkers in Acute Respiratory Distress Syndrome (ARDS) and in acute lung injury. During the exudative phase of ARDS, diffuse alveolar damage and loss of cellular integrity trigger an intense inflammatory reaction associated with induction and release of cytokines and chemokines (38). Several inflammatory cytokines have been studied as potential biomarkers in patients with ARDS; however, the evidence suggests that their predictive value for development of lung injury is weak. Markers of alveolar cell injury, endothelial cell activation, bronchiolar cell damage, extracellular matrix fragmentation and activation of the coagulation cascade. During the proliferative phase of ARDS, biomarkers reflecting growth factor release, cellular proliferation and pro-fibrotic activity may provide prognostic information. Because of the complexity of the pathophysiology of acute lung injury, biomarker combinations may be needed to derive clinically useful information.

Vij and Noth (39) discuss promising new biomarkers for patients with Idiopathic Pulmonary Fibrosis (IPF). Several markers that reflect pulmonary injury (such as surfactant proteins and Krebs von den Lungen-6 Antigen), matrix degradation (matrix metalloproteinases-1 and -7), inflammation (the CC chemokines CCL18 and CCL22), fibrogenesis, aberrant angiogenesis (such as Vascular Endothelial Growth Factor/VEGF) and active matrix remodeling (including matricellular proteins such as osteopontin and periostin) have been suggested as markers of potential interest in the serum and bronchoalveolar lavage (BAL). Their clinical value in early diagnosis, prognosis, subtyping and treatment of IPF patients needs to be tested in large prospective clinical studies.

Although functional indicators, such as forced expiratory volume in one second (FEV1), are established predictors of prognosis in patients with chronic obstructive pulmonary disease (COPD), they do not correlate well with the patient's clinical condition or symptomatic status (40). Thus, there is a need for biomarkers both to identify subtypes of COPD on a pathophysiologic basis, but also to provide information on disease activity and the clinical course. Rosenberg and Kahlan (41) review the current status of biomarkers in COPD and discuss the future prospects for discovery and implementation of new markers in clinical

practice. Markers of inflammatory activity (such as sputum neutrophil count and serum levels of the lung-predominant CC chemokine CCL18) may have prognostic implications and may guide treatment reflecting activating of immunoinflammatory signals. Moreover, measurement of desmosine levels in urine, sputum or serum may reflect elastin turnover providing information on pulmonary matrix degradation. Development of integrative indices may prove valuable in assessment of patients with COPD.

Biomarkers in inflammatory bowel disease (IBD)

Iskandar and Ciorba (42) review the use of biomarkers in IBD. Although diagnosis and evaluation of patients with IBD is primarily based on clinical assessment, routine laboratory tests and endoscopy and biopsies, several currently available serum and fecal biomarkers may provide complementary information. Inflammatory markers (such as CRP and fecal leukocyte markers) may help in differentiating between IBD and non-inflammatory etiologies of diarrhea and may assist in monitoring disease activity. New biomarkers are needed to assist clinicians in diagnosis and treatment. Considering our limited understanding of the etiology of IBD, characterization of such biomarkers may also provide important pathophysiologic insights.

Biomarkers in diabetes

The role of biomarkers in diabetes is reviewed by Lyons and Basu (43). The authors focus on the established role of hemoglobin A1c (HbA1c) in diabetes care as an indicator of the presence and severity of hyperglycemia. Development and validation of new metabolic biomarkers reflecting the biochemical consequences of diabetes and the biomolecular modifications induced by chronic hyperglycemia could represent a major advance in the field. Tissue-specific biomarkers may greatly contribute to the diagnosis and evaluation of patients with diabetic complications.

Biomarkers in systemic lupus erythematosus (SLE)

Ahearn and co-workers (44) review the role of biomarkers in SLE. The authors stress the importance of developing and validating new biomarkers in the management of patients with SLE. The complexity of the pathogenesis of the disease, the challenges in lupus diagnosis, the difficulties in providing prognostic information and in predicting response to treatment explain why introduction of new biomarkers for patients with SLE is so important. Identification of genetic biomarkers of SLE susceptibility may eventually provide insights into pathogenesis and contribute to recognition of distinct subpopulations of SLE patients. Recent investigations have identified new markers of immune dysregulation that may be associated with disease activity in subsets of lupus patients. Much like in diabetes, discovery of biomarkers capable of predicting organ-specific involvement would be of outstanding significance in management of patients with SLE.

Challenges and future directions

Over the last few decades we have witnessed an explosion in biomarker discovery. In all fields of clinical medicine, numerous potential markers were proposed on the basis of

“hypothesis-driven” approaches. The recent development of high throughput technologies has further accelerated the pace of discovery resulting in a huge number of putative markers. Unfortunately neither the research community, nor the health care environment have developed the capabilities necessary to test the large volume of potential biomarkers in large populations of patients (11). Thus, introduction of biomarkers in clinical practice is hampered by the enormous costs of biomarker validation and by the absence of objective prioritization criteria. Regardless of the attractiveness of the underlying concept, the choice of which markers to validate is often determined by commercial considerations (11).

Discovery and implementation of transformative new biomarkers in the clinic requires strong collaborative relations between scientists, clinicians and industry. The – omics revolution can provide us with a myriad of promising candidates but cannot guide us towards their implementation. In addition to rapid effective and systematic approaches for clinical validation, there is a need to study and establish links between the purported biomarker and the pathophysiologic basis of the disease of interest. Biomarkers are most informative when they provide insights into activation of specific pathways, thus serving as windows into the molecular basis of the disease.

Considering the complexity of most common conditions, it is clear that single biomarker assays are unlikely to have transformative effects in clinical practice. In the future, implementation of multimarker approaches assessing the major aspects of the pathophysiology of the disease may provide clinicians with the information needed for diagnosis, prognostic evaluation and treatment. For example, future development of pathophysiologically relevant multimarker panels may transform clinical evaluation and treatment of patients with acute myocardial infarction (MI). Despite the heterogeneity of the population suffering an acute MI and the complexity of pathophysiology of the disease, current treatment is standardized. Adjustments of the treatment strategy are primarily based on clinical evaluation, routine laboratory tests and the use of imaging strategies to assess cardiac function and ischemia. However, these indicators are not sufficient to predict development of cardiac remodeling and heart failure in patients suffering an acute MI. In a pathophysiologically-oriented biomarker-guided approach, clinical decision making would be guided by multimarker panels providing information on multiple pathologic processes including cardiomyocyte necrosis, the presence of ischemia, plaque vulnerability, pro-arrhythmic tendencies, the reparative response, matrix deposition and metabolism. Biomarker selection would be informed by pathophysiologic insights derived through basic research. Such a strategy would allow the clinician to distinguish patients more likely to develop dilative remodeling due to impaired resolution of post-infarction inflammation (45) and overactive matrix-degrading pathways from those who may exhibit dominant pro-fibrotic responses likely to result in prominent diastolic dysfunction (46). Development and implementation of such ambitious efforts will undoubtedly face many challenges, but may eventually fulfill the visionary goal of personalized medicine.

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Figure 1.

Schematic representation of the biomarker development pipeline. Traditional hypothesis-driven approaches and high throughput technologies suggest thousands of candidate biomarkers. Lists of putative markers are prioritized and undergo systematic testing to establish the consistency of the association between marker and disease (qualification) and to study the sensitivity and specificity of the indicator in a larger number and a broader

range of samples (verification). The few candidates that survive verification undergo a lengthy and expensive process of rigorous clinical validation.