**Biomarkers in Cardiovascular Clinical Trials: Past, Present, Future**

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**BACKGROUND:** Cardiovascular (CV) clinical trials are instrumental in understanding treatment effects and offer insights into the natural progression of CV disease. Biomarkers are a critical component of patient selection, end point definition, and safety monitoring, and clinical trials provide a platform for the discovery and validation of new biomarkers that may augment the understanding of disease mechanisms, risk stratification, and/or clinical decision-making.

**CONTENT:** We review the roles that biomarkers have played in CV clinical trials and roles that CV clinical trials have played and will continue to play in the discovery and validation of biomarkers and their implementation in clinical practice. Large biobanks containing multiple specimen types are increasingly being created from patients enrolled in clinical trials, and such biobanks, when coupled with advances in molecular techniques and bioinformatics, promise to accelerate our understanding of CV disease mechanisms and to help fuel the discovery and development of novel therapeutic targets and biomarkers of risk and treatment response.

**SUMMARY:** The past, present, and future of biomarkers and clinical trials have been and will remain intertwined. Biomarkers were once the workhorses of patient selection and end point definition in clinical trials; more recently, clinical trials have been the proving ground for individual biomarkers. Attention to biobanking and the application of modern informatics and molecular techniques to samples collected within clinical trials will usher in the era of stratified and personalized medicine.

Clinical trials are imperative in the process of developing new treatments and treatment strategies in cardiology. The results of large-scale randomized clinical trials have led to remarkable advances in cardiovascular (CV) care, as well as to a better understanding of the natural history of CV disease (CVD) and the associations of various risk factors and complications with outcomes. Many trials in cardiology use easily measurable outcomes, such as mortality; however, in part to manage sample size or as signals in early-phase trials, most trials use other clinically meaningful outcomes in composite end points. These outcomes, such as myocardial infarction (MI), often rely on definitions that incorporate the measurement of biomarkers. In addition, many trials rely on biomarker measurements (e.g., LDL cholesterol, high-sensitivity C-reactive protein (hsCRP), or troponin assays) to select patients for inclusion. In this way, biomarkers and clinical trials have been inextricably linked throughout their evolution.

A working group from the NIH 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” (1). The ideal biomarker should be easily measured, provide information in addition to features that are readily apparent, and assist in the management of patients (2). Although the coronary anatomy determined by angiography or the pattern on a 12-lead electrocardiogram can be considered a biomarker in the strictest

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2 Nonstandard abbreviations: CV, cardiovascular; CVD, CV disease; MI, myocardial infarction; hsCRP, high-sensitivity C-reactive protein (assay); BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; CK-MB, cardiac-specific isoenzyme of creatine kinase; GUSTO-IIa, Global Use of Strategies to Open Occluded Coronary Arteries IIa (trial); TIMI-IIIb, Thrombolysis in Myocardial Ischemia IIIb (trial); ACS, acute coronary syndrome; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38; CAD, coronary artery disease; CARE, Cholesterol and Recurrent Events (trial); AFCAp/TeaCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; PRINCE, Pravastatin Inflammation/CRP Evaluation (trial); PROTECT, Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (trial); COMET, Carvedilol or Metoprolol European Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition in Patients with Unstable Coronary Artery Disease; TACTICS-TIMI 18, Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (trial); CHECKMATE, Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I (trial); OPUS, Orbofliban in Patients with Unstable Coronary Syndromes (trial); GRACE, Global Registry of Acute Coronary Events; TIMIACS, Timing of Intervention in Acute Coronary Syndromes (trial); JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (trial); CAST, Cardiac Arhythmia Suppression Trial; HERS, Heart and Estrogen/Progestin Replacement Study.

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Interpretation of the term, “biomarker” within the CV field frequently refers to circulating molecules in the blood. Many diseases, such as asthma, cancer, and diabetes rely on biomarkers not only for diagnosis but also for prognosis and monitoring disease progression and the response to therapy. In this review, we describe the integration of biomarkers specifically in CV clinical trials—past, present, and future.

Biomarkers Past

Over the years, blood-based biomarkers have played an increasing number of important roles in clinical trials. In addition to refining our understanding of CVD mechanisms, they assist in both identifying study populations and defining intermediate end points (infarct size, suppression of inflammation) in phase 2 clinical trials and in identifying nonfatal clinical end points (e.g., MI) in later-phase work. The cases of troponin, hsCRP, B-type natriuretic peptide (BNP), and N-terminal pro-BNP (NT-proBNP) are prime examples of the importance of clinical trials in the development of novel biomarkers, and that work has led to their widespread incorporation in both clinical trials and clinical practice as tools for diagnosis, risk stratification, and refinement of our understanding of disease mechanism and treatment response.

Clinical Trials and the Evolution of Troponin

One of the most recognized of biomarker roles in clinical trials is the definition of the MI end point. For years, the gold standard for diagnosis of myocardial necrosis was the cardiac-specific isoenzyme of creatine kinase (CK-MB). Previously, the myocardial fraction of lactate dehydrogenase and even aspartate aminotransferase were used to diagnose myocardial necrosis. As early as 1992, it was becoming clear that increased concentrations of troponin, a novel biomarker with myocardium-specific isoforms, was common in patients with unstable angina and that this increase was associated with an increased occurrence of future major cardiac events (3).

Two early clinical trials, GUSTO-IIa (Global Use of Strategies to Open Occluded Coronary Arteries IIa) and TIMI-IIIB (Thrombolysis in Myocardial Infarction IIIIB) (4, 5) played a major role in solidifying the prognostic importance of troponin increase in patients with acute coronary syndrome (ACS), whether or not they were classified as having experienced an MI according to a conventional clinical, electrocardiographic, and CK-MB assessment. Not only did troponin measurement detect more patients with myocard necrosis, these patients also had adverse outcomes with severities that were proportional to the degree of troponin increase (6, 7). Thus, the integration of the biomarker substudies that focused on troponin within these clinical trials provided unbiased systematic and detailed follow-up that confirmed troponin to be a marker of myonecrosis that was more diagnostically sensitive than CK-MB and solidified the relationship of troponin to the risk of future adverse outcomes. Consequently, the measurement of biomarkers of myocardial necrosis moved from simply a diagnostic role to one of assessing prognosis in ACS patients.

Subsequent trials reconfirmed these relationships and provided evidence that troponin measurement could identify groups of patients who would experience an enhanced benefit from more-aggressive antithrombotic therapy and an invasive evaluation strategy (8–13). Table 1, which summarizes the results of these trials, focuses on the reduced rates of primary end points in patients with increased troponin concentrations who received the more intensive therapies. Coupled with its greater diagnostic sensitivity for myonecrosis, its greater myocardial specificity, and its prognostic implications, troponin has now supplanted CK-MB as the biomarker of choice for both the diagnosis and risk stratification of ACS patients (14, 15).

Despite its role in clinical trials, end point definition remains a topic of much discussion, and trials have begun to explore the effects of incorporating the universal definition of MI in end point definition. In an analysis from the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) trial, which compared prasugrel with clopidogrel in ACS patients undergoing percutaneous coronary intervention, application of the universal definition of MI to adjudicate the MI end point showed that most new or recurrent MIs were type 1 (spontaneous) or type 4a (periprocedural coronary intervention) events. There were very few type 2 (secondary) events. Regardless of infarct size, prasugrel reduced MI events compared with clopidogrel for both spontaneous and periprocedural MIs, but there was no treatment effect among patients with type 2 MIs (16).

Clinical Trials and the Inflammatory Hypothesis

The inflammatory process has been implicated extensively in the pathogenesis of atherosclerosis and ACS (17). Pathologic studies have identified an active local inflammatory process in atherosclerotic plaque, as well as a more systemic inflammatory process in patients with coronary artery disease (CAD) manifested by increased concentrations of CRP, interleukin-6, serum amyloid A, CD40 ligand, and other proteins of the inflammatory cascade (18–20). Of these biomarkers, CRP is the most studied, and high-sensitivity assays for measuring CRP are now widely available.
The association of hsCRP with CV events was initially studied most intensively in clinical trials of populations of patients with stable CAD and in primary-prevention populations, but it has also been studied in trials of ACSs (21–23). The Cholesterol and Recurrent Events (CARE) trial evaluated the effect of pravastatin on CAD death and nonfatal MI in post-MI patients (24). Embedded within this trial was the collection of blood samples for hsCRP assay. This trial was the first secondary-prevention trial to demonstrate the association of hsCRP concentrations with recurrent CAD events and that patients treated with statins had lower hsCRP concentrations with recurrent CAD (25). Additionally, statin therapy had a greater clinical benefit when the CRP concentration measured with an hsCRP assay was increased. Subsequently, the AFCAPs/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) primary-prevention trial found statin therapy to be associated with reduced hsCRP concentrations, regardless of initial cholesterol concentration, and there was a greater treatment effect when CRP concentrations were increased, regardless of the baseline LDL cholesterol concentration (26). This hsCRP-lowering effect of statins was demonstrated prospectively with pravastatin in the PRINCE (Pravastatin Inflammation/CRP Evaluation) trial (27), and the relationship between statin treatment and lower hsCRP concentrations has also been observed for other statins, including simvastatin and atorvastatin (28). These observations and others from within early clinical trials have provided empirical support for the inflammatory hypothesis in CVD and, along with observations of its incremental contribution to risk stratification in population cohorts, have fueled the development of the hsCRP assay into a commercially available test for clinical risk stratification.

**BNP as a Biomarker of Neurohormonal Activation**

BNP is a neurohormone produced in the ventricular myocardium in response to dilation and pressure overload, and its plasma concentration correlates with the magnitude of pressure and/or volume overload. Assays for both BNP and NT-proBNP are available and have been extensively studied in clinical trials. The results of a landmark trial of heart failure, in which bedside testing for BNP was shown to have a 96% negative predictive value for the diagnosis of heart failure in the emergency department and to add incrementally to clinical factors in a model for predicting the diagnosis of heart failure, launched the use of BNP in clinical practice (29, 30). Additional studies confirmed that BNP could augment the clinical judgment of the severity of heart failure presentation and the assessment of prognosis in patients presenting with heart failure (30, 31). Additionally, NT-proBNP has been used in other trials, such as the PROTECT (Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy) trial, to refine a role for this marker in guiding outpatient management of chronic heart failure (32).

Heart failure, a reduced ejection fraction, and presentation with cardiogenic shock have long been associated with worse outcomes among patients with ACS (33, 34). As markers of neurohormonal activation, BNP and NT-proBNP were subsequently studied within clinical trials of ACS as adjuncts to risk stratification and have been associated with short- and long-term mortality in ACS patients, even after adjusting for the presence of congestive heart failure (35, 36). This

| Table 1. Trials assessing differential treatment benefit among patients with and without increased troponin concentrations. |
|-----------------|----------------|----------------|------------------|----------------|-----------------|
| **Trial**       | **Treatment**  | **Biomarker**  | **Outcome**       | **Rates of end point, treated vs not treated (P)** |
| PRISM* [Heeschen et al. (8)] | Tirofiban     | Troponin T     | Death or MI at 30 days | 3.5% vs 13.7% (<0.001) |
| CAPTURE [Hamm et al. (9)]       | Abciximab     | Troponin T     | Death or MI at 30 days | 5.8% vs 19.6% (0.001) |
| TiMI 11B [Morrow et al. (10)]  | Enoxaparin    | Troponin I     | Death, MI, or urgent revascularization at 14 days | 21% vs 40% (0.03) |
| TACTICS-TIMI 18 [Morrow et al. (11)] | Early invasive | Troponin I     | Death, MI, or hospitalization for ACS at 30 days | 7.4% vs 16.2% (<0.001) |
| PARAGON-B [Newby et al. (12)]  | Lamifiban     | Troponin T     | Death, MI, or severe recurrent ischemia at 30 days | 11% vs 19.4% (0.013) |
| ISAR-REACT 2 [Kastrati et al. (13)] | Abciximab    | Troponin T     | Death, MI, or urgent target vessel revascularization at 30 days | 13.1% vs 18.3% (0.02) |

* PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management (trial); CAPTURE, c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (trial); PARAGON-B, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network–B (trial); ISAR-REACT 2, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (trial).
relationship was also demonstrated in the setting of chronic heart failure, for which the Carvedilol or Metoprolol European Trial (COMET) found an association between increased NT-proBNP concentrations and higher all-cause mortality (37). In the TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18) trial, which randomized patients to early interventional vs early conservative treatment for non–ST-elevation ACS, not only did BNP concentrations predict the risk of early and 6-month mortality, higher BNP concentrations also correlated with tighter culprit stenoses and left anterior descending coronary artery involvement (22, 38). Thus, clinical trials have played a key role in the development of BNP and NT-proBNP as clinically useful biomarkers for the diagnosis and prognosis of heart failure and ACS, and ongoing trials continue to refine their roles in clinical decision-making and for monitoring treatment in heart failure patients.

**Clinical Trials and the Concept of Multidimensional Risk Stratification**

One of the first trials to clearly demonstrate that using a multimarker strategy could improve risk stratification for subsequent clinical events was CHECKMATE (Chest Pain Evaluation by Creatine Kinase-MB, Myoglobin, and Troponin I) (39). In this study, 3 biomarkers of myonecrosis with differing kinetics and diagnostic sensitivity and specificity (myoglobin, CK-MB and troponin I) were measured simultaneously in 1005 patients presenting with ischemic symptoms. The investigators found that use of the 3 biomarkers in combination not only identified more patients with myonecrosis than either a single-marker strategy or CK-MB plus troponin I, but also better discriminated risk for subsequent 30-day death or MI. This concept of simultaneously testing multiple biomarkers subsequently evolved to multidimensional risk stratification with biomarkers that report on multiple distinct pathways thought to be active in the pathogenesis of CVD and ACSs. In particular, the combination of troponin (myonecrosis), hsCRP (inflammation), and BNP/NT-proBNP (neurohormonal activation)—all of proven diagnostic and prognostic value through testing in clinical trials—have been evaluated as part of multidimensional biomarker testing. Table 2 summarizes the clinical trials that served as a vehicle for the discovery and incorporation of important biomarkers in stratified clinical care.

**Biomarkers Present**

Of the multiple phases proposed for development of a biomarker for use in clinical practice (41), these studies have shown that troponin, hsCRP, and BNP/NT-proBNP satisfy the important criterion of adding diagnostic and/or prognostic information to readily available clinical features and routine laboratory testing. In some cases, they may be relevant in guiding treatment decisions. The ability to embed these studies within clinical trials has been critical to this development. Since the beginning of the new millennium, numerous individual biomarkers have moved from hypothesis to proof of concept, often within the context of clinical trials (42–44). The movement of these markers to clinical utility in routine practice has been slow, however. It has become increasingly clear that simply providing a new way to diagnose disease or to predict risk is not sufficient. Rather—as with troponin in ACS, hsCRP in inflammatory acute illness, and BNP/NT-proBNP in heart failure—a biomarker must provide information that augments standard clinical and routine laboratory studies and must do so such that the testing alters practice and, as the highest hurdle, leads to improved outcomes that justify the costs of testing.

In addition, the evolution and availability of genomics, proteomics, and metabolomics has accelerated the ability to identify new putative markers for diagnosis and risk stratification. For example, metabolites that identify patients with ischemia have been discovered via microfluidic metabolomics (45), and expression profiling of cultured cells and platelets has identified ST2 (an interleukin-1 receptor family member) and myeloid-related protein 14 as potential biomarkers of inflammation and platelet activation, respectively, that could be important for diagnosis or prognosis in ACS (46). A gene expression profile that discriminates patients with CAD from those without it and estimates the severity of CAD has also been developed and prospectively validated (47). For any of these biomarkers to become part of routine clinical practice, however, further demonstration of their incremental contribution to risk assessment, their utility in treatment decisions, and the cost-effectiveness of their testing awaits confirmation in the context of future randomized clinical trials.

Still, biomarkers today play an important role in planning and developing new CV clinical trials. Many trials use biomarkers to define study populations for use in testing new therapies. For example, prompted by the demonstration in earlier studies that the treatment
effect of glycoprotein IIb/IIIa inhibitors appeared enhanced among patients who had increased troponin values at baseline (12), subsequent ACS trials of these agents and others have used baseline troponin measurements as an inclusion criterion to enrich the trial population with patients at high risk for events and to identify patients most likely to benefit from treatment (49, 50). In addition, biomarkers, including necrosis markers such as troponin (51, 52) and serum creatinine (52), are key components of risk scores that have been developed and/or validated in clinical trial populations. In the case of the Global Registry of Acute Cor-

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<td>2nd SYMPHONY [Cantor et al. (67)]</td>
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**Table 2.** Selected examples of cardiovascular clinical trials demonstrating roles for biomarkers in diagnosis, prognosis, identification of differential response to therapy, and biomarker-guided therapy.

- *STE, ST elevation; NSTE, non-ST elevation; PCI, percutaneous intervention; SYMPHONY, Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes (trials); PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management (trial); CAPTURE, c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (trial); PARAGON-B, Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network B (trial); ISAR-REACT 2, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (trial).
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Annually Events (GRACE) risk score, its incorporation as a prespecified assessment of global risk at baseline led to the identification of a subgroup of patients who experienced enhanced benefit from a very early invasive strategy in the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial (53).

Similarly, the earlier data showing the relationship between hsCRP and statin treatment and benefit led to the use of hsCRP as an inclusion criterion for testing a specific hypothesis in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial. In this trial, hsCRP concentrations were used to identify a study population thought to be at high risk for CV events despite normal cholesterol concentrations (54). Not only did treatment with rosvastatin lower serum LDL cholesterol and CRP concentrations, it also produced an almost 50% reduction in the combined primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes, compared with placebo.

Presently, there is much debate regarding the use of biomarkers as surrogate end points in clinical trials. Owing to the cost and time burden of event-driven clinical trials, many investigators rely on biomarkers that correlate with risk or a presumed mechanism in order to identify differences between therapies. Changes identified in surrogate markers in the setting of CV clinical trials, however, do not always translate well into clinical end points. A prime example occurred in the CAST (Cardiac Arrhythmia Suppression Trial), in which suppression of premature ventricular contractions (thought to be a good surrogate for ventricular arrhythmias and sudden cardiac death) with class Ic antiarrhythmics in MI survivors actually led to increased mortality compared with placebo (55).

Similarly, lowering of LDL cholesterol and increases in HDL cholesterol (biomarker surrogates believed to be key intermediates on the pathway to atherosclerotic events) with Premarin in the Heart and Estrogen/Progesterin Replacement Study (HERS) failed to reduce ischemic events overall and may have increased early ischemic events (56). Thus, biomarkers may be useful for screening for both favorable and unfavorable effects of therapy, but in general, CV safety and the effectiveness of new treatments or treatment strategies should be confirmed in randomized clinical trials with meaningful clinical outcomes.

In other areas, strategy trials, in which a new treatment strategy and a standard approach are randomly assigned within groups defined by biomarker-testing results, have not been as successful. For example, the use of genetic testing for mutations affecting the metabolism of warfarin to guide dosing has not shortened the time to a therapeutic interval or decreased bleeding risk, compared with standard approaches to warfarin dosing (57, 58). Additionally, 2 recent trials of platelet function testing to guide the dosing of clopidogrel or the use of prasugrel in patients with high residual platelet function on clopidogrel have been limited by low rates of overall events and have not provided the evidence needed for including such testing in routine clinical practice (59, 60).

Biomarkers Future

CV clinical trials increasingly and frequently serve as a platform for collecting samples from enrolled patients for future use. Although most published studies from analyses of these samples have reported the results of individual or at most a few targeted biomarkers with an effect on outcomes or treatment, this process of sample collection is vital for providing material for use in developing novel biomarkers for future clinical use and for improving our understanding of the pathogenesis of CVD. Unfortunately, the incorporation of sample collection in randomized clinical trials in CV medicine has been highly variable to date, a fact reflecting both financial realities and corporate interests; however, the principle of biobanking focusing on the preservation of biologic material for future investigations yet to be determined or beyond the imagination or technical possibilities at the time of collection is an essential concept, the importance of which is increasingly being recognized (61).

Although the incorporation of biobanking into clinical trials is not yet routine, the collection of various biological specimen types (including whole blood for DNA, stabilized whole blood for RNA, serum, plasma, and other specimens) as relevant to trial design and operations could generate a unique resource for future studies of mechanisms of disease pathways, biomarker discovery and development, and, potentially, the identification of new treatment targets as an outgrowth of the former. In particular, that the process of drug development has become increasingly difficult is evidenced by the fact that since the introduction of statins in 1987, only 4 classes of major CV drugs (angiotensin receptor blockers, BNP mimics, glycoprotein IIb/IIIa inhibitors, and direct renin inhibitors) have become available (62). There are numerous reasons for this state of affairs, including the large costs and long timelines associated with drug development and the high attrition rates in preclinical and early clinical trials. These limitations exemplify the need for a more targeted approach to CV drug development. This approach may incorporate novel biomarkers of efficacy or risk in early-phase clinical trials as initial biological signals for moving forward with additional testing of a new compound or for using mechanistic information.
gleaned from the study of large sample collections from within clinical trials of specific disease states. One approach that is becoming more common is that of systems biology, the science of establishing multiple genomic datasets that may be intersected and queried with sophisticated informatics approaches in order to establish causal associations of gene pathways with disease (62). In addition to genetic information, this approach uses RNA profiling, proteomics, and metabolomics. This consideration highlights the importance of collecting multiple specimen types within clinical trial biobanking efforts.

A potential use of biomarker information for drug development lies in the field of pharmacogenomics, in which the efficacy and toxicity of novel drug therapies in populations are predicted by their biomarker profile, which may be used to guide treatment. This strategy has been used with mixed success for such commonly prescribed medications as warfarin, statins, β-blockers, and angiotensin-converting enzyme inhibitors (63–65). As our ability to target pathways in drug development improves, the incorporation of “omics” technologies will improve our prediction of efficacy and safety in targeted populations and the development of biomarker tests that guide treatment. This approach will lead to a more “personalized” approach to the delivery of CV care. In response to the growing enthusiasm for linking biomarkers with therapeutic decisions, the US Food and Drug Administration recently issued its draft guidance on in vitro companion diagnostics (66), which defines companion diagnostics as tests that (a) “identify patients who are most likely to benefit from a particular therapeutic product,” (b) “identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product,” or (c) are used to “monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.” Clinical trials at all phases will be required to meet these needs in parallel with drug development or to adapt existing biomarker tests to new purposes as companion diagnostics.

Conclusions

Clinical trials have played an important role in the evolution of novel biomarkers and in the generation of evidence to bring them to clinical utility. Biomarkers also serve key functions in clinical trial operations, including population selection and end point definition. In this way, biomarkers and clinical trials will continue to be inextricably intertwined. Routine biobanking in the context of clinical trials, coupled with the use of advanced analytical platforms for biomarker discovery and an emphasis on understanding disease pathways through the use of sophisticated bioinformatics tools and advanced techniques for data analysis, will move us ever closer to an era of stratified informatics for clinical utility and an emphasis on understanding disease pathways through the use of sophisticated bioinformatics tools and advanced techniques for data analysis, will move us ever closer to an era of stratified bio-informatics tool

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