Biomarkers in acute medicine

Louella Vaughan

Abstract

Biomarkers represent a major technological innovation in medicine. This article discusses the definition and uses of biomarkers, particularly their role in diagnosis, risk stratification and management of disease. It reviews the current roles of the seven most commonly used biomarkers in the acute setting (troponin, creatine kinase, myoglobin, brain natriuretic peptide, D-dimer, C-reactive protein, procalcitonin). The article looks briefly at the utility of point-of-care testing, which, despite concerns about accuracy, can help to risk-stratify patients more efficiently at the point of presentation. Biomarkers currently in development for diagnosis and prognostication across a spectrum of disease are surveyed.

Keywords Biomarkers; brain natriuretic peptide; C-reactive protein; creatine kinase; D-dimer; diagnosis; procalcitonin; risk stratification; troponin

Key points

- Correct interpretation of biomarker results depends on understanding the reason why the test was taken — screening, diagnosis, prognosis or monitoring
- Biomarkers appear to be most effective when incorporated into robustly tested clinical algorithms
- Panels of biomarkers and the newly emerging fields of proteomics, metabolomics and metagenomics are likely to replace single protein biomarkers. Not only are these likely to perform better diagnostically, but they also will offer the opportunity to more highly personalize therapeutic regimens

Introduction

The development of biomarkers represents one of the great technological developments in medicine. They are potentially useful at every stage of the disease process (screening, diagnosis, prognosis, monitoring) and possibly in most disease states. Despite the explosion in number of biomarkers in development, very few are routinely used in the acute clinical setting. This article reviews the potential uses of biomarkers, outlines those currently in use in the acute setting and surveys promising new biomarkers.

Definitions of biomarkers

The American National Institute of Health defines a biomarker as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention or other healthcare intervention'.[1] This very broad definition covers such diverse processes as the identification of specific DNA/RNA gene sequences, detection of antibodies and measurement of organic metabolites. Most biomarkers used in clinical practice tend to be single proteins, which may be a direct or indirect result of disease processes. However, there is increasing research around proteomics, metabolomics and metagenomics as 'snapshot' protein, metabolite and microbial flora profiles appear to be strongly correlated with certain disease states and predictive of outcomes.[2]

Uses of biomarkers

A biomarker can serve one or more purposes (Table 1). It is vital to remember not only that any particular biomarker can serve one or all of these roles in any given disease, but also that the role of the biomarker can change with different pathologies (Table 2). Lack of awareness of these differences can lead to misdiagnosis and/or poor clinical care. For example, troponin is diagnostic, prognostic and used experimentally as a surrogate endpoint in acute coronary syndrome (ACS), but is useful as a prognostic marker only in patients with pulmonary embolism (PE).

Common biomarkers

Given the large numbers of potential biomarkers, the number demonstrated to be useful in the acute setting is surprising small. For example, >100 distinct molecules have been proposed as being useful in the diagnosis and management of sepsis, but only C-reactive protein (CRP) is routinely used at present.[3]

Troponin

Troponin is a contractile protein of the cardiac myofibril that leaks into the general circulation when myocytes become ischaemic. It is not, therefore, usually found in patients with normal physiology and is almost invariably a marker of pathology.[3,4] As well as being highly sensitive and specific for myocardial ischaemia, it is strongly associated with increased risk of subsequent death, acute myocardial infarction (AMI), need for revascularization, and readmission following ACS.[3] In 2000, it replaced creatine kinase (CK) as the preferred biomarker for the detecting all forms of myocardial ischaemia.[4]

All patients with suspected myocardial ischaemia should have a serum troponin measurement, the timing of which depends on the local assay. The new generation, high-sensitivity troponin assays (hs-Tn) are capable of identifying as little as 3 pg/ml of protein and become positive within 3–4 hours of the onset of

***Louella Vaughan** MB BS MPhil DPhil FRACP FRCP is Senior Research Fellow, Northwest London CLAHRC, UK. Research interests include diagnosis and management of the acutely unwell patient, patient safety, medicines management. Competing interests: she has been a co-investigator on projects indirectly funded by Alere and Brahms (biomarker samples analysed at no cost); Alere has provided travel grants to her junior staff for attendance at an educational symposium.*

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Uses of biomarkers

- **Screening**
  Identification of a patient with an increased probability of having a disease or one who might warrant further investigation; detecting risk before the development of disease
- **Diagnosis**
  Identification of the presence of a pathological state or process in order to establish a diagnosis. Alternatively, a biomarker may assist in ruling out a disease
- **Risk stratification/prognostication**
  Identification of patients at higher risk of mortality or certain morbidities. This may include the use of biomarkers to classify, grade or stage disease, as well as using biomarkers to assist in the selection of treatment modalities
- **Disease monitoring**
  Biomarkers may respond dynamically to the severity of the disease state. This can help to predict disease flares, assist with diagnosis when patients present with interim illnesses and/or titrate therapeutic regimens
- **Drug monitoring**
  Biomarkers may respond dynamically to the use of certain drugs, providing a means to monitor the response to a given intervention and/or titrate therapeutic regimens
- **Surrogate end points**
  If biomarkers correlate consistently with patient outcomes, the marker can be useful as a surrogate outcome measure, particularly in the research setting

Table 1

Uses of common biomarkers in the acute setting

	Diagnosis	Risk stratification/prognosis	Disease monitoring
Troponin	ACS	ACS	
	Myocardial infarction	Myocardial infarction	
	Myocarditis/pericarditis	Congestive cardiac failure	
		Myocarditis/pericarditis	
		PE	
		Chronic obstructive pulmonary disease	
		Pneumonia	
		Sepsis	
		Systemic inflammatory response syndrome	
		Renal disease	
CK/myoglobin	ACS	ACS	
	Myocardial infarction	Myocardial infarction	
Brain natriuretic peptide	Congestive cardiac failure	Congestive cardiac failure	Congestive cardiac failure
		ACS	
		Myocardial infarction	
		Syncope	
		PE	
		Chronic obstructive pulmonary disease	
		Sepsis	
		Systemic inflammatory response syndrome	
D-Dimer	Venous thromboembolic disease	PE	
	Aortic dissection	Aortic dissection	
		Upper gastrointestinal bleeding	
		Acute bowel ischaemia	
C-reactive protein	Infection	Infection	Infection
		Coronary artery disease	Solid tumours
		Solid tumours	Aortic dissection
Procalcitonin	Infection	Infection	Infection

Table 2

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