

Personalised Medicine and the Future of Healthcare – Reflections on the Role of Biomarkers

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Abstract

The concept of personalised healthcare, namely targeting medical interventions based on novel biomarkers, is appropriately considered to be of pivotal importance for the future of healthcare. It represents an iterative extension in the evolution of medicine towards an increasingly differentiated assessment of patients and diseases based on the use of novel biomarkers, which are increasingly becoming available based on recent progress in molecular and cell biology and associated technologies. While the topic of biomarker-guided personalised medicine is receiving a high degree of visibility, certain fundamental considerations regarding the requirements for such markers are often not afforded sufficient attention. In particular, the qualitative and quantitative information content and the long-term predictive characteristics that are needed for a useful biomarker are commonly not addressed. Consideration of these requirements suggests that dynamically modulated markers, such as proteins, are most likely to provide these attributes, but also that the nature of these requirements creates a significant hurdle to finding and validating such markers.

Keywords

Personalised healthcare, biomarkers, diagnostics, prognostics, sensitivity, specificity, statistical significance, genome-wide association studies

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What Is New and Not So New About Personalised Healthcare?

Over the last few years we have witnessed increasing enthusiasm for the idea of personalised healthcare, sometimes approaching irrational exuberance with claims of a radically new approach to the practice of medicine. However, the concept of treating each patient in a targeted, 'personalised' fashion to achieve an optimal healthcare outcome is conceptually nothing revolutionary, and has indeed been the noble quest of every physician since time immemorial. In the early days of medical practice when diagnoses were rather crude, this was arrived at mainly by an iterative, retrospective, empirical adjustment of the therapeutic approach based on success or failure of a treatment, but the goal of optimising the treatment of the individual was the same.

With the emergence of a new, science-driven breed of medicine in the late 19th century we began to understand aetiological factors at the level of physiology, gross anatomy, histology, microbiology and biochemistry, and thus gained mechanistic insight into disease processes. This allowed the shift from a differentiation based on retrospective insights gleaned by trial and error to a prospectively differentiated approach to diagnosing and treating disease. This concept, captured under the term 'differential diagnosis', encapsulated an increasingly sophisticated, science-based diagnostic approach to the patient that allowed more tailored, and thus more successful, therapeutic interventions. The last century also witnessed the emergence of the recognition that non-disease-related inter-individual differences based on inheritance may also

play a role in the likelihood of responding to a certain treatment: empirical observations led to differential recommendations regarding the choice of diuretic agents based on ethnic background, and the role of cytochrome P450 isoenzymes in between-patient differences in drug metabolism was uncovered.

What we are pursuing today as personalised medicine is yet another iteration of this relentless move towards a more differentiated approach based on a deeper understanding of disease heterogeneity and patient-patient differences, this time based on the major progress in our fundamental understanding of biology on the molecular level that occurred during the latter third of the last century. These developments may be regarded as revolutionary change, or perhaps more accurately as evolutionary steps. The more measured evolutionary view helps to avoid hyperbole with its inherent danger of raising exalted expectations, leading to unfulfilled promises and disappointment. However, to some extent the revolutionary perspective is important as well: unless we approach innovation with sufficient enthusiasm, it is very difficult to muster the support and resources that are critical to allow the viability of a new idea to be interrogated in the first place. Carefully pairing a non-risk-averse approach with responsible expectation management is critical for the ultimate success of the modern concept of personalised healthcare.

This article attempts to cast a balanced light on the important opportunities but also the limitations of our current drive towards personalised healthcare.

Biomarkers, An Array of Beacons Guiding Us Towards Personalised Healthcare – Which Marker When?

Biomarkers are conceptually not so new either if we view them, in a rather generic sense, as physicochemical indicators or characteristics that help us recognise and distinguish disease processes and choose our interventions in order to restore or maintain the health of our patients. Thus, body temperature serves as an example of a biomarker that we have known about for eons, and others, more and more sophisticated, followed as medicine and science intermarried: blood pressure, blood sugar, haematoxylin–eosin (H–E)-stained biopsies, results of imaging studies and microbial cultures – the list goes on. Advances in assay technologies and platforms robust enough to be deployed in everyday clinical practice led to the discovery of molecular markers in the last few decades. Today the term biomarker is sometimes used as if it referred only to this newest of clinical tools; however, the palette of useful new biomarkers deserves special attention, as we can expect radically different degrees of usefulness from members of different subgroups.

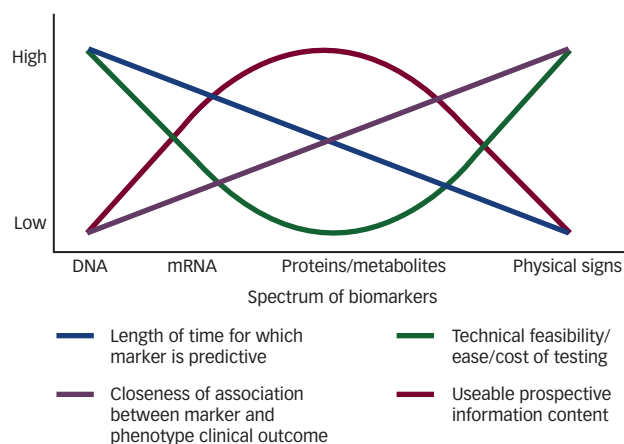
On one end of the biomarker spectrum, the most highly informative biomarkers may be viewed as those that assess biology/pathology at the highest level of physiological integration, such as body temperature or blood pressure, i.e. physical signs (see *Figure 1*). By their very nature, these markers – being most closely associated with the actual health outcome – tend to be indicative of a current condition (such as elevated temperature for sepsis) or of a relatively short-term health outcome (such as death as a consequence). While they may serve to guide preventative or therapeutic interventions in the short term, they are of limited value in providing predictive or prognostic information for medical decisions and actions relevant to longer time-frames.

At the other end of the spectrum of biomarkers are DNA variants, such as single nucleotide polymorphisms (SNPs) or copy number variations (CNVs) (see *Figure 1*). These most basic building blocks of life are also those most remote from, and thus least reflective of, integrated physiological processes. The early days in the modern era of biomarker science tended to focus strongly on DNA – not surprisingly, as progress in this field was most rapid. Also, DNA markers are relatively straightforward to assay: the analyte is highly stable, the markers (with the exception of somatic mutations) are not dynamic but static and their read-out is easily interpretable. DNA markers are qualitative and dichotomous – a sequence variant is either present or not, allowing a digital read-out. In rare, monogenic Mendelian disease the information content they convey in predicting future health outcomes can be paradigmatically powerful, with literally black or white prognostic accuracy.

However, when it comes to common complex diseases – the highly prevalent ailments such as diabetes, osteoarthritis, arteriosclerosis or asthma that are the focus of public health concerns with regard to both disease burden and healthcare expenditure – DNA markers have so far largely disappointed. Interrogations of a very large number of DNA markers carried out in recent years with the help of genome-wide association studies in many of these disorders have, by and large, revealed rather modest associations and thus had no direct impact on personalising healthcare.¹

On a conceptual level, this should not come as a surprise: the DNA sequence is arguably the least nuanced, not to say crude, factor

Figure 1: Attributes of Different Classes of Biomarker



affecting the programming of the infinitely subtle variations and modulations that govern integrated regulation of physiology and biology on the level of the whole organism. We know that the vast majority of biological modulation takes place downstream of the genetic blueprint, at the level of messenger RNA (mRNA) and proteins. Functional states as well as environmental variables modify gene products at every step along the cascade from DNA to protein. Thus, DNA markers, being largely static and furthest removed from the complex dynamic interplay of these downstream factors, can in most cases be expected to contain rather limited information content compared with markers found further along this cascade. The increasing information content along the cascade from gene to protein is mirrored by the molecular diversity of the classes of molecules involved – rising from 25,000 genes in the genome to an estimated 100,000 or more mRNAs, and an order of magnitude more distinct proteins by the time post-translational modifications and chemically distinct functional states are considered. The price to be paid for the increasingly dynamic and differentiated information available along this value chain is the increasingly complex and, generally, expensive array of analytical approaches and platforms needed to assess these higher-order markers. In return, these more diverse and complex markers, particularly proteins, can be expected to convey more comprehensive, meaningful, integrated information on the state of health and disease than is available at the level of the gene itself.

An example may illustrate the respective merits and shortcomings of the panoply of biomarkers that can be used in a given disease. In the treatment of patients with adult-onset diabetes, blood sugar levels are arguably the most highly integrated biomarker that is directly indicative of the state of the disease and of its physiological–metabolic consequences at any particular time-point. Blood glucose measurements are helpful in managing the disease in a realtime fashion by guiding the timing and dose of insulin administration as needed; however, they are of little or no value in long-term prediction of the occurrence of the disease, and of very limited help in predicting its course once it has occurred. On the other hand, while a number of DNA variants have recently been shown in large studies to be associated with an elevated risk of contracting non-insulin-dependent diabetes, the effect of each of them is far too small – i.e. they are individually too unreliable as predictors – to be useful in clinical practice. Positioned between the extremes of DNA variants and clinical outcome as indicated by metabolic phenotype (blood glucose), there is a protein marker, glycated haemoglobin (HbA_{1c}),

which has long been recognised as the most informative biomarker for the disease. While more difficult to measure than either blood glucose or a DNA variant, HbA_{1c} is widely used as an indicator of mid- to long-term treatment efficacy as well as disease prognosis.

Thus, biomarkers that provide the richest source of prospective information about complex biological processes will likely be those that straddle the divide between highly reductionist ones, such as DNA, and highly integrated ones, such as realtime disease-state read-outs. Such highly informative biomarkers are expected to be dynamic with regard to both quantitative and qualitative characteristics. For this reason, and because they are expected to commonly be present in low concentrations, they will be challenging to measure.² Assaying them is therefore likely to require sophisticated tools and approaches with requirements for sensitivity (lower limits of detection and quantification) and accuracy far beyond those applicable to less differentiated markers.

Statistical Significance versus Magnitude of Effect – What Makes a Meaningful Biomarker?

In addition to the requirements for analytical accuracy are what we may call the biomedical, or clinical–epidemiological, attributes that determine its validation as a biomarker. A differentiated and contextual view of these requirements is of prime importance, particularly as it applies to the use of the marker – in other words, whether the marker will be viewed as a research tool or lend itself to being deployed in the clinic to guide medical decision-making in the care of individuals.

The evaluation and determination of a biomarker's utility has suffered historically from a chasm in the perspectives and terminology applied by the different communities interested in these markers. Academic research and investigative epidemiology, concerned about basic mechanisms of disease and about public health, tend to focus primarily on statistical significance in their evaluation of the relevance of a marker–phenotype association. They understand that when studying large populations, even a small magnitude of effect, if real, can contribute new insights regarding disease mechanisms or new strategies for disease prevention. For clinicians treating patients, on the other hand, statistical significance, while essential, is by no means sufficient. Rather, since they deal with individual persons rather than whole populations, they require a very high level of reliability of any marker to be used for responsible medical decision-making – an attribute that translates into a clinically meaningful magnitude of effect. Thus, clinicians appropriately apply a different standard in judging the usefulness of a biomarker for individual patients than that needed by academics seeking to understand new mechanisms of disease or by public health professionals who can effect positive change in a population's health through interventions that benefit only a subset of the whole group.

Too often, the understanding of what a biomarker may or may not deliver is lost in translation between vernaculars used by these different constituencies with their very different goals and points of view. The academic community commonly uses odds ratios (ORs) or relative risk (RR) to assess the impact of biomarkers, and tends to be mainly concerned with ascertaining statistical significance with regard to these metrics. Their attention has therefore, appropriately, been focused on the development of statistical algorithms that allow the reliable recognition of small expected differences in the face of

analysing many markers – a challenge inherent in genome-wide association studies where hundreds of thousands of markers are assayed in parallel. This focus on statistical tools is indeed justified by the fact that the ORs that were found in a large number of genome-wide association studies for common complex disease were almost universally of very modest magnitude, with numbers generally very close to unity. ORs between 1.1 and 1.5 dominate the results of these studies.¹ Based on the potential new mechanistic insights that these findings – if they reflect causative relationships – may allow, their publication in premier journals is certainly justified. Their importance from the viewpoint of basic biomedical research cannot be overemphasised, and from a public health perspective, small effects that are applicable to large groups are of well-established relevance.

By contrast, the metrics for biomarker relevance and the associated terminology that physicians and other healthcare providers use are very much based on the magnitude of effect with which a biomarker correlates with a clinical entity or outcome. Thus, rather than ORs, they use as their reference point in the assessment of a marker's value metrics such as sensitivity and specificity, or positive and negative predictive value (PPV and NPV, respectively). Clinically useful markers generally will have a sensitivity and specificity of at least 75%. Markers with a performance less than this will be viewed as yielding too many false-negative or false-positive results to be useful for responsible medical decision-making in most situations.

If one reconciles the metrics used by the two communities and translates the two terminologies, it quickly becomes evident that a wide gap exists between what academics and clinicians consider as relevant. Thus, an OR in the range of 1.1–1.5 translates to sensitivity and specificity values of very little more than 50%, while a 75% sensitivity and specificity equates to an OR of about 10. Clearly, from the perspective of the physician confronted with the dilemma of responsible decision-making for individual patients, the results of most genome-wide association studies are of unclear value at best. Using them would be similar to basing these decisions on a coin toss. Given the high hurdles clinicians set for new biomarkers, it is also fair to predict that only a small minority of markers investigated will provide the kind of information content that is required to qualify as a clinically useful marker.

It is fair to speculate that the high requirements placed on information content necessary to qualify for clinical applicability will more likely be met by markers reflecting higher degrees of information integration. As elucidated above, this will tend to favour biomarkers that are qualitatively and quantitatively modulated and thus positioned somewhere downstream from the reductionist and static DNA-based markers (see *Figure 1*). While markers more closely associated with the actual disease state or outcome, such as body temperature, blood pressure, or blood glucose will, by definition, provide higher levels of sensitivity and specificity, their utility is limited by the fact that they measure the present state rather than predict future outcomes.

Truly valuable markers that will be useful in guiding medical decisions will be characterised by high levels of both sensitivity and specificity as well as a being robust predictors of meaningful clinical outcomes over the long term. It may be expected that generally there will be trade-offs between these two attributes: the longer the time-frame over which a biomarker is asked to predict outcomes, the less

perfectly it will perform with regard to sensitivity and specificity. It will therefore always be critical to take into consideration the clinical context in which the marker will be used in order to choose one with the optimal balance among these test characteristics.

For example, a biomarker used to decide on the choice of cancer therapy (A versus B) will need to provide sufficiently reliable prospective information at the start of treatment regarding the likelihood of success with either treatment A or treatment B. However, in all likelihood it will not be able to be held to the same standards of sensitivity or specificity as a marker used to assess treatment response on a more realtime basis. Reverting to the diabetes example, the value of blood glucose – despite very high sensitivity and specificity for realtime monitoring – is mitigated by its lack of longer-term information content regarding the disease. The DNA variants that have been associated with increased risk of diabetes may be interrogated starting at birth to assess the lifetime risk of diabetes (i.e. in a predictive fashion covering a very long time-frame), but the sensitivity and specificity they provide with respect to predicting disease occurrence is extremely low. The protein HbA_{1c}, neither as sensitive and specific as blood glucose nor displaying the long-term quality of DNA markers, strikes a clinically useful balance between information content and predictive attributes, a quality that is reflected by its widespread use to assess future health outcomes in patients with diabetes.

Conclusion

The pivotal role of biomarker research for future progress in healthcare is now widely recognised. Indeed, biomarkers are, in essence, nothing other than a reflection of new, increasingly sophisticated and differentiated insights into the molecular pathology of disease: the discovery that a new molecular pathway is relevant to a disease renders all the members of this pathway as potential biomarkers. Although the likelihood that any one novel biomarker will cross the threshold of sensitivity and specificity required for clinical applicability is modest, it will happen from time to time. When the occasional very powerful biomarker is discovered, it will profoundly affect the practice of medicine. Thus, the search for biomarkers should be a routine part of the investigation of each new disease or treatment, and it would be a fundamentally flawed approach to fail to deploy systematically the new and powerful tools for investigation of biomarkers that are at now our disposal. Meaningful biomarkers have

the potential to increase treatment efficacy and safety as well as to increase the cost-efficacy of healthcare expenditures.

The challenges for biomarker science are clear and rather daunting. Those markers that ultimately will provide the kind of information content that will qualify them in the clinical arena as diagnostic or prognostic tools will need to satisfy high standards with regard to both sensitivity/specificity and prediction of health outcomes on a prospective timeframe. Importantly, these requirements will have to be judged and adjusted in a context-specific way – different clinical applications will require different qualities of biomarkers. In considering the attributes that will render a biomarker truly useful, it may be argued that protein markers are likely to dominate the field, with the associated cost and complexity of assaying these most demanding markers.

Successfully realising the promise of biomarker-driven personalised healthcare will require a highly collaborative and integrated multidisciplinary coalition of basic scientists, clinical investigators, pharmaceutical and diagnostic/device industry specialists, healthcare professionals and payers. Last, but by no means least, patient preferences and societal values must play a key role in guiding this effort, since improving lives is the ultimate test of the value of biomedical innovation. **n**



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