Editorial

Development and validation of new biomarkers: major opportunities for health-care scientists

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Reflecting significant advances in technology and substantial research investment in discovery programmes, thousands of new biomarkers with diagnostic potential have been identified over the last 30 years. However, only a tiny fraction of these – among them CA125, prostate specific antigen (PSA) and troponin – have successfully joined the routine clinical biochemistry repertoire, and often only after considerable delay.

Reasons for this were considered at a multidisciplinary 'Perspectives in Clinical Proteomics' conference convened in March 2010 under the auspices of the Wellcome Trust.[1] While primarily focusing on biomarkers identified using proteomic technologies, conclusions developed during the conference and subsequent retreat[2] are equally relevant to the introduction of biomarkers identified by other routes. Among issues highlighted were the pressing need for more thorough and systematic evaluation of new biomarkers and the importance of early involvement of health-care scientists, both of which are briefly considered here. A more detailed report[3] is available as an open access publication with key points summarized here (Table 1). The proceedings of a recent International Federation of Clinical Chemistry and Laboratory Medicine Bergmeyer Conference on the same topic are also relevant.[4]

Why are so few new biomarkers implemented in routine clinical practice?

Failure to provide convincing evidence of the clinical and financial benefits of introducing a new test and the weakness of many published studies were identified as major factors relevant to the slow uptake of new biomarkers.[3] Serious limitations include initial failure to address clinically important questions where a novel biomarker could improve clinical outcome (i.e. not asking 'the right question' and instead devoting valuable resources to clinical questions for which existing tests provide adequate information),[5] lack of rigorous early investigation of preanalytical factors (i.e. biomarker stability and specimen requirements, diurnal and intraindividual variation, etc.),[6] deficiencies in study design leading to different types of bias (e.g. inappropriate selection of specimens and/or cohorts of patients and/or healthy subjects),[7] absence of independent verification of results (i.e. not confirming reproducibility in different laboratories and patient cohorts)[7] and failure of investigators to evaluate whether the application of the biomarker would change clinical practice to the benefit of patients or the health service as a whole.

Many of these problems can be reduced by adherence to the Standards for Reporting of Diagnostic Accuracy guidelines.[8] However, the critical importance of study design and independent verification of results has recently been brought into sharp focus by two examples, specifically from the field of genomics but with much broader implications. In the first, three cancer trials have been suspended following doubts about the validity of microarray data on which the trials were based.[9] Relevant to this, the Scientists for Reproducible Research Working Group recommends that journal editors require study authors to supply more detailed information, including the entire data set on which experiments were based, to enable other groups to reproduce reported results.[9]

In the second example, when pharmacological and epidemiological evidence regarding the association between *CYP2D6* inhibition and risk of breast cancer recurrence was objectively reviewed, a number of causes of possible bias in different studies were identified.[10] The significant diversity observed in studies, including differences in how oestrogen-receptor expression was determined (e.g. whether by biochemical or immunohistochemical techniques, which have different positive predictive values), led the authors to conclude that recommending *CYP2D6* genotyping of candidates for adjuvant tamoxifen therapy – a recommendation with significant clinical and cost implications – may have been premature.[10]

What is being done to improve the situation?

The barriers impeding the introduction of new biomarkers in clinical practice are essentially the same as those inhibiting their use in drug development. To address the latter, the American Association for Cancer Research, the US Food and Drug Administration and the US National Cancer Institute (NCI) proactively convened a Cancer Biomarkers

Table 1 Successful introduction of a new biomarker into routine practice – key requirements[3]

- Proactive collaboration involving research laboratory, diagnostics industry, clinical laboratory and clinical staff.
- Recognition that some tests may be most appropriately provided by specialist laboratories.
- Rigorous investigation of preanalytical requirements at the earliest possible stage of evaluation.
- Analytical performance documented in detail.
- Well-documented evidence of clinical utility and cost-effectiveness in populations representative of those which will be encountered in clinical practice.
- Evidence of the likely beneficial effect of the new test on the patient pathway, i.e. evidence of the additional diagnostic or predictive information it will provide when supplementing or replacing existing tests.
- Fulfilment of appropriate regulatory requirements.

Collaborative (CBC), which has recently published an excellent and comprehensive Consensus Report on advancing the use of biomarkers for cancer drug development.[11] The recommendations made by the CBC in eight critical areas (Table 2) are equally relevant to biomarkers being developed for clinical use in diagnosis (early detection, disease classification), prediction (response, adverse effects of treatment) and monitoring (response, progression). Development, adoption and implementation of the CBC recommendations clearly will require well-coordinated national and international communication and collaboration among clinicians, research and routine laboratorians, staff from pharmaceutical and diagnostics industries, regulatory agencies and other stakeholders including patients and health-care providers. Lines of communication to enable such dialogue, as commenced through the CBC initiative, may not yet be widely in place but should be actively developed.

How can health-care scientists contribute?

As staff at the interface between the clinic and the laboratory, health-care scientists are uniquely well placed to contribute at all stages of discussions related to the rapid and timely introduction of effective new biomarkers into publicly funded health-care systems. There is no point in expending valuable resources in identifying a new biomarker for a particular application unless its measurement is likely to be clinically relevant and improve patient outcome.[5] Early dialogue between laboratorians and clinicians to establish where in a given patient pathway a new biomarker could best make an effective contribution to clinical care is therefore essential. Identification of post-transplant renal rejection, for example, still relies on serial creatinine measurements but more sensitive and specific early biomarkers could be highly cost-effective if they identified problems earlier, reducing the need for later expensive intervention and/or hospitalization.

As emphasized above, from the earliest stages of development of a potential new biomarker it is critically important to ensure that studies in both preanalytical and analytical phases are rigorous and comprehensive and that all major variables are thoroughly investigated. In relation to the first requirement in Table 2, health-care scientists can help to specify the preanalytical and other quality requirements for specimen biobanks, and can also highlight the potential of the clinical laboratory as a source of biological material for research. With sufficient will, encouragement from decision makers and modest financial investment, hospital laboratory infrastructures could readily support efficient collection of such material, provided arrangements for appropriate specimen selection, clinical documentation, consenting of patients and funding were assured. An excellent prototype infrastructure facilitating such collaboration

Table 2 Desirable requirements for advancing the use of biomarkers in clinical practice

Preanalytical requirements and specimen biobanks

- Established nationally or internationally agreed quality requirements for biological specimens acquired for research and means of assessing their quality;
- Infrastructure supportive of collection of biological specimens for research.

Analytical performance

- Defined best practice for analytical validation of different analytes and technologies;
- Quality systems for use in assay validation.

Standardization and harmonization

- Terminology for biomarker validation and qualification;
- Common data standards;
- A universally agreed clinical data set for specimens in high-quality biobanks;
- A simple efficient informed consent process and documentation.

Bioinformatics

- Working models for biomarker development to facilitate development of appropriate bioinformatics tools.

Collaboration and data sharing

- A model precompetitive consortium to facilitate sharing of scientific information and research operations;
- Incentives to encourage collaborations among pharmaceutical or diagnostics industry sponsors, clinical research sponsors and regulatory authorities;
- Sharing of methodological and experimental biomarker data in public databases.

Regulatory issues

- Best practice standards relating to co-development of therapeutics and diagnostics;
- Best practice standards for composite assays involving more than one biomarker.

Stakeholder education and communication

- Increased awareness of the value and need for collection of biological specimen by patients and health-care providers;
- Increased awareness and understanding of the importance of analytical validation and quality control.

Science policy

- Identification of areas and/or processes likely to encourage biomarker development;
- Improved funding for collection of biological specimens and diagnostic tests;
- Consideration of how to maintain patient confidentiality requirements without adversely affecting biomarker research.

After the recommendations of the AACR-FDA-NCI Cancer Biomarkers Collaborative[11]

already exists through the UK National Cancer Research Network (NCRN) (http://science.cancerresearchuk.org/index.htm), with an associated Cancer Research UK project currently assessing the use of genomic markers to inform selection of therapy for patients with a wide range of cancers.

Analytically, the procedures for internal quality control, external quality assessment, audit and laboratory accreditation that are taken for granted in routine clinical laboratories provide readily modifiable templates for studies of new biomarkers.

As a new biomarker moves closer towards routine implementation, it is important to recognize that the realities of research and routine laboratory settings differ significantly and techniques well suited to the former may be impossible to implement in the latter.[3] Where workloads are likely to be small, where a biomarker is relevant only in rare clinical conditions, where the test is technically difficult or requires specialist equipment and/or where clinical interpretation is complex and requires specialist expertise, it may be most appropriate for a new biomarker to be provided by specialist referral laboratories, as exemplified by the network of Supra-Regional Assay Service laboratories in the UK.[3] Such provision may also be desirable for tests that are in transition from research to routine practice and those using new technologies such as plasma nucleic acid analysis.[12]

A sound business case is of course required to support the introduction of a new routine test, which is unlikely to be adopted unless there is clear evidence that its measurement will improve patient outcome (in terms of survival and/or quality of life) and/or will significantly decrease costs in another part of the patient pathway (e.g. by obviating the need for more expensive imaging tests or by selecting those patients likely to benefit from expensive drugs). The majority (60–70%) of medical decisions rely on laboratory testing,[13] which represents only about 2% of the health-care budget,[5] but relating extra expenditure in the laboratory (e.g. for a new test) to resulting savings in another department or discipline (e.g. for expensive drugs) is particularly difficult. More effective means of assessing potential savings and returning these to the laboratory budget are urgently required, with proactive involvement of health-care scientists in such discussions being highly desirable.

Major opportunities for the future

Various means of fast-tracking new biomarkers into routine clinical practice are being explored, with involvement of many stakeholders including the NHS Technology Adoption Centre and National Institute for Health and Clinical Excellence in the UK and the National Institutes of Health and the NCI in the USA.

The UK National Institute for Health Research is currently funding a three-stranded research programme with the specific remit of exploring how best to achieve fast-tracking of new biomarkers with a sound evidence base into routine use in the NHS.[14] The project aim is to develop a rigorous evidence-based approach to biomarker evaluation in the context of renal cancer, renal transplantation and liver disease. In the first strand, statisticians and health economists are considering the minimum data requirements for assessment of a new biomarker. The second strand focuses on the identification and early biochemical work-up of potentially useful new biomarkers using appropriately collected and biobanked specimens, while the third strand involves a clinical trial statistically powered to establish whether introduction of a new triple test for early liver fibrosis would benefit the NHS. Involvement of interested parties at all stages of this project is welcome, together with early collaboration with partners in the diagnostics industry. It is hoped that the project will encourage spin-off research applications in these and other areas where new biomarkers could be beneficial, also providing valuable and timely opportunity to reinvigorate research activity in clinical laboratories, activity which has recently been highlighted as a core NHS role.[15]

As we move towards a new era of personalized medicine,[16] the development of multiple new potential biomarkers is continuing apace. It is not yet clear how quickly benefits for patients or for health-care provision will follow this rapid scientific advance. However, a rigorous and efficient evaluation pathway, with active involvement of clinicians and health-care scientists who will be employing these tests in clinical practice, is an essential prerequisite for success in this field.

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