Biomarker Discovery in Emergency Care – A Suggested Development Pathway

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Research article

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Abstract

Background: Biomarkers are widely used in medical diagnosis with rigorous pathways for the identification, development. However, there are no published pathways for emergency care.

Aim: We aim to synthesise the existing literature on biomarker development in order to produce a Biomarker Development Pathway for a physiological biomarker relevant to emergency care.

Methods: Medline, BIOSIS, the National Center for Biotechnology Information databases and the Web of Science for relevant articles. Material published on websites was searched using two internet search engines (Google Scholar and Ask). Websites of organisations involved in biomarker development were also 'hand searched' for relevant information.

Results: We identified 536 papers, of which 14 were relevant to the methodology of biomarker development. One additional paper was found by hand searching from websites.

Conclusions: There were no papers that explored the specific requirements for the development of a physiological biomarker in emergency care. The biomarker development pathway published here will guide emergency care researchers in a sequential approach to biomarker development, enable description of the stage of their technology development in grant applications, and give technology development companies a clear route 'downstream' to clinical use.

Background

Biomarkers are widely used in medical diagnosis, with the term conventionally applied to a "biochemical measurement" (BNP etc). However a biomarker in fact has a much wider definition as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[1] Within clinical chemistry, cancer and clinical genetics there are rigorous pathways for the identification, development and characterisation of a biomarker. These are seen as a fundamental underpinning for biomarker development and provide the standards by which a potential new biomarker can be judged. The concepts underpinning these pathways seem to be entirely appropriate for emergency care, although in the emergency situation the later evaluation stage probably needs a pragmatic rather than explanatory approach.[2] However there are no published pathways developed specifically for emergency care and none of the current pathways consider the development of novel physiological markers.

In emergency care measurements of physiology are an important part of the process of diagnosis, whether individually (such as measurement of oxygen saturation) or in combination (such as an 'Early Warning Score'). According to the broad definition these measurements of pathophysiology can also be thought of as biomarkers. A number of new technologies which provide novel physiological measurements in emergency care are being developed and marketed. Either as single measurements or as patterns of change they are sold as providing valuable extra information in emergency care, however

there is no development pathway for a physiological biomarker in emergency care so it can be difficult for a clinician to understand whether or not a new measurement is of any benefit. Lack of a clear development pathway also makes it difficult to researchers to produce the data required for evaluation of clinical utility.

This paper aims to synthesise the existing literature on biomarker development in order to produce a Biomarker Development Pathway for a physiological biomarker relevant to emergency care.

Methods

A literature search was undertaken using the search strategy in Table 1. Abstracts of papers identified were read for relevance and the references of relevant papers were used to identify further relevant publications. Searches were undertaken of Medline, BIOSIS, the National Center for Biotechnology Information databases and the Web of Science. Material published on websites was searched using two internet search engines (Google Scholar and Ask). Websites of organisations involved in biomarker development were also 'hand searched' for relevant information. Abstracts were scanned to identify those that were relevant.

There is no quality grading system for this type of publication, so relevant papers were simply categorised into (1) those that were the result of a formal consensus process (with a defined consensus methodology used), (2) those that were the result of an informal consensus process (clinical conference or other meeting), and (3) publications of an individual/group.

Results

The search strategy identified 536 papers, of which 14 were relevant to the methodology of biomarker development (Figure 1). There were no papers which explored the specific requirements for the development of a physiological biomarker in emergency care. One additional paper was found by hand searching from websites.

Of the 15 papers relevant to the methodology of biomarker development there was one paper that was the product of a formal consensus process, three that were the result of an informal consensus, and 11 that were publications by an individual/group (Table 2).

The pathways found were then amalgamated and the language changed to be appropriate for emergency care (Figure 2).

Discussion

When considering the evaluation of a biomarker the ideal pathway depends on how the marker might be used in clinical practice. There are three basic ways in which a biomarker could be useful in emergency care with each of these different types of biomarker requiring a slightly different development pathway:

a) As a *Diagnostic Biomarker* – to define whether or not the patient has a specific condition.

b) As a *Co-diagnostic Biomarker* – to risk stratify patients with a particular condition, or to define a subgroup that might benefit from a particular intervention.

c) As a *Treatment Target Biomarker* – to define a goal for therapy in a specific condition.

The conventional language used to describe a biomarker development pathway is heavily influenced by the biochemical methods that are usually used. The stages are:

1) Prototype Design and Discovery – the technological development required to measure a new parameter.

2) Biomarker Identification – comparison of a broad range of measurements using the new technology between a small group of 'disease' (usually advanced stage disease) and 'normal' subjects in order to identify parameters (potential biomarkers) that might differentiate.

3) Biomarker Qualification – the quantification of the relationship between biomarker and disease (to see if the potential biomarker will 'qualify' as clinically useful).

a. Retrospective studies (maybe from a disease registry) looking at the biomarker in patients with known outcomes (disease or normal).

b. Prospective studies in a representative group (all disease severities) using biomarker to predict outcome (disease or normal).

4) Efficacy Trials – to quantify the effect of biomarker use on outcomes.

Prototype Design and Discover is often undertaken by technologists without medical input. There are some notable exception in emergency care where emergency physicians are involved at the forefront of technological development[3], but it is unfortunately more common for an emergency physician to be approached at a later stage of technology development where the technologists have developed a device and are thinking about how a device might be applied in clinical care. Many of the technology development companies are small or medium sized enterprises (SMEs) who do not have the expertise or resources to undertake proper clinical evaluation. There is a stark contrast with the development of a new drug, where the pharmaceutical industry has large resources and expertise to lead on the combined development and testing of their new product in the clinical situation. The NIHR Healthcare Technology Co-operatives aim to link clinicians with technology companies, with the trauma (University of Birmingham) and cardiovascular (King's College) HTCs being the most relevant for emergency medicine.

Biomarker Identification is the process of taking a first look at the data produced and identifying any potentially useful variables. This stage in the Biomarker Development Pathway has its origins in biochemical and genetic technologies, where advances in technology in genomics, proteomics and

metabolomics now allow the measurement of many thousands of variables. It is impossible to evaluate all of these variables, so the process of Biomarker Identification (with samples from patients with advanced disease) gives an initial filtering, usually based on quantitative methods but without the ability to look at aspects such as the clinical significance of the associations found. At this stage there is also an evaluation of both biological plausibility (does the putative biomarker fit with what we think we know of the disease process) and clinical plausibility (is there the potential for the putative biomarker to be useful in clinical care). With so many variables being measured it is certain that false positive association will be found at this stage.

Biomarker Qualification is the process by which the relationship between the proposed biomarker and the specific disease is quantified. The potentially confusing term 'Qualification' is derived from the biochemical literature, being used as the biomarker was said to 'qualify' for clinical use. This is observational study with well-defined inclusion criteria and definition of the endpoints of 'disease' or 'normal'. These studies are usually in two stages, with a retrospective case-control analysis of whether 'real world' patients (not just those with advanced disease) know to have the disease have different levels of the biomarker from normals, followed by a prospective analysis (cohort study) of whether the biomarker can identify the disease.

Efficacy trials (randomised Controlled Trials) are the final part of the Biomarker Development Pathway, and are unfortunately often missed out. However tempting it is to market a product that can "make a diagnosis" after the biomarker qualification procedures it is not sufficient to simply show that there is a good relationship between the Biomarker and the disease. In order to influence clinical practice it must be shown that the use of the Biomarker improves patient outcome (in the same way as a new drug would be expected to show a benefit before being marketed).

The terminology used in these four key stages of biomarker development can be altered to fit with emergency care research as shown in Figure 2. This Biomarker Development Pathway integrates the technology and clinical elements, with a combination of medical device developments and clinical studies at each stage. This emphasises the need for close collaboration between emergency physicians and those developing the methods and technologies, this collaboration being more likely to be effective if it is initiated as early as possible within the pathway. For example if a company first meets a clinician with a fully formed product it is unlikely that it will have been optimised for the clinical situation.

The different stages of biomarker development have different potential sources of funding (Table 3). There is a complex funding landscape as the development of a biomarker crosses the intersections between Industry / Public funding and basic science / clinical research. Early contact with the relevant research program manager is the best way to navigate between the various organisations – there may initially seem to be both overlapping functions and gaps, however the different organisations are increasingly well co-ordinated and will either collaborate or signpost the researcher to the most appropriate place.

Conclusion

There were no papers that explored the specific requirements for the development of a physiological biomarker in emergency care. The biomarker development pathway published here will guide emergency care researchers in a sequential approach to biomarker development, enable description of the stage of their technology development in grant applications, and give technology development companies a clear route ‘downstream’ to clinical use.

Abbreviations

BBSRC: Biotechnology and Biological Sciences Research Council

DCS: Developmental Clinical Studies

DPFS/DCS: Developmental Pathway Funding Scheme/Developmental Clinical Studies

EPSRC: Engineering and Physical Science Research Council

HTA: Health Technology Assessment

MRC: Medical Research Council

NIHR EME: National Institute for Health Research Efficacy and Mechanisms Evaluation

SMEs: small or medium sized enterprises

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TJC conceived the research question and undertook pathway development. MHE undertook literature search and evidence synthesis. Both authors contributed to manuscript write-up and critical revision. All authors have read and approved the manuscript.

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Tables

Table 1 Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present		
1	exp Biological Markers/st [Standards]	167
2	(biomarker* adj2 develop*).ti.	333
3	"develop* biological marker*".mp.	11
4	"develop* of biological marker*".mp.	47
5	"authenti* biological marker*".mp.	0
6	"authenti* of biological marker*".mp.	0
7	"validat* biological marker*".mp.	12
8	"validat* of biological marker*".mp.	23
9	"biological marker* validat*".mp.	0
10	"biological marker* authenti*".mp.	0
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	568
12	limit 11 to english language	536

Table 2 Characteristics of included studies

Study	Type	Field	Year	Journal
Sin[4]	Individual / group	Pulmonary medicine	2015	American Journal of Respiratory and Critical Care Medicine
Poste[5]	Informal consensus	N/A	2015	Expert Review of Molecular Diagnostics
Kelloff[6]	Individual / group	Urology	2015	Urologic Oncology: Seminars and Original Investigations
Henrotin[7]	Individual / group	Physical therapy	2016	Biomarkers
Drabovich[8]	Individual / group	Laboratory medicine	2015	Biochimica et Biophysica Acta
Amur[9]	Individual / group	Drug research	2015	Clinical Pharmacology & Therapeutics
Taube[10]	Formal consensus	Cancer research	2009	Journal of the National Cancer Institute
Rifai[11]	Individual / group	Laboratory medicine	2006	Nature Biotechnology
Phillips[12]	Informal consensus	Drug research	2006	Nature Reviews
Ramachandra[13]	Individual / group	Cardiovascular Disease	2006	Circulation
Gutman[14]	Individual / group	Cancer research	2006	Nature Reviews
Dunckley[15]	Individual / group	Neurology	2005	Drug Discovery Today
Barker[16]	Individual / group	Cancer research	2003	Annals of the New York Academy of Sciences
Pepe[17]	Individual / group	Cancer research	2001	Journal of the National Cancer Institute
Biomarkers Definitions Working Group[1]	Informal consensus	N/A	2001	Clinical Pharmacology & Therapeutics

Table 3 Potential Sources of Funding for Biomarker Development

Stage of Development	Potential funding source
Prototype Design and Discovery (a)	Engineering and Physical Science Research Council (EPSRC) Biotechnology and Biological Sciences Research Council (BBSRC) Medical Research Council (MRC) Program Boards Industry
Biomarker identification (b)	MRC Research Boards MRC Developmental Pathway Funding Scheme (DPFS) Industry
Biomarker Qualification	MRC Research Boards MRC Developmental Pathway Funding Scheme/Developmental Clinical Studies (DPFS/DCS)
Efficacy Trials (c)	MRC Developmental Clinical Studies (DCS) National Institute for Health Research Efficacy and Mechanisms Evaluation (NIHR EME) NIHR Health Technology Assessment (HTA)

Footnotes to Table 3:

a) Choice here depends on the level of engineering risk and the breadth of applicability.

b) If the technology development is more risky/time consuming/costly than the initial clinical studies funding is more likely to be DPFS. Development of late stage technology is the focus of DPFS.

c) A 'proof of concept' study would probably be DCS, a multi-center follow up study would be EME and a trial with health economic analysis would be HTA.

Figures

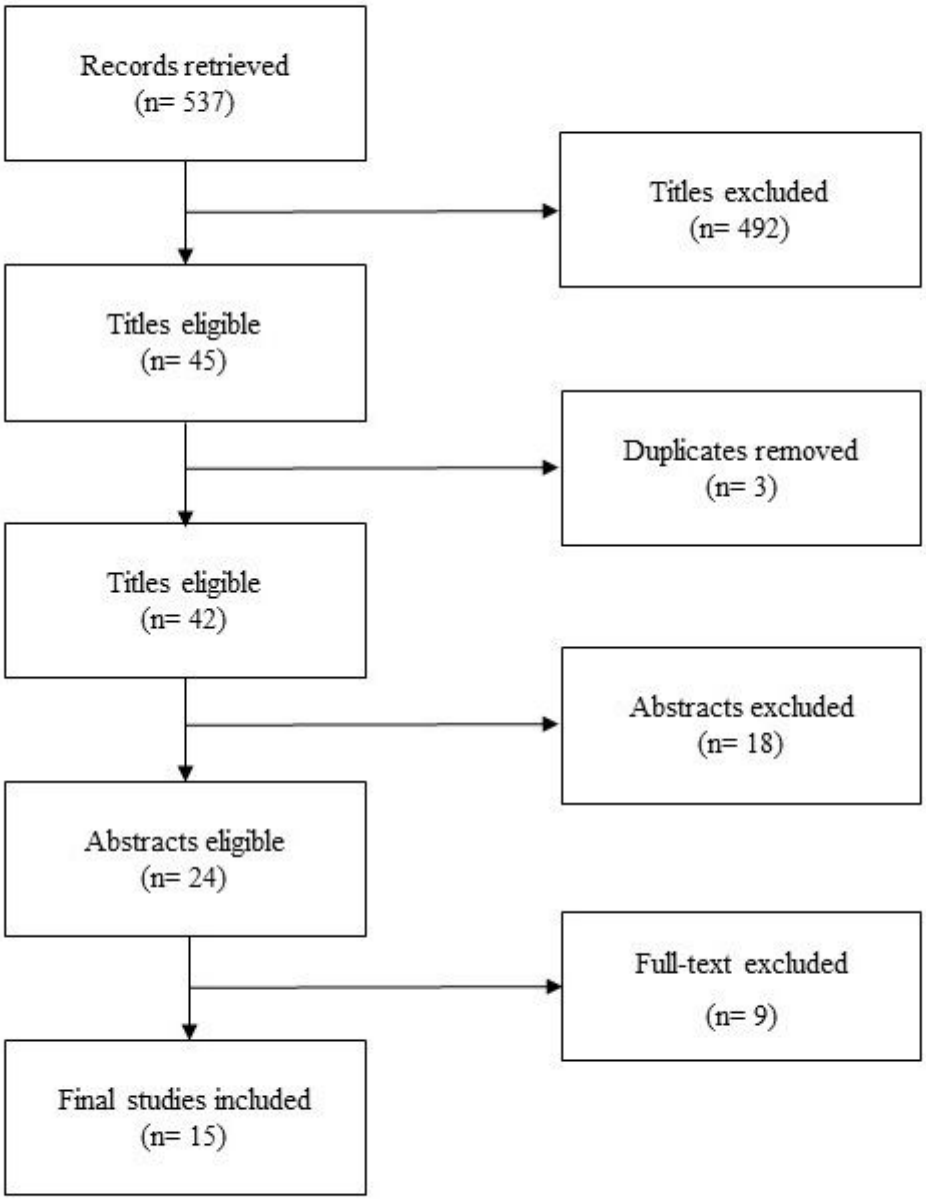

Figure 1

Screening process

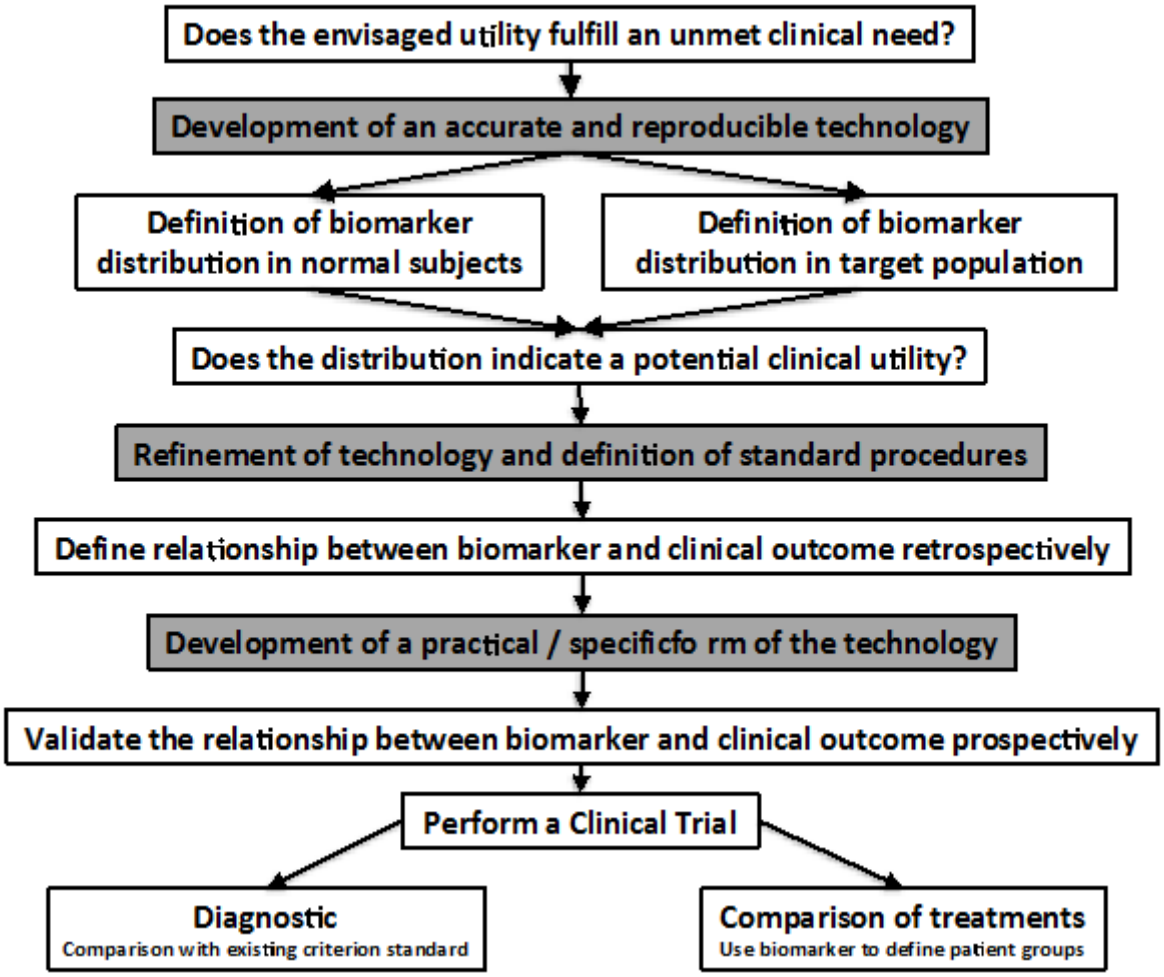

Figure 2

Biomarker Development Pathway for Emergency Care (technology development steps in grey)

Supplementary Files

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- PRISMA2009checklist.doc