Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

10-Nov-2008

English - Or. English

DIRECTORATE FOR SCIENCE, TECHNOLOGY AND INDUSTRY
COMMITTEE FOR SCIENTIFIC AND TECHNOLOGICAL POLICY

DSTI/STP/BIO(2008)39
Unclassified

Working Party on Biotechnology

ANALYTICAL PAPER: EVIDENCE BASE AND KNOWLEDGE SHARING

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This analytical paper was submitted for discussion at the workshop on Policy Issues in the Development and Use of Biomarkers in Health held on 6-7 October 2008 in Hinxton, United Kingdom. It is submitted for information to the WPB.

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JT03254960

English - Or. English

NOTE BY THE SECRETARIAT

This analytical paper was submitted as background material for discussion at the expert workshop organised by the Biotechnology Division on "Policy Issues in the Development and Use of Biomarkers in Health" held in Hinxton, United Kingdom on 6-7 October, 2008. This workshop contributes to the fulfillment of Output Result 5 of the 2007-2008 PWB entitled "Analytical and policy reports on the impact of molecular markers and targeted therapies on Biomedicine".

This analytical paper, written by the PHG Foundation, discusses how to improve knowledge-sharing in order to create a base of evidence for biomarker evaluation. It lays the groundwork by describing models of databases that could be used to collate knowledge about biomarkers.

This analytical paper, along with others developed for the Biomarker Workshop, will be used as input for the Policy Report entitled "Policy issues in the Development and Use of Biomarkers in Health" that will be submitted to WPB in early 2009.

Delegates to the Working Party on Biotechnology are invited to:

- **Note** the analytical paper.

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1. Introduction

The purpose of this paper is to summarise the importance of developing an evidence base for *biomarkers* and medical diagnostic tests, and of sharing this knowledge in an efficient and transparent manner. Specifically, the paper will cover the following key areas:

1. The need to set-up an accessible and consistent evidence base for biomarker tests
2. Examples of different approaches
3. Government involvement in access and transparency
4. Mechanisms to generate the relevant data

The paper is presented, not by way of a definitive proposal, but as a mechanism for stimulating debate and discussion.

2. Issues

There are a number of challenges associated with the construction and accessibility of an evidence base for biomarkers, which need careful consideration:

- Scope of evidence base, *i.e.* national versus international;
- Funding to set up an evidence base;
- Format and structure of the evidence base;
- Access and knowledge sharing within the evidence base;
- Responsibility for setting up and maintaining the evidence base;
- Oversight of content and quality control within the evidence base;
- Target audience and principal beneficiaries, *e.g.* the public, physicians, biomarker developers, *etc*;
- Level(s) of transparency required for different audiences;
- Requirement for a horizon scanning function;
- Logistical issues regarding standardisation, integration and coordination between different data and study formats for different biomarkers;
- Interoperability between different systems (*e.g.* national versus international);
- Confidentiality and IP issues surrounding the development of novel biomarkers;
- Industry incentives to share evidence for the clinical performance of biomarkers

3. Need for an evidence base and knowledge sharing

There is currently significant variability in the scrutiny of biomarker tests both before and after entry into the market. This lack of consistency discourages innovation on the part of biomarker developers, and may lead to inappropriate adoption and use of biomarkers by healthcare providers, thus unnecessarily increasing health costs and potentially harming patients.

Due to their variety and complexity, evaluation of diagnostic tests is significantly more complex than drug evaluation; a test may be effective for one purpose, or in one population, but not another. However, unlike the extensive requirements for clinical trials of new therapeutics, novel biomarkers and medical tests often have minimal evidence of clinical performance and lack a robust evaluation process. Currently, no national or international agency takes full responsibility for ensuring clinical validity and utility of biomarker tests; although there are a number of national and international bodies involved in test evaluation, their coverage is by no means exhaustive and each has its own specific remit and perspective, making it almost impossible to make evidence-based decisions or comparisons between tests. There is also a lack of communication between the different bodies and it is unclear where ultimate responsibility for test evaluation lies. As a growing number of biomarkers are discovered, of ever increasingly complexity, physicians and policy-makers will be insufficiently prepared to evaluate, implement and interpret such tests effectively.

This problem is even more apparent with direct-to-consumer (DTC) tests. Currently, providers of tests sold directly to the public (rather than via a trained medical intermediary) are not required to provide anything in the way of evidence that the test gives clinically useful information. In many cases, the test may be at best useless, and at worst, misleading or even harmful to the individual concerned.

Standards for evaluation of biomarkers vary considerably, in part because there is no overarching leadership in the field. Therefore, generating an authoritative evidence base of all biomarkers used in medical testing, with clear and transparent standards, would significantly improve the situation. A minimum standard of information associated with a biomarker could be agreed, and knowledge gaps explicitly highlighted within the evidence base, so as to make it clear where evidence is lacking and more data are required.

To best serve the needs of different stakeholders, there is a general consensus regarding the importance of knowledge sharing and access to this evidence base. There is a need for consistency and transparency in the way biomarkers are assessed and validated to assist not only health service professionals, providers and patients, but also to provide much needed clarity for commercial organisations and academic researchers who wish to bring ensure their innovations are used effectively. Although it is currently unclear whose responsibility it should be to set-up, resource and promote knowledge sharing and access to biomarker data, numerous stakeholders will need to be involved, and ultimately governments may be required to oversee and coordinate the process.

4. Approaches to knowledge sharing

A number of different infrastructures may be utilized to maximize the utility and knowledge sharing capacity of a biomarker evidence base. Two possible models are presented here, based on existing international systems. The first is a centralised model with a central information hub (for example, an online database), into which a network of organisations can feed evidence and expertise. The second is a decentralised model, in which an overarching organisation has responsibility for setting standards that can be ratified by independent stakeholders, but does not itself serve as an evidence base.

Both models require consideration of consistency and interoperability between different systems or stakeholders, and it is possible that a mixture of the two models may be required to best serve national and international interests. A number of different compliance mechanisms are possible for each model (see the accompanying paper on Regulation), including mandatory compliance that is legally enforceable under law, incentive-driven compliance that is supported by financial or legal incentives, and informal or voluntary compliance such as self-governance.

4.1 Centralised database

One potentially attractive structure for a shared evidence base is an online database, which provides a central hub for evidence on biomarker test evaluation with links to other relevant sources of information. This database may be entirely open and collaborative, allowing anyone access to modify entries (*e.g.* internet wiki model), or formally managed and curated, with multiple different levels of user access (*e.g.* numerous bioinformatics resources). There are numerous examples of online publically accessible databases that provide information on different aspects of clinical medicine, many of which are integrated through extensive online networks to other databases, and also serve as repositories for research information. Many of these sites could provide a model or infrastructure upon which to develop a database of information on emerging diagnostic tests. Examples of a small subset of relevant sites and a brief description of their remit are given below.

4.1.1 Biology and disease

Multiple public sites exist specifically to host current information about human biology and disease. Data from the Human Genome Project (*www.ensembl.org*) and associated projects to catalogue human genetic variation, such as the HapMap (*www.hapmap.org*) and the database of Genotype and Phenotype (*ncbi.nlm.nih.gov/dbgap*), are available online. These sites provide links to relevant literature and other databases containing information about gene products and disease associations. Amongst numerous linked databases, the Online Mendelian Inheritance in Man (*www.ncbi.nlm.nih.gov/omim*) catalogues all known disease with a genetic component, providing information on genes and disorders, as well as links to raw research data. Both the UK and the US have extensive online national medical libraries (*www.library.nhs.uk* and *www.nlm.nih.gov* respectively) that integrate information from different sources. More specific databases also exist, such as the European site Orphanet (*www.orpha.net*), which provides information on rare diseases and orphan drugs to both patients and professionals. It has a range of information covering research projects, approval status, accredited tests and clinical laboratories that offer them.

4.1.2 Research publications

A number of searchable public databases of research publications are available, of which the largest is probably PubMed (*www.ncbi.nlm.nih.gov/pubmed*), which contains over 17 million citations to date. Additionally, there is currently a worldwide trend towards open access publishing amongst scientific journals. Various different models have been developed to achieve this end – from instant public access, to delayed access after the first year of publication – and the cost of publication is usually covered through research grants from funding bodies. Moreover, the not-for-profit Public Library of Science (*www.plos.org*) was specifically set up to provide high quality, peer-reviewed, open access journals.

4.1.3 Diagnostic Tests

There are already a few sites that provide information on diagnostic tests. The most comprehensive is Labtests online (*www.labtestsonline.com*), which is primarily aimed at patients but is also used by professionals. There are different sites for different countries, which have been tailored dependant upon

practices in that region. More specific sites also exist, such as the United Kingdom Genetic Testing Network (*www.ukgtn.nhs.uk*), which is aimed at providing information on tests for hereditary single gene disorders, including their test evaluation process. The EuroGenTest website (*www.eurogentest.org*) also provides information on genetic testing, including a list of relevant databases, and facilitates the harmonization of standards and practices throughout the EU through recommendations about quality standards and interoperability.

4.1.4 Therapeutics

Stringent regulatory requirements for extensive clinical trials of new therapeutics already exist, and many academic journals require that trials are registered with online databases – such as the US ClinicalTrials.gov (*www.clinicaltrials.gov*) and Current Controlled Trials (*www.controlled-trials.com*) – prior to publication of results. Information on approved therapeutics is available in a number of registries, such as the British National Formulary (*www.bnf.org*), which is also widely available in hard copy, and the US Drug information portal (*druginfo.nlm.nih.gov*). These sites have searchable databases that provide information on prescribing, dispensing and administering approved medicines, as well as links to information on a variety of subjects including consumer health, clinical trials, literature and information from governmental resources.

4.1.5 Evidence-based medicine

There are several sites, such as the BMJ Clinical evidence (*clinicalevidence.bmj.com*) and the Turning Research Into Practice database (*www.tripsdatabase.com*), which seek to answer clinical questions by providing an evidence base for them. These sites search available resources and provide information on the current state of knowledge in the form of systematic reviews, evidence based synopsis, and core primary research. The Cochrane Collaboration (*www.cochrane.org*) provides access to all their systematic reviews and meta-analyses, including a lay summary of the key findings.

4.2 Decentralised standardisation

Under a decentralised model, there would be no central storage of evidence for biomarker evaluation. Instead, evidence is held by individual stakeholders (be they test developers or national test evaluation centres) all of whom have the option to sign-up and adhere to an agreed set of standards against which biomarkers must be evaluated. A central organisation could take overall responsibility for setting the consensus standards, without actually collecting the evidence itself; such an organisation could also have responsibility for ensuring that individual stakeholders adhere to these standards. Compliance through standardisation can occur through international harmonisation or informal self-governance (see accompanying paper on Regulation) and may simply require that stakeholders sign up to a common set of rules regarding transparency and standards for evaluation. It could also take the form of professional standards or a code of practice.

Importantly, consistency between data from different stakeholders is paramount to the efficient and reliable functioning of a decentralised system. The ability of diverse systems and organisations to work together relies on interoperability, i.e. the ability of all the components to exchange information and be able to use the information that has been exchanged. The barriers to achieving interoperability are both inter- and intra-organisational and relate to standardisation, co-ordination and communication. Much work has already done by into achieving interoperability standards in bioinformatics, particularly by the European Bioinformatics Institute (EBI), such as the Distributed Annotation System (DAS). The Centers for Disease Control and Prevention (CDC) have also set up the Public Health Information Network (PHIN) to provide an interoperable information system for the many organisations involved in public health. At the core of PHIN are accepted health data and technical standards including Systematized Nomenclature of

Medicine (SNOMED), Health Level 7 (HL7), and Logical Observation Identifier Names and Codes (LOINC).

An example of this decentralised model is the Public Population Project in Genomics (P3G), a not-for-profit international consortium for the development and management of a multidisciplinary infrastructure for comparing and merging results from population genomics studies. Its motto is transparency and collaboration and its main objective is the creation of an open, public and accessible knowledge database. The members of the consortium are public organisations involved in genetic epidemiology studies or biobanks, each with their own independent governance structure and objectives, who must comply with the objectives and requirements of P3G.

Another example is the International Organisation for Standardisation (ISO), a network of over 150 member countries with over 17,000 internationally agreed standards ranging over a wide range of technologies. ISO standards are developed by technical committees, comprising experts from the industrial, technical and business sectors as well as representatives of government agencies, testing laboratories and consumer associations. Although adherence to ISO standards is voluntary (as ISO is a non-governmental organisation and as such has no power to enforce implementation of its standards), many are mandated by individual governments and often form part of national regulatory frameworks, providing an internationally recognised mark of excellence.

A mixture of centralised and decentralised models is also possible, as evidenced by The Cartagena Protocol on biosafety, a comprehensive regulatory system for ensuring the safe transfer, handling and use of genetically modified organisms (GMOs) across borders. The aim of this protocol is to ensure that a country has all the information it needs in order to make an informed decision on whether or not to import a GMO. Exchange of information about biosafety, regulatory regimes and risk assessment occurs via the Biosafety Clearing House, an internet-based system enabling knowledge sharing and transparency between governments, and has links to other pertinent resources. Such a system does not involve a large centralised database, but requires stakeholders to provide relevant data in order for national regulatory authorities to make informed decisions. The availability of documents, such as final reports and risk assessments, to all parties (national and international) allows global comparisons. In addition, positive assessments of products may serve as a form of endorsement in such an arena, and could serve as an incentive to release data.

5. Access and transparency

Currently, what little evidence exists on biomarkers is often confidential, which makes it near impossible for policy-makers and health providers to make evidence-based decisions about healthcare provisions. Transparency regarding the level of evidence associated with a biomarker, and the standard to which it has been evaluated, would allow new biomarkers to be properly assessed and compared. Systems should be established to ensure that the data are appropriately analysed and evaluated against agreed standards, and that details of the evidence and standards required are placed in the public domain. It is important to note that in order for information to be ‘transparent’ it must be clearly understandable; therefore careful consideration should be given to the target audience(s) in order to decide upon the optimum level(s) of transparency.

Ultimately, submission of results to an evidence base could be a pre-requisite for funding of any relevant research project. Government funders and reimbursers of health services as well as clinicians could then be discouraged from using tests that are not backed by appropriate clinical evidence.

In the longer term, the issues of intellectual property and reimbursement surrounding diagnostics will need to be addressed, so that diagnostic companies have an appropriate incentive both to develop and thoroughly evaluate new diagnostic tests.

6. Generation of data and standards

The generation of appropriate clinical data about test performance is crucial to evidence-based decision making. However, there are a number of steps required to ensure adequate evaluation. Firstly, coordination is necessary to agree appropriate protocols for generating and assessing data for evaluation as well as standards to which biomarker evaluation and performance should adhere.

Secondly, relevant data for evaluation (see accompanying paper on Clinical Evaluation) must be generated and assessed. Where evidence is missing for the clinical validity and utility of tests, it is currently unclear whose responsibility it is (or should be) to generate new data. Whereas significant research funding is available to develop biomarker-disease associations, there is a gap in the provision of a system for the systematic evaluation of the clinical performance of biomarker tests. Internationally, there are a number of different health technology assessors – including the UK National Institute of Clinical Excellence (NICE), the European network for Health Technology Assessment (EUnetHTA), the US Preventative Service Task Force (USPSTF) and the International Network of Agencies for Health Technology Assessment (INAHTA) – but none have sufficient resources to carry out a thorough clinical evaluation of all biomarkers.

Since these data are generally expensive and slow to generate, public-private partnerships between industry and clinical scientists might be a possible solution to this problem. A way is therefore needed to bring industry and the public sector together, to discuss such issues and to determine the roles and responsibilities of the various stakeholders. Policy reform is urgently needed to establish systems and resources to generate evidence of test performance, and to agree the respective roles and responsibilities of government, statutory regulators, public bodies, academia and the commercial sector.

7. Conclusion

There is a need for an evidence base for collating and evaluating evidence associated with diagnostic biomarkers. Key to this database is the principle of access and knowledge sharing, to allow patients, physicians and policy-makers to make informed choices about healthcare priorities. Governments must work to ensure transparency in test evaluation and consistency of evidence, and any knowledge gaps should be explicitly highlighted, so as to make it clear where evidence is lacking and more data are required.

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