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Biomarkers

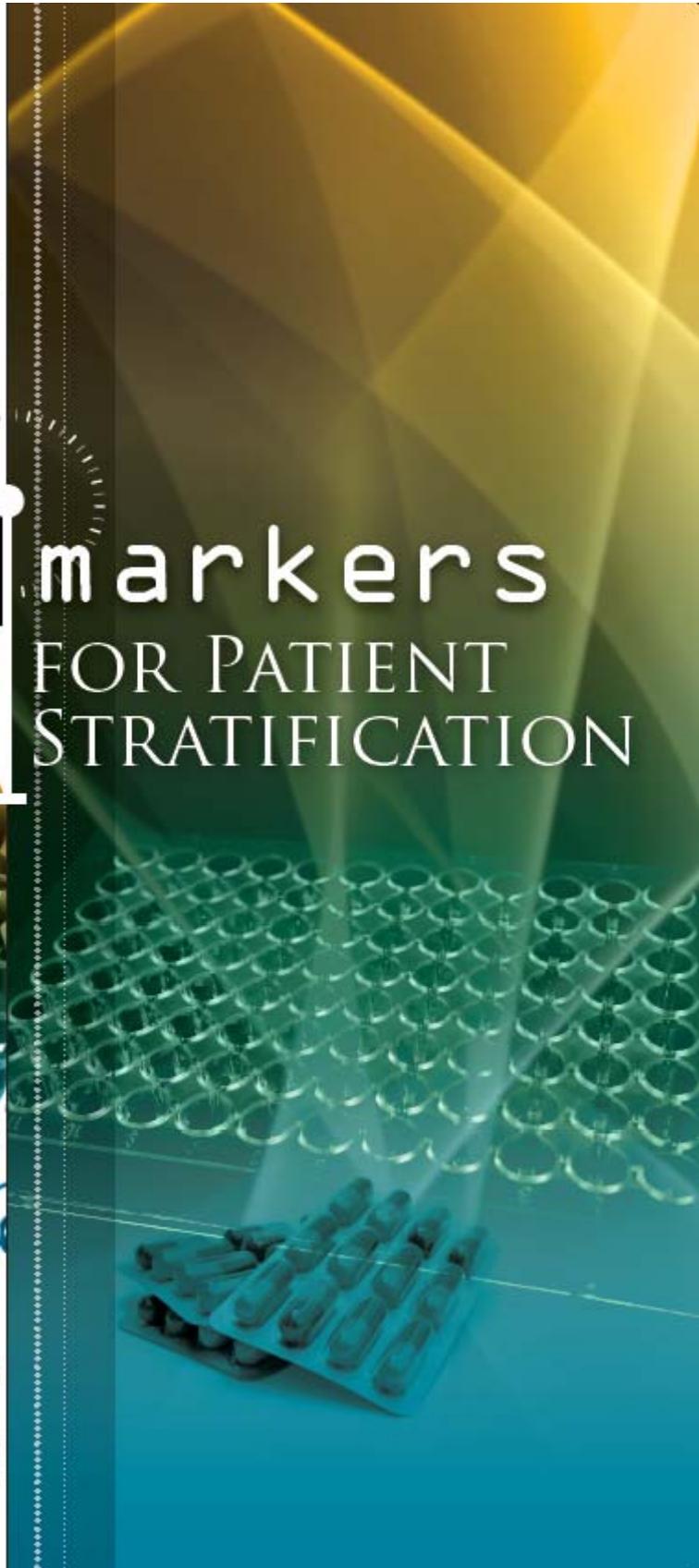
FOR PATIENT STRATIFICATION



Organisers:



European Commission
Health Research Directorate



SUMMARY REPORT

**"Stratification biomarkers in
personalised medicine"**

Workshop to clarify the scope for stratification biomarkers and to identify bottlenecks in the discovery and the use of such biomarkers.

European Commission, DG Research - Brussels, 10-11 June 2010

Summary Report

Despite advances in pharmacology, not all patients respond favourably to drugs. A proportion of patients under therapy don't benefit from their treatment or experience an adverse reaction to the medication. However, progress in the understanding of disease mechanisms and drug actions are opening opportunities to match therapies to patient populations, and thus pave the way towards a more personalised medicine.

Personalised medicine may be defined as “a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention”.

In this context, the use of biomarkers can help identifying patients that are more likely to respond favourably to a given therapy. Until now, biomarkers have been used in clinical practice to describe both normal and pathological conditions. Increasingly, they find application in order to stratify different patient groups in terms of clinical response, so as to develop personalised, preventive or therapeutic strategies.

The workshop "Stratification biomarkers in personalised medicine" that was held at the European Commission in Brussels on 10th and 11th June 2010 brought together experts from different fields and perspectives in order to stimulate an open discussion about the evolution of this rapidly expanding area, in which biomarkers are used to adapt therapies to the characteristics of patient populations.

The purpose of the workshop was to clarify the scope for stratification biomarkers and to identify barriers in the process from biomarker discovery to their use in clinical trials and in medical practice. It aimed at building a vision for 2020, identifying bottlenecks for reaching the goal and discussing the role of EU-funded research therein.

The debate allowed clarifying concepts and issues, outlining a vision for the next ten years and identifying bottlenecks in research and development. The main outcomes of the workshop are presented hereafter.

Research perspectives; Identification of a vision for 2020 and bottlenecks

1) Definition of biomarkers

A biomarker is a biological characteristic, which can be molecular, anatomic, physiologic, or biochemical. These characteristics can be measured and evaluated objectively. They act as indicators of a normal or a pathogenic biological process. They allow assessing the pharmacological response to a therapeutic intervention. A biomarker shows a specific physical trait or a measurable biologically produced change in the body that is linked to a disease or a particular health condition.

A biomarker may be used to assess or detect:

- A specific disease as early as possible – **diagnostic biomarker** (HCV RNA after infection)
- The risk of developing a disease – **susceptibility/risk biomarker** (BRCA1-breast cancer)

- The evolution of a disease (indolent vs. aggressive) – **prognostic biomarker** (HER-2-breast cancer) – but it can be predictive too
- The response and the toxicity to a given treatment – **predictive biomarker** (EGFR-NSCLC/gefitinib, DPD-gastrointestinal cancer/fluoropyrimidines)

2) **Definition of stratification in the frame of personalised medicine.**

Stratification is the identification of a group of patients with shared “biological” characteristics by using molecular, biochemical and imaging diagnostic testing to select the optimal management for the patients and achieve the best possible outcome in terms of (based on the category and disease characteristics):

- Risk assessment and prevention
- Achievement of the optimal treatment outcome

3) **Methodologies and approaches for new stratification biomarkers**

Genomics and other "omics" technologies have largely contributed to the identification and the development of biomarkers. Due to genetic causes of variability among individuals, genotyping and gene expression analysis are indeed key elements of the emergence of personalised medicine. However, genomic technologies have limitations (functional significance of genetic variants, false negatives, etc) and cannot encompass all approaches for the development of stratification biomarkers. A multiplex approach integrating various technologies (“omics”, phenotype studies, imaging, functional in vivo studies, etc.) should be privileged. Stratification biomarkers can be identified by several means in pre-clinical studies, epidemiological studies or clinical trials. Ideally, their identification should happen as early as possible in the workflow of drug discovery and development. Preclinical identification of stratification biomarkers combines the understanding of disease and drug mechanisms with the unique characteristics of the individual. Hence, the challenge is to include the development of stratification biomarkers into the concept of disease prevention and drug development. In addition, we should distinguish between biomarkers and assays. Biomarkers need to be qualified and properly detected before they can be used in the clinics. Therefore, the applicability of a qualified biomarker relies also on the development of a robust assay. Consequently, the development chain including the discovery of the stratification biomarker, the development of the assay and the qualification of the marker should preferably start in the preclinical phase and the selected stratification biomarkers be explored in clinical trials. In fact, insufficient knowledge of drug action mechanisms and/or unavailability of necessary data can preclude the early identification of stratification biomarkers. In practice, signatures that predict toxicity or efficacy can be identified afterwards. For example, therapies targeting the Epidermal Growth Factor Receptor have been first approved before it was demonstrated that mutations in KRAS cancer gene were associated to failures of the relevant therapies in metastatic colorectal carcinoma. This example shows that well-designed retrospective analysis of data from prospective randomized controlled trials can bring forward effective treatments to biomarker defined subgroups of patients in a timely manner. However, retrospective analyses are often criticised for being flawed by confounding factors and potential bias in patient selection. It is agreed that retrospective studies are much less desirable than prospective studies but potentially useful. All-comers designs are optimal in situations where preliminary evidence of treatment benefit is missing and/or the reproducibility of the associated biomarker assay is not demonstrated (e.g., EGFR expression and tyrosine kinase inhibitors in lung cancer). These trial designs allow also identifying the most effective therapy from a panel of

regimens (e.g. chemotherapy options in breast cancer). In conclusion, flexible paradigms could be considered where clinical trial designs could be adapted to the emergence of new data.

4) Needs, domains of application and relevant expertise

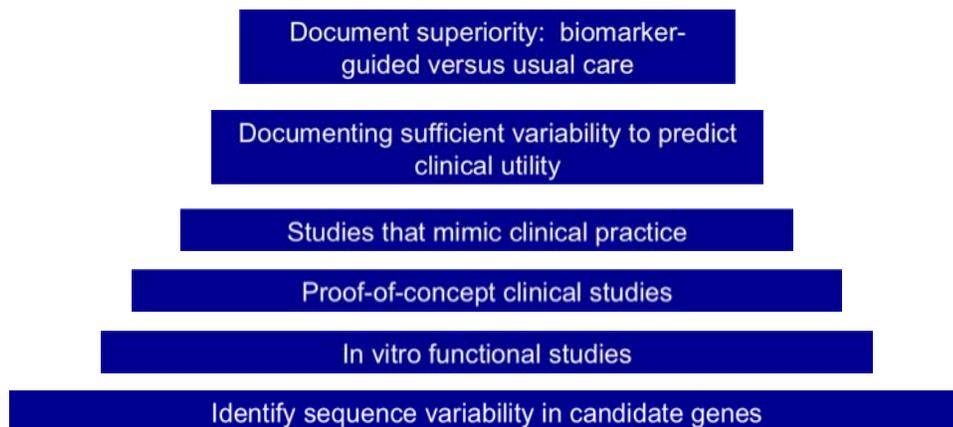
The therapeutic fields where stratified medicine is expected to take off first are oncology, secondary complications of diabetes, cardiovascular diseases and neurodegenerative diseases. Though, the development of stratified medicine is largely dependant of the identification and the qualification of pertinent biomarkers in these areas. Regrettably, only a few studies on biomarkers have proved to be sufficiently powered to detect differences among genetic variants and/or the function of gene products. In addition, these studies are often fraught with flaws and doubts with respect to the choice of genetic polymorphism, the issue of germ lines vs. somatic variants, the suitability of standard clinical endpoints, ethnical issues, etc. It's also worth mentioning that the scientific community is not well structured in this area and insufficiently involved in European joint initiatives. The creation of interactive networks would help making progress.

5) Identification of research bottlenecks

Several bottlenecks have been identified:

1. Technical feasibility, quality of the specimen collected and bioassay performance

Recent advances in "omics" technologies have provided powerful tools to search new biomarkers that can allow predicting the response to a drug. A clinical approach for the qualification of potential biomarkers is the following:



Research is needed at any level of this sequence. But the way is long and difficult from the identification of a new biomarker, or a set of biomarkers, to the development of a valid and reliable clinical assay that can serve as a companion diagnostics in drug development. Before they can be evaluated in clinical trials, presumptive biomarkers are submitted to a difficult process of verification and assay development. Therefore the involvement of professionals in diagnostics is determinant for the development of valid, i.e. sensitive and specific companion diagnostics.

Important steps for the reliability of bio-molecule analysis are also the collection, the storage and the transport of clinical samples. There is a need for standardisation of pre-analytical procedures and anticipation during clinical trials in view of ulterior bio-molecular analysis.

2. Access to bio-banks

The development of tests for biomarkers requires access to biological resources where samples are carefully processed, stored and documented. Information on the patients and access to anonymous medical records of the donors are needed. If bio-banks are flooded with extensive data, appropriate softwares are required to support the capture of these datasets. Beyond the issue of information, the problem is that bio-banks provide samples for research projects that were not initially defined. Therefore good practices requirements should be met and standardisation is deemed necessary.

3. Data acquisition, management and analysis

Stratified medicine relies heavily on data analysis and the amount of medically relevant data that are available electronically increases dramatically. However, these data are generated in complex forms and are acquired and recorded in various ways. Incompatibility among research databases, electronic medical records and laboratory information management systems is then an issue. The challenge is to organise electronic data and to make them usable for research. Open and standardised databases are required to make use of all available data in order to identify stratification biomarkers and to stratify clinical trial recruitment.

Another challenge is to deal with the generation of large amount of concomitant and complex data generated by "omics", phenotyping and imaging technologies (multiple readouts). Traditional statistical methods are based on single signal assays. There is a need to implement new statistical methods to cope with multi-signal assays

4. Insufficient partnership between industry and academia

Biomarkers are the keystone of stratified medicine. Now, as for any new medical product, the development of bioassays follows a pathway that begins with basic research and moves toward preclinical and clinical stages. Although biomarkers can be identified in clinical phases, the discovery of new biomarkers is often ground in knowledge generated by academic basic research. A better understanding of disease mechanisms is crucial in this respect. It is obvious that neither the pharmaceutical industry nor the diagnostic manufacturers can support alone the continuum that leads to stratified medicine. Therefore, a stronger cooperation between public and private sectors is needed.

c) Is there a place for basic research?

The discovery of effective predictive biomarkers is fostered by the understanding of disease mechanisms, taking into account that most diseases are complex and polygenic, and by the development of technological platforms. Progress in basic biomedical science and in technology can contribute to advance personalised medicine. The need of interactions between basic research and technological research, with clinical science is obvious and should be encouraged.

Towards development; Identification of a vision for 2020 and bottlenecks

1) Validation and biomarker qualification

Since biomarkers of safety and efficacy are becoming tools in drug development, it is necessary to determine whether these biomarkers can qualify for applications in clinical trials. Qualification is defined as “a conclusion that the biomarker data submitted support use of the biomarker in drug discovery, drug development or post approval studies and where appropriate, in regulatory decision making” (*ICH E-16*). A definition of validation was proposed during the workshop. Validation would refer to "establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a biomarker that meets its pre-determined specifications and quality attributes.

The concept of qualification is dynamic and evolving. It takes into account the context and the intended use. The process through which the European Medicine Agency takes multiple avenues:

- CHMP (*Committee for Medicinal Products for Human Use*) qualification opinion (formal)
- CHMP qualification advice (formal)
- Informal advice (for "Omics")

The main issues identified for qualification are the followings:

- Lack of sufficient rigor for translation to drug development
- Lack of adequate description of sampling / data generation / statistical methods
- Poor power/ cherry picking/ bias
- Independent pockets of research with poor collaboration

Ideally, predictive biomarkers should be available at an early stage of the drug development. Thus, biomarker qualification should be initiated timely. Noteworthy, the EMA process for the biomarker qualification is separated from the approval procedure for companion diagnostics, which is covered by the In Vitro Devices directive (IVD 98/77/EC). Standards for companion diagnostic tests are not so well established. However, specific requirements have been identified:

- High analytical validity
- Appropriate sensitivity and specificity
- Clinical validity/ Clinical utility
- Ability to influence treatment plan
- Possibly free of environmental & clinical factors

2) Intellectual Property Right issues

1. Potential conflicts

The implementation of stratified medicine requires investment and risk taking. There are several actors, not excluding academia, who have a vested interest. Because it links the measurement of predictive biomarkers to drug therapy, stratified medicine leads to cooperation between pharmaceutical and diagnostic companies. It creates new opportunities for value creation but how should it be separated if drugs and diagnostics are co-developed and marketed together? Who would own the biomarkers and/or the companion diagnostic tests? To what extent biomarkers would be in the public domain? It

is an emerging landscape where conflicts of interest should be properly anticipated and where openness to public-private partnership should be considered.

2. Precompetitive research

The Innovative Medicines Initiative has been mentioned as an interesting paradigm of public-private partnership to overcome identified research bottlenecks in the drug development, and to support pre-competitive industrial research and development. In this context, "pre-competitive pharmaceutical research and development should be understood as research on the tools and methodologies used in the drug development process" (*Council Regulation (EC) No 73/2008*). Cooperation of multiple disciplines in public-private partnership is deemed essential. With the aim of allowing stratified medicine becoming reality, open access to qualified stratification biomarkers should be considered. In addition, clinical trials could be conducted for the qualification of existing biomarker candidates that are in the public domain.

3) Identification of bottlenecks

1. Uncertainties

Despite expectations born a decade ago, there are only a few successes in stratified medicine up to now and its implementation proves to be challenging in many aspects. Numerous factors are considered in making decisions. Indeed the pharmaceutical sector becomes increasingly aware of the potential benefits of stratified medicine but it seems inhibited by uncertainties. In addition to the above mentioned obstacles in research, the regulatory framework, intellectual property issues, the uncertain impact on the market and doubtful commercial advantages contribute to create an unclear landscape that seems to prevent the main stakeholders to clearly move forward.

2. Regulatory framework

Co-development of drugs and companion diagnostics might need timely and coordinated approval decisions from different bodies to meet the requirements of joint clinical trial schemes and eventually the approval of both the drug and its associated test. In addition, the path to get a stratified indication approved is not always clear. In this respect, the status of retrospective analysis deserves clarification. Besides, the concept of qualification is evolutionary and clear guidelines are missing. Therefore, the regulatory authorities should be contacted early enough to provide input, give advice and hence allow adjusting strategies on time.

3. Problem of incentives

Stakeholders are becoming more and more aware of the potential impact of stratification biomarkers in drug development and the expected benefits of stratification for the patients. However, stratified medicine includes inherent challenges and is weighed down by scientific, economic and regulatory uncertainties. Without incentives, the main driving forces, in particular the pharmaceutical and diagnostic industries, may not invest adequately in research and development.

Conclusions

In summary:

- Development of stratification biomarkers is a vital concept to facilitate disease prevention and drug development
- A better understanding of disease mechanism and drug action is important,
- The importance of genetic variants of a gene product should be validated by functional studies,
- It is necessary to facilitate data sharing and to create coherent data sets. The development of a European database on biomarkers could help,
- The development of imaging platforms is of major interest in "in vivo" personalized approaches,
- Pre-analytical and analytical procedures require gold standards, quality assurance schemes and standardisation of technical procedures,
- Prospective approach is preferred but often difficult. Retrospective analysis can be useful,
- Needs for statistical and bioinformatics tools have been identified,
- It is important to bring stakeholders into common research projects (i.e. pharmaceutical companies, diagnostic manufacturers and research institutions,). Collaborative research and public-private partnerships should be encouraged and supported,
- Stratification biomarkers should be identified and qualified at early development stages,
- Clinical trials would be needed for the qualification of current biomarker candidates,
- Communication with Regulatory Authorities is strongly recommended,
- Stratification can increase market potential but they are many technical, scientific, medical, economical and regulatory uncertainties,
- Incentives are essential to allow stratified medicine becoming a reality.

Keywords for the future:

With the aim of defining a vision for the future, the following keywords have been identified:

- **Sensitivity and specificity** – There is a need to improve knowledge of the disease and apply appropriate technology to increase specificity and sensitivity of the biomarker, i.e., the proportion of true negatives and true positives that are correctly identified by the test.
- **Cost** – Stratification biomarkers should help saving money (tailored treatments and speed up drug development).
- **Validation/qualification** of biomarkers as well as clinical and laboratory procedures – tissue collection, standardization of technologies, prospective clinical trials.

- **Incorporation** of biomarkers in clinical guidelines. Biomarkers should change clinical practice – pharmaceutical and diagnostic companies, scientific societies and regulatory agencies should play a role.
- **Knowledge** – Education is needed in this field – Novel professional profiles should be identified – Open access to large datasets.
- **Focus** – Priorities should be made – Oncology, secondary complications of diabetes, cardiovascular diseases, neurodegenerative diseases are probably the major areas
- **Interaction** between all stakeholders is necessary.
- **Basic research** should be oriented to solve clinical needs.