Biomarkers

Introduction

A biological marker is something that can be reliably measured and that can tell us something about a person's health or disease state: for instance, the presence of a disease, a physiological change, response to a treatment, or a psychological condition. For example, glucose levels are used as a biomarker in managing diabetes, and brain images can provide information about the progression of Multiple Sclerosis. Biomarkers are used in many scientific fields, and are used in different ways at different stages of medicines development. The accuracy of biomarkers can vary; therefore, not all biomarkers are suitable for medicines development.

Biomarkers can be used to measure:

- Normal biological processes in the body (heart rate, blood pressure, temperature),
- Disease (pathological) processes in the body (for example, disease stage), **or**
- A person's response to a treatment or medicine.

Some examples of biomarkers are:

- Biological substances ('biochemicals') such as enzymes (biological substances that cause a change in the body), which may be found in the blood or in tissue samples (often used in cancer)
- Genetic (DNA) changes
- Medical images, such as Magnetic Resonance Imaging (MRI) or X-ray

Aims of biomarker use

The two main aims of using biomarkers in medicines development are:

1. Improving the processes of medicines development

Clinical trials seek to measure patients' responses to a treatment. If it is not possible to measure the response directly, biomarkers may provide an alternative way of measuring an outcome (they serve as surrogate endpoints).

There are advantages of using validated biomarkers as surrogate endpoints, including that:

- They might be able to be measured earlier, more easily, or frequently with higher precision
- They may be less affected by other treatments, reduce the size of sample required, and allow researchers to make faster decisions
- There are important ethical advantages in using biomarkers as surrogate endpoints in diseases with poor prognoses.

A strong example of the use of a biomarker as a surrogate endpoint comes from the development of antiretroviral medicines for HIV and AIDS. Previously, studies would have been based on hard clinical endpoints such as the progression of the HIV infection to AIDS and/or patient survival. Now, cell changes (such as levels of 'CD4 lymphocytes') and changes in the levels of HI-virus RNA in plasma can be used as surrogate endpoints.

2. Tailoring treatment to individuals

Biomarker research is helping to improve how well we can predict a person's risk of disease, how a disease might

progress once it is diagnosed, and how an individual will respond to a medicine. This will enable safer and more effective treatment decisions.

For example:

- Blood sugar levels in a patient’s blood can be used to monitor if an individual is responding to diabetes treatment
- Magnetic Resonance Imaging (MRI) scans of a patient’s brain can be used to monitor the progress of the disease in Multiple Sclerosis.

In addition, many new biomarkers are being discovered and used during the development of new medicines. Many of these use genomics (analyses of changes occurring at the gene level), proteomics (analyses of changes on the protein level), and/or metabolomics (analyses of differences in chemical molecules that play an important role in body/cell function).

Biomarkers in medicines development

Cancer (oncology) research was one of the first areas where the use of such biomarkers was adopted. Biomarkers are used to make exploratory trials (early trials, Phase II Proof of Concept trials) of medicines more efficient. Only a limited number of biomarkers can be used for clinical endpoints in a confirmatory trial (late-stage trials, Phase III). Biomarkers may be used in late-stage trials in combination with clinical outcomes (clinical endpoints).

For some medicines, only a minority of patients might respond. It is important to identify these patients for clinical trials using biomarker measures.

Uses and benefits of biomarkers in

medicines development

Companion diagnostics

Companion diagnostics are tests that are validated and approved for marketing alongside a new medicine.

The tests may help to:

- Select patients likely to respond to a medicine
- Exclude those patients likely to have an adverse reaction
- Determine the best dose for a patient

Many companies developing targeted therapies for cancer have also begun to consider the potential benefits of developing a diagnostic to pair with that treatment. The trend is to develop medicines and companion diagnostics together, rather than have both developments happen in isolation.

Medicines

At each stage of the development of a new medicine, many compounds under investigation will fail and will not be taken further. Biomarkers have the potential to increase the efficiency of medicines development.

- **Speeding up clinical trials**
  Biomarkers can be used to detect an effect (or lack of effect) earlier and more frequently than if only a clinical outcome (endpoint) is used. For example:
    - A panel of biomarkers has been used in the early phases of a clinical trial for a psoriasis treatment. The biomarkers included ‘epidermal thickness’ (thickness of the outer layer of skin) and the activity levels of several genes. These were both measured in tissue samples.
- **Streamlining clinical trials**

Biomarkers are used to identify those patients who are most suitable for a treatment. Specifically, genomic biomarkers can be used to:

  - Identify patients with a particular disease sub-type or severity
  - Exclude patients at increased risk of serious side effects (adverse reactions) – for example, melanoma patients are at risk of their condition getting worse if their tumours do *not* have a certain mutation in the 'BRAF' gene and they treated with kinase inhibitors
  - Identify patients with a high chance of benefiting from a particular medicine

- **Improving our understanding**
  Biomarkers can improve understanding of how new medicines work and may lead to novel approaches to medicines development in both non-clinical and clinical phases
- **Improving the ethics of trial recruitment**
  Biomarkers can help exclude people who won't benefit from starting a non-helpful treatment, thus providing an ethical benefit.
- **Improving trial monitoring and stopping unhelpful trials early**
  Biomarkers may help decide whether to stop a trial early if there is no benefit to be gained by the patients in the trial.
- **Speeding up authorisation**
  A medicine that is having a positive effect may be authorised sooner based on information provided by biomarkers and therefore may be prescribed earlier to patients who will benefit.

Challenges of using biomarkers in

medicines development

As the use of biomarkers in pharmaceutical research grows, companies face new technical, regulatory, and ethical challenges.

Technical challenges

- Biomarkers used in clinical trials must be validated through scientific evidence to ensure that the biomarker test is sufficiently accurate, reliable, sensitive, and specific.
- Need to ensure that the biomarker is a valid measure. For instance, if a certain biomarker is to be used to predict how severe a disease may get, is there enough evidence of this 'predictive ability' with this biomarker?
- The IT systems for data management and data analysis must be reliable and fast in order to cope with the amount of data generated. All biomarker measurements must be correctly linked with individual patients.
- In cases where the use of a companion diagnostic is required for a new medicine to be prescribed, a new platform or kit for testing patients in the clinic may need to be developed. IT will usually need to be available for use during the large confirmatory trials of the medicine (Phase III), and it must also be validated and tested for accuracy and clinical usefulness.

Regulatory challenges

The regulation of the use of novel methods such as biomarkers in medicines development is evolving. 'Biomarker' and 'surrogate endpoint' are not interchangeable terms. For a biomarker to be used as a surrogate endpoint, studies will be done to assess the direct relationship of the biomarker with:

- The development of the disease

- A treatment intervention with an important clinical endpoint.

The European Medicines Agency (EMA) has built up considerable experience in assessing the potential benefits and limitations of the use of biomarkers for regulatory purposes. Developers of novel biomarkers are being encouraged to engage with regulators at an early stage, and they can submit their plans to use biomarkers to the EMA.

Validating biomarkers to meet regulatory standards can be complex and expensive. This is especially challenging if a biomarker is intended to be used as a surrogate endpoint. In this case, a dedicated clinical trial is required, designed to test the link between the biomarker and the clinical endpoint.

In the EU, medicines and diagnostics are regulated differently. Licensing a medicine and its companion diagnostic together adds an extra layer of complexity to the approval process.

Ethical challenges

Many of the ethical issues that arise in biomarker research are those linked to the storage and use of tissue samples, and the associated handling of personal medical data.

Additionally, wider concerns have been raised about the impact of targeted medicine (which is largely based on biomarker research). As targeted treatments only bring benefits to the sub-population of patients that respond to them, the challenge is to ensure that medicines are developed for those who fall outside of this sub-population.

Further Resources

[glossary_exclude]

- Education Task Force, Industry Pharmacogenomics Working

Group (2012). *Understanding the intent, scope, and public health benefits of exploratory biomarker research. A guide for IRBs/IECs and investigational site staff.* Retrieved 13 October 2023 from https://i-pwg.org

Attachments

- Presentation: Biomarkers
  Size: 393,107 bytes, Format: .pptx
  A presentation describing biomarkers, which can be adapted for own use.

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