

# Thought Leadership

**An introductory guide to biomarkers, precision, personalised and stratified medicine.**



**Professor Richard Kennedy**  
Global VP of Biomarker Development, Almac Diagnostic Services

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**The application of biomarkers to improve patient outcomes is now common in clinical trials and is rapidly being adopted into clinical practice.**

Although most of what is being described in articles and at conferences is fairly straight forward, clinicians and scientists as well as the regulatory bodies in the US and EU tend to use what can be seen as fairly obscure terminology. In this article I have attempted to provide some clarity to this evolving field, particularly for those without a medical or scientific background. Several of the examples I use are in the area of cancer medicine, mainly because this has been at the forefront of biomarker development and also because I am a Medical Oncologist and cancer researcher by training. The concepts, however, are the same for the application of biomarkers to all human diseases. For more detailed explanations of concepts covered here I would recommend the [FDA website](#) that has various useful articles.

First of all we need to tackle the contentious issue of **personalised medicine** versus **precision medicine** versus **stratified medicine**. I have been on scientific advisory panels that have spent hours debating these terms with no resolution so it is not surprising there is considerable variation as to how they are used. Accepting that some people will disagree I have found the most useful way to think about these as the following:



- a. Precision medicine:** Selection of the best approach to managing a patient based on biological measurements (biomarkers). For example: a person's genome is sequenced or a protein is measured in their blood and a specific drug is given that is known to work with their unique biology. It can also involve repeated monitoring of disease markers to allow tailoring of a treatment to an individual. For example, a specific cancer related gene mutation or protein may be detected in blood and disappear when successful treatment has been given.
- b. Personalised medicine:** Selection of the best approach to managing a specific patient, based on available biological information about the patient as well as a patient's personal preferences, environmental factors, social factors and other factors that may affect the treatment choice. This can be thought of an extension of precision medicine to a holistic approach. An example may be the choice of a prophylactic salpingo-oophorectomy (surgical removal of fallopian tubes and ovaries) in an individual who has tested positive for the BRCA1 or BRCA2 mutation, who has a family history of ovarian cancer, is aware of the relative risk of developing ovarian cancer themselves and has decided to have no pregnancies in the future.
- c. Stratified medicine:** Selection of the best approach to managing a group of patients. It can be considered a step towards precision and personalised medicine and is often used for treatment selection in clinical trials. Stratified medicine accepts that the treatment selected has a net effect of benefiting a group of patients as a whole but may not benefit every individual within the group. An example may be the use of the estrogen receptor to select hormone treatment in breast cancer. The majority (70%) will benefit, but it is accepted that some will not.

## Biomarkers

These are required for precision, personalised and stratified medicine. Again there are multiple definitions for these, many that are quite complex.

[The official FDA definition is here](#) and the [European Medicines Agency \(EMA\) discusses biomarkers here](#).

Basically a biomarker is something you measure to let you know if a person is healthy, not healthy, at risk of becoming unhealthy or if unhealthy is responding to a treatment. Biomarkers can be anything that can be measured in a person and can range from DNA, RNA, Protein, metabolites measured from samples such as blood, tumour material, urine or saliva to imaging such as digital pathology and radiology with special contrast agents. Other examples are blood pressure as a biomarker for risk of heart disease and blood sugar and HBA1c as biomarkers for risk of diabetes related health problems.

Biomarkers can be qualitative or quantitative.

**Qualitative biomarkers** are either present or not. For example a KRAS mutation can either be measured in a cancer or not. **Quantitative biomarkers** measure something using a continuous scale. For example a blood sugar is measured as a numerical concentration in blood. Tumour mRNA is often measured as a number relative to a control mRNA for which the level is known. Quantitative biomarkers will usually have associated values which represent “**cut-offs**” above (or sometime below) which is considered abnormal (biomarker positive).

A working classification of biomarkers is given in the following table. Each would require an article to describe them fully, but it is worth discussing prognostic and predictive biomarkers in more detail as these often cause confusion.

**A prognostic biomarker** is used to estimate the outcome for a patient in the absence of a treatment. For example, if a patient has surgery for breast cancer how likely are they to be cured without further (adjuvant) chemotherapy?

The Oncotype Dx and MammaPrint assays are examples of prognostic biomarkers used to help answer this question.

**A predictive biomarker** is used to estimate the benefit for a **specific treatment**. When a predictive biomarker is registered with a regulatory body (such as the FDA) along with an associated drug to select appropriate patients it is referred to as a companion diagnostic and is on-label for the drug. Using the breast cancer example again, HER2 overexpression (predictive biomarker positive) indicates potential benefit from trastuzumab (Herceptin) treatment. HER2 overexpression is a companion diagnostic on-label for trastuzumab and the FDA require it is tested prior to prescribing this drug. [The FDA discuss these definitions and the use of companion diagnostics further here](#).

A common point for confusion is where a specific intervention such as chemotherapy is shown to have an overall benefit in a high risk population as identified by a prognostic biomarker. This does not necessarily mean the biomarker is “predictive” for the treatment. For example, the breast cancer prognostic biomarkers mentioned earlier will identify high-risk patients who should be offered adjuvant chemotherapy (The low risk patients are unlikely to develop recurrent disease and therefore will not need chemotherapy). The actual benefit for chemotherapy used for an individual high-risk patient however is unknown as the prognostic biomarker does not measure the biology that determines sensitivity or resistance to chemotherapy. Rather it is designed to predict the aggressiveness of a tumour and its likelihood of metastatic spread. This means that the overall response rate is probably less than 50% for standard adjuvant chemotherapy in the high risk population. Ideally a predictive biomarker that measures mechanisms of sensitivity or resistance would be used along with the prognostic biomarker to select the correct chemotherapy for the patient’s specific tumour.

Biomarker	Use	Examples
Susceptibility	Is patient at risk of disease?	BRCA1 mutation and risk of breast cancer. CAG Repeats and Huntington's Disease.
Diagnostic / Biomarker	Is disease present?	D-Dimer measurement and deep venous thrombosis PSA and presence of prostate cancer.
Prognostic	Is treatment needed?	HBA1C levels and complications of diabetes. MammaPrint assay and risk of breast cancer recurrence.
Predictive	Which treatment?	KRAS mutation and cetuximab resistance in colon cancer. ER and response to tamoxifen in breast cancer.
Pharmacogenomic	Is treatment safe?	The CYP2C9*3 single nucleotide polymorphism in germline DNA reduces warfarin metabolism by 90% increasing the risk of overtreatment and bleeding.
Pharmacodynamic/ response	Is the treatment as prescribed working at a biological level?	Loss of Ki67 as marker of decreased proliferation in cancer. Blood pressure as a response to anti-hypertensives.
Monitoring biomarker	Is there a change in the disease with time?	Hepatitis C virus ribonucleic acid (HCV-RNA) for assessing patients with chronic hepatitis C.
Physiological	Is the patient fit for treatment?	Renal function tests prior to platinum-based chemotherapy.



## Biomarker Validation

This again is an area of much confusion with several different terms used. There are, however, two main aspects to proving a biomarker is fit for purpose that can be summarised as:

- I. Analytical validation.** This is the proof that the biomarker is technically robust (ie it measures what it is supposed to reliably). This is what the [Clinical Laboratory Improvement Amendments \(CLIA\) legislation](#) is primarily focussed on in the US. Indeed, in order to be able to use a biomarker for the selection of patient treatment in many US states, including clinical trials, the assay must be compliant with CLIA biomarker validation requirements. This typically includes:
  - a. Accuracy** - does the biomarker measure what it is supposed to? Usually it needs to be compared to another measurement technique to demonstrate comparable data.
  - b. Precision** - does the biomarker give the same result for the same sample every time it is run or is the technology/process "noisy" with a lot of variation?
  - c. Analytical Sensitivity** - what is the minimum amount of biological material (eg DNA from blood) that is required to give a reliable result?
- II. Clinical Validation.** This is proof that the biomarker can be used for the clinical purpose for which it has been designed. The FDA and EMA require adequate clinical validation before a biomarker can be routinely used in the clinic. The process usually involves the application of the biomarker to a patient population that is entirely different (**the validation dataset**) to that used for the purpose of discovery and development (**the training dataset**). The true ability of the biomarker to guide precision medicine can be estimated in terms of [sensitivity](#) (ability to identify those patients with an adverse outcome and distinct from "analytical sensitivity" mentioned above) and [specificity](#) (ability to identify those who do not have the adverse outcome). Sometimes the validation can be given in terms of a [Hazard Ratio \(HR\)](#) which is a measure of the biomarker's ability to predict the risk of developing an adverse event over time such as cancer recurrence, stroke, death etc. A **P-Value** indicates the level of statistical certainty that the biomarker is performing, with a value of less than 0.05 conventionally indicating it is working as expected.

Historically clinical validation has often been poorly performed with the same patient population being used for the purposes of discovery and clinical validation.

This approach, rather unsurprisingly, demonstrates the biomarker working very well in this defined group of patients and is referred to as “**overfitting**”. The problem is that when someone then applies the overfitted biomarker to a separate group of patients it can fail due to differences between the populations the investigators were not aware of.

For example, a centre may collect patient samples using a specific protocol that is not used elsewhere resulting in any locally developed biomarkers only working in that centre. Overfitting is avoided by ensuring the clinical validation patient population is entirely different from that used for biomarker discovery. In addition, a third party should be used to apply the biomarker independently from the original investigators using a pre-specified, locked protocol to prevent any unintended experimental bias.

One area of confusion is the use of the term “**Biomarker verification**” that is sometimes used interchangeably with the “Biomarker validation”.

[Biomarker verification is best reserved for the analysis of a sample set to ensure that a diagnostic lab can run a commercially available biomarker accurately and to the manufacturer’s specification.](#)

For example, a lab may acquire kits from a vendor to measure HER2 amplification. They will need to show that they generate comparable results to other labs when analysing a set of verification samples before offering the assay to patients.

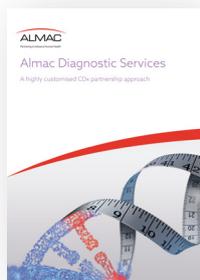
## Conclusion

This article has covered some of the main concepts of biomarker application which will hopefully orientate those new to the field and provide a working knowledge. There are, of course nuances specific to certain situations that are covered elsewhere in more detail.

**Please contact Almac Diagnostic Services if you would like to discuss any of the points raised.**

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## Contact us:

### UK

Almac Group  
19 Seagoe Industrial Estate  
Craigavon  
BT63 5QD  
United Kingdom

### US

Almac Group  
4238 Technology Drive  
Durham  
NC 27704  
United States of America

diagnostics@almacgroup.com  
+44 28 3833 7575

diagnostics@almacgroup.com  
+1 (919) 294 0230