

# THE ROLE OF PROGNOSTIC AND PREDICTIVE MARKERS IN CANCER

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## Abstract

New genomic and proteomic technologies have led to important therapeutic advances in oncology. This article describes how the discovery of molecular prognostic markers to classify an individual patient's risk of disease events and predictive markers to classify response to specific treatment options are used to guide the selection of treatment and identify targets for the development of new molecular-targeted therapies. Prognostic markers can be used to determine the need for further treatment. Patients at very low risk of disease events can safely avoid treatment if risks of adverse events outweigh the estimated benefits. Alternatively, high-risk patients may benefit from a more aggressive treatment regimen. Predictive markers are used to select the most appropriate treatment by identifying patients most likely to respond and avoiding treatment for patients unlikely to respond or those at unacceptably high risk of adverse events. The clinical value of molecular markers depends on a series of factors: the reproducibility of the laboratory methods used for marker measurement; the accuracy of the marker to classify patient prognosis or response to treatment compared to conventional clinico-pathological criteria; its validity when used in independent populations; and the impact of using this information to guide treatment selection on patient outcomes. Randomised control trials are essential to assess the effectiveness and optimal use of prognostic and predictive markers and biomarker-guided therapies.

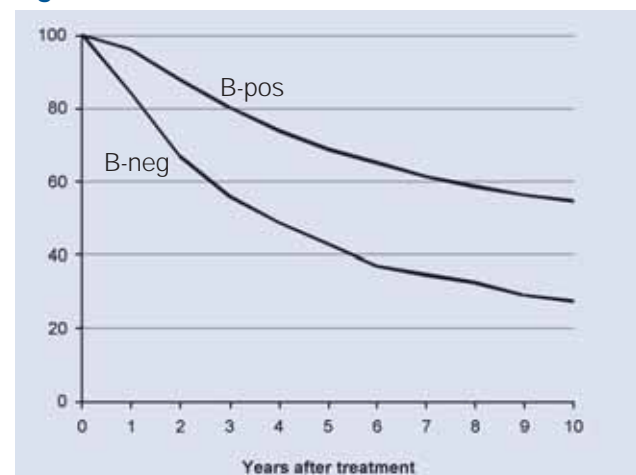
The clinical management of the patient with cancer is largely based on the use of a standardised set of clinical and pathological criteria for diagnosis and classification of the extent of disease. Cancer staging systems have been developed to organise this information in a clinically meaningful way to estimate patient prognosis and guide the selection of effective treatments. However, patients with the same diagnosis and pathological characteristics can show wide variability in clinical outcomes and response to treatment. The use of new genomic and proteomic technologies for the investigation of the molecular mechanisms of disease and response to therapies has led to the discovery of molecular markers for more accurate classification of a patient's risk of disease events (prognostic markers) and response to specific treatment options (predictive markers). Here, we describe the role of prognostic and predictive markers for the selection of existing treatments and the identification of novel molecular targets for the development of new treatments in oncology.

## Discovery and validation of molecular markers

The term 'biomarker' can be used to refer to any characteristic that can be objectively measured as an indicator of normal or pathological biological processes or the response to a therapy.<sup>1</sup> In oncology, biomarkers can include: basic clinical characteristics such as patient gender, age, weight and smoking status; inherited (germline) gene mutations or variants that predispose to cancer or response to treatment; and the pathological and molecular characteristics of the tumour. Potential candidate tumour markers include somatic mutations of the DNA sequence and epigenetic changes such as DNA methylation, that modify gene function in critical pathways involved in cancer pathogenesis or treatment action; or downstream DNA products such as levels of messenger ribonucleic acid or protein expression.

The discovery of a molecular marker begins by demonstrating that the presence, absence or level of the marker is associated with outcomes such as survival time or tumour response, with further evidence required to determine its clinical role (figure 1). Initial biomarker

**Figure 1:** Identification of biomarkers



*Interpretation: Patients testing positive for Biomarker B (B-pos) have a better outcome on treatment A than patients with testing negative (B-neg). Log-rank test  $P < 0.01$*

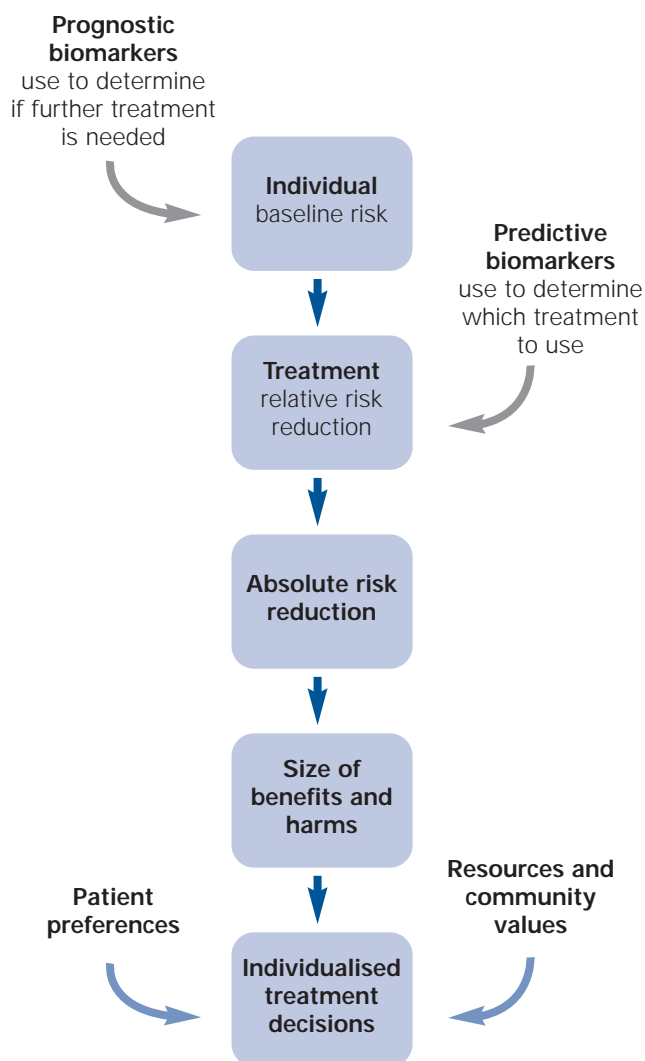
*Additional evidence is needed to determine the clinical role of biomarker B.*

*Outstanding questions include:*

- Does biomarker B identify patients with a better prognosis; or does it predict which patients will respond to treatment A?
- Should biomarker B be used to select which patients should receive treatment A?
- Should treatment A be recommended to all B-positive patients?
- How does biomarker B compare to conventional clinico-pathological criteria to guide treatment decisions?

studies are often undertaken retrospectively using specimens collected from a convenience sample of patients who may have received different treatments. The initial exploratory analysis may investigate large numbers of candidate markers. False positives are therefore common and there is a serious potential for over-fitting data when developing explanatory models, in particular, if few patients are available or few events have occurred. Thus, marker development involves an assessment of the reproducibility of the laboratory assay used for its measurement and validation of its discriminatory capabilities in independent populations.<sup>2,3</sup> After validation, the clinical role of the marker will depend on whether it provides prognostic or predictive information or both.<sup>4</sup> As displayed in figure 2 and discussed in the following sections, prognostic information can be used to determine the need for additional treatment, whereas predictive information can be used to select which treatment to use. The clinical value of using this information to guide the selection of treatment is tested in clinical trials. This evidence and other factors such as patient preferences, the resources of the health system and community values can then be used to individualise treatment decisions in the clinic (figure 2).

**Figure 2:** *The role of prognostic and predictive markers to guide individualised treatment decisions*



## Prognostic markers

Prognostic markers can be used to classify patient risk of, or time to, cancer death and/or other disease events independent of the effects of treatment. For example, involvement of regional lymph nodes in patients with solid tumours is routinely used as a prognostic marker for survival.

In addition to the immediate value of prognostic information to help address patient questions about the expected natural history of their disease, prognostic markers can be used to identify patients at very low risk of disease events who can safely avoid treatment, or high-risk patients who may benefit from more aggressive treatment. For example, in women with early breast cancer, the absence of axillary lymph node metastasis together with other favourable prognostic markers, such as small size and low tumour grade, help to identify women at low risk of disease recurrence. These women may safely avoid adjuvant chemotherapy if the small benefits are unlikely to outweigh the harms of treatment-related adverse events. Alternatively, the presence of axillary node involvement can be used to identify high risk women who may benefit from the addition of more aggressive adjuvant chemotherapy regimens.

In theory, the absolute benefits of a treatment (eg. the number of disease events avoided per 1000 patients treated) are proportional to patient prognosis (absolute risk reduction = baseline risk x relative risk reduction from treatment, figure 2). Although in some situations where treatment is used to extend survival, the reverse may be true and low-risk patients will receive the maximum absolute life years gained. The other exception is if the effects of the planned treatment differ according to patient prognosis. Conclusions about the role of a prognostic marker therefore rely on additional evidence from randomised control trials (RCTs) to assess whether it also predicts treatment response.

Returning to the example of nodal status, RCTs comparing adjuvant chemotherapy with no chemotherapy in women with early breast cancer report that node-positive women have a higher annual death rate than node-negative women within each arm of the trial, but response to chemotherapy is similar for each group (figure 3a).<sup>5</sup> These results indicate that nodal status can provide important prognostic information to help decisions about whether further treatment is needed, but does not identify subgroups of women in whom chemotherapy will be more (or less) effective. Ideally, predictive markers could be used to select which chemotherapy regimen the patient is most likely to respond to.

Biomarkers that have a strong association (ie. show a high relative risk), for disease events may not necessarily be good at discriminating between patients at high or low-risk of these events, or may be no better than conventional tests.<sup>6</sup> Once a promising new molecular biomarker is identified, studies conducted in representative patient populations are needed to compare its prognostic accuracy with conventional

clinico-pathological markers. Further, the clinical value of this information depends on whether it leads to the use of more effective or safer treatments. Ideally, the efficacy of biomarker-guided treatment strategies can be addressed by prospective RCTs.

This is the rationale for the MINDACT trial, an RCT designed to assess the clinical value of a prognostic 70-gene signature for classifying risk of metastases in women with node negative early breast cancer.<sup>7</sup> A multi-centre retrospective analysis of data from a well-defined patient population indicates that this gene signature provides more accurate information for risk classification than conventional clinico-pathological staging systems alone.<sup>8</sup> The MINDACT trial will compare patient outcomes when this prognostic marker is used to guide the selection of adjuvant chemotherapy versus conventional criteria. It will also provide data to explore whether the marker also predicts response to standard chemotherapy regimens. Conclusions from these secondary analyses will depend on whether there is sufficient power to test for treatment interactions by marker status.

Prognostic markers can also have a role in the design of clinical trials. For example, they can be used to selectively recruit high-risk patients in order to maximise the efficiency of the trial to provide evidence about treatment efficacy.

## Predictive markers

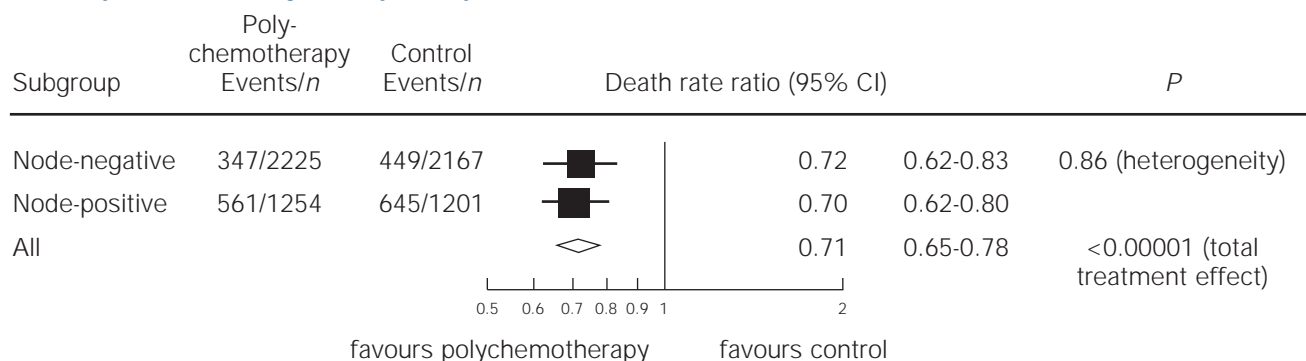
Predictive markers classify patients according to their predicted response or resistance to a treatment. Conventionally, treatments are selected using evidence from RCTs demonstrating their effectiveness in clinically representative populations. Unfortunately, even the most promising therapies that report a highly statistically significant and clinically relevant reduction in the risk of disease events are unlikely to benefit all patients. Some patients will still experience the disease event despite treatment, while others will not regardless of treatment received, and all patients will be at risk of treatment side-effects. The use of predictive markers clearly has enormous clinical implications to optimise the selection of treatments to those patients most likely to respond and avoid the use of treatment in patients unlikely to respond, or those at high risk of

treatment-related adverse events. Non-responders may benefit from the earlier use of alternative therapies or can be identified as a population in need for the development of new treatments.

When an association between biomarker status and patient outcomes is first discovered in a group of patients who have all received treatment as shown in figure 1, it is not possible to conclude whether the marker is prognostic, predictive or both. RCTs designed to compare the effects of treatment between subgroups of patients classified by their biomarker status with a test for interaction (or heterogeneity) are needed to address this question. In some cases, a prognostic marker also predicts treatment response because it is also a therapeutic target. For example, oestrogen receptor expression provides prognostic information in women with early breast cancer and RCTs have provided evidence that it predicts response to hormonal therapy.<sup>5</sup> The discovery of a prognostic marker can also lead to the subsequent development of a molecular-targeted therapy. For example, the discovery that multiple gene copies/high level of expression of the HER-2/NEU gene protein is associated with poor prognosis in women with breast cancer, led to the development of trastuzumab, an antibody to HER-2/NEU.<sup>9,10</sup> Initial 'targeted' trials conducted in HER2-positive women with metastatic breast cancer have provided proof-of-concept evidence about the efficacy of trastuzumab and the use of the marker to select women for treatment.<sup>11</sup> Furthermore, 'non-targeted' trials comparing treatment response in HER2-positive and HER2-negative women would provide stronger evidence of its predictive ability.

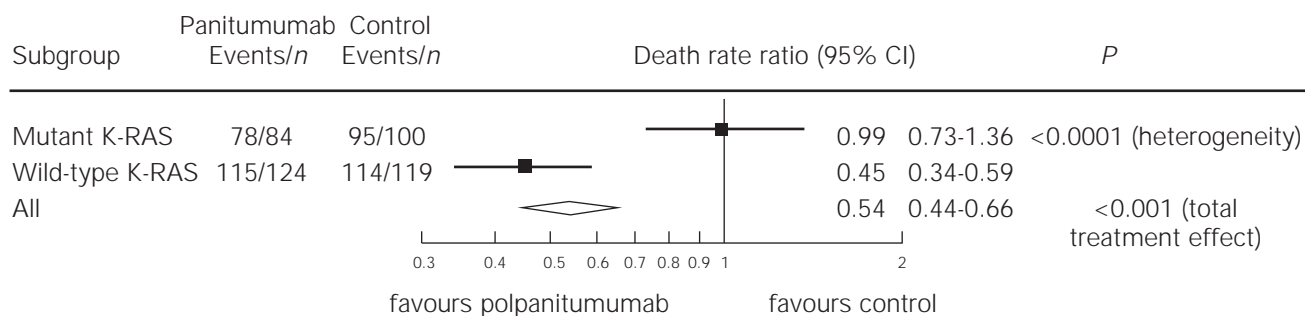
For further illustration of these concepts, consider the development of treatments targeting epidermal growth factor receptor (EGFR) expression following the discovery that abnormal EGFR-mediated cell signalling has a critical role in tumorigenesis. A recent targeted trial of the EGFR inhibitor panitumumab in patients with EGFR-positive metastatic, chemotherapy refractory colorectal cancer, resulted in only a modest improvement in progression-free survival time compared to best supportive care alone.<sup>12</sup> A subsequent retrospective analysis of archival tissue samples from trial participants observed treatment response varied according to tumour K-RAS mutation status.<sup>13</sup> No

**Figure 3a:** Prognostic marker – annual breast cancer mortality for polychemotherapy versus no chemotherapy in women with early breast cancer aged <50 years, by nodal status.<sup>1</sup>



1. Data extracted from EBCTG 2005<sup>5</sup>

**Figure 3b:** Predictive marker – progression-free survival for panitumumab + best supportive care versus best supportive care in patients with metastatic colorectal cancer, by K-RAS mutation status.<sup>1</sup>



1. Data for total treatment effect for trial participants (N=463) extracted from Van Cutsem et al 2007.<sup>14</sup>  
Data for subgroup analysis by K-RAS mutation status (N=427) extracted from Armado et al 2008.<sup>15</sup>

treatment effect was observed among patients with the K-RAS mutation indicating this marker may have a more important role than EGFR-status for treatment selection (figure 3b).

Finally, it is important to emphasise that the molecular pathways involved in carcinogenesis are complex. There are a growing number of examples where promising markers are yet to find a role in clinical practice. For example, p53 gene mutations are common in many cancers and have an important role in pathways involved in tumorigenesis that are also treatment targets, strongly suggesting its value as a prognostic and predictive marker. Even so, its role in improving treatment selection has not yet been established.<sup>16</sup> Thus, even the most compelling biological hypotheses regarding the prognostic or predictive ability of a marker, or the effectiveness of a molecular-targeted treatment need to be formally assessed in clinical trials to determine its optimal clinical use.

## Conclusions

The discovery of clinically-relevant prognostic and predictive markers and the development of molecular-targeted therapies have led to important therapeutic advances in oncology. Two fundamental challenges for the development of new markers are firstly, the need for sound validation of the marker as a reproducible, accurate and independent classifier of prognosis and/or treatment response, and secondly, the need for advances in the efficiency of clinical trial designs for assessing the effectiveness of biomarker-guided therapies. Ultimately, the goal of individualised therapy will only be possible if these two challenges are adequately addressed.

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