PIP Digest

Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer

Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

UNDERSTANDING CANCER: Biomarker Basics

This PIP Digest defines various types of biomarkers and describes their importance for cancer prevention, detection, diagnosis, and treatment. Biomarker research is an emerging field that requires rigorous evaluation to identify truly useful tests for prevention and treatment.

Key concepts

- Definition of a biomarker
- Types and functions of biomarkers
- The role of biomarkers in precision medicine

Related PIP Digests

- Clinical Trials: Precision Medicine and Clinical Trials
- Understanding Cancer: Tumour Heterogeneity

A biomarker (short for "biological marker") is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention."[1] The last part of this definition is most relevant to cancer.

Biomarkers can be based on:

- Molecules or proteins found in blood, body fluids, or tissues (sometimes called signature molecules)
- How tissues and cells appear under a microscope
- How tissues and cells appear via image scans
- Overall states such as body temperature or body mass

Cancer-related biomarkers include aspects of tumours themselves, substances associated with or released by them as well as substances released by the body in response to a tumour.

Biomarkers serve many purposes:

- Susceptibility or risk biomarkers indicate potential for developing cancer.

[1] Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics,* 69(3):89-95.

- Diagnostic biomarkers help detect and diagnosis cancers.
- Prognostic biomarkers predict how aggressive a cancer will become as well as odds of reoccurrence
- Predictive biomarkers reveal how a person will respond to certain cancer treatments and help identify optimal treatments and doses. Certain predictive biomarkers related to treatments and dosages receive the separate classification of pharmacodynamic biomarkers.

Biomarkers can also be used to monitor the progression of your cancer or your response to treatment — in terms of both effectiveness and safety.

An "ideal" biomarker is:

- repeatable/reliable
- valid and clinically useful
- safe and easy to measure
- applicable across gender, ethnic, and age groups
- beneficial to individuals and the healthcare system by reducing disease burden and costs

The table on the next page provides more information the key considerations of biomarkers with different functions.

Uses of Biomarkers in Cancer Drug Discovery

Biomarkers routinely guide cancer drug discovery research. For example, a **risk biomarker** gene for a certain subtype of cancer could help focus research into drugs that inhibit that gene's protein coding.

Biomarkers can also be "surrogate endpoints," standing in for the effects of a drug on cancer progression and survival."[2] Whether or not a biomarker consistently changes in response to a drug helps determine if an experimental treatment should proceed to clinical trials. Such biomarker-based research can be game-changing by reducing time and money spent on dead-end trials and speeding up the drug development pipeline.

Biomarkers have also shown great potential to improve precision medicine — *delivering the right treatment to the right person at the right time*. Biomarker research related to cancer subtypes is critical to tailored treatment approaches. Given cancer's complexity, the most effective research increasingly involves clusters of biomarkers or biomarker signatures that are measured and monitored throughout a patient's journey.

[2]Research Advocacy Network. (2010). *Biomarkers in Cancer: An Introductory Guide for Advocates.* Plano, TX.

<table>
<tr><th>BIOMARKER TYPE/FUNCTION</th><th>KEY CONSIDERATIONS</th></tr>
<tr><td>Risk/susceptibility</td><td>

People at risk may not actually develop cancer for many years.
The usefulness of risk/susceptibility biomarkers is related to the availability of effective interventions that reduce cancer risk. The BRCA1/2 mutation, for example, is used to evaluate the likelihood of developing breast and ovarian cancers. Lifestyle, nutritional, or other preventive interventions like surgery may be used to reduce risk.

</td></tr>
<tr><td>Diagnostic</td><td>

A perfect diagnostic biomarker test would be able to accurately detect cancer in all patients with cancer (100% of people with cancer would test positive – this is called “sensitivity”) and no patients without cancer would be diagnosed with cancer (100% of the people without cancer would test negative – this is called “specificity”). A test with low sensitivity will miss people with cancer who might benefit from treatment while a test that is not very specific may involve more invasive diagnostic procedures and sometimes unnecessary treatments in patients who do not have cancer.

<table>
<tr><th></th><th>Test says person has cancer</th><th>Test says person does not have cancer</th></tr>
<tr><td>Person has cancer</td><td>TRUE POSITIVE</td><td>FALSE NEGATIVE</td></tr>
<tr><td>Person does not have cancer</td><td>FALSE POSITIVE</td><td>TRUE NEGATIVE</td></tr>
</table>

In practice, no biomarker test has perfect sensitivity and specificity. While there is often a lot of media coverage on promising diagnostic tests at early stages in the research lifecycle, the reality is that very few make their way to the clinic.

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<tr><td>Prognostic</td><td>

Biomarkers such as tumour size, number of lymph nodes positive for tumour cells, and presence of metastasis have traditionally been used to indicate cancer prognosis.
Increasingly, molecular indicators or signatures measured on tumours themselves are being used.
Prognostic biomarkers may indicate that you need further treatment, but they are not related to decisions about which treatments you may need.

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<tr><td>Predictive</td><td>

Predictive biomarkers apply to a wide variety of interventions to both prevent and treat cancer. This includes drugs, biologics, medical devices, and medical procedures as well as behavioral and dietary modifications.
Establishing that a biomarker can predict a treatment's effect usually requires a randomized trial - that is, patients with and without the biomarker are randomly assigned to either the novel intervention or a control treatment.
Predictive biomarkers are also used in studies of exposures or in studies of the unintended effects of treatments. For example, a test that measures your likelihood of getting lung cancer based on your exposure to asbestos would be predictive. Identifying which cancer patients are at risk of heart damage from cancer treatments is another example of a predictive biomarker.

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Liquid Biopsy

On the vanguard of cancer biomarker research is the quest for a clinically viable liquid biopsy – that is, a test that can detect and isolate cancer cells or pieces of DNA from a tumor that are circulating in the blood. This research is made possible because of newly developed techniques and advances in genomic research.

From a patient perspective, a liquid biopsy has great advantages over traditional biopsies or surgical procedures, which are invasive, may result in complications, or may not even be doable when a person becomes very sick or the tumour is inaccessible.

Liquid biopsies hold promise as diagnostic, prognostic, and predictive biomarkers, and there are Canadian researchers who are world leaders in this work!

References:

- FDA-NIH Biomarker Working Group. *BEST (Biomarkers, Endpoints, and other Tools) Resource* [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Co-published by National Institutes of Health (US), Bethesda (MD). Last Updated: May 2, 2018. Available at: http://www.biostatsolutions.com/wp-content/uploads/2016/11/Bookshelf_NBK326791.pdf
- Research Advocacy Network. (2010). *Biomarkers in Cancer: An Introductory Guide for Advocates*. Plano, TX. Available at : https://cancer.wisc.edu/research/wp-content/uploads/2019/05/Biomarkers-in-Cancer.pdf

Check out these short videos for more information on biomarkers:

- Merck in Canada / Merck au Canada. *What Are Cancer Biomarkers?* (YouTube) November 8, 2017 [2:20 minutes] https://www.youtube.com/watch?v=T1FJ2UT6mXM
- Genentech. *Understanding Biomarkers*. (YouTube) May 18, 2011 [5:49 minutes] https://www.youtube.com/watch?v=gqG4cUMw6Og
- European Cancer Patient Coalition ecpcTV. *Cancer Biomarkers in the Era of Personalised Medicines*. (YouTube) March 29, 2018 [4:08 minutes] https://www.youtube.com/watch?v=t_7wuuZAQAg

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