Biomarkers in Cancer Care

Danielle Fournier, DNP, APRN, AGPCNP-BC, AOCNP



Objectives

- 1. Review foundational cancer genomic concepts
- 2. Discuss the role of cancer biomarkers throughout the cancer care spectrum
- 3. Explore biomarker testing technologies currently in use



Genomics Foundations

Cancer is a disease of the genome

Cancer results from uncontrolled cellular growth caused by genetic variants

Variants can be inherited or acquired

Germline v. Somatic Variants

Germline Variants

- Inherited from reproductive cells (egg or sperm)
- Variants can be transferred from parent to offspring
- Hereditary

Somatic Variants

- Genetic change that occurs after conception to any non-reproductive cell
- Not hereditary: Variants are not passed to offspring
- Sporadic or random
- Most common cause of cancer

(NCI, n.d.)

Genomic Driver Variants

- *Driver variants* are associated with propelling tumorigenesis
- *Passenger variants* do not contribute to tumorigenesis
- Do not all behave the same

(Ostroverkhova et al., 2023)

- Vary between cancer types and subtypes
- May only drive oncogenesis in combination with other variants
- May work quickly or remain latent for long periods of time



Hallmarks of Cancer



(Hanahan & Monje, 2023)

Variant Classification for Pathogenicity

Type of Variant	Description
Pathogenic	Directly impacts the development of disease, and additional evidence is not expected to alter the classification of this variant
Likely Pathogenic	Very likely impacts the development of disease, but scientific evidence is currently insufficient to prove this conclusively
Uncertain Significance	There is currently not enough information to support a more definitive classification.
Likely Benign	Not expected to influence the development of disease, but there is not strong enough scientific evidence to prove this conclusively
Benign	Does not cause development of disease, and additional evidence is not expected to alter classification of this variant

https://www.ons.org/genomics-taxonomy/variant-subcategories



What is a Biomarker?



A molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease



Genes, proteins, and other substances



May be used to see how well the body responds to a treatment for a disease or condition

(NCI, n.d.)





Susceptibility Biomarkers

- Increased or decreased risk of developing disease in an individual who DOES NOT yet have that disease
- Guides preventive strategies including cancer screening practices and risk reduction interventions
- Examples:
 - Germline *BRCA1/BRCA2* variants:
 - Breast, ovarian, prostate, pancreatic cancer and melanoma
 - Human papilloma virus (HPV):
 - Cervical, anal, oropharyngeal, penile, vaginal and vulvar cancers
 - Germline Neurofibromatosis 1 (*NF1*) variants:
 - Breast cancer , peripheral nerve sheath tumors, and gastrointestinal stromal tumors (GIST)

(FDA-NIH Biomarker Working Group, 2016; NCCN, 2024)

Diagnostic Biomarkers

- Used to detect or confirm presence of a disease
- Can identify disease sub-types
- Test before or at time of diagnosis
- Examples:
 - Philadelphia (Ph) chromosome
 - Chronic myeloid leukemia (CML)
 - Estrogen receptor (ER), progesterone receptor (PR), or HER2 expression
 - Breast cancer subtypes



Prognostic Biomarkers

- Indicates an increased or decreased likelihood of a future clinical event
 - Disease recurrence
 - Disease progression
 - Overall survival
- Measured at or after diagnosis
- Examples:
 - CEA Poor survival in colorectal, breast and lung cancer
 - *TP53* Poor overall survival across multiple cancer diagnoses
 - MYC Adverse prognosis in multiple myeloma





Predictive Biomarkers

- Used to predict response or non-response to treatment
- Test prior to treatment selection
 - First line setting or after disease progression
- Assist in informing patient care decisions and personalizing therapy





Predictive Biomarkers

- ALK rearrangement- alectinib, brigatinib, lorlatinib, ceritinib, crizotinib
- **BRAF** dabrafenib/trametinib, encorafenib/binimetinib, vemurafenib
- EGFR osimertinib, afatinib, erlotinib, gefitinib
- KRAS G12C sotorasib, adagrasib
- MET Exon 14 Skipping capmatinib, tepotinib
- **RET** selpercatinib, pralsetinib, cabozantinib
- HER2 fam-trastuzumab deruxtecan
- NTRK1/2/3 larotrectinib, entrectinib, repotrectinib
- **ROS1** ceritinib, crizotinib, entrectinib, repotrectinib
- PD-L1 atezolizumab, cemiplimab, ipilimumab/nivolumab, nivolumab, pembrolizumab

Response/Monitoring Biomarkers

- Measured repeatedly to assessing status of a disease or for evidence of exposure to a medical product or an environmental agent
- Helps to identify disease response, recurrence, or progression
- Test during and after completion of treatment
- Examples:
 - **PSA** Prostate cancer
 - AFP Hepatocellular carcinoma
 - CEA Gastric cancer
 - ctDNA- Colorectal cancer





Safety Biomarkers

- Measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect
- Testing during therapy
- Examples:
 - LFTs to monitor for hepatotoxicity on immunotherapy
 - Ejection fraction to monitor for cancer-therapy related cardiac dysfunction
 - Corrected QT interval to monitor for QT prolongation on TKI therapy







(Zhou et al., 2024)

Biomarker Testing Technologies



Next-Generation Sequencing (NGS)

- Technology used to sequence DNA and/or RNA to detect genomic variants
- Allows for sequencing of multiple genes simultaneously
- Superior sensitivity and improved cost-effectiveness over single gene assays



(Cheng et al., 2023; Qin, 2019)

Other Biomarker Testing Modalities

Testing Modality:	Tests for:	Description:
Immunohistochemistry (IHC)	Protein overexpression	 Uses antibodies to check for certain cell surface antigens in a sample of tissue Antibodies are usually linked to an enzyme or a fluorescent dye After the antibodies bind to the antigen in the tissue sample, the enzyme or dye is activated and can then be seen under a microscope.
Polymerase Chain Reaction (PCR)	DNA/RNA sequence and abundance	 Method to make many copies of a piece of DNA from a sample that contains small fragments of that DNA The DNA is amplified so it can be detected and studied in greater detail
Fluorescence in Situ Hybridization (FISH)	DNA/RNA sequence and location in cells	 Pieces of DNA that contain a fluorescent dye (probe) are made in the laboratory and are added to a tissue sample The probe binds to its corresponding sequence on the chromosome in the sample and activated the dye is visible under a special light

(NCI, n.d.)

Liquid Biopsy

- Laboratory test done to look for cancer cells or cancer cellular fragments released into a person's body fluids
- Advantages:
 - Minimally-invasive
 - Allows for serial testing
- Currently used in the advanced/metastatic setting to identify actionable genomic variants



(Bertoli et al., 2023; Santini et al., 2023)



Additional Resources

JADPRO Patient Resources on Biomarker Testing:

<u>https://patiented.advancedpractitioner.com/biomarker</u>

NCI Dictionary of Genetics Terms:

<u>https://www.cancer.gov/publications/dictionaries/genetics-dictionary</u>

ONS Genomics and Precision Oncology Learning Library:

<u>https://www.ons.org/learning-libraries/precision-oncology</u>

ONS Biomarker Database

<u>https://biomarkers.ons.org/biomarkers/</u>

National Human Genome Research Institute (NHGRI) – Introduction to Genomics

<u>https://www.genome.gov/About-Genomics/Introduction-to-Genomics</u>



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Thank you!

dmfournier@mdanderson.org @DFournierNP

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