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BIOMARKERS:

PATHWAY TOWARD TARGETED THERAPY

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Introduction

Biomarkers - including molecular, histologic, radiographic, or physiologic characteristics - are measurable indicators of biological processes and play a pivotal role in modern medicine. They provide researchers and clinicians with a greater understanding of health outcomes among subgroups.[1] Biomarkers themselves serve as tools that function in a wide range of roles, such as diagnosis, prognosis, and monitoring of diseases. While traditional approaches relying on broad population data often miss important individual variations in treatment response, the identification of biomarkers allows for a more targeted approach and increases certainty of response regarding specific subgroups. Continuous advancements in genomic and bioinformatic technologies enable the discovery of novel biomarkers that represent the target of new treatments, further stratifying patients into different clinical subgroups, and allowing the development of targeted therapy with higher certainty regarding regulatory approval and clinical decision-making.

In such a context, the drug effectiveness will be different among patients who express the biomarker compared to those who do not. This differential efficacy related to the biomarker expression (i.e., an effect modification) is one important aspect of precision medicine.[2] It represents a biological interaction between the drug and the biomarker, which enhances the drug's effectiveness for a specific subgroup. Given the critical role of biomarkers, it is essential to carefully navigate the steps involved in evidence generation, regulatory submission, and health technology assessment.

While biomarkers are foundational to precision medicine, they are not synonymous with it. Precision medicine refers to the broader framework of using individual variability (e.g., genetic, environmental, or lifestyle factors) to guide medical decisions, whereas biomarkers are the concrete signals, such as a genetic mutation or protein expression, that inform those decisions.

Similarly, *personalized medicine* often implies treatments uniquely crafted for individuals, whereas biomarker-guided therapies target defined subgroups sharing a specific biological trait. Biomarker-guided therapy has already shaped the landscape of oncology, reducing the uncertainty of various oncological products' effectiveness and minimizing the use of unnecessary therapies. Within advanced non-small cell lung cancer, for instance, sequential testing has increased five-year survival from 2% to 5-7%, and multigene testing has increased five-year survival from 2% to 13-19%.[3]

This article focuses specifically on biomarkers as *effect modifiers* and their role in optimizing therapeutic strategies. By focusing on biomarkers as tools in biomarker-guided therapy, we can examine their utilization in enhancing drug development, regulatory decision-making, and clinical practice as one aspect of precision medicine.

Biomarkers in Oncology

Various oncological reviews have classified cancer biomarkers into prognostic or predictive biomarkers:

- Prognostic biomarkers provide insights into disease course or outcomes outside of the intervention.[4,5]
- Predictive biomarkers are useful for evaluating drug responses within different subgroups.[4,5]
    - Predictive biomarkers allow us to understand their role as effect modifiers in one aspect of precision medicine.

Within oncology, biomarkers allow for the shift towards precision medicine, which allows for more targeted interventions, leading to improved treatment outcomes and reduced adverse effects.[6] The power of these biomarkers lies in their ability to guide treatment selection, maximizing benefit while minimizing harm.

Examples of biomarkers that have previously been used in mutation-guided therapy across select cancers include[6]:

- EGFR, ALK, and ROS1 mutation in lung cancer.
- HER2, BRCA1/2, and PIK3CA for breast cancer.
- KRAS/NRAS/BRAF mutations for colorectal cancer.

Predictive biomarker detection used for response in immunotherapy, such as seen in PD-L1, has also been approved by the FDA for various types of cancers.[7] However, the journey of biomarker discovery and application does not end with identification. It continues with ongoing investigation and integration of advanced technologies like artificial intelligence. A study showed that integrating genomics, transcriptomics, proteomics, and metabolomics results in better detection of cancer subtypes and prediction of response to treatments.[8] The advancements of artificial intelligence will work hand in hand with the development of biomarker-guided therapy and precision medicine. The ultimate goal of these efforts is to enhance treatment efficacy and reduce adverse effects, thereby improving patient outcomes.

The use of biomarker-guided therapy can improve outcomes in patients with advanced cancer through the improvement of survival times, resulting in lower patient costs with higher progression-free survival.[9] One way precision medicine in oncology is utilized is through the guidance of biomarkers, biomarker-guided therapy in oncology introduces "extra value" beyond standard cost-effectiveness measures, including[10,11]:

Value of knowing/personal utility[12]

- Provides confidence for risk-averse patients about treatment responses.
- Reduces uncertainty, giving responders greater peace of mind.
- Improves adherence among responders.
- Helps non-responders avoid ineffective treatments and adverse effects.

Insurance value[13,14]

- Protects patients from catastrophic financial loss due to high treatment costs.
- Prevents health declines from lack of coverage.

Other relevant value concepts not specific to biomarker-guided therapy include[15,16]

- Value of hope
- Scientific spillovers
- Real option value

The path to integrating biomarkers into clinical practice is not without its challenges, particularly when it comes to regulatory approval and standardization.

Regulatory Approach to Biomarkers

The United States Food & Drug Administration (FDA) has two regulatory pathways within the Center of Drug Evaluation and Research (CDER) for the integration of biomarkers into drug development.[17] The biomarkers can be integrated through the drug approval process, or they can be approved through the Biomarker Qualification Program.

The **Resources for Biomarker Requestors** page by the FDA provides different qualification stages and submission requirements for biomarker usage.[18]

The first pathway involves drug developers who can utilize biomarkers within clinical trials to answer questions regarding their drug, additionally, the CDER may consider the use of biomarkers in approved product labeling.[17] Novel biomarkers require the drug developer to be responsible for all aspects of the biomarker development.

With the second pathway, registering a biomarker through the **Biomarker Qualification Program** allows the biomarker to be used in multiple drug development programs. Qualified biomarkers are required to undergo a formal regulatory process to ensure that they can be interpreted and applied correctly within medical product development and regulatory review.[19] The Biomarker Qualification Program works with the requestor in guiding biomarker development.

An example of an approved biomarker within the Biomarker Qualification Program is seen in a guidance document from the FDA, which outlines the context of use for plasma fibrinogen levels for the target population/studies; in this case, it would be investigational studies for exacerbations and/or all-cause mortality in COPD patients.[20] The recommendations outline the use of plasma fibrinogen, measured at baseline, as a "prognostic biomarker to select patients with COPD at high risk for exacerbations and/or all-cause mortality for inclusion in interventional clinical trials."

At the moment, only prognostic markers have been approved within the Biomarker Qualification Program, with predictive markers either pending approval or withdrawn.

The European Medicines Agency (EMA) also outlines information and methodological issues regarding pharmacogenomic biomarkers.[21] In this **Reflection Paper**, they distinguish predictive biomarkers as characteristics that determine if a patient is a good candidate for treatment through biomarker testing.

The qualification of predictive biomarkers requires researchers to clearly define what the biomarker will be used for, and information on the subgroups that will respond to the biomarker-guided therapy.[22]

Additionally, the paper outlines methodological challenges in biomarker use, including:

- **Sample Collection Variability**
  - Assay differences or biomarker misclassification may lead to invalid results.[21]
- **Validation Requirements**
  - Exploratory study findings must be confirmed in prospective pivotal clinical trials to assess clinical efficacy.[21]
  - Trials should establish:
    - Biomarker-treatment interaction.
    - Predictive value and clinical utility of the biomarker.
    - Basis of association between biomarker and response.
- **Cut-off Points & Subgroup Validation**
  - If biomarker-response relationships are not predefined, cut-off points (identifying biomarker-positive subgroups) must be validated in a second independent trial.[21]

Overall, the insights from regulatory bodies on the different pathways allow drug developers to understand how biomarkers can aid in regulatory approval for the use of the biomarkers themselves or within drug submission. These clinical strategies come with unique study designs, costs of select assays, and the question of clinical utility based on the acquisition of the biomarkers, further adding to the considerations required in biomarker-guided therapies.

Study Designs Used for Assessing Biomarker Assays

Biomarker-guided therapy relies on a range of study designs, and the pathway from discovery to application within a clinical setting can vary depending on the researcher's goals. The exploratory or discovery phase of biomarker research can begin with in vitro/in silico testing on patient tumors or retrospective analysis of healthcare data, and then the biomarkers can be validated with basket trials where one specific drug is tested within multiple cancer types that all share the same biomarker or within umbrella trials where multiple targeted therapies are tested in specific biomarker-defined subgroups.[23]

We outline here in **Table 1** the basket and umbrella trials suggested by the FDA for the efficient development of oncological drugs and biologics based on one or more cancer/tumor types for biomarker-guided therapy.[24]

Table 1. Study Designs for Validating Biomarkers as Effect Modifiers

Design	Purpose	Key Features	Biomarker Validation Focus	Example
Basket Trial	Test a single therapy across multiple cancers with a shared biomarker.	- Single-arm or randomized. - Adaptive arms (add/drop cancer groups).	- Efficient for rare biomarkers. - Supports tumor-agnostic approvals.	Vemurafenib for BRAF V600+ nonmelanomas[25]
Umbrella Trial	Test multiple therapies in a single cancer type stratified by biomarkers.	- Randomized sub-studies with a common control - Adaptive arms (add/drop therapies).	- Validates multiple biomarkers at once. - Compares targeted therapies and standard of care.	PIK3CA/CDK4/FGFR in squamous NSCLC[26]

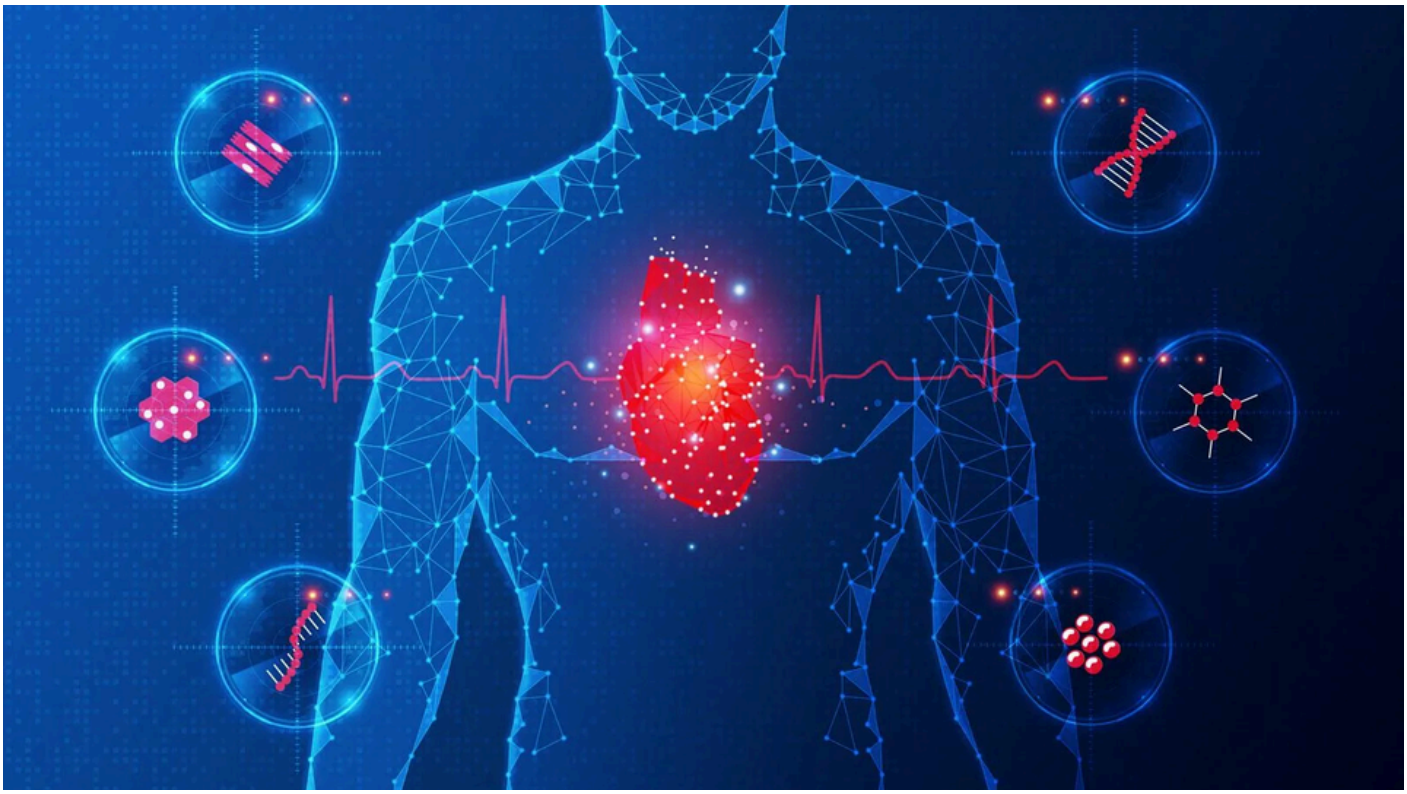
On top of the study design used, the FDA has other considerations to include in the design[24]:

1. **Common Control Arms**
   - Recommended for efficiency in evaluating multiple drugs at the same time.
   - Should reflect the current standard of care (SOC) for interpretability with U.S. medical practice.
   - Protocol must adapt if SOC changes mid-trial due to new drug approvals.
2. **Novel Drug Combinations Being Investigated**
   - Require strong scientific rationale and dose optimization.
   - Dose-finding phases must occur before efficacy evaluation.
3. **Drug Targeting Multiple Biomarkers**
   - Biomarker tests must be analytically validated before starting the trial.
   - Pre-specify rationale for allocating patients eligible for multiple biomarkers based on the mechanism of action.
   - Must interpret and address prognostic implications of co-occurring biomarkers.
4. **Adaptive Arm Modifications**
   - Protocols may add/drop arms based on interim analyses or external new data.
   - Requires predefined rules for modification in the Statistical Analysis Plan (SAP).
5. **Independent Data Monitoring Committees**
   - Independent Data Monitoring Committees (IDMCs) are mandatory for trials supporting market application.
   - IDMCs monitor safety/efficacy, recommend arm discontinuation, and ensure ethical conduct.

With biomarker-guided treatment strategies and the development of studies come the economic costs of select assays, and the question of clinical utility is affected by the use of cost-efficient biomarkers.[27] Trial designs that compare a validated biomarker with a cheaper alternative can determine more cost-effective measures within biomarker-guided therapy. The study design is essentially broken down into two phases.[27] In the first phase, patients in both the experimental arm and the control arm are assessed using a standard, validated biomarker assay and an alternative, cheaper one, with the standard biomarker guiding treatment for the experimental arm. Prior to the conclusion of the trial, the accuracy of the two biomarker assays is analyzed and is then used to choose the biomarker for the remainder of the trial. The trial design essentially allows investigators to determine if a cheaper alternative assay would accurately detect the predictive biomarker of interest in comparison to the validated, more costly biomarker assay. The integration of novel biomarkers, regulatory pathways, and clinical utility assessment with cheaper biomarker alternatives allows for more efficient application of biomarkers towards precision medicine.

Conclusion

Biomarker use highly depends on distinguishing the role of the biomarkers within specific subgroups, the validation of the cost-effective assays, and working closely with regulatory bodies for approval. To use biomarkers effectively in treatment, it is important to first validate whether they predict outcomes among subgroups and ensure test accuracy through adaptive trials. The design of biomarker-guided studies can help identify likely responders, while engaging regulators early to clarify approval pathways allows for efficient applications of biomarkers for drug approval. Post-approval, biomarkers can demonstrate real-world value by showing how biomarkers prevent ineffective treatments and reduce adverse effects while improving outcomes compared to traditional one-size-fits-all approaches. Future work should integrate multiomic data, discovering new biomarkers for resistant cancers, and standardize testing protocols while addressing tumor heterogeneity and reimbursement barriers to make biomarker-guided oncology more practical and impactful.



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