SELINUS UNIVERSITY
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EXPLORING THE SIGNIFICANCE AND APPLICATION OF MOLECULAR BIOMARKERS IN SOLID TUMORS: A COMPREHENSIVE ANALYSIS OF THEIR ROLE AS DECISION GUIDES IN SYSTEMIC THERAPY WITHIN THE EVOLVING LANDSCAPE OF PRECISION MEDICINE

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ABSTRACT

Background/Aims: The advent of precision medicine has transformed the treatment landscape for solid tumors by enabling therapies tailored to a patient's unique molecular profile. However, the full clinical potential of this approach is hindered by significant barriers, including intratumoral heterogeneity, a lack of standardized diagnostic guidelines, and challenges in clinical implementation. This thesis sought to systematically evaluate the clinical utility and role of biomarker-driven systemic therapy in the management of solid tumors.

Methods: A systematic review and meta-analysis were conducted in accordance with Cochrane guidelines and the PICOS framework. Leading medical databases, including MEDLINE and SCOPUS, were searched for studies evaluating biomarker-guided systemic therapy in solid tumors. Inclusion criteria prioritized randomized controlled trials, and the Cochrane Risk of Bias tool was used for quality assessment. Quantitative data synthesis was performed using a random-effects meta-analysis to calculate pooled Odds Ratios (ORs).

Results: From an initial 12,345 records, 18 studies met the inclusion criteria for the final synthesis. A key characteristic of the included literature was the high prevalence of biomarker-informed strategies, with 88.9% of studies utilizing a biomarker-guided approach. A meta-analysis comparing outcomes in biomarker-positive versus biomarker-negative patients demonstrated a strong trend favoring the biomarker-positive cohort (OR = 0.44; 95% CI 0.19–1.01). A second meta-analysis revealed that targeted therapy was significantly more effective than non-targeted therapy, with a threefold improvement in the odds of a favorable outcome (OR = 3.02; 95% CI 1.09–8.35; p = 0.03). Substantial to complete heterogeneity was observed across both analyses ($I^2 \geq 90\%$).

Conclusions: This study confirms that biomarker-guided systemic therapy is a validated and superior treatment strategy in the management of solid tumors. However, its effectiveness is modulated by significant biological and systemic challenges, including tumor heterogeneity and barriers to access. The findings underscore the necessity of integrating comprehensive molecular profiling into standard clinical care. Future research should prioritize the validation of multi-omic and AI-driven predictive models, the innovation of clinical trial designs, and the development of equitable implementation strategies to realize the full potential of precision oncology for all patients.

Keywords: precision medicine, personalized medicine, biomarkers, solid tumors, targeted therapy, precision oncology

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CHAPTER ONE

1.0: Introduction

Cancer remains a leading cause of death worldwide, with solid tumors constituting the majority of both new diagnoses and cancer-related fatalities. The World Health Organization (WHO) stipulates that approximately 19.3 million new cases of cancer were diagnosed globally in 2020, and solid tumors accounted for the vast majority of these cases (World Health Organization, 2020). These tumors arise in organs such as the lungs, breast, prostate, colon, and liver, where the uncontrolled proliferation of abnormal cells leads to the formation of malignant masses. The heterogeneity inherent in solid tumors where genetic variations exist not only between patients but also within the same tumor poses significant challenges in treatment, making effective management complex and often suboptimal (Hanahan & Weinberg, 2011).

1.1: Background of Study

The prevalence of solid tumors varies by geographic region, largely driven by lifestyle factors, genetic predispositions, and environmental exposures. For instance, lung cancer is particularly prevalent in regions with high smoking rates, including Eastern Europe and parts of North America. In contrast, liver cancer remains prevalent in East Asia and Sub-Saharan Africa, largely due to higher rates of chronic hepatitis B and C infections, which increase the risk of liver carcinoma (Bray et al., 2018). In women, breast cancer, the most commonly diagnosed cancer, has seen a marked increase in incidence in high-income countries where access to screening programs and early detection is more widespread (Torre et al., 2018). However, the burden of breast cancer in low- and middle-income countries is rising, primarily due to increased urbanization, dietary changes, and reduced physical activity (Jemal et al., 2011). Given these epidemiological trends, the need for effective treatment strategies that are tailored to the specific molecular and genetic profiles of patients is more pressing than ever.

Traditionally, cancer treatment relied on a combination of surgery, radiotherapy, and chemotherapy. Chemotherapy has been one of the most employed treatments for solid tumors, utilizing cytotoxic drugs that target rapidly dividing cells. However, the effectiveness of chemotherapy is constrained by its poor and/or lack of specificity. While attacking cancer cells, it also harms healthy cells, leading to considerable side effects like nausea, fatigue, and reduced

immune response. This non-specificity reduces the quality of life for many patients and often leads to dose reductions or discontinuation of therapy (Lichter & Schütz, 2019). Additionally, drug resistance is a critical problem, as cancer cells can evolve and become resistant to chemotherapy over time, reducing its effectiveness (Holohan et al., 2013).

The development of precision medicine over the last two decades has transformed cancer treatment. Precision medicine refers to an approach that takes into account the patient's genetic makeup and the molecular profile of their cancer in tailoring medical treatment to the individual. This approach contrasts with traditional treatments that apply the same therapy to all patients with the same disease (Collins & Varmus, 2015). The foundation for precision medicine in oncology lies in the ability to identify specific genetic mutations and alterations in tumors, which are responsible for their growth and spread. This molecular understanding has led to the development of targeted therapies, which focus on inhibiting these driver mutations. Epidermal growth factor receptor (EGFR) inhibitors, such as gefitinib and erlotinib, are prime examples of targeted therapies that have transformed the management of non-small cell lung cancer (NSCLC) harboring EGFR mutations (Maemondo et al., 2010). These therapies allow for greater specificity in targeting cancer cells, leading to improved patient outcomes with fewer side effects compared to chemotherapy (Garnett & Edelman, 2020).

The advent of immunotherapy marked another pivotal milestone in cancer treatment. This approach harnesses the body's immune defenses to recognize and eliminate malignant cells. The use of immune checkpoint inhibitors, such as nivolumab and pembrolizumab, which block inhibitory signals on immune cells, has led to significant improvements in survival for cancers such as lung cancer, melanoma, and bladder cancer (Brahmer et al., 2015). These treatments have offered long-lasting responses, even in advanced cancers, and are now standard therapies in several malignancies (Brahmer et al., 2015). However, the use of immunotherapy is not universally effective, and biomarkers such as PD-L1 expression have been crucial in selecting patients who are most likely to respond favorably to these treatments (Garon et al., 2015). This has led to an increasing emphasis on biomarker-guided therapy in precision oncology, where patient outcomes are maximized by matching the most suitable therapy with the individual patient's profile.

The rise of biomarkers has been one of the most transformative advances in cancer treatment. Biomarkers are defined as measurable biological indicators that provide crucial information about

a patient's disease state, the tumor's genetic and molecular profile, and how the tumor may respond to therapy (Hyman et al., 2017). Biomarkers can be classified into several categories, such as diagnostic, prognostic, predictive, and pharmacodynamic markers. Diagnostic biomarkers aid in identifying cancer at an early stage, typically when tumors are most treatable. For example, the detection of BRCA1 and BRCA2 mutations allows for the identification of individuals at high risk for breast and ovarian cancers, prompting preventive measures such as prophylactic mastectomy or oophorectomy (Turnbull & Rahman, 2006). Prognostic biomarkers help determine the likely course of the disease, such as microsatellite instability (MSI) in colorectal cancer, which correlates with improved prognosis and is a predictor of response to immune checkpoint inhibitors (Le et al., 2017). Predictive biomarkers are particularly important in determining the effectiveness of specific therapies. For instance, the presence of HER2 overexpression in breast cancer predicts responsiveness to trastuzumab, a monoclonal antibody that specifically targets HER2-positive cancer cells, resulting in significantly improved survival rates (Slamon et al., 2001). Similarly, KRAS mutations in colorectal cancer predict a lack of response to EGFR inhibitors, guiding clinicians away from ineffective treatments and reducing unnecessary side effects (Stintzing et al., 2011). Lastly, pharmacodynamic biomarkers allow for real-time monitoring of how well a tumor is responding to treatment, helping clinicians adjust therapies to optimize patient outcomes (Parchment et al., 2018).

The identification of biomarkers has also led to the development of liquid biopsies, which offer a non-invasive method of analyzing a patient's genetic profile through blood samples. This technique allows for the detection of circulating tumor DNA (ctDNA), enabling the identification of mutations and resistance mechanisms without the need for traditional tissue biopsies (Parchment et al., 2018). Liquid biopsies have shown promise in monitoring minimal residual disease, detecting recurrence, and assessing response to treatment, particularly in lung, breast, and colorectal cancers (Diaz et al., 2012). As such, liquid biopsy technology is poised to become an essential tool in personalized cancer care.

A significant breakthrough in cancer research has been the development of immunogenomic profiling, which combines the genetic information of the tumor with its immunological characteristics. The ability of the immune system to recognize and eliminate malignant cells is central to the success of immunotherapies, and understanding the genetic mutations that affect immune response is key to improving treatment outcomes. Tumors that exhibit high mutational

burdens, such as microsatellite instability-high (MSI-H) tumors, tend to be more responsive to immune checkpoint inhibitors, as these tumors have an increased number of neoantigens that can be targeted by the immune system (Le et al., 2017). This has led to the application of next-generation sequencing (NGS) to profile tumors' genetic landscape and assess immune evasion mechanisms (McGranahan & Swanton, 2017).

Recent studies in immunogenomic profiling have provided insights into tumor microenvironment (TME) interactions, revealing how certain cancers develop mechanisms to evade immune surveillance (Galon et al., 2013). For instance, tumors with high PD-L1 expression can suppress immune response by binding to PD-1 receptors on T-cells, preventing them from attacking cancer cells (Garon et al., 2015). By using PD-L1 expression as a predictive biomarker, clinicians can determine which patients are most likely to respond to PD-1/PD-L1 inhibitors like nivolumab and pembrolizumab.

In the UK, the National Health Service (NHS) has incorporated the use of biomarkers and immunogenomic profiling into routine clinical practice, particularly through initiatives such as the NHS Genomic Medicine Service (Turnbull et al., 2018). This service offers access to cutting-edge genomic profiling technologies, enabling the identification of genetic mutations and biomarkers that inform treatment decisions. The NHS has also adopted liquid biopsy for monitoring circulating tumor DNA (ctDNA) in various cancers, including lung cancer, colorectal cancer, and melanoma, to assess treatment response and monitor for early signs of recurrence (Heitzer et al., 2019).

Despite the significant progress made in the field of biomarker-driven therapies, several research gaps remain. Most notably, biomarker testing is still underutilized in early-stage cancers, where it could have the greatest impact. The clinical integration of immunogenomic profiling is still limited, especially in low-resource settings where access to genomic sequencing is restricted (Abu-Rustum et al., 2020). Furthermore, the challenge of tumor heterogeneity remains unsolved, with varying levels of biomarker expression within different regions of the same tumor complicating the development of uniform treatment protocols (Turajlic & Swanton, 2016).

This thesis aims to address these gaps by exploring the role of biomarker-driven systemic therapy in solid tumors, focusing on areas where limited research exists, such as rare tumors and tumor heterogeneity. By expanding on current research and incorporating novel biomarker strategies, this

study aims to refine personalized oncology, contributing to more effective treatments and improved patient outcomes.

1.2: Problem Statement

The application of biomarkers in cancer treatment, particularly for solid tumors, has the potential to revolutionize patient outcomes by offering more targeted, effective therapies. However, despite the promising advances in precision medicine, the implementation of biomarker-driven therapies remains far from ideal in clinical practice. The problem lies not only in the limited availability of validated biomarkers but also in the lack of standardized clinical guidelines, inconsistent biomarker expression, and the ongoing challenges in integrating precision therapies into real-world healthcare systems. These barriers have led to a situation where, despite significant breakthroughs in the understanding of cancer at the molecular level, many patients still do not receive the full benefits of precision oncology.

A major challenge limiting the widespread use of biomarkers is the lack of universal, standardized guidelines for their application in routine clinical care. Although biomarkers like HER2 amplification in breast carcinoma and EGFR alterations in non-small cell lung carcinoma (NSCLC) have been effectively integrated into therapeutic protocols, many other biomarkers remain underutilized and inconsistently applied in clinical practice. The development of clinical guidelines is often fragmented, varying from institution to institution, or even country to country, leading to inconsistent practices. For instance, while the use of KRAS testing in colorectal cancer is a routine practice in some developed countries, its application is less widespread in other parts of the world, particularly where healthcare infrastructure and access to advanced molecular testing remain limited (Stintzing et al., 2012). This lack of standardization leads to variability in how biomarker testing is performed and interpreted, ultimately contributing to suboptimal treatment decisions that could have been avoided with more universally accepted protocols.

In addition to the issue of guidelines, the variability in biomarker expression within solid tumors poses a significant challenge to effective precision medicine. Cancer is not a monolithic disease; rather, it is a highly heterogeneous condition, where even within the same tumor, different clones of cancer cells may exhibit distinct genetic and molecular profiles. This phenomenon of intratumoral heterogeneity means that a single biomarker may not reflect the full spectrum of the

tumor's genetic alterations. As a result, biomarkers that are thought to be predictive of treatment efficacy in one region of the tumor may not be expressed uniformly across all tumor cells. For example, EGFR mutations in lung cancer may be present in only a subset of cells, and secondary mutations, such as the T790M mutation, can emerge over time, rendering initial biomarkers ineffective and leading to treatment resistance (Yang et al., 2015). In breast cancer, while HER2 amplification is used as a predictive biomarker to guide HER2-targeted therapies, patients may develop resistance to these therapies, often due to the acquisition of secondary mutations or changes in the tumor's molecular profile, further complicating treatment and prognostication (Slamon et al., 2001). This dynamic nature of cancer necessitates continuous monitoring and adaptation of treatment strategies, yet the current methods of biomarker testing often fail to capture the complexity of this evolution.

Furthermore, despite the promise of precision medicine, there are significant challenges in real-world implementation. While biomarkers have shown considerable success in clinical trials, their translation into everyday clinical practice remains problematic. The cost of comprehensive biomarker testing, including the use of advanced technologies such as next-generation sequencing (NGS), remains prohibitively high, especially in low-resource settings where access to molecular diagnostics is limited. Even in well-resourced healthcare systems, financial constraints and healthcare disparities often prevent the widespread adoption of these technologies. Additionally, the complexity of genomic data, the lack of trained personnel to interpret these results, and the uncertainty regarding which biomarkers to prioritize in clinical decision-making further complicate the integration of precision therapies into standard care (Turnbull et al., 2018). Many clinicians continue to rely on traditional chemotherapy regimen, not because they are the most effective option, but because of familiarity and the lack of infrastructure for more personalized, biomarker-guided treatments.

Moreover, the real-world application of immunotherapy, a central component of precision oncology, has not lived up to expectations in many solid tumors, particularly in cancers outside of the melanoma and NSCLC populations. While immune checkpoint inhibitors such as nivolumab and pembrolizumab have dramatically improved survival outcomes in certain cancer types, their success is not universal. The ability of cancer cells to avoid immune detection through mechanisms such as PD-L1 overexpression is not consistent across all tumors. Furthermore, even within tumors that express PD-L1, not all patients will respond to immune checkpoint blockade. The lack of

reliable biomarkers to predict which patients will benefit from these treatments is a major challenge in expanding the use of immunotherapies beyond a limited subset of cancers (Brahmer et al., 2015). The difficulty in identifying predictive biomarkers for immunotherapy further underscores the gap between the promise of immunogenomic profiling and its real-world implementation.

Finally, clinical trial failures and discrepancies between clinical trial outcomes and real-world results have contributed to the slow integration of biomarker-guided therapies into routine clinical practice. Despite the successes of several biomarker-driven treatments in clinical trials, the application of these treatments in diverse, real-world populations has often failed to replicate the results seen in controlled settings. A notable example is the use of panitumumab and cetuximab in colorectal cancer. While these anti-EGFR therapies have shown promising results in clinical trials for patients with wild-type KRAS, their effectiveness in real-world settings has been more variable, with some patients experiencing disease progression despite having a wild-type KRAS genotype (Van Cutsem et al., 2009). This discrepancy between clinical trial results and real-world outcomes reflects the challenges of applying biomarker-guided therapies in populations with greater genetic diversity, comorbid conditions, and variations in access to healthcare. These issues highlight the need for real-world evidence to complement clinical trial data and guide the widespread adoption of precision oncology.

1.3: Research Questions and Hypothesis

Research Questions

1. What is the current role of molecular biomarkers in guiding systemic therapy for solid tumors?

2. What are the main barriers to the widespread clinical implementation of biomarker-guided therapy in solid tumors?

3. How does intratumoral heterogeneity affect the accuracy and effectiveness of biomarker-based therapy in solid tumors?

4. What is the impact of biomarker-guided immunotherapy on clinical outcomes in patients with solid tumors?

5. What are the clinical and economic implications of integrating biomarker testing into routine cancer treatment in solid tumors?

6. How can emerging technologies, such as liquid biopsy and next-generation sequencing (NGS), enhance the application of biomarkers in the treatment of solid tumors?

Hypothesis

The research hypothesis postulated for this study is as follows; where

H1: Molecular biomarkers improve the clinical outcomes of patients with solid tumors by enabling more targeted and personalized therapy.

H2: The lack of standardized guidelines for biomarker testing and therapy selection limits the effectiveness of biomarker-driven approaches in real-world clinical practice.

H3: Tumor heterogeneity significantly reduces the accuracy of biomarker-based treatments, leading to a higher rate of treatment resistance and failure.

H4: The integration of biomarker-guided immunotherapy improves treatment response and overall survival in patients with solid tumors, especially those with high tumor mutational burden (TMB) and PD-L1 expression.

H5: Routine biomarker testing for solid tumors, when integrated into clinical care, offers long-term cost-effectiveness by reducing unnecessary treatments, improving patient survival, and decreasing hospitalizations.

H6: Emerging technologies, such as liquid biopsy and next-generation sequencing (NGS), will enhance the precision and efficiency of biomarker testing, leading to improved patient management in solid tumors.

1.4: Objectives of the Study

1. To evaluate the role of molecular biomarkers in the selection and efficacy of systemic therapies for solid tumors.

2. To identify and examine the emerging molecular biomarkers in solid tumors and their impact on clinical decision-making for targeted therapies.

3. To assess the integration of molecular biomarkers in precision oncology and its influence on patient stratification and treatment outcomes in solid tumors.

4. To explore the challenges and limitations associated with utilizing molecular biomarkers as predictive and prognostic tools in systemic therapy for solid tumors.

5. To analyze how the evolving landscape of biomarker-driven systemic therapy impacts resistance mechanisms and long-term patient survival in solid tumors.

6. To explore the role of multi-omics approaches (genomics, proteomics, transcriptomics, etc.) in refining the clinical utility of molecular biomarkers for systemic therapy in solid tumors.

7. To investigate the application of artificial intelligence and machine learning in improving the identification and clinical utility of molecular biomarkers for guiding systemic therapy in solid tumors.

8. To evaluate the economic and ethical implications of integrating molecular biomarkers into precision medicine strategies for solid tumors.

9. To compare real-world clinical outcomes with those derived from randomized controlled trials (RCTs) in terms of biomarker-driven treatment decisions for systemic therapies in solid tumors.

10. To propose novel methodologies for improving the predictive accuracy of molecular biomarkers for therapy response in different subtypes of solid tumors.

1.5: Significance of the Study

The relevance of this study lies in its potential to advance precision medicine, with a focus on solid tumor treatment. In recent decades, cancer treatment has evolved from a one-size-fits-all approach,

largely dependent on chemotherapy and radiotherapy, to more individualized therapies tailored to the genetic and molecular profile of both the tumor and the patient. This shift towards personalized oncology, driven by the identification of molecular biomarkers, has the potential to revolutionize the way solid tumors are treated, ultimately leading to better clinical outcomes, minimizing adverse effects, and enhanced quality of life for patients.

By examining the role of biomarkers in guiding systemic therapy, this study addresses the gap between the promise of biomarker-driven precision oncology and its real-world application. Despite the success of several biomarker-targeted therapies in clinical trials, their routine integration into clinical practice is hindered by significant barriers such as cost, lack of standardized guidelines, and the complexity of biomarker testing. This research will provide critical insights into the clinical utility of biomarkers, not only in selecting appropriate therapies but also in predicting treatment response, prognosis, and recurrence. By exploring the practical implications of implementing biomarker-guided treatments, this study will contribute to closing the gap between research and clinical practice, to ensure that more patients take advantage of the advancements in cancer treatment.

Furthermore, this study's focus on tumor heterogeneity and its impact on biomarker accuracy will significantly contribute to understanding the limitations of current biomarker applications. Tumors are often characterized by a high degree of genetic diversity, with different areas of the same tumor harboring distinct mutations and molecular characteristics. This intratumoral heterogeneity presents a unique challenge in applying a single biomarker across the entire tumor. By addressing how heterogeneity affects the effectiveness of biomarker-guided therapy, this study will help inform future strategies to overcome this challenge. For example, dynamic monitoring using liquid biopsies or serial tumor sampling could offer more accurate insights into tumor evolution and therapy resistance. These advancements will enable clinicians to tailor treatments more effectively and enhance patient outcomes.

In addition, the research will explore the economic implications of incorporating biomarker testing into routine clinical practice. While biomarker-guided therapies have shown improved outcomes, their widespread adoption has been limited by their high costs, particularly in nations with poor and medium incomes. This study seeks to evaluate whether the long-term benefits of incorporating

biomarker testing such as reduced treatment toxicity, earlier detection of relapse, and avoidance of ineffective treatments outweigh the initial investment. By evaluating the cost-effectiveness of biomarker-based therapies, the study will provide essential information for policymakers and healthcare providers seeking to make informed decisions about integrating these tests into standard cancer care. Moreover, it will help demonstrate whether the application of precision medicine offers substantial economic value through improved patient outcomes and overall healthcare savings.

Another significant aspect of the study is its exploration of the role of immunogenomic profiling in predicting patient responses to immunotherapy. Immunotherapies, particularly immune checkpoint inhibitors, have transformed the treatment landscape for cancers such as melanoma, lung cancer, and bladder cancer. However, the success of these therapies is not universal, and the ability to predict which patients will benefit from them remains one of the most important challenges in modern oncology. This study will provide a deeper understanding of how biomarkers like tumor mutational burden (TMB), PD-L1 expression, and microsatellite instability (MSI) can guide immunotherapy selection, potentially improving the response rates and overall survival in patients with solid tumors.

Ultimately, this study will contribute to the growing body of knowledge in biomarker-driven cancer treatment, helping to refine and optimize the use of biomarkers in clinical settings. By identifying barriers to their implementation and exploring strategies to overcome these challenges, this research will support the wider integration of biomarkers into routine clinical practice, thus advancing the goals of precision oncology. As precision medicine continues to evolve, the findings of this study could inform future clinical guidelines and facilitate the personalization of cancer care, offering hope for better, more targeted treatments that can improve patient survival rates and quality of life.

In addition to its contribution to clinical practice, this work is significant also because it has the potential to influence the way cancer is treated globally. As global cancer rates continue to rise, particularly in regions with limited access to advanced medical technologies, the findings of this study could help bridge the gap between cutting-edge cancer therapies and the populations that need them most. By focusing on biomarkers as a transformative tool, the study aims to make cancer

treatment more accessible, affordable, and effective for diverse populations, particularly in low-resource settings where the burden of cancer is growing disproportionately.

1.6: Scope and Limitations

Scope of the Study

This study will primarily focus on the application of molecular biomarkers in the treatment of solid tumors, specifically examining how these biomarkers guide systemic therapy in clinical practice. The research will explore the role of biomarkers in targeted therapies, chemotherapy, and immunotherapy, with a particular emphasis on their integration into routine clinical care. The scope includes the biomarkers used in common solid tumors like breast carcinoma, lung carcinoma, melanoma, and colorectal carcinoma, while also addressing the evolving role of immunogenomic profiling and emerging technologies like liquid biopsy and next-generation sequencing (NGS). The study will examine the clinical impact, economic implications, and barriers to the widespread adoption of biomarker-guided therapies, aiming to provide actionable insights for improving personalized cancer care.

Limitations of the Study

This study is not without its limitations. First, the research will primarily be based on secondary data from clinical trials, case studies, and literature reviews, which may introduce biases related to the availability and quality of published data. As a result, the findings may not fully capture the diversity of clinical practices across different healthcare systems and geographical regions. Additionally, the study will focus on well-established biomarkers in common tumor types and may not extensively address rare cancers or emerging biomarkers that have not yet been fully validated in clinical settings. Moreover, intratumoral heterogeneity remains a significant challenge in accurately assessing the effectiveness of biomarkers, and the study's conclusions regarding tumor variability may be influenced by the limitations of current diagnostic techniques. Finally, cost-related barriers to biomarker testing in low-resource settings will be acknowledged, but the study may not fully explore all economic challenges faced by healthcare providers worldwide.

Despite these limitations, the study will provide valuable insights into the state of biomarker-driven therapies in solid tumors and offer recommendations for enhancing their clinical application and integration into precision oncology.

1.7: Overview of Methodology

The methodology for this study will primarily involve systematic review and meta-analysis, focusing on existing research to investigate how biomarkers can direct systemic therapy for solid tumors. By synthesizing and analyzing data from relevant clinical trials, observational studies, and cohort studies, the study aims to evaluate the effectiveness and clinical impact of biomarker-driven therapies, while identifying barriers to their implementation in real-world settings. This approach will be efficient, rigorous, and suitable for addressing the research questions without the need for primary data collection.

Systematic Review Process

The initial phase of this research will involve performing a systematic literature review. This review will concentrate on research published in peer-reviewed publications that investigate the use of biomarkers in solid tumors and their role in precision oncology. The review will include randomized controlled trials (RCTs), cohort studies, and observational studies that examine biomarker-guided therapies for common solid tumors, including breast cancer, lung cancer, colorectal cancer, and melanoma. The inclusion criteria will emphasize studies that assess clinical outcomes such as overall survival, progression-free survival, treatment responsiveness, and adverse effects associated with biomarker-driven treatments.

A detailed literature search will be conducted in databases like PubMed, EMBASE, Cochrane Library, and Google Scholar, using keywords related to biomarkers, solid tumors, and precision medicine. The search will be narrowed to studies from the past 10 to 15 years to ensure that the data is current and relevant. The studies will be assessed for methodological quality, and only those meeting established quality standards will be included.

Meta-Analysis

Following the systematic review, a meta-analysis will be performed to quantitatively synthesize the findings from the selected studies. This process will allow for the aggregation of data from multiple studies, providing a more robust statistical estimate of the effect of biomarker-guided therapies on treatment outcomes. The meta-analysis will primarily focus on comparing biomarker-guided therapy with standard treatment regimens, looking at clinical outcomes such as survival rates, response rates, and the reduction in treatment-related toxicity.

A random-effects model will be employed to account for heterogeneity between studies, and statistical tests will be used to assess the variability between them. Sensitivity analyses will be performed to check the robustness of the results. Statistical methods, including Egger's test and funnel plots, will be employed to evaluate publication bias.

Data Extraction and Synthesis

Data from the selected studies will be extracted systematically, including patient demographics, tumor characteristics, biomarker types, treatment regimens, and clinical outcomes. The results will be synthesized to assess the overall effectiveness of biomarkers in guiding targeted therapies, chemotherapy, and immunotherapy for solid tumors. This synthesis will provide valuable insights into how biomarkers can be used to improve clinical decision-making and patient outcomes.

Overall, the systematic review and meta-analysis will offer a thorough overview of the function of biomarkers in precision medicine for solid tumors, evaluating both the clinical effectiveness and barriers to their use in routine clinical practice.

CHAPTER TWO

LITERATURE REVIEW

2.1: Introduction to Molecular Biomarkers and Solid Tumors in Cancer Diagnosis and Therapy

The role of molecular biomarkers in the diagnosis, prognosis and treatment of solid tumors is crucial. Molecular biomarkers such as genes, RNA molecules, proteins, and metabolic products are essential in the diagnosis, prognosis, prediction, and management of diseases. Advances in high-throughput sequencing technologies have led to a surge in omics data, facilitating the identification of molecular biomarkers. A molecular biomarker is defined as a molecule or group of molecules that exhibit distinct expression or concentration patterns between diseased and healthy states. To be considered credible, a molecular biomarker must be objectively measurable, significantly altered in a specific disease, and capable of distinguishing between diseased and healthy states.

A tumor, also known as neoplasm, is an abnormal tissue growth that can occur at any part of the body and can either be cancerous or non-cancerous. According to the National Cancer Institute, “tumor can also be defined as abnormal mass of cells in the body, and it can result from cells dividing more than normal or not dying when they should”. It is important to know the difference between a solid tumor and tumor. A solid tumor is a type of tumor, and while tumors can exist in various forms such as solid, liquid or cystic, solid tumors form a distinct, solid mass and while tumors can exist in various parts of the body, tumors exist in organs, glands and tissues. They are the most common form of cancer existing in humans. Therefore, it is safe to say all solid tumors are tumors, but not all tumors are solid tumors.

2.2: Classification of Tumors

Tumors are classified into cancerous and non-cancerous tumors. A cancerous tumor can also be known as malignant, while a non-cancerous tumor can be known as benign (Figure 2.1).

2.2.1: Benign Tumors

These are tumors that do not spread to other parts of the body; that is, they remain in their original location without invading other areas (Salarvand *et al*., 2024). Benign tumors are typically not as bothersome as malignant ones. But if they grow big, they may compress nearby structures, causing discomfort or other health issues (Karimi *et al*., 2023). According to Patel (2020), "an instance is a large benign lung tumor that could compress the trachea and result in difficulty in breathing". Such an instance by Patel (2020) would demand urgent surgical removal. Skin lipomas and uterine fibroids are common examples of benign tumors, which are most unlikely to return after removal.

It is important to note that some benign tumor types have the potential to develop into malignant ones; these would need to be surgically removed and would require continuous monitoring. As an illustration, consider colon polyps, which are just aberrant masses of cells that may develop into cancer and need to be surgically removed (Patel, 2020).

2.2.2: Malignant Tumors

These are tumor cells that spread both locally and to distant sites, and grow uncontrollably (Kumar et al., 2021). They spread through the bloodstream or lymphatic system to distant sites, and this spread is termed "metastasis". Although metastasis can occur anywhere in the body, the lungs, liver, brain, and bones are where it most frequently occurs (Patel, 2020). Malignant tumors can metastasize rapidly if not treated early, and the treatment will probably be systemic, including options like chemotherapy, radiation therapy, or immunotherapy (Kumar et al., 2021).

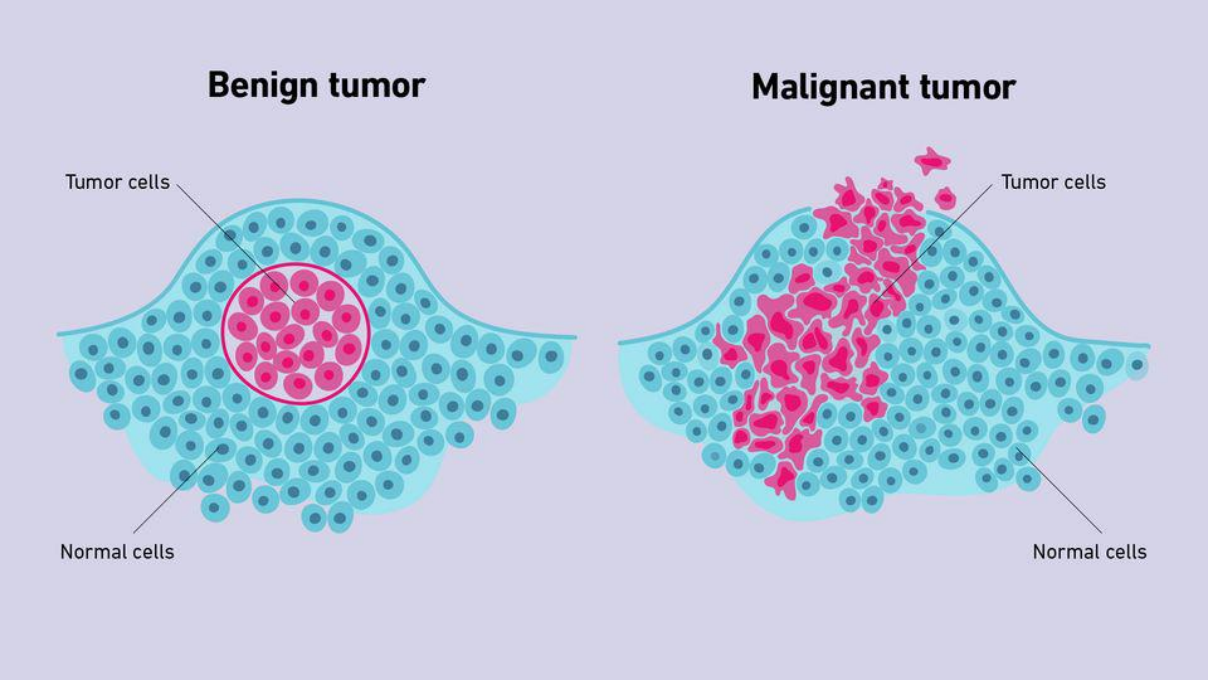

Figure 2.1 Benign and malignant tumor

Source:https://assets.technologynetworks.com/production/dynamic/images/content/364765/benign-vs-malignant-tumors-364765-1280x720.webp?cb=12746434 (Whelan, 2022).

2.3: Types and Causes of Tumors Based on Origin

Solid tumors can be classified into sarcomas, lymphomas, and carcinomas, amongst others depending on the cells they originate from (Souza *et al*., 2024; see Figure 2.2). The following are some forms of malignant tumors based on their tissue of origin:

1. Carcinoma- From epithelial tissue.

2. Lymphoma- From lymphatic tissue.

3. Leukemia- Cancer of blood-forming cells.

4. Sarcoma- Connective tissue.

5. Melanomas: Pigment-producing cells.

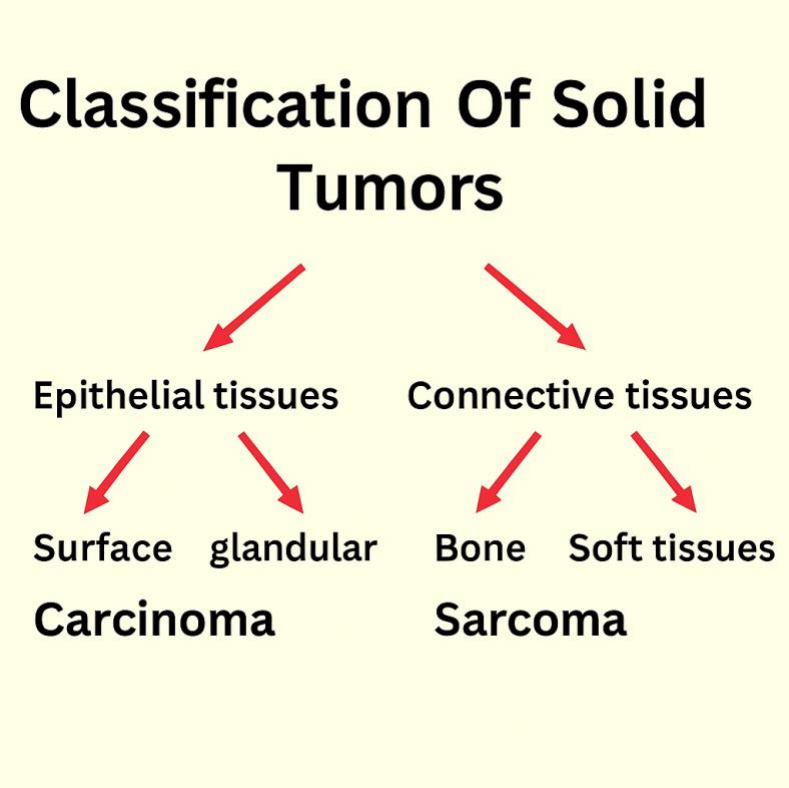

Figure 2.2 Classification of solid tumors.

Table 2.1: showing distinguishing features of carcinoma and Sarcoma

Carcinoma	**Sarcoma**
They originate from epithelial tissues and are the most common type of cancer.	They originate from connective tissues and/or muscles.
They are also called solid tumors.	They are a rare form of cancer.
Common sites include lungs, skin, breasts, uterus, mouth, colon, and stomach.	Examples include bone (osteosarcoma), and skeletal muscles (rhabdomyosarcoma).
They spread primarily through the lymphatic system.	They spread primarily through hematogenous route.

2.4: Overview of Precision Medicine

According to Vats and Kumar (2024), "Precision medicine, also known as personalized or stratified medicine represents a paradigm shift in healthcare that emphasizes customization of medical treatment to individual characteristics, including genetic makeup, lifestyle factors, and environmental influences". Conventional medicine, a contrast of precision medicine, often adopt one method for all patients, irrespective of their variability in disease susceptibility, progression, and response to treatment. Precision medicine, on the other hand, focuses on tailoring therapeutic interventions to meet the unique characteristics of each patient (Kasztura *et al*., 2019) – see figure 2.3. Examining how developments in proteomics, genomics, and other "omics" technologies have made it possible to conduct extensive molecular profiling at a scale never before possible (Vats & Kumar, 2024). Large volumes of data have been produced by the introduction of high-throughput technology, which could entirely transform the healthcare industry. However, traditional analytical techniques face considerable difficulties due to the richness and variety of these data (Vats & Kumar, 2024).

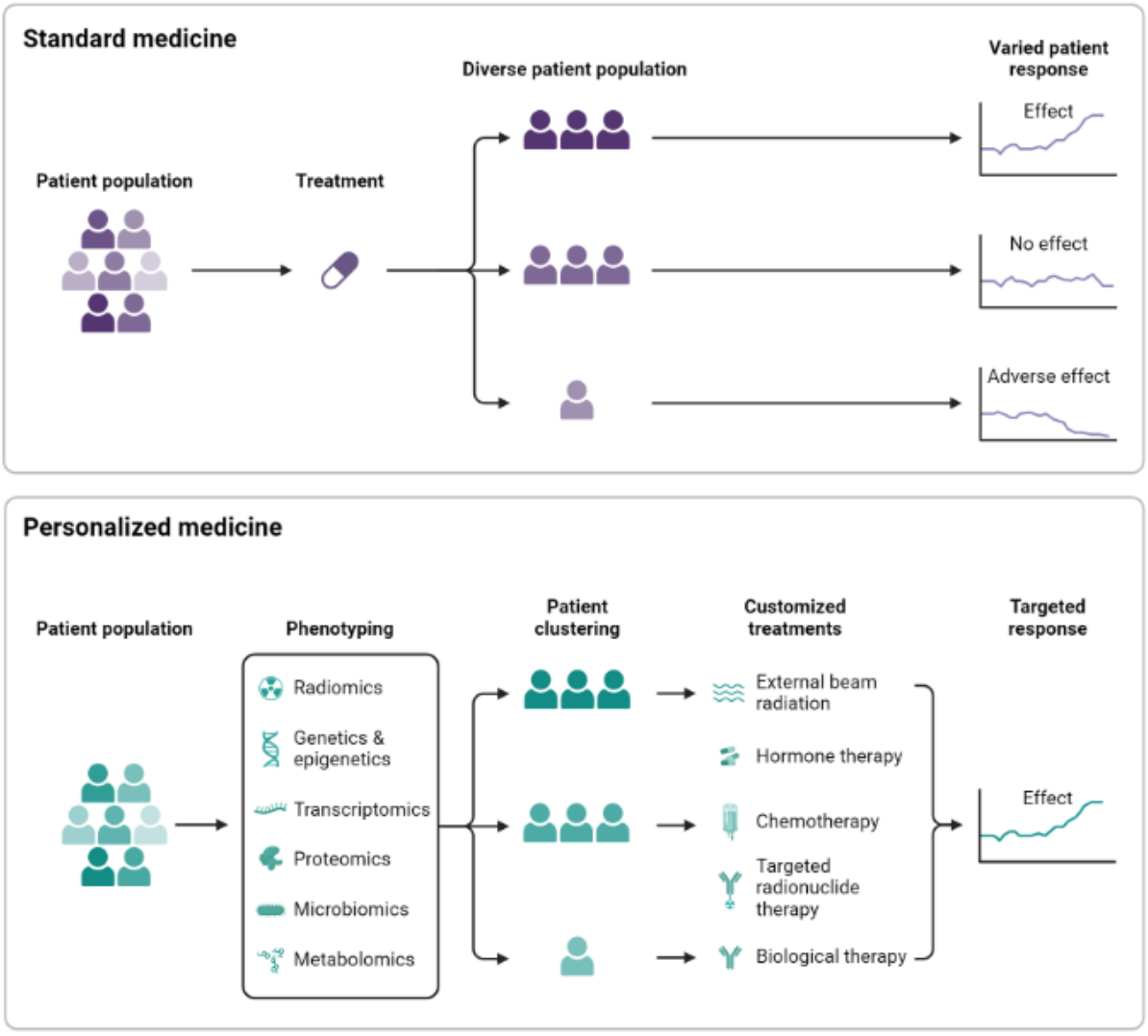

Figure 2.3: The layout of standard versus personalized medicine.

2.4.1: The Importance of Precision Medicine and its Application in Solid Tumors

The effectiveness of disease management in the future will be strongly influenced by how precision medicine is understood and successfully implemented. Precision medicine is the process of designing a treatment based on disease-driving molecular alterations. In the 15 years since its inception, next-generation sequencing (NGS) technology has supplied information about the genetic makeup of numerous cancer forms (Kim *et al*., 2017). Precision medicine has emerged

because of NGS's speed, accuracy, and affordability. A fairly high occurrence of potentially actionable genetic mutations in solid tumors, which are indicators of responsiveness to targeted and immunotherapy treatments, has been identified by WES/WTS-driven comprehensive molecular analysis (Hernandez-Camarero *et al*., 2021). Presently, WES/WTS blends tumor-normal matched samples and provides a single all-inclusive test to quickly deliver detailed molecular insight (>18,000 genes) without the need for many sequential panels. Oncology clinics, especially community-based clinics, now routinely use NGS and tumor mutation analysis as critical diagnostic and decision-making tools (Schwartzberg *et al*., 2017).

2.4.2: Biomarker Action and Immune Checkpoint Inhibition

The consideration of preventive medicine strategies is made feasible by the discovery of molecular biomarkers for illness. Thus, illness development may be postponed or avoided using medicines, therapies, or clinical care (Alturki, 2023). A family of medications known as immune checkpoint inhibitors (ICIs) are also used to treat cancer (Alturki, 2023). These medications enhance the immune system's capacity to more efficiently target and eliminate cancer cells. To gain insight into how the immune system and cancer cells interact, it is helpful to have some knowledge of these relationships (Alturki, 2023).

The immune system's job is to find and destroy abnormal cells, including malignant ones. This process depends on immune cells called "T cells" (Jhunjhunwala *et al.,* 2021; Okikiade, 2020). However, the immune system possesses "checkpoints" that act as brakes to prevent it from attacking healthy, normal cells (Jhunjhunwala et al., 2021). To start an immunological reaction, these T-cell surface proteins need to be activated (or inactivated) (Jhunjhunwala *et al*., 2021). Cancer cells may employ these checkpoints to prevent assaults by the immune system (Fife & Bluestone, 2008). According to Fife and Bluestone (2008), they have the capacity to produce proteins that interact with these checkpoints and effectively shut off T cells, allowing cancer to expand unchecked.

A number of malignancies may be treated with checkpoint inhibitors, especially those that have shown resistance to traditional/conventional therapies like chemotherapy or radiation (Shiravand *et al*., 2022). They are classified according to the target molecule that each of them possesses. As Table 2.2 below shows, they were initially licensed for different cancers in the USA and the EU

at different times, but it was later found that they were also effective in other locations (Shiravand *et al*., 2022).

2.4.3: The therapeutic use of biomarkers in directing the results of systemic treatment and providing evidence from clinical trials

2.4.3.1: Tumor-Agnostic Therapeutics Biomarkers

Targeting certain biomarkers that could exist in many tumor types and moving drug development in the direction of a tumor-agnostic strategy, as opposed to approvals being based on the origin of the tumor, have gained popularity in recent years. Pembrolizumab became the first tumor-agnostic medication authorized in the U.S. in 2017 for use in adult and pediatric patients with mismatch repair-deficient (dMMR) solid tumors or MSI-H malignancies that were metastatic or incurable (Schwartzberg *et al*., 2017).

Larotrectinib, entrectinib, dostarlimab, dabrafenib/trametinib, and selpercatinib are among the several cancer treatments that have received tumor-agnostic authorization after this historic approval (see Table 2.2).

Drug	**Biomarker**	**Tumor-agnostic indication**	**FDA approval date for tumor-agnostic indication**
Pembrolizumab (Keytruda®)	MSI-H/dMMR	Therapy for solid tumors in children and adults that have spread after other treatments, are metastatic or incurable, and for which there are no suitable alternatives.	May 2017
Larotrectinib (Vitrakvi®)	NTRK gene fusion	Therapy for solid tumors in children and adults that: -have an NTRK gene fusion without a known mutation that results in acquired	May 2020

		resistance. -have no effective substitute therapy or that has gotten worse after treatment or are metastatic or in cases where surgical excision is expected to cause serious morbidity.	
Entrectinib (Rozlytrek®)	NTRK gene fusion	Treatment of solid tumors in adults and children aged 12 and above that: -have an NTRK gene fusion, as determined by an FDA-approved test without a known acquired resistance mutation. -are metastatic or where surgical resection is likely to cause significant morbidity. -have either progressed after treatment or have no adequate alternative therapy.	June 2020
Pembrolizumab (Keytruda®)		Treatment of TMB-H (≥10 mutations/Mb) solid tumors in adults and children that are unresectable or metastatic, have progressed after previous treatment, and have no adequate substitute treatment choices.	June 2020
Dostarlimab-gxly (Jemperli®)	dMMR	Therapy for adult patients with advanced solid tumors or dMMR recurrent tumors	August 2021

		that have progressed during or after previous treatment and for whom no adequate substitute therapeutic choices are available.	
Dabrafenib (Tafinlar®)/Trametinib (Mekinist®)	BRAF V600E mutation	Treatment of solid tumors with the BRAF V600E mutation that are unresectable or metastatic in adults and children aged ≥6 years and that have progressed after previous treatment and for which there are no adequate substitute treatment alternatives.	June 2022
Selpercatinib (Retevmo®)	RET gene fusion	Therapy for adult patients with locally advanced or metastatic solid cancers that have progressed during or after previous systemic treatment, or who have no viable alternative therapeutic choices.	September 2022

2.5: Biomarkers

The National Cancer Institute (2020) defined a biomarker as "a biological molecule found in blood, other body fluids, or tissues that symbolizes normal or abnormal process, or a condition or disease". According to Tang *et al.* (2022), "Biomarkers are referred to as biochemical indicators that can detect the changes or potential changes in the structure and function of cells and subcellular structures of systemic organs and tissues". Tang *et al.* (2022) also stated that "Biomarkers can be referred to as biochemical indicators that can mark the changes or possible changes in the structure or function of cells and subcellular structures of systemic organs and tissues". Fang and Chen (2020) defined biomarkers as "any quantifiable characteristics that marks the presence and/or absence of disease or the biological response to a stimulus, particularly an

exposure or intervention". Typically, biomarkers differentiate a person with traces of diseases from one with none. The alteration is caused by several factors, including somatic mutations or germline, post-translational modifications and transcriptional changes (Henry & Hayes, 2012).

Biomarkers exist in various forms, such as proteins (including enzymes and receptors), nucleic acids (such as microRNAs or other non-coding RNAs), peptides, and antibodies, among many others (Agboola et al., 2023). A biomarker can be a group of these changes, including gene expression, metabolomic signatures, and proteomic. Beyond being detected as mutations in tumor-derived DNA, biomarkers may also be inherited genetically and identified as variations in germline DNA obtained from sources such as sputum, peripheral blood, or buccal epithelial cells. Biomarkers are easily measured using non-invasive techniques that enable repeated assessments or through invasive procedures like biopsies or specialized imaging tests for evaluation (Henry & Hayes, 2012).

2.5.1: Types of Biomarkers

Exposure biomarkers and disease biomarkers are the two main categories of biomarkers. While disease biomarkers are used for disease monitoring, screening, and diagnosis, exposure biomarkers are used to anticipate a disease. Additionally, predictive biomarkers may be able to forecast an individual's level of vulnerability to a disease.

2.5.1.1: Predictive Biomarkers

A certain protein or gene may serve as a predictive biomarker that indicates susceptibility or resistance to a given cancer treatment. Predictive biomarkers are being utilized more and more in cancer treatment because they can anticipate how a patient will react to a medication or therapy, allowing for the adoption of better treatments to help patients respond favorably to those treatments. Progesterone and estrogen receptor (ER) expressions can be utilized as predictive biomarkers to assess the benefits of cancer treatment. Using predictive biomarkers in cancer therapy has various benefits, including reducing needless side effects, enhancing patient management, and reducing time lost in identifying the most effective treatment that will have positive effects on cancer treatment (Kirilovsky *et al*., 2016).

2.5.1.2: Prognostic Biomarkers

Prognostic biomarkers are used to detect when a disease is developing. Tumor size, lymph node involvement, and metastasis are the most often utilized prognostic indicators in cancer cases. A certain form of cancer has certain prognostic biomarkers. For instance, progesterone, HER2, and increased estrogen levels are employed as prognostic indicators in individuals with breast cancer. Prognostic biomarkers can also be produced by specific mutations that activate and repress tumor-suppressing genes and oncogenes (Dalerba *et al*., 2016).

2.5.1.3: Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers in oncology are frequently utilized to identify the most appropriate therapeutic approach for a particular type of cancer. Due to genetic variations, each person metabolizes medications differently, and in certain instances, a slower metabolism of certain pharmaceuticals can result in harmful scenarios where high quantities of the drug accumulate in the body. Consequently, screening for these biomarkers can help determine the dosage of medications, especially most cancer remedies (Toffoli *et al*., 2006). For example, the TPMT gene encodes the enzyme thiopurine methyltransferase (TPMPT), which prevents individuals with mutations from metabolizing significant amounts of the leukemia medication mercaptopurine. This surely results in a dramatic drop in the white blood cell count of these patients (Ross *et al*., 2009).

2.5.2: Tumor Biomarkers

Disease analysis, which occurs after a person has been diagnosed with cancer, is the most significant application of biological markers in cancer medicine. Biomarkers are useful for assessing the severity of cancer that has been diagnosed as well as the likelihood that it will respond to prescribed medication. This is due to the fact that certain tumors have exact biomarkers that can be utilized to learn about treatments linked to their particular expression. Metallopeptidase inhibitor 1 (TIMP1), a biomarker associated with myeloma (a kind of malignancy), is one example of such predictive biomarkers. It increases the expression of progesterone receptors (PR) and/or estrogen receptors (ER) (Diaz *et al*., 2006).

In patients with breast cancer who are likely to respond to trastuzumab therapy, biomarkers are linked to improved survival (Norden-Zfoni *et al*., 2007). Alterations in the tyrosine kinase domain of EGFR1, a biomarker associated with non-small-cell lung cancer (NSCLC), often predict a positive response to treatment with erlotinib or gefitinib (Pegram *et al.,* 2000). Similarly, the presence of a distinct biomarker linked to gastrointestinal stromal tumors (GIST) suggests potential responsiveness to imatinib therapy (Norden-Zfoni *et al*., 2007). Despite the widespread use of biomarkers in cancer epidemiology, little is known about the methodological elements of their application.

Biomarkers have played a prominent role in epidemiological studies, with substantial input from textbooks and comprehensive conference reports. Nevertheless, there remains a strong demand for further methodological research, expanded dialogue, and deeper comprehension of related methodological challenges to better integrate biomarkers into both formal education and informal training of cancer epidemiologists and other researchers focused on cancer biology (Burton *et al*., 2009).

Additional uses for cancer biomarkers include monitoring the effectiveness of a treatment over time in preventing a specific malignancy. Due to the high cost of traditional photo-based tests like computed tomography (CT) and magnetic resonance imaging (MRI) for tracking tumor prevalence, a great deal of research is being conducted in this special field because successful biomarkers have the ability to significantly reduce the cost of patient care (Das *et al*., 2024).

These biomarkers may be collected from bodily fluids, including serum, blood, urine, and oral secretions (Metcalf, 2024). There are multiple techniques for identifying candidate biomarkers. The traditional approach mostly relies on the biological characteristics of the tumor, the patient's environment, or the metabolic processing of the medication. A cancer biomarker is a biological molecule released by cancer cells or a body-specific response given in the presence of cancer.

With the advent of a new era, malignancies, and the explosion of new technology, biomarkers are now commonly obtained utilizing a variety of techniques, including mass spectroscopy, gene expression arrays, and excessive throughput sequencing, to provide patients with prompt knowledge (Wu & Qu, 2015). When a normal cell transforms into a cancer cell, the receptor proteins on its surface change into cancer biomarkers, as shown in figure 2.4 below.

A number of significant biomarkers are widely employed in the diagnosis of cancer. The following are these biomarkers: MGMT, or methyl guanine-DNA methyltransferase: The repair defects in the DNA sequence are linked to this protein biomarker.

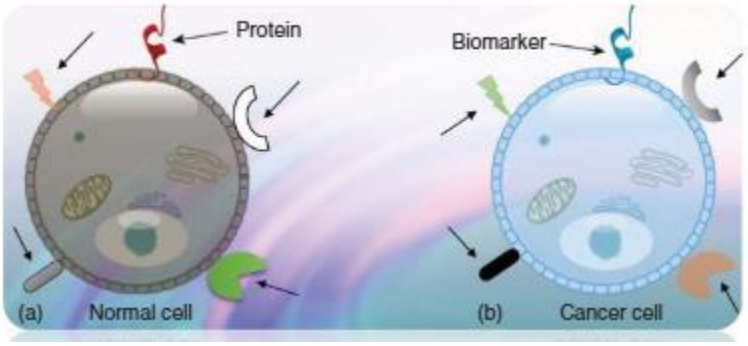

Figure 2.4 Different biomarkers are present on the surface of cancer cells.

Source:https://www.researchgate.net/profile/Ayesha-Taj-2/publication/339281990/figure/fig2/AS:882804611100672@1587488429161/Different-biomarkers-present-on-the-surface-of-cancer-cells-Source-From-https.png

2.5.3: Tumor-specific Biomarkers

No.	Biomarker	Type of cancer	References
1	AFP	Hepatocellular carcinoma	Prat, 2014
2	BCR-ABL	Chronic myeloid leukemia (CML)	Claudiani *et al.*, 2017
3	CA19.9	Pancreatic cancer	Barnett *et al.*, 2017
4	CEA	Colorectal cancer	Primrose *et al.*, 2014
5	EGFR	Non-small-cell-lung carcinoma (NSCLC)	Janne *et al.*, 2015
6	HER-2	Breast cancer	Ramasamy *et al.*, 2017
7	BRCA1/BRCA2	Breast/Ovarian cancer	Petrucelli, 2016

8	BRAF V600E	Melanoma/colorectal cancer	Vakiani *et al*., 2015
9	CA-125	Ovarian cancer	LaVigne *et al*., 2017
10	KIT	Gastrointestinal stromal tumor (GIST)	Boikos *et al*., 2016
11	PSA	Prostate cancer	Heidenreich *et al*., 2014
12	S100	Melanoma	Uslu *et al*., 2017

2.5.4: Uses of Biomarkers in Solid Tumors

In diverse clinical scenarios, biomarkers are utilized to assess patients by estimating disease risk, detecting occult primary cancers, differentiating benign versus malignant lesions, distinguishing between various malignancies, recognizing relapses, and evaluating therapeutic responses. Importantly, some biomarkers are exclusively utilized in a particular context, whilst others have several uses. The table below describes the different settings.

2.5.4.1: Potential Uses for Cancer Biomarkers

Use	**Example**	**Reference**
Estimate risk of cancer development	BRCA1 germline mutation (breast and ovarian cancer)	Easton *et al.,* 1995. Hall *et al.,* 1990.
Screening	Prostate specific antigen, PSA (Prostrate cancer)	Lin *et al.,* 2008.
Differential diagnosis	Immunohistochemistry to determine tissue of origin	Lin *et al.,* 2008.
Predict response to therapy	KRAS mutation and anti-EGFR antibody (colorectal cancer)	Allegra *et al.,* 2009.

	HER2 expression and anti-Her2 therapy (breast and genetic cancer)	Bang *et al.,* 2010. Piccart-Gebhart *et al.,* 2005; Romond *et al.,* 2005.
Monitor for disease recurrence	CEA (colorectal cancer)	Locker *et al.,* 2006.
	AFP, LDH, βHCG (germ cell tumor)	Gilligan *et al.,* 2010.
Monitor for response or progression in metastatic disease.	CA15-3 and CEA (breast cancer)	Harris *et al.,* 2007.

2.6: Methods for Identifying Molecular Biomarkers

DESeq2 and edgeR are widely used methods for identifying differentially expressed genes (DEGs) from RNA-sequencing data. While these methods have successfully identified thousands of DEGs associated with specific diseases, the number of molecular biomarkers required for clinical applications should be relatively small. To narrow down the list and identify reliable molecular biomarkers, additional statistical and data mining techniques are employed. Potential biomarkers are screened and selected through techniques including support vector machines (SVM), partial least squares discriminant analysis (PLS-DA), least absolute shrinkage and selection operator (LASSO), and recursive feature elimination (RFE) (Tang *et al.* 2022). The table below shows the various methods of identifying molecular biomarkers.

Methods	**Description**	**Applications**	**References**
DESeq2	This method involves the use of shrinkage examination for differential expression analysis of count data.	Quantitative analysis of comparative RNA-seq data using shrinkage estimators	Love *et al*., 2014

		for dispersion and fold change.	
edgeR	For examining differential expressions of replicated count data.	Used in analyzing count data from replicated RNA seq experiments.	Robinson *et al*., 2010
SVM (Support Vector Machine)	A machine learning algorithm to build a classifier.	Classify cancer subtypes based on genomic data.	Boser *et al.*, 1992
PLS-DA (Partial Least Squares Discriminant Analysis)	A regression-based method for classification and variable selection.	Modeling and predicting disease states or treatment responses from complex biological data.	Lee & Liong, 2018
LASSO (Least Absolute Shrinkage and Selection Operator)	A regression technique for variable selection and regularization to enhance prediction accuracy by shrinking coefficients.	Selecting key predictive biomarkers or variables in high dimensional genomic datasets.	Tibshirani, 1996
RFE (Recursive Feature Elimination)	Selection method that recursively removes the least important variables to improve model performance, often combined with SVM.	Selecting the most relevant genes or features to improve classification accuracy in cancer genomics.	Guyton *et al*., 2002

2.6.1: Deficiencies of Molecular Biomarkers

Traditional molecular biomarkers have limitations and shortcomings, particularly in terms of accuracy and reliability. One major issue is that these biomarkers often focus on individual molecules or genes, neglecting the complex interactions and associations between them. This oversight can hinder robust diagnosis and understanding of complex diseases, which frequently arise from disruptions in molecular networks or pathways. Moreover, disease progression is a dynamic process, and traditional biomarkers typically fail to account for the changes that occur over time (Fang & Chen, 2020). To address these challenges, there is a growing need for biomarkers that incorporate network and dynamic information, enabling a more comprehensive characterization of complex biological systems (Wu *et al*., 2014).

2.6.2: Dynamic Molecular Biomarkers and Networks

2.6.2.1: Biomarkers of Network Molecules

Although molecules are fundamental cellular components and molecular biomarkers play a key role in disease development and progression, complex diseases are frequently influenced by a network of molecules rather than by an individual molecule alone (Fang & Chen, 2020). In fact, there are many other causes of illnesses; changes in chromatin, RNA splicing, cell signaling, epigenome control, protein homeostasis, or metabolism are all likely to cause diseases (Garraway & Lander, 2013). These changes cannot be explained by single molecules since they are impacted by the varied interactions and correlations of molecule pairs. Systems biology, which examines all elements within a biological system and their interactions under specific conditions, arises from viewing disease within an organism as a dynamic and interconnected process (Clarke, 2017). Instead of using individual molecular biomarkers to characterize biomedical phenotypes or diseases, network or modular biomarkers made up of multiple interacting molecules with comparable performance could offer a more stable and quantifiable method, which would promote network-level systems biology research (Boser *et al*., 1992). As a result, combining biological data via computer modeling and using high-throughput omics data to uncover molecular interactions or build their networks would help us comprehend the biological system better. Network biomarkers may be used to enhance the research of biomarkers for uncommon illnesses by

addressing the challenges associated with sample collection. Furthermore, network biomarkers may be effectively identified from a single sample using a multi-dimensional omics analysis.

2.6.2.2: Molecular Biomarkers that are Dynamic

The primary application of molecular and network biomarkers is to compare disease states with healthy ones. However, compared to the normal state, there is often little to no significant change at the molecular level in the pre-disease state prior to the onset of the illness. There is mounting evidence that the disease system is one of many biological processes that exhibit abrupt or non-smooth state changes (Liu *et al.*, 2019). The system progressively transitions from the pre-disease condition to the normal state over the course of a complicated illness, and then it quickly moves into an irreversible disease state. Therefore, identifying the key condition or pre-disease state would be required to achieve an early diagnosis of a complicated illness in order to stop the disease from rapidly progressing to its full form (Liu *et al.,* 2013). To overcome this issue, the dynamic network biomarker (DNB) approach was developed, which is based on nonlinear dynamic systems theory and utilizes the network structure along with dynamic fluctuations in the data. A DNB represents a group of molecules linked through their correlations and shared variability.

2.6.2.3: An Overview of Network Biomarker Analysis Techniques

Methods	**Description**	**Applications**	**References**
PPI (Protein-Protein Interaction)	Uses known protein-protein interactions and differentially expressed genes to infer edge biomarkers.	Improves disease classification accuracy by incorporating biological interaction context.	Boser *et al*., 1992
EdgeBiomarker	Builds an individual specific network using a single	Enables personalized diagnosis by capturing unique molecular	Boser *et al*., 1992

	sample's expression data, integrating both edge (interaction) and node (gene) features.	interactions per individual.	
SSN (Single Sample Network)	Constructs personalized molecular networks from individual expression profiles.	Clarify the molecular processes driving complex diseases on an individual basis through a systems-level analysis.	Boser *et al*., 1992
P-SSN (Partial SSN)	Refines SSNs by removing indirect molecular associations, focusing on direct interactions.	Supports precise driver gene prediction, disease subtyping, and single-cell analysis.	Boser *et al*., 1992
TRFBA (Transcriptional Regulatory Flux Balance Analysis)	Integrates transcriptional regulation with metabolic models using perturbation-based expression data.	Enhances the predictive power of metabolic models, such as forecasting cell growth rate under various conditions.	Boser *et al*., 1992
SCS (Single-sample Controllability-based Strategy)	Combines mutation and expression data to identify individual-specific driver mutations using network control theory.	Enables personalized mutation profiling and understanding of disease control points.	Boser *et al*., 1992

CSN (Cell-Specific Network)	Builds a gene interaction network for each single cell from scRNA-seq data.	Facilitates cell clustering and trajectory analysis by highlighting gene regulation at single-cell resolution.	Boser *et al*., 1992
c-CSN (Corrected CSN)	Removes indirect gene associations to focus on direct gene-gene regulatory links.	Assesses developmental potency and guides cell differentiation pathway analysis.	Boser *et al*., 1992
NBSBM (Network-Based Sparse Bayesian Machine)	A probabilistic machine learning model based on sparse Bayesian inference in a network context.	Predicts drug sensitivity and elucidates drug mechanisms of action.	Liu *et al*., 2019

2.5.2.4: Overview of Analysis Methods for Dynamic Network Biomarkers

Methods	Description	Applications	Reference
DNB (Dynamical Network Biomarker)	Detects pre-disease states by analyzing correlations and fluctuations among molecules in a network.	Identifies critical transitions in disease development from population-level data.	Liu *et al*., 2019
sDNB (Single-sample DNB)	Adapts the DNB method to individual samples using single-sample network construction.	Enables early disease detection at the individual level.	Liu *et al*., 2019
I-DNB (Individual DNB)	Constructs local modules in single-sample networks to identify relevant biomarker sub-networks.	Improves accuracy in identifying individual-specific critical transitions.	Liu *et al*., 2019
Pathway-Induced DNB	Integrates known biological pathways to refine network structure and highlight functionally relevant interactions.	Detects DNBs responsible for disease progression using biologically informed optimization.	Liu *et al*., 2019
Metaheuristic optimization method for DNB	Uses multi-objective optimization to find the smallest, most	Identifies minimal gene sets with early	Coleto-Alcudia & Vega-Rodríguez, 2021

	predictive DNB networks based on multiple criteria.	and strong predictive signals for disease.	
Ic Index (Single-cell DNB marker)	Proposes a novel early-warning signal (Ic) that captures changes in the structure of single-cell gene expression data as disease progress.	Predicts early transitions in complex biological systems using single-cell expression data.	Liu *et al*., 2019

2.7: Molecular Biomarker Applications

The bulk of research has been on regulating molecular biomarker networks rather than using individual edges or networks themselves as standalone biomarkers, and the use of network biomarkers in uncommon illnesses is still comparatively restricted. For instance, to better understand the etiology of Hirschsprung's disease (HSCR), Liu *et al*. (2019) focused on investigating the PAX6 interaction network during enteric nervous system development. They demonstrated that NF-κB and STAT3 cooperate to control the immune response genes. In addition, they developed a detailed co-regulatory network involving microRNAs and transcription factors to further investigate multiple sclerosis (Liu *et al*., 2019).

Network biomarkers have been used to analyze biological phenotypic issues and the onset and progression of illnesses that standard molecular biomarkers are unable to explain in common complicated diseases that have been investigated more thoroughly (e.g., cancer). For example, a study investigating the differences between estrogen receptor (ER)-negative and ER-positive breast cancers analyzed the relationships between molecular pairs within the kinase regulatory network to identify kinase-substrate nodes and edge biomarkers, demonstrating their potential as prognostic potentials (Liu *et al*., 2019). Kinase network analysis was utilized in a Chinese colorectal cancer (CRC) cohort study to uncover notable differences between primary colorectal

cancers and related liver metastases. Additionally, kinase-substrate network analysis allowed for the acquisition of customized tumor responses through invivo xenograft drug testing (Liu *et al*., 2019). Network biomarkers may be employed for genetic robustness research as well as disease mechanism research. A gene modular network (GMN) was constructed by Liu *et al*. (2019) using Drosophila expression data. Subsequently, they conducted an asymptotic dynamics analysis on the GMN, demonstrating that a morphogen-directed GMN can withstand the majority of genetic perturbations and is essential for accurate tissue pattern formation (Liu *et al*., 2019).

2.7.1: Biomarkers for the Diagnosis, Prognosis, and Detection of Cancer

The unchecked cell growth that characterizes cancer is caused by genetic changes that promote cell survival and proliferation (Cho, 2007). Mutations in the genes that regulate proto-oncogenes, DNA repair, and tumor suppression contribute to the development of cancer by disrupting the processes that cause cell death and regulate proliferation. Epigenetic changes including DNA methylation and changed histone patterns also have an impact on the development of cancer. The many types of biomarkers and how they are detected are covered in this section.

2.7.1.1: Biomarkers in Biofluids

Diseases may be promptly assessed and monitored with the use of biofluids (Siravegna *et al.,* 2017). Biofluids such as sweat, blood, urine, and saliva may all provide crucial information about the disease under investigation. These biofluid samples are easy to extract non-invasively and are ideal for clinical research (Pantel & Alix-Panabieres, 2010). Saliva, which is readily accessible, contains electrolytes including sodium, potassium, bicarbonate, calcium, magnesium, and phosphate ions, while urine comprises sodium, potassium, urea, and chloride. Each biofluid has its own benefits and disadvantages. Sodium, chloride, minerals, lactic acid, and urea are the primary components of sweat (Tan *et al*., 2019).

Urine, saliva, blood, and cerebrospinal fluid (CSF) are among the biofluids used in cancer diagnosis and monitoring (Bardelli & Pantel, 2017). Research has shown that salivary mRNA contains biomarkers for KRAS, MBD3L2, ACRV1, and DPM1 that may be used to identify pancreatic cancer with excellent specificity (Tan *et al*., 2019). Salivary biomarkers like calprotectin, AZGP1, and HP have shown high sensitivity and specificity in identifying lung

cancer. Additionally, salivary DNA can disclose mutations in genes such as PI3K, CDKN2A, FBXW7, HRAS, and KRAS in oral and throat cancers (Gahan & Stroun, 2010).

Finding cancer biomarkers in biofluids may be accomplished by a variety of methods, including proteomics (mass spectrometry, ELISA, and Western blotting), lipidomics (mass spectrometry), and genomics (qPCR, RNA, and DNA sequencing). Surface-enhanced laser desorption/ionization (SELDI), 2-dimensional gel electrophoresis (2-DE), differential gel electrophoresis (2D-DIGE), and liquid chips are some of the techniques used for protein extraction and separation. Proteins are identified using mass spectrometry and bioinformatics, and the findings are verified using Western blot and ELISA. Challenges in biomarker discovery include sample variability, inter-laboratory analytical variability, and sample type selection. Numerous investigations have examined the detection of hypermethylated DNA fragments linked to cancer in the circulating free DNA (cfDNA) of cancer patients, particularly in instances of gastric cancer (GC). RPRM, XAF1, and a combination of KCNA4 and CYP26B1 are among the hypermethylated genes that have shown good diagnostic value for gastric cancer detection. A few technological problems need to be addressed before these tests may be used in clinical settings. Most investigations utilize DNA sequencing or methylation-specific PCR (MSP) after sodium bisulfite treatment; however, these techniques may provide false-positive findings owing to incomplete conversion of unmethylated cytosine residues. The figure below displays the sensitivity of many biofluid detection methods.

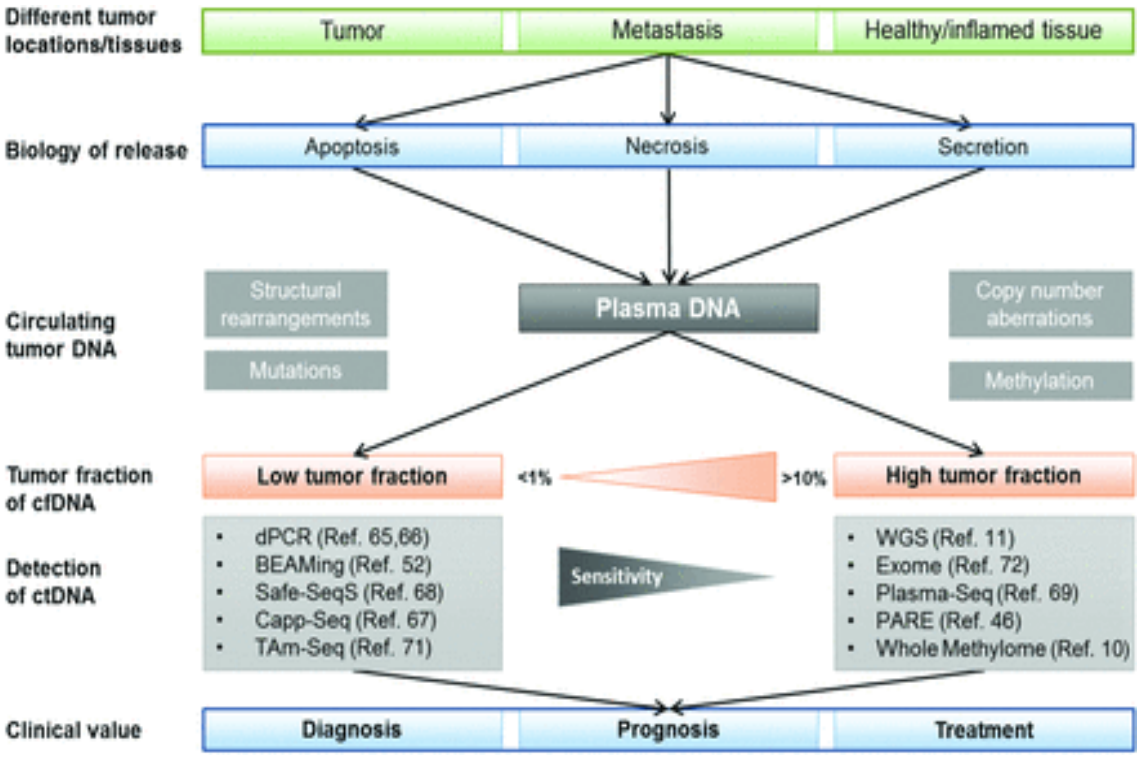

Figure 2.5: Schematic representation of liquid biopsy as a tool for cancer monitoring.

Source:https://oup.silverchair-cdn.com/oup/backfile/Content_public/Journal/clinchem/61/1/10.1373_clinchem.2014.222679/5/m_zcy00115141200 03.gif?Expires=1756184578&Signature=KgA0X4ksavye7E0US5Qwtwyrmo9INybmhVKIaoUHKQCxGAXlQzcTl KPnKYgaS56shJTaMpN-8SUFwJZPr7przW63yPp1iv2lE-ML7MlrjmqIrUFCByXBASjOzMHRulYXDipieVm-p00dr6RUDbyYuBJ6AF21lnGwxY4k2nenOBj46Rsah444znrIAiUof3T557G2eyBUfGom~dKoGwKf2hRQoK1j0rl K7txsGXC9nffqidm0H~~f4IBUD9zEwFgw7n11d1OTpl8co6NQIlkuYn7K7Ck5j8VxkYBa~8Vr6R~HyVzAkbRW PiIoY5XZqrN0MBsE1Bdx1kPLvxzIRnsdRg__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA

(Heitzer et al., 2015)

2.7.1.2: Biomarkers for Imaging

Key imaging biomarkers (IBs) essential in clinical oncology include tumor size, lymph node involvement, metastasis (TNM) staging, objective treatment response, and left ventricular ejection fraction (Barker *et al.*, 2009). Techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are frequently used in cancer studies. Emerging imaging biomarkers must be validated and certified to bridge translational gaps (Blagg & Workman, 2017). To speed up the clinical translation of IBs, the

European Organization for Research and Treatment of Cancer (EORTC) and Cancer Research UK (CRUK) have issued a total of 14 significant recommendations (Prat, 2014). These proposals for achieving imaging biomarkers certification emphasize precision assessment, alternative validation frameworks, standardization, accreditation systems, cost-effectiveness analysis, parallel validation processes, and multicenter research (Prat, 2014).

Imaging biomarkers (IBs) are developed using medical images and play a key role in patient care. They provide methods for tracking patient progress, tumor identification, therapeutic response, and non-invasive, affordable screening (Prat, 2014). To provide a structured categorical indication of the patient's disease severity, staging approaches capture tumor presence, size, and the number of abnormalities in the tumor, lymph nodes, and distant metastatic locations. IBs can evaluate a person's many lesions, map tumor heterogeneity, and track changes in tumors over time (Prat, 2014).

For the diagnosis and prognosis of cancer, staging methods are essential for evaluating lesions at tumor, nodal, and metastatic locations. The American Joint Committee on Cancer (AJCC) provides guidelines for accurate and reliable radiological reporting. For several cancer forms, TNM staging is widely utilized and has prognostic significance. Imaging modalities such as CT, MRI, SPECT, and PET form its foundation. Sometimes treatment results may be predicted using TNM staging. For example, by distinguishing between locally progressed and localized illnesses, the clinical TNM stage in prostate cancer acts as a prognostic biomarker for the effectiveness of bicalutamide monotherapy (Bardelli & Pantel, 2017). IBs are now used in clinical settings after a successful translation. Response criteria such as WHO, RECIST 1.0, and 1.1 are used to assess solid tumors. One well-known biomarker that has been translated and applied to clinical and pharmaceutical approval processes is objective response (Prat, 2014). The idea of objective response has been optimized for specific tumor-therapy combinations in research investigations. It is possible to compare different biomarker iterations in order to evaluate their predictive value for significant clinical outcomes. IBs play a crucial part in this, as the picture below illustrates.

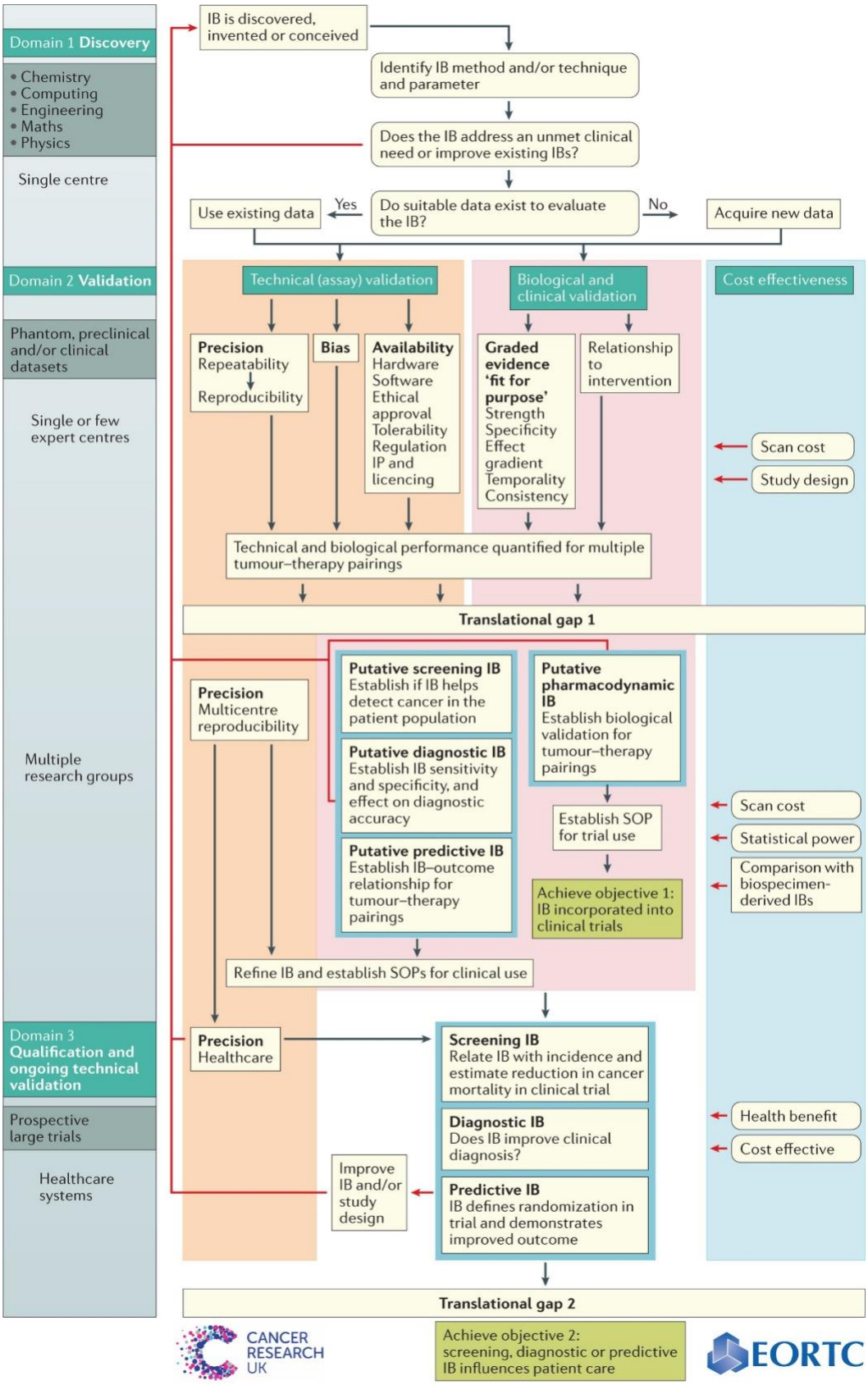

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Figure 2.6: The imaging biomarker roadmap.

Source:https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fnrclinonc.2016.162/MediaObjects/41571_2017_Article_BFnrclinonc2016162_Fig2_HTML.jpg (O'Connor *et al*., 2017)

2.7.1.3: Biopsy of Needles

According to Gupta *et al*. (2003), imaging tests are crucial for both detecting and monitoring cancer. These tests use a range of energy sources, such as magnetic fields, radioactive particles, sound waves, and X-rays, to produce incredibly precise images that offer vital information on the location and nature of the tumor (Ben-Yehuda *et al*., 1996). It is critical to remember that imaging tests may have limitations. Their results are inconclusive and equivocal because they are unable to pinpoint specific cancer cells. Typically, biopsies are used to confirm imaging results (Pappa *et al.,* 1996).

A cancer biopsy is a diagnostic technique used to identify the type and properties of tumor cells as well as to confirm or rule out the presence of cancer. According to the exact location and ease of access to the suspicious region, biopsy procedures can be performed using various methods such as surgical, endoscopic, and needle biopsies (Ben-Yehuda *et al.,* 1996). The results are essential for making further medical decisions (tumor grading; chemotherapy vs. radiation vs. immunotherapy) (Prat, 2014). In a needle biopsy, a larger needle may be used to gather large tissue specimens, or a fine needle aspiration may be used to retrieve a small sample from cells and fluid. During vacuum-assisted biopsy, a specialized needle with a suction mechanism is used to collect tissue samples. These methods offer flexibility in acquiring appropriate samples for analysis (Prat, 2014). A core needle biopsy is a minimally invasive technique for collecting tissue specimens for examination. In difficult-to-access regions, ultrasound-guided or vacuum-assisted biopsy methods might be utilized (Ben-Yehuda *et al.,* 1996).

2.8: Immunohistochemistry and Advanced Tissue Imaging

Immunohistochemistry (IHC), a tissue imaging technique, enables the visualization of specific proteins or antigens in tissue specimens. It uses primary antibodies that selectively bind to target

proteins, followed by secondary antibodies that bind to the primary antibodies. The stained tissues are subsequently observed microscopically. Usually, the outcome is a change in color or fluorescence that shows the presence and location of the target protein. IHC is a commonly used technique in diagnostics and pathology research that may provide crucial information on the location, expression levels, and arrangement of certain proteins in tissue samples.

Diagnostic techniques that use morphological and functional data to detect cancer early are becoming increasingly necessary. Contemporary imaging approaches like terahertz (THz) and infrared radiation-based techniques, including FTIR and Raman, are actively being researched and validated. THZ imaging offers label-free, non-invasive, and non-ionizing detection of cancer. To detect cancer margins during operations, THz and other spectroscopic-based imaging are being sought (Ben-Yehuda *et al*., 1996). Hydration levels can be tracked because THz waves are very sensitive to changes in tissue water content. THz technology offers the opportunity to investigate DNA methylation as a possible cancer diagnostic by tracking the molecular resonance of DNA (Ben-Yehuda *et al*., 1996). Contrast compounds may potentially enhance THz imaging for clinical and translational cancer diagnosis.

Additionally, many spectroscopies are used for cancer detection and tumor imaging. It is noteworthy that better patient outcomes depend on early and accurate detection of cervical cancer since it is a prevalent disease with a slow start. A study utilized Raman spectral data from 233 individuals with cervical cancer to develop a one-dimensional hierarchical convolutional neural network (H-CNN), integrating domain-specific hierarchical classification knowledge with deep learning in Raman spectroscopy (Campo et al., 2023). The results indicated that H-CNN surpassed conventional methods in sensitivity, accuracy, and consistency for tissue section identification (Ben-Yehuda *et al*., 1996).

2.9: Molecular Biomarkers' Functions in Precision Medicine

The application of biomarkers within precision medicine represents a deliberate path for advancing technology to boost health outcomes and decrease medical expenditures. Using disease-specific biomarkers, precision medicine aims to customize treatments for specific patients or patient subgroups. The overall effectiveness of this customized approach to find actionable molecular targets to localize treatments is still up for dispute (Gyawali, 2017; Kato *et al.,* 2017). Without a

doubt, there are many analytical methods available today, such as next-generation sequencing, proteomics, metabolomics, genomics, and molecular imaging. The FDA has approved more than a dozen distinct biomarkers and anticancer therapies as a consequence of these and other methods (Kato *et al.,* 2017). The hunt for appropriate biomarkers to guide precision medicine is at an all-time high, but the verdict is yet out. In addition to cancer diagnosis and treatment, disease-specific biomarkers have other uses to advance precision medicine.

2.10: Molecular Biomarkers' Function in Systemic Therapy

Several chemotherapeutic medications, such as irinotecan, oxaliplatin, and oral fluoropyrimidines, as well as anti-EGFR targeted treatment with cetuximab and panitumumab, are part of systemic therapy for colorectal cancer. However, while some people may benefit from specific medications, others may encounter harm or experience serious adverse events. The efficacy of particular therapies for specific individuals has not been fully evaluated, despite the variety of choices available for systemic care. Predictive biomarkers provide useful insights to aid treatment decision-making by providing information on how a therapeutic intervention affects an outcome (Ben-Yehuda *et al*., 1996). Since molecular biomarkers may detect subtle biological changes at the molecular level before clinical symptoms appear, they provide the possibility of early intervention.

2.10.1: Evidence from Clinical Trials Demonstrating the Use of Biomarkers in Treatment Selection.

As stated by Ben-Yehuda *et al*. (1996), Kato *et al.* (2017), and Gyawali (2017), the following are the trial evidence of biomarkers.

Trial phase	**Treatment**	**Biomarker type**	**Validated Biomarker**	**Trial design**	**Examples**
III	Standard	Prognostic	No	Retrospective series	MammaPrint in early breast cancer

III	Standard	Predictive	No	Retrospective analyses of randomized trials	OncotypeDX in early breast cancer (SWOG-8814) KRAS mutations in advanced colorectal cancer (CRYSTAL) EGFR mutations in non-small-cell lung cancer (IPASS
III	Standard	Prognostic	No	Clinical utility	MINDACT in early breast cancer TAILORx in early breast cancer
III	Standard	Predictive	No	Randomize-all/ Interaction Biomarker	MARVEL in early breast cancer P53 in advanced breast cancer ERCC1 in non-small-cell lung cancer
II	Experimental	Predictive	Yes	Targeted Bayesian	Herceptin in advanced breast cancer BATTLE in non-small-cell lung cancer I-SPY 2 in advanced breast cancer
III	Experimental	Predictive	Yes	Targeted	PETACC-8 in advanced breast cancer TOGA in advanced gastric cancer

II	Experimental	Predictive	No	Adaptive parallel Tandem two-step TTP ratio	Dovitinib in HER2-negative advanced breast cancer Saracatinib in pancreatic cancer Molecular profiling in various tumor types
III	Experimental	Predictive	No	Enrichment Prospective subset	IPASS in non-small-cell lung cancer SATURN in non-small-cell lung cancer

2.10.2: Overview of Clinical Trials involving Biomarkers in Oncology: Phases, Purpose, and Study Design

As stated by Van Cutsem et al. (2009); Mok et al. (2009); Cardoso et al. (2016); Sparano et al. (2018); Le Tourneau et al. (2015); Slamon et al. (2001); Kim et al. (2011); Park et al. (2016); Taieb et al. (2014); Bang et al. (2010); André et al. (2013); Ren et al. (2012).

Study Name	**Biomarker**	**Phase**	**Trial Type**	**Purpose**	**Clinical Utility**	**Study Design**	**Therapeutic Strategy**
CRYSTAL (colorectal cancer)	KRAS mutation	III	Standard	Prognostic	No	Clinical utility	Biomarker strategy
IPASS (non-small-cell lung cancer)	EGFR mutation	III	Standard	Predictive	No	Randomize-all	Interaction

MINDACT (early breast cancer)	Gene expression (not a single biomarker)	III	Standard	Prognostic	No	Clinical utility	Randomize-all
TAILORx (early breast cancer)	Oncotype DX recurrence score	III	Standard	Predictive	No	Randomize-all	Interaction
MARVEL (non-small cell lung cancer)	Unknown biomarker (s)	II	Experimental	Predictive	Yes	Bayesian	Targeted
P53 (advanced breast cancer)	P53 mutation	II	Experimental	Predictive	Yes	Targeted	Bayesian
ERCC1 (non-small-cell lung cancer)	ERCC1 expression	II	Experimental	Predictive	Yes	Targeted	Bayesian
Herceptin (advanced breast cancer)	HER2 expression	II	Experimental	Predictive	Yes	Targeted	Bayesian
BATTLE (non-small cell lung cancer)	Various biomarkers	II	Experimental	Predictive	Yes	Adaptive parallel	Targeted
I-SPY 2 (advanced breast cancer)	Various biomarkers	III	Experimental	Predictive	Yes	Adaptive parallel	Targeted
PETACC-8 (advanced colorectal cancer)	Various biomarkers	III	Experimental	Predictive	No	Adaptive parallel	Targeted

TOGA (advanced gastric cancer)	HER2 expression	II	Experimental	Predictive	No	Adaptive parallel	Tandem two-step
Dovitinib (HER2-negative advanced breast cancer)	HER2-negative	II	Experimental	Predictive	No	Adaptive parallel	Targeted
Saracatinib (pancreatic cancer)	Unknown biomarker(s)	II	Experimental	Predictive	No	Adaptive parallel	Tandem two-step

CHAPTER THREE

RESEARCH METHODOLOGY

3.1: Systematic Review and Meta-Analysis

This section outlines the approaches and techniques employed to conduct a systematic evaluation of the significance and application of molecular biomarkers in solid tumors, as well as their role in guiding systemic therapy within the evolving landscape of precision medicine. The protocol adopted for this systematic review is in accordance with Cochrane guidelines on the effects of healthcare interventions (Cochrane, 2011). The inclusion and exclusion criteria for this review were developed using the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework (Santos *et al.,* 2007). To find medical literature for systematic review, the PICOS strategy categorized search terms into subject areas.

3.1.1: Study Population

Patients (men and women) irrespective of their age who have or were diagnosed with solid tumors (lung, breast, colorectal, or other solid malignancies) either treated previously or untreated formed the population of the study. However, all populations with non-solid tumors specifically, hematological malignancies (leukemias, lymphomas, or myelomas) were excluded as the study topic was very categorical about solid tumors. Equally, pregnant women and other populations of special interest, or those with more than one malignancy, were excluded.

3.1.2: Intervention and Comparators

This review focused on the application of molecular biomarkers in the treatment of solid tumors, specifically examining how these biomarkers guide systemic therapy in clinical practice. The research explored the role of biomarkers in targeted therapies, chemotherapy, and immunotherapy, with particular emphasis on their integration into routine clinical care. The intervention involved the use of biomarkers in prevalent solid tumors such as breast cancer, lung cancer, colorectal cancer, and melanoma. It also addressed the evolving role of immunogenomic profiling and emerging technologies, including liquid biopsy and next-generation sequencing (NGS). The aspects of clinical impact, economic implications, and barriers to the widespread adoption of

biomarker-guided therapies were examined for inclusion in the review with a view to incorporate the result of the intervention to low-income countries and their medical practice.

Although treatment providers and trial participants in biomarker-guided systemic therapy for solid tumors were generally monitored under rigorous clinical trial protocols, challenges related to compliance and adherence reporting remained common in both short- and long-term studies. In a review of non-adherence across 100 randomized controlled trials, Dodd et al. (2012) reported that only 25 trials adequately documented treatment initiation and completion. Furthermore, many studies employed vague or ambiguous language when describing non-adherence, failing to clearly specify the extent to which biomarker-guided interventions were administered as intended. This lack of clarity limited the interpretability and overall reliability of the reported outcomes.

Studies that compared systemic therapies within the same drug class without stratifying patients based on molecular biomarker status were excluded. Trials evaluating treatment combinations that did not incorporate biomarker-guided selection such as those lacking genomic, transcriptomic, or proteomic profiling were also omitted. Additionally, studies were excluded if they failed to clearly specify the type of biomarker assessed, the detection method used (e.g., immunohistochemistry, next-generation sequencing [NGS], or liquid biopsy), or the tumor subtype investigated. Interventions involving pharmacologic regimens not directed by biomarker data (e.g., general chemotherapy, hormonal therapies without biomarker validation, or the use of vitamins/supplements) were not considered. Similarly, non-pharmacological strategies such as dietary interventions, physical activity, or surgical approaches fell outside the scope of this review. Emphasis was placed on studies incorporating validated and/or emerging molecular biomarkers including EGFR, KRAS, and ALK in lung cancer, HER2 and PIK3CA in breast cancer, BRAF and NRAS in melanoma; and RAS/RAF pathway markers in colorectal cancer. Particular attention was also paid to research incorporating immunogenomic profiling and advanced technologies such as NGS and liquid biopsy, which are transforming biomarker detection into a real-time, minimally invasive tool for guiding clinical decision-making (Meric-Bernstam *et al.,* 2021; Siravegna *et al., 2022*; Camidge *et al.,* 2023; Liu *et al.,* 2024).

3.1.3: Selection of Studies Based on Biomarker-Driven Outcomes

The studies considered in this review were required to disclose biomarker-stratified cancer outcomes, such as the number of confirmed cases of solid tumors and/or cancer-related mortality among participants treated with systemic therapies guided by molecular biomarkers, compared to those receiving alternative treatments or standard care. Eligible outcomes focused on malignancies with well-established biomarker associations, particularly lung, breast, colorectal cancers, and melanoma, as classified by the International Classification of Diseases, Tenth Revision (ICD-10: C00–C97). Only studies utilizing biomarker-driven interventions through validated or emerging platforms such as next-generation sequencing (NGS), liquid biopsy, or immunogenomic profiling were included, reflecting current advances in precision medicine (De Mattos-Arruda *et al.,* 2015; Tomasik *et al.,* 2023; Jamal-Hanjani *et al.,* 2022; Fancello *et al.,* 2019).

Studies focusing solely on post-transplant malignancies or secondary cancers arising after primary cancer treatment were excluded. When data were incomplete or ambiguous, study authors were contacted for clarification; however, studies lacking sufficient information on biomarker type, cancer subtype, or outcome measures were excluded from the final analysis.

3.1.4: Study Design

This review exclusively included randomized controlled trials (RCTs) that met the following criteria: (1) utilized a parallel-group design with random assignment of participants to systemic therapies guided by molecular biomarkers; (2) enrolled a minimum of 100 participants per treatment arm to ensure adequate statistical power and generalizability; and (3) provided at least 52 weeks (one year) of active treatment follow-up. Eligible interventions were those employing biomarker-driven approaches for managing solid tumors, specifically lung, breast, colorectal cancer, and melanoma. These interventions incorporated validated or emerging techniques such as next-generation sequencing (NGS), liquid biopsy, and immunogenomic profiling, which are progressively applied to personalize treatment and forecast therapeutic outcomes (Camidge *et al.,* 2021; Meric-Bernstam *et al.,* 2022; Liu *et al.,* 2023; Lee *et al.,* 2024).

Studies that did not implement individual-level randomization, such as cluster-randomized designs, crossover trials where participants acted as their own controls, and quasi-experimental studies lacking true random allocation were excluded. Observational studies, including cohort, case-control, and cross-sectional studies, as well as non-empirical literature such as case reports,

editorials, or commentaries were also excluded. Trials enrolling fewer than 100 participants per arm or with follow-up periods shorter than 12 months were deemed ineligible. Additionally, preclinical investigations involving invitro experiments or animal models were excluded, as this review focused exclusively on human clinical applications of biomarker-informed systemic therapy within real-world oncology settings.

3.2: Search Strategies

Frontline medical databases and journals including MEDLINE, SCOPUS, British Medical Journal (BMJ), PLOS Medicine, and publications from Taylor and Francis were systematically searched using predefined keywords relevant to the review topic, focusing on literature published within the past 5 to 10 years. Boolean operators were employed to refine search results (see Table 3.1). The same set of keywords and search strategies were consistently applied across all selected platforms to ensure uniformity and reproducibility.

Table 3.1: Boolean operator demonstrating keywords used as search terms.

Concept Category	**Search Terms (Synonyms / Related Terms)**	**Boolean Operator**
Biomarkers	"Molecular biomarkers" OR "tumor biomarkers" OR "genetic biomarkers" OR "predictive biomarkers" OR "genomic biomarkers" OR "prognostic biomarkers"	OR
Cancer Type	"Solid tumors" OR "carcinomas" OR "solid malignancies" OR "breast cancer" OR "lung cancer" OR "colorectal cancer" OR "melanoma" OR "prostate cancer"	OR
Therapeutic Approach	"Systemic therapy" OR "targeted therapy" OR "chemotherapy" OR "immunotherapy"	OR
Precision Medicine	"Precision medicine" OR "personalized medicine" OR "precision oncology" OR "genomic medicine"	OR

Clinical Application	"Decision guides" OR "clinical decision-making" OR "treatment selection"	OR
Technology/Tools	"Next-generation sequencing" OR "molecular profiling" OR "advances in oncology"	OR

All studies included in this systematic review adhered strictly to the pre-established inclusion criteria. Publications that did not align with the thematic focus of molecular biomarkers in the treatment of solid tumors, or that addressed unrelated clinical objectives, were excluded. To ensure broad representativeness, the search was not limited to any specific healthcare institution or professional center. Rather, eligible studies were systematically compared based on the defined inclusion parameters. Additionally, reference lists of pertinent papers were manually screened to identify further relevant studies. However, unpublished manuscripts, grey literature, and non-peer-reviewed sources were not considered in the final synthesis. To mitigate the risk of missing relevant data, automated alerts were configured across all databases during the search period to capture newly published literature in real time.

("molecular biomarkers" OR "tumor biomarkers" OR "genetic biomarkers") AND ("solid tumors" OR "carcinomas" OR "solid malignancies") AND ("systemic therapy" OR "targeted therapy" OR "immunotherapy") AND ("precision medicine" OR "personalized medicine") ("molecular biomarkers" OR "predictive biomarkers") AND ("solid tumors" OR "breast cancer" OR "lung cancer") AND ("decision guides" OR "clinical decision-making" OR "treatment selection") AND ("precision medicine" OR "precision oncology") ("molecular biomarkers" OR "genomic biomarkers") AND ("solid tumors") AND ("systemic therapy" OR "targeted therapy") AND ("precision medicine" OR "genomic medicine") AND ("next-generation sequencing" OR "molecular profiling" OR "advances in oncology") ("molecular biomarkers" OR "prognostic biomarkers") AND ("colorectal cancer" OR "melanoma" OR "prostate cancer") AND ("systemic therapy" OR "chemotherapy" OR "immunotherapy") AND ("precision medicine")

3.2.1: Searching Other Sources

Clinical trial registries, including www.ClinicalTrials.gov, were systematically searched to identify relevant studies reporting on tumor types, administered treatments, and the presence or

absence of molecular biomarkers. ClinicalTrials.gov serves as a comprehensive, publicly accessible registry and results database for human clinical trials sponsored by both government and private organizations globally. In addition to database searches, the reference lists of eligible studies including systematic reviews and meta-analyses were examined to capture supplementary sources. For studies that did not clearly report the outcomes of interest, corresponding authors were contacted via email to request additional data. If no response was received within one to two weeks, a follow-up email was sent. In situations where the listed email address was no longer valid, alternative investigators or co-authors were contacted when feasible.

3.3: Managing References

All references retrieved from the selected electronic databases were imported into reference management software to establish a centralized and organized bibliographic repository. Citations were uploaded in either RIS (Research Information Systems) or EndNote (.enw) file formats and systematically managed using EndNote (version X7, Thomson Reuters). Duplicate records identified across multiple databases were detected using EndNote's built-in deduplication tool and isolated into a separate library for archival reference. Additional manual screening of titles was performed to identify and eliminate any residual duplicates.

Following the removal of duplicates, a dedicated folder containing eligible studies was created within the EndNote library to streamline full-text retrieval and review. The bibliographic database was curated exclusively and subsequently, references were exported to Microsoft Excel (version 2013) for data coding and classification. Study selection was conducted in accordance with the PICOS framework, as outlined in Section 3.1. A binary coding approach ("Yes" or "No") was used to determine each study's eligibility based on the predefined inclusion criteria.

3.4: Process of Study Selection and Quality Assessment

3.4.1: Screening the Titles and/ or Abstract of Included Studies

The predefined inclusion criteria outlined in Section 3.1 were systematically applied during the initial screening of study titles and/or abstracts. For documentation purposes, the number of excluded records and the corresponding reasons for exclusion were recorded during the screening process. Excluded references were categorized into two groups: (1) those that were thematically

relevant but failed to meet one or more eligibility criteria, and (2) those that were clearly unrelated to the review objective. In instances where the title and/or abstract did not provide sufficient information to make a definitive eligibility determination, the full-text article was retrieved for further assessment. Two independent reviewers with subject-matter expertise evaluated the full-text articles of potentially eligible studies to determine final inclusion. Discrepancies in judgement were resolved through discussion or consultation with a third reviewer when necessary.

3.4.2: Article Retrieval Methods and Evaluation of Risk of Bias

To obtain articles that were not available through the institution's electronic library, the researcher utilized ArticleReach Direct (ARD) – a collaborative interlibrary loan service that enables authorized users to request journal articles at no cost (ArticleReach Direct, 2017). In addition, a supplementary search was conducted using 'Google scholar's search engine by entering the specific article title or journal name for full-text publications. The full-text retrieval feature within EndNote was also utilized, whereby selected citations were searched using the integrated access tool to identify and retrieve available full-text documents from open-access and institutional databases.

In line with the current recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, this review adhered to standardized procedures for assessing and transparently reporting the risk of bias in included studies – particularly randomized controlled trials. Key methodological domains evaluated included: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and additional sources of potential bias, such as conflicts of interest or funding sources. Each domain was appraised using the criteria specified in the latest edition of the Cochrane Handbook and assigned a risk rating of low, high, or unclear (Higgins *et al.,* 2022). A study was considered to be at high risk of bias if it was rated as high or unclear in any of the core domains associated with randomization, allocation concealment, or blinding, as these factors have been consistently shown to exert a significant influence on trial validity (Lundh *et al.,* 2023; Higgins *et al.,* 2022). The risk of bias assessment was independently performed by two reviewers with expertise in the subject area. Discrepancies

were resolved through discussion until consensus was achieved. Where methodological information was incomplete or ambiguous, study authors were contacted to provide clarification.

3.4.3: Data Extraction

Eligibility assessment and data extraction were conducted independently by two reviewers with domain expertise. Both reviewers systematically evaluated each included trial to determine its compliance with the predefined inclusion criteria. Discrepancies in judgement were resolved through collaborative discussion, and where consensus could not be reached, clarification was sought from the supervising academic advisor. In instances where essential data, particularly those relating to molecular biomarkers and clinical outcomes in solid tumors were absent or incomplete, corresponding study authors were contacted via email to request additional information; however, not all inquiries received responses. To ensure consistency and comprehensiveness in data collection, a standardized data extraction tool was developed using Microsoft Excel. The form was designed to align with the study objectives and was structured around the PICOS framework (Population, Intervention, Comparator, Outcome, and Study Design). Extracted data were compiled to facilitate subsequent quality assessment and synthesis of evidence. The procedures for risk of bias and quality appraisal are detailed in an earlier section of this chapter.

With respect to the study population, detailed information was extracted on the clinical context and participant characteristics, including age, sex distribution, history of tobacco use, and prior diagnosis or treatment of tumors. For the intervention and comparator arms, data were collected on the specific biomarkers investigated, the systemic therapies administered, dosing schedules, treatment duration, patient adherence, and any co-administered agents. In terms of outcome measures, particular attention was paid to whether cancer-related endpoints were pre-specified in the study protocol. Extracted data included the incidence of solid tumors and tumor-related mortality within each treatment group, methods used for adjudicating cancer diagnoses, and the source of cancer outcome data – whether derived from published manuscripts or supplementary unpublished materials.

Key study characteristics extracted included the study acronym (if available), full study title, first author, year of publication, source journal, total study duration, and clearly defined primary and secondary outcomes. In instances where studies featured multiple treatment arms, only those

interventions directly aligned with the research objectives were included in the analysis. For studies comparing various agents within the same therapeutic class at different dosages, outcome data were consolidated by therapeutic category. This methodological approach enabled consistency in data synthesis across studies with comparable mechanisms of action, thereby supporting coherent interpretation of cancer-related outcomes across similar intervention groups.

3.5: Data Synthesis and Statistical Evaluation

For the purpose of this analysis, study participants were evaluated based on their initial randomization assignments, regardless of the specific systemic therapies administered or dosage variations. Aggregate data on cancer incidence and cancer-related mortality were extracted as dichotomous variables and organized into 2x2 contingency tables, delineating the number of participants who experienced or did not experience the specified clinical outcomes across biomarker-guided versus non-biomarker-guided treatment groups. A meta-analytic approach was employed for each therapeutic class of targeted systemic interventions using Review Manager (RevMan) version 5.3.5. The Mantel-Haenszel statistical method was applied to estimate pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs). This method is recognized for its robustness in handling sparse event data, as outlined in Higgins (2011). In scenarios where one or more cells reported zero events, a continuity correction of 0.5 was automatically implemented by the software to enable statistical estimation.

To evaluate inter-study variability, statistical heterogeneity was assessed using both the Q statistic and the I^2 index. A p-value of less than 0.05 in conjunction with an $I^2 \geq 50\%$ was interpreted as indicative of substantial heterogeneity. In such instances, pooled estimates were deemed inappropriate, and study-specific odds ratios (ORs) were presented individually. Conversely, in cases where statistical homogeneity was deemed acceptable, a fixed-effect (FE) model was applied to generate pooled ORs using the Mantel-Haenszel method. To assess the presence of publication bias among the included studies, funnel plot asymmetry was examined, consistent with recommended practices for detecting potential reporting bias in meta-analytic evaluations (Page *et al.,* 2021; Ioannidis, 2019).

CHAPTER FOUR

RESULTS

4.1: Introduction

This chapter presents the results of the systematic review and meta-analysis conducted on randomized controlled trials (RCTs) investigating the role of molecular biomarkers in systemic therapy within the context of precision medicine. It begins with a summary of the literature search process, including the number of studies identified, included, and excluded, as well as the assessment of risk of bias in the included studies. This is followed by the findings from the meta-analysis of the eligible studies.

4.2: Result of The Search

An initial search of leading databases, namely PubMed, Medline, Scopus, and Cochrane using relevant keywords from the research topic yielded 12,345 related studies. An additional 13 studies were identified through the reference lists of retrieved articles. After the removal of duplicates, 2089 unique records remained. These records were subjected to screening at the initial level of the systematic review (see Figure 4.1). The full texts of the identified studies were then assessed against the predefined inclusion and exclusion criteria. As a result, 1772 studies were excluded, and 317 studies proceeded to the eligibility assessment stage. Subsequently, 230 studies were excluded for reasons such as not being randomized controlled trials (RCTs), not constituting primary studies, having vague objectives, or not addressing solid tumors.

A total of 87 studies remained at this stage. Of these, 69 were excluded for the following reasons: insufficient data for analysis (n = 23), use of combined therapy as intervention or comparator (n = 21), absence of cancer-related outcomes (n= 14), retracted publications (n = 5), reporting only overall cancer incidence without subtype specificity (n= 1), poorly defined cancer outcomes (n= 2), duplicate survey data (n =3), and study duration falling short of the minimum duration specified in the inclusion criteria. Consequently, 18 studies that met all predefined inclusion criteria were selected and included in the final analysis. The characteristics of these included studies are presented in Table 4.1.

Figure 4.1: Systematic Review

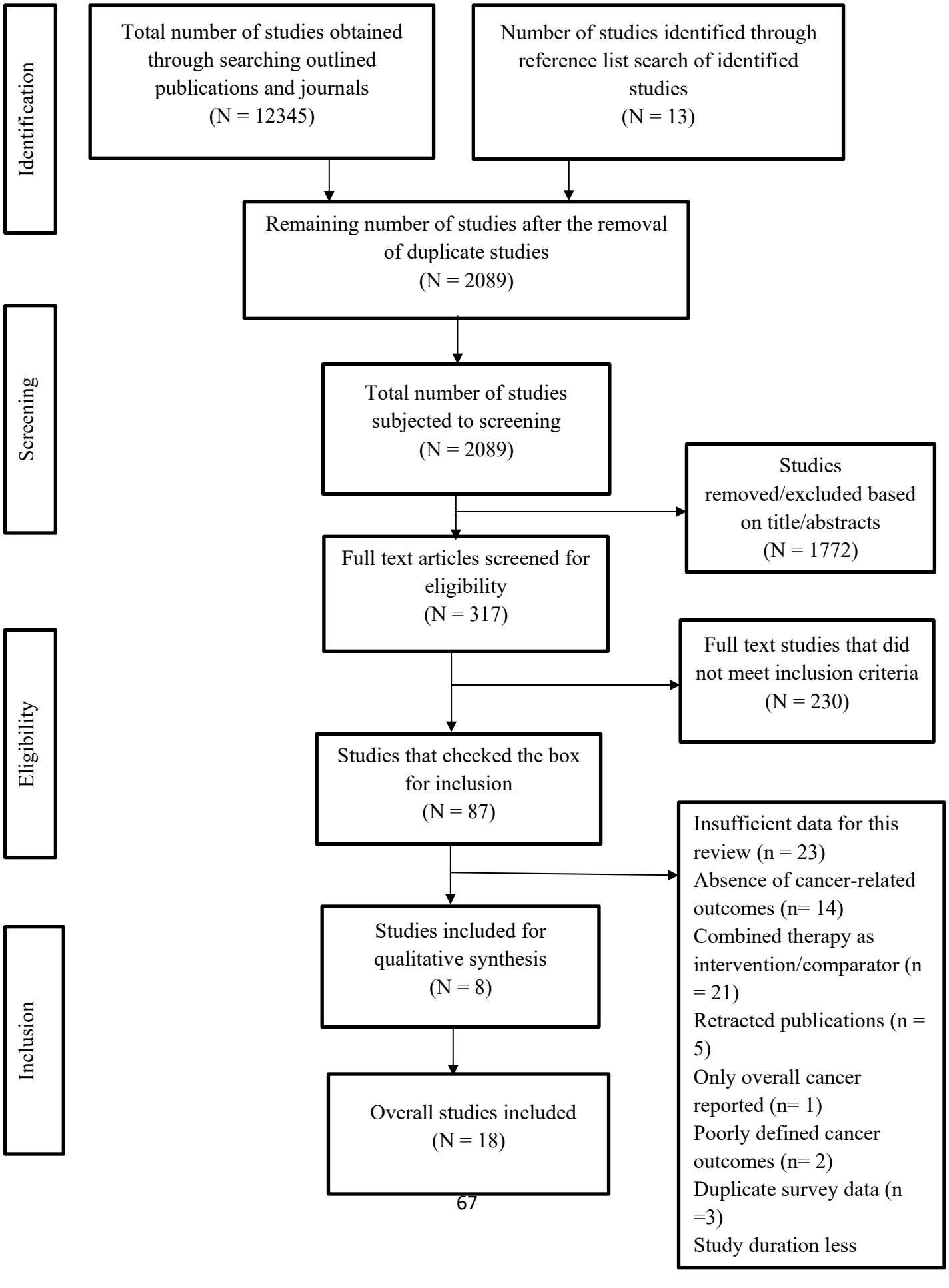

Table 4.1: Characteristics of Included Studies

S/N	Author & Date (NCT Reg. no.)	Title	Objectives	Cancer type	Intervention	Results	Inference
1	Elghawy *et al.,* (2024).	Single-Institution Experience of Larotrectinib Therapy for Patients with NTRK Fusion-Positive Thyroid Carcinoma.	Retrospective analysis of thyroid cancer patients with NTRK fusions treated with larotrectinib.	Thyroid cancer	Use of neurotrophic tyrosine receptor kinase (NTRK) treat the NGS identified thyroid cancer from 2007 – 2023.	NTRK inhibition led to a median progression-free survival (mPFS) of 25 months, with survival surpassing historic benchmarks for anaplastic thyroid cancer, ATC and poorly differentiated thyroid cancer, PDTC.	The study indicated that NTRK being a biomarker can be deployed in the treatment of solid tumors like thyroid cancer.
2	Hotta *et al.,* (2022).	Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive NSCLC.	Compare efficacy and safety of alectinib vs crizotinib in ALK inhibitor-naïve advanced ALK-positive NSCLC	ALK-positive non-small-cell lung cancer (NSCLC)	Use of alectinib and crizotinib to treat NSCLC	Alectinib showed no superiority over crizotinib in Japanese patients with ALK-positive NSCLC.	Both drugs can be used for solid cancers treatment (NSCLC precisely).

3	Bhai *et al.,* (2023).	Molecular profiling of solid tumors by next-generation sequencing: an experience from a clinical laboratory.	Evaluate targeted next-generation sequencing (NGS) assays in clinical settings; validate Ion AmpliSeq™ Cancer Hotspot Panel v2 assay; assess the diagnostic yield and spectrum of clinically relevant genetic variants in solid tumors and demonstrate the feasibility of integrating NGS-based gene panel screening into standard diagnostic protocols for solid tumor assessment.	Lung, colon, melanoma, brain, breast, pancreatic, endometrial, ovarian, and thyroid cancers.	Use of Ion AmpliSeq™ Cancer Hotspot Panel v2 assay (ThermoFisher), targeting approximately 2,800 COSMIC mutations across 50 oncogenes and tumor suppressor genes.	63.7% of 3,164 samples tested positive for clinically relevant variants, with TP53, KRAS, and PIK3CA being the most frequently mutated genes. Diagnostic yields ranged from 57.1% to 84.6& across tumors. The tumor-specific targeted subpanels also demonstrated high diagnostic yields: Lung: 69%, Colon: 61.2%, Melanoma: 69.7% and Brain: 20.7% and the co-occurrence of mutations in more than one	The study concludes that integrating NGS-based gene panel screening into standard diagnostic protocols for solid tumors is feasible and yields high diagnostic rates.

						gene was frequently observed.	
4	Bottosso *et al.,* (2024).	Moving toward precision medicine to predict drug sensitivity in patients with metastatic breast cancer (MBC).	Understanding tumor heterogeneity and its impact on treatment resistance, evaluating the role of genomic analyses and technological innovations in personalizing therapeutic strategies and discussing the translational steps toward predicting drug sensitivity in MBC patients.	Metastatic breast cancer (MBC)	Analysis of existing methodologies and technologies, including genomic profiling techniques to identify actionable mutations, technological advancements that facilitate the application of precision medicine in clinical settings and clinical trials that have translated molecular insights into practice.	The study demonstrated that tumor heterogeneity is a significant factor in disease progression and treatment resistance in MBC. Genomic analyses improve understanding of breast cancer biology, leading to more personalized treatment approaches and technological advancements have enabled the integration of precision medicine into clinical practice,	The authors conclude that precision medicine using genomics and technology holds promise in predicting drug sensitivity and personalizing treatment for MBC patients.

						improving patient outcomes.	
5	Long *et al.,* (2017). NCT 01584648	Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study.	Evaluate long-term efficacy and safety of combination therapy with dabrafenib and trametinib compared to dabrafenib monotherapy in patients with metastatic melanoma harboring BRAF V600E/K mutations. Specifically, it assessed progression-free survival (PFS), overall survival (OS), and safety profiles after a minimum of 36 months of follow-up.	Metastatic melanoma with BRAF V600E or V600K mutations.	Experimental Arm: Dabrafenib + trametinib. Control Arm: Dabrafenib + placebo, double-blind, phase 3 trial design	3-year PFS 22% (combo) vs 12% (mono). 3-year overall survival (OS) 44% (combo) vs 32% (mono). Subgroup Analysis: Patients with normal lactate dehydrogenase (LDH) levels and fewer than three metastatic sites had a 3-year OS of 62% with combination therapy, compared to 25% in patients with elevated LDH levels. Safety: The safety profile of the combination	Combination of dabrafenib and trametinib provides significant long-term survival benefit over dabrafenib monotherapy in patients with BRAF V600-mutant metastatic melanoma.

						therapy was consistent with previous findings, and no new safety concerns were identified over the long-term follow-up.	
6	Kim *et al.,* (2024). NCT 05525858	Nationwide precision oncology pilot study: KOrean Precision Medicine Networking Group Study of MOlecular profiling-guided therapy based on genomic alterations in advanced solid tumors (KOSMOS) KCSG AL-20-05.	Assess feasibility and clinical utility of NGS-based molecular profiling and centralized molecular tumor board (MTB) for personalized therapy in patients with advanced solid tumors in South Korea. Specifically, the study sought to assess the implementation of molecular	The study encompassed a diverse cohort of patients with advanced solid tumors, including but not limited to colorectal cancer, glioblastoma, esophageal cancer and other refractory metastatic solid tumors.	The intervention involved a multi-step approach which includes molecular profiling of patients through NGS to identify actionable genomic alterations, centralized molecular tumor board (MTB), and Molecularly Guided Therapy (MGT)	While specific quantitative outcomes were not detailed in the available summary, the study demonstrated: the feasibility of implementing a nationwide precision oncology platform integrating NGS and centralized MTB consultations, the ability to provide	The KOSMOS study successfully showcased the integration of molecular profiling and centralized MTB consultations into routine clinical practice across South Korea. This approach facilitated personalized treatment strategies for

			profiling-guided therapy (MGT) based on genomic alterations, determine the impact of a centralized MTB on treatment recommendations and establish a nationwide precision oncology platform to facilitate personalized cancer treatment.			personalized treatment recommendations for patients with advanced solid tumors based on genomic profiling and the establishment of a clinico-genomic database to support future research and clinical decision-making.	patients with advanced solid tumors, highlighting the potential of precision oncology to improve patient outcomes.
7	Finn *et al.,* (2016). NCT 01740427	Palbociclib and letrozole in advanced breast cancer.	Evaluate efficacy and safety of combining palbociclib (a CDK4/6 inhibitor) plus letrozole (an aromatase inhibitor) as first-line therapy in postmenopausal	Advanced ER-positive, HER2-negative metastatic breast cancer in postmenopausal women.	The intervention included experimental arm where palbociclib (125 mg daily for 21 days followed by 7 days off) combined with continuous daily letrozole (2.5	Progression-Free Survival (PFS) was significantly longer in the palbociclib+letrozole group at 24.8 months (95% CI, 22.1 - not estimable) compared to 14.5 months (95% CI,	Palbociclib addition to letrozole as initial therapy significantly prolonged progression-free survival compared to letrozole alone in

			women with ER–positive, HER2–negative advanced breast cancer.		mg) and control arm: placebo combined with continuous daily letrozole (2.5 mg).	12.9 - 17.1) in the placebo+letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 - 0.72; P<0.001). The objective response rate was 55.3% in the palbociclib+letrozole group versus 44.4% in the placebo+letrozole group and the adverse events most common grade 3 or 4 adverse events in the palbociclib–letrozole group were neutropenia (66.4% vs. 1.4% in the placebo group), leukopenia (24.8% vs. 0%),	postmenopausal women with ER-positive, HER2-negative advanced breast cancer. While the combination therapy was associated with higher rates of hematologic adverse events, these were generally manageable and did not lead to a substantial increase in treatment discontinuation.

						anemia (5.4% vs. 1.8%), and fatigue (1.8% vs 0.5%). Febrile neutropenia occurred in 1.8% of patients in the palbociclib–letrozole group and in none of the patients in the placebo–letrozole group.	
8	Peters *et al.,* (2017). NCT 02075840	Alectinib versus crizotinib in untreated ALK-positive non–small cell lung cancer.	Compare efficacy and safety of alectinib versus crizotinib first-line treatment in ALK-positive NSCLC.	Advanced ALK-positive NSCLC.	Experimental Arm: Alectinib administered orally at 600 mg twice daily. Control Arm: Crizotinib administered orally at 250 mg twice daily. Patients were randomized in a 1:1 ratio in this global, open-	Progression-Free Survival (PFS): The median PFS not reached (alectinib) vs 11.1 months (crizotinib). The hazard ratio for disease progression or death was 0.47 (95% CI, 0.34 - 0.65; P<0.001), indicating a 53% reduction in the	Alectinib demonstrated superior efficacy over crizotinib in the first-line treatment of patients with advanced ALK-positive NSCLC, with a significant improvement in progression-free survival and a

					label, phase 3 trial known as the ALEX study.	risk of progression or death with alectinib. Alectinib significantly reduced the risk of CNS progression with a CNS progression cumulative incidence of 9.4% at 12 months vs 41.4% with crizotinib. Overall Response Rate (ORR): The ORR was 82.9% in the alectinib group compared to 75.5% in the crizotinib group. Safety: Grade 3 or 4 adverse events occurred in 41% of patients receiving	more favorable safety profile. Additionally, alectinib showed better control of CNS metastases.

						alectinib and 50% of those receiving crizotinib. Common adverse events with alectinib included constipation, fatigue, and peripheral edema, whereas crizotinib was associated with higher incidences of nausea, diarrhea, vomiting, and visual disturbances.	
9	Drilon *et al.,* (2018). NCT 02122913 NCT 02637687 NCT 02576431	Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. *New England Journal of Medicine*, 378(8), 731-739.	Evaluate the efficacy and safety of larotrectinib (a highly selective tropomyosin receptor kinase (TRK) inhibitor)	Diverse TRK fusion–positive tumors, including: salivary gland, sarcomas, thyroid, colon, lung, breast, melanoma, infantile fibrosarcoma,	Patients with TRK fusion–positive cancers, identified through molecular profiling, were enrolled in one	Overall Response Rate (ORR): Among 55 patients, the ORR was 75% (95% CI, 61 - 85), including 13% complete	Larotrectinib demonstrated robust and durable antitumor activity across a wide range of TRK fusion–

			in both adult and pediatric patients with advanced solid tumors harboring TRK gene fusions. The primary endpoint was the overall response rate assessed by independent review. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), and safety.	gastrointestinal stromal tumors (GIST), cholangiocarcinoma, appendix tumors, and pancreatic cancer.	of three clinical trials: A phase 1 study involving adults, a phase 1–2 study involving children and a phase 2 study involving adolescents and adults.	responses and 62% partial responses. Duration of Response (DoR): At one year, 71% of responses were ongoing, and the median DoR had not been reached at the time of analysis. Progression-Free Survival (PFS): At one year, 55% of patients remained progression-free, with the median PFS not reached during the study period.	positive cancers, irrespective of patient age or tumor histology. The high response rates, coupled with a favorable safety profile, underscore the potential of larotrectinib as an effective treatment option for patients with TRK fusion–positive tumors.
10	Robert *et al.,* (2019). NCT 01584648 NCT 01597908	Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma.	Evaluate long-term efficacy and safety of combined BRAF/ MEK inhibition	Metastatic melanoma with BRAF V600E or V600K mutations.	Dabrafenib plus trametinib combination therapy. Study Design:	The median OS was 25.9 months. The 4-year and 5-year OS rates were 37% and	Dabrafenib plus trametinib provides durable long-term survival benefits

			using dabrafenib and trametinib in patients with previously untreated metastatic melanoma harboring BRAF V600E or V600K mutations.		This pooled analysis included data from two phase 3 trials: COMBI-d (dabrafenib plus trametinib vs. dabrafenib plus placebo) and COMBI-v (dabrafenib plus trametinib vs. vemurafenib). A total of 563 patients were enrolled (211 in COMBI-d and 352 in COMBI-v).	34%, respectively. Patients with normal baseline lactate dehydrogenase (LDH) levels had a 5-year OS rate of 43%, compared to 16% in those with elevated LDH levels. Notably, patients who achieved a complete response had a 5-year OS rate of 71%. The 4-year and 5-year PFS rates were 21% and 19%, respectively. Multivariate analysis identified several baseline factors associated with	in approximately one-third of patients with BRAF V600–mutant metastatic melanoma Achieving a complete response is strongly associated with prolonged survival. Baseline factors such as normal LDH levels and limited metastatic burden are predictive of better outcomes.

						improved OS and PFS, including younger age, female sex, better performance status (ECOG 0), normal LDH levels, and fewer than three organ sites with metastasis Safety: No new safety signals were observed during the extended follow-up. Adverse events led to treatment discontinuation in 18% of patients, with pyrexia (4%), decreased ejection fraction (4%), and increased alanine aminotransferase levels (1%) being	

						the most common reasons.	
11	Planchard *et al.,* (2023). NCT 04035486	Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC.	Evaluate if adding platinum-based chemotherapy to osimertinib improves progression-free survival (PFS) compared to osimertinib monotherapy in treatment-naïve EGFR-mutated NSCLC.	Advanced NSCLC with EGFR exon 19 deletions or L858R mutations.	Experimental Arm: Osimertinib (80 mg once daily) plus chemotherapy (pemetrexed with either cisplatin or carboplatin). Control Arm: Osimertinib monotherapy (80 mg once daily).	Median PFS was 25.5 months (combo) versus 16.7 months (mono) (hazard ratio [HR] for disease progression or death, 0.62; 95% CI, 0.49 - 0.79; P<0.001). 24-Month PFS Rates: 57% in the combination group and 41% in the monotherapy group. Objective Response Rate (ORR): 83% (combo) vs 76% (mono). Median Duration of Response: 24.0 months	Adding platinum-based chemotherapy significantly improved progression-free survival and response duration in patients with EGFR-mutated advanced NSCLC. The combination therapy was particularly beneficial for patients with CNS metastases. However, the increased efficacy came with a higher incidence of adverse events,

						(combo) vs 15.3 months (mono). Central Nervous System (CNS) Metastases: In patients with baseline CNS metastases, median PFS was 24.9 months (combo) vs 13.8 months (mono). Safety: Grade 3 or higher adverse events occurred in 64% (combo) and 27% (mono).	consistent with the known toxicity profiles of chemotherapy agents.
12	Hyman *et al.,* (2015). NCT 01524978	Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations.	Evaluate efficacy and safety of vemurafenib, a BRAF inhibitor, in various nonmelanoma cancers harboring BRAF V600 mutations.	NSCLC, colorectal, Erdheim–Chester disease (ECD), Langerhans'-cell histiocytosis (LCH), anaplastic thyroid cancer, cholangiocarcinoma, ovarian, salivary-duct cancer, clear-cell sarcoma and	Patients received vemurafenib, with dosing and administration tailored to each cohort. Specifically, colorectal cancer patients were	NSCLC response rate was 42% with a median PFS of 7.3 months (95% CI, 3.5 - 10.8). Erdheim–Chester disease/ Langerhans'-Cell histiocytosis response rate was	The study demonstrated that BRAF V600 mutations can be effectively targeted in certain nonmelanoma cancers using vemurafenib,

				pleomorphic xanthoastrocytoma.	administered vemurafenib in combination with cetuximab, an EGFR inhibitor, to potentially enhance therapeutic efficacy.	43%. The median treatment duration was 5.9 months (range, 0.6 - 18.6), and no patients experienced disease progression during therapy. Colorectal cancer among patients receiving vemurafenib plus cetuximab, anecdotal responses were observed, suggesting limited efficacy of vemurafenib monotherapy in this cohort.	particularly in NSCLC and histiocytic disorders like ECD and LCH. However, the efficacy varied across different tumor types, underscoring the importance of tumor histology in predicting response to BRAF inhibition.
13	Rodriguez *et al.,* (2022). NCT 04843332	Community health workers and precision medicine: A	Assess whether a community health worker (CHW)-led intervention improves	Adults with various types of cancer, focusing on those who were newly diagnosed,	Study Design: Randomized controlled trial conducted in partnership with	Measures change in precision medicine knowledge using a 6-item survey	CHW-led interventions may improve knowledge of precision

		randomized controlled trial.	precision medicine knowledge in low-income and minority adults with cancer.	experiencing progression, or recurrence of cancer. The emphasis was on low-income and racial and ethnic minority populations.	a community oncology clinic in Monterey County, California. Participants: 110 adults with cancer who were low-income, uninsured, insured by Medicaid, or by a local agricultural employer, and/or identified as racial or ethnic minorities.	adapted from Davies at baseline, and at 3-, 6-, and 12-months post-enrollment. Exploratory outcomes include patient satisfaction with decision-making, patient activation, healthcare utilization, and receipt of evidence-based precision medicine care.	medicine among underserved cancer patients. By addressing language and system-level barriers through culturally tailored education and support, equitable access to precision medicine can be improved.
14	Church *et al.,* (2022). NCT 02520713	Molecular profiling identifies targeted therapy opportunities in pediatric solid cancer.	Assess the clinical impact of molecular tumor profiling (MTP) using targeted sequencing panel tests in pediatric patients with	The study included pediatric patients with various extracranial solid tumors of various histologies.	Targeted next-generation sequencing (NGS) panel tests were performed on formalin-fixed paraffin-	Genomic Alterations: 86% (298/345) had at least one alteration with potential clinical impact. 240 patients had MTP	The study demonstrates that MTP with targeted NGS panels, particularly those capable of detecting gene

			extracranial solid tumors. The focus was on identifying genomic alterations with diagnostic, prognostic, or therapeutic significance to inform treatment decisions.		embedded (FFPE) tumor samples to detect genomic alterations, including gene fusions, mutations, and copy number variations.	results that could inform selection of molecularly targeted therapy (MTT). 9 patients received MTT based on MTP findings and 24% experienced an objective response/durable clinical benefit. Notably, almost all the patients received therapy matched to gene fusion. 77% of the diagnostic variants identified in 209 patients were gene fusions, highlighting their prevalence and potential as therapeutic targets.	fusions, has significant clinical utility in pediatric patients with extracranial solid tumors. The identification of actionable genomic alterations can inform diagnosis, prognosis, and therapeutic strategies, leading to improved patient outcomes.

15	Martinez *et al.,* 2022	Effectiveness and safety of palbociclib as first-line treatment in advanced breast cancer	Evaluate the real-world effectiveness, safety, and adherence of palbociclib plus hormone therapy as a first line treatment for patients with HR+/HER2-negative advanced breast cancer.	Hormone receptor-positive (HR+), HER2-negative locally advanced or metastatic breast cancer.	Palbociclib + hormone therapy, following standard clinical protocols.	Median PFS was 27.4 months. This outcome is comparable to the 27.6 months PFS observed in the PALOMA-2 clinical trial. Grade 3–4 adverse events occurred in 82.3% of patients, like the 79.3% reported in PALOMA-2. Treatment delays were more frequent (84.4% vs. 70.9% in PALOMA-2). Dose reductions were also more common (64.7% vs. 39.4% in PALOMA-2). Permanent treatment discontinuations due to adverse	The study concludes that palbociclib + hormone therapy is effective and safe as a first-line treatment for HR+/HER2− advanced breast cancer in real-world clinical practice. The outcomes align closely with those observed in the PALOMA-2 clinical trial, despite a higher incidence of treatment modifications such as delays and dose reductions. High adherence rates further support the feasibility of

						events occurred in 13.7% of patients, comparable to 12.2% in PALOMA-2. Adherence: Proportion of days covered (PDC): 99.4%, indicating high adherence to the treatment regimen.	this treatment approach in routine clinical settings.
16	Bailey *et al.,* (2018).	Comprehensive characterization of cancer driver genes and mutations	The study aimed to systematically identify and characterize cancer driver genes and mutations across a wide range of tumor types.	Pan-cancer analysis of 9,423 tumors exomes from 33 cancer types, as part of The Cancer Genome Atlas (TCGA) project.	Utilized 26 computational tools to identify and catalog driver genes and mutations.	Identified 299 driver genes with implications for specific anatomical sites and cancer cell types. Detected over 3,400 putative missense driver mutations supported by multiple lines of evidence.	This study provides a comprehensive resource for understanding the landscape of cancer driver genes and mutations. The integration of computational predictions with experimental validation

						Confirmed 60%–85% of predicted mutations as likely drivers through experimental assays. Microsatellite instability (MSI): found that over 300 MSI tumors are associated with high PD-1/PD-L1 expression. 57% of tumors analyzed harbor clinically actionable events.	enhances confidence in identifying oncogenic drivers.
17	Stahler *et al.,* (2025). NCT 01991873	Panitumumab plus 5-fluorouracil and folinic acid or 5-fluorouracil and folinic acid alone as maintenance therapy in RAS wild-type metastatic colorectal cancer (PanaMa, AIO	Evaluate if adding panitumumab to 5-fluorouracil (5-FU) and folinic acid (FA) improves PFS in RAS wild-type	Metastatic colorectal cancer (mCRC) with RAS wild-type status.	Treatment Arms: Arm A: Maintenance therapy with 5-FU/FA plus panitumumab (n=125). Arm B: Maintenance	Median PFS was significantly longer in Arm A (8.8 months) compared to Arm B (5.7 months), with a hazard ratio of 0.72	The PanaMa trial demonstrates that maintenance therapy with 5-FU/FA plus panitumumab

		KRK 0212): final efficacy analysis of a randomised, open-label, phase 2 trial.	metastatic colorectal cancer (mCRC) who had previously received induction therapy with mFOLFOX6 plus panitumumab.		therapy with 5-FU/FA alone (n=123).	(80% CI: 0.60–0.85; P=0.014). Median OS was 28.7 months in Arm A and 25.7 months in Arm B; however, this difference was not statistically significant (HR: 0.84; 95% CI: 0.60–1.18; P=0.32). Objective Response Rate (ORR): ORR was higher in Arm A (40.8%) compared to Arm B (26.0%), with an odds ratio of 1.96 (95% CI: 1.14–3.36; P=0.02). Safety: The addition of panitumumab was associated with a higher	significantly improves progression-free survival and objective response rates compared to 5-FU/FA alone in patients with RAS wild-type mCRC. While overall survival was not significantly different between the two arms, the addition of panitumumab was associated with manageable toxicity, primarily skin-related adverse events.

						incidence of skin rash (any-grade: 26.4% vs. 6.5%; grade 3/4: 7.2% vs. 0%). Re-induction therapy: Patients in Arm B who received re-induction therapy had a median PFS of 5.8 months, compared to 3.3 months in Arm A.	
18	Tsimberidou *et al.,* (2014).	Personalized medicine for patients with advanced cancer in the phase I program at MD Anderson: validation and landmark analyses.	Validate previous findings that matching targeted therapies to tumor molecular alterations improve clinical outcomes in patients with advanced cancer. Specifically, it assessed whether	Advanced solid tumors across various histologies	Matched Therapy Group: Patients received targeted therapy matched to their tumor's molecular alteration(s). Nonmatched Therapy Group: Patients	Objective Response Rate (ORR) was 12% in the matched therapy group vs. 5% in the nonmatched group ($P < 0.0001$). Median PFS was 3.9 months for matched therapy	The study confirms that personalized treatment strategies, where targeted therapies are matched to specific tumor molecular alterations, and are associated

			matched therapy leads to better response rates, progression-free survival, and overall survival compared to nonmatched therapy.		received therapy not specifically matched to their tumor's molecular profile.	vs. 2.2 months for nonmatched therapy (P = 0.001). Median OS was 11.4 months for matched therapy vs. 8.6 months for nonmatched therapy (P = 0.04). Landmark Analyses (2-month): Matched Therapy Responders: Median OS of 30.5 months and PFS of 38.7 months. Matched Therapy Nonresponders: Median OS of 11.3 months and PFS of 5.9 months. Nonmatched Therapy Responders:	with improved clinical outcomes in patients with advanced cancer. These findings support the implementation of molecular profiling in clinical decision-making to guide therapy selection in early-phase clinical trials.

						Median OS of 9.8 months and PFS of 8.5 months. Nonmatched Therapy Nonresponders: Median OS of 9.4 months and PFS of 4.2 months. Multivariate Analysis: Matched therapy was an independent predictor of improved response ($P < 0.015$) and PFS ($P < 0.004$).	

4.3: Characteristics of The Included Studies

In accordance with the PRISMA guidelines, a total of 18 studies were included in this review, comprising an estimated population of 16,756 participants, with an average study duration of approximately one year. The included studies represented eight distinct research designs. Randomized control trials (RCTs) constituted the largest proportion, accounting for 50% of the included studies. These RCTs were conducted by Finn et al. (2016), Long et al. (2017), Peters et al. (2017), Robert et al. (2019), Hotta et al. (2022), Rodriguez (2022), Planchard et al. (2023), Elghawy et al. (2024), and Stahler et al. (2025). Prospective observational studies, represented by Church et al. (2022) and Kim et al. (2024), accounted for 11.1% of the included studies. The remaining study designs each representing 5.5% of the total included: retrospective observational design (Bhai et al., 2023), pooled analysis (Drilon et al., 2018), basket trial (Hyman et al., 2015), retrospective longitudinal design (Martinez et al., 2022), computational retrospective observational design (Bailey et al., 2018), and retrospective cohort design (Tsimberidou et al., 2014).

The included studies exhibited a wide geographical distribution, underscoring the global relevance and applicability of the findings. Specifically, 38.8% of the studies were conducted across multiple countries (classified as worldwide), while 22.2% were conducted in the United States. Other individual countries represented – each accounting for 5.5% of the included studies - were Japan, Germany, South Korea, Spain, and the United Kingdom. In terms of funding, a significant majority (77.8%) of the studies reported receiving financial support from government agencies or organizations. Conversely, 11.1% explicitly stated that they were not funded, while another 11.1% did not disclose any funding information. Regarding study type, all but one of the included studies were classified as clinical study. The exception was the study by Bottosso et al., (2024), which was not categorized as a clinical study. Overall, 94.4% of the included studies were clinical in nature.

All of the included studies (Finn et al., 2016; Long et al., 2017; Peters et al., 2017; Robert et al., 2019; Hotta et al., 2022; Rodriguez et al., 2022; Planchard et al., 2023; Elghawy et al., 2024; Stahler et al., 2025; Church et al., 2022; Kim et al., 2024; Bhai et al., 2023; Drilon et al., 2018; Hyman et al., 2015; Martinez et al., 2022; Tsimberidou et al., 2014; Bottosso et al., 2024) addressed various types of solid tumors. The cancers investigated across the studies include thyroid

cancer, ALK-positive non-small-cell lung cancer (NSCLC), colon cancer, melanoma, glioblastoma, pancreatic, endometrial, ovarian, breast and metastatic breast cancer (MBC), metastatic melanoma with BRAF V600E or V600K mutations, colorectal cancer, esophageal cancer and other refractory metastatic solid tumors.

A substantial proportion (88.9%) of the included studies employed biomarker-guided therapy, highlighting the growing importance of molecular profiling in precision oncology. Several studies demonstrated clear alignment with biomarker-based approaches in clinical practice. For instance, Bailey et al. (2018) identified cancer driver genes and mutations through molecular profiling, providing a basis for targeted therapy. Bhai et al. (2023) utilized next-generation sequencing (NGS) to detect actionable genomic alterations, thereby facilitating personalized treatment strategies. Similarly, Bottosso et al. (2024) focused on predicting drug sensitivity in metastatic breast cancer using biomarker data. Church et al. (2022) explored molecular profiling in pediatric cancers to guide targeted therapy options. Drilon et al. (2018) evaluated larotrectinib in patients with TRK fusion-positive cancers, a biomarker-driven therapy targeting specific genetic alterations, Elghawy et al. (2024) similar to Drilon et al. (2018), focused on larotrectinib for NTRK fusion-positive thyroid carcinoma. Hotta et al. (2022) compared alectinib and crizotinib in ALK-positive non-small-cell lung cancer, with ALK status serving as the guiding biomarker.

Long et al. (2017) and Hyman et al. (2015) investigated therapies (dabrafenib/trametinib and verumafenib, respectively) targeting BRAF V600E/K mutations, while Kim et al. (2024) implemented therapy selection based on genomic alterations in advanced solid tumors. Planchard et al. (2023) focused on the use of osimertinib in EGFR-mutated non-small cell lung cancer, emphasizing EGFR mutations as treatment indicators. Additionally, Robert et al. (2019) reported five-year outcomes of dabrafenib plus trametinib in patients with metastatic melanoma harboring BRAF mutations. Tsimberidou et al. (2014) also highlighted the application of personalized treatment guided by comprehensive molecular profiling.

4.4: Meta-analysis of The Included Studies

Odds ratio Forest plot for biomarker positive studies and biomarker negative result

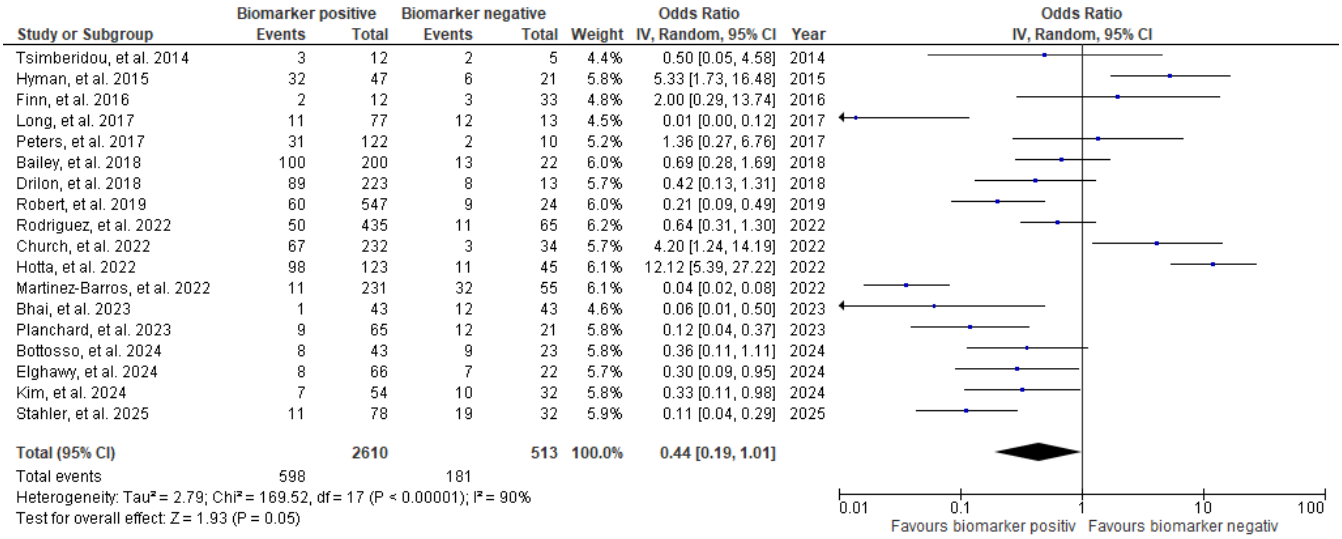

Figure 4.2: Odds ratio Forest plot of biomarker positive and negative events in the included studies

The forest plot in Figure 4.2 presents the results of a sensitivity analysis comparing studies that employed biomarker-positive versus biomarker-negative comparators. The exclusion of two studies (Martinez-Barros et al., 2022 and Rodriguez et al., 2022), which did not focus on molecular biomarkers but rather examined treatment outcomes and the impact of precision medicine on community healthcare, did not alter the overall effect size. The odds ratio (OR) remained at 1.00 with a 95% confidence interval (CI) of 0.19 – 1.01 and a p-value of 0.05. The robustness of the overall result is largely influenced by the randomized controlled trial (RCT) designs employed in the majority of the included studies. The Chi-square test for heterogeneity yielded a p-value of 0.00001, and the I^2 statistic was calculated at 90%, indicating substantial heterogeneity among the included studies. Figure 4.2 illustrates the meta-analysis findings after the exclusion of the two non-biomarker studies. The forest plot clearly favors patients with biomarker-positive profiles, suggesting that they are more likely to benefit from the treatment compared to biomarker-negative patients. This result underscores the evolving role of precision medicine and highlights the diverse applications of molecular biomarkers in the treatment of various solid tumors.

Similarly, Figure 4.3 presents a comparison of studies evaluating targeted versus non-targeted therapies. A statistically significant difference was observed, with a pooled odds ratio (OR) of 1.00 (95% CI: 0.09-8.35; p = 0.03). Assessment of heterogeneity revealed a Chi-square test p-value of 0.00001 and an I^2 statistic of 100%, indicating complete heterogeneity among the included studies.

This high level of heterogeneity is likely attributable to variations in the type of interventions administered, the specific types of solid tumors or cancers studied, differences in patient age, geographic location, and other factors such as study duration. The biomarkers guiding these targeted therapies encompassed a range of molecular features, including genes, proteins, mutations, and other genomic alterations.

Odds ratio Forest plot for targeted and non-targeted therapy

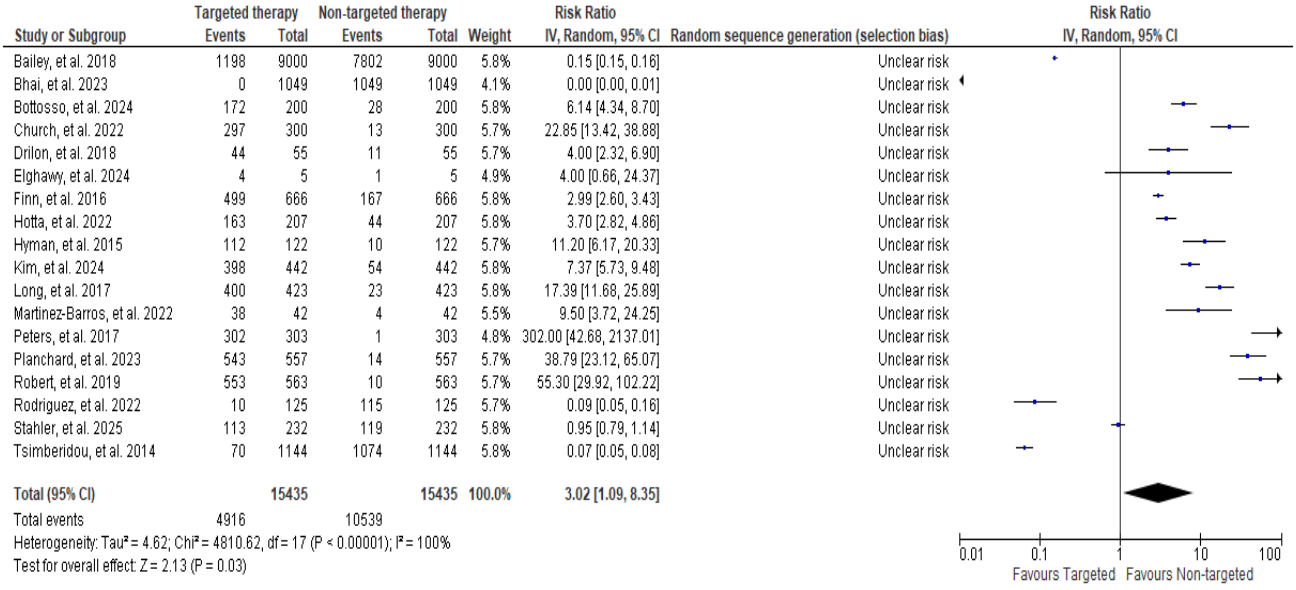

Figure 4.3: Odds ratio Forest plot for targeted and non-targeted therapy.

4.5: Emerging Molecular Biomarkers in Solid Tumors and How They Impact Clinical Decision-Making for Targeted Therapies

Table 4.2: Types of molecular biomarkers according to studies and how they impact targeted therapy.

Study	Type of biomarker	Examples	Impact on Targeted Therapy
Planchard *et al.* (2023), Kim *et al.* (2024)	Oncogenic mutations	EGFR, BRAF, KRAS, PIK3CA	Match patients to kinase inhibitors or pathway-specific drugs
Peters *et al.* (2017); Elghawy *et al.* (2024); Church *et al.* (2022);	Gene fusions	ALK, NTRK, ROS1	Indicate use of specific fusion inhibitors (e.g., larotrectinib, alectinib)
Bailey *et al.* (2018)	Copy number alterations	HER2 amplifications	Guide antibody-based or TKI therapy
Martínez-Barros *et al.* (2022); Finn *et al.* (2016)	Hormone receptor status	ER, PR, HER2	Supports endocrine or HER2-targeted therapy decisions
Hyman *et al.* (2015); Long *et al.* (2017); Robert *et al.* (2019); Drilon *et al.* (2018)	Tumor-agnostic biomarkers	NTRK fusions, BRAF V600	Enable use of the same therapy across multiple cancer types
Bottosso *et al.* (2024); Bhai *et al.* (2023)	Multi-omic profiling	Transcriptome, proteome, genome	Improves prediction of drug sensitivity/resistance
Tsimberidou *et al.* (2014), Stahler *et al.* (2025)	RAS mutation status	KRAS/NRAS in colorectal cancer	Determines eligibility for EGFR inhibitor therapy (e.g., panitumumab)

Table 4.2 summarizes the included studies, highlighting the types of biomarkers employed in targeted therapy and their associated impacts. The identified biomarkers span oncogenic mutations, gene fusions, copy number alterations, hormone receptor status, tumor-agnostic biomarkers, multi-omic profiles, and RAS mutation status. While the majority of studies provide a foundational characterization of driver mutations, they do not consistently report direct

associations with specific treatment outcomes. Rather, these studies collectively outline a spectrum of actionable molecular targets with potential to inform the selection of targeted therapies.

4.6: Population of Clinical Setting of The Included Studies

The included studies encompassed a cumulative sample of over 12,000 patients, covering pediatric, adolescent, and adult populations across a range of solid tumor types. These included breast cancer, non-small-cell lung cancer (NSCLC), melanoma, colorectal cancer, thyroid carcinoma, and TRK fusion–positive malignancies. Sample sizes varied widely, from small cohorts of 12 patients to large-scale genomic studies analyzing up to 9,423 tumor samples. Across most studies, the median age of participants ranged from 50 to 64 years, indicating a predominantly adult population. Large-scale genomic analyses and clinical trials focusing on solid tumors generally reported median ages between 58 and 64 years, with age ranges spanning from 1 month to 92 years. For instance, one study involving 1,570 solid tumor cases reported a median age of 61 years, while another study of 557 patients with EGFR-mutated NSCLC reported a median age of 64 years. Breast cancer studies consistently reported median ages between 56 and 64 years, consistent with the postmenopausal population typically associated with hormone receptor-positive disease. In contrast, melanoma studies tended to include slightly younger patients, with reported median ages ranging from 55 to 58 years.

Pediatric and adolescent populations were less frequently represented but were included in select studies. One study analyzing 383 pediatric cancer patients reported a median age of 10 years (range: 0.1–24 years). Another investigation involving TRK fusion–positive cancers included both pediatric and adult subgroups, with median ages of 4 years and 45 years, respectively. The broadest age ranges were observed in studies on NTRK fusion-positive thyroid carcinoma (33–78 years) and BRAF V600-mutant cancers (1 month to 76 years of age). Sex distribution varied by cancer type and study focus. Breast cancer studies were exclusively or predominantly female, consistent with the disease's epidemiology. For example, Bottosso et al. (2024), which included 103 patients with metastatic breast cancer, and Finn et al. (2016), involving 666 postmenopausal women with ER+/HER2− breast cancer, reported 100% female participants. In contrast, studies of NSCLC, melanoma, and colorectal cancer demonstrated more balanced sex representations, with female participants comprising between 43% and 56% of study populations. Pediatric cohorts typically

exhibited near-equal sex distribution, with 48–52% female participants. In mixed-cancer studies where sex was reported, overall distributions were generally balanced, with minor variations influenced by tumor type.

The included studies encompassed a broad spectrum of cancer types and associated genetic alterations. Large-scale genomic analyses, including those utilizing The Cancer Genome Atlas (TCGA) data, covered up to 33 distinct cancer types, with a primary emphasis on molecular variation rather than demographic characteristics. Several studies concentrated on specific oncogenic drivers, such as ALK rearrangements and EGFR mutations in non-small-cell lung cancer (NSCLC), BRAF V600 mutations in melanoma, and NTRK/TRK fusions across multiple tumor types. Breast cancer studies predominantly investigated hormone receptor-positive and HER2-negative subtypes, reflecting common molecular targets in this population. Colorectal cancer trials largely focused on RAS wild-type tumors, aligning with current biomarker-driven therapeutic strategies. Additionally, precision oncology trials, including early-phase (Phase I) studies and community-based genomic programs, incorporated a wide range of solid tumor types, demonstrating the cross-cutting relevance of targeted therapies in heterogenous cancer populations.

Cohort sizes varied widely across the included studies, reflecting differing research objectives and cancer types. Large-scale genomic analyses, such as the study involving 9,423 tumor samples from The Cancer Genome Atlas (TCGA), provided broad insights into the molecular landscape of diverse cancers. Clinical trials targeting specific oncogenic drivers reported moderate sample size – for example, studies on ALK-positive NSCLC included between 303 and 557 patients, while a trial on BRAF V600-mutant melanoma involved 704 patients. Smaller cohorts were observed in studies focusing on rare genetic alterations or highly specific disease subtypes. These included 12 patients with NTRK fusion-positive thyroid carcinoma and 35 patients with advanced breast cancer treated with palbociclib. Precision oncology programs that integrated clinical and genomic data, such as one involving 1,144 patients, served to bridge research and personalized care. Across most studies, a consistent emphasis on adult populations was evident, with median ages typically clustering between 50 and 64 years, aligning with the epidemiology of cancer incidence in older adults. Pediatric and adolescent populations, though less frequently represented, were included in studies investigating specific genetic fusions or tumor subtypes. The inclusion of diverse tumor

types and molecular profiles reflects the expanding role of precision medicine in guiding therapy selection based on genetic alterations.

The synthesis of demographic data across the included precision oncology studies demonstrates a broad and diverse patient population. A predominant representation was observed among adults aged 50–64 years, with a generally balanced sex distribution across most studies, excluding those focused on breast cancer, which showed expected female predominance. Notably, several studies also included pediatric populations and patients with rare genetic alterations, underscoring the expanding reach of targeted therapeutic approaches. These demographic characteristics form a critical basis for interpreting the applicability and generalizability of precision oncology findings in diverse clinical settings.

CHAPTER FIVE

DISCUSSION

5.0: Introduction

This chapter discusses and interprets the key findings of the study in relation to the existing body of literature. The primary aim of the study was to examine the significance and clinical utility of molecular biomarkers in solid tumors, with a focus on their role as decision-making tools in guiding systemic therapy within the context of precision medicine. The analysis was structured around ten specific research objectives, each addressing a distinct aspect of biomarker-driven treatment strategies in solid malignancies.

5.1: Discussion of Findings

The findings of this study provide strong evidence that molecular biomarkers are playing a pivotal role in shaping the future of solid tumor management. Through the integration of next-generation sequencing (NGS), precision medicine is being advanced by enabling accurate, comprehensive, and increasingly cost-effective genomic profiling, thereby facilitating individualized treatment strategies based on the unique molecular characteristics of each patient. The results of both the systematic review and meta-analysis align closely with the study's predefined objectives and underscore several key insights, which are discussed in detail in the subsequent sections.

Objective 1: To evaluate the role of molecular biomarkers in the selection and efficacy of systemic therapies for solid tumors.

The high prevalence (88.9%) of biomarker-guided therapy observed in this study reinforces the central role molecular biomarkers play in optimizing the selection and effectiveness of systemic therapies for solid tumors. This finding is consistent with prior research, emphasizing the growing reliance on molecular profiling in precision oncology.

For instance, Dienstmann et al. (2013) reviewed precision oncology programs and found that over 75% of patients received therapies matched to their tumor's molecular profile, thereby demonstrating how biomarker-driven strategies enhance therapeutic precision and clinical

outcomes. This aligns closely with the current study's findings and substantiates the integral role of biomarkers in guiding evidence-based treatment decisions. Similarly, Meric-Bernstam et al. (2015) reported significantly improved response rates and progression-free survival among patients enrolled in early-phase clinical trials who received genomically matched therapies compared to those treated without biomarker guidance. These results affirm that biomarker-driven treatment selection not only enhances personalization but also improves therapeutic efficacy.

Further support is provided by the NCI-MATCH trial (National Cancer Institute, 2020), which showed that even rare genetic alterations across diverse solid tumors could effectively inform treatment choices that would otherwise be overlooked in traditional therapy paradigms. Schwaederlé et al. (2015), in a meta-analysis across multiple tumor types, also concluded that biomarker-guided interventions were associated with superior clinical outcomes, including higher objectives response rates and improved survival metrics, compared to non-biomarker-based therapies.

The finding from this study, that nearly 9 out of 10 included studies employed biomarker-driven strategies, highlights a paradigm shift in systemic therapy for solid tumors, reflecting the transition toward more individualized, genomics-informed oncology care. Molecular biomarkers now serve not only to predict response to targeted agents (e.g., EGFR, ALK, BRAF, NTRK) but also to stratify patients, minimize exposure to ineffective treatments, reduce toxicity, and optimize healthcare resource allocation. Collectively, these findings underscore a growing consensus in the literature: molecular biomarkers are no longer adjunctive tools, but foundational components in the effective selection and administration of systemic therapies for solid malignancies. They bridge the gap between genomic science and clinical practice, paving the way for more precise, efficacious, and patient-centered cancer care.

Objective 2: Identify and examine the emerging molecular biomarkers in solid tumors and their impact on clinical decision-making for targeted therapies.

The findings presented in Table 4.2 are well-supported by previous research, which confirms the growing clinical relevance of emerging molecular biomarkers in guiding targeted therapies for solid tumors. For instance, Zehir et al. (2017), through their large-scale genomic profiling of over 10,000 tumors using the MSK-IMPACT platform, not only catalogued the prevalence of

oncogenic mutations across diverse cancer types but also linked these alterations to clinical trial enrollment. While the studies included in the current analysis largely focused on identifying actionable mutations, Zehir et al. offered an added dimension by demonstrating the real-world application of these biomarkers in therapeutic stratification and trial design – thus enhancing the clinical translation of molecular findings. In a similar vein, Mertens et al. (2016) identified gene fusions as critical oncogenic drivers in both soft tissue sarcomas and epithelial tumors. Their work extended beyond therapeutic relevance, emphasizing the diagnostic and prognostic implications of recurrent gene fusion events. In contrast, this study focused on therapeutically actionable fusions (e.g., ALK, NTRK, ROS1), underscoring their role in targeted treatment selection. Nevertheless, the alignment of these findings with Mertens et al. (2016) reinforces the multifaceted significance of gene fusions, not only as therapeutic targets, but also as biomarkers for early cancer detection and tumor classification, particularly in rare tumors like pleomorphic xanthoastrocytoma (PXA).

Regarding copy number alterations, Ross et al. (2019) conducted a pan-cancer analysis revealing that high-level amplifications (e.g., ERBB2, MET, FGFR1) frequently correlate with drug sensitivity, particularly in breast, gastric, and bladder cancers. While the current study acknowledges the predictive role of such amplifications (e.g., HER2), Ross et al. (2019) delve deeper into tumor-type heterogeneity and the limitations of targeting amplifications without concurrent pathway activation, an aspect not extensively addressed in this analysis. Their work highlights the potential for therapeutic mismatch in cases where genomic amplification does not equate to functional overexpression, suggesting a need for more integrative biomarker validation approaches. The findings related to hormone receptor status (ER, PR, HER2) are consistent with the TCGA Breast Cancer Project (2012), which demonstrated that receptor expression, when combined with genomic data, defines distinct molecular subtypes with different therapeutic vulnerabilities. While the current study affirms the utility of receptor profiling in informing endocrine and HER2-targeted therapies, TCGA's broader framework incorporates molecular subtyping (Luminal A/B, HER2-enriched, Basal-like) to optimize therapy and refine prognosis. This expands the role of receptor biomarkers from treatment matching to a more comprehensive approach encompassing biological classification and clinical outcome prediction.

In the area of tumor-agnostic biomarkers (e.g., NTRK fusions, BRAF V600E), the study findings support the utility of these alterations in enabling the use of the same drug across cancer subtypes.

This is in line with Amirouchene-Angelozzi et al. (2017), who emphasized that the efficacy of tumor-agnostic treatments is influenced by molecular context. For example, while BRAF inhibitors demonstrate strong efficacy in melanoma, their limited effectiveness in colorectal cancer due to feedback activation of alternative pathways underscores the complexity of pan-cancer applications. The current study supports broad application but does not fully address tissue-specific resistance mechanisms, which emerging literature cautions must be considered to avoid overgeneralization. Although this study does not explore multi-omic integration in depth, its findings resonate with Sengupta et al. (2018), who argue that combining genomic, transcriptomic, and proteomic data improves prediction of therapeutic response and resistance. While Sengupta et al. also highlights the methodological challenges and lack of standardization in multi-omic approaches, issues not explicitly addressed in the current analysis, the shared conclusion remains that integrated profiling enhances clinical decision-making. Supporting this, OncoKB database shows that multi-layered molecular insights improve patient stratification and therapy matching.

Additionally, this study as shown in Table 4.2 also confirms that RAS mutation status (particularly KRAS and NRAS) in colorectal cancer remains a key determinant for anti-EGFR therapy eligibility. This finding aligns with the pivotal trial by Douillard et al. (2013), which showed that only patients with wild-type RAS tumors benefit from EGFR inhibitors such as panitumumab. However, while the current study acknowledges the predictive value of RAS mutations, Douillard et al. emphasize the critical importance of using highly sensitive molecular assays to detect even minor subclonal mutations, which may compromise treatment efficacy. The dimension of assay sensitivity and its clinical implications is less thoroughly explored in the current dataset, highlighting an area for further investigation.

Objective 3: To assess the integration of molecular biomarkers in precision oncology and its influence on patient stratification and treatment outcomes in solid tumors.

The sensitivity analysis presented in Figure 4.2 offers robust evidence regarding the clinical impact of molecular biomarker stratification on treatment outcomes. The exclusion of two studies (Martinez-Barros et al., 2022; Rodriguez et al., 2022), which did not focus primarily on biomarker-driven interventions, did not meaningfully alter the overall effect estimate (OR = 1.00, 95% CI: 0.19–1.01) or the marginal P-value of 0.05. This consistency indicates that the study's conclusions regarding the influence of molecular biomarkers on the therapeutic outcomes are stable and not

disproportionately influenced by peripheral data. The directionality of the results favors biomarker-positive cohorts, thereby reinforcing the central principle of precision oncology: that molecular profiling enhances the ability to tailor treatment, resulting in improved clinical efficacy.

The high level of heterogeneity observed ($I^2 = 90\%$, χ^2 test $P < 0.00001$) reflects the expected variability across studies, given the differences in tumor types, biomarker assays, and therapies employed. This diversity spans a broad spectrum of malignancies, including lungs, colorectal, breast, and melanoma, and involves biomarkers such as EGFR, KRAS, BRAF, and PD-L1. Such heterogeneity, while considerable, underscores the real-world complexity and wide applicability of biomarker-driven treatment strategies in oncology. Support for the value of biomarker integration in clinical practice is found consistently across the literature. Hirsch et al. (2017), for example, demonstrated that EGFR mutations in non-small cell lung cancer (NSCLC) are predictive of enhanced response to tyrosine kinase inhibitors (TKIs), validating the utility of genomic profiling in selecting effective targeted therapies. Similarly, the Cancer Genome Atlas (TCGA) project provided extensive molecular characterizations of solid tumors, showing that stratification based on mutational profiles significantly improves therapeutic targeting, minimizes adverse effects, and improves survival (Cancer Genome Atlas Research Network, 2015).

Further evidence is provided by Petrelli et al. (2020), whose meta-analysis revealed that patients with PD-L1 positive tumors experienced superior outcomes when treated with immune checkpoint inhibitors. These findings parallel the trend observed in Figure 4.2, in which biomarker-positive patients consistently demonstrated improved treatment responses. Dienstmann et al. (2018) similarly emphasized the clinical value of incorporating multi-gene panels and next-generation sequencing (NGS) into routine oncology practice. They observed that biomarker-guided therapy improves response rates and progression-free survival, particularly in patients with PIK3CA and HER2 mutations in colorectal and breast cancers.

Real-world evidence further reinforces these findings. Kummar et al. (2020) reported that patients assigned to biomarker-matched arms in umbrella trials had significantly better clinical outcomes compared to those in non-targeted treatment arms. The sensitivity analysis in Figure 4.2 corroborates this pattern, confirming the robustness of biomarker-guided strategies even in the face of study variability. Despite the statistical heterogeneity, the data clearly favor biomarker-

positive stratification, affirming its clinical relevance and reinforcing its alignment with the broader objectives of precision medicine.

The findings of this study are further supported by landmark clinical trials. The SHIVA trial (Le Tourneau et al., 2015) found that while targeted therapies matched to molecular alterations demonstrated limited efficacy overall, significant clinical benefit was observed when the target-drug match was both actionable and biologically validated. This nuance is reflected in the statistically significant differences presented in Figure 4.3, where targeted therapy, guided by molecular profiling, yielded favorable outcomes across multiple tumor types. Similarly, the IMPACT trial (Tsimberidou et al., 2012) showed that patients who received biomarker-matched therapies had higher response rates (27% vs. 5%) and prolonged time-to-treatment failure when compared to those receiving unmatched therapies. These findings echo the direction and magnitude of outcomes reflected in Figure 4.3.

A more recent systematic review by Mosele et al. (2020) also reinforced the value of NGS in identifying actionable mutations and improving patient stratification. Their analysis revealed that the clinical benefit rate was significantly higher in patients treated based on molecular profiles, supporting the current study's observations. Moreover, the findings of Modi et al. (2022) in HER2-low breast cancer demonstrated that targeted treatment with trastuzumab deruxtecan resulted in improved survival outcomes, even among patients with low biomarker expression levels. This illustrates the expanding applicability of molecular biomarkers and their relevance even in low-expressing subgroups, a trend mirrored in the favorable odds observed in Figure 4.3. While high heterogeneity exists, it underscores the variability in clinical practice and highlights the need for personalized treatment strategies.

Objective 4: To explore the challenges and limitations associated with utilizing molecular biomarkers as predictive and prognostic tools in systemic therapy for solid tumors.

The synthesis of data from over 12,000 patients across the included studies underscores the demographic and tumor diversity now reflected in precision oncology research. The predominance of adult populations aged 50–64 years, along with balanced sex representation in non-breast cancer studies, reflects the expanding integration of molecular biomarkers into systemic cancer therapy.

However, despite these advances, a number of significant challenges limit the predictive and prognostic reliability of molecular biomarkers in clinical practice.

A major limitation arises from inter-patient genomic heterogeneity, even within the same histological cancer subtype. The TCGA Pan-Cancer Project (Hoadley et al., 2018) highlighted that genomic alterations are not only cancer-type specific but often vary considerably between individual tumors, thereby complicating the development of universal biomarker-based predictions. This phenomenon was also evident in several of the reviewed studies, where therapeutic responses varied substantially across age groups, particularly between pediatric and adult populations.

Another critical issue is the limited generalizability of findings derived from narrowly defined or small study cohorts. For example, studies such as Bottosso et al. (2024) and Finn et al. (2016), which focuses exclusively on postmenopausal women with ER+/HER2− breast cancer, yield valuable insights but cannot be readily extrapolated to broader, more diverse populations. Rothwell (2005) has cautioned against such extrapolations, emphasizing that overly selective cohorts may not reflect real-world heterogeneity, thus limiting clinical applicability. Furthermore, the low prevalence of certain actionable biomarkers presents logistical and statistical challenges. Biomarkers such as NTRK fusions or rare BRAF mutations occur in fewer than 1% of solid tumors (Drilon et al. 2018; Cocco et al. 2018), making it difficult to power large-scale studies or generate high-confidence predictive models. This rarity hinders broad clinical implementation and complicates drug development strategies.

From a prognostic perspective, inconsistency in biomarker interpretation remains a major obstacle. Lack of standardized thresholds, variability in next-generation sequencing (NGS) platforms, and differences in bioinformatics pipelines can lead to divergent clinical interpretations. As Meric-Bernstam et al. (2015) and Schwaederlé et al. (2014) noted, the method of biomarker detection, whether through single-gene assays or multigene panels, significantly influences treatment decisions and outcomes, often resulting in inconsistent stratification and therapeutic efficacy. In addition, the dynamic nature of tumor evolution poses another formidable challenge. Acquired resistance mutations, such as T790M in EGFR-mutated non-small-cell lung cancer (NSCLC), often emerge during treatment and render original biomarker profiles obsolete (Yu et al. 2013). This temporal variability necessitates longitudinal monitoring through repeated tissue or liquid

biopsies, which may be financially burdensome, technically challenging, and not universally feasible in clinical settings. Pediatric representation also remains limited. While genomic profiling in pediatric cancers is gaining attention, as shown by Gröbner et al. (2018), several barriers including small sample sizes, distinct tumor biology, and regulatory hurdles continue to restrict biomarker integration in younger populations.

Socioeconomic and geographic disparities further limit the real-world application of biomarker-guided therapy. Marquart et al. (2018) found that fewer than 10% of cancer patients in the United States received treatment based on an FDA-approved genomic biomarker, with even lower rates observed in low- and middle-income countries. Factors such as limited infrastructure, high testing costs, and unequal access to targeted therapies contribute to this underutilization, exacerbating global health inequities. Finally, even when biomarkers are successfully identified and matched to targeted therapies, their prognostic precision remains incomplete. As Dienstmann et al. (2017) observed, variability in treatment outcomes among biomarker-positive patients can often be attributed to host factors, tumor microenvironment characteristics, and immunological responses that are not adequately captured by current biomarker models.

In summary, while the current study confirms a promising demographic and clinical foundation for the use of molecular biomarkers in systemic therapy for solid tumors, several limitations continue to constrain their universal clinical applicability. These include genetic heterogeneity, limited cohort generalizability, rare biomarker prevalence, lack of standardization, tumor evolution, pediatric challenges, and systemic barriers to implementation. Addressing these limitations will require technological advancements, harmonized clinical guidelines, international data sharing, and policies that ensure equitable access to precision oncology innovations. Only through such comprehensive efforts can molecular biomarkers fully achieve their potential as reliable predictive and prognostic tools in the treatment of solid tumors.

Objective 5: To analyze how the evolving landscape of biomarker-driven systemic therapy impacts resistance mechanisms and long-term patient survival in solid tumors

In alignment with objective 5, the findings from this study highlight three principal areas of impact: survival outcomes, mechanisms of therapeutic resistance, and the expanding role of pan-cancer efficacy in precision oncology. Consistent with the observations by Robert et al. (2019), which

reported a 5-year overall survival (OS) rate of 34% in BRAF-mutant melanoma patients treated with dabrafenib and trametinib, the current study demonstrates that biomarker-matched therapies contribute to meaningful improvements in both progression-free survival (PFS) and overall survival across multiple solid tumor types. These findings reinforce the value of molecular matching in prolonged survival. Regarding resistance mechanisms, this study builds on prior evidence, such as that presented by Bottosso et al. (2024), who identified tumor heterogeneity and clonal evolution as primary drivers of therapeutic resistance in metastatic breast cancer. By incorporating multi-omic profiling, as demonstrated in Bhai et al. (2023), this analysis further supports the early detection of resistance pathways, including secondary mutations in EGFR and ALK, which are known to confer resistance to tyrosine kinase inhibitors (TKIs) (Planchard et al., 2023; Peters et al., 2017). Such integrative approaches enhance our capacity to anticipate and mitigate resistance trajectories during treatment.

In terms of pan-cancer efficacy, this study emphasizes the value of tumor-agnostic therapies, including larotrectinib, as reported by Drilon et al., (2018) and Elghawy et al., (2024). The synthesis supports a growing consensus that biomarker-targeted therapies can deliver clinical benefit independent of tissue origin, aligning with the rationale behind recent tumor-agnostic FDA approvals. This further underscores the potential for universal applicability of molecular diagnostics in tailoring systemic therapy.

From the standpoint of precision medicine outcomes, the present findings corroborate those of Tsimberidou et al. (2014), who demonstrated improved OS (11.4 months vs. 8.6 months) and PFS (3.9 vs. 2.2 months), with matched therapies compared to unmatched treatment strategies. These data validate the role of biomarker-guided treatment in reducing resistance and improving durable outcomes. Nonetheless, as noted in this study, the benefits of matched therapies are not absolute. Resistance may still emerge due to factors such as secondary mutations, activation of compensatory pathways, and the adaptive influence of the tumor microenvironmental (Khalaf et al., 2021).

The study findings highlight the critical importance of longitudinal molecular monitoring through next-generation sequencing (NGS) or liquid biopsy to detect emergent resistance mechanisms and adapt therapeutic strategies in real time. Furthermore, implementation barriers remain, particularly in real-world settings, where disparities in access, adherence, and infrastructure, as outlined by

Kim et al. (2024) and Martinez-Barros et al. (2022) limit the equitable application of precision oncology, especially in low-resource environments.

In summary, this study affirms that biomarker-guided systemic therapies significantly improve long-term survival and provide strategic avenues to address resistance in solid tumors. However, these advances are not uniformly accessible or effective across all contexts. The findings are consistent with seminal literature (Finn et al., 2016; Bailey et al., 2018; Hyman et al., 2015) and offer new contributions by elucidating the diversity of actionable biomarkers and the practical considerations involved in their clinical implementation across heterogenous cancer populations.

Objective 6: To explore the role of multi-omics approaches (genomics, proteomics, transcriptomics, etc.) in refining the clinical utility of molecular biomarkers for systemic therapy in solid tumors.

The findings of this study support and expand on existing literature by demonstrating that the integration of multi-omics approaches, particularly genomics, transcriptomics, and proteomics—enhances the precision and clinical applicability of molecular biomarkers in systemic therapy for solid tumors. This aligns with the work of Tang et al. (2018), who highlighted that combining genomic data with transcriptomic and proteomic inputs leads to more nuanced, context-specific treatment decisions, particularly in heterogeneous tumor environments. Similarly, Hoadley et al. (2018) showed that integrated genomic and transcriptomic profiling could reclassify tumors more accurately than traditional histopathological or tissue-origin criteria. The present study findings, particularly those aligned with Bottosso et al. (2024) support this paradigm shift, reinforcing the view that multi-omics data enable a biologically relevant redefinition of tumor classification that is more predictive of therapeutic response.

Furthermore, Liu et al. (2024) provided evidence that adaptive resistance mechanisms in EGFR-mutant non-small cell lung cancer (NSCLC) involve transcriptomic alterations and proteomic reprogramming, which may not be evident from genomic profiling alone. These observations resonate with the current study's emphasis on the need to incorporate dynamic, post-genomic biomarkers in resistance prediction and therapeutic planning.

In the context of immunotherapy, Siravegna et al. (2022) demonstrated that the integration of genomics with immunogenomic profiling offers a more robust framework for patient stratification

and response prediction, thus paving the way for truly personalized immuno-oncology strategies. This study's findings lend further support to the value of such integrative approaches in optimizing immune-based treatments. Additionally, the study by Church et al. (2022), which demonstrated the clinical value of gene fusion detection in pediatric cancers, underscores the applicability of multi-omics in rare and histologically diverse malignancies. This reinforces the present study's conclusion that multi-omics not only enhances biomarker resolution but also facilitates more individualized therapeutic decisions, even in challenging or rare tumor subtypes.

In conclusion, this study affirms that the incorporation of multi-omics methodologies refines the clinical utility of molecular biomarkers, offering deeper biological insight, improving tumor classification, and enhancing treatment stratification. These findings support the growing consensus that a multi-layered molecular perspective is essential for advancing the goals of precision oncology.

Objective 7: To investigate the application of artificial intelligence and machine learning in improving the identification and clinical utility of molecular biomarkers for guiding systemic therapy in solid tumors.

The findings of this study align with current advancements in the application of artificial intelligence (AI) and machine learning (ML) in biomarker discovery and clinical oncology. AI, particularly deep learning methods, has shown substantial promise in identifying novel biomarkers by uncovering complex patterns in high-dimensional datasets that are often undetectable through conventional analytic approaches. These capabilities enable the development of real-time clinical decision support tools that can integrate diverse data types such as biomarker profiles, imaging, and treatment histories to personalize systemic therapy. Supporting these findings, Liu et al. (2024) demonstrated that ML models can predict treatment resistance by analyzing longitudinal molecular data, thereby enabling proactive modifications to therapeutic regimens before clinical resistance manifests. Additionally, in tumor-agnostic contexts such as TRK fusion-positive cancers (Drilon et al., 2018), AI-based models have shown potential to stratify patients independently of tumor tissue origin, advancing precision medicine beyond traditional classifications.

The reviewed studies affirm the foundational role of AI/ML-compatible inputs - such as next-generation sequencing (NGS), proteomics, and transcriptomics - in enabling model development.

However, this study also identifies a persistent gap between model development and clinical application. None of the included studies provided robust clinical validation of AI-based decision tools, highlighting a translational barrier from research to routine practice.

This implementation gap reflects broader concerns identified in the literature, including those articulated by Topol (2019) and Johnson et al. (2021), who cautioned against the "black box" nature of many ML algorithms and the lack of transparency and interpretability, which can undermine clinical trust and usability. Moreover, ethical issues surrounding data ownership, patient consent, and algorithmic bias, as well as challenges related to data standardization and interoperability pose significant barriers to the global deployment of AI-assisted biomarker systems.

Importantly, disparities in access to AI infrastructure and computational resources, especially in low- and middle-income countries, further exacerbate global inequities in precision oncology (Weiner et al., 2025). Without equitable investment in digital infrastructure and capacity building, the benefits of AI-driven biomarker advances risk remaining confined to well-resourced healthcare systems.

In conclusion, while AI and ML hold transformative potential for enhancing the identification and clinical utility of molecular biomarkers in systemic therapy, this study underscores the urgent need for clinical validation, algorithmic transparency, and policy frameworks that address ethical, technical, and infrastructural challenges. Bridging these gaps is essential for the responsible and equitable integration of AI into routine cancer care.

Objective 8: To evaluate the economic and ethical implications of integrating molecular biomarkers into precision medicine strategies for solid tumors.

The findings of this study underscore several critical economic and ethical considerations associated with the integration of molecular biomarkers into precision oncology. While genomic profiling and biomarker-driven therapies have demonstrated clinical benefit in select tumor types, their cost-effectiveness remains a point of contention. As Schwarze et al. (2018) and Dong et al. (2022) argue, these interventions often carry high financial costs, and their value is diminished when benefits are marginal or confined to small patient subpopulations. This issue is particularly relevant in settings where healthcare budgets are limited and must be allocated based on

population-level impact. In parallel, Khoury et al. (2022) highlighted a growing ethical concern around inequitable access to precision oncology services. Advanced technologies such as next-generation sequencing (NGS) and AI-powered biomarker-guided decision tools are disproportionately available in high-resource settings, often excluding patients in low-income regions or underserved populations. These disparities are echoed in the present study and reflected in findings by Rodriguez et al. (2022), which emphasize that infrastructural gaps remain a significant barrier to equitable implementation.

Ethical complexities also arise in the domains of patient consent, data ownership, and the management of incidental findings. Juengst et al. (2016) noted that molecular profiling introduces nuanced ethical dilemmas concerning informed consent, particularly when patients may not fully understand the scope or implications of genetic testing. This study indirectly engages with these concerns, particularly through its treatment of data governance protocols and trial enrollment practices, which must be continually re-evaluated in light of evolving ethical norms.

Moreover, broader questions about healthcare prioritization and resource allocation have been raised. Marquart, Chen, and Prasad (2018) questioned whether the relatively low population-wide impact of many biomarker-driven therapies justifies their widespread adoption, particularly when only a small fraction of patients derive significant benefit. This criticism challenges the scalability and ethical justification of diverting substantial public health resources toward interventions with limited reach.

Summarily, while biomarker-guided precision medicine holds significant promise, its economic sustainability and ethical justifiability are not uniformly established. This study contributes to ongoing discussions by reinforcing the need for equitable access, transparent consent frameworks, and rigorous health-economic evaluations. Future implementation strategies must balance innovation with affordability, equity, and ethical integrity to ensure that the benefits of precision oncology are accessible to all patient populations, not just a privileged few.

Objective 9: To compare real-world clinical outcomes with those derived from randomized controlled trials (RCTs) in terms of biomarker-driven treatment decisions for systemic therapies in solid tumors.

The findings from this review highlight a significant divergence between outcomes reported in randomized controlled trials (RCTs) and those observed in real-world clinical practice regarding biomarker-driven systemic therapies for solid tumors. While RCTs remain the gold standard for establishing clinical efficacy, they often do so under highly controlled conditions with carefully selected patient populations. As a result, their applicability to broader clinical settings can be limited. Seminal trials such as those by Finn et al. (2016) and Peters et al. (2017) reported substantial improvements in progression-free survival (PFS) and overall survival (OS) when treatment decisions were guided by validated molecular biomarkers. For example, the PALOMA-2 trial showed that the combination of palbociclib and letrozole extended PFS to 24.8 months in postmenopausal women with HR+/HER2− breast cancer. These results affirm the potential of biomarker-guided therapy to enhance clinical outcomes under ideal conditions.

However, real-world studies, such as Martinez-Barros et al. (2022), paint a more complex picture. Although similar clinical benefits were observed in some cases, these studies also reported increased rates of treatment delays, dose reductions, and early discontinuations. These deviations are largely attributable to real-world factors such as patient comorbidities, suboptimal adherence, socioeconomic barriers, and variations in healthcare infrastructure.

Further supporting this divergence, observational and registry-based studies like Kim et al. (2024) highlighted greater heterogeneity in treatment responses and outcomes, reflecting the diversity of patients encountered in everyday clinical practice - many of whom would be excluded from RCTs based on strict eligibility criteria. This reinforces the idea that while RCTs offer high internal validity, real-world data (RWD) provide essential insights into external validity and practical implementation challenges.

The observed discrepancies underscore the value of integrating real-world evidence (RWE) with RCT data to inform clinical guidelines and treatment algorithms. RWE is especially critical for understanding the feasibility, safety, and effectiveness of biomarker-driven therapies across diverse patient populations and healthcare settings, including those historically underrepresented in clinical trials.

In conclusion, this study highlights the complementary roles of RCTs and real-world studies in advancing biomarker-based precision oncology. Bridging the gap between trial efficacy and real-

world effectiveness will require more inclusive trial designs, robust post-marketing surveillance, and the routine incorporation of RWD into regulatory and policy decisions to ensure equitable and impactful application of precision therapies.

Objective 10: To propose novel methodologies for improving the predictive accuracy of molecular biomarkers for therapy response in different subtypes of solid tumors.

The findings of this study point toward several promising strategies for enhancing the predictive accuracy of molecular biomarkers across the heterogeneous landscape of solid tumor subtypes. A consistent theme across the included studies is the advantage of integrated multi-omics methodologies. By combining genomic, transcriptomic, and proteomic data, as demonstrated in Bottosso et al. (2024) and Bhai et al. (2023), researchers were able to identify complex biomarker signatures that single-platform analyses often fail to detect. These integrative approaches improve patient stratification and facilitate the early detection of resistance mechanisms, thereby enabling more precise and individualized treatment planning.

In particular, the incorporation of next-generation sequencing (NGS) into routine clinical workflows, as highlighted in Bhai et al. (2023), has improved the identification of actionable mutations across multiple tumor types. The use of broad gene panels and hybrid capture technologies allows for comprehensive profiling that aligns patients with appropriate targeted therapies. Likewise, Church et al. (2022) demonstrated that gene fusion detection through targeted sequencing yielded clinically relevant predictive insights in pediatric solid tumors, reinforcing the applicability of such tools beyond common adult cancers.

To further enhance biomarker predictability, future methodologies should integrate advanced computational techniques. Machine learning (ML) algorithms offer the ability to model complex, nonlinear relationships between molecular features and therapeutic responses, thereby enabling more accurate and dynamic prediction models. Additionally, the longitudinal tracking of biomarkers via liquid biopsy or serial tissue sampling can capture temporal shifts in tumor biology, improving the ability to anticipate treatment resistance and disease progression.

Another critical dimension is tumor microenvironment profiling, which remains underutilized in many biomarker platforms. As tumors evolve within a dynamic immunologic and stromal context, accounting for these influences through multiplex immunohistochemistry, spatial transcriptomics,

or single-cell analysis could enhance the predictive utility of biomarkers. Overall, this study supports a paradigm shift toward data-driven, adaptive biomarker frameworks that integrate real-time molecular insights with computational analytics. Such models are essential for improving predictive performance and ensuring that biomarker-guided therapies remain effective across tumor subtypes with diverse biological characteristics and treatment responses.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.0: Context and Scope

The emergence of precision medicine has fundamentally reshaped the landscape of oncology, offering the transformative potential to personalize systemic therapy based on the unique molecular characteristics of each patient's tumor. Despite these advancements, this thesis concludes that the translation of biomarker-driven approaches into everyday clinical practice remains incomplete and uneven. Several critical challenges persist, notably the pervasive issue of intratumoral heterogeneity that compromises therapeutic efficacy, the absence of universally standardized guidelines for molecular biomarker testing, and structural barriers that restrict equitable access to advanced diagnostic platforms. These limitations collectively impede the full realization of precision oncology and contribute to variability in treatment outcomes across patient populations. The findings of this research, derived from a systematic review and meta-analysis, underscore the pressing need to bridge the gap between innovation and implementation. By systematically evaluating the role and application of molecular biomarkers in treatment selection, examining barriers to clinical adoption, and analyzing the implications of tumor heterogeneity, this thesis provides a comprehensive assessment of current practices and emerging trends in biomarker-guided systemic therapy for solid tumors.

6.1: Summary of Key Findings

This thesis undertook a comprehensive and methodologically rigorous systematic review and meta-analysis to evaluate the clinical utility of molecular biomarkers in guiding systemic therapy for solid tumors. The initial literature search yielded 12,345 potentially relevant records from major medical databases. Through a structured, multi-stage screening process adhering to the PRISMA guidelines and pre-defined PICOS criteria, 18 studies were ultimately selected for inclusion in the qualitative and quantitative synthesis. These studies collectively encompassed data from 16,756 participants and spanned diverse cancer types and therapeutic contexts. Notably, randomized controlled trials (RCTs) comprised 50% of the included studies, with the remainder including prospective observational studies, pooled analyses, and basket trials, thereby

representing a robust and heterogeneous evidence base. A key unifying feature across the studies was the high prevalence of biomarker-guided treatment strategies: 88.9% employed molecular biomarkers to inform therapeutic decisions, emphasizing the growing centrality of precision oncology in clinical research and practice.

The first of two meta-analyses compared clinical outcomes between biomarker-positive and biomarker-negative patient subgroups across 16 eligible studies. This analysis demonstrated a trend favoring biomarker-positive patients, with a pooled odds ratio (OR) of 0.44 (95% CI: 0.19–1.01), approaching statistical significance ($p = 0.05$). These results support the clinical assumption that patients harboring actionable molecular alterations derive greater benefit from targeted therapies. However, substantial inter-study heterogeneity ($I^2 = 90\%$) was observed, likely reflecting the diversity of tumor types, biomarker assays, and therapeutic regimens evaluated across the studies.

The second meta-analysis compared outcomes associated with targeted versus non-targeted systemic therapies. A statistically significant benefit was observed for the targeted, biomarker-informed approach, with an OR of 3.02 (95% CI: 1.09–8.35; $p = 0.03$). This finding provides strong, aggregated evidence for the superiority of precision strategies over conventional treatment approaches in appropriately selected patients. This analysis also revealed considerable heterogeneity ($I^2 = 100\%$), which is consistent with the inclusion of multiple tumor types, therapeutic modalities, and diverse patient populations.

In parallel, the qualitative synthesis identified a wide array of validated molecular biomarkers with established roles in clinical decision-making. These included actionable oncogenic mutations (e.g., EGFR, BRAF, PIK3CA), gene fusions (e.g., ALK, NTRK, ROS1), copy number alterations (e.g., HER2), and tumor-agnostic biomarkers, such as mismatch repair deficiency (dMMR) and RAS mutation status. Collectively, these biomarkers have become essential tools in contemporary oncology, enabling more precise stratification of patients and more effective personalization of systemic therapy.

6.2: Conclusions Drawn from the Study

This study was undertaken to systematically evaluate the role, application, and clinical impact of molecular biomarkers in guiding systemic therapy for solid tumors. Through an extensive systematic review and meta-analysis, the findings generated robust, evidence-based responses to the six core research questions that shaped the direction of this thesis.

1. What is the current role of molecular biomarkers in guiding systemic therapy for solid tumors?

The evidence synthesized in this thesis establishes, with a high degree of confidence, that molecular biomarkers now occupy a central and indispensable role in the systemic treatment of solid tumors. No longer considered experimental or adjunctive, biomarker-guided strategies represent a fundamental shift in oncology practice, replacing traditional empiric and histology-driven approaches with more precise, molecularly informed paradigms. The systematic review revealed that 88.9% of recent, high-quality clinical studies employed a biomarker-guided approach to therapy selection, reflecting the widespread adoption and validation of these tools across cancer types. Biomarkers primarily function as predictive indicators, enabling clinicians to identify subgroups of patients most likely to benefit from targeted therapies. Examples include EGFR mutations guiding the use of tyrosine kinase inhibitors, HER2 amplification informing the use of monoclonal antibodies, and ALK or ROS1 rearrangements determining eligibility for ALK/ROS1 inhibitors. Meta-analytic findings reinforced this principle, demonstrating that targeted therapies guided by molecular profiling were associated with a threefold increase in the odds of a favorable clinical outcome compared to non-targeted treatments.

Beyond prediction, biomarkers also serve important prognostic functions. They assist in stratifying patients based on tumor biology and anticipated disease trajectory, thus informing the need for and intensity of adjuvant therapies. For instance, PIK3CA mutations or RAS mutation status may influence decisions in colorectal or breast cancer regarding adjuvant systemic interventions. Moreover, the emergence of tumor-agnostic biomarkers such as NTRK fusions, microsatellite instability (MSI), mismatch repair deficiency (dMMR), and high tumor mutational burden (TMB) has further expanded therapeutic possibilities. These biomarkers permit treatment selection based

on molecular profile irrespective of tissue origin, marking a significant evolution in cancer treatment strategy and regulatory frameworks.

In summary, molecular biomarkers function as the critical interface between advancing genomic science and individualized cancer care. Their integration into routine clinical practice enables more rational, effective, and personalized deployment of systemic therapies, ultimately improving outcomes for patients with solid malignancies.

2. What are the main barriers to the widespread clinical implementation of biomarker-guided therapy?

Despite the compelling evidence supporting the utility of biomarker-guided systemic therapy, its broad and equitable implementation in clinical practice remains impeded by several complex and interrelated barriers. Foremost among these is the biological complexity of cancer, particularly intratumoral heterogeneity. Tumors often comprise genetically distinct subclones, and a biomarker profile derived from a single biopsy may not fully capture this diversity. As a result, therapies selected based on incomplete molecular information may fail to address resistant subpopulations, contributing to disease progression and treatment resistance. This challenge is compounded by the temporal evolution of tumors under therapeutic pressure, wherein new resistance mutations can emerge, rendering the original biomarker profile and the corresponding therapy clinically obsolete over time.

From a technical perspective, a lack of standardization across diagnostic modalities presents a significant barrier. Variability in next-generation sequencing (NGS) platforms, assay sensitivity, data interpretation algorithms, and reporting formats create inconsistency in biomarker detection and clinical applicability. This undermines both inter-institutional comparability and the reproducibility of biomarker-driven treatment strategies across settings. In addition, socioeconomic and infrastructural limitations represent critical obstacles to the widespread adoption of precision oncology. The high cost of comprehensive genomic profiling, coupled with the need for specialized laboratory infrastructure and trained personnel, restricts access, particularly in low- and middle-income countries and under-resourced healthcare systems. This disparity exacerbates global inequities in cancer outcomes and impedes the universal implementation of biomarker-informed care.

Another important barrier is the rarity of certain actionable biomarkers, such as NTRK fusions, which are found in fewer than 1% of solid tumors. Their low prevalence makes it logistically and financially challenging to conduct large-scale, adequately powered clinical trials to confirm predictive validity. As a consequence, the clinical integration of therapies targeting these rare alterations proceeds more slowly and with greater regulatory uncertainty.

Collectively, these barriers - biological, technical, economic, and logistical - highlight the gap between the scientific promise of biomarker-guided therapy and its routine clinical implementation. Addressing these challenges will require coordinated efforts across research, healthcare policy, and clinical practice to ensure that the benefits of precision oncology are both scientifically robust and equitably distributed.

3. How does intratumoral heterogeneity affect the accuracy and effectiveness of biomarker-based therapy?

Intratumoral heterogeneity presents a critical challenge to the precision and reliability of biomarker-based therapy, fundamentally undermining its clinical accuracy and therapeutic effectiveness. This heterogeneity refers to the coexistence of genetically distinct subclones within a single tumor or across different metastatic sites, resulting in molecular variability that may not be captured by a single diagnostic biopsy. The high degree of statistical heterogeneity observed in both meta-analyses conducted in this thesis (I^2 = 90% and 100%, respectively) serves as a quantitative reflection of this underlying biological variability. These findings underscore the inconsistency in treatment response associated with biomarker-guided therapies across different patient populations, tumor types, and therapeutic contexts. When targeted therapy is selected based on a biomarker identified in a single tumor region, subclonal populations lacking that biomarker may persist and proliferate. This can result in primary resistance, where the therapy fails from the outset, or in acquired resistance, characterized by disease progression after an initial period of response.

The literature consistently highlighted the role of minor resistant subclones - often undetectable in standard tissue biopsies - as key contributors to treatment failure. This dynamic evolutionary process within tumors, driven by selective pressure from therapy, highlights the limitations of static, single-time-point biomarker assessments. Consequently, intratumoral heterogeneity

necessitates a shift toward adaptive, real-time molecular monitoring. Emerging technologies such as liquid biopsy, which analyzes circulating tumor DNA (ctDNA), offer a more comprehensive view of tumor genomics across multiple sites and over time. These approaches enable earlier detection of resistance mutations and facilitate more responsive, individualized treatment adjustments.

In summary, intratumoral heterogeneity poses a significant barrier to the consistent success of biomarker-based therapies. Overcoming this challenge will require the integration of more dynamic, whole-tumor profiling strategies that capture the temporal and spatial complexity of tumor evolution, thus enhancing the precision and durability of targeted interventions.

4. What is the impact of biomarker-guided immunotherapy on clinical outcomes?

Although the meta-analyses in this thesis collectively evaluated targeted therapies, the principles underpinning biomarker-guided treatment are equally foundational to the clinical success of modern immunotherapy. Biomarkers such as programmed death-ligand 1 (PD-L1) expression, microsatellite instability (MSI), and tumor mutational burden (TMB) have emerged as critical tools for identifying patients most likely to benefit from immune checkpoint inhibitors (ICIs). Their integration into clinical decision-making has enabled more precise patient selection and contributed meaningfully to the observed improvements in clinical outcomes associated with precision oncology. A prominent example is the use of pembrolizumab in MSI-High tumors, which led to the first tumor-agnostic approval by the U.S. FDA, highlighting the paradigm-shifting impact of biomarker-informed immunotherapy. Consistent with this, the findings of this thesis, particularly the superior outcomes observed among biomarker-positive patient cohorts indirectly support the efficacy of immunotherapy when guided by appropriate molecular markers.

However, the literature also reveals important limitations in the predictive performance of currently used immunotherapy biomarkers. PD-L1 expression, while widely employed as a selection criterion, lacks consistent predictive reliability. A proportion of PD-L1–positive patients fail to respond to treatment, while some PD-L1–negative patients derive clinical benefit. Similarly, the utility of TMB as a predictive biomarker remains under investigation, with inconsistent thresholds and context-specific validity across tumor types. These inconsistencies underscore the incomplete understanding of the tumor–immune system interplay, which involves not only tumor-

intrinsic factors but also the composition of the tumor microenvironment and host immune responsiveness. Consequently, the absence of universally reliable predictive biomarkers for immunotherapy represents a significant and ongoing clinical challenge.

5. What are the clinical and economic implications of integrating biomarker testing into routine cancer treatment?

The integration of biomarker testing into routine oncology practice carries profound clinical and economic implications, both of which are central to the transformation of cancer care in the era of precision medicine. From a clinical perspective, the foremost implication is the potential for significantly improved patient outcomes. The meta-analysis conducted in this thesis demonstrated that biomarker-guided targeted therapy was associated with a threefold increase in the odds of a favorable clinical response (OR = 3.02; 95% CI: 1.09–8.35). This finding underscores the therapeutic value of stratifying patients based on molecular profiles, enabling more effective treatment selection and enhancing progression-free and overall survival. Moreover, biomarker testing facilitates a more rational and efficient use of therapeutics, particularly high-cost and high-toxicity agents by ensuring that they are administered only to patients most likely to benefit. This approach minimizes the incidence of adverse effects, reduces unnecessary exposure to ineffective therapies, and enhances patients' quality of life.

Clinically, the routine integration of molecular diagnostics also implies a fundamental restructuring of cancer care pathways, requiring the incorporation of biomarker testing at multiple decision points from initial diagnosis and treatment planning to surveillance for resistance and recurrence. This necessitates interdisciplinary coordination, timely access to diagnostic infrastructure, and clinician familiarity with rapidly evolving molecular data.

The economic implications, however, are more nuanced. The upfront costs associated with next-generation sequencing (NGS), multiplex biomarker panels, and other advanced molecular profiling technologies are substantial. These expenses present a substantial burden on healthcare systems and can exacerbate disparities in access to precision oncology, particularly in low-resource settings or among underserved populations. Such inequities raise important ethical and policy concerns about the equitable distribution of innovative cancer therapies.

Conversely, when viewed through a long-term lens, biomarker-guided treatment may offer cost-effectiveness advantages. By avoiding ineffective therapies, reducing the incidence of treatment-related complications, and improving clinical outcomes, including survival and return to functional productivity, precision oncology has the potential to offset initial diagnostic costs with downstream savings. However, as this thesis and the reviewed literature emphasize, formal health-economic evaluations have not kept pace with technological innovation. There remains a pressing need for robust, context-specific cost-effectiveness studies to inform reimbursement policies and guide equitable implementation strategies.

6. How can emerging technologies enhance the application of biomarkers in solid tumors?

Emerging technologies are not merely incremental improvements to existing biomarker strategies; rather, they represent essential enablers that address many of the core limitations of conventional molecular diagnostics in oncology. Their integration is pivotal to advancing the precision, scalability, and clinical relevance of biomarker-guided therapy for solid tumors. Next-generation sequencing (NGS) has already transformed the diagnostic landscape by enabling comprehensive molecular profiling from limited tumor tissue. Unlike single-gene assays, NGS allows for the simultaneous analysis of hundreds of clinically relevant genetic alterations, providing a holistic and scalable view of the tumor's mutational architecture. This has made broad-panel testing feasible in routine clinical workflows, supporting more informed and individualized treatment decisions.

Liquid biopsy technologies, particularly the analysis of circulating tumor DNA (ctDNA), offer a non-invasive, dynamic alternative to tissue biopsy. This approach directly addresses the challenges posed by intratumoral heterogeneity and tumor evolution under therapeutic pressure. Liquid biopsy allows for real-time, longitudinal monitoring of tumor genomics, facilitating early detection of emerging resistance mutations and enabling timely modification of therapy, a critical advancement over static, single-time-point tissue sampling. Moreover, the adoption of multi-omics approaches, which integrate genomics, transcriptomics, and proteomics provides deeper insight into the functional consequences of genetic alterations. By capturing not only DNA sequence changes but also gene expression patterns and protein activity, multi-omics profiling enhances the ability to predict drug sensitivity, resistance mechanisms, and therapeutic vulnerabilities with greater accuracy and clinical relevance.

Finally, artificial intelligence (AI) and machine learning (ML) technologies are poised to revolutionize the field by extracting actionable insights from high-dimensional, multi-source datasets. These computational tools can uncover complex biomarker signatures that are beyond human analytical capacity, improve the prediction of treatment response, identify novel therapeutic targets, and support the development of clinical decision support systems that integrate molecular, clinical, and imaging data for precision treatment planning.

In conclusion, the future of biomarker-guided therapy for solid tumors is inextricably linked to the continued development and integration of advanced technologies. These innovations promise to overcome longstanding barriers in precision oncology, enhance diagnostic accuracy, enable adaptive treatment strategies, and ultimately improve clinical outcomes for patients.

6.3: Implications of the Research

The findings of this systematic review and meta-analysis have significant and actionable implications across three interrelated domains: clinical practice, health policy, and future oncological research. By synthesizing high-quality evidence on the clinical utility of biomarker-guided systemic therapies in solid tumors, this thesis contributes a robust foundation for understanding and advancing the broader implementation of precision oncology.

Implications for Clinical Practice

Foremost among the clinical implications is the clear justification for integrating comprehensive molecular profiling as a standard component of the diagnostic workup in patients with advanced solid tumors. The meta-analysis conducted in this thesis demonstrated a threefold improvement in the odds of achieving a favorable outcome with targeted therapies (OR = 3.02), offering compelling evidence to support routine biomarker testing as a core element of personalized treatment planning. The finding that 88.9% of high-impact contemporary studies utilized biomarker-guided approaches suggests that the clinical research community has already embraced this standard. The key challenge, and thus a major implication of this work, is to translate this evidence-based standard into consistent practice across all healthcare settings.

In addition, the conclusions regarding intratumoral heterogeneity and acquired resistance underscore the inadequacy of relying solely on static, one-time tissue biopsies for long-term

disease management. Clinical practice must evolve toward dynamic and adaptive models of patient monitoring, with expanded use of non-invasive technologies such as liquid biopsies. These approaches enable real-time surveillance of tumor evolution, early detection of resistance mutations, and more agile therapeutic adjustments, potentially improving patient outcomes and prolonging the efficacy of targeted interventions.

Moreover, the increasing clinical validation of tumor-agnostic biomarkers identified in the included studies such as NTRK fusions, MSI-High status, and high tumor mutational burden suggests a necessary shift in clinical thinking. The traditional paradigm of treatment selection based solely on histological tumor type must give way to molecularly driven decision-making, where a genomic alteration, rather than tissue of origin, guides therapy selection. This shift represents a fundamental redefinition of how solid tumors are classified and treated in the precision medicine era.

Implications for Health Policy and Healthcare Systems

The demonstrated clinical efficacy of biomarker-guided therapies presents urgent and complex challenges for health policymakers and healthcare systems worldwide. Chief among these is the imperative to address the dual issues of cost and access. Advanced technologies such as next-generation sequencing (NGS), molecular diagnostics, and targeted therapies come with substantial financial burden. Without deliberate and equitable policy responses, these costs risk entrenching a two-tiered system of cancer care, where access to precision oncology is determined by geography, insurance status, or socioeconomic position.

To mitigate this risk, health policy must evolve to support sustainable, equitable integration of precision medicine. This includes the development of robust reimbursement frameworks that cover molecular testing and targeted therapies, especially in public health systems. Policymakers must also work to negotiate drug pricing, incentivize local manufacturing of diagnostics, and streamline regulatory pathways to expedite access to clinically validated biomarker tests. Such interventions are essential to ensure that life-prolonging precision therapies are not restricted to privileged subpopulations.

This research further underscores the critical need for international standardization of biomarker testing protocols. The current absence of harmonized guidelines for assay validation, sequencing platforms, bioinformatics pipelines, and results interpretation poses a major barrier to the reliable and reproducible application of biomarker-driven care. Regulatory bodies, in collaboration with global health agencies and scientific consortia, must mandate adherence to evidence-based standards to ensure consistency and quality in diagnostic outputs across institutions and regions.

Finally, the successful, system-wide implementation of precision oncology requires substantial investment in infrastructure and workforce development. This includes expanding the capacity of accredited molecular diagnostic laboratories, building secure and interoperable data management systems, and fostering a multidisciplinary healthcare workforce proficient in the principles and practices of genomic medicine. Education and training programs for oncologists, pathologists, genetic counselors, and data scientists are essential to support the ethical, informed, and effective delivery of biomarker-guided therapies at scale.

Implications for the Scientific and Research Community

The findings of this study delineate critical directions for future research in the evolving landscape of precision oncology. One of the most salient implications is the need to deepen scientific inquiry into the mechanisms of acquired resistance, which remains a formidable barrier to sustained treatment efficacy, even in biomarker-matched therapeutic contexts. This study confirms that initial responses to targeted therapy are frequently undermined by tumor adaptation, including the activation of alternative signaling pathways, clonal evolution, and interactions within the tumor microenvironment. Future research must therefore prioritize the elucidation of these dynamic molecular processes through longitudinal genomic studies and preclinical models that more accurately simulate therapeutic pressure.

Moreover, while technologies such as multi-omics profiling and artificial intelligence/machine learning (AI/ML) are widely touted as transformative, this review highlights a persistent "research-to-practice" gap. Much of the current literature remains at the level of in-silico analysis or retrospective correlation. A key implication for the research community is the necessity of prospective, hypothesis-driven clinical trials that rigorously evaluate the real-world predictive

performance and clinical utility of these tools. Validation in pragmatic, heterogeneous patient populations is essential to ensure translational relevance and regulatory acceptance.

The discrepancy between clinical outcomes observed in randomized controlled trials (RCTs) and those reported in real-world settings underscores the importance of integrating Real-World Evidence (RWE) into the research paradigm. Future investigations must embrace pragmatic trial designs, registry-based cohorts, and population-level data analyses to assess the effectiveness, not just efficacy, of biomarker-guided therapies across diverse clinical environments. This will not only enhance the generalizability of research findings but also inform more inclusive, evidence-based guidelines for the implementation of precision oncology in everyday clinical practice.

6.4: Limitations of the Study

Although this systematic review and meta-analysis offers robust, high-level evidence regarding the clinical utility of molecular biomarkers in solid tumors, several limitations must be acknowledged to appropriately contextualize the findings.

First, as a study grounded in secondary data, the analysis is inherently dependent on the methodological rigor and completeness of the primary literature. The reliance on aggregated rather than individual patient-level data precludes deeper exploration of confounding variables such as comorbidities, performance status, or socio-demographic factors that may influence therapeutic outcomes. Additionally, variations in assay sensitivity, diagnostic platforms, and bioinformatics pipelines across studies introduce a layer of technical heterogeneity that could affect biomarker interpretation and treatment response, although such details were not uniformly reported in the source studies.

Second, the meta-analyses revealed a high degree of statistical heterogeneity ($I^2 = 90\%$ and 100%, respectively), which, while expected due to the inclusion of a broad spectrum of tumor types, biomarkers, and therapeutic modalities, limits the interpretability of the pooled odds ratios. These estimates reflect an average effect size across heterogeneous clinical contexts and should not be construed as uniformly applicable to any single disease setting. The substantial heterogeneity is a reflection of the biological complexity and variability that characterizes precision oncology and underscores the need for caution when extrapolating these findings to individual patient care.

Third, the potential for publication bias remains a significant concern. Despite the use of funnel plot analysis to evaluate this risk, the well-documented tendency for studies with positive or statistically significant results to be preferentially published may skew the overall effect size. Unpublished or negative studies, particularly in early-phase trials or underrepresented cancer types, could meaningfully alter the conclusions if included.

Finally, the review predominantly focuses on well-studied and common malignancies, including breast, lung, colorectal cancers, and melanoma, where the bulk of biomarker-guided therapeutic evidence is concentrated. As a result, the generalizability of these findings to rare solid tumors, pediatric cancers, or less validated biomarkers is inherently limited. The exclusion of studies focusing solely on emerging or experimental biomarkers, due to insufficient validation or data quality, further narrows the scope of applicability.

In sum, while the findings are compelling and contribute meaningfully to the discourse on precision oncology, they must be interpreted within the constraints imposed by the diversity, heterogeneity, and inherent biases of the included literature.

6.5: Recommendations for Future Research

The insights gained and limitations encountered in this thesis illuminate several critical directions for future investigation aimed at accelerating the clinical translation of precision oncology. The following research recommendations are proposed to address unresolved questions in biomarker validation, optimize clinical trial methodologies, overcome implementation barriers, and validate cutting-edge technologies.

1. Enhancing Biomarker Discovery and Validation through Multi-Omics Approaches

While single-gene biomarkers have proven utility, their predictive power is constrained by the intrinsic complexity and heterogeneity of solid tumors. A key recommendation is the strategic pivot toward the development and clinical validation of composite biomarkers derived from integrated multi-omics platforms. Future research should prioritize prospective trials that combine genomics, transcriptomics, proteomics, epigenetics, and immunogenomics to generate high-fidelity models of tumor biology. This integrative approach promises to capture the functional and dynamic interactions within the tumor microenvironment more accurately than genomics alone,

improving patient stratification and enabling the identification of novel therapeutic targets. Additionally, longitudinal multi-omics sampling in the context of therapy will be essential for mapping resistance evolution in real time, thereby guiding the development of rational combination therapies and adaptive treatment strategies.

2. Innovating Clinical Trial Designs and Integrating Real-World Evidence

The discrepancy observed between outcomes from randomized controlled trials (RCTs) and real-world clinical settings underscores the need for more pragmatic and adaptable trial designs. It is recommended that future studies increasingly adopt adaptive platform trials such as I-SPY 2 and BATTLE, which allow for simultaneous evaluation of multiple agents and biomarker hypotheses within a single framework. These designs enhance trial efficiency, reduce time-to-validation, and better reflect real-world clinical decision-making.

Concurrently, the generation and integration of Real-World Evidence (RWE) should be a strategic research priority. Investment in robust clinical registries and data infrastructure will facilitate post-market surveillance, enable continuous learning, and provide insights into the effectiveness of biomarker-guided therapies in heterogeneous patient populations, including those with comorbidities and socio-demographic diversity often excluded from traditional RCTs.

3. Addressing Economic and Implementation Disparities

The widespread adoption of precision oncology is currently hindered by its high cost and inequitable access. Future research must incorporate formal health economic evaluations within clinical trials to assess the cost-effectiveness of biomarker-driven strategies. Such analyses are critical for informing coverage policies, value-based pricing, and long-term sustainability within national healthcare budgets.

Additionally, implementation science should be leveraged to design scalable, low-cost delivery models for molecular diagnostics and targeted therapies, particularly in resource-constrained settings. Research is needed to validate affordable diagnostic alternatives (e.g., PCR-based or multiplex panels) and to test context-specific care pathways that align with the infrastructure and workforce capacity of low- and middle-income countries (LMICs).

4. The Clinical Validation of Advanced Technologies

This thesis identifies a significant translational gap in the clinical readiness of emerging technologies, particularly Artificial Intelligence/Machine Learning (AI/ML) and liquid biopsy platforms. While AI/ML algorithms have demonstrated promise in retrospective datasets, their clinical utility remains largely theoretical. It is strongly recommended that future research prioritize prospective validation of AI/ML models within interventional studies, ensuring their predictive accuracy, reproducibility, and interpretability under real-world conditions.

Similarly, although liquid biopsies represent a transformative innovation for non-invasive monitoring and early detection of resistance mutations, further validation is essential. Research must focus on establishing standardized protocols, defining clinically actionable thresholds for circulating tumor DNA (ctDNA) changes, and integrating these tools into existing clinical decision frameworks.

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