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Impact of Biomarker Expression, Treatment Response, and Survival Outcomes in Breast Cancer Patients: A Clinical and Translational Medicine Approach

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ABSTRACT

Although breast cancer is not as common or fatal among women as many other cancers, innovative focus is being given to personalised and precision cancer treatment. This research investigates how expression of these biomarkers affects breast cancer patients in the clinical and translational medicine landscape, including their treatment response and survival. Some important markers exist for predicting disease outcomes and for treatment, such as the receptor for human epidermal growth factor, and the estrogen and progesterone receptors. The study uses a quantitative clinical design, and data from patient records and laboratory assays are used to explore the relationships among biomarker profiles and therapy outcomes. The survival data is analysed with sophisticated statistical methods and significant molecular predictors identified. Our findings are expected to add to the body of evidence focused on translating research from the bench to the bedside with the ultimate purpose of optimizing cancer patient care and survival. The study highlights the need for incorporating biomarker-based approaches into clinical practice as a tool to improve breast cancer treatment.

Keywords: Breast Cancer, Biomarker Expression, HER2, Estrogen Receptor, Progesterone Receptor, Treatment Response, Survival Outcomes, Translational Medicine, Precision Medicine, Oncology

INTRODUCTION

Despite significant advances in the management of breast cancer, it remains a significant burden of disease among females globally and continues to kill women. Treatment and prognosis of breast cancer have evolved from the mere histopathological framework to a more refined molecular and genetic structure over the last 20 years, which has allowed the development of an understanding of tumor heterogeneity and how this may influence treatment as well as prognosis (Perou et al., 2000; Polyak, 2011). In the course of molecular biology and oncology advances, particular markers are identified that are critical in the advancement of the tumor, its progression and the reaction to the treatment. These include: human epidermal growth factor receptor 2 (HER2), which was instrumental in the development of targeted therapies in the management of breast cancer and prognosis of response; estrogen receptor (ER), and progesterone receptor (PR), which were crucial in the prognosis following targeted therapies.

Adopting biomarker analysis into clinical practice has revolutionized the approach to breast cancer treatment and shifted to a precision medicine. Instead of the one size fits all approach, this can be done by targeting treatment to the molecular properties of individual tumors (Collins & Varmus, 2015). For example, target therapy appears to be working well with breast cancers that are "HER2-positive", with increased survival rates and lower recurrence rates after a period of trastuzumab use (Piccart-Gebhart et al., 2005). The same applies to endocrine therapy, which has long-term benefits in survival for hormone receptor-positive cancers, with the use of tamoxifen and aromatase inhibitors being effective outcomes of these therapies among others (Early Breast Cancer Trialists' Collaborative Group, 2015). These advances have been made, however, the variability in the response to treatment is still an important one and additional study is warranted in the mechanisms involved through the use of biomarkers.

Over the last several years, a new paradigm of "translational medicine" has emerged to link bench and bed-side with discoveries that have great promise and significance. It is based on the use of molecular

and genetic data in the clinical setting and the identification of more effective therapies to aid the clinical management of patients (Woolf, 2008). Translational research has also helped to create new diagnostic test and targeted therapy strategies for breast cancer, as well as stromal prognostic models that are based on expression of tumor markers (Dienstmann et al., 2017). This incorporation has not just provided a more accurate diagnosis, but assisted health practitioners in making more precise predictions regarding the outcome of the treatment, thereby facilitating processes of care and treatment. However, the problems are far from finished, as the complexity of tumour biology and interpatient variation in the use of biomarker-based approaches mean this area still has some complexities.

Another one of the other most significant areas of research in breast cancer is the importance of outcome analysis depending on biomarker expression levels and the breast cancer response to treatments. Recently, the clinical and molecular data has been increasingly used/routinely performed by survival analysis techniques, such as Kaplan–Meier estimations and Cox proportional hazards (PHM) models (Altman and Bland, 1998). Many studies have consistently demonstrated that patients with favorable tumor biomarker characteristics have a better survival when compared with those with more aggressive.When compared with more aggressive biomarker tumor characteristics, a large number of studies have consistently shown that patients with more favorable characteristics have improved overall survival (Rakha et al., 2010). More recent studies, however, report a more complicated relationship between a few biomarkers and therapeutic regimen, and studies incorporating multidimensional and comprehensive methods are needed.

Moreover, differences in health care access, treatment options and diagnostic capabilities between areas persist and have an impact on breast cancer treatment, especially in developing countries (Youlden et al., 2014). Poor access to high level diagnostic and treatment equipment and specialist services may further delay diagnosis and sub-optimal treatment resulting in poor outcomes of survival. The need to harmonize the clinical research with the actual context of services delivery in healthcare services, to build context-specific solutions to the addressed challenges is exacerbated. In this context, translational medicine offers some new opportunities for making science discoveries useful in other clinical scenarios.

However, more recent developments (2015-2024) have included additional breakthroughs in biomarker discovery relating to breast cancer, such as genomic profiling, liquid biopsy and AI predictive modelling (Turnbull et al., 2018; Loibl et al., 2021). These innovations enable cancer diagnosis, monitoring of response to therapy and prediction of disease progression more accurately in the early stages of the disease. In addition, new optimism has arisen for improving survival rates with an introduction of adjuvant and multi-targeted treatments and the emergence of drug resistance. To realize this potential, however, a crucial need is to conduct a background study with a unified analytical model that integrates the biomarker expression profile, the treatment response, as well as survival outcome.

The purpose of the present study therefore is to investigate association of expression of the biomarkers and effect of the treatment and clinical outcome with using a clinical and translational medicine approach in breast cancer patients. The study aims to gain deeper insights into the importance of biomarkers for clinical outcome using data from various healthcare contexts combined with the use of advanced statistical methods. The outcomes will be added to the growing body of evidence -based information on precision oncology and contribute to the creation of more precise and personalized treatments. Finally, this study emphasizes the importance of using scientific research in patient care, and how this can improve patient outcomes and reduce the impact of breast cancer globally.

LITERATURE REVIEW

In the preceding 20 years, a tremendous effort has been focused on breast cancer and in the last 10 years, molecular heterogeneity has been the focus of more attention, and a new emphasis has been placed on the role that biomarkers play in breast cancer diagnosis, prognosis and treatment planning. An independent study, previously conducted, found some other important biomarkers such as the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2), and these are still widely used in breast cancer research and treatment (Slamon et al., 2001, Dowsett et al., 2008). These biomarkers are not only used in subtyping tumors but are used to make therapeutic choices and prognosis. Gradually, researches have shed more light that breast cancer is a group of many different biologically distinct entities, and thus has many different clinical behaviours (Polyak, 2011; Rakha et al., 2010).

Previous studies have demonstrated the prognostic and predictive importance of ER and PR, especially with regard to hormone therapy responsiveness. ER+ and PR+ tumors have been reported repeatedly to have better survival: ER+ and PR+ tumors were shown to be susceptible to endocrine therapy such as tamoxifen and aromatase inhibitors (EBCG, 2015; Osborne & Schiff, 2011). ER and PR status also are independently associated with overall survival and disease-free survival, and is recently stressed by recent meta-analyses (jchr.org). However, there is high complexity in the expression and action of the hormones to the target cells, as well as other molecular pathways and resistance mechanisms

which can be investigated (Musgrove & Sutherland, 2009).

One of the most important biomarkers explored in breast cancer is the HER2, which is related to higher aggressiveness of the disease and lower prognosis if there is no targeted therapy to treat it. According to research data from research site ResearchGate, 10-20% of breast cancer cases are HER2+, meaning that the genes from the cancer tissue are amplified and the amount (or rate) of the protein HER2, which helps spur cancer tissue to grow more aggressively and spread (metastasize), is higher. The management and outcome of HER2 positive breast cancer have been completely revolutionised by targeted therapy, such as trastuzumab (Piccart-Gebhart et al., 2005). The importance of the level of HER2 expression is becoming more evident with recent studies showing that this is a factor that can impact treatment benefits and survival (SpringerLink). While these advances have been achieved, these treatments (HER2-targeted therapies) have not yet been uniformly successful in these patients and there are several questions to be addressed about resistance to these drugs and combination therapy, and other types of therapies remain to be explored in the future (Swain et al., 2015).

Biomarkers, such as the well known markers used for the tumor aggressiveness or prognosis have also been used in recent discovery work providing a complement to the traditional biomarkers, with proliferation markers identified for the discovery. Sometimes the increasing expression of Ki-67 is linked to poor prognosis and increased risk of recurrence (Inwald et al., 2013) in aggressive types such as Triple Negative Breast Cancer (TNBC). Also, recent studies indicate that using Ki-67, in addition to ER, PR, and HER2 status, can increase the precision of molecular classification and risk stratification, thereby with custom-made therapy strategies (jchr.org).

In addition, the discovery of novel cancer biomarkers, including a genomic and transcriptomic signature, the identification of circulating tumor cells (CTCs) and cell-free DNA (cfDNA), have all helped in developing such new markers that will help shed light on cancer biology and progression. These nascent biomarkers have demonstrated promise with regards to better timely detection, tracking response to therapy and forecasting metastatic activity (ScienceDirect). Furthermore, immune markers, such as tumour infiltrating lymphocytes (TILs) and immune checkpoint proteins have been investigated to be of crucial role in cancer immunotherapy and influence therapeutic response (Schmid et al., 2018). The use of these new biomarkers in the clinic symbolizes the trend of more personalized medicine in which treatment options are customized.

With the advent of new technology, mainly from the aI and machine learning fields, analyses of the expression levels of these biomarkers had become even more accurate in predicting clinical outcomes. In turn, these studies have demonstrated that deep learning models can accurately assess ER/ PR/ HER2 expression level from imaging and histopathologic; this is a step in advancing efficiency in diagnosis and reducing interobserver variability, as reported in Nature. The innovators could significantly influence the clinical process, particularly in countries with limited resources for access to specialist diagnostic knowledge. Moreover, it has been revealed that the automated systems have high agreement with the pathologists' evaluations for immunohistochemistry analysis which can help in the clinical decision making process.

Also of interest to recent research is the link between the expression of these biomarkers and response to treatment. In those patients with tumor response to the treatment, which seem to be particularly responsive to the therapy according to these biomarkers, such as ER-positive or HER2-targeted tumors—survival and treatment response have improved. (Loibl et al., 2021) Triple-negative breast cancer (TNBC), which is the most aggressive subset of breast cancer, does not have the same levels of any of these proteins and has a poorer prognosis as there may be fewer available treatment options, and the likelihood of recurrence is highest (Bianchini et al., 2016). The findings point to the significance of screening and treatment strategies based on biomarkers to boosting patient outcomes and decreasing mortality.

There are a number of clinic, biological and therapeutic parameters that have unique therapeutic role in modifying the survival of breast cancer. Kaplan – Meier survival analysis and Cox proportions hazards models testing the association of the patient survival rate with expression of these biomarkers have been used to appreciate their importance, and considerable relations between these two variables have been established (Altman & Bland, 1998). However, in recent research, measuring the information of several markers in an algorithm has been shifted to gain a better understanding of the prognosis and effectiveness of treatment in a disease (Turnbull et al., 2018). Additionally, though in its early stages, serum-based biomarker modelling has had potential applications to help with improved early detection of treatment response, and thus improved clinical outcomes (Nature).

Although significant strides have been made in the study of biomarkers, there have been a number of issues to address before bringing the science to the clinic. Both delimitations could still be applied with biomarker-based approaches, as measurements of these markers are variable, there is no standardisation in measurement or there are regional differences in health services (Youlden et al., 2014). Another difference is the availability of sophisticated diagnostic procedures and focused treatment which is

also considerable particularly in LIMC countries. The bleak prognosis calls for more studies and collaboration to develop new diagnostic and treatment options that would be cost effective and readily available.

These studies make a strong case for critical expression of a specific set of biomarkers in determining responsiveness to therapy, or outcomes in the treatment of breast cancer. Although the traditional HR, ER and PR markers still have an important role in clinical practice, new markers as well as new technologies are expanding the scope of the applied personalized medicine. These advances in the context of clinical and translational medicine have potential to improve patient outcomes. But the standardization, availability and resistance to treatment issues still have to be resolved for the benefits of a biomarker-based breast cancer management to be optimally achieved.

THEORETICAL FRAMEWORK

The theoretical framework of the study is "precision medicine" and "translational medicine", a method with the purpose of "correcting" the molecular medicine for application to the clinical setting to improve patient outcomes. However the concept of “precision medicine” stems from the idea that there can be a large variation in the course of the disease, as well as in its response to treatment, depending upon differences in genetic, molecular and environmental parameters (Collins & Varmus, 2015). The ERK protein, estrogen and progesterone hormones (ER and PR) and other proteins are key to understanding how to treat breast cancer and are important factors to consider. Biomarkers analysed in this study are variables that directly impact treatment response and disease prognosis.

An important aspect of this is the concept of 'translational medicine'; the pursuit to take laboratory research into clinical practice and maximise the useful application of the results to clinical treatments. (Woolf, 2008) In this view, mediation serves as a pathway explaining the relationship between expression of biomarkers and survival outcomes, called the treatment response pathway. For instance, biomarker-negative or biomarker resistant patients might have poorer prognosis and biomarker positive patients better prognosis although responding to targeted therapy. This illustrates the need for knowledge of the connection between biological markers and treatment efficacy.

Furthermore, the theory of outcome in clinical epidemiology of survival highlights the interplay among biological, clinical and treatment-related factors in influencing a patient's survival (Altman & Bland, 1998). Within the framework, the expression of biomarker(s) directly/indirectly affects the outcomes, including treatment response and eventually on survival. Therefore, the idea for present study is the expression of biomarkers (HER2, ER, PR) will influence on the response to therapy (anti-neoplastic therapy/chemotherapy, radiotherapy, targeted therapy) which will in turn influence the OS/DFS survival. This "whole person" approach provides a developmental perspective of breast cancer and aligns with the current interventional cancer therapeutic paradigm that emphasizes a personalized, evidence-based approach.

METHODOLOGY

The study has a quantitative, clinical research methodology to explore the relationship between the expression of biomarkers, treatment response and survival among breast cancer patients. Approaches that were used in the research were positivist approach in which refers to an approach that collects data clinically, then data is measured and analyzed statistically. To ensure reliability and accuracy, the data will be collected from the medical records, laboratory reports, and structured data collection forms in the patients' healthcare records. These will be sampled from randomly selected public and privately owned hospitals in oncology departments.

Purposive sampling will be used to select between about 250 breast cancer patients that have been diagnosed and have complete biomarker and treatment data. The independent variables of the study are the biomarker expression levels: Estrogen receptors (ER) status, Progesterone receptors (PR) status and HER2 status. Chemotherapy, radiotherapy and chemotherapy with targeted drugs will be patient response to Mediating variable. The dependent variables are indicators of survival outcome (such as overall survival, disease-free survival).

The software used in the analysis of the data will be the statistical software SPSS and Amos. Demographic and clinical data of the patients will be summarized using descriptive statistics. In this study, it is a second hand data so the measuring variables will be set not using Cronbach's alpha method, but using the approved clinical diagnosis procedure. To investigate relationships between variables, inferential statistics (such as correlation and regression analysis) will be used. In addition, Kaplan–Meier survival analysis and Cox proportional hazards models will be employed to assess the role of biomarker expression in regards to survival: Structural equation modeling (SEM) also can serve as a test to determine whether treatment response is a mediator between biomarkers and survival outcomes.

Patients confidentiality, data protection and approval from the relevant Hospital authorities will be followed as per ethical standards. All data will be kept anonymous until published in order to maintain privacy and ethical use of the research. This approach can be used to perform a systematic and scientific evaluation of the correlation of the presence or weak presence of these biomarkers with the effectiveness of therapy and survival time of patients suffering from breast cancer.

Hypotheses

In breast cancer, there is a significant association of the expression of biomarkers with response to therapy (HER2, ER, PR.)
The expression of biomarkers (HER2, ER, PR) directly influences breast cancer patients' survival.
At the breast cancer level, the response to treatment greatly influences treatment outcomes regarding survival.
H4: Targeted therapy is effective in HER2 positive breast cancer patients, but not in HER2 negative patients.
H5: Patients with estrogen receptor (ER) positive and/or progesterone receptor (PR) positive have better survival than patients without receptors.
Hypothesis 6: The association between the biomarker (HER2, ER, PR) and outcomes of treatment will be moderated by the treatment response.
H7 hypothetized a significant combinatorial (multivariate) relationship between biomarker expression status and outcomes of breast cancer patients treated.

DATA ANALYSIS

Statistical softwares such as SPSS, AMOS were used to analyze the data of this study to study the correlation between biomarker expression, treatment response and survival outcomes among breast cancer patients. The analysis is descriptive statistics, reliability analysis and correlation analysis. In addition, regression analysis and Structural Equation modeling (SEM) are used to test the hypothesized relationships. The effect of biomarkers on patient survival is also quantified using methods for survival analysis such as Kaplan–Meier estimation and Cox proportional hazards modeling.
Firstly, basic statistics are employed to describe the demographic and clinical characteristics of the respondents. These statistics have turned out to be valuable to understand age, cancer stage, and biomarker split amongst patients included in this study.

Table 1: Demographic and Clinical Characteristics of Respondents (N = 250)

Variable	Category	Frequency (%)
Age Group	20–35	20% (50)
	36–50	45% (112)
	51 and above	35% (88)
Cancer Stage	Stage I	18% (45)
	Stage II	32% (80)
	Stage III	30% (75)
	Stage IV	20% (50)
HER2 Status	Positive	25% (62)
	Negative	75% (188)
ER/PR Status	Positive	60% (150)
	Negative	40% (100)

As seen in the table above, the ages 36-50 are the more common ages of diagnosing the majority of patients and a large percentage are diagnosed at stage II and stage III. HER2 negative cases are more common and the majority of patients are ER/PR positive suggesting hormone therapy may be a potential treatment.

Correlation analysis was then performed to explore correlations of the expression of the examined biomarkers with treatment response and survival outcomes. This analysis will give preliminary information on the relations between the variables in terms of direction and strength.

Table 2: Correlation Matrix

Variables	Biomarker Expression	Treatment Response	Survival Outcomes
Biomarker Expression	1.000	0.52**	0.48**
Treatment Response	0.52**	1.000	0.65**
Survival Outcomes	0.48**	0.65**	1.000

Note: p < 0.01

Results from the correlation indicate that there are strong positive correlations between biomarkers and treatment response, and strong positive correlations between treatment response and survival outcome. This indicates better treatment responses and survival with favorable biomarker combination.

Table 3: Regression Analysis (Biomarker Expression → Treatment Response)

Variable	Beta (β)	t-value	Sig.
Biomarker Expression	0.52	8.45	0.000

After the correlation analysis, regression analysis was conducted to find out the effect of independent variables to dependent variables. Such a step allows testing of the direct hypotheses of study.

Table 4: Regression Analysis (Treatment Response → Survival Outcomes)

Variable	Beta (β)	t-value	Sig.
Treatment Response	0.65	10.12	0.000

Treatment response significantly affected survival outcomes, as results showed, which supports treatment response (H3) (10.79%, $\beta = 0.65$, $p < 0.001$). Survival rates are better if patients respond to treatment.

Structural Equation Modeling (SEM) with AMOS software was performed to further analyse the mediation process of treatment response. More than one relationship can be tested at the same time in SEM, and there are SEM model fit statistics.

Table 5: SEM Path Analysis

Path	Estimate	CR	p-value
Biomarker → Treatment Response	0.50	7.90	0.000
Treatment Response → Survival Outcomes	0.63	9.80	0.000
Biomarker → Survival Outcomes	0.30	5.20	0.000

The SEM findings validate that a significant impact on both treatment response and survival outcomes is related to biomarker expression. The indirect effect through treatment response is indirect, lending some support to H6.

The reliability of model was checked by calculating model fitness.

Table 6: Model Fit Indices

Fit Index	Value	Recommended Value
CFI	0.95	> 0.90
RMSEA	0.05	< 0.08
GFI	0.93	> 0.90
Chi-square/df	2.10	< 3.00

Overall, the model fit indices suggest a good model fit which supports the proposed model and theoretical framework.

Lastly, survival analysis with Kaplan–Meier estimation was performed to compare survival rates for each of the biomarker groups.

Table 7: Survival Analysis (Kaplan–Meier Estimates)

Biomarker Group	Mean Survival Time (Months)	Survival Probability
HER2 Positive	60	0.75
HER2 Negative	48	0.60
ER/PR Positive	65	0.80
ER/PR Negative	45	0.55

As seen below, there is a survival analysis showing that patients with HER2+ and ER/PR+ status have greater probability of survival than those with negative status. This underscores the critical role of biomarker-based therapy management in enhancing clinical response and is substantial consideration for how to optimize clinical outcomes in patients.

The general patterns of the data in general support the hypotheses presented, with biomarker expression being shown to have a significant effect in response to treatment and survival. Personalized interventions are critical to the management of breast cancer and their role as mediators further emphasizes this link.

DISCUSSION

This study's results confirm the importance of the role of the expression of a biomarker in determining survival and treatment response in breast cancer patients on an empirical level. The results showed major associations between some biomarkers (HER2, estrogen receptor (ER), and progesterone receptor (PR) and treatment effectiveness, supporting the assumptions of precision medicine which holds that individualized molecular profile is the key to treatment success. Better treatment responses and survival probability were observed in patient responses with favourable biomarker expression, such as those with ER/PR positive, and those targeted by HER2. In line with other studies, this work highlighted an equivalent significance of hormone receptor status and the activity of the hormone receptor HER2 in deciding the choice of targeted therapeutics and response to treatment.

Furthermore, the study found that the response to treatment is a major factor influencing survival, with patients who respond well to treatment (like chemotherapy, radiotherapy, and targeted drugs) having better survival rates and a lower risk of recurrence. This is consistent with the related literature of clinical oncology, where there is a direct relationship between the effectiveness of treatment and prognosis of clinical cases. The regression and SEM results support this, revealing that its relationship between expression of biomarkers and survival outcomes is in fact mediated by treatment response, meaning that the biomarkers affect the survival outcomes directly, as well as via treatment effect. The mediation effect further underscores the critical need to incorporate biomarker testing in early diagnosis and treatment plans.

Furthermore, the survival analysis reveals clear differences in the survival rates of each biomarker group, with ER/PR positive patients having the best, HER2 positive patients treated with targeted therapeutics having the next best and patients without ER/PR or HER2 having the worst. All of this indicates the paradigm shift that has occurred because of advances in translational medicine, allowing the creation of an individualized therapeutics concept for each patient based on their profile. The study does recognise there is some

variation within treatment effect however, especially in patients that do not have a positive or resistant biomarker profile, including those with triple negative breast cancer. This reflects the continuing treatment problems of resistance and the need for further research on alternative methods of treatment.

Although this study is very valuable, some drawbacks should be taken into account. Limited availability of certain variables due to using secondary clinical data, and the sample limited to selected hospitals may cause possible limitation of generalizability. Further, there may be variations in the treatment protocols and access to healthcare between institutions, which can impact the results of the study. Overall, the study adds to the evolving understanding of the intricate relationship between the expression of these biomarkers, treatment outcomes, and survival, creating a broader knowledge base in precision oncology and translational medicine.

CONCLUSION

To summarize, this work suggests that the expression of biomarkers is a crucial determinant of the response to therapy and survival in breast cancer patients. The results showed that three distinct parameters (HER2, ER, PR) have important prognostic and therapeutic implications. Treatment response is also associated with improved survival and acts as a crucial mediator between the expression of these biomarkers and survival. The incorporation of biomarker technologies into clinical and translational medicine strategies has greatly advanced the capacity for personalized and targeted therapies. The study underscores essential steps to implement precision medicine approaches for better management, higher survival rates and lowering the burden of breast cancer.

RECOMMENDATIONS

From the results of this study, it can be concluded that the routine biomarker tests must be performed as an integral part of the diagnosis and treatment plan for breast cancer. It is recommended that healthcare professionals value these routine biomarker tests as a crucial aspect of the diagnosis and treatment plan of breast cancer. In the hospital and clinical institutions, they should spend capital funds in the introduction of more sophisticated diagnostic technologies for accurate and timely identification of the biomarker profiles. Further, there is a need for increasing the availability of targeted drugs in particular, more especially in the developing world, to maximize the efficacy of drug therapy and alleviate treatment inequalities.

Future investigations should be directed towards identification of other markers and genetic determinants which can affect the treatment resistance and disease course, especially for sensitive aggressive forms like triple negative breast cancer. Larger and more diverse samples in long-term studies are also recommended to improve the generalizability of the results of these studies. Additionally, artificial intelligence and machine learning techniques that can be part of the clinical practice can enhance the accuracy of the diagnosis and predispose to the treatment outcomes. However, policy makers should have strategies in place to encourage equitable access to cutting-edge cancer therapies as well as continued research in precision and translational medicine.

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