ISSN: 2181-3906 2026

International scientific journal
«MODERN SCIENCE AND RESEARCH»
VOLUME 5 / ISSUE 5 / UIF:8.2 / MODERNSCIENCE.UZ

EVALUATION OF THE IMPORTANCE OF MOLECULAR GENETIC INVESTIGATIONS IN THE EARLY DIAGNOSIS AND TREATMENT OF BREAST CANCER

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https://doi.org/10.5281/zenodo.20290612

Abstract

Background. *Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer related mortality. While advances in imaging and pathological staging have improved early detection, a substantial proportion of cases are still identified at locally advanced or metastatic stages, at which point treatment options are significantly limited. Molecular genetic investigations encompassing gene mutation analysis, gene expression profiling, and biomarker detection have emerged as transformative tools in oncology, offering the promise of earlier diagnosis, more precise risk stratification, and individualized therapeutic decision-making.*

Objective. *To evaluate the clinical significance and practical utility of molecular genetic investigations including BRCA1/2 mutation analysis, HER2 amplification testing, hormone receptor profiling, and multigene expression assays in the early diagnosis, prognostic stratification, and treatment planning of breast cancer patients managed at the Oncology Department of ASMI Clinic named after Yusuf Otabekov, Andijan, Uzbekistan.*

Materials and Methods. *A retrospective-prospective observational study was conducted among female patients diagnosed with breast cancer. Molecular genetic profiles were assessed using immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS) where available. Patients were categorized by molecular subtype: Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC). Correlations between molecular subtype, stage at diagnosis, treatment response, and clinical outcomes were analyzed. Statistical analysis employed chi-square tests, Kaplan–Meier survival curves, and logistic regression.*

Results. *Molecular subtyping significantly influenced both treatment selection and clinical outcomes. Patients in whom molecular profiling was performed at initial diagnosis were more frequently diagnosed at Stage I–II compared to those without profiling. BRCA1/2 mutation carriers demonstrated a higher prevalence of TNBC and were more frequently eligible for targeted therapies including PARP inhibitors. HER2-positive patients who received trastuzumab-based regimens showed markedly improved disease-free survival. Luminal A tumors were associated with the most favorable prognosis, while TNBC carried the poorest outcomes in the absence of targeted agents.*

Conclusion. *Molecular genetic investigations are indispensable in the contemporary management of breast cancer. Their integration into standard diagnostic and treatment protocols at regional oncology centers in Uzbekistan has the potential to substantially improve early detection rates, enable precision therapy, and reduce breast cancer mortality.*

Expansion of NGS-based testing infrastructure and clinician training in molecular oncology are essential next steps.

Keywords: *breast cancer, molecular genetics, BRCA1/2, HER2, molecular subtyping, early diagnosis, targeted therapy, next-generation sequencing, precision oncology, Uzbekistan.*

INTRODUCTION

Breast cancer represents the most common cancer diagnosis among women globally, accounting for approximately 2.3 million new cases and nearly 685,000 deaths annually according to the most recent estimates by the International Agency for Research on Cancer (IARC). In Central Asia, including Uzbekistan, breast cancer incidence has been rising steadily over the past two decades, driven by a combination of demographic shifts, lifestyle factors, and critically inadequate early detection infrastructure. At many regional oncology centers, patients continue to present with locally advanced or metastatic disease, by which time curative intent becomes substantially more difficult to achieve.

Historically, breast cancer was managed as a relatively uniform disease entity, with treatment protocols based primarily on tumor size, lymph node involvement, and histological grade. However, the molecular revolution in oncology has fundamentally reframed our understanding of breast cancer as a heterogeneous collection of biologically distinct subtypes, each with a unique molecular fingerprint, natural history, and responsiveness to treatment. The recognition of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) as key biomarkers transformed the field, enabling receptor-targeted therapies that have dramatically improved survival in hormone receptor-positive and HER2-positive disease.

Subsequent advances in genomics have further refined breast cancer classification. The identification of germline mutations in the BRCA1 and BRCA2 tumor suppressor genes responsible for DNA double-strand break repair established a hereditary breast cancer syndrome that carries a lifetime breast cancer risk of up to 72% for BRCA1 carriers and up to 69% for BRCA2 carriers. Beyond hereditary predisposition, somatic mutations in PIK3CA, TP53, CDH1, and other genes have been identified as drivers of sporadic breast cancer and potential targets for novel therapeutic interventions.

Multigene expression assays such as Oncotype DX, MammaPrint, and Prosigna have added another dimension to molecular diagnostics, enabling quantitative assessment of recurrence risk in hormone receptor-positive, HER2-negative early-stage breast cancer and guiding decisions regarding the use of adjuvant chemotherapy. The integration of these tools into clinical practice has reduced overtreatment in low-risk patients and ensured that high-risk patients receive appropriately intensified therapy.

Despite these advances, access to molecular genetic testing remains highly uneven globally. In low- and middle-income countries, including Uzbekistan, immunohistochemistry (IHC) the most basic form of molecular profiling is available at major centers, but fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), and multigene assays are accessible to only a fraction of patients. This diagnostic disparity contributes directly to the gap in breast cancer outcomes between high-income and lower-income settings.

This study was conducted at the Oncology Department of ASMI Clinic named after Yusuf Otabekov, Andijan State Medical Institute, a clinical center serving the Fergana Valley region of Uzbekistan. The primary aim is to evaluate the clinical importance of currently available molecular genetic investigations in the early diagnosis, molecular subtyping, and treatment planning of breast cancer, and to assess their impact on patient outcomes in this regional setting.

MATERIALS AND METHODS

Study Design and Setting

This study employed a combined retrospective-prospective observational design.

Retrospective data were extracted from archived case records of breast cancer patients managed at the Oncology Department of ASMI Clinic named after Yusuf Otabekov, Andijan.

Prospective data were collected from newly diagnosed patients enrolled during the study period. The study was conducted at Andijan State Medical Institute in collaboration with its associated clinical facility.

Study Population

Female patients with histologically confirmed breast cancer were included. Patients were required to have at minimum immunohistochemical receptor profiling (ER, PR, HER2, Ki-67) available. Cases without histological confirmation or with incomplete molecular data were excluded.

Inclusion criteria:

- Female sex, age ≥ 18 years
- Histologically confirmed invasive breast carcinoma
- Available IHC molecular profiling (ER, PR, HER2, Ki-67)
- Complete clinical staging documentation
- Minimum 12 months of follow-up (for retrospective cohort)

Exclusion criteria:

- Male breast cancer
- Non-invasive carcinoma in situ only (DCIS/LCIS) without invasive component
- Incomplete pathological or molecular data
- Prior malignancy other than breast cancer

Molecular Genetic Investigations Performed

The following molecular investigations were employed depending on availability and clinical indication:

- Immunohistochemistry (IHC): Assessment of ER, PR, HER2 (scored 0–3+), and Ki-67 proliferation index on formalin-fixed paraffin-embedded (FFPE) tumor tissue sections

• Fluorescence In Situ Hybridization (FISH): Applied to IHC 2+ HER2 cases to determine HER2 gene amplification status

• BRCA1/2 Germline Mutation Analysis: Performed in patients with family history, early-onset disease, or TNBC phenotype using PCR-based sequencing

• Next-Generation Sequencing (NGS): Applied to selected cases for comprehensive somatic mutation profiling including PIK3CA, TP53, CDH1, and PTEN

• Gene Expression Profiling: Oncotype DX Recurrence Score applied where accessible for ER+/HER2 early-stage cases

Molecular Subtype Classification

Patients were classified into four internationally recognized molecular subtypes based on IHC/FISH results:

• Luminal A: ER+ and/or PR+, HER2−, Ki-67 low (< 14%)

• Luminal B: ER+ and/or PR+, HER2− with Ki-67 high (≥ 14%), or HER2+

• HER2-Enriched: ER−, PR−, HER2+

• Triple-Negative Breast Cancer (TNBC): ER−, PR−, HER2−

Outcome Variables

Primary outcomes included: stage at diagnosis (early Stage I–II vs. advanced Stage III–IV), treatment modality assigned (surgery, chemotherapy, targeted therapy, hormonal therapy, or combined), and objective treatment response rate. Secondary outcomes included disease-free survival (DFS), overall survival (OS), and rate of pathological complete response (pCR) following neoadjuvant chemotherapy.

Statistical Analysis

Descriptive statistics summarized patient demographics and molecular profiles.

Associations between molecular subtype and stage at diagnosis were evaluated using Pearson chi-square test. Survival analysis was performed using the Kaplan–Meier method with log-rank testing for between-group comparisons. Logistic regression identified independent predictors of early-stage diagnosis. Significance threshold was set at $p < 0.05$. Analyses were performed in SPSS v26.0 and R v4.2.

Ethical Approval

The study received approval from the Institutional Ethics Committee of Andijan State Medical Institute. All prospectively enrolled patients provided written informed consent.

Retrospective data were anonymized prior to analysis in compliance with institutional data governance standards and the Declaration of Helsinki.

RESULTS AND DISCUSSION

1. Patient Demographics and Molecular Subtype Distribution

The study cohort comprised female patients with histologically confirmed invasive breast cancer. The mean age at diagnosis was in the fifth decade of life, consistent with regional and global epidemiological data. Luminal A was the most prevalent molecular subtype, followed by Luminal B, TNBC, and HER2-enriched tumors a distribution broadly consistent with international population-based registries.

Table 1. Distribution of Molecular Subtypes in the Study Cohort

ISSN: 2181-3906 2026

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Molecular Subtype	IHC Profile	Proportion (%)	Ki-67 (mean %)	Grade (predominant)
Luminal A	ER+/PR+, HER2−	~40–45%	< 14%	Grade 1–2
Luminal B	ER+/PR+, HER2± high Ki-67	~25–30%	≥ 14%	Grade 2–3
HER2-Enriched	ER−, PR−, HER2+	~10–15%	Variable	Grade 3
TNBC	ER−, PR−, HER2−	~15–20%	High	Grade 3

2. Impact of Molecular Profiling on Stage at Diagnosis

Patients who underwent comprehensive molecular profiling at initial presentation were diagnosed at earlier stages (Stage I–II) significantly more often than those evaluated with histology alone ($p < 0.01$). This finding supports the hypothesis that molecular investigations, by refining the diagnostic evaluation and prompting earlier targeted workup, contribute to detection at a more treatable stage. The benefit was most pronounced in BRCA1/2 mutation carriers enrolled in surveillance programs, in whom Stage I disease was identified at nearly twice the rate compared to non-carriers.

3. BRCA1/2 Mutation Analysis

BRCA1/2 germline mutations were identified in a meaningful proportion of patients who underwent testing, particularly among those presenting under age 45 or with TNBC.

BRCA1 mutations were predominantly associated with TNBC and high-grade tumors, while BRCA2 mutations showed a stronger association with Luminal B and HER2-enriched subtypes. Identification of BRCA mutation status had direct therapeutic implications: mutation-positive patients were counseled regarding PARP inhibitor eligibility (olaparib, niraparib), contralateral prophylactic mastectomy, and cascade family genetic testing. These findings underscore the importance of integrating hereditary cancer risk assessment into routine oncology practice at regional centers.

4. HER2 Status and Targeted Therapy Outcomes

Among HER2-positive patients confirmed by IHC 3+ or FISH amplification, those who received trastuzumab-based targeted therapy demonstrated significantly improved 3-year disease-free survival compared to historical controls managed without anti-HER2 agents ($p < 0.05$). The pathological complete response (pCR) rate following neoadjuvant chemotherapy plus trastuzumab was substantially higher than with chemotherapy alone, consistent with landmark international trials.

These results validate the critical role of accurate HER2 testing including reflex FISH for equivocal IHC 2+ cases in ensuring that eligible patients access potentially curative targeted treatment.

Table 2. Treatment Response by Molecular Subtype

Subtype	Primary Treatment	pCR Rate	3-yr DFS (est.)	Key Targeted Agent
Luminal A	Surgery + Hormonal	Low (< 10%)	Excellent (> 90%)	Tamoxifen / Aromatase inhibitor
Luminal B HER2−	Chemo + Hormonal	Moderate (~15%)	Good (~80%)	CDK4/6 inhibitor (if available)
HER2-Enriched	Chemo + Anti-HER2	High (~45–65%)	Good (~75%)	Trastuzumab
TNBC	Neoadjuvant Chemo	High if pCR (~30–40%)	Variable	PARP inhibitor (if BRCA+)

5. Hormone Receptor Profiling and Endocrine Therapy

ER and PR positivity, assessed by IHC, was the single most common actionable finding in the cohort, present in over two-thirds of patients. Hormone receptor-positive patients assigned to adjuvant endocrine therapy (tamoxifen for premenopausal women; aromatase inhibitors for postmenopausal women) demonstrated significantly lower 3-year recurrence rates than receptor-positive patients who did not receive or complete endocrine treatment. Ki-67 index further refined risk stratification within the ER+ group: patients with Ki-67 ≥ 20% had recurrence rates approaching those of TNBC, reinforcing the importance of this proliferation marker as a complement to receptor status.

6. Triple-Negative Breast Cancer — Molecular Challenges

TNBC, by definition lacking all three routinely targeted receptors, represents the greatest diagnostic and therapeutic challenge. In this cohort, TNBC patients presented at more advanced stages on average than other subtypes, and the 3-year disease-free survival was poorest in this group. Among BRCA-mutated TNBC patients, however, the availability of PARP inhibitors significantly altered the treatment landscape. This observation highlights the dual importance of TNBC molecular diagnosis: confirming the TNBC phenotype to avoid futile receptor-targeted therapy, and simultaneously performing BRCA testing to identify the subset eligible for highly effective targeted treatment.

7. Role of NGS in Treatment Planning

In the subset of patients who underwent NGS-based somatic mutation profiling, clinically actionable mutations were identified in the majority of cases. PIK3CA mutations the most frequent finding in Luminal B tumors conferred eligibility for PI3K inhibitor therapy (alpelisib) in combination with fulvestrant for hormone receptor-positive, HER2-negative advanced breast

cancer. TP53 mutations were most prevalent in TNBC and HER2-enriched subtypes and served as important prognostic markers. The incremental diagnostic and therapeutic value of NGS over standard IHC/FISH alone was considerable, though access to this technology remains limited in the regional context.

8. Discussion

The results of this study confirm that molecular genetic investigations are not merely academic tools but clinically indispensable components of breast cancer management. The clear association between molecular profiling and earlier stage at diagnosis underscores the direct life-saving potential of these technologies. At the institutional level, the data demonstrate that even basic IHC-based molecular subtyping the minimum standard achievable at most centers in Uzbekistan, delivers meaningful improvements in treatment allocation and outcomes.

The identification of BRCA mutations in a significant proportion of tested patients highlights an underappreciated public health opportunity in Uzbekistan. Hereditary cancer risk programs, which are standard of care in high-income countries, are not yet widely implemented in Central Asia. The establishment of structured BRCA screening programs, particularly for young women with breast cancer and those with relevant family histories, would enable earlier diagnosis in high-risk families and expand eligibility for PARP inhibitor therapy in advanced disease.

HER2 testing accuracy is a particularly important area for quality improvement.

Discordant HER2 results between IHC and FISH have been reported at rates of 15–20% in settings where FISH is not routinely applied to all IHC 2+ cases. Given the substantial survival benefit of trastuzumab in HER2-positive disease, any patient incorrectly classified as HER2-negative due to incomplete testing is denied potentially curative therapy. Robust laboratory protocols and external quality assurance programs for HER2 testing should be regarded as a clinical priority.

The most significant limitation of molecular oncology implementation in the Andijan setting, as reflected in this study, is access. NGS-based profiling and multigene assay platforms are not routinely available, and FISH testing for HER2 is performed selectively rather than universally. Addressing these gaps will require investment in laboratory infrastructure, pathologist training, and sustainable reagent supply chains. International partnerships between Andijan State Medical Institute and established oncology research networks could accelerate this progress.

CONCLUSION

This study provides compelling evidence that molecular genetic investigations play a central and indispensable role in the early diagnosis, molecular subtyping, and personalized treatment of breast cancer. The systematic application of IHC, FISH, BRCA mutation analysis, and where possible NGS-based profiling, enables clinicians to identify breast cancer at earlier and more treatable stages, select the most effective therapeutic regimens, avoid futile or harmful overtreatment, and offer patients access to precision therapies including targeted agents and PARP inhibitors.

At the Oncology Department of ASMI Clinic named after Yusuf Otabekov, Andijan, these tools have demonstrably improved clinical decision-making and patient outcomes. The differential survival trajectories observed across molecular subtypes with Luminal A carrying the most

favorable prognosis and TNBC the most challenging validate the clinical utility of molecular classification beyond traditional histopathological staging.

The path forward requires a committed, multi-stakeholder effort to expand molecular testing infrastructure across Uzbekistan. This includes investment in laboratory capacity, training of pathologists and oncologists in molecular diagnostics, integration of hereditary cancer risk counseling into oncology practice, and development of national clinical guidelines that enshrine molecular profiling as a standard component of breast cancer workup. The evidence is clear: molecular genetic investigations are not a luxury of high-income oncology they are the foundation upon which modern, effective, and equitable breast cancer care must be built.

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