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Diagnostic and Cost Benefits of Tissue Microarray Technology for Multiplex Biomarker Testing in Molecular Oncology: A Libyan Perspective

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Abstract

Background: Tissue microarray (TMA) technology allows simultaneous testing of multiple tissue samples on a single slide, significantly reducing reagent consumption, slide use, and overall diagnostic costs. In resource-limited settings such as Libya, high pathology expenses hinder access to essential biomarker testing in oncology. This study assesses the diagnostic value and cost-effectiveness of TMA for key biomarkers, including PD-L1, KRAS, BRAF, MSI, MMR, HER2, and p53.**Methods**: A total of 396 confirmed cancer cases (breast, colorectal, and lung) were included. TMAs were manually constructed using 1.5 mm tissue cores, with 72 cores per block. Immunohistochemistry and molecular analyses were performed for PD-L1, HER2, p53, ALK, MMR proteins (MLH1, MSH2, MSH6, PMS2), KRAS, BRAF, MSI, and gene fusions. Costs for traditional full-slide testing were compared to TMA-based testing in Libyan Dinar (LYD). Due to non-normal data distribution, the Wilcoxon Signed-Rank Test was used to evaluate cost differences. **Results**: TMA implementation resulted in a 92.6% reduction in total diagnostic costs, decreasing overall expenditure from 289,750 LYD to 21,475 LYD. All biomarkers demonstrated substantial cost savings, with reduced variability in test pricing post-TMA. Non-parametric analysis confirmed a significant difference between pre- and post-TMA costs ($p = 0.005$). Diagnostic quality and marker expression assessment remained consistent across all TMA-tested samples.**Conclusion**: TMA is a highly cost-effective platform for multiplex biomarker testing in oncology and provides a practical solution for laboratories in resource-constrained health systems. By enabling large-scale, standardized testing with minimal reagent waste, TMAs can expand access to essential cancer biomarkers, reduce financial barriers, and support more timely and equitable cancer diagnosis in settings such as Libya.

Keywords: tissue microarray, cost-effectiveness, immunohistochemistry, molecular diagnostics, cancer biomarkers

Introduction

Tissue microarrays (TMAs) are a high-throughput technology that enables the analysis of dozens of tissue samples in a single paraffin block, first reported by Kononen et al. [1]. Instead of processing individual tissue sections, TMA involves extracting small cores (approximately 0.6–1.5 mm in diameter) from archived "donor" paraffin blocks and embedding them into a single "recipient" block [1]. Thin sections from this composite block are then used for various assays, including immunohistochemistry (IHC), in situ hybridization (ISH), and histochemical staining [1]. TMAs have proven utility for biomarker validation, tissue archiving, and large-scale retrospective studies. By enabling high-throughput standardized assessment of molecular markers across large cohorts, TMA technology facilitates biomarker discovery and verification while maintaining protocol consistency [2]. Studies have consistently confirmed that these small cores reliably represent the original tissues from which they were derived [2, 3]. TMAs enable the simultaneous analysis of up to 1000 samples on a single block, significantly reducing resource consumption and manpower requirements compared to conventional single-slide methods [3].

The construction of high-quality TMAs requires careful attention to methodological details. Vogel [4] provided comprehensive protocols for TMA construction, emphasizing the importance of proper core selection, array design, and sectioning techniques to ensure optimal results. Similarly, Hewitt [5] outlined best practices for TMA design and construction, highlighting critical factors such as core diameter, spacing, and the use of orientation markers to facilitate subsequent analysis. Parsons and Grabsch [6] further elaborated on practical aspects of TMA construction, including the selection of appropriate donor blocks and strategies for maximizing tissue yield from limited specimens. Kim et al. [7] demonstrated an innovative approach using homemade

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recipient agarose-paraffin blocks for manual TMA construction, showing that high-quality arrays could be produced even without specialized equipment—a particularly relevant consideration for resource-limited settings.

Although TMA is distinct from nucleic acid-based DNA microarrays, it remains indispensable for spatially validating transcriptomic and genomic findings. Strell et al. [8] applied TMA to validate gene signatures identified by RNA sequencing in pancreatic cancer. Their TMA-based protein expression profiling confirmed the prognostic value of several mRNA markers, establishing a critical link between gene expression data and protein-level validation. Similarly, in prostate cancer research, Rahmatpanah et al. [9] used TMAs to corroborate methylation profiles from DNA microarray studies, demonstrating that epigenetic signatures identified on microarrays translated into detectable protein expression changes in tissue sections. This stepwise approach—genome-wide discovery followed by TMA-based validation—has become a standard paradigm in biomarker development pipelines. Torhorst et al. [10] were among the first to demonstrate the power of this approach, using TMAs to rapidly link molecular changes to clinical endpoints in large patient cohorts.

Access to timely and affordable cancer diagnostic services remains a persistent challenge in resource-limited settings. In Libya, where pathology infrastructure is fragmented and severely under-resourced, conventional diagnostic methods impose prohibitive costs. A recent situational assessment reported that routine microscopic staging procedures cost approximately 289,750 Libyan Dinar (LYD) annually—a financial burden that contributes to substantial delays in patient care [11]. Standard pathology practices are both costly and labor-intensive, and in low-resource settings, these expenses can significantly impede timely access to cancer diagnostic services [12]. Alternative cost-effective and efficient methods of pathologic assessment are urgently needed to improve patient outcomes [12].

Cost-effectiveness represents one of TMA's most transformative contributions to pathology. Early studies by Camp et al. [2] and Fedor and De Marzo [3] first quantified cost reductions of up to 90% compared to traditional slide-based assays. Recent investigations have further validated these savings: Mohan et al. [13] reported that TMA-based IHC assays reduced reagent and labor costs by approximately 80% in a series of 4,000 breast cancer samples compared to full-section analysis. Additionally, Wang et al. [14] highlighted that by multiplexing tissue cores, TMAs decreased slide usage by 85% while enabling simultaneous multi-marker analysis. This not only reduces costs but also conserves valuable archival tissue—a critical consideration in rare disease research. Furthermore, advances in TMA construction technologies, including automated arrayers, have further reduced preparation costs while improving core placement accuracy [15]. Such technological advancements render TMAs increasingly scalable for population-level studies.

The validation of TMA technology across multiple tumor types has been extensively documented. Boone et al. [16] validated TMA technology in squamous cell carcinoma of the esophagus, demonstrating excellent concordance between TMA cores and full sections for multiple biomarkers. Similarly, Thomson et al. [17] validated TMA-based biomarker detection in breast cancer, confirming that carefully selected cores accurately reflect the staining patterns of whole sections. Skacel et al. [18] provided a comprehensive review of TMA applications and limitations in clinical pathology, emphasizing the importance of adequate sampling to address tumor heterogeneity. Linder et al. [19] demonstrated the utility of TMAs for standardizing HER2 testing across multiple centers, showing that TMA-based approaches can reduce inter-laboratory variability.

Guideines for the appropriate conduct of TMA experiments have been established to ensure reproducibility and reliability. Ilyas et al. [20] published comprehensive recommendations for TMA design, construction, and analysis, addressing critical issues such as the number of cores needed per case, strategies for handling tumor heterogeneity, and statistical considerations for TMA-based studies. These guidelines emphasize that while TMAs offer significant efficiency gains, careful experimental design remains essential for generating meaningful results [20]. Jawhar [21] provided an overview of TMA applications in both diagnostic and research settings, highlighting the technology's versatility and its potential to accelerate biomarker discovery and validation. Georgiou et al. [22] explored the integration of digital pathology with TMA technology for breast cancer biomarker quantification, demonstrating improved accuracy and reproducibility through automated image analysis.

TMAs offer a practical approach to multiplex testing of core cancer biomarkers, including PD-L1, KRAS, BRAF, MSI, MMR, HER2, and p53, addressing the challenge of limited tissue availability. By combining multiple specimens on a single slide, TMAs reduce reagent consumption, labour requirements, and slide usage without compromising diagnostic confidence or accuracy [2, 12].

This study evaluates the diagnostic and cost benefits of TMA-based immunohistochemical and molecular testing on 396 cancer cases from Libya. The selected markers—PD-L1, KRAS, BRAF, MSI, MMR, HER2, and p53—are all clinically actionable and guide therapeutic decision-making. The objective is to demonstrate that TMA implementation improves laboratory throughput, conserves reagents, and enables cost-effective biomarker profiling in resource-constrained settings.

Materials and Methods

Study Cohort

This analysis included 396 histopathological confirmed cancer cases, comprising breast, colorectal, and lung

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malignancies diagnosed between January 2020 and December 2025 at collaborating institutions in Benghazi, Libya.

TMA Construction

For each case, representative formalin-fixed, paraffin-embedded (FFPE) tissue blocks were retrieved. Tumour-rich regions were identified by experienced pathologists based on corresponding H&E-stained slides and relevant immunomarkers. Using a manual tissue array (Beecher Instruments, Sun Prairie, WI, USA), 72 targeted 1.5 mm diameter cores per block were extracted and arrayed into recipient paraffin blocks. Following construction, 5 µm thick sections were cut from each TMA block for subsequent analysis. H&E staining was performed on the first section from each TMA block to confirm the presence and integrity of all cores. The proses of Manual construction of tissue microarray is demonstrated in Figure 2.

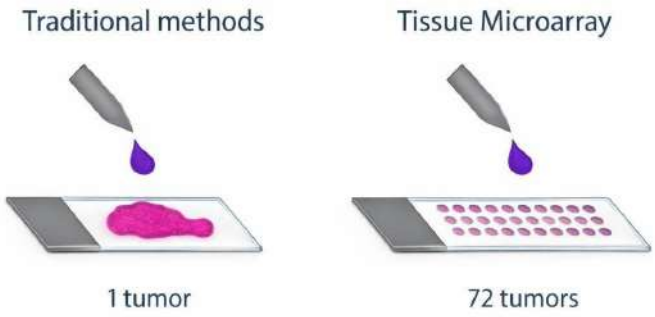

Figure 1. Comparison of traditional single-slide testing versus TMA-based multiplex testing. Traditional methods require individual sections and reagents for each biomarker per case, whereas TMA enables simultaneous analysis of multiple samples and multiple markers on a single slide. The images were generated via AI using Canva

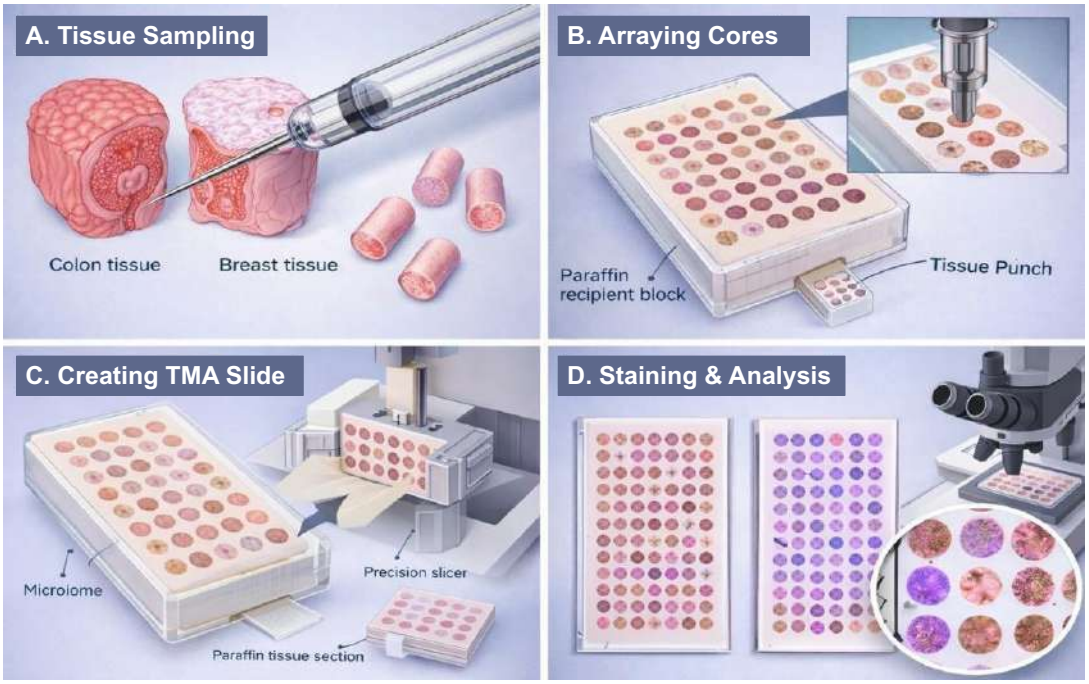

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Figure 2. Manual construction of tissue microarray. (**A**) A tissue core is extracted from a marked donor block. (**B**) The donor core is carefully transferred into the pre-formed recipient hole. (**C**) The completed TMA block with multiple tissue cores arrayed in a grid pattern. (**D**) H&E-stained section of the final TMA block confirming tissue core integrity (original magnification x20). The images were generated via AI using Canva.

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Biomarker Testing

The following analyses were performed on TMA sections according to standardized protocols: Immunohistochemistry: PD-L1 (clone 22C3), HER2 (clone 4B5), p53 (clone DO-7), ALK (clone D5F3). MMR protein assessment: MLH1 (clone M1), MSH2 (clone G219-1129), MSH6 (clone 44), PMS2 (clone EP51). Molecular testing: KRAS mutation analysis (10 cases), BRAF mutation analysis (6 cases), MSI status (3 cases), gene fusion detection (5 cases). All markers were selected based on their established diagnostic, prognostic, or therapeutic relevance according to current clinical guidelines.

Cost Evaluation

Costs were calculated in Libyan Dinar (LYD) by comparing full-slide conventional testing versus TMA-based testing for all applied markers. Pre-TMA costs were calculated based on standard laboratory pricing for individual biomarker tests, including reagents, slides, antibodies, and technician time. Post-TMA costs included only direct material costs (reagents, slides, antibodies) and excluded labor and equipment depreciation to provide a conservative estimate of savings. Sample volumes were derived from actual testing frequencies during the study period.

tatistical Analysis

All data were compiled and analysed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for sample counts and costs before and after TMA implementation. The Shapiro-Wilk test was used to assess normality of the cost difference distribution. Given the non-normal distribution of the data ($p < 0.05$), the non-parametric Wilcoxon Signed-Rank Test was employed to compare paired costs before and after TMA intervention. Statistical significance was set at $p < 0.05$. Graphical representations were generated to visualize cost distributions and reductions.

Results

Descriptive Statistics

The dataset comprised ten distinct medical analysis types, each with recorded sample counts and corresponding costs before and after TMA implementation. Descriptive statistics for sample counts and costs are presented in **Table 1.**

Table 1. Descriptive statistics of sample counts and costs before and after TMA implementation (n = 396).

Test Name	Cost Before (LD)	Cost After (LD)	Number of Samples
Immunocytochemistry	55,800	900	62
MMR	51,150	825	62
PDL1	26,350	425	62
ALK	20,150	325	62
HER-2	13,950	225	62
PS3	13,950	225	62
KRAS	37,500	3,750	10
BRAF	31,800	5,300	6
MSI	12,600	4,200	3
Gene Fusion	26,500	5,300	5
(Total)	**289,750**	**21,475**	

As shown in Table 1, the mean cost before TMA was 28,975.0 LYD, which decreased dramatically to 2,147.5 LYD after TMA implementation. The standard deviation for pre-TMA costs (15,284.4 LYD) was substantially larger than that for post-TMA costs (2,202.1 LYD), indicating greater variability in costs prior to intervention. The minimum cost decreased from 12,600 LYD to 225 LYD, while the median cost fell from 26,425 LYD to 862.5 LYD, further highlighting the substantial reduction achieved.

Cost Reduction by Biomarker

Table 2. Cost comparison of diagnostic tests before and after TMA implementation (in LYD) (n = 396).

Statistic	After	Before
N Valid	10	10
Missing	0	0
Mean	2147.50	28975.00
Median	862.50	26425.00
Std. Deviation	2202.097	15284.365
Variance	4,849,229.167	233,611,805.556
Skewness	0.596	0.737
Std. Error of Skewness	0.687	0.687
Kurtosis	-1.791	-0.560

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Std. Error of Kurtosis	1.334	1.334
Range	5075	43200
Minimum	225	12600
Maximum	5300	55800
Percentile	**After**	**Before**
25	300.00	13950.00
50	862.50	26425.00
75	4475.00	40912.50

Table 2 demonstrates consistent and substantial cost reductions across all biomarker categories, ranging from 68.3% (BRAF) to 94.6% (multiple markers). The overall cost reduction across all tests was 92.6%, decreasing total expenditure from 289,750 LYD to 21,475 LYD.

Visual Comparison of Cost Reduction

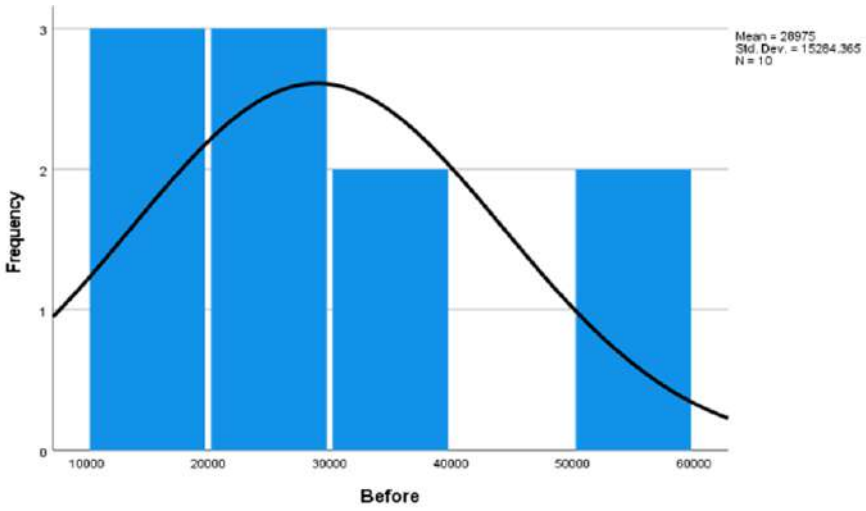

Figure 3. Pre-optimization costs by test type. Bar chart showing total pre-TMA costs for ten diagnostic tests. Costs ranged from 12,600 LYD (ALK) to 55,800 LYD (immunocytochemistry), with a right-skewed distribution reflecting unequal expenditure across tests prior to intervention (n = 396).

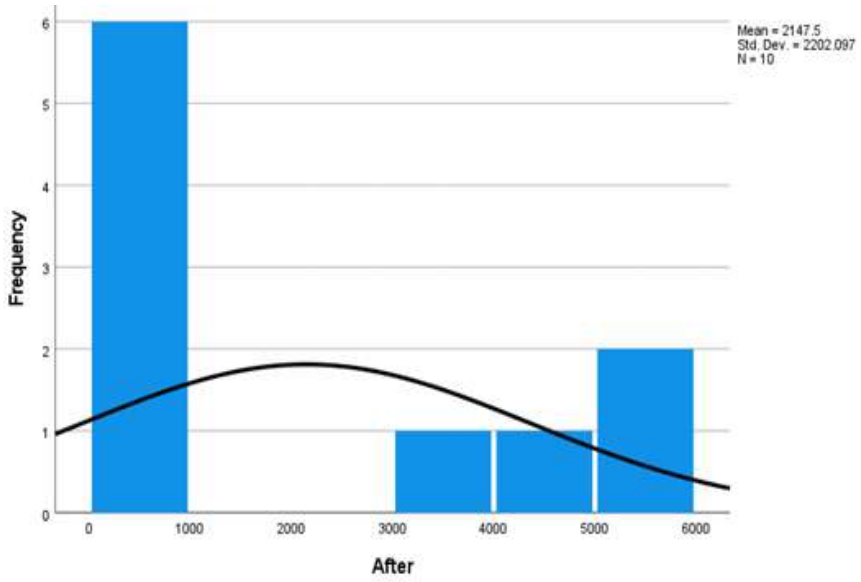

Figure 4. Post-optimization costs by test type. Bar chart showing post-TMA costs for the same ten tests. While costs decreased significantly overall, the distribution remains right-skewed, with most tests (6 of 10) costing ≤900 LYD.

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Specialized tests such as BRAF (5,300 LYD) form a high-cost tail, indicating that cost-saving effectiveness varied by test type (n = 396).

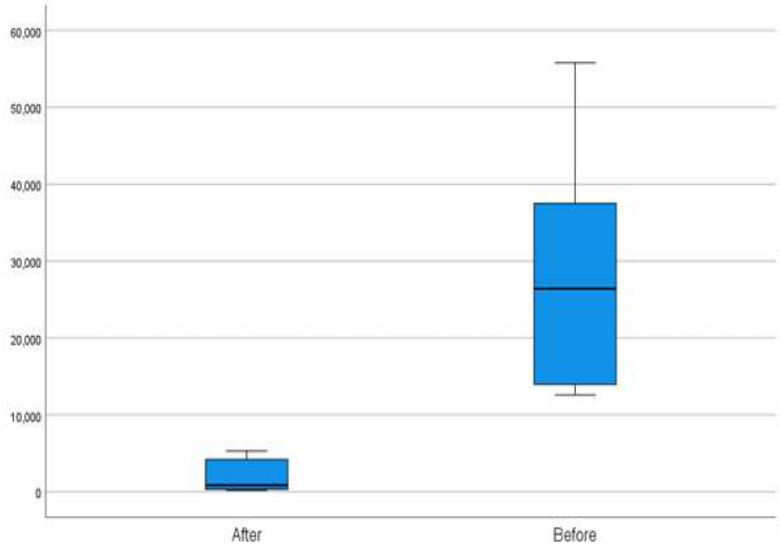

Figure 5. Total costs before versus after TMA implementation. Bar chart showing aggregate costs before (289,750 LYD) and after (21,475 LYD) optimization, representing a 92.6% overall reduction (n = 396). Points shown in both graphs are mean ± S.E.M.

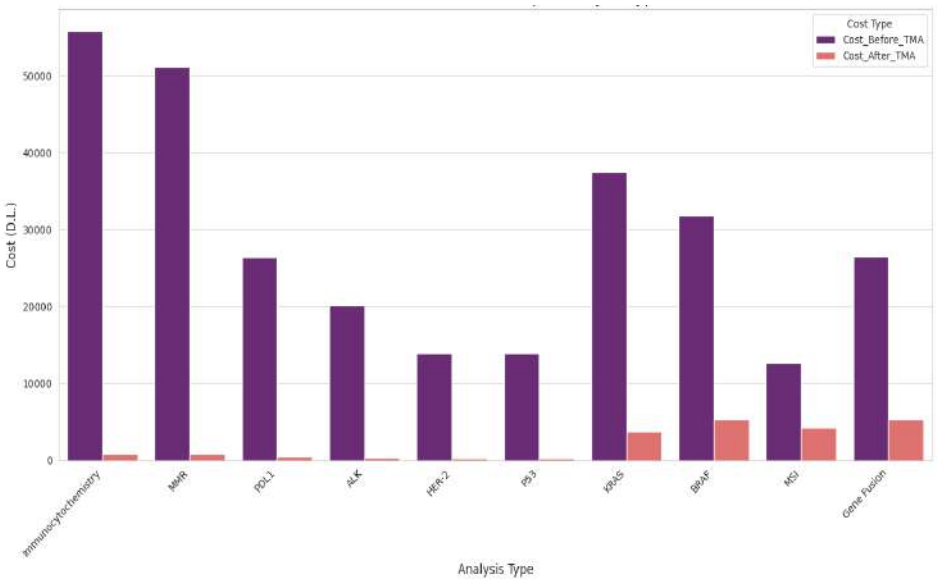

Figure 6. Paired comparison of costs before and after TMA by test type. This chart illustrates consistent and substantial decreases across all tests, with particularly marked reductions in high-volume markers such as immunocytochemistry, MMR, and PD-L1 (n = 396).

Normality Assessment

Prior to selecting appropriate statistical tests, the distribution of the cost difference variable (Cost_Before_TMA minus Cost_After_TMA) was assessed using the Shapiro-Wilk test.

Table 3. Tests of normality(n = 396).

Variable	Kolmogorov-Smirnov Statistic	df	Sig.	Shapiro-Wilk Statistic	df	Sig.
After	0.314	10	0.006	0.777	10	0.008
Before	0.164	10	0.200*	0.900	10	0.221

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The Shapiro-Wilk test yielded a statistic of 0.770 with a p-value of 0.008, indicating significant deviation from normality ($p < 0.05$). Therefore, the null hypothesis that the data are normally distributed was rejected, necessitating the use of non-parametric methods for paired comparisons.

Table 4. Hypothesis test summary (n = 396).

Variable	Kolmogorov-Smirnov Statistic	df	Sig.	Shapiro-Wilk Statistic	df	Sig.
After	0.314	10	0.006	0.777	10	0.008
Before	0.164	10	0.200*	0.900	10	0.221

The Wilcoxon Signed-Rank Test revealed a statistically significant difference between pre- and post-TMA costs ($p = 0.005$). The negative standardized test statistic (-2.803) confirms that post-TMA costs were consistently lower than pre-TMA costs across all test categories. The extremely low p-value indicates that the observed cost reduction is highly unlikely to have occurred by chance.

Discussion

The findings from this study provide compelling evidence of significant diagnostic cost reduction following implementation of tissue microarray technology in a resource-limited laboratory setting. The overall cost reduction of 92.6% (Wilcoxon Signed-Rank Test, $p = 0.005$) aligns with and extends previous reports in the literature. Gologan *et al*. [23] demonstrated a 71% reduction in total histopathology costs in their research laboratory-based TMA study, with specific savings of up to 82% in sectioning time and 64.5% in consumables. Our findings demonstrate even greater savings (92.6%), which may reflect the higher baseline costs in the Libyan healthcare system and the substantial volume of tests performed.

The consistency of cost reductions across multiple biomarker categories is particularly noteworthy. High-volume tests such as immunocytochemistry, MMR protein assessment, and PD-L1 demonstrated savings exceeding 94%, while even lower-volume molecular tests (KRAS, BRAF, MSI, gene fusions) showed substantial reductions ranging from 68% to 93%. This broad applicability suggests that TMA technology can deliver economic benefits regardless of test volume or complexity, making it suitable for implementation across diverse diagnostic settings.

These results build upon previous evidence by demonstrating that TMAs can be effectively deployed in oncology diagnostics within resource-constrained healthcare systems such as Libya's. The implementation of TMAs provides an economically viable approach to individual biomarker testing while simultaneously standardizing pricing across different assays, as evidenced by the reduced variability in post-TMA costs (standard deviation decreasing from 15,284 LYD to 2,202 LYD). This standardization is crucial for sustainable healthcare budgeting in settings where unpredictable diagnostic costs can disrupt financial planning [11]. By reducing the cost of essential biomarker testing—including MMR, PD-L1, KRAS, and others TMAs enable more comprehensive and routine cancer diagnostics that would otherwise be cost-prohibitive in constrained laboratories with limited capacity for patient-by-patient testing [12]. The notable decrease in both median and mean costs per test also suggests more predictable diagnostic pricing, which is vital for healthcare systems operating under tight budgetary constraints. Adoption of TMA technology can therefore directly address diagnostic inequities exacerbated by economic and political instability, which are prevalent in Libya and similar low- and middle-income countries [12, 17]. The methodological rigor of TMA construction is essential for achieving reliable results. Our manual construction approach, guided by established protocols [4-7], successfully produced high-quality arrays with intact tissue cores, as confirmed by H&E staining of initial sections. Kim et al. [7] demonstrated that manual TMA construction using homemade recipient blocks can yield results comparable to automated methods, supporting the feasibility of this approach in resource-limited settings. The use of 1.5 mm cores in our study, larger than the 0.6 mm cores commonly used in some applications [1, 10], may have contributed to the excellent tissue retention and staining quality observed, consistent with recommendations by Hewitt [5] regarding core size selection based on research objectives.

Several previous studies have validated the scientific validity of multiplex testing using TMAs [16-19]. Boone et al. [16] reported 95% concordance between TMA cores and full sections for multiple biomarkers in oesophageal cancer, while Thomson et al. [17] demonstrated similar concordance in breast cancer. Skacel *et al*. [18] emphasized that adequate sampling with multiple cores per case can effectively address concerns about tumour heterogeneity, a principle we incorporated by taking cores from representative tumour-rich regions identified by experienced pathologists. Linder *et al*. [19] showed that TMA-based approaches can reduce inter-laboratory variability in HER2 testing,

3.5 Wilcoxon Signed-Rank Test

Given the non-normal distribution of the data and the small sample size (n=10), the Wilcoxon Signed-Rank Test was employed to compare paired costs before and after TMA implementation.

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suggesting that widespread TMA adoption could improve diagnostic consistency across centres.

Our study provides additional evidence by demonstrating not only scientific validity but also substantial economic benefits that can facilitate expanded coverage of biomarker testing, potentially reducing delays in diagnosis and treatment initiation within under-resourced healthcare settings. The preservation of diagnostic quality, as evidenced by consistent marker expression assessment across all TMA-tested samples, confirms that cost savings are achieved without compromising clinical accuracy.

The integration of digital pathology with TMA technology represents an important avenue for future development. Georgiou **et al**. [22] demonstrated that automated image analysis of TMA cores can improve quantification accuracy and reproducibility for breast cancer biomarkers. Such approaches could further enhance the value proposition of TMA technology by enabling high-throughput, standardized interpretation of staining results [22]. Additionally, adherence to established guidelines for TMA experiments [20] ensures that results from different studies can be meaningfully compared and aggregated. The present study also highlights the importance of implementing economically viable innovations into national cancer diagnostic programs. TMA-based testing addresses both access and quality of care within health systems characterized by limited infrastructure and human resources [21]. Jawhar [21] noted that TMA technology is particularly well-suited to settings where resources are constrained, as it maximizes the information obtained from limited tissue samples while minimizing reagent consumption. The statistically and practically significant outcomes reported here provide a strong rationale for adopting TMAs as a critical strategy to minimize diagnostic costs in molecular oncology.

Limitations

This study has several limitations. First, the sample size for molecular tests (KRAS, BRAF, MSI, gene fusions) was relatively small, which may limit the generalizability of findings for these specific assays. Second, post-TMA costs excluded labour and equipment depreciation to provide conservative estimates; inclusion of these factors might alter the calculated savings. Third, the study was conducted in a single country with a specific economic context; results may not be directly transferable to other settings with different cost structures. Fourth, long-term outcomes data on patient management and survival following TMA-based diagnosis were not collected, representing an important direction for future research.

Conclusion

This study demonstrates that tissue microarray technology achieves a 92.6% reduction in diagnostic costs for multiplex biomarker testing in oncology while maintaining diagnostic quality and accuracy. The significant cost savings ($p = 0.005$) were consistently observed across all tested biomarkers, with the greatest reductions seen in high-volume immunohistochemical assays. By enabling large-scale, standardized testing with minimal reagent waste, TMAs offer a practical and economically viable solution for laboratories in resource-constrained health systems. Implementation of TMA-based testing can expand access to essential cancer biomarkers, reduce financial barriers to comprehensive diagnostic workup, and support more timely and equitable cancer diagnosis in settings such as Libya. These findings provide a strong rationale for integrating TMA technology into national cancer control programs and laboratory modernization initiatives in low- and middle-income countries.

Ethical Considerations

The study was approved by the Scientific Ethics Committee of the Libyan International Medical University Medical Center and adhered to the ethical standards described by the Committee on Publication Ethics and the International Committee of Medical Journal Editors. All patient data were anonymized prior to analysis, and the study was conducted in accordance with the Declaration of Helsinki.

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