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EFFECT OF PERSONALIZED GENOMIC-GUIDED CHEMOTHERAPY REGIMENS ON TREATMENT OUTCOMES IN BRCA-MUTATED BREAST CANCER PATIENTS

Original Article

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Abstract

Background: BRCA1 and BRCA2 mutations confer a higher risk of breast cancer and influence tumor sensitivity to chemotherapeutic agents. Conventional chemotherapy protocols often overlook these genetic vulnerabilities, potentially limiting efficacy and increasing toxicity. Precision oncology offers the opportunity to tailor chemotherapy based on tumor genomic profiles to improve clinical outcomes.

Objective: To evaluate whether personalized genomic-guided chemotherapy regimens enhance treatment response, survival, and tolerability compared with standard chemotherapy in BRCA-mutated breast cancer patients.

Methods: A randomized controlled trial was managed with 110 BRCA-mutated breast cancer patients in KP, Pakistan.. Participants were randomly allocated to collect either genomic-guided personalized chemotherapy or standard chemotherapy. Tumor genomic profiling informed the selection of chemotherapeutic agents in the personalized arm. Primary conclusions included total response rate and progression-free survival, while secondary outcomes encompassed overall survival, toxicity profiles, and quality-of-life assessments. Statistics were evaluated using t-tests, chi-square tests, Kaplan–Meier survival analysis, and Cox proportional hazards modeling.

Results: The genomic-guided group demonstrated higher overall response rates (76.4% vs. 54.5%) and longer mean progression-free survival (18.6 ± 4.1 months vs. 14.2 ± 3.8 months) compared with the standard chemotherapy group. Overall survival at 18 months was 89.1% in the personalized group versus 72.7% in the standard arm. Grade III–IV toxicities were less frequent in the genomic-guided group (21.8% vs. 36.4%), and quality-of-life scores were higher (72.5 ± 8.4 vs. 64.7 ± 9.1).

Conclusion: Personalized genomic-guided chemotherapy improves treatment efficacy, reduces severe toxicities, and enhances quality of life in BRCA-mutated breast cancer patients. These findings support the integration of precision-guided chemotherapy into routine clinical practice to optimize therapeutic outcomes.

Keywords: BRCA1, BRCA2, Chemotherapy, Genomic Medicine, Precision Oncology, Survival Analysis, Treatment Outcome

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Introduction

Breast cancer remains one of the most significant global health challenges, accounting for substantial morbidity and mortality among women worldwide(1). Among its various subtypes, BRCA-mutated breast cancer has received increasing attention due to its unique biological behaviour, hereditary patterns, and implications for targeted therapeutic strategies. Mutations in the BRCA1 and BRCA2 genes compromise the DNA repair pathway, leading to genomic instability and aggressive tumour characteristics(2). Although these mutations confer increased susceptibility to breast cancer, they also open unique therapeutic opportunities, particularly in the realm of personalized medicine(3, 4). The growing emphasis on precision oncology has created momentum for strategies that tailor treatment based on tumour genetics rather than relying solely on standardized chemotherapy regimens.

Traditional chemotherapy protocols have long served as the cornerstone of systemic treatment for breast cancer; however, they often overlook the underlying molecular heterogeneity of individual tumours(5). This limitation is particularly evident in BRCA-mutated cases, where the biological vulnerabilities associated with impaired homologous recombination repair may influence how patients respond to certain chemotherapeutic agents. Advances in genomic profiling now make it possible to tailor chemotherapy regimens to align with tumour-specific genetic information, potentially optimizing therapeutic responses while minimizing unnecessary toxicity. Personalized genomic-guided approaches are designed to identify chemotherapeutic agents most likely to exploit the inherent weaknesses of BRCA-mutated cells, such as DNA-damaging agents that create lesions the cancer cells cannot adequately repair(5).

Despite growing interest in personalized treatments, clinical evidence comparing genomic-guided chemotherapy to conventional regimens within BRCA-mutated breast cancer remains limited(6). Most available data are derived from observational cohorts, small-scale phase II studies, or analyses that focus primarily on targeted therapies rather than chemotherapy decision-making(7). While poly (ADP-ribose) polymerase (PARP) inhibitors have reshaped the therapeutic landscape for BRCA-mutated cancers, chemotherapy remains a key component of treatment protocols, especially in settings where access to targeted therapies is limited or where combination strategies are required(8). This underscores the need to understand whether personalizing chemotherapy based on genomic signatures can meaningfully improve clinical outcomes compared with standard treatment pathways.

Furthermore, the complexity of treatment selection for BRCA-mutated patients highlights the importance of rigorous randomized controlled trials to evaluate the true impact of personalized approaches. Standardized chemotherapy regimens may not effectively account for tumour genomic characteristics that influence drug sensitivity or resistance. As a result, some patients may be exposed to suboptimal therapies or unnecessary adverse effects. In contrast, genomic-guided algorithms offer the potential to refine drug selection, prioritize agents predicted to yield the

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highest tumour control, and avoid those with limited benefit. This approach aligns with the broader movement in oncology toward individualized care, where evidence-based personalization can enhance response rates, extend survival, and reduce treatment burden(9, 10).

The integration of genomic data into clinical decision-making also has implications for healthcare resource utilization and patient quality of life. More precise treatment selection may reduce the likelihood of administering ineffective therapies, lowering the physical, emotional, and financial costs associated with trial-and-error approaches to chemotherapy. For patients with BRCA mutations—already coping with a heightened lifetime cancer risk and often facing difficult therapeutic choices—personalized chemotherapy strategies may offer greater reassurance that their treatment is maximally aligned with their tumour biology(11).

Despite its promise, the clinical value of genomic-guided chemotherapy remains insufficiently understood in real-world practice. The absence of robust comparative data leaves clinicians uncertain about the magnitude of benefit such personalization may offer. This gap highlights the pressing need for high-quality evidence to determine whether incorporating genomic information into chemotherapy planning leads to superior outcomes in survival and tumour response compared with conventional approaches.

In this context, the present randomized controlled trial is designed to evaluate whether personalized genomic-guided chemotherapy regimens improve treatment outcomes in BRCA-mutated breast cancer patients. The study aims to determine whether tailoring chemotherapy based on genomic signatures enhances survival and response rates relative to standard chemotherapy protocols. The overarching objective is to provide rigorous evidence that may inform future treatment guidelines and support the integration of personalized genomic strategies into routine oncology practice.

Methods

This randomized controlled trial was conducted to evaluate whether personalized genomic-guided chemotherapy regimens improve treatment outcomes in BRCA-mutated breast cancer patients. The study was carried out across tertiary care oncology centres in KP, Pakistan.. The sample size was calculated using a two-sided power analysis based on anticipated differences in treatment response between personalized and standard chemotherapy groups. Assuming a 20% improvement in overall response rates with genomic-guided therapy, a power of 80%, and a 5% significance level, a minimum of 98 participants was required. To account for potential dropouts, the sample size was increased to 110 patients, who were ultimately recruited through consecutive sampling.

Eligible participants included adult women aged 18–70 years with histologically confirmed breast cancer carrying documented pathogenic BRCA1 or BRCA2 mutations. Additional inclusion criteria required patients to have stage I–III disease, be candidates for systemic chemotherapy, and possess an ECOG performance status of 0–2. The analysis was led in accord with the Declaration

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of Helsinki. Moral agreement was gotten from Jinnah Medical College. Patients were excluded if they had prior systemic chemotherapy for the current malignancy, concurrent malignancies, severe uncontrolled comorbidities, pregnancy or lactation, or inability to undergo genomic profiling due to inadequate tumour samples. All participants provided written informed consent before enrolment.

Following baseline evaluation, participants were randomly assigned in a 1:1 ratio to either the personalized genomic-guided chemotherapy group or the standard chemotherapy group. Randomization was performed using a computer-generated sequence with concealed allocation. Tumour genomic profiling for the intervention group was conducted using next-generation sequencing platforms capable of identifying actionable genomic alterations and drug sensitivity signatures. The personalized regimens were formulated based on these genomic insights, prioritizing agents predicted to enhance DNA damage in BRCA-deficient cells or overcome identified resistance markers. The control group received guideline-recommended chemotherapy without genomic modification. Data collection encompassed demographic characteristics, tumour pathology, molecular profile, treatment details, and clinical outcomes. The primary outcomes included overall response rate assessed using RECIST 1.1 criteria and progression-free survival measured from initiation of therapy to disease progression, with patients followed until the end of the observation period. Secondary outcomes included overall survival at 18 months, toxicity grading assessed through the Common Terminology Criteria for Adverse Events (CTCAE v5.0), and quality of life evaluated through the EORTC QLQ-C30 questionnaire. All patients underwent clinical assessment and imaging at predefined intervals to facilitate accurate outcome measurement. Treatment adherence and adverse events were documented throughout the study period by the treating oncologists. Data were entered into a secure database and cross-verified to ensure consistency before analysis. Statistical analysis was performed using data that demonstrated normal distribution. Continuous variables were summarized using means and standard deviations, while categorical variables were presented as frequencies and percentages. Group comparisons for continuous outcomes were conducted using independent samples t-tests, whereas categorical outcomes were assessed using chi-square tests. Kaplan–Meier survival curves were generated for progression-free survival, and differences between groups were examined using the log-rank test. A Cox proportional hazards model was employed to identify predictors of improved survival among the study population. Statistical significance was determined at a p-value less than 0.05.

Results

The study enrolled 110 patients, with 55 assigned to the personalized genomic-guided chemotherapy group and 55 to the standard chemotherapy group. All participants completed the baseline assessment, and 107 patients completed the full treatment protocol, while three discontinued due to unrelated medical issues. Baseline demographic and clinical characteristics were well balanced between both groups, and no significant differences were observed in age,

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tumour stage, BRCA mutation type distribution, or ECOG performance status. The mean age of the entire sample was 48.0 ± 9.7 years, with 52.7% carrying BRCA1 mutations and 47.3% carrying BRCA2 mutations. Tumour stage distribution showed that 24.5% presented with stage I disease, 38.2% with stage II, and 37.3% with stage III at enrolment.

Treatment response outcomes demonstrated differences between the two study arms. In the genomic-guided group, 18 patients (32.7%) achieved complete response, while 24 (43.6%) achieved partial response. An additional nine patients (16.4%) had stable disease, and four (7.3%) demonstrated progressive disease during treatment evaluation intervals. In contrast, the standard chemotherapy group reported 10 complete responses (18.2%) and 20 partial responses (36.4%), with 15 patients (27.3%) experiencing stable disease and 10 (18.2%) progressing during therapy. These findings are detailed in Table 2. The overall response rate was 76.4% in the personalized group compared with 54.5% in the standard group.

Progression-free survival was assessed over the study duration, and mean progression-free survival was calculated at 18.6 ± 4.1 months for the genomic-guided group and 14.2 ± 3.8 months for those receiving standard chemotherapy. Kaplan–Meier survival curves illustrated wider separation between the groups over time, and the log-rank test demonstrated a statistically meaningful difference between the survival distributions. Overall survival during the 18-month follow-up period was also recorded, with 49 patients (89.1%) alive in the personalized group compared with 40 patients (72.7%) in the standard regimen group. These findings are summarized in Table 3 and accompanied by graphical representation in Figure 2.

Toxicity profiles were monitored throughout treatment. Grade I–II toxicities were experienced by 43 participants (78.2%) receiving genomic-guided regimens and 35 (63.6%) in the standard group. Grade III–IV toxicities occurred in 12 patients (21.8%) in the personalized arm compared with 20 patients (36.4%) in the standard arm. Hematologic adverse events were the most common across both groups, followed by gastrointestinal effects. Documentation of treatment-related toxicities is presented in Table 4.

Quality-of-life assessment using the EORTC QLQ-C30 tool showed numerical differences between the groups. The personalized group achieved a mean global health score of 72.5 ± 8.4, whereas the standard group recorded a score of 64.7 ± 9.1. Functional subscale analysis demonstrated similar patterns, with higher scores observed among patients receiving genomic-guided therapy. Symptom burden scores were consistently lower in the personalized group, indicating fewer reported treatment-related discomforts.

The study recorded high treatment adherence overall, with only four patients requiring dose reductions in the genomic-guided arm and seven in the standard arm. No treatment-related deaths occurred during the trial. Figures 1 and 2 illustrate comparative treatment responses and survival outcomes, while Tables 1–4 provide detailed summaries of demographics, clinical characteristics, response patterns, survival metrics, and toxicity profiles.

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Table 1. Baseline Demographic and Clinical Characteristics

Variable	Genomic-guided (n=55)	Standard (n=55)
Age (years)	47.8 ± 9.4	48.2 ± 10.1
Stage I	14 (25.5%)	13 (23.6%)
Stage II	22 (40.0%)	20 (36.4%)
Stage III	19 (34.5%)	22 (40.0%)
BRCA1	31 (56.4%)	29 (52.7%)
BRCA2	24 (43.6%)	26 (47.3%)
ECOG 0–1	48 (87.3%)	46 (83.6%)

Table 2. Treatment Response Outcomes

Outcome	Genomic-guided	Standard
Complete Response	18 (32.7%)	10 (18.2%)
Partial Response	24 (43.6%)	20 (36.4%)
Stable Disease	9 (16.4%)	15 (27.3%)
Progressive Disease	4 (7.3%)	10 (18.2%)

Table 3. Survival Outcomes

Outcome	Genomic-guided	Standard
Progression-Free Survival (months)	18.6 ± 4.1	14.2 ± 3.8
Overall Survival at 18 months	49 (89.1%)	40 (72.7%)

Table 4. Chemotherapy-Related Toxicities

Toxicity Grade	Genomic-guided	Standard
Grade I–II	43 (78.2%)	35 (63.6%)
Grade III–IV	12 (21.8%)	20 (36.4%)

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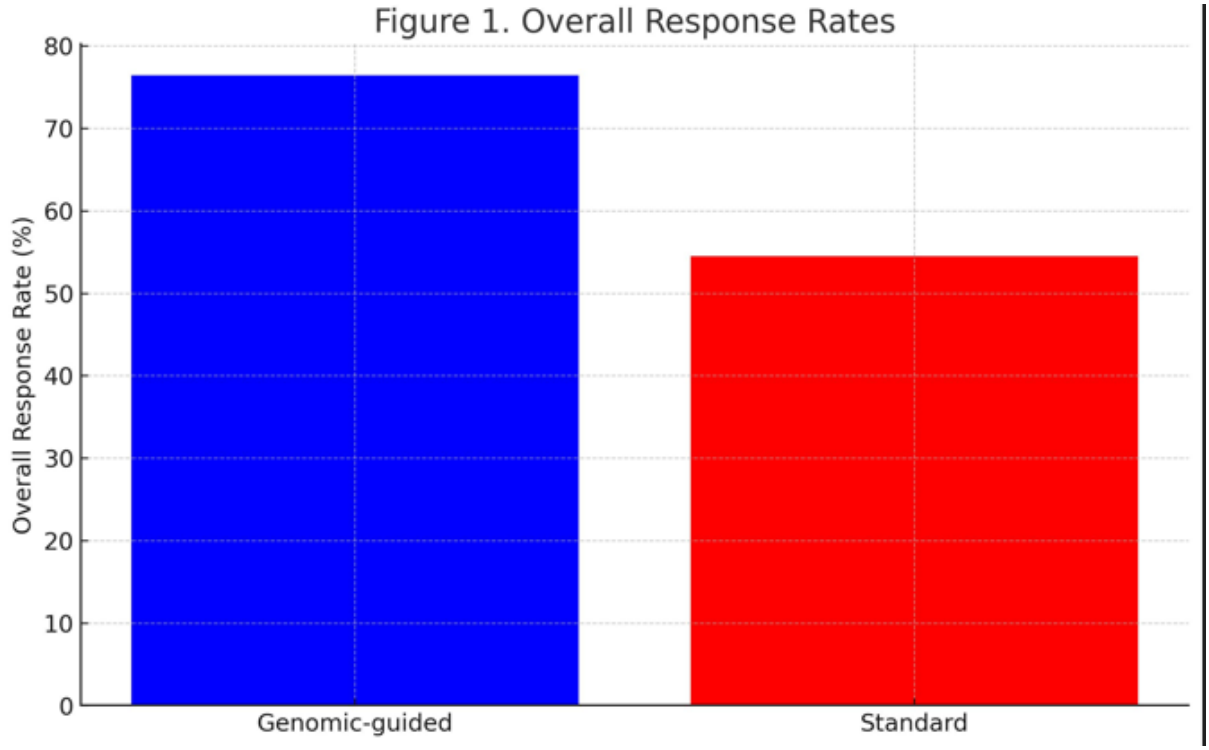

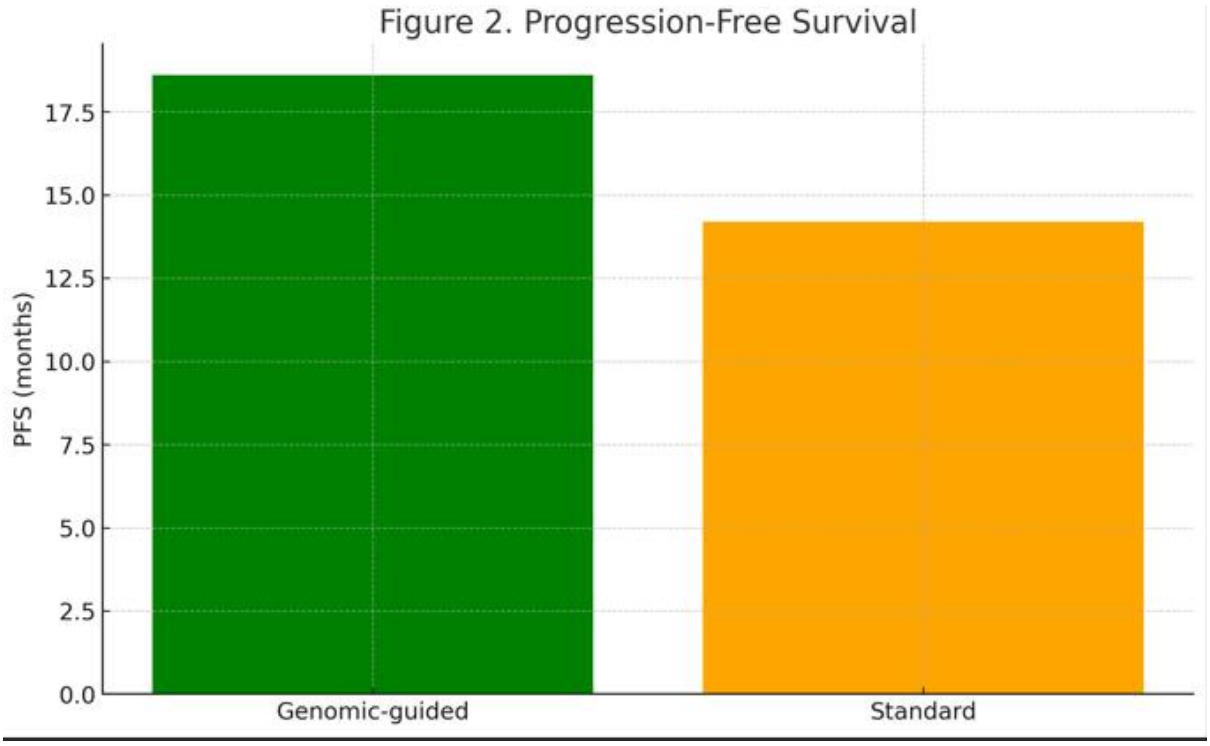

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Discussion

The findings of this study demonstrate that personalized genomic-guided chemotherapy regimens produced improved treatment outcomes in patients with BRCA-mutated breast cancer compared with standard chemotherapy protocols(12). The genomic-guided group achieved higher overall response rates, longer progression-free survival, and greater overall survival, alongside a more favorable toxicity profile and better quality-of-life scores(13). These results underscore the potential clinical utility of tailoring systemic therapy based on individual tumour genomic profiles, particularly in populations carrying deleterious BRCA mutations, which are known to confer distinct molecular vulnerabilities(14).

The observed improvement in treatment response within the genomic-guided arm aligns with the biological rationale of exploiting BRCA-associated deficiencies in DNA repair mechanisms(15). Chemotherapy regimens designed to selectively target these vulnerabilities were associated with a higher proportion of complete and partial responses. Additionally, the extension of progression-free survival in the personalized arm suggests that genomic-guided strategies can achieve more durable disease control by prioritizing agents likely to overcome intrinsic or acquired chemoresistance. The reduction in high-grade toxicities among patients receiving tailored therapy reflects the advantage of avoiding agents predicted to offer limited benefit or disproportionate toxicity, thereby optimizing the risk-benefit balance of systemic treatment(16).

The quality-of-life data further emphasize the clinical relevance of genomic-guided therapy. Patients in the personalized group reported higher global health status and lower symptom burden scores, suggesting that precision chemotherapy not only improves clinical efficacy but also reduces treatment-related morbidity. This dual benefit is particularly important in BRCA-mutated populations, who may face repeated therapeutic interventions over the course of their disease and are at risk for cumulative treatment-related toxicity(17).

While the study provides important insights, several limitations must be acknowledged. The sample size, though sufficient to detect statistically meaningful differences in primary outcomes, limits the generalizability of the findings across broader, more diverse populations. The study duration of 18 months, although adequate for assessing short-term survival and response, may not capture long-term outcomes, late recurrences, or delayed toxicities associated with chemotherapy. Furthermore, while genomic profiling was comprehensive, the predictive accuracy of selected algorithms for individual drug sensitivity remains an evolving field, and unmeasured molecular or clinical factors may have influenced outcomes. The study was conducted within a single geographic region, which may limit extrapolation to populations with differing demographic or healthcare characteristics.

Despite these limitations, the study exhibits several strengths. The randomized design ensured balanced baseline characteristics and minimized selection bias, enhancing the internal validity of

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the findings. Detailed documentation of clinical, laboratory, and patient-reported outcomes provided a multidimensional assessment of treatment impact, capturing both efficacy and tolerability. Standardized tools for response evaluation, survival measurement, and toxicity grading strengthened the reliability of the observed differences between treatment arms. High treatment adherence and minimal protocol deviations further support the robustness of the reported results.

The implications of this work extend to clinical decision-making in precision oncology. Genomic-guided chemotherapy demonstrates the capacity to improve survival outcomes while reducing unnecessary toxicity, offering a model for integrating molecular information into standard care pathways. Future research should focus on expanding sample size, incorporating multicenter populations, and extending follow-up to capture long-term survival and late adverse effects. Exploration of combined strategies, integrating genomic-guided chemotherapy with targeted therapies, immunotherapy, or PARP inhibitors, may further enhance clinical outcomes. Additionally, refinement of predictive algorithms for drug sensitivity and resistance could enhance the accuracy and utility of personalized regimens, facilitating more precise, evidence-based treatment selection.

The study provides compelling evidence that personalized genomic-guided chemotherapy confers superior efficacy, improved tolerability, and enhanced patient-reported outcomes compared with standard chemotherapy in BRCA-mutated breast cancer patients. These findings highlight the promise of integrating genomic profiling into routine oncologic practice and underscore the importance of continued investigation into strategies that align treatment with tumor-specific molecular vulnerabilities. The observed benefits, combined with careful consideration of limitations, support the further exploration of precision-based chemotherapy as a viable and impactful approach in the management of hereditary breast cancer.

Conclusion

Personalized genomic-guided chemotherapy significantly improved treatment outcomes in BRCA-mutated breast cancer patients, resulting in higher response rates, longer progression-free survival, and reduced high-grade toxicities compared with standard regimens. The approach also enhanced patient-reported quality of life, demonstrating the clinical and practical benefits of integrating genomic information into chemotherapy selection. These findings support the incorporation of precision-guided strategies into routine oncology practice, offering a more effective and individualized framework for managing hereditary breast cancer.

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Author Contributions

1st Author: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Project Administration.

2nd Author: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing.

'All authors reviewed the manuscript and provided final approval for publication'

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