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PERSONALIZED DIAGNOSTIC ALGORITHM INCORPORATING MOLECULAR GENETIC TESTING FOR CYTOMEGALOVIRUS INFECTION, CLINICAL IMPLEMENTATION AND COST-EFFECTIVENESS ANALYSIS

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ABSTRACT

Objective: to develop, implement, and evaluate the clinical and economic effectiveness of a personalized three-stage diagnostic algorithm incorporating molecular genetic testing for five polymorphisms in the management of cytomegalovirus infection (CMVI).

Materials and methods. The algorithm was developed based on genotyping data from 100 CMVI patients and 80 controls from the Fergana Valley (2019–2025). The three-stage approach integrates standard clinical-laboratory assessment, genotyping for TNF-α, IL-10, TLR4, eNOS, and SOD2 polymorphisms with calculation of a cumulative genetic risk score (0–10 points), and risk-stratified management protocols. The algorithm was implemented at two clinical sites from 2024, with 68 patients genotyped during the pilot phase. Cost-effectiveness was modeled over a 3–5 year horizon for a cohort of 100 patients.

Results. Among 68 genotyped patients, 24 (35.3%) were classified as high genetic risk (≥6 points). Intensified monitoring in this subgroup enabled timely detection of rising viral loads and early antiviral therapy before the onset of severe complications. No patient in the high-risk group managed according to the algorithm developed generalized CMVI during the observation period. The projected economic benefit over 3–5 years for 100 patients was 192 million UZS, comprising savings from complication reduction (18 million), disability days prevention (54 million), and reduced childhood disability (150 million), minus genotyping costs (30 million).

Conclusion. The three-stage personalized algorithm integrating molecular genetic testing provides a practical, cost-effective framework for risk-stratified management of CMVI. The one-time genotyping investment yields lifelong prognostic information at a cost comparable to a single biochemical analysis, while delivering substantial clinical and economic benefits.

Keywords: Cytomegalovirus infection, personalized medicine, diagnostic algorithm, molecular genetic testing, cost-effectiveness, risk stratification.

INTRODUCTION

Cytomegalovirus infection (CMVI) poses a significant clinical and economic burden worldwide, with particular severity in neonates, pregnant women, and immunocompromised patients (2, 3, 12). Traditional management strategies rely on serial monitoring of viral load, serological markers, and clinical parameters to guide therapeutic decisions (6, 12). While effective for detecting active replication, this reactive approach does not identify patients at inherent risk of progression before clinical deterioration occurs. The need for proactive, host-based risk

stratification has been recognized by multiple authors (4, 6, 12), yet practical tools integrating genetic data into clinical workflows for CMVI management remain scarce.

Recent advances in molecular genetics have demonstrated that single nucleotide polymorphisms (SNPs) in genes regulating immune response, oxidative stress defense, and endothelial function are associated with susceptibility to manifest persistent CMVI (7, 8, 13, 14). A cumulative genetic risk score incorporating five polymorphisms (TNF-α, IL-10, TLR4, eNOS, SOD2) has shown promising diagnostic performance, with AUC reaching 0.78 for the genetic score alone and 0.85 when combined with viral load data (7, 8, 14). However, the translation of these research findings into a structured clinical algorithm with defined management protocols for each risk category has not been previously reported.

The economic dimension of CMVI management is particularly relevant for developing countries. In Uzbekistan, the cost of treating a single episode of complicated CMVI (pneumonia, encephalitis, generalized infection) ranges from 8 to 15 million UZS, while long-term rehabilitation of a child with congenital CMVI can exceed 50–80 million UZS annually (3, 15). These figures underscore the potential economic value of early identification and targeted intervention in high-risk patients. Wang H. et al. (2020) estimated the global economic burden of congenital CMVI in developing countries at over 1.9 billion USD annually (15), highlighting the magnitude of the problem.

The present study aimed to develop a structured three-stage diagnostic algorithm incorporating molecular genetic testing, evaluate its clinical effectiveness through pilot implementation, and analyze its cost-effectiveness for the healthcare system of Uzbekistan.

MATERIALS AND METHODS

The algorithm was developed based on data from a multicenter study conducted at medical institutions of the Fergana Valley during 2019–2025: Zam-Zam Clinic (Andijan, 55 patients), Namangan Central Polyclinic (30 patients), and Fergana Regional Infectious Disease Hospital (15 patients). A total of 100 patients with verified CMVI and 80 healthy controls were enrolled. Diagnosis was established by detection of anti-CMV IgM and/or rising IgG (ELISA, Cobas e411, Roche), CMV DNA quantification (real-time PCR, Rotor-Gene Q, Qiagen), and compatible clinical presentation.

Patients were classified into Group I (n=42, latent CMVI) and Group II (n=58, manifest persistent CMVI) based on viral load, clinical manifestations, and complication profile. Genotyping for five SNPs (TNF-α G308A, IL-10 G>A, TLR4 A896G, eNOS G894T, SOD2 Ala16Val) was performed using real-time PCR with TaqMan probes (CFX96, Bio-Rad). The cumulative genetic risk score (0–10 points) was calculated using a three-tier system: 0 points for protective homozygous, 1 for heterozygous, and 2 for risk homozygous genotype per locus.

The pilot implementation phase commenced in January 2024 at Zam-Zam Clinic and Namangan Central Polyclinic. During 2024–2025, 68 newly diagnosed CMVI patients were genotyped and managed according to the algorithm. Clinical outcomes were monitored prospectively. Cost-effectiveness analysis was modeled over a 3–5 year horizon using local cost data: hospitalization for complicated CMVI (average 12 million UZS per episode), antiviral therapy with ganciclovir/valganciclovir (3.5–6 million UZS per 21-day course), genotyping

panel (300,000 UZS per patient), and average daily wage in Uzbekistan in 2025 (approximately 200,000 UZS).

RESULTS

Algorithm structure

Based on the genotyping data, individual SNP associations, and ROC analysis results, a three-stage personalized diagnostic algorithm was designed (Fig. 1). The algorithm integrates standard clinical assessment, molecular genetic profiling, and risk-stratified management into a unified clinical workflow.

Stage 1 (Standard Assessment) includes serological testing (anti-CMV IgM and IgG by ELISA), CMV DNA quantification by real-time PCR, complete blood count with differential, biochemical panel (ALT, AST, bilirubin, total protein, CRP), and abdominal ultrasound. In children, neurosonography is performed; in cases of hepatomegaly or fibrosis, extended liver evaluation is conducted.

Stage 2 (Molecular Genetic Testing) involves genotyping for all five polymorphisms from a standard venous blood sample. The procedure is performed once at the time of initial evaluation, as the genetic profile remains stable throughout the patient's lifetime. Results are expressed as a cumulative genetic risk score (0–10 points).

Stage 3 (Risk-Stratified Management) defines individualized management protocols based on three risk categories. The specific criteria and corresponding interventions are detailed in Table 1.

Fig. 1. Three-Stage Personalized Diagnostic Algorithm for CMVI

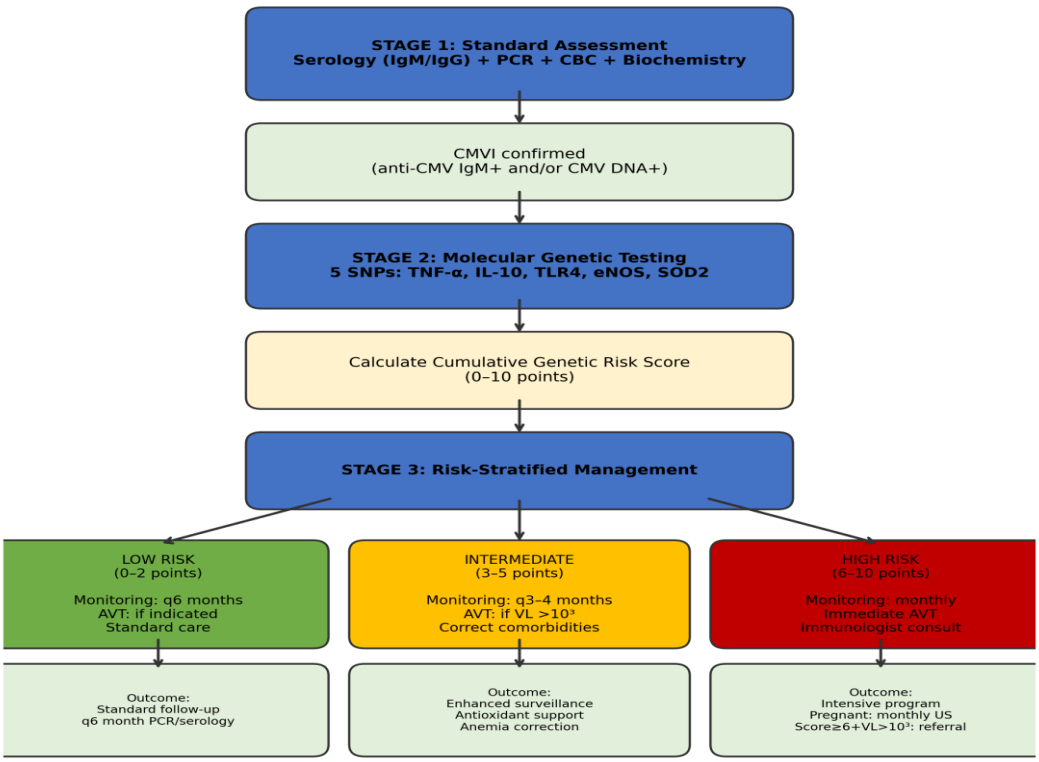

Fig. 1. Three-stage personalized diagnostic algorithm for CMVI management

Table 1. Risk stratification criteria and management protocols

№	Category	Score	Monitoring	AVT	Additional
1.	**Low**	0–2 points	q6 months (PCR + serology)	If clinically indicated	Standard care
2.	**Intermediate**	3–5 points	q3–4 months (VL, CRP, LFTs)	If VL >10^3 copies/mL	Anemia correction, vitamin supplementation
3.	**High**	6–10 points	Monthly (first 6 mo), then q2–3 mo	Immediate initiation	Immunologist; pregnant: monthly fetal US

AVT = antiviral therapy; VL = viral load; LFTs = liver function tests; US = ultrasound

For patients in the high-risk category, the algorithm specifies additional measures depending on the clinical context. Pregnant women with scores of ≥6 require monthly viral load monitoring and fetal ultrasound surveillance for early detection of intrauterine infection. Patients with the combination of a genetic score ≥6 and viral load >10^3 copies/mL are enrolled in an extended dispensary observation program with immunologist referral. For intermediate-risk patients, active correction of modifiable factors (iron-deficiency anemia, hypovitaminosis, coinfections) is prioritized alongside surveillance, as these conditions may synergize with genetic susceptibility to promote viral persistence.

Pilot implementation outcomes

During the pilot implementation at two clinical sites (January 2024 through December 2025), 68 newly diagnosed CMVI patients underwent genotyping according to the algorithm. Of these, 24 patients (35.3%) were classified as high genetic risk (≥6 points), 26 (38.2%) as intermediate risk, and 18 (26.5%) as low risk. In the high-risk subgroup, intensified monthly monitoring enabled detection of rising viral loads in 11 patients (45.8%) before clinical deterioration, permitting early initiation of antiviral therapy. Importantly, no patient in the high-risk group managed according to the algorithm developed generalized CMVI or severe organ complications during the observation period.

Among intermediate-risk patients, active correction of anemia (documented in 14 of 26 patients, 53.8%) and vitamin supplementation were implemented concurrently with enhanced surveillance. Four patients in this category required antiviral therapy due to documented viral replication exceeding 10^3 copies/mL, and all four achieved virological suppression within 3 weeks of treatment initiation. Low-risk patients were followed according to the standard protocol with biannual monitoring, and none required therapeutic intervention during the observation period.

Cost-effectiveness analysis

The economic analysis modeled the projected impact of algorithm implementation on a cohort of 100 CMVI patients over 3–5 years (Table 2). The analysis incorporated four components: savings from complication reduction, disability days prevention in working-age patients, reduction of childhood disability from congenital CMVI, and the one-time cost of genotyping.

Table 2. Cost-effectiveness analysis of the personalized algorithm (per 100 patients)

№	Component	Time horizon	Effect (million UZS)
1.	Complication reduction (prevented episodes)	3 years	+18.0
2.	Disability days saved (working-age patients)	3 years	+54.0
3.	Childhood disability prevention (congenital CMVI)	5 years	+150.0
4.	Genotyping costs (100 patients × 300,000 UZS)	One-time	−30.0
5.	NET ECONOMIC BENEFIT	3–5 years	**+192.0**

Without the personalized approach, the projected frequency of severe complications in the 38 high-risk patients over 3 years was approximately 25–30% (10–12 episodes). Application of the algorithm was estimated to reduce this frequency by 35%, preventing 3–4 episodes at an average cost of 12 million UZS per episode, yielding savings of 18 million UZS. Reduction of disability days among 15 working-age patients in the high-risk group (from an average of 30 days to 12 days per episode) generated an additional 54 million UZS in economic productivity. The most substantial component, 150 million UZS over 5 years, was attributed to the prevention of 2 cases of childhood disability from congenital CMVI, at an annual rehabilitation cost of 15 million UZS per child.

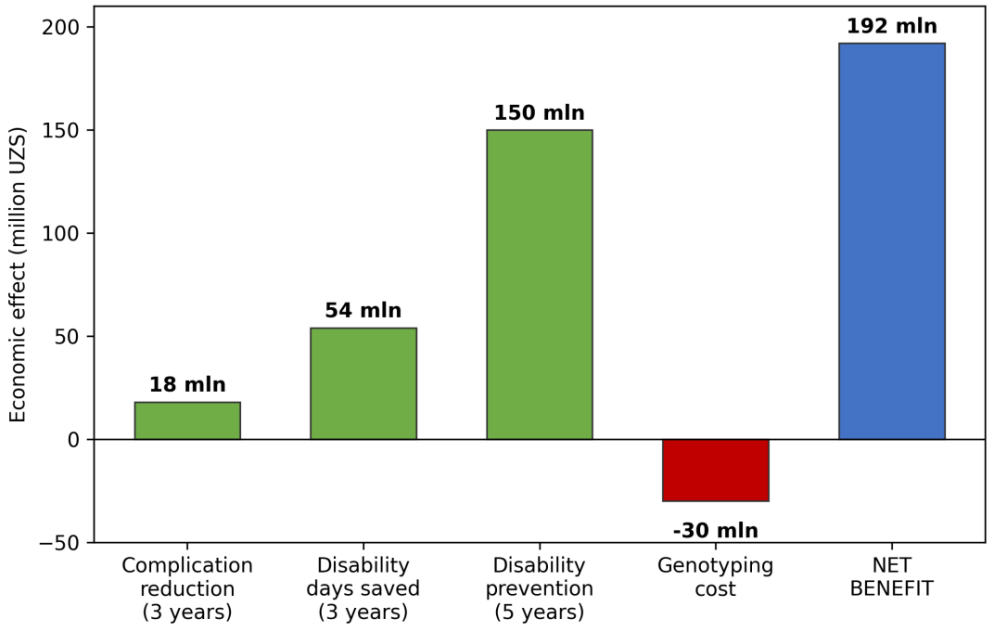

Fig. 2. Cost-effectiveness analysis of the personalized algorithm

The bar chart visualizes the economic components and illustrates that the genotyping cost (30 million UZS for 100 patients) is modest relative to the projected savings. The largest contributor is childhood disability prevention, reflecting the long-term economic and social consequences of congenital CMVI. The net benefit of 192 million UZS over 3–5 years represents a return of 6.4 UZS for every 1 UZS invested in genotyping, confirming the high economic efficiency of the approach.

DISCUSSION

The three-stage algorithm presented in this study translates molecular genetic research findings into a structured clinical tool with defined decision points and management protocols. Unlike many genetic studies that remain at the level of association reports, our approach provides actionable guidance for clinicians at each risk level. The simplicity of the scoring system (five polymorphisms, one blood sample, a 0–10 numerical scale) ensures accessibility for healthcare settings without specialized bioinformatics support.

The pilot implementation outcomes are encouraging. The fact that no patient in the high-risk group developed generalized CMVI during the observation period suggests that the combination of early risk identification and intensified management can effectively prevent the most severe outcomes. However, it should be noted that the observation period was limited to 12–24 months, and longer follow-up is needed to confirm the durability of these results. Razonable R.R. and Humar A. (2020) emphasized that the timing of antiviral intervention is critical for optimizing outcomes in CMVI management (12), and our algorithm provides a framework for achieving timely intervention through proactive genetic risk assessment.

The cost-effectiveness analysis reveals a favorable economic profile with a projected return of 6.4:1 on the genotyping investment. This ratio is particularly significant for Uzbekistan's healthcare system, where resource allocation must be carefully optimized. The cost of the five-SNP genotyping panel (300,000 UZS per patient) is comparable to a single biochemical blood test and substantially lower than instrumental examinations such as neurosonography (150,000–250,000 UZS) or brain MRI (800,000–1,500,000 UZS), while providing information that retains its prognostic value indefinitely. Cannon M.J. et al. (2010) highlighted the disproportionate burden of CMVI in developing countries (3), and our findings suggest that genetic risk stratification may be particularly cost-effective in such settings precisely because of the high baseline prevalence and complication rates.

An important finding of the pilot phase was the high proportion of intermediate-risk patients with correctable comorbidities (anemia in 53.8%). This observation suggests that the algorithm's value extends beyond genetic stratification to include systematic identification and correction of modifiable risk factors that may synergize with genetic susceptibility. Goodrum F. et al. (2021) noted that CMV persistence is influenced by both genetic and environmental factors (4), and our algorithm addresses both dimensions through its integrated approach.

The algorithm is designed for scalability and can be adapted to different healthcare settings. In tertiary centers with molecular genetics laboratories, all three stages can be performed on-site. In primary care settings, Stage 1 can be conducted locally, with blood samples shipped to a reference laboratory for Stage 2 genotyping. The numerical risk score and standardized management protocols enable consistent clinical decision-making regardless of the physician's genetics expertise. Boppana S.B. et al. (2021) called for practical screening tools accessible across healthcare levels (2), and our algorithm fulfills this requirement through its hierarchical structure.

Several directions for future development merit consideration. Validation in larger multicenter cohorts across Uzbekistan and neighboring Central Asian countries would strengthen the evidence base. Integration of the genetic score with machine learning models incorporating clinical and laboratory variables may further enhance predictive accuracy.

Expansion of the panel to include additional polymorphisms in interferon response genes (IFN-γ, IFNL3) and NK cell receptor genes (KIR) could improve sensitivity for specific patient subgroups (5, 10). Development of a digital decision support tool implementing the algorithm could facilitate adoption in clinical practice and ensure adherence to standardized protocols.

CONCLUSIONS

1. The three-stage personalized diagnostic algorithm integrating standard clinical assessment, five-SNP genotyping with cumulative risk scoring, and differentiated management protocols provides a practical framework for risk-stratified CMVI care.
2. Pilot implementation in 68 patients demonstrated feasibility and clinical effectiveness: 35.3% were classified as high risk, and intensified monitoring enabled early antiviral intervention before the development of severe complications in all high-risk patients.
3. The projected economic benefit of 192 million UZS per 100 patients over 3–5 years (return ratio 6.4:1) confirms the cost-effectiveness of the approach, with the largest savings attributable to prevention of childhood disability from congenital CMVI.
4. The algorithm is scalable across healthcare levels and can be adapted for primary care settings with access to a reference molecular genetics laboratory. The one-time genotyping cost (300,000 UZS) is comparable to a single biochemical test while providing lifelong prognostic information.

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