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IMPLEMENTATION OF A GENOTYPE-GUIDED MANAGEMENT PROTOCOL FOR CYTOMEGALOVIRUS INFECTION: PILOT OUTCOMES AND HEALTH ECONOMIC PROJECTIONS IN UZBEKISTAN

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Background

Cytomegalovirus infection (CMVI) imposes a substantial clinical and economic burden on healthcare systems, particularly in developing countries where seroprevalence approaches 85–95% and resources for prolonged antiviral therapy and rehabilitation are limited (1, 7). Traditional management strategies rely on serial monitoring of viral load and serological markers to guide therapeutic decisions, constituting a reactive approach that identifies deterioration only after it has occurred (3, 6). The cost of treating a single episode of complicated CMVI (pneumonia, encephalitis, generalized infection) in Uzbekistan averages 8–15 million UZS, while long-term rehabilitation of a child with congenital CMVI can exceed 50–80 million UZS annually (7). Wang H. et al. (2020) estimated the global economic burden of congenital CMVI in developing countries at over 1.9 billion USD per year (7), underscoring the magnitude of the problem and the potential value of preventive strategies.

Recent research has demonstrated that a cumulative genetic risk score incorporating five single nucleotide polymorphisms (TNF-α, IL-10, TLR4, eNOS, SOD2) achieves an AUC of 0.78 for predicting manifest persistent CMVI,

rising to 0.85 when combined with viral load data (4, 5). These findings provide a scientific foundation for developing a structured clinical algorithm that translates genetic research into actionable management protocols. However, the practical implementation of genotype-guided CMVI management and its economic implications have not been previously evaluated. The present study aimed to develop a three-stage personalized diagnostic algorithm incorporating molecular genetic testing, assess its clinical effectiveness through pilot implementation, and project its cost-effectiveness for the healthcare system of Uzbekistan.

Objective: to develop, implement, and evaluate the clinical feasibility and health economic impact of a genotype-guided three-stage management protocol for CMVI in the Fergana Valley.

Materials and methods

The algorithm was developed based on genotyping data from 100 CMVI patients and 80 controls enrolled at three medical institutions of the Fergana Valley during 2022–2025. Diagnosis was verified by detection of anti-CMV IgM/IgG (ELISA, Cobas e411, Roche) and CMV DNA quantification (real-time PCR, Rotor-Gene Q, Qiagen). Genotyping for five SNPs was performed using TaqMan probes on CFX96 (Bio-Rad). The cumulative genetic risk score (0–10 points) was calculated using a three-tier system per locus: 0 for protective homozygous, 1 for heterozygous, 2 for risk homozygous genotype.

The algorithm comprises three sequential stages. Stage 1 (Standard Assessment) includes serology, PCR, complete blood count, biochemistry, and abdominal ultrasound. Stage 2 (Molecular Genetic Testing) involves one-time genotyping of five SNPs from a standard venous blood sample with calculation of the

cumulative risk score. Stage 3 (Risk-Stratified Management) defines individualized protocols for three categories: low risk (0–2 points, monitoring every 6 months, antiviral therapy if clinically indicated), intermediate risk (3–5 points, monitoring every 3–4 months, antiviral therapy if viral load exceeds 10^3 copies/mL, active correction of anemia and hypovitaminosis), and high risk (6–10 points, monthly monitoring for the first 6 months, immediate antiviral therapy initiation, immunologist referral, and monthly fetal ultrasound for pregnant women).

Pilot implementation commenced in January 2024 at Zam-Zam Clinic (Andijan) and Namangan Central Polyclinic. During 2024–2025, 68 newly diagnosed CMVI patients were genotyped and managed according to the protocol. Cost-effectiveness was modeled over a 3–5 year horizon using local cost data: hospitalization for complicated CMVI (average 12 million UZS per episode), antiviral therapy course (3.5–6 million UZS), genotyping panel (300,000 UZS per patient), and average daily wage (approximately 200,000 UZS in 2025).

Results and discussion

Among 68 genotyped patients, 24 (35.3%) were classified as high genetic risk (≥6 points), 26 (38.2%) as intermediate, and 18 (26.5%) as low risk. The high-risk proportion is consistent with the original study cohort data, supporting the reproducibility of the scoring system in an independent patient sample. 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 ganciclovir/valganciclovir therapy. This is a critical finding, as Razonable R.R. and Humar A. (2020) emphasized that the timing of antiviral intervention is the principal determinant of treatment outcomes in CMVI (6). No patient in the high-risk group managed according to the algorithm developed

generalized CMVI or severe organ complications during the observation period, suggesting that proactive genetic risk identification combined with intensified surveillance can effectively prevent the most severe outcomes.

Among intermediate-risk patients, active correction of anemia (documented in 14 of 26, 53.8%) and vitamin supplementation were implemented concurrently with enhanced surveillance. Four patients in this category required antiviral therapy due to viral replication exceeding 10^3 copies/mL, and all achieved virological suppression within 3 weeks. This observation highlights that the algorithm's value extends beyond genetic stratification to systematic identification of modifiable risk factors that synergize with genetic susceptibility. Goodrum F. et al. (2021) noted that CMV persistence is influenced by both genetic and environmental factors (3), and our protocol addresses both dimensions. Low-risk patients followed standard biannual monitoring, and none required therapeutic intervention during the observation period, confirming that resource allocation can be safely reduced for genetically favorable patients.

The cost-effectiveness analysis projected four economic components over 3–5 years for a cohort of 100 patients. Complication reduction (prevention of 3–4 severe episodes at 12 million UZS each) yielded savings of 18 million UZS over 3 years. Reduction of disability days among 15 working-age high-risk patients (from 30 to 12 days per episode) generated 54 million UZS in economic productivity. The largest component, 150 million UZS over 5 years, was attributed to prevention of 2 cases of childhood disability from congenital CMVI at an annual rehabilitation cost of 15 million UZS per child. Against these benefits, the one-time genotyping cost for 100 patients totaled 30 million UZS (300,000 UZS per patient). The net projected economic benefit was 192 million UZS, representing a return of 6.4 UZS for every 1 UZS invested in genotyping. This ratio is particularly significant for resource-constrained healthcare settings

such as Uzbekistan, where Cannon M.J. et al. (2010) documented the disproportionate burden of CMVI in developing countries (1).

The algorithm is designed for scalability across healthcare levels. In tertiary centers with molecular genetics laboratories, all three stages can be performed on-site. In primary care, Stage 1 is conducted locally with blood samples shipped to a reference laboratory for genotyping. The numerical score and standardized 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 hierarchical structure fulfills this requirement. The genotyping cost of 300,000 UZS is comparable to a single biochemical blood test and substantially lower than neurosonography (150,000–250,000 UZS) or brain MRI (800,000–1,500,000 UZS), while providing information that retains prognostic value throughout the patient's lifetime. Future directions include validation in larger multicenter cohorts, development of weighted scoring using machine learning, integration of interferon response genes (IFN-γ, IFNL3) and KIR receptors into the panel (8), and creation of a digital clinical decision support tool to facilitate adoption.

Conclusions

1. The three-stage genotype-guided management protocol is clinically feasible: pilot implementation in 68 patients demonstrated effective risk stratification (35.3% high risk), with intensified monitoring enabling early antiviral intervention and prevention of severe complications in all high-risk patients.
2. 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.

3. The algorithm is scalable across healthcare levels, with a one-time genotyping cost comparable to a single biochemical test while providing lifelong prognostic information, making it particularly suitable for resource-constrained healthcare systems with high CMV seroprevalence.

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