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Original Article

Prevalence and Impact of *TPMT* and *NUDT15* Gene Polymorphisms on Consolidation Phase Chemotherapy in Pediatric ALL

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Abstract

Introduction Acute lymphoblastic leukemia (ALL) is the most frequently occurring cancer in children, with cure rates exceeding 90%. The consolidation phase (CP) plays a vital role in lowering relapse rates. However, chemotherapy in this phase is commonly delayed due to toxicities related to 6-mercaptopurine (6-MP). The metabolism of 6-MP depends on enzymes encoded by the thiopurine S-methyltransferase (*TPMT*) and nucleoside diphosphate (*NUDT15*) (nudix hydrolase 15) genes. Inherited variations in these genes are known to impact drug metabolism, affecting effectiveness and toxicity.

Objectives This study was conducted to determine the prevalence of notable *TPMT* and *NUDT15* gene variants in pediatric patients with ALL from North Karnataka. It also aimed to evaluate the association of these polymorphisms with chemotherapy interruptions and related toxicities during the CP.

Materials and Methods This longitudinal analysis included 106 patients newly diagnosed with ALL. Genetic screening for *TPMT* and *NUDT15* mutations was carried out before the initiation of treatment. Data collected included the total 6-MP dose administered during CP, the number of delayed treatment days, frequency of febrile neutropenia (FN) episodes, and their duration.

Results Over a period of 2.5 years, 106 patients were enrolled. The male-to-female ratio was 1.52, and the average age was 7.19 ± 4.08 years. Variants in *NUDT15* and *TPMT* were found in 24.5 and 3.77% of cases, respectively. Those with genetic mutations had an average CP delay of 13.5 days and experienced more FN episodes, with a statistically significant difference ($p = 0.002$).

Conclusion The frequency of *TPMT* and *NUDT15* mutations in this group was higher than in previous Indian reports. These gene variants were linked to longer treatment

Keywords
- 6-MP toxicity
- chemotherapy delay
- consolidation phase
- *NUDT* polymorphism
- *TPMT* polymorphism

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delays and increased toxicity during CP. We propose that *TPMT* and *NUDT* polymorphism analysis should be performed upfront at diagnosis, so that consolidation delays can be minimized and toxicities can be reduced, which may improve the overall outcome.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy with a cure rate of more than 90%. The management of ALL involves a structured treatment regimen, typically divided into several phases, which include induction, consolidation, interim maintenance, delayed intensification, and maintenance. Each phase plays a crucial role in achieving remission, preventing relapse, and ensuring long-term survival.[1,2] The induction phase aims to rapidly reduce the leukemia burden and achieve complete remission. Once remission is achieved, the consolidation phase (CP) follows, which is designed to eliminate any remaining leukemia cells. This phase is critical in reducing the risk of relapse and solidifying the gains made during induction therapy. The goal is to further intensify the treatment to eradicate residual disease, preventing leukemia cells from surviving and proliferating during remission.[1,3]

Consolidation chemotherapy typically involves a combination of drugs, which include 6-mercaptopurine (6-MP), cytarabine, intrathecal methotrexate, cyclophosphamide, and L-asparaginase if the patient falls in the high-risk category.[2,4] 6-MP is often administered over several weeks to months, depending on the risk stratification. It is a thiopurine drug, which is metabolized by enzymes encoded by genes such as thiopurine S-methyltransferase (*TPMT*) and nucleoside diphosphate (*NUDT15*). Genetic polymorphisms in these genes have been identified as significant factors influencing drug metabolism, efficacy, and toxicity profiles. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines elaborate 6-MP dosage regimen, frequency of administration, and dose reduction based on pharmacogenomic impact.[5] The variability in response to thiopurine treatment can lead to severe side effects, especially myelotoxicity, which is dose-limiting with a narrow therapeutic index. This side effect may delay chemotherapy regimens and impact patient morbidity, prolong hospitalization, and impact overall morbidity.[6,7]

These variations can result in adverse reactions or insufficient therapeutic response, which in turn may necessitate dose adjustments. Understanding the impact of chemotherapy during the CP, alongside genetic factors that affect drug metabolism, is essential for optimizing treatment protocols. *TPMT* polymorphisms are more common worldwide and have been established as the main factor affecting 6-MP metabolism. *NUDT15* polymorphisms are the most common in East Asian countries, followed by South Asian countries.[8–10] There are a limited number of studies from India in this regard. Two studies from Vellore and Chandigarh have reported 14 and 9.5% prevalence of *NUDT15* polymorphism in children with ALL, respectively.[6,11,12] The effect of these mutations on the delay in the consolidation therapy and treatment outcomes has not been studied. Moreover, there are no studies from North Karnataka regarding these polymorphisms in children with ALL and the effect of the polymorphism on the CP delay in India.

In this study, we aim to study the prevalence of *TPMT* and *NUDT15* gene polymorphisms and assess their impact on chemotherapy delay and morbidities such as febrile neutropenia (FN) during the CP of treatment in patients with ALL. This study is an attempt to understand the genetic factors that influence thiopurine metabolism, which will help optimize therapeutic strategies, minimize adverse effects, and improvisation of chemotherapy regimens.

Materials and Methods

Objectives

The primary objective of the study was to study the prevalence of *TPMT* and *NUDT15* gene polymorphisms, and the secondary objective was to study the chemotherapy delay and toxicities due to *TPMT* and *NUDT15* polymorphisms during CP of chemotherapy.

Study Design and Setting

This was a longitudinal study conducted on 106 children aged 1 to 18 years with newly diagnosed ALL at the pediatric hematology oncology unit in a tertiary care hospital. All these children were treated as per the Indian Childhood Collaborative Leukemia Group protocol. The children who had received allopurinol after the induction phase of chemotherapy and those who did not give consent to participate in the study were excluded.

The epidemiological and clinical data of the patients were documented in a standardized proforma. All the patients who were eligible for the study underwent upfront *TPMT* and *NUDT15* variant detection at the time of diagnosis.

Three mL of blood was collected in EDTA vacutainers, following which DNA was extracted using standard methods.

Genomic DNA was amplified, including regions of the *TPMT* and *NUDT15* genes. Bidirectional sequencing was carried out using 3500/3730 XL Genetic Analyzer (Applied Biosystems) to detect common variant alleles in these genes. Dose of 6-MP was noted for the entire CP of chemotherapy. Furthermore, the number of FN, other cytopenias, the number of days of delay in CP, the number of episodes, and the duration of FN were noted. They were followed up until the end of the CP of chemotherapy. However, further research is

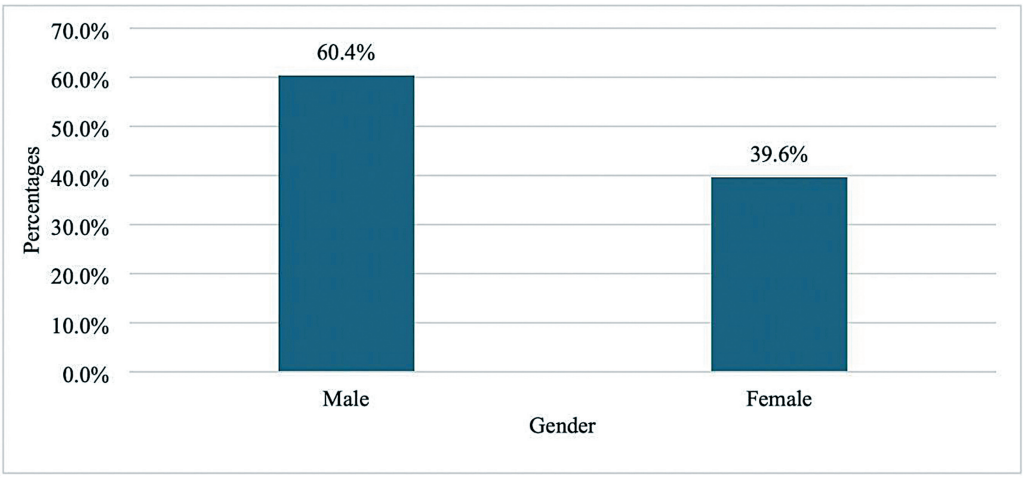

Fig. 1 Bar chart of gender in the study population ($n = 106$).

underway in which patients will be followed up for up to 5 years postmaintenance chemotherapy, resulting in a total timeline of 8 years.

Expected Outcomes

The primary outcome is the prevalence of *TPMT* and *NUDT15* gene polymorphisms.

The secondary outcome is chemotherapy delay and toxicities due to *TPMT* and *NUDT15* polymorphisms during the CP of chemotherapy.

Ethics

The study was approved by the ethics committee (KAHER/EC/22-23/272) dated November 21, 2022. We obtained written informed consent from the parents of the patients in their own vernacular language. All procedures involving human participants in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical Analysis

All quantitative variables were checked for normal distribution within each category of explanatory variable by using Shapiro–Wilk's test. The p-value of >0.05 was considered as anormal distribution. For nonnormally distributed quantitative parameters, the median values were compared between study groups using Mann–Whitney's U test (two groups). The p-value of < 0.05 was considered statistically significant. IBM SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, New York, United States: IBM Corp) was used for statistical analysis.

Results

A total of 128 patients were diagnosed with ALL over a period of 2.5 years, out of which 0.17% ($n = 22$) of patients did not give consent to participate, so a total of 106 patients were enrolled in our study. Among them, 60.4% ($n = 64$) were males and 39.6% ($n = 42$) were females (►**Fig. 1**). The male-to-female ratio was 1.52. The mean age of the study population ($n = 106$) was 7.19 ± 4.08 years. A total of 87.7% ($n = 93$) of patients had pre-B ALL and 12.3% ($n = 13$) had T ALL. Regarding the risk stratification in our study population, 38.68% ($n = 41$) of patients belonged to the high-risk category, 58.49% ($n = 62$) were in the intermediate-risk category, and 2.83% ($n = 3$) belonged to the standard-risk category. Out of the 106 patients with ALL, 30 (28.3%) were found to have either *NUDT15* or *TPMT* polymorphisms. Among these patients, 24.5% ($n = 26$) and 3.77% ($n = 4$) had *NUDT15* and *TPMT* polymorphisms, respectively (►**Table 1**). The mean duration of delay in consolidation chemotherapy was 13.5 days for patients with polymorphisms, and these patients experienced a higher number of FN episodes compared with those without polymorphisms. This difference was statistically significant, with a p-value of 0.002 (►**Table 2**).

Discussion

CP is critical in reducing the risk of relapse, but CP chemotherapy in this phase is often interrupted and delayed due to 6-MP-related toxicity. 6-MP is an important part of the consolidation and delayed intensification phase of chemotherapy, and is the backbone of maintenance phase chemotherapy.[2,3] Hence, 6-MP-related toxicities have a significant impact on treatment outcome. There are a few studies from Western world and a few from India, which highlight the impact of 6-MP-related toxicities due to *NUDT* and *TPMT* polymorphisms affecting 6-MP metabolism during the maintenance phase, but there is a lack of research on these polymorphisms during CP.[7,8] Hence, we decided to study *TPMT* and *NUDT-15* polymorphism prevalence and assess their impact on chemotherapy delay and morbidities such as FN during the CP.

6-MP belongs to the thiopurine group of drugs, with a typical dosage in CP being 50 to 60 mg/m^2 per day. The adverse effects of 6-MP include alopecia, hepatotoxicity, pancreatitis, and myelosuppression. Myelosuppression is a dose-limiting toxicity with a narrow therapeutic index.[13,14]

Table 1 Descriptive analysis of polymorphism in the study population ($n = 106$)

Polymorphism	Frequency	Percentage
Present	30	28.3%
Absent	76	71.6%
Polymorphism type		
NUDT	26	24.5%
TPMT	4	3.7%
NUDT polymorphism		
Homozygous	1	0.9%
Heterozygous	25	23.5%
TPMT polymorphism		
Homozygous	1	0.9%
Heterozygous	3	2.8%

Abbreviations: NUDT, nucleoside diphosphate; TPMT, thiopurine S-methyltransferase.

Variation in the degree of myelosuppression is observed between individual children, especially from different ethnicities. This variation is mostly attributed to genetic polymorphisms in enzymes involved in the metabolism of 6-MP. It is well established that *TPMT* and *NUDT15* polymorphisms affect 6-MP dosing and toxicity. Other genetic variants in the *ITPA* and *MRP4* genes may affect 6-MP metabolism and are common in the Asian population.[9,11,12,14] However, their effect on 6-MP-induced myelotoxicity is controversial and requires further research.

TPMT enzyme converts 6-MP to its inactive metabolite 6-methylmercaptopurine nucleotide. *TPMT* genetic polymorphisms, which reduce enzymatic activity, lead to increased levels of active metabolite of 6-MP, that is, 6-thioguanine (6-TG), which is responsible for myelosuppression. TPMT 1^* is a wild-type allele. TPMT 2^*, $3A^*$, $3B^*$, and $3C^*$ alleles account for 95% of significant polymorphisms. These variants are responsible for more frequent cytopenia, FN, and 6-MP interruption. Hence, dose reduction is advised in these patients (►**Fig. 2**).[6]

Guidelines developed by CPIC recommend a normal dose for normal metabolizers. For intermediate metabolizers, a 30 to 70% reduction is recommended for 6-MP and a 30 to 50% reduction for 6-TG. Poor metabolizers receiving 6-MP or 6-TG should receive a 90% reduction in dose with drug administration three times per week in order to avoid adverse drug reactions (ADRs) (►**Table 3**). Pre-emptive patient testing is highly recommended either to avoid ADRs in case of malignant disease or to reduce the time needed for upward titration of drug dosage. Recent in-depth research has focused on interindividual differences in drug-metabolizing enzymes to adjust drug dosage and therapy.[15]

NUDT15 polymorphisms are also known to affect 6-MP dosing and toxicity. *NUDT15* dephosphorylates cytotoxic metabolite thioguanine triphosphate into nontoxic monophosphate. Genetic polymorphisms with low *NUDT15* enzyme activity lead to the accumulation of active metabolites, leading to myelosuppression. It is well known that *TPMT* polymorphisms are more common in Caucasians as compared with Asians.[8,9,11] In the Indian population, studies done on the normal population and children with ALL have reported 1 to 4.5% frequency of *TPMT* polymorphisms associated with low to intermediate enzyme activity.[5,9,11] Many studies from Western countries have shown that *TPMT* polymorphisms are associated with low enzyme activity

Table 2 Comparison of median of number of FN in consolidation between polymorphism ($n = 106$), polymorphism type ($n = 30$), NUDT polymorphism ($n = 26$), and TPMT polymorphism ($n = 4$)

Parameter	**Polymorphism (IQR)**		**p-Value**
	Present ($n = 30$)	**Absent ($n = 76$)**	
Number of FN in consolidation	2 (1–3)	1 (1–2)	0.007
Delay in consolidation	13.50 (4–16.25)	7 (2–12)	0.002
Parameter	**Polymorphism type (IQR)**		***p*-Value**
	NUDT ($n = 26$)	**TPMT ($n = 4$)**	
Number of FN in consolidation	2 (1–3)	2 (1.25–11)	0.975
Delay in consolidation	13.50 (4–16.25)	10.50 (3.5–18.25)	0.976
Parameter	**NUDT polymorphism (IQR)**		***p*-Value**
	Homozygous ($n = 1$)	**Heterozygous ($n = 25$)**	
Number of FN in consolidation	3 (3–3)	2 (1–3)	0.692
Delay in consolidation	43 (43–43)	13 (4–16)	0.077
Parameter	**TPMT polymorphism (IQR)**		**p-Value**
	Homozygous ($n = 1$)	**Heterozygous ($n = 3$)**	
Number of FN in consolidation	1 (1–1)	2 (2–2)	0.500
Delay in consolidation	5 (5–5)	16 (3–16)	1.000

Abbreviations: FN, febrile neutropenia; IQR, interquartile range; NUDT, nucleoside diphosphate; TPMT, thiopurine S-methyltransferase.

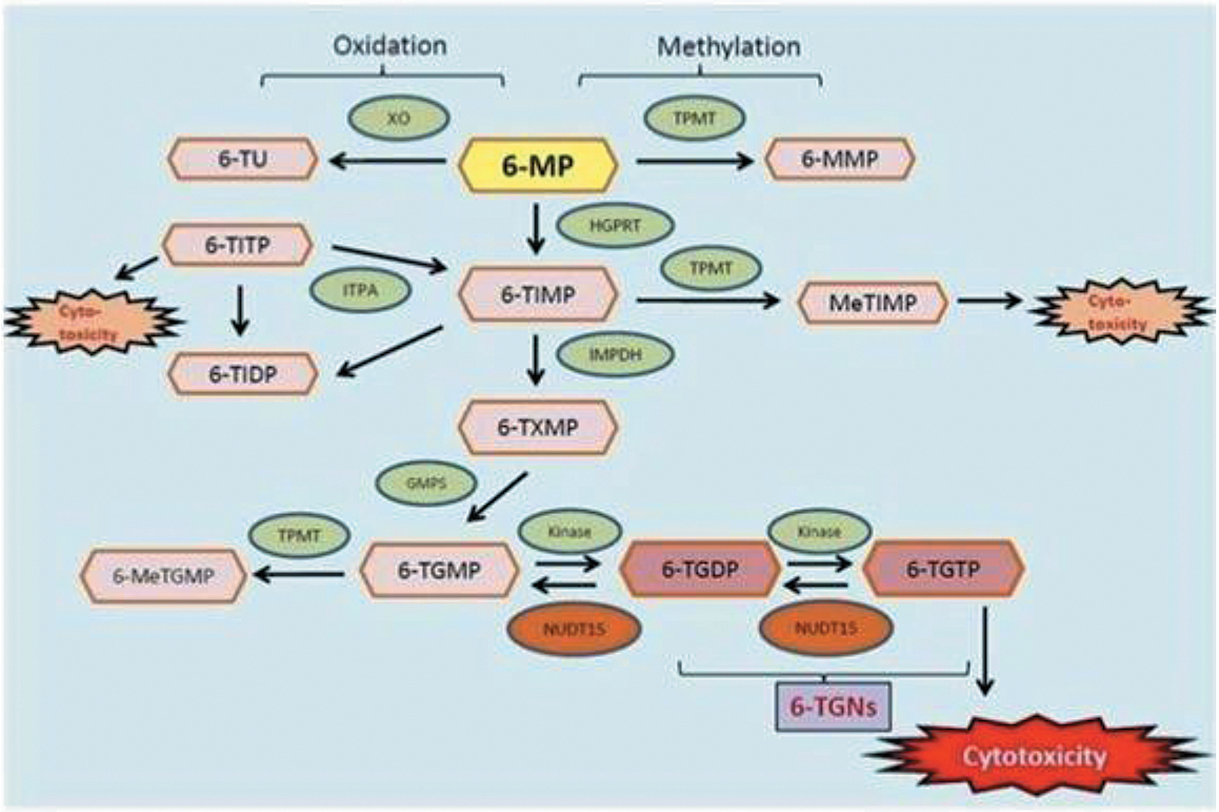

Fig. 2 Metabolism of 6-MP. GMPS, GMP-synthase; HPRT, hypoxanthine phosphoribosyl transferase; IMPDH, inosine-5-monophosphate; ITPA, inosine triphosphate pyrophosphatase; 6-MeTG, 6-methyl thioguanine; 6-MMP, 6-methylmercaptopurine; 6-MP, 6-mercaptopurine; NUDT15, nucleoside diphosphate–linked moiety X-type motif 15; 6-TGDP, 6-thioguanine diphosphate; 6-TGMP, 6-thioguanine monophosphate; 6-TGNs, 6-thioguanine nucleotides; 6-TGTP, 6-thioguanine triphosphate; 6-TIDP, 6-thioinosine 5-diphosphate; 6-TIMP, thioinosine 5-monophosphate; TPMT, thiopurine S-methyltransferase; 6-TU, 6-thiouric acid; XO, xanthine oxidase. (Adapted from Singh et al.[6])

resulting in increased risk of cytopenia, FN, and 6-MP interruption. Homozygous variants need a significant (10%) reduction in the dose of 6-MP. Similarly, Indian studies have also shown the need for dose reduction in the *TPMT* polymorphism group.

Interestingly, *TPMT* polymorphisms protect against hepatotoxicity and mucositis.[11,12,14]

Apart from *TPMT* polymorphisms, *NUDT15c.415C>T(p.R139C)* variant was found to be associated with 6-MP intolerance in Asian children, on a genome-wide association study in the Children's Oncology Group COG cohort. *NUDT15*2 (p.V18_V19 insGV* and *c.415C>T)*, **3(C.415C>T)*, and **9 (c.50 dd GAG TCG)* polymorphisms are associated with loss-of-function *NUDT15* enzyme activity. *NUDT15* variants are common in Asian populations and Hispanic populations; higher prevalence is seen in East Asian countries, followed by South Asian countries. On the contrary, *NUDT15* polymorphisms are rare in the Caucasian population. *NUDT*3* is the commonest variant seen in the Asian population.[6,7,14]

A study from North India reported a *NUDT15* polymorphism prevalence of 9.5% in children, all of whom were heterozygous, and a *TPMT* polymorphism prevalence of 3.1% during the maintenance phase of chemotherapy.[11] Additionally, a study from Vellore showed a *NUDT15* polymorphism prevalence of 14%. This is notably lower than the 24.5% prevalence for *NUDT15* and 3.7% for *TPMT*

Table 3 CPIC guidelines on 6-MP dosage regimen

TPMT phenotype/genotype	Dosing recommendation 6-MP	Dosing recommendation 6-TG
Normal metabolizer (two functional alleles)	Start with normal dose	Start with normal dose
Intermediate metabolizer (one functional alleles)	Start with 30–70% reduced dose	Start with 90% reduced dose, thrice weekly
Poor metabolizer (no functional alleles)	Start with 90% reduced dose, thrice weekly	Start with 90% reduced dose, thrice weekly

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; TPMT, thiopurine S-methyltransferase.

observed in our study.[12] The incidence of FN episodes was higher in children with polymorphisms (6.7%) compared with those without (1.3%) the polymorphism. Further, the mean delay in the CP was found to be 13.5 days, which was significantly longer in children with polymorphisms compared with those without it. However, there are no studies regarding the impact of these mutations on the treatment delay and toxicities during CP.

The strengths of our study include the fact that there are very few studies on *TPMT* and *NUDT15* polymorphisms in India, and those that do exist primarily focus on the maintenance phase. Our study is the first from India to be conducted during the CP. This study revealed a very high prevalence rate of the *NUDT15* polymorphism (24.5%), which significantly impacted treatment duration and led to increased toxicities. Therefore, our study is of great importance, as it emphasizes the need for upfront screening for these polymorphisms and subsequent dose reduction of 6-MP according to CPIC guidelines. This approach could help reduce toxicities, minimize delays in the CP, and ultimately lower the relapse rate.

Regarding future research, the impact of *TPMT* and *NUDT15* genetic polymorphisms on 6-MP dosing, toxicity, event-free survival, and relapse risk in children with ALL warrants further exploration. The limitations of our study include its single-center design and small sample size, which means that additional research is needed to establish more accurate prevalence rates during the CP of chemotherapy. We also could not evaluate single-nucleotide polymorphisms related to *ITPA* polymorphism, which accounts for the gray areas that need attention for further studies.

Conclusion

The prevalence of *NUDT15* and *TPMT* mutations was found to be 24.5 and 3.8%, respectively. These polymorphisms were also associated with a significant delay in consolidation chemotherapy, and these patients experienced a higher number of FN episodes compared with those without polymorphisms. We propose that *TPMT* and *NUDT* polymorphism analysis should be done upfront at diagnosis, so that consolidation delays can be minimized and toxicities can be reduced, which may improve the overall outcome.

Authors' Contributions

A.S. was responsible for data collection, establishing clinical diagnosis, planning investigations, management, and follow-up. N.M. provided guidance and support. H.K. was responsible for clinical care of the patient and writing the manuscript. A.D. was responsible for clinical care of the patient and data collection. V.B. and S.B. were responsible for planning the study and providing guidance in manuscript preparation.

Patient Consent

Patient consent has been received.

Conflict of Interest

None declared.

Acknowledgments

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