Instillation Strategies for Non-Muscle-Invasive Bladder Cancer in the Bacillus Calmette-Guerin Shortage Era: A Simple Solution for BCG Discontinuation

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Objective: Among intravesical instillation protocol in patients with non-muscle-invasive bladder cancer (NMIBC), chemotherapy agents have been widely used during the bacillus Calmette-Guérin (BCG) shortage era since the patient might under the risk of BCG discontinuation. This study evaluates the efficacy of incomplete BCG instillation compared with pure chemotherapy instillation protocol.

Materials and Methods: Patients newly diagnosed with intermediate- and high-risk NMIBC who received incomplete BCG intravesical instillation or chemotherapy instillation were retrospectively included. Patients were divided into three groups according to different intravesical instillation schedules: [BCG only], [BCG + Chemo], and [Chemo only]. Comparisons between these three groups were performed. Bladder recurrence-free survival (RFS) was analyzed as the primary endpoint.

Results: A total of 475 patients who received intravesical instillations were enrolled. Compared to the [Chemo only] group, the [BCG + Chemo] group had significantly better bladder RFS (p = 0.027). Multivariate analysis of recurrence revealed the [BCG + Chemo] regimen has a hazard ratio 0.381 (95% CI 0.154–0.941, p = 0.037). The total instillation number >12 was associated with better RFS (p = 0.001) compared with other instillation numbers.

Conclusion: For NMIBC patients facing the risk of unexpected BCG instillation interruption, instead of starting instillation with chemotherapy agents, receiving BCG first till stoppage then shifting to chemotherapy agents is recommended.

Keywords: bladder cancer, NMIBC, intravesical instillation, intravesical chemotherapy, BCG, bladder recurrence

Introduction

Bladder cancer (BC) is the 11th most commonly diagnosed cancer in the world, with an estimated 549,393 new cases diagnosed per year. The worldwide age-standardized incidence rates (per 100,000 people/year) are 9.0 for men and 2.2 for women. In newly diagnosed cases, non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75%.

In NMIBC, the first treatment step is to perform an adequate high-quality transurethral resection of bladder tumour (TUR-BT), which aims to achieve both tumour staging and tumour excision as radical as possible. TUR-BT is a critically important step since it provides staging, therapeutic, and prognostic benefits.
Following TUR-BT, more efforts should be made to prevent patients from progressing to muscle-invasive bladder cancer (MIBC) and to maintain quality of life. Progression to MIBC during the management of NMIBC has been shown to significantly increase the risk of disease-specific mortality.\textsuperscript{8}

Among the existing modalities, intravesical bacillus Calmette-Guérin (BCG) is one of the most effective methods widely utilized in the adjuvant setting following TUR-BT for intermediate- and high-risk NMIBC, with a response rate of approximately 50%.\textsuperscript{9–11}

Since the first landmark study demonstrating the efficacy of BCG, its dose and schedule have not changed much.\textsuperscript{12} The European Association of Urology (EAU) guidelines suggest 6 weekly instillations as an induction, followed by a maintenance schedule for better efficacy,\textsuperscript{13–15} while a complete schedule may require 36 months.\textsuperscript{16} However, mainly due to the significant toxicity of BCG, only 16% of patients can complete the whole treatment course.

In addition to toxicity, which hinders the continuation of BCG instillation, a global BCG shortage is problematic. Not only does the global demand for BCG exceed the supply but closures of BCG plants in 2012 and 2014, a reduction of production in 2015, and the withdrawal of a large BCG manufacturer in 2017 have further led to worldwide shortages of BCG.\textsuperscript{17}

Many strategies have been studied as alternatives to BCG instillation; these include changes in the BCG schedule or using other instillation agents such as chemotherapy, with the latter being widely used in this BCG shortage era. For patients who initiated a BCG instillation protocol but discontinued it due to shortage or toxicity, some had shifted to a chemotherapy instillation protocol, but others stopped instillation management. To our best knowledge, outcome analysis between intravesical chemotherapy and incomplete BCG instillation was limited. Therefore, we developed a retrospective study to compare the outcomes of patients with NMIBC who received chemotherapy instillation only and those who received initial BCG instillation but discontinued. We aim to determine which strategies would have more therapeutic benefits.

**Materials and Methods**

**Patients**

We conducted a retrospective study and enrolled consecutive patients with newly diagnosed BC from January 2005 to December 2018 in a single tertiary medical centre. We reviewed the medical charts of patients with NMIBC (T1, Ta, and Tis) who were considered eligible for intravesical instillation therapy after TUR-BT. Low-risk NMIBC defined by EAU guideline was excluded since no further instillation needed as guideline suggestion.\textsuperscript{13} Other exclusion criteria include patients who completed the whole course of BCG instillation and those with a previous urothelial carcinoma history or any other active malignancy history in the last five years. All patients received an immediate single dose of intravesical chemotherapy within 24 hours after TUR-BT. All patients were well evaluated and discussed in our urology-oncology multidisciplinary meeting. The management of these patients followed the clinical guidelines for bladder cancer.

This study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital. The requirement for patient consent to review their medical records was waived by the IRB of Chang-Gung Memorial Hospital due to the retrospective nature of the study. The data collection confidentiality agreement fulfilled the requirements of the Declaration of Helsinki.

**Data Collection**

General preoperative characteristics, including sex, age, body height, body weight, and body mass index (BMI), were recorded. Data on tumour-related parameters, such as tumour stage, tumour histology, pathological grade, and intravesical instillation data, including the number of BCG instillations and chemotherapy instillations, and total intravesical instillations, were also recorded.

All patients received regular follow-up with cystoscopy every three months in the first two years, then every six months for another two years, and annually thereafter. Bladder local recurrence was the primary endpoint, while patients were followed for recurrence-free survival (RFS) until the final analysis. RFS was defined as the period from the date of diagnosis to bladder recurrence. In the absence of a confirmation of bladder recurrence, RFS was censored on the last date at which the patient was known to be recurrence-free.
Intravesical Instillation Dosage and Protocol

The protocol of BCG instillation consisted of weekly doses of 81 mg BCG (TICE strain) for six weeks in the induction course and three weekly instillations at months 3, 6, 12, 18, and 24 in the maintenance course following induction treatment. Patients who did not complete this protocol were regarded as BCG discontinuation.

The chemotherapy instillation protocol also consisted of six weekly intravesical instillations as the induction course and monthly instillations at months 3 to 14 as the maintenance course. The chemotherapy agent used in the intravesical instillation included epirubicin (50 mg), mitomycin C (40 mg), and doxorubicin (30 mg). Only a single drug was used in each instillation.

Statistical Analyses

Patients were divided by the initiation with chemotherapy or BCG instillation protocol. There were two results in the BCG instillation group when facing BCG discontinuation, one is no further instillation plan, and the other is shifting to chemotherapy instillation. Therefore, the total enrolled population could be divided into three groups according to different intravesical instillation (IVI) schedules: [BCG only], [BCG + Chemo], and [Chemo only]. The patients’ general characteristics and tumor-related parameters in the three subgroups were compared. We compared the difference between each group with the Pearson chi-square test, Fisher’s exact test, an independent $t$-test, and a one-way analysis of variance (ANOVA). Bladder RFS was determined with the Kaplan–Meier survival test. A multivariable Cox regression analysis would be conducted to identify independent predictors of recurrence, using backward selection to eliminate non-significant variables ($p$-value >0.1). We regarded $p$ values less than 0.05 as significant in each analysis. All statistical analyses were performed using IBM SPSS Statistics 22.

Results

Initially, 2779 patients with BC were assessed in this study, and 475 patients with NMIBC who received sequential intravesical induction and/or maintenance instillations were further analysed. The enrolment flowchart is illustrated in Figure 1.

![Flowchart of patients enrolment](https://doi.org/10.2147/CMAR.S383627)

Figure 1 Flowchart of patients enrolment. Among the enrolled patients with NMIBC, those who did not receive intravesical instillation or have complete instillation records were excluded. The remaining eligible patients were divided into three subgroups based on their instillation regimen.
Among the enrolled patients, the male-to-female ratio was 2.67, with a mean age at diagnosis of 66.6 years. Detailed general characteristics, such as body height, body weight, and BMI, are listed in Table 1.

Among the patients with NMIBC receiving intravesical instillations, 47.2% had stage Ta disease, 51.8% had stage T1 disease, and only 1.1% had pure stage Tis disease. Low-grade and high-grade tumors accounted for 31.4% and 62.5%, respectively. A total of 161 patients (33.9%) eventually experienced bladder recurrence throughout the follow-up period. The mean follow-up period was 40.1 ± 29.1 months. Other detailed parameters are listed in Table 1.

The patients' general characteristics and tumor-related parameters in the [BCG only], [BCG + Chemo], and [Chemo only] subgroups were compared and listed in Table 2. It showed no significant difference between these three groups of patients in body weight, body height, BMI, gender, age, and tumor grade. In the composition of the tumor stage, the [Chemo only] group had a significantly lower ratio of patients with stage T1 disease compared to the [BCG only] and [BCG + Chemo] groups.

As for the counts of instillation, the [BCG + Chemo] and [BCG only] patients received statistically equal BCG instillation counts (10.2 and 9.3, respectively), while the [Chemo only] patients received significantly more chemotherapy instillation counts than the [BCG + Chemo] group. Generally, the [BCG + Chemo] patients received statistically more total IVI counts than [BCG only] and [Chemo only] patients (16.7 vs 10.2 and 11.4, respectively).

Concerning bladder RFS in different instillation regimen, the [BCG only] group showed an insignificant difference towards higher RFS than the [Chemo only] group (p value = 0.118). In addition, the [BCG + Chemo] group showed

### Table 1 Patients' General Characteristics and Tumour-Related Parameters

| Variable                        | Mean/Number | SD | Range/Percentage |
|---------------------------------|-------------|----|------------------|
| **Patients' general characteristics** |             |    |                  |
| Total number                    | 475         |    |                  |
| Sex                             |             |    |                  |
| Male                            | 376         |    | 79.2%            |
| Female                          | 99          |    | 20.8%            |
| Age (years)                     | 66.6        | 12.3| 19–97            |
| Height (cm)                     | 162.7       | 7.6 | 141–182          |
| Weight (kg)                     | 66.5        | 12.0| 38–121           |
| BMI (kg/cm²)                    | 25.0        | 3.6 | 16.4–41.9        |
| **Tumour-related parameters**   |             |    |                  |
| T stage                         |             |    |                  |
| Ta                              | 224         |    | 47.2%            |
| T1                              | 246         |    | 51.8%            |
| Tis                             | 5           |    | 1.1%             |
| Grade                           |             |    |                  |
| Low                             | 149         |    | 31.4%            |
| High                            | 297         |    | 62.5%            |
| Unknown                         | 29          |    | 6.1%             |
| Chemotherapy agent              |             |    |                  |
| Epirubicin                      | 197         |    | 41.5%            |
| Mitomycin C                     | 152         |    | 32.0%            |
| Doxorubicin                     | 17          |    | 3.6%             |
| Bladder recurrence              |             |    |                  |
| Yes                             | 161         |    | 33.9%            |
| No                              | 314         |    | 66.1%            |
| Instillation agent              |             |    |                  |
| BCG only                        | 109         |    | 22.9%            |
| BCG + chemo                     | 29          |    | 6.1%             |
| Chemo only                      | 337         |    | 70.9%            |
| Follow-up (months)              | 40.1        | 29.1|                 |

**Abbreviations:** BCG, bacillus Calmette-Guérin; BMI, body mass index.
higher RFS than the [BCG only] group but no statistical significance as well (p value = 0.222). The [BCG + Chemo] group had significantly better bladder RFS than the [Chemo only] group (p value = 0.027). The Kaplan–Meier survival plots are illustrated in Figure 2A.

The association of intravesical instillation number and bladder RFS was also evaluated, with the findings that total instillation number >12 had statistically higher RFS than instillation numbers 1–6 and 7–12 (p = 0.006 and <0.001, respectively). However, there was no significant difference between the latter two groups (p = 0.707). These findings are illustrated in Figure 2B as Kaplan–Meier survival plots.

### Table 2 Difference Analysis Between Instillation Subgroups

|                          | BCG Only (N = 109) | BCG + Chemo (N = 29) | Chemo Only (N = 337) | p value |
|--------------------------|--------------------|----------------------|----------------------|---------|
|                         | Mean/Number | SD/Percentage | Mean/Number | SD/Percentage | Mean/Number | SD/Percentage |
| Body weight (kg)         | 65.7        | 10.1          | 66.3        | 12.2          | 66.7        | 12.5          | 0.734 |
| Body height (cm)         | 162.7       | 7.2           | 162.4       | 7.3           | 162.8       | 7.8           | 0.962 |
| BMI (kg/cm²)             | 24.8        | 3.2           | 25.0        | 3.7           | 25.1        | 3.8           | 0.745 |
| Sex                      |             |               |             |               |             |               |
| Male                     | 87          | 79.8%         | 22          | 75.9%         | 267         | 79.2%         | 0.896 |
| Female                   | 22          | 20.2%         | 7           | 24.1%         | 70          | 20.8%         |       |
| Age (years)              | 67.5        | 11.0          | 65.7        | 10.1          | 66.4        | 12.9          | 0.650 |
| T stage                  |             |               |             |               |             |               |
| Ta                       | 37          | 34.3%         | 8           | 27.6%         | 179         | 53.8%         | < 0.01 |
| T1                       | 71          | 65.7%         | 21          | 72.4%         | 154         | 46.2%         |       |
| Tumour grade             |             |               |             |               |             |               |
| Low                      | 27          | 27.0%         | 7           | 25.0%         | 115         | 36.2%         | 0.270 |
| High                     | 73          | 73.0%         | 21          | 75.0%         | 203         | 63.8%         |       |
| IVI with BCG             | 10.2        | 5.0           | 9.3         | 6.6           | –           | –             | 0.460 |
| IVI with chemo           | –           | –             | 7.4         | 5.5           | 11.4        | 5.1           | < 0.01 |
| Total IVI                | 10.2        | 5.0           | 16.7        | 7.7           | 11.4        | 5.2           | < 0.01 |

**Abbreviations:** BCG, bacillus Calmette-Guérin; BMI, body mass index; IVI, intravesical instillation.

**Figure 2** Kaplan–Meier survival curve of bladder recurrence free survival. Recurrence free survival (RFS) analysis according to (A) the instillation subgroup and (B) different total intravesical instillation numbers. The vertical reference line indicates RFS, and the horizontal reference line indicates the duration (days) of follow-up. The *Among the p-value interpretations indicates statistical significance.
In the multivariate Cox regression analysis of bladder recurrence, female had a hazard ratio (HR) 0.568 (95% confidence interval (CI) 0.353–0.915, p-value = 0.02) and high-grade tumor had an HR 1.992 (95% CI 0.353–0.915, p-value = 0.02). The [BCG + Chemo] instillation regimen also revealed an HR 0.381 with 95% CI 0.154–0.941, and the p-value is 0.037. The HR of total intravesical instillation number is 0.958 (95% CI 0.926–0.991, p-value = 0.012). The details of Cox regression are listed in Table 3.

The efficacy of different chemotherapy agents (epirubicin, mitomycin C, and doxorubicin) was also analyzed. All patients receiving these three agents had statistically similar characteristics (Table 4). Among the three agents, mitomycin C had a nonsignificant association with higher RFS (Figure 3).

### Table 3 Univariate and Multivariate Cox Regression Analysis of Recurrence

|                  | Univariate |                      | Multivariate |                      | p value |
|------------------|------------|-----------------------|--------------|-----------------------|---------|
|                  | Hazard Ratio (95% CI) | p value | Hazard Ratio (95% CI) | p value |
| **Age (years)**  | 1.002 (0.986–1.017) | 0.181 | – | – | |
| **Sex**          | Male | Reference | – | Reference | – | |
|                  | Female | 0.738 (0.494–1.104) | 0.140 | 0.568 (0.353–0.915) | 0.020 |
| **BMI (kg/cm²)** | 0.997 (0.955–1.041) | 0.897 | – | – | |
| **T stage**      | Ta | Reference | – | Reference | – | |
|                  | T1 | 1.442 (1.050–1.980) | 0.024 | – | |
| **Tumour grade** | Low | Reference | – | Reference | – | |
|                  | High | 1.670 (1.160–2.405) | 0.006 | 1.992 (1.324–2.997) | 0.001 |
| **IVI regimen**  | Chemo only | Reference | – | Reference | – | |
|                  | BCG + Chemo | 0.408 (0.180–0.927) | 0.032 | 0.381 (0.154–0.941) | 0.037 |
|                  | Total IVI | 0.952 (0.924–0.981) | 0.001 | 0.958 (0.926–0.991) | 0.012 |

**Abbreviations:** BCG, bacillus Calmette-Guérin; BMI, body mass index; IVI, intravesical instillation; CI, Confidence Interval.

### Table 4 Difference Analysis Between Chemotherapy Agent Subgroups

|                  | Epirubicin (N = 197) | Mitomycin C (N = 152) | Doxorubicin (N = 17) | p value |
|------------------|-----------------------|-----------------------|----------------------|---------|
| **T stage**      | Mean/Number | SD/Percentage | Mean/Number | SD/Percentage | Mean/Number | SD/Percentage | 0.293 |
| Ta                | 94 | 47.7% | 84 | 55.3% | 9 | 52.9% |
| T1                | 99 | 50.3% | 68 | 44.7% | 8 | 47.1% |
| **Tumour grade** | Low | 61 | 31.0% | 52 | 34.2% | 9 | 52.9% | 0.336 |
|                  | High | 126 | 64.0% | 90 | 69.2% | 8 | 47.1% |
| **IVI with chemo** | 11.0 | 5.3 | 10.9 | 5.3 | 13.3 | 5.3 | 0.201 |
| **Total IVI**    | 11.6 | 5.8 | 11.9 | 5.3 | 13.3 | 5.3 | 0.482 |

**Abbreviation:** IVI, intravesical instillation.
Discussion

In the instillation treatment of NMIBC, the dose and schedule of BCG instillation have changed only minimally since its very first use 40 years ago. Multiple trials have been conducted to address its toxicity and global shortages and have tried to reduce the usage of BCG instillations by, for example, reducing the dose, shortening the length of the treatment course, or reducing the number of instillations.

The EORTC 30962 trial aimed to determine whether a reduced dose (one-third) could achieve similar efficacy to full-dose BCG. The results supported that a one-third dose could provide a non-inferior effect in preventing progression and survival. However, the dose reduction strategy had a weakness: preparing a one-third dose in a reliable and aseptic closed system is nearly impossible, which majorly impedes dose reduction.

In addition to dose reduction, studies have focused on shortening the length of the BCG course. In addition to the BCG induction course, the maintenance course is also vital and was reported to have a lower 5-year progression rate than the induction course alone, with the latter having a 5-year progression rate of up to 11%. Schedules modified with a single instillation per maintenance cycle for three years have been shown to be no better than those with an induction course alone. Most recently, the NIMBUS, a randomized trial studying the effects of a reduced number of instillations, demonstrated that a reduced instillation schedule was inferior to a standard instillation schedule and was halted by the EAU Research Foundation.

In addition to changing the BCG instillation schedule, intravesical chemotherapy instillation has also been considered an alternative for NMIBC. Chemotherapy agents used as intravesical instillations began in the 1960s to prevent BC recurrence. A single immediate postoperative intravesical instillation (SI) of chemotherapy has been shown to reduce the 5-year recurrence rate by 14%, from 59% to 45% in a systematic review and meta-analysis of 2278 patients. Different chemotherapies with mitomycin C (MMC), gemcitabine, epirubicin, or pirarubicin have shown beneficial effects.

Although SI can effectively prevent recurrence, the efficacy of induction and maintenance intravesical chemotherapy instillations is inferior to that of BCG instillation. In a meta-analysis of 39 trials, induction chemotherapy instillation was associated with a decrease in the risk of recurrence only, while BCG instillation was associated with a reduction in the risks of recurrence and progression. Regarding maintenance instillation, compared to patients receiving BCG instillation, those receiving chemotherapy instillation had a higher rate of disease recurrence.

However, practice might change during the global shortage of BCG since inadequate BGC instillation was proved to have more recurrence events. In the BCG shortage era between October 2013 and December 2016, there was an

![Figure 3 Kaplan-Meier survival curves according to different chemotherapy agents. Recurrence analysis between different chemotherapy agents in the (A) [BCG + Chemo] subgroup and (B) all subgroups regardless of the chemotherapy instillation. The *Among the p-value interpretations indicates statistical significance.](https://doi.org/10.2147/CMAR.S383627)
increased rate of BC recurrence, and the total cost of care for NMIBC patients was noted.26 Therefore, initiating the chemotherapy instillation protocol seems reasonable in this situation but lacks evidence support.

Our study focused on a standard clinical dilemma encountered in the real world: in the high probability of BCG discontinuation, whether due to a BCG shortage or intolerance to toxicity, should we subsequently initiate intravesical chemotherapy instillation instead? In this study, patients in the [Chemo only] group initiated a chemotherapy protocol and the [BCG only] group received BCG instillation without any subsequent replacement agents even though intolerance or a BCG shortage was encountered. On the other hand, patients in the [BCG + Chemo] group represented those who received BCG instillation. However, they experienced intolerant BCG side effects or an unexpected BCG shortage and had to shift to subsequent chemotherapy instillation. Patients in [BCG only] and [BCG + Chemo] groups were statistically similar in general characteristics and disease patterns, including the number of BCG instillations.

Based on the results, although patients who received initial chemotherapy instillation had a higher percentage of Ta tumors while those who received BCG were T1 dominant, the latter seemed to have better bladder RFS although the difference was not statistically significant (p value = 0.119). Besides, the additional chemotherapy instillations in patients in whom BCG was discontinuated could have led to significantly better RFS than pure chemotherapy instillation (Figure 2A). Total IVI numbers might be a confounding factor in these results, since the [BCG + Chemo] group had significantly more total IVI numbers than the [Chemo only] group. However, multivariate Cox regression analysis revealed that both instillation regimen and total IVI numbers were independent predictors of bladder recurrence (Table 3), supporting the thesis that [BCG + Chemo] regimen should have priority of consideration over [Chemo only] regimen.

Since total intravesical instillation number is identified as predictive of bladder recurrence, the precise instillation number that would have better RFS aroused further investigation. We found that instillation more than 12 times had significantly higher RFS than other instillation numbers. However, this result should be interpreted carefully as the frequency and duration of instillation are also associated with the outcome. An optimal instillation schedule of BCG following chemotherapy needs further evaluation.

Very few studies have directly compared the efficacy of different chemotherapy agents in intravesical instillations. In a meta-analysis comparing BCG and chemotherapy agents, the risk of recurrence after BCG was equivalent to that after MMC (RR 0.95, 95% CI 0.81–1.11), but patients who received BCG had a lower rate of recurrence than those who received doxorubicin (RR 0.31, 95% CI 0.16–0.60), epirubicin (RR 0.54, 95% CI 0.40–0.74) and thiotepa (RR 0.38, 95% CI 0.19–0.76).15 Our study also demonstrated that intravesical instillations with MMC could achieve better bladder RFS than epirubicin and doxorubicin (Figure 3).

The retrospective study design limited the evidence level of this research. Although we performed statistical analyses to confirm the equivalence between subgroups, selection bias still existed and may have interfered with the results. The number of patients who received BCG instillation followed by chemotherapy instillation was relatively small. The results could be more robust if the sample size is expanded.

**Conclusion**

The BCG shortage has already impacted the outcome of BC patients and has become one of the most challenging issues for urologic oncologists. The COVID-19 pandemic is in full swing and is causing a further global BCG shortage crisis. In this era, instead of initiating a chemotherapy instillation protocol, we still recommend starting with BCG instillation for those with intermediate- and high-risk NMIBC. Shifting to chemotherapy agents if unexpected BCG interruption occurs is a simple strategy to apply in the clinic and can potentially reduce bladder recurrence.

**Abbreviations**

BC, bladder cancer; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; Tis, carcinoma in situ; Ta, non-invasive papillary carcinoma; T1, tumour invasive to the lamina propria; EAU, European Association of Urology; IRB, institutional review board; TUR-BT, transurethral resection of bladder tumour; BCG, bacillus Calmette-Guérin; MMC, mitomycin C; BMI, body mass index; RFS, recurrence-free survival.
Data Sharing Statement
All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate
This study was conducted in accordance with the ethical principles mentioned in the Declaration of Helsinki (2013). This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB Number: 202100259B0).

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Disclosure
The authors declare that they have no competing interests in this work.

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