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ORIGINAL ARTICLE

Risk of metachronous advanced lesions after resection of diminutive and small, non-advanced adenomas

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KEYWORDS
Diminutive;
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Summary
Background and aims: Current post-polypectomy surveillance interval guidelines do not discriminate between 1—2 diminutive (1—5 mm) and small (6—9 mm) non-advanced adenomas. This study compared the risk for metachronous advanced lesions in these groups.
Methods: Patients with 1—2 diminutive, non-advanced adenomas and no further advanced lesions, and patients with no polyps at baseline colonoscopy were retrospectively analyzed to determine the rate of metachronous advanced lesions. These were defined as the combined rate of colon cancer, advanced adenoma and ≥ 3 non-advanced adenomas at surveillance colonoscopy. Polyp size was measured either subjectively by the endoscopist or by pathology-based measurements.
Results: Among patients with diminutive (n = 395) and small polyps (n = 110), advanced lesions were found in 68 patients (17.2%) and 16 patients (14.5%), respectively (P = 0.53), during a mean follow-up of 4.3 ± 0.9 years. In contrast, advanced lesions were observed in 33 patients (6.6%) in the no polyp group (n = 505), significantly lower than diminutive (P = 0.000) and small polyp groups (P = 0.002), despite a mean follow-up duration of 6.1 ± 1.9 years. The rate of metachronous advanced lesions was also similar between patients with 1—3 mm polyps (16%) versus 7—9 mm polyps (15.8%).
Conclusions: Our findings suggest that among patients who underwent polypectomy of up to 2 non-advanced adenomas, those with diminutive and small polyps have the same risk of metachronous advanced lesions; thus, supporting uniform recommendations for surveillance colonoscopy for these lesions.

Abbreviations: CRC, colorectal cancer; TA, tubular adenoma; LGD, low-grade dysplasia; NAA, non-advanced adenoma; OR, Odds ratio.

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Introduction

Most, if not all, colorectal cancers (CRC) arise from preexisting adenomas. Therefore, early detection and complete removal of adenomatous polyps reduce the incidence of CRC [1,2]. Although diminutive (1—5 mm) and small (6—9 mm) polyps demonstrate a lower frequency of advanced histological features compared with large (> 10 mm) polyps [3,4], complete removal of all polyps is recommended in clinical practice.

According to American Gastroenterology Association and European guidelines [5], patients with 1—2 tubular adenomas (TA) with low grade dysplasia (LGD) < 10 mm represent a low-risk group for metachronous advanced adenomas and CRC; therefore, a 5- to 10-year interval is recommended for surveillance. This recommendation was based on large prospective and population-based studies [6—9] that mostly compared the risk for advanced adenomas and CRC in patients with low-risk adenomas (i.e. 1—2 TA-LGD < 10 mm) and high-risk adenomas (i.e. the presence of polyp > 10 mm or with villous histology or high-grade dysplasia) at baseline colonoscopy. However, most studies did not categorize patients whose largest polyp size was diminutive versus small on screening examination.

A recent retrospective study from Israel [10] that included 443 patients whose worst finding was 1—2 TA-LGD < 10 mm, found advanced neoplasia in follow-up colonoscopy in 3.5% of the 1—2 diminutive polyps group versus 9.8% in the 1—2 small polyps group [hazard ratio (HR): 3.97]. However, they were not matched to healthy population undergoing screening colonoscopy. Additionally, the size of the polyp that was used for stratification was determined by subjective estimation of the endoscopist, which has potential bias.

Thus, the aim of this study was to stratify the risk for advanced neoplasia at follow-up colonoscopy for patients who had no polyps or whose most advanced polyps at baseline colonoscopy were 1—2 diminutive and small TA, and to evaluate the risk factors for their development.

Patients and methods

This retrospective study was conducted at Meir Medical Center, Kfar Saba, Israel, which serves a population of about 850,000 people. Approximately 5,000 colonoscopies are performed annually by 15 senior gastroenterologists. The adenoma-detection rate at screening colonoscopy for average-risk population, was confirmed 25% from 2005 through 2013. This study was approved by the Institutional Ethics Committee.

The methods of data collection were described in detail by our group in a recent study [11]. Briefly, data were collected from electronic medical records for patients undergoing colonoscopy from 2005 through 2015. Cases included adult patients above the age of 18 years who had a documented polyp at baseline colonoscopy and a surveillance colonoscopy from 1 to 5 years later, which is the longest recommended interval for adenomas. The indication for baseline colonoscopy was not limited to screening and included symptomatic patients as well. We included only patients with a diagnosis of 1—2 small or diminutive TA at baseline colonoscopy. Patients were excluded if they had previous colonoscopies before the study period with detected polyps, any advanced polyp, serrated polyp or > 2 small TA's at baseline colonoscopy, history of inflammatory bowel disease, a known hereditary syndrome or a history of CRC or bowel resection for other indications. Patients were also excluded if they had poor bowel preparation as determined by the endoscopist, or incomplete examinations at either of the two colonoscopies.

Data retrieved from the electronic medical records included demographic information, history of colon cancer in first-degree relatives, diabetes (based on A1C hemoglobin > 7% or the use of anti-diabetic therapy), chronic aspirin use and indication for colonoscopy. We categorized the indications into three sub-groups: screening, non-bleeding complaints (abdominal pain, change in bowel habits or loss of weight) and signs of bleeding (iron deficiency and either occult or overt rectal bleeding). Information regarding the procedures included quality of bowel preparation and details regarding polyps (number, size and histology). When more than one polyp was found, the larger was used for categorization.

Based on the findings at baseline colonoscopy, we compared patients with 1—2 diminutive (1—5 mm) and small (6—9 mm) NAA. The control group consisted of age-matched patients at a 1:1 ratio, with negative screening baseline colonoscopy who had a follow-up colonoscopy at 5- to 10-year intervals, within the study period at our institute. The outcome of the study was the rate of metachronous advanced lesions, defined as the combined rate of CRC, advanced adenoma and $\geq$ 3 NAA at surveillance colonoscopy in each study group. Since the assessment or measurement of a polyp size around 5 mm can be difficult and is largely inaccurate, we performed a sub-group analysis and compared these outcome measures between the extremes of each group, i.e. 1—3 mm and 7—9 mm polyps at baseline colonoscopy.

Colonoscopy procedure

Bowel preparation included a liquid preparation solution (polyethylene glycol [PEG] or sodium pico-sulfate), oral laxatives and enemas. The cleansing level was graded based on a validated 4-level scale. Excellent, good or fair preparations were considered adequate, while patients with poor cleansing level were excluded. According to departmental policy, all polyps, regardless of size or location, were resected during the procedure and sent to pathology.

Method of polyp resection was at the discretion of the endoscopist, but as a rule, cold forceps or snare polypectomy was recommended for the resection of 1—5 mm polyps and snare polypectomy, either cold or hot, was recommended for removal of polyps 6—9 mm.

Assessment of polyp size

The determination of polyp size that was used for polyp stratification was based on subjective estimation by the endoscopist, either using open forceps or unaided visual estimation, and when available, by objective pathology-based measurements using a ruler. Whenever there was a dis-

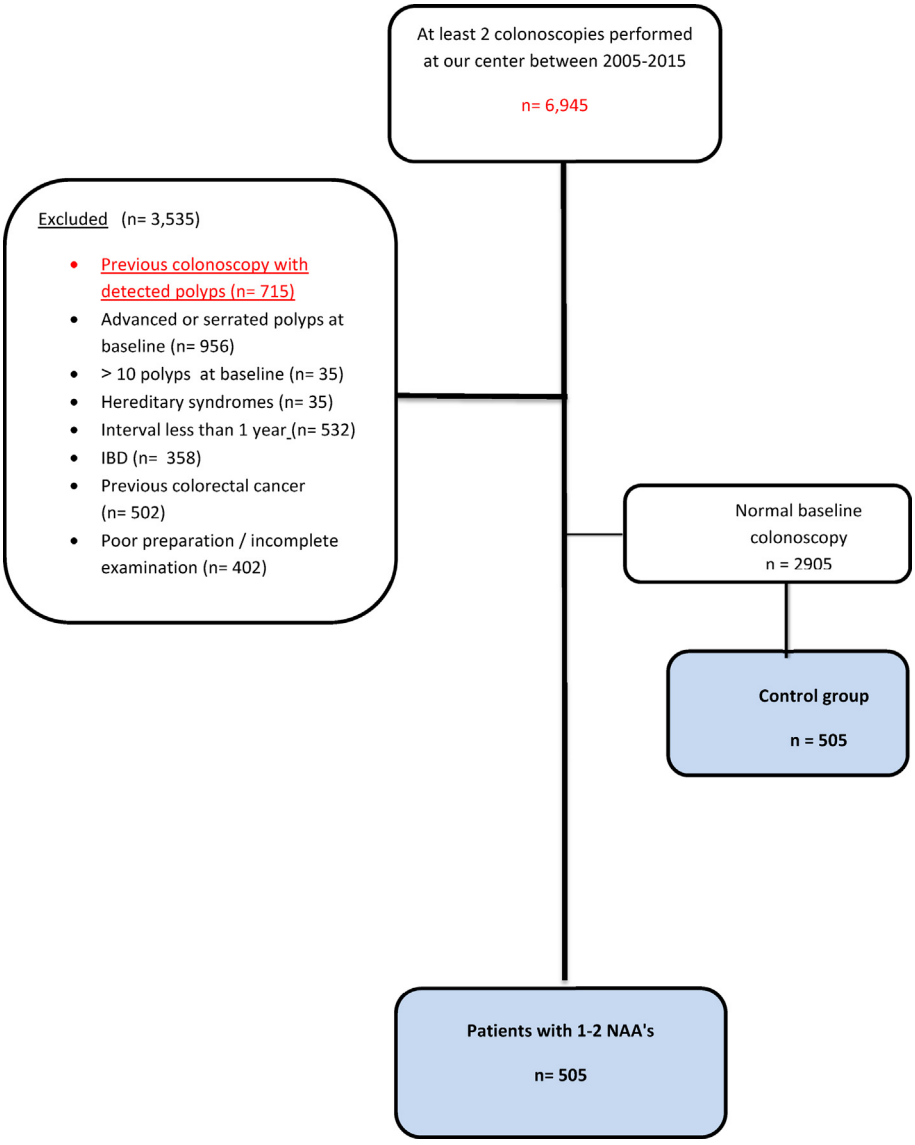

Figure 1 Flow chart of the patients undergoing at least two colonoscopies who were included in the study groups.

crepancy between the two, we considered the pathologist's measurement the more reliable.

Recommended surveillance interval

Recommendations for post-polypectomy surveillance interval agreed with the accepted AGA guidelines, i.e. 5 years. However, a follow-up colonoscopy at shorter interval was performed if the resection border was not clear of dysplasia according to the pathology report or the preparation was only fair. In these cases, a 1- to 3-year interval was recommended, at the discretion of the endoscopist.

Statistical analysis

Results were expressed as frequencies and percentage for categorical data and mean ± standard deviation for continuous parameters. Differences between two groups were analyzed by Pearson Chi^2 test or Fisher's exact test for non-metric variables and by *t*-test or Mann-Whitney test, each when appropriate, and for more than two groups, comparisons using one-way ANOVA. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. All statistical tests were two-sided at an α-level of 0.05.

Results

After ineligible patients were excluded, 505 patients with 1—2 NAA who appeared to satisfy the inclusion criteria were evaluated (Fig. 1), of which 395 had diminutive polyps and 110 had small polyps. The control group consisted of 505 patients with negative baseline colonoscopy. The mean age (± SD) of the study population was 60.2 ± 9.2 years and 46.3% were males.

Among 395 patients with diminutive polyps, 249 had 1—3 mm polyps that were removed with forceps, and 146 had

Table 1 Background demographics and clinical characteristics of the study groups at baseline colonoscopy.

Characteristic	Diminutive polyp, *n* (%) (*n* = 395)	Small polyp, *n* (%) (*n* = 110)	No polyp, *n* (%) (*n* = 505)	*P*-value
Age (mean ± SD), years	60.87 ± 9.51	60.13 ± 9.27	59.77 ± 8.91	0.21
Male sex	194 (49.1)	58 (52.7)	213 (42.3)	0.05[a]
Family history colon cancer	156 (39.5)	46 (41.8)	203 (40.2)	0.54
Indication				
Screening	216 (54.7)	53 (48.2)	297 (58.8)	0.017[b]
Non-bleeding symptoms	93 (23.5)	23 (20.9)	114 (22.5)	
Bleeding symptoms	86 (21.8)	34 (30.9)	94 (18.7)	
Aspirin	107 (27.1)	37 (33.6)	160 (31.7)	0.22
Diabetes	61 (15.4)	16 (14.5)	61 (12.1)	0.36
Preparation quality				
Excellent/good	306 (77.7)	87 (79.1)	395 (78.2)	0.26
Fair	89 (22.3)	23 (20.9)	110 (21.8)	

[a] Between diminutive/small polyp groups and no polyp group.
[b] Between small polyp group and no polyp group.

4—5 mm polyps that were removed with forceps (55 patients) or snares (91 patients). All small polyps (110 patients) were removed with snares. Thus, subjective estimation for polyp size was obtained in 304 patients (60.1%) in whom polyps were removed with forceps, and pathological assessment was achieved in 201 patients (39.8%) in whom polyps were resected with snare.

The demographic parameters, indication for baseline colonoscopy and other factors related to the risk for dysplastic lesions are depicted in Table 1 for the three groups. There were no age differences among the groups, as well as proportions of family history of CRC, aspirin use and diabetes. Male sex was more prevalent in the diminutive and small polyp groups (49.1% and 52.7%, respectively) compared with controls (42.3%, $P = 0.05$). Bleeding symptoms were more common in the small polyp group (30.9%) than in the control group (18.7%, $P = 0.017$) and not significantly than in the diminutive polyp group (21.8%, $P = 0.13$).

Findings at surveillance colonoscopy are shown in Table 2. During a mean follow-up of 4.3 ± 0.9 years, metachronous advanced lesions (the sum of ≥ 3 NAA, advanced adenomas and colorectal cancer) were found in 84 patients (16.6%), among all patients with 1—2 NAA at baseline. Advanced lesions were observed in 68 patients (17.2%) with diminutive polyps and 16 (14.5%) patients with small polyps ($P = 0.53$). The components of the advanced lesions did not differ significantly as well between these groups. We further analyzed the findings at surveillance colonoscopy for patients with 1—3 mm vs. 7—9 mm polyps at baseline. As shown in Table 3, these groups did not differ regarding the risk for any metachronous advanced lesions or its components thereof. In contrast, advanced lesions were observed in 33 patients (6.6%) in the control group, significantly lower than in the diminutive ($P < 0.001$) and small ($P = 0.002$) polyp groups, with a longer mean follow-up duration (6.1 ± 1.9 years, $P < 0.001$) between procedures (Table 2). Indications for follow-up colonoscopy in the control group included family history of CRC in 202 patients (40%), non-bleeding symptoms in 186 patients (37%), bleeding symptoms in 70 patients (14%) and no symptoms in 47 patients (9%).

Table 2 Findings at surveillance colonoscopy of the study groups.

Finding	Diminutive polyp, *n* (%) (*n* = 395)	Small polyp, *n* (%) (*n* = 110)	No polyp, *n* (%) (*n* = 505)	*P*-value
No findings	250 (63.4)	76 (69.1)	420 (83.2)	< 0.001[a]
1—2 non-advanced adenomas	77 (19.4)	18 (16.4)	52 (10.2)	< 0.001[b]
≥ 3 non-advanced adenomas	15 (3.8)	1 (0.9)	3 (0.6)	0.001[b]
Advanced adenomas	50 (12.6)	13 (11.8)	26 (5.1)	0.01[c]
Villous histology	37 (9.3)	10 (9.0)	23 (4.5)	
Size ≥ 10 mm	45 (11.3)	11 (10.0)	23 (4.5)	< 0.001[b]
High-grade dysplasia	8 (2.0)	3 (2.7)	5 (0.9)	
Colorectal cancer	3 (0.8)	2 (1.8)	4 (0.9)	0.36
Any advanced lesion	68 (17.2)	16 (14.5)	33 (6.6)	0.002[c]
				< 0.001[b]
Colonoscopy interval (mean ± SD), years	4.36 ± 0.92	4.25 ± 0.96	6.14 ± 1.91	< 0.001[a]

[a] Between diminutive/small polyp groups and no polyp group.
[b] Between diminutive polyp group and no polyp group.
[c] Between small polyp group and no polyp group.

Table 3 Findings at surveillance colonoscopy of patients with 1—3 mm and 7—9 mm polyps at baseline colonoscopy.

Finding	1—3 mm polyp, *n* (%) (*n* = 249)	7—9 mm polyp, *n* (%) (*n* = 63)	*P*-value
No findings	164 (65.9)	43 (68.3)	0.72
1—2 non-advanced adenomas	45 (18.1)	10 (15.9)	0.68
≥ 3 non-advanced adenomas	6 (2.4)	1 (1.6)	0.85
Advanced adenomas	32 (12.8)	8 (12.6)	0.97
Colorectal cancer	2 (0.8)	1 (1.6)	0.56
Any advanced lesions	40 (16.0)	10 (15.8)	0.65

Table 4 Univariate analysis for the association of demographics and background diseases with any advanced lesion at surveillance colonoscopy.

Variable	Patients, *n*	Any advanced lesions, *n* (%)	Odds ratio (OR)	95% Confidence interval (CI)	*P*-value
Male gender					
No	541	61 (11.2)	1 (ref)	0.63—1.33	0.72
Yes	469	56 (11.9)	1.03		
Family history of colon cancer					
No	603	79 (13.1)	1 (ref)	0.44—1.02	0.06
Yes	407	38 (9.3)	0.67		
Aspirin use					
No	705	81 (11.4)	1 (ref)	0.85—2.27	0.15
Yes	305	36 (11.8)	1.09		
Diabetes					
No	868	98 (11.2)	1 (ref)	0.75—2.17	0.36
Yes	142	19 (13.3)	1.28		
Bowel preparation					
Excellent/good	788	82 (10.4)	1 (ref)	1.14—2.38	0.03
Fair	222	35 (15.7)	1.52		

Serrated polyps were found in 3 patients on surveillance colonoscopy (2 in the diminutive polyp group and 1 in the control group at baseline), and none of those polyps showed dysplasia or were ≥ 10 mm in size.

A univariate analysis was performed for the association of metachronous advanced lesions with baseline demographic and clinical variables (Table 4). Fair preparation was the only risk factor that was associated with metachronous advanced lesions, and it was significant after adjustment for age, time of surveillance colonoscopy and the presence of polyps (OR 1.49, CI 1.10—2.45, *P* value: 0.02).

Discussion

The findings of this study indicate that patients who underwent polypectomy of up to 2 NAA compared to those with at least one 1—5 mm polyp have the same risk of metachronous advanced lesion compared with those who had 6—9 mm polyps. As expected, their risk was significantly increased in comparison with patients with negative baseline colonoscopy. This study supports the current recommendations for surveillance colonoscopy after polypectomy [5] which do not discriminate between diminutive and small NAA.

As opposed to this study, a previous Israeli study [10] found an increased risk for advanced neoplasia in surveillance colonoscopy for patients with 1—2 small compared with diminutive NAA (9.8% and 3.5%, respectively; hazard ratio 3.97). Additionally, the rate of advanced neoplasia in both groups was considerably lower in that study compared with the current findings. Some differences exist between the two reports. First, the main outcome measure in their study was advanced neoplasia, which included advanced polyps and CRC, while in our study we considered ≥ 3 NAA in the definition of advanced lesions. However, only 0.9—3.8% of our patients developed ≥ 3 NAA, which is less than the differences in rate observed between the studies. Second, the median time to follow-up colonoscopy in their study was 32 months and 46% of the study group underwent the procedure earlier than recommended, while it was 52 months in this study. Shorter than recommended surveillance intervals can lead to underestimation of the true rate of metachronous advanced neoplasia had the procedure been performed as recommended, due to lack of time to grow. Indeed, the rate of metachronous non-advanced neoplasia in their study was considerably higher than in the current study among patients with polyps (23.3—31.1% and 16.4—19.4%, respectively). This might reflect the shorter interval, and consequently less time, for a polyp to become advanced.

Another difference was in the estimation of polyp size for categorization. While Sneh Arbib et al. based polyp size on visual estimation by the endoscopists (with its inherent inaccuracies in polyp estimates and consequent potential misclassification of polyps), in the current study we assessed almost 40% of the polyps by objective pathological measurements, while the other 60% were subjectively assessed and removed with forceps; thus, unlikely to be > 5 mm. Therefore, there was less potential for bias and misclassification between diminutive and small polyps. Indeed, when we further compared the extremes of each these groups, in order to decrease the bias from inaccurate measurements, the rate of advanced lesions was comparable between the two groups. The main problem with visual estimation of polyps is overestimation. Anderson et al. [12] demonstrated that 46% of polyps estimated as ≥ 1 cm on endoscopy, were actually 1 cm on pathology, while only 3.9% of polyps estimated as < 1 cm on endoscopy were larger. Nonetheless, even when measuring an ex situ polyp in pathology, inaccuracy can still arise due to potential shrinkage when electrocauterization is used for polypectomy or from formalin fixation. However, most studies have demonstrated no significant differences between fresh (post-excision) and fixed polyp measurements [13—15].

Several prospective studies [7,9] found lower rates (5.2—6.1%) of advanced neoplasia at surveillance colonoscopy, in patients with baseline low-risk adenomas, than this study did. Potential factors that can explain the dissimilarities are differences in quality measures of the endoscopies, differences in polyp estimates or interval between colonoscopies and variations in the definition of the outcome measure. In addition, incomplete resection of polyps should be considered as well. Several studies have compared cold forceps polypectomy and cold or hot snare polypectomy for the removal of diminutive and small polyps [16—19]. Although forceps polypectomy is a therapeutic option for removal of diminutive polyps, it is associated with significant rates of incomplete polyp resection. Although previous trials revealed a markedly incomplete resection rate (29—38%) [20—22], more recent studies have shown lower rates (9—18%) [16,17]. Moreover, complete resection was achieved in almost all 1—3 mm polyps [17]. Snare polypectomy was shown to decrease the risk of incomplete diminutive polyp removal by 60% in a recent review [23], and by 79% in randomized trials, compared with forceps polypectomy [18,19], making it a very effective method for all small polyps, especially those > 3 mm. In our study, all 1—3 mm and about a third of 4—5 mm polyps were removed by forceps; thus, increasing the risk of incomplete resection as a potential factor in the development of metachronous advanced lesions.

Although advanced adenoma is an important surrogate marker and a precursor of carcinoma, and as such, can be used as a primary outcome measure in follow-up studies, the actual aims of screening and surveillance colonoscopy are to reduce CRC incidence and mortality. The rate of interval cancer in this study was < 1% (5/505) in the baseline polyp group and 0.9% (4/505) in the no polyp group, with no significant difference between small and diminutive polyp groups. This rate is comparable to that of a large cohort study that reported an interval cancer rate of 0.8% after polypectomy of low-risk adenomas [24]. The randomized European Polyp Surveillance trial (EPOS) is commencing. In this trial, the primary outcome among subjects with low-risk adenoma will be CRC incidence between years 5 and 10.

Among background demographics and clinical variables at baseline colonoscopy, fair preparation was the only independent risk factor that was associated with metachronous advanced lesions. This confirms the importance of the quality of bowel preparation in detecting small polyps and in reducing the rate of advanced neoplasia at follow-up.

The current study has few limitations. In addition to potential bias in misclassification of polyps as mentioned above, the retrospective design, the relatively small cohort and the fact that it was performed in a single referral center, prevent it from being completely generalizable. Additionally, we do not have, and therefore did not adjust for, endoscopist-related quality measures (adenoma-detection rate, retrieval time), although all the procedures were performed by senior gastroenterologists with complete cecal intubation and at least fair preparation. Despite these limitations, our findings suggest a comparable risk of advanced polyps and CRC on follow-up among patients with baseline 1—2 diminutive and small NAA, which was both higher than patients with no polyps at baseline. Thus, the current recommendation for 5-year interval, which do not discriminate between the two, seems to be appropriate. Clearly, the most problematic factors to adjust retrospectively in this issue are the interval between colonoscopies and the exact polyp size. Thus, prospective studies with predetermined intervals for repeat colonoscopy and a direct measurement of the polyp (e.g. by computed tomography colonography or video-capsule endoscopy) before resection, are needed.

Disclosure of interest

The authors declare that they have no competing interest.

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