WHAT THIS PAPER ADDS

In this study, where a cohort of 3,268 men invited to screening at age 65 was re-invited and re-screened at age 70, AAA prevalence rose from 1.5% at age 65 to 2.4% at age 70, and AAA had developed among 0.7% men with <25 mm at age 65, and among 52.5% of men with sub-aneurysmal (25—29 mm) aortas at age 65. Screening was safe with high 5-year surgery rates for screening detected AAA (50%) in conjunction with no observed peri-operative mortality and ruptured AAA occurring only among non-attenders.

Objective: Acquiring contemporary data on prevalence and natural history of abdominal aortic aneurysms (AAA) is essential in the effort to optimise modern screening programmes. The primary aim of this study was to determine the fate of a 65-year-old male population 5 years following an invitation to an aortic ultrasound (US) examination.

Methods: In this population-based cohort-study, men were invited to US examination at age 65, and were re-invited at age 70. Mortality, AAA repair, and risk factors were recorded. An AAA was defined as a diameter ≥30 mm, and a sub-aneurysmal aorta as 25—29 mm.

Results: In 2006—2007, 3,268 65-year-old men were invited, and 2,736 (83.7%) were examined. After 5 years, 24 had completed AAA repair (6 died within 0—4 years), an additional 239 had died, and 194 had moved. Thus, 2,811 70-year-old men were re-invited, and 2,247 (79.9%) were examined. The AAA prevalence increased from 1.5% at 65 to 2.4% (95% CI: 1.8 to 3.0) at 70, and of sub-aneurysmal aortas from 1.7% at 65 to 2.6% (2.0 to 3.3), at 70. Of 2,041 with <25 mm at 65, 0.7% had an AAA at 70. Of 40 with a sub-aneurysmal aorta at 65, 52.5% progressed to AAA at 70. In a Cox regression analysis, sub-aneurysmal aorta at 65 (hazard ratio [HR] 59.78) and smoking (HR 2.78) were independent risk factors for AAA formation. Among 44 with AAA at 65, 22 completed AAA repair with no 30-day mortality.

Conclusion: AAA screening in a contemporary setting was safe at 5 years, with a single AAA rupture observed among non-attenders. Men with a screening detected AAA had a high repair rate and high non-AAA related mortality. AAA-formation was common among men with sub-aneurysmal dilatation, indicating a possible need for surveillance of this group.

INTRODUCTION

Evidence from randomised controlled trials (RCT) and observational studies demonstrate that screening elderly men for abdominal aortic aneurysm (AAA) reduces long-term mortality from ruptured AAA.1–5 The most widespread strategy, one-screening of men at age 65, is partially or fully implemented in several countries.6 This specific strategy is, however, not evidence-based and several aspects need further research, such as the threshold diameter for surveillance, the long-term natural course of those screened normal as well as the fate of those not attending the screening programme.

Since the start of a AAA screening programme targeting 65-year-old men in the County of Uppsala, Sweden, in 2006,7 a pending longitudinal cohort-study was initiated offering all men in the County of Uppsala AAA screening every 5-years, at the ages of 65, 70, 75, and 80 years.

The primary aim of this first report from that initiative was to determine the fate of a 65-year-old male population 5 years following an invitation to an aortic ultrasound (US) examination. The specific aims were to study (1) the rate of de novo AAA formation following a normal scan, (2) the rate of AAA events, and (3) the mortality rate. A
secondary aim was to analyse risk factors associated with AAA formation.

PATIENTS AND METHODS

In the County of Uppsala all men born 1941 and 1942, identified in the National Population Registry, were invited to screening for AAA with US at age 65 years (primary screening cohort) during the years 2006 and 2007. Individuals with an infrarenal aortic diameter $\geq 25$ mm were scheduled for US surveillance at regular intervals, 25–29 mm after 5 years, 30–39 mm after 2 years, 40–44 mm after 1 year, 45–49 after 6 months, and $\geq 50$ mm every 3 months. Surgery was considered at 55 mm or more, or in individuals with symptomatic or rapidly expanding AAA.

The cohort of men born in 1941–1942 was re-invited during the years 2011–2012 for an US examination of the abdominal aorta at age 70 years. Individuals with a history of AAA repair were excluded from invitation. No other exclusion criteria were used.

The maximum antero-posterior diameter of the infrarenal aorta was recorded using the leading edge to leading edge principle. An AAA was defined as a maximum infrarenal diameter of 30 mm or more. A diameter of 25–29 mm was classified as a sub-aneurysmal aorta.

Information on smoking habits, family and medical history, as well as current medication was collected at ages 65 and 70 from those attending screening. Smoking status was classified as never, former, or current. Medical history consisted of self-reported history of coronary artery disease (angina pectoris or myocardial infarction), hypertension, hyperlipidaemia, cerebrovascular disease (stroke or transient ischaemic attack), claudication, diabetes mellitus (dietary or medical treatment), renal insufficiency, and chronic obstructive pulmonary disease.

Mortality data were retrieved from the National Population Registry. Information on AAA repair of screening detected and opportunistically detected AAA (detected outside of screening programme) was retrieved from the Swedish Vascular Registry (Swedvasc) for the past 5 years.

Statistical analysis

Differences in proportions were analysed with uncorrected chi-square test and results presented with 95% confidence intervals (95% CI). Independent-sample Student $t$ test was used for comparison of continuous data. Risk factors associated with AAA formation with $p < 0.1$ in a univariable analysis were entered as covariates into a Cox proportional hazards regression model; where hazard ratios (HR) and

Figure 1. Trial profile. AAA = abdominal aortic aneurysm; iAAA = intact abdominal aortic aneurysm; rAAA = ruptured abdominal aortic aneurysm; US = ultrasound.
95% CI were calculated. A p value < .05 was considered statistically significant. Statistical analysis was performed with SPSS PC version 20.0 (IBM, Armonk, NY, USA). The study was approved by the ethical committee of the Uppsala/Örebro region.

RESULTS

Attendance, prevalence, diameters, deaths, and AAA repair

In the National Population Registry, 3,270 65-year-old men were identified. Two men had a history of AAA repair, one for a ruptured AAA at age 64 and one for intact AAA with unknown date of surgery, and they were not invited and thus excluded from the study. Of the remaining 3,268 invited men, 2,736 (83.7%, 95% CI: 82.5 to 85.0) attended and completed a valid US examination, of whom 2,702 (98.8%, 95% CI: 98.3 to 99.2) also completed a health questionnaire. In one individual the aorta could not be visualised and he did not attend at age 70, and he was excluded. The mean infrarenal aortic diameter at age 65 was 18.5 mm (95% CI: 18.3 to 18.6). The trial profile and main outcome are displayed in Fig. 1.

After 5 years, 23 had completed elective AAA repair, of whom five subsequently had died of non-AAA-related causes, and one had undergone ruptured AAA repair and died during surgery. In addition, 239 men were reported dead without a history of AAA repair. Thus, of all men invited at age 65 years, 245 had died resulting in a 5-year mortality of 7.5% (95% CI: 6.6 to 8.4) (see Table 3 for causes of death). Of the remaining 2,811 men re-invited to an US examination at age 70, 2,247 (79.9%, 95% CI: 78.5 to 81.4) attended. The total prevalence of AAA at age 70 was 2.4% (95% CI: 1.8 to 3.0), and of a sub-aneurysmal aorta 2.6% (95% CI: 2.0 to 3.3). The mean infrarenal aortic diameter at age 70 years was 19.4 mm (95% CI: 19.3 to 19.6), significantly larger than at age 65 (p < 0.001). The relative 5-year mortality in the respective sub-groups is displayed in Fig. 2.

Men not attending screening at age 65 years

Among 532 men invited, but not attending at age 65, one had completed elective repair of an opportunistically detected AAA (66 mm) at age 66 and died 2 years later of non-AAA-related causes. One had emergency repair for a ruptured 70 mm AAA at age 69 and died during surgery. Another 94 men died before age 70, in all 96 of 532 (18%, 95% CI: 14.8 to 21.3). A total of 153 non-attenders attended US examination at age 70, 35.1% (95% CI: 30.6 to 39.6) of the survivors. One of these had an AAA (45 mm) opportunistically detected at age 69, and one had a sub-aneurysmal aorta (28 mm expanding to a 34 mm AAA at age 70) opportunistically detected at a trauma CT examination at age 66. In addition, two AAA and three sub-aneurysmal aortas, previously unknown, were detected. Thus, at age 70 years a total of four men (2.6%, 95% CI: 0.7 to 6.6) had an AAA, of whom one exceeded 40 mm, and three (2.0%, 95% CI: 0.4 to 5.6) had a sub-aneurysmal aorta. The distribution of risk factors in this subgroup did not differ from those attending at both 65 and 70, except for a significantly higher current smoking rate in this group, 18.5% (95% CI: 12.3 to 24.8) versus 9.0% (95% CI: 7.8 to 10.2, p = .0001).

Men screened <25 mm at age 65 years

Among the 2,041 subjects attending re-screening, 42 (2.1%, 95% CI: 1.5 to 2.7) had a sub-aneurysmal aorta, and 15 (0.7%, 95% CI: 0.4 to 1.1) an AAA. All but one AAA were less than 40 mm.

Figure 2. Relative mortality. AAA = abdominal aortic aneurysm. Error bars indicate 95% confidence interval.
Men screened 25–29 mm at age 65 years
Among those re-examined at age 70, three (7.9%, 95% CI: 1.7 to 21.4) individuals were found to have diameters less than 25 mm, 14 (36.8%, 95% CI: 21.8 to 54.0) were still classified as sub-aneurysmal aortas, and 21 (55.3%, 95% CI: 38.3 to 71.4) had expanded to an AAA. Of these, 15 (39.5%, 95% CI: 24.0 to 56.6) were 30–39 mm and six (15.8%, 95% CI: 6.0 to 31.3) were 40–54 mm.

Men with an AAA at age 65 years
Of the 44 patients with an AAA at age 65, a total of 11 (25.0%, 95% CI: 13.2 to 40.3) died of non-AAA related causes within 5 years, including four who had completed intact AAA (iAAA) repair. In addition to one man examined at age 65 with a known AAA that had been under surveillance for 4 years, 43 previously unknown AAA were detected at screening. The 5-year events of the men with AAA are displayed in Fig. 3. Twenty-two of 44 (50.0%, 95% CI: 34.6 to 65.4) AAA detected or known at age 65 completed iAAA repair during the study.

AAA formation
A total of 2,059 men with an aortic diameter of less than 30 mm at age 65 and complete data on risk factors were included in a risk factor analysis for AAA formation. In the univariable analysis of men, stratifying those not expanding to an AAA (n = 2,023) versus those who did develop AAA (n = 36) after 5 years, resulted in a sub-aneurysmal aorta at age 65, current smoking, and claudication displaying association (p < .05) with the risk of expansion to an AAA (Table 1).

In a subsequent multivariable Cox proportional hazards regression analysis, including risk factors with p < .10 in the univariable analysis, the infrarenal aortic diameter at age 65 or a sub-aneurysmal aorta at age 65, and current smoking were the only independent risk factors for expansion to an AAA within 5 years (Table 2).

With a surveillance threshold of 25 mm at the age of 65, 21 of 36 (58.3%, 95% CI: 40.8 to 74.5) individuals developing AAA after 5 years would have been identified. The risk of expanding from an aorta <30 mm to an AAA within 5 years according to infrarenal aortic diameter at age 65 is displayed in Fig. 4.

DISCUSSION
In this first report from an on-going population-based cohort study started in 2006 in the County of Uppsala in Sweden, we report on the fate of a 65-year-old male population 5 years following an invitation to an aortic US examination. High attendance at both primary screening at age 65 and re-screening at age 70, in combination with

<table>
<thead>
<tr>
<th>Aortic diameter/risk factors/medication at age 65 years</th>
<th>Normal aorta at 70 years</th>
<th>Normal aorta at 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2,023</td>
<td>N = 36</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Mean aortic diameter (mm)</td>
<td>18.0 mm (17.9 to 18.1)</td>
<td>24.8 mm (23.6 to 26.0)</td>
</tr>
<tr>
<td>Sub-aneurysmal aorta (25–29 mm)</td>
<td>0.8 (0.4 to 1.2)</td>
<td>58.3 (41.4 to 75.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11.7 (10.3 to 13.1)</td>
<td>41.7 (24.7 to 58.6)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>9.7 (8.4 to 11.0)</td>
<td>19.4 (5.9 to 33.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.2 (34.1 to 38.3)</td>
<td>44.4 (27.4 to 61.5)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>22.3 (20.5 to 24.2)</td>
<td>30.6 (14.7 to 46.4)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>3.9 (3.1 to 4.8)</td>
<td>8.3 (0 to 17.8)</td>
</tr>
<tr>
<td>Claudication</td>
<td>1.1 (0.6 to 1.5)</td>
<td>5.6 (0 to 13.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7.3 (6.1 to 8.4)</td>
<td>5.6 (0 to 13.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10.3 (9.0 to 11.6)</td>
<td>8.3 (0 to 17.8)</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>0.6 (0.3 to 1.0)</td>
<td>0 (0 to 0)</td>
</tr>
<tr>
<td>Treatment with anti-platelet agent or anti-coagulant</td>
<td>17.9 (16.2 to 19.6)</td>
<td>22.2 (8.0 to 36.5)</td>
</tr>
<tr>
<td>Treatment with lipid lowering agent</td>
<td>18.7 (17.0 to 20.4)</td>
<td>22.2 (8.0 to 36.5)</td>
</tr>
</tbody>
</table>

TIAs = transient ischaemic attack.

| Table 2. Cox proportional hazards multivariable regression analysis of risk factors associated with the risk of expanding to an abdominal aortic aneurysm (AAA) within 5 years in men screened normal at 65 years. |
|-------------------------------------------------------|--------------------------|--------------------------|
| Risk factor                                           | HR 95% CI                 | p                        |
| Current smoker                                        | 2.78 (1.38 to 5.57)       | .004 a                    |
| Sub-aneurysmal aorta at 65 years                      | 59.78 (29.87 to 119.63)   | <.0001 a                  |
| Infrarenal aortic diameter at 65 years                | 1.66 (1.53 to 1.82)       | <.0001 a                  |
| Coronary disease                                      | 1.44 (0.58 to 3.57)       | .433                      |
| Claudication                                          | 0.59 (012 to 2.95)        | .525                      |
| HR = hazard ratio.                                    |                           |                           |

a Independent, significant risk factors.
b Diameter-related variables were entered separately one at a time into the model. Values of non-diameter-related hazard ratios are presented from analysis together with variable "Sub-aneurysmal aorta at 65 years".
The clearly dominant risk factor for AAA formation within 5 years was the presence of a sub-aneurysmal aorta at age 65, which increased the risk of AAA formation 60-fold, more than 20 times higher than the increased risk attributed to smoking. In a report by Lederle et al., a cohort of subjects in the American ADAM-study, aged 50–79 years, with extensive risk factor data, cross-linked with registry-based information on AAA repair and mortality, delivers a detailed and reliable coverage of relevant events in the studied cohorts. In the study, four main subgroups of special interest emerge.

Men not attending screening at age 65

In this report, by use of personal identification numbers and cross-referencing the national population registry, the mortality of the non-attenders could be reliably calculated, and was higher (×2.4) than that of the entire cohort, consistent with previous older reports of increased mortality among non-attenders. The non-attenders at 65 were the source of all three opportunistically detected AAA, one having iAAA repair, as well as the only rupture observed in the studied cohort, suggesting effort should be spent on further increasing attendance rates in AAA screening programmes.

Approximately one-third subsequently attended at age 70, and apart from more active smokers this group was similar to the group that attended at both 65 and 70, in risk factor distribution as well as in AAA prevalence.

Men screened normal at age 65 and re-screened at age 70

In general, this group of individuals with <25 mm aortas appears to comprise healthier individuals, suggested by the lower 5-year mortality rate (5.1%, or ×0.7 that of the entire cohort). In a prospective cohort study of 8,146 men aged 65–74 in the Scottish Highlands by Duncan et al. in 2012, a similar mortality of 7.2% was observed for men with <25 mm after a mean 7.4 years. In that study a mortality of 8% was observed for the entire cohort, also similar to our entire cohort’s mortality of 7.5%, although the Scottish cohort was older and had a higher rate of smoking.

Despite a diameter below 25 mm at age 65, 0.7% of the men in our study developed AAA after 5 years. In addition, 2.1% progressed to sub-aneurysmal aortas after 5 years. Displaying small diameters, they pose no relevant threat of rupture at age 70. They are, however, not entirely without risk of developing clinically relevant AAA later in life, as observed in Gloucestershire where 80 (0.16%) of 50,130 65-year-old men screened with <26 mm, either had AAA repair or died of rupture after a median time of 13 years. Likewise, in the Multicentre Aneurysm Screening Study (MASS), late ruptures in men screened <25 mm markedly contributed to diminishing the protective effect of the screening programme after approximately 8 years.

The more benign nature of AAA developed from <25 mm aortas is also supported by Hafez et al. in a comprehensive long-term follow-up of men aged 65–77 screened normal (<30 mm) in Chichester. The mean time from screening to AAA repair or AAA death was 13.2 years in the men with aortas <25 mm as opposed to those with aortas 25–29 mm where the corresponding time was 9.7 years. In that study the rate of de novo AAA formation after approximately 5 years among those screened <30 mm was 2.8%, twice that observed in our study (1.3%), possibly reflecting differences in risk factor profiles.

Men with aortas 25–29 mm (AiFs)

A group with sub-aneurysmal aortas (25–29 mm) consistently displayed a high rate of progression to an AAA in a recently published multicentre observational study. The authors combined data on 1,696 individuals with sub-aneurysmal aortas from eight screening programmes in Europe, and reported that 60% developed AAA within 5 years, and that 8% had AAA of >54 mm after 13 years. This compares with the rate in this report of 53% (21/40) after 5 years of follow-up. No one exceeded 54 mm and no AAA events were observed, so far reaffirming a continued use of our re-scanning interval of no less than 5 years for this group. In this report, the majority (58%) of de novo AAA after 5 years were identified with a surveillance threshold of 25 mm, which indicated re-scanning after 5 years of the men with aortas 25–29 mm at age 65; constituting merely 1.5% (n = 40) of all men examined at age 65. In contrast, to identify the remaining 42% of de novo AAA, all men with diameters of 18–24 mm would need re-examination, constituting an additional 56% (n = 1,535) of all men screened at 65. However, although cost-efficiency of this 25 mm-threshold at first glance would appear reasonable, the unclear balance of increased longevity in elderly versus the observed higher all-cause mortality in this group indicates a need for further long-term study of these cohorts to determine the risk of progressing to clinically relevant AAA disease in a contemporary context. In the absence of firm contemporary data on disease progression for this group in a time of changing epidemiology, it would seem reasonable to include men with aortic diameters of 25 mm or more at the age of 65 in a continued surveillance programme.

<30 mm at initial screening (n = 2,622) were re-screened after 4 years at a mean age of 67.17 In that study, current smoking (OR 3.09) and coronary disease (OR 1.81) were independent risk factors for AAA formation, similar to our findings, although they did not include aortic diameter in the multivariable regression analysis. Other reports have also indicated smoking and initial aortic diameter as important risk factors for aortic expansion.15,18,19 It should be emphasised, however, that the changing epidemiology of AAA disease8,20 makes it important to reinvestigate phenomena of importance for designing AAA screening programmes. As expected, the risk of expanding to an AAA increased proportionally as diameters neared 30 mm (Fig. 4). Our findings are still based on relatively few cases, and other risk factors with impact on expansion may emerge as the cohort study increases in numbers and length of observation.

Men with AAA

The 5-year rate of surgery for screening detected AAA (50%) was higher in this report than what could be estimated for MASS at 5 years (25%),12,21 and in the Danish Viborg AAA screening trial at 4 years (24%). However, circumspection in this comparison is called for, as these studies did not exclusively screen 65-year-old men, but men aged 65—74 with corresponding variations in fitness for surgery. Referencing Fig. 2 in this study, the 5-year rate of surgery for AAA 30—39 mm at detection was 20%, which compares with a 38% 10-year rate for this specific size segment reported in 2012 by Darwood et al., in a 20-year experience from the Gloucestershire screening programme for 65-year-old men. For AAA of 40—54 mm at age 65, this report’s 5-year rate is 83%, exceeding the 10-year rate (66%) observed in Gloucestershire.7 Allowing for relatively few observed AAA in this report’s cohort, this might imply a contemporary higher eligibility for AAA surgery among screened men, associated with an increased use of endovascular aneurysm repair (EVAR) permitting elective surgery in more frail patients, and maybe also overall healthier subjects.22—24 With no ruptures among men with screening detected AAA in addition to no peri-operative mortality despite high rate of surgery, taking part in the first 5 years of the screening programme appeared safe. All deaths, including those occurring after AAA repair, were from non-AAA-related causes in this group. This fact, together with a relative all-cause mortality in this group of 3.3 confirms observations of non-AAA-related causes of death dominating among individuals with AAA.25,26

Malignancy and cardiac disease were the main causes of death among non-attenders and attenders; however, diabetes and neurological degenerative disease was more common among non-attenders. The only observed AAA rupture (died during surgery), as well as two aortic ruptures with unspecified location occurred among non-attenders (Table 3).

A limitation of this study is the fairly small number of cases, making the risk factor analysis for AAA formation prone to type II statistical error. This may explain why numerical differences in coronary disease, hypertension, hyperlipidaemia, and stroke or transient ischaemic attack (TIA) did not reach statistical significance. Nevertheless, smoking and aortic diameter were clearly important risk factors for AAA formation within 5 years. In addition, misclassification of disease as a result of erroneous ultrasound measurement occurred to some extent in this study. Three individuals with sub-aneurysmal aortas and one with an AAA at age 65 were in fact individuals with normal diameters at age 70. Ultrasound has an inherent inaccuracy of a few millimetres,27 and visualisation in some individuals is

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Non-attender at age 65</th>
<th>Aortic diameter &lt;25 mm at age 65</th>
<th>Sub-aneurysmal aorta (25—29 mm)</th>
<th>AAA</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 96</td>
<td>n = 136</td>
<td>n = 2</td>
<td>n = 11</td>
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<td>0</td>
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<td>Malignancy</td>
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<td>2.1</td>
<td>1</td>
<td>0.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

AAA = abdominal aortic aneurysm. (% is proportion of deaths within subgroup.

a In one man, who was electively repaired for AAA without complications in the follow-up period and died after 4 years and 10 months, the cause of death was unknown.
known to be difficult. The level of misclassification was low and acceptable, however, with an estimated positive predictive value of 97.6% of infrarenal US examination at age 65 years. This fact further indicates the need for a safety margin in surveillance, in order not to erroneously exclude individuals with early AAA disease.

CONCLUSION
This population-based cohort study confirms recent findings of a changed epidemiology with lower AAA prevalence at age 65, to be true also at the age of 70. AAA formation was fairly common among men with an aortic diameter below 30 mm, especially among subjects with a sub-aneurysmal (25—29 mm) aorta indicating a possible need for surveillance of this subgroup. A threshold of 25 mm for surveillance identified a majority of individuals later developing AAA. Aortic size at age 65 and smoking were important independent risk factors for AAA formation, although other factors may emerge when this cohort study is expanded in numbers and length of observation. The results of the first 5 years of AAA screening indicate that the programme is safe; with documented AAA rupture occurring only among non-attenders. Furthermore, a high rate of repair of screening detected AAA was observed with no 30-day mortality; however, with a high overall mortality in that subgroup.

CONFLICT OF INTEREST
None.

FUNDING
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