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Original Study

Impact of Short-Term Computerized Cognitive Training on Cognition in Older Adults With and Without Genetic Risk of Alzheimer's Disease: Outcomes From the START Randomized Controlled Trial

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A B S T R A C T

Objectives: To establish the impact of a 3-minute computerized cognitive training program (START) on cognition in older adults with and without genetic risk of Alzheimer's disease.
Design: Two-arm randomized controlled trial of the START program.
Setting and Participants: Remote online trial in adults older than 50 taking part from home.
Methods: The trial compared the START program with placebo in 6544 people older than 50. Primary outcome was executive function measured through Trailmaking B, with other secondary cognitive measures. Genetic risk profile and ApoE4 status were determined by Illumina Array.
Results: START conferred benefit to executive function, attention, memory, and a composite measure, including in people with the ApoE4 genotype.
Conclusions and Implications: The 3-minute START task offers a means of supporting cognitive health in older adults and could be used at scale and within a precision medicine approach to reduce risk of cognitive decline in a targeted way.

Progressive cognitive decline represents a considerable public health issue.[1] The disparity between projected mild cognitive impairment (MCI) prevalence and diagnostic rates indicates that 99% of people with MCI never receive a diagnosis, and do not reach health services until they decline.[2,3] There is a tangible opportunity to intervene early with interventions to reduce dementia risk and promote a wider community-based awareness of the need to protect brain health. The potential impact of a strategy to delay the clinical onset of symptoms, even by a few months, could be extremely significant from a population perspective, would achieve substantial financial saving at a societal level,[4] and complements ongoing work to develop disease-modifying pharmacological therapies for dementia.

A recent Lancet Commission estimated that 40% of population-attributable dementia risk was related to modifiable risk factors.[5] To realize and maximize the impact of preventive strategies in cognitive health, the role of precision medicine is key. In the context of Alzheimer's disease (AD) the best established risk genetic risk factor is the

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ApoE4 gene, which confers 3.5-fold increased risk in heterozygotes and a 10-fold increased risk in homozygotes.[6] Polygenic Risk Scores (PRSs) for AD are also well defined and increasingly straightforward to identify on a large scale,[7] raising the opportunity for precision medicine and targeting of preventive interventions to individuals with specific risk profiles. This approach would also require interventions that are scalable, affordable, and effective to enable rollout across large population groups of at-risk individuals.

One potential opportunity for maintaining cognitive function and preventing progressive cognitive decline, highlighted by the Lancet Commission in 2020, is cognitive training (CT).[5] Trials of CT have reported significant benefit to cognition and function in older adults,[8,9] with meta-analyses indicating an effect size in cognition of 0.16.[10] This magnitude of benefit, if generalizable to overall cognitive performance, would be considerable at a population level. This would rely on delivery through a model involving modest cost and broad reach, which makes an online or app-based CT program particularly suitable. We developed this concept by building a computerized CT intervention that specifically targeted reasoning ability (ReaCT). A large online randomized controlled trial (RCT) in 6742 participants reported significant benefit to reasoning, other aspects of cognition, and instrumental activities of daily living in older adults over 6 months.[11]

This work supports the hypothesis that CT that targets reasoning or executive function may achieve greater generalizable and real-life benefits. However, trials of CT have been hampered by considerable loss of engagement over the longer term. The use of smartphones means that people now engage with apps and devices frequently, but in short bursts of activity. There is therefore a strong rationale for examining the impact of a single-task brief intensive training approach that individuals could use as part of a proactive lifestyle choice to protect their cognition. A shorter program, requiring just 3 minutes per day, would likely improve longer term engagement and could be rapidly adopted into the global CT market. This is particularly pertinent due to the enormous commercial market for CT programs, for example Lumosity alone reports more than 100 million users of their platform.[12] However, few of these programs have any research-based evaluation and do not specifically target executive function.

This study sought to establish whether short-term computerized CT in Verbal Reasoning Training (START), an intensive executive function task, conferred benefit to cognitive performance. Pilot work conducted using data from the online PROTECT-UK study has already indicated cognitive benefits using this task frequently over a short period. This study evaluates this further in a large RCT and examined whether treatment response to the CT program was influenced by ApoE4 genotype and known polygenic risk factors for AD. This represents a high-priority step toward a precision medicine approach to cognitive health. The study hypothesis was that the START intervention would provide significant benefit to cognition, both directly to executive function and transferably to other cognitive domains.

Methods

Study Design

This study was a parallel double-blind online RCT to establish the impact of short-term intensive online Grammatical Reasoning Training (START) on cognition and function in adults older than 50. The study compared an executive function training task with a control treatment. The study was approved by the South West Central Bristol Research Ethics Committee under the UK Health Research Authority (Ref 16/SW/0311). The protocol is registered on the Clinicialtrials.gov database (Ref: NCT03661190).

Participants

Adults older than 50 in the United Kingdom were invited to take part through the UK online aging cohort, PROTECT. This age criterion was selected based on known cognitive trajectories in aging, and ensured adults in the trial were within the target age range for preclinical cognitive changes associated with aging. All participants were already registered on the PROTECT cohort and were invited to the trial by e-mail correspondence as part of the consent for contact in place in the PROTECT cohort. Eligible participants were older than 50, without a diagnosis of dementia, and had access to a computer and the internet. Interested individuals registered and provided consent for the study through an ethically approved digital consent process embedded on the PROTECT website. Participants then accessed the trial by navigating to the START trial area on their online dashboard. Automated emails were scheduled to remind participants to access the CT package and to complete their cognitive assessments.

Treatment Interventions

Participants were randomized to receive either the Verbal Reasoning CT task (START) or a control task for 6 weeks. The START intervention consisted of a Verbal Reasoning cognitive task which challenges individuals to mentally reason the relationships among different shape combinations assigned to grammatical statements (Figure 1). The task took approximately 3 minutes to complete and was completed on a third-party website. The control group completed a basic picture-matching task that was designed to provide the same level of engagement, but without the training effects seen with the START intervention.[10] Participants were encouraged to complete their training once a day during the 6-week period of the trial.

Outcome Measures

Outcome measures were completed at baseline and 6 weeks. Data were collected irrespective of how many CT sessions a participant completed. All outcome measures were completed online through the PROTECT cohort platform.

Primary Outcome Measure

The primary outcome measure was executive function and task-switching as measured by a computerized version of the well-validated Trailmaking B task in which a participant connects an alternating sequence of alphanumeric characters. Total time and accuracy are captured and combined to provide a total score.

Participants were shown 32 images depicting a circle and a square. On each trial the square would either be shown within the outline of the square, or vice versa. Each image was accompanied by text describing the image, which could be either true or false. The difficulty of each image depended on the complexity of the grammatical statement in the text. 16 of the image/statement combinations were simple questions (e.g. 'the circle is bigger than the square', 'the square contains the circle') and 16 were more grammatically complex questions (e.g. 'the circle is not bigger than the square; 'the square does not contain the circle'). Half of each type of trial were true and half were false. Participants responded to the task using keyboard keys.

Fig. 1. Description of the START CT Task.

Secondary Outcome Measures

Secondary cognitive outcomes were measured at baseline and 6 weeks using a wider computerized cognitive test system consisting of 7 cognitive tests described in full in previous papers.[11,13,14] The test system included measures of attention and reaction time (Digit Vigilance, Simple and Choice Reaction Time), spatial working memory (Paired Associate Learning), numerical working memory (Digit Span), and episodic memory (Picture Recognition) delivered through the third-party CogTrack system[15,16] (Table 1). Outputs from these individual tests were combined to create a form of the validated composite cognitive measure, Factors of Longitudinal assessment of Attention, Memory, and Executive Function (FLAME).[17]

Sample Size

The sample size calculation was based on our published study of online CT in adults older than 50 that showed significant benefit to reasoning, memory, and function.[18] Based on an effect size of 0.11, 4826 participants would be required to provide 90% power at a 2-sided 0.01 significance level.

Randomization and Masking

Participants were randomly assigned in equal proportions via computerized simple randomization to receive START or control. This was achieved using a computer-generated randomization sequence to eliminate allocation bias. Participants were blind to which group they were allocated to. The online format enabled complete allocation concealment from investigators and participants.

DNA Sampling and Analysis

Saliva samples were collected by post and DNA extracted by the National Institute for Health Research South London and the Maudsley National Health Service Biomedical Research Centre. Genotyping was performed using the Illumina Global Screening Array with custom content (including directly genotyped single nucleotide polymorphisms [SNPs], rs429358 and rs7412, to determine *APOE* status).

Standard genotype quality control (QC) steps were followed before *APOE* genotypes were determined. A detailed description of genotyping, QC, and imputation is provided in a previous publication.[19] Individual-level QC steps included call-rate (98%) filtering, relatedness, excess heterozygosity, and gender mismatch. Individuals not of European ancestry were excluded. Variant-level QC included call-rate (98%) and Hardy-Weinberg deviation ($P < .00001$). Genotypes were imputed to the 1000 Genomes European reference panel using the Michigan imputation server and genotype phasing using Eagle. Variants were restricted to SNPs only, with a minor allele frequency (MAF) > 0.001. An absolute cutoff of 0.7 was applied to the imputation quality of variants (R^2 as reported by the Michigan imputation server). The number of variants remaining after QC was 9,415,055. *APOE* genotype was determined from SNPs rs429358 and rs7412, which were genotyped directly on the Global Screening Array (GSA) array.

Table 1
Description of Secondary Cognitive Tests (CogTrack)

Cognitive Test Name	Cognitive Domain	Description
Digit Vigilance	Reaction time/ Attention	The participant is instructed to monitor a rapidly appearing series of digits presented one at a time in the center of the screen. At the start of the task the "target" digit is presented on the right-hand side of the screen and remains there throughout. The subject is instructed to press the RIGHT arrow keyboard key as quickly as possible every time a target digit appears in the series of digits, even if the target digit is no longer displayed. The digits are presented in an unpredictable order at the rate of 150 per minute, and there are 15 targets every minute. The task records the number of correct detections (hits), the speed of these correct detections, and all responses made in error (false alarms).
Simple Reaction Time	Reaction time	An arrow pointing to the RIGHT (with YES inside) is presented in the center of the screen at brief but unpredictable intervals. The participant is instructed to place the right forefinger lightly on the RIGHT arrow key on the keyboard and to press the key as quickly as possible to the occurrence of the stimulus. Each stimulus remains on the screen until the RIGHT arrow is presented. A fixed number of stimuli is used with randomly varying intervals between 1 and 3.5 seconds. The task takes approximately 2 minutes to complete.
Choice Reaction Time	Reaction time/ Attention	The task similar to Simple Reaction Time with the exception that each stimulus can be either an arrow pointing to the RIGHT (with YES inside) or an arrow pointing to the LEFT (with NO inside). The participant is asked to place the left forefinger on the left arrow keyboard key and the right forefinger on the right arrow keyboard key. The participant is instructed to press the appropriate key as quickly and accurately as possible. A fixed number of stimuli is used with randomly varying intervals between 1 and 3.5 seconds. The task records the number and the speed of correct responses and lasts approximately 2 minutes.
Paired Associate Learning	Spatial working memory	Participants are shown objects, one per "window" in a grid. Then they see the series of objects, one at a time in a random order, and select the correct "window" where the object had previously appeared. This version uses a ratchet-style approach, each successful trial is followed by one with more objects to recall and each unsuccessful trial is followed by the same number of objects as in the unsuccessful attempt. The outcome measure is the average number of correct object-place associations ("paired associates") in the trials that were successfully completed. Participants are allowed 3 errors before the test terminates.
Digit Span	Numerical working memory	A series of numbers is shown to the participant who then enters the numbers in the same sequence as they appeared using a number keypad. The test uses a ratchet-style approach in which each successful trial is followed by a new sequence that is one digit longer than the last and each unsuccessful trial is followed by a new sequence that has the same number of digits as the unsuccessful trial. This allows an accurate estimate of digit span to be made quickly. The outcome measure is the average number of digits in all successfully completed trials. Participants are allowed 3 errors before the test terminates.
Delayed Picture Recognition	Episodic memory	A series of 20 pictures of everyday scenes and objects is presented on the screen at the rate of 1 every 3 seconds. The participant is instructed to pay close attention to the detail of each picture. There are no responses for this part of the task. Then, after the 3 attention tests have been performed (approximately 7 minutes later) the 20 original pictures are presented mixed with the 20 similar pictures. Each picture has a closely similar paired picture, and the participant is instructed to press the RIGHT arrow keyboard key whenever an original picture is presented, or the LEFT arrow keyboard key if it is a different one. The accuracy of responses is recorded, as is the speed of all appropriate responses. The 2 parts of the task together take approximately 4 minutes.

Table 2
Cohort Characteristics for the START Trial

Characteristic	START Group, n = 3279	Control Group, n = 3265
Age	62.4 (7.23)	62.5 (7.08)
Mean (SD)		
Sex n (%)		
Male	662 (20)	664 (20)
Female	2617 (80)	2601 (80)
Educational attainment		
Mean (SD)	3.28 (1.40)	3.23 (1.36)

Data Analysis

The association between cognitive profiles and intervention was assessed through a linear model of cognition score change from baseline and intervention status, with baseline, sex, and age (as linear variable) as covariates. The fitted model was used to calculate the differences between the estimated marginal means of the cognition scores corresponding to the intervention groups. In addition to reporting the individual cognitive scores, the intervention effects were also calculated on the FLAME composite score, derived from the published composite model described elsewhere.[17] The R package emmeans was used for the analysis. Results are reported as Cohen's D effect sizes with corresponding 95% confidence intervals and associated *P* values.

To examine the association of genetic risk factors on intervention response ApoE4 genotype (including heterozygotes and homozygotes) and PRS scores were examined for the linear correlation with cognitive scores as described in detail elsewhere.[20] Here, the top 6 principal components of relatedness were added as covariates in addition to sex and age. As a positive control, the AD PRS was also compared with baseline scores to confirm correlation. Results are reported as slope, slope standard error of the mean (SEM), and associated *P* value.

Results

Cohort Characteristics

A total of 6544 participants were consented to the study, of whom 79% were female, with an average age of 62 (SD 7.1); 3279 participants were randomized to the START intervention group and 3265 were randomized to the control group. There were no significant differences between characteristics of the 2 groups. The baseline characteristics of the study participants are described in Table 2 and flow of participants through the study is presented in Figure 2. Genotype data (Illumina GSA) were available for 617 study participants. The trial ended after the last follow-up assessment of the last participant was completed.

Impact of START on Cognitive Outcomes

Analysis showed significant benefits to cognition in the START intervention group compared to the control group at 6 weeks. In the primary outcome of executive function measured by the Trailmaking task the ReaCT intervention conferred significant benefit compared with the control task with a Cohen's D Effect Size (ES) of 0.23 ($P <$ .000).

In the secondary outcome measures the treatment group also showed significantly better performance compared with the control group in numerical working memory (ES0.14, $P <$ .000), spatial working memory (ES0.10, $P =$ .0043), attention (ES0.10, $P =$ .0052) and episodic memory (ES0.12, $P <$ .000). The difference between groups was also significant in the FLAME composite measure (ES 0.09, $P =$ .0097). Full cognitive outcomes are described in Table 3.

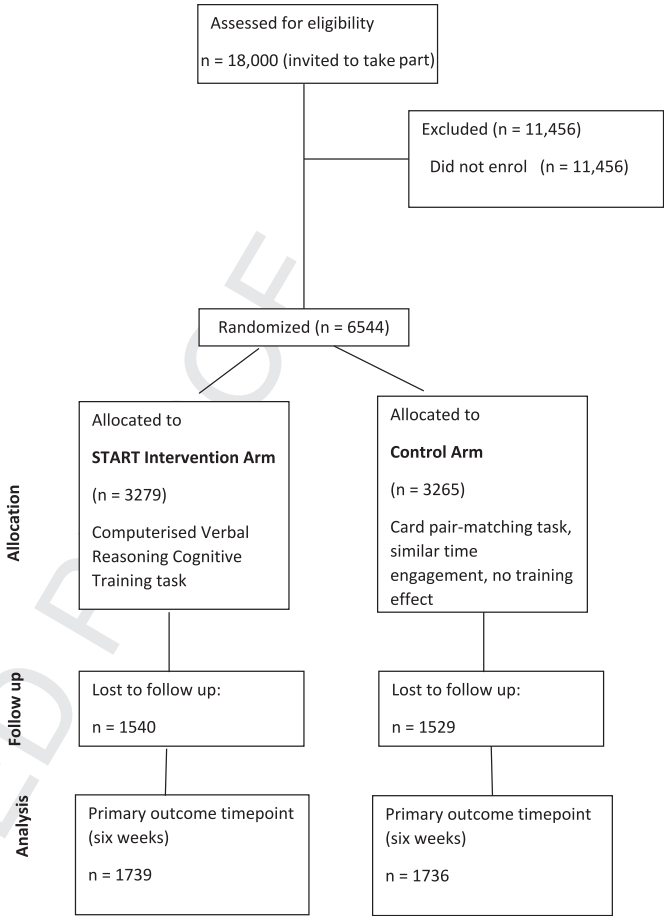

Fig. 2. CONSORT chart showing flow of participants through the START trial.

Impact of the START Intervention on Cognition in People With the ApoE4 Genotype

A subgroup analysis was conducted in people with the heterozygotic and homozygotic ApoE4 genotype with more limited power to detect change. The START intervention conferred significant benefit to the cognitive composite measure with larger effect sizes than the whole cohort (ES 0.17, $P =$ .035) (Table 3). There was also significant benefit to executive function as measured by the Trailmaking task (ES 0.24, $P <$ .004), attention measured by the Choice Reaction Time task (ES 0.22, $P =$ .0076) and episodic memory measured by the Picture Recognition task (ES0.22, $P =$ .0064) although benefit was not seen in measures of numerical and spatial working memory.

Impact of AD PRS on Treatment Response

The positive control analysis showed significant inverse association between the AD PRS and cognitive performance on the cognitive composite score, reaction time, and numerical working memory (Table 4). Analysis of cognitive change in the START treatment group showed an enhanced treatment effect on spatial working memory (B 0.043, SEM 0.020, $P =$ .031) in people with the AD PRS, and no worsening of effects in any other cognitive domain.

Discussion

This study reports the findings from a large-scale online RCT of a computerized Grammatical Reasoning CT task in older adults. The

Table 3
Impact of the START Intervention on Executive Function (Primary Outcome) and Cognition (Secondary Outcomes) at 6 Weeks in the Whole Cohort and People With the ApoE4 Genotype

Cognitive Outcome Measure	Cognitive Domain	Cohen's D Effect Size (CI)	*P*	Cohen's D Effect Size (CI)	*P*
		Whole Cohort, n = 3475		ApoE4, n = 617	
Trailmaking	Executive function	0.23 (0.30–0.16)	<.0001	0.24 (0.41, −0.078)	.004
Digit Span	Numerical working memory	−0.14 (−0.07, −0.20)	<.0001	0.10 (−0.06, −0.25)	.24
Paired Associate Learning	Spatial working memory	0.10 (0.16–0.03)	.0043	0.02 (0.14, −0.18)	.82
Choice Reaction Time	Attention	−0.10 (−0.02, −0.16)	.0052	0.22 (−0.06, −0.38)	.0076
Delayed Picture Recognition	Episodic memory	−0.12 (−0.05, −0.18)	<.0001	0.22 (−0.06, −0.38)	.0064
FLAME composite		0.09 (0.15–0.02)	.0097	0.17 (0.33–0.01)	.035

results show a clear benefit conferred by the intervention on executive function, working memory, episodic memory, and attention, as well as a composite cognitive measure after 6 weeks' use of the training task. The magnitude of this benefit is comparable with that seen with in-person CT programs.[8] Combined with the accessibility of the online format, this raises the potential for large-scale app-based rollout of START as an effective public brain health intervention. Importantly, the brevity and accessibility of this 3-minute task highlights its potential for widespread adoptability and uptake on a large scale in the context of the increasingly widespread pattern of short, intensive device use behavior. Furthermore, the program begins to suggest enhanced effectiveness in people with the ApoE4 risk genotype, potentially raising the opportunity for precision medicine approaches in this group of high-risk individuals within a public brain health initiative.

The improvements to executive function align to the cognitive domain that the START Grammatical Reasoning task is designed to train, so in part this outcome likely reflects a direct cognitive benefit from the CT, generalized to a substantially different executive function test. The START task also elicited improvements in working memory, episodic memory, and attention, demonstrating a global impact on key cognitive domains. It also translated to significant improvements in an established composite cognitive measure that has been shown to be sensitive to cognitive decline and trajectory.[17] These findings align with our previous work including the large-scale trial of the multi-game ReaCT program that demonstrated similar transferable cognitive benefits in the treatment group over a 6-week period. We also demonstrated transferable benefits to function, measured through the instrumental activities of daily living scale, after 6 months.[18] Although it is possible that similar transferable benefit would be seen with the START intervention but a longer period of follow-up would be needed to evaluate this.

This builds on the evidence base that shows generalizability of benefit from CT and shows that this benefit can be achieved even when using a single focused 3-minute task. Users increasingly engage with devices such as smartphones in short, sharp bursts, with frequent distractions and rapid switching between tasks. A 3-minute task offers the means to embed a healthy lifestyle intervention into this time-poor behavior, and therefore has the potential to retain users in the long term, particularly if presented in an engaging front-end design with well-considered engagement mechanisms to encourage regular use.

Table 4
Association of Outcomes in the START Treatment Group With Alzheimer's PRS at Baseline and in Comparison With Change at 6 Weeks

Timepoint	Outcome Measure	ß	SEM	*P* Value
Baseline	FLAME composite	−0.059	0.023	.009
	Reaction time	0.049	0.023	.034
	Numerical working memory	0.049	0.022	.026
Six weeks	Spatial working memory	0.043	0.020	.0031

The effect sizes reported in this study are modest compared with RCTs of clinical interventions but highly impactful in the context of a public health intervention.[21] This is particularly important for mental health and psychological impacts where a small shift in performance translates to a large change in prognosis or trajectory.[22] In this context, the effect size of 0.23 achieved in this study indicates the potential for significant population-level benefits.

A key objective of the study was to evaluate whether there was any difference in treatment response in individuals with different levels of genetic risk for AD, as a means of exploring the potential for a precision medicine approach to CT use. In the subgroup of people with the ApoE4 genotype, the START intervention conferred significant benefit to all cognitive domains except working memory, with effect sizes comparable to or numerically larger than the overall cohort. Risk reduction measures for AD will likely be most effective when targeted to known at-risk groups, and these findings indicate that use of CT by individuals with ApoE4, who represent the largest nonmodifiable risk group for AD, elicits equal, if not greater, benefit compared with non-ApoE4 carriers. This raises the possibility of applying CT as a targeted precision medicine intervention in at-risk groups alongside a broader population-level rollout.

Analysis of the PRS data suggests an enhanced treatment response in people with a higher AD PRS in spatial working memory, and no difference in impact on any other domain despite the unfavorable genetic profile. The PRS score incorporates ApoE4 but builds on the ApoE4 subgroup analysis by enabling an evaluation that examines genetic risk across the full cohort, confirming an equivalent or improved response to CT in higher risk individuals.

This study has provided robust outcomes from a large clinical trial; however, some limitations must be acknowledged. The study recruited from a self-selected cohort, the PROTECT-UK study, with a demographic range that equates to higher educational attainment, lower ethnic diversity, and higher proportion of women than the overall UK population and so caution should be taken when applying generalized interpretations across a more diverse population. The study also reported 50% attrition at 6 weeks, which is consistent with other digital studies and similar across treatment groups. This highlights the importance of implementing further enhancements to improve engagement with online training interventions in this population group to achieve effective large-scale rollout.

Conclusions and Implications

Overall, this RCT demonstrates the benefit of a 3-minute intense executive training task for executive function and other key elements of cognition, with a suggestion of potentially enhanced benefits in people with at-risk genotypes. This highlights opportunities for public brain health interventions.

Disclosure

C.B. has received consulting fees from Acadia pharmaceutical company, AARP, Addex pharmaceutical company, Eli Lily, Enterin pharmaceutical company, GWPharm, H.Lundbeck pharmaceutical company, Novartis pharmaceutical company, Janssen Pharmaceuticals, Johnson and Johnson pharmaceuticals, Novo Nordisk pharmaceutical company, Orion Corp pharmaceutical company, Otsuka America Pharm Inc, Sunovion Pharm. Inc, Suven pharmaceutical company, Roche pharmaceutical company, Biogen pharmaceutical company, Synexus clinical research organization, and tauX pharmaceutical company; and research funding from Synexus clinical research organization, Roche pharmaceutical company, Novo Nordisk pharmaceutical company and Novartis pharmaceutical company. A.C. discloses financial relationships with Suven and Janssen pharmaceutical companies for consultancy work. H.B. discloses employment by CogTrack. G.W., A.P., B.C., and A.H. report no financial relationships with commercial interests.

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