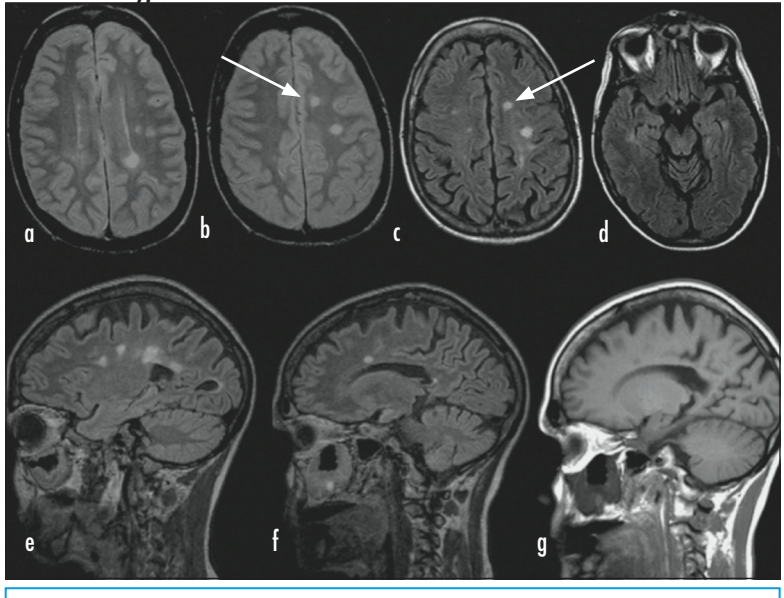
Negotiating the radiologically isolated syndrome

Multiple sclerosis, always challenging, hands down a particular gauntlet with the concept of the radiologically isolated syndrome. This article discusses what it is, recent developments in the field and how these patients should be managed.

The radiologically isolated syndrome was first formally described in 2009 (Okuda et al, 2009) to characterize a growing number of individuals who presented with brain magnetic resonance imaging (MRI) findings similar to those observed in patients with multiple sclerosis but who clinically had no suspicion of having multiple sclerosis (*Figure 1*). This is distinct from those who had experienced a first episode of inflammatory demyelination (e.g. optic neuritis), now termed the clinically isolated syndrome. Since its description, several cohort studies have been published suggesting that individuals with radiologically isolated syndrome are at a high risk (around 30% in 2–5 years) of developing multiple sclerosis (Okuda et al, 2009, 2014; Lebrun et al, 2009, 2012). It is because of this, and the rising use of brain MRI, that radiologically isolated syndrome has become an area of interest to doctors in many specialities, as this article now describes.

Figure 1. a and b. Initial images of a 46-year-old patient who presented with headache and was then followed for an incidental meningioma. She was asymptomatic and had suffered no previous events. c–g. Magnetic resonance imaging appearances 9 years later, with evolution of lesions, but again without any symptoms. Arrows indicate sites of white matter hyperintensities.



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Case presentation

A 50-year-old woman comes to your clinic with ongoing severe headache. She has no additional neurological symptoms and a normal examination. She reports having a cousin with possible multiple sclerosis. You arrange an MRI scan of the brain, and a few weeks later receive this report (hopefully delivered to you initially rather than directly copied to the patient): 'Multiple white matter hyperintensities consider multiple sclerosis.' How best to proceed? Does she have multiple sclerosis?

Examining the 'isolated' in radiologically isolated syndrome

The term 'radiologically isolated syndrome' is arguably a misnomer since presentation is commonly detected as a result of a routine investigation for a presenting symptom not attributable to multiple sclerosis. A systematic review of several cohorts of patients with radiologically isolated syndrome confirmed that headache is overwhelmingly the most common presenting complaint in about half the cases (Granberg et al, 2013b).

Whether standard headache can be considered an early manifestation of multiple sclerosis is currently debated. While an association with migraine has been observed in a meta-analysis (Pakpoor et al, 2012) and stabbing type headache has been associated with development of multiple sclerosis relapse in one review (Klein et al, 2013), this finding was not observed by Putzki et al (2009). Coupled with the generally held acceptance that headache is not demyelinating in aetiology has meant that it is not widely considered a cardinal feature of multiple sclerosis.

The MRI fingerprint of multiple sclerosis – ovoid white matter hyperintensities (see arrows on *Figure 1*) – is found frequently in headache patients. A 2013 retrospective cohort study of 326 American patients aged 10–55 years, who presented with headache, found that around half had evidence of at least one white matter hyperintensity while 2% could be categorized as having radiologically isolated syndrome according to the Okuda criteria (*Table 1*) (Liu et al, 2013). This may suggest that

there is an overrepresentation of headache among individuals with radiologically isolated syndrome.

A second more recently appreciated feature of radiologically isolated syndrome is an association with cognitive impairment. Decline of mental function is thought to be present in 43–70% of individuals with multiple sclerosis and has been recognized as a common finding among patients with radiologically isolated syndrome, often going undetected by patients and relatives (Lebrun et al, 2010). In one small French study, 62% of patients with radiologically isolated syndrome were found to have impaired cognitive functioning in at least one domain (Lebrun et al, 2010) and significant decline predicts conversion from clinically isolated syndrome to multiple sclerosis (Zipoli et al, 2010).

Common or uncommon?

The prevalence of radiologically isolated syndrome is still being illuminated. Since the 1960s there have been several pathological studies investigating multiple sclerosis-type brain lesions found incidentally at autopsy. These have put the prevalence rate at between 0.08 and 0.3% (Georgi, 1961; Engell, 1989; Gilbert and Sadler, 1983; Johannsen et al, 1996). As the data were collected retrospectively through case notes, it is possible that these figures may be subject to inflation through missed presentations. However, a similar prevalence rate (in terms of orders of magnitude) has also been found in large cohorts reporting incidental MRI findings (Morris et al, 2009; Wasay et al, 2011).

It is reasonable to assume that rates of occurrence of radiologically isolated syndrome fluctuate regionally in a manner akin to multiple sclerosis and clinically isolated syndrome. However, prevalence rates of radiologically isolated syndrome are profoundly influenced by both the criteria used for diagnosis and the field power of the MRI system used (Liu et al, 2013; Gabelic et al, 2014).

A recent study from a neurological outpatients clinic in New York used 3T MRI as opposed to 1.5T to discern if there was a significant difference in the prevalence of radiologically isolated syndrome in 82 healthy relatives of patients with multiple sclerosis matched against 150 healthy controls (Gabelic et al, 2014). Healthy relatives had lesions meeting the Okuda criteria in 2.9% of cases, a proportion which echoed the findings of a previous study from Sardinia (de Stefano et al, 2006). However, 2.4% of the healthy controls also met the criteria, around a 30–40-fold increase in the prevalence reported by a large meta-analysis of over 15 000 individuals as well as several other studies which used 1.5 T MRI or less (Morris et al, 2009; Wasay et al, 2011; Granberg et al, 2013a). This figure was even higher (3.7%) when alternative (Swanton) diagnostic criteria were used. It has been postulated that the trial's recruitment of volunteers working at the clinic rather than the general population could be responsible for the greatly increased prevalence of radiologically isolated syndrome seen in the healthy controls (Granberg et al, 2013b). However, it is much more probable that the higher field power of the diagnostic imaging was responsible for the inflated findings. As the field strength of mainstream MRI scanners moves from 1.5T to 3T (and perhaps 7T in the not too distant future), it is likely that this may be paralleled by an increased number of patients meeting the diagnostic criteria for radiologically isolated syndrome.

There is also a growing importance of having agreed standards for standardized criteria. The Okuda Criteria A for radiologically isolated syndrome (*Table 1*) states that a diagnosis may be considered in cases where the MRI shows evidence of ovoid, well-circumscribed lesions which are >3 mm and fulfil three out of four Barkhof–Tintore criteria (*Table 2*) (Okuda et al, 2009). In applying the Barkhof–Tintore criteria to MRI performed on a small cohort of headache patients, there was a three-fold increase in the number of reported cases when the definition of 'periventricular lesions' was extended to included white matter hyperintensities within 3 mm of the ventricles rather than just directly touching the ventricles (Liu et al, 2013).

As MRI becomes more sensitive, more precise diagnostic criteria will be required to adequately distinguish between non-significant proliferations of white matter intensities on MRI and those which may evolve into mul-

Table 1. Definition of radiologically isolated syndrome

The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria	1. Ovid, well-circumscribed and homogeneous foci with or without involvement of the corpus callosum
	2. T2 hyperintensities measuring >3 mm and fulfilling Barkhof criteria (at least three out of four) for dissemination in space
	3. CNS white matter anomalies not consistent with a vascular pattern
No historical accounts of remitting clinical symptoms consistent with neurological dysfunction	
The MRI anomalies do not account for clinically apparent impairments in social, occupational or generalized areas of functioning	
The MRI anomalies are not the result of the direct physiological effects of substances (recreational drug abuse, toxic exposure) or a medical condition	
Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum	

MRI = magnetic resonance imaging. From Okuda et al (2009)

Table 2. Barkhof–Tintore criteria – these have the greatest accuracy in predicting clinically definite multiple sclerosis in three or more positive parameters

At least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium-enhancing lesion
At least one or more infratentorial lesion
At least one or more juxtacortical lesion
At least three or more periventricular lesions

tiple sclerosis. At present this may come in two forms: first by adding further layers of specificity to radiological markers and second through potentially characterizing lesions according to their metabolic state. In an example of the former, de Stefano and colleagues (2011) characterized white matter lesions in patients with radiologically isolated syndrome and multiple sclerosis using quantitative MRI metrics such as brain volume and magnetization transfer, a non-specific indicator of tissue integrity. When compared with healthy controls, patients with radiologically isolated syndrome have significantly lower total brain volume than controls ($P<0.0001$) and a distinctly higher magnetization transfer ratio when directed towards brain lesions. This research needs to be extended to individuals who report white matter hyperintensity but do not meet the criteria for radiologically isolated syndrome but it provides evidence of magnetization transfer as an excellent diagnostic tool (de Stefano et al, 2011).

Using a second approach, an Italian study has used proton magnetic resonance spectroscopic imaging to quantify the ratio of N-acetyl-aspartate to creatinine in patients with radiologically isolated syndrome (Stromillo et al, 2013). N-acetyl-aspartate is a putative marker for neuroaxonal integrity and a diminished ratio is observed in white matter lesions seen in multiple sclerosis. Among 23 individuals with radiologically isolated syndrome, intralesional N-acetyl-aspartate:creatinine ratios were significantly depressed compared to health controls. Fascinatingly, patients with radiologically isolated syndrome also showed a profound global deficit (lesional or perilesional, normal-appearing white matter and cortical grey matter) in N-acetyl-aspartate:creatinine ($P<0.005$). This was on a comparable level to multiple sclerosis, which may point to a more widespread process of neuroaxonal damage than previously observed (Okuda and Vrenken, 2013).

Weighing up the multiple sclerosis risk

In light of our evolving understanding of radiologically isolated syndrome and the widening diagnostic net, risk stratification of individuals is essential to aid decisions about intensity of follow up, guide patient counselling and develop potential treatment options in the future.

Prospective cohort studies of patients with radiologically isolated syndrome are still relatively immature. However, several studies have put the overall risk of conversion to clinically isolated syndrome or multiple sclerosis at around 30% at 2–5 years, with two thirds showing radiological progression (Lebrun et al, 2009; Okuda et al, 2014). Nevertheless, rates of conversion vary widely in respect to specific parameters.

The Radiologically Isolated Syndrome Consortium (RISC) has recently published the largest clinical study to date (Okuda et al, 2014). In a group of 451 subjects from 21 cohorts, age 11–74 years, mean follow-up time 4.4 years, multivariate analysis found three parameters to be significantly associated with risk first clinical presentation:

1. Cervical or thoracic spinal cord lesions
2. Male sex
3. Age less than 37 years.

Existence of one, two or three risk factors conferred approximately a 10%, 50% and >80% risk of progression at 5 years respectively (Kaplan–Meier curve, *Figure 2*). Younger age (Okuda et al, 2009) and spinal lesions (Okuda et al, 2009, 2011; Maia et al, 2012) have both been shown to be predictive in previous studies. However, oligoclonal bands or pathological immunoglobulin G (IgG) index on CSF and infratentorial lesions were not predictive of progression, contrary to previous findings (Lebrun et al, 2009; Okuda et al, 2009).

In addition to these, several other factors from other studies confer risk of progression:

4. Pathological visual evoked potentials (Lebrun et al, 2009)
5. Pregnancy (Lebrun et al, 2012)
6. Lesion load (Maia et al, 2012).

It is worth mentioning that the RISC did not show familial history to be a significant marker for risk progression once multivariate analysis was performed, although a theoretical overrepresentation of relatives of patients with multiple sclerosis is conceivable, since a family history of multiple sclerosis may provoke investigation. However, as the prevalence of individuals with first-degree relatives with multiple sclerosis was 10% in the study (Okuda et al, 2014) it is unlikely to be solely the result of selection bias.

What to do next?

Management of radiologically isolated syndrome is delicate and should be carefully deliberated. The syndrome must be considered a diagnosis of exclusion rather than a default. The first and most important step is to reassess the patient with full history and examination to rule out undisclosed pathology. Excluding differentials such as age-related vascular changes, infection and other inflammatory (e.g. sarcoid) and vasculitic processes is mandatory, through the normal channels (*Table 3*). In conjunction, treatment of the presenting complaint should clearly be the priority. A detailed discussion with a neuroradiologist is essential. If radiologically isolated syndrome is still suspected, further neurological investigation or referral is appropriate, particularly cervical and thoracic MRI. Cognitive examination, e.g. the Brief International Cognitive Assessment for multiple sclerosis test which takes around 15–20 minutes to complete, is an excellent indicator of cognitive decline in multiple sclerosis (Benedict et al, 2012).

Similarly, CSF examination is useful both to rule out other disease and to look for unmatched oligoclonal bands or raised IgG index present in around two thirds of individuals with radiologically isolated syndrome. However, its use as a predictor of progression is unclear as stated above (Lebrun et al, 2009).

After that, the crux decision surrounding radiologically isolated syndrome is either 'wait and see' or 'follow' as

enunciated by Sellner et al (2010). 'Wait' entails no formal ongoing investigation but an appropriate discussion about the possible future risk of clinically isolated syndrome or multiple sclerosis. Clear dialogue with patients is vital (Chataway, 2010).

'Follow' involves a scheduled MRI at 6 and 24 months with further investigations and the possibility of treatment should the patient develop further MRI lesions – dissemination in time. *Figure 3* shows an adaptation of the Sellner algorithm. Considering the age, gender and radiological findings of the test patient mentioned earlier it would seem reasonable for her to be placed in the 'wait' category should she have a normal cervical and thoracic MRI.

Pre-emptive treatment with disease-modifying therapies such as interferon-β or the new oral agents is, at present, controversial. In favour of treatment are:

1. The favourable outcomes seen in relapsing remitting multiple sclerosis and clinically isolated syndrome with early use of disease-modifying therapies
2. The increasing awareness that (on a metabolic level at least) the brain is globally affected in radiologically isolated syndrome
3. The high rate of progression seen in certain patient subsets.

Although not common in the UK, off-label use of disease-modifying therapies in patients with radiologically isolated syndrome is occasionally seen; this was as many as 17% of individuals in the multinational RISC study (Okuda et al, 2014).

It is certainly plausible that in the future we may see routine treatment of a select subset of patients with radiologically isolated syndrome, but this will require wider prospective, randomized data analysis.

Table 3. Diagnostic tests to rule out alternative causes of white matter hyperintensities

Chest X-ray
Inflammatory markers (e.g. C-reactive protein, erythrocyte sedimentation rate)
Autoimmune screen
Hepatitis serology
HIV serology
Serum angiotensin-converting enzyme level
CSF sample
Carotid doppler

Figure 2. Kaplan–Meier survival analysis in n=451 patients with radiologically isolated syndrome with the end point of time to a first clinical event by (a) the presence of spinal cord lesions, (b) age at first magnetic resonance image demonstrating anomalies suggestive of demyelinating disease, (c) sex and (d) stratified based on presence of no, one, two or three risk factors. From Okuda et al (2014).

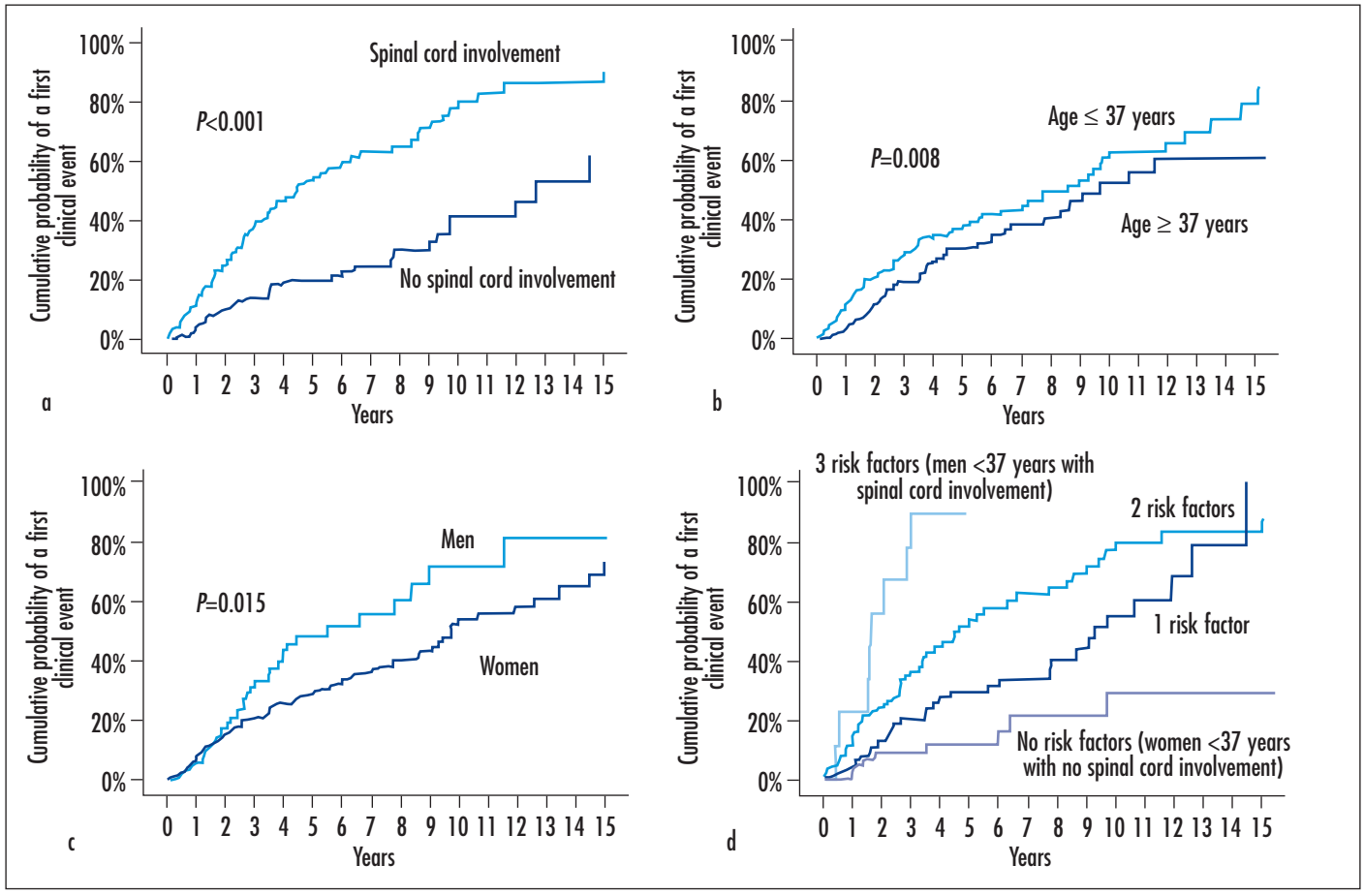
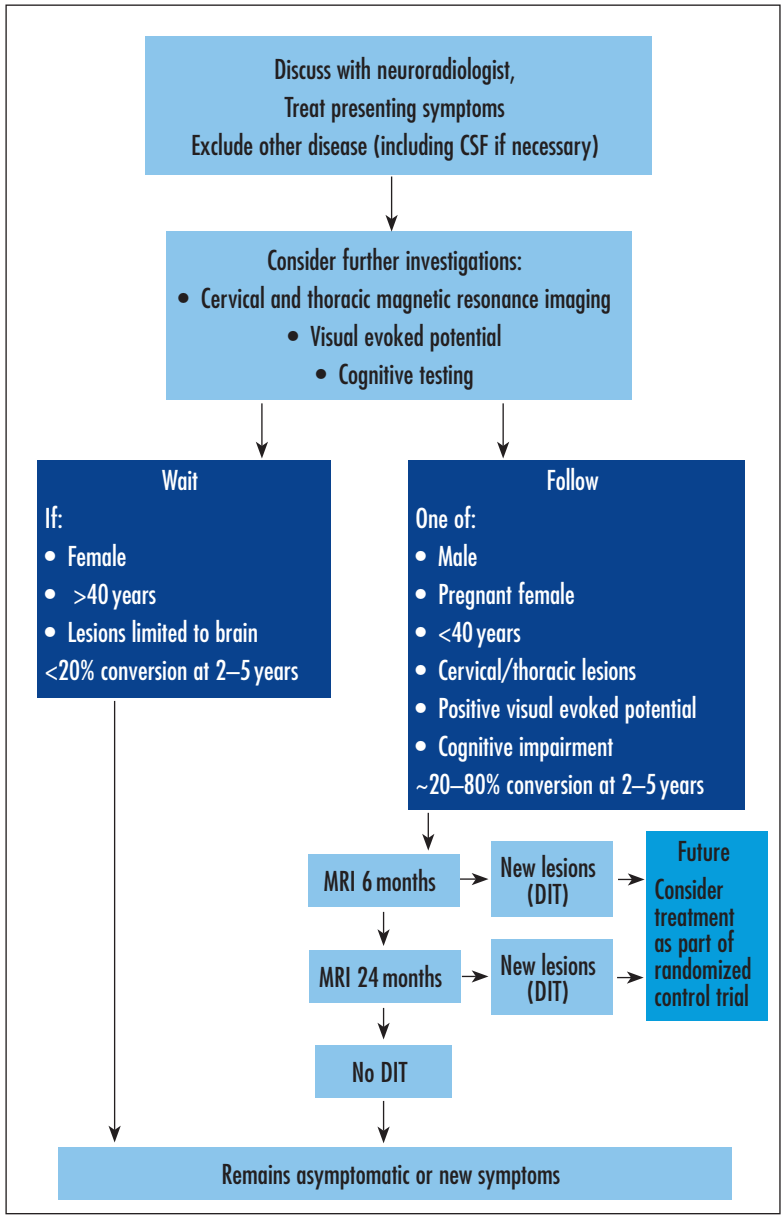


Figure 3. Suggested management algorithm in cases with no neuro-inflammatory (multiple sclerosis) disturbance but magnetic resonance imaging (MRI) positive (modified from Sellner et al, 2010). DIT = dissemination in time.



KEY POINTS

- Exclude other disease and treat the presenting symptoms, e.g. headache.
- Discuss magnetic resonance imaging results with a neuroradiologist.
- The risk of progression to multiple sclerosis should be discussed with the patient.
- Consider visual evoked potentials and cervical or thoracic magnetic resonance imaging to help with decisions regarding intensity of follow up.
- Cognitive testing is a useful adjunct to diagnosis and may unmask previously undetected deficits.
- Further discussion on the basis of perceived risk of progression and patient preference.
- Management with disease-modifying therapies is not recommended for any group at present but this may change in the future.

Conclusions

The radiological isolated syndrome is an evolving and difficult area. With the rapid increase in the use and field power of MRI, the incidence of radiologically isolated syndrome will continue to rise. Improved diagnostic criteria, prospective studies and novel investigation techniques are needed to help stratify the risk of progression to clinical manifestation, inform management strategies and minimize improperly classified subjects. This will increase the clarity of management to both clinician and patient alike. However, as always, the priority is to treat the presenting symptom. **BJHM**

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Conflict of interest: none.

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