The Canadian Journal of Neurological Sciences (2024), 1–6
doi:10.1017/cjn.2024.312

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Analysis of Clinical Utility of Functional MRI in Neurosurgical Decision-Making in Focal Epilepsy

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ABSTRACT: ***Background:*** Functional MRI (fMRI) has proven valuable in presurgical planning for people with brain tumors. However, it is underutilized for patients with epilepsy, likely due to less data on its added clinical value in this population. We reviewed clinical fMRI referrals at the QEII Health Sciences Center (Halifax, Nova Scotia) to determine the impact of fMRI on surgical planning for patients with epilepsy. We focused on reasons for fMRI referrals, findings and clinical decisions based on fMRI findings, as well as postoperative cognitive outcomes. ***Methods:*** We conducted a retrospective chart review of patients who underwent fMRI between June 2015 and March 2021. ***Results:*** Language lateralization represented the primary indication for fMRI (100%), with 7.7% of patients also referred for motor and sensory mapping. Language dominance on the side of resection was observed in 12.8% of patients; in 20.5%, activation was adjacent to the proposed resection site. In 18% of patients, fMRI provided an indication for further invasive testing due to the risk of significant cognitive morbidity (e.g., anterograde amnesia). Further invasive testing was avoided based on fMRI findings in 69.2% of patients. Cognitive outcomes based on combined neuropsychological findings and fMRI-determined language dominance were variable. ***Conclusion:*** fMRI in epilepsy was most often required to identify hemispheric language dominance. Although fMRI-determined language dominance was not directly predictive of cognitive outcomes, it helped identify patients at low risk of catastrophic cognitive morbidity and those at high risk who required additional invasive testing.

RÉSUMÉ : Analyse de l'utilité clinique de l'IRM fonctionnelle dans les cas d'épilepsie focale en ce qui concerne les prises de décision relatives à la neurochirurgie. ***Contexte :*** L'imagerie par résonance magnétique fonctionnelle (IRMf) se révèle particulièrement utile en phase préopératoire chez les personnes souffrant d'une tumeur cérébrale. Toutefois, cette technique est sous-utilisée chez les patients atteints d'épilepsie, probablement en raison d'une collecte moindre de données sur la valeur clinique ajoutée de l'examen dans cette population. Aussi avons-nous procédé à une analyse clinique des demandes d'IRMf au QEII Health Sciences Center (Halifax, Nouvelle-Écosse) dans le but de déterminer l'incidence de cet examen sur la planification chirurgicale dans les cas d'épilepsie. Ont été retenus les motifs des demandes d'IRMf, les constatations et les décisions cliniques fondées sur les résultats de l'examen ainsi que les résultats cognitifs postopératoires. ***Méthode :*** Il s'agit d'une étude rétrospective de dossiers de patients qui ont subi une IRMf entre juin 2015 et mars 2021. ***Résultats :*** La latéralisation du langage constituait le principal motif des demandes d'IRMf (100 %), auquel s'ajoutait une cartographie motrice et sensorielle dans 7,7 % des cas. La zone de domination du langage était du côté de la résection chez 12,8 % des patients, et l'activation, adjacente au siège proposé de résection dans 20,5 % de l'échantillon. Dans 18 % des cas, l'IRMf a fourni des indications d'autres examens effractifs en raison de risques d'une morbidité cognitive grave (p. ex. l'amnésie antérograde). Par contre, les résultats de l'IRMf ont permis d'éviter des examens exploratoires effractifs additionnels chez 69,2 % des patients. Les résultats cognitifs fondés sur l'association d'observations neuropsychologiques et de la zone de domination du langage déterminée par l'IRMf se sont révélés variables. ***Conclusion :*** Les demandes d'IRMf visaient principalement à déterminer la domination hémisphérique du langage dans les cas d'épilepsie. Bien que la détermination de la latéralité du langage par l'IRMf n'ait pas été associée à une valeur prévisionnelle directe quant aux résultats cliniques, elle a néanmoins permis de repérer les patients à faible risque de morbidité cognitive catastrophique et ceux à risque élevé chez qui d'autres examens effractifs s'imposaient.

Keywords: Epilepsy surgery; functional MRI; neuropsychology; neuroimaging; neurosurgery

(Received 2 April 2024; final revisions submitted 30 August 2024; date of acceptance 11 September 2024)

Introduction

Functional MRI (fMRI) is a noninvasive means of identifying regions (or hemispheres) of the brain associated with cognitive, motor or sensory functions using a standard MRI scanner. fMRI is founded on the physiological principle of neurovascular coupling, whereby the increased metabolic activity of neurons in response to a specific task or activity causes dilation of nearby blood vessels. This increases the ratio of oxyhemoglobin to deoxyhemoglobin in the region.[1] Increased oxyhemoglobin affects the magnetic resonance signal, which is detectable in an MRI scanner using blood-oxygen-level-dependent (BOLD) contrast.[2] By imaging the entire brain

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Cite this article: O'Grady C and Omisade A. Analysis of Clinical Utility of Functional MRI in Neurosurgical Decision-Making in Focal Epilepsy. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2024.312

rapidly (usually between 1and 4 seconds), changes in BOLD contrast can be correlated to when tasks are being performed. Thus, regions of the brain associated with different tasks can be identified and desired cognitive functions associated with those tasks extrapolated.

This method has found great utility in neuroscience research. It has continued to also gain popularity as a clinical tool, especially in neurosurgical planning when anatomical localization of brain functions in relation to the projected resection area is required to identify/minimize neurological, cognitive or functional morbidity. The clinical "added value" of fMRI has been well-documented in surgical decision-making for tumor resections, demonstrating its impact on noninvasively defining resection boundaries.[3–5] In contrast to tumors, the clinical added value in presurgical planning for focal epilepsy has not been fully elucidated. Benjamin et al. (2017) describe presurgical functional mapping in patients with tumors and epilepsy but do not describe its impact on treatment planning or outcomes.[6] Furthermore, none of the studies take into consideration the neuropsychological outcomes of surgery in relation to preoperative mapping.

This manuscript presents our experience using fMRI for preoperative mapping in Halifax, Nova Scotia, over a 6-year period since this method was implemented here in 2015. We completed a retrospective review of presurgical fMRI's performed between June 2015 and March 2021 for the purposes of surgical planning in patients with focal epilepsy with the aim of answering the following questions:

1. What was the reason for fMRI referral as part of presurgical planning?
2. How often did fMRI activation coincide with the cortical area of prospective resection?
3. What was the impact on clinical care?
    i. How did it impact surgical decision-making?
    ii. Did fMRI reduce the need for invasive testing, such as cortical stimulation (CS) or intracarotid testing?

For the patients who had completed both pre- and post-operative neuropsychological assessments by the end of the study period, cognitive outcomes are also reported.

The goal of this manuscript is to help inform clinical centers considering routinely employing fMRI as a presurgical tool in patients with medically resistant focal epilepsy by demonstrating its added value to clinical decision-making with regard to surgical planning.

Methods

This study was approved by the Nova Scotia Health Authority REB. A chart review of all patients who underwent fMRI at the QEII Health Sciences Centre in Halifax, Nova Scotia, between June 2015 and March 2021, was conducted to select those with focal epilepsy. Due to some overlap between focal epilepsy and tumors, a patient was classified as having "epilepsy" if the lesion would not have been resected save for the fact it was causing seizures. This classification approach resulted in a sample of 39 patients.

The following information was gathered from the patient charts: age, sex, handedness, side and location of the epileptogenic region, proposed area of resection and if surgery was pursued. Core fMRI information gleaned included the reason for requesting fMRI, the type of fMRI requested (i.e., language or motor/sensory), fMRI results, how fMRI impacted surgical planning and decisions regarding further testing (i.e., if it progressed to invasive testing or if invasive procedures were likely no longer required). In patients who completed neuropsychological assessments both before and after surgery ($n = 9$) prior to March 2021, those results were documented as well.

fMRI details

At our center, fMRI images were collected on a 3 tesla GE MR 750 imaging machine with echo-planar pulse sequences with the following parameters: TR/TE = 2000/25 msec, FOV = 22 cm, FA = 77 degrees, 48 axial slices (3 mm) and in-plane voxel resolution = 1.72 mm. Parameters of the high-resolution anatomical T1 scan collected at the same as the functional data were as follows: TR/TE = 8.3/3.3 msec, FOV = 22 cm, FA = 12 degrees and 80 axial slices (1 mm) and in-plane voxel resolution = 0.86 mm. Data processing and analyses were completed with AFNI software.[7] Processing was done using the general linear model developed by Friston et al.[8] Main processing steps included (1) rigid body realigned of all frames to the first volume, (2) slice timing correction, (3) spatial smoothing using a Gaussian kernel FFull Width Half Maximum (FWHM) 4.0 mm, (4) removal of low-frequency signal drift and (4) registration to a high-resolution anatomical T1 image. The processing pipeline is illustrated in detail in Omisade et al. (Figure 2).[9] The language fMRI paradigm is detailed in Omisade et al. (Figure 1)[9] and involves three language tasks (phonemic word generation, sentence completion and naming to description) as well as two control tasks (finger tapping and pattern discrimination). The motor/sensory task is illustrated in Appendix Figure 1 and includes three "task" conditions (tongue movement, unilateral finger tapping and unilateral ankle flexion) as well as two control tasks (pattern discrimination and number discrimination).[10]

fMRI maps were determined by collapsing activation across the task conditions and comparing it to activation collapsed across control conditions. For language scans, laterality was determined by first thresholding to the top 1–3 percentile t-stats prior to evaluation by a neuropsychologist skilled in fMRI interpretation. The laterality index, used by authors in research, is not used for clinical interpretation of scans, which must incorporate not only the broader clinical context but also exclude active voxels that are clearly spurious or unrelated to language function or make note of potential false negative findings due to clinical or pathological factors. Scans that had significant spurious activation that was clearly not related to relevant functional regions (such as in the ventricles or unpredictably scattered throughout in small collections of voxels) were considered uninterpretable. Following thresholding, the determination of language laterality was made by comparing the relative amount of activation in both left and right canonical language areas (such as the temporal lobes, angular gyrus and inferior frontal gyrus). The motor and sensory paradigms were thresholded in the same manner, but activation was considered in the pre- and postcentral gyri as well as supplementary motor and sensory regions.

Results

Demographic information

Age, sex, location of the epileptogenic region and completion or non-completion of surgery for each of the 39 patients are presented in Table 1.

Table 1. Demographic and clinical information

Patient	Age/sex	Epileptogenic region	Surgery completed Y/N
1	26M	Right frontal	Y
3	41F	Left temporal	Y
3	30M	Right parietal	Y
4	42M	Right temporal and insula	Y
5	31M	Left frontal	Y
6	48F	Right temporal	Y
7	22M	Right temporal	Y
8	38F	Right parietal	Y
9	25F	Right temporal and insula	Y
10	44F	Left temporal	Y
11	41M	Left temporal	N
12	21F	Left temporal	Y
13	39M	Left*	N
14	55M	Right temporal	Y
15	54F	Right temporal	N
16	22F	Right*	N
17	58F	Right temporal	N
18	25F	Left temporoparietal	N
19	35F	Right frontal	N
20	30M	Right temporal	Y
21	46F	Left frontal	Y
22	35F	Temporal**	N
23	64M	Left frontal	N
24	43F	Left temporal	Y
25	39F	Temporal**	N
26	40M	Left temporal	N
27	36M	Left frontal	Y
28	26F	Left temporal	Y
29	22F	Left parietal	N
30	42M	Right temporal	N
31	29M	Right parietal	Y
32	30F	Undetermined***	N
33	54M	Right temporal	N
34	39F	Left temporal	N
35	54F	Left temporal	Y
36	52M	Left frontal	N
37	56M	Right temporal	Y
38	60M	Left temporal	Y
39	29M	Right temporal	N

Male (M), female (F), Y (yes, proceeded to surgery), N (no, did not proceed to surgery).
*Seizure focus lateralized, but not localized at the time of the study.
**Probable seizure focus (lobe) identified, but not clearly lateralized at the time of the study.
***Neither the side nor the lobe of seizure focus unknown at the time of the study.

Reason for fMRI referral as part of surgical planning

The reasons for fMRI, as outlined in the clinical requisitions and detailed in Table 2, were not mutually exclusive in the epilepsy population (i.e., the same patients may have been referred for several reasons).

Table 2. Reason for fMRI referral

Reason for FMRI	% Of sample
Unclear language dominance	30.8
Neuropsychology discordant with EEG	33.3
Potential surgical interference with “eloquent” areas	51.2
Language	100
Motor/sensory	7.7

All patients with epilepsy who were considered for surgery completed comprehensive neuropsychological assessments as standard of care. These assessments are completed to document a presurgical cognitive baseline and to help predict the risk of cognitive decline (especially in language and memory functions). As such, the main goals include (i) determining hemispheric language dominance, (ii) localizing areas of neurocognitive dysfunction and (iii) determining concordance between areas of dysfunction identified on testing with the location of seizure onset identified on electroencephalogram (EEG).

For patients with epilepsy, the indication for fMRI was closely intertwined with the results of neuropsychology. Although there are numerous factors that help determine the cognitive risk of epilepsy surgery, operations in the dominant hemisphere are inherently more risky with respect to potential functional declines. As such, if hemispheric language dominance was unclear (e.g., in cases of ambidexterity or other indicators of atypical language representation), fMRI was recommended for this purpose. Second, when neuropsychological findings are incongruent with the known or suspected side of seizure onset based on other clinical exams, this poses challenges for both confirmation of the onset zone and determination of surgical risk. For instance, a right-handed individual with right temporal lobe epilepsy may show a weakness in verbal memory relative to visual memory. In cases like this, a language fMRI would be recommended to confirm left hemisphere language dominance. Atypical language distribution seen in fMRI would explain the discrepant findings and preclude the need for invasive memory testing.

fMRI activation in relation to eloquent cortex targeted for resection

The frequency of overlap between fMRI activation with functionally significant areas of prospective resection is detailed in Table 3.

Patients with epilepsy demonstrated a greater-than-expected variability in language dominance relative to the healthy population.[11,12] Activation directly overlapping the area of the proposed resection was relatively uncommon. For most patients, the main goal was to lateralize language to help interpret conflicting neuropsychological results, rather than to “map” language due to a suspected overlap with the proposed area of resection in an eloquent region.

Impact on preoperative clinical care

fMRI was deemed to contribute to preoperative decision-making if (i) it led to the use of invasive testing, like CS or intracarotid testing (i.e., etomidate speech and memory testing, eSAM),[13] which would otherwise not have been done, or (ii) it helped avoid invasive procedures that otherwise would have been necessary. This data is summarized in Table 4.

Table 3. FMRI outcomes

Outcome	% Of sample
Language laterality	
Left	69.2
Right	12.8
Bilateral	17.9
Activation in/adjacent to site of planned resection	20.5
Temporal lobe activation in dominant hemisphere	12.8
Results cannot be interpreted*	7.7

*The cause for uninterpretable findings could not be determined in any of the cases based on clinical information, observation of performance in the scanner and the post-scan interview (e.g., age, seizure, motion, noncompliance, etc.). In all cases, the hemodynamic response was low, resulting in insufficient variability in t-values for meaningful thresholding, and large amounts of scattered activation were noted.

Table 4. Impact of fMRI in inclusion/exclusion of invasive testing

	% Of sample
eSAM* needed	10.3
Cortical stimulation (extra- or intraoperative)	7.7
No invasive testing	69.2

*Etomidate speech and memory test (eSAM).

In patients with epilepsy, fMRI was more likely to help avoid invasive testing since clarification of language dominance in relation to the side of seizure onset and neuropsychological performance was usually sufficient to predict the cognitive risk of surgery. However, fMRI also helped identify several patients who did require invasive testing to avoid or predict the risk of catastrophic cognitive deficit (e.g., anterograde amnesia) and functional disability following surgery. For patients whose fMRI scans could not be interpreted for technical reasons, the recommended course of action was to treat the surgical hemisphere as dominant for the determination of resection margins (e.g., limiting the posterior extent of a temporal lobe resection). For patients judged to be at risk for anterograde amnesia following a dominant temporal lobe resection, eSAM was recommended. Within our sample, we do not have a record of patients with successful fMRI's who required CS.

Neuropsychological outcomes

Out of the 39 patients, 9 completed both preoperative and a postoperative comprehensive neuropsychological assessments. The predicted[19] and actual outcomes on relevant tasks are summarized in Table 5.

Cognitive outcomes in patients who had completed both pre- and postoperative neuropsychological evaluations were variable and often did not correspond to the expected changes in cognition in three of the patients. Specifically, patient 35 experienced improvement in naming following a dominant temporal lobe resection, patient 24 showed a decline in both verbal and visual memory following a nondominant temporal lobe resection, while patient 37 showed improvement in visual memory following a nondominant temporal resection. Comparison of predicted versus actual outcomes was not possible for patient 8, who had extra-temporal surgery, and in cases with bilateral language dominance identified on fMRI. However, two out of the three patients with bilateral language did not demonstrate any marked change in their cognition following left temporal lobe surgery, which is a contrast to patients with lateralized language, all of whom showed some type of change.

Despite the variability of cognitive outcomes, none of the patients experienced catastrophic memory loss or aphasia after having undergone neuropsychological testing, fMRI and, when indicated following fMRI, invasive testing.

Discussion

This retrospective chart review was completed with the goal of documenting the added value of presurgical fMRI in clinical decision-making in patients with medically intractable epilepsy. To the best of our knowledge, while the added clinical value of fMRI has been well-documented in tumor surgery,[3–5] it has not yet been evaluated in epilepsy.

Our first question probed the reason for fMRI referrals. With regard to patients with epilepsy, this was almost always an extension of neuropsychological testing since neuropsychology is a core element of presurgical evaluation in this patient population. Thus, for patients with epilepsy, fMRI acted as an adjunct to neuropsychology when results were unclear or insufficient to predict cognitive risk.

In examining typical fMRI findings, we have noted that it was successful in identifying atypical language representation, which cannot be reliably determined using markers like handedness or neuropsychological performance (though these factors may lead to a suspicion of atypical distribution). This is consistent with literature suggesting that language re-organization is prevalent in patients with focal epilepsy originating in the language-dominant hemisphere.[11,12] fMRI was also successful in identifying critical regions that should be avoided during surgery, particularly those around the proposed surgical resection site, which is in keeping with presurgical fMRI findings in tumor surgery.[3–5]

fMRI replaced invasive procedures in the majority of patients with epilepsy (69.2%) because it was often used to corroborate information already gleaned from neuropsychology and other clinical factors (i.e. handedness, region of seizure onset, etc.) and provided additional information that would otherwise have been gleaned from invasive procedures like intracarotid tests. It also helped identify those patients who were at higher risk of catastrophic cognitive impairment, mostly amnesia, following surgery, and who required invasive testing.

Aside from identifying people at risk for catastrophic cognitive decline (e.g., anterograde amnesia), which necessitated further testing, prediction of less severe cognitive outcomes in patients who had completed both pre- and postoperative neuropsychological evaluations demonstrated a greater variability than anticipated between predicted outcomes based on preoperative neuropsychological scores and fMRI determination of language dominance. In part, this variability may be due to a very limited sample size. However, it is also likely that this variability reflects a large number of factors that are likely to impact cognitive function in epilepsy both before and after surgery including (i) time between preoperative assessment and surgery, as well as seizure control during this time. Longer time frames and worse seizure control, as well as types of seizures that occur during this time (e.g., focal, generalized tonic-clonic, status epilepticus), may alter cognitive function between the assessment and the surgery, thereby confounding comparisons between pre- and postoperative

Table 5. Neuropsychological outcomes following focal resections

Patient	Language dominance	Resection site	Expected change	Actual change
35	Left	Left temporal	Language Verbal memory	Improvement in naming[a]
10	Left	Left temporal		Decline in story learning and retention[b], word list learning and retention[c]
6	Left	Right temporal	Visual memory	Decline in delayed recall of designs[d]
24	Left	Right temporal		Verbal and visual memory decline on all tasks
37	Left	Right temporal		Visual memory improved on all tasks
8	Left	Right parietal	N/A	No change
2	Bilateral	Left temporal	N/A	No change
12	Bilateral	Left temporal	N/A	No change
26	Bilateral	Left temporal		Verbal memory decline on all tasks, improvement in face recognition memory [e]

[a]Boston Naming Test[14]; [b]WMS-IV Logical Memory I and II[15]; [c]Rey Auditory Verbal Learning Test[16]; [d]Aggie Figural Learning Test[171]; [e]Munn Faces[18].

outcomes; (ii) seizure control following surgery. Ongoing or worse seizures following the operation are likely to result in a greater and broader decline than anticipated based on the resection alone. By contrast, good seizure control may result in cognitive improvement in one or more areas, especially after a nondominant resection; (ii) changes in medication between preoperative testing and surgery and between surgery and postoperative testing; and (iv) preferential selection of patients for fMRI based on complex neuropsychological findings. As noted previously, referral for fMRI in patients with epilepsy is closely linked to their performance on neuropsychological testing in relation to other clinical variables and the proposed resection site. As such, our sample over-represents patients with complex or hard-to-interpret cognitive profiles, which may impact the accuracy of postoperative outcome predictions. Finally, out of the nine patients who completed neuropsychological testing, one had extra-temporal surgery, and three had bilateral language representation. At this time, there is insufficient data in the literature to predict postoperative cognitive outcomes in such cases. However, the absence of cognitive change in two out of the three patients with bilateral language and left temporal resection is notable because it provides some support for the "protective" impact of language bilaterality or, at the very least, for bilateral language serving as a marker for better cognitive outcomes.

The variability in cognitive outcomes does not negate the usefulness of fMRI in helping predict cognitive outcomes following epilepsy surgery. Rather, these findings highlight the importance of considering all aspects of a patient's epilepsy and seizure management when discussing predicted changes and interpreting postoperative outcomes. In this sense, the role of fMRI in epilepsy surgery somewhat is more nuanced than in tumor surgery, where cognitive outcomes are less likely to be affected by long wait times before cognitive testing and surgery, or other variable disease factors before or after the operation. Furthermore, while in tumor surgery, the main role of fMRI is to delineate resection margins to avoid eloquent areas; in epilepsy surgery, it is most often used to define the language-dominant hemisphere and is rarely used to significantly alter the surgical approach. Research to date has generally shown better seizure control with greater resection margins but no significant differences in the degree of lost function in temporal lobe epilepsy surgery;[20,21] therefore, the focus in presurgical evaluation of patients with epilepsy has been language laterality. As such, the relationship between fMRI findings and cognitive outcomes is likely to be less precise.

This study has a number of limitations. The main limitation is the retrospective nature of this work. Our chart reviews were limited by the details included in the health records and clinic notes, which varied significantly between patients and care providers. The reason for referral for fMRI was often derived from the comments on requisition forms, which had variable levels of detail. Other times, it was derived from chart checks and comments from rounds. These may not have represented various conversations about patient care that weren't documented, such as in meetings between clinicians. In many cases, there was significant detail across different sources, but for others, there was much less information. Similarly, when charting, clinicians typically do not reference what tests are not needed for their patients. As such, it was not always possible to determine the course of clinical care in the absence of fMRI unless it was explicitly discussed in the medical chart. It is likely that our findings underestimate the impact of fMRI on surgical planning due to a lack of sufficient detail. Furthermore, a larger sample is required to evaluate the relationship of fMRI findings to postoperative cognitive outcomes, with the emphasis on examining the interactions between fMRI results, preoperative cognitive performance and epilepsy-related disease and treatment variables. Finally, since fMRI findings are directly contingent on paradigm design, post-processing pipeline decisions (e.g., thresholding) and interpretation and reporting approaches (e.g., entirely automated vs. expert review), the added value of this method may vary among sites. The clinical utility of fMRI in epilepsy surgery may be enhanced by designing paradigms that are more closely linked to cognitive outcomes of interest.

Conclusions

At our center, fMRI impacted clinical care and presurgical decision-making in over 50% of the patients who underwent this procedure. For patients with epilepsy, fMRI reduced the need for invasive tests, increasing patient safety and potentially reducing wait times for surgery if invasive testing is not required. Future directions in clinical fMRI include the development of valid and efficient paradigms focusing on other significant cognitive functions, particularly memory, which may further reduce the need for invasive testing, especially for patients with epilepsy.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.312.

Author contributions. C.O.: Conceptualization, data collection and analysis, writing of the original manuscript and manuscript revisions.

A.O.: Study supervision and management, conceptualization, data collection and manuscript revisions.

Funding statement. Dr O'Grady's work on this project was supported by the Dalhousie University Faculty of Medicine Gladys Osman Estate Studentship. This project was otherwise unfunded.

Competing interests. The authors have no competing interests or conflicts of interest to declare.

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