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Basic science

Estimating overdiagnosis in giant cell arteritis diagnostic pathways using genetic data: genetic association study

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‡See Supplementary Appendix 1, available at *Rheumatology* online, for a list of the UK GCA Consortium.

Abstract

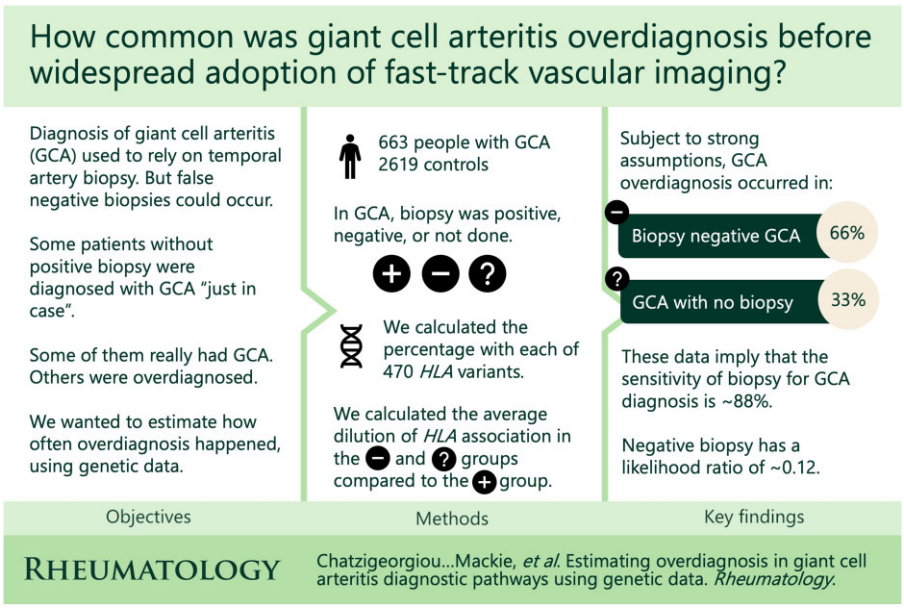
Objectives: GCA can be confirmed by temporal artery biopsy (TAB) but false negatives can occur. GCA may be overdiagnosed in TAB-negative cases, or if neither TAB nor imaging is done. We used HLA genetic association of TAB-positive GCA as an 'unbiased umpire' test to estimate historic overdiagnosis of GCA.

Methods: Patients diagnosed with GCA between 1990 and 2014 were genotyped. During this era, vascular imaging alone was rarely used to diagnose GCA. HLA region variants were jointly imputed from genome-wide genotypic data of cases and controls. Per-allele frequencies across all HLA variants with $P < 1.0 \times 10^{-5}$ were compared with population control data to estimate overdiagnosis rates in cases without a positive TAB.

Results: Genetic data from 663 GCA patients were compared with data from 2619 population controls. TAB-negative GCA ($n = 147$) and GCA without TAB result ($n = 160$) had variant frequencies intermediate between TAB-positive GCA ($n = 356$) and population controls. For example, the allele frequency of HLA-DRB1*04 was 32% for TAB-positive GCA, 29% for GCA without TAB result, 27% for TAB-negative GCA and 20% in population controls. Making several strong assumptions, we estimated that around two-thirds of TAB-negative cases and one-third of cases without TAB result may have been overdiagnosed. From these data, TAB sensitivity is estimated as 88%.

Conclusions: Conservatively assuming 95% specificity, TAB has a negative likelihood ratio of around 0.12. Our method for utilizing standard genotyping data as an 'unbiased umpire' might be used as a way of comparing the accuracy of different diagnostic pathways.

Graphical abstract



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Keywords: giant cell arteritis, HLA, temporal artery biopsy, overdiagnosis.

Rheumatology key messages

- Under certain conditions and assumptions, overdiagnosis can be estimated using genetic data.
- The sensitivity of temporal artery biopsy for detecting GCA was estimated to be about 88%.
- Without vascular imaging, GCA may often be overdiagnosed in biopsy-negative patients.

Introduction

GCA is a vasculitis of older people [1] which can present with a variety of symptoms including headache, scalp tenderness, jaw ache, ocular ischaemia, fever and weight loss [2]. Where GCA is strongly suspected, it should be treated with high-dose glucocorticoids pending further investigation. The 'diagnostic momentum' thus created can make it difficult to reverse the diagnosis if the temporal artery biopsy (TAB) subsequently proves negative and yet no better explanation for the presenting symptoms is found. Some patients with genuine GCA do have a negative TAB [3], often attributed to patchy arterial involvement or 'skip lesions' [4, 5]. The sensitivity of a unilateral TAB was estimated from bilateral TAB studies to be 87% [6] although this might be overestimated due to the frequently symmetrical nature of arterial involvement in GCA. The concept that GCA can spare the temporal arteries even in cranial GCA is supported by 18-flurodeoxyglucose PET (18-FDG-PET) studies assessing the cranial arteries (temporal, maxillary, occipital, vertebral): temporal artery 18-FDG uptake in GCA is not universal, even when other cranial arteries are involved [7].

Sometimes there is no evidence of any cranial artery involvement in GCA [8]; this extracranial or 'large-vessel' GCA subset is usually diagnosed with vascular imaging [9, 10]. Vascular imaging is now also recommended as first-line investigation for cranial GCA, but where imaging and TAB give discordant or unexpected results, expert clinical judgement of GCA probability is crucial [11].

Where confirmatory tests are equivocal or negative, but pre-test probability is high, a clinical diagnosis of GCA may be justified by the desire to avoid preventable sight loss [12]. The cost of this strategy is that some patients will be overdiagnosed. Adoption of better tests including vascular imaging should improve the overall diagnostic accuracy of the pathway, but so far no method has been established that can demonstrate reduction in overdiagnosis.

We previously demonstrated that TAB-positive GCA is strongly associated with genetic variants in the HLA region including the single nucleotide polymorphisms rs9268905 [$P = 1.9 \times 10^{-54}$, per-allele odds ratio (OR) = 1.79] located between *HLA-DRA1* and *HLA-DRB1*, rs477515 ($P = 4.0 \times 10^{-40}$, OR = 1.73) located in the intergenic region between *HLA-DRB1* and *HLA-DQA1*, and the *HLA-DRB1**04 allele ($P = 6.8 \times 10^{-38}$, OR = 1.92) [13]. HLA region genotyping is not currently performed in routine care for GCA diagnosis; therefore, genotype cannot directly influence diagnostic decisions and can act as an 'unbiased umpire' [14]. In this study, we sought to estimate the extent of GCA overdiagnosis during the era before widespread adoption of vascular imaging as a first-line test in GCA diagnostic pathways.

Methods

Study population

The UK GCA Consortium was designed as a genetic epidemiology study. Ethical approval was received from the Yorkshire and Humber–Leeds West Research Ethics Committee (REC Ref. 05/Q1108/28). Patients were eligible for the study if diagnosed with GCA by a consultant rheumatologist or ophthalmologist, without requiring any specific diagnostic criteria as none has been validated for GCA. Patients were identified from clinic lists and searches of TAB records from histopathology databases. After provision of written informed consent, clinical data and TAB result were determined by casenote review. TAB result was determined from the clinical records as 'positive', 'negative' or 'no result'. The 'no result' category included cases where no biopsy was done, no temporal artery biopsy was done (no arterial tissue received for processing) or where no clear TAB result was determinable despite complete review of the patient's medical records.

Population control data came from two sources: 1430 individuals from the 1958 British Birth Cohort (58BC), who were born in England, Wales and Scotland during one week in 1958; and 1500 healthy blood donors from the United Kingdom Blood Service for the Wellcome Trust Case Control Consortium (WTCCC) [15, 16] (Supplementary Methods, available at *Rheumatology* online).

The genetic data from the TAB-positive GCA cases have been previously included in two international collaborative studies [13, 17]. In this study, we focus on the cases that received a 'clinical diagnosis' of GCA: the TAB-negative and 'no TAB result' cases that still received a GCA diagnosis.

Genotyping and quality control

Genomic DNA was extracted from blood samples by standard methods [13]. Cases and controls were genotyped separately with the use of two versions of the Illumina chip (Infinium Human core 24 Beadchip, HumanCore-12v1-0_A). The same quality filters [18] were independently applied to the raw data from each cohort using PLINK version 1.9 (Supplementary Methods, available at *Rheumatology* online). The genome-wide Manhattan plot for GCA susceptibility is dominated by the signal from the HLA region in chromosome 6 (chr6: 29–34 Mb on build 36/hg18) [19] and therefore we chose to focus on the HLA region in our analysis. In this region, there is strong linkage disequilibrium. The allele type for each HLA gene can be inferred from SNP genotyping results by imputation.

HLA imputation

Classical HLA alleles were determined from the single nucleotide polymorphism (SNP) data by imputation. Genotypic

data from both cases and controls were jointly imputed across the extended MHC using the SNP2HLA imputation method, using the Beagle software package [20, 21] (Supplementary Methods, available at *Rheumatology* online). Post-quality control filter thresholds were set to remove variants with a minor allele frequency <0.01 and variants with an information score <0.8 [13]. After this was done, 159 classical HLA alleles and 6730 SNPs remained. Variants from the association analysis of TAB positive cases *vs* controls spanning the entire HLA region with $P < 1.0 \times 10^{-5}$ were used in order to estimate the misclassification rate.

Association analysis using different case definitions

Firstly, to determine whether the TAB result was associated with specific HLA alleles imputed across extended haplotypes, we compared the strength of association (OR) and allele frequencies of susceptibility and protective HLA alleles in TAB-positive GCA, TAB-negative GCA and GCA with no TAB result.

Estimation of misclassification rate

Because of the extensive linkage disequilibrium within the HLA region, different genetic variants within this region are not independent of one another, and so cannot be treated as independent variables. On the other hand, selection of only a few, very strong HLA associations of TAB-positive GCA would have potentially introduced 'winner's curse' bias [22]. To address this, for each TAB-defined subset of the GCA cases, the proportion of patients misclassified as GCA was estimated by taking the average effect size across all the variants with $P < 1.0 \times 10^{-5}$ (per-allele association of TAB-positive GCA cases with controls). This conservative approach acknowledges the non-independence of alleles and SNPs from each other, while avoiding loss of potentially informative data. The proportions of 'genuine' GCA cases in the TAB-negative GCA and GCA without TAB groups, p_n and p_x, were calculated from the allele frequencies in TAB-positive cases and controls (Supplementary Methods, available at *Rheumatology* online) [23]. For simplicity, we assumed an additive gene–dose model in our analyses: although HLA-DRB1*04 may have a dominant effect [24] we could not assume this was also true of other HLA variants.

Assumptions made

For the purposes of analysis we assumed (i) a 100% specificity of TAB (no false-positive TAB), (ii) the group of GCA cases without positive TAB comprises a mixture of 'genuine' GCA and 'overdiagnosed' GCA, (iii) all 'genuine' GCA cases share the same HLA associations, (iv) 'overdiagnosed' cases have a similar distribution of HLA variants as the control population and (v) HLA status did not influence clinical diagnosis.

Results

After quality control, we had genetic data for 663 cases of GCA and 2619 population controls. GCA patients were diagnosed between 1991 and 2014, before vascular US or PET/CT were widely available in the UK. Indeed, only eight of the cases had their GCA confirmed by a positive imaging test, which was not necessarily performed at the time of diagnosis (one US, three CT angiography/magnetic resonance angiography and four PET/CT). Table 1 gives clinical data on the TAB-positive GCA ($n = 356$), TAB-negative GCA ($n = 147$) and cases of GCA without any TAB result ($n = 160$). The cases were recruited from 29 centres, with 18 centres recruiting 10 or more patients. The proportion of TAB-positive cases ranged from 13% to 90%; the proportion of cases diagnosed without any TAB result ranged from 0% to 52%. This may have reflected clinical heterogeneity in referral routes and variations in diagnostic practice, as vascular imaging was rarely used.

HLA allele associations

The HLA association of TAB-positive GCA patients was similar to that described in previous studies, including the large international study to which we had contributed TAB-positive cases [13]. *HLA-DQA1*01*, *HLA-DQB1*05* and *HLA-DQB1*06* alleles had a protective effect; *HLA-DQA1*03*, *HLA-DQB1*03* and *HLA-DRB1*04* were associated with GCA susceptibility (Table 2, 'TAB positive' column).

TAB-negative GCA showed a pattern of HLA allelic associations in the same direction as TAB-positive GCA, but the effect was generally diluted: for each HLA allele, the strength of association was diminished (closer to the null OR of 1.0). The ORs for GCA with no biopsy result were generally intermediate between those for TAB-positive and TAB-negative GCA (Table 2, columns for TAB negative, no TAB result).

Single-nucleotide polymorphisms

Associations with the three SNPs (rs9268969, rs9275184, rs477515) previously reported as being associated with biopsy-confirmed GCA [13, 17] were markedly diluted for TAB-negative GCA, to the extent that only rs9275184 (located between *HLA-DQA1* and *HLA-DQA2*) retained

Table 1. Clinical features of GCA patients included in the analysis

	TAB positive ($n = 356$)	TAB negative ($n = 147$)	No TAB result ($n = 160$)
Female sex, *n* (%)	248 (69.7)	106 (72.1)	117 (73.1)
Age at diagnosis, median (IQR), years	72.5 (69; 78)	68 (63; 76)	71 (65; 76)
Year of initial treatment with steroids, median (IQR)	2009 (2005; 2012)	2010 (2007; 2012)	2010 (2006; 2012)
Evidence of GCA from vascular imaging tests[a], *n* (%)	16 (4.5)	14 (9.5)	18 (11.2)
Presence of polymyalgic symptoms[b], *n* (%)	119 (33.4)	58 (39.5)	72 (45.0)
Presence of jaw or tongue claudication[b], *n* (%)	235 (66.0%)	63 (42.9%)	82 (51.2)
CRP (mg/l), median (IQR)	69.5 (35; 127)	32 (7; 91)	53 (23; 118)
ESR (mm/h), median (IQR)	65 (44; 93)	47 (23; 78)	59 (36; 84)

[a] Results of vascular imaging tests were recorded only in 65 GCA cases.
[b] Coded as present, absent or missing; for these variables <5% were coded as missing. IQR: interquartile range; TAB: temporal artery biopsy.

Table 2. Examination of classical HLA alleles associated with biopsy positive GCA in additional GCA diagnostic subgroups

		Positive TAB ($n = 356$) *vs* controls ($n = 2619$)			Negative TAB ($n = 147$) *vs* controls ($n = 2619$)			No TAB result ($n = 160$) *vs* controls ($n = 2619$)		
Classical HLA allele	MAF_{ctrl}	MAF_{pos}	OR_{pos}	P_{pos}	MAF_{neg}	OR_{neg}	P_{neg}	$MAF_{unknown}$	$OR_{unknown}$	$P_{unknown}$
HLA-DQA1*01	0.38	0.23	0.50	8.07×10^{-14}	0.34	0.83	0.14	0.28	0.62	0.0001
HLA-DQA1*0102	0.19	0.12	0.57	5.43×10^{-06}	0.16	0.80	0.18	0.11	0.53	0.0006
HLA-DQA1*03	0.21	0.33	1.85	2.37×10^{-12}	0.28	1.42	0.0086	0.29	1.49	0.0020
HLA-DQA1*0301	0.21	0.33	1.85	2.37×10^{-12}	0.28	1.42	0.0086	0.29	1.49	0.0020
HLA-DQB1*03	0.35	0.49	1.76	2.65×10^{-12}	0.41	1.28	0.04	0.41	1.29	0.0282
HLA-DQB1*0301	0.18	0.25	1.46	6.00×10^{-4}	0.21	1.17	0.28	0.21	1.18	0.24
HLA-DQB1*0302	0.11	0.18	1.83	1.59×10^{-08}	0.17	1.62	0.0029	0.17	1.65	0.0013
HLA-DQB1*05	0.15	0.08	0.52	4.75×10^{-06}	0.14	0.95	0.79	0.13	0.84	0.32
HLA-DQB1*06	0.23	0.15	0.58	7.68×10^{-07}	0.20	0.80	0.15	0.15	0.56	0.0004
HLA-DRB1*04	0.20	0.32	1.96	5.13×10^{-14}	0.27	1.48	0.0038	0.29	1.65	0.0001
HLA-DRB1*0401	0.12	0.20	1.94	1.54×10^{-09}	0.14	1.28	0.17	0.17	1.65	0.0017
HLA-DRB1*0404	0.05	0.09	2.16	4.97×10^{-07}	0.08	1.77	0.019	0.07	1.64	0.038

P_: *P*-value from the logistic regression of each subgroup of cases (positive, negative, unknown) with the control individuals. OR: per-allele odds ratio assuming an additive model; MAF: minor allele frequency.

statistical significance at $P < 0.05$ (Table 3, 'negative TAB' column). Again, ORs for GCA with no biopsy result were intermediate between those observed for TAB-positive GCA and TAB-negative GCA (Table 3, 'no TAB result' column).

Estimation of misclassification rates

A total of 470 HLA variants were associated with TAB-positive GCA compared with controls at a per-allele threshold of $P < 1.0 \times 10^{-5}$. We estimated the proportion p_n of 'genuine' cases among TAB-negative GCA as 0.33 (S.D. 0.23) and proportion p_x of 'genuine' cases in GCA without TAB result as 0.67 (S.D. 0.15).

Discussion

In this study, we used HLA genotyping data to estimate the proportion of clinically diagnosed GCA patients who are overdiagnosed. Of 503 cases in our study who had a TAB, 356 (71%) were recorded as positive; this is in line with the '77% sensitivity' of TAB reported in a meta-analysis [25]. Our question was: how many of those diagnosed with 'TAB-negative GCA' really had GCA? We found, by demonstrating dilution of the known genetic associations with biopsy-positive GCA, that subject to strong assumptions, about two-thirds of biopsy-negative GCA cases, and one-third of GCA cases without a biopsy result, may have been overdiagnosed.

The Merriam-Webster dictionary defines overdiagnosis as 'the diagnosis of a condition or disease more often than it is actually present'. Overdiagnosis/overtreatment ('just in case' treatment) is a rational response to diagnostic uncertainty, because GCA-related visual loss is a feared consequence. Under such circumstances, the greater the diagnostic uncertainty, the more overdiagnosis is likely to occur.

Our estimate depends on several assumptions which are limitations of our approach. (i) We assumed a 100% specificity of TAB (no false-positive TAB). This assumption has been called into question by a reliability study in which discordant classifications of TAB images as positive/negative were made by a panel of pathologists [26]. Standardized reporting templates for TAB might address this. (ii) We assumed that the group of GCA cases without positive TAB comprises a mixture of 'genuine' GCA and 'overdiagnosed' GCA. This could be an oversimplification if there are 'halfway-house' disease states including potentially PMR [10]. (iii) We assumed that all genuine GCA cases share the same HLA associations, but there is probably genetic heterogeneity within this disease. This is a major limitation of our approach. Large-vessel involvement was previously suggested in small studies to have a different pattern of HLA association [8], although a more recent study had failed to confirm this [27]. Takayasu arteritis does appear to have a different HLA association compared with GCA [19, 28], but the cases in our study were all of an age-range compatible with GCA rather than Takayasu arteritis. (iv) We assumed 'overdiagnosed' cases have a similar distribution of HLA variants to population controls. Although there is global variation of population HLA frequencies [24], our cases and controls both came from the UK. (v) We assumed that HLA genotype did not influence clinical diagnosis. This assumption seems reasonable, since the clinical diagnosis of GCA was an inclusion criterion for UK GCA Consortium, and HLA typing is not an accepted test for GCA diagnosis in clinical practice. The HLA genotyping done for this study was only done in retrospect and the results of the HLA genotyping were not returned to the clinical care team.

As a rational response to uncertainty, GCA overdiagnosis arises from the limitations of the diagnostic tests available [29]. Given an estimated GCA prevalence of 52 per 100 000 in the over-50s [1], with just over 25 million over-50s living in the UK (2021 data [30]), this would equate to 13 000 people in the UK who have ever been diagnosed with GCA. Extrapolating from our findings reported here, up to 3500 of these people may have been overdiagnosed and therefore been exposed to the harms of long-term glucocorticoid therapy. We would hope that the greater adoption of vascular imaging for GCA since 2007–14 has reduced GCA overdiagnosis rates; this could be tested by repeating our study in a contemporary cohort.

Conventionally, the fact that 71% of GCA patients in our cohort had a positive TAB would have been interpreted as TAB having a sensitivity of 71% for GCA diagnosis. However, removing 'overdiagnosed' cases from the denominator yields a 'true sensitivity' of TAB for detecting GCA of around 88%, comparable to the 87% 'true sensitivity' estimated by studies of bilateral TAB [6]. Sensitivity and

Table 3. Previously-reported independent SNP associations in the HLA region among subsets of GCA classified according to TAB result [13, 17]

				All cases ($n = 663$) *vs* controls ($n = 2619$)			Positive TAB ($n = 356$) *vs* controls ($n = 2619$)			Negative TAB ($n = 147$) *vs* controls ($n = 2619$)			No TAB result ($n = 160$) *vs* controls ($n = 2619$)		
SNP	BP	Gene/Intergenic region	MAF_{CTRL}	MAF_{all}	OR_{all}	P_{all}	MAF_{pos}	OR_{pos}	P_{pos}	MAF_{neg}	OR_{neg}	P_{neg}	MAF_{unk}	OR_{unk}	P_{unk}
rs477515	32677668	*HLA-DRB1/HLA-DQA1*	0.35	0.46	1.54	2.99×10^{-12}	0.50	1.84	4.14×10^{-14}	0.37	1.09	0.49	0.44	1.43	0.002
rs9268969	32542328	*HLA-DRA1/HLA-DRB1*	0.37	0.47	1.49	1.99×10^{-10}	0.51	1.78	1.03×10^{-12}	0.38	1.06	0.61	0.44	1.34	0.01
rs9275184	32762692	*HLA-DQA1/HLA-DQA2*	0.11	0.18	1.75	5.48×10^{-11}	0.18	1.83	1.53×10^{-08}	0.17	1.62	0.003	0.17	1.64	0.001

P_: *P*-value from the logistic regression of each subgroup of cases (positive, negative, unknown) with the control individuals; BP: base pair position; MAF: minor allele frequency; OR: per-allele odds ratio assuming an additive model; MAF: minor allele frequency; SNP: single nucleotide polymorphism.

specificity are alternatively expressed as likelihood ratios. A negative likelihood ratio is the ratio of pre-test odds to post-test odds, given a negative test result. With a 88% 'true sensitivity' and conservatively assuming a TAB specificity of 95%, we estimate the negative likelihood ratio for TAB as 0.12 (previous best estimate was 0.23 [31]). To give an illustrative example, a pre-test GCA probability of 20%, 50% or 80% would be downgraded by a negative TAB result to a post-test probability of 3%, 11% or 34%, respectively.

Could HLA genotyping be useful in clinical practice to improve accuracy of estimation of pre-test probability? *HLA-DRB1**04, which was the strongest allelic association, is fairly common in the general Northern European population. In the context of a patient with suspected GCA, knowing their *HLA-DRB1**04 status would only allow a small diagnostic shift (positive and negative likelihood ratios of *HLA-DRB1**04 ~1.79 and 0.76, respectively [27]). At best, this would need to be combined with symptoms, signs and standard laboratory tests to incrementally improve diagnostic accuracy [2]. We used 470 *HLA* variants to generate the best estimate we could; but because of strong linkage disequilibrium and multiplicity of testing, it is not possible to identify the optimal variant(s) from our data.

Our results provide a benchmark for estimating GCA overdiagnosis rates during the era before widespread adoption of temporal artery US. Future studies of HLA frequencies in GCA cohorts diagnosed via pathways involving vascular imaging could ascertain whether diagnostic accuracy has improved with contemporary diagnostic pathways. Within cohorts diagnosed during the same time period, the accuracy of different classification criteria for GCA could also be compared; HLA variant/allele frequencies in the subgroup classified as GCA by the 1990 ACR criteria might be compared with HLA variant/allele frequencies in the subgroup classified as GCA by the 2022 ACR/EULAR classification criteria. Unbiased tests have a useful role to play in such comparisons [14].

Lastly, our approach might be extended to evaluate diagnostic pathways or classification criteria for other diseases where the gold-standard test is highly specific but insensitive, and where a strong genetic association is present.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data access requests should be directed to the corresponding author.

Contribution statement

Design, concept: C.C., A.W.M., S.L.M., J.H.B. Analysis: C.C., J.H.B., A.W.M., S.L.M. Clinical expertise: A.W.M., S.L.M. Writing manuscript: C.C., A.W.M., S.L.M., J.H.B., J.M. Manuscript review: C.C., A.W.M., S.L.M., J.H.B., J.M.

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