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EXTENDED REPORT

# Should I send my patient with previous giant cell arteritis for imaging of the thoracic aorta? A systematic literature review and meta-analysis

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## ABSTRACT

**Objectives** To review the literature in order to estimate how many previously unknown thoracic aortic aneurysms (TAAs) and thoracic aortic dilatations (TADs) might be detected by systematic, cross-sectional aortic imaging of patients with giant cell arteritis (GCA).

**Methods** A systematic literature review was performed using Ovid Medline, Embase and the Cochrane Library. Studies potentially relevant to TAA/TAD were evaluated by two authors independently for relevance, bias and heterogeneity. Meta-analysis was performed using a random-effects model to estimate pooled prevalence.

**Results** Two analyses of routinely collected administrative data suggested a threefold risk of TAA/dissection in GCA compared with controls. In GCA cohorts without systematic imaging, 2–8% had TAA. In the two best-reported studies, aneurysm dissection/rupture occurred in 1% and 6% of GCA cases. Aortic imaging studies had a variety of TAA/TAD definitions, imaging methods and time points. There were limited data on age-matched controls. Three studies suggested that male sex may be a risk factor for TAA/TAD in GCA. On average, five to ten patients with GCA would need aortic imaging to detect one previously unknown TAA/TAD.

**Conclusions** The data support an association between GCA and TAA/TAD compared with age-matched controls, but the true relative risk, and the time course of that risk, remains unclear. It is also unclear whether chest radiography is a sufficiently sensitive screening tool. Clinicians should retain a high index of suspicion for aortic pathology in patients with GCA. Before ordering imaging, clinicians should consider whether, and how, detecting aortic pathology would affect a patient's management.

## INTRODUCTION

Giant cell arteritis (GCA) is an age-related, large-vessel vasculitis with a well-described association with aortitis. In an autopsy study, half the cases with aortitis also had some evidence of polymyalgia rheumatica (PMR)/GCA,[1] while, in a surgical series, one-third of cases with active, non-infectious aortitis were attributed to GCA.[2] CT studies reveal aortic thickening (presumed aortitis) in 45–65% of patients with GCA at diagnosis,[3 4] and an ultrasound study revealed abnormality of the abdominal aorta in 90% of patients with GCA at diagnosis.[5] The ascending aorta shows impaired elastic properties even at presentation of GCA.[6]

In the population, normal aortic diameter increases by 1 mm/decade.[7 8] The incidence of thoracic aortic aneurysm (TAA), dissection and rupture together has been estimated for the Swedish population at 0.16 per 1000 person-years in men, and 0.09 per 1000 person-years in women, with a median age at diagnosis of 71 years and 40% overall still unruptured at diagnosis.[9] Abdominal aortic aneurysm (AAA) is observed in about 5% of men over 65 in ultrasound screening programmes.[10]

Patients with GCA appear to have an elevated incidence of aortic aneurysm, particularly TAA, compared with the general population; the aneurysm may only be discovered some years after GCA diagnosis, in the event of (often fatal) dissection or rupture.[11 12] This late aneurysm development in GCA might be a consequence of cumulative inflammatory damage to the smooth muscle and/or elastic laminae of the aortic wall, although it has also been proposed that the aortic inflammation in GCA is secondary to atrophy of the aortic smooth muscle.[13] There is pathological evidence of active giant cell aortitis in many reported cases of aortic dissection/rupture; also, patients with increased aortic fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) at GCA diagnosis are more likely to develop aortic dilatation later.[14]

Over time, aortic aneurysms in general enlarge by 1–10 mm/year[15–17]; there are few data on whether this may occur more rapidly in TAAs that are caused by aortitis. It is important that the blood pressure of patients with TAA is aggressively controlled to avoid excessive aortic strain. Patients with unrepaired TAAs in general have a 1-, 3- and 5-year survival of approximately 65%, 36% and 20%,[15 18] although this depends on many factors including aneurysm size.[17] There are few data on mortality attributable to TAA that is caused by aortitis. If a TAA ruptures, 76% of patients die within 24 h, whether or not they reach the operating table.[15] In atherosclerotic TAA, surgery is usually considered at >55 mm for ascending aortic TAA and >60 mm for descending aortic TAA, or in TAAs that grow at >10 mm/year.[15] For all these reasons, it is relevant to ask whether, how and when we should screen our patients with GCA for TAA. Here we focus on TAA rather than AAA because the imaging necessary for TAA diagnosis is potentially more burdensome for both patients and the health service, compared with the relative ease of diagnosing AAA.

Current UK guidelines for management of GCA suggest a chest radiograph every 2 years to screen for TAA,[19] but chest radiography is not a very sensitive test for detecting TAA, with a sensitivity of

only 60% even in symptomatic patients,[20] and is therefore not an ideal screening tool. Other commentators have suggested yearly two-view chest radiography plus abdominal ultrasound.[21] Conversely, American guidelines recommend CT or MRI of the thoracic aorta in the initial evaluation of GCA.[22] The evidence for both recommendations is graded at C (expert opinion). In the face of this discrepancy in expert opinion, we reviewed the evidence for cross-sectional imaging (CT or MRI) for TAA in patients who have received a diagnosis of GCA.

## METHODS

A systematic review protocol was written (see online data supplement), and Ovid Medline (1948 to September 2011), Embase Classic+Embase (1947 to 2011 September 26) and the Cochrane Library were searched on 27 September 2011 (see online appendices 1–3 for search terms used). In the absence of formal studies of TAA screening programmes, observational studies were included. Meeting abstracts from international rheumatology meetings (2006–2011) were also searched. From the search output, potentially relevant studies were defined as those concerning human subjects over 40 years of age, with a diagnosis of GCA or PMR. Finally, the search was updated on 21 April 2012 using PubMed Medline.

Any potentially relevant studies were assessed in abstract form by two authors separately (SLM and CTP) for relevance to the research question. Criteria for exclusion were: not about humans, age <40 years, no clinical evidence of GCA (isolated giant cell aortitis only detected on histology, without clinical symptoms of GCA, was not counted as GCA for the purposes of this review), or no mention of aortic dilatation, aneurysm or dissection. Remaining studies were sorted into study type (analyses of routinely collected population-level administrative data, GCA cohorts without systematic imaging (ie, where not all patients were imaged), and imaging studies in which all patients with GCA were imaged, either once or repeatedly. Duplicate results were identified by sorting citations alphabetically. If reports from the same centre had significant overlap, the most relevant report was chosen for inclusion in the final analysis. Case studies and small case series of up to six relevant cases were retrieved where possible to check reference lists. Studies were excluded if they were not relevant to our question of whether patients with a prior diagnosis of GCA on clinical grounds may be at risk of developing aneurysm subsequently.

Data were extracted systematically from the included studies by authors SLM and CTP, including evaluation of risk of bias. Risk of bias in the estimate of aneurysm prevalence was assessed first by evaluating study design: whether the way patients were identified and recruited to the study appeared likely to influence this estimate. For example, studies in which consecutive patients presenting within a defined population were included were considered to have low risk of bias, whereas those in which patients were selected because of clinical features of large-vessel GCA were judged to be at high risk. Where relevant, we also assessed differences in potential confounders (eg, age, sex, smoking) between patients with GCA and non-GCA controls, but this was not used to exclude studies from the primary analysis. Some reports differentiated TAA from thoracic aortic dilatation (TAD). The primary outcome of interest was the combined incidence of TAA/TAD because both of these may require surgical repair.[23]

Pooled prevalence was estimated in Stata SE V.12.0 by weighted pooling of the imaging studies (excluding those studies judged to have a high risk of bias) using the metan command.[24] It was assumed for the purposes of this summary analysis that the definitions of GCA and of TAA/TAD were equivalent in pooled studies, but we also repeated the analysis restricted only to reports where all patients with GCA were biopsy proven. Statistical heterogeneity was assessed using the $I^2$ statistic; even if no significant statistical heterogeneity was found, a random-effects model was used to calculate pooled prevalence because statistical heterogeneity could have been missed because of small numbers. The pooled prevalence estimation was then repeated using only those studies published as full articles.

## RESULTS

A total of 296 results (citations) were obtained from the Medline search and 504 results from Embase. No relevant results were identified from the Cochrane Library search. After combination of the search outputs and removal of duplicates, this yielded 517 results. Results were then sequentially excluded as follows: not about humans (n=2); patients under 40 years (n=33); no GCA or PMR (n=110); and no mention of aortic dilatation, aneurysm, TAD, TAA or dissection (n=79). This left 293 references, to which 51 further references were added, collated from the reference lists of articles reviewed in full-text, from conference abstracts and from papers newly published during the preparation of this manuscript. This process yielded 39 reports on the frequency of TAA or AAA in GCA, 33 reports on the frequency of GCA in aneurysms (including surgical series), 142 case reports or small case series, 103 reviews, and 28 deemed not relevant for miscellaneous reasons (most commonly that the article was not about patients with a clinical diagnosis of GCA who were later found to have developed aneurysm).

Thirty-nine reports on the frequency of aneurysm in GCA were retrieved in full-text (except for meeting abstracts). Where two reports appeared to describe the same group of patients, the report giving the fullest data was selected. Reports with data relevant to our question were two reports from large administrative databases, nine studies where not all patients were imaged, and nine imaging studies. There were not enough data to address all the outcome measures prespecified in the protocol.

In an analysis of routinely collected data from administrative databases, the adjusted HR of thoracic or abdominal aneurysm/dissection over a 3-year period following the diagnosis of GCA, compared with that seen in the general population, was 3.2.[25] Data on 4566 GCA cases and 18 264 matched controls from the US Nationwide Inpatient Sample, reported so far in abstract form only, gave an OR for TAA/dissection of 3.28 (95% CI 2.05 to 5.24).[26] The estimated incidence of TAA in GCA was 0.1 per 100 person-years in one administrative dataset,[25] but 1 per 100 person-years in two single-centre studies.[11 27]

In nine studies of GCA where not all patients were imaged (the two largest studies with consecutive recruitment of GCA cases are shown in table 1; other studies are listed in online appendix 4), aneurysms were detected by review of medical records (and usually confirmed by imaging, resection or autopsy) in 2–8% of patients with GCA. Ascertainment of GCA diagnosis and definitions of aneurysm/dilatation varied. For example, 'aneurysmal disease' was defined in one report as 'aneurysm and/or dissection'[27] and it was difficult to separate out these two factors; reports of 'dissecting aneurysm' were particularly hard to interpret. In a specialist referral centre,[28] 5% of patients with GCA had TAA, and 6% had dissection/rupture.

Nine imaging studies[3–5 14 23 29–32] had a variety of aneurysm/dilatation definitions, imaging protocols and time points (table 1). In some studies, TAA/TAD and AAA were both reported (table 1): in the following description, the word 'aneurysm' is used to mean thoracic and/or abdominal aneurysm. The frequency of TAA/TAD in age-matched controls was 2/22 (9%)[3] and 2/28 (7%).[23]

**Table 1** Studies included in the final analysis

| Reference | Female/total, n/N (%) | Age at GCA diagnosis, mean (range) | Ascertainment of GCA | Ascertainment of aortic aneurysm/ dilatation | Definition of aneurysm/ dilatation | Time since GCA diagnosis to imaging/aneurysm | Newly identified aneurysm or dissection (F, females with TAA/TAD where information given) | Dissection or rupture, N (%) | Risk of bias estimate of aneurysm prevalence |
|---|---|---|---|---|---|---|---|---|---|
| Prieto-Gonzalez *et al*[4] | 27/40 (68%) | 79 (57–92) | Biopsy proven | CT aortogram | See note 1 | Within 3 days of treatment | 6 (6 TAD, 0 AAD) (1F) | 0 | Low |
| Agard *et al*[3] | 17/22 (77%) | 74 (61–86) | Biopsy proven | CT aortogram | See note 2 | Within 4 weeks | 4 (2 TAA, 2 TAD, 0 AAA/AAD) | 0 | Low |
| Garcia-Martinez *et al*[23] | 40/54 (74%) | 77 (63–91) | Biopsy proven | CXR+abdominal USS ±CT | See note 3 | Median 5.4 (4–10.5) years | 12 (4 TAA, 7 TAD, 1 AAA) (5F) | 0 | Low |
| Karamagkiolis *et al*[29] | NR/49 | 73.5 (SD 4.5) | NR | Annual CT thorax and abdomen | NR | 7 years | 4 (4 TAA, 1 AAA) | 0 | Unclear (meeting abstract) |
| Both *et al*[30] | 86/105 (82%) | 65.2 | ACR criteria, or limb stenosis | MRA thorax | NR | 31 (1–157) months | 18 (18 TAA) | 0 | Low |
| Koenigkam-Santos *et al*[31] | NR/28 | 69 (36–84) | ACR criteria; or PMR with additional features suggesting large-vessel disease | MRA thorax | NR | NR | 0 (0 TAA) | 0 | High |
| Blockmans *et al*[14] | 32/46 (70%) | 73 (49–85) | Biopsy proven | Aortic CT | See note 4 | 46.7 (SD 29.9) months | 11 (11 TAD) | 0 | High |
| Schmidt *et al*[32] | 23/33 (70%) | 73 (58–88) | ACR criteria (except 2) | Abdominal USS | NR | At diagnosis | 2 (2 AAA) | 0 | Low |
| Agard *et al*[5] | 25/30 (83%) | 69 (61–90) | Biopsy proven | Abdominal USS | See note 5 | Within 8 weeks | 8 (4 AAA, 4 AAD) | 0 | Low |
| Gonzalez-Gay *et al*[27] | 113/210 (54%) | 75 | Biopsy proven | Records review (not all patients imaged) | NR; overlap with dissection | 57 (0–162) months | 20 (16 TAA, 6 AAA) | 2 (1) | Low |
| Nuenninghoff *et al*[28] | NR | NR | ACR criteria (except 2) | Pathology or imaging (not all patients imaged) | NR | 10.9 (TAA), 6.3 (AAA) | 20 (9 TAA, 11 AAA) | 10 (6) | Low |

Note 1. TAD: >4 cm in ascending aorta, at least 4 cm in aortic arch or descending aorta; AAD: diameter at least 3 cm in abdominal aorta. Loss of normal progressive reduction in the abdominal aortic calibre was also considered as dilatation.
Note 2. TAA: aortic dilatation with loss of wall parallelism according to New York Heart Association (NYHA) criteria. TAD: radiologist-defined abnormal dilatation without loss of wall parallelism.
Note 3. TAA: focal dilatation of aortic wall. TAD: diffuse dilatation with diameter >4 cm in ascending aorta, or at least 4 cm in arch and descending aorta.
Note 4. TAD: diameter of ascending aorta >4 cm.
Note 5. AAA: dilatation of the aorta, either saccular or fusiform, with loss of aortic wall parallelism (NYHA definition). AAD: radiologist-defined abnormal dilatation without loss of wall parallelism.
AAA, abdominal aortic aneurysm; AAD, abdominal aortic dilatation; ACR, American College of Rheumatology; CXR, chest x-ray; MRA, magnetic resonance angiogram; NR, not reported; PMR, polymyalgia rheumatica; TAA, thoracic aortic aneurysm; TAD, thoracic aortic dilatation; USS, ultrasound scan.

**Table 2** Pooling of the prevalence of newly identified thoracic abdominal aneurysm or thoracic abdominal dilatation, using data from imaging studies

| Study | TAA/TAD prevalence (95% CI) by binomial exact method, % | TAA/TAD prevalence in meta analysis (95% CI), % | Model 1 (4 full reports and 1 meeting abstract) weighting, % | Model 2 (4 full reports only) weighting, % | Model 3 (biopsy-proven GCA only), % |
|---|---|---|---|---|---|
| Prieto-Gonzalez *et al*[4] | 15.0 (5.7 to 29.8) | 15.0 (3.9 to 26.1) | 15.22 | 20.45 | 39.49 |
| Agard *et al*[3] | 18.2 (5.2 to 40.3) | 18.2 (2.1 to 34.3) | 7.52 | 9.64 | 18.61 |
| Garcia-Martinez *et al*[23] | 20.4 (10.6 to 33.5) | 20.4 (9.6 to 31.1) | 16.07 | 21.71 | 41.90 |
| Karamagkiolis *et al*[29] | 8.2 (2.3 to 19.6) | 8.2 (0.5 to 15.8) | 29.04 | – | – |
| Both *et al*[30] | 17.1 (10.5 to 25.7) | 17.1 (9.9 to 24.4) | 32.15 | 48.20 | – |
| Estimated pooled prevalence (95% CI), % | | | 14.8 (10.3 to 19.3) | 17.5 (12.5 to 22.5) | 17.8 (10.9 to 24.8) |
| Number of patients needed to be imaged in order to pick up one new thoracic aortic aneurysm or dilatation, calculated from pooled prevalence (95% CI) | | | 6.8 (5.2 to 9.7) | 5.7 (4.4 to 8.0) | 5.6 (4.0 to 9.2) |

Model 1: goodness-of-fit $\chi^2$ value heterogeneity was 4.49, p>$\chi^2$=0.34. $I^2$ (variation in prevalence attributable to heterogeneity)=10.8%.
Model 2: goodness-of-fit $\chi^2$ value heterogeneity was 0.49, p>$\chi^2$=0.92. $I^2$ (variation in prevalence attributable to heterogeneity)=0.0%.
Model 3: goodness-of-fit $\chi^2$ value heterogeneity was 0.47, p>$\chi^2$=0.791. $I^2$ (variation in prevalence attributable to heterogeneity)=0.0%.
GCA, giant cell arteritis; TAA, thoracic aortic aneurysm; TAD, thoracic aortic dilatation.

The period of maximal TAA/TAD risk remains unclear. Without systematic imaging, the median time between GCA diagnosis and thoracic aortic dissection/rupture was 1.1 years, and the median time between GCA diagnosis and discovery of unruptured TAA was 10.9 years.[28] In one report, the period of highest risk was the first 5 years after GCA diagnosis, with fewer aneurysms occurring between 5 and 7 years after GCA diagnosis,[33] but, in another report, all aneurysms developed between 5 and 7 years after GCA diagnosis[29]; both these reports are so far published only as meeting abstracts.

Results of the pooled prevalence estimations are shown in table 2. Excluding reports at high risk of bias, on average about seven (95% CI 5 to 10) patients would need to be screened to detect one TAA/TAD.

Reported predictors of aneurysm/dilatation (see table 1 for whether this relates to TAA/TAD alone or all aneurysms) were male gender,[4 14 23 26 29] younger age at diagnosis of GCA,[27] increasing time since diagnosis of GCA,[14] earlier cessation of prednisolone,[23] hypertension[27] (also, those with TAA/TAD[4] were stated in a later report[34] to all have had a history of hypertension, although significance testing was not performed), hyperlipidaemia,[28] lack of hyperlipidaemia,[23] coronary artery disease,[28] not being prescribed aspirin at GCA diagnosis,[29] increased aortic FDG uptake by PET at GCA diagnosis,[14] aortic regurgitant murmur at GCA diagnosis,[28] a combination of polymyalgic symptoms and elevated laboratory markers of inflammation (erythrocyte sedimentation rate >100 mm/h and/or haemoglobin concentration <11 g/dl and/or platelet count >450×$10^9$/l) at GCA diagnosis,[27] and lower erythrocyte sedimentation rate and higher haemoglobin concentration (but no difference in C-reactive protein or interleukin 6 levels) at the time of aneurysm screening.[23] The most reliable information about predictors is likely to come from the series where consecutive patients with GCA were all imaged (see table 1). However, the small study numbers means that CIs are wide, making interpretation of even statistically significant findings difficult—for example, the only two systematic imaging studies of TAA in GCA in which data on gender ratio of TAA/TAD give ORs (95% CI) for male gender as 16.2 (1.6 to 160.2)[4] and 7.0 (1.7 to 28.5).[23] Also, correction for multiple testing has not been performed on any of these data. All in all, the information on clinical predictors of aneurysm must be considered preliminary and highlights an important gap in the published evidence.

## DISCUSSION

This systematic literature review suggests that, on average, pooling studies with a mixture of time points, five to ten patients with GCA would need cross-sectional imaging to identify one TAA/TAD. In one of the imaging studies,[23] patients received a chest radiograph, which was compared with a chest radiograph at diagnosis, and contrast CT scan of the chest was then performed on those 28 patients with radiological suspicion of aneurysm from the latest chest radiograph. This CT scan showed significant structural abnormalities of the thoracic aorta in 11 of the 28 patients imaged. It is unknown how many of the remaining 26 patients in that study who had apparently normal chest radiographs also had TAA/TAD. Estimates of the absolute risk of TAA in GCA are relatively low in routinely collected administrative data, although such studies are limited by the quality of their clinical coding. It is plausible that, in routine clinical practice compared with specialist centres, asymptomatic TAAs may be more likely to remain undetected, and deaths from aortic dissection may be mistakenly attributed to myocardial infarction. Conversely, index case effects, referral bias and publication bias could inflate estimates derived from the studies based in specialist centres. Systematic imaging studies of consecutive patients are therefore critical.

The suggestion that patients who receive lower doses of steroids are more likely to develop aneurysm later[23] raises the question of whether subclinical aortitis may possibly lead to aortic damage even in patients whose GCA is clinically quiescent. Otherwise, there is little to guide assessment of those at greatest risk: many of the reported predictors of aneurysm could be confounded by known associations of TAA in general (male gender and hypertension; smoking is a further predictor of AAA).

These data are limited by the absence of any controlled trials of aneurysm screening in GCA. The next best sources of evidence are the reports of imaging studies, which are limited by their small size and heterogeneity (including time point of imaging, modality of imaging and definition of aneurysm/dilatation). Genetic heterogeneity in the background population may introduce further unknown variability—for example, *HLA-DRB1**04 may be associated with both inflammatory and non-inflammatory AAA in the general population, with an OR of 2.5 and 2.0, respectively.[35] *HLA-DRB1**04 is also associated with GCA with an OR of similar magnitude.[36] Given the surprisingly high incidence of aneurysms at diagnosis of GCA (table 1), it would be

interesting to determine the extent to which the association between GCA and aneurysm can be explained by *HLA-DRB1**04. It is important to remember that the existence of a statistical association between GCA and aneurysm does not necessarily imply direct causation (in either direction). It would be helpful to have longitudinal data from GCA inception cohorts, where symptomatic/laboratory response to therapy is evaluated as a candidate predictor of aneurysm risk; the existing data[23] suggest that suppression of conventional laboratory markers may not be a very good guide to future aneurysm risk.

There remains much that is unknown about aneurysm in GCA. Even the mechanism of aneurysm is debated; the assumption that aneurysm arises from direct inflammation-related damage to elastin has recently been challenged by a hypothesis that aneurysm may arise proximal to a stiff, inflamed aortic segment.[4] Estimates of the prevalence of aneurysm in GCA could be biased by index case effects and by selectively including individuals with other risk factors for TAA. The way the risk changes following the diagnosis of GCA also remains unclear. Assumptions about the rate of progression, extrapolated from the natural history of TAA in the absence of GCA, may not hold true, since GCA causes damage to the internal elastic lamina. Establishing what diameter of TAA/TAD carries a significant risk of dissection or rupture may prove a challenge. Lastly, it remains unclear whether chest radiography is actually sensitive enough to pick up TAAs in routine clinical practice, as opposed to research studies designed to pick up TAAs, in which over half of all patients with GCA in the study ended up receiving a CT.[23] Those with aortic abnormalities on CT did not all have surgery.[23] It is not known how many TAAs may be missed by chest radiography. Whether routine imaging can be generally recommended must also take into account resource use, including costs, scanning and reporting time, patient acceptability of each imaging modality, and the risks of ionising radiation or intravenous contrast (depending on the imaging modality selected). In view of all these unknowns, further research would seem useful, with the aim of defining a protocol that would detect a TAA before it grows large enough to cause aortic insufficiency, congestive cardiac failure, dissection or rupture. In this way there would be time to control the blood pressure to reduce the risk of progression, and to make plans for future corrective surgery if appropriate.

In conclusion, the limited data available suggest that there is a significant risk of aneurysm in GCA, but the precise risk and time course of that risk remain unclear. AAA can be detected by ultrasonography, but chest radiography may miss many TAAs, raising the question of whether patients with known GCA should have a CT or MRI to image the aorta. We suggest that clinicians, rather than ordering thoracic imaging for every patient with previous GCA, should first have a clear idea of how the result of that imaging would change the management of the individual patient. There remains a significant research agenda to further define exactly when and how any imaging should be performed.

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# Should I send my patient with previous giant cell arteritis for imaging of the thoracic aorta? A systematic literature review and meta-analysis

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**Notes**