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REVIEW ARTICLE

Quantitative computed tomography and opportunistic bone density screening by dual use of computed tomography scans

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Summary Central dual-energy X-ray absorptiometry (DXA) of the lumbar spine and proximal femur is the preferred method for bone mineral density (BMD) testing. Despite the fracture risk statistics, osteoporosis testing with DXA remains underused. However, BMD can also be assessed with quantitative computed tomography (QCT) that may be available when access to DXA is restricted. For patients undergoing a primary CT study of the abdomen or pelvis, a potential opportunity exists for concurrent BMD screening by QCT without the need for any additional imaging, radiation exposure, or patient time.
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Introduction

Central dual-energy X-ray absorptiometry (DXA) of the lumbar spine and proximal femur is the preferred method for bone mineral density (BMD) testing. Despite the fracture risk statistics, osteoporosis testing with DXA remains underused [1,2]. However, BMD can also be assessed with other radiologic imaging tools, such as quantitative computed tomography (QCT) that may be available when access to DXA is restricted [3]. Originally, QCT was developed as a methodology using single thick (around 10 mm) CT image slices angled to sample the vertebrae and to avoid the cortical end plates. However, this mode of operation has now been largely superseded by the use of volume images covering regions of interest at the spine or hip.

For patients undergoing screening CT colonography (CTC), a potential opportunity exists for concurrent BMD screening by QCT without the need for any additional imaging, radiation exposure, or patient time [4]. In addition, there are a number of indications for CT imaging for which there is a large overlap between the need for a CT scan and a patient having risk factors for osteoporosis. By utilizing volume-based QCT methodology rather than the older single-slice protocols, use may also be made of these CT images for BMD measurement by QCT [5,6]. Such dual use of CT images could increase screening rates or, alternatively, preclude the need for DXA screening in some individuals.

Previous studies combining standard CT imaging and QCT have generally focused on BMD measurement at the

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lumbar spine [7,8] for which QCT provides a volumetric BMD measure of the trabecular vertebral bone in isolation. This can have an advantage of superior sensitivity due to the higher turnover rate of trabecular bone [9], but QCT T-scores on average are somewhat lower than DXA T-scores for the same age, and the established World Health Organization (WHO) classification of osteoporosis by DXA T-score is not appropriate [10]. By contrast, at the proximal femur, QCT three-dimensional (3D) data may be used to derive a projectional two-dimensional (2D) image of the proximal femur, and this image may be analysed using standard DXA region of interests (ROIs) to determine DXA-equivalent "computed tomography X-ray absorptiometry (CTXA)" areal BMD (aBMD) values in g/cm^2 [11]. Using this method, the WHO T-score classifications may be applied and the aBMD measures may be included in FRAX calculations.

The workflow associated with such dual use of CT scans may be improved using "phantom-less" or "asynchronous" calibration methods, so that the BMD measurement does not need to be planned in advance of the CT scan. In addition, using such methods, it is possible to make use of archived CT scans retrospectively [12]. Finally, the use of intravenous (IV) contrast-enhanced CT images for QCT is usually contraindicated and a measurement bias has been shown at the spine [13]. However, some recent studies suggest that for measurements made at the hip, the measurement difference due to contrast enhancement may not be clinically significant, further widening the utility of CT scans for BMD measurement [14].

Standard QCT

QCT may be performed on any CT scanner with the use of a calibration phantom and dedicated analysis software. The patient is usually examined in the supine position, lying on the phantom, usually with a water- or gel-filled cushion between the phantom and patient to avoid CT reconstruction (Figure 1). Calibration phantoms are required to transform the attenuation measured in Hounsfield units into BMD values. When the patient and phantom are examined at the same time, the process may be described as "simultaneous calibration". Three of the most frequently used calibration phantoms for this purpose are the solid-state Cann—Genant phantom (Mindways Software Inc., Austin, TX, USA) containing five potassium phosphate-equivalent density phases; the five-phase solid-state calcium hydroxyapatite phantoms developed by Image Analysis Inc. (Columbia, KY, USA); and the phantom developed by Kalender et al [15] utilizing two calcium hydroxyapatite phases. This latter phantom is used by Siemens (Siemens Healthcare, Erlangen, Germany) for their commercial QCT product. BMD measurements from different types of calibration phantoms are not interchangeable, unless a cross-calibration calculation is performed.

Single-slice QCT

Single-slice QCT was the original QCT methodology, which was developed on single-slice CT scanners for trabecular
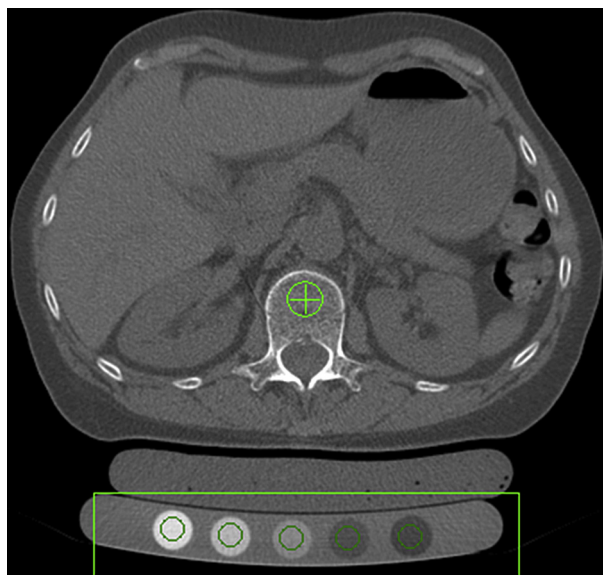

Figure 1 Simultaneous calibration involves the patient lying on top of a calibration phantom, in this case, a five-phase Cann—Genant phantom. A gel-filled bolus bag fills the air gap between the phantom and lumbar region.

BMD measurements at the lumbar spine. Using the standard methodology, single sections of three to four consecutive vertebrae from T11 to L4 are scanned [16] (Figure 2). A typical acquisition involves 10-mm slice thickness with a gantry tilt used to derive midvertebral sections parallel to the vertebral end plates. The gantry tilt is selected interactively by the technologist from the lateral scout view.

Single-slice QCT protocols generally have radiation doses that are higher than those of DXA, although these doses are smaller than many other radiographic procedures. Low-
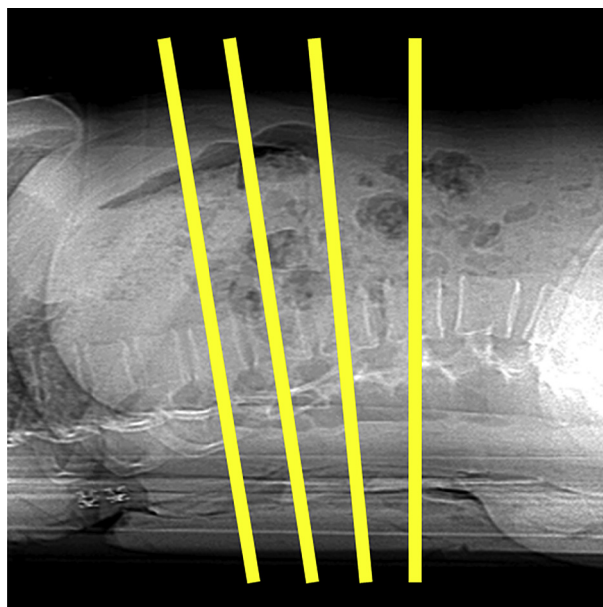

Figure 2 Single-slice quantitative computed tomography protocols typically use a series of three to four 10-mm slices angled parallel to the vertebral end plates.

dose protocols using 80 kVp (or 120 kVp) and 120 mAs (or 150—200 mAs) result in effective doses of less than 200 µSv [16]. By way of comparison, DXA has radiation doses in the order of 10—15 µSv for the spine and hip. However, QCT has lower exposure doses than many other standard radiology procedures: an anteroposterior lumbar spine radiograph has a dose of 700 µSv and a standard abdominal CT has an exposure dose of the order of 8000 µSv [17].

Although radiation exposure dose can be substantially lower with single-slice QCT compared with volumetric QCT (vQCT), which is described in the next section, a substantial disadvantage with single-slice BMD analysis by 2D QCT is the lower precision compared with that of DXA (1.5—4% vs. 1%), which results in a larger least significant change required to detect significant changes in BMD (6—11% vs. 3%). This, however, is partially offset by the fact that metabolic activity of trabecular bone is higher and that even lower precision single-slice QCT is usually adequate to monitor longitudinal changes that are in the same range as those found with DXA.

Of course, it should be noted that, in the context of opportunistic screening by the dual use of a CT scan, exposure dose is not an issue because a CT scan has already been performed for some other purpose. However, although a single, angled slice could be extracted from a volumetric CT of the abdomen for secondary computation of BMD at the spine, the lower precession means that vQCT is the favoured method.

Volumetric QCT

vQCT or 3D QCT has increased precision and is easier to perform compared with single-slice QCT. A contiguous volume with a slice thickness of 1—3 mm with no CT gantry tilt is typically scanned (Figure 3). At the lumbar spine,
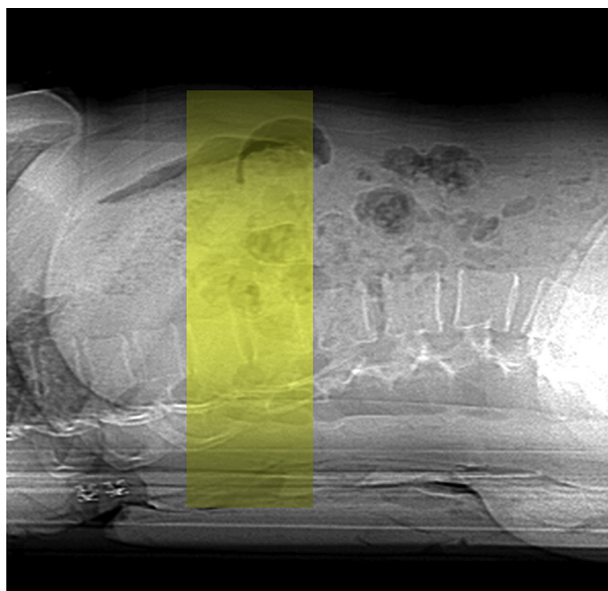
protocols usually include only two vertebrae between T11 and L4, often L1 and L2, to reduce dose while achieving measurement precision noninferior or superior to that reported for single-slice QCT [16]. Typical values are in the order of 80—120 kVp and between 50 and 200 mAs. Using these parameters, the dose has been estimated using pharmaceutical clinical trials protocols with 1-mm slice width to be as high as 1.5 mSv for the spine and 2.5—3 mSv for the hip [16]. For a fixed noise level, exposure, and consequently dose, decreases inversely to slice thickness. Thus, doses of under 1 mSv for 2.5—3.0-mm slice thicknesses commonly used for clinical QCT are achievable. This is consistent with lower doses on the order of 0.3—0.6 mSv for the spine described by one of the CT manufacturers [18]. The precision for trabecular BMD measurements by vQCT is superior to 2D slice-based QCT, which is comparable with that of DXA [16].

At the spine, QCT provides a volumetric BMD measure of the trabecular vertebral bone in isolation (Figure 4). This can have an advantage of superior sensitivity because of the higher turnover rate of trabecular bone [9] and can also avoid the confounding effects of joint-space narrowing, osteophytes, aortic calcification, and other extraosseous calcification that can artificially raise a DXA spine BMD measurement [19—21]. However, the measurement of isolated trabecular bone means that QCT T-scores are somewhat lower, on average, than DXA T-scores for the same age [10], and the established WHO classification of osteoporosis by DXA T-score is not appropriate. To facilitate the interpretation of QCT spine results, the American College of Radiology has in 2008 and 2013 published guidelines for the performance of QCT [22]; based on these guidelines, volumetric trabecular BMD values from 120 mg/cm^3 to 80 mg/cm^3 are defined as osteopenia and BMD values less than 80 mg/cm^3 as osteoporosis.

Projectional QCT: Hip

By contrast, at the proximal femur, 3D QCT data may be used to derive a projectional 2D image of the proximal femur (Figure 5), and this image may be analysed using standard DXA ROIs to determine DXA-equivalent CTXA aBMD values in g/cm^2. Because the correlations between these calculated BMD values of the proximal femur and those obtained by DXA are extremely high, the WHO T-score

Figure 3 For three-dimensional volumetric quantitative computed tomography protocols, a contiguous volume with a slice thickness of 1—3 mm with no computed tomography gantry tilt is typically scanned.

Figure 4 At the spine, a region of interest used measures the trabecular bone mineral density in isolation.
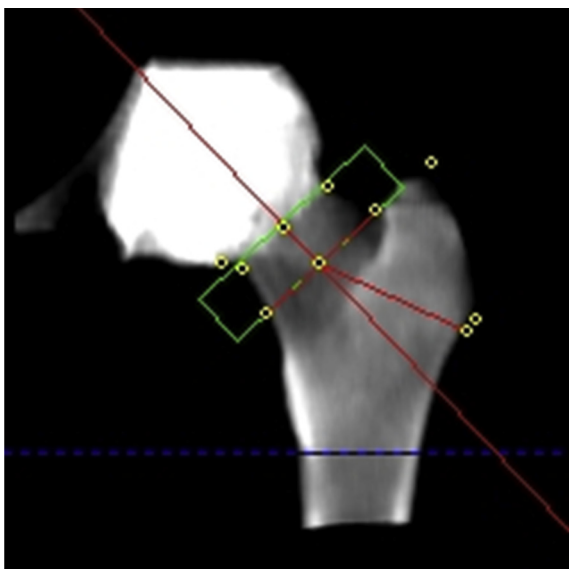
Figure 5 At the hip, computed tomography can produce projectional data that are used with region of interests similar to dual-energy X-ray absorptiometry (DXA), to provide DXA-equivalent areal bone mineral density measurements and T-scores.

classifications may be applied [23]. The precision of projectional hip BMD values has been found to be slightly better than DXA in the same patients [10,13,22], probably because of hip rotation being performed by software rather than at the time of acquisition. Areal CTXA BMD measurements from hip QCT are included in the FRAX tool [24], and hip BMD conversion equations are available between Hologic and Lunar DXA and QCT. In addition, the 2008 and 2013 American College of Radiology QCT Practice Guidelines state that QCT at the hip also provides aBMD with DXA-equivalent T-scores.

Calibration methods

The usual protocol of scanning a calibration phantom with a patient for QCT can be problematic for the dual use of CT images. In particular, the requirement for phantom placement must be known prior to scanning the patient, and the workflow including the patient positioning associated with a regular CT imaging protocol must be altered. There is, therefore, a considerable advantage in not requiring a phantom to be scanned simultaneously with the patient. If a phantom is not scanned simultaneously with the patient, either a separate scan of a calibration phantom (asynchronous calibration) must be performed, or an "internal" or "phantom-less" calibration based on the Hounsfield units of several tissues within the body may be applied.

Although previous studies have indicated that uncalibrated Hounsfield units values from CT scanners may be used for the opportunistic screening of low bone mass [4], the use of a calibration standard means that the derived aBMD results and T-score computations will be consistent across CT scanners from different manufacturers and also consistent at different scanning X-ray energies [25].

Internal BMD calibration

The principal behind QCT utilizing internal calibration is to use CT values of internal tissues as references for the BMD calibration. In general, the method relies on the patient's paraspinal muscle and subcutaneous fat as calibration references and uses the peak of a best-fit Gaussian distribution to the muscle and fat histograms, respectively, for the calibration [26].

Only two technical studies on the use of internal calibration have been published, and both of these were of measurement at the spine [26,27]. The original method reported by Boden et al [27] was made commercially available by IRIS Inc. (Myersville, MD, USA). This method has been used by Gudmundsdottir et al [28] to investigate age-related vertebral BMD changes in Icelandic women and by Hopper et al [29] to explore the possibility of opportunistic screening using contrast-enhanced and noncontrast abdomen and pelvic scans. The method has been provided as a QCT solution on Philips CT scanners (Philips Healthcare, Cleveland, OH, USA) and has been used in this format by Pickhardt et al [8] for opportunistic screening.

Despite the convenience of using an internal calibration standard, there are some disadvantages to the method. The reproducibility of external phantom systems is generally superior to that of internal calibration systems because of the underlying differences in muscle attenuation related to variations in atrophy, fat infiltration, and hydration [26]. In addition, although Weber et al [14] presented the use of CT scans of inflammatory bowel disease patients for projectional aBMD measurement at the hip, the internal reference standards that were used are not described and no established calibration standards for use at the pelvis for the analysis of BMD at the proximal femur have yet been presented in peer-reviewed literature.

Asynchronous BMD calibration

An alternative to either simultaneous calibration or the use of internal calibration standards is the method of using an external calibration standard but scanned in an "asynchronous" mode at a different time from the patient scan [30]. In a recent study on asynchronous calibration [31], T-scores derived from CTXA were compared with T-scores obtained from DXA. Correlation between DXA and CTXA T-scores was as high as the correlation of T-scores between different DXA scanners, indicating that asynchronous calibration of the CT images was very successful in that study. The period between the CT scans of the patients and those of the external calibration phantom were reported as being approximately 4 years, which indicates good CT scanner stability over this period.

Dual use of CT scans

The usual procedure for a producing a dedicated QCT hip BMD acquisition uses an anterior—posterior computed radiograph or localizer obtained by the scanner from the iliac crest to a few centimetres past the lesser trochanter. At the spine, a lateral localizer is used to define a volume covering two contiguous vertebral levels. A contiguous

series of CT images are then acquired from the superior femoral head to approximately 1 cm below the lesser trochanter with a 2.5—3.0-mm slice thickness and spacing between images. For opportunistic screening or dual use of CT images, CT volume images may be sampled using software tools such as SlicePick (Mindways Software Inc., Austin, TX, USA) to produce a simulated projection anterior—posterior image to locate the femoral head and lesser trochanter or to produce a simulated projection lateral image to locate vertebral levels in the same way as using a localizer. A contiguous set of slices is then chosen covering this region for BMD analysis (Figure 6).

In the context of CTC screening, for which there is an obvious overlap in the screened population due to age [12], the changes required to normalize CTC workflow to facilitate QCT of the hip are easily accommodated and comprise asynchronous calibration scans performed periodically (e.g., monthly), ensuring that the CTC scan volume appropriately includes the entire anorectal junction so that the lesser trochanters are imaged, which is often a standard protocol in CTC imaging.

Influence of contrast media

Many of the existing CT abdominal and pelvic CT scans that might be used for the diagnosis of low BMD have been acquired after IV contrast administration. Because contrast media increase X-ray absorption, it would be expected that BMD values in perfused areas such as the trabecular

Figure 6 A volume at the hip or spine may be manually segmented from standard computed tomography scans covering a region from the top of the acetabulum to below the lesser trochanter, or a pair of contiguous vertebral levels, using the SlicePick tool from Mindways.

compartment of the vertebrae will increase, and QCT bone density measurement is contraindicated for patients undergoing IV contrast CT scans. While trabecular bone is measured at the spine, projectional measurement of BMD at the hip incorporates both cortical and trabecular bone. Thus, it is generally expected that vBMD measurement by QCT at the spine should be more affected than aBMD measured by QCT at the hip.

Of the studies to date that investigated the feasibility of dual use of CT images [4,7,8,13,14,26,29,31—33], around a half have addressed the issue of dealing with the potential for IV contrast to increase BMD measurement [13,14,26,32,33]. Most of these previous studies on the effect of IV contrast on QCT measurement have focused on BMD measurement at the lumbar spine, and to date only a few studies have addressed this issue at the hip [13,14,33]. In the study by Gruber et al [33], the measurement made was volumetric BMD at the hip and this was compared with DXA measurement. No projection method was employed to measure a DXA-equivalent aBMD from QCT data. Although both the other studies [13,14] did produce aBMD measurements by projection from vQCT, Weber et al [14] used an internal calibration standard, and Bauer et al [13] used an external calibration standard within the patient scan for simultaneous calibration.

The previous study by Bauer et al [13] used BMD measurements obtained from vQCT of the spine and hip and correlated them with those derived from nondedicated contrast-enhanced standard CT data sets to derive a calibration factor for vQCT. Based on linear regression, a correlation coefficient of $r = 0.98$ was calculated for lumbar BMD with the equation BMD (QCT) $= 0.96 \times$ BMD (MD—CT) $- 20.9$ mg/cm^3. The investigators concluded that with the conversion factors, reliable vBMD measurements can be calculated for the spine from routine abdominal and pelvic CT data sets. However, the absolute numbers show considerable divergence because of the presence of the contrast in the vertebral bone marrow.

Habashy et al [30] reported a similar additive bias of 20 mg/cm^3 to 23 mg/cm^3 in volumetric spine BMD estimates for a paediatric population. This group reported a cross-calibration equation including compensation for IV contrast volume: BMD (QCT) $=$ BMD (with contrast) $- 35.3$ mg/cm^3 $+ 0.14$ mg/cm^3/mL $\times$ (IV contrast volume in millilitre). A standard error of the estimate of 10.79 mg/cm^3 was reported for the prediction of standard externally calibrated QCT BMD estimates from QCT BMD estimates derived in the presence of IV contrast agent. Assuming a standard deviation of 26 mg/cm^3 for a 1 T-score unit change implies a standard error of about 0.4 T-score units for this standard error. This degree of uncertainty compares favourably to a precision of 0.4 T-score units reported by Kiebzak et al [36] for femoral neck T-scores obtained across DXA units from different manufacturers. While evidence exists supporting the notion of screening for low bone mass based on lumbar spine QCT BMD estimates obtained in the presence of IV contrast agent, this finding is tempered by results from Acu et al [34] that show a significant time dependency to such BMD measurements relative to the time since IV contrast agent injection.

At the hip, Bauer et al [13] showed a coefficient of $r = 0.99$ with the equation BMD (QCT) $= 0.99 \times$ BMD (MDCT) $- 12$ mg/cm^2 ($p < 0.01$). In their study, Weber et al

[14] found that DXA- and contrast-enhanced CT enterography-generated T-scores for femoral neck BMD were highly correlated ($R^2 = 0.84$, $p < 0.0001$), with a linear agreement and no significant offset from the origin. Interestingly, the large study by Pickhardt et al. [4] based on the use of CT values without any calibration stated that IV contrast did not affect the ability of CT to distinguish patients with low BMD from those with normal BMD.

Conclusion

The potential clinical implications of extracting BMD data from routine CT examinations are very wide ranging as virtually any unenhanced abdominopelvic CT scan could presumably be employed. Given the enormous patient volume of body CT scanning currently performed in older adults for a wide variety of clinical indications, this represents a unique opportunity to expand osteoporosis screening. Importantly, this opportunistic screening requires no additional patient time or radiation exposure, and very little time from radiology staff, further enhancing the clinical yield of the CT scan; and one clear advantage of CT over DXA BMD screening is its ability to accurately identify unsuspected osteoporotic compression fractures, which clearly diagnose osteoporosis independent of the patient's DXA T-score [35].

Classically, QCT has utilized an in-scan phantom for simultaneous calibration because of instabilities in CT equipment. In particular, differences in table height from scan to scan of a given patient can at least partly be compensated with a simultaneous calibration. In the last decade or so, CT scanner stability has improved a great deal, which has led to the possibility of asynchronous calibration methods. There are a number of potential advantages in avoiding the need for the placement of a calibration device beneath the patient by allowing for calibration using a phantom to take place asynchronously. Asynchronous calibration can achieve the following:

- Simplify radiology facility workflow by avoiding the need for CT calibration phantom and table pad placement.
- Reduce the risk of needing to rescan a patient due to improper placement of a CT calibration phantom.
- Reduce overall patient exposure to ionizing radiation by combining a medically appropriate bone density study with another medically necessary CT study utilizing the same CT scan covering the abdomen (spine), pelvis (proximal femur), or abdomen and pelvis.
- Allow for retrospective extraction of bone density information from CT scans of the abdomen and/or pelvis acquired for other purposes, again resulting in an overall reduction in exposure of a patient to ionizing radiation.

However, retrospective analysis of existing CT scans must still be treated with some caution without some knowledge of the scanner stability between patient and phantom scans. Further investigation is required to assess the impact that IV contrast might have on BMD measurement by QCT evaluation at both the spine and the hip. However, if the use of postcontrast CT scans can be validated for BMD evaluation, particularly for the use of projectional aBMD at the hip—for which there appears to be little or no significant change—the clinical impact would be accentuated even further.

Conflicts of interest

Both authors are employees and shareholders of Mindways Software Inc., Austin, TX, USA.

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