Opportunistic Screening of Low Bone Mineral Density From Standard X-Rays

CME

VISUAL ABSTRACT

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Abstract

Background: Osteoporosis, characterized by loss of bone mineral density (BMD), is underscreened. Osteoporosis and low bone mass are diagnosed by a BMD T-score $\leq$ –2.5, and between –1.0 and –2.5, respectively, at the femoral neck or lumbar vertebrae (L1-4), using dual energy x-ray absorptiometry (DXA). The ability to estimate BMD at those anatomic sites from standard radiographs would enable opportunistic screening of low BMD (T-score $<$ –1) in individuals undergoing x-ray for any clinical indication.

Methods: Radiographs of the lumbar spine, thoracic spine, chest, pelvis, hand, and knee, with a paired DXA acquired within 1 year, were obtained from community imaging centers (62,023 x-ray–DXA pairs of patients). A software program called Rho was developed that uses x-ray, age, and sex as inputs, and outputs a score of 1 to 10 that corresponds with the likelihood of low BMD. The program's performance was assessed using receiver-operating characteristic analyses in three independent test sets, as follows: patients from community imaging centers (n = 3,729; 83% female); patients in the Canadian Multicentre Osteoporosis Study (n = 1,780; 71% female); and patients in the Osteoarthritis Initiative (n = 591; 50% female).

Results: The areas under the receiver-operating characteristic curves were 0.89 (0.87-0.90), 0.87 (0.85-0.88), and 0.82 (0.79-0.85), respectively, and subset analyses showed similar results for each sex, body part, and race.

Conclusion: Rho can opportunistically screen patients at risk of low BMD (at femoral neck or L1-4) from radiographs of the lumbar spine, thoracic spine, chest, pelvis, hand, or knee.

Key Words: Bone mineral density, machine learning, opportunistic screen, x-ray

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INTRODUCTION

Osteoporosis, a disease characterized by the loss of bone mineral density (BMD), affects 200 million lives globally [1]. Its prevalence in the United States, in men and women aged 50 years and older, is 15% and 4%, respectively, and with the aging population, its incidence and prevalence are rising [2].

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Dr Bilbily and Dr Cicero contributed equally.

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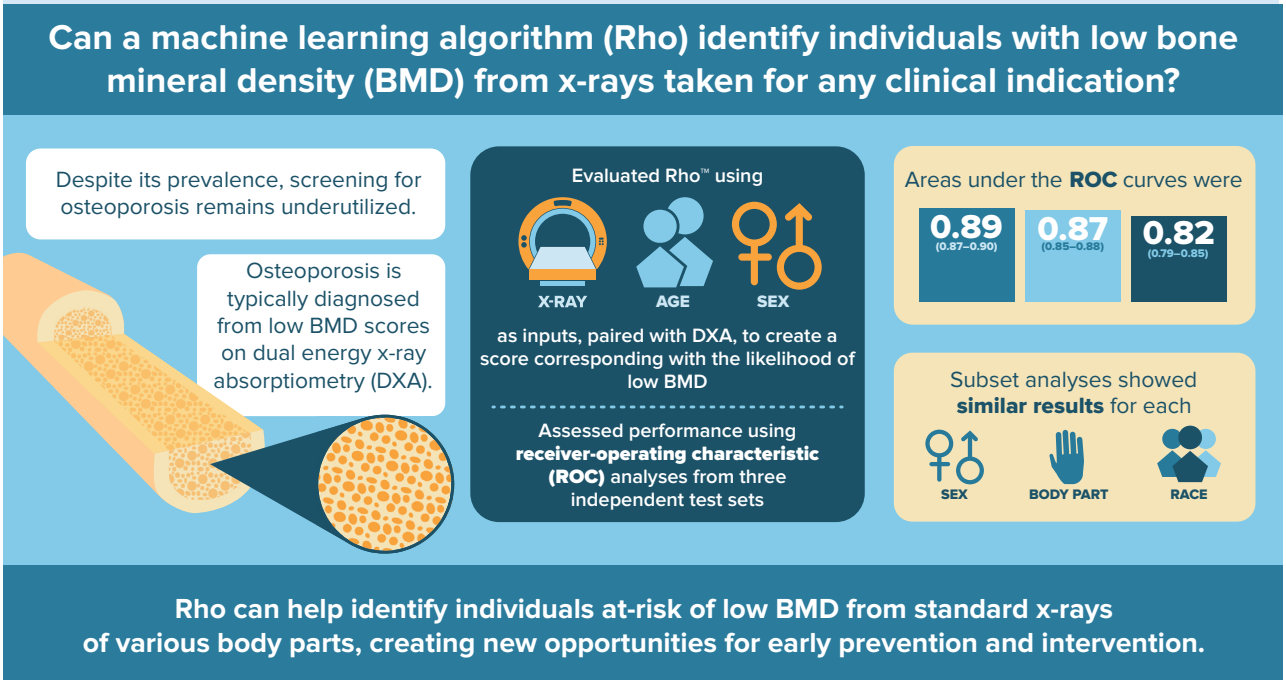
Visual Abstract



In their lifetime, up to 50% of women and 22% of men will suffer an osteoporotic fracture [3]. Of patients who suffer an osteoporotic hip fracture, almost one-third die within 1 year [4]. Currently, to identify those at risk, a clinician conducts a clinical fracture risk assessment, and if appropriate, refers a patient for dual-energy x-ray absorptiometry (DXA) for diagnosis. The US Preventive Services Task Force recommends BMD testing by DXA for women aged 65 and older, and for younger women with certain clinical risk factors [5], but screening rates are low, and osteoporosis is underdiagnosed [6]. Among women who are privately insured, fewer than 25% of those eligible are screened [7]. The US Preventive Services Task Force makes no recommendation for screening for men [5], and thus, men's screening rates are also low [8]. In Canada, DXA is indicated for women and men aged 65 and older, and for younger adults with clinical risk factors for fracture, including those found to have low bone density on radiograph [9]. Both lifestyle and pharmacologic therapy are available for prevention and treatment.

Deep convolutional neural networks have been trained by multiple research groups to learn the complex features of bone and soft tissue attenuation used to estimate BMD and T-score from standard x-rays [10-13]. Health Canada recently licensed Rho (16 Bit, Toronto, Canada), a machine learning–based opportunistic prescreener for low BMD, as a class II software-as-a-medical device, and it is commercially available in Canada. A regulatory submission is under review by the FDA; Rho is not available for sale in the United States. When installed on an institution's network, Rho connects to the PACS by leveraging the DICOM standard. Rho automatically detects, downloads, and analyzes eligible x-rays (defined as frontal x-rays of the chest, lumbar spine, thoracic spine, pelvis, hand, or knee in patients aged 50 years or older) as soon as they are acquired. Rho generates a score from 1 to 10; the higher the score, the higher the likelihood that the patient has low BMD (defined as a DXA T-score < -1 at L1-4 or femoral neck [FN]). The Rho score is included in a one-page report that is automatically sent back to the PACS and is directly viewable by radiologists in their existing clinical workflow at the time of x-ray reporting. Radiologists can choose to include Rho's finding in their report if the patient has a high likelihood of having low BMD. Inclusion of such a finding could prompt the referring physician to conduct a clinical fracture risk assessment, and if necessary, refer the patient for DXA BMD analysis. By initiating a fracture risk assessment, Rho could help improve low osteoporosis screening rates.

Here, we describe the development of Rho, report on its performance in three independent datasets, and describe how use of this device can improve clinical care.

Table 1. Test set characteristics

Characteristic	TNI		CaMos		OAI	
	Women	Men	Women	Men	Women	Men
x-ray–DXA pairs, n	3,111	618	1,258	522	293	298
Age, y (mean [SD])	66.8 (9.7)	72.5 (9.0)	70.1 (8.2)	68.3 (8.3)	65.9 (8.5)	64.8 (9.2)
% with low BMD	84.6	60.7	75.4	40.4	50.5	28.2
x-ray types						
Chest PA	1,092 (35.1)	239 (38.7)	N/A	N/A	N/A	N/A
Hand AP	210 (6.8)	40 (6.5)	N/A	N/A	78 (26.6)	72 (24.2)
Knee AP	498 (16.0)	74 (12.0)	N/A	N/A	120 (41.0)	124 (41.6)
Lumbar AP	643 (20.7)	148 (23.9)	714 (56.8)	315 (60.3)	N/A	N/A
Pelvis AP	393 (12.6)	64 (10.4)	N/A	N/A	95 (32.4)	102 (34.2)
Thoracic AP	275 (8.8)	53 (8.6)	544 (43.2)	207 (39.7)	N/A	N/A

Values are n (%), unless otherwise indicated. AP = anteroposterior; BMD = bone mineral density; CaMos = Canadian Multicentre Osteoporosis Study; DXA = dual energy x-ray absorptiometry; N/A = not available; OAI = Osteoarthritis Initiative; PA = posteroanterior; TNI = True North Imaging.

METHODS

Datasets

True North Imaging (TNI) Community Imaging Centre data. This retrospective study was performed using de-identified digital radiographs and DXA-derived BMD values of the lumbar vertebrae L1 to L4 (L1-4) and FN from adult patients collected from 19 community imaging centers in Ontario, Canada from January 1, 2010 to January 1, 2021. The study was approved by an independent review board (Veritas, Montreal, Canada), with a waiver of informed consent. An individual's x-rays were paired to a DXA report when the absolute value of Δt (time between x-ray and DXA) was less than 1 year. We assumed that a Δt of up to 1 year was acceptable, given the typically slow rate of bone loss in most patients. The dataset was then split by geographically separated imaging clinics into a *training and validation set* (from 13 TNI centers, hereafter referred to as TNI13, in Kitchener, Cambridge, and Waterloo) and a *test set* (from 6 TNI centers, hereafter referred to as TNI6, in Toronto). Any x-ray–DXA pairs that were not exclusively from TNI6 or TNI13 were discarded.

TNI population for algorithm development. TNI13 data were used to develop the Rho algorithm, to estimate the BMD of both L1-4 and FN from an x-ray of the lumbar spine, thoracic spine, chest, pelvis, knee, or hand (ie, one of six body parts), using DXA values as the reference standard (n = 62,023 x-ray–DXA pairs; Table S1). TNI13 has a higher prevalence of low BMD than the general population (Table S2), as cases are derived from a population of individuals who have had a DXA (and thus already are suspected of being at risk of low BMD).

TNI population for algorithm testing. The TNI6 x-ray–DXA pairs were limited to those aged 50 years and older (n = 8,715 x-ray–DXA pairs). When multiple pairs were available from a single patient, we kept only one pair (see Supplemental Digital Content), to avoid bias in performance of the algorithm due to pseudo-replication (n = 3,729).

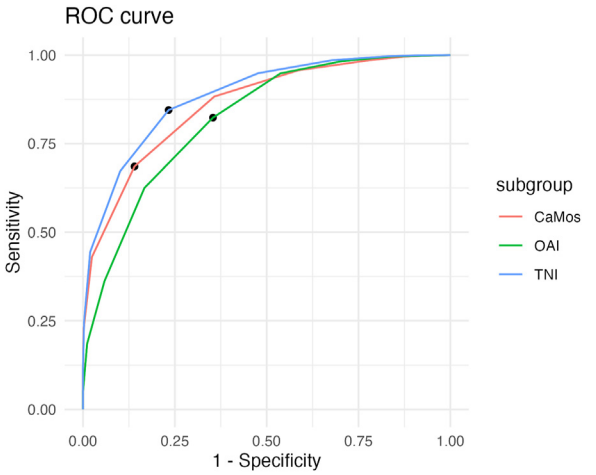


Fig. 1. Receiver operating characteristic (ROC) curves for Rho score predicting low bone mineral density (T-score < –1) in three independent datasets. Areas under the curve (AUC) and 95% confidence intervals are presented for the three datasets. True North Imaging (TNI; *n* = 3,729) AUC: 0.89 (0.87-0.90); Canadian Multicentre Osteoporosis Study (CaMos; *n* = 1,780) AUC 0.87 (0.85-0.87); Osteoarthritis Initiative (OAI; *n* = 591) AUC 0.82 (0.79-0.85).

Table 2. AUC using Rho score or age as a predictor of low BMD in different races

Analysis Group	*n*	Low BMD, *n*	AUC With Age as Predictor	AUC With Rho Score as Predictor	Optimal Rho Score Cutpoint*
TNI6					
Women	3,111	2633	0.62 (0.60-0.65)	**0.89 (0.88-0.91)**	6 (6-6)
Men	618	375	0.58 (0.54-0.62)	**0.82 (0.79-0.85)**	6 (6-6)
CaMos					
Women	1,258	948	0.64 (0.61-0.67)	**0.85 (0.84-0.87)**	7 (7-7)
Men	522	211	0.52 (0.40-0.63)	**0.81 (0.72-0.88)**	6 (6-6)
OAI					
Women	293	148	0.71 (0.66-0.76)	**0.82 (0.78-0.85)**	6 (6-6)
Men	298	84	0.68 (0.62-0.74)	**0.80 (0.75- 0.84)**	5 (5-5)

*To minimize the absolute difference between sensitivity and specificity.
Boldface indicates significance. AUC = area under the receiver operating characteristic curve; BMD = bone mineral density; CaMos = Canadian Multicentre Osteoporosis Study; OAI = Osteoarthritis Initiative; Rho = machine learning–based software program (16 Bit, Toronto, Canada); TNI6 = a test set from 6 True North Imaging centers in Toronto.

Canadian Multicentre Osteoporosis Study (CaMos) population for algorithm testing. A subset of CaMos [14] data with x-ray–DXA pairs were identified (see Supplemental Digital Content). Informed consent was obtained from each participant, and the study was approved by the institutional review board of each participating institution. The current study was approved by an independent review board (Veritas, Montreal, Canada). The subset included participants with digital x-rays of lumbar or thoracic spine aged 50 years and older. We kept only one x-ray–DXA pair per individual (n = 1,780).

Osteoarthritis Initiative (OAI) population for algorithm testing. A subset of the OAI [15] data with x-ray–DXA pairs were identified (see Supplemental Digital Content). Informed consent was obtained from each participant, and the study was approved by the institutional review board of each participating institution. The subset included participants aged 50 years or older with x-rays of the pelvis, hand, or knee. All participants came from the progression subcohort, meaning they had symptomatic tibiofemoral knee OA data at baseline. BMD was measured only at the FN; thus, in this dataset, reference-standard low BMD was defined based on FN BMD T-score < –1. We kept only one x-ray–DXA pair per individual (n = 591).

BMD Reference Standard

Patients were classified as having low BMD if either L1-4 or FN had a BMD T-score < –1, as measured by DXA. BMD T-scores were derived using peak bone mass at L1-4 or FN from National Health and Nutrition Examination Survey (NHANES) female reference values [16,17]. BMD values measured using GE densitometers (GE Healthcare, Madison, WI) were converted to a Hologic base (Hologic Inc, Marlborough, MA) using clinically accepted methods [18].

Machine-learning Algorithm

Rho (developed by 16 Bit [A.B., C.S., M.C.]) was trained using a single machine-learning algorithm (see Supplemental Digital Content) using data from all eligible body parts (chest, thoracic, lumbar, hand, knee, pelvis) of the TNI13 dataset. A k-fold training approach was taken, with k = 4. Validation splits were used to select model parameters that minimized mean absolute error between the model-derived BMD estimates and the DXA BMD measures at both L1-4 and FN.

Algorithm Output

The algorithm outputs a Rho score, rather than a T-score, as it is not intended to diagnose or rule out disease. The Rho score ranges from 1 to 10 and correlates with a patient's likelihood of having low BMD (T-score < –1).

Statistical Analyses

Area under the receiver operating characteristic curve (AUC). The AUC is an effective way to summarize the overall diagnostic performance of a test and is the most appropriate metric in assessing the test's ability to correctly rank order subjects within a population. The 95% confidence intervals were verified with bootstrap resampling (n = 4,000) with replacement. The minimum number of bootstrap samples [19] (10^2/alpha) for an alpha of 0.025 is 4,000. The R package cutpointr [20] was used to calculate the 95% confidence intervals on the AUC using 4,000 bootstraps using in-bag values in the AUC_b column of

Table 3. AUC using age or Rho score as a predictor of low BMD in different races

Race	AUC With Rho Score as Predictor	AUC With Age as Predictor
White (n = 5423)	0.87 (0.86-0.88)	0.59 (0.58-0.61)
Asian (n = 163)	0.93 (0.89-0.96)	0.50 (0.38-0.61)
Other (n = 317)	0.85 (0.81-0.89)	0.60 (0.53-0.67)
Black (n = 181)	0.85 (0.80-0.90)	0.69 (0.62-0.76)
Hispanic (n = 16)	0.96 (0.88-1.00)	0.46 (0.33-0.82)

AUC = area under the receiver operating characteristic curve; BMD = bone mineral density; Rho = machine learning–based software program (16 Bit, Toronto, Canada).

the bootstrap results. The algorithm takes as input an x-ray image, age, and sex. On average, BMD is lower in women than in men, and it decreases with age. To confirm the value of the x-ray image as input into the Rho score, we calculated AUC by age in sex-specific groups to compare with the AUC by Rho score in sex-specific groups.

Sample size and power. Based on the results of each of the four folds during algorithm development, we expected to achieve an AUC of 0.85. We proposed a null hypothesis, or performance goal (PG) for the AUC to be > 0.75 (ie, the lower bound of the 95% confidence interval must be ≥ to the PG). For an AUC point estimate of 0.85 and a PG of 0.75, to achieve 80% power at a one-sided alpha of 0.025, we require 98 negative cases and 98 positive cases (PASS 2021 Power Analysis and Sample Size Software [2021], NCSS, Kaysville, UT). All three datasets had at least 98 negative and 98 positive cases; thus, we are adequately powered for this analysis. Analyses were conducted in relevant subsets, including sex, age decade, x-ray type, and race.

Statistical analyses were performed by C.S., in R, version 4.2.2.

RESULTS

In TNI6, female patients were younger than male patients, and in CaMos and OAI, male patients and female patients were similar in age. In all datasets, as expected, female patients versus male patients had lower BMD, and a higher frequency of low BMD (Table 1). Additional characteristics of body mass index, BMD, and race can be found in Supplemental Digital Content (Tables S3-S5).

The Rho score achieved an AUC of 0.89 (0.87-0.90), 0.87 (0.85-0.87), and 0.82 (0.79-0.85) in the TNI6, CaMos, and OAI datasets, respectively, at classifying low BMD (Fig. 1). Subset analyses by sex, age decade, and x-ray type in the three test sets showed that the AUCs for identifying patients with low BMD were similar—∼0.80 or higher (Tables S6-S8; four subsets had 0.76 < AUC < 0.80; however, each of those four sets was not adequately powered, as they did not have 98 negative cases and 98 positive cases). The Rho score achieved a higher AUC than age, supporting the contribution of the image to the risk score generated (Table 2). When these groups were further divided by age decade, the AUCs for the Rho score all remained similar for each decade (∼0.8), whereas those for age were lower (Table S9).

When the three independent datasets are pooled to increase numbers of x-ray–DXA pairs in racial subgroups, the Rho score achieved an AUC ∼0.8 for the races studied (Table 3).

Sensitivity and specificity of Rho will depend on the Rho score threshold at which a site considers a patient to be at high risk for low BMD. The Rho score in the TNI dataset that minimized the absolute difference between sensitivity and specificity was 6 (Table S6). Table 4 shows the numbers of true and false negatives and positives in the three datasets when this threshold was applied.

The Rho report that is sent to PACS for a radiologist's consideration displays the patient's Rho score, as well as the results from the TNI6 dataset: a graph of the frequency of low BMD (defined by the reference standard, ie, DXA T-score < −1) for the TNI6 patients within each Rho score bin (Fig. S1). For example, 2 of 64 TNI6 patients with a Rho score of 1 (3.1%) had low BMD by DXA, whereas 518 of 613 TNI6 patients with a Rho score of 6 (85%) had low BMD by DXA.

Table 4. Confusion matrix for a Rho score of 6

Dataset	True Positive	False Negative	False Positive	True Negative
TNI	2,541	467	168	553
CaMos	1,024	135	222	399
OAI	145	87	60	299

CaMos = Canadian Multicentre Osteoporosis Study; OAI = Osteoarthritis Initiative; Rho = machine learning–based software program (16 Bit, Toronto, Canada); TNI = True North Imaging.

DISCUSSION

Our study demonstrates that Rho can identify individuals who are at risk of low BMD (defined as DXA BMD T-score < −1 at FN or L1-4) from standard x-rays of various body parts with high diagnostic performance. Results were similar in x-rays of each studied body part (chest, lumbar spine, thoracic spine, pelvis, hand, and knee), ie, even when the FN and L1-4 are not included in the image. Rho's performance in three independent datasets, with different sexes, ages, and races, supports the generalizability of the algorithm. AUC was >0.80 in three independent datasets; TNI6 had a higher prevalence than that in the general population, CaMos had a

prevalence similar to that in the general population, and OAI had a lower prevalence than that in the general population. These results suggest that the algorithm will perform well when implemented in various populations.

This study assessed the performance of an opportunistic screening tool in men and women aged 50 years and older. This age category was chosen partly by design of the preexisting datasets used (ie, CaMos), and due to the fact that most women undergo menopause at this age. The AUC provides an indication of overall diagnostic performance of a test and is the most appropriate metric in assessing a test's ability to correctly rank order subjects within a population; however, sensitivity and specificity of Rho will depend on the Rho score threshold at which a site considers a patient to be at high risk for low BMD. Given that the information provided would otherwise not be obtained, no cost is associated with a true negative or false negative. A true positive potentially saves costs associated with a future osteoporotic fracture (to both the health care system [treatment and rehabilitation] and the individual [potential loss of income or quality of life]). The cost of a false positive includes the time of a radiologist to report the finding, and the time of the patient and physician for a clinical fracture risk assessment. The latter, however, is recommended to be conducted in this age group [21]: a finding of high fracture risk by clinical assessment is an indication for DXA referral in adults aged <65 years (for women in the United States [6], and for both sexes in Canada [9]). Further research is necessary to determine the optimal age for this kind of opportunistic screening, which is likely to vary by jurisdiction based on a variety of health economic factors.

Opportunistic screening of osteoporosis using CT scans, eg, for colonography or lung cancer screening, has been FDA-cleared and is reimbursed by Medicare in the United States [22]. To the best of our knowledge, no such tool has been cleared for opportunistic screening using standard x-ray. Given the high frequency with which standard x-rays, and in particular chest x-rays, are performed, such screening has the potential for widespread integration into clinical practice.

To our knowledge, this is one of the first large studies to use machine learning to predict L1-4 and FN BMD as a means to identify patients at risk for having low BMD, from a variety of standard x-rays, even when the FN and L1-4 are not included in the image. Some studies have used pelvic [10,11] or lumbar [11,13] x-rays, and have shown utility in predicting BMD in those body parts. Other researchers have had success predicting BMD from chest x-rays [12]. Strengths of Rho include its use of end-to-end machine learning without any manual image preprocessing, landmarking, or segmentation systems, and its achievement of a high AUC despite the variety of x-ray inputs, many of which do not include the anatomic sites traditionally used for bone-density assessment (FN and L1-4).

The current study has several limitations. First, DXA BMD values have several sources of error, including variability among both manufacturers [23] and operators, and the impact of degenerative change or aortic calcification; nonetheless, this method is considered the gold standard for BMD measurement. Second, in the OAI dataset, reference-standard low BMD (T-score < -1) was based on the BMD T-score at the FN only (rather than considering the lowest of L1-4 or FN), as L1-4 BMD was not measured. We do not expect that additionally considering L1-4 would greatly affect the results, as a previous study in a US population showed no significant difference in prevalence of low BMD when defining low BMD using FN only versus the lowest of FN and lumbar spine BMD [2]. Strengths of the study include the use of three independent datasets, x-rays of multiple body parts, and analyses to assess performance in relevant subsets, including race. Although the study included relatively small numbers of participants/patients representing traditionally underrepresented subgroups in studies evaluating medical devices, the results suggest that similar performance would be seen in race-based subsets.

TAKE-HOME POINTS

- Incorporating use of a machine-learning algorithm that can identify individuals at-risk of having low BMD by analyzing standard x-rays of the lumbar spine, thoracic spine, chest, pelvis, hand, or knee into clinical practice could provide opportunistic screening of low BMD in patients who undergo radiography for a variety of clinical indications.
- Inclusion of an at-risk finding in a radiologist's report could prompt a referring physician to conduct a clinical assessment of fracture risk.
- An opportunistic screening tool such as this opens a window for early prevention and intervention strategies to slow the rate of bone loss.
- Ultimately, this approach can decrease the incidence of fragility fractures leading to significant health care cost savings and minimizing the morbidity and mortality associated with these fractures.

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ADDITIONAL RESOURCES

Additional resources can be found online at: https://doi.org/10.1016/j.jacr.2023.07.024.

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