Abstract—We describe a novel method of estimating reduced bone mineral density (BMD) from dental panoramic tomograms (DPTs), which show the entire mandible. Careful expert width measurement of the inferior mandibular cortex has been shown to be predictive of BMD in hip and spine osteoporosis and osteopenia. We have implemented a method of automatic measurement of the width by active shape model search, using as training data 132 DPTs of female subjects whose BMD has been established by dual-energy X-ray absorptiometry. We demonstrate that widths measured after fully automatic search are significantly correlated with BMD, and exhibit less variability than manual measurements made by different experts. The correlation is highest towards the lateral region of the mandible, in a position different from that previously employed for manual width measurement. An receiver-operator characteristic (ROC) analysis for identifying osteopenia ($T < -1$; BMD more than one standard deviation below that of young healthy females) gives an area under curve (AUC) value of 0.64. Using a minimal interaction to initiate active shape model (ASM) search, the measurement can be made at the optimum region of the mandible, resulting in an AUC value of 0.71. Using an independent test set, AUC for detection of osteoporosis ($T < -2.5$) is 0.81.

Index Terms—Active shape model (ASM), bone mineral density (BMD), dental panoramic tomogram (DPT), inferior mandibular cortex (IMC), osteopenia, osteoporosis, segmentation.

I. INTRODUCTION

OSTEOPOROSIS is a general loss of bone mineral density and can lead to an increased risk of fracture. Based on factors such as previous fracture, family history, and height loss. Patients deemed to be at risk are referred for bone mineral density (BMD) assessment using dual-energy X-ray absorptiometry (DXA). However, there has recently been great interest among dental researchers in the possibility of identifying those at risk of reduced BMD from dental radiographs since mandibular BMD is related to systemic BMD [1].

Fig. 1 shows an example of a dental panoramic tomogram (DPT) of a normal patient and Fig. 2 shows a close up of the right mandible. Fig. 3 shows a schematic of Fig. 2—the cortical region in this diagram is referred to as the inferior mandibular cortex (IMC). There is evidence that the thickness of this cortex is related to systemic BMD and hence causes osteoporosis [2]. Fig. 4 shows the equivalent view of Fig. 2 for a patient with osteoporosis—the mandibular cortex is much harder to perceive visually as it is both thinner and less distinct from the mandible as a whole. In particular, the thickness of the mandibular cortex at a point closest to the mental foramen, referred to as the mental index (MI), (Fig. 3) has been found to be the best indicator of low BMD compared to the equivalent indices at the gonion (GI) and the antegonion (AI) (Fig. 1) [2].

There is considerable room for subjectivity in the precise placement of the MI measurement; the mental foramen is a very indistinct feature, and the endosteal border can become very
indistinct in cases of osteoporosis (Fig. 4). These factors do not pose significant problems for an expert radiologist. However, for general dental practitioners (GDP), they lead to considerable variability in MI measurement, even with individual training, and so routine assessment of low BMD risk from dental radiographs by GDPs is not practical [4].

Dentists use a large number of radiographs, accounting for 32% of all medical radiological examinations in the U.K. [5], opening the possibility of obtaining valuable medical information about patients’ osteoporotic status from a routine radiological examination. Here, we describe an automatic method of measuring radiographic indices using computer image analysis that is sensitive to mandibular BMD, and hence, systemic osteoporosis.

Our approach is to use an active shape model (ASM) method [7] to locate the upper and lower borders of the inferior mandibular cortex, and hence measure its thickness.

II. DATA

The patient data set had been collected for a previous study [3] and consisted of 132 consecutive female patients aged between 45–55 who attended the University Dental Hospital of Manchester for routine dental treatment.

Fig. 3. Schematic diagram of the dental tomogram shown in Fig. 2, showing the point at which the inferior mandibular cortex thickness is measured by dentists (mandibular index MI).

Fig. 4. Portion of a DPT showing the same region of the mandible as in Fig. 2, but for a patient with osteoporosis. Note the thinning of the inferior mandibular cortex compared with Fig. 2.

A. Radiographic Examination

All of the patients received a radiological examination of the mandible using a DPT. All radiographs were performed using either a Cranex DC-3 unit (Soredex Orion Corporation, Finland) or a Planmeca PM 2002C unit (Planmeca, Finland) using the same film/cassette combination. The films were digitized using a Kodak LS85 digitizer (Eastman Kodak, Rochester, NY) at a resolution of 25.64 pixels/mm.

B. BMD Assessment

One hundred and twenty six females had central DXA of the proximal femur and lumbar spine on the GE Lunar DPX-L (GE Lunar Corporation, Madison, Wisconsin). BMD measurements at each site were compared to the manufacturers reference data to give a T-score value, which is the number of standard deviations the BMD measure lies from the sex-matched young adult mean value. Using the World Health Organisation criteria, patients are defined as osteopenic if their T-score value is between −1 and −2.5 and osteoporotic if their T-score value is less than −2.5. In this study, patients were categorized by the lowest T-score value at either the total hip or lumbar spine (L1-L4). Of the 126 patients with BMD measurements, 79 were normal, 42 were osteopenic, and five were osteoporotic.

III. ASM METHOD

A. Point Distribution Model (PDM)

The ASM method has been extensively documented already elsewhere [7]–[9], and only a brief description will be given here. At its core is a PDM that describes the principal modes of variation of a set of landmark points used to describe the object of interest. The model is “trained” using points placed on a training set of example shapes, usually manually (see Section III-B), at anatomically consistent locations around the border of the object (see for example, Fig. 1). The points are concatenated into a single shape vector \( x = (x_1, y_1, x_2, y_2, \ldots, x_n, y_n) \) for each of the training examples, after alignment to a common coordinate frame, where \( n \) is the number of points. New example shapes can be generated from a principal component analysis of the covariance matrix generated from the shape vectors, thus

\[
\begin{align*}
  x &= \bar{x} + Pb \\
  \bar{x} &= \mathbb{E}X \\
  \sigma^2 &= \mathbb{E}(X - \bar{x})^2
\end{align*}
\]

where \( \bar{x} \) is the mean shape, \( P \) is the \( n \times t \) matrix of the \( t \) most significant eigenvectors \( P_1, P_2, \ldots, P_t \) of the covariance matrix, and \( b \) is a vector of parameters \( b_1, b_2, \ldots, b_t \) describing the weights assigned to each eigenvector to describe a particular shape. Equation (1) shows that \( b \) is equivalent to \( x \) as a shape description. Each eigenvector \( P_i \) corresponds to a “mode of variation” in the observed shapes in the training set. Varying the values of \( b_1, b_2, \ldots, b_t \) allows us to generate shapes within the observed range. For example Fig. 5 shows the effect of varying \( b_1 \) by \( \pm 3\sigma \) around its mean value, while keeping \( b_2, \ldots, b_t \) at their mean values. This mode of variation principally represents the range from narrow to broad mandible shape. Other modes represent different characteristics of the observed shape.
This results in a set of shape parameters $b$, and so constrains the new example to shapes that can be generated by the PDM. However, though this restricts variation in shape to the axes dictated by the eigenvectors of the PDM, it does not limit how far along each of these axes the new shape lies. This means that whilst the PDM cannot generate any possible shape (like a circle or a star), it can produce examples of mandibles with features exaggerated beyond anything that are likely to be found.

Realistic limits on how far along each of the shape axes to go are determined from the training set. For each example shape in the training set there is a shape vector $b$, and so, each $b_i$ has a variance determined by its eigenvalue $\lambda_i$. We would therefore expect the sum

$$\sum_{i=1}^{l} \frac{b_i^2}{\lambda_i}$$

(3)

to follow a $\chi^2$ distribution. Thus, by setting a limit on this sum, and using the area under the $\chi^2$ distribution below this limit, we can retain a desired percentage of the variance observed in the training set for new example shapes. The value of this limit is discussed below in Section III-D.

The above process is iterated until changes in landmark positions are sufficiently small, the precise threshold depending on the application. In this case, ten iterations were found to be sufficient to reduce changes in position to approximately 0.2 pixels (0.026 mm).

The abundance of confounding structure in the images results in the location of incorrect edges during ASM search. While the imposition of shape constraints reduces the effects of such erroneous detections, both speed and accuracy of search can be affected by the detection of “outlier” points. Rogers and Graham [11] have shown that robust estimation of model parameters can lead to much more accurate fits in these circumstances. Here, we use a version of ASM search that uses M-estimators [10] to fit the model parameters in (2), using the method described in [11].

Briefly, the process of estimating the parameters $b$ for a given shape $x$ proceeds by minimizing the residuals $r = (x - x_0)$ where $x_0$ is the current set of model points. In the M-estimator method a set of weights $\omega$ are calculated based on the standard deviation of the residuals $\sigma$, and thus

$$\omega_i = \begin{cases} 
1, & r_i < \sigma \\
\sigma / |r_i|, & \sigma \leq r_i < 3\sigma \\
0, & r_i \geq 3\sigma 
\end{cases}$$

(4)

These weights are then used to determine the influence of each point on the estimation of the model parameters. Since the inferior border of the IMC is far more clearly defined than the superior border (Fig. 2), the search is divided into two phases. The first phase uses a model built from the points on the inferior border only to locate that edge, defining the overall shape and pose of the mandible. This result is used as the initialization of phase 2, which is a search using the complete model of the IMC to obtain the positions of both inferior and superior borders.
**D. Experimental Procedure**

To test the ability of an ASM search to segment an unseen example, i.e., one not used in the training set, a leave-one-out methodology is employed. Here, the model is trained on all examples except the one to be tested, and this is repeated for all examples in the data set.

Two versions of the ASM search described in Section III-C were tested experimentally on the data set.

The first was a free search without any manual initialization points. The ASM search for the inferior border of the IMC (phase 1) was initialized from the mean position and pose of the training data. For some images, the correct shape and pose are some distance from this starting point. ASM search uses a multiresolution coarse-to-fine search strategy in such circumstances [7], and that was employed in this case. The results of this search were then used to initialize a full endosteal border ASM search by warping the mean example of the full endosteal PDM such that its lower edge matched the results of the lower edge ASM fit. We refer to fits determined this way as “unconstrained fits” or “UFits.” An example of a UFit search result showing start condition and final results is shown in Fig. 6.

The second version used four manually defined reference points on the lower mandible edge at the left and right AG and MF as starting points. To start the phase 1 search, the mean example of the lower mandible border PDM was stretched and positioned such that its AG and MF points matched the manually placed start points. An edge-based ASM search was then initiated, making no further reference to the manual points during the search. The full endosteal border ASM search was then initiated from the results of the phase 1 search in the same way, as described in the unconstrained fits.

The use of this straightforward interaction allowed us to decouple the effects of location and shape in ASM search. Starting the search so close to the true position guarantees that the search will finish up with the correct pose. The quality of ASM fit is determined solely by the ability of the PDM to represent the variation in shape that occurs among the images. We refer to fits determined this way as “constrained fits” or “4PFits.” An example of the results of a 4PFit showing the initial start condition and final search result is shown in Fig. 7.

There are a number of parameters, which need to be set in an ASM search such as sample profile length, degree of PDM shape constraint (3), number of resolution levels, etc., and the optimum values for these were found empirically.

For the unconstrained multiresolution fit, a shape constraint of 99% (see Section III-C) was required to provide sufficient flexibility to accommodate the variation in shapes while retaining sufficient shape constraint to avoid unfeasible matches arising from the spurious edge features close to the mandible. However, for the full resolution fitting of the complete mandibular cortex model in either the 4PFit method or the UFit method, a constraint of 100% was necessary for the model to be able to describe the fine detail of the endosteal border accurately and give the best sensitivity to bone mineral density.

This is effectively a removal of model parameter constraint since the tail of the $\chi^2$ distribution goes on to infinity, however, this still restricts the shapes to those possible along the axes of variation within the PDM (see Section III-C above). This high degree of model flexibility was possible since the second phase search started very close to the correct position, and so, only the mandibular cortical edges would be within reach of the search profiles of the models.

**E. Image Resolution**

The panoramic dental tomograms were scanned from film at a resolution of 25.64 pixels/mm. At this resolution, the film grain is visible, contributing a source of noise in the images, which was found to interfere with ASM search. To overcome this, a degree of smoothing was necessary. Dental panoramic radiography in digital format is becoming increasingly used; these images typically have a resolution of 8.8 pixels/mm, and hence, it is appropriate to evaluate the effectiveness of the method for segmenting images at the current digital resolution. Experiments over a range of subsampled resolutions on the data set showed that reducing the resolution by Gaussian smoothing and subsampling, to that of the digital radiographs had little effect on the model fit accuracy, as measured by the point-to-point difference,
and no effect on the sensitivity to reduced BMD, which is indicated by ROC analysis. Therefore, the results presented in the following sections are based on a 30% reduced resolution of 7.69 pixels/mm, which is approximately equivalent to digital radiographs.

IV. RESULTS

In common with many studies in medical image analysis, we define “accuracy” to mean conformity with expert medical annotation. To compare the model fits with the manual annotation we use the mean point-to-point, and the mean point-to-curve difference between the manually placed points and those resulting from the model fit in order to estimate the accuracy of the model fit. Since our goal is to measure mandibular cortical thickness, we also compare the measurements of thickness derived from model fits with those from manual annotation. The thickness is measured as the distance between corresponding points on the lower and upper border of the mandibular cortex. The comparison is done using a Bland and Altman plot [12], where the difference between two sets of measurements are plotted against their mean. From this analysis, the bias is measured as the mean of the differences between the two sets of measurements being compared, and the limits of agreement are the mean difference $\pm 1.96 \sigma$ [12]. As an example, Fig. 10 shows the Bland–Altman plot for the Manual 1–2 comparison.

For the Manual-UFit comparison, the point-to-point differences are large—more than twice that of the manual inter-observer reliability. This is because the unconstrained fits are able to successfully find the correct location and shape of the mandible, but may not find the correct scale. Because, the mandible exhibits a strong grey-level edge along its lower border, there is strong evidence in the image for the position of a point orthogonal to the mandibular edge, but there are no features such as edges to characterize the position of a particular point along the edge of the mandible, i.e., its correct medio-lateral position with respect to the AG and MF landmarks. This is borne out in the difference between point-to-point and point-to-curve differences when comparing manual annotations. This means that once the lower mandible ASM has adhered to the mandible edge, there is no motivation in the search mechanism to stretch or contract to the correct scale. This suggests that an unconstrained ASM fit will accurately measure a portion of the cortical thickness, but that the exact anatomical region of the mandibular cortex that is being measured cannot be guaranteed. This is demonstrated in Fig. 8 where the results of an unconstrained fit are plotted against the target image, along with the user defined AG and MF points. The upper and lower borders of the IMC has been correctly located, but the points are displaced laterally with respect to the AG and MF points. Fig. 9 shows the equivalent image for a 4PFit—here anatomical correspondence is always guaranteed by the initialization points.

4) Fit1-Fit2—the 4PFit involves user interaction, and hence, there is a certain degree of subjectivity involved in the exact placement of the four initialization points. To estimate the magnitude of this effect, we perform two 4PFits, each initialized by a different observer.

Each of the above comparisons were made for the whole region of the mandible annotated, (i.e., the AG-MF region), and separately the MF points, as these are the points used in manual measurement. The point-to-point and point-to-curve differences are presented as “mean value (standard deviation).” For comparison of cortical thickness measurements using the Bland–Altman plots, the bias is the mean of the differences between the two sets of measurements being compared, and the limits of agreement are the mean difference $\pm 1.96 \sigma$ [12]. As an example, Fig. 10 shows the Bland–Altman plot for the Manual 1–2 comparison.

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### Table I

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Region</th>
<th>Point Fit Accuracy Results</th>
<th>Cortical Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual 1-2</td>
<td>AG-MF</td>
<td>2.45 (2.45)</td>
<td>0.31 (0.33)</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>2.19 (3.00)</td>
<td>0.38 (0.38)</td>
</tr>
<tr>
<td>Manual-UFit</td>
<td>AG-MF</td>
<td>5.73 (4.57)</td>
<td>0.49 (1.58)</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>0.71 (0.70)</td>
<td>0.45 (0.56)</td>
</tr>
<tr>
<td>Manual-4PFit</td>
<td>AG-MF</td>
<td>0.59 (0.54)</td>
<td>0.31 (0.40)</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>0.71 (0.70)</td>
<td>0.45 (0.56)</td>
</tr>
<tr>
<td>Fit1-Fit2</td>
<td>AG-MF</td>
<td>2.31 (2.44)</td>
<td>0.14 (0.24)</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>2.23 (2.99)</td>
<td>0.27 (0.41)</td>
</tr>
</tbody>
</table>

Point differences are presented as mean value (standard deviation).
Thus, the point-to-curve differences and bias and limits of agreement for the AG-MF region are only slightly higher than those of the Manual-Fit and the Manual 1–2 comparison, but the search result is more accurate than the point-to-point differences would suggest. Because the location along the mandible edge cannot be guaranteed in the unconstrained fit, the results for the MF are of little meaning and so are not included in this case.

For the Manual-4PFit, the point-to-point differences are much lower than inter-observer (Manual 1–2) equivalent. This is because between two observers there is much greater subjectivity in the position of the points along the mandibular border than there is in their distance from the border. Hence, the point-to-curve differences for Manual 1–2 comparison are much lower than the point-to-point differences, and are comparable with those of the Manual-4PFit comparison.

For the Manual-4PFit comparison, the bias in the cortical thickness measurement is larger than the manual inter-observer bias suggesting a systematic difference between the maximum gray-level gradient, and the edge perceived by the human observers. For the AG-MF region, the limits of agreement are slightly lower than the Manual 1–2 comparison, but consider-

ably larger for the MF points. Closer inspection of the model fits suggests these larger limits of agreement are due to poor ASM location of the upper MF points, most probably due to image noise in this region caused by the shadow of the spine.

For the Fit1-Fit2 comparison, the point-to-point differences are similar to those of the Manual 1-2 comparison, since subjectivity in point position along the mandibular border has been reintroduced by the use of two sets of initialization points. However, the point-to-curve difference and the bias and limits of agreement for the AG-MF region are much lower than the other comparisons (Table I).

B. Sensitivity To Reduced BMD

1) BMD Correlations: Table II shows the correlation coefficients (Pearson’s) between the cortical thickness measurements and the BMD values for the hip, spine, and the minimum BMD T-score of the two sites (see Section II-B). Figures in bold exceed the $p = 0.05$ threshold, and figures with a “*” exceed the $p = 0.01$ threshold.

None of the cortical thickness measurements derived from the MF points show significant correlation, whereas, the AG-MF measurements do. For the hip and spine BMDs, the 4PFit
performs better than the manual measurements, or the UFit measurements.

Fig. 11 demonstrates how the correlation between cortical thickness and BMD of the hip varies with position along the mandible for the manual and 4PFit results. The cortical thickness measurements show greatest sensitivity to BMD in the lateral halves of the mandible, and least around the MF points. This would suggest that the MF points are not the optimal place to measure cortical thickness in the detection of osteoporosis. A similar pattern is observed for the spine BMD, and the minimum T-score of the two sites.

2) Roc Analysis: Because, the number of osteoporotic patients is so small (5) in this data set, it is difficult to generate a meaningful ROC curve using osteoporosis as the categorical variable, and so, in the following analysis, the osteoporotic and osteopenic patients are combined into a “reduced BMD” group of 47.

Fig. 12 shows the relationship between position along the mandible and the area under the ROC curve derived from the cortical thickness at that position. The overall pattern is similar to the results for direct BMD correlation (Fig. 11) in that the sensitivity of cortical thickness measurement to reduced BMD are optimal in the lateral halves of the mandible. Fig. 13 shows the ROC curves obtained using the cortical thickness averaged over this optimum region of the mandible for both manual and 4PFit points yielding an area under the curve (AUC) of 0.66 and 0.71, respectively. Analysis of the original films corresponding to this data set using the traditional visual methods yielded an AUC of 0.63 [3].

Fig. 14 shows the resulting ROC curve for reduced BMD using the mean cortical thickness obtained from the unconstrained model fit as the discriminating parameter. Compared to the equivalent from the four-point initialized model fit, the two curves are indistinguishable ($p = 0.60$).

V. DISCUSSION

One problem that all studies of this kind face is the lack of absolute ground-truth against which to test the proposed measurement technique. Within the limits of this study, the average results from two expert manual observers is the only reference we have against which to test the ASM model fit in its ability to measure cortical width. Therefore, all measurements of fit accuracy presented depend on the accuracy of the manual measurements. The sensitivity of the ASM method to BMD and its ability to detect osteopenia, however, can be compared...
directly with the objective DXA measurements, independently of the subjectivity of expert image interpretation.

We can conclude from the above that it is possible to accurately measure the width of the inferior mandibular cortex in panoramic dental tomograms using an edge-based ASM method. For these measurements to have an exact anatomical correspondence, four manually placed initialization points are required. This is a reasonable level of interaction, since only the lower mandible edge need be identified—a clearly visible feature in all patients—and the points only need to be placed close to the border, not exactly on it, since the ASM search will locate the exact position of the local edge anyway.

Correlation of the cortical thickness with the BMD measured from the spine or hip was highest for the lateral portion of the AG-MF region of the mandible. The results of the 4PFit were an improvement on the manual measurements when compared with both hip and spine BMD, and the fully automatic unconstrained model fit yielded correlations equivalent to the manual results. This indicates that even in the cases where there is reduced anatomical correspondence between the model position and the mandible, width measurements still produce useful information on BMD.

The ROC analysis appears to confirm the conclusion that the lateral portion of the AG-MF region of the mandible is the optimum area from which cortical thickness is measured. This effect is more pronounced for the model fit results than the manual measurements, as model fitting in the MF region is relatively poor due to noise mostly from the shadow of the spine.

It is conceivable that this observation reflects real physiological effects. For example, the cortical bone in this region medial to the antegonial point AG may be more sensitive to the systemic effects of skeletal osteoporosis. In other regions such as that adjacent to the mental foramen, the local musculature may preserve bone due to local functional stimulation.

The low number of osteoporotic patients in this data set make it difficult to derive meaningful ROC analysis for detection of osteoporosis, as the statistical confidence intervals tend to be large. Development of the model fitting method was performed on this data set, because it represents a realistic sample of routine panoramic dental tomograms from patients likely to benefit from low BMD screening.

Fig. 15 shows an ROC curve for detecting osteoporosis \( (T < -2.5) \), generated using DPTs from 50 osteoporotic and 50 nonosteoporotic individuals, who did not contribute to the training set. This allows us to conduct a limited experiment on truly “unseen” images, and to make a preliminary evaluation of the diagnostic efficacy in detecting osteoporosis. The resulting ROC curve has a larger area \( (AUC = 0.81) \) than those shown above since the more severe condition of osteoporosis is being used as the discriminating factor rather than osteopenia. Traditional measurement of the cortical thickness by five experts from the original films yields an AUC of between 0.61 and 0.68 for the same 100 individuals. Traditional manual analysis of data from 653 subjects yielded an AUC range of 0.71–0.78 [16].

As this research was intended to develop a clinical tool for diagnosis, it is worth considering from a dentist’s perspective, and in the context of everyday practice. Most dentists currently use radiographs on film. There has, however, been a steady proliferation of digital radiology in dentistry over the last 15 years, and it is appropriate to develop computed methods of image analysis for dental use.

It should be remembered that the manual measurements made for this study were the result of expert annotation and that the direct measurement techniques that have received previous research attention [14] require time and care to give a result. Furthermore, the repeatability of such measurements may not be acceptable.

Osteoporosis diagnosis is not part of everyday dental practice, and hence, any involvement in this task should be facilitated for
the dentist. Measurement of cortical width will only be practical if it is fully automatic or very nearly so. The limited and straightforward interaction described here may be sufficiently unobtrusive to be practical. However, the results of automatic search indicate that useful measurement can be made without the involvement of dentist. The improved specificity and sensitivity arising from being able to make measurements at anatomically precise locations holds out the possibility of improved diagnostic performance. The ASM method does of course require training by experts, however this has already been done in this study and is not required for further applications of the method. The application of the trained model to the unseen dataset described earlier demonstrates this.

There have been calls [15] for improving access to dual-energy X-ray absorptiometry for individuals at risk of osteoporosis. Dentists are in a unique position to carry out fortuitous identification of patients at risk of osteoporosis and make a contribution to general healthcare. This research offers the potential to facilitate this process. Further work is in progress, collecting DPT’s and DXA measurements from a large patient sample to establish the diagnostic validity of our technique and the diagnostic threshold appropriate for clinical practice.

REFERENCES


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