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A new method to measure anatomic knee alignment for large studies of OA: data from the Osteoarthritis Initiative

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SUMMARY

Objective: To develop and validate a new and improved software method to rapidly determine femur–tibia angle (FTA).
Methods: Three readers, two skilled and one unskilled, without any formal medical training, measured FTA in 142 subjects from the Osteoarthritis Initiative (OAI). The reader reliability was assessed using the intra-class correlation coefficient (ICC), root mean square standard deviation (RMSSD), and Bland–Altman plots, comparing the existing and new FTA methods. Gender-specific linear regression assessed the relationship of FTA with the hip–knee–ankle angle (HKA).
Results: The ICC (RMSSD) for intra- and inter-reader reproducibility of the existing FTA method was 0.96 (0.77°) and 0.92 (1.38°), respectively, and for the new technique was 0.98 (0.25°) and 0.98 (0.37°), with similar results for all three readers. Bland–Altman 95% limits of agreement were greater than ±2° for the existing, and ±1° for the new method. The *r*-value for the relation of FTA to HKA was 0.68 and 0.72 for the existing and new methods, respectively. Varus (HKA $\leq -2°$)/neutral ($-2° <$ HKA $< 2°$)/valgus (HKA $\geq 2°$) alignment based on predicted HKA agreed moderately with measured HKA (weighted kappa = 0.53), and had moderate sensitivity (73%) and specificity (84%) for varus malalignment. The new FTA was related to HKA using a linear equation with a slope of 0.98 and an offset of 4.0°.
Conclusions: Since it is largely automated and uses unambiguous anatomical landmarks, the new method is highly reproducible and can be made on a standard posteroanterior (PA) knee radiograph by a relatively unskilled reader.

Significance and innovation

- Tibiofemoral alignment is an important risk factor for knee OA progression.
- The hip–knee–ankle angle (HKA) or mechanical axis is the gold standard measurement but requires a full-length lower-limb radiograph.
- We present and validate a new software method based on automated image analysis to measure knee alignment using the standard radiograph that is more reproducible than the existing methods and can be used in very large studies of OA since it is fast and requires a minimal amount of reader training.

Introduction

Knee osteoarthritis (OA) is one of the major health problems in the United States affecting between 7 and 17 percent of individuals[1]. Knee radiography is widely used in studies to confirm diagnosis and to follow progression of OA longitudinally[2]. Knee malalignment has been established as a potent risk factor for the progression of knee OA[3–7], and is also used by surgeons to determine the intra-operative axial alignment of the lower extremity for total knee replacements[8]. Recent studies have examined the relationship of knee malalignment with structural outcomes from magnetic resonance imaging (MRI). Studies of subjects from the Multicenter Osteoarthritis Study (MOST) have shown that knee malalignment is associated with enlarging bone marrow lesions[9], and that valgus alignment is associated with lateral compartment cartilage loss[10]. The goal of our study is to report and validate a new method that can be used to quantify knee alignment for large studies of knee OA.

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The gold standard measure of knee malalignment is the hip–knee–ankle angle (HKA) or mechanical axis measured from a full-length lower-limb radiograph[11,12]. This angle is computed by drawing line segments on a full-limb film connecting the center of the femoral head with the center of the knee above the tibial spines to the center of the talus bone in the ankle[13]. The HKA measurement requires a full limb radiograph, which is generally not available, and causes substantially more radiation exposure than a standard posteroanterior (PA) or AP knee radiograph that covers just the area near the knee joint. The femur–tibia angle (FTA or anatomic axis) can be used to assess knee alignment using a standard knee radiograph[14]. FTA has also been shown to predict the risk of incident, and progressive knee OA[6,15,16] and shows a moderate correlation with HKA[15,17]. Existing FTA methods require placing a point in the center of the knee joint, usually defined with respect to the tibial spines and/or femoral notch, and the centers of the tibia and femur shafts are determined at fixed distances (often 10 cm) from the center of the joint.

Difficulties in accurately defining the landmarks and differences in positioning of the knee joints impact the test–retest reliability of knee alignment measurements[17]. Due to the shorter length of line segments used to calculate the angles of the FTA method compared to the full-limb HKA method, FTA is much more sensitive to variations in locating the center point of the knee. For example, a difference of 2 mm in the location of the center point approximately translates into a half of a degree shift in the FTA, assuming a 10 cm distance from the center point to the landmarks on the shafts. Since this shift is inversely proportional to the length of line segments used to measure the angle, it is substantially smaller for the HKA method. The appearance of the tibial spines can differ substantially due to natural variation, effects of disease and variability in knee positioning, so an experienced reader is required to achieve consistent point placement. Figure 1 shows examples of such cases; difficulties are caused by osteophytes, oblique projections, and overlap with the femur, among other factors. While an expert with experience interpreting knee radiographs may be able to consistently determine appropriate landmarks on some of these examples, a less skilled reader cannot be expected to perform this task. The issue of tibial spine appearance and its effect on FTA remain unaddressed in the literature to the best of our knowledge.

The Osteoarthritis Initiative (OAI) (http://www.oai.ucsf.edu/) is a large National Institutes of Health and Industry funded study of nearly 5000 subjects followed over 96 months. Radiological imaging including MRI and knee radiography is performed at seven visits (baseline, 12, 24, 36, 48, 72, and 96 months); there are over 41,000 individual knee radiographic images in the first five visits alone. The OAI and other large studies of OA will require methods that can handle the vast amount of imaging data they produce.

We have developed and validated a new fast software method to determine FTA on standard PA knee radiographs that mitigates some of the difficulties associated with the existing FTA methods. The aim of this study was to develop and validate a new and improved software method to rapidly determine FTA.

Methods

The new method is based on a dimensionless Cartesian coordinate system developed for location-specific joint space width (JSW) measurements[18] (Fig. 2). The x-axis of the coordinate system is a line tangent to the distal margin of the medial and lateral femoral condyles and the y-axis is perpendicular to the x-axis and tangent to the medial margin of the medial femoral epicondyle; a perpendicular line parallel to the lateral margin of the lateral femoral epicondyle defines $x = 1.0$. Once the coordinate system is established, any point in the image can be assigned an x and y value.

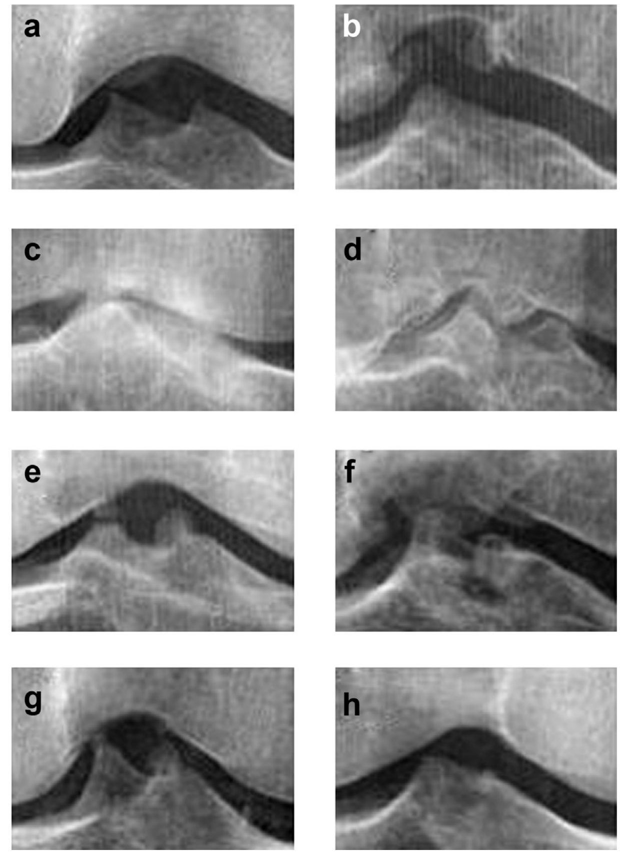

Fig. 1. Examples of the tibial spine radiographic appearance. (a) is the ideal case where the tips of both spines are clearly seen. Other images show the difficult but common cases. Difficulties are caused by osteophytes (d, e, f, and g), oblique or lack of prominent projections (b and h), and overlap with the femur (c, d, and f), among other reasons.

The femur axis is defined as a line passing through $\{x = 0.5, y = 0.0\}$ and perpendicular to the y-axis (Fig. 2). In practice FTA is independent of the intersection point since it is calculated as the angle between the femur and tibia axes. To define the tibia axis, the reader placed two points on the medial and lateral sides of the tibia at a distance of 1 cm below the lowest (most distal) point on the tibial plateau and the mid point between the two points is calculated. A further two points are placed on the medial and lateral sides of the tibial shaft at a distance of 10 cm from the tibial plateau, and a second mid point calculated. The tibial axis is defined as the line connecting these two mid points (see Fig. 2).

The study used subjects from the Progression Cohort of the OAI (OAI datasets 0.1.1, 0.B.1, and 1.B.1) where HKA measurements were available from the OAI public data release. HKA measurements were from the publically released OAI dataset (flXR_KNEEALIGN_COOKE01, Version 1.2). The HKA was measured according to the method by Cooke *et al.*[13]. Kellgren and Lawrence grades were from the OAI dataset (kXR_SQ_BU01 dataset, Version 1.5), and participant demographics were from the OAI dataset (ALLCINICAL00, Version 0.2.2). We excluded 54 images where the center of the knee was less than 10 cm from the lower edge of the image, leaving 266 total knees from 142 subjects for the final analysis.

The study used three readers. Reader 1 (TI) performed the measurements twice with the new procedure and two times using the existing method described in McDaniel *et al.* ("Method-B")[17]. Reader 2 (JLi) performed a single measurement with each of the two methods. Readers 1 and 2 were researchers with M.D. training, both with extensive experience in musculoskeletal radiography and using digital tools for image analysis. A third reader evaluated

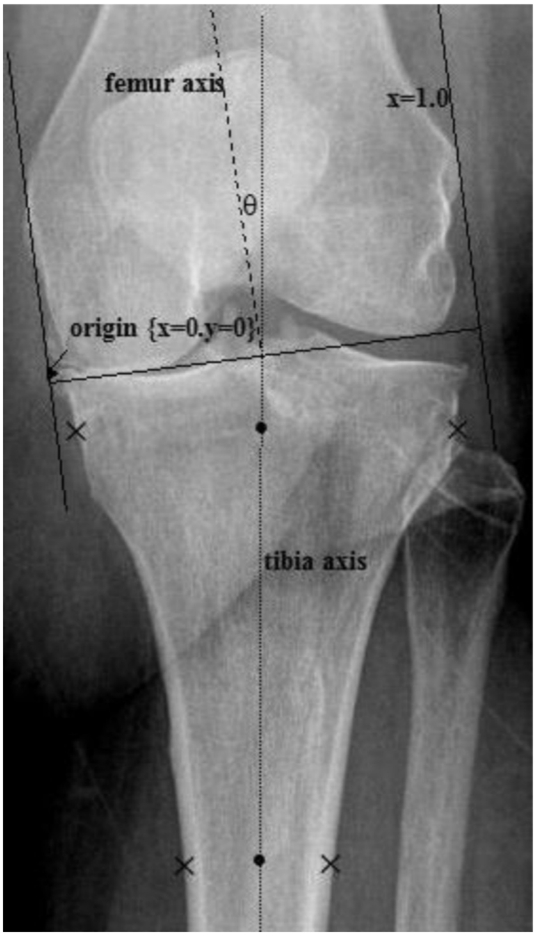

Fig. 2. Image showing the tibia and femur axes as defined by the new method. The femur axis is perpendicular to a line tangent to the base of the femoral condyles, and centered between the outer margins of the medial and lateral femoral epicondyles. The tibia axis is defined by first marking points (×'s) on the outer margins of the tibia at 1 cm and 10 cm below the projected tibial plateau. The axis is the line connecting the mid points of the marked locations. θ is the alignment angle and is a negative number for varus alignment.

the images once using the new method, but only after Reader 1 had set up the coordinate system; therefore her task was limited to placing points on the tibial shaft. Reader 3 had a 2-year associate degree with no formal training in the medical field. The purpose of the third reader was to determine whether a relatively unskilled individual could use the method to measure FTA accurately, once the location-specific JSW method had been accomplished by a more experienced reader.

Statistical analysis

SAS software (v9.2) was used for the analyses. Inter- and intra-reader reproducibility was assessed using intra-class correlation coefficients (ICC) and by the root mean square standard deviation (RMSSD), as well as by analysis of Bland–Altman plots and 95% limits of agreement. The use of FTA to predict HKA and limb malalignment was analyzed using linear regression modeling and assessment of slopes, intercepts and variance explained (R2). Gender differences were also examined in the use of the model:

$$\text{HKA} = \text{slope} \times \text{FTA} + \text{intercept} \quad (1)$$

By adding an interaction term between FTA and gender in SAS PROC GLM, which allowed gender-specific models to be generated and also allowed testing of the significance of any differences between the male-specific model and the female-specific model for predicting HKA. These gender-specific models were then used to calculate a predicted HKA value for each knee, which was classified into a predicted malalignment status based on HKA thresholds of $\leq -2°$ for varus and $\geq \pm 2°$ for valgus, with neutral alignment being HKA less than $\pm 2°$ from zero.

Table I
Characteristics of the study subjects and knees. Data for this table are taken from OAI public use datasets

Age (SD)		61.5 (9.8) years
BMI (SD)		30.0 (4.3)
Gender		
Male/Female		70/72
Race		
White/African American/other		117/22/3
Alignment from full-limb radiograph	Male (knees)	Female (knees)
Varus (HKA $\leq -2°$)	75 (60%)	38 (27%)
Neutral (HKA between $-2°$ and $+2°$)	38 (30%)	60 (42%)
Valgus (HKA $\geq +2°$)	13 (10%)	42 (30%)
Kellgren and Lawrence grade	Male (knees)	Female (knees)
0	16 (13%)	13 (9%)
1	14 (11%)	25 (18%)
2	38 (30%)	53 (38%)
3	47 (37%)	40 (26%)
4	11 (9%)	9 (6%)

Results

Descriptive statistics

The 142 participants, 82% Caucasian, were on average overweight. In the almost equal numbers of men and women, both genders had slightly over 70% of knees with definite radiographic OA (KLG $\geq$ 2), but more men were varus than women and more women were valgus than men (Table I). Gender-specific mean values of FTA were typically 5–6° more negative (varus direction), for the new method of measuring FTA, compared to the existing FTA method, while the standard deviations were smaller for the new method (Table II). The reader time for measuring FTA using the new method was less than 20 s per knee once the coordinate system was established.

Reliability of FTA measurement

Bland–Altman plots in Fig. 4 show that 95% limits of agreement for the new method of measuring FTA are slightly over $\pm 1°$. Comparing Fig. 3 with Fig. 4, the 95% limits of agreement for the

Table II
Descriptive statistics, in degrees, for measurement of mechanical axis (HKA) as well as anatomic axis FTA (Reader 1 data) using the existing method as well as the new method described in this paper

Measurement	*N*	Mean	SD	Median	Twenty fifth percentile	Seventy fifth percentile
HKA						
Men	126	−2.58	3.56	−3.10	−5.30	−0.30
Women	140	−0.11	3.76	0.25	−2.05	2.20
FTA (existing method)						
Men	126	−0.51	3.64	−0.16	−3.49	1.9
Women	140	1.64	3.50	1.36	−0.30	3.85
FTA (new method)						
Men	126	−5.91	2.57	−6.20	−7.66	−3.94
Women	140	−4.94	2.97	−5.16	−7.19	−2.97

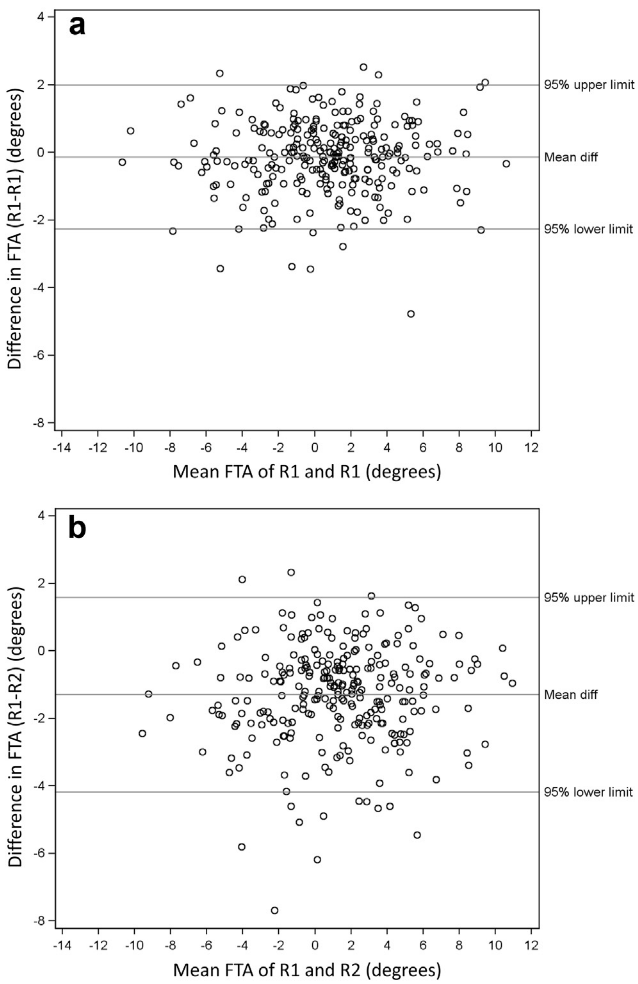

Fig. 3. Showing Bland–Altman plots and 95% limits of agreement (dashed lines) for agreement for (a) intra-reader (R1 vs R1), and (b) inter-reader (R1 vs R2) measurement of FTA using the existing method.

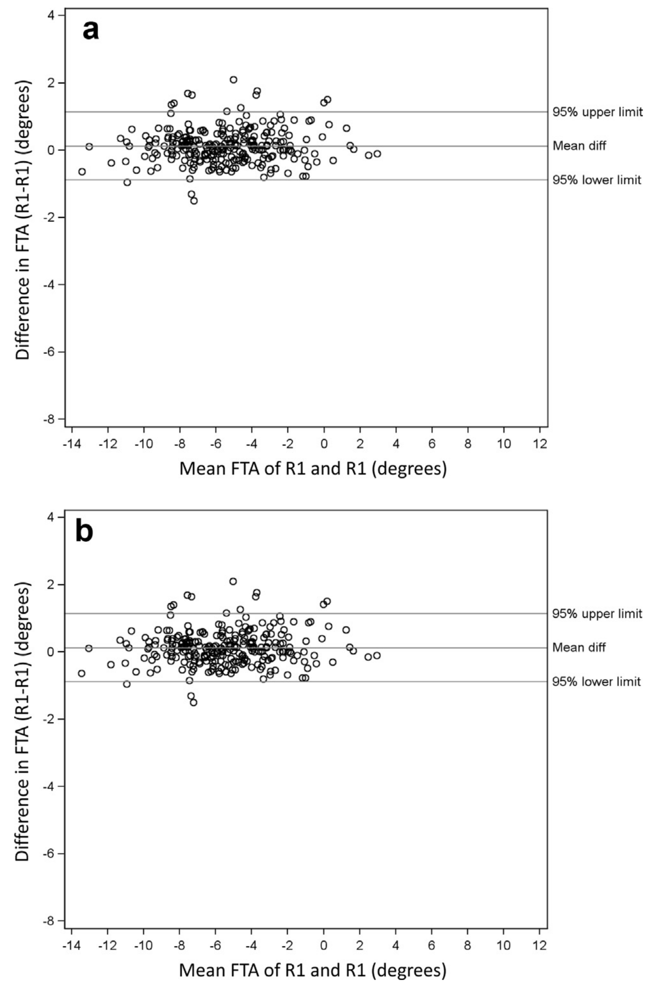

Fig. 4. Showing Bland–Altman plots and 95% limits of agreement (dashed lines) for agreement for (a) intra-reader (R1 vs R1), and (b) inter-reader (R1 vs R2) measurement of FTA using the new method.

new method of measuring FTA were between two times more reliable (intra-reader) and three times more reliable (inter-reader) than the old method. For the new method, the limits of agreement for intra- and inter-reader reliability were similar at just over $\pm 1^\circ$ (Fig. 4), and since the mean differences for this are both close to zero, this value represents the smallest detectable difference. ICCs and values for RMSSD mirror those findings (Table III). For the new method, comparing Reader 3 to Reader 2 showed results very similar to those presented for Reader 1 vs Reader 2, with ICCs $\geq$ 0.98 and with limits of agreement about 1° (data not shown). This suggests that using an unskilled reader to perform the final step of the method does not decrease the performance.

Estimating HKA from FTA

Table IV shows results from regression models using FTA to predict HKA for each reader. For all 266 knees (men and women combined), the overall *r*-value was 0.68 for the old method and 0.72 for the new method, but the slopes and intercepts for the old method and new method were substantially different. In particular, the slope for the new method was very close to 1, compared to the existing FTA method where the slope was close to 0.7.

Models allowing for an interaction with gender showed a significant effect for both the existing FTA method ($P < 0.008$, Reader 1) and the new FTA method ($P < 0.009$, Reader 1), and the results of the models with this interaction term are also in Table II showing the gender effect on the prediction of HKA using FTA. In particular note that for the new FTA method the slope remains close to 1 but the intercepts for male and females are slightly over 1° different. The gender effect was similar for Readers 2 and 3.

Use of the gender specific model for predicting alignment (varus vs neutral vs valgus from HKA) using the new FTA method are shown in Table V with 66% of knees correctly classified (weighted kappa = 0.53). No varus knees were predicted to be valgus and only five valgus knees were predicted to be varus. The models were reasonably accurate in predicting varus alignment (sensitivity = 79%, specificity = 84%) but less accurate for valgus knees (sensitivity = 40%, specificity = 94%). The model was poor at predicting valgus alignment in men; of 13 valgus knees in men, only one

Table III
Reader reproducibility. The table presents the ICC results with the RMSSD values in parentheses

	Intra-reader reproducibility (Reader 1)	Inter-reader reproducibility (Reader 1–Reader 2)	Inter-reader reproducibility (Reader 3–Reader 2)
Existing method ICC (RMSSD)	0.96 (0.77°)	0.92 (1.38°)	N/A
New method ICC (RMSSD)	0.98 (0.25°)	0.98 (0.37°)	0.99 (0.31°)

Table IV
Results for linear regressions for the use of FTA to predict HKA. Model for "All" does not include gender or interaction terms

		Reader 1	Reader 2	Reader 3
Existing FTA method				
All ($N = 266$)	Intercept	−1.7°	−2.7°	N/A
	Slope (β)	0.70	0.73	N/A
	R-square	0.46	0.46	N/A
Male ($N = 126$)	Intercept	−2.3°	−3.6°	N/A
	Slope (β)	0.59	0.63	N/A
	R-square	0.36	0.40	N/A
Female ($N = 140$)	Intercept	−1.3°	−2.0°	N/A
	Slope (β)	0.73	0.74	N/A
	R-square	0.46	0.50	N/A
New FTA method				
All ($N = 266$)	Intercept	4.0°	4.3°	4.2°
	Slope (β)	0.98	1.01	0.99
	R-square	0.52	0.53	0.52
Male ($N = 126$)	Intercept	2.7°	3.0°	2.9°
	Slope (β)	0.90	0.92	0.91
	R-square	0.43	0.44	0.45
Female ($N = 140$)	Intercept	4.6°	4.9°	4.8°
	Slope (β)	0.95	0.99	0.97
	R-square	0.56	0.58	0.58

was predicted to be valgus. An analysis using the existing FTA method and regression models gave similar results for agreement (weighted kappa = 0.47).

Discussion

The new method for assessing FTA demonstrated substantially improved inter- and intra-reader reproducibility compared to an existing FTA method, with higher ICCs and lower RMSSD values and Bland–Altman plots showing substantially narrower limits of agreement within and between readers than the existing FTA measurement method. The results for Reader 3 indicated that there was no loss of reliability when the less trained reader was used for the final step of the procedure. The new method does not require landmarks placed in the tibial spines, and can be performed by a relatively unskilled reader once the coordinate system is defined for location-specific JSW.

This implies that a large number of subjects can be evaluated relatively inexpensively if the location-specific JSW procedure has previously been performed, as is the case for the OAI. Placing the coordinate system itself adds less than 30 s for each knee for a trained reader.

The improvement in reader reproducibility is not surprising given that the alignment axes are determined automatically by easily perceived anatomical landmarks as opposed to reader judgment of a center point for the knee that is based on a frequently complicated anatomical structure. Each of the landmarks (margins of the femoral condyles and the tibia shaft) used to establish the new FTA measurement is a well-defined bone edge with minimal room for ambiguity.

Table V
Predicted alignment using new FTA method and gender-specific regression models vs alignment from actual HKA measurement. Weighted kappa = 0.53 (95% CI: 0.54, 0.61)

Alignment from predicted HKA	Alignment from actual HKA		
	Varus (≤−2°)	Neutral (−2° to +2°)	Valgus (≥2°)
Varus (≤−2°)	89	22	5
Neutral (−2° to +2°)	24	64	28
Valgus (≥2°)	0	12	22

The marginal improvement in the correlation with HKA ($r = 0.68$ existing method, $r = 0.75$ new method) may also be due to this fundamental difference between the two methods. Of additional interest is the nature of the linear relationship between FTA and HKA (Table IV) as both the slope and intercept appear to be method dependent. It is notable that the slope of the new method was close to 1, which implies that degree differences in FTA measured using the new method are roughly equivalent to the same degrees differences in HKA. However, the magnitude of the offset (intercept) was larger compared to the existing method, reflecting the differences in the fundamental geometry of each technique. The values of the slope and intercept, *per se*, do not reflect the performance of either method, rather they provide a way to use FTA to estimate HKA in order to determine if knees are malaligned. For such use we would stress that it is crucial to use both model parameters since using the intercept (or offset) alone will potentially produce inaccurate results.

The significant differences in the intercepts from the regression equations for the male and female participants is noteworthy, and suggests that in this sample of knees, gender-specific equations for estimating HKA from FTA are needed. A similar result was observed by Kraus *et al.*[14]. While this finding may reflect true gender differences in lower limb anatomy, as also suggested in other studies, the small number of valgus knees from men in the sample studied may have impacted our results. Our results in the linear regression models suggest that there is a significant interaction of gender on the prediction of HKA from FTA, at least in the sample of knees studied in this paper. Further work is needed in larger samples including more men with valgus knees to determine the best way to estimate malalignment using our new FTA method.

Our results for the new FTA method indicate that it performs as well as, or better than existing methods of measuring FTA from standard radiographs, in reliability and relationship to alignment assessed by HKA. McDaniel *et al.*[17] examined five different methods of determining the center point of the knee with respect to the tibia spines or femoral notch for measuring FTA. For the existing method, that study found a similar correlation of FTA to HKA ($r = 0.65$) compared to our results using the same method ($r = 0.68$). The authors did not quote a slope value. The reproducibility values for the existing FTA method were also slightly higher (inter-reader ICC = 0.96 and intra-reader ICC = 0.98) compared to our results for the existing method but, for the new method, there was very little difference between the inter- and intra-reader reproducibility. Felson *et al.*[15] also found a moderate correlation between FTA and HKA using an existing method ($r = 0.66$) and a similar agreement as in our study in terms of classification of alignment status estimated from FTA and alignment based on HKA measures. Direct comparisons between different studies are of limited use unless the subjects and radiographs are identical; factors such as radiographic technique and knee positioning method, disease status, and the general quality of the acquisition are likely to cause the difficulties shown in Fig. 1, and affect the reliability and accuracy of the measurement.

For future studies it will be important to establish the clinical validity of the new method by reproducing the results from studies that have shown a significant association between knee alignment and OA progression[3,15]. With our limited data we have observed a hint of gender differences for the methods. Studies with larger datasets could shed light on potential gender effects as well as the relationship with variables such as age, OA severity, and body-mass index (BMI). Finally, it will be possible to measure the progression of FTA longitudinally for studies where standard radiography is available at multiple time points. For example, it will be feasible to provide measurements for all knee radiographs in the OAI for which the location-specific JSW has been measured (over 25,000 knee radiographic images).

A limitation of the method is that it relies on the coordinate system set up for location specific JSW; additional time is necessary if this step has not already been performed. However, setting up the coordinate system using our software is substantially automated and can be performed independent of measuring JSW. The measured improvement of the new technique may be affected by the skills and level of training obtained by the readers we used. We did not investigate the repositioning reproducibility of the method using duplicate radiographs, as these were not available. Rotation of the knee could potentially affect all components of the anatomical landmarks that are used for the method. Our method will not be able to detect or account for most bowing of the femur since the angle is determined using landmarks below the typical location of bowing. Furthermore we cannot claim that it is a perfect surrogate for the HKA, which is the preferred measurement. These limitations are also true for the traditional FTA method. However, we believe our results justify this method where full-limb radiographs are unavailable, a common occurrence.

Our method was validated using radiographs acquired with the fixed flexion protocol knee position; using a different positioning protocol may not produce the same results. Since longitudinal full-limb radiographs were not available from the OAI, the study is cross sectional. For our method we excluded knees where there was not sufficient coverage of the tibia shaft. For this reason there is the possibility of a bias in our results, but a similar problem exists for the conventional FTA measurement. However, this exclusion is due to poor radiography acquisition and is likely to be random with respect to relationships of interest. By comparison, our method may be an improvement since we do not need to exclude images where the femur shaft is not visible. This initial validation study used a modest number of subjects. Future more highly powered studies may shed light on these issues.

In summary, we have developed and validated a new software method to rapidly determine FTA that may expedite the measurement of alignment from knee radiographs from large studies such as the OAI. We found substantially improved inter- and intra-reader reproducibility compared with the existing method and higher correlation with the HKA. With the new method, very little difference was observed between the inter- and intra-reader precision suggesting a robust technique. The new FTA was related to HKA using a linear equation with a slope of 0.98 and an offset of 4.0°. Malalignment is an important indicator of disease progression and treatment outcome and this new method will help make high quality knee alignment data more readily available.

Author contributions

Study conception and design: *Iranpour – Boroujeni, Lynch, Nevitt, Duryea*
Acquisition of data: *Iranpour – Boroujeni, Li, Lynch, Nevitt, Duryea*
Analysis and interpretation of data: *Lynch*, *Nevitt*, *Duryea*
Drafting the article or revising it critically for important intellectual content: *Iranpour – Boroujeni*, *Li*, *Lynch*, *Nevitt*, *Duryea*
Final approval of the version of the article to be published: *Iranpour – Boroujeni*, *Li*, *Lynch*, *Nevitt*, *Duryea*
J Duryea (jduryea@bwh.harvard.edu) takes responsibility for the integrity of the work as a whole.

Conflict of interest statement

The authors declare that they have no conflicting interests.

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