

## Position Development Paper

# Official Positions for FRAX<sup>®</sup> Clinical Regarding Prior Fractures

*From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX<sup>®</sup>*

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### Abstract

The 2010 Position Development Conference addressed four questions related to the impact of previous fractures on 10-year fracture risk as calculated by FRAX<sup>®</sup>.

- Does the number of past fractures affect future fracture risk?
- Does the severity of past vertebral fractures affect future fracture risk?
- Does the site of past fractures affect future fracture risk?
- Should the family history of fracture be expanded to include additional sites, additional family members, or account for age at fracture?

To address these questions, PubMed was searched on the keywords “fracture, epidemiology, osteoporosis.” Titles of retrieved articles were reviewed for an indication that risk for future fracture was discussed. Abstracts of these articles were reviewed for an indication that one or more of the questions listed above was discussed. For those that did, the articles were reviewed in greater detail to extract the findings and to find additional past work and citing works that also bore on the questions. The official positions and the supporting literature review are presented here. FRAX<sup>®</sup> underestimates fracture probability in persons with a history of multiple fractures (good, A, W). FRAX<sup>®</sup> may underestimate fracture probability in individuals with prevalent severe vertebral fractures (good, A, W). While there is evidence that hip, vertebral, and humeral fractures appear to confer greater risk of subsequent fracture than fractures at other sites, quantification of this incremental risk in FRAX<sup>®</sup> is not possible (fair, B, W). FRAX<sup>®</sup> may underestimate fracture probability in individuals with a parental history of non-hip fragility fracture (fair, B, W). Limitations of the methodology include performance by a single reviewer, preliminary review of the literature being confined to titles, and secondary review being limited to abstracts. Limitations of the evidence base include publication bias, overrepresentation of persons of European descent in the published studies, and technical differences in the methods used to identify prevalent and incident fractures. Emerging topics for future research include fracture epidemiology in non-European populations and men, the impact of fractures in family members other than parents, and the genetic contribution to fracture risk.

**Key Words:** FRAX; past fractures; fracture risk; vertebral morphometry; family history.

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## Introduction

It is beyond dispute that prior fractures increase the risk of future fractures. The robustness of past fracture as a predictive factor is reflected in its inclusion as a variable in the present version of the FRAX<sup>®</sup> tool (1–3). Moreover, parental history of hip fracture is also included in FRAX (2,3). Yet, there are several important questions regarding personal or family history of fracture that remain unanswered in the present model.

The goal of the FRAX model is to provide a simple, point of care decision support tool that can help busy clinicians assess an individual patient's 10 year risk of hip or major osteoporotic fracture. At present, the FRAX model includes past fracture as a dichotomous variable, with an added note that vertebral fractures are more predictive of future fractures than are fractures at other sites. This properly reminds the clinician that not all fractures are equal, a view that is clearly supported by the evidence review. The evidence summarized below provides additional guidance for clinicians as they interpret FRAX risk estimates. It is worth noting that several reports have noted that FRAX tends to underestimate fracture risk (4,5). In the future, appropriate refinement of the model would help address the conservative fracture risk estimates generated by the FRAX model.

## Methodology & Data sources

In a series of meetings held in advance of the position development conference, the clinical task force developed a set of key questions to be addressed. The key questions structured the scope of the literature review and discussion at the conference.

The PubMed database was searched on the keywords “fracture, epidemiology, osteoporosis.” Titles of retrieved articles were reviewed for an indication that risk for future fracture was discussed. Abstracts of these articles were reviewed for an indication that one or more of the questions listed below was discussed. For those that did, the articles were reviewed in greater detail to extract the findings and to find additional past work and citing works that also bore on the questions. Limitations of the methodology include use of only a single reviewer, preliminary review of the literature being confined to titles, and secondary review being limited to abstracts.

In addition to the limitations of the evidence review, limitations of the primary evidence should also be acknowledged. These include publication bias, overrepresentation of persons of European descent in the published studies, and technical differences in the methods used to identify prevalent and incident fractures. The criteria for establishing the existence of a fracture is particularly noteworthy with regard to vertebral fractures.

There are several important questions regarding personal or family history of fracture that remain unanswered in the present model. These include:

1. Does the *number* of past fractures affect future fracture risk?
2. Does the *severity* of past vertebral fractures affect future fracture risk?

3. Does the *site* of past fracture affect future fracture risk?
4. Should the family history of fracture be expanded to include *additional sites, additional family members, or account for age at fracture*?

This list of questions is by no means exhaustive; other topics related to past fractures are worthy of discussion and might merit inclusion in future versions of FRAX. In particular, the issues of whether additional fracture risk related to past fracture diminishes over time and whether past fracture confers equivalent risk to men and women are important but have not been addressed.

## Official Statements

**Question:** Does the number of past fractures affect future fracture risk?

**Official Position:** There is a relationship between number of prior fractures and subsequent fracture risk. FRAX underestimates fracture probability in persons with a history of multiple fractures.

**Grade:** Good, A, W

**Question:** Does the *severity* of past vertebral fractures affect future fracture risk?

**Official Position:** There is a relationship between severity of prior vertebral fractures and subsequent fracture risk. FRAX may underestimate fracture probability in individuals with prevalent severe vertebral fractures.

**Grade:** Good, A, W

**Question:** Does the *site* of past fracture affect future fracture risk?

**Official Position:** While there is evidence that hip, vertebral, and humeral fractures appear to confer greater risk of subsequent fracture than fractures at other sites, quantification of this incremental risk in FRAX is not possible.

**Grade:** Fair, B, W

**Question:** Should the family history of fracture be expanded to include *additional sites, additional family members, or account for age at fracture*?

**Official Position:** FRAX may underestimate fracture probability in individuals with a parental history of non-hip fragility fracture.

**Grade:** Fair, B, W

## Rationale

There is an extensive literature on past fractures as predictors of future fractures. The review below is limited to investigations that explicitly address one or more of the questions listed above.

Available evidence clearly demonstrates that both number of fractures and severity of vertebral fractures affect future fracture risk. Hip, vertebral, and humeral fractures appear to confer greater risk of subsequent fracture than fractures at other sites, although the evidence base is not as extensive as for fracture number or fracture severity.

## Reviews of the Topic

Klotzbuecher *et al.* reviewed studies published between 1966 and 1999 to identify studies that related prior fracture occurrence to future fracture risk, and reanalyzed the data for all sites that had been investigated 2 or more times (6). The reanalysis used a random effects model for individual studies and estimated relative risk and estimated 95% confidence intervals for each site. They broke down the data by site of prior fracture and site of incident fracture. Across sites, prior fracture approximately doubled subsequent fracture risk. However, prior vertebral fracture increased future vertebral fracture risk approximately 4-fold. Further, several of the reviewed studies demonstrated that the risk increased as a function of the number of prior vertebral fractures. There was a suggestion that multiple fractures at other sites also increased subsequent fracture risk. Limitations of this review include heterogeneity of the methods used in the original investigations, inclusion of retrospective data, and limited availability of data in males.

A meta-analysis of 9 cohorts enrolling patients of European descent compared distal radius fractures and vertebral fractures as predictors of hip fractures in postmenopausal women and men over 50 (7). Fractures at both these sites increase the risk of future hip fracture. Notable results include a generally stronger association of past fracture with future fracture in men than women, and that this gender-specific difference is limited to the distal radius (relative risk of approximately 3.2 in men and 1.5 in women), with overlapping confidence intervals for the risk attributable to past vertebral fractures (point estimates of relative risk approximately 3.5 in men and 2.2 in women).

Kanis *et al.* performed a meta-analysis of previous fracture as a predictor of future fracture, using primary data from 11 studies including more than 60,000 patients (8). These authors found that prior fracture increases the risk of future fracture, that adjustment for BMD has minimal impact on the predictive power of prior fracture, and that the prior fracture contribution to subsequent fracture risk is similar in women and men. One important finding of this analysis is that with advancing age, the risk attributable to prior fracture declines.

A meta-analysis of the impact of family history of fracture on fracture risk (9) including over 30,000 subjects in prospective epidemiological studies showed a consistent, modest increase in fracture history when there was a family history of fracture. The relative risk attending a positive family history was higher for history of hip fracture relative to fractures at other sites, and the relative risk declined with age.

## Number of Past Fractures

In a cohort study of Hawaiian women of Japanese descent, a single past vertebral fracture increased risk of future vertebral fractures approximately 5-fold, while 2 past vertebral fractures increased the risk approximately 12-fold (10). These risks were reduced to approximately 2.5-3-fold and 7-fold, respectively after adjustment for calcaneal BMD measured by single photon absorptiometry.

In a trial of etidronate therapy for osteoporosis in postmenopausal women of European descent, presence of 1 or 2 vertebral fractures at entry increased the risk of subsequent vertebral fracture more than 7-fold, while the presence of more than 2 prevalent fractures further increased the incident fracture risk (11).

In the Study of Osteoporotic Fractures, the number of prevalent vertebral fractures robustly predicted new vertebral fracture risk but predicted hip and non-vertebral fractures less robustly, and was not associated with Colles' fracture risk (12).

In the FIT trial of alendronate, the number of prevalent vertebral fractures at study entry was associated with incident vertebral fractures during the trial (13). The risk relationship was not affected by treatment assignment.

Among women in the EVOS study, a single prevalent vertebral deformity conferred a relative risk of 4.5 for hip fracture, while the relative risk among those with 2 or more vertebral deformities was 7.2 (14). The increased risk attending multiple v single vertebral deformities was also evident at other sites, albeit with lower relative risks.

In a pooled analysis of placebo subjects in 4 trials of osteoporosis drugs, number of prevalent vertebral fractures was associated with incident vertebral fracture risk (15).

In EPOS, a single prevalent vertebral deformity increased the risk of future vertebral fracture 3.3-fold, two increased the risk 9.8-fold, and three or more increased the risk 23.2-fold (16).

In the placebo group of the MORE trial of raloxifene, the number of prevalent vertebral fractures in MORE trial placebo group predicted vertebral fracture risk (17).

In a pooled analysis of placebo patients in MORE and the Fracture Prevention Trial, number of vertebral fractures at study entry increased the 21 month risk of incident morphometric vertebral and clinical non-spine fractures increased as a function of number of fractures (18). This relationship held regardless of T-score.

Among placebo subjects in a clinical trial of teriparatide, incident vertebral fractures were associated with the number of prevalent vertebral fractures (19). Treatment greatly attenuated fracture risk regardless of number of fractures at study entry.

In a Japanese population-based cohort study of 712 women aged 50–79, the fully adjusted relative risk of future fracture was 2.35 in the presence of a single prevalent deformity and increased to 4.89 in the presence of 2 or more prevalent vertebral deformities (20). These authors also found that the relative risk is greater among younger women than among older women.

Postmenopausal Korean women attending an osteoporosis clinic receiving treatment, display an increasing risk of incident fracture as a function of the number of prevalent vertebral fractures (21). This risk is independent of age and BMD.

## Severity of Past Vertebral Fractures

Severity of prevalent vertebral fracture predicted new vertebral, hip, and all non-vertebral fractures in SOF (12).

In a nested case-control study of incident fractures (22), increasing spinal deformity determined by a combination of number and severity of morphometric vertebral abnormalities increased incident fracture risk. This risk was independent of BMD.

In EPOS, loss of anterior and mid-vertebral body height conferred a greater risk of future vertebral fracture than did loss of posterior vertebral body height (16). Rating severity of fractures by Z-score from normal height, more severe prevalent deformities conferred a greater risk of future fracture.

Severity of prevalent vertebral fracture in MORE trial placebo group predicted both vertebral and nonvertebral fracture risk (17).

In a pooled analysis of placebo patients in MORE and the Fracture Prevention Trial, the 21 month risk of incident morphometric vertebral and clinical non-spine fractures increased as a function of the semi-quantitative severity of prevalent fracture (18). This relationship held regardless of T-score, and also held when the spinal deformity index, a composite measure of number and severity of vertebral fractures was used as the input variable.

Among placebo subjects in a clinical trial of teriparatide, incident vertebral fractures were associated with the severity of prevalent vertebral fractures (19). Treatment greatly attenuated fracture risk regardless of fracture severity at study entry.

Placebo subjects in the SOTI and TROPOS studies demonstrated incident fracture risks that increased as a function of the spinal deformity index (SDI), a composite measure of number and severity of prevalent vertebral fractures (23).

In a Finnish nested case-control study of 7000 persons aged 30 and above at ascertainment, severe, but not mild or moderate prevalent vertebral fractures increased subsequent risk of hip fracture over the ensuing ~25 years (24).

A potential problem with implementation attends the difficulty of correctly identifying mild vertebral deformities (25). These are difficult to read, even by skilled individuals. It is therefore likely that primary care physicians and other users of the FRAX tool will misclassify some of these. It is uncertain how large an effect this would have on the model's predictions.

### **Sites of Past Fractures**

A Swedish registry-based case-control study of women and men suffering distal forearm fractures demonstrated a relative risk of hip fracture of about 1.5 in women and about 2.3 in men (26).

A Rochester, Minnesota-based population cohort study of persons with initial distal forearm fractures (27) showed that women had a 1.4-fold increase in hip fracture risk and men had a 2.7-fold increase in risk. In women, the risk was increased only among those aged 70 or greater at the time of the distal forearm fracture. Risk of vertebral fractures was even greater following distal forearm fracture, increasing 5.2-fold in women and 10.7-fold in men.

In EPOS, prevalent vertebral deformities were more predictive of fractures within 3 levels of the deformity than at

more distant sites (16). So, for example, a prevalent deformity at T10 was more predictive of a future fracture between T7 and L1 than at other sites.

An HMO-based study of men over age 60 compared the relative risk of limb fracture following humeral, distal radius, hip, and ankle fractures with no fractures over the prior 2 years (28). Humeral fractures were most strongly associated with future limb fractures, with a relative risk of about 4. Hip and wrist fractures conferred relative risks of approximately 3 and 2, respectively, while ankle fractures were not associated with future fractures.

In a Swedish cohort study, the site of prior fracture had a significant impact on the relative risk of future fracture (29). Moreover, the risk of subsequent fracture following vertebral, humerus, and hip fractures varies with site of the subsequent fracture. Finally, the risk is highest in the first year following the initial fracture and tends to decrease over time.

In a life-table analysis of hip fracture risk following distal forearm or vertebral fracture, spinal fracture conferred a greater future risk in women, while distal forearm fracture conferred greater future risk in men (30).

In EPOS, rib fractures increased the risk of hip, humeral, and all limb fractures in women (31). Similar trends were observed in men, but the low number of events in men precluded the trend from achieving statistical significance.

In SOF, the relative risk of future fracture was greater for subjects with prevalent vertebral deformity than for those with baseline histories of non-spine, non-hip fractures (32). In both groups, there was an increased relative risk of fracture that appeared to decline with time since the initial event.

In DOES, relative risk of future fracture depended on the site of first fracture (33). In both women and men, hip fractures conferred the greatest subsequent fracture risk in both genders, followed by vertebral fractures. In women, ankle fractures did not increase future fracture risk, while in men rib fractures were not predictive of subsequent fractures.

In a retrospective cohort study of over 21000 persons in the Manitoba provincial health registry, all traditional osteoporotic fractures were predictive of future fractures over a 10-year period (34). However, distal forearm fractures were both more common and less predictive than fractures at other sites, conferring a relative risk of approximately 1.5, compared with a relative risk of approximately 2.5 at other sites. The lower predictive power of forearm fractures may reflect their occurrence at an earlier age.

In the Study of Osteoporotic Fractures, proximal humeral fracture increased the risk of hip fracture 6-fold over the subsequent year, but had no impact on subsequent hip fracture risk (35).

In MrOS, past history of rib fracture significantly increased the risk of subsequent rib fractures (36). Past fracture at any site also significantly increased the risk of new rib fractures.

Among Japanese nursing home residents, appendicular fractures other than the hip doubled the adjusted hazard ratio for hip fracture (37).

### Expanded Family History

Available evidence regarding fractures in family members other than parents is extremely limited. Evidence regarding fractures at sites other than the hip is also limited, as are data incorporating age at fracture. These are important gaps in our knowledge of fracture epidemiology, and should be addressed in future research.

In a meta-analysis of 7 cohorts comprising nearly 35000 subjects, parental fractures at all sites increased fracture relative risk to 1.17 (9). The increased risk was independent of BMD. The relative risk for hip fractures was 1.54.

In EVOS, maternal history of hip fracture caused an approximate 30% increase in the risk of prevalent vertebral deformity in both men and women (38). A similar trend was observed for paternal history of hip fracture, but because of a small number of events, this relationship was not statistically significant.

In a Swedish twin study, fracture risk displayed variable heritability based on fracture site and age of fracture (39). The heritability approached 0.7 for hip fractures in those under age 70 and fell to 0.2 for all fractures. Vertebral fractures also showed relatively high heritability. The heritability was robust to correction for covariates.

In MrOS, neither maternal nor paternal fracture history was associated with rib fracture risk (36).

Over 100 genes have been associated with either low BMD or fracture risk, and some of these findings are now sufficiently consistent and robust to consider that genotypic information may soon be used in clinical practice to predict fracture risk. In a recent meta-analysis of GWAS studies (40), 5 genes, *SOST*, *SPPI* (*OPN*), *LRP5*, *TNFRSF11A* (*RANK*), and *TNFSF11* (*RANKL*) each included one or more alleles that displayed consistent associations with fracture. While this is not specifically use of past fracture to predict future fracture risk, it is clear that within the next decade genotypic information will be able to provide substantial ancillary data to guide treatment decisions.

### Additional Questions for Future Research

#### 1. Revision of the FRAX Model

Revising the FRAX model is beyond the scope of the Position Development Conference and this review. However, the FRAX model is constantly being reassessed and is subject to periodic updates. One or more of the questions addressed here may ultimately be included in a revised FRAX model. Such revision will depend not only on the evidence supporting the change, but also on whether the revision can be incorporated into the risk calculator while preserving its ease of use.

#### 2. Data in Men Are Limited

Although data in men are now being gathered, the existing literature is based on approximately twice as many women as men. Further, since the fracture rate in women exceeds that in men, many more events have occurred in women than in men. Therefore, there is an extremely high priority to epidemiological work exploring fracture risk in men.

#### 3. Data Regarding Wider Family History Are Limited

Very few data are available regarding the impact of fractures occurring in family members other than parents. This is also true regarding the impact of age at fracture in all family members. It seems intuitive that a family history of fractures in the 6<sup>th</sup> decade has more impact on fracture risk than a similar history in the 9<sup>th</sup> decade. However, to our knowledge, no data exist to support this idea.

As genetic risk factors continue to emerge, there is a clear need to determine whether identified high-risk alleles stand up in the large epidemiologic cohorts, and to determine the extent to which these are independent of other covariates that have already been studied.

#### 4. Data Regarding Persons of Non-European Descent Are Limited

Existing data are highly skewed toward persons of European descent. Obtaining similar data in other ethnic groups is clearly a high priority topic for future research.

### In Summary

There is compelling evidence that past fractures increase future fracture risk. It seems clear from existing data that number of past fractures, severity of past vertebral fractures, and site of prior fracture all impact future fracture risk. Parental fractures also increase fracture risk, but the relationship is most robust for hip fractures. Multiple gaps in present knowledge provide attractive topics for future research.

### Acknowledgments

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## Appendix 1. Position Conference Members

**Organizers:** Didier B. Hans (Chair), Cyrus Cooper (Co-chair), Sanford Baim, Bess Dawson-Hughes, John A. Kanis, William D. Leslie, Marjorie M. Luckey, Rene Rizzoli,

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**Expert Panel:** John P. Bilezikian (Moderator), Socrates E. Papapoulos (Co-moderator), Jonathan D. Adachi, Robert D. Blank, Roland Chapurlat, Wu (Paulo) Chih-Hsing, Edward Czerwinski, Adolfo Diez Perez, Hans P. Dimai, Ghada El-Hajj Fuleihan, Saeko Fujiwara, Ruxandra M. Ionescu, John A. Kanis, Mike McClung, Sergio Ragi-Eis, Jan Stepan, Kenneth G. Saag, John T. Schousboe, Wei Yu, Cristiano Zerbini.

**Supporting Person:** Peter D. Brown (ISCD), Patrice McKenney (IOF), Helena Johansson, Judit Nagy, Anders Oden and Denys A. Wahl.