

## Original Article

# Worldwide Fracture Prediction

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## Abstract

The substantial increase in the burden of non-communicable diseases in general and osteoporosis in particular, necessitates the establishment of efficient and targeted diagnosis and treatment strategies. This chapter reviews and compares different tools for osteoporosis screening and diagnosis; it also provides an overview of different treatment guidelines adopted by countries worldwide. While access to dual-energy X-ray absorptiometry to measure bone mineral density (BMD) is limited in most areas in the world, the introduction of risk calculators that combine risk factors, with or without BMD, have resulted in a paradigm shift in osteoporosis screening and management. To-date, forty eight risk assessment tools that allow risk stratification of patients are available, however only few are externally validated and tested in a population-based setting. These include Osteoporosis Self-Assessment Tool; Osteoporosis Risk Assessment Instrument; Simple Calculated Osteoporosis Risk Estimation; Canadian Association of Radiologists and Osteoporosis Canada calculator; Fracture Risk Assessment Calculator (FRAX); Garvan; and QFracture. These tools vary in the number of risk factors incorporated. We present a detailed analysis of the development, characteristics, validation, performance, advantages and limitations of these tools. The World Health Organization proposes a dual-energy X-ray absorptiometry-BMD T-score  $\leq -2.5$  as an operational diagnostic threshold for osteoporosis, and many countries have also adopted this cut-off as an intervention threshold in their treatment guidelines. With the introduction of the new fracture assessment calculators, many countries chose to include fracture risk as one of the major criteria to initiate osteoporosis treatment. Of the 52 national guidelines identified in 36 countries, 30 included FRAX derived risk in their intervention threshold and 22 were non-FRAX based. No universal tool or guideline approach will address the needs of all countries worldwide. Osteoporosis screening and management guidelines are best tailored according to the needs and resources of individual countries. While few countries have succeeded in generating valuable epidemiological data on osteoporotic fractures, to validate their risk calculators and base their guidelines, many have yet to find the resources to assess variations and secular trends in fractures, the performance of various calculators, and ultimately adopt the most convenient care pathway algorithms.

**Key Words:** Fracture risk calculator; FRAX; guidelines; risk factors.

*Since manuscript submission, revised guidelines from both the ACP and RACGP, which incorporate fracture risk, have been published. RACGP. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 yr of age (2nd edition). The Royal Australian College of General Practitioners 2017. Available online: <http://www.racgp.org.au/your-practice/guidelines/musculoskeletal/osteoporosis/> (Accessed June, 2017); Qaseem A, Forciea MA, McLean RM, Denberg TD. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Annals of Internal Medicine*. 2017 June 6.*

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## Introduction

Osteoporosis, a major public health problem of aging populations, incurs staggering social and economic costs worldwide. The 2015 Global Burden of Disease Study reported a substantial increase in population growth, and in life expectancy from 61.7 (61.4–61.9) yr in 1980 to 71.8 (71.5–72.2) yr in 2015, worldwide (1). Osteoporosis disease burden exceeds that of several non-communicable diseases combined. In postmenopausal women, osteoporotic fractures are more common than stroke, myocardial infarction, and breast cancer combined (2).

In 2000, there were 9 million osteoporotic fractures worldwide: 1.4 million were clinical vertebral fractures, 1.7 million at the forearm and 1.6 million at the hip (3,4), with a projected increase to 2.6 million hip fractures by 2020, and to 4.5 million vertebral fractures in 2050 (5). These fractures incur substantial morbidity and mortality for vertebral and hip fractures (4,6–8). Projected hip fracture risk may increase by 4-folds in some regions, with a parallel explosion in incurred costs, considering such fractures, let alone other fractures (9). As an example, total costs incurred from hip fractures worldwide were estimated at US\$34.8 billion in the late 90s, and projected to exceed 130 billion dollars by 2050 (10). Prevention and treatment are therefore key to contain the social and financial consequences of this taxing disease on our aging societies.

Risk calculators combining risk factors have resulted in a paradigm shift in non-communicable diseases management for almost 3 decades. Examples include the Gail calculator for breast cancer, and the Framingham followed by the Reynolds and Arteriosclerotic Cardiovascular Disease calculators for cardiovascular diseases. The osteoporosis field has similarly experienced a similar shift, with the launch of fracture risk calculators (FRCs) over the last 10 yr (11), and the introduction of intervention thresholds for osteoporosis drug therapy, in many national guidance documents based on these calculators (12–15). Several fracture risk assessment tools have been developed that incorporate varying numbers of risk factors, with or without bone mineral density (BMD) (9,11–13,16,17), and these have been extensively discussed in prior chapters in this special issue. We will briefly review dual-energy X-ray absorptiometry (DXA) and non-DXA based fracture risk assessment tools commonly used today, intervention thresholds and their use in guidelines, and discuss related considerations and challenges this approach raises.

## Methods

### Literature Search

Medline was the primary search engine for the topic *Fracture Risk Assessment*; Medline, BMJ Best Practice, and Dynamed were search engines for the topic *Osteoporosis Guidelines Worldwide*, and we used Medline, PubMed, and EMBASE to conduct a systematic review on *Incidence rate ratios for major osteoporotic fractures (hip, clinical spine,*

*humerus, and wrist) and hip fractures*. Medical Subject Headings (MeSH) terms and keywords for these concepts, and Boolean operators “and” and “or” were used in different combinations to ensure completeness of the search (Appendix 1) (15). We contacted international bone experts for their input on relevant articles in foreign languages, other related publications, and work in progress (see Acknowledgments). For FRAX-based guidelines, we also accessed other various resources detailed in Appendix 1. We also reviewed the regional International Osteoporosis Foundation (IOF) audits posted on the IOF website, including: The Asian Audit (2009), The Asia–Pacific Regional Audit (2013), The Eastern European and Central Asian Regional Audit (2010), The Latin America Regional Audit (2012), and the Middle East and Africa Regional Audit (2011). Guidelines for secondary causes of osteoporosis were excluded.

### Major Osteoporotic Fracture (MOF) and Hip Fractures Ratios

For data extraction, computation of ratios and quality rating, please see Appendix 1 (18,19).

For all 3 searches, we also used relevant references selected from the reference lists of the retrieved articles and from authors' libraries.

## Overview of FRAX Tools

### Low BMD (T-Score) as a Predictor of Fractures

DXA-derived BMD is the single best predictor of fractures, and as BMD decreases, fracture risk increases by 1.5–2.5 folds (20). However, although such risk gradient, expressed as relative risk per standard deviation decrease in BMD, seems comparable across populations (20–22), it does not provide information about absolute hip fracture risk, a risk that may vary widely with age (23,24), gender, ethnicity, and geographic location (4,25,26). The World Health Organization (WHO)'s operational definition of osteoporosis is that of a DXA-derived T-score  $\leq -2.5$ , using the National Health and Nutrition Examination Survey (NHANES) universal database (27), but the appropriate reference database for T-score calculation in non-Caucasians is unclear, an important consideration for intervention thresholds worldwide. Furthermore, the above WHO operational definition is neither specific nor sensitive in identifying subjects at high risk for fragility fractures. Indeed, subjects from some regions (e.g., Asia, Middle East, and Africa), have low DXA derived T-scores, even after adjustment for body size, yet are at lower risk for fractures than Caucasians (28–33). Conversely, many subjects with hip fractures do not have osteoporosis by T-score (34). BMD combined with clinical risk factors can increase the predictive ability of some risk calculators (35–38).

Central DXA-derived BMD (T-score), may not be available for risk assessment in many countries and regions with scarce health-care resources, and some tools that use

as little as 2–3 clinical risk factors (e.g., Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI]), can perform very well to identify subjects with low BMD (11). Thus, Asian countries use OST for Asians (OSTA), as a quick screening tool validated in Asians, in their osteoporosis risk assessment algorithms, as detailed below.

### **FRCs (With or Without BMD)**

Several papers and systematic reviews have reported on the large number of fracture risk assessment tools available, and examined characteristics worthy of consideration when selecting a fracture risk tool as screening for risk assessment (11,12,16,39–43). Traditional and newer measures to assess performance of tools include discrimination (distinguishing high from low risk individuals) calibration (agreement between predicted and observed rates), reclassification, and clinical usefulness (44). Other characteristics relevant to calibration include independent validation and ability of the tool to be customized, taking into account country-specific epidemiology and life expectancy for better model fit.

In his recent systematic review, Rubin et al identified a total of 48 tools, 20 of which had been externally validated, and only 6 had been tested more than once in a population-based setting (11). Three of these 6 validated tools are non-DXA-based and aim at identifying subjects with low BMD (OST, ORAI, and Simple Calculated Osteoporosis Risk Estimation), and 3 predict fracture risk, 2 include DXA BMD as an optional entry (FRAX and Garvan) and 1 does not (QFracture). Section 3 of this special issue reviews FRAX and Garvan fracture prediction tools in detail, along with an additional chapter “Additional fracture prediction tools” that covers other risk calculators. It includes Simple Calculated Osteoporosis Risk Estimation, ORAI, QFracture, Canadian Association of Radiologists and Osteoporosis Canada (CAROC) calculator, OST, and the United States Preventive Services Task Force tool.

Table 1 summarizes the main features of Garvan, FRAX, and QFracture, including characteristics of their derivation cohorts (age range and gender), input, output (hip fracture, any fracture, MOF), time interval for fracture prediction (yearly, 5 yr, 10 yr), and performance. One aspect of performance characteristics expressed as area under the curve (AUC) or C statistic, is included in Table 1, as reported in 3 studies that directly compared these tools within the same cohorts (36,41,43,45). Additional details on the 3 studies, and other tool performance characteristics, are provided in section “Comparative Studies of Risk Assessment Tools” below. For a thorough review of the tools’ development, validation, advantages, and limitations, we refer the reader to Appendix 2 (Tool Performance in Systematic Reviews (11,16,40), and FRAX Calibration in Cohorts Worldwide (12,15,39,46–52), other relevant chapters in this special issue, and to other papers (11–13,16,40,53).

FRAX characteristics includes its reliance on meta-analyses to assess the impact of the clinical risk factors

included in the tool on fracture risk, its incorporation of fracture and mortality interaction terms, competing mortality risk, and ability to be customized to specific countries/populations (15,54). FRAX has 68 calculators, calibrated for use in 63 countries worldwide, and is available in 33 languages (FRAX v3.11, released 7.11.2016). Whereas FRAX enters risk factors into the model as dichotomous variables, Garvan includes a dose response for number of prior fractures and falls (0, 1, 2,  $\geq 3$ ) (55,56), and QFracture allows a dose response for smoking (4 levels), alcohol intake (5 levels), and type of diabetes (type 1 or 2) (39). QFracture has been shown to accurately predict fracture risk in older people in the UK up to the age of 85 yr, although it does not take mortality into account (57). All 3 tools are available online (Table 1); the original QFracture calculator was withdrawn from the Internet in 2012 and replaced by the updated QFracture tool. FRAX is the only algorithm that is not public.

### **FRAX Worldwide**

The World Bank lists a total of 170 countries, excluding states and islands in Polynesia, Micronesia, Melanesia, Greenland, and the Vatican, of these 170, 63 countries adopted FRAX calculators. Although many societies and organizations surveyed in this review endorse the use of FRAX tools, they do not necessarily incorporate them in their guidelines for drug intervention. Indeed, many still favor the use of diagnostic thresholds, reflected in a personal history of fragility fracture, or T-score  $\leq -2.5$ , as intervention thresholds. This is explained by the abundance of evidence for drug efficacy in clinical trials using the above criteria.

FRAX: This is the most commonly used fracture risk assessment tool worldwide; a finding explained by its adaptation to country-specific epidemiology. Of the 63 countries with FRAX calculators: 33 (out of 37) are in Europe; 12 (out of 35) in Asia-Pacific; both US and Canada in North America, 7 (out of 29) in Latin America; and 8 (out of 67) in the Middle East and Africa (<https://www.shef.ac.uk/FRAX/index.aspx>, Accessed: March 21, 2017). FRAX adaptation to country calibration, taking into account country-specific epidemiology of fractures, has resulted in a major paradigm shift in osteoporosis management, with incorporation of FRAX-based risk assessment as an indicator to initiate osteoporosis drug therapy, in many but not all countries (15) (see “Fracture Risk Assessment as the Basis for Osteoporosis Guidelines Worldwide” below).

Few countries, such as Australia, China, Malaysia, Scotland, Singapore, the UK, and the US, specify other tools for screening but do not use them for treatment intervention, whereas guidelines from Canada, New Zealand, and the Philippines, also use them for setting treatment intervention thresholds (Table 2) (58–67). We describe where and how these tools are used for risk assessment, and in the following section their contribution to defining intervention thresholds in guidelines, worldwide.

**Table 1**  
Characteristics of Garvan, FRAX, and QFracture Tools

Calculator	N risk factors	Risk factors (excluding BMD)	BMD	Gender age (yr)	Development cohort Validation cohort	N validation studies Countries ethnicity	Output	Prediction time	AUC/C-Statistic <sup>a</sup>
<b>Garvan</b> <a href="http://www.garvan.org.au/bone-fracture-risk">www.garvan.org.au/bone-fracture-risk</a>	4	Age, gender, prior fracture, fall	Optional	M/F	DUBBO epidemiologic study, Australia	6 (in 3 countries)	Any fracture: hip, wrist, clinical vertebrae, forearm, metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, or sternum fractures	5 and 10 yr	<b>Bolland et al (41)</b> - Hip fx <sup>a</sup> (BMD) 0.67 - Garvan-defined osteoporotic fx (BMD) 0.64 <b>Sambrook et al (43)</b> - Hip fx (no BMD) 0.76 - MOF (no BMD) 0.63 <b>Dagan et al (45)</b> - Hip fx (no BMD) 0.71
				60–96	1358 Females 858 Males	Caucasian	Hip fracture		
<b>FRAX</b> <a href="http://www.shef.ac.uk/FRAX">www.shef.ac.uk/FRAX</a>	10	Age, gender, BMI, prior fracture, parental history of hip fracture, alcohol >3 units, smoking, glucocorticoid use, RA, secondary osteoporosis	Optional	M/F	9 development cohorts <sup>b</sup> from Europe, North America, Japan, and Australia, N = 46,340	26 (in 9 countries)	MOF: spine, hip, humerus, or forearm fractures	10 yr	<b>Bolland et al (41)</b> - Hip fx (no BMD) 0.67 - Hip fx (BMD) 0.70 - FRAX-defined osteoporotic fx (no BMD) 0.62 - FRAX-defined osteoporotic fx (BMD) 0.64 <b>Sambrook et al (43)</b> - Hip fx (no BMD) 0.78 - MOF (no BMD) 0.61 <b>Dagan et al (45)</b> - Hip fx (no BMD) 0.82 - MOF (no BMD) 0.71
				40–90	11 validation cohorts N = 230,486 N = 1,208,528 person-yr	Not in Middle East or Africa, Mostly Caucasian	Hip fracture		
<b>QFracture (not available)</b>	18	Age, gender, BMI, parental history hip fracture or other fractures, falls, smoking, alcohol, type 2 DM, asthma, cardiovascular disease, chronic liver disease, RA, GI malabsorption, use of tricyclics, HRT, or corticosteroids, endocrine problems, menopause	No	M/F	357 UK general practices 2.2 million	3 (in 2 countries)	Any fracture: clinical spine, hip, distal forearm, or humerus fractures	1–10 yr	<b>Dagan et al (45)</b> - Hip fx (no BMD) 0.88 - MOF (no BMD) 0.75
				30–85	178 practices for internal validation	Caucasian	Hip fracture		
<b>QFracture Update</b> <a href="http://www.qfracture.org">www.qfracture.org</a>	31	Above, plus 13 other risk factors	No	M/F	UK general practices 3 million	1 (in 1 country)	Any fracture: hip, vertebral, proximal humerus, or distal radius Hip fracture	1–10 yr	Not available

Abb: BMD, bone mineral density; BMI, body mass index; FRAX, fracture risk assessment.

<sup>a</sup>Tool performance in studies reporting head-to-head comparisons with area under the curve (AUC); concordance statistic (C-statistic). Abbreviations and definitions: DM, Diabetes Mellitus; fx, fracture; GI, gastro-intestinal; HRT, hormone replacement therapy; MOF, major osteoporotic fractures; RA, rheumatoid arthritis; Garvan-defined osteoporotic fractures (Bolland et al (41)); fractures of the hip, vertebrae (symptomatic), forearm, metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, or sternum; FRAX-defined osteoporotic fractures (Bolland et al. (41)); fractures of the shoulder, hip, or forearm and clinical vertebral; MOF (Sambrook et al. (43)); fractures of the spine, forearm, hip, proximal humerus, or upper arm; MOF (Dagan et al. (45)); fractures of the hip, vertebrae, distal radius, or proximal humerus.

<sup>b</sup>AUC from FRAX cohorts (36); 9 development cohorts: AUC for hip fracture (no BMD) 0.67; hip fracture (BMD) 0.78; MOF (no BMD) 0.62; MOF (BMD) 0.63; 11 validation cohorts: AUC for hip fracture (no BMD) 0.65; hip fracture (BMD) 0.74; MOF (no BMD) 0.58; MOF (BMD) 0.60.

**Table 2**

Countries With FRAX Calculators that Use other Fracture Risk Assessment Tools

Country	CAROC	Garvan	OSTA	QFracture
Australia		+		
Canada	+			
China			+	
Malaysia			+	
New Zealand		+		
Philippines			+	
Scotland				+
Singapore			+	
Taiwan			+	
UK				+
US		+		

*Abbr:* CAROC, Canadian Association of Radiologists and Osteoporosis Canada; FRAX, fracture risk assessment; OSTA, Osteoporosis Self-Assessment Tool for Asians.

- Tools other than FRAX used in treatment guidelines.
- Tools other than FRAX used for fracture risk assessment.

**CAROC:** Canadian Association of Radiologists and Osteoporosis Canada tool is a simplified version of FRAX that is based on age, gender, prior fragility fracture, glucocorticoid use, and BMD. It was developed and validated in Canadian men and women, and was highly concordant, about 90%, in risk categorization with FRAX (68). Differences, when they occur, usually relate to the presence of 1 or more risk factors that contribute to the Canadian version of the FRAX tool but that are not considered in the 2010 version of CAROC. CAROC categorizes 10-yr MOF risk as low (<10%), moderate (10–20%), and high (>20%) (58). Although less complete than FRAX, it is easier to use, does not require computer or web access, and is more widely available on densitometry machines across Canada. The national guidelines state that the 2010 version of CAROC or the Canadian version of the WHO FRAX tool can be used in Canada (grade A). Because the software for the Canadian version of the WHO FRAX tool is not widely available on BMD machines in Canada, the 2010 version of CAROC tool is the preferred national risk assessment system for BMD reporting (58).

**OSTA:** Although a screening tool for low BMD, OSTA is also used in the Philippines for treatment intervention (Table 2). OSTA is recommended to screen postmenopausal Asian women, given the constraints in the measurement of BMD, and the lack of cost-effective evidence for population-based screening using BMD (60,61,65,67,69). OSTA was validated in 8 Asian regions, including China, Hong Kong, Korea, Malaysia, the Philippines, Singapore, Taiwan, and Thailand. In the validation study, 61% of individuals in the high-risk category had osteoporosis as opposed to 15% in the moderate risk category and 3% in

the low-risk category, and the AUC varies between 0.65 and 0.85 (61,67,69). Although the tool was developed for postmenopausal Asian women, it is applicable to Asian men. The OSTA score incorporates information on age and weight (age-weight), and based on the derived score subjects are stratified into high (>20), moderate (0–20), and low-risk (<0) categories. Women, who are found to be in the high-risk category, and those in the moderate risk with an additional risk factor, should perform a DXA scan, whereas no BMD is necessary in the low-risk group. In China, Malaysia, Singapore, and Taiwan, OSTA is used for osteoporosis screening, while guidelines for treatment are based on T-scores, history of fragility fractures, or absolute risk (60,61,67,69), similarly to the other countries worldwide (Tables 3 and 4) (58–62,64–67,69–112). The Philippines is the only country that recommends treatment based on a high OSTA score, if BMD is not available (65).

**QFracture:** According to the National Institute for Clinical Excellence (NICE), the absolute risk for fragility fracture in the UK can be assessed with QFracture for subjects between ages 30 and 85 yr, and with FRAX for ages 40 and 90 yr (112). In Scotland, the Scottish Intercollegiate Guidelines Network recommend fracture-risk assessment, preferably using QFracture, prior to DXA, in subjects with clinical risk factors for osteoporosis and in whom anti-osteoporosis treatment is being considered (62). QFracture is the calculator of choice in Scotland due to its ability to provide predictions in a wide spectrum of age groups (30–99 yr, based on the updated QFracture tool (113), and its allowance for calculation of risk over varying time frames (1–10 yr) (62).

**Garvan:** This risk calculator is commonly used in Australia as recommended by the Royal Australian College of General Practitioners (59), and is incorporated in the New Zealand osteoporosis guidelines (66). In New Zealand, either FRAX or Garvan could be used to determine the 10-yr hip fracture risk, as both calculators allows the calculation to be performed in the absence of BMD measurements (66). The US Endocrine society recommends the use of Garvan (as an alternative to FRAX), for predicting fracture risk in men with osteopenia in the absence of fragility fracture (64). This was, in part, based on the validation study in Australia that revealed that FRAX underestimates fracture risk in men (114).

### FRAX Calibration in Cohorts Worldwide

Several studies have independently assessed the performance of FRAX to predict fracture incidence in various populations from the US, the UK, France, Denmark, and Canada, as summarized in Appendix 2 (39,46–51), and reviewed elsewhere (12,13,15,16,40,115,116). In general, as detailed in Appendix 2, the performance of FRAX, captured by AUC, was consistently superior for hip fracture as compared to MOF, in most studies. Adding BMD to the tool did not consistently nor substantially improve tool performance (39,46–51).

### Comparative Studies of Risk Assessment Tools

We review studies that directly compared key performance characteristics of 4 validated FRAX tools, in large cohorts, to-date.

1. **FRAX and CAROC:** The performance of the 2 calculators were assessed in Canadian Multicenter Osteoporosis Study (CaMOS; over 6000 individuals) and Manitoba BMD (over 39,000 individuals) cohorts, mean age 65.5(9.5) yr (68). Ten-year fracture outcomes in both cohorts showed good discrimination and calibration for both CAROC (6.1%–6.5% low risk, 13.5%–14.6% in moderate risk, and 22.3%–29.1% in high-risk individuals) and FRAX (6.1–6.6% in low risk, 14.4–16.1% in moderate risk, and 23.4–31% in high-risk individuals). Reclassification from the CAROC risk category to a different risk category under FRAX occurred in less than 5% in low risk, 20–24% in moderate risk, and 27–30% in high risk (68). Reclassified individuals had 10-yr fracture outcomes that were still within or close to the original nominal-risk range (68). The same group evaluated the performance of the 2 tools, in a cohort of 34,060 subjects, with a mean follow-up of 9.8 yr, during which 3905 individuals sustained fractures, and the investigators compared observed vs predicted fractures (117). There was a high concordance between FRAX Canada and CAROC, percent agreement for identical risk categorization was seen in 85% of the overall study population, 90% in those without additional CAROC risk factors, and 69% in those with additional CAROC risk factors (117). Thirty-six individuals would have needed to be assessed with FRAX rather than CAROC to yield an improvement in risk stratification. Net reclassification improvement favored FRAX over CAROC, and in no situation was there any worsening of net reclassification overall when using FRAX instead of CAROC.
2. **FRAX, Garvan, other simple models:** The performance of FRAX and Garvan were compared in a prospective 5-yr calcium trial conducted in 1422 women from New Zealand, mean age 74.2 yr, with a femoral neck T-score of  $-1.3$  (41). FRAX performance was evaluated with and without BMD, whereas that of Garvan was inclusive of BMD. The accuracy of the calculators was assessed by testing for significant deviation from the identity line for observed/predicted fractures. Both calculators had comparable, moderate, discriminative ability, with an AUC for hip fractures of 0.67 (0.60–0.75) for Garvan with BMD, 0.70 (0.64–0.77) for FRAX with BMD, and 0.69 (0.63–0.76) for FRAX without BMD. For all fractures (combining FRAX-defined and Garvan-defined osteoporotic fractures), the AUC was 0.63 (0.60–0.66) for Garvan, 0.62 (0.59–0.66) for FRAX with BMD, and 0.60 (0.57–0.63) for FRAX without BMD. FRAX (with and without BMD) underestimated MOF, FRAX with BMD tended to underestimate hip fractures (except for high-end probability point estimate,  $p < 0.01$ ), while FRAX without BMD tended to overestimate them ( $p = 0.18$ ). The Garvan calculator more closely approximated the identity line for MOF than FRAX (with and without BMD), but overestimated hip fractures ( $p < 0.01$ ). AUC for a risk tool that only inputs age and BMD was comparable (41). The power of the study was relatively limited with 279 osteoporotic MOF and only 57 hip fractures occurring over the follow-up of 8.8 yr (41).
3. **The C index (an index identical to AUC for dichotomous variables) for FRAX, Garvan, and a simple tool based on age and prior fracture, were compared in the Global Longitudinal Study of Osteoporosis in Women international cohort using risk factors only, without BMD (43).** The cohort was based in 723 primary care centers in 10 countries over 3 continents (Europe, North America, and Australia) and comprised 19,586 women, 60 yr and older, followed annually for 2 yr. The 2-yr estimates were derived from 10-yr estimates from FRAX and Garvan assuming linearity of fracture rate over 10 yr. The C index for hip fracture was 0.78 for FRAX with BMD and 0.76 for Garvan, and lower for MOF with values of 0.62 and 0.63, respectively. Neither algorithm was better than age and prior fracture alone.
3. **The Garvan and CAROC:** Garvan was independently externally validated in the CaMOS (118). Over 6000 women and men were followed for a mean of 8.3–8.6 yr. The concordance between predicted risk with the Garvan and actual fracture events (Harell C statistic) for low trauma fractures was 0.69 for women and 0.70 for men, and for hip fractures 0.80 in women and 0.85 in men. The net re-classification index favored Garvan FRC over CAROC in men (118).
4. **FRAX-QFracture:** The performance of the 2 tools was compared in the QResearch database using FRAX 2008 version. In general, FRAX was shown to overestimate hip fracture risk in the UK QResearch database in most decile risk categories, in both genders, with exception of good predictive accuracy, in women only, in the highest 2 decile risk categories (119). In contrast, QFracture more accurately predicted hip fractures across all age categories. No direct comparison was performed for MOF. FRAX underestimated the 10-yr fracture risk in older people compared with both QFracture and Garvan calculator (120). The latter finding was attributed to the fact that FRAX, in contrast to other calculators, takes the mortality rate of the general population into account. However, QFracture has been shown to accurately predict fracture risk in older people up to the age of 85 yr, although mortality is not part of the tool (57).
5. **FRAX, Garvan, and QFracture:** The performance of the 3 tools, without BMD for FRAX and Garvan, was examined in a retrospective electronic health records database from a health-care organization in Israel (45).

The study population consisted of over 1 million subjects, 54% were women, aged 50–90, followed over 5 yr from 2010 to 2014, during which 7.7% (N = 81,564) MOF occurred and 2.7% (N = 28,091) hip fractures occurred. The AUC for hip fractures was 0.83 for QFracture, 0.82 for FRAX, and 0.78 for Garvan. The AUC for MOF were 0.71 for QFracture and 0.71 for FRAX. All tools underestimated fracture risk, observed to predicted ratios, were closest to 1 (1.6–1.9) for FRAX in women, across all age groups, with a much wider range from 1.1 to 3.7 for QFracture, and from 2.7 to 6.9 for Garvan, with a gradual decrease in this ratio with increasing age.

Possible explanations for differing performances by the 3 main tools are developmental differences, namely, FRAX only includes a competing mortality risk, in addition to differences in the input, output, and time interval between them. Both FRAX and Garvan can include BMD. QFracture and Garvan include falls, an important consideration in the elderly. Garvan incorporates a dose risk effect for falls and fractures, and QFracture does the same for smoking, alcohol, and diabetes. QFracture uses numerous secondary causes of osteoporosis, while there are only few in FRAX, and less in Garvan. For FRAX and QFracture the output is MOFs, while for Garvan the output is any osteoporotic fracture (hip, clinical spine, wrist, metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, and sternum). QFracture provides an annual fracture risk, but for Garvan and FRAX, a linear increase in fracture risk with time of follow-up was assumed to derive fracture probabilities over shorter periods. Finally, tool performance is most optimal when tested in a population of similar characteristics to that where it was developed. This is true for AUC for QFracture in the UK, and AUC for Garvan in Australia and New Zealand.

## FRAX as the Basis for Osteoporosis Guidelines Worldwide

Osteoporosis diagnosis and treatment were, to a large extent, and still are in many countries, driven by a history of fragility fractures (requiring a low BMD concomitantly for some), or in individuals who had not experienced fragility fractures, by a low DXA BMD T-score. A low T-score cutoff  $\leq -2.5$ , the WHO BMD operational diagnostic threshold for osteoporosis (27), was adopted and retained by many guidelines (82), while others use lower T-score cutoffs (Tables 3 and 4).

Risk calculators have as an intervention threshold allowed the introduction of case finding strategies, identifying high-risk individuals for treatment. Since their advent, several societies and organizations have incorporated absolute fracture risk assessment strategies in their revised osteoporosis treatment guidelines. This approach, pioneered in the UK, the US, and Canada, was based on FRAX. To date, 4 main FRAX-based intervention strategies

have been proposed. All concur to treat individuals with fragility fractures. In individuals without fractures, the UK National Osteoporosis Guideline Group (NOGG) model uses an age-dependent translational approach that treats individuals without fractures at thresholds equivalent to those defined in a subject of similar age, BMI of 25 kg/m<sup>2</sup>, and who experienced a fragility fracture (79). The National Osteoporosis Foundation (NOF) model in the US uses a clinical and cost-effectiveness approach based on T-scores  $\leq -2.5$  at the lumbar spine or hip, and in the absence of osteoporosis on fixed thresholds (82). A threshold of 10-yr hip fracture FRAX probability of  $\geq 3\%$  was selected based on cost-effectiveness analyses, and the 10-yr MOF FRAX probability of  $\geq 20\%$  was derived from it (121). The Canadian national guidelines are based on risk stratification (low risk is 10-yr MOF  $< 10\%$ , moderate risk between 10% and 20%, and high risk if MOF  $> 20\%$ ), with recommendations to consider treatment of individuals at high risk and for those at moderate risk in light of additional considerations (risk factors and patient preferences) (58). Ten-year fracture outcomes in CaMOS and Manitoba cohorts revealed good discrimination and calibration for both CAROC and FRAX for these 3 risk categories (68). Lebanese national guidelines introduced a hybrid model, with a fixed MOF threshold ( $\geq 10\%$ ) under age 70 yr, and an age dependent model after 70 yr (90). The aim of the hybrid model was to avoid treating subjects  $< 70$  yr, at low risk for MOF ( $< 10\%$ ), if an age-dependent model was adopted for all age groups. The UK has explored a hybrid model, with an age-dependent threshold until age 70 and a fixed threshold after that (122). The aim of such approach was to reduce inequity in access to therapy in elderly subjects, but this approach has not been adopted in the UK NOGG guidance.

We reviewed a total of 82 guidelines and academic papers, and 52 were used in this review. The total numbers of guidelines exceeds the number of countries because some countries have more than 1 set of guidelines (e.g., the UK and the US, Tables 3 and 4).

## Country-Specific Guidelines

Of the 36 countries with guidelines, 21 countries have guidelines that included FRAX (with or without T-scores, Table 3), and the remaining 15 were T-score based (Table 4). The UK appears in Tables 3 and 4 due to different approaches used by NICE and NOGG. Most guidelines include fragility fractures as an indication to treat, regardless of T-score or other risk calculators. We therefore divide the retrieved guidelines into guidelines that use FRAX (Table 3) and those that do not (Table 4).

## Guidelines That Use FRAX (With and Without T-Score)

Of the 21 countries with FRAX-based guidelines, 8 countries are from Europe (France (70), Greece (71), Poland

**Table 3**  
Intervention Thresholds in Countries With FRAX-Based Guidelines

Country Organization	T-score database FRAX calculator	Target population Intervention threshold
France (70) <i>French National Authority for Health (HAS)</i>	T-Score: NHANES III FRAX France	Postmenopausal women - Previous severe osteoporotic fracture (femur, humerus, spine, 3 ribs, tibia, pelvis) - Other nonsevere osteoporotic fractures (wrist and other sites) ▶ T-score $\leq -3$ at LS or femur - Absence of nontraumatic osteoporotic fractures, evaluate risk factors for osteoporosis or high-risk for fall ▶ T-score $\leq -3$ at LS or femur ▶ T-score $> -3$ at LS or femur and MOF age-dependent FRAX threshold <sup>a</sup>
Greece (71) <i>Greek National Medicine Agency Endorsed by Central Health Council of Greece</i>	T-score: NS FRAX Greece	Postmenopausal women, and men age $\geq 50$ yr - Vertebral or hip fracture - More than 1 other fragility fracture - T-score $\leq -2.5$ (total hip, FN, LS) - Osteopenia, and an MOF FRAX probability $\geq 20\%$ and hip FRAX probability $\geq 3\%$ - Osteopenia with MOF FRAX probability between 10% and 20% with: ▶ Asymptomatic fracture diagnosed through lateral or lumbar X-ray ▶ Wrist fracture at age $\geq 65$ ▶ Lumbar BMD lower than hip BMD ▶ $>5\%$ decrease in BMD $<1$ yr ▶ Breast cancer ▶ High risk for falls
Poland (72) <i>Multidisciplinary Osteoporotic Forum</i>	T-score: NS FRAX Poland: FRAX-BMI algorithm for the Polish population	Postmenopausal women, and men age $\geq 50$ yr - Any existing osteoporotic fracture - Absolute risk of fractures $>10\%$ (absolute risk of fracture is estimated based on BMI, clinical risk factors, including BMD, and other independent risk factors) - The decision to start treatment must be preceded by confirmation of fracture by an X-ray or VFA scan of the vertebra [A] <sup>b</sup>
Portugal (73) <i>Order of Physicians</i>	T-score: NS FRAX Portugal	Postmenopausal women, and men aged $\geq 50$ yr - Previous fragility fracture - T-score $< -2.5$ at the LS or FN by DXA - Osteopenia and MOF FRAX probability $>20\%$ or hip FRAX probability $>3\%$
Slovenia (74,75) <i>Adopted by the Expanded Professional Board of Internal Medicine of Slovenia</i>	T-score: NS FRAX UK	Postmenopausal women, and men age $\geq 50$ yr - Previous hip or vertebral fracture (clinical or morphometric) - In the absence of fractures: ▶ A range of age-dependent and gender-specific T-score thresholds (e.g., T-score $\leq -2.5$ at age $>70$ yr, but $\leq -4$ at younger ages 50–60 yr for women) <sup>c</sup> ▶ FRAX probability with cutoffs of $>20\%$ for MOF or $>5\%$ hip probabilities
Switzerland (76,77) <i>Association Suisse Contre l'Osteoporose</i>	T-score: NS FRAX Switzerland	Postmenopausal women, and men age $\geq 50$ yr -Subject with fracture ▶ Vertebral or hip fracture ▶ Peripheral fracture atraumatic assess absolute fracture risk -Subject without fracture ▶ T-score $\leq -2.5$ at LS or FN ▶ MOF age-dependent FRAX threshold <sup>a</sup>
Turkey (78) <sup>d</sup> <i>Turkish Endocrinology and Metabolism Association endorsed by the Turkish Government</i>	T-score: NHANES III, young female reference data FRAX Turkey	Postmenopausal women, and men age $\geq 50$ yr - Previous fragility fracture - T-score $\leq -2.5$ <sup>c</sup> - Fixed threshold MOF $>20\%$ and hip $>3\%$
UK (79,90) <i>NOGG</i>	T-score: NHANES III FRAX UK	Postmenopausal women, and men age $\geq 50$ yr - Previous fragility fracture (hip, spine, and forearm) - In patient without fractures ▶ Age-dependent FRAX threshold <sup>a</sup>

(Continued)

**Table 3**  
(Continued)

Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Asia-Pacific		
China- Hong Kong (60) <i>Osteoporosis Society of Hong Kong</i>	T-Score: Asian normative database FRAX Hong Kong	Postmenopausal women - Prior low-energy hip or vertebral fractures - T-score of $\leq -2.5$ at the LS or proximal femur by DXA scan - T-score between $-1$ and $-2.5$ , and MOF FRAX probability $>20\%$ or hip FRAX probability $>3\%$
Japan (81) <i>Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation</i>	T-score: T-score of $-2.5$ is approximately equivalent to 70% of the YAM reference database FRAX: NS	Postmenopausal women, and men age $\geq 50$ yr - Previous fragility fracture (femur or vertebrae) - Previous fragility fractures (other than femur or vertebrae) and BMD $<80\%$ of YAM - Absence of nontraumatic fragility fractures and $70\% \leq$ BMD $<80\%$ and family history of femoral fracture - Absence of nontraumatic fragility fractures and $70\% \leq$ BMD $<80\%$ and MOF FRAX probability $\geq 15\%$ (patient age $>75$ ) - Absence of nontraumatic fragility fractures and BMD $<70\%$ of YAM
Malaysia (61) <i>Ministry of Health</i>	T-score: Comparison with YAM reference database FRAX: Use of ethnic specific algorithms (e.g. Singapore Chinese or Hong Kong Chinese, Singapore Malay, Singapore Indian) until local data are available	Postmenopausal women - Previous low trauma hip, vertebral, or wrist fracture - T-score $< -2.5^c$ - Osteopenia and MOF FRAX probability $>20\%$ or hip FRAX probability $>3\%$ - If FRAX not accessible may treat patients if $>65$ yr with multiple risk factors
New Zealand (66) <i>Osteoporosis New Zealand</i>	T-score: Healthy young adults FRAX New Zealand	Postmenopausal women age $\geq 65$ yr, and men aged $\geq 75$ yr - Previous osteoporotic fracture - T-score $\leq -2.5^c$ - Hip FRAX/Garvan 10-yr probability $\geq 3\%$
Philippines (65) <i>Osteoporosis Society of the Philippines Foundation and the Philippine Orthopedic Association</i>	T-Score: NS FRAX Philippines	Postmenopausal women - Among those with BMD examination, recommend treatment if patient has: ▶ Vertebral compression fracture/s evident on VFA or confirmed through radiograph (clinical osteoporosis) [quality of evidence—high] <sup>b</sup> ▶ T-score of $< -2.5$ [quality of evidence: high] ▶ T-score between $-1$ and $-2.5$ , with a history of previous fracture [quality of evidence: high], or secondary causes associated with high fracture risk [quality of evidence: high], or MOF FRAX probability $>20\%$ or hip FRAX probability $>3\%$ [quality of evidence: moderate] - Among those without BMD: ▶ High-risk category on OSTA tool where central BMD not available [quality of evidence: low] MOF FRAX probability $>20\%$ or hip FRAX probability $>3\%$ [quality of evidence: moderate]
Taiwan (69) <i>Taiwanese Osteoporosis Association</i>	T-score: Asian female database FRAX Taiwan	Postmenopausal women, and men age $\geq 50$ yr - Osteoporotic fracture after age 50 yr - If $>1$ risk factor measure BMD to ascertain risk, treat if hip FRAX probability $\geq 3\%$ or MOF FRAX probability $\geq 20\%$

(Continued)

**Table 3**  
(Continued)

North America		
Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Canada (58) <i>An expert panel, consisting of members of the Osteoporosis Canada Scientific Advisory Council, members of stakeholder organizations, family physicians and experts from across Canada</i>	T-score: NHANES III FRAX Canada	Postmenopausal women, and men age $\geq 50$ yr - Previous fragility fracture of the hip or vertebra, and those with more than 1 fragility fracture are and are at high risk for future fractures [B] <sup>b</sup> - MOF FRAX probability $>20\%$ [D] - MOF FRAX probability between 10% and 20% (moderate risk), should be evaluated in terms of patients' preference and for additional risk factors and treated accordingly [C]
US (82) <i>Expert committee of the National Osteoporosis Foundation (NOF)</i>	T-score: NHANES III FRAX US White, Black, Hispanic, and Asian	Postmenopausal women, and men age $\geq 50$ yr - Hip or vertebral (clinical or asymptomatic) fractures - T-scores $\leq -2.5$ at FN, total hip, or LS by DXA - Postmenopausal women and men age $\geq 50$ yr with osteopenia at the FN, total hip, or LS by DXA, and MOF FRAX probability $\geq 20\%$ or hip FRAX probability $\geq 3\%$ AAACE, NAMS, ACOG/AHRQ, ICSI, and the Endocrine Society adopted the NOF (64,82–86)
Latin America		
Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Argentina (87) <i>la Asociación Argentina de Osteología y Metabolismo Mineral y la Sociedad Argentina de Osteoporosis</i>	T-score: NHANES III FRAX Argentina	Postmenopausal women, and men age $\geq 50$ yr - Previous fragility fracture of the hip or vertebra - After ruling out secondary causes of osteoporosis; treatment is considered when MOF FRAX probability $\geq 20\%$ and/or hip FRAX probability $\geq 3\%$
Mexico (88,89) <i>Centro Nacional De Programas Preventivos y Control De Enfermedades (CENAPRECE)</i>	T-score: Healthy population age 20–35 yr FRAX Mexico	Women and men age $\geq 50$ yr - Previous fragility fracture - T-score $\leq -2.5$ <sup>c</sup> - Age-dependent FRAX threshold <sup>a</sup>

(Continued)

**Table 3**  
(Continued)

Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Lebanon (90) OSTEOS and Ministry of Health	T-score: NHANES III FRAX Lebanon	Postmenopausal women - Age $\leq 70$ yr, MOF FRAX probability of 10% - Age $> 70$ yr, age-dependent FRAX threshold <sup>a</sup>
Saudi Arabia (91) Saudi Osteoporosis Society (SOS)	T-Score: US/Northern European and other reference data FRAX USA-White version	Postmenopausal women and men with osteoporosis - Osteopenia and fragility fracture - T-score $\leq -2.5$ at spine, femur or 1/3 radius, by DXA - MOF FRAX probability $\geq 20\%$ or hip FRAX probability $\geq 3\%$
South Africa (92) National Osteoporosis Foundation of South Africa (NOFSA)	T-scores: NHANES III, young female reference data The FRAX: surrogate country should be used, based on the likelihood that it is representative of the index country	Postmenopausal women, and men age $\geq 50$ yr - Prior fragility fracture at spine, hip, wrist, pelvis, humerus, or rib [2] <sup>b</sup> - T-score $\leq -2.5$ <sup>c</sup> - Age $> 75$ yr - Age 65–75 yr and $\geq 2$ clinical risk factors - T-score $\leq -2.5$ at spine, hip, or forearm [1] - If a subject is clearly of British, German, or Dutch descent, it is reasonable to use the model using this index country and hip FRAX probability of 3%–5% [2]

Abbr: AACE, American Association of Clinical Endocrinologist; ACOG, American College of Obstetricians and Gynecologists; AHRQ, Agency for Health care Research and Quality; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; FRAX, fracture risk assessment; ICSI, Institute for Clinical Systems Improvement; LS, lumbar spine; MOF, major osteoporotic fracture; NAMS, North America Menopause Society; NHANES, National Health and Nutrition Examination Survey; NS, not specified; OSTA, Osteoporosis Self-Assessment Tool for Asians; OSTEOS, Lebanese Society for Osteoporosis and Metabolic Bone Disorders; VFA, vertebral fracture assessment; YAM, young adult mean.

<sup>a</sup>Age-dependent FRAX threshold: in patients without fractures, the age-dependent intervention threshold for MOF or hip fracture is set at the age-specific fracture probability equivalent to women with a prior fragility fracture and BMI (25 kg/m<sup>2</sup>).

<sup>b</sup>Grade as reported in the referenced guidelines.

<sup>c</sup>T-score skeletal site not specified in the referenced guidelines.

<sup>d</sup>Personal communication with Dr. Dilek Gogas, Osteoporoz Ve Metabolik Kemik Hastaliklari Tani Ve Tedavi Kilavuzu; Osteoporoz ve Diğ er Metabolik Kemik Hastaliklari Ç alıřma Grubu tarafından hazırlanmıřtır (2016). Available online: [http://www.turkendokrin.org/files/METABOLIK\\_KH\\_BOOK\\_web.pdf](http://www.turkendokrin.org/files/METABOLIK_KH_BOOK_web.pdf) (Accessed March, 2017).

(72), Portugal (73), Slovenia (74,75), Switzerland (76,77), Turkey (78), and the UK (63,79)); 6 from Asia-Pacific (China-Hong Kong (60), Japan (81), Malaysia (61), New Zealand (66), the Philippines (65), and Taiwan (69)); 3 from the Middle East and Africa (Lebanon (90), Saudi Arabia (91), South Africa (92)); 7 from North America (1 from Canada (58) and 6 from the US (64,82–86)); and 2 from Latin America (Argentina (87), and Mexico (88,89)). Many of these were issued by national osteoporosis societies and some were endorsed by national health authorities (e.g., France, Greece, Lebanon, Malaysia, and New Zealand; Table 3).

The use of FRAX is without any consideration for T-score, in Argentina (87), Lebanon (90), Poland (72), Turkey (78), the UK (79), and Saudi Arabia (91), while other countries also kept T-score thresholds in their considerations to intervene, such as Canada (58), China-Hong Kong (60),

France (70), Greece (71), Japan (81), Malaysia (61), Mexico (88,89), New Zealand (66), Portugal (73), the Philippines (65), Slovenia (74,75), South Africa (92), Switzerland (76,77), Taiwan (69), and the US (64,82–85). The T-score threshold, while often set at  $\leq -2.5$ , or even lower, take into account other considerations (age, risk factors). It was set at  $\leq -3$  in France (70) (Table 3), or was based on a range of age-dependent T-scores in the UK NICE guidance (112) (Table 4).

While France and Switzerland adopted the UK NOGG translational approach of an age-dependent FRAX-based intervention threshold, in accordance with the IOF, European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) guidelines (123,124), several others in Europe, and most in Asia, chose the US fixed NOF intervention thresholds of  $\geq 3\%$  for hip fracture FRAX probability and  $\geq 20\%$  for MOF FRAX probabilities.

**Table 4**  
Intervention Thresholds in Countries with non-FRAX-Based Guidelines

Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Austria (93) <i>Academia</i>	T-score: NHANES III, young healthy population FRAX Austria	Postmenopausal women - Previous vertebral or hip fracture - T-score of $-2.5$ at LS, hip
Belgium (94) <i>Belgian Bone Club</i>	T-score: NHANES III, female database 20–29 yr FRAX Belgium	Postmenopausal women - Prevalent vertebral fracture - T-score $<-2.5$ at LS, hip
Denmark (95,96) <i>Danish Bone Society</i>	T-score: NS FRAX Denmark	Population not specified - Prior fragility fracture of the hip or spine - T-score $\leq -2.5$ at total hip or spine with an accredited risk factor - T-score $\leq -4$ and no clinical risk factors
Germany (97) <i>Academia</i>	T-score: NHANES III, female database 20–29 yr FRAX Germany	Postmenopausal women age $\geq 50$ yr, and men age $\geq 60$ yr - 30% 10-yr risk for hip fractures and vertebral fractures, calculated using the DVO 2006 model - Gender and age-specific T-scores with the consideration of other risk factors
Italy (98,99) <i>SIOMMS, Academia</i>	T-score: NS FRAX Italy	Postmenopausal women - History of previous osteoporotic fracture - T-score $\leq -3$ plus other risk factors (family history of fragility fractures, RAs, or others) <sup>a</sup> - Hip BMD or calcaneal ultrasonography $<-4$
Ireland (100) <i>Ireland Osteoporosis Society</i>	T-score: NS FRAX—Ireland	Population not specified - T-score of $-2.5^a$
The Netherlands (101) <i>Academia</i>	T-score: NHANES III, for the hip FRAX Netherlands	Postmenopausal women, and men age $\geq 50$ yr - Postmenopausal women with 1 or more osteoporotic vertebral fractures or an increased risk and a T-score $<-2.5^a$ - Women older than 70 yr with Z-score $<-1.0$ with other risk factors - Men with severe osteoporosis (vertebral fracture and T-score $<-2.5$ )
Romania (102) <i>Academia</i>	T-Score: NS FRAX Romania	Population not specified - T-score $\leq -2.5^a$
Slovakia (103) <i>Ministry of Health</i>	T-score: NS FRAX Slovakia	Postmenopausal women - Previous osteoporotic fracture
Spain (104,105) <i>Spanish Society of Rheumatology; Spanish Menopause Society</i>	T-score: NHANES III FRAX Spain	Postmenopausal women - Presence of fragility fracture [A] <sup>b</sup> - T-score $\leq -2.5$ at spine and/or femur [A] - Osteopenia (T-score between $-1.0$ and $-2.5$ ) if any of the predictive scales indicate a high risk for fracture [2 B]
UK (106,112) <i>National Institute for Health and Clinical Excellence (NICE)</i>	T-score: NHANES III FRAX UK	Postmenopausal women aged $\geq 65$ yr, and men aged $\geq 75$ yr - Drug-specific intervention thresholds based on clinical risk factors for fractures, age, gender, and varying T-score cutoffs

(Continued)

**Table 4**  
(Continued)

Asia-Pacific		
Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Australia (59,107) <i>The Royal Australian College of General Practitioners</i>	T-score: NHANES III FRAX Australia	Postmenopausal women, and men aged $\geq 50$ yr - Previous fragility fractures, BMD recommended but not essential to start treatment ▶ Vertebral fractures ▶ Any fracture following minimal trauma - In the absence of fracture: ▶ Assess major risk factors, age ( $\geq 70$ yr), and BMD to evaluate absolute fracture risk (nomograms used)
India (108) <i>Indian Menopause Society</i>	T-score: NHANES III, Caucasian women aged 20–29 yr FRAX India	Postmenopausal women - $>5$ yr post menopause, with T-score between $-1$ and $-2.5$ at hip or spine, and 1 major risk factor or 2 other risk factors - $<5$ yr post menopause, with or without 1 major risk factor or 2 other risk factors, and T-score $\leq -2.5$ at hip or spine - $<5$ yr post menopause, with a T-score $< -2.5$ at hip or spine and a fragility fracture
Singapore (67) <i>Ministry of Health</i>	T-score: Asian reference database FRAX Singapore	Postmenopausal women - Previous fragility fracture [A] <sup>b</sup> - Absolute risk for fracture is high (calculator and thresholds not clearly defined) - T-score $\leq -2.5^a$ [A] <sup>b</sup> - Other factors to consider in making a decision to treat: age ( $>65$ yr); high risk for bone loss; high risk for falls (male with OP to be referred to specialized clinic)
Latin America		
Country Organization	T-score database FRAX calculator	Target population Intervention threshold
Brazil (109–111) <i>Ministry of Health</i>	T-score: NS FRAX Brazil	Postmenopausal women - Low-impact fracture of the femur, hip, or vertebrae (clinical or morphometric) radiologically confirmed - T-score $\leq -2.5$ at FN or spine - T-score between $-1.5$ and $-2.5$ at FN or spine, in patients aged $\geq 70$ yr if they have suffered 2 or more falls in the last 6 months

Abbr: BMD, bone mineral density; DVO, Deutschsprachigen Wissenschaftlichen Osteologischen; FN, femoral neck; FRAX, fracture risk assessment; LS, lumbar spine; NHANES, National Health and Nutrition Examination Survey; OP, osteoporosis; RA; rheumatoid arthritis; SIOMMS, The Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases.

<sup>a</sup>T-score skeletal site not specified in the referenced guidelines.

<sup>b</sup>Grade as reported in the referenced guidelines.

Most of these guidelines refer to the US NOF, or UK NOGG guidance, for the selection of their cutoffs, without any other specific justification for their use in the countries concerned. The New Zealand Osteoporosis Society defines a 10-yr hip fracture risk of 3%, using FRAX or Garvan calculators, as an intervention threshold based on pharmaco-economic analyses (66). A fixed threshold approach is currently recommended in Greece, but a cost-effectiveness biphasic model was recently developed (125);

Turkey has a fixed FRAX model and is considering an age-dependent model (78).

#### T-Score-Based Guidelines

The following countries do not incorporate FRAX or any other risk calculator in their current guidelines: Austria (93), Australia (59), Belgium (94), Brazil (109–111), Denmark (95), Germany (97), India (108), Ireland (100), Italy (98,99), the Netherlands (101), Romania (102),

Singapore (67), Slovakia (103), Spain (104,105), and the UK (112) (Table 4). Few countries use FRAX as a support tool in assessing subjects; for example, Spain where a 10-yr FRAX-based MOF of 15% is considered high risk in the Spanish population (104), and Italy uses DeFRA an updated version of FRAX (99).

### *Countries With FRAX Calculator but Without Guidelines*

Twenty-five countries have country-specific FRAX calculators but do not have published osteoporosis guidelines. In Europe, these are Armenia, Belarus, Croatia, Czech Republic, Estonia, Hungary, Iceland, Israel, Malta, Moldova, Norway, Russia, and Ukraine; in Latin America, these are Colombia, Ecuador, and Venezuela; in the Middle East-Africa, these are Iran, Jordan, Kuwait, Morocco, Palestine, Tunisia, and the United Arab Emirates; and in Asia-Pacific, these are Sri-Lanka and Thailand (<https://www.shef.ac.uk/FRAX/index.aspx>, Feb 28, 2016). Another 6 countries have FRAX calculators, but their guidelines are published in non-English language: Chile, Finland, Indonesia, Lithuania, the Netherlands, South Korea, and Sweden.

### *Countries With Guidelines but Without FRAX Calculator*

Saudi Arabia, South Africa, Malaysia, and Slovenia do not have a FRAX calculator, but have FRAX-based guidelines (see section below “Countries with Limited Data”). Bulgaria has published guidelines in non-English language, but does not have a country-specific FRAX calculator.

## **Regional Guidelines**

### *Europe*

The “European Guidance for the Diagnosis and Management of Osteoporosis in Postmenopausal Women” was developed by the IOF and ESCEO. The guideline recommends that clinical risk factors and fracture probability be assessed as a first step; subjects with high fracture probability, based on age-dependent FRAX thresholds, should be considered for drug therapy. Subjects with intermediate fracture probability should perform a BMD, after which fracture probability is reassessed, and those at high risk should be referred to treatment (123,124).

The Deutschsprachigen Wissenschaftlichen Osteologischen 2014 guidelines were issued by the Organization of Scientific Osteological Societies of the German-Speaking countries which include Austria, Germany, and Switzerland (126). They target postmenopausal women and men age 60 yr or older, and use an alternative risk assessment approach, taking into account age and gender-specific DXA T-score cutoffs, and risk factors (9 risks, 9 diseases, 3 drugs). T-score cutoffs are adjusted downward (0.5 T-score adjustment per risk factor to a maximum T-score of -2). The guidelines recommend

treatment for patient with single or multiple vertebral fractures or proximal femur fracture and a DXA T-score  $<-2.0$  at lumbar spine, or hip; a 10-yr risk for vertebral or proximal femoral fracture  $>30\%$  when DXA T-score  $<-2.0$  at lumbar spine, or hip; if a patient is on glucocorticoids with a T-score  $\leq-2.5$  (126).

### *Latin America*

The “Iberoamerican Consensus on Osteoporosis: Prevention, Diagnosis, and Treatment” developed by Iberoamerican Society of Osteology and Mineral Metabolism in 2009, recommends treatment to postmenopausal women if they have at least 1 fragility fracture; had no prior fractures and 1 or more risk factors (besides menopause); had BMD T-score of less than or equal to  $-2.0$  by DXA at the spine or hip; had no prior fractures or detectable risk factors, if their DXA T-score  $\leq-2.5$  in one of the main axial skeletal sites. It also recommended treatment to postmenopausal women and men with osteoporosis; and to individuals older than 80 yr with a Z-score  $<-1.5$  (127).

### *Middle East*

The “Middle East and North Africa Consensus on Osteoporosis” was developed by members of patient-based or scientific osteoporosis societies from 13 countries from the Middle East and North Africa. They recommend consideration of osteoporosis treatment based on patient’s age, history of fragility fracture especially at the spine; BMD results at the spine and hip, with no specific T-score cutoff. The authors expressed uncertainty regarding the best local database to use (local vs other when defining osteoporosis) (128).

The systematic review of Kanis et al (15) had identified a total of 82 guidelines or academic papers that used or explored FRAX as risk assessment tools. Our review revealed 52 guidelines in 36 countries (Tables 3 and 4). We only considered the most recent set of guidelines for any national society within a country, as applicable, papers published in English, French, Spanish, and German, or that had an English abstract, and excluded from Tables 3 and 4 publications that were not directly relevant to guidelines (such as epidemiologic and cost-effectiveness studies), and references/websites with a broken link.

## **Challenges in FRAX Worldwide**

The possibility of customizing FRAX to country-specific epidemiology, in terms of hip fracture incidence, life expectancy, and incorporating updates taking into account changes in these variables, is particularly attractive. But this advantage needs to be assessed in light of several considerations.

### **MOF/Hip Incidence Rate Ratios**

The UK, Sweden, Switzerland, the US, Japan, and Mexico are reported to have robust epidemiologic data on the MOF,

spine, forearm, and humerus fracture (54). For other countries, current FRAX models are based on the assumption that age- and gender-specific patterns for MOF fractures are similar to those in Sweden (54). We conducted a systematic review (see Appendix 1) to evaluate this assumption, and identified 27 papers describing the incidence of hip and other MOF, by gender and age categories, in various countries worldwide, and none from the Middle East or Latin America. We discuss findings from 6 large studies in 3 different continents, spanning a wide range of hip fracture incidence. In addition to Sweden, we describe results from Switzerland, the UK, the US, Canada, and Japan. We computed MOF/hip ratios obtained from most recent papers describing the epidemiology of the MOFs in these countries (129–142), with the exception of Switzerland, where we selected the older study that is more representative of the general population (142).

We described the method used to calculate MOF/hip ratios in Appendix 1, and the various studies in Appendix 3 (129–142).

### Summary of Results

MOF/hip ratios decreased with age, across all studies/countries, ranging from 8.9 to 23 in women, and 7.9 to 11 in men, at age 50–54 yr, and down to 1.4–2.6 in women and 1.2–2.4 in men, at 85+ yr (Fig. 1 and Appendix 3). Exceptions include Japan, and because no hip fractures were identified in 2 age categories in women (50–54 yr and 60–64 yr) and in 1 age category in men (50–54 yr), we could not calculate the MOF/hip ratio. Ratios were higher in women compared with men across all ages. In general, the highest ratios were registered in Canada, but there was wide variation between genders, by age group and country of origin, which does not allow a general conclusion (Fig. 1, Panels A and B) and (Appendix 3).

### Interpretation and Limitations

The observed differences in ratios between countries may represent true variability in fracture risk and fracture patterns. However, our findings are limited by the quality (captured by quality score in Appendix 3) the heterogeneity in data sources and data collection in individual studies, including differences in study design (retrospective vs prospective), sample size, study period and duration, the fracture identification method, the type of fracture included (osteoporotic vs any fractures), and the recruitment settings (inpatient only, vs inpatient and outpatient). Fracture site definition and method of identification also could have varied between studies. This was definitely the case for vertebral fractures (some identified clinical, whereas others included morphometric as well). Although the occurrence of more than 1 MOF was taken into account when calculating the incidence of any MOF in 1 study (130), we could not evaluate the possibility of such overlap in other studies, because it was not reported. Finally, the period during which the studies were conducted, differed significantly. The studies

from Sweden, Switzerland, and the UK were conducted before year 2000; those in Canada, the US, and Japan 15–20 yr later. Therefore, the effect of changes in lifetime expectancy and secular trends in fracture incidence, detailed below, on the observed differences in ratios cannot be excluded.

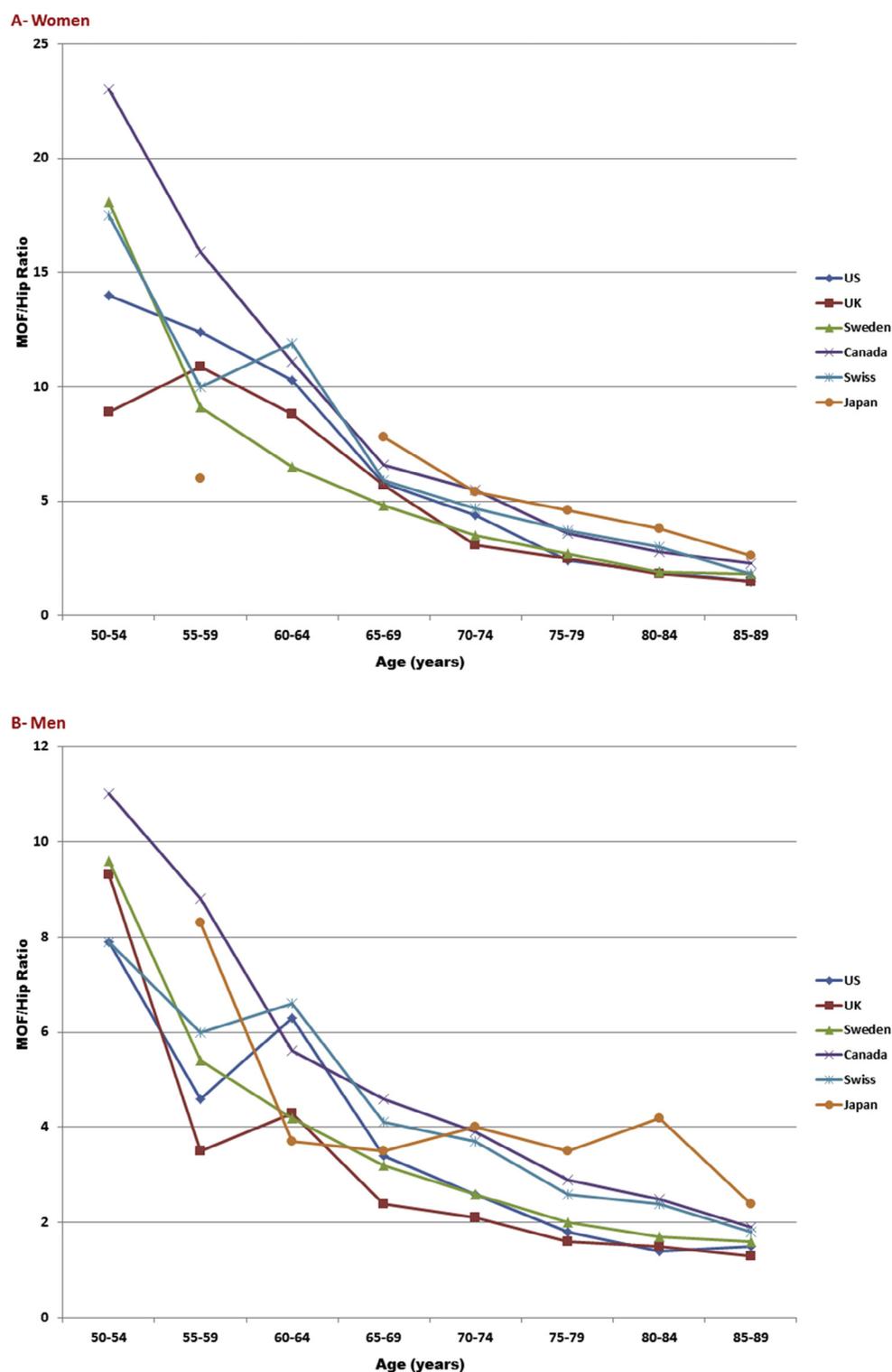
Disparate information was provided regarding study representativeness of the general population. Singer et al evaluated the incidence of MOF in 2.5% of the general population in Edinburg (134), the US NIS database represents 20% of hospital discharges (130), the Swiss Federal Office of Statistics in Switzerland cover more than 80% of registered patients (142), and the Manitoba Population Health Research Repository includes information from nearly all Manitoba citizens (132). Details from the remaining countries were not provided. The effect of ethnicity on fracture incidence has been previously described (143–145). However, the effect of ethnicity on fracture incidence by gender and age category, and thus on MOF/hip ratios, were not assessed systematically to the best of our knowledge in any study.

### Implications to FRAX Assumption on MOF/Hip Ratios

The real impact of such observed differences in MOF/hip ratios on FRAX-derived MOF estimates is unclear. It depends on how this information is entered into the FRAX calculator (type of function used, linear, exponential, quadratic, etc.). Because the FRAX algorithm is not public this is currently not known. The study by Leslie et al (133) reported that Swedish MOF/hip ratios were significantly lower than Canadian MOF/hip ratios, by 19% in men and 23% in women, differences that were largest in the younger age groups (132). The authors suggested such differences will have implications in fracture risk estimation and intervention rates. Our comparisons illustrate this diversion of the curves at younger age groups, and more so in women than men. For example, in the case of men, the MOF/hip ratio in Canadians was 1.26-folds higher than the Americans at age 85–89 yr, and reached 1.39-folds in the age category 50–54 yr. Similar comparisons in the case of women, Canadian vs UK, revealed a 1.5-folds difference in the older and a much larger, 2.6-folds difference, in the younger age groups (Fig. 1 and Appendix 3). Nevertheless, notwithstanding our lack of clear understanding of the effect of differences in MOF/hip ratios worldwide on FRAX calibration for MOF in a specific country, it would be best to rely on country-specific high-quality data, for non-hip fractures, when available. This is reflected in the Joint Official Positions of the International Society for Clinical Densitometry (ISCD) and the IOF on FRAX (18).

### Moving Targets in FRAX Worldwide

Geographic variations within and between countries in fracture rates, secular trends in such rates, and death hazards have important implications in terms of tool



**Fig. 1.** Represents the MOF-to-hip ratio in women (**A**) and in men (**B**). The dark blue line represents data from the United States (130); the red line represents data from the UK (134); the green line represents data from Sweden (141); the purple line represents data from Canada (132); the light blue line represents data from Switzerland (142); the orange line represents data from Japan (138). In Japan, for women at the age categories of 50–54 and 60–64, and in men at the age category of 50–54, the incidence of hip fracture was 0; therefore, the MOF-to-hip ratio could not be calculated for these age categories. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

calibration in general, and of country-specific FRAX calculators in particular. The data on fracture outcomes for most risk assessment tools was collected in the 1990s and 2000s and may not reflect the current performance of these tools to date. Secular trends also make it imperative to periodically reassess and update country-specific FRAX calculators, taking such changes into account. This is compounded by an added layer of complexity due to the changing population mix within many countries worldwide, the result of migration, and inter-racial marriages across the globe.

### *Geographic Variations and Secular Trends in Fractures*

There are wide variations in hip rates fractures within (up to 2-folds) and between (10–15 folds) countries worldwide, but the reasons for such differences are not clear (4,26,54,146–156). Secular trends in hip fractures further compound the picture. After a steep rise in age-adjusted rates in western populations, a decrease was noted between the mid-70s and 90s. In contrast, scarce data from Asia and South America reveal a continuous rise in hip fracture rates, with the exception of Hong Kong and Taiwan (156–158).

### *Racial Differences in Fracture Rates*

The impact of race and ethnicity on fracture epidemiology and longevity are well recognized and have been extensively discussed (18,26,156). Thus, the choice by certain countries to have ethnic-specific FRAX models, such as in the US (Caucasian, Black, Hispanic, Asian), China (China and Hong Kong), and Singapore (Chinese, Malay, Indian).

Recent data from the US suggest that, while hip fracture rates are declining among Caucasians, there has been an increase in age- and gender-specific hip fracture risk in Hispanic Americans from California (159), possibly related to social admixture. If confirmed, then the Hispanic model may need revision or the Caucasian model used instead (18). Secular trends in other fractures (157), although less well characterized, will also affect FRAX-derived hip and MOF estimates.

All other countries with FRAX calculators to date use a single model, which ideally should be built using country-specific population-based high-quality representative data that include all ethnicities. Experts have argued that in some instances, a single-country model may be preferred, recognizing the potential impact of ethnic differences on FRAX interpretation (54). However, considering the constant flux of immigrants from Africa and Asia into western continents, there may be an advantage in using the FRAX tool of the country of origin, especially in first- and possibly second-generation immigrants. As an example, the incidence of hip fracture rates between 1987 and 2002 were twice as high in 2.8 million Swedish born compared with 270,000 foreign-born residents, even after 40 yr of residence (160).

### *Secular Trends in Longevity*

In 2015, global average life expectancy at birth was 71.4 yr (73.8 yr for women and 69.1 yr for men), 60.0 yr in the WHO African region, and 76.8 yr in the WHO European region (1). It increased by 5 yr between 2000 and 2015, the fastest rise since the 1960s. The increase was greatest in the WHO African Region, where life expectancy increased by 9.4 yr to 60 yr, driven mainly by improvements in child survival, and expanded access to antiretroviral drugs. This will affect FRAX calibration.

### *Changes in Calibration and FRAX Performance*

Kanis et al proposed that systematic errors in FRAX calibration may have minimal impact on the rank order of fracture probabilities produced by the FRAX tool, as shown by comparison of the original and revised US FRAX tool (161). Such errors would, however, impact absolute FRAX-derived fracture probabilities, and thus daily practice at the individual and public health level, the latter because of a major impact on cost-effectiveness analyses (15). Indeed, Leslie et al showed that small changes in FRAX calibration, for example, as little as 10%, had a large effect on the number of individuals qualifying for treatment (162). The importance of high-quality data that best represents country-specific epidemiology was further underscored in a study directly comparing 8 national FRAX tools for fracture prediction and treatment qualification in 36,730 Canadian women, mean age  $65.7 \pm 9.8$  yr, enrolled in the Manitoba BMD program. For hip fracture prediction, good calibration was observed for FRAX Canada, the US, France, the UK, Australia, but the risk was overestimated using FRAX Sweden and underestimated using FRAX China (163). For MOF prediction, even greater differences were seen; FRAX Sweden had the largest overestimation and FRAX China the largest underestimation. Even relatively small calibration differences had a large effect on risk categorization and treatment qualification (163).

### *FRAX in Countries With Limited Data*

The ISCD-IOF FRAX International Task Force recommended that in the absence of a FRAX model for a particular country, a surrogate country that is most representative of the index country in terms of hip fracture rates should be selected (18,54). The Task Force also recommends that the FRAX model should incorporate the death hazard of the index country. Mortality data are available for nearly all countries, based on either data from the national Ministries of Public Health and WHO life tables (Life expectancy by country, WHO 2012). Poland had initially adopted the entire UK FRAX model as its surrogate country, without adjustment for death hazard for Poland. This approach was evaluated retrospectively in a convenience sample of 501 women who had BMD and clinical risk factors 9–12 yr prior. The tool was demonstrated to overestimate fracture risk, with an expected/observed ratio of

1.79 (CI = 1.44–2.21) for calculations with BMD and 1.94 (1.45–2.54) without BMD (164), again underscoring the importance to gather country-specific data.

Countries that currently have a FRAX calculator based on the use of surrogate country for risk assessment are India, Palestine, and Sri Lanka. Palestine calculator is based on FRAX Jordan, while India and Sri Lanka use the Singapore FRAX calculator for Indians, and WHO life expectancy tables are used for all 3 (John A. Kanis, personal communication). No data are available to evaluate the impact of such approach on fracture risk assessment in these countries.

Although the majority of countries with FRAX-based guidelines for treatment have a country-specific FRAX-calculator, 4 countries did not and used alternatives. Malaysia and South Africa followed the recommendations of the ISCD-IOF FRAX International Task Force recommendations. Malaysia used that of a neighboring country, Singapore (61), and South African guidelines by the National Osteoporosis Foundation of South Africa advised the use of a FRAX calculator from a surrogate country (92), reflecting the individual's descent. Slovenia elected to use FRAX UK as a surrogate country based on the fact that the epidemiology of fractures in Great Britain is similar to that in Slovenia (75). Surprisingly, guidelines from Saudi Arabia recommended the use of a US FRAX calculator, and US-based intervention thresholds of 20% for 10-yr MOF risk and 3% for hip fracture risk of 3% (91). The paper noted the lack of reliable hip fracture data from Saudi Arabia, but there was no discussion for any consideration for the use of a surrogate country from the Middle East region.

## Summary and Remaining Questions

Osteoporosis disease management has undergone a major paradigm shift pursuant to the advent fracture assessment tools over the last decade. FRAX is by far the most widely validated, and used, Fracture risk assessment tool worldwide. The FRAX calculator is available in 63 countries, and FRAX-based risk assessment is included in over 25 osteoporosis guidelines, in countries spanning 5 continents. Several more are on the horizon. FRAX was validated almost exclusively in Caucasian populations, and in Japan. No fracture risk tools have been validated in other ethnic groups. FRAX performance, using AUC statistics (AUC 0.6–0.8), or predicted probability/observed fracture incidence rates, is moderate, and in general superior for hip fracture as compared with MOF, thus questioning the assumption that MOF/hip ratios are comparable worldwide. The performance of FRAX is similar to Garvan, while that of QFracture maybe better. Garvan has been externally validated in Australia, New Zealand, and Canada, whereas QFracture has only been validated in the UK and Ireland.

FRAX underestimates fracture probability in the elderly, due to the incorporation of competing mortality, an

approach that may have its disadvantages, considering that life expectancy is difficult to predict at the individual level. A shorter time interval for predicted fracture probability may be preferable in the elderly. Despite the ability of FRAX to be customized to country-specific epidemiology, namely, hip fracture and life expectancy, there is no evidence for its superiority over simple tools. This is true when FRAX is compared with the CAROC tool in Canada, and the Garvan calculator in Australia, New Zealand, and Canada. Some studies reveal that even more parsimonious tools, age and BMD (Study of Osteoporotic Fractures [SOF] cohort), or age and prior fracture (GLOW cohort), perform as well as more complex ones. The performance of FRAX in special populations, for example, patients with multiple medical problems, and the elderly in nursing homes, is not known. Similarly, its predictive ability in countries from the Middle East, Latin America, and Africa, remain to be explored. Finally, the performance of FRAX in patients on treatment is not well characterized.

## What Should a Country Consider to Improve Fracture Prediction Now and in the Future?

Tool selection is the result of a trade-off between simplicity and ease of application, complexity with enhanced performance, taking into account ease of access/availability, and cost. Simple tools may be favored in the public health setting (age, BMI, smoking), whereas more complex ones, which include additional risk factors, may be better suited for clinical practices. However, this has not been systematically investigated.

Fracture risk assessment is not static, and tool calibration has to follow this dynamic process. In countries where fracture risk tools have been validated, and adopted, periodic check on model performance, and recalibration, taking into account changing population demographics, lifestyle, migration, and inter-racial population mix, is recommended. In countries with multiple ethnic groups, the decision to use a single tool (e.g., Canada), or to calibrate a tool to different specific ethnic groups (e.g., the US, Singapore) is complex. Country-specific current fracture incidence rates for both hip and MOF, which take into account secular trends, and changing longevity, are crucial to optimize FRAX tool performance. The addition of BMD did not consistently improve FRAX tool performance across studies. It thus is not warranted at the population level, especially in countries with scarce resources. Exceptions may include obese subjects (SOF study). BMD may not be necessary in young subjects. The time to screen level fracture risk score without BMD (FRAX without BMD  $\geq 9.3\%$ ) for 10% of Women's Health Initiative participants was 16 yr for those aged 55–59 yr, and 6.3 yr for those aged 60–64 yr (165). BMD screening is also not necessary in older subjects with high FRAX probabilities because they tend to have low BMD (166).

A 2-step approach, reserving BMD testing to subjects at moderate risk, based on clinical risk factors, is attractive. It was adopted by NOGG in the UK, and validated

in the Manitoba cohort (MOF FRAX 10%–19%) (167). This 2-step approach is currently being tested in the Risk-Stratified Osteoporosis Strategy Evaluation Study trial randomizing 35,000 women aged 65–80 yr to risk factor screening, followed by DXA, in subjects with an MOF of 15% (168).

Countries where tools have not been validated are best advised to establish population-based cohorts to validate simple tools (age, gender, BMI, and prior fragility fracture) and compare their performance to more complex ones, such as FRAX, with and without BMD. While mass screening with BMD is not cost-effective, the utility of fracture risk prediction, with and without BMD, requires additional research, in general, and in non-Caucasians, in particular. The 2-tier approach, with validation of a quick screening tool, as was done with OSTA in Asian populations, and its use in osteoporosis risk assessment algorithms in other populations is very attractive.

### **How Should a Country Use Fracture Prediction Tools in Guidelines for Treatment?**

Prevalent vertebral fractures, or a hip BMD T-score  $\leq -2.5$  in the absence of fractures, were the main criteria for entry into previous pivotal phase III randomized osteoporosis trials. They were traditionally adopted indications to treat osteoporosis in many countries worldwide, and will remain until results from new trials, designed differently, become available. The clinical implications for this T-score cutoff on fracture risk probability vary widely by age, gender, presence of other risk factors, and, importantly, ethnicity. Therefore, BMD T-score, as a single criterion, was and should be dropped from the list of indications to intervene with drug therapy, in many countries, especially non-Caucasian populations. It remains, however, a useful adjunct to clinical risk factors (age, gender, BMI, fractures) in certain situations, such as in subjects at moderate risk by clinical risk factors. Since the launch of FRAX in 2008, several countries have incorporated absolute FRAX into their care pathways, albeit with scarce evidence to do so. The Screening of Older Women for Prevention of Fracture study is a UK, 7-center, 5-yr randomized controlled trial that aims to assess the effectiveness and cost-effectiveness of FRAX in selecting subjects for drug intervention based on thresholds in a community-based screening program (169). In preliminary analyses, FRAX screening was not associated with a significant reduction in the primary endpoint of all clinical fractures, but was associated with a significant reduction in hip fractures, Relative Risk Ratio 27%,  $p < 0.001$  (170).

The rationale for the inclusion of FRAX in current osteoporosis guidelines is often not clear. An optimal approach takes into account strength of the evidence, and tries to balance social health equity, with health-care resources and economics. In the case of FRAX, fixed, age-dependent, and hybrid models have been selected in the UK, the United States, Canada, New Zealand, and Lebanon, taking into

account current evidence from trials (T-scores), translational (the UK), cost-effectiveness (the United States, New Zealand), or other considerations. Cost-effectiveness analyses have been explored in various countries, such as Greece (125), France (171), Portugal (172), Sweden (173), Switzerland (77), the UK (174,175), the United States (121), and Europe (176,177).

The incorporation of risk assessment tool in guidelines is as dynamic as FRAX is. The ultimate approach depends on country-specific considerations, and will vary widely between countries. We propose that a reiterative process that examines the respective advantages and disadvantages of various approaches, and ultimately defines the most optimal one to develop guidelines, is best suited. The FRAX hybrid risk assessment model, adopted in the Lebanese guidelines and explored in the UK, illustrates such reiterative process. Guidelines present physicians with a framework and assist them in implementing a structured, evidence-based approach, taking into account country-specific recommendations. They do not supersede the Art and Science of Medicine, a practice that tailors therapy to patients taking into account their preferences, and individual risk profile.

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## Appendix 1

### Methodology

#### Fracture Risk Assessment (FRAX)

Medline was the primary search engine; the concepts used included osteoporotic fractures, risk assessment, tools,

with the application of Medical Subject Headings (MeSH) and keywords in different combination to ensure search completeness. A total of 964 were retrieved, their titles and abstracts reviewed, and a total 214 articles were selected for further full-text review. The selection of the final list was based on whether papers were published between 2000 and 2017, in English (or had an English abstract), but manuscripts in French or German were also included.

### *Osteoporosis Guidelines Worldwide*

We applied the terms osteoporosis and guidelines, to Medline (1946 to February 28, 2017), BMJ Best Practice, and Dynamed. MESH and keywords were applied with Boolean operators “and” and “or” as applicable. This was coupled with a thorough review of the list of publications posted on the International Osteoporosis Foundation (IOF) website, the content and reference list of the systematic review by Kanis et al (15). We reviewed the regional IOF audits posted on the IOF website, including The Asian Audit (2009), The Asia–Pacific Regional Audit (2013), The Eastern European and Central Asian Regional Audit (2010), The Latin America Regional Audit (2012), and the Middle East and Africa Regional Audit (2011). We contacted international bone experts for their input on relevant articles in foreign languages, and other related publications (see Acknowledgments). For FRAX-based guidelines, we accessed the online FRAX-calculator <https://www.shef.ac.uk/FRAX/tool.jsp>, identified countries with a FRAX calculator, searching for corresponding national guidelines documents. The Medline search resulted in a total of 3373 references, titles and abstracts were screened, and 161 publications reviewed, from which 49 were selected. BMJ Best Practice database search resulted in 47 guidelines, 2 were selected for further review; Dynamed database search resulted in 90 guidelines, 16 were selected for further review. An additional 15 guidelines were selected from the list of guidelines available on the IOF website. A total of 82 guidelines were reviewed in full, and 52 references were included in this chapter.

### *Incidence Rate Ratios for Major Osteoporotic Fractures (MOFs)/Hip Fractures*

We conducted a systematic search for epidemiologic studies discussing the incidence of major osteoporotic (MOF) and hip fractures. Medline, PubMed, and EMBASE were the electronic databases searched, and the concepts hip fractures; non-hip fractures; MOFs; epidemiology; and osteoporosis were used. MeSHs and keywords for these concepts, and Boolean operators “and” and “or” were used in different combinations to ensure completeness of the search. Medline search resulted in 1963 articles; PubMed in 2112 articles; and EMBASE in 3423 articles; a total of 5544 articles were screened by title and abstract after removal of duplicates; and 321 articles were selected for full-text review. We abstracted data for the crude incidence rates of hip, vertebral, humerus, and wrist fracture, by gender and age

category in duplicate. When the incidence of any MOF was not provided in the paper, we calculated the incidence of any MOF as the sum of the incidence of the 4 fractures. Then, we calculated the ratio of the incidence of MOF to the incidence of hip fractures. When the paper provided data on the fracture rates (per person-year), we derived the fracture incidence using the following formula: Risk =  $[1 - e^{(-\text{Rate} \times \text{time})}]$  using e base (2.718)]. [http://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713\\_diseasefrequency/EP713\\_DiseaseFrequency5.html](http://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_diseasefrequency/EP713_DiseaseFrequency5.html)

For all 3 searches, we also used relevant references others selected from the reference lists of the retrieved articles and from authors’ libraries.

### *Quality Rating of the Included Studies for Assessment of Ratios for MOFs/Hip Fractures*

We assessed the quality of the studies using a quality score that incorporates items that have been previously developed to rate the quality of studies on hip fracture incidence for the FRAX International Task Force Statement (18). The original items were related to study design (retrospective vs prospective), representativeness (whether the study is population-based or multi-center), study duration ( $\leq 1$  yr vs  $> 1$  yr), ethnicity definition, method used to identify fractures (use of International Classification of Diseases codes or not) (18). We have added 1 additional item to the aforementioned score one related to the definitions of osteoporotic fractures and another one for the period during which data on the various MOF fractures were collected (within 3 yr, or more than 3 yr apart for various MOF fractures reported within the same study). The latter was to account for the possibility of secular trends in fracture rates that may affect validity of derived MOF/hip incidence rate ratios.

## **Appendix 2**

### **2A—Systematic Reviews on Tool Performance**

Three systematic reviews have assessed the most commonly used fracture risk assessment tools to date. The area under curve (AUC) varied between 0.63 and 0.69 in 2 studies using the Garvan tool, between 0.62 and 0.69 in 3 studies using FRAX, while QFracture had the largest AUC varying between 0.79 and 0.82 for capturing major osteoporotic fracture (MOF) (11). Nayak et al reported a mixed performance for FRAX in different populations, good calibration of Garvan in populations in New Zealand and Canada, and good calibration for QFracture in a large national sample in the UK (16). Authors of both reviews concluded there was no compelling evidence for superiority of complex tools compared to that simpler ones (11,14). Marques et al performed a systematic review with 10 meta-analyses for FRAX using 15 studies, 3 for Garvan using 5 studies, and 4 for QFracture using 3 studies (40). They demonstrated that QFracture had the largest AUC for hip

fracture, above 0.80, for both genders in most studies. In women, the AUC for Garvan with bone mineral density (BMD) ranged between 0.67 and 0.80, AUC for FRAX with BMD between 0.70 and 0.88, and that for FRAX without BMD between 0.64 and 0.89. The AUC for FRAX in men without BMD ranged between 0.69 and 0.76. Heterogeneity was moderate to high in 9/10 FRAX meta-analyses, with the exception of 1 for FRAX combining studies for men in the US (Mr Os) and Denmark. Pooled AUC for 10-yr hip fracture prediction in women with BMD using FRAX including 5 studies, with 115,611 participants, was 0.79 (0.73–0.85), and for Garvan using 2 studies with 5574 participants 0.74 (0.61–0.87). AUC in women using QFracture including 3 studies, with 1,779,154 participants, was 0.89 (0.88–0.89), and for FRAX without BMD including 9 studies, with 131,224 participants, was 0.74 (0.68–0.80). A similar trend was noted for men using QFracture and FRAX without BMD. Heterogeneity was quite elevated exceeding 70% for all meta-analyses except for FRAX in men. Pooled estimates could not be derived for MOF in view of the fact that their definition differed from one tool to the other (40). The differences in AUCs outlined above are in large part probability explained by the variability in the populations in which they were tested (most heterogeneity in FRAX and least in QFracture), and the larger number of clinical risk factors in QFracture, and thus better risk stratification.

## 2B—FRAX Calibration in Cohorts Worldwide

Several studies have independently assessed the performance of FRAX to predict subsequent fractures in various populations (12,15). We summarize findings from studies conducted in Europe and North America; those from the UK, Canada, and Denmark were based on population cohorts that may be more representative of their countries.

1. In the UK, data from the prospective open cohort based on general practices revealed that in general, FRAX overestimated hip fracture risk in the low-to-moderate risk categories in women and men aged 10–85 yr; the ratios were close to unity in the highest risk categories (39).
2. In France, FRAX performance was examined in 867 women from the Os des Femmes de Lyon cohort (46), and in 2651 women from the Menopause et Os study (47). AUC for MOF derived from femoral neck BMD (FN BMD) was 0.74 (0.71–0.77), from FRAX without BMD 0.75 (0.71–0.79), and from FRAX with BMD 0.78 (0.72–0.82) (46). AUC derived from hip-BMD for MOF was 0.66 (0.60–0.73), and from FRAX with BMD 0.63 (0.56–0.69) (47).
3. In Denmark, FRAX performance without BMD was examined using the registry linkage system in a random sample of 3636 women. The overall predicted 10-yr hip fracture probability was 7.6% and identical to the observed risk, with no significant differences by age group, using the Swedish version of FRAX. However, when the 10-yr hip fracture probability was recalculated using the UK version, the predicted values were significantly lower than the observed risk (5.6% for predicted vs 7.6% for observed risk;  $p$  value <0.001). There was a significant variation between age groups in the predicted 10-yr fracture probability by the UK version, for age groups 61–70 ( $p = 0.032$ ) and 71–80 yr ( $p < 0.001$ ), underscoring the importance of country-specific calibration. MOF rates were not available (48).
4. In Canada, the performance of the Canadian FRAX tool was evaluated in 2 large cohorts, the Canadian Multicenter Osteoporosis Study (CaMOS) and the Manitoba BMD referral population. Both studies showed predicted fracture risks that were consistent with observed rates (49). In the Manitoba cohort, a cohort independent from the original FRAX derivation database that consisted of 36,730 women and 2873 men, the AUC for hip fractures derived from FRAX with BMD was 0.83 (0.82–0.85), and that for MOF 0.69 (0.68–0.71). The AUC for hip fractures without BMD was 0.79 (0.78–0.81), and that for MOF was 0.66 (0.65–0.67) (49).
5. In the United States, FRAX with BMD fracture discrimination was evaluated in over 6049 women partaking in SOF, with a mean follow-up of 9.03 yr, both in obese and nonobese subjects. Receiver operating characteristic analysis revealed there was no difference between obese and nonobese women in fracture prediction by FRAX, with and without BMD. BMD improved hip fracture prediction in obese more than nonobese. For obese women, the AUC for hip fracture was 0.66 (0.59–0.73) without BMD and 0.76 (0.70–0.81) with BMD, and for MOF it was 0.63 (0.59–0.68) without BMD and 0.70 (0.66–0.74) with BMD. For nonobese women, the AUC for hip fracture was 0.69 (0.67–0.71) without BMD and 0.73 [0.71–0.76] with BMD, and for MOF the AUC was 0.63 (0.61–0.65) without BMD, and 0.68 (0.66–0.70) with BMD (50). In both groups, predicted fracture probability was lower than observed for hip fractures, more so when FRAX with BMD was used, but there was good calibration for MOF fracture prediction. In MrOS, 5891 men were followed over an average of 8.4 yr. In contrast to SOF, hip fracture discrimination was better than that for MOF. The AUC C statistics were significantly higher both for hip (0.77) and MOF (0.69) for calculations with BMD, as compared to without BMD (0.67 and 0.63, respectively,  $p < 0.001$ ). Predicted quintile probabilities closely approximated cumulative incidence of hip fractures (observed/predicted ratio ranging from 0.9 to 1.10) but FRAX performance for MOF was less optimal. FRAX without BMD overestimated observed incidence rate (observed/predicted 0.7–0.9), and the addition of BMD did not improve the differences observed (0.7–1.1) (51).

6. Australia and New Zealand: please see main text “Comparative Studies of Risk Assessment Tools.”

Most validation studies have used ROC curves, an approach that has been criticized, citing that sources of error include variability in sample size and follow-up in the various cohorts, selection bias, and the need to standardize by age, to name a few (52). Other potential reasons for differences between observed incidence rates and FRAX-predicted probabilities include the fact that FRAX algorithm derives a probability that incorporates death hazard which is not equivalent with fracture incidence (15), the accuracy of the fracture hazards and death hazards, and their secular trends, FRAX model assumptions (hip/non-hip ratios, etc.), all of which can affect FRAX calibration as detailed below. Furthermore, the above studies do not allow a head-to-head comparison, to allow solid conclusions. This is covered in the main text “Comparative Studies of Risk Assessment Tools.”

### 2C—Hip to Non-Hip Incidence Rate Ratios

*Study description:* In Sweden, information on fracture incidence came from 2 retrospective studies (141). For hip fractures it was from the National Bureau of Statistics (141), and for other MOF it was taken from the Malmo study, collecting data from the Department for Diagnostic Radiology (129,141). Data for the US was from the large Nationwide Inpatient Sample (NIS) (130) that provided updated hip fracture incidence, for the year 2006 (130). Humeral and wrist fractures incidence were from the older Minnesota study (1989–1991) (131), which applied a 10%–20% discount to account for fracture overlap (>1 MOF occurring in the same individual) (130). Vertebral fracture incidences were estimated using the hip/vertebral fracture ratios from the Malmo study (129). These findings were

used to update the US FRAX calculator (130). Canadian MOF/hip ratios were as reported from a retrospective population-based study in Manitoba-Canada (132). Fracture rates registered in Manitoba are considered to be representative of the fracture rates in Canada (133). FRAX Canada uses hip fracture rates reported in a population-based study (2000–2005) (133), and non-hip fracture rates derived from US data, assuming that fracture ratios are the same in Canada and the US (FRAX Canada). Fracture incidence rates for the UK were as described in a prospective study conducted in Edinburgh (134). FRAX UK uses this study results for the incidence of hip, forearm, and humeral fractures, and derived vertebral fracture rates, assuming that the ratio of clinical vertebral-to-hip fracture is the same in the UK and in Sweden (135). For Switzerland, fracture incidence was from a study that combined information from the Swiss Federal Office of Statistics inpatient database, and the Swiss OsteoCare prospective nationwide survey that collected information for both inpatients and outpatients (142). FRAX Switzerland was built incorporating data from these 2 sources (136,137). For Japan, inpatient and outpatient incidence of hip and other MOF was as reported in a recent prospective survey conducted in Sakaiminato-Japan (138). FRAX Japan incorporated older data for hip (139), forearm, and humeral fracture (140), and used vertebral fracture incidence derived from Swedish data (FRAX Japan). All these studies extended over more than 1 yr, and data on the 4 MOFs were collected within a period of less than 3 yr, with the exception of Sweden (129,141). International Classification of Diseases codes were used to identify fractures in studies from the US, Switzerland, and Canada (130,132,142), a direct search of radiology centers was used in Sweden and in the UK (129,134), and a survey was used in Japan (138). With the exception of Japan and the UK (134,138), traumatic fractures were excluded (130,132,141,142).

### Appendix 3

#### MOF to Hip Ratios in 6 Countries by Gender and Age Categories

##### Women

Country/study yr	Author/yr	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90 +	Quality score
US NIS 2006 (130)	Ettinger (2010)	14.0	12.4	10.3	5.8	4.4	2.4	1.9	1.5		5
UK 1992-1993 (134)	Singer (1998)	8.9	10.9	8.8	5.7	3.1	2.5	1.8	1.5	1.4	3
Sweden 1996/ Malmo1987-1994 (141)	Kanis (2001)	18.1	9.1	6.5	4.8	3.5	2.7	1.9	1.8	—	2
Canada 2000-2007 (132)	Lam (2014)	23.0	15.9	11.1	6.6	5.5	3.6	2.8	2.3	1.9	5
Switzerland 2000 (142)	Lippuner (2009)	17.5	10.0	11.9	5.9	4.7	3.7	3.0	1.8	—	7
Japan 2010-2012 (138)	Tsukutani (2015)	—	6.0	—	7.8	5.4	4.6	3.8	2.6		5

##### Men

Country	Author/yr	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90 +	Quality score
NIS 2006 (130)	Ettinger (2010)	7.9	4.6	6.3	3.4	2.6	1.8	1.4	1.5		5
UK 1992-1993 (134)	Singer (1998)	9.3	3.5	4.3	2.4	2.1	1.6	1.5	1.3	1.2	3
Sweden 1996/ Malmo1987-1994 (141)	Kanis (2001)	9.6	5.4	4.2	3.2	2.6	2.0	1.7	1.6	—	2
Canada 2000-2007 (132)	Lam (2014)	11.0	8.8	5.6	4.6	3.9	2.9	2.5	1.9	—	5
Switzerland 2000 (142)	Lippuner (2009)	7.9	6.0	6.6	4.1	3.7	2.6	2.4	1.8		7
Japan 2010-2012 (138)	Tsukutani (2015)	—	8.3	3.7	3.5	4.0	3.5	4.2	2.4		5

##### Quality Score:

- Multicenter or population-based (Yes = 1)/(No = 0)
- Study design (Prospective = 1)/(retrospective = 0)
- Ethnicity (defined = 1; not defined = 0)
- Duration (for data collection 1 or more fractures; >1 yr = 1, <1 yr = 0)
- All fractures data collected during a period of 3 yr (Yes = 1, No = 0)
- Definition of the included fractures as osteoporotic (osteoporotic fractures defined and included (yes = 1), all types of fractures included (0))
- Method used to define fracture (ICD = 1)/(other definition or no definition = 0)

The scoring system represents a modified version of a score previously used by Cauley et al (18) for rating quality of hip fracture incidence studies. For further details on differences between studies, please refer to text.