

## FRAX™ and the Assessment of Fracture Probability: An Introduction

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FRAX™ is a computer-based algorithm (<http://www.shef.ac.uk/FRAX>) that provides models for the assessment of fracture probability in men and women (1-3). The approach uses easily obtained clinical risk factors to estimate 10-year fracture probability. The estimate can be used alone or with BMD to enhance fracture risk prediction. In addition to fracture risk, FRAX™ uses Poisson regression to derive hazard functions of death. These hazard functions are continuous as a function of time which permits the calculation of the 10-year probability of hip, clinical spine, humerus or wrist fracture and the 10-year probability of hip fracture. Some of the risk factors affect the risk of death as well as the fracture risk. Examples include increasing age, low BMD and smoking. In the case of age and BMD, the effect is modest since the two hazard functions have an opposing influence on fracture probability. Other risk engines calculate the probability of a clinical event (e.g., a myocardial infarct) without taking into account the possibility of death from other causes. In addition, the FRAX™ model can be calibrated for different countries (1;3).

Probability of fracture is calculated in men or women from age, body mass index (BMI) computed from height and weight and dichotomized risk variables that comprise:

- a prior fragility fracture
- parental history of hip fracture
- current tobacco smoking
- ever long-term use of oral glucocorticoids
- rheumatoid arthritis
- other causes of secondary osteoporosis
- daily alcohol consumption of 3 or more units daily

Femoral neck BMD can additionally be entered either as a Z-score or a T-score. **The transformation of Z- to T-score and vice versa is derived for the NHANES III database for female Caucasians aged 20-29 years** (4). It is important to note that the relationship between T-score and Z-score is not linear (as sometimes assumed by reference ranges), and the T-score should be used unless account has been taken of this non-linearity. When entered, calculations give the 10-year probabilities as defined above with the inclusion of BMD.

FRAX™ has been constructed using information derived from the primary data of nine population based cohorts from around the world, including centers from North America, Europe, Asia and Australia and has been validated in 11 independent cohorts with a similar geographic distribution with in excess of 1 million patient years (5). The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors, as well as interaction between risk factors, and thereby to optimize the accuracy whereby fracture probability can be computed. The large sample permits the examination of the general relationship of each risk factor by age, sex, duration of follow up and, for continuous variables (BMD and BMI), the relationship of risk with the variable itself in a manner hitherto not possible. The use of primary data also eliminates the risk of publication bias.

In addition to the clinical risk factors, fracture probability varies markedly in different regions of the world (6). Thus the FRAX™ models need to be calibrated to those countries where the epidemiology of fracture and death is known. **At present, FRAX™**

**models are available for China, France, Italy, Japan, Spain, Sweden, Turkey, and the UK and US.** Other models are being developed, but there are relatively few other countries with sufficient information to construct FRAX™ models (3), and these are listed below according to categories of risk:

- (a) Very high risk (*e.g.*, Denmark, Iceland, Norway, *Sweden, United States*).
- (b) High risk (*e.g.*, Australia, Canada, Finland, Germany, Greece, Hungary, *Italy*, Kuwait, Netherlands, Portugal, Singapore, Switzerland, Taiwan, *UK*).
- (c) Moderate risk (*e.g.*, Argentina, *China, France*, Hungary, Hong Kong, *Japan, Spain*).
- (d) Low risk (*e.g.*, Cameroon, Chile, Korea, *Turkey, Venezuela*).

Each category of risk has been represented in the FRAX™ models currently available (in italics, above). Thus in the absence of a FRAX™ model for a particular country, a surrogate country should be chosen, based on the likelihood that it is representative of the index country. (Note from the Editor: FRAX™ users should be aware that, for a given patient's profile, the calculated probability of fracture will therefore vary substantially according to the country of reference that is chosen).

There are several other caveats and limitations that should be mentioned. Several of the clinical risk factors identified take no account of dose-response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risk associated with excess alcohol consumption and the use of glucocorticoids is dose-responsive (7;8). In addition, the risk of fracture increases progressively with the number of prior fractures (9). These limitations should be recognized when interpreting the FRAX™ result in the clinic.

It should also be acknowledged that there are many other risk factors that might be considered for incorporation into assessment algorithms. **At present the FRAX™ tool limits BMD to that measured**

**at the femoral neck.** This is a result of the wealth of data available for this site. It has the advantage that for any given age and BMD, the fracture risk is approximately the same in men and women (10). Because of this, **the T-score is derived from a single reference standard (the NHANES III database for female Caucasians aged 20-29 years) as widely recommended** (11). (Note from the Editor: *i.e.*, including for men. Hence FRAX™ users should be careful if the T-score for a given patient was derived from local reference data or from any other source than NHANES). There are, however, other bone measurements that provide information on fracture risk. These include BMD at other skeletal sites, ultrasonography, quantitative computed tomography and the biochemical indices of bone turnover. The available information was too sparse to provide a meta-analytic framework for the present version of FRAX™, but other assessment tools should be incorporated into risk assessment algorithms when they are more adequately characterized.

Provision is made for the inclusion of many secondary causes of osteoporosis. A distinction is made between rheumatoid arthritis and other secondary causes. Rheumatoid arthritis carries a fracture risk over and above that provided by BMD (12). Whereas this may hold true for other secondary causes of osteoporosis, the evidence base is weak. For this reason, the other secondary causes of osteoporosis are conservatively assumed to mediate fracture risk as a result of low BMD. It is assumed that they increase fracture risk in a manner similar to patients with rheumatoid arthritis. **However, when BMD is entered into the FRAX™ equations, no weight is accorded by these other secondary causes** (1).

For these reasons, the FRAX™ tool should not be considered as a gold standard, but rather as a platform technology on which to build as new validated risk indicators become available. Notwithstanding, the present model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with BMD.

**The application of this methodology to clinical practice will demand a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds).** These are currently being developed for Europe, Japan, the UK and US (13-17). Intervention thresholds based on cost-effectiveness analyses, e.g., the UK and US, may not be applicable to other countries since the 10-year probability of fracture varies markedly in different countries (6). Intervention thresholds would also change with differences in costs, particularly fracture costs, which vary markedly worldwide. There is also the issue of affordability or willingness to pay for a strategy (3). For all these reasons, it is important to define intervention and assessment thresholds on a country by country basis that takes into account the setting for service provision and willingness to pay, as well as considerations of absolute costs. (Note from the Editor: Accordingly, intervention thresholds will likely vary from less than 10% to 30% or more in different countries).

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