Review

# Validation and further development of the WHO 10-year fracture risk assessment tool in Italian postmenopausal women: project rationale and description

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## ABSTRACT

*The threshold for pharmacological intervention for osteoporosis remains controversial. Tools predicting the future risk of new fractures are increasingly used to establish a convenient individual risk/benefit ratio for a long term treatment. FRAX® is likely to become the most widely used tool for assessing fracture risk also for the WHO endorsement. The inevitable limitations will not hamper its value. As for any tool like this a continuous process of validation and further development is highly warranted. The predictive and clinical value of FRAX® has to be tested in individual countries by exploring also the inclusion of additional specific relatively uncommon risk factors.*

*The DeFRA project is intended to validate in a large cohort of postmenopausal women a new algorithm derived from FRAX®. Both, the coefficients of continuous variable and the gradients for clinical risk factors should not be considered as conclusive for the routine clinical use. The new tool will be offered for the routine clinical use only at the completion of the DeFRA project, requiring the prospective collection of at least 60.000 patient-years. Here we report the rational and the design of the project.*

### Introduction

The number of fragility fractures has been continuously increasing in western countries and a further increase in numbers is anticipated within the next few years due to the rising ageing of the population (1).

Population interventions are recommended only to tackle extremely frequent risk factors, such as vitamin D deficiency in the elderly (2), or when the recommendations are of general health benefit, such as giving-up smoking, moderate physical activity, and a calcium rich diet. A case-finding approach for a pharmacological treatment appears to be obligatory, at least with the available drugs. This problem has been approached by the health authorities of some countries, like Italy and France, by granting drug reimbursement only for patients with a higher risk of fractures. Patients with prevalent vertebral and hip fracture and/or with very low levels of bone mineral density (BMD) were deemed to be at an adequately high risk. In countries where drug reimbursability is not regulated and all registered drugs are automatically reimbursed, the threshold for pharmacological intervention is often recommended by scientific societies on the basis of low BMD values. Thus, for example, the North-America Osteoporosis Foundation (NOF) recommended initiating therapy in patients with a T-score of -2.5 or lower in the lumbar vertebrae, hip, or distal one third radius (3).

However, it was soon realised that low BMD was only modulating the effect of other relevant risk factors such as age, previous fracture and corticosteroid therapy. By analysing data from large epidemiological studies or their meta-analysis it was found that the combination of several risk factors could substantially enhance fracture predictability, allowing the development of tools to predict the future risk of fracture in postmenopausal women.

Most of the earlier tools were based on the analysis of single database such as the SOF (4) the Rotterdam (5), the DUBBO (6) and the WHI studies (7)

or on a Canadian cohort (8). It was also found to be more convenient to express the risk over a given lag time (typically 5 or 10 years) rather than in terms of relative risk.

On February 21, 2008, the World Health Organisation (WHO) unveiled the Fracture Risk Assessment Tool (FRAX®) to calculate the percent 10-year probability of a patient sustaining a fracture (10YFR) of the hip or other bones (9-12). The databases used included 59,232 subjects, 249,898 person-years, 957 hip fractures, and 3,495 osteoporotic fractures. Due to the size of the study population and also to the WHO endorsement, FRAX® is likely to become the reference tool for assessing fracture risk in most countries. The first national organisation endorsing FRAX® was the NOF (13) that revised its guidelines for the management of patients with osteopenia in the United States and recommended initiating therapy in patients with osteopenia if the 10-year probability of sustaining a hip or other major osteoporotic fractures equaled or exceeded 3% and 20%, respectively (14). The NOF recommendations to initiate therapy in patients with osteoporosis (*i.e.* with evidence of a fragility fracture or a T-score of -2.5 or lower in the lumbar vertebrae, hips, or distal one third radius) have not changed.

### *Risk factors included in the FRAX® model*

At present the FRAX® permutation is specific for a number of countries (9) and it is achieved by simply multiplying the risk of the reference population by a fixed factor. Thus, for example, the permutation of the risk for the Italian population is 35% lower than that of Swedish women for any level of risk.

When calculating the 10YFR for both sexes, the FRAX® tool takes 3 continuous variables and 7 categorical risk factors into consideration. The continuous variables are:

1. Age: between 40 and 90.
2. Body mass index (body weight divided by square height)
3. BMD: Only hip measurements are considered, but the 10YFR can be calculated without including the BMD in the permutation.

**Table I.** Approximate gradients associated with each clinical risk factor (CRF) in FRAX®. The 10-year fracture risk derived from the computation of the 3 continuous variables is multiplied by the specific gradient whenever the CRF occurs. The gradient apparently does not change when multiple CRF are present.

| | FRAX® Risk gradients (with BMD) | | FRAX® Risk gradients (without BMD) | |
|---|---|---|---|---|
| | Hip fracture | Multiple fractures | Hip fracture | Multiple fractures |
| Previous fractures | 1.55 | 1.50 | 2.1 | 2 |
| Family history | 2.12 | 1.64 | 2.1 | 1.7 |
| Smoking | 1.63 | 1.15 | 1.4 | 1.15 |
| Glucocorticoid therapy | 1.80 | 1.58 | 2.1 | 1.7 |
| Rheumatoid arthritis | 1.42 | 1.28 | 1.7 | 1.4 |
| Secondary osteoporosis | 1 | 1 | 1.7 | 1.4 |
| Alcohol >3 units/day | 1.50 | 1.25 | 1.4 | 1.2 |

These 3 variables are strongly inter-correlated and give rise to an algorithm that is not disclosed on the FRAX® web site, but that can be roughly derived from the tables published in the WHO Technical report (9) and in several publications (10-12). The value of this algorithm with the 3 continuous variables (age, BMD and BMI) cannot be compared with data published in the literature but it requires a prospective validation.

The FRAX® includes also 7 clinical dichotomous risk factors (clinical risk factors or CRFs):

1. History of fragility fractures (yes/no answer): A fragility fracture is a fracture sustained after falling from a height not exceeding the body height or occurring after minimal or no trauma. The answer should be yes if the patient has sustained any fragility fractures;
2. Parental history of hip fractures (yes/no answer): The answer should be yes if a blood parent has sustained a hip fracture;
3. Current corticosteroid therapy (yes/no answer): The intake of corticosteroids is ranked as yes if the patient has been on prednisone or its equivalent, at least 5 mg daily for at least 3 months;
4. Rheumatoid arthritis;
5. Current cigarette smoking (yes/no answer);
6. Current alcohol abuse: 3 or more units of alcohol a day (yes/no answer);
7. Conditions leading to bone demineralisation (yes/no answer): The following are included in the FRAX® model: insulin dependent diabetes mellitus, menopause before the age of 45 years, hypogonadism, chronic malnutrition, malabsorption, chronic liver disease, and untreated long-standing hyperthyroidism.

The risk gradients attributed to the CRFs by FRAX® were roughly extrapolated from a few simulated cases of FRAX®, and are listed in Table I.

### *Major advantages of the FRAX® tool*

Until the FRAX® tool became available, the only guidelines existing to determine whether or not a patient should be treated relied heavily on the patient's T-score for BMD or the presence of a vertebral fracture. This, however, meant over-treating many relatively young women with low BMD but at low risk of fracture. When the decision to start treatment is taken, this is expected to be extended over several years, and it can be predicted that the long-term medication could potentially outweigh the possible benefits of the therapy if the risk is not adequately estimated. In many countries for economic restrains the drug reimbursement policy is based on stringent pharmaco-economic analysis (see for example in the UK the NICE, http://www.nice.org.uk/), that might be appropriately processed by making use of tools like FRAX®.

Treatment compliance with osteoporosis treatment is typically rather low and this is often due to lack of motivation. In addition, the interpretation of the DXA results varies among different densitometric centres and this is often perceived by other specialists as a sign of poor clinical and scientific evidence!

From this point of view the main advantage of the FRAX® tool is that it provides objective and reproducible documentation of the severity and potential impact of the disease. In addition, by using the FRAX® tool, only those at a substantially increased risk of fracture will be further investigated and treated. The patients and their treating clinicians are more likely to appreciate the impact of the disease if they know the probability of sustaining, for instance, a hip fracture as opposed to a relative risk.

In conclusion, the broad diffusion of FRAX® or similar tools might be of great help to improve the way osteoporosis management will be perceived by patients, caregivers, and health care providers.

*Limitations of the FRAX® tool*

Although the FRAX® tool represents a major step forward in the management of osteoporosis, it has significant limitations which may undermine its usefulness:

1. The 10-YFR can be calculated without including the BMD evaluation even though the predictability of risk factors for low BMD is rather poor (15) and mostly driven by body weight. To establish the treatment threshold the FRAX® without BMD evaluation might be considered acceptable in countries where dual x-ray absorptiometry (DXA) scans are not readily available. However, in such countries even the treatment of patients with established or severe osteoporosis is often a remarkable achievement! Furthermore, the Hip Intervention Program (HIP) study on risedronate has eloquently shown that the fracture risk is not significantly reduced when patients are treated merely based on the presence of risk factors (16). Thus, in countries where DXA scans are available the FRAX® without BMD should be used only for more convenient selection of patients in whom a DXA evaluation is warranted (17) while its use for selecting patients for treatment should not be recommended.
2. Spine BMD or quantitative ultrasound (US) assessments are not included in the FRAX® permutation, since the algorithm was established only on the hip BMD values. However, in some conditions hip BMD cannot be obtained or only US devices are available. In these cases permutation algorithms allowing the use also of spine BMD or US values would be warranted.
3. Parental history of hip fractures appears to be intuitively associated with the life spans of the relatives since the risk of hip fracture rises exponentially with ageing. This limitation is tapered by the theoretical longer, genetically determined, life expectancy, which, paradoxically is a risk factor for hip fracture!
4. The risk associated with previous fractures raises a number of problems. With FRAX® the answer should be either yes or no, but it is not clear weather silent mild morphometric vertebral compression fracture (18) detected by chance by DXA Vertebral Fracture Assessment or by an x-ray, should be included. At present, the program does not differentiate whether the patient has sustained several fragility fractures or a single asymptomatic morphometric vertebral fracture. It is well known that the risk of fractures increases with the number and type of previous fractures sustained (19) and for the presence of multiple simultaneous fractures (20).
5. Some major risk factors for fractures are not taken into account, such as the risk of falling, and the use of medication likely to interfere with the state of alertness, equilibrium, or cognitive functions. These risk factors are only partially encompassed by age.
6. Rheumatoid arthritis is considered by FRAX® as an important risk factor. Other similar conditions are not considered, not because they are unharmful for the skeleton but rather because they are not sufficiently frequent to be detected as a risk factors in epidemiological studies. Thus, the lack of permutation with other similar diseases (psoriatric arthritis) or less common rheumatic diseases (spondyloarthritis, Lupus, systemic sclerosis) is an objective limitation of the tool that should be avoided by an approximation based on common sense, for example, by attributing the same risk gradient to these conditions.
7. Corticosteroid therapy is possibly one the most prominent fracture risk. FRAX® does not differentiate the risk according to the dose and the duration of treatment. Larger doses and longer duration should have more weight than a smaller dose for a shorter duration. Similarly, if the patient has been on one or more courses of corticosteroids in the past is not taken into account. The attributed gradient risk by FRAX® is considerably lower (at least 50% lower) than that found in the few available studies or in the placebo harm of randomised clinical trials (21).
8. The database used for FRAX® development is rather large, but inevitably a number of risk factors are overlooked, not because they are unimportant, but simply because they are rare. In addition to some rheumatic diseases (see point 6) other risk factors definitely associated with increased fracture risk include the use of a number of drugs (heparin, anti-retroviral agents), history of some diseases associated with even transient immobilisation or poor nutrition. In addition, it seems logical to think that the nature or strength of risk factors for fracture may vary according to the women's age and /or the type of fracture. For example, parity and previous hormone replacement therapy is more likely to affect the risk of fracture early after menopause, but not at a more advanced age (22).
9. The FRAX® tool is potentially a process in evolution, but it is not clear who is committed to this. The disclosure of the algorithm would allow the large scale planning of a process of validation and further development, with the possible inclusion of new risk factors.

In conclusion, the recent availability of FRAX®, with the additional value associated with the WHO endorsement, is in many countries likely to considerably alter the way in which patients who are candidates for pharmacological treatment for osteoporosis are iden-

tified. Indeed, for the first time it is possible to obtain a value, the 10YFR, that can be used also by health authorities to work out a cost-benefits analysis. The validation process is critically important for any tool of this kind and the validation should be both universal and country (or ethnic group) specific.
The lack of flexibility remains a critical limitation of FRAX®. A flexible tool should allow the adjustment of risk gradients or even the inclusion of new risk factors, agreed with the local health authorities. In addition the validation process is critically important for any tool of this kind and the validation should be both universal and country (or ethnic) specific. The disclosure of the algorithm remains the preliminary step to encourage people to start the process of validation and further development of FRAX® locally. Alternatively, all major research centres will continue to elaborate their own algorithm with an inevitable huge loss of resources and opportunities.

## Validation and evolution of FRAX®: the DeFRA project

FRAX® is a trade mark and the structure of the algorithm is not disclosed and this hampers the validation and the further development of the tool. However, in order to commence its validation, the steering committee of the Italian osteoporosis guidelines consented to temporarily rely on the rough approximation of the FRAX® algorithm (derived FRAX® or DeFRA) thanks to the processing of the many examples published in the WHO Technical Report (9-12). This led to the development of the algorithms reported below (Table II and III) derived from the continuous variables (age, BMD T-score and BMI). The independent variable was set as the logarithm of the 10YRF rather than the natural number in order to obtain only positive results of the estimated risk. We compared the results obtained by using the DeFRA functions with those obtained by FRAX® and the Garavan fracture risk predicting tool (6) also freely available on line (http://www.garvan.org.au/bone-fracture-risk) in 50 simulated cases without CRFs. The Defra results were almost superimposable to those obtained by FRAX® but approximately 20 and 50% lower than those obtained by the Garavan tool, while keeping fixed the BMI values (results not shown).
These algorithms cannot be compared or tested again other similar tools or studies and the only realistic approach is to make the best possible use of it, while waiting for a prospective validation.
In the process of validation by the DeFRA project, it appears useful to make use, in addition to hip BMD, also of spine BMD and quantitative ultrasound. In Table III are reported the permutation algorithms that are used when the only bone measurements available are spine BMD (spine BMD T score; data from Adami *et al*., in preparation) or phalangeal ultrasonography as assessed by the DBM Sonic 1200 machine (QUST score; IGEA, Carpi, Italy) (23).
The risk gradients attributed to the CRFs adopted by FRAX® appear to be occasionally somewhat inconsistent with data derived from some important epidemiological studies including also Southern European populations (see "Limitations of the FRAX® tool"). A reasonable approach appears to be a re-setting of all gradients and the inclusion of other important risk factors in order to be in the best condition for a validation and further development of the predicting tool (Table IV).
Thus, the gradients were re-assessed by analysing data from large epidemiological studies and from meta-analysis.
The risk factors for fragility fractures are quite numerous. In a recent review of 170 studies 80 factors were identified. However, in most cases the association was rather weak and the relative risk was greater than 2 in only 15% of the risks (12, 24). Some risk factors are associated only with a reduction in BMD values. Other risk factors are partially or totally BMD independent. Only the latter will be properly analysed for the DeFRA tool which does obligatory include the BMD evaluation in the algorithm.
For most CRFs the risk gradient may vary according to the type of fracture. The risk of falling or extra-skeletal risk factors thus play a role in many appendicular fractures while they are of little importance for vertebral fractures (12, 25). However, for both FRAX® and DeFRA, so called multiple clinical fractures encompass both clinical vertebral fractures and appendicular fractures.

## Gradients for clinical risk factors suggested for the DeFRA project

*Previous fragility fractures*

After the age of 40, the history of a previous fracture is one of the strongest CRF for new incident fractures. (4, 19, 26-31). The mean RR is 2.2, but the value depends on age and on the site and number of previous fractures (19, 30, 32). Thus, for example, the risk of new vertebral fractures rises from 5-fold to 15-fold as compared to age matched women by increasing the number of prevalent vertebral deformities from one to 3-4 (33). The risk is mostly BMD independent and in general the adjustment for BMD values decreases the risk by only 10–20% (26, 34).
In conclusion, previous fractures, apparently of any kind, are associated in the FRAX® with a 50% increased risk of hip or multiple fractures. This appears to be somewhat underestimated even for BMD-adjusted values, particularly for patients with previous hip or multiple vertebral fractures.

*Family history of fracture*

A parental history of fracture (particularly a family history of hip fracture) confers an increased risk of fracture that is independent of BMD (35).
In an analysis of ten prospective cohorts (35), a family history of hip fracture in parents was associated with a significant risk both of all osteoporotic fractures (RR 1.54; 95CI=1.25–1.88) and of hip fracture (RR=2.27; 95% CI=1.47–3.49); the risk did not significantly change when adjusted for BMD.
A parental history of any fracture was associated with a modest but significantly increased risk of any osteoporotic fracture (RR=1.18, 95% CI=1.06–1.31), and of hip fracture (RR=1.49, 95% CI=1.17–1.89) (35). A recent review (36) found that a maternal history of any fracture was associated with an increased risk of any fracture (RR up to 1.3) and hip fracture (RR up to 1.7); a

**Table II.** Algorithm for the estimation of Ln (natural logarithm) of the 10 year risk (10YR) of either hip or multiple major fractures (as defined by FRAX®) as worked out from the tables published in the WHO technical report.

*ln* 10YR hip fracture = 0.121 age -0.000455 age$^2$-1.512 Tscore -0.162 Tscore$^2$ -0.0045 Tscore$^3$ -7.538

*ln* 10 YR of multiple major fractures = (-0.001 age$^3$ /1000) +0.050 age-0.246 Tscore+0.032 Tscore$^2$ +0.003 Tscore$^3$ +0.012 BMI -1.75

T-score: BMD T score at either the femoral neck or the total hip as assessed by Dual x-ray absortiometry (DXA).

**Table III.** Algorithms used for the permutation of the spine BMD and QUST score to T-score at the hip.

Hip BMD T score = 0.429 spine BMD T score – 0.016 Age +0.152

Hip BMD T score = 0.120 QUSTscore + 0.107 BMI – 0.030 Age -2.565

**Table IV.** Gradients associated with each clinical risk factor (CRF) for the DeFRA project.

| DeFRA Risk gradients | Hip fracture | Multiple clinical fractures |
|---|---|---|
| Family history of hip fracture[1] | 1.6 | 1.2 |
| Corticosteroid use: >5 mg prednisone equivalents [2] | 2.5 | 2.5 |
| Corticosteroid use: <5mg >2.5 mg prednisone equivalents[2] | 1.8 | 1.6 |
| One previous vertebral o hip fracture[3] | 2.2 | 2.2 |
| More than 1 previous hip or vertebral fracture[3] | 4.0 | 4.0 |
| Previous non-traumatic non-hip non-vertebral fracture[3] | 1.4 | 1.4 |
| Alcohol (>3 units /day)[4] | 1.5 | 1.2 |
| Smoking <10 cigarettes /day[5] | 1.2 | 1.0 |
| Smoking >10 cigarettes /day[5] | 1.9 | 1.5 |
| Rheumatoid and psoriatic arthritis, ankylosing spondyloarthritis, any connective tissue diseases. | 1.3 | 1.2 |

[1]Parental history of hip fractures (yes/no answer). [2]Applicable to patients on corticosteroid therapy for more than 3 months. Prior treatment courses are not considered. [3]A fragility fracture is a fracture sustained after falling from a height not exceeding the body height or occurring after minimal or no trauma. Morphometric (even asymptomatic) moderate or severe (Genant- method) vertebral fractures are also included. [4]Currently drinking 3 or more units of alcohol. A unit of alcohol is defined as a 285 mL glass of beer, a 120 mL glass of wine, a 60 mL measure of aperitif, or a 30 mL measure of spirit. [5]Current smoking only: previous smoking is not considered.

If pharmacological treatment for postmenopausal osteoporosis is or has been implemented, the estimated risk should be lowered by 30%.

Limits for the use of DeFRA:

- Only postmenopausal women.
- Age less than 90 years of age.
- Absence of the following conditions known to increase fracture risk:
  - o Malabsorption syndromes o chronic malnutrition;
  - o Any type of advanced malignancy;
  - o Type 1 diabetes or Type 2 diabetes poorly controlled;
  - o Renal insufficiency (Serum creatinine >2 mg/dl);
  - o Primary hyperparathyroidism;
  - o Severe liver dysfunction;
  - o Osteogenesis imperfecta or juvenile idiopathic osteoporosis iatrogenic hyperthyroidism.

stronger association was observed for a maternal history of hip fracture (RR up to 1.5 for any fracture and RR up to 2.0 for hip fracture).

In conclusion, the gradient risk attributed by FRAX® to family history of any kind of fragility fracture is 1.6 and 2.1 for multiple, clinical and hip fracture, respectively. This gradient is somewhat higher than that found in many epidemiological studies, and might have been driven by the higher incidence of hip fracture in elderly northern cohorts as compared to that typical of southern European populations. Genetically determined life expectancy also plays an important role particularly for hip fractures.

*Smoking*

Smoking is a risk factor for fractures, and in particular for hip fracture, in part due to its negative effects on BMD and BMI. However, smoking increases fracture risk even independently of age, BMD and BMI (37). In most studies, the relative risk decreases with time since smoking cessation (38), a finding consistent with the reversibility of its detrimental effect on the skeleton.

In a meta-analysis including 50 cohort, case-controlled, and cross-sectional studies on 512,399 subjects, fracture risk was significantly increased in current smokers for all fracture types combined (pooled relative risk 1.26, 95% CI 1.12–1.42) and for hip (1.39, 95% CI 1.23–1.58) and spine fractures (1.76, 95% CI 1.10–2.82), but not for wrist fractures (0.86, 95% CI 0.46–1.60) (37). In a subsequent analysis of 59,232 men and women (74% female) from ten prospective cohorts followed for a total of 250,000 person-years (37), current smoking was associated with a significantly increased risk of any fracture compared to non-smokers (RR=1.13; 95% CI 1.01–1.25 after adjustment for age and BMD) and especially for hip fracture (RR=1.60; 95% CI=1.27–2.02). In general the RR for hip fractures is higher (by 10 to 40%) than the RR for any fracture.

In most cases, the studies reporting on the daily amount smoked show a dose-dependent increase in fracture risk, even though the RR vary considerably according to the fracture type studied and the dose intervals examined (number of cigarettes per day, years smoked and pack years) (38). For a daily smoking dose up to 10–15 cigarettes per day, the RR is close to 1 for all fractures, and averages 1.2 for hip fractures. With higher doses, the RR for all fractures is approximately 1.5 and varies between 1.35 and 3.2 for hip fractures (38); a reasonable estimate of RR for hip fracture could be a value 25% higher than the RR for any fracture (1.9).

In conclusion, the gradient risk attributed by FRAX® to current smoking is close to that found in most epidemiologic studies. However, a dose-dependency (number of cigarettes smoked) has been reported and we suggested

that this should be taken into account on the common sense basis.

*Alcohol*

Alcoholism is widely considered as a risk factor for osteoporotic fractures and low bone density, with effects varying in a non linear way according to intake. The risk of fracture has also been associated with extra-skeletal factors, such as way of life and increased risk of falling (39). Generally no significant increase in risk is observed at daily intakes of less than 3 units (40, 41). Above this threshold, alcohol intake is associated with an increased risk of any osteoporotic fracture (RR adjusted for BMD=1.36, 95% CI 1.13–1.63), or hip fracture (RR=1.70, 95% CI 1.20–2.42) (40, 41). However, the frequency of women reportedly consuming more than 2 units of alcohol per day is low (4%) If alcohol intake is assessed as a continuous variable, each additional unit of intake above 1 unit daily increases the risk of hip fracture by 7% and the risk of any fracture by 5% (40).

The gradient risk attributed by FRAX® to alcohol intake (>3 units per day) in the BMD independent model is close to that found in most epidemiologic studies and adopted also by DeFRA.

*Falls*

Most fractures are the result of falls and an increased propensity to fall is an important BMD independent risk of fractures (25, 42). Thus, an increased risk of falling is an important risk factor of fracture.

The risk of falling increases with age (43), which is included in the FRAX® model. Living in a nursing home increases the risk of falling by 2–3 fold, but this might be due to co-morbidities encompassed by the other risk factors included in FRAX®.

In elderly people who experience a fall, the risk of falling again within a year is 2–3 times higher (44). Even when not responsible for a fracture, a fall in a very elderly person is associated with loss of self-confidence and depression which contribute to the increased risk of falling (45).

A number of additional risk factors of falling in the elderly have been identified by both NOF and NICE (46-47). These include environmental factors, specific diseases and pharmacological treatments. Vitamin D deficiency is an important fully preventable risk of falling (48).

In conclusion, FRAX® does not attribute any risk gradient to the propensity of falling. It is likely that age encompasses most of the risk associated with falls. However, the role of previous falls as an important risk of additional falls and fractures has not been fully characterised. Thus the number of falls per year has to be included in a process of validation of the FRAX®.

*Glucocorticoid treatment*

Osteoporosis and an increased fracture risk is one of the most serious complications of oral glucocorticoid (GC) treatment. In the last few years, some large epidemiological studies and meta-analyses have allowed new insights into the role played by factors such as the cumulative dose, the daily dose, the treatment duration, the existence of a threshold dose, the role of underlying diseases, and the predictive value of BMD. In a large retrospective cohort study, Van Staa *et al*. showed that the increased risk of fracture in patients using oral GC is more strongly related to daily dose than to the cumulative dose and a monotonic relationship was observed between daily oral GC dose and the risk of any fractures, without any apparent dose threshold (48). A daily dose lower than 2.5 mg of prednisone equivalent was found to have no influence on the number of incident fractures (49), but this might have been due to lack of statistical power. Daily doses between 2.5 and 5 mg increased fracture risk by 20% (50). Hip fracture risk rose from 1.77 at daily doses of 2.5–7.5 mg, to 2.27 at doses of 7.5 or greater. Clinical vertebral fracture risks were 2.59 for a daily dose less than 2.5 mg, 2.59 for 2.5–7.5 mg, and 5.18 at doses ≥7.5 mg. The role of age and menopausal status is more controversial with some studies reporting that the relative risk does not change with age and (51) and others underlying the strong negative effect on the risk associated with advancing age (52, 53).

Particularly relevant for the development of a fracture risk esteem is also the observation that the risk of fracture increases soon after starting GC therapy (52) and it is significant within the 3 months. The rapid onset of the increased risk is balanced by the observation that the negative effect of GC on fracture risk is also rapidly reversible by treatment discontinuation and independent of the underlying disease and prior cumulative dose (52). The rapid offset of skeletal effects might lower the estimates of fracture risk when the study sample encompasses subjects who discontinued GC treatment (51).

Another source of fracture risk underestimate may be the low diagnostic accuracy and sensitivity of the few epidemiological studies performed so far. By design these studies considered only clinical fractures but only a limited proportion of spine fractures are symptomatic or the symptoms led to an x-ray evaluation for the conclusive diagnosis. This may explain the substantial greater incidence observed in the placebo groups of clinical trials, as compared to that estimated from epidemiological studies.

From an analysis of the placebo groups of randomised clinical trials it was found that GC users had considerably higher risks of vertebral fracture at the same levels of BMD than controls (20, 54). The RR, particularly among postmenopausal women and men was higher than 3 for any BMD value.

In establishing the risk of fracture associated with GC therapy, the underlying diseases for which GC treatment is prescribed must be taken into account. A number of these conditions, such as rheumatoid arthritis, other inflammatory arthropathies, and Crohn's disease increase the fracture risk independently of GC treatment through the systemic release of inflammatory cytokines. Other diseases for which GC are usually prescribed, *e.g*. skin disorders and allergies, probably do not contribute to fracture risk because the systemic release of cytokines is low (55). In the same way, the increased risk of falling related to GC treatment (53) and the neurological or articular impairment of the underlying disease represent a further aspect

over and above the increased fracture risk conferred by GC treatment *per se*. In the FRAX® tool only rheumatoid arthritis is included as a CRF. To estimate the fracture risk at individual level the interplay between GC therapy and underlying disease is complex and must be considered while attributing a risk gradient to some of the above mentioned conditions.

In conclusion the risk gradient attributed by FRAX® to GC therapy seems to be underestimated, even taking into account that the gradient was attributed on top of what was attributed to underlying diseases (rheumatoid arthritis and some of the so-called secondary osteoporosis disorders), age and BMD values. The lack of a gradients for GC daily doses (prednisone equivalents) lower than 5 mg or higher than 7.510 mg also requires reassessment.

*Rheumatoid arthritis and other rheumatologic diseases*

*Rheumatoid arthritis*. Several early studies documented an increased fracture risk in subjects with rheumathoid arthritis (RA): the RRs are 1.51 and 2.60 for hip and vertebral fractures, respectively (56-58).

In the early studies the role played by RA itself and GC therapy or functional limitation was not analysed. The more recent prospective cohort studies performed in the general population give more consistent information about the relationship between RA and fragility fractures.

In a meta-analysis based on various prospective studies (CAMOS, DOES, Sheffield cohort population studies) it was shown that RA is a significant risk factor for osteoporotic fracture (RR=1.45) and hip fracture (RR=1.95) (59, 60). The RR persisted after adjustement for GC use and BMD (1.35 for osteoporotic fracture and 1.46 for hip fracture). These risk gradients are in line with the more recent data obtained from two prospective cohort studies, the Rotterdam study (4157 women) and the Longitudinal Aging Study Amsterdam (LASA; 762 women) in which women were followed for 6-9 years. Indeed, the contribution of RA as a risk factor for fracture showed coefficients for fragility OP fractures (1.3) and for hip fractures (1.4) (5) similar to those obtained by the previously mentioned meta-analysis (59-62) and subsequently included in the FRAX® algorithm.Interestingly patients with RA appears to be more susceptible to bisphosphonate associated osteonecrosis of the jaw (63).

*Systemic lupus erythematosus (SLE)*. A high prevalence of osteoporosis in patients with SLE has been reported by most studies (64). Although many cross-sectional studies found that corticosteroids are the major determinants of low bone mass in patients who have SLE, it has also been shown that there is an inverse association between disease damage and BMD in SLE women that is independent of corticosteroid use (65).

Women with SLE are at increased risk for fractures as compared to the general population. In larger studies, the prevalence of self-reported fractures in SLE ranges from 9.1% (66) to 12.3% (67), and the occurrence of radiographically identified vertebral fractures is as high as 20% (65). In the most extensive retrospective, population-based study in 702 women followed for 5951 person-years, the odd ratio for fracture risk in the cohort with SLE, as compared with control women of similar age, was 4.7 (67). Variables that were significantly associated with fracture were older age at diagnosis, longer disease duration, menopause and longer exposure to corticosteroids. On the other hand another epidemiological study showed that only age, disease duration and reduced BMD (but not steroid exposure ) were predictors of fractures in multivariate analysis (65). Finally, a cross-sectional study confirmed the important role of disease duration as an essential risk factor for fractures and showed only a limited association between BMD status and fractures in 304 women with SLE. In line with prior reports (64, 67) a high proportion of women with normal BMD experienced vertebral and non-vertebral fractures. Taken together all these results indicate that, even though GC therapy and low BMD are important risk factors for fractures in SLE women, the disease itself is an important risk factor of fragility fractures.

*Ankylosing spondylitis (AS) and spondyloarthropathies (SspAs)*. Despite extra-osseous new bone formation being considered a hallmark of AS, osteoporosis is a well-recognised feature that occurs even in the early, mild form of AS and leads to an increased rate of fractures. Patients with spinal involvement associated with other SspAs have often been included as small subgroups in larger samples of patients who have AS. The few longitudinal studies on BMD demonstrated a greater bone loss in patients who had active disease and a correlation between serum inflammatory parameters, bone resorption markers, and decrease in BMD (68, 69). As a consequence of osteoporosis, vertebral compression fractures are reported frequently in AS, although in clinical practice they are probably underdiagnosed, because the pain associated with them is attributed to exacerbations of the spondylitic process.

Vertebral fractures seem to be the predominant clinical consequence of osteoporosis in patients with AS, even though the systemic inflammatory process which is the most significant pathogenetic mechanisms is expected to involve the entire skeleton.

A retrospective population-based study shows an increased vertebral fracture (VF) relative risk as great as 7.6 in comparison with the expected fracture incidence in the same community (70). In a more recent large primary care-based nested case control study (231,778 fracture cases and 231,778 age-sex-mached controls) 758 patients with AS had an increased risk of clinical vertebral fracture (OR:3.26) while the risk for nonvertebral fractures (*i.e.* forearm and hip fractures: RR:1.21 and 0,77, respectively) was not significantly increased (71). In another recent study the increased vertebral fracture risk in AS was found to be almost totally BMD independent (72).

*Systemic sclerosis (SSc)*. Several studies have reported that SSc, a connective tissue disorder, is associated with osteoporosis (62). The reduced bone mass may be related to a chronic inflammation state, decreased physical activity, low body mass index, earlier menopause, decreased vitamin D syn-

thesis in the fibrotic skin and glucocorticoid therapy. A recent survey (73) assessing demographics, diagnosis and investigations for osteoporosis and risk factors for OP in 129 SSc patients, and 230 RA subjects, indicated that the prevalence of OP in patients with SSc (19.4%) was comparable ($p$=0.38) to those with RA (16.7%). In addition there were no differences between groups in reports of fracture (35% Ssc, 37% RA; $p$=0.5). All these analyses were adjusted for age. These data suggest that the burden of osteoporosis and fragility fractures in SSc might be similar to that of RA.

*Psoriatic arthritis (PsA).* Studies concerning skeletal involvement in PsA subjects are scanty, probably because osteoporosis is a less frequently recognised feature in these subjects. With regard to oligo/polyarthritic subsets, in a recent report that used DXA to quantify periarticular BMD in patients who had early disease, periarticular bone loss occurred both in patients with RA and those with PsA to the same extent (74). Few studies have investigated generalised osteoporosis in PsA. While some authors (75) found no difference in lumbar and femoral neck BMD in 52 patients who had peripheral PsA compared with controls, other investigators (76) examining 186 patients who had nonaxial PsA found that the prevalence of osteoporosis was 11% in young women, 47% in postmenopausal women, and 29% in men. Bone loss was more evident at the lumbar level in young women, whereas a reduced femoral neck BMD was detectable only in postmenopausal subjects. Besides well-recognised risk factors for osteoporosis, such as age, years since menopause, and body mass index, the only variable that was related specifically to disease that was predictive of osteoporosis risk was a disability index that is related to articular function (HAQ score). The similarities between PsA and RA in terms of association between disease activity, disability and prevalence of OP suggest that as for RA, PsA might be identified as a potential unappreciated clinical risk factor for fracture.

In conclusion, among rheumatologic disorders, the FRAX® identification of RA as a unique clinical risk factor with the exclusion of other rheumatic diseases is justified by the epidemiology of these conditions, but may represent an objective limitation, particularly when applied in a rheumatology unit .

Patients with other rheumatologic diseases such as SLE, AS and SspAs or SSc are definitely at increased risk for fragility fractures in part independent of BMD and GC use. It seems reasonable to temporarily attribute the same risk gradient attributed to RA to the above mentioned rheumatic inflammatory diseases.

*Secondary osteoporosis*

FRAX® attributes a fixed risk gradients for a number of clinical conditions known to be associated with somewhat increased risk of fracture. For DeFRA it was decided to leave out (exclusion criteria) all these and other conditions (see below) for the esteem of the 10YFR. The low incidence of all these conditions is unlikely to provide sufficient data also for the project of validation of the tool.

## Other information recorded for the validation of DeFRA

DeFRA should be used only in postmenopausal women aged 50 to 90 but not in men (77). In addition to the continuous (age, BMD and BMI) and categorical variables (CRFs) collected for the estimation of 10YFR by DeFRA, in order also to adjust for fracture associated mortality (78), the following additional findings will be recorded for the validation of the tool:

- Type of pharmacological treatment implemented (the global adherence should be ranked as <50%; 50–75%; >75% (indicates prevalent treatment).
- Simplified calcium intake questionnaire (79).
- Simplified sun exposure questionnaire (79).
- Number of falls that occurred during the last year.
- Intake of vitamin D supplements (estimated yearly intake ranked as: <50,000 U; 50,000 to 200,000 U; 200,000 to 500,000 U; 500,000 to 900,000 U; >900,000 U.
- Mean calcium supplement intake during last year, taking into account global adherence, ranked as: None; <300 mg/day; 300–600 mg/die; >600 mg/die.

All centres participating in the project will be asked to re-assess all patients at least one year later. During the follow-up visits the following additional findings will be recorded:

- Cumulative number and type of incident fractures (for vertebral fractures indicate the severity of the deformity and whether this is a new fracture or a worsening of a previous deformity)
- Duration of follow-up.

## Conclusions

The algorithms derived mostly from FRAX® and called DeFRA should be intended as temporary and requiring continuous revisions that might be implemented during the validation study. A rough esteem of the statistical power, assuming the variance in the gradients reported above, indicates that for the validation of the diagnostic tool at least 60.000 patient-years are needed. Only when this data is obtained and the results analysed, the DeFRA tool might be offered for use in a routine setting and to the Italian health authorities for re-setting the Nota 79, regulating the reimbursability of osteoporosis treatment.

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