GAPS AND SOLUTIONS IN BONE HEALTH

A Global Framework for Improvement

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International Osteoporosis Foundation

WHAT IS OSTEOPOROSIS?

Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture. Osteoporosis causes a net loss of bone strength, as a result even a slight bump or fall can lead to a broken bone (referred to as a fragility fracture). Osteoporosis has no signs or symptoms until a fracture occurs – this is why it is often called a 'silent disease'.

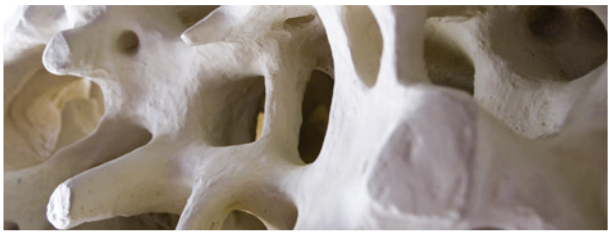
Osteoporosis affects all bones in the body; however, fractures occur most frequently in the vertebrae (spine), wrist and hip. Osteoporotic fractures of the pelvis, upper arm and lower leg are also common. Osteoporosis itself is not painful but the broken bones can result in severe pain, significant disability and even mortality. Both hip and spine fractures are associated with a higher risk of death - 20% of those who suffer a hip fracture die within 6 months after the fracture.

A Common Disease

It is estimated that worldwide an osteoporotic fracture occurs every three seconds. From 50 years of age, one in three women and one in five men will suffer a fracture in their remaining lifetime. For women, the risk of hip fracture is higher than the risk of breast, ovarian and uterine cancer combined. For men, the risk is higher than the risk for prostate cancer. Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture.

A Growing Public Health Problem

The risk of sustaining a fracture increases exponentially with age due not only to the decrease in bone mass, but also due to the increased rate of falls among the elderly. The elderly represent the fastest growing segment of the population and as life expectancy increases for the majority of the world's population, the financial and human costs associated with osteoporotic fractures will increase dramatically unless preventive action is taken.



NORMAL BONE

OSTEOPOROTIC BONE

TABLE OF CONTENTS

FOREWORD

Bone health in 2016: Gaps and solutions

This Report provides a comprehensive, global overview of the state of osteoporosis care for individuals at high-risk of suffering fragility fractures. Ten 'gaps' have been identified which can be clustered into four major themes:

1. CASE FINDING AND MANAGEMENT:

- Gap 1: Secondary fracture prevention
- Gap 2: Osteoporosis induced by medicines
- Gap 3: Diseases associated with osteoporosis
- Gap 4: Primary fracture prevention for individuals at high risk of fracture

2. PUBLIC AWARENESS:

- Gap 5: The importance of staying on treatment
- Gap 6: Public awareness of osteoporosis and fracture risk
- Gap 7: Public awareness of benefits versus risks of osteoporosis treatment

3. GOVERNMENT AND HEALTH SYSTEM ISSUES:

- Gap 8: Access and reimbursement for osteoporosis assessment and treatment
- Gap 9: Prioritization of fragility fracture prevention in national policy

4. LACK OF DATA:

- Gap 10: The burden of osteoporosis in the developing world

During 2016, the first of the Baby Boomers will celebrate their 70th birthdays. As a direct consequence, the increasing burden of fragility fractures will place severe strains on the capacity and finances of healthcare systems. Thankfully, this is a catastrophe that would be entirely preventable if the solutions to each gap identified in this report were to be implemented worldwide.

With regard to case finding and management, widespread implementation of Fracture Liaison Services and Orthogeriatrics Services would ensure that healthcare systems can always respond to the first fragility fracture, in order to prevent the second. Healthcare professionals and patients are aware of which medicines the patient has been prescribed. Accordingly, when drugs that have an adverse effect on bone health are necessarily used to manage other conditions, adherence to the numerous clinical guidelines available to prevent bone loss and fractures should be the norm. Among individuals who suffer diseases in which osteoporosis is a common comorbidity, osteoporosis and fracture risk assessment should be a standard component of managing the disease in question. Finally, fracture risk assessment tools, such as FRAX®, are now readily available to pre-emptively identify those individuals who are at high-risk of suffering their first fragility fracture.

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Public awareness of osteoporosis, and the fragility fractures it causes, is low in many countries. A determined global effort is required, involving healthcare professionals and their organisations, patient societies and policymakers, to provide the public with clear, consistent and compelling messages regarding bone health. The most obvious initial target group for such messages comprises those individuals who have been initiated on osteoporosis treatment, to ensure that they stay on that treatment. For many people, the association between osteoporosis and fracture risk is not clear. A pressing need also exists for evidence-based communications which highlight the risk that untreated osteoporosis poses to sufferers' quality and quantity of life.

In contrast with other comparable common non-communicable chronic diseases, osteoporosis has often not attracted a commensurate level of attention from health providers and governments. Given the current and imminent future burden imposed by this disease, that is a position which policymakers can no longer afford to take. Access to treatment cannot be impeded by inadequate access to bone mineral density testing, or inadequate reimbursement policies for treatments. Further, osteoporosis and fragility fracture prevention should feature as a National Health Priority in all countries. Action is needed now, and not in 10 or 20 years' time when it will already be too late.

Finally, given current projections indicating that the burden of fragility fracture will shift to the developing world over the next four decades, it is imperative that governments, key opinion leaders and national patient societies work together now to ensure that epidemiological data are available to inform policy development in these countries.

There is much to be done. However, all ten of these gaps have been closed somewhere in the world. The task now facing all of us is to ensure the dissemination and adoption of these best practice examples, adapted for local considerations, in order to tackle the current, and future, burden of fragility fractures worldwide.

GAP 1:
SECONDARY FRACTURE PREVENTION

One fracture leads to another, which means that people who suffer fragility fractures today are at high risk of suffering second and subsequent fractures in the future.

Highly effective osteoporosis treatments - which substantially reduce fracture risk - have been available for 20 years, but are often not routinely offered to fragility fracture sufferers.

Fracture Liaison Service and Orthogeriatrics Service models of care have been successfully developed in many countries to close the secondary fracture prevention care gap.

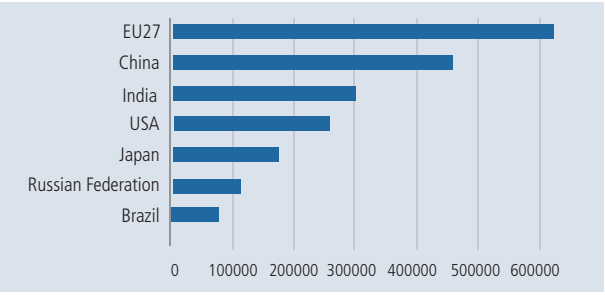
Fragility fractures are common and expensive

The clinically important consequence of osteoporosis is a fragility fracture. Fragility fractures, also referred to as low or minimal trauma fractures, usually happen as a result of a fall from standing height, and occur most commonly at the spine, wrist, hip, humerus (upper arm) or pelvis. Among people over 50 years of age, half of women and a fifth of men will suffer a fragility fracture during their remaining lifetime[1-3]. Arguably, hip fractures impose the greatest burden on sufferers and their families:

- Fewer than half of people who survive a hip fracture will walk unaided again[4] and in many cases they will never regain their former degree of mobility[5].
- A year after hip fracture, 60% of sufferers require assistance with activities such as feeding, dressing or toileting, and 80% need help with activities such as shopping or driving[6].
- Between 10-20% of sufferers will become residents of care homes in the year following a hip fracture[7-9].
- Mortality 5 years after hip or vertebral fracture is about 20% in excess of that expected; Most excess deaths occur in the first 6 months after hip fracture[6].

As shown in figure 1, recent estimates of the annual incidence

Figure 1. Recent estimates of hip fracture incidence for the EU27[10] and major countries[11-17]



of hip fracture in the European Union[10] and some of the most populous countries elsewhere[11-17] highlight the scale of the current burden, a burden which is set to grow rapidly as the world's population ages.

The economic burden imposed by fragility fractures is staggering:

EUROPEAN UNION: In 2010, the 27 countries of the EU – the current EU28 countries prior to Croatia's entry - were estimated to have spent €37 billion on fragility fractures, a cost which is expected to increase by 25% by 2025[10].

USA: The cost of fragility fractures in the United States in 2015 was estimated to be in excess of US$20 billion[18]. Analysis suggests that Medicare bears 70% of the costs of fracture and osteoporosis-related care[19].

CHINA: In 2010, the cost imposed by fractures among people with osteoporosis was estimated to be in excess of US$9 billion, which is expected to rise to US$25 billion by 2050[11].

However, fragility fractures need not be an inevitable consequence of ageing.

Secondary fractures can be prevented

Since the 1990s, a broad range of effective treatments for osteoporosis have become available throughout the world. Osteoporosis treatments can be taken as daily, weekly or monthly tablets, or as daily, quarterly, six-monthly or annual injections. Several Cochrane Collaboration systematic reviews of secondary fracture prevention (i.e. reduction in rates of refracture) have been published for alendronate[20], etidronate[21] and risedronate[22]. The findings of the Cochrane reviews are summarized below, including reference to relative risk reduction (RRR: a halving of fracture risk on treatment represents an RRR of 50%) and absolute risk reduction (ARR: the absolute percentage difference in fracture rates between those treated and those receiving placebo, which depends upon the background fracture risk of the population studied):

- **Alendronate:** Clinically important and statistically significant reductions in vertebral (RRR 45%, ARR 6%), non-vertebral (RRR 23%, ARR 2%), hip (RRR 53%, ARR 1%) and wrist fractures (RRR 50%, ARR 2%) were observed, designated as 'gold' level evidence.
- **Etidronate:** A statistically significant reduction was observed only for vertebral fractures (RRR 47%, ARR 5%). The level of evidence for all outcomes was designated 'silver'.
- **Risedronate:** Statistically significant reductions in vertebral (RRR 39%, ARR 5%), non-vertebral (RRR 20%, ARR 2%) and hip (RRR 26%, ARR 1%) fractures were observed. The level of evidence was designated 'gold' for vertebral and non-vertebral fractures, and 'silver' for hip and wrist fractures.

A Cochrane systematic review of intravenous **zoledronate** - administered as an annual infusion - for postmenopausal osteoporosis, is planned but was not available at the time this report was written[23]. The HORIZON Pivotal Fracture Trial (PFT) evaluated zoledronate for the treatment of postmenopausal osteoporosis[24]. Whilst the majority (>60%) of study participants had at least one prevalent vertebral fracture at recruitment, this was not specifically a secondary fracture prevention trial. However, the HORIZON Recurrent Fracture Trial (RFT) evaluated

zoledronate for treatment of individuals who had undergone repair of a hip fracture and were unable or unwilling to take an oral bisphosphonate[25]. Statistically significant reductions in any new clinical fracture (RRR 35%, ARR 5.3%), clinical non-vertebral fracture (RRR 27%, ARR 3.1%) and new clinical vertebral fracture (RRR 46%, ARR 2.1%) were observed. A non-significant trend towards reduction in hip fracture (RRR 30%, ARR 1.5%) was observed. The safety analysis revealed a statistically significant reduction in deaths from any cause for the individuals treated with zoledronate (RRR 28%, ARR 3.7%).

A Cochrane systematic review for **denosumab** – administered as a six-monthly sub-cutaneous injection - for postmenopausal osteoporosis, is also awaited[26]. The FREEDOM study evaluated denosumab for the treatment of postmenopausal osteoporosis[27]. Whilst almost half (45%) of study participants had at least one prevalent vertebral fracture on recruitment, this was not specifically a secondary fracture prevention trial. A post-hoc analysis of this study ascertained the impact of denosumab on the occurrence of secondary fragility fractures[28]. A statistically significant reduction in any secondary fragility fracture (RRR 39%, ARR 6.8%) was observed. Significant reductions were also observed for the sub-groups of participants who had vertebral fractures (RRR 35%, ARR 6.6%) and non-vertebral fractures (RRR 34%, ARR 6.1%) at baseline.

Raloxifene is currently the only selective estrogen receptor modulator (SERM) used in clinical practice for fracture prevention. Among the sub-group of women in the MORE study who had a prevalent vertebral fracture at baseline, those receiving the licensed 60 mg dose of raloxifene suffered significantly fewer new vertebral fractures compared to placebo (RRR 30%, ARR 6%)[29]. No significant difference was observed for rates of non-vertebral fractures for women treated with raloxifene as compared to placebo. With regard to **hormone replacement therapy (HRT)**, there is no specific evidence in the secondary fracture prevention setting.

The parathyroid hormone (PTH) analogue **teriparatide** - administered by subcutaneous injection once daily - is an anabolic agent which directly stimulates osteoblastic bone formation. Teriparatide was evaluated for the treatment of postmenopausal osteoporosis among women with at least one vertebral fracture at baseline[30]. Participants who received the licensed dose of 20 µg per day suffered significantly fewer new vertebral fractures (RRR 65%, ARR 9.3%) and non-vertebral fragility fractures (RRR 53%, ARR 2.9%).

Finally, a pre-planned sub-analysis of postmenopausal women with osteopenia and a prevalent vertebral fracture, who were recruited to the SOTI[31] and TROPOS[32] studies of **strontium ranelate**, reported a significant reduction in the incidence of new vertebral fractures (RRR 37%, ARR 8.1%)[33, 34]. The SOTI study evaluated strontium ranelate specifically in a secondary prevention population, because all participants had radiographic evidence of at least one vertebral fracture. However, no statistically significant effect of treatment was observed on the incidence of non-vertebral fractures. Approximately 55% of women recruited to the TROPOS study had a history of any vertebral or non-vertebral fracture. However, the impact of treatment on this prevalent fracture sub-group of the study population was not reported.

Thus, a diverse array of effective osteoporosis treatments is available to reduce the risk of second and subsequent fractures among individuals presenting with their first fragility fracture.

The care gap

In 2012, an IOF report issued for World Osteoporosis Day was devoted to the global Capture the Fracture® Campaign[35, 36]. Approximately half of hip fracture patients suffer a prior fragility fracture in the months or years before breaking their hip[37-40], representing an obvious opportunity and, indeed, imperative for assessment and intervention to prevent future fractures. The report also cited numerous audits undertaken across the world to establish what proportion of fracture patients received the osteoporosis care that they needed: in the absence of a systematic approach, less than a fifth received such care. Whilst some exciting progress has been made to close this care gap many publications and initiatives since 2012 bear testament to the fact that there is still a huge amount of work to be done throughout the world:

> 'Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture. The majority of fragility fracture patients never learn what caused their fracture to happen, or receive treatment to prevent it from happening again. Evidently, this is a missed opportunity to identify and treat those at greatest risk of disabling and costly secondary fractures.'[35]
>
> *Professor Cyrus Cooper*

ASIA: China[41], Japan[42-44], South Korea[45-47], Thailand[48]

EUROPE: Austria[49, 50], France[51, 52], Germany[53], Italy[54-56], Ireland[57, 58], Norway[59, 60], Spain[47], Sweden[61], Switzerland[62], UK[63-69]

MIDDLE EAST: Saudi Arabia[70]

NORTH AMERICA: Canada[71-74], USA[47, 62, 75-87]

OCEANIA: Australia[88-91], New Zealand[91-93]

Since the turn of the century, clinically effective models of care have been developed in many countries to close the secondary prevention care gap in a highly cost-effective manner.

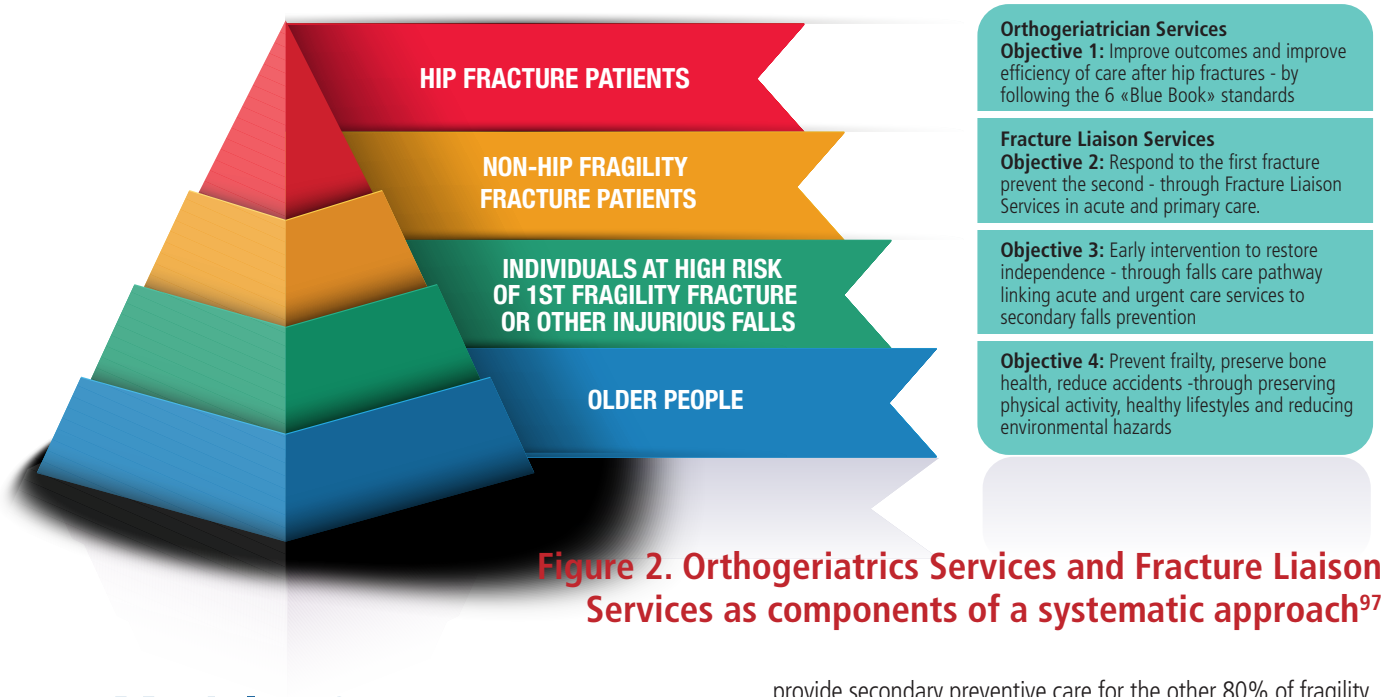


Figure 2. Orthogeriatrics Services and Fracture Liaison Services as components of a systematic approach[97]

Models of care: Orthogeriatrics Services and Fracture Liaison Services

In response to the well documented secondary fracture prevention care gap, innovators throughout the world have developed models of care designed to ensure that health systems respond to the first fracture to prevent second and subsequent fractures:

- **Orthogeriatrics Services (OGS):** The need for effective orthopaedic – geriatric co-care of patients admitted to hospital with hip fractures is well recognised in professional guidance[94-96]. Such models of care focus on expediting surgery, ensuring optimal management of the acute phase through adherence to a care plan overseen by senior orthopaedic and geriatrician/internal medicine personnel, and delivery of secondary fracture prevention through osteoporosis management and falls prevention.
- **Fracture Liaison Services (FLS):** The Fracture Liaison Service (FLS) model of care has also been adopted in many countries. The purpose of an FLS is to ensure that all patients aged 50 years or over, who present to urgent care services with a fragility fracture, undergo fracture risk assessment and receive treatment in accordance with prevailing national clinical guidelines for osteoporosis. The FLS also ensures that falls risk is addressed among older patients through referral to appropriate local falls prevention services.

These two service models are entirely complementary. As adoption of OGS for hip fracture sufferers becomes more widespread, OGS are increasingly likely to deliver secondary preventive care for these patients. As hip fractures constitute approximately 20% of all clinically apparent fragility fractures, in health systems which have implemented an OGS, FLS will provide secondary preventive care for the other 80% of fragility fracture sufferers who have experienced fractures of the wrist, humerus, spine, pelvis and other sites. This 'division of labour' is illustrated in the falls and fractures pyramid in figure 2, which was first presented in policy developed by the Department of Health for England in 2009[97]. A similar approach has been advocated in Australia[98], Canada[73], New Zealand[93] and the United States [99, 100].

Secondary fracture prevention – and OGS and FLS as a reliable means to deliver this care to fracture patients – has featured in a growing number of clinical guidelines and government policies.

Guidelines, policy and national secondary fracture prevention initiatives

During the last 15 years, the number of clinical guidelines from societies and policies from governments which highlight the importance of secondary fracture prevention has increased considerably. Furthermore, a number of national campaigns to drive widespread adoption of OGS and/or FLS have been undertaken. Examples from several countries include:\

AUSTRALIA AND NEW ZEALAND: Clinical guidelines from the Australian Commission on Quality and Safety in Healthcare[101-103], Australian and New Zealand (ANZ) Hip Fracture Registry[95] and Royal Australian College of General Practitioners[104]. Policy initiatives in Australia from state governments in New South Wales[98, 105], South Australia[106] and Western Australia[107-109]. A position paper and call to action from the ANZ Bone and Mineral Society[91]. An Australian national alliance focused on secondary fracture prevention is in development in 2016[110]. A FLS implementation initiative developed by the ANZ Bone and Mineral Society[111]. A multi-

sector initiative in New Zealand focused on implementation of OGS and FLS[112, 113]. An ANZ Clinical Care Standard for hip fracture[114].

CANADA: Clinical guidelines from Osteoporosis Canada[115]. A FLS implementation initiative led by Osteoporosis Canada[73], including Quality Standards for FLS endorsed by many learned societies[74].

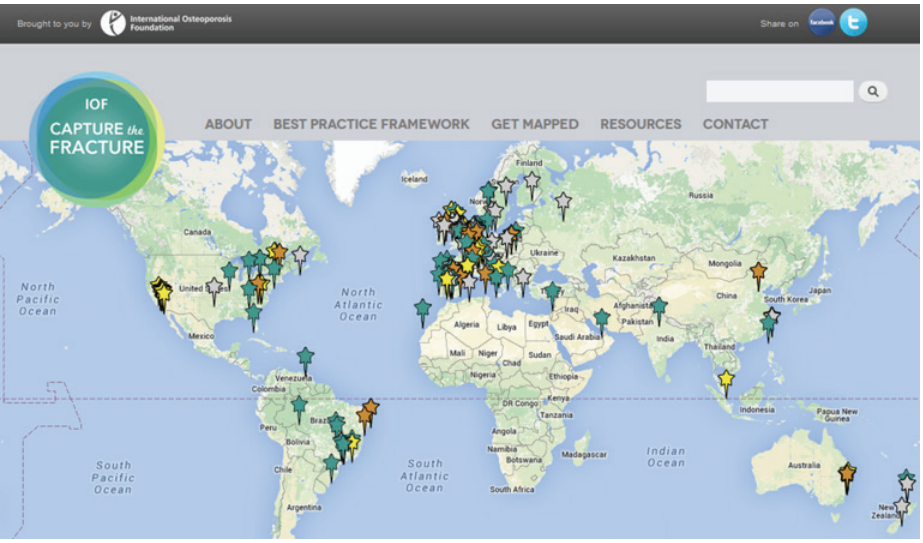
JAPAN: The Japanese Osteoporosis Society developed an accreditation programme for physicians and coordinators working in Osteoporosis Liaison Services (which deliver FLS and a systematic approach to primary fracture prevention)[116].

SINGAPORE: The Osteoporosis Patient Targeted and Integrated Management for Active Living (OPTIMAL) Programme was funded by the Singapore Ministry of Health to deliver secondary fracture prevention in the 5 public hospitals in existence in Singapore in 2008[117]. The programme was subsequently expanded to include the 18 polyclinics in Singapore.

UNITED KINGDOM: Clinical guidelines from the National Institute for Health and Care Excellence (NICE)[118-123] and the National Osteoporosis Guideline Group (NOGG)[124]. Establishment and government funding of the National Hip Fracture Database (NHFD)[125]. Policy from the Department of Health[97, 126] and financial incentives for primary[127] and secondary care[128]. British Orthopaedic Association Standards for Trauma (BOASTs) on hip fracture care[129] and FLS[130]. Clinical Standards for FLS from the National Osteoporosis Society (NOS)[131], in addition to a NOS FLS Toolkit[132] and NOS FLS Service Development Team.

UNITED STATES OF AMERICA: Clinical guidelines from the Endocrine Society[133] and National Osteoporosis Foundation (NOF)[134]. Following the Surgeon General's Report on Bone Health in 2004[2] and subsequent publication of the National Action Plan on Bone Health in 2008[135], the National Bone Health Alliance (NBHA) was formed in late 2010[85]. NBHA has developed an award winning disease awareness campaign relating to secondary fracture prevention, 2Million2Many[136], and an FLS implementation initiative, Fracture Prevention CENTRAL[137]. Quality measures have been developed by The Joint Commission and endorsed by the National Quality Forum[138]. NBHA and NOF have developed a Qualified Clinical Data Registry (QCDR) which is approved by the Centers for Medicare and Medicaid Services (CMS)[86]. The QCDR is focused on measuring, reporting and improving patient outcomes in osteoporosis and post-fracture care. NOF has developed a FLS accreditation programme[139].

Figure 3. The Capture the Fracture® Programme Map of Best Practice in March 2016[142]



The IOF Capture the Fracture® Programme

The IOF Capture the Fracture® Programme aims to support implementation of FLS throughout the world. During the last 4 years, the programme has gained considerable momentum. The key elements of Capture the Fracture® are:

- **Website:** The Capture the Fracture® website - www.capture-the-fracture.org - provides a comprehensive suite of resources to support healthcare professionals and administrators to establish a new FLS or improve an existing FLS.
- **Webinars:** An ongoing series of webinars provide an opportunity to learn from experts across the globe who have established high-performing FLS and contributed to development of guidelines and policy on secondary fracture prevention.
- **Best Practice Framework:** The Best Practice Framework (BPF), currently available in 8 major languages, sets an international benchmark for FLS by defining essential and aspirational elements of service delivery. The BPF serves as the measurement tool for IOF to award 'Capture the Fracture® Best Practice Recognition' in celebration of successful FLS worldwide. The 13 globally-endorsed standards of the BPF have been published in *Osteoporosis International*[140]. The BPF tool has been tested in a range of health settings across the globe. Initial findings during the first 12 months confirmed a significant heterogeneity in service provision and highlighted the importance of a global approach to ensure high quality secondary fracture prevention services[141].

The BPF Map of Best Practice shown in figure 3 has recognised FLS from across the world[142]. IOF encourages leaders of FLS to share their experience through a submission for Best Practice Recognition at http://www.capture-the-fracture.org/best-practice-framework.

GAP 2:
OSTEOPOROSIS INDUCED BY MEDICINES

Many widely used medicines have been associated with decreases in bone mineral density and/or increased fracture incidence, although these links have not been proven as causal in every case. Such evidence has been reported for the following classes of agents:

- Glucocorticoids
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors
- Thiazolidinediones
- Anticonvulsants
- Medroxyprogesterone acetate
- Hormone deprivation therapy
- Calcineurin inhibitors
- Chemotherapies
- Anticoagulants

A 2014 review described the potential pathogenesis of bone loss associated with all of these classes of medicines[143]. This report will focus on three very commonly used agents: glucocorticoids for a range of conditions, androgen deprivation therapy for treatment of prostate cancer in men, and aromatase inhibitors for treatment of hormone receptor-positive breast cancer in women.

Glucocorticoid-induced osteoporosis

Pathogenesis of glucocorticoid-induced osteoporosis

Glucocorticoids (GCs) affect function and numbers of the three major types of bone cells[143]:

- **Osteoclasts:** Stimulation by GCs results in prolonged survival of osteoclasts leading to excessive bone resorption, particularly in trabecular bone in the spine.
- **Osteoblasts:** By reducing the recruitment of the precursors to osteoblasts the number of mature osteoblasts is reduced, resulting in decreased bone formation.
- **Osteocytes:** Osteocyte apoptosis (cell death) is triggered by GCs and may contribute to an increase in fracture risk prior to a reduction in bone mineral density (BMD).

In 2014, Henneicke and colleagues published a detailed review of the direct and indirect effects of GCs on bone[144].

Glucocorticoid use and fracture incidence

GCs are very commonly used to control inflammation in the setting of a broad range of conditions including autoimmune, dermatological and respiratory diseases, and malignancies and organ transplants. Estimates suggest that 1 in 13 adults aged 18 years and over have been prescribed an oral GC at some stage of their life[145].

Up to 30-50% of patients receiving chronic glucocorticoid therapy experience clinically apparent fragility fractures and/or asymptomatic vertebral fractures, making GC-induced osteoporosis the leading cause of secondary osteoporosis[146]. Meta-analysis has shown previous GC use to be associated with a relative risk of 2 for any fracture at the age of 50 years and 1.7 at the age of 85 years[147]. For osteoporotic fracture the range of relative risk is 2.6 and 1.7; and for hip fracture 4.4 and 2.5 for the same age groups.

Prevention and treatment of glucocorticoid-induced osteoporosis

Clinical guidelines for the prevention and treatment of GC-induced osteoporosis are available in many countries, including Austria[148], Australia[149], Belgium[150], Brazil[151], France[152], Japan[153], The Netherlands[154], Spain[155], UK[124] and the United States[156]. Furthermore, the European League Against Rheumatism (EULAR)[157] and a Joint Guideline Working Group of IOF and the European Calcified Tissue Society (ECTS)[158] have produced internationally relevant guidance. Whilst the detail of individual guidelines varies somewhat, the common theme is that individuals receiving chronic GC therapy are at increased risk of fracture on account of taking GCs, and, in a significant proportion, the risk is great enough to warrant the offer of preventive treatment.

> Despite widely available guidelines a significant care gap exists worldwide in prevention and treatment of GC-induced osteoporosis.

The care gap

In 2014, a systematic literature review of osteoporosis management among GC users evaluated studies conducted between 1999 and 2013[145]. Among the various studies reviewed, the proportion of patients reported to have received BMD testing ranged from 0% to 60%, and osteoporosis treatment ranged from 0% to 78%. The majority of studies (>80%) identified that less than 40% of chronic oral GC users underwent BMD testing or osteoporosis treatment. Accordingly, despite widely available guidelines a significant care gap exists worldwide in prevention and treatment of GC-induced osteoporosis.

Quality improvement initiatives

It is clear that major efforts are now required to close the GC-induced osteoporosis care gap. Healthcare professionals, health administrators and policymakers should seek to audit what proportion of long term GC users in their health systems are currently receiving guideline-based care. The following quality improvement initiatives from Australia and the United States could inform efforts to routinely deliver best practice elsewhere:

AUSTRALIA: A multifaceted education programme delivered in Tasmania, which incorporated academic detailing of general practitioners and community pharmacists, increased the use of osteoporosis prevention strategies in long term oral GC users[162]. The use of osteoporosis treatments was 31% prior to the intervention, increasing to 57% after the intervention (highly significant, $p<0.0001$).

UNITED STATES OF AMERICA: The Geisinger Health System in the United States implemented an organized programme of care - GIOP (Glucocorticoid-Induced Osteoporosis Program) – in order to improve preventive care for members[163]. The programme goals were to identify patients at risk of fracture, provide education, redesign and implement new pathways of care, and monitor outcomes. Key outcomes at 12 months included:

- Patient retention of knowledge, frequent exercise, and 25(OH)-vitamin D concentrations all significantly improved.
- A significant decrease in GC dose was observed.
- 91% of patients considered at high fracture risk were taking a bisphosphonate or teriparatide at 1 year, and 96% of patients overall were adherent to their prescribed regimen of calcium, vitamin D, and prescription treatment, where indicated.

Androgen Deprivation Therapy-induced osteoporosis

Pathogenesis of Androgen Deprivation Therapy-induced osteoporosis

Androgen Deprivation Therapy (ADT), in the form of gonadotropin-releasing hormone agonists (GnRHs), limits the production of testosterone and estradiol, leading to chemical castration[143]. GnRHs elicit this effect by reducing secretion of luteinizing hormone and follicle-stimulating hormone. This is a consequence of GnRHs binding to GnRH receptors in the pituitary gland and downregulating the gonadotropin-producing cells.

Androgen Deprivation Therapy use and fracture incidence

Prostate cancer is the most common non-cutaneous malignancy in men, with 1 in 6 men being diagnosed during their lifetime[164]. Approximately half of men diagnosed with prostate cancer will receive ADT at some stage after diagnosis[165]. In 2014, a meta-analysis of relevant studies reported that between 9% and 53% of survivors had osteoporosis[166]. A rapid decline in BMD is observed during the first year of ADT treatment[167]. A cohort study based on medical claims data from Medicare beneficiaries in the United States compared fracture rates for men with non-metastatic prostate cancer who initiated GnRH agonist treatment against a comparison group who did not receive GnRH agonist treatment[168]. The men treated with GnRHs had statistically significantly higher rates of any clinical fracture (relative risk [RR]: 1.2), vertebral fractures (RR: 1.5) and hip/femur fractures (RR: 1.3). Longer duration of treatment also conferred greater fracture risk.

Prevention and treatment of Androgen Deprivation Therapy-induced osteoporosis

Clinical guidelines relating to the prevention and treatment of ADT-induced osteoporosis are available in many countries, including Australia[169], Belgium[170], Canada[171], New Zealand[169], UK[172] and the United States[173, 174]. Furthermore, the European Society for Medical Oncology has produced internationally relevant guidance[175].

The care gap

The care gap for ADT-induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and GC-induced osteoporosis care gaps discussed above. However, local studies have been conducted in several countries, including Canada[165, 176-178], India[179] and the United States[180-183]. The rates of BMD testing and/or osteoporosis treatment varied from 9% to 59%, with on average less than a quarter of ADT treated men receiving appropriate care.

Quality improvement initiatives

Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in urology departments to establish what proportion of ADT treated patients have undergone osteoporosis assessment and received guideline-based care. A quality improvement initiative from the United States could inform efforts to routinely deliver best practice elsewhere[184]. In 2002, Kaiser Permanente Southern California (Kaiser SoCal) implemented the Healthy Bones Model of Care (HBP). This programme identifies individuals at high fracture risk and delivers guideline-based care in a systematic fashion. All Kaiser SoCal patients with prostate cancer newly diagnosed between 2003 and 2007

were identified through a cancer registry. Two study cohorts were subsequently created: any patient who had a bone density test at most 3 months before the first administration of ADT was assigned to the HBP group, and a contemporaneous control group was comprised of all others (the non-HBP group). The incidence of hip fracture was 70% lower in the HBP group compared to the non-HBP group.

Aromatase Inhibitor-induced osteoporosis

Pathogenesis of Aromatase Inhibitor-induced osteoporosis

Aromatase inhibitors (AIs) reduce estrogen levels by inhibition of the peripheral conversion of androgens to estrogens. This results in lower estrogen levels with a consequent increase in bone turnover and bone loss.

Aromatase Inhibitor use and fracture incidence

Breast cancer is the most common neoplasm and primary cause of cancer-related mortality in women, affecting 1 in 8 women worldwide[185]. AIs currently represent the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer[186]. The annual rate of bone loss observed for women taking AIs of around 2.5% is elevated compared to healthy postmenopausal women who lose about 1% to 2% per year[187]. Analysis of the Women's Health Initiative Observational Study compared fracture rates among breast cancer survivors with women with no history of breast cancer at baseline[188]. After adjustment for factors related to hormone levels, risk of falls, prior fracture history, medication use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was 15%. Studies comparing two commonly used AIs, anastrozole[189] and letrozole[190], with tamoxifen have reported significant increases in fracture risk for the AI treated patients. A comparative study of anastrozole with exemestane showed similar fracture rates[191]. A position paper from the European Society from Clinical and Economical Aspects of Osteoporosis (ESCEO) has comprehensively documented studies on the skeletal effects of aromatase inhibitors[187].

Prevention and treatment of Aromatase Inhibitor-induced osteoporosis

Clinical guidelines relating to the prevention and treatment of AI-induced osteoporosis are available in many countries, including Belgium[170], China[192], Germany[193], Italy[194], Lithuania[195], UK[196] and the United States[173]. Furthermore, ESCEO has produced internationally relevant guidance[187].

The care gap

The care gap for AI-induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and GC-induced osteoporosis care gaps discussed above. However, local studies have been conducted in several countries, including the UK[197] and the United States[198-200]. The largest of these studies reported that less than half (44%) of women underwent BMD testing within 14 months of continuous AI use for at least 9 months[200]. Furthermore, 75% and 66% of women failed to have BMD tests done during the second and third annual time periods after continuous AI use for almost 2 and 3 years, respectively.

Quality improvement initiatives

Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in oncology departments to establish what proportion of AI treated patients have undergone osteoporosis assessment and received guideline-based care. The following quality improvement initiatives from Italy and the United Kingdom could inform efforts to routinely deliver best practice elsewhere:

ITALY: In 2011, investigators from Florence developed a database to monitor delivery of care for patients treated with tamoxifen and AIs, and those treated with AIs as first line therapy[201]. This will enable evaluation of:

- Effectiveness of bisphosphonate therapy, particularly intravenous zoledronate.
- The impact of treatment on BMD, bone turnover markers and fracture rates.

UNITED KINGDOM: In 2007, investigators from London reported their experience with a software system to close the AI-induced osteoporosis care gap[197]. The installation of a text recognition system on oncology department secretaries' computers enabled automation of delivery of guideline-based care for patients undergoing treatment for breast cancer. Women aged between 50 and 80 years were automatically referred to an Osteoporosis Nurse Specialist for assessment and management. The software system automatically inserted text into the oncology department letters to the patients' primary care physicians (PCP), advising the PCP that their patient would be receiving osteoporosis care. The PCPs of patients aged over 80 years were recommended to initiate osteoporosis treatment without undertaking a BMD test. Implementation of this system resulted in a 10-fold increase in the proportion of breast cancer patients referred for osteoporosis management.

GAP 3:
DISEASES ASSOCIATED WITH OSTEOPOROSIS

There are many health problems which can increase an individual's risk of developing osteoporosis and suffering fragility fractures[202]. These include a broad array of disorders: autoimmune, digestive and gastrointestinal, endocrine and hormonal, hematologic, neurological, mental illness, cancer and AIDS/HIV. This report will focus on six common disorders: chronic obstructive pulmonary disease (COPD), diseases of malabsorption, rheumatoid arthritis (RA), primary or secondary hypogonadism, dementia and diabetes.

Chronic obstructive pulmonary disease

The World Health Organization (WHO) estimates that 65 million people have moderate to severe COPD worldwide[203]. The two main types of COPD are chronic bronchitis and emphysema. Smoking is the primary cause of COPD, but up to a fifth of COPD may be attributable to occupational exposure to industrial pollutants and dust[204].

A systematic literature review established the average prevalence of osteoporosis among COPD sufferers to be 35%[205]. Vertebral fractures, the most common fragility fracture, is of particular significance for patients with COPD. In such patients with already compromised lung function, a single vertebral fracture is estimated to reduce the vital capacity by 9%[206]. Of additional concern is the observation that hip fracture sufferers who have COPD experience significantly increased post-hip fracture mortality. A study from the Veteran's Affairs (VA) Health System in the United States reported that severe COPD patients had mortality at 12 months of 40%, compared to 31% in mild COPD and 29% in non-COPD subjects[207]. Notably, this study also found that osteoporosis was known prior to the hip fracture for only 3% of participants, a care gap which has also been documented in the Netherlands[208, 209].

In 2015, in response to the lack of specific guidelines for management of osteoporosis among COPD sufferers, a Dutch Working Group comprised of clinical experts in the field of COPD and fracture prevention published a 5-step approach which includes case finding, risk evaluation, differential diagnosis, therapy and follow-up[210]:

Diseases of malabsorption

Celiac disease is one of the most common genetic disorders in the West and is estimated to affect 1% of the population in the United States[211]. Worldwide, 5 million people live with Crohn's disease and ulcerative colitis, conditions known as inflammatory bowel diseases (IBD)[212].

Low bone mass is highly prevalent amongst sufferers of celiac disease[213] and Crohn's disease[214, 215]. Many factors contribute to this association: in Crohn's disease these include intestinal resection and the resulting malabsorption of vitamin D and other nutrients, weight loss, chronic inflammation with increased levels of circulating cytokines, and frequent use of glucocorticoids. The major causes of osteoporosis amongst sufferers of malabsorption include malnutrition of calcium, vitamin D, protein and other nutrients, and the accompanying weight deficit. The incidence of fractures reported in a large study of celiac sufferers is elevated compared to non-sufferers, with increases of 90% and almost 80% for hip and wrist fractures, respectively[216]. Similarly, the incidence of fracture among IBD sufferers is 40% higher than in the general population[217]. Studies from Austria[218] and the United States[219] have reported that less than a quarter of IBD sufferers underwent BMD testing.

> The incidence of fractures reported in a large study of celiac sufferers is elevated compared to non-sufferers, with increases of 90% and almost 80% for hip and wrist fractures, respectively.

Clinical guidelines relating to the prevention and treatment of osteoporosis in celiac disease are available in Canada[220], Germany[221], UK[222] and the United States[223, 224]. Guidelines relating to the prevention and treatment of osteoporosis in inflammatory bowel disease (IBD) are available in the UK[222] and IBD and other gastrointestinal diseases in the United States[223-225].

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) affects between 0.5% and 1% of adults in the developed world[226] and resulted in about 49,000 deaths globally in 2010[227]. The onset of RA most commonly occurs in women during their forties and somewhat later in men.

Sufferers of RA have lower BMD than healthy controls and the degree of bone loss observed is correlated with disease severity[228]. Pro-inflammatory cytokines released into the circulation from the inflamed synovium are thought to cause the bone loss. A study undertaken with the British General Practice Research Database evaluated fracture incidence in more than 30,000 RA sufferers[229]. As compared to a control group, the RA sufferers' risk

of hip fracture and vertebral fracture was increased 2-fold and 2.4 fold, respectively[229]. Currently, RA is the only cause of secondary osteoporosis in the FRAX® algorithm that is considered a predictor of fracture independent of bone density[230].

RA sufferers frequently take GCs. Investigators in the VA Health System in the United States thus evaluated osteoporosis treatment among a cohort of 9,600 veterans with RA[231]. Fewer than half had received preventive treatment for osteoporosis. Similar studies from Canada[232, 233], Finland[234], Germany[235], Mexico[236], South Korea[237] and the United States[238, 239] have also reported sub-optimal assessment and/or treatment of osteoporosis in RA sufferers.

Clinical guidelines which include the prevention and treatment of osteoporosis in RA are available in Brazil[240], Germany[235], South Africa[241] and Spain[242]. Furthermore, EULAR has produced internationally relevant guidance[157].

Hypogonadism

Hypogonadism describes a diminished functional activity of the gonads – the testes in males and ovaries in females – which results in diminished sex hormone biosynthesis. Hypogonadism presents in two forms:

Primary hypogonadism: Results from defects of the gonads e.g. Klinefelter's syndrome in males and Turner syndrome in females.

Secondary hypogonadism: Resulting from hypothalamic or pituitary defects e.g. Kallmann syndrome in males and females, and anorexia in females.

The prevalence of hypogonadism has been estimated as 20% among men in their sixties and 30% among men in their seventies[243]. In 2013, investigators from the United States used data from Clinformatics DataMart (CDM), which is one of the largest commercial health insurance populations, to examine androgen prescribing patterns in the United States during the period 2001 to 2011[244]. Testosterone replacement therapy (TRT) use in men had risen to almost 4% of men in their sixties. Of particular concern was the observation that, of men newly prescribed TRT, only three-quarters had their serum testosterone level measured in the preceding 12 months (from 2001 through 2011). This assessment gap prompted production of a critical update of the 2010 Endocrine Society clinical practice guidelines for male hypogonadism[245]. In relation to osteoporosis, the update to the guideline stated '… trials published since 2010 reinforce the positive effects of TRT on BMD and muscle strength, but the effects on the risk of fracture in men with osteoporosis remain unexamined.'

In 2015, the Italian Society of Endocrinology published guidelines on androgen replacement therapy in adult male hypogonadism[246]. This guideline stated that '… testosterone supplementation should be combined with currently available treatments for individuals at high risk for complications, such as those with osteoporosis and/or metabolic disorders.'

Dementia

In December 2013, the first G8 Dementia Summit was convened in London, UK. Alzheimer's Disease International (ADI) provided a policy brief for heads of government attending the Summit[247]. The estimated number of people living with dementia in 2013 was estimated to be 44.4 million, a figure set to increase to 75.6 million and 135.5 million by 2030 and 2050, respectively. The largest increases in the projected number of dementia sufferers will be in East Asia and Sub-Saharan African regions. By 2050, the proportion living in what are currently low and middle income countries will increase to 71%, compared to 62% in 2013. In 2010, the global societal cost of dementia was US$604 billion, representing 1% of global GDP[248], and 486,000 people died as a result of dementia worldwide[227].

A significant overlap exists between sufferers of dementia and older people at high risk of injurious falls and fractures; this is particular evident amongst patients presenting with hip fracture. A UK study published in 2009 found that during a 12 month period, 66% of participants with dementia had a fall compared with 36% of age-matched controls[249]. Furthermore, the incidence of falls in dementia was nine times higher than that observed among a control group. The incidence of hip fracture among patients with

> The incidence of hip fracture among patients with Alzheimer's disease has been reported to be almost three times higher than amongst cognitively healthy peers.

Alzheimer's disease has been reported to be almost three times higher than amongst cognitively healthy peers[250]. In a meta-analysis, the prevalence of dementia amongst older hip fracture patients was estimated to be 19%[251]. The prevalence of cognitive impairment was estimated at 42%. In 2007, the Scottish Hip Fracture Audit reported on the prevalence of dementia amongst hip fracture patients[252]. Over a quarter (28%) of patients had a documented

past medical history of dementia, which the authors indicated was likely to be a significant underestimate of actual prevalence on account of the poor diagnosis rates for dementia documented at that time.

In 2011, a monograph on the subject of dementia, falls and fractures summarised the current evidence[253]:

- Persons with dementia suffer more falls, more fractures and higher post-fracture mortality than those without dementia, yet they are under-assessed for falls risk factors and are less likely to receive treatment for osteoporosis.
- Falls and fracture patients have a high prevalence of dementia and cognitive impairment, yet do not routinely receive cognitive assessment and, consequently, frequently miss an opportunity for a diagnosis of dementia to be made.

Subsequent studies from Canada[254], Finland[255], UK[67] and the United States[256] have added to the evidence that osteoporosis is infrequently diagnosed and treated in people living with dementia. As illustrated in this section of the current report, guidelines have been developed for management of osteoporosis in several diseases where osteoporosis is a common comorbidity. As the population of dementia sufferers is set to grow spectacularly in the coming decades, evidence-based guidelines for the management of osteoporosis - and falls risk - in dementia must be drafted and implemented as soon as possible.

Diabetes

In 2015, the International Diabetes Federation (IDF) estimated that there were 415 million adults aged 20 to 79 years with diabetes worldwide, including 193 million who are undiagnosed[257]. Data were not available to report the precise proportion of type 1 and type 2 diabetes globally. However, in high-income countries approximately 87% to 91% of all people with diabetes are estimated to have type 2 diabetes[258-261]. Diabetes was estimated to have caused 5 million deaths and have cost between US$673 billion and US$1,197 billion

> In light of the staggering number of individuals already affected, evidence-based guidelines for the management of osteoporosis in type 2 diabetes must be drafted and implemented as soon as possible

in healthcare spending. Left unchecked, IDF estimates that by 2040 there will be 642 million people living with the disease.

Evidence is growing to suggest that diabetes and osteoporosis share pathophysiological mechanisms. The osteoblast-specific secreted protein, osteocalcin (OC), has been shown in animal studies to influence bone metabolism, glucose metabolism and fat mass[262, 263], though the role in humans remains unknown[264]. Individuals with type 2 diabetes have increased fracture risk, up to three times greater than that of non-diabetics for hip and other non-vertebral fractures[265, 266]. Why this should be so is not completely understood because there is strong evidence of normal to high BMD at both the hip and spine in type 2 diabetics[265, 267].

In 2016, Bouxsein and colleagues published a comprehensive review on skeletal fragility in type 2 diabetes which provides several important take home messages[268]:

- Despite often having normal to high BMD, individuals with type 2 diabetes have increased fracture risk irrespective of sex, race or ethnicity. Accordingly, BMD measurements may underestimate skeletal fragility in type 2 diabetics.
- There is little data available on the optimum management of osteoporosis in type 2 diabetes.
- In the absence of evidence to the contrary, management should adhere to the established principles of management of postmenopausal osteoporosis.

Given the scale of the threat posed to public health by diabetes, self-evidently, efforts to prevent the disease must be a priority for health systems worldwide. However, in light of the staggering number of individuals already affected, evidence-based guidelines for the management of osteoporosis in type 2 diabetes must be drafted and implemented as soon as possible.

GAP 4:
PRIMARY FRACTURE PREVENTION FOR INDIVIDUALS AT HIGH RISK OF FRACTURE

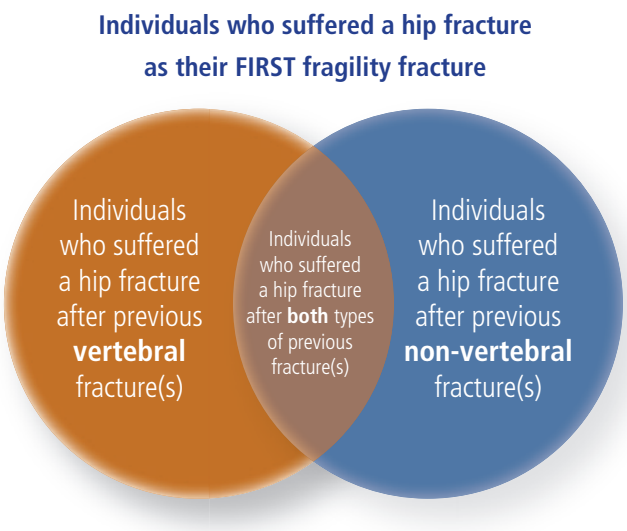
As discussed in Gap 1 of this report, there is an enormous amount of work to be done to close the secondary fracture prevention care gap worldwide. IOF is of the firm belief that secondary prevention is the single most important, immediate mechanism to directly improve patient care and reduce spiraling fracture related healthcare costs. The ultimate goal in the longer term would be the prevention of the first fracture, and advances in fracture risk assessment during the last decade provide a platform for development of clinically effective and, crucially, cost-effective approaches.

In order to ensure that a primary fracture prevention programme has the potential to be cost effective, consideration must be given to which first fragility fracture is to be prevented. Primary prevention of hip fracture is likely to be more cost-effective than primary prevention of wrist fracture, because hip fractures cost considerably more to manage than wrist fractures. In this regard, consideration must be given to what proportion of all hip fractures occur as an individual's first fragility fracture at any skeletal site, as illustrated in the Venn diagram in figure 4.

Whilst definitive data to populate such an analysis are not available, the following illustration is consistent with the current evidence-base:

- Approximately 50% of hip fracture patients have suffered clinically apparent fragility fracture(s) prior to breaking their hip, which was usually a non-vertebral fracture[37-40].
- Conservative interpretation of studies from Spain and Japan suggests that a further 10%[269] to 25%[270] of hip fracture patients may have suffered previous vertebral fractures – the majority of which are not recognised or diagnosed as such[271] – but have not suffered clinically apparent non-vertebral fractures.
- Therefore, 25-40% of hip fracture patients may have suffered the hip fracture as their first overt fragility fracture at any skeletal site.

Figure 4. Distribution of prior fracture history among hip fracture patients



This analysis highlights the challenge faced by efforts to pro-actively case-find the relatively small proportion of individuals who are likely to suffer a hip fracture as their first fragility fracture. It should also be noted that fragility fractures at sites other than the hip impose a significant burden on older people. Vertebral fractures lead to many adverse consequences for sufferers, including[272]:

- Back pain, loss of height, deformity, immobility and increased number of hospital bed days[273, 274].
- Reduced quality of life resulting from loss of self-esteem, distorted body image and depression[275-278].
- A significant negative impact on activities of daily living[279, 280].

Studies from Australia[281], Canada[282] and the international Global Longitudinal Study of Osteoporosis in Women (GLOW)[283] have all reported significant reductions in health-related quality of life among individuals who have suffered fragility fractures at all skeletal sites. Accordingly, a robust clinical case exists for primary prevention of all major osteoporosis fractures, defined as hip, clinical vertebral, wrist or proximal humerus fractures. Pragmatic approaches to case-finding individuals at high risk of suffering these fractures as their first fracture include:

- **Gap 2:** Osteoporosis induced by medicines: Systematic case-finding of individuals at high fracture risk in this group.
- **Gap 3:** Diseases associated with osteoporosis: Systematic case-finding of individuals at high fracture risk in this group.
- **Absolute fracture risk calculation**: Systematic application of tools such as FRAX® to risk stratify the older population.

The SCOOP trial, which is currently ongoing in the UK, will provide valuable insights on primary fracture prevention strategies[284]. This pragmatic, randomised controlled trial (RCT) is following more than 12,000 women aged 70 to 85 years over a five-year period. The study will assess the effectiveness and cost-effectiveness of a community-based screening programme which utilises the FRAX® algorithm and BMD measurement to assess 10-year probability of fracture.

Information specifically concerned with the extent of the primary fracture prevention care gap is not available. Given the pervasive and persistent secondary fracture prevention care gap documented in Gap 1, it would be reasonable to assume that the primary fracture prevention care gap among high risk individuals is at least as wide. While not specific to primary fracture prevention, information regarding national use of FRAX® and national prescribing levels provide an indication of overall assessment and treatment rates within a country. Importantly, a major report on osteoporosis in the European Union (EU) published in 2013 revealed that for the 12 month period from November 2010 to November 2011 uptake of FRAX® was sub-optimal in all EU countries, including those for which FRAX®

models were available[10]. More recent information on the usage of FRAX® is illustrated in figure 5.

The 2013 EU report also documented national prescribing levels[10]. These data, in combination with an algorithm which calculated the number of patients who were eligible for treatment in each of the 27 EU member states at the time, enabled estimation of the potential treatment gap for each country in 2010. This approach assumed that all those treated were actually eligible for treatment and not at a lower level of risk, so may have underestimated the treatment gap among high risk patients. In total in the EU, 10.6 million out of 18.4 million women who were eligible received treatment. Among men, 1.7 million men out of the 2.9 million men who were eligible received treatment. The inferred treatment gaps for each EU member state are illustrated for women and men in figure 6.

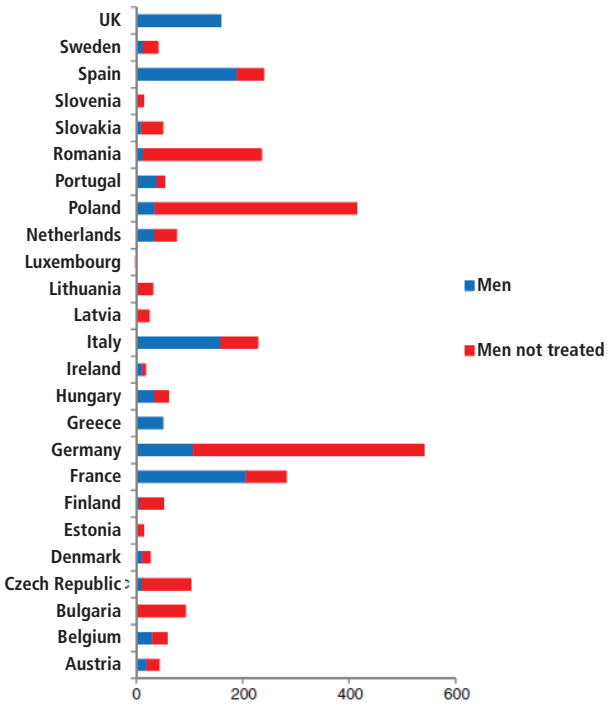
Most clinical guidelines cover both secondary fracture prevention and primary fracture prevention. A notable exception is guidance from NICE in the UK, which first published guidance specifically on primary fracture prevention[285] in 2008 to complement existing secondary prevention guidance[119, 286].

Several health systems have implemented systematic approaches to primary fracture prevention targeted at high risk individuals in parallel to secondary prevention efforts. The Kaiser Permanente Healthy Bones Program[287] and Geisinger Health System Hi-ROC Program[288] provide high-performing examples of this approach.

Figure 5. FRAX® sessions per 100,000 of population by country for April 2015 to March 2016

[Google Analytics]

Figure 6. The EU osteoporosis treatment gap in 2010[10].



Estimated number (in thousands) of men treated (blue) and patients eligible for treatment that are not treated (red) in 2010

Estimated number (in thousands) of women treated (blue) and patients eligible for treatment that are not treated (red) in 2010

Adapted from Arch Osteoporos (2013) 8:136 Hernlund E et al. with permission of Springer

GAP 5:
THE IMPORTANCE OF STAYING ON TREATMENT

The focus of this report thus far has been upon care gaps which result in individuals at high risk of fragility fracture not undergoing assessment and/or not receiving osteoporosis treatment. This section considers a different, but common challenge in the chronic disease arena: ensuring that individuals who are initiated on treatment actually stay on treatment.

Two measures of adherence to treatment are commonly used in studies:

- **Persistence:** Defined as either the time to treatment discontinuation or as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g. 30, 60 or 90 days).
- **Compliance:** Defined as the ability of a patient to adhere to the dosing, timing and conditions described by the prescriber or in accordance with the medicine's patient information leaflet. One measure of compliance is the medication possession ratio (MPR). MPR is usually defined as the number of days of medication available to the patient, divided by the number of days of observation.

In routine clinical practice, both persistence and compliance with osteoporosis treatment are sub-optimal, a phenomenon previously reported for other classes of widely-used medicines including antihypertensives[289] and statins[290]. Approximately half of patients initiated on osteoporosis treatment do not follow their prescribed treatment regimen and/or discontinue treatment within a year[291]. This is particularly notable on account of the flexibility of dosing options of widely available osteoporosis treatments, which can be taken as daily, weekly or monthly tablets, or as daily, quarterly, six-monthly or annual injections. Intravenous or sub-cutaneous routes of administration provide a means to ensure 100% adherence with treatment, as long as a robust system is in place to administer the initial injection and reliably arrange follow-up injections at appropriate intervals. It has been estimated that improved adherence in the United States would reduce fracture rates by 25%, equating to approximately 300,000 fewer fractures per year and generate savings of US$3 billion[292].

In 2013, the Medication Adherence and Persistence Special Interest Group of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) undertook a systematic literature review of interventions to improve osteoporosis medication adherence[293]. Interventions identified which may improve adherence were:

- Simplification of dosing regimens
- Electronic prescriptions
- Patients decision aids
- Patient education

Patients were most persistent with medications which had the least frequent dosing regimens[294-296]. The use of electronic prescriptions in combination with verbal counselling was associated with a 2.6-fold improvement in short-term compliance compared to verbal counselling alone[297]. A study from the United States evaluated use of a patient decision aid in combination with usual primary care practice compared to usual primary care practice alone[298]. While adherence at 6

months was similar for both groups, the proportion with more than 80% adherence was significantly higher with the decision aid. With regard to the impact of patient education, it should be noted that the largest and least biased studies reviewed showed only marginal improvement in adherence[299-302].

The impact of FLS on adherence has been evaluated in several studies[303-307]. Among patients managed by an FLS after fracture, between 74% and 88% remained on treatment at 12 months, and between 64% and 75% at 24 months. These data reinforce the notion that a 'teachable moment' exists after individuals have suffered a fragility fracture which can be capitalized upon by an FLS to improve adherence to treatment. The FLS team at Concord Hospital in Sydney, Australia also compared adherence among patients initiated on treatment by the FLS who were subsequently followed up by either the FLS or local primary care physicians (PCPs)[305]. Notably, persistence at 24 months was similar in both groups leading the investigators to conclude that the main function of an FLS is to initiate a management plan for osteoporosis after fractures occur. If effective communication between the FLS and local PCPs is established, PCPs are well-placed and willing to manage osteoporosis care in the long term after initial recommendations are provided by the FLS.

GAP 6:
PUBLIC AWARENESS OF OSTEOPOROSIS AND FRACTURE RISK

In recent years, a number of studies have been undertaken to characterise awareness of osteoporosis and fracture risk among older people. In 2008, investigators from a non-profit Health Maintenance Organization (HMO) in the Northwest United States sought to evaluate key stakeholder perspectives on osteoporosis care after a fracture[308]. These stakeholders included fracture patients, quality and other healthcare managers, PCPs, and orthopaedic clinicians and staff. Both patients and PCPs commented that confusion of osteoporosis with osteoarthritis was common. Furthermore, this confusion led to the perception that osteoporosis is a benign consequence of ageing.

In 2010, Canadian investigators evaluated osteoporosis knowledge among older fracture patients who were treated by orthopaedic surgeons at two major teaching hospitals in Ontario[309]. Fracture patients were asked two questions:

1 - Do you know what osteoporosis is?

2 - If Yes, what do you think it is?

The overwhelming majority of respondents (91%, 115/127) said that they knew what osteoporosis was. Among these individuals, 75% gave responses that were considered to be correct. Individuals who had reported a diagnosis of osteoporosis or a higher education level were more likely to provide a correct definition, however, the odds reduced with age. Almost 40% of the interview participants completed a 'Facts on Osteoporosis Quiz'. Notably, less than half (41%) of those who took the quiz knew that a person who had suffered a spine fracture was at increased risk of suffering a fracture in the future as compared to a fracture-free individual.

The acute rehabilitation setting could provide an opportunity to improve post-fracture osteoporosis treatment. In this setting, investigators from Boston in the United States assessed fracture patients' willingness to participate, free of charge, in a secondary fracture prevention programme[310]. Less than half of eligible patients chose to participate, with reluctance to take another medication cited as the most common reason for not doing so.

In New Zealand, patients' and doctors' perceptions of appropriate intervention thresholds for fracture risk have been surveyed[311]. Stark differences were evident. An absolute risk of 50% for both major osteoporotic and hip fractures was identified by patients as meriting drug treatment, as compared an absolute risk of 10% among doctors. Further, patients determined that an effective drug would achieve a relative risk reduction of 50%. On this basis, patients in New Zealand would consider taking treatment for osteoporosis only when the absolute reduction in fracture risk was 25%.

The international GLOW study has compared self-perception of fracture risk with actual risk among more than 60,000 postmenopausal women in 10 countries in Europe, North America, and Australia[312]. Key findings included:

- Among women reporting a diagnosis of osteopenia or osteoporosis, only 25% and 43%, respectively, thought their risk was increased.
- Among women whose actual risk was increased based on the presence of any one of seven risk factors for fracture, the proportion who recognized their increased risk ranged from 19% for smokers to 39% for current users of glucocorticoid medication.
- Only 33% of those with at least 2 risk factors perceived themselves as being at higher risk.

These studies are illustrative of the evidence base relating to awareness of fracture risk among older people. The findings of some studies are in conflict with others. Knowledge gaps are evident among some groups but not others. Efforts to improve awareness need to provide clear, evidence-based messages. Disease awareness campaigns (DACs) such as 2Million2Many from the NBHA in the United States provide an innovative example of implementing this approach[136]. The key messages for 2Million2Many are very simple and compelling:

- Every year, there are 2 million bone breaks that are no accident (in the USA).
- They are the signs of osteoporosis in people as young as 50.
- But only 2 out of 10 get a simple follow-up assessment.
- Together we can break osteoporosis before it breaks us. But we must speak up. Remember: Break a bone, request a test.

The impact of the 2Million2Many campaign cannot be assessed in isolation, because pursuant to the launch of this campaign in 2012, NBHA and NOF launched a major FLS implementation initiative in 2013[137] and a Qualified Clinical Data Registry focused on outcomes in osteoporosis and post-fracture care in 2014[86]. In 2015, the National Committee on Quality Assurance (NCQA) published a report on post-fracture osteoporosis care for women for the period 2007 to 2014[313]. Together these initiatives resulted in a significant improvement in post-fracture care in the United States.

An initial focus of DACs should be to drive awareness throughout the population of the world that fracture begets fracture. If all individuals aged 50 years or over know that suffering a first fragility fracture significantly increases their risk of suffering second and subsequent fractures, up to one half of all people who will suffer hip fractures in the future could be aware of that risk, and be proactive in taking steps to lower it.

GAP 7:
PUBLIC AWARENESS OF BENEFITS VERSUS RISKS OF OSTEOPOROSIS TREATMENT

Numerous RCTs and Cochrane Collaboration systematic reviews have demonstrated the efficacy and safety of treatments for osteoporosis. However, in the last decade use of these treatments among individuals at high risk of fracture has been significantly impacted by reports relating to rare side effects, including osteonecrosis of the jaw (ONJ), atrial fibrillation (AF) and atypical femur fracture (AFF). The importance of vigilant monitoring of the occurrence of side effects cannot be overstated. That being said, the benefits of anti-osteoporosis therapies for the prevention of fragility fractures in high risk individuals significantly outweigh harm potentially attributable to these medicines.

ONJ has primarily been observed among patients taking high doses of bisphosphonates for treatment of bone metastases rather than osteoporosis. It is very rare in the context of treatment for osteoporosis. In fact, Swedish investigators estimated that an average Swedish dental practice (of 1,234 patients) would encounter one osteoporosis patient with new oral bisphosphonate-related ONJ every 62nd year[314]. In 2015, an International Task Force estimated the incidence of ONJ in the osteoporosis population to be 0.001% to 0.01%, which was marginally higher than the incidence observed in the general population of <0.001%[315].

With regards to atrial fibrillation, an increase in risk was observed for zoledronic acid infusions compared to placebo in the HORIZON-PFT Trial (1.3% vs. 0.5%, p<0.001)[24]. However, a meta-analysis of 26 RCTs of oral bisphosphonates reported no increase in risk of AF[316].

> ‘Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years.’

The occurrence of AFF has also been the subject of considerable debate within the media. Current estimates suggest that atypical fractures occur in 3 to 50 cases per 100,000 person years for bisphosphonate users[317, 318]. Investigators from Kaiser Permanente in the United States analysed a large population of bisphosphonate users to explore the relationship between duration of therapy and risk of AFF[317]. Age-adjusted incidence rates for an AFF were 1.78 per 100,000 person years (95% confidence interval [CI], 1.5-2.0) with exposure from 0.1 to 1.9 years, which increased to 113.1 per 100,000 person years (95% CI, 69.3-156.8) with exposure from 8 to 9.9 years. The authors concluded that the incidence of AFF increases with longer duration of bisphosphonate use, but this risk should be counterbalanced with the proven benefits in terms of fracture reduction.

In 2016, the impact of US Food and Drug Administration (FDA) safety-related announcements on the use of bisphosphonates after hip fracture was the subject of a short report[319]. A large sample of hip fracture patients insured by United HealthCare were analysed. Overall, the proportion of hip fracture patients treated with bisphosphonates after their hip fracture occurred declined from 15% in 2004 to 3% in the last quarter of 2013. A significant decline in bisphosphonate prescribing was observed after the 2007 FDA announcement relating to AF, which continued after the 2010 FDA announcement relating to atypical fractures. The authors concluded that given the clinical importance of the secondary prevention of hip fracture, these results highlight the need to weigh benefits versus harms of bisphosphonates and to improve the communication of drug safety information with both clinicians and patients.:

This is the crux of this issue, and demonstrates a failure to counter adverse coverage of rare side effects of osteoporosis treatments across media platforms. The risk-benefit calculation for treatment of osteoporosis among individuals who are at high risk of suffering fragility fractures, including life changing and life threatening hip fractures, significantly favours treatment[320-323]. Clinicians and patients need to be able to objectively discuss and evaluate the risk benefit calculation for the patient’s individual circumstances when making collaborative treatment decisions. Having ready access to absolute fracture risk calculation tools such as FRAX® can make such discussions far more tailored – and meaningful - to individual patients. It requires all those involved in the care of osteoporosis patients to ensure clear, balanced communication of these issues both to individual patients and more widely when opportunities arise.

GAP 8:
ACCESS AND REIMBURSEMENT FOR OSTEOPOROSIS ASSESSMENT AND TREATMENT

During this decade, IOF has undertaken a series of regional audits throughout the world[10, 324-329]. These audits have evaluated epidemiology, costs and the burden of osteoporosis in the regions, and have included an overview of access and reimbursement to treatment. A summary is provided for each region below. With regard to the current situation in North America, Osteoporosis Canada and the National Osteoporosis Foundation in the United States have provided summaries.

Asia-Pacific

The most recent IOF Asia-Pacific Regional Audit was published in 2013[324]. The audit noted that reimbursement varied greatly across the region, ranging from zero to 100% reimbursement for the most commonly prescribed medications. There were also differences between public and private insurance, with only partial reimbursement being offered, or restrictive criteria applied, such as age or history of prior fracture.

Access to BMD testing can also have a significant impact on access to osteoporosis treatment. In this regard, the audit noted that many countries were seriously under-resourced in terms of DXA scanners. Further, BMD testing is not fully reimbursed in many countries, which serves as another barrier to accessing treatment.

Eastern Europe and Central Asia

The IOF Eastern European and Central Asian Regional Audit was published in 2010[325]. Throughout the region availability and access to osteoporosis treatment was extremely limited. In the Russian Federation, while treatment was free of charge for individuals with severe osteoporosis, salmon calcitonin was the only treatment available.

In most countries, BMD testing was only accessible in the main cities, yet in about one-third of the countries, more than 40% of the population resides in a rural area. Further, in countries without reimbursement, the majority of the population cannot afford DXA examinations.

European Union

In 2013, IOF and the European Federation of Pharmaceutical Industry Associations (EFPIA) undertook a comprehensive audit of the EU member states at the time[10, 326, 327]. While most treatments were reimbursed in most countries, full reimbursement was provided in only 7 member states. In the remaining countries, the level of reimbursement varied from zero in Malta, up to 100% for selected treatments in Luxembourg and Spain.

As illustrated in figure 7, access to BMD testing varied dramatically across the continent. The survey found that about half of countries in the EU had the recommended number of DXA scanners to adequately serve their populations. However, given that information was not available on the specific use of these scanners (i.e. for routine clinical service provision or for research purposes), or levels of staffing in DXA units, it is likely that a majority of countries did not have adequate access to BMD testing to implement national clinical guidelines for osteoporosis.

Latin America

The IOF Latin American Regional Audit was published in 2012[328]. Bisphosphonates were widely available throughout the region with considerable variability in reimbursement policy. Other osteoporosis therapies such as selective estrogen receptor modulators (SERMs), parathyroid hormone analogues (PTH), hormone replacement therapy (HRT), and strontium ranelate were also available, but access was often restricted.

Access to BMD testing was limited to urban areas throughout the region with availability estimates ranging from 1 to 10 devices per 1 million inhabitants.

Middle East and Africa

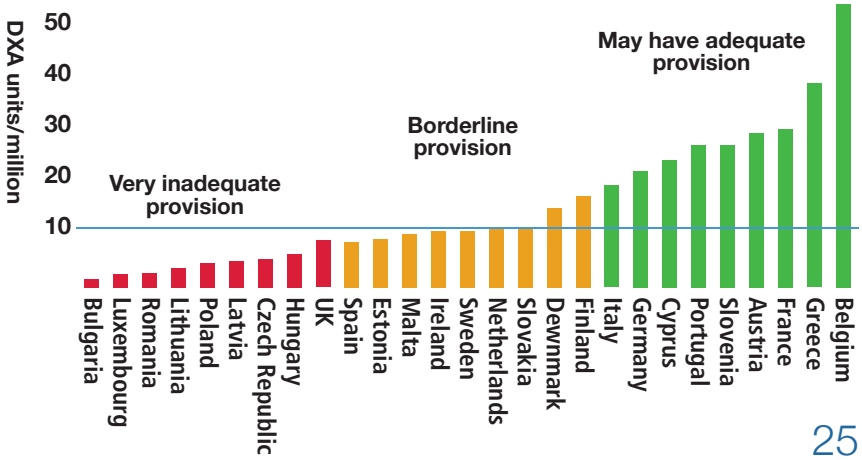
The IOF Middle East and Africa Regional Audit was published in 2011[329]. The situation documented in this region was very heterogeneous. Some countries had a very good reimbursement policy for diagnostic tools and therapies, while in other countries there was absolutely no reimbursement available and patients had to pay for all diagnostic tests and treatment.

North America

In Canada there is no single national healthcare system. Healthcare falls under the independent jurisdiction of each of the 10 provinces and 3 territories. There is reimbursement for many of the oral bisphosphonates in all Canadian provinces for seniors who are indicated for such treatment. However, coverage for other osteoporosis medications such as denosumab and zoledronic acid is quite variable depending on the province/territory.

In the United States reimbursement for treatment varies greatly depending on each patient's health plan. Health care reform is evolving from fee for service to supporting improved quality, prevention and care coordination with financial incentives (or penalties) to encourage healthcare professionals and health systems to report on and improve patient outcomes. There are a number of quality measures focused on osteoporosis and post-fracture care but performance around these measures remain low compared to other major chronic diseases. Further, a major drop in reimbursement for DXAs performed in the office setting has led to a drop in the number of providers and more than 1 million less DXAs performed.

Figure 7. Access to DXA scanners in the EU in 2010[326]



n.b. DXA units per million of the general population in 2010 based on sales of DXA in the EU supplied by manufacturers. The horizontal line denotes a minimum service requirement[330]. Adapted from Arch Osteoporos (2013) 18:144 Kanis JA et al. with permission from Springer.

GAP 9:
PRIORITIZATION OF FRAGILITY FRACTURE PREVENTION IN NATIONAL POLICY

The IOF regional audits provide comprehensive information on the level of priority afforded to fragility fracture prevention by governments throughout the world[10, 324-329].

Asia-Pacific

The most recent IOF Asia-Pacific Regional Audit was published in 2013[324]. At the time, the governments of just 4 of the 16 countries represented in the audit had designated osteoporosis as a national health priority: Australia (2002), Chinese Taipei (2005), Singapore (2009) and China (2011). Since 2013, significant progress has also been made in New Zealand[112].

Eastern Europe and Central Asia

The IOF Eastern European and Central Asian Regional Audit was published in 2010[325]. At the time, of the 21 countries presented in the audit, only 2 (Republic of Belarus and Bulgaria) considered osteoporosis as a health priority.

European Union

As illustrated in in the IOF-EPFIA Audit 2013[10, 326, 327], the majority of member states (18/27) did not recognize osteoporosis or musculoskeletal diseases as a national health priority (NHP). Of those member states that had developed a NHP, the focus was on nutrition (6 countries), falls prevention (4 countries), exercise (4 countries) and the implementation of FLS (2 countries).

Latin America

The IOF Latin America Regional Audit 2012 [328] showed that osteoporosis was a NHP in only 3 of the 14 countries in the audit: Brazil, Cuba and Mexico. Although osteoporosis guidelines were available in 9 of the 14 countries, they were only government endorsed in Bolivia and Cuba.

Middle East and Africa

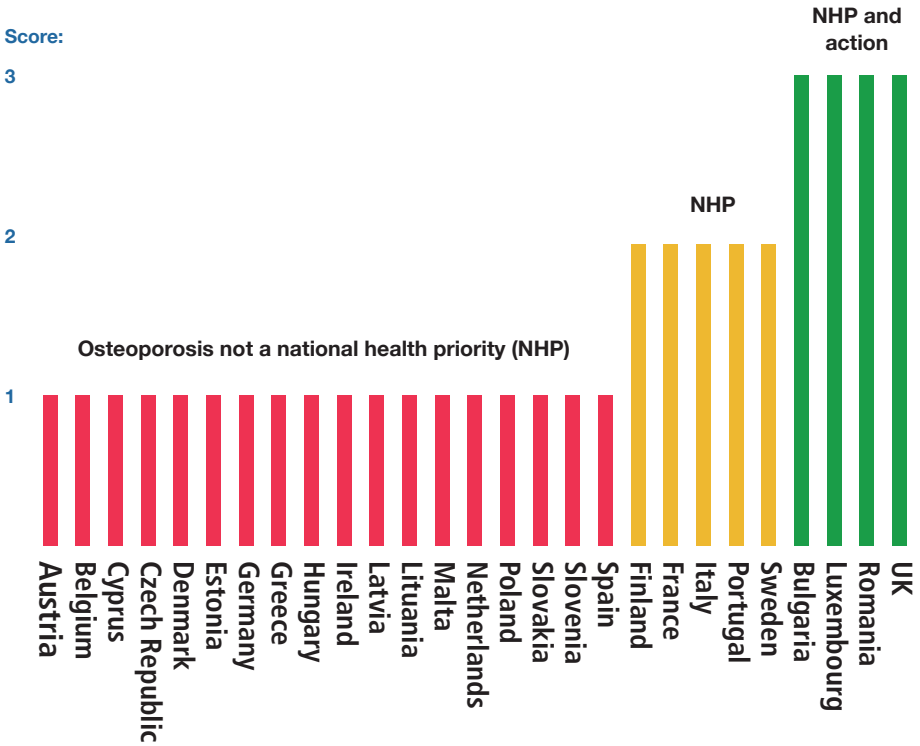
The IOF Middle East and Africa Regional Audit 2011[329] found that osteoporosis was considered a health priority in only 3 out of the 17 countries included in this audit: Iran, Iraq and Jordan. Osteoporosis guidelines were endorsed by governments in Egypt, Lebanon and South Africa, with approval pending for guidelines in Iran and Iraq.

North America

Healthcare in Canada falls under the independent jurisdiction of each of the 10 provinces and 3 territories. There is therefore no national governmental policy on osteoporosis or fracture prevention. However, Osteoporosis Canada (OC) is actively promoting implementation of effective FLS as a priority. OC will soon be launching an FLS Registry to showcase Canadian FLS meeting all 8 of the *Essential Elements for Fracture Liaison Services*[331].

In the United States, despite a landmark report by the Surgeon General in 2004[2] and the specific recommendations from key national and scientific societies [132,133,134] intended to prioritize and improve osteoporosis and fracture prevention, implementation has been poor. Many patients are not given the necessary information about prevention and are not receiving appropriate testing to diagnose osteoporosis or establish osteoporosis risk. Most importantly, a majority of patients who have osteoporosis-related fractures are not being diagnosed with osteoporosis and are not receiving any of the Food and Drug Administration (FDA)-approved, effective therapies.

Figure 8. National health priorities for osteoporosis or musculoskeletal diseases in the EU in 2013[326].



Adapted from Arch Osteoporos (2013) 18:144 Kanis JA et al. with permission of Springer

GAP 10:
THE BURDEN OF OSTEOPOROSIS IN THE DEVELOPING WORLD

> The developing world is set to bear the brunt of the burden of osteoporosis as the world's population rapidly ages during the first half of this century. Accordingly, it is ironic that few data on fracture rates exist in many developing countries. The IOF regional audits provide valuable insights in this regard[324, 325, 328, 329].

Asia-Pacific

There is an urgent need at the national level to accurately quantify osteoporosis and fracture prevalence in many countries of this region. India will become the most populous country in the world in the next few decades, and life expectancy of Indians is set to increase considerably[324]. In 2013, a study of the incidence of hip fracture in the Rohtak district of North India[12] found that among individuals aged 50 years or over, the crude incidence was 159 per 100,000 in women and 105 per 100,000 in men. Application of these rates to the United Nations Population Projection for India for 2015[13] suggests that the number of hip fractures in men and women in 2015 was 121,000 and 185,000 cases, respectively. Efforts by the Indian Society for Bone and Mineral Research (ISBMR) to conduct multicentre, large-scale hip fracture incidence studies will provide robust fracture epidemiology to inform policy development. The IOF Asia-Pacific Regional Audit 2013 also reported a paucity of fracture data for Malaysia, Pakistan, Sri Lanka, Thailand and Vietnam[324].

Eastern Europe and Central Asia

In 2010, the IOF Eastern European and Central Asian Regional Audit stated[325]: So the under recognition of osteoporosis on the part of governments and healthcare professionals in the region is mainly due to the lack of solid epidemiological and economic data on the costs and burden of the disease.

In 2012, work undertaken to inform development of a FRAX® model for the Russian Federation provided estimates of fracture incidence for Russia[16]. The total number of hip fractures estimated to have occurred in 2010 (112,000) was expected to rise to 159,000 in 2035. The estimated number of major fractures was expected to rise from 590,000 to 730,000 over the same time interval. The investigators highlighted that these estimates were based on extrapolation of robust fracture information collected in Yaroslavl and Pervouralsk to the entire population of the Russian Federation. Multi-centre, large-scale epidemiological studies should be undertaken in Russia and other countries in the region to inform policy development.

Latin America

The IOF Latin American Regional Audit identified a major lack of data on fracture incidence in the region in 2012[328]. Only 8 of the 14 countries in the audit had published hip fracture incidence data, and many of the studies were out-dated and non-population based. Further, there were virtually no data available on the status of vertebral fractures in 8 of the 14 audited countries.

In 2015, work undertaken to inform development of a FRAX® model for Brazil provided estimates of hip fracture incidence for Brazil[17]. There were estimated to be 80,640 hip fractures in 2015, of which 23,422 were in men and 57,218 in women. In 2040, the number of hip fractures was expected to rise to 55,844 in men and 141,925 in women, a rise of 238 and 248 %, respectively.

Middle East and Africa

The IOF Middle East and Africa Regional Audit identified a major lack of data on fracture incidence in the region in 2011[329]. Only 6 of the 17 countries in the audit had published hip fracture incidence data. Further, prevalence rates for vertebral fractures were available for only 3 countries.

References

1. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone.* Dec 2001;29(6):517-522.

2. Office of the Surgeon General. Bone Health and Osteoporosis: A Report of the Surgeon General. In: US Department of Health and Human Services, ed. Washington; 2004.

3. Kanis JA, McCloskey EV, Johansson H, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* Oct 19 2012.

4. Osnes EK, Lofthus CM, Meyer HE, et al. Consequences of hip fracture on activities of daily life and residential needs. *Osteoporos Int.* Jul 2004;15(7):567-574.

5. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J Gerontol.* May 1990;45(3):M101-107.

6. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med.* Aug 18 1997;103(2A):12S-17S; discussion 17S-19S.

7. Autier P, Haentjens P, Bentin J, et al. Costs induced by hip fractures: a prospective controlled study in Belgium. Belgian Hip Fracture Study Group. *Osteoporos Int.* 2000;11(5):373-380.

8. Cree M, Soskolne CL, Belseck E, et al. Mortality and institutionalization following hip fracture. *J Am Geriatr Soc.* Mar 2000;48(3):283-288.

9. Kiebzak GM, Beinart GA, Perser K, Ambrose CG, Siff SJ, Heggeness MH. Undertreatment of osteoporosis in men with hip fracture. *Arch Intern Med.* Oct 28 2002;162(19):2217-2222.

10. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden : A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos.* Dec 2013;8(1-2):136.

11. Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010-2050. *Osteoporos Int.* Jul 2015;26(7):1929-1937.

12. Dhanwal DK, Siwach R, Dixit V, Mithal A, Jameson K, Cooper C. Incidence of hip fracture in Rohtak district, North India. *Arch Osteoporos.* 2013;8:135.

13. United Nations Department of Economic and Social Affairs Population Division. *World Population Prospects: The 2015 Revision, DVD Edition.* New York 2015.

14. Stevens JA, Rudd RA. The impact of decreasing U.S. hip fracture rates on future hip fracture estimates. *Osteoporos Int.* Oct 2013;24(10):2725-2728.

15. Orimo H, Yaegashi Y, Hosoi T, et al. Hip fracture incidence in Japan: Estimates of new patients in 2012 and 25-year trends. *Osteoporos Int.* Jan 5 2016.

16. Lesnyak O, Ershova O, Belova K, et al. Epidemiology of fracture in the Russian Federation and the development of a FRAX model. *Arch Osteoporos.* Dec 2012;7(1-2):67-73.

17. Zerbini CA, Szejnfeld VL, Abergaria BH, McCloskey EV, Johansson H, Kanis JA. Incidence of hip fracture in Brazil and the development of a FRAX model. *Arch Osteoporos.* 2015;10:224.

18. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res.* Mar 2007;22(3):465-475.

19. Blume SW, Curtis JR. Medical costs of osteoporosis in the elderly Medicare population. *Osteoporos Int.* Jun 2011;22(6):1835-1844.

20. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev.* 2008(1):CD001155.

21. Wells GA, Cranney A, Peterson J, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev.* 2008(1):CD003376.

22. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev.* 2008(1):CD004523.

23. Albergaria BH, Gomes Silva BN, Atallah ÁN, Fernandes Moça Trevisani V. Intravenous zoledronate for postmenopausal osteoporosis (Protocol). *Cochrane Database of Systematic Reviews.* 2010(1):1-8.

24. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* May 3 2007;356(18):1809-1822.

25. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* Nov 1 2007;357(18):1799-1809.

26. Bennett TG, Le Marshall K, Khan F, Wark JD, Brand C. Denosumab for the treatment and prevention of postmenopausal osteoporosis (Protocol). *Cochrane Database of Systematic Reviews.* 2012(8):1-10.

27. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* Aug 20 2009;361(8):756-765.

28. Palacios S, Kalouche-Khalil L, Rizzoli R, et al. Treatment with denosumab reduces secondary fracture risk in women with postmenopausal osteoporosis. *Climacteric.* Dec 2015;18(6):805-812.

29. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* Aug 18 1999;282(7):637-645.

30. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* May 10 2001;344(19):1434-1441.

31. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med.* Jan 29 2004;350(5):459-468.

32. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab.* May 2005;90(5):2816-2822.

33. Seeman E, DeVogelaer JP, Lorenc RS, et al. Strontium ranelate: the first anti-osteoporotic agent to reduce the risk of vertebral fracture in patients with lumbar osteopenia. Paper presented at: IOF World Congress on Osteoporosis, 2004; Rio de Janeiro, Brazil.

34. Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess.* Feb 2007;11(4):1-134.

35. Akesson K, Mitchell PJ. *Capture the Fracture: A global campaign to break the fragility fracture cycle.* Nyon,: International Osteoporosis Foundation; 2012.

36. International Osteoporosis Foundation. Capture the Fracture® Programme website. http://www.capture-the-fracture.org/. Accessed 4 March 2016.

37. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. *Clin Orthop Relat Res.* Jul-Aug 1980(150):163-171.

38. Port L, Center J, Briffa NK, Nguyen T, Cumming R, Eisman J. Osteoporotic fracture: missed opportunity for intervention. *Osteoporos Int.* Sep 2003;14(9):780-784.

39. McLellan A, Reid D, Forbes K, et al. *Effectiveness of Strategies for the Secondary Prevention of Osteoporotic Fractures in Scotland (CEPS 99/03)*: NHS Quality Improvement Scotland; 2004.

40. Edwards BJ, Bunta AD, Simonelli C, Bolander M, Fitzpatrick LA. Prior fractures are common in patients with subsequent hip fractures. *Clin Orthop Relat Res.* Aug 2007;461:226-230.

41. Wang O, Hu Y, Gong S, et al. A survey of outcomes and management of patients post fragility fractures in China. *Osteoporos Int.* Nov 2015;26(11):2631-2640.

42. Hagino H, Sawaguchi T, Endo N, Ito Y, Nakano T, Watanabe Y. The risk of a second hip fracture in patients after their first hip fracture. *Calcif Tissue Int.* Jan 2012;90(1):14-21.

43. Sakuma M, Endo N, Oinuma T, et al. Incidence of osteoporotic fractures in Sado, Japan in 2010. *J Bone Miner Metab.* Mar 2014;32(2):200-205.

44. Baba T, Hagino H, Nonomiya H, et al. Inadequate management for secondary fracture prevention in patients with distal radius fracture by trauma surgeons. *Osteoporos Int.* Jul 2015;26(7):1959-1963.

45. Kim SH, Ko YB, Lee YK, et al. National utilization of calcium supplements in patients with osteoporotic hip fracture in Korea. *J Bone Metab.* Nov 2013;20(2):99-103.

46. Kim SR, Park YG, Kang SY, Nam KW, Park YG, Ha YC. Undertreatment of osteoporosis following hip fractures in jeju cohort study. *J Bone Metab.* Nov 2014;21(4):263-268.

47. Kim SC, Kim MS, Sanfelix-Gimeno G, et al. Use of osteoporosis medications after hospitalization for hip fracture: a cross-national study. *Am J Med.* May 2015;128(5):519-526 e511.

48. Angthong C, Rodjanawijitkul S, Samart S, Angthong W. Prevalence of bone mineral density testing and osteoporosis management following low- and high-energy fractures. *Acta Orthop Traumatol Turc.* 2013;47(5):318-322.

49. Gosch M, Druml T, Nicholas JA, et al. Fragility non-hip fracture patients are at risk. *Arch Orthop Trauma Surg.* Jan 2015;135(1):69-77.

50. Brozek W, Reichardt B, Zwerina J, Dimai HP, Klaushofer K, Zwettler E. Antiresorptive therapy and risk of mortality and refracture in osteoporosis-related hip fracture: a nationwide study. *Osteoporos Int.* Jan 2016;27(1):387-396.

51. Erny F, Auvinet A, Chu Miow Lin D, et al. Management of osteoporosis in women after forearm fracture: data from a French health insurance database. *Joint Bone Spine.* Jan 2015;82(1):52-55.

52. Viprey M, Caillet P, Canat G, et al. Low Osteoporosis Treatment Initiation Rate in Women after Distal Forearm or Proximal Humerus Fracture: A Healthcare Database Nested Cohort Study. *PLoS One.* 2015;10(12):e0143842.

53. Haasters F, Prall WC, Himmler M, Polzer H, Schieker M, Mutschler W. [Prevalence and management of osteoporosis in trauma surgery. Implementation of national guidelines during inpatient fracture treatment]. *Unfallchirurg.* Feb 2015;118(2):138-145.

54. Parri S, Cianferotti L, Marcucci G, et al. The T.A.R.Ge.T. project: a regional program to reduce hip fracture in elderly patients. Main results of retrospective phase. *Clin Cases Miner Bone Metab.* Jan-Apr 2015;12(1):34-42.

55. Beraldi R, Masi L, Parri S, Partescano R, Brandi ML. The role of the orthopaedic surgeon in the prevention of refracture in patients treated surgically for fragility hip and vertebral fracture. *Clin Cases Miner Bone Metab.* Jan 2014;11(1):31-35.

56. Degli Esposti L, Sinigaglia L, Rossini M, et al. Adherence to therapeutic and diagnostic recommendations in patients with femur fracture and at risk of re-fracture or death: results of an analysis of administrative databases. *Reumatismo.* 2012;64(1):18-26.

57. National Office of Clinical Audit. Irish Hip Fracture Database (IHFD). https://www.noca.ie/audits. Accessed 7 March 2016.

58. Irish Medical Times. An undiagnosed and untreated condition. *Irish Medical Times* [http://www.imt.ie/clinical/2013/10/an-undiagnosed-and-untreated-condition.html. Accessed 8 March 2016.

59. Hoff M, Skurtveit S, Meyer HE, et al. Use of anti-osteoporotic drugs in central Norway after a forearm fracture. *Arch Osteoporos.* 2015;10:235.

60. Devold HM, Sogaard AJ, Tverdal A, Falch JA, Furu K, Meyer HE. Hip fracture and other predictors of anti-osteoporosis drug use in Norway. *Osteoporos Int.* Apr 2013;24(4):1225-1233.

61. Jonsson E, Eriksson D, Akesson K, et al. Swedish osteoporosis care. *Arch Osteoporos.* 2015;10:222.

62. Maier S, Sidelnikov E, Dawson-Hughes B, et al. Before and after hip fracture, vitamin D deficiency may not be treated sufficiently. *Osteoporos Int.* Nov 2013;24(11):2765-2773.

63. All Wales Osteoporosis Advisory Group. *All Wales Audit of Secondary Prevention of Osteoporotic Fractures 2012.* Aberystwyth 2012.

64. Bryson DJ, Nichols JS, Ford AJ, Williams SC. The incidence of vitamin D deficiency amongst patients with a femoral neck fracture: are current bone protection guidelines sufficient ? *Acta Orthop Belg.* Aug 2013;79(4):470-473.

65. Mettyas T, Carpenter C. Secondary prevention of osteoporosis in non-neck of femur fragility fractures: is it value for money? A retrospective, prospective and cross-sectional cohort study. *J Orthop Surg Res.* 2013;8:44.

66. Elvey MH, Pugh H, Schaller G, Dhotar G, Patel B, Oddy

MJ. Failure in the application of fragility fracture prevention guidelines. *Ann R Coll Surg Engl.* Jul 2014;96(5):381-385.

67. Klop C, Gibson-Smith D, Elders PJ, et al. Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000-2010. *Osteoporos Int.* Jul 2015;26(7):1919-1928.

68. Royal College of Physicians. Fracture Liaison Service Database (FLS-DB). https://www.rcplondon.ac.uk/projects/fracture-liaison-service-database-fls-db. Accessed 7 March 2016.

69. National Osteoporosis Society. The Falls and Fractures Alliance. https://www.nos.org.uk/about-us/public-affairs/falls-and-fractures-alliance. Accessed 7 March 2016.

70. Sadat-Ali M, Al-Omran A, Al-Bakr W, Azam MQ, Tantawy A, Al-Othman A. Established Osteoporosis and Gaps in the Management: Review from a Teaching hospital. *Ann Med Health Sci Res.* Mar 2014;4(2):198-201.

71. Leslie WD, Brennan SL, Prior HJ, Lix LM, Metge C, Elias B. The post-fracture care gap among Canadian First Nations peoples: a retrospective cohort study. *Osteoporos Int.* Mar 2012;23(3):929-936.

72. Leslie WD, Giangregorio LM, Yogendran M, et al. A population-based analysis of the post-fracture care gap 1996-2008: the situation is not improving. *Osteoporos Int.* May 2012;23(5):1623-1629.

73. Osteoporosis Canada. *Make the FIRST break the LAST with Fracture Liaison Services* 2013.

74. Osteoporosis Canada. *Quality Standards for Fracture Liaison Services in Canada.* Toronto: Osteoporosis Canada; 2014.

75. Guggina P, Flahive J, Hooven FH, et al. Characteristics associated with anti-osteoporosis medication use: data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) USA cohort. *Bone.* Dec 2012;51(6):975-980.

76. Shepherd AJ, Cass AR, Ray LA, Tan A, Wilkinson GS. Treatment for older men with fractures. *Osteoporos Int.* Mar 2012;23(3):1041-1051.

77. Liu SK, Munson JC, Bell JE, et al. Quality of osteoporosis care of older Medicare recipients with fragility fractures: 2006 to 2010. *J Am Geriatr Soc.* Nov 2013;61(11):1855-1862.

78. Antonelli M, Einstadter D, Magrey M. Screening and Treatment of Osteoporosis After Hip Fracture: Comparison of Sex and Race. *J Clin Densitom.* Mar 20 2014.

79. Balasubramanian A, Tosi LL, Lane JM, Dirschl DR, Ho PR, O'Malley CD. Declining rates of osteoporosis management following fragility fractures in the u.s., 2000 through 2009. *J Bone Joint Surg Am.* Apr 2 2014;96(7):e52.

80. Dirschl DR. Shame on us! Men need osteoporosis care, too! Commentary on an article by Carl M. Harper, MD, et al.: "Distal radial fractures in older men. A missed opportunity?". *J Bone Joint Surg Am.* Nov 5 2014;96(21):e186.

81. Harper CM, Fitzpatrick SK, Zurakowski D, Rozental TD. Distal radial fractures in older men. A missed opportunity? *J Bone Joint Surg Am.* Nov 5 2014;96(21):1820-1827.

82. National Committee for Quality Assurance. *The State of Health Care Quality Report 2014.* Washington D.C. 2014.

83. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis Medication Use after Hip Fracture in U.S. Patients between 2002 and 2011. *J Bone Miner Res.* Feb 18 2014.

84. Wilk A, Sajjan S, Modi A, Fan CP, Mavros P. Post-fracture pharmacotherapy for women with osteoporotic fracture: analysis of a managed care population in the USA. *Osteoporos Int.* Aug 12 2014.

85. Lee DB, Lowden MR, Patmintra V, Stevenson K. National Bone Health Alliance: an innovative public-private partnership improving America's bone health. *Curr Osteoporos Rep.* Dec 2013;11(4):348-353.

86. National Osteoporosis Foundation, National Bone Health Alliance, CECity. The NOF and NBHA Qualified Clinical Data Quality Improvement Registry (QCDR). https://www.medconcert.com/content/medconcert/FractureQIR/. Accessed 9 March 2016.

87. Mears SC, Kates SL. A Guide to Improving the Care of Patients with Fragility Fractures, Edition 2. *Geriatr Orthop Surg Rehabil.* Jun 2015;6(2):58-120.

88. Scarvell JM, Van Twest MS, Stanton SF, Burski G, Smith PN. Prevalence of undisclosed osteoporosis in patients with minimal trauma fractures: a prospective cohort study. *Phys Sportsmed.* May 2013;41(2):38-43.

89. Tulk C, Lane P, Gilbey A, et al. Improving osteoporosis management following minimal trauma fracture in a regional setting: The Coffs Fracture Card Project. *Aust J Rural Health.* Dec 2013;21(6):343-349.

90. Watts JJ, Abimanyi-Ochom J, Sanders KM. *Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022.* Glebe, NSW: Osteoporosis Australia; 2013.

91. Mitchell PJ, Ganda K, Seibel MJ. *Australian and New Zealand Bone and Mineral Society Position Paper on Secondary Fracture Prevention Programs.* In press 2015.

92. Health Quality and Safety Commission. Atlas of healthcare variation: Falls. http://www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/falls/. Accessed 2 April 2015.

93. Osteoporosis New Zealand. *Bone Care 2020: A systematic approach to hip fracture care and prevention for New Zealand.* Wellington 2012.

94. British Orthopaedic Association, British Geriatrics Society. *The care of patients with fragility fracture* 2007.

95. Australian and New Zealand Hip Fracture Registry (ANZHFR) Steering Group. *Australian and New Zealand Guideline for Hip Fracture Care: Improving Outcomes in Hip Fracture Management of Adults.* Sydney: Australian and New Zealand Hip Fracture Registry Steering Group; 2014.

96. Kates SL, Mears SC, Sieber F, et al. A Guide to Improving the Care of Patients with Fragility Fractures. *Geriatric Orthopaedic Surgery & Rehabilitation.* 2011;2(1):5-37.

97. Department of Health. Falls and fractures: Effective interventions in health and social care. In: Department of Health, ed; 2009.

98. New South Wales Agency for Clinical Innovation Musculoskeletal Network. NSW Model of Care for Osteoporotic Refracture Prevention. Chatswood, NSW; 2011.

99. National Osteoporosis Foundation. *The Surgeon General's Report: 10 years later.* Washington DC 2014.

100. Mitchell PJ, Cooper C, Dawson-Hughes B, Gordon CM, Rizzoli R. Life-course approach to nutrition. *Osteoporos Int.* Dec 2015;26(12):2723-2742.

101. Australian Commission on Safety and Quality in Health Care. *Preventing Falls and Harm From Falls in Older People: Best Practice Guidelines for Australian Hospitals* 2009.

102. Australian Commission on Safety and Quality in Health Care. *Preventing Falls and Harm From Falls in Older People: Best Practice Guidelines for Australian Residential Aged Care Facilities* 2009.

103. Australian Commission on Safety and Quality in Health Care. *Preventing Falls and Harm From Falls in Older People: Best Practice Guidelines for Australian Community Care* 2009.

104. Royal Australian College of General Practitioners, National Health and Medical Research Council. *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men.* Melbourne 2010.

105. New South Wales Agency for Clinical Innovation. *The Orthogeriatric Model of Care: Summary of Evidence 2010.* North Ryde 2010.

106. Statewide Orthopaedic Clinical Network and Rehabilitation Clinical Network. Models of Care for Orthopaedic Rehabilitation - Fragility Fractures General Orthopaedic Trauma and Arthroplasty. In: Government of South Australia, SA Health, eds. Adelaide; 2011.

107. Government of Western Australia. Orthogeriatric Model of Care. In: Department of Health Aged Care Network, ed. Perth; 2008.

108. Government of Western Australia. Falls Prevention Model of Care for the Older Person in Western Australia. In: Department of Health Falls Prevention Health Network, ed. Perth; 2008.

109. Government of Western Australia. Osteoporosis Model of Care. In: Department of Health Musculoskeletal Diabetes & Endocrine Falls Prevention and Aged Care Health Networks (WA), ed. Perth; 2011.

110. Seibel MJ. First National Forum on Secondary Fracture Prevention; 20 November 2015, 2015; Rydges Hotel, Sydney Airport, Sydney, NSW.

111. Australian and New Zealand BOne and Mineral Society. Secondary Fracture Prevention Program Initiative. http://www.fragilityfracture.org.au/. Accessed 21 March 2016.

112. Mitchell PJ, Cornish J, Milsom S, et al. BoneCare 2020: A systematic approach to hip fracture care and prevention for New Zealand. *3rd Fragility Fracture Network Congress 2014*. Madrid, Spain.; 2014.

113. Osteoporosis New Zealand. *Fracture Liaison Services Resource Pack.* Wellington: Osteoporosis New Zealand; 2014.

114. Australian Commission on Safety and Quality in Health Care, Health Quality & Safety Commission. *Draft Hip Fracture Care Clinical Care Standard.* Canberra 2015.

115. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ.* Nov 23 2010;182(17):1864-1873.

116. Suzuki A. [Osteoporosis liaison service]. *Nihon Rinsho.* Oct 2015;73(10):1765-1769.

117. Chandran M, Tan MZ, Cheen M, Tan SB, Leong M, Lau TC. Secondary prevention of osteoporotic fractures--an "OPTIMAL" model of care from Singapore. *Osteoporos Int.* Nov 2013;24(11):2809-2817.

118. National Institute for Health and Clinical Excellence. *Denosumab for the prevention of osteoporotic fractures in postmenopausal women: NICE Technology Appraisal Guidance 204.* 2010.

119. National Institute for Health and Clinical Excellence. *Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance 161 (amended).* 2011.

120. National Institute for Health and Clinical Excellence. *Hip fracture: The management of hip fracture in adults. NICE Clinical Guideline 124.* 2011.

121. National Institute for Health and Clinical Excellence. *Osteoporosis: assessing the risk of fragility fracture. NICE clinical guideline 146.* London 2012.

122. National Institute for Health and Clinical Excellence. *Quality standard for hip fracture care. NICE Quality Standard 16.* London, England. 2012.

123. National Institute for Health and Clinical Excellence. *Falls: assessment and prevention of falls in older people. NICE clinical guideline 161.* London 2013.

124. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. *Maturitas.* Aug 2013;75(4):392-396.

125. Royal College of Physicians. *National Hip Fracture Database (NHFD) annual report 2015.* London 2015.

126. Department of Health. Fracture prevention services: an economic evaluation.; 2009.

127. BMA, NHS Employers, NHS England. *2015/16 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): Guidance for GMS contract 2015/16.* London 2015.

128. Chamberlain M, Pugh H. Improving inpatient care with the introduction of a hip fracture pathway. *BMJ Qual Improv Rep.* 2015;4(1).

129. British Orthopaedic Association. *BOAST 1 (version 2): Hip fracture.* London 2012.

130. British Orthopaedic Association, National Osteoporosis Society. *BOAST 9: Fracture Liaison Services.* London 2014.

131. Gittoes N, McLellan AR, Cooper A, et al. *Effective Secondary Prevention of Fragility Fractures: Clinical Standards for Fracture Liaison Services.* Camerton: National Osteoporosis Society; 2015.

132. National Osteoporosis Society. Fracture Liaison Service Implementation Toolkit. https://www.nos.org.uk/health-professionals/fracture-liaison-service/implementation-toolkit. Accessed 8 March 2016.

133. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* Jun 2012;97(6):1802-1822.

134. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* Oct 2014;25(10):2359-2381.

135. National Coalition for Osteoporosis and Other Bone Diseases. *National Action Plan on Bone Health: Recommendations from the Summit for a National Plan on Bone Health.* Washington DC 2008.

136. National Bone Health Alliance. 2Million2Many. http://www.2million2many.org/. Accessed 8 March 2016.

137. National Bone Health Alliance. Fracture Prevention CENTRAL. http://www.nbha.org/fpc. Accessed 8 March 2016.

138. National Quality Forum. NQF-Endorsed Measures for Endocrine Conditions Final Report. http://www.qualityforum.org/Publications/2015/11/NQF-Endorsed_Measures_for_Endocrine_Conditions_Final_Report.aspx. Accessed 8 March 2016.

139. National Osteoporosis Foundation. Fracture Liaison Service Pathway Certificate Program. http://nof.org/ISO-FLS/fls-program. Accessed 8 March 2016.

140. Akesson K, Marsh D, Mitchell PJ, et al. Capture the Fracture: a Best Practice Framework and global campaign

to break the fragility fracture cycle. *Osteoporos Int.* Aug 2013;24(8):2135-2152.

141. Javaid MK, Kyer C, Mitchell PJ, et al. Effective secondary fracture prevention: implementation of a global benchmarking of clinical quality using the IOF Capture the Fracture(R) Best Practice Framework tool. *Osteoporos Int.* Nov 2015;26(11):2573-2578.

142. International Osteoporosis Foundation. Map of best practice. http://www.capture-the-fracture.org/map-of-best-practice. Accessed 8 March 2014.

143. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. *Ther Adv Musculoskelet Dis.* Oct 2014;6(5):185-202.

144. Henneicke H, Gasparini SJ, Brennan-Speranza TC, Zhou H, Seibel MJ. Glucocorticoids and bone: local effects and systemic implications. *Trends Endocrinol Metab.* Apr 2014;25(4):197-211.

145. Albaum JM, Youn S, Levesque LE, Gershon AS, Cadarette SM. Osteoporosis management among chronic glucocorticoid users: a systematic review. *J Popul Ther Clin Pharmacol.* 2014;21(3):e486-504.

146. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int.* Oct 2007;18(10):1319-1328.

147. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res.* Jun 2004;19(6):893-899.

148. Rintelen B, Bobacz K, Hofle G, et al. [Prophylaxis and therapy of the glucocorticoid-induced osteoporosis - a review of recent guidelines]. *Wien Klin Wochenschr.* Nov 2011;123(21-22):633-644.

149. Sambrook PN, Diamond T, Ferris L, et al. Corticosteroid induced osteoporosis. Guidelines for treatment. *Aust Fam Physician.* Aug 2001;30(8):793-796.

150. Devogelaer JP, Goemaere S, Boonen S, et al. Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. *Osteoporos Int.* Jan 2006;17(1):8-19.

151. Pereira RM, Carvalho JF, Paula AP, et al. Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. *Rev Bras Reumatol.* Aug 2012;52(4):580-593.

152. Briot K, Cortet B, Roux C, et al. 2014 update of recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis. *Joint Bone Spine.* Dec 2014;81(6):493-501.

153. Suzuki Y, Nawata H, Soen S, et al. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. *J Bone Miner Metab.* Jul 2014;32(4):337-350.

154. Geusens PP, de Nijs RN, Lems WF, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. *Ann Rheum Dis.* Mar 2004;63(3):324-325.

155. Sosa Henriquez M, Diaz Curiel M, Diez Perez A, et al. [Guide for the prevention and treatment of glucocorticoid-induced osteoporosis of the Spanish Society of Internal Medicine]. *Rev Clin Esp.* Jan 2008;208(1):33-45.

156. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken).* Nov 2010;62(11):1515-1526.

157. Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis.* Dec 2013;72(12):1905-1913.

158. Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporos Int.* Sep 2012;23(9):2257-2276.

159. Gudbjornsson B, Juliusson UI, Gudjonsson FV. Prevalence of long term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Ann Rheum Dis.* Jan 2002;61(1):32-36.

160. Buckley LM, Marquez M, Feezor R, Ruffin DM, Benson LL. Prevention of corticosteroid-induced osteoporosis: results of a patient survey. *Arthritis Rheum.* Aug 1999;42(8):1736-1739.

161. Hougardy DM, Peterson GM, Bleasel MD, Randall CT. Is enough attention being given to the adverse effects of corticosteroid therapy? *J Clin Pharm Ther.* Jun 2000;25(3):227-234.

162. Naunton M, Peterson GM, Jones G, Griffin GM, Bleasel MD. Multifaceted educational program increases prescribing of preventive medication for corticosteroid induced osteoporosis. *J Rheumatol.* Mar 2004;31(3):550-556.

163. Newman ED, Matzko CK, Olenginski TP, et al. Glucocorticoid-Induced Osteoporosis Program (GIOP): a novel, comprehensive, and highly successful care program with improved outcomes at 1 year. *Osteoporos Int.* 2006;17(9):1428-1434.

164. Stangelberger A, Waldert M, Djavan B. Prostate cancer in elderly men. *Rev Urol.* Spring 2008;10(2):111-119.

165. Damji AN, Bies K, Alibhai SM, Jones JM. Bone health management in men undergoing ADT: examining enablers and barriers to care. *Osteoporos Int.* Mar 2015;26(3):951-959.

166. Lassemillante AC, Doi SA, Hooper JD, Prins JB, Wright OR. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. *Endocrine.* Apr 2014;45(3):370-381.

167. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab.* Aug 2002;87(8):3656-3661.

168. Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol.* Nov 1 2005;23(31):7897-7903.

169. Grossmann M, Hamilton EJ, Gilfillan C, Bolton D, Joon DL, Zajac JD. Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. *Med J Aust.* Mar 21 2011;194(6):301-306.

170. Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer -- a consensus paper of the Belgian Bone Club. *Osteoporos Int.* Nov 2007;18(11):1439-1450.

171. Duncan GG, Corbett T, Lukka H, Warde P, Pickles T. GU radiation oncologists consensus on bone loss from androgen deprivation. *Can J Urol.* Feb 2006;13(1):2962-2966.

172. National Institute for Health and Care Excellence. *NICE Clinical Guideline 175: Prostate cancer: diagnosis and management.* London 2014.

173. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. *J Natl Compr Canc Netw.* Aug 2013;11 Suppl 3:S1-50; quiz S51.

174. Resnick MJ, Lacchetti C, Bergman J, et al. Prostate cancer survivorship care guideline: American Society of Clinical Oncology Clinical Practice Guideline endorsement. *J Clin Oncol.* Mar 20 2015;33(9):1078-1085.

175. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J, Group EGW. Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.* Sep 2014;25 Suppl 3:iii124-137.

176. Panju AH, Breunis H, Cheung AM, et al. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. *BJU Int.* Mar 2009;103(6):753-757.

177. Van Tongeren LS, Duncan GG, Kendler DL, Pai H. Implementation of osteoporosis screening guidelines in prostate cancer patients on androgen ablation. *J Clin Densitom.* Jul-Sep 2009;12(3):287-291.

178. Al-Shamsi HO, Lau AN, Malik K, et al. The current practice of screening, prevention, and treatment of androgen-deprivation-therapy induced osteoporosis in patients with prostate cancer. *J Oncol.* 2012;2012:958596.

179. Pradhan MR, Mandhani A, Chipde SS, Srivastava A, Singh M, Kapoor R. Bone densitometric assessment and management of fracture risk in Indian men of prostate cancer on androgen deprivation therapy: Does practice pattern match the guidelines? *Indian J Urol.* Oct 2012;28(4):399-404.

180. Yee EF, White RE, Murata GH, Handanos C, Hoffman RM. Osteoporosis management in prostate cancer patients treated with androgen deprivation therapy. *J Gen Intern Med.* Sep 2007;22(9):1305-1310.

181. Dhanapal V, Reeves DJ. Bone health management in prostate cancer patients receiving androgen deprivation therapy. *J Oncol Pharm Pract.* Mar 2012;18(1):84-90.

182. Morgans AK, Smith MR, O'Malley AJ, Keating NL. Bone density testing among prostate cancer survivors treated with androgen-deprivation therapy. *Cancer.* Feb 15 2013;119(4):863-870.

183. Suarez-Almazor ME, Peddi P, Luo R, Nguyen HT, Elting LS. Low rates of bone mineral density measurement in Medicare beneficiaries with prostate cancer initiating androgen deprivation therapy. *Support Care Cancer.* Feb 2014;22(2):537-544.

184. Zhumkhawala AA, Gleason JM, Cheetham TC, et al. Osteoporosis management program decreases incidence of hip fracture in patients with prostate cancer receiving androgen deprivation therapy. *Urology.* May 2013;81(5):1010-1015.

185. McGuire A, Brown JA, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. *Cancers (Basel).* 2015;7(2):908-929.

186. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol.* Jan 20 2010;28(3):509-518.

187. Rizzoli R, Body JJ, DeCensi A, et al. Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper. *Osteoporos Int.* Nov 2012;23(11):2567-2576.

188. Chen Z, Maricic M, Bassford TL, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. *Arch Intern Med.* Mar 14 2005;165(5):552-558.

189. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* Dec 2010;11(12):1135-1141.

190. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol.* Feb 10 2007;25(5):486-492.

191. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. *J Clin Oncol.* Apr 10 2013;31(11):1398-1404.

192. Xiu B-H, Consensus Expert Group For Prevention D, Treatment Of Bone L, Osteoporosis In Postmenopausal Breast Cancer Patients After Aromatase Inhibitor T. [Expert group consensus: prevention, diagnosis and treatment of bone loss and osteoporosis in postmenopausal breast cancer patients after aromatase inhibitor therapy]. *Zhonghua Zhong Liu Za Zhi.* Nov 2013;35(11):876-879.

193. Dachverband Osteologie. *DVO guideline 2009 for prevention, diagnosis and therapy of osteoporosis in adults* 2014.

194. Vescini F, Attanasio R, Balestrieri A, et al. Italian association of clinical endocrinologists (AME) position statement: drug therapy of osteoporosis. *J Endocrinol Invest.* Mar 11 2016.

195. Juozaityte E, Aleknavicius E, Janciauskiene R, et al. Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer: a consensus of Lithuanian medical oncologists, radiation oncologists, endocrinologists, and family medicine physicians. *Medicina (Kaunas).* 2014;50(4):197-203.

196. Reid DM, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. *Cancer Treat Rev.* 2008;34 Suppl 1:S3-18.

197. Dolan AL, Mohammed M, Thakur K. Novel way to implement bone assessment guidelines to identify and manage patients receiving aromatase inhibitors using FITOS software. *Osteoporos Int.* 2007;18(Suppl 3):S282-S283. Abstract P242A.

198. Tham YL, Sexton K, Weiss HL, Elledge RM, Friedman LC, Kramer RM. The adherence to practice guidelines in the assessment of bone health in women with chemotherapy-induced menopause. *J Support Oncol.* Jun 2006;4(6):295-298, 304.

199. Gibson K, O'Bryant CL. Screening and management of osteoporosis in breast cancer patients on aromatase inhibitors. *J Oncol Pharm Pract.* Sep 2008;14(3):139-145.

200. Spangler L, Yu O, Loggers E, Boudreau DM. Bone mineral density screening among women with a history of breast cancer treated with aromatase inhibitors. *J Womens Health (Larchmt).* Feb 2013;22(2):132-140.

201. Giusti F, Ottanelli S, Masi L, Amedei A, Brandi ML, Falchetti A. Construction of a database for the evaluation and the clinical management of patients with breast cancer treated with antiestrogens and/or aromatase inhibitors. *Clin Cases Miner Bone Metab.* Jan 2011;8(1):37-50.

202. National Osteoporosis Foundation. Diseases and Conditions that May Cause Bone Loss. http://nof.org/articles/5. Accessed 14 March 2016.

203. World Health Organization. Chronic respiratory diseases: Burden of COPD. http://www.who.int/respiratory/copd/burden/en/. Accessed 14 March 2016.

204. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* Oct 15 2002;156(8):738-746.

205. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J.* Jul 2009;34(1):209-218.

206. Leech JA, Dulberg C, Kellie S, Pattee L, Gay J. Relationship of lung function to severity of osteoporosis in women. *Am Rev Respir Dis.* Jan 1990;141(1):68-71.

207. Regan EA, Radcliff TA, Henderson WG, et al. Improving hip fractures outcomes for COPD patients. *COPD.* Feb 2013;10(1):11-19.

208. Graat-Verboom L, Spruit MA, van den Borne BE, et al. Correlates of osteoporosis in chronic obstructive pulmonary disease: An underestimated systemic component. *Respir Med.* Aug 2009;103(8):1143-1151.

209. Graat-Verboom L, van den Borne BE, Smeenk FW, Spruit MA, Wouters EF. Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. *J Bone Miner Res.* Mar 2011;26(3):561-568.

210. Romme EA, Geusens P, Lems WF, et al. Fracture prevention in COPD patients; a clinical 5-step approach. *Respir Res.* 2015;16:32.

211. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology.* Dec 2006;131(6):1981-2002.

212. World IBD Day. Inflammatory Bowel Disease: World IBD Day - 19 May. http://worldibdday.org/. Accessed 15 March 2016.

213. Stazi AV, Trecca A, Trinti B. Osteoporosis in celiac disease and in endocrine and reproductive disorders. *World J Gastroenterol.* Jan 28 2008;14(4):498-505.

214. Schoon EJ, van Nunen AB, Wouters RS, Stockbrugger RW, Russel MG. Osteopenia and osteoporosis in Crohn's disease: prevalence in a Dutch population-based cohort. *Scand J Gastroenterol Suppl.* 2000(232):43-47.

215. Siffledeen JS, Fedorak RN, Siminoski K, et al. Bones and Crohn's: risk factors associated with low bone mineral density in patients with Crohn's disease. *Inflamm Bowel Dis.* May 2004;10(3):220-228.

216. West J, Logan RF, Card TR, Smith C, Hubbard R. Fracture risk in people with celiac disease: a population-based cohort study. *Gastroenterology.* Aug 2003;125(2):429-436.

217. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. *Ann Intern Med.* Nov 21 2000;133(10):795-799.

218. Kirchgatterer A, Wenzl HH, Aschl G, et al. Examination, prevention and treatment of osteoporosis in patients with inflammatory bowel disease: recommendations and reality. *Acta Med Austriaca.* 2002;29(4):120-123.

219. Etzel JP, Larson MF, Anawalt BD, Collins J, Dominitz JA. Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. *Inflamm Bowel Dis.* Oct 2011;17(10):2122-2129.

220. Fouda MA, Khan AA, Sultan MS, Rios LP, McAssey K, Armstrong D. Evaluation and management of skeletal health in celiac disease: position statement. *Can J Gastroenterol.* Nov 2012;26(11):819-829.

221. Pfeilschifter J. [Diagnosing osteoporosis: what is new in the 2014 DVO guideline?]. *Dtsch Med Wochenschr.* Nov 2015;140(22):1667-1671.

222. British Society of Gastroenterology. *Guidelines for osteoporosis in inflammatory bowel disease and coeliac disease* 2007.

223. American Gastroenterological Association (AGA) Committee on Osteoporosis in Gastrointestinal Disease. American Gastroenterological Association medical position statement: guidelines on osteoporosis in gastrointestinal diseases. *Gastroenterology.* Mar 2003;124(3):791-794.

224. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. *Gastroenterology.* Mar 2003;124(3):795-841.

225. Bernstein CN, Katz S. *Guidelines for osteoporosis and inflammatory bowel disease. A guide to diagnosis and management for the gastroenterologist (monograph).* American College of Gastroenterology; 2003.

226. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet.* Sep 25 2010;376(9746):1094-1108.

227. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2012;380(9859):2095-2128.

228. Lodder MC, de Jong Z, Kostense PJ, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. *Ann Rheum Dis.* Dec 2004;63(12):1576-1580.

229. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum.* Oct 2006;54(10):3104-3112.

230. Broy SB, Tanner SB, Members FRDC. Official Positions for FRAX(R) clinical regarding rheumatoid arthritis from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). *J Clin Densitom.* Jul-Sep 2011;14(3):184-189.

231. Caplan L, Hines AE, Williams E, et al. An observational study of glucocorticoid-induced osteoporosis prophylaxis in a national cohort of male veterans with rheumatoid arthritis. *Osteoporos Int.* Jan 2011;22(1):305-315.

232. Watt J, Thompson A, Le Riche N, Pope J. There is still a care gap in osteoporosis management for patients with rheumatoid arthritis. *Joint Bone Spine.* Jul 2014;81(4):347-351.

233. Roussy JP, Bessette L, Bernatsky S, Rahme E, Lachaine J. Rates of non-vertebral osteoporotic fractures in rheumatoid arthritis and postfracture osteoporosis care in a period of evolving clinical practice guidelines. *Calcif Tissue Int.* Jul 2014;95(1):8-18.

234. Hamalainen H, Kautiainen H, Pohjolainen T, Virta L, Jarvenpaa S, Puolakka K. Use of osteoporosis drugs in patients with recent-onset rheumatoid arthritis in Finland. *Clin Exp Rheumatol.* Sep-Oct 2011;29(5):835-838.

235. Heberlein I, Demary W, Bloching H, et al. [Diagnosis and treatment of osteoporosis and rheumatoid arthritis in accordance with German guidelines. Results of a survey of patients, primary care physicians and rheumatologists]. *Z Rheumatol.* Sep 2011;70(7):592-601.

236. Gamez-Nava JI, Zavaleta-Muniz SA, Vazquez-Villegas

ML, et al. Prescription for antiresorptive therapy in Mexican patients with rheumatoid arthritis: is it time to reevaluate the strategies for osteoporosis prevention? *Rheumatol Int.* Jan 2013;33(1):145-150.

237. Lee JH, Sung YK, Choi CB, et al. The frequency of and risk factors for osteoporosis in Korean patients with rheumatoid arthritis. *BMC Musculoskelet Disord.* 2016;17(1):98.

238. Solomon DH, Katz JN, Cabral D, Patrick AR, Bukowski JF, Coblyn JS. Osteoporosis management in patients with rheumatoid arthritis: Evidence for improvement. *Arthritis Rheum.* Dec 15 2006;55(6):873-877.

239. Ledwich LJ, Clarke K. Screening and treatment of glucocorticoid-induced osteoporosis in rheumatoid arthritis patients in an urban multispecialty practice. *J Clin Rheumatol.* Mar 2009;15(2):61-64.

240. Pereira IA, Mota LM, Cruz BA, et al. 2012 Brazilian Society of Rheumatology Consensus on the management of comorbidities in patients with rheumatoid arthritis. *Rev Bras Reumatol.* Aug 2012;52(4):474-495.

241. Hodkinson B, Van Duuren E, Pettipher C, Kalla A, South African R, Arthritis A. South African recommendations for the management of rheumatoid arthritis: an algorithm for the standard of care in 2013. *S Afr Med J.* Aug 2013;103(8 Pt 2):576-585.

242. Loza E, Lajas C, Andreu JL, et al. Consensus statement on a framework for the management of comorbidity and extra-articular manifestations in rheumatoid arthritis. *Rheumatol Int.* Mar 2015;35(3):445-458.

243. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of A. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab.* Feb 2001;86(2):724-731.

244. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med.* Aug 12 2013;173(15):1465-1466.

245. Seftel AD, Kathrins M, Niederberger C. Critical Update of the 2010 Endocrine Society Clinical Practice Guidelines for Male Hypogonadism: A Systematic Analysis. *Mayo Clin Proc.* Aug 2015;90(8):1104-1115.

246. Isidori AM, Balercia G, Calogero AE, et al. Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology. *J Endocrinol Invest.* Jan 2015;38(1):103-112.

247. Alzheimer's Disease International. *Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050.* London, UK 2013.

248. Wimo A, Prince M. *World Alzheimer Report 2010: The Global Economic Impact of Dementia.* London, UK: Alzheimer's Disease International; 2010.

249. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One.* 2009;4(5):e5521.

250. Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. *Age Ageing.* Jan 2011;40(1):49-54.

251. Seitz DP, Adunuri N, Gill SS, Rochon PA. Prevalence of Dementia and Cognitive Impairment Among Older Adults With Hip Fractures. *Journal of the American Medical Directors Association.* Mar 7 2011.

252. NHS National Services Scotland. *Scottish Hip Fracture Audit Rehabilitation Report 2007.* 2007.

253. Mitchell PJ, Bateman K. *Dementia, falls and fractures: Integrated approaches to improve quality and reduce costs.* Camberley, UK 2012.

254. Knopp-Sihota JA, Cummings GG, Newburn-Cook CV, Homik J, Voaklander D. Dementia diagnosis and osteoporosis treatment propensity: a population-based nested case-control study. *Geriatr Gerontol Int.* Jan 2014;14(1):121-129.

255. Tiihonen M, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S. Incidence and Duration of Cumulative Bisphosphonate Use among Community-Dwelling Persons with or without Alzheimer's Disease. *J Alzheimers Dis.* Mar 1 2016.

256. Gleason LJ, Menzies IB, Mendelson DA, Kates SL, Friedman SM. Diagnosis and treatment of osteoporosis in high-risk patients prior to hip fracture. *Geriatr Orthop Surg Rehabil.* Jun 2012;3(2):79-83.

257. International Diabetes Federation. *IDF Diabetes Atlas Seventh Edition.* Brussels, Belgium 2015.

258. Evans JM, Newton RW, Ruta DA, MacDonald TM, Morris AD. Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabet Med.* Jun 2000;17(6):478-480.

259. Boyle JP, Engelgau MM, Thompson TJ, et al. Estimating prevalence of type 1 and type 2 diabetes in a population of African Americans with diabetes mellitus. *Am J Epidemiol.* Jan 1 1999;149(1):55-63.

260. Bruno G, Runzo C, Cavallo-Perin P, et al. Incidence of type 1 and type 2 diabetes in adults aged 30-49 years: the population-based registry in the province of Turin, Italy. *Diabetes Care.* Nov 2005;28(11):2613-2619.

261. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. *Diabet Med.* Sep 2015;32(9):1119-1120.

262. Lee NK, Sowa H, Hinoi E, et al. Endocrine regulation of energy metabolism by the skeleton. *Cell.* Aug 10 2007;130(3):456-469.

263. Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. *Proc Natl Acad Sci U S A.* Apr 1 2008;105(13):5266-5270.

264. Booth SL, Centi A, Smith SR, Gundberg C. The role of osteocalcin in human glucose metabolism: marker or mediator? *Nat Rev Endocrinol.* Jan 2013;9(1):43-55.

265. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. *Osteoporos Int.* Apr 2007;18(4):427-444.

266. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol.* Sep 1 2007;166(5):495-505.

267. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur J Epidemiol.* May 2012;27(5):319-332.

268. Shanbhogue VV, Mitchell DM, Rosen CJ, Bouxsein ML. Type 2 diabetes and the skeleton: new insights into sweet bones. *Lancet Diabetes Endocrinol.* Feb 2016;4(2):159-173.

269. Sosa Henriquez M, Saavedra Santana P, grupo de trabajo en osteoporosis de la Sociedad Espanola de Medicina I. [Prevalence of vertebral fractures in hip fracture patients]. *Rev Clin Esp.* Oct 2007;207(9):464-468.

270. Imai N, Endo N, Hoshino T, Suda K, Miyasaka D, Ito T. Mortality after hip fracture with vertebral compression fracture is poor. *J Bone Miner Metab.* Dec 14 2014.

271. Delmas PD, van de Langerijt L, Watts NB, et al. Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. *J Bone Miner Res.* Apr 2005;20(4):557-563.

272. Mitchell PJ, Dolan L, Sahota O, et al. *Breaking Point Report 2015.* London: Breaking Point Editorial Board; 2015.

273. Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med.* May 15 1998;128(10):793-800.

274. Lips P, Cooper C, Agnusdei D, et al. Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporos Int.* 1999;10(2):150-160.

275. Gold DT. The nonskeletal consequences of osteoporotic fractures. Psychologic and social outcomes. *Rheum Dis Clin North Am.* Feb 2001;27(1):255-262.

276. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T. The association of bone mineral density and depression in an older population. *J Am Geriatr Soc.* Jun 2001;49(6):732-736.

277. Lyles KW. Osteoporosis and depression: shedding more light upon a complex relationship. *J Am Geriatr Soc.* Jun 2001;49(6):827-828.

278. Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ, 3rd. Impact of hip and vertebral fractures on quality-adjusted life years. *Osteoporos Int.* Dec 2001;12(12):1042-1049.

279. Hall SE, Criddle RA, Comito TL, Prince RL. A case-control study of quality of life and functional impairment in women with long-standing vertebral osteoporotic fracture. *Osteoporos Int.* 1999;9(6):508-515.

280. Adachi JD, Ioannidis G, Olszynski WP, et al. The impact of incident vertebral and non-vertebral fractures on health related quality of life in postmenopausal women. *BMC Musculoskelet Disord.* Apr 22 2002;3:11.

281. Abimanyi-Ochom J, Watts JJ, Borgstrom F, et al. Changes in quality of life associated with fragility fractures: Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS). *Osteoporos Int.* Jun 2015;26(6):1781-1790.

282. Tarride JE, Burke N, Leslie WD, et al. Loss of health related quality of life following low-trauma fractures in the elderly. *BMC Geriatr.* 2016;16(1):84.

283. Roux C, Wyman A, Hooven FH, et al. Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *Osteoporos Int.* Dec 2012;23(12):2863-2871.

284. Shepstone L, Fordham R, Lenaghan E, et al. A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening older women for the prevention of fractures: rationale, design and methods for the SCOOP study. *Osteoporos Int.* Oct 2012;23(10):2507-2515.

285. National Institute for Health and Clinical Excellence. *Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance 160 (amended).* 2011.

286. National Institute for Health and Clinical Excellence. *Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Technology appraisal guidance 87.* 2005.

287. Dell R, Greene D, Schelkun SR, Williams K. Osteoporosis disease management: the role of the orthopaedic surgeon. *J Bone Joint Surg Am.* Nov 2008;90 Suppl 4:188-194.

288. Olenginski TP, Maloney-Saxon G, Matzko CK, et al. High-risk osteoporosis clinic (HiROC): improving osteoporosis and postfracture care with an organized, programmatic approach. *Osteoporos Int.* Feb 2015;26(2):801-810.

289. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am J Hypertens.* Nov 2006;19(11):1190-1196.

290. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol.* Oct 2014;78(4):684-698.

291. Seeman E, Compston J, Adachi J, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. *Osteoporos Int.* Jun 2007;18(6):711-719.

292. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med.* Feb 2009;122(2 Suppl):S3-13.

293. Hiligsmann M, Salas M, Hughes DA, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. *Osteoporos Int.* Dec 2013;24(12):2907-2918.

294. Cooper A, Drake J, Brankin E, Investigators P. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract.* Aug 2006;60(8):896-905.

295. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* Jan 2012;23(1):317-326.

296. Kendler DL, McClung MR, Freemantle N, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. *Osteoporos Int.* Jun 2011;22(6):1725-1735.

297. Hill DA, Cacciatore M, Lamvu GM. Electronic prescribing influence on calcium supplementation: a randomized controlled trial. *Am J Obstet Gynecol.* Mar 2010;202(3):236 e231-235.

298. Montori VM, Shah ND, Pencille LJ, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. *Am J Med.* Jun 2011;124(6):549-556.

299. Nielsen D, Ryg J, Nielsen W, Knold B, Nissen N, Brixen K. Patient education in groups increases knowledge of osteoporosis and adherence to treatment: a two-year randomized controlled trial. *Patient Educ Couns.* Nov 2010;81(2):155-160.

300. Shu AD, Stedman MR, Polinski JM, et al. Adherence to osteoporosis medications after patient and physician brief education: post hoc analysis of a randomized controlled trial. *Am J Manag Care.* Jul 2009;15(7):417-424.

301. Solomon DH, Iversen MD, Avorn J, et al. Osteoporosis

telephonic intervention to improve medication regimen adherence: a large, pragmatic, randomized controlled trial. *Arch Intern Med.* Mar 26 2012;172(6):477-483.

302. Yuksel N, Majumdar SR, Biggs C, Tsuyuki RT. Community pharmacist-initiated screening program for osteoporosis: randomized controlled trial. *Osteoporos Int.* Mar 2010;21(3):391-398.

303. Boudou L, Gerbay B, Chopin F, Ollagnier E, Collet P, Thomas T. Management of osteoporosis in fracture liaison service associated with long-term adherence to treatment. *Osteoporos Int.* Jul 2011;22(7):2099-2106.

304. Eekman DA, van Helden SH, Huisman AM, et al. Optimizing fracture prevention: the fracture liaison service, an observational study. *Osteoporos Int.* Feb 2014;25(2):701-709.

305. Ganda K, Schaffer A, Pearson S, Seibel MJ. Compliance and persistence to oral bisphosphonate therapy following initiation within a secondary fracture prevention program: a randomised controlled trial of specialist vs. non-specialist management. *Osteoporos Int.* Apr 2014;25(4):1345-1355.

306. Dehamchia-Rehailia N, Ursu D, Henry-Desailly I, Fardellone P, Paccou J. Secondary prevention of osteoporotic fractures: evaluation of the Amiens University Hospital's fracture liaison service between January 2010 and December 2011. *Osteoporos Int.* Oct 2014;25(10):2409-2416.

307. Chandran M, Cheen M, Ying H, Lau TC, Tan M. Dropping the Ball and Falling Off the Care Wagon. Factors Correlating With Nonadherence to Secondary Fracture Prevention Programs. *J Clin Densitom.* Jan 2016;19(1):117-124.

308. Feldstein AC, Schneider J, Smith DH, et al. Harnessing stakeholder perspectives to improve the care of osteoporosis after a fracture. *Osteoporos Int.* Nov 2008;19(11):1527-1540.

309. Giangregorio L, Thabane L, Cranney A, et al. Osteoporosis knowledge among individuals with recent fragility fracture. *Orthop Nurs.* Mar-Apr 2010;29(2):99-107.

310. Berry SD, Misra D, Hannan MT, Kiel DP. Low acceptance of treatment in the elderly for the secondary prevention of osteoporotic fracture in the acute rehabilitation setting. *Aging Clin Exp Res.* Jun 2010;22(3):231-237.

311. Douglas F, Petrie KJ, Cundy T, Horne A, Gamble G, Grey A. Differing perceptions of intervention thresholds for fracture risk: a survey of patients and doctors. *Osteoporos Int.* Aug 2012;23(8):2135-2140.

312. Siris ES, Gehlbach S, Adachi JD, et al. Failure to perceive increased risk of fracture in women 55 years and older: the Global Longitudinal Study of Osteoporosis in Women (GLOW). *Osteoporos Int.* Jan 2011;22(1):27-35.

313. National Committee for Quality Assurance. *The State of Health Care Quality 2015.* Washington D.C. 2015.

314. Ulmner M, Jarnbring F, Torring O. Osteonecrosis of the jaw in Sweden associated with the oral use of bisphosphonate. *J Oral Maxillofac Surg.* Jan 2014;72(1):76-82.

315. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res.* Jan 2015;30(1):3-23.

316. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: a meta-analysis. *PLoS One.* 2015;10(4):e0122646.

317. Dell RM, Adams AL, Greene DF, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. *J Bone Miner Res.* Dec 2012;27(12):2544-2550.

318. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. *J Bone Miner Res.* Aug 2013;28(8):1729-1737.

319. Kim SC, Kim DH, Mogun H, et al. Impact of the US Food and Drug Administration's Safety-Related Announcements on the Use of Bisphosphonates after Hip Fracture. *J Bone Miner Res.* Mar 11 2016.

320. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med.* May 13 2010;362(19):1761-1771.

321. Abrahamsen B. Older women who use bisphosphonate for longer than 5 years may have increased odds of a subtrochanteric or femoral shaft fracture, but absolute risk is low. *Evid Based Med.* Dec 2011;16(6):168-169.

322. Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis. *N Engl J Med.* Jan 21 2016;374(3):254-262.

323. Reyes C, Hitz M, Prieto-Alhambra D, Abrahamsen B. Risks and Benefits of Bisphosphonate Therapies. *J Cell Biochem.* Jan 2016;117(1):20-28.

324. International Osteoporosis Foundation. *The Asia-Pacific Regional Audit: Epidemiology, costs and burden of osteoporosis in 2013.* Nyon, Switzerland 2013.

325. International Osteoporosis Foundation. *The Eastern European & Central Asian Regional Audit: Epidemiology, costs & burden of osteoporosis in 2010* 2011.

326. Kanis JA, Borgstrom F, Compston J, et al. SCOPE: a scorecard for osteoporosis in Europe. *Arch Osteoporos.* Dec 2013;8(1-2):144.

327. Svedbom A, Hernlund E, Ivergard M, et al. Osteoporosis in the European Union: a compendium of country-specific reports. *Arch Osteoporos.* Dec 2013;8(1-2):137.

328. International Osteoporosis Foundation. *The Latin America Regional Audit: Epidemiology, costs & burden of osteoporosis in 2012.* Nyon, Switzerland 2012.

329. International Osteoporosis Foundation. *The Middle East & Africa Regional Audit: Epidemiology, costs & burden of osteoporosis in 2011* 2011.

330. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. *Osteoporos Int.* Mar 2005;16(3):229-238.

331. Osteoporosis Canada. Essential Elements of Fracture Liaison Services (FLS). http://www.osteoporosis.ca/fls/wp-content/uploads/Osteoporosis-Canada-Essential-Elements-of-an-FLS.pdf. Accessed 6 May 2016.

CALL TO ACTION

The ten care gaps described in this report, together with their associated solutions, provide a new Global Framework for tackling the impending catastrophic burden that will be placed on the world's population and economy by fragility fractures. At the national level policymakers, healthcare professionals' organisations and national osteoporosis societies can use this framework to identify local gaps in the provision of best practice for the populations that they serve. Where currently absent, development of national strategies to close these gaps can be informed by the numerous international examples of clinical guidelines and quality improvement initiatives which have been highlighted in this report. It must be emphasised that this document is not an end in itself, but is instead best viewed as a call to action. The solutions to many of the problems we face have been identified and at least partly implemented, but not yet fully at a sufficient level to impact the approaching fracture tsunami. In the words of Leonardo da Vinci, "Knowing is not enough. We must apply. Being willing is not enough. We must do." The time for optimal management of bone health is now.

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