

Final Report

PATIENT PERCEPTION OF VALUE IN HEALTHCARE: OSTEOPOROSIS AND BONE FRAGILITY

*A Patient-Oriented Value (POV™) Report
Prepared by Connect 4 Strategies, LLC on behalf of*

National Osteoporosis Foundation

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About the National Osteoporosis Foundation

The National Osteoporosis Foundation (NOF) is the nation's leading resource for patients, health care professionals and organizations seeking up-to-date, medically sound information and program materials on the causes, prevention and treatment of osteoporosis. Established in 1984 as America's only voluntary, nonprofit health organization dedicated to reducing the widespread prevalence of osteoporosis, the foundation has grown to include a network of diverse stakeholders that support its goals to increase public awareness and knowledge, educate physicians and health care professionals, and support research activities concerning osteoporosis and bone health related areas.

Our Policy Institute brings together the expertise, resources, and perspective of the full spectrum of bone health stakeholders to advocate for health policy initiatives that promote bone health and reduce both the personal and financial costs of fragility fractures. As payers signal an increased focus on curbing health care costs, external value assessments and patient preference information have gained increasing importance -- and are often at odds with each other. NOF seeks to model a foundational economic analysis that reflects patient goals and preferences, and is capable of more accurately ascertaining value for treatment options that reach the large, untreated population and/or address the treatment needs of higher-risk patients.

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1. Executive Summary

1.1 Rationale and Background

1.1.1. *Bone Fragility is an Emerging Public Health Crisis*

NOF's 2014 update to its bone fragility prevalence data, revealed that an estimated 10.2 million adults in the U.S. have osteoporosis and another 43.4 million have low bone mass. This means 54 million U.S. adults, representing 50 percent of the U.S. adult population over age 50, are at risk of a fragility fracture.¹ Our healthcare system is armed with both the tools to detect and diagnose low bone mass and osteoporosis, and an understanding of the risk factors signaling the need for testing and treatment. Individuals in whom osteoporosis is detected have a variety of therapeutic options to effectively address their condition and reduce their risk of a fragility fracture.

Despite our ability to identify and manage osteoporosis, Medicare patients continue to suffer fragility fractures at an alarming rate, with an annual cost estimate of \$52 billion.² NOF finds it particularly jarring that a significant majority of US hip fracture patients are released from the inpatient setting without any evaluation for osteoporosis; most do not receive evaluation or treatment within the 12 months following the fracture.³ While over 80% of patients with an acute myocardial infarction receive diagnosis, evaluation and therapy, less than 20 percent of those with an acute hip fracture are diagnosed or treated for their underlying bone fragility. These patients are at a particularly high risk of future fractures due to failure to treat and manage progression of this chronic condition.

Individuals experiencing a fragility fracture have a marked decrease in quality of life and an increased likelihood of functional impairment, morbidity, and mortality. For the health system, the costs are significant; for patients, fragility fractures can have a catastrophic impact on the duration and quality of their lives. For otherwise-healthy patients, an osteoporotic hip fracture can change the trajectory of where and how they age.

- Typically, half of women with hip fracture do not recover full functionality post-fracture;
- Approximately 1 in 5 older adults will die within the year following a hip fracture;
- Although men have a lower incidence of hip fracture, they are at an increased risk of associated mortality;

¹ Office of the Surgeon General (US) (2004) Bone health and osteoporosis: a report of the Surgeon General. Office of the Surgeon General (US), Rockville (MD). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK45513/>.

² Lewiecki, E. M., Ortendahl, J. D., Vanderpuye-Orgle, J. , Grauer, A. , Arellano, J. , Lemay, J. , Harmon, A. L., Broder, M. S. and Singer, A. J. (2019), Healthcare Policy Changes in Osteoporosis Can Improve Outcomes and Reduce Costs in the United States. JBMR Plus. doi:[10.1002/jbm4.10192](https://doi.org/10.1002/jbm4.10192)

³ Office of the Surgeon General (US) (2004) Bone health and osteoporosis: a report of the Surgeon General. Office of the Surgeon General (US), Rockville (MD). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK45513/>.

- Despite clinical practice guidelines, only 23% of women age 67 or older who have an osteoporosis-related fracture receive either a BMD test or a prescription for a drug to treat osteoporosis in the 6 months after a fragility fracture;
- Hip fractures disproportionately occur among women age 80 and older, yet this group is the least likely to receive recommended care and remain at an unnecessarily high risk for subsequent fracture.

Solomon, et al.,⁴ reported a 50% decline over a 10-year period in prescriptions for osteoporosis-related medications related to the treatment of hip fractures. Poor patient compliance is also a major concern given that fewer than half of patients prescribed bisphosphonate therapy adhere to their treatment regimen.⁵⁶ While we expect the quality of our healthcare to improve with introduction of new diagnostic and treatment options, the care gap in osteoporosis has actually worsened over time. Given the risks of untreated or poorly treated osteoporosis, identification of barriers to effective treatment is an essential component of reducing the human and financial costs associated with fragility fractures.

1.1.2 Challenges in Incorporating the Patient Voice Impact the Validity of Frameworks Evaluating Osteoporosis Treatments

Patient-centered care has been recognized as a key element in delivering high-quality, high-value treatment, and was incorporated into several initiatives within the Affordable Care Act legislation. Many studies have shown that placing patients at the center of care results in greater participation in clinical decision-making, as well as higher patient satisfaction. While value frameworks have been developed to guide pricing and reimbursement decisions by key stakeholders in healthcare delivery, they are frequently criticized for not being sufficiently patient-centered. Value frameworks typically utilize data from randomized controlled trials to assess the comparative value of emerging therapies in disease states with multiple treatment options. While these clinical endpoints are important, patients may value other aspects of treatment that are not captured in clinical trials.⁷⁸

The Institute for Clinical and Economic Review (ICER) acknowledged in its 2017 framework update that patient preferences are often not captured in clinical trial data. ICER's framework refinement included contextual consideration of clinical outcomes that are important to patients, but stopped short of fully incorporating patient preference information into the Quality Adjusted Life Years formula driving its bottom-line assessments. The nature of the osteoporosis patient population, and extent to which costs of untreated bone fragility continue to burden the healthcare system make it particularly important for value frameworks to incorporate relevant, real-world data and patient preference information into the assumptions and other inputs that ultimately drive efforts to quantify value in osteoporosis treatments. The emergence of additional bone-building treatment options

⁴ Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fractures in patients between 2002 and 2011. *J Bone Miner Res.* 2014;29(9):1929e1937.

⁵ Wade SW, Curtis JR, Yu J, et al. Medication adherence and fracture risk among patients on bisphosphonate therapy in a large United States health plan. *Bone.* 2012;50(4):870e875.

⁶ Kothawala PK, Badamgarav E, Ryu S, Miller RM, Halbert RJ., Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clin Proc.* 2007;82(12):1493e1501.

⁷ Schnipper, L.E., et al., Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. *Journal of Clinical Oncology*, 2016. 34(24): p. 2925-2934.

⁸ Institute for Clinical and Economic Review, Overview of the ICER Value Assessment Framework and Update for 2017-2019. 2017.

further underscores the importance of focusing on treatment context, including fracture risk, treatment duration, and real-world medication persistence.

- Devising a base-case that assumes 100% persistence for existing treatments fails to accurately identify value of new treatments addressing the currently untreated population and the 30-60% of patients discontinuing treatment;
- Selecting comparators that, like zoledronic acid (ZA), slow bone loss rather than build new bone ignores the treatment context and urgency of addressing bone fragility for patients at particularly high risk of fracture;
- Patient preference considerations in osteoporosis treatment can identify pharmacologic agents that patients are willing to start and likely to continue for optimum therapeutic benefit. This is an essential driver of value assessment validity in a chronic, progressive disease state with a significant proportion of untreated patients and high rates of treatment discontinuation;
- Osteoporosis is a chronic disease, that like other chronic conditions, can be effectively treated but is not cured. It requires lifelong management, with treatment selected to address patient-specific, and potentially changing, needs over time;
- A recent NOF survey of 2200+ patients and caregivers found that 43% of patients had been prescribed two or more osteoporosis medications throughout their treatment, underscoring the unique circumstances for many osteoporosis patients whose fracture risk, treatment tolerance, and therapeutic needs may change over time.

1.2. Objectives

The goal of this project was to investigate how patients valued and prioritized various attributes associated with osteoporosis therapy across the treatment journey, including side effects, affordability, mechanism of action, and cost, in their treatment decisions.

The NOF reached out to the patient and caregiver community to explore the preferences that drive treatment decisions and persistence, including the all-too-frequent decision to decline treatment or diagnostic testing. We believe that this important information should play a pivotal role in any treatment value assessments that are intended to or could have the effect of shaping access.

1.3 Key Findings

The results of this survey revealed several overarching themes related to treatment decision-making in osteoporosis:

- Individuals at risk for a fragility fracture are primarily concerned that a fracture will trigger loss of the ability to live independently;
- Individuals with a previous fracture are particularly concerned about their risk for a subsequent fracture – 50% reported limiting their activities to reduce risk;
- Despite participant knowledge of their increased fracture risk, concerns that a fracture could severely limit quality of life, and awareness of treatment options, the vast majority of patients, including those at highest risk of a fragility fracture (i.e., those who have experienced a previous fracture after age 50), remain untreated;

- Participants across the risk spectrum for a fragility fracture identified dual mode of action, i.e., having both anabolic (bone building) and antiresorptive (slowing bone breakdown) as the most desirable attribute, and low out-of-pocket cost as attribute least likely to drive a treatment decision;
- Though overall treatment rates are low, participants with a fracture history were most likely to report a high level of willingness to consider starting an osteoporosis treatment regimen (as compared to those who had not fractured);
- Individuals reporting an unwillingness to consider treatment were overwhelmingly likely to have expressed concern with, or to have experienced, side effects; and
- Formulation and dosing frequency preferences were unexpectedly divergent, underscoring the importance of ensuring that individuals at greatest risk of fragility fracture have sufficient options to enable access to a treatment to which they will adhere.

These key findings illuminate many of the factors that are most meaningful to patients as they determine whether to start and continue with treatment for osteoporosis or low bone density. These considerations are particularly salient for osteoporosis patients who can choose from many different types of treatment regimens but all-too-frequently decline treatment altogether. Value frameworks for osteoporosis treatments tend to rely on inputs that extrapolate clinical trial data and discount real-world experience, running counter to the contextual considerations and circumstances that are most meaningful to patients. Valuing, comparing, and selecting a therapy based only on clinical endpoints such as response to treatment over potentially divergent timeframes ignores what may be the most important factor in determining an osteoporosis treatment's value – whether or not patients will be willing to start treatment and remain treated long enough to realize better outcomes. Moreover, unless value assessments include real-world data on patient adherence to existing treatments in the inputs driving those assessments, conclusions on value will likely mischaracterize the benefits to patients of existing treatments and result in suboptimal valuation of newer options.

2. Methods

This project utilized a brief survey instrument to collect key information from individuals suffering from, or within the demographic at high risk for, bone fragility and osteoporosis. Participant responses were included in, or excluded from, the data collection and analysis based on answers to the initial screening question on each individual's personal experience with osteoporosis testing, diagnosis, or treatment, and history of fractures after age 50.

2.1 Methodology and Approach

Individuals electing to participate submitted responses electronically. A brief description of bone fragility and treatment options was presented before participants were prompted to answer the first survey question. This introductory information was adapted from educational content prepared by the NOF and reads as follows:

Your skeleton is an active vital organ. It keeps you healthy through a constant process of repair, renewal, and mineral release. This process is called remodeling. The bone remodeling cycle consists of two distinct stages:

- *bone resorption (breakdown and removal) and*
- *bone formation (generation of new bone).*

As we age, the remodeling process can become unbalanced. More old bone gets removed than new bone gets created. Over time, this leaves bones weaker and more likely to break.

The goal of osteoporosis therapy is to try to restore the balance of resorption and formation. It can be done by:

- *slowing resorption through use of antiresorptive medication or*
- *promoting bone formation using anabolic medication.*

By doing so, these therapies lower the risk for fractures, which is the goal of treatment.

The survey instrument consisted of an initial “screening” question followed by a set of inquiries designed to illuminate predominating reasons for osteoporosis undertreatment, patient awareness of risks associated with low bone density, and medication attributes most likely to encourage or discourage a patient to start and maintain a therapeutic regimen. It is described in greater detail below and attached as Attachment 2.

2.2 Study Population

Participants 50 years of age or older with a previous fragility fracture, a self-reported diagnosis of low bone density or osteoporosis, previous treatment or testing experience, or a clinician recommendation of one or more bone health interventions were included in the data analysis.

We excluded individuals from participation if they failed to answer all questions or failed the screening question.

Specific inclusion and exclusion criteria are as follows:

Inclusion Criteria

Has, since reaching age 50:

- Had a fracture of the wrist, shoulder, hip or spine from a fall.
- Taken Vitamin D and/or calcium for low bone density
- Had blood tests to measure calcium or Vitamin D level
- Been on hormone therapy such as estrogen
- Undergone an imaging study to evaluate bone mineral density (e.g., DXA scan)
- Taken a prescription medication (or had one administered by injection) for low bone density

- Received an osteoporosis diagnosis from a health care provider **or**
- Been identified by a health care provider as having low bone density and/or being at high risk for a fragility fracture

Exclusion Criteria

Failed to meet inclusion criteria above
Failed to complete all relevant survey questions

2.3. Sample Size

The NOF recruited participants by utilizing its database of constituents⁹ that includes patients, caregivers and healthcare professionals, explaining NOF's interest in better understanding "value" in osteoporosis care from the patient perspective through a survey instrument. The email, sent on April 26, 2019, clarified that the NOF was seeking survey responses from patients. "Reminder" emails were sent on April 26th and May 13th.

Of the approximately 3,000 constituents for whom NOF can confirm receipt of the invitation, i.e., opening the participation request, 386 clicked on the link to the survey. 338 individuals, self-identified as patients, submitted survey responses, with 323 of those respondents meeting the criteria for inclusion in the analysis. Each participant was assigned a unique Respondent ID, and their IP address was identified and recorded to guard against duplicate submissions. The number of participants is likely sufficient to capture a diversity of opinion and experiences, and to reflect the experience and values of individuals across the osteoporosis patient journey.¹⁰

2.4. Survey Development

The survey instrument was designed to investigate patients' treatment decisions from the emergence of initial risk factors through disease maintenance and monitoring, including the decision on whether or not to begin or continue osteoporosis treatment. The instrument was adapted from a similar survey administered by Mora, et al.,¹¹ and included questions designed to solicit patient information on experience with testing for and diagnosis of low bone density, health provider recommendations on treatment, treatment experience, and for patients at high risk of a fragility fracture who remain untreated, reasons for declining therapy, interest in exploring treatment, and desirable attributes that would motivate treatment decisions. The survey instrument is described below and attached as Addendum 2.

⁹ The 22,800 "constituents" in NOF's database include individuals and entities with an interest in osteoporosis. This includes patients, caregivers, providers, and other stakeholders.

¹⁰ See, Patient Perceptions and Preferences for Osteoporosis Treatment, Ariana N. Mora, BA, Philip E. Blazar, MD,, Jenna C. Rogers, MPH, Brandon E. Earp, MD (2019)

¹¹ Patient Perceptions and Preferences for Osteoporosis Treatment, Ariana N. Mora, BA, Philip E. Blazar, MD,, Jenna C. Rogers, MPH, Brandon E. Earp, MD (2019)

Table 1: Survey Instrument Questions

Domain	Objective	Question
Risk Assessment	Participant screening	<p>Check Yes, No or Unsure for each. Since reaching AGE 50 I have:</p> <ul style="list-style-type: none"> • Had a fracture of my wrist, shoulder, hip or spine from a fall. • Taken Vitamin D and/or calcium for low bone density • Had blood tests to measure calcium or Vitamin D level • Been on hormone therapy such as estrogen • Undergone an imaging study to evaluate bone mineral density (e.g., DXA scan) • Taken a prescription medication (or had one administered by injection) for low bone density • Been told by a health care provider that I have osteoporosis • Been told by a health care provider that I have low bone density or that I am at high risk for a fragility fracture
Testing, Diagnosis, and Treatment Experience	Differentiate provider-driven from patient-driven treatment decisions	<p>Check Yes, No or Unsure for each. A physician treating me has recommended or offered:</p> <ul style="list-style-type: none"> • Vitamin D and/or calcium for low bone density • Blood tests to measure calcium or Vitamin D level • Hormone therapy such as estrogen • Imaging study to evaluate bone mineral density (e.g., DXA scan) • A prescription medication (including one administered by injection) for low bone density
Treatment Decision Making	Patient preference on formulation and frequency	<p>On a scale of 1 (most preferred) to 7 (least preferred) when starting a new medication, do you prefer:</p> <ul style="list-style-type: none"> • Medication by mouth daily • Medication by mouth once a week • Medication by mouth once a month • Subcutaneous injection (inject medication under skin) every 6 months • Subcutaneous injection once a month • Subcutaneous injection every day • Intravenous infusion (administer medication through a vein) taken once a year

Informed Decision Making	Participant knowledge of risks associated with bone fragility, concerns, and treatment attitudes	<p>Check ALL THAT APPLY.</p> <ul style="list-style-type: none"> • I am concerned that bone fragility could cause me to have a fracture that makes it difficult to live independently. • The possibility that my bone fragility increases the chance of a fracture has made me less active than I used to be. • I am aware that I am at risk for a fracture, but do not currently take medication to strengthen my bones • I am aware of the medications currently available to address osteoporosis, but have either decided not to take them or have stopped taking osteoporosis medication.
Treatment Decision Making	Patient reasons for not treating low bone density or osteoporosis.	<p>Answer ONLY if you DO NOT currently take a prescription medication for low bone density. Check ALL THAT APPLY. I am NOT taking a prescription medication(s) to treat low bone density because:</p> <ul style="list-style-type: none"> • No medical provider has recommended or prescribed one • It was recommended, but another physician, dentist, physical therapist or health care provider told me not to • I'm afraid of potential side effects to these medications • These medications are too expensive • I don't think I need to take them • I feel I'm already taking too many medications • I stopped taking these medications because of side effects • I was told by a physician or health care provider that I do not need to keep taking these medications
Treatment Decision Making	Patient willingness to consider treatment.	<p>Answer ONLY if you DO NOT currently take a prescription medication for low bone density. On a scale of 0 (not willing) to 10 (very willing) how willing would you be to start a new medication to treat or prevent low bone density?</p>
Treatment Decision Making	Patient preference on product attributes	<p>Rank the following medication attributes based upon what is most important to you in choosing to take a prescription medicine for osteoporosis or osteopenia with 1 being the most important attribute and 6 being the attribute least likely to encourage you to take the medication:</p> <ul style="list-style-type: none"> • Reduces risk of hip fracture • Reduces risk of spine (vertebral) fracture • Rapidly reduces fracture risk • Has dual effect – increases bone formation AND decreases bone loss • Low out-of-pocket cost • Lack of bothersome side effects

2.5. Participant Recruitment

The NOF recruited participants from individuals within its database. Potential participants received an email from the NOF asking that recipients self-identifying as patients consider survey participation; (Attachment 1); a follow-up email reinforced the NOF's particular interest in recruiting participants who had suffered a fragility fracture within the previous five (5) years.

The NOF's email to potential participants included a link to the survey instrument. Participant responses were assigned a unique numeric identifier. The online survey instrument recorded the participant's IP address, the date, start time for answering the survey questions, and the time the participant completed and submitted their responses.

Although participants were not compensated for their time, NOF's recruitment email offered a \$5.00 Starbucks gift certificate to the first 50 respondents completing the survey instrument.

NOF has an online Privacy Policy that is used to report on how information collected from those who register on our website and for our e-newsletters will be used and stored. Additional information can be found here - <https://www.nof.org/privacy-policy/>.

3. Results

3.1. Study Sample

Approximately 22,800 people were sent emails over the course of three weeks. The distribution list consisted of patients, caregivers and healthcare professionals – asking for patient feedback. 323 individuals submitting responses to the survey met the inclusion criteria. Their responses are included in the tables and charts at Attachment 3. The sample included 73 individuals with responses on fracture history after age 50 indicating a high probability of previous fragility fracture.

Using the NOF database to recruit participants appears to have yielded a participant group that is far more likely to be aware of osteoporosis and treatment options than the general public. The reported rates of DXA, diagnosis, and recommendation of a prescription drug to treat osteoporosis are far higher than those within the general public, likely due to sampling methodology. Unfortunately, the care gap remains clear and consistent with general population statistics. Despite relative success at diagnosing osteoporosis and recommending/prescribing treatment, individuals with knowledge of a high risk for fragility fracture tend to remain untreated. Even for those with known high fracture risk/osteoporosis and for those with a prior fracture, current medication use is very low.

For several of the analyses in this report, we segmented participants into subgroups: 1) all participants; 2) participants without a fracture history reporting provider-diagnosed osteoporosis or provider-identified risk of fragility fracture; and 3) participants with a history indicating likely previous fragility fracture.

Table 2: Participant Characteristics: Healthcare Experience and Risk Factors

Characteristics	N=313	%
Previous likely fragility fracture	73	23.3
Taken calcium or Vitamin D for low bone density	271	86.5
Blood test – calcium or Vitamin D	277	88.5
Hormone replacement therapy	98	31.3
Have had a DXA scan at least once	269	85.9
Have taken prescription meds for osteoporosis	187	59.7
Provider diagnosed osteoporosis	185	59.1
Provider identified patient as having low bone density or at high risk for fragility fracture	180	57.5

3.2 Testing, Diagnosis, and Treatment Experience Among Participants

Table 3: Participant Characteristics

Clinician Recommended or Offered:	All Participants N=323	Provider Dx Osteoporosis or High Fracture Risk (no fracture history) N=148	Previous Fracture N=73
<i>Vitamin D and/or calcium for low bone density</i>	264 (81.7%)	138 (93%)	66 (90.4%)
<i>Blood tests to measure calcium or Vitamin D level</i>	265 (82%)	128 (86.5%)	59 (80.8%)
<i>Hormone therapy such as estrogen</i>	71 (21.9%)	33 (22%)	18 (24.6%)
<i>Imaging study to evaluate bone mineral density (e.g., DXA scan)</i>	266 (82.3%)	141 (95%)	63 ((86.3%)
<i>A prescription medication (including one administered by injection) for low bone density</i>	205 (63.4%)	117 (79%)	55 (75.3%)
<i>Currently taking osteoporosis medications</i>		20 (13.5%)	19 (26%)

Of the 73 participants who have had a likely previous fragility fracture, all but 8 have received an osteoporosis diagnosis from their health care provider, and of the remaining 8, 4 have been told that they are at high risk of a future fragility fracture and 1 was unsure. 1 of the 3 participants without an osteoporosis diagnosis or identification of increased fracture risk, as well as the “unsure” participant, report having been prescribed medication to treat low bone density.

3.3 Participant General Awareness of Osteoporosis Risks, Treatment Availability

The vast majority of participants expressed concerns about their risk of a fragility fracture and the potential that this injury might interfere with their ability to live independently. Among individuals with a fracture history, these concerns are more likely to impact an individual’s activity level. Over half of participants with a fracture history report having curtailed their activity level due to concerns about a subsequent fracture.

A significant proportion of participants with a fracture history reported that they:

- Have been less active than previously due to fracture risk concerns;
- Are concerned that bone fragility could contribute to a fracture that might make it difficult to live independently;
- Are aware of medications currently available to treat osteoporosis; and
- Despite awareness of their increased fracture risk and the medications available to manage it, do not treat their bone fragility.

The disconnect between awareness that osteoporosis is a serious, but treatable disease, and treatment rate suggests an unmet need for osteoporosis treatments that patients are willing to take and that sufficiently address their concerns about fracture risk.

Table 4: Participant Concerns, Awareness, and Attitudes on Treatment

Check ALL THAT APPLY.	All Participants	Provider Diagnosed Osteoporosis or High Fracture Risk (no fracture history) N=148	Participants w/ Fracture History
I am concerned that bone fragility could cause me to have a fracture that makes it difficult to live independently.	243 (75%)	111 (75%)	64 (87.6%)
The possibility that my bone fragility increases the chance of a fracture has made me less active than I used to be.	104 (32%)	43 (29%)	37 (50.7%)
I am aware that I am at risk for a fracture, but do not currently take medication to strengthen my bones.	95 (29.4%)	50 (33.8%)	22 (30%)

I am aware of the medications currently available to address osteoporosis, but have either decided not to take them or have stopped taking osteoporosis medication.	103 (32%)	53 (35.8%)	27 (37%)
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Responses of participants with a fracture history revealed an interesting predominant characteristic correlating with current treatment status – 16 of the 19 participants reporting that they are currently treating their bone fragility indicated that (1) they were concerned that a fragility fracture could jeopardize their ability to live independently AND (2) concerns about bone fragility have made them less active than they used to be. This correlation did not extend at all to participants with no fracture history who had a diagnosis of osteoporosis or clinician-communicated high risk of fragility fracture.

Despite general awareness of the potential impact that untreated bone fragility can have on ability to retain independence and activity level, a relatively high number of participants appear not to pursue treatment or to stop their medication regimen. 42 of the 73 (56%) participants with a fracture history indicated that they were not currently taking osteoporosis medications despite reporting concerns that their bone fragility would threaten their independent living status. All but 5 (88%) of that set of participants indicated that they were aware of treatment options.

The trend was similar among individuals with a diagnosis of osteoporosis or clinician warning regarding low bone density, but no fracture history. The majority of participants expressed knowledge of their fracture risk, concerns that bone fragility could impact quality of life, and awareness of treatment options, yet these individuals are likely to forego or stop treatment.

3.4. Key Drivers for Participant Decisions to Decline to Start or Stop Osteoporosis Treatment

Although low rates of currently-treated osteoporosis prevailed across subpopulations, there does not appear to be a single, simple factor or clear set of factors driving the persistent undertreatment patterns. Resolving the osteoporosis care gap requires a multi-pronged approach combining education/outreach to providers and patients with advancement of treatment options that are attractive to patients. Although treatment cost was not identified as a major factor overall, it is interesting to note that cost was most frequently reported as a concern among participants at highest risk, i.e., those with a fracture history. Side effects, however, were the most frequently-cited rationale for not pursuing osteoporosis treatment – participants identified either fear of or experience with side effects as a major factor in their decision. Over 22% of currently-untreated individuals with a history of a previous fracture report that they discontinued treatment due to side effects.

Health care providers appear to play a significant role in the care gap as well. Interestingly, the likelihood of having not been offered treatment was higher in individuals with a fracture history than in those with diagnosed osteoporosis or provider-identified fracture risk (24.1% and 13.3%, respectively), despite the fact that the overwhelming majority of participants with a previous fracture were told by their provider that their low bone density put them at risk of a future fracture.

Table 5: Participant Reasons for Not Starting or Discontinuing Treatment

I am NOT taking a prescription medication(s) to treat low bone density because:	<i>All Participants</i>	<i>Provider Diagnosed Osteoporosis or High Fracture Risk (no fracture history) N=128</i>	<i>Participants with Previous Fracture (N=54)</i>
No medical provider has recommended or prescribed one	82 (25.4%)	17 (13.3%)	13 (24.1%)
It was recommended, but another physician, dentist, physical therapist or health care provider told me not to	20 (6.2%)	11 (8.6%)	5 (9.3%)
I'm afraid of potential side effects to these medications	85 (26.3%)	46 (36%)	18 (33.3%)
These medications are too expensive	26 (8%)	10 (7.8%)	10 (18.5%)
I don't think I need to take them	39 (12%)	8 (6.3%)	4 (7.4%)
I feel I'm already taking too many medications	8 (2%)	4 (3.1%)	4 (7.4%)
I stopped taking these medications because of side effects	32 (10%)	17 (13.3%)	12 (22.2%)
I was told by a physician or health care provider that I do not need to keep taking these medications	39 (12%)	21 (16.4%)	8 (14.8%)

3.5 Patient Preferences on Medication Formulation and Dosing Frequency

There was a great deal of diversity in participant responses to their formulation and frequency preferences. Of note, each of the choices presented was identified as a preferred formulation and dose by a subset of participants. While self-administered, oral formulations may have been preferred by many patients, others appear to prefer physician-administered products. Subcutaneous injections were favored at a 6-month frequency, but disfavored when presented as a daily injection. Monthly oral formulations were viewed as preferable to a monthly subcutaneous injection. Interestingly, the relative convenience of annual intravenous formulations did not drive a preference to this formulation and frequency – monthly subcutaneous injections were viewed nearly-as, or more, favorably than annual infusions. Daily subcutaneous injections were viewed least favorably across participant subgroups.

It is important to caution that even the most favorably-viewed formulations were perceived by some patients as undesirable, just as many participants expressed a clear preference for widely disfavored formulations such as daily subcutaneous injections or annual infusions. Comparing treatment options on efficacy demonstrated through clinical trials without considering formulation, dose frequency, or treatment duration to optimal response would, therefore, tend to drive conclusions away from real-world value of new products that might appeal to patients and close the treatment gap.

Table 6: Participant Preferences – Formulation and Dosing Frequency

On a scale of 1 (most preferred) to 7 (least preferred) when starting a new medication, do you prefer:	<i>All Participants</i>	<i>Provider Diagnosed Osteoporosis or High Fracture Risk (no fracture history) N=148</i>	<i>Participants with Previous Fracture</i>
Medication by mouth daily	3.4	3.4	3.04
Medication by mouth once a week	2.91	2.98	2.93
Medication by mouth once a month	2.59	2.66	2.75
Subcutaneous injection (inject medication under skin) every 6 months	3.32	3.21	3.29
Subcutaneous injection every month	4.59	4.53	4.76
Subcutaneous every day	6.14	6.03	6.46
Intravenous infusion (administer medication through a vein) taken once a year	4.84	4.98	4.46

3.6 Willingness of Currently Untreated Participants to Start an Osteoporosis Treatment

Participants reporting that they are not currently taking prescription medications for osteoporosis were asked to score their willingness to start a new osteoporosis medication on a scale from 0 (unwilling) to 10 (very willing). Some participants wrote in “not willing” or “very willing” instead of assigning a numeric ranking to their response – in these instances, we substituted a “1” for “not willing;” and a “9” for “very willing” in tabulating responses.

Responses on this inquiry yielded the greatest divergence between individuals with an osteoporosis or bone fragility diagnosis, but no fracture history, and participants who had suffered at least one previous fracture. The divergence was particularly pronounced at the top and bottom of the scale, with 27% of the no-fracture subgroup reporting a high level of unwillingness to start a new medication compared to just 7% of their previous-fracture counterparts. While 56% of participants with a previous fracture reported willingness to start a new treatment (and 38% expressing that they would be very willing), only 32% of the no-fracture subgroup indicated a willingness to treat their diagnosed osteoporosis (21% were very willing).

When we correlated reported willingness with views or experience on treatment side effects, we found that 20 of the 25 “very unwilling” no-fracture participants had reported that they were either afraid of treatment side effects or that they had stopped taking osteoporosis medications due to side effects. Although very few participants with a history of fracture reported being very unwilling to start a new medication, 2 out of the 3 who did cited side effects as a concern.

The proportion of patients at highest risk of a fragility fracture (i.e., individuals with a fracture history) who remain untreated despite a high level of willingness to start a new medication appears to signal an unmet need that would enhance the value proposition of new market entries that align with patient preferences.

Table 7: Participant Willingness to Start an Osteoporosis Medicine

On a scale of 0 (unwilling) to 10 (very willing) how willing would you be to start a new osteoporosis medication?	Osteoporosis or Bone Fragility Diagnosis (No Fracture History). (N=94)	History of Previous Fracture (N=45)
Very Unwilling (0-2)	25 (27%)	3 (7%)
Somewhat Unwilling (3-4)	12 (13%)	7 (16%)
Neutral (5-6)	27 (29%)	10 (22%)
Somewhat Willing (7-8)	10 (11%)	8 (18%)
Very Willing (9-10)	20 (21%)	17 (38%)

3.7 Preference on Medication Attributes that Would Encourage or Discourage Use

Participants were relatively consistent across subpopulations with respect to the medication attributes they felt were most and least important. Responses in all subgroups indicated that a medication with a dual effect of increasing bone formation and decreasing bone loss would be viewed favorably and that this attribute would be important in determining whether or not to start a medication. Although out-of-pocket costs can impede access for some patients, low financial burden was ranked by all groups as the least important attribute when making a treatment decision. Although a significant number of participants reported that side effect profiles of existing treatment options discourage their use, lack of bothersome side effects was ranked as the 4th most important attribute in all subgroups.

The only attribute with a difference in ranking between subgroups was “rapidly reduces fracture risk.” This attribute was ranked higher among participants who had a history of previous fracture and had, at some point, taken a prescription medication for low bone density.

Table 8: Participant Preferences -- Medication Attributes

What is most important to you in choosing to take a prescription medicine for low bone density. 1= most important attribute; 6 = the attribute least likely to encourage you to take the medication	All Participants	Osteoporosis or Low Bone Density (no fracture history)N=148	Previous Fracture; Have Taken Rx for bone fragility	Previous Fracture; Treatment Naïve
Reduces risk of hip fracture	3.26 (3)	3.31 (3)	3.38 (5)	3.31 (3)
Reduces risk of spine (vertebral) fracture	3.19 (2)	3.06 (2)	2.87 (2)	3.2 (2)
Rapidly reduces fracture risk	3.38 (4 – tie)	3.53 (5)	2.92 (3)	3.4 (5)
Has dual effect – increases bone formation decreases bone loss	2.61 (1)	2.23 (1)	2.33 (1)	2.67 (1)
Low out-of-pocket cost	4.46 (6)	4.62 (6)	4.59 (6)	4.33 (6)
Lack of bothersome side effects	3.38 (4 – tie)	3.36 (4)	3.84 (4)	3.33 (4)

4. Conclusions

Participant responses identified multiple factors as both facilitators of and barriers to value in osteoporosis treatment. Cost and side effect profile were critically important for a small subset of participants. However, when making decisions about care and treatment, our findings revealed that a dual effect of building bone while also reducing bone loss is the attribute participants would find most important in deciding to start a new.

Participants, particularly those who have had a likely previous fragility fracture, overwhelmingly expressed concern that they will suffer a fragility fracture that will threaten their ability to live independently, with many indicating that the fear of another fracture has made them less active. Unfortunately, the vast majority of participants reporting factors associated with high risk for fragility fracture were not currently taking osteoporosis medication. Among individuals without a fracture history who have been told by a health care provider that they have low bone density, just 13% report

that they are currently treating bone fragility. Fracture history doubled the likelihood of current osteoporosis treatment to 26%, which is still far below what the standard of care should be.

There was a great deal of divergence among participants on preferred formulation and frequency for osteoporosis medications, indicating that retaining patient choice is an important factor in optimizing osteoporosis treatment. Participant responses on preferred attributes of treatments indicated that a medication's ability to both build new bone and reduce resorption were of highest importance for individuals at greatest risk of a future fracture, followed by reduction in vertebral and hip fractures. Side effects and costs were, overall, the least important attributes, although for patients in whom this is especially important, high side effect and/or cost burden severely limit willingness to start and stay on treatment. – side effects were frequently cited as a reason for not taking, or stopping, osteoporosis medications. Individuals expressing an unwillingness to start osteoporosis treatment disproportionately identified fear of, or experience with, medication side effects.

When asked about preferences on attributes that would drive a decision to begin taking a new osteoporosis medication, participants indicated that a dual mechanism of building bone and reducing resorption would be the attribute most likely to encourage product use. Low out-of-pocket cost was identified as the least important factor.

Participants at higher risk for a fragility fracture expressed a relatively high level of willingness to start an osteoporosis treatment, despite the fact that the overwhelming majority of these individuals are not currently treating their low bone density. The high percentage of high-risk participants reporting that a health care provider had recommended a prescription medication or that they had, at some point in time, taken a prescription osteoporosis medication contrasted sharply with the proportion of participants currently treating this chronic condition.

The osteoporosis care gap is clearly a complex problem requiring multi-pronged strategies that include outreach to increase awareness among at-risk individuals and the providers responsible for their health care. This survey, however, appears to indicate that even when awareness of risks and available treatments are high, most individuals at risk for a fragility fracture choose not to take, or stop taking, medications needed to reduce their risk of a catastrophic injury. Patient preferences and treatment options that address the range of those preferences, therefore, are an important factor in the overall and comparative value of existing and pipeline treatments.

5. Strengths and Limitations

The NOF database used for initial contact in the participant recruitment process includes a broad set of individuals and entities with an expressed interest in bone health and osteoporosis, and is a poor barometer for response rate to the invitation for patient survey participation. Similarly, recruiting participants from NOF's database has yielded a participant population that is more aware of osteoporosis and its associated risks, more likely to have had testing and a diagnosis, and better informed of treatment options than the general public. Their healthcare experience, with respect to seeking and receiving care consistent with clinical guidelines is aligned with what would be expected from a highly motivated, well-informed subset of patients and is not likely generalizable to the population at large.

Despite use of a potentially enriched participant population from a disease awareness standpoint, the overall rate of self-identified osteoporosis patients currently treating the disease was in line with general population estimates. We believe that patient preferences in this population, including those driving decisions to start, stop, or continue a treatment regimen are particularly relevant as they are informed by participant's knowledge of the disease and its risks as well as their healthcare experience, and likely reflect real-world experience with the benefits and short-comings of existing options.

Attachment 1: NOF Communication to Potential Survey Participants

Dear Friends of NOF:

We grow increasingly concerned over the rising trend in defining value for patients without their input and using it to reduce access to new treatments. With this survey, NOF is asking patients to participate in defining value for themselves rather than having it defined for us! Please join us in making every effort to have our voices heard on what matters to patients, with respect to what treatments are on the market now and what may be developed in the future.

We would appreciate your response to a short survey about value in healthcare and treatment for osteoporosis. Thank you for everyone who has responded! If you have not had the chance, please follow this link: <https://www.surveymonkey.com/r/ValueInHealthcare> to complete the short survey. It should take no more than 10 minutes to complete.

The first 50 people to respond will receive an electronic \$5 Starbucks gift card (must include your email address if you want to be eligible for the gift card).

Thank you for your opinions!

Best regards,
The NOF Team

Attachment 2: Survey Content

Introductory Text:

Your skeleton is an active vital organ. It keeps you healthy through a constant process of repair, renewal, and mineral release. This process is called remodeling. The bone remodeling cycle consists of two distinct stages:

- bone resorption (breakdown and removal) and
- bone formation (generation of new bone).

As we age, the remodeling process can become unbalanced. More old bone gets removed than new bone gets created. Over time, this leaves bones weaker and more likely to break.

The goal of osteoporosis therapy is to try to restore the balance of resorption and formation. It can be done by:

- slowing resorption through use of antiresorptive medication or
- promoting bone formation using anabolic medication.

By doing so, these therapies lower the risk for fractures, which is the goal of treatment.

1. Check Yes, No or Unsure for each. Since reaching AGE 50 I have:

- Had a fracture of my wrist, shoulder, hip or spine from a fall.
- Taken Vitamin D and/or calcium for low bone density
- Had blood tests to measure calcium or Vitamin D level
- Been on hormone therapy such as estrogen
- Undergone an imaging study to evaluate bone mineral density (e.g., DXA scan)
- Taken a prescription medication (or had one administered by injection) for low bone density
- Been told by a health care provider that I have osteoporosis
- Been told by a health care provider that I have low bone density or that I am at high risk for a fragility fracture

2. Check Yes, No or Unsure for each. A physician treating me has recommended or offered:

- Vitamin D and/or calcium for low bone density
- Blood tests to measure calcium or Vitamin D level
- Hormone therapy such as estrogen
- Imaging study to evaluate bone mineral density (e.g., DXA scan)
- A prescription medication (including one administered by injection) for low bone density

3. **On a scale of 1 (most preferred) to 10 (least preferred) when starting a new medication, do you prefer:**

- Medication by mouth daily
- Medication by mouth once a week
- Medication by mouth once a month
- Subcutaneous injection (inject medication under skin) every 6 months
- Subcutaneous injection once a month
- Subcutaneous injection every day
- Intravenous infusion (administer medication through a vein) taken once a year

4. **Check ALL THAT APPLY.**

- I am concerned that bone fragility could cause me to have a fracture that makes it difficult to live independently.
- The possibility that my bone fragility increases the chance of a fracture has made me less active than I used to be.
- I am aware that I am at risk for a fracture, but do not currently take medication to strengthen my bones
- I am aware of the medications currently available to address osteoporosis, but have either decided not to take them or have stopped taking osteoporosis medication.

Answer questions 5 and 6 ONLY if you DO NOT currently take a prescription medication for low bone density.

5. **Check ALL THAT APPLY. I am NOT taking a prescription medication(s) to treat low bone density because:**

- No medical provider has recommended or prescribed one
- It was recommended, but another physician, dentist, physical therapist or health care provider told me not to
- I'm afraid of potential side effects to these medications
- These medications are too expensive
- I don't think I need to take them
- I feel I'm already taking too many medications
- I stopped taking these medications because of side effects
- I was told by a physician or health care provider that I do not need to keep taking these medications

6. **On a scale of 0 (not willing) to 10 (very willing) how willing would you be to start a new medication to treat or prevent low bone density?**

7. Rank the following medication attributes based upon what is most important to you in choosing to take a prescription medicine for low bone density (osteoporosis or osteopenia) with 1 being the most important attribute and 6 being the attribute least likely to encourage you to take the medication:

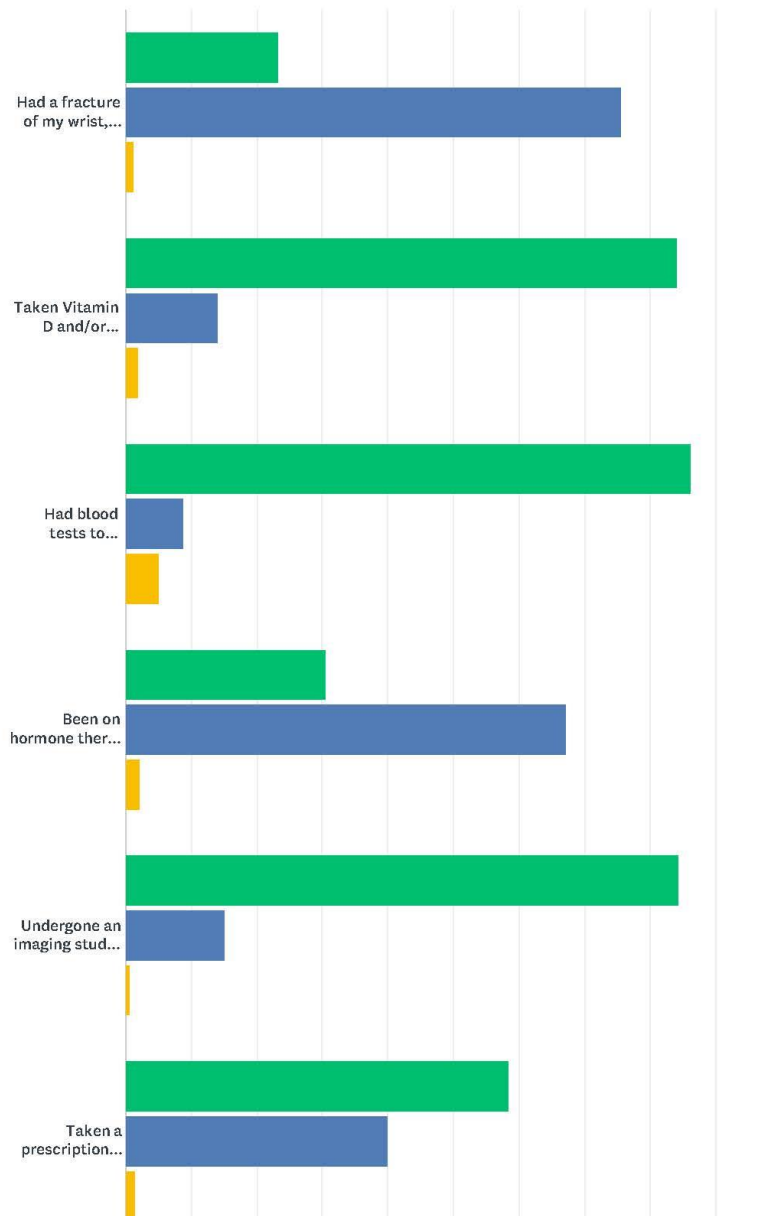
- Reduces risk of hip fracture
- Reduces risk of spine (vertebral) fracture
- Rapidly reduces fracture risk
- Has dual effect – increases bone formation AND decreases bone loss
- Low out-of-pocket cost
- Lack of bothersome side effects

Attachment 3: Topline Results of Survey

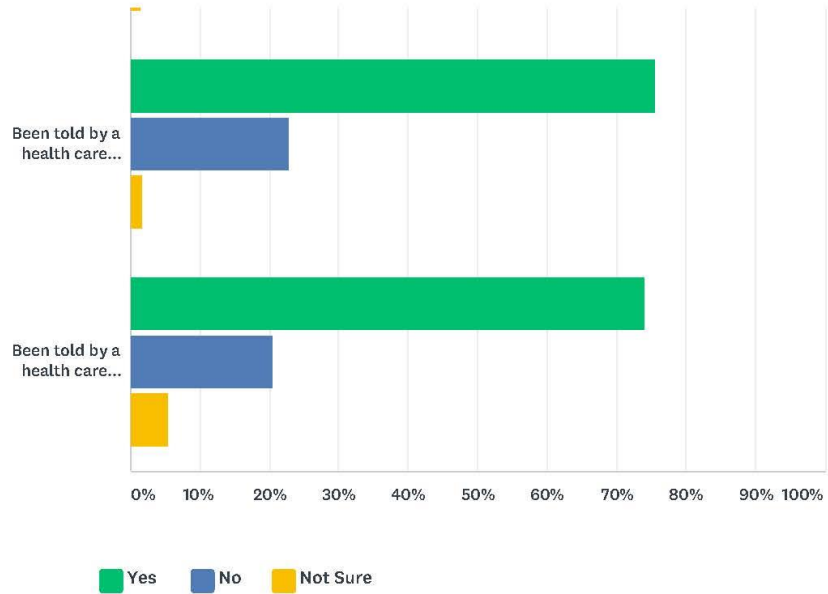
Value in Healthcare Survey

Q1 We are especially interested in hearing from patients who have had at least one previous fragility fracture (had a fracture of wrist, shoulder, hip or spine from a fall after reaching age 50), as well as those who have been told by a health care practitioner that they have osteoporosis. Check Yes, No or Unsure for each. Since reaching AGE 50 I have:

Answered: 323 Skipped: 1



Value in Healthcare Survey

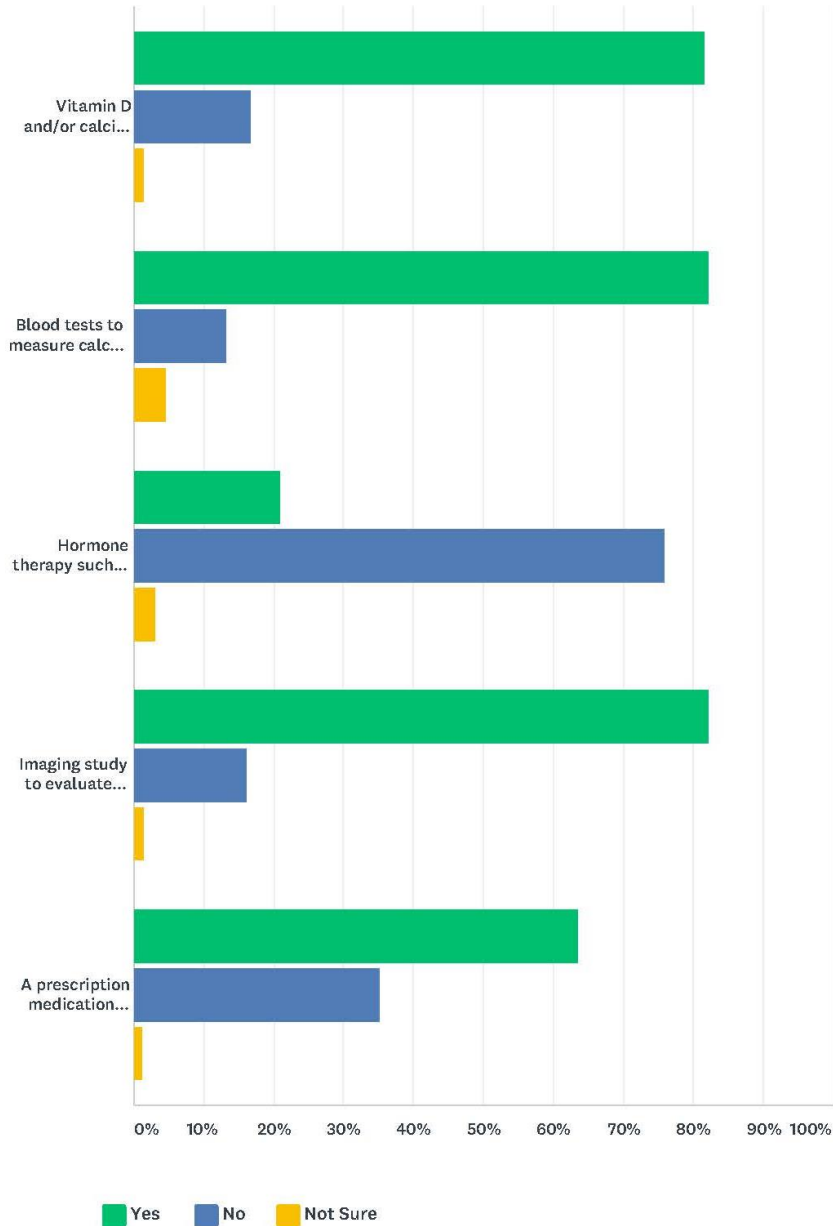


	YES	NO	NOT SURE	TOTAL	WEIGHTED AVERAGE
Had a fracture of my wrist, shoulder, hip or spine from a fall.	23.13% 74	75.63% 242	1.25% 4	320	1.78
Taken Vitamin D and/or calcium for low bone density	84.16% 271	13.98% 45	1.86% 6	322	1.18
Had blood tests to measure calcium or Vitamin D level	86.29% 277	8.72% 28	4.98% 16	321	1.19
Been on hormone therapy such as estrogen	30.63% 98	67.19% 215	2.19% 7	320	1.72
Undergone an imaging study to evaluate bone mineral density (e.g., DXA scan)	84.33% 269	15.05% 48	0.63% 2	319	1.16
Taken a prescription medication (or had one administered by injection) for low bone density	58.44% 187	40.00% 128	1.56% 5	320	1.43
Been told by a health care provider that I have osteoporosis	75.51% 185	22.86% 56	1.63% 4	245	1.26
Been told by a health care provider that I have low bone density or that I am at high risk for a fragility fracture	74.07% 180	20.58% 50	5.35% 13	243	1.31

Value in Healthcare Survey

Q2 Check Yes, No or Unsure for each. A physician treating me has recommended or offered:

Answered: 323 Skipped: 1



	YES	NO	NOT SURE	TOTAL	WEIGHTED AVERAGE
Vitamin D and/or calcium for low bone density	81.68% 263	16.77% 54	1.55% 5	322	1.20

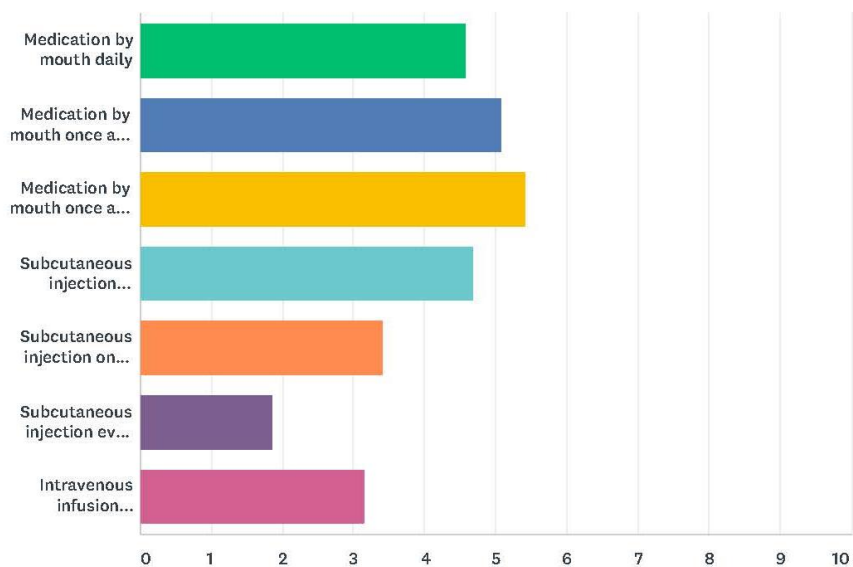
Value in Healthcare Survey

Blood tests to measure calcium or Vitamin D level	82.13%	13.17%	4.70%		
	262	42	15	319	1.23
Hormone therapy such as estrogen	21.00%	75.86%	3.13%		
	67	242	10	319	1.82
Imaging study to evaluate bone mineral density (e.g., DXA scan)	82.24%	16.20%	1.56%		
	264	52	5	321	1.19
A prescription medication (including one administered by injection) for low bone density	63.55%	35.20%	1.25%		
	204	113	4	321	1.38

Value in Healthcare Survey

Q3 On a scale of 1 (most preferred) to 7 (least preferred) rank when starting a new medication, what your preference is:

Answered: 311 Skipped: 13

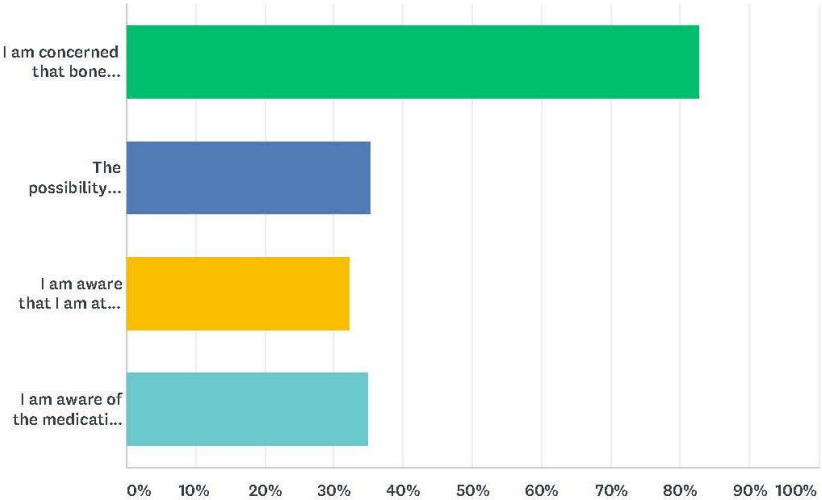


	1	2	3	4	5	6	7	TOTAL	SCORE
Medication by mouth daily	30.96% 74	8.37% 20	21.76% 52	5.44% 13	8.37% 20	11.30% 27	13.81% 33	239	4.59
Medication by mouth once a week	12.30% 30	43.03% 105	13.93% 34	11.89% 29	11.07% 27	6.15% 15	1.64% 4	244	5.09
Medication by mouth once a month	30.08% 74	14.23% 35	35.37% 87	11.38% 28	5.69% 14	2.03% 5	1.22% 3	246	5.41
Subcutaneous injection (inject medication under skin) every 6 months	23.20% 58	13.60% 34	6.80% 17	35.20% 88	11.20% 28	6.00% 15	4.00% 10	250	4.68
Subcutaneous injection once a month	2.17% 5	6.52% 15	9.57% 22	15.65% 36	43.91% 101	21.74% 50	0.43% 1	230	3.40
Subcutaneous injection every day	1.28% 3	0.85% 2	1.28% 3	6.81% 16	5.96% 14	36.60% 86	47.23% 111	235	1.86
Intravenous infusion (administer medication through a vein) taken once a year	17.84% 48	7.06% 19	5.20% 14	8.18% 22	8.55% 23	11.52% 31	41.64% 112	269	3.16

Value in Healthcare Survey

Q4 Check ALL THAT APPLY:

Answered: 292 Skipped: 32

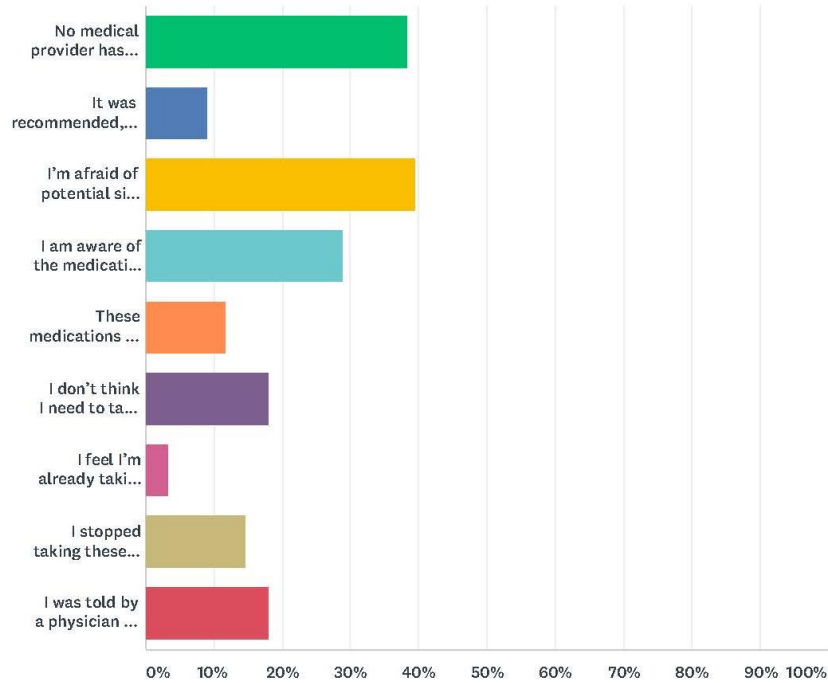


ANSWER CHOICES	RESPONSES
I am concerned that bone fragility could cause me to have a fracture that makes it difficult to live independently.	82.88% 242
The possibility that my bone fragility increases the chance of a fracture has made me less active than I used to be.	35.27% 103
I am aware that I am at risk for a fracture, but do not currently take medication to strengthen my bones.	32.19% 94
I am aware of the medications currently available to address osteoporosis, but have either decided not to take them or have stopped taking osteoporosis medication.	34.93% 102
Total Respondents: 292	

Value in Healthcare Survey

Q5 Answer questions 5 and 6 ONLY if you DO NOT currently take a prescription medication for low bone density. Check ALL THAT APPLY. I am NOT taking a prescription medication(s) to treat low bone density because:

Answered: 212 Skipped: 112

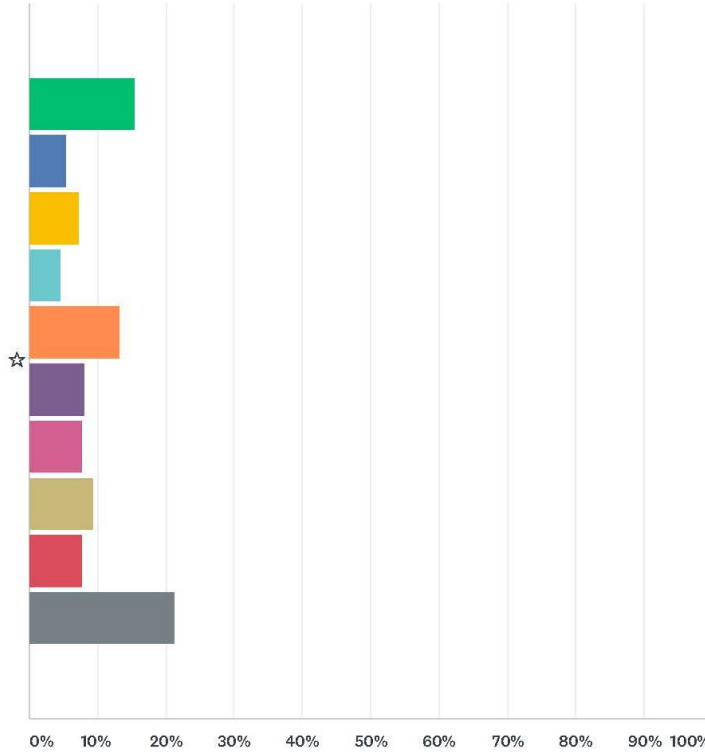


ANSWER CHOICES	RESPONSES
No medical provider has recommended or prescribed one	38.21% 81
It was recommended, but another physician, dentist, physical therapist or health care provider told me not to	8.96% 19
I'm afraid of potential side effects to these medications	39.62% 84
I am aware of the medications currently available to address osteoporosis, but have either decided not to take them or have stopped taking osteoporosis medication.	28.77% 61
These medications are too expensive	11.79% 25
I don't think I need to take them	17.92% 38
I feel I'm already taking too many medications	3.30% 7
I stopped taking these medications because of side effects	14.62% 31
I was told by a physician or health care provider that I do not need to keep taking these medications	17.92% 38
Total Respondents: 212	

Value in Healthcare Survey

Q6 On a scale of 0 (not willing) to 10 (very willing) how willing would you be to start a new medication to treat or prevent low bone density?

Answered: 221 Skipped: 103



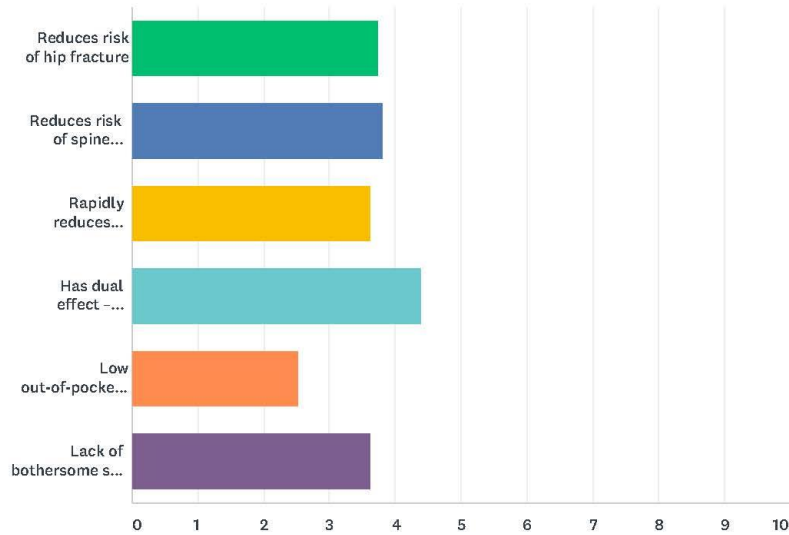
■ Not Willing
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ (no label)
 ■ Very Willing

	NOT WILLING	(NO LABEL)	(NO LABEL)	(NO LABEL)	(NO LABEL)	(NO LABEL)	(NO LABEL)	(NO LABEL)	(NO LABEL)	VERY WILLING	TOTAL	WEIGHTED AVERAGE
☆	15.38%	5.43%	7.24%	4.52%	13.12%	8.14%	7.69%	9.50%	7.69%	21.27%	221	5.0
	34	12	16	10	29	18	17	21	17	47		

Value in Healthcare Survey

Q7 Rank the following medication attributes based upon what is most important to you in choosing to take a prescription medicine for low bone density (osteoporosis or osteopenia) with 1 being the most important attribute and 6 being the attribute least likely to encourage you to take the medication:

Answered: 304 Skipped: 20



	1	2	3	4	5	6	TOTAL	SCORE
Reduces risk of hip fracture	18.03% 42	15.88% 37	22.75% 53	18.45% 43	15.45% 36	9.44% 22	233	3.74
Reduces risk of spine (vertebral) fracture	13.39% 32	27.20% 65	15.48% 37	21.76% 52	15.48% 37	6.69% 16	239	3.81
Rapidly reduces fracture risk	13.25% 33	16.47% 41	26.91% 67	19.28% 48	10.44% 26	13.65% 34	249	3.62
Has dual effect – increases bone formation AND decreases bone loss	40.55% 103	13.78% 35	11.81% 30	19.29% 49	7.48% 19	7.09% 18	254	4.39
Low out-of-pocket cost	5.53% 14	12.25% 31	9.49% 24	9.88% 25	28.85% 73	33.99% 86	253	2.54
Lack of bothersome side effects	26.84% 73	14.34% 39	12.87% 35	6.99% 19	17.65% 48	21.32% 58	272	3.62