Evidence Gaps Research Taxonomy Table
Research to Address Evidence Gaps in Preventive Services for the USPSTF
Topic: Screening for Osteoporosis to Prevent Fractures

To fulfill its mission to improve health by making evidence-based recommendations for preventive services, the USPSTF routinely highlights the most critical evidence gaps for creating actionable preventive services recommendations. The USPSTF often needs additional evidence to create the strongest recommendations for everyone, especially those with the greatest burden of disease. In some cases, clinical preventive services have been well studied, but there are important evidence gaps that prevent the USPSTF from making recommendations for specific populations.

In this table, the USPSTF summarizes the gaps in the evidence for screening for osteoporosis to prevent fractures that need to be addressed to advance the health of the nation. For each of the evidence gaps listed below, the USPSTF provides guidance to researchers and funders on the types of studies needed to expand the evidence in screening for osteoporosis to prevent fractures.

Although there are several tools that are designed to predict fracture risk or identify osteoporosis, the USPSTF is calling for the development of new and accurate risk assessment tools. It is crucial that such tools are developed and validated using contemporary cohorts that are broadly representative of the U.S. population, as detailed in the table. Because of the limitations and potential bias inherent in race-based risk assessment tools, newly developed tools should not use race as a variable. If risk is found to vary across population groups, it would be important to determine what the underlying cause(s) are.

The research taxonomy is intended to provide general guidance to investigators. Investigators are encouraged to develop research designs that are responsive to the research taxonomy outlined in the table, in collaboration with their research teams and areas of expertise and experience. The research developed will be reviewed according to standard USPSTF criteria for inclusion in its evidence report; inclusion criteria are summarized in the final Research Plan (https://www.uspreventiveservicestaskforce.org/uspstf/document/final-research-plan/osteoporosis-screening-prevent-fractures) and Procedure Manual (https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual).

Research Gap	Key Questions* or Contextual Questions	Direct/ Indirect Pathway†	Type of Gap	Study Characteristics	Population	Intervention/ Comparison	Outcomes/Timing	Setting
More research is needed on the benefits and harms of screening and of different screening strategies:	---	---	---	---	---	---	---	---
• Studies are needed on the benefits and harms of screening for osteoporosis or fracture risk to prevent osteoporotic fractures and related morbidity and mortality in men.	KQ1, KQ3	Direct	Grade assignment	Randomized, controlled trials; controlled clinical trials	Adult males; studies should include racial and ethnic groups representative of U.S. population to allow for preplanned subgroup analyses	Compare screening with no screening; screening modalities may include DXA, fracture risk assessment tool‡, or combinations of imaging and risk assessment	KQ1: All-cause mortality Fracture-related mortality Fractures (all-cause, hip, major osteoporotic fractures§, clinical vertebral fractures, any clinical fragility fractures) Fracture-related morbidity (e.g., disability) KQ3: Overdiagnosis resulting in unnecessary treatment Radiation exposure Anxiety from labeling	Settings applicable to U.S. primary care

Research Gap	Key Questions* or Contextual Questions	Direct/ Indirect Pathway†	Type of Gap	Study Characteristics	Population	Intervention/ Comparison	Outcomes/Timing	Setting
• Research is needed on the benefits and harms of screening using BMD alone vs. fracture risk assessment tools alone vs. combination of BMD and fracture risk assessment in postmenopausal women.	KQ1, KQ3	Direct	Health equity, grade assignment	Randomized, controlled trials; controlled clinical trials	Postmenopausal females; studies should include racial and ethnic groups representative of the U.S. population and sufficient numbers of women younger than age 65 years to allow for preplanned analyses by age and by race and ethnicity	Compare different screening strategies; for example, screening using DXA BMD alone vs. screening using formal fracture risk assessment tool‡ alone vs. screening using both vs. two-step screening (risk assessment followed by DXA)	KQ1: All-cause mortality Fracture-related mortality Fractures (all-cause, hip, major osteoporotic fractures§, clinical vertebral fractures, any clinical fragility fractures) Fracture-related morbidity (e.g., disability) KQ3: Overdiagnosis resulting in unnecessary treatment Radiation exposure Anxiety from labeling	Settings applicable to the United States
Research is needed to develop and validate new primary care–feasible risk assessment tools that accurately predict risk of hip and non-hip major osteoporotic fractures in women and men.	KQ2a	Indirect	Grade assignment, health equity	Large, nationally representative observational cohorts of U.S. population for development of new risk assessment tools Prospective, large, nationally representative cohorts of U.S. population for validation of new risk assessment tool Cohorts for both risk assessment tool development and validation should include populations	Adult females and males; racial and ethnic groups representative of U.S. population	Compare risk assessment tool predicted incidence with observed fracture incidence from nationally representative and verified sources	Predictive accuracy: Calibration outcomes (e.g., observed vs. expected ratio, calibration slope, calibration plot, Hosmer-Lemeshow goodness-of-fit, overall prediction model performance [e.g., Brier score, explained variation {R^2}]) Discrimination outcomes (e.g., c-statistic, discrimination slope, sensitivity, specificity, area under the receiver operating characteristic curve) Studies should observe cohort members for at least 5 years (i.e., be of sufficient duration) to determine incident fracture status and enroll sufficient numbers of persons to ensure an adequate number of hip or	Settings applicable to U.S. primary care

Research Gap	Key Questions* or Contextual Questions	Direct/ Indirect Pathway†	Type of Gap	Study Characteristics	Population	Intervention/ Comparison	Outcomes/Timing	Setting
				broadly representative of the U.S. population and sufficient numbers of postmenopausal women younger than age 65 years and men to be able to report on accuracy in each of these groups Observational cohorts for both risk assessment tool development and validation should include sufficient numbers of transgender persons to better understand and report on accuracy in this group			major osteoporotic fracture events for accurate risk prediction.	
Research is needed to develop and validate new primary care–feasible risk assessment tools that accurately identify osteoporosis in women and men.	KQ2c	Indirect	Grade assignment, health equity	Large, nationally representative observational cohorts of U.S. population for risk assessment tool development Prospective, large, nationally representative cohorts of U.S. population for risk assessment tool validation	Adult females and males; racial and ethnic groups representative of U.S. population	Compare risk assessment tool with DXA-measured BMD at the femoral neck (T-scores based on NHANES III reference range) or lumbar spine	Discrimination outcomes (e.g., c-statistic, discrimination slope, sensitivity, specificity, area under the receiver operating characteristic curve) No longer than 8 weeks between risk assessment and BMD measurement	Settings applicable to U.S. primary care

Research Gap	Key Questions* or Contextual Questions	Direct/ Indirect Pathway†	Type of Gap	Study Characteristics	Population	Intervention/ Comparison	Outcomes/Timing	Setting
				Cohorts for both risk assessment tool development and validation should include populations broadly representative of the U.S. population and sufficient numbers of postmenopausal women younger than age 65 years and men to be able to report on accuracy in each of these groups. Observational cohorts for both risk assessment tool development and validation should include sufficient numbers of transgender persons to better understand and report on accuracy in this group.				
Decision analysis studies are needed to help inform the optimal start and stop ages and screening interval in women.	KQ2d, CQ1	Direct, indirect	Grade assignment, other (modify topline by age to start and stop; specify screening interval)	Large, nationally representative cohorts of U.S. population and RCTs applicable to U.S. population for model development Prospective, large, nationally	Adult females; racial and ethnic groups representative of U.S. population	Compare screening strategies by start and stop ages and screening interval	Benefits: All-cause mortality Fracture-related mortality Fractures (all-cause, hip, major osteoporotic fractures§, clinical vertebral fractures, any clinical fragility fractures) Fracture-related morbidity (e.g., disability)	Settings applicable to U.S. primary care

Research Gap	Key Questions* or Contextual Questions	Direct/ Indirect Pathway†	Type of Gap	Study Characteristics	Population	Intervention/ Comparison	Outcomes/Timing	Setting
				representative cohorts of U.S. population for model validation			Harms: Overdiagnosis resulting in unnecessary treatment Radiation exposure Anxiety from labeling	
Research is needed on the benefits and harms of pharmacotherapy to prevent fractures in men with primary osteoporosis and without a history of fragility fractures.	KQ4, KQ5	Indirect	Grade assignment	Randomized, controlled trials; controlled clinical trials	Adult males; studies should include racial and ethnic groups representative of the U.S. population	Bisphosphonates with FDA-approved indications for the treatment of osteoporosis (i.e., alendronate, ibandronate, risedronate, zoledronic acid), denosumab, compared with placebo	KQ4: All-cause mortality Fracture-related mortality Fractures (all-cause, hip, major osteoporotic fractures§, clinical vertebral fractures, any clinical fragility fractures KQ5: Total adverse events Total serious adverse events Specific serious adverse events: major cardiovascular events (i.e., myocardial infarction, stroke, cardiovascular death), atrial fibrillation, osteonecrosis of the jaw, atypical femur fractures, incident gastrointestinal cancer, serious gastrointestinal events, rebound fractures after discontinuing denosumab treatment Discontinuations because of adverse events	Settings applicable to U.S. primary care

*Key questions are an integral part of the approach to conducting systematic reviews that the USPSTF uses in its recommendation process. Along with the analytic framework, these questions specify the logic and scope of the topic, and are critical to guiding the literature searches, data abstraction, and analysis processes. (https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual)

†The direct pathway is typically derived from RCTs of the targeted screening or preventive intervention that adequately measure the desired health outcomes in the population(s) of interest. If certainty for net benefit cannot be derived from the direct pathway, then the USPSTF determines if the evidence is sufficient across the key questions and linkages in the indirect pathway to determine overall certainty.

‡Using a fracture risk assessment tool that has been evaluated in at least two independent cohorts external to the development cohort.

§Major osteoporotic fracture is typically defined as fractures of the hip, wrist, and humerus and clinical vertebral fractures.

Abbreviations: BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; FDA=U.S. Food and Drug Administration; KQ=key question; NHANES=National Health and Nutrition Examination Survey; RCT=randomized, controlled trial; USPSTF=U.S. Preventive Services Task Force.