American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

CLINICIAN'S GUIDE

The objective of this guide is to provide a summary of the ACR 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis, which have been reviewed and endorsed by the American Society for Bone and Mineral Research.

Clinical Issue

Although glucocorticoids may effectively be used in the management of many inflammatory conditions, their use is associated with significant morbidity and mortality. Osteoporosis, with resultant fractures, constitutes one of these morbid complications and is associated with significant pain and disability. A rapid decline in bone mineral density (BMD) begins within the first 3 months of glucocorticoid use and peaks at 6 months, followed by a slower, steady loss with continued use. An increased risk of both vertebral and nonvertebral fractures has been reported with dosages of prednisolone or equivalent as low as 2.5-7.5 mg daily, and this risk may relate more strongly to daily rather than to cumulative doses of glucocorticoids. However, there has been some controversy regarding the dose at which an increased risk of fracture occurs, as some smaller studies have found no appreciable decline in bone density with mean daily 8.0 mg dosages of prednisone, or prednisone <5 mg/day. In a large meta-analysis, prior and current use of oral glucocorticoids increased the risk of any type of fracture, with no significant difference in relative risk between men and women.

Scope

This guide addresses the most salient clinical questions discussed in the recommendations, which are for adult patients receiving oral glucocorticoid therapy. Medications approved for use in the treatment of osteoporosis in the US, Canada, or the European Union as of August 28, 2008 are included. The following are not included in either the recommendations or this guide: 1) therapies that were approved for use in the treatment of osteoporosis after August 28, 2008; 2) discussions of GIOP in the transplant and pediatric populations; and 3) inhaled glucocorticoids.

Methodology

These recommendations were developed based on a rigorously conducted systematic review of research papers published between January 1966 and August 28, 2008 and the subsequent work of a primary Core Executive Panel (CEP). The CEP utilized the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method, with the assistance of 2 expert panels – the Expert Advisory Panel, which framed the development of the recommendations, and the Task Force Panel, which voted on the specific recommendations. The aim of the RAND/UCLA Appropriateness Method is to combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of a treatment based on patient-specific symptoms, medical history, and test results. The method combines a systematic review of the scientific literature with expert opinion and yields specific criteria of appropriateness that can be used as the basis for practice guidelines. The AGREE instrument was used to help assure that the updated recommendations covered all the important domains and attributes. The AGREE instrument grades elements of validity and includes 6 sections: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Full details regarding the methods used can be found in the full paper.

Rating the strength of evidence

Specific grades are included in order to reflect the level of evidence supporting each recommendation:

- **Level A**: data were derived from multiple randomized controlled trials (RCTs) or a meta-analysis
- **Level B**: data were derived from a single RCT or nonrandomized study
- **Level C**: data were derived from consensus, expert opinion, or case series

Although few RCTs were performed exclusively in premenopausal patients, many studies did include premenopausal women as part of the overall cohort. These studies were, therefore, included when determining the evidence grade for recommendations for premenopausal women and men younger than age 50 years.

INTENDED USE

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Why new GIOP recommendations?

The ACR last published recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis in 2001. Several developments in recent years support the need for a reappraisal and update of the 2001 recommendations:

- Additional therapies and new data on therapies included in the previous recommendations have become available.
- Updated approaches to identify patients at highest risk for fracture have been developed.
  - Bone density alone may not be the sole reliable diagnostic approach for some patients receiving glucocorticoids, because fracture in patients receiving glucocorticoids may occur independently of a decline in bone mass.
  - In 2008, the National Osteoporosis Foundation incorporated the 10-year absolute probability of fracture, calculated by the FRAX tool, into their guidelines for the treatment and prevention of osteoporosis and included glucocorticoid use as a clinical risk factor. The FRAX tool uses updated, evidence-based estimates of absolute fracture risk and was created for the purpose of quantitatively integrating numerous clinical factors into a clinically useful risk prediction model.
- Guideline development methodology has evolved from a more informal consensus approach to a more rigorous process.

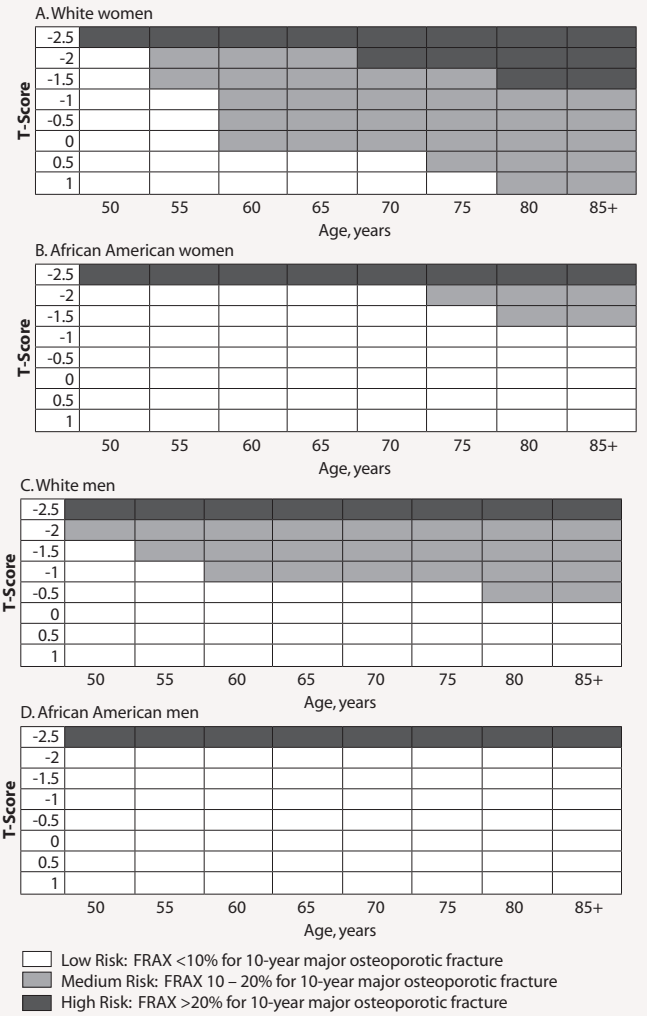
What has changed from 2001 to 2010?

- **Expanded recommendations for counseling and monitoring**
  - The 2001 recommendations included counseling those patients receiving glucocorticoid therapy on smoking cessation or avoidance, limiting excessive alcohol intake, weight-bearing activities, calcium and vitamin D intake and supplementation, and obtaining baseline and follow up BMD measurement. Recommendations for counseling and monitoring are now expanded to include fall risk assessment, height and 25-hydroxyvitamin D measurement, evaluation for prevalent and incident fragility fractures, and consideration for vertebral fracture assessment or radiographic imaging of the spine and calcium and vitamin D supplementation for any duration of glucocorticoid use.
- **Updated pharmacologic recommendations**
  - Updated pharmacologic recommendations are delineated for postmenopausal women and men over age 50 years, premenopausal women not of childbearing potential and men under the age of 50 years with a history of a fragility fracture, and premenopausal women of childbearing potential with a history of a fragility fracture.
  - The newer therapies zoledronic acid and teriparatide are now recommended along with alendronate and risedronate for the treatment of GIOP, while the previously included therapies estrogen replacement and testosterone are no longer endorsed.
- **Recommendations now guided by patient's overall clinical risk instead of T-scores alone**
  - Because other factors in addition to BMD, such as age and weight, contribute to fracture risk, these recommendations are guided in part by the FRAX score or patients' overall clinical risk profiles. This represents an advance over previous recommendations, which relied on T scores.

Assessing fracture risk

The Expert Advisory Panel recommended the use of either the FRAX* tool to define low-, medium-, and high-risk patients or the reliance by clinicians upon examples of patients that were typical of low, medium, and high risk categories *(as shown in Figure 2).*

Figure 2. Typical examples of postmenopausal women and men age ≥50 years with a history of glucocorticoid use at high, medium, and low risk of fracture in the absence of other risk factors in A, white women, B, African American women, C, white men, and D, African American men. High, medium, and low risk patient classification based on an approximation of FRAX 3.0 using age, sex, race, T score, and the presence of glucocorticoids for the calculation, with all other risk factors in the FRAX calculation absent. For example, a 65-year-old white man receiving glucocorticoids with a T score of –1.5 at the total hip would be considered a medium-risk patient if other risk factors listed in Table 1 were absent. Recommendations for this type of medium-risk patient are found in Tables 2, 3, and 4.



Using the FRAX calculator, the Expert Advisory Panel defined a 10-year risk of a major osteoporotic fracture of 10% or less as low risk, 10-20% as medium risk, and greater than 20% or a T score of less than or equal to –2.5 or a history of a fragility fracture as high risk (which is the threshold for cost-effective treatment recommended by the National Osteoporosis Foundation).

Fracture risk in the "typical patient" (Figures 2A-D) may be increased in patients who have additional risk factors that were presumed to be absent in the scenarios considered (such as low BMI, parental history of hip fracture, current smoking, and consuming three or more alcoholic drinks per day). Since FRAX uses an average glucocorticoid dose to calculate the 10-year probability of a major osteoporotic fracture, those receiving higher doses are likely to have a greater absolute fracture risk than estimated by the FRAX. Higher cumulative glucocorticoid dose and intravenous pulse glucocorticoids may also increase the risk of fractures. A declining central BMD measurement that exceeds the least significant change may be another reason that clinicians would move a patient to a higher risk category. These factors (Table 1) need to be considered in the health care provider's assessment of the patient and may shift an individual into a greater risk category (low→medium, or medium→high).

Table 1. Clinical factors that may shift an individual to a greater risk category for glucocortcoid-induced osteoporosis.

- Low body mass index
- Parental history of hip fracture
- Current smoking
- ≥3 alcoholic drinks per day
- Higher daily glucocorticoid dose
- Higher cumulative glucocorticoid dose
- Intravenous pulse glucocorticoid usage
- Declining central bone mineral density measurement that exceeds the least significant change

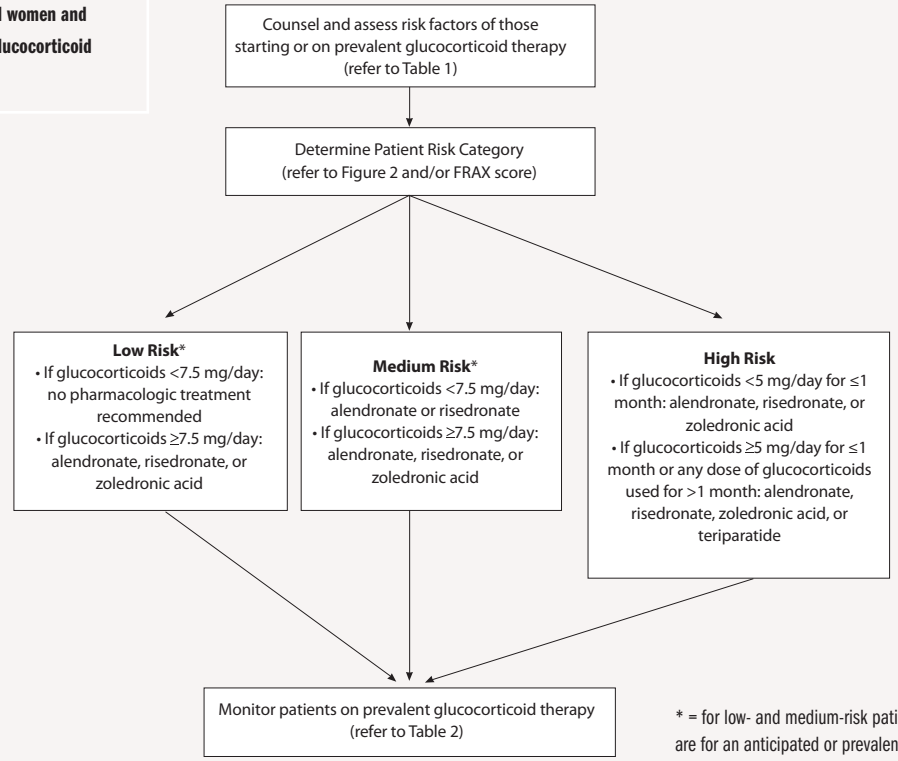
***FRAX:** WHO Fracture Risk Assessment Tool. URL: http://www.shef.ac.uk/FRAX/.

Recommendations

Only positive statements were included in the recommendations. Absence of any recommendation should not be construed to suggest that a treatment was inappropriate in particular settings; the absence of a recommendation generally implied only inadequate or conflicting evidence.

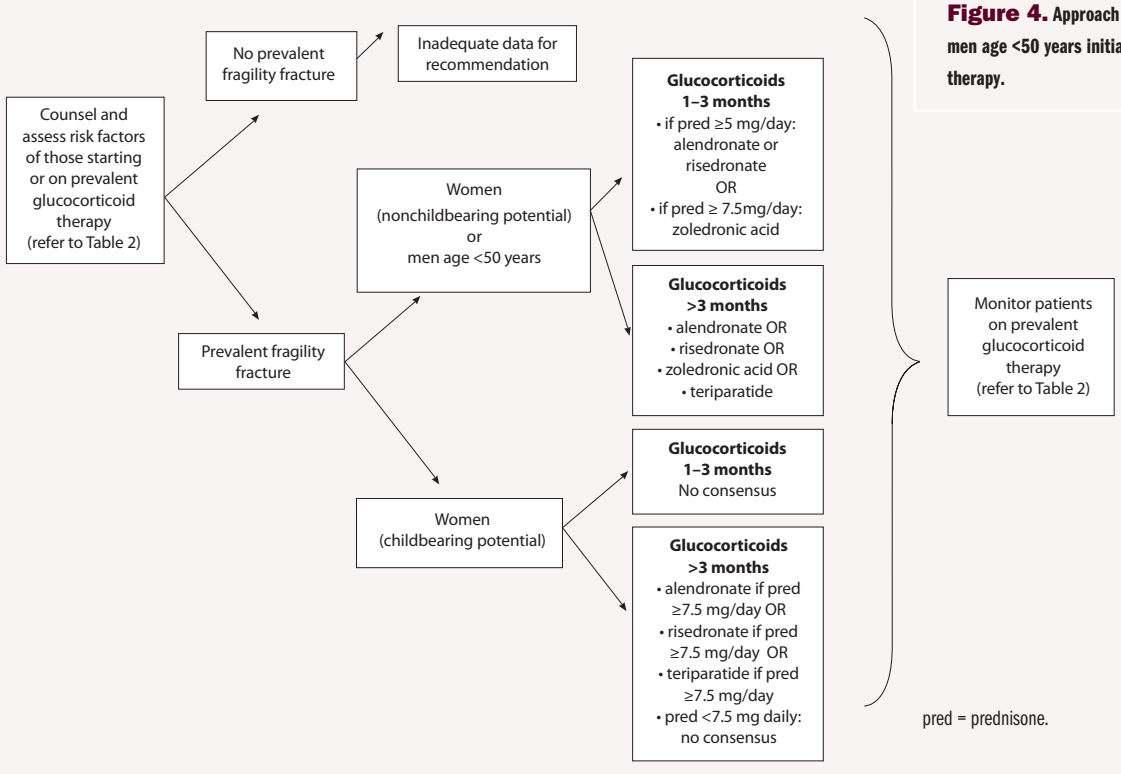
Figures 3 and 4 represent proposed approaches to the management of GIOP.

Figure 3. **Approach to postmenopausal women and men age >50 years initiating or receiving glucocorticoid therapy.**



* = for low- and medium-risk patients, recommendations are for an anticipated or prevalent duration of ≥3 months of glucocorticoids.

Figure 4. **Approach to premenopausal women and men age <50 years initiating or receiving glucocorticoid therapy.**



pred = prednisone.

Assessing fracture risk

The 17 recommendations concerning counseling for lifestyle modifications and follow up of patients receiving glucocorticoids are shown in Tables 2 and 3.

Table 2. **Recommendations on counseling for lifestyle modification and assessment of patients starting glucocorticoids at any dose with an anticipated duration ≥3 months.**

Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (>2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) 1,200-1500 mg/day*	A
Vitamin D supplementation*	A

* Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration of >3 months.

Table 3. **Recommended monitoring for patients receiving prevalent glucocorticoid therapy for a duration of ≥3 months.**

Recommendation	Level of evidence
Consider serial bone mineral density testing	C
Consider annual serum 25-hydroxyvitamin D measurement	C
Annual height measurement	C
Assessment of incident fragility fracture	C
Assessment of osteoporosis medication compliance	C

The recommendations for low-, medium- and high-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years are shown in Table 4.

Table 4. **Pharmalogic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of ≥3 months, or prevalent glucocorticoid therapy of a duration of at least 3 months (unless otherwise noted).**

Recommendations	Level of evidence
Low-risk patient	
Alendronate for ≥7.5 mg/day prednisone	A
OR	
Risedronate for ≥7.5 mg/day prednisone	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
Medium-risk patient	
Alendronate for any dose of glucocorticoids	A
OR	
Risedronate for any dose of glucocorticoids	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
High-risk patient†	
Alendronate	A
OR	
Risedronate	A
OR	
Zoledronic acid*	B
OR	
Teriparatide‡	B

* Head-to-head comparison data available in the Discussion section of the full paper.

† Any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients.

‡ For ≥5 mg/day prednisone with a duration ≤1 month and for any dose of glucocorticoids with a duration >1 month. Head-to-head comparison data available in the Discussion section of the full paper.

Recommendations for premenopausal women and men age <50 years with a history of fragility fracture are included in Table 5. There was inadequate evidence to make recommendations for patients in these populations who did not have a history of fragility fracture.

Table 5. **Recommendations for premenopausal women and men under age 50 years with a history of fragility fracture.**

Recommendations	Grade of recommendation
1-3 MONTHS OF GLUCOCORTICOIDS	
Nonchildbearing potential	
Alendronate if receiving prednisone ≥5 mg/day	A
OR	
Risedronate if receiving prednisone ≥5 mg/day	A
OR	
Zoledronic acid if receiving prednisone ≥7.5 mg/day	B
Childbearing potential*	
≥3 MONTHS OF GLUCOCORTICOIDS	
Nonchildbearing potential	
Alendronate for any dose	A
OR	
Risedronate for any dose	A
OR	
Zoledronic acid for any dose†	B
OR	
Teriparatide for any dose†	B
Childbearing potential	
Alendronate if prednisone ≥7.5 mg/day	A
OR	
Risedronate if prednisone ≥7.5 mg/day	C
OR	
Teriparatide if prednisone ≥7.5 mg/day†	C

* Inadequate data

† Head-to-head comparison data available in the Discussion section of the full paper.

The recommendations for premenopausal women and younger men are constrained by the paucity of evidence for fracture risk and the treatment of GIOP in this population. The absence of specific recommendations should not be construed as counseling against treatment for premenopausal women and young male patients, but as an indication of the need for further research.

Limitations

- **FRAX:** The categorization of high, medium, and low risk for fracture assessment of patients is based largely on the FRAX tool, and there are limitations to FRAX that are important to consider:
  - Several of the clinical risk factors contributing to FRAX do not take into account dose response but use "average" dose or exposure. However, there is good evidence that the risk associated with alcohol consumption and glucocorticoid use is dose related.
  - The computer modeling underlying FRAX uses only the bone density value for the hip. This may be an issue in GIOP because patients receiving glucocorticoids frequently lose bone mass in the spine before the hip, leading to a possible underestimation of fracture risk. Thus, FRAX alone cannot replace clinical judgment in risk stratification.
- **Medication risks for individual patients:** These updated recommendations have added a greater number of thresholds around glucocorticoid dosing, reflecting the populations studied in clinical trials and the differing risk-benefit values of the agents. While the recommendations support the use of a variety of therapies, all medications have their own risk profiles that need to be considered when evaluating individuals.
- **Quality of available evidence:** Every set of recommendations is limited by the quality of the available evidence, and in many situations additional clinical judgment will influence the application of these proposed recommendations.

Further research needed

Despite significant advances in the understanding of the epidemiology of GIOP and despite an increased number of higher-quality clinical trials in recent years, gaps in knowledge still exist. Some of the areas where further research is needed include:

- Fracture risk and treatment of GIOP in premenopausal women and men younger than age 50 years, including 1) definition of the risk factors that influence fracture propensity in these populations; 2) the long term safety of medications used to treat GIOP in these populations; and 3) the risk of these medications to a fetus, either from current or previous exposure
- Incremental impact of various rheumatic diseases such as rheumatoid arthritis on GIOP risk
- Use of osteoporosis therapies for patients with chronic renal insufficiency and a creatinine clearance level <30 mg/minute
- The risk of and treatment for patients who receive intermittent pulse or intramuscular glucocorticoids without daily oral doses

Glucocorticoid-induced osteoporosis is an undertreated condition. With more than an estimated one million patients in the US receiving a prescription for glucocorticoids yearly, GIOP has wide-reaching consequences. The goal of these recommendations is to improve awareness and increase the rate of counseling and treatment of GIOP. It is anticipated that GIOP recommendations will undergo future revisions as new evidence is developed, which will further the aim of improving care for patients treated with glucocorticoids.

For more information

For electronic copies of this Clinician's Guide, the full recommendation paper, or details about the evidence review and guideline development process, visit http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658 and view the November 2010 issue of *Arthritis Care & Research*.

Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG. American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care Res (Hoboken) 2010;62:1515-1526.

Authors

JENNIFER M. GROSSMAN,[1] REBECCA GORDON,[2] VEENA K. RANGANATH,[1] CHAD DEAL,[3] LIRON CAPLAN,[4] WEILING CHEN,[1] JEFFREY R. CURTIS,[5] DANIEL E. FURST,[1] MAUREEN MCMAHON,[1] NIVEDITA M. PATKAR,[5] ELIZABETH VOLKMANN,[1] AND KENNETH G. SAAG[5]

[1]Jennifer M. Grossman, MD, Veena K. Ranganath, MD, Weiling Chen, MA, Daniel E. Furst, MD, Maureen McMahon, MD, MSc, Elizabeth Volkmann, MD: University of California, Los Angeles; [2]Rebecca Gordon, MD: VA Greater Los Angeles Healthcare System and University of California, Los Angeles; [3]Chad Deal, MD: Cleveland Clinic, Cleveland, Ohio; [4]Liron Caplan, MD: University of Colorado, Denver; [5]Jeffrey R. Curtis, MD, MPH, Nivedita M. Patkar, MD, MSPH, Kenneth G. Saag, MD, MSc: University of Alabama, Birmingham.

Dr. Deal has received consultant fees, speaking fees, and/or honoraria (more than $10,000 each) from Lilly, Amgen, and Genentech. Dr. Curtis has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Eli Lilly and Procter & Gamble, and (more than $10,000 each) from Novartis, Amgen, Roche/Genentech, and Merck. Dr. Saag has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Merck, Lilly, Novartis, Aventis, Genentech, AstraZeneca, Pfizer, and Horizon.

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