

Abstracts of the NIH-FDA Conference “Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications”

Factors Influencing the Optimal Use of Surrogate Markers and Models

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In the current development climate, there is increasing pressure to select the successful from the unsuccessful development candidates at the earliest possible stage and to base dose selection rationally rather than empirically. The use of surrogates and models potentially can facilitate these decisions by demonstrating dose-concentration-response relationships early in well-controlled experiments. However, the predictive value of data from a surrogate or model is likely to be imperfect. Factors likely to determine the utility of such an approach include validation aspects such as the construct, criterion, and face validity of the measurement. However, there are other less quantitative and objective aspects that may affect surrogate or model utility in drug development. Even relatively imperfect surrogates may need to be used in assessing drugs of high medical need, or where hard clinical endpoints are difficult to achieve (e.g., due to the large sample size required). Another factor is the culture of the developing organization (e.g., its attitude toward scientific and commercial risk) and whether the scientific/analytical approach predominates over a heuristic one. One obstacle to the increasing use of surrogates and models is the basic tension between the extent of validation of the measurement and the degree of clinical need for the intervention (i.e., the best validated surrogates exist for a well-served therapeutic need). However, even in areas of unmet therapeutic need where the understanding of the biology of the disease is incomplete, the maximal value of surrogates and models will arise when there is an integrated approach to the development and use of novel techniques throughout the preclinical and clinical development programs. This requires clinical pharmacologists to be closely involved with the work of the preclinical scientists well before the compound is due to go into humans and the assistance of the scientists to develop and use appropriate laboratory techniques in clinical studies. This integrated approach is not the dominant mode in the current pharmaceutical industry, but it is likely to be the source of competitive advantage in the future. Case examples will be presented that illustrate how decisions about the development potential of a novel drug can be made even from data of imperfect predictive value.

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The Importance of Markers in Drug Discovery and Development

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The availability and use of validated markers of disease progression and severity as well those demonstrating drug activity and response can be crucial during drug development for a new chemical entity (NCE). This can be especially important when NCEs are being evaluated in patients with common, chronic, and progressive diseases through clinical trials that can involve large numbers of patients over prolonged periods of time to detect an effect on disease progression, severity, and outcome response. Getting an early readout on the efficacy of an NCE in development cannot facilitate prudent use of patient and financial resources, but it can provide early feedback to discovery to validate the importance of a new mechanism of action, especially for an unprecedented therapeutic approach. We recently established a collaboration in the area of Alzheimer's disease (AD) in search of markers,

hoping that such markers could contribute to the design and interpretation of clinical trials as well as uncover important new targets in AD.

The Prospective Search for Alzheimer's Disease Biomarkers

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Despite many recent advances in the understanding of the biology of Alzheimer's disease (AD), the diagnosis of AD still depends on clinical criteria and is confirmed only by biopsy or autopsy. Although the clinical diagnosis of an experienced clinician is accurate to a level of 80 to 85 percent, it is often delayed by the heterogeneous symptom profile at presentation and the current lack of antemortem biologic markers of the disease process. As new and more targeted therapies emerge for the treatment of the underlying biochemical changes associated with AD (i.e., accumulation of beta-amyloid peptide and hyperphosphorylated tau protein), the need for biomarkers to aid in the diagnosis, prognosis and evaluation of treatment effectiveness has become a rate-limiting factor in the development and advance of therapeutic studies. This talk will describe the rationale behind and progress to date in a collaborative study developed between the National Institute of Mental Health and industry designed to use standard and novel techniques to examine the spinal fluid of AD patients over the course of their illness compared with controls. In addition, this study involves a longitudinal view of a special group of normal subjects at risk for developing AD in the hope of isolating specific biomarkers that will have potential value both as diagnostic and surrogate markers.

Use of Modern Proteomics to Discover Protein Biomarkers of Disease

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Proteins secreted by diseased cells or tissues have long been considered central to the detection, differential diagnosis, and assessment of disease. Approaches to discovering disease-specific proteins in human blood, cerebrospinal fluid, and so forth have to date been constrained by (1) the predominance of albumin and IgG, (2) the lack of reproducible methods for the high-resolution separation and detection of serum proteins, and (3) the lack of analytical methods to characterize at the molecular level trace levels of disease-specific proteins. These limitations have largely been overcome through technological advances in modern proteomics. These advances will be described and exemplified with reference to Alzheimer's disease.

Definitions and Conceptual Model

Biomarkers and Surrogate Endpoints

- Overview
- Definitions
- Conceptual Model
- Biomarkers as Surrogate Endpoints: Possible Relationships

Overview

A review of the scientific literature reveals that there are many terms and meanings used when describing the measurement of biological parameters and their substitution for clinical endpoints in clinical trials. In an effort to develop an effective dialogue to discuss the topics presented in the conference, a working group on definitions¹ was organized. The working group developed terminology and a conceptual model that were recommended to serve as the convention for discussion at this conference.

Definitions

Biomarker (Biological Marker) — A characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Clinical Endpoint — A characteristic or variable that measures how a patient feels, functions or survives.

Surrogate Endpoint — A biomarker intended to substitute for a clinical endpoint.

Global Assessment — Evaluation of risk and benefit balance for a patient or a group of patients.

Conceptual Model

A conceptual model was developed to demonstrate the potential interactions of biomarkers and surrogate endpoints (Figure 1). Biomarkers used in evaluating a therapeutic intervention may have utility in assessing safety or efficacy. In fact, some biomarkers may have dual functions that assess efficacy for some interventions and safety for others. A subset, represented by the quadrant of the biomarker sphere, may achieve the status of a surrogate endpoint in a clinical trial. Surrogate endpoint status is evaluated by considering those factors that relate to the ability of a biomarker to accurately substitute for a clinical endpoint. The evidence supporting the linkage of a biomarker to a clinical endpoint may be derived from epidemiologic studies, clinical trials, in vitro analyses, animal models, and simulated biological systems. Many biomarkers have been proposed as potential surrogate endpoints, but relatively few are likely to achieve this status because of the complexity of disease mechanisms and the limited capability of a single biomarker to reflect the collective impact of multiple therapeutic effects on ultimate outcome. The evaluation of the risk and benefit balance of an intervention on a biomarker employed as a surrogate endpoint for a patient or group of patients is referred to as the “global intervention assessment”. Scenarios for the relationships of biomarkers as surrogate endpoints are shown in Figure 2.

¹ Definitions Working Group: Arthur Atkinson (NIH-Clinical Center); Wayne Colburn (MDS Harris); Victor De Gruttoia (Harvard School of Public Health); David DeMets (University of Wisconsin, Madison); Gregory Downing (Office of Science Policy, NIH); Daniel Hoth, John Oates (Vanderbilt University); Cari Peek (Georgetown University); Robert Schooley (University of Colorado); Bert Spilker (Pharmaceutical Research and Manufacturers of America); Janet Woodcock (Center for Drug Evaluation and Research, FDA); Scott Zeger (Johns Hopkins University School of Public Health).

Conceptual Model of Biomarkers and Surrogate Endpoints

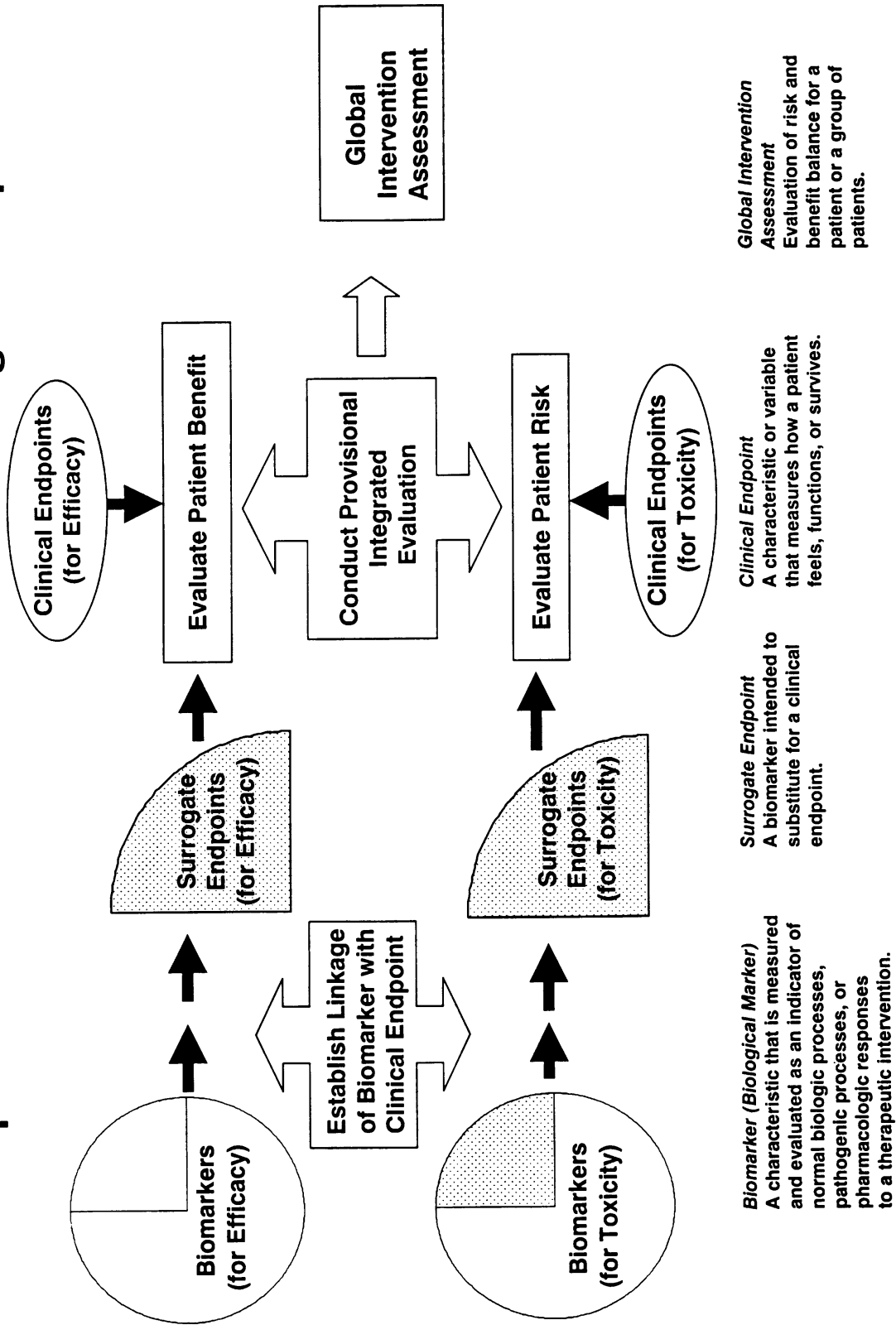


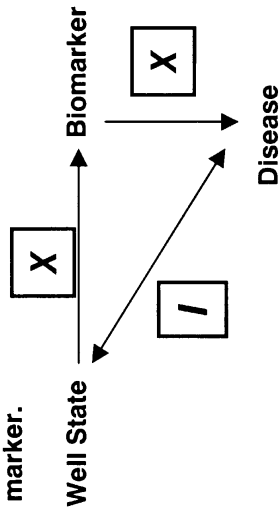
Figure 1.

Biomarkers as Surrogate Endpoints: Possible Relationships



Type of Relationships

A. Unreliable interaction between marker and endpoint in response to the intervention. Intervention affects disease but does not affect marker.



Prostate-specific antigen is a useful biomarker for prostate cancer detection but unreliable as an indicator of response to various treatments.

B. Intervention affects disease through an effect on the biomarker. The full effect of the intervention is observed by assessing the marker.



None known at present.

Value of the Biomarker

Biomarker of no value as a surrogate endpoint but may be useful in exploratory studies.

Biomarker is an ideal surrogate endpoint.

I = Affected by intervention
 X = Not affected by intervention
 U = Unintended effect of intervention

Figure 2.

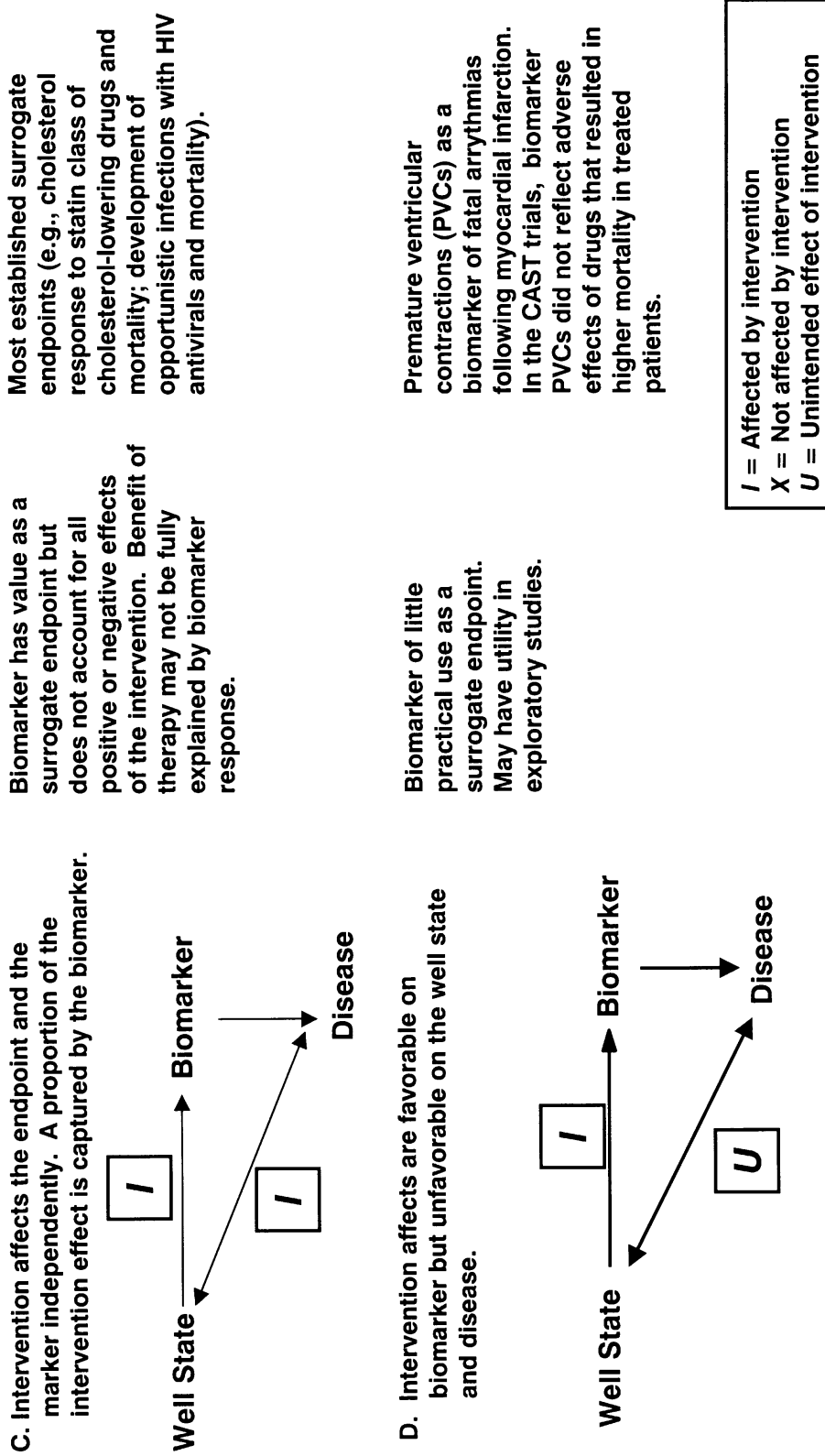


Figure 2 (continued).

Osteoporosis Biomarkers and Surrogate Endpoints

Objectives

- Assess the current status of biomarkers as surrogate endpoints in clinical trials of osteoporosis interventions
- Address future needs and opportunities in the assessment of bone structure and function using imaging technologies
- Translate advances in the understanding of osteoporosis pathogenesis into improved clinical measures to assess change in bone mineralization status
- Consider current measures of bone absorption and reabsorption as biomarkers and surrogate endpoints in osteoporosis clinical trials
- Develop strategies to stimulate research on biomarkers and their use as surrogate endpoints in clinical trials for osteoporosis interventions

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Surrogate Endpoints for Treatment-Induced Change in Risk of Osteoporotic Fractures: Introduction

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Bone mass, measured in a number of ways, is strongly associated with the risk of fracture. In addition, biochemical markers of bone resorption and formation can be measured in urine or serum. Single measurements of these markers are related to the subsequent risk of fracture. To be useful surrogates for the effect of treatment on the risk of fracture, changes in these markers during treatment should predict changes in the risk of fractures. This session will review the evidence that changes in these markers predict changes in risk of fracture. In addition, we will review how well two common outcomes, changes in vertebral dimensions on x-ray and changes in stature during treatment, predict change in risk of nonspinal fractures and morbidity. The goals of the session are to review the state of the art in biomarkers and surrogate endpoints for change in fracture risk and identify key questions that still need to be addressed.

Osteoporosis: Biomarkers and Surrogate Endpoints

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Biochemical markers of bone turnover reflect bone remodeling at the skeletal level and provide information about bone formation (by the osteoblast) and resorption (by the osteoclast). Important formation markers include serum bone alkaline phosphatase (BAP) and serum osteocalcin or bone-gla-protein (OC). Specific markers of bone resorption include urinary pyridinoline crosslinks (Pyr), urinary deoxypyridinoline crosslinks (dPyr), and their amino- and carboxy-terminal telopeptides NTx and CTx. Serum formation markers are secreted by the osteoblast and are subject to less biologic variation. Diurnal variation of serum BAP is also less evident. Urine assays of resorption markers usually show high biologic variability, and their clinical usefulness is also limited due to diurnal variation. Potential uses of these markers are to (1) predict bone loss at menopause to identify “fast” versus “slow” bone losers, (2) monitor response to antiresorptive therapy in postmenopausal osteoporosis, (3) estimate fracture risk, (4) predict changes in bone mineral density to antiresorptive therapy, and (5) monitor compliance with treatment. However, biochemical markers provide little or no help in the diagnosis of osteoporosis. Significant changes in biochemical markers are generally observed within 3 to 6 months of treatment with antiresorptive drugs in postmenopausal osteoporosis. In response to treatment, changes in formation markers lag behind changes in resorption markers. Conflicting data in the literature preclude the use of these markers as surrogate of any efficacy endpoints in clinical practice. The clinical utility of these markers other than in postmenopausal osteoporosis has not been clearly demonstrated. Future long-term longitudinal studies with measurements of specific markers of bone formation and resorption will lead to a better understanding of their clinical usefulness.

Is Change in Bone Mineral Density an Adequate Surrogate for Assessing the Effect of Antiresorptive Medications on Fracture Risk?

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Bone mineral density (BMD) has been shown to be a strong predictor of future fracture risk, and it has been thought that antiresorptive drugs that reduce fracture risk do so by improving bone mineral density. In fact, the U.S. Food and Drug Administration and other regulatory agencies base their approval of some medications solely on showing effectiveness for BMD. If the pathway of action of a drug in reducing risk is solely through its effect on BMD, then a drug's effect on BMD should accurately predict its effect on fracture risk. To test this hypothesis, we compared the BMD effects to vertebral fracture effects from a large number of recent clinical trials of osteoporosis medications. To compile a comprehensive list of trials, we performed MEDLINE searches of the published literature, examined abstracts from major meetings over the past 2 years, and queried experts in the field. We included all trials of antiresorptive medications that were large enough to have at least five fractures per treatment. A total of 11 trials of 6 medications, which randomized a total of about 19,000 women, were included. We correlated the active/placebo BMD difference to the log of the relative risk for the observed fracture effect and performed a weighted linear regression analysis. There were two major findings from this analysis. First, we found that, in general, the studies that showed the largest BMD effects tended to show the largest fracture reductions. However, despite the large number of studies, the correlation was only moderate and was only marginally statistically significant ($p = .09$). Second, we found that the changes in BMD were too small to account for the large decreases in fracture risk found in these trials. This suggests that factors other than BMD must account for at least some of the action of these drugs. To confirm these results, we performed an analysis using the method of Freedman and colleagues to estimate the proportion of the fracture effect that could be explained by the change in BMD in a large trial of alendronate. The results showed that change in BMD could explain only 15 to 17 percent of the effect of alendronate. We conclude that BMD only is not an adequate surrogate for assessing the potential effects of a drug on fracture risk. Since no other surrogates are presently available, trials with fracture endpoints are necessary to ascertain how effective a drug will be in reducing fracture risk.

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Quantitative Ultrasound as a Surrogate Endpoint for Fracture Risk in Osteoporosis Studies

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Osteoporosis is an enormous and growing public health concern. In the United States alone, it is estimated that 25 million postmenopausal women are at risk for fracture due to low bone mass. Despite the increased awareness of osteoporosis and expansion in clinical bone densitometry, only a minority of these individuals at risk are diagnosed, because traditional bone densitometry scans are not yet available to all patients who might benefit from knowledge of their skeletal status. Thus, it is clear that there is a growing need for bone densitometry techniques that can increase access to bone density testing. Quantitative ultrasound (QUS) has recently been introduced and shows promise as a tool for widespread screening and evaluation of skeletal status as it is quick, easy to use, portable, and free from ionizing radiation and requires a relatively low capital investment. Moreover, due to the nature of the interaction between ultrasound and bone, QUS may reflect skeletal properties that are distinct from bone mineral density. Devices currently approved by the U.S. Food and Drug Administration include those designed to assess bone at the heel and tibia. Prospective studies indicate that heel QUS is a strong predictor of hip fracture risk, with risk ratios (RR = 2.0) similar to those obtained from femoral BMD. However, there are few data available to evaluate whether QUS can be used to monitor therapeutic response and thus whether changes in QUS are predictive of changes in fracture risk. Randomized clinical trials incorporating QUS, BMD, and fracture as outcome measures are required to fully evaluate the potential clinical utility of QUS.

Assessment of Trabecular Bone Using Magnetic Resonance Imaging: Role in the Study of Osteoporosis

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Currently bone mineral density (BMD) testing is the most common clinical diagnostic for assessing skeletal status and fracture risk; however, there is strong evidence that trabecular bone structure may be of importance in osteoporosis (Kleerekoper et al. 1985; Parfitt 1982, 1987; Hodgkinson and Currey 1990), and considerable effort is being expended in developing techniques to assess trabecular bone microarchitecture noninvasively. In addition, bone macroarchitecture and changes in trabecular bone microarchitecture may play a role in and affect the biomechanical competence of trabecular bone. The heterogeneity in the microarchitecture of trabecular bone is primarily governed by physiological function and mechanical loading on the skeleton. This results in trabecular bone microarchitecture being dependent on the anatomic site, as well as having a directional anisotropy of the mechanical properties and architecture (Zhu et al. 1994; Ciarelli et al. 1991; Martens et al. 1983; Schoenfeld et al. 1974; Goldstein 1987). Traditionally, trabecular structure has been assessed using a two-dimensional analysis of histomorphometry sections obtained from iliac crest biopsies. However, the anisotropy of trabecular orientation and connectivity of trabecular bone, which is a three-dimensional (3-D) quantity, is likely to play an important role in determining bone strength. With recent hardware and software advances, magnetic resonance (MR) images with spatial resolutions of 80 to 200 μm and slice thicknesses of 300 to 700 μm , which resolve the trabecular structure, have been obtained both in vitro and in vivo. In conjunction with 3-D image processing and an understanding of the mechanisms of image formation, these high-resolution images may be used to quantify trabecular bone architecture. In addition to obtaining standard stereological measures such as trabecular bone volume, mean trabecular width, mean trabecular spacing, mean intercept length as a function of angle, parameters such as 3-D connectivity as

measured by the Euler number, fabric tensor in three dimensions, and texture-related parameters such as fractal dimension may be derived from such images. In vitro, quantitative measures of trabecular architecture derived from such images have been compared with those obtained from higher resolution 18 μm images and with those with biomechanical properties. In vivo, high-resolution MR techniques combined with standard techniques of stereology and texture analysis have been used to determine the relationship between trabecular bone structure parameters, age, and measures of BMD and osteoporotic status. Furthermore, these structure measures may be combined with density measures to assess the added role of trabecular microarchitecture, as well as combined with finite element modeling to predict mechanical properties of bone. The issues associated with longitudinal assessment of trabecular bone structure in vivo are complex and will be discussed. Recent results emphasize the need for studies to establish the role of bone structure in understanding the pathophysiology of osteoporosis, and the mechanism of therapeutic action clearly warrants further investigation. However, with the recent advances in technology and research, the potential of combining MR imaging with 3-D image analysis provides a potentially unparalleled tool for this purpose.

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Radiographically Detected Vertebral Deformities and Loss of Stature as Surrogate Endpoints in Osteoporosis

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The primary objective of osteoporosis treatment and prevention is to reduce the risk of clinical fractures and their associated morbidity, including pain, limitation of activity, and disability. Although hip fractures cause the greatest morbidity, a wide variety of other fractures are common in elderly persons and also result in substantial morbidity. Radiographically detected vertebral deformities are the most common fracture in elderly patients, a hallmark of osteoporosis, and the primary fracture endpoint in most clinical trials of osteoporosis treatments. However, a large proportion of these radiographically detected deformities are asymptomatic; an even larger proportion escape clinical detection, and their clinical and functional impact remains uncertain. We will examine evidence for the validity of radiographically detected vertebral deformities as surrogate endpoints for clinical fractures and the morbidity caused by osteoporosis. What is the morbidity associated with vertebral deformities? What is the

relationship between deformities and clinical spine fractures and between deformities and other clinical fractures? How well do the treatment effects observed for vertebral deformities agree with the effects of the same treatment on clinical spine fractures and on other clinical fractures? Do we see effects of treatment on morbidity related to spine fractures? Does a reduction in deformities or spine fractures explain the effect observed on morbidity? Similarly, we will examine the validity of loss of stature as a valid surrogate endpoint for radiographically detected vertebral deformities or spine fractures.

Biological Markers of Bone Turnover: Clinical Value of Biochemical Markers

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Bone turnover markers could have clinical utility in setting treatment for osteoporosis if they predicted response to treatment or allowed monitoring of response. So far, these markers have been evaluated against another surrogate marker, bone mineral density in clinical trials. They need to be evaluated against the probability of sustaining a fracture. The markers could be used to evaluate efficacy of treatment and to enhance compliance. We need to know the relationship of response to variability to characterize an individual's response. We need to know whether excessive dosage is harmful such that titration of treatment to response is a valid exercise. We need to know whether compliance is enhanced by treatment monitoring. We need to conduct studies that monitor bone turnover after cessation of therapy to understand how long treatment effects persist. Finally, we could use markers to evaluate anabolic treatments for osteoporosis, not just to identify such compounds in the short term, but also to devise the optimal dosing regime.

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Biological Markers of Bone Turnover: Current Status as Surrogate Endpoints in Clinical Trials

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In the setting of clinical trials, biochemical markers of bone turnover should be considered validated surrogate efficacy parameters for compounds where the primary mechanism of action is antiresorptive (or where at least a significant proportion of the antifracture efficacy is presumed to be mediated by this mechanism). Substantial evidence supports a key role of enhanced bone turnover in the pathogenesis of osteoporosis and osteoporotic fractures:

- Estrogen deficiency is associated with an increased rate of bone turnover, whether measured histomorphometrically or by use of biochemical markers (Eriksen et al. 1990; Eastell et al. 1988; Riis 1996; Garnero et al. 1994; Riis et al. 1996). With any imbalance between resorption depth and wall thickness, any increase in activation frequency will be associated with an increased rate of decline in bone mass. In addition, estrogen deficiency is associated with an increase in the degree of negative bone balance at each BMU, which, together with the increased activation frequency, further exacerbates the rate of decline in bone mass.
- Increased bone turnover is predicted to decrease bone strength (and increase fracture risk) independently of its effect to decrease bone mass (e.g., via an increased number of resorption spaces, decreased ability of trabeculae to withstand buckling loads due to the presence of resorption lacunae, and decreased trabecular connectivity due to increased perforation) (Einhorn 1992; Parfitt et al. 1983; Riggs et al. 1996).

This biomechanical theory has been supported by several prospective studies in which patients in the highest quartile for bone turnover demonstrated a significantly increased relative risk for either hip or vertebral fractures. The predictive value of increased bone turnover was as predictive of fracture risk as decreased bone mineral density (BMD) and was independent of BMD; hence, the risk of high turnover was additive to that imposed by low bone mass (Garnero et al. 1995; Ross et al. 1997). Data from prospective fracture trials have shown that the fracture efficacy demonstrated is substantially greater than that predicted by the increased BMD alone (Cummings et al. 1996). Both the magnitude and the time course of the fracture efficacy observed are inconsistent with the entire effect being mediated only or substantially by increased BMD and support the concept that the efficacy derives primarily from the substantial and rapid decrease in bone turnover (Black et al. 1996). For antiresorptive agents, there appears to be a relationship between the magnitude of the turnover suppression and the magnitude of the fracture efficacy. Thus, in the clinical trial setting, markers of bone turnover constitute validated surrogates for the clinical endpoint of fractures. Recommendations for future study/analysis include quantification of the relationship between bone turnover decrease and reduction in fracture risk, as well as studies to evaluate the validity of turnover markers as efficacy surrogates for anabolic agents.

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