

Appendix II

Summary of Valid Scientific Evidence Supporting Recommendation

NOTE: Copies of these articles ARE INCLUDED in this submission.

They are in the same order as listed here.

See Book 2 of 3 for 1 thru 47 and Book 3 of 3 for 48 thru 88.

1. **Ann Laskey, M and Prentice, A: Do appendicular bone measurements reflect changes in the axial skeleton? The use of dual-energy x-ray absorptiometry and ultrasound measurements during lactation. Journal of Clinical Densitometry. 7:296-301, 2004.** The authors monitor change in bone in lactating women for up to one year using DXA and the McCue CUBA. What the study showed was that while the DXA results show significant loss with lactation, BUA measured by the CUBA does not change over this time period. The study serves to show the CUBA is safe and precise when used to monitor change over time.
2. **Andrew, T, et al: Linkage and association for bone mineral density and heel ultrasound measurements with a simple tandem repeat polymorphism near the osteocalcin gene in female dizygotic twins. Osteoporosis International. 13:745-754, 2002.** The authors follow the effect of a tandem repeat polymorphism near the osteocalcin gene on DXA measured bone density and the results of measurements made with the McCue CUBA and find similar changes after menopause. The study serves to show the CUBA is safe and can identify similar results between groups.
3. **Arden, NK, et al: Polymorphisms of the vitamin D receptor gene do not predict quantitative ultrasound of the calcaneus or hip axis length. Osteoporosis International. 6:334-337, 1996.** The authors examine the relationship between polymorphisms of the vitamin D receptor gene and hip axis length measured by DXA and measurements by the McCue CUBA in 189 healthy female twin pairs. The authors do not find a detectable relationship between the polymorphism and the bone results. The study serves to show the CUBA is safe and can identify similar results between groups.
4. **Aspray, TJ, et al: Comparison of ultrasound measurements at the heel between institutional adults with mental retardation and control subjects. Bone. 22:665-668, 1998.** The authors use the McCue CUBA to examine 170 subjects with mental retardation and 108 control subjects. The authors found that the population of subjects with mental retardation showed a marked reduction of BUA. The study serves to show the CUBA is safe and can identify differences between groups.
5. **Barr, RJ, et al: Screening elderly women for risk of future fractures—Participation rates and impact on incidence of falls and fractures. Calcified Tissue International. 76:243-248, 2005.** The authors investigate the impact of BUA assessment with the McCue CUBA in future fall and fracture incidence in a population of elderly women. What the authors find is that those subjects who were examined by the McCue CUBA tolerated the test without problem and seemed to experience a reduction in increased age-associated fall and fracture rate. The study serves to show the CUBA is safe and makes an impact on the subject evaluated.
6. **Bayer, M and Kutilek, S: Ultrasound transmission through the os calcis in children: Which side should we measure? Calcified Tissue International. 61:441-442, 1997.** The authors use the McCue CUBA to examine left and right heel differences in measured results in a population of 373 children. An average difference of 11% was found between the left and right heel indicating that follow-up studies should be done on same side. The study serves to establish procedure and shows the CUBA is safe.
7. **Bennell, KL, et al: Acute and subacute changes in the ultrasound measurements of the calcaneus following intense exercise. Calcified Tissue International. 63:505-509, 1998.** The authors use the McCue CUBA to examine BUA and VOS in a population of 111 marathon runners and 28 nonrunning controls. The study reports that the runners have significantly higher BUA than nonrunners and that immediately after the marathon and returned to baseline levels after 5-6 days. The study serves to show the CUBA is safe and reflects differences between groups and over time.

8. **Bernaards, CM, et al: Smoking and quantitative ultrasound parameters in the calcaneus in 36-year-old men and women. Osteoporosis International. 15:735-741, 2004.** The authors examine the effect of smoking in a population of 174 men and 187 women using the McCue CUBA. The study shows that while DXA shows no effect of smoking, a reduced SOS was found in smoking men and women and a reduced BUA was found in lifetime female smokers. The authors suggest that smoking may have a negative effect on bone that is first noticed by ultrasound results. The study serves to show the CUBA is safe and reflects differences in bone.
9. **Brooke-Wavell, K, et al: Commencing, continuing and stopping brisk walking: Effects on bone mineral density, quantitative ultrasound of bone and markers of bone metabolism in postmenopausal women. Osteoporosis International. 12:581-587, 2001.** The authors examine the effect of a walking exercise program on DXA measured bone density and measurements by the McCue CUBA. The results show that on starting exercise BUA—but not BMD—was increased but that in the second year no further changes occurred. Subjects who stopped exercising showed a significant decrease in BMD but not BUA. The study serves to show the CUBA is safe and reflects differences between groups and over time.
10. **Burston, B, et al: Determination of a standard site for the measurement of bone mineral density of the human calcaneus. Journal of Anatomy. 193:449-456, 1998.** The authors examine the precision of measurements made by the McCue CUBA at different anatomical sites of the heel. The study establishes a site where these measurements can be made with consistent precision. The study serves to establish procedures with the CUBA.
11. **Daly, RM, et al: Influence of high impact loading on ultrasound bone measurements in children: A cross-sectional report. Calcified Tissue International. 60:401-404, 1997.** The study uses the McCue CUBA to examine 33 gymnasts and 40 normoactive controls to see if the highly active develop differences in bone. The gymnast showed significantly greater VOS results than seen in the control but did not show differences in BUA. The study serves to show the CUBA is safe and reflects differences between groups.
12. **De Hart, R and Gonzalez, EH: Osteoporosis: Point-of-Care testing. Annals of Pharmacotherapy. 38:473-481, 2004.** The authors review the literature and report that ultrasonometry—including the McCue CUBA—is safe and can be used to assess patients. The authors note that when overseen by a physician the evaluation can meet reimbursement under CPT Code 76977 for assessment of disease. The article serves to show that the CUBA is accepted and safe when assessing patients.
13. **Dhonukshe-Rutten, RAM, et al: Homocysteine and vitamin B₁₂ status relate to bone turnover markers, broadband ultrasound attenuation, and fractures in healthy elderly people. Journal of Bone and Mineral Research. 20:921-929, 2005.** A population of 1,321 subjects underwent measurement with the McCue CUBA with homocysteine and bone marker assessment. Later follow-up showed that a combination of high plasma levels of homocysteine and low vitamin B₁₂ were related to a low BUA, increased bone turnover markers and high fracture risk. The study serves to show that the CUBA is safe and able to identify subjects with conditions that may produce high fracture risk.
14. **Dolan, AL, et al: Assessment of bone in Ehlers Danlos Syndrome by ultrasound and densitometry. Annals of Rheumatic Diseases. 57:630-633, 1998.** This study examined 23 patients with Ehlers Danlos Syndrome using the McCue CUBA to examine if this condition affected bone. The study confirmed that these patients show significantly lower BUA and VOS results than seen in the controls. These patients may be at increased risk of osteoporosis. The study serves to show that the CUBA is safe and identifies patients with poorer bone.
15. **Drysdale, IP, et al: Bilateral variation in calcaneal broadband ultrasound attenuation—Part II: As measured by three bone densitometers employing ultrasound or x-ray. Journal of Clinical Densitometry. 4:337-341, 2001.** The study examined the left to right heel difference in three heel scanners—including the McCue CUBA. The study confirmed earlier studies that show that there can be a significant left to right heel difference in normal subjects. This demonstrates that care should be taken in documenting which heel is being evaluated. The study serves to establish procedures that should be used in studies done with the CUBA.

16. **Etherington, J, et al: The effects of 10 weeks military training on heel ultrasound and bone turnover. *Calcified Tissue International*. 64:389-393, 1999.** To assess the effect of significant exercise the study evaluated 40 military trainees over 10 weeks using the McCue CUBA. The study confirmed that those subjects who completed the 10 weeks showed a significant decrease in VOS and a nonsignificant increase in BUA indicating some response to the heavy activity. Of the subjects that did not complete the training program because of injury, the authors note that they had a significantly lower VOS on entry to the program. The study serves to show the CUBA is safe and effectively shows differences over time.
17. **Falcini, F, et al: Comparison of quantitative calcaneal ultrasound and dual energy x-ray absorptiometry in the evaluation of osteoporotic risk in children with chronic rheumatic diseases. *Calcified Tissue International*. 67:19-23, 2000.** The authors examine 53 rheumatic disease patients with the McCue CUBA and DXA over one year. Both CUBA assessed BUA the DXA studies were significantly lower than seen in control subjects. Changes in BUA and DXA-measured BMD over the year were significantly correlated. The authors note that the CUBA results effectively reflect the condition of these patients. The study serves to show the CUBA is safe and show differences in time.
18. **Garcia, AR, et al: Bone ultrasound in healthy women and bone mass related factors. *Medicina Clinica*. 113:285-289, 1999.** The authors use the McCue CUBA to examine BUA in 136 premenopausal and 119 postmenopausal women and find that in this population BUA is most strongly related to age and body weight. The study serves to show the CUBA is safe and effective.
19. **Gluer, CC, et al: Peripheral measurement techniques for the assessment of osteoporosis. *Seminars in Nuclear Medicine*. 27:229-247, 1997.** The authors evaluate the role of peripheral technology—including the McCue CUBA—in the assessment of osteoporosis. Briefly, the authors note that ultrasound is safe (no radiation risk) and a good reflector of fracture risk but may not reflect changes with treatment over time. The study serves to show that the CUBA is safe and can be useful in assessing fracture risk.
20. **Gonnelli, S and Cepollaro, C: The use of ultrasound in the assessment of bone status. *Journal of Endocrinologic Investigation*. 25:389-397, 2002.** The authors evaluate the role of ultrasound based technology—including the McCue CUBA—in the assessment of osteoporosis. Briefly, the authors note that ultrasound is safe (no radiation risk) and a good reflector of fracture risk but may not reflect changes with treatment over time. The study serves to show that the CUBA is safe and can be useful in assessing fracture risk.
21. **Graafmans, WC, et al: The influence of physical activity and fractures on ultrasound parameters in elderly people. *Osteoporosis International*. 8:449-454, 1998.** The authors evaluated the left and right heel in 710 elderly subjects using the McCue CUBA. The authors report significant left to right heel differences in these subjects. The authors also demonstrate BUA and VOS are related to levels of physical activity so that as the subject becomes less active values decrease with increasing risk of fracture. The study serves to establish procedures for clinical protocol and shows that the CUBA is safe and can be useful in assessing fracture risk.
22. **Graafmans, WC, et al: Ultrasound measurements in the calcaneus: Precision and its relation with bone mineral density of the heel, hip, and lumbar spine. *Bone*. 19:97-100, 1996.** The study uses the McCue CUBA to evaluate precision and the relationship between bone density, BUA and fracture. The study finds that short and long-term precision are good and that a low BUA predicted a low hip BMD. In addition, subjects with known vertebral fracture were found to have lower BUA values than subjects without vertebral fracture. The study serves to establish precision obtained with the CUBA and documents that effectiveness of the system.
23. **Greenfield, DM and Eastell, R: Risk factors for ankle fracture. *Osteoporosis International*. 12:97-103, 2001.** Trying to establish risk factors for ankle fracture, the authors examine the ankle fracture in elderly subjects by DXA and Ultrasound—using the McCue CUBA—but find no direct evidence to explain which subjects will fracture. The authors note, however, that ankle fractures are not generally considered typical of osteoporotic fractures. The study serves to show the CUBA is safe.

24. **Greenspan, SL, et al: Precision and discriminatory ability of calcaneal bone assessment technologies. Journal of Bone and Mineral Research. 12:1303-1313, 1997.** The study uses a number of heel scanning systems—including the McCue CUBA—to examine a population of 53 young normal women and 108 postmenopausal women with osteoporosis. While precision among systems was variable—the McCue CUBA reported a %CV of 4.37%—all five systems were able to discriminate between osteoporotic patients and young normal controls so that subjects with osteoporosis could be identified. The study serves to show the CUBA is precise and safe.
25. **Hausler, KD, et al: Water bath and contact methods in ultrasonic evaluation of bone. Calcified Tissue International. 61:26-29, 1997.** The study compares ultrasound methods using water-bath or contact methods (McCue CUBA). The authors report that results obtained by the water bath and contact methods are highly correlated. The study serves to show the CUBA performs effectively.
26. **Hausler, KD, et al: Relationship between static histomorphometry and ultrasound in the human calcaneus. Calcified Tissue International. 64:477-480, 1999.** The study examines the relationship between histomorphometric bone distribution and measurements made by the McCue CUBA. The authors examined 15 cadaveric heels with the CUBA and histomorphometry and conclude that there is no significant correlation between BUA or VOS and cancellous bone structure measured by histomorphometry. The study serves to show that the CUBA is assessing something other than histomorphometry assessed structure.
27. **Hodgkinson, R, et al: The ability of ultrasound velocity to predict the stiffness of cancellous bone in vitro. Bone. 21:183-190, 1997.** The authors use the McCue CUBA to examine possibility that VOS may provide some indication of stiffness. The authors examine 18 bovine cubes with the CUBA and find that the VOS measurement can give structure specific information. The study serves to show that measurements made by the CUBA can reflect bone properties.
28. **Howard, GM, et al: Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements: A twin study. Journal of Bone and Mineral Research. 13:1318-1327, 1998.** Examining 93 sets of twins, the authors use the McCue CUBA to examine genetic and environmental contributions to BUA and VOS. The authors find as much as an 80% genetic influence on variance in ultrasound parameters. The study serves to show that measurements made by the CUBA are reflecting properties largely related to genetic factors.
29. **Howard, GM, et al: Influence of handedness on calcaneal ultrasound: Implications for assessment of osteoporosis and study design. Osteoporosis International. 7:190-194, 1997.** The authors examine 264 subjects using the McCue CUBA to determine the influence of handedness on parameters measured by heel ultrasound. The authors found significant differences between left and right heel BUA but found no difference between left and right heel VOS. The authors recommend that studies using calcaneal ultrasound standardize the side being examined to eliminate side dependence. The study serves to set an examination protocol and shows that the CUBA is safe and precise.
30. **Hunter, D, et al: A randomized controlled trial of vitamin D supplementation on preventing postmenopausal bone loss and modifying bone metabolism using identical twin pairs. Journal of Bone and Mineral Research. 15:2276-2283, 2000.** The authors examine the effect of two years of vitamin D supplementation in healthy young women using DXA and the McCue CUBA and found that vitamin D supplementation did not produce any significant change in BMD or BUA in the two years. The study serves to show that the CUBA is safe and reflects changes in bone.
31. **Ingle, BM and Eastell, R: Site-specific bone measurements in patients with ankle fracture. Osteoporosis International. 13:342-347, 2002.** The authors studied 31 healthy post-menopausal women and 31 post-menopausal women with a history of ankle fracture by DXA and ultrasound using the McCue CUBA. The authors found no difference between healthy and fractured subjects in DXA or BUA but did see that fractured subjects had reduced VOS measurements that may reflect structural changes that relate to fragility. The study serves to show that the CUBA is safe and reflects the condition of bone.

32. **Ingle, BM, et al: Changes in bone mass and bone turnover following ankle fracture. Osteoporosis International. 10:408-415, 1999.** The authors studied 14 elderly subjects with ankle fracture over a period of one year by DXA and ultrasound using the McCue CUBA. There was a significant decrease in BMD at the ankle and trochanter and VOS and BUA after the fracture. At 52 weeks BMD at the ankle and VOS were back to baseline but trochanteric BMD and BUA did not return to baseline. This study serves to show that the CUBA is safe and reflects what is happening to bone.
33. **Ingle, BM, et al: Differential effects of primary hyperparathyroidism on ultrasound properties of bone. Osteoporosis International. 13:572-578, 2002.** The authors studied 25 postmenopausal women diagnosed with primary hyperparathyroidism and 95 control subjects by DXA and ultrasound using the McCue CUBA. At diagnosis the hyperparathyroid subjects showed hand and spine BMD and heel BUA significantly lower than controls. At one year postoperation hand and spine BMD and heel BUA showed significant increases and returned towards normal postmenopausal values. The study serves to show that the CUBA is safe and reflects what is happening to bone.
34. **Jakes, RW, et al: Patterns of physical activity and ultrasound attenuation by heel bone among Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk): population based study. British Medical Journal. 322:140-144, 2001.** The study examined the relationship between activity level and BUA measured by the McCue CUBA in 5,210 subjects. The authors find that subjects with increased physical activity showed higher BUA results building a case to consider promoting activity as an intervention behavior. The study serves to show that the CUBA is safe and reflects what is happening to bone.
35. **Jawed, S, et al: Quantitative heel ultrasound variable in powerlifters and controls. British Journal of Sports Medicine. 35:274-275, 2001.** The authors compare ultrasound parameters measured by the McCue CUBA in a population of 24 powerlifters to results from 21 sedentary controls. When adjusted for analysis the authors find both BUA and VOS were significantly higher in the powerlifters than seen in the sedentary controls. The study serves to show that the CUBA is safe and reflects what is happening in bone.
36. **Johansen, A and Stone, MD: The effect of ankle oedema on bone ultrasound assessment at the heel. Osteoporosis International. 7:44-47, 1997.** The authors examine the effect of oedema on ultrasound measurements using the McCue CUBA. Eleven subjects with oedema were repeatedly evaluated with rubbing of the area between studies. The authors found significant reduction in VOS and BUA with reduced oedema. The study serves to develop a protocol and shows that the CUBA is safe. Note that the CUBA now addresses the issue of oedema by repeatedly pressing the target area prior to ultrasound sampling.
37. **Keen, RW, et al: Evidence of association and linkage disequilibrium between a novel polymorphism in the transforming growth factor β 1 gene and hip bone mineral density: a study of female twins. Rheumatology. 40:48-54, 2001.** The authors examine a population of 1,706 twins by DXA and ultrasound (McCue CUBA) to establish if bone is related to TGF- β 1. The study shows that subjects that were homozygous for the TGF- β 1 C allele showed a 4% reduction in femur neck BMD but showed no difference in spine, forearm or ultrasound parameters. The study serves to show that the CUBA is safe and reflects what is happening to bone.
38. **Khaw, KT, et al: Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. Lancet. 363:197-202, 2004.** This study examined a population of 14,824 with the McCue CUBA and over 1.9 years of follow-up was able to relate BUA to fracture risk over the follow-up period. Subjects with the lowest 10% of BUA had a relative risk of fracture of 4.44 compared to those with the highest 30% of BUA. Furthermore, a decrease of 1 SD in BUA was associated with a relative risk of fracture of 1.95 confirming a continuous relationship between BUA and fracture risk. The study serves to show that the CUBA is safe and reflects what is happening to bone.

39. **Knapp, KM, et al: An investigation of unique and shared gene effects on speed of sound and bone density using axial transmission quantitative ultrasound and DXA in twins. *Journal of Bone and Mineral Research*. 18:1525-1530, 2003.** This study the heritability of DXA measured BMD and McCue CUBA measured BUA in a study population of 215 pairs of twins. The study showed heritability of 0.58 for BUA and between 0.72 and 0.77 for axial BMD in this population. The study serves to show that the CUBA is safe and reflects what is happening to bone in this population.
40. **Langton, CM and Langton, DK: Male and female normative data for ultrasound measurement of the calcaneus within the UK adult population. *British Journal of Radiology*. 70:580-585, 1997.** The authors examine ultrasound parameters in a population of 169 male and 210 female subjects between 20 and 80 years using the McCue CUBA. Female data shows a peak between 30 and 39 years of age and then shows a steady fall thereafter. Results from male subjects show less age related dependence. The study serves to show that the CUBA is safe and reflects what is happening to bone.
41. **Langton, CM and Langton, DK: Comparison of bone mineral density and quantitative ultrasound of the calcaneus: Site-matched correlation and discrimination of axial BMD status. *British Journal of Radiology*. 73:31-35, 2000.** Using traditional DXA and the McCue CUBA the authors examine 91 postmenopausal women referred for DXA assessment. Using ROC analysis the authors find that heel DXA (0.814) was only slightly better than heel BUA (0.791) in identifying osteoporotics. The study serves to show that the CUBA is safe and reflects what is happening to bone.
42. **Langton, CM and Njeh, CF: Sound-tissue interaction—The physical basis of bone ultrasonometry and limitations of existing methods. *Journal of Clinical Densitometry*. 1:295-301, 1998.** The authors review the concepts of velocity measurements and broadband attenuation assessed in the bone ultrasound systems—including the McCue CUBA. The study serves to show that the CUBA is safe and reflects what is happening to bone as effectively as most other ultrasound systems.
43. **Langton, CM, et al: Prediction of mechanical properties of the human calcaneus by broadband ultrasonic attenuation. *Bone*. 18:495-501, 1996.** The authors evaluate the relationship between mechanical properties and BUA measured in 20 excised human calcanei with the McCue CUBA. An interesting finding was that power law relationship between BUA and apparent density. The study serves to show that the CUBA reflects what is happening in bone.
44. **Martin, JC, et al: A comparison of radial peripheral quantitative computed tomography, calcaneal ultrasound, and axial dual energy x-ray absorptiometry measurements in women aged 45-55 yr. *Journal of Clinical Densitometry*. 2:265-273, 1999.** The authors are evaluating how pQCT assessment of the forearm may reflect bone loss in early menopause. The study evaluated 119 perimenopausal women by pQCT, Spine and Hip DXA and ultrasound—using the McCue CUBA. The study demonstrated menopausal subjects showed significantly lower spine, hip and BUA results than seen in the premenopausal subjects. Additionally, pQCT showed the major radial bone mineral content losses in the subcortical region. The study serves to show that the CUBA is safe and reflects what is happening in bone.
45. **Martin, JC, et al: Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: Comparison with axial measurements. *British Journal of Rheumatology*. 36:43-49, 1997.** The authors evaluated bone loss measured by pQCT, ultrasound—using the McCue CUBA—and traditional DXA in postmenopausal women with rheumatoid arthritis. The study examined 29 control subjects, 21 patients with rheumatoid arthritis that had not been treated with corticosteroids and 25 patients with rheumatoid arthritis being treated with corticosteroids. Bone mass was significantly reduced in all rheumatoid arthritis patients by pQCT (31%), heel BUA (31%), heel VOS (6.6%) and femur neck (15.4%) but not spine. The study serves to show that the CUBA is safe and reflects what is happening in bone.
46. **Martin, JC and Reid, DM: Appendicular measurements in screening women for low axial bone mineral density. *British Journal of Radiology*. 69:234-240, 1996.** The authors evaluated bone measured by pQCT, ultrasound—using the McCue CUBA—and traditional DXA in a perimenopausal population of 216 women to see if peripheral assessments would reflect what is happening in the axial skeleton. The authors found that neither pQCT or ultrasound effectively reflected the spine or hip DXA assessment. The

study serves to show that the CUBA is safe but that reflection of axial bone density is not by a simple direct relationship.

47. **McCloskey, E, et al: Effects of Clodronate on vertebral fracture risk in osteoporosis: A 1-year interim analysis. *Bone*. 28:310-315, 2001.** This one-year report on a clinical trial examining the effect of Clodronate examines changes evaluated by DXA and ultrasound—using the McCue CUBA—in a randomized population of 677 patients. DXA based assessments are indicating that at one year Clodronate is increasing spine and hip BMD. Although only 135 patients have undergone a one year CUBA assessment, it seems BUA showed a 3.4% increase in the treatment group—compared to 0.2% in the placebo group—that proved not to be significant. The study serves to show that the CUBA is safe and may with time reflect response to treatment.
48. **McCloskey, E, et al: Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: Results of a double-blind, placebo-controlled 3-year study. *Journal of Bone and Mineral Research*. 19:728-736, 2004.** This three-year report on a clinical trial examining the effect of Clodronate examines changes evaluated by DXA and ultrasound—using the McCue CUBA—in a randomized population of 677 patients. DXA based assessments indicate Clodronate increases spine BMD. At three years CUBA assessment demonstrates significantly increased heel BUA in treated subjects. The study serves to show that the CUBA is safe and may with time reflect response to treatment.
49. **Miller, CG: Methodology for the clinical assessment of medical instrumentation—Evaluating ultrasonometers. *Journal of Clinical Densitometry*. 1:309-316, 1998.** The author reviews eight ultrasonometers (including the McCue CUBA) examining system precision and applicability to the market. In general, these systems are found to be safe and find some role in the international marketplace.
50. **Mughal, MZ, et al: Comparison between broad-band ultrasound attenuation of the calcaneum and total body bone mineral density in children. *Acta Paediatrica*. 85:663-665, 1996.** The authors examine BUA—measured with the McCue CUBA—and DXA-based total body bone density in a population of 58 children. BUA was found to be significantly correlated with total body bone density. The study serves to show that the CUBA is safe and reflects what is happening in bone.
51. **Mughal, MZ, et al: Assessment of bone status using the contact ultrasound bone analyzer. *Archives of Diseases in Childhood*. 76:535-536, 1997.** The authors examine BUA—measured with the McCue CUBA—in a normal population of 367 children and find the result increase with age and are significantly correlated with age, height and weight. The study serves to show that the CUBA is safe and reflects what is happening in bone.
52. **Mulherin, D, et al: Identification of risk factors for future fracture in patients following distal forearm fracture. *Osteoporosis International*. 14:757-760, 2003.** The authors examined 148 subjects with distal forearm fracture assessing falls risk, future hip fracture risk and heel ultrasound BUA—using the McCue CUBA. The authors found that about 85% of subjects with low BUA were later confirmed osteopenic or osteoporotic by DXA. The authors also noted that the older and less ambulatory subjects would likely not have visited a DXA facility had they not first found the reduced ultrasound BUA. The study serves to show that the CUBA is safe and can motivate patients to pursue further assessment or treatment.
53. **Naganathan, V, et al: Gender differences in the genetic factors responsible for variation in bone density and ultrasound. *Journal of Bone and Mineral Research*. 17:725-733, 2002.** The authors examine a population of male and female twins (identical and nonidentical same-sex pairs and non-identical opposite-sex pairs) by axial and forearm DXA and heel ultrasound—using the McCue CUBA—to assess a role of genetic factors in variations of bone. The authors find that variations in DXA and ultrasound results in identical twins and like-sex non-identical twins were similar for both males and females suggesting little difference in the variance explained by genetics. The study serves to show that the CUBA is safe and can be used to evaluate bone.

54. **Naganathan, V, et al: Quantitative heel ultrasound as a predictor for osteoporosis. Medical Journal of Australia. 171:297-300, 1999.** This study evaluated 326 healthy subjects using DXA and the McCue CUBA. Depending on the variables being compared, the sensitivity and specificity of ultrasound measures varied in identifying the DXA-based osteoporotic, osteopenic and normal subject. The study serves to show that the CUBA is safe.
55. **Naganathan, V, et al: Peak bone mass is increased in the hip in daughters of women with osteoarthritis. Bone. 30:287-292, 2002.** The authors compare DXA-based bone density and ultrasound BUA and VOS in daughters of women with confirmed osteoarthritis to daughters of those without osteoarthritis. These daughters of women with osteoarthritis had significantly higher BMD when adjusted for BMI in the total hip, femur neck and Ward's regions but did not show significant differences in trochanteric region, spine or heel ultrasound. The study suggest that the observed higher BMD in older subjects with osteoarthritis may be due in part to a higher peak bone mass in some regional sites. The study serves to show that the CUBA is safe and reflects what is happening to bone.
56. **Nguyen TV and Eisman, JA: Genotype-sex interactions in the determination of bone mineral density and quantitative ultrasound measurements. Journal of Vietnamese Medicine. 1:8-19, 2001.** The authors examine male and female monozygotic and dizygotic twins to determine if DXA-assessed density and ultrasound assessed parameters—evaluated by the McCue CUBA—are genetically related. The authors report that both DXA and ultrasound parameters are highly heritable traits with some sharing between parameters. The study serves to show that the CUBA is safe and reflects what is happening in bone.
57. **Njeh, CF, et al: Comparison of six calcaneal quantitative ultrasound devices: Precision and hip fracture discrimination. Osteoporosis International. 11:1051-1062, 2000.** The authors compare precision and hip fracture discrimination of six heel ultrasound systems—including the McCue CUBA. The authors found precision on the CUBA to be 4.11% for BUA and 4.84% for VOS. All six ultrasound systems gave similar, statistically significant hip fracture discrimination for both VOS and BUA. The study serves to show that the CUBA is safe and reflects what is happening in bone.
58. **Njeh, CF, et al: Prediction of human femoral bone strength using ultrasound velocity and BMD: An in vitro study. Osteoporosis International. 7:471-477, 1997.** The authors examine excised femur head stiffness and strength using BMD-based DXA and ultrasound-based VOS using the McCue CUBA. What the authors report is that both BMD and VOS are individually and when combined are significant predictors of stiffness and strength. The authors suggest that these combined technologies may improve osteoporosis risk assessment. The study serves to show that the CUBA is reflecting what is happening in bone.
59. **Njeh, CF and Langton, CM: The effect of cortical endplates on ultrasound velocity through the calcaneus: An in vitro study. British Journal of Radiology. 70:504-510, 1997.** The authors examine a set of excised heel bones to determine what component of the bone is modifying results of ultrasound velocity in the McCue CUBA. Heel samples examined were whole (soft tissue removed), core (cylindrical sample), can (cancellous sample without cortex) and def (defatted cancellous sample). The authors find heel ultrasound velocity is determined mainly by the cancellous bone component. The study serves to show how measurements on the CUBA relate to bone composition.
60. **Nurmi-Lawton, JA, et al: Evidence of sustained skeletal benefits from impact-loading exercise in young females: A 3-year longitudinal study. Journal of Bone and Mineral Research. 19:314-322, 2004.** The authors examine the effect of substantial gymnastic activity on bone in a population of 23 young females compared to 33 normal young females. Bone parameters were evaluated over three years by DXA and heel ultrasound—using the McCue CUBA. Although smaller and lighter than the controls, at three years gymnasts showed 13-28% higher bone density and 45% higher for BUA. The study serves to show the CUBA is safe and reflects what is happening to bone.

61. **Ohishi, T, et al: Ultrasound measurement using CUBA Clinical System can discriminate between women with and without vertebral fractures. Journal of Clinical Densitometry. 3:227-231, 2000.** This study evaluated a population of 114 postmenopausal women with DXA and the McCue CUBA. The population included some women with spine fracture and some without. There was no significant difference between ultrasound and DXA parameters in discriminating subjects with fracture. The study serves to show the CUBA is safe and reflects the condition of bone.
62. **Pluijm, SMF, et al: Effects of gender and age on the association of apolipoprotein E ϵ 4 with bone mineral density, bone turnover and the risk of fractures in older people. Osteoporosis International. 13:701-709, 2002.** This study examined whether the presence of apolipoprotein E ϵ 4 was associated with a reduced BMD, lower BUA or VOS measured by the McCue CUBA or high bone turnover and high fracture risk. The authors report that in the presence of apolipoprotein E ϵ 4 females had lower BMD at several sites while younger (65-69 years) men showed lower BMD at the femur neck. In women no difference was found in BUA or VOS with apolipoprotein E ϵ 4 status while only the oldest men showed higher BUA and VOS in the presence of apolipoprotein E ϵ 4. The study serves to show the CUBA is safe and reflects the condition of bone.
63. **Pluijm, SMF, et al: Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. Osteoporosis International. 9:550-556, 1999.** A population of 710 elderly subjects was evaluated by the McCue CUBA with follow-up interviews over a mean period of 2.8 years. Multivariate analysis identified low BUA values and immobility as the strongest predictor of hip or other fracture. The study serves to show the CUBA is safe and reflects the condition of bone.
64. **Sambrook, PN, et al: Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxyvitamin D status, bone mass, and renal function in the frail and very old: A cohort study. Journal of Clinical Endocrinology and Metabolism. 89:5477-5481, 2004.** The authors investigate the role of parathyroid hormone, vitamin D status, BUA measured by the McCue CUBA and renal function on mortality in a population of 842 very old men and women. While there appears to be a role for parathyroid hormone in mortality, the other variables did not solely demonstrate a significant relationship with mortality. The study serves to show the CUBA is safe and reflects what is happening in bone.
65. **Sone, T, et al: Calcaneus as a site for the assessment of bone mass. Bone. 22 S:155S-157S, 1998.** The authors review the use of ultrasound based assessment of the heel noting that—while ultrasound may be much slower than DXA in establishing change over time—these assessments can provide useful information about bone quality. The review serves to show that ultrasound may be useful in reflecting what is happening to bone.
66. **Stagi, S, et al: Changed bone status in human immunodeficiency virus type 1 (HIV-1) perinatally infected children is related to low serum free IGF-1. Clinical Endocrinology. 61:692-699, 2004.** This study evaluated a population of HIV-1 children (one group with severe clinical symptoms and one group with mild or no clinical symptoms) using the McCue CUBA to see if skeletal status could be assessed. The authors found that children with mild or no clinical symptoms showed bone similar to controls while those with severe symptoms showed significantly reduced BUA and serum total and free IGF-1. The study serves to show the CUBA is safe and reflects what is happening in bone.
67. **Stewart, A, et al: Bone density and bone turnover in patients with osteoarthritis and osteoporosis. Journal of Rheumatology. 26:622-666, 1999.** The study compares bone assessed by DXA and ultrasound—using the McCue CUBA—in a population of 30 normal subjects and patients with osteoarthritis (30) and osteoporosis (30). The study finds that compared to normals and osteoarthritis subjects, osteoporotics had significantly reduced bone density by DXA and BUA by ultrasound. The study serves to show the CUBA is safe and reflects what is happening in bone.

68. **Stewart, A, et al: Cervical and trochanteric hip fractures: Bone mass and other parameters. Clinical Rheumatology. 18:201-206, 1999.** The study examines 310 hip fracture patients with DXA and heel ultrasound (McCue CUBA) to determine if there are parameters that relate to cervical and trochanteric hip fractures. Patients with cervical fracture demonstrated significantly higher BUA and total body BMD than patients with trochanteric fractures. The study serves to show the CUBA is safe and reflects what is happening in bone.
69. **Stewart, A and Reid, DM: Precision of quantitative ultrasound: Comparison of three commercial scanners. Bone. 27:139-143, 2000.** The study examines precision and the Monitoring Time Interval for three ultrasound systems—the McCue CUBA, the Lunar Achilles+ and the DTU-One. Precision with the three systems was similar. Monitoring Time Interval for BUA and VOS on the McCue CUBA was just over five years. The study serves to establish precision obtained with the CUBA and documents the estimated Monitoring Time Interval that can be employed on the system.
70. **Stewart, A and Reid, DM: Quantitative ultrasound or clinical risk factors—which best identifies women at risk of osteoporosis? British Journal of Radiology. 73:165-171, 2000.** A sample of 250 women referred for assessment of osteoporosis were evaluated by the McCue CUBA, DXA and Clinical Risk Assessment. ROC analysis demonstrated that BUA was a good predictor of spine and hip BMD with Clinical Risk Assessment being a significantly poorer predictor of BMD. The study serves to show the CUBA is safe and reflects the usefulness of the system to identify what is happening in bone.
71. **Stewart, A, et al: Predicting a second hip fracture—The potential role of dual x-ray absorptiometry, ultrasound, and other risk factors in targeting of preventive therapy. Journal of Clinical Densitometry. 2:363-370, 1999.** This study evaluated DXA bone density, heel ultrasound parameters and various clinical parameters to predict a second hip fracture among 394 patients with an initial hip fracture. The study demonstrated that low femur neck BMD, total body BMD, BUA—measured by the McCue CUBA—and poor mobility scores were significant predictors of a second hip fracture. The study serves to show the CUBA is safe and reflects what is happening in bone.
72. **Stewart, AD, et al: Correcting calf girth discriminates the incidence of falling but not bone mass by broadband ultrasound attenuation in elderly female subjects. Bone. 31:195-198, 2002.** This study used BUA measured by the McCue CUBA to grade subjects who have fallen within the past 12 months. Subjects with lower BUA are more likely to have fallen and will have spent less time on their feet per day and will have a smaller corrected calf girth. Corrected calf girth may be a useful assessment to identify subjects in whom to take steps to prevent future falls. The study serves to show the CUBA is safe and reflects what is happening in bone.
73. **Strelitzki, R, et al: Ultrasonic measurement: An evaluation of three heel bone scanners compared with a bench-top system. Osteoporosis International. 6:471-479, 1996.** The study evaluated the BUA and velocity parameters on three ultrasound scanners—McCue CUBA, Lunar Achilles and the UBA 375. All three systems were able to discriminate porosity differences of at least 3%; however, the values measured for the same porosity by the different systems differ. To some extent the authors suggest these differences relate to differences in technology and to a lack of standardization among manufacturers. The study serves to show the CUBA reflects differences in porosity.
74. **Strelitzki, R and Truscott, JG: An evaluation of the reproducibility and responsiveness of four ‘State-of-the-Art’ ultrasonic heel bone measurement systems using phantoms. Osteoporosis International. 8:104-109, 1998.** The authors examined the reproducibility of measurements done with four ultrasonometers, including the McCue CUBA, and found that the CUBA generate very repeatable results. The study serves to show the CUBA generates precise measurements.
75. **Taal, MW, et al: Usefulness of quantitative heel ultrasound compared with dual-energy x-ray absorptiometry in determining bone mineral density in chronic haemodialysis patients. Nephrology, Dialysis and Transplantation. 14:1917-1921, 1999.** The study evaluated ultrasound assessment—using the McCue CUBA—and DXA in a population of 88 dialysis patients. A relatively high negative predictive

value suggests ultrasound assessment can reliably screen out patients unlikely to have an osteoporotic BMD. The relatively low positive predictive values, however, mean that subjects classified as osteoporotic by ultrasound will require DXA assessment to confirm. The study serves to show the CUBA is safe and can effectively identify subjects without osteoporosis.

76. **Te Velde, SJ, et al: Birth weight and musculoskeletal health in 36-year-old men and women: Results from the Amsterdam Growth and Health Longitudinal Study. Osteoporosis International. 15:382-388, 2004.** The authors investigate the relationship between birth weight and musculoskeletal health in an adult population using DXA and ultrasound assessment using the McCue CUBA. The study could not establish a relationship between birth weight and BMD, BUA or muscle strength in the adult. The study serves to show the CUBA is safe and reflects what is happening in bone.
77. **Tomkinson, A, et al: Changes in bone mineral density in the hip and spine before, during, and after the menopause in elite runners. Osteoporosis International. 14:462-468, 2003.** The authors evaluated changes in DXA assessed BMD and ultrasound assessed BUA and VOS—using the McCue CUBA—in a population of perimenopausal elite runners. Postmenopausal runners not on hormone replacement therapy lost BMD from the femur neck and spine at the expected rates while heel BUA and VOS remained near young normal values. The study serves to show the CUBA is safe and reflects what is happening in bone.
78. **Trivedi, DP, et al: Effect of four monthly oral vitamin D₃ (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. British Medical Journal. 326:469-474, 2003.** Examining 238 subjects with ultrasound—using the McCue CUBA—the authors evaluate the effect of vitamin D supplementation over five years in older men and women. While serum vitamin D was higher in the treated group, analysis of the full population shows no significant difference in BUA or VOS between treated and placebo subjects at five years. The study serves to show the CUBA is safe and reflects what is happening in bone.
79. **Tromp, AM, et al: Quantitative ultrasound measurements of the tibia and calcaneus in comparison with DXA measurements at various skeletal sites. Osteoporosis International. 9:230-235, 1999.** The authors examine compare tibial and heel ultrasound and with DXA measurements of the spine, hip and whole body in a population of 109 elderly men and women. Heel ultrasound measurements—obtained with the McCue CUBA—show higher correlations with DXA measurements than seen with the tibial ultrasound. The study serves to show the CUBA is safe and reflects what is happening in bone.
80. **Tuzun, S, et al: Evaluation of bone with quantitative ultrasound in healthy Turkish children. Turkish Journal of Pediatrics. 45:240-244, 2003.** Using the McCue CUBA the authors examine BUA in 80 girls and 61 boys between 6 and 12 years of age. The authors find BUA increases linearly with age with boys having a significantly greater BUA by age 7. The study serves to show the CUBA is safe and reflects what is happening in bone.
81. **Van der Poest Clement, E, et al: Alendronate in the prevention of bone loss after a fractures of the lower leg. Journal of Bone and Mineral Research. 17:2247-2255, 2002.** The authors evaluate the effect of alendronate treatment on bone loss at one year after lower leg fractures as measured by DXA of the hip and ultrasound—using the McCue CUBA—BUA and VOS. The authors showed that alendronate prevented DXA measured bone loss at one year while placebo showed significant loss in the injured limb. Similarly, alendronate prevented BUA and VOS reduction in the injured limb over the one year period. The study serves to show the CUBA is safe and reflects what is happening in bone.
82. **Warden, SJ, et al: Efficacy of low-intensity pulsed ultrasound in the prevention of osteoporosis following spinal cord injury. Bone. 29:431-436, 2001.** The authors investigate whether ultrasound stimulation can prevent heel bone loss—measured by DXA or ultrasound measured BUA and VOS—in 15 patients with spinal cord injury. The authors find that spinal cord injury results in significant DXA measured bone loss and ultrasound measured BUA and VOS. Treatment with pulsed ultrasound was not overcome spinal cord injury induced heel osteoporosis. The study serves to show the CUBA is safe and reflects what is happening in bone.

83. **Warden, SJ, et al: Quantitative ultrasound assessment of acute bone loss following spinal cord injury: A longitudinal pilot study. Osteoporosis International. 13:586-592, 2002.** The authors investigate early heel bone loss in 15 male subjects with spinal cord injury. DXA assessed bone loss and ultrasound measured BUA and VOS—measured by the McCue CUBA—were examined over six weeks. Rapid bone loss was confirmed over the six weeks by DXA assessed BMD and ultrasound assessed BUA and VOS. The study serves to show the CUBA is safe and reflects what is happening in bone.
84. **Welch, A, et al: Calcaneum broadband ultrasound attenuation relates to vegetarian and omnivorous diets differently in men and women: an observation from the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Osteoporosis International. 16:590-596, 2005.** The authors examine a population of 6,369 men and 5,379 postmenopausal women with the McCue CUBA and examine the influence of a vegetarian and omnivorous diet on BUA. The authors find that while there is no difference among women, vegetarian men on a high soya diet have a significantly lower BUA. The study serves to show the CUBA is safe and reflects what is happening in bone.
85. **Welch, A, et al: Broadband ultrasound attenuation (BUA) of the heel bone and its correlates in men and women in the EPIC-Norfolk cohort: a cross-sectional population-based study. Osteoporosis International. 15:217-225, 2004.** This study is one of the largest studies available and uses the McCue CUBA to evaluate a population of 15,668 middle age and older men and women. The study confirmed that men generally have a higher BUA than women and with history of fracture have a lower BUA than subjects without fracture. The study serves to show the CUBA is safe and reflects what is happening in bone.
86. **Wilson, SG, et al: A genome-screen of a large twin cohort reveals linkage for quantitative ultrasound of the calcaneus to 2q33-37 and 4q12-21. Journal of Bone and Mineral Research. 19:270-277, 2004.** The authors examine ultrasound assessed BUA and VOS—measured with the McCue CUBA—in a cohort of 2,134 twins and carry out a genome-screen to identify linkage for BUA or VOS. The assessment showed linkage to BUA to 2q33-37 and for VOS to 4q12-21. The study serves to show the CUBA is safe and reflects what is happening in bone.
87. **Zochling, J, et al: Quantitative ultrasound measurements of bone: Measurements error, discordance, and their effects on longitudinal studies. Osteoporosis International. 15:619-624, 2004.** This study using the McCue CUBA scanner to do follow-up studies on 56 elderly subjects over 2.2 years found the scanner to be highly reliable and sensitive to longitudinal change in the very elderly. The study serves to show the CUBA is safe and can be used to reflect what is happening in bone over time.
88. **Zochling, J, et al: Quantitative ultrasound of the calcaneus and falls risk in the institutionalized elderly: Sex differences and relationship to vitamin D status. Osteoporosis International. 13:882-887, 2002.** The authors examine BUA and VOS—measured with the McCue CUBA—in a population 65 to 104 years old including 294 elderly men and 899 elderly women. The authors find that BUA is about 30% higher in men than in women. The authors also find no significant decline in BUA or VOS with age in men while BUA declines at 2.8%-4.7% per decade and 1% per decade for VOS. The study serves to show the CUBA is safe and reflects what is happening in bone.