

1 scientist, would be the one to say, "Yes; the clinician, I
2 think, must always have that option." I think what we are
3 probably looking at are different scenarios. I think I am
4 looking here at a population-based scenario to prevent hip
5 fracture.

6 I think that we have got to bear in mind that the
7 clinician will see other cases of secondary osteoporosis, et
8 cetera. So I think we need to be going some way along sort
9 of having a sort of narrow definition but I think it
10 shouldn't be exclusive in any way.

11 DR. GARRA: Thank you. Any other questions?

12 Thank you very much.

13 Our next speaker is Dr. Richard Mazess from Lunar
14 Corporation talking about sources of variation and T-scores.

15 **Sources of variation in T-scores**

16 DR. MAZESS: For the panel, I will introduce
17 myself. My name is Dick Mazess.

18 [Slide.]

19 I started out working in bone densitometry 37
20 years ago with John Cameron at the University of Wisconsin.
21 About seven years later, or about 30 years ago, I developed
22 what was the prototype for the first bone densitometer that
23 we ultimately gave to Norland Corporation and became,
24 really, the first commercial bone densitometer in the United
25 States.

1 About a decade later, in 1980, I founded Lunar
2 Corporation and I am currently president of that corporation
3 thereby compounding my earlier error. Currently, there are
4 about 25,000 to 30,000 densitometers in the world of which
5 about one-third are located in the U.S. These are dedicated
6 densitometers.

7 So it is really a concern how do we deal with
8 these different instruments.

9 [Slide.]

10 I thought I would give you a little bit of
11 historical background because this is something that we also
12 developed about the same time we developed the first
13 densitometer. This is the first indication of fracture risk
14 which we developed for the forearm measurements. This was
15 developed from our normative data and indicated something
16 about the risk of fracture with the green zone being normal,
17 the yellow zone being intermediate and the red zone being
18 osteoporotic.

19 So I think this is the precursor of what we
20 currently have with the WHO categories. So, not only were
21 we responsible for the epidemic of densitometry but for the
22 erroneous propagation of T-scores.

23 [Slide.]

24 A decade later, when we became aware of spine
25 density and the fact that there was a real gradient of risk,

1 we changed this view a little bit and had a larger gradient
2 in which serious osteoporosis was not recognized until the
3 patient was three standard deviations below the young-normal
4 level. But, still, there was the same idea that the
5 deviation from the young-normal or young-adult level was
6 really the serious consideration for clinical use.

7 So the use of this concept, what now is called the
8 T-score concept, is something that goes back, really, almost
9 30 years and was certainly used 20 years ago in some of the
10 first commercial instruments.

11 [Slide.]

12 I think the problem we are having today is not
13 with that concept assessing abnormality in relation to young
14 adults--that is something that is very commonly done in
15 medicine--but, really, how do we use these thresholds, how
16 do we assess risk on the basis of these things and can we do
17 it uniformly.

18 At the beginning of this decade, the World Health
19 Organization proposed defining a threshold of -2.5 SD for
20 osteoporosis. I won't talk about osteopenia, but
21 osteoporosis was defined at -2.5 SD. It was really based on
22 radius BMD. It was not based on spine or femur BMD. It
23 defined the lowest quintile of the population of post-
24 menopausal white women. It was not designed, I believe, to
25 apply to men or to other ethnic groups.

1 This shows the relationship between fracture risk,
2 hip-fracture incidence, actually, from the EPIDOS study and
3 either femur-neck BMD or ultrasound stiffness. You can see
4 the gradient of risk is very similar for both ultrasound and
5 for femur BMD in this particular study.

6 I think the interesting thing to look at is that
7 the gradient is relatively shallow until you get to very low
8 levels, until you get to this -2.5 SD level. So there seems
9 to be some intrinsic value in defining a threshold where the
10 gradient of risk seems to increase and there is some greater
11 diagnostic value.

12 [Slide.]

13 With regard to fracture-risk differences, the WHO
14 categories for white women may not apply for males, as we
15 know, and for non-white groups. So I think that is clear
16 now. There is another problem that people have alluded to
17 and talked about. This same criterion defines the lowest,
18 roughly, 15 to 20 percent of post-menopausal white women
19 and, as Dr. Looker and others have shown, Dennis Black, it
20 defines different prevalences depending upon the skeletal
21 site.

22 In fact, I would propose that you take a look at
23 the difference between BMC and BMC at the same skeletal site
24 and you will find the difference of prevalence, whether you
25 are using area density or just the bone-mineral content in

1 grams. Same site, same reference population, you will get a
2 different T-score.

3 Even when -2.5 SD T-score defines similar
4 prevalences of women, the risk of fracture may, in fact,
5 differ. So this is something that Dennis Black talked
6 about, the need for, perhaps, getting an iso-risk criterion.

7 [Slide.]

8 I want to talk a little bit about the T-score
9 differences among skeletal sites. This is using the T-score
10 at age 65 or the average age for post-menopausal women for
11 different sites. You can see quite a bit of difference
12 from--this is the average from about -0.5 to -2.0. Some
13 sites, such as Ward's triangle and the lateral spine, have a
14 very low T-score whereas others, such as the finger and os
15 calcis BMD are relatively high.

16 The forearm, the femur neck, stiffness of the os
17 calcis, the ABT spine, are sort of in an intermediate level.
18 These differences really correspond to differences of aging
19 loss. This shows the T-score versus age for sites with slow
20 loss, what I call normal loss, and fast loss.

21 This simply reflects the loss rates at these
22 different skeletal sites and is not a function of population
23 differences or reference data or any of these things. It
24 simply is 75 to 90 percent of the variance in T-scores is
25 probably associated simply with aging loss.

1 [Slide.]

2 Another way to look at this is in terms of normal
3 curves, slow loss, normal loss, fast loss. Obviously, those
4 sites with a relatively slow loss will have a very small
5 tail below the -2.5 threshold. Those with very fast loss
6 will have a large proportion of individuals below that
7 threshold.

8 This simply illustrates the problem that everyone
9 was talking about earlier that you can't equate T-scores. I
10 think that T-scores have really been defined for sites with
11 relatively normal aging loss, sites like the Ward's triangle
12 on the femur are different than the trochanter on the femur.
13 So now we are talking about minor differences at the same
14 skeletal site can cause big differences in terms of the T-
15 score that you have.

16 The trochanter has a very slow rate of loss and a
17 T-score of -0.6 whereas the Ward's triangle has the T-score
18 of -1.9 in older women and a very high rate of loss.

19 [Slide.]

20 This shows the disparity graphically at different
21 ages. You can see that there is quite a bit of difference.
22 This is, I think, a clinical problem that we are
23 encountering even without going to questions of how do we
24 deal with fracture risk. We are seeing a different
25 prevalence of abnormality with these different skeletal

1 measurements.

2 [Slide.]

3 As Dr. Genant pointed out, one can normalize to a
4 group of post-menopausal women and, in fact, the
5 International Committee on Densitometry Standardization has
6 proposed and approved such an isoprevalence approach to try
7 to standardize on women at age 65, which Dr. Genant
8 proposed. This shows the effect of standardizing at a Z-
9 score of -0.84, something like that, which defines the
10 lowest quintile of the post-menopausal population.

11 If, in fact, you do that, you can get isoprevalent
12 values for all the different skeletal sites that are
13 available today.

14 [Slide.]

15 Some of these differences I just will repeat.
16 Most of the differences are due to aging loss. Some
17 differences are due to small differences of anatomical
18 location. Some manufacturers, for example, use the L1 to L4
19 sequence on the spine whereas others use the L2 to L4
20 sequence. And there can be small differences associated
21 with that.

22 There can be differences associated to the precise
23 location of the femur neck on the proximal femur. So those
24 are small effects. The major effect is aging loss. There
25 is some effect of the standard deviation in young adults and

1 the choice of which group you use as a young adult, 20 to
2 39, 20 to 49. Those things are complicated and we really do
3 need some standardization in that area.

4 The sampling is generally not a problem as far as
5 I can see among manufacturers. In general, sample sizes
6 exceed 500 for white women for most manufacturers. There is
7 very little difference between volunteers and random
8 testing. We have looked at this several times. We have
9 also looked at the use of exclusionary criteria versus
10 taking all comers. There is very little difference in terms
11 of mean values although, obviously, it can increase or
12 standard deviation by taking all comers.

13 One of the key things, I think, that has not been
14 addressed is the requirement to take samples from a variety
15 of different geographical locations. I think some of the
16 defects that have occurred in the past have come from a
17 manufacturer getting a reference population from one
18 location, one geographic location. A specific bone
19 densitometer or a specific geographic location, may differ.
20 I think we need to broaden our scope here and use multiple
21 samples in order to get a good reference population that is
22 more representative.

23 [Slide.]

24 This shows just some spine and femur T-scores. I
25 think, from the USA, Northern Europe, the NHANES data for

1 femur neck, they are completely concordant. The results
2 from the hologic and Lunar databases are completely
3 concordant on spine and femur T-scores. So I don't think
4 geography makes a big difference and I don't think, in the
5 case of our reference data--we have about 13,000 women
6 included in that. I don't think it really makes very much
7 difference right now in terms of having a large sample.

8 [Slide.]

9 T-score differences; I shouldn't say that this is
10 really--it is probably fracture risk differences. I think
11 we have a problem and some of those solutions are being
12 addressed. First of all, I think these WHO categories--the
13 T-scores are useful and the Z-scores are useful. They have
14 been used clinically for 20 years and we should keep them.

15 But the WHO categories really are restricted to, I
16 think, white women at the present time. We simply don't
17 have enough information on males or on other ethnic groups
18 to use those categories and those groups.

19 Secondly, I believe those categories really apply
20 to certain sites with normal aging loss and it simply causes
21 confusion and a lot of problem when we use those categories
22 for sites with either very rapid loss such as the lateral
23 spine and Ward's triangle are very slow loss, like the
24 trochanter and a finger.

25 I think this is a need to develop some other type

1 of approach such as Dennis Black has talked about, in terms
2 of prevalence, identifying a group such as the 20th centile,
3 the lowest quintile of the population. There are a great
4 deal of advantages for defining this which is, I think, the
5 reason that the committee on standardization really wanted
6 to follow through.

7 First, from a manufacturer's point of view, it is
8 really easy to do. Everybody has the information already so
9 it is very easy to identify the lowest quintile in a
10 population. Secondly, you can do that for males and
11 females. You can say this is the lowest quintile of males.
12 This is the lowest quintile of females. This is the lowest
13 quintile of blacks. This is the lowest quintile of
14 Hispanics.

15 It is very easy to do and we don't need a lot of
16 information on fracture risk. I think, ideally in a perfect
17 world, having risk-based analysis like world peace would be
18 ideal but I don't know if we are going to achieve it in my
19 lifetime.

20 It would be great to have an assessment of
21 fracture risk that everybody could agree on but we already
22 see that there are disputes, whether we should be talking
23 about spine fracture, hip fracture. I'm sure the
24 manufacturers of forearm densitometers will say, "We really
25 ought to be thinking about Colley's fractures."

1 So everybody will have their particular fracture
2 that they want to focus on and I think there is going to be
3 a lot of controversy here before we come to any kind of
4 agreement. I think, as a step, the isoprevalence type of
5 approach may be an intermediary step that one could define,
6 and manufacturers, without calling the T-scores, could
7 probably define the lowest quintile in the older population
8 very readily and then move with the help of the NOF and the
9 ISCD to define the fracture-risk approach.

10 Thank you.

11 DR. GARRA: Thank you.

12 Are there any questions?

13 DR. GENANT: Dick, an issue that has surfaced
14 several times is what is the major contributor to the
15 discrepancies in T-score-based classification. You have
16 implicated the variable age-related loss and, certainly,
17 that is a major factor.

18 But I think that, perhaps, potentially even more
19 important is the somewhat unpredictable and non-systematic
20 relationship in a given individual between the density as
21 measured with the types of techniques that we use at one
22 site and other sites.

23 I think that is reflected even if you take a young
24 population and you look at the correlations of BMD from one
25 site to another site. The standard error of the estimate

1 there, you have potentially 15, 20 percent error around that
2 so I think that indicates that simply with the types of
3 measurements that we do, that there is variation from
4 individual to individual and how the forearm relates to the
5 spine, to the hip, et cetera.

6 DR. MAZESS: I would agree. I think we have 206
7 bones in the body and 206 potential clinical interpretations
8 on an individual at least. Once we start subdividing the
9 bones, we end up with more and looking at different indices.
10 But I think what I was trying to address is not the fact of
11 the great individual variability because, obviously, we see
12 patients all the time who have low spine density due to
13 steroids or due to immobilization.

14 Or you see people with low heel values due to
15 diabetic arthropathy, for example. So this happens
16 clinically where you will see particular areas that are
17 going to be anomalous and there is a great deal of
18 individual heterogeneity. I am talking about, really, what
19 is the reason for these differences on the average amongst
20 all the sites. I think, in the average, the biggest source
21 of variation is just differences in aging loss and very
22 little of the problem is really due to any of these other
23 factors.

24 DR. FAULKNER: I was wondering, too--we can't even
25 agree on the number of bones in the body because not

1 everyone has 206, anyway. So how are we supposed to lose at
2 the same rates?

3 DR. MAZESS: We could mandate it.

4 DR. FAULKNER: That will happen later today. Lack
5 of standardization in the field of densitometry; do you feel
6 that this is also contributing to this confusion?

7 DR. MAZESS: Actually not because I think we have
8 had a great deal of effort towards standardization through
9 the work of UCSF. The manufacturers have intercalibrated
10 and standardized. I feel very confident about the
11 intercalibration of the units.

12 Typically, the densitometry units measuring at the
13 same site correlate 0.98, roughly--0.97, 0.98. We just
14 finished another study. The correlations and
15 intercalibration are very high.

16 There are some small differences among
17 manufacturers in terms of what is chosen as the young-adult
18 reference value. I prefer to take 20 to 39 because it is
19 more inclusive. The standard deviation is a little bigger
20 and you get a little lower prevalence of abnormality. So
21 you don't alarm as many people as you do if you take the so-
22 called peak BMD.

23 In fact, if you try to take peak BMD, you really
24 do have a problem because many skeletal sites, the peak BMD
25 actually occurs at 17 years of age.

1 Also we heard--I think Alan Tenenhouse indicated
2 that there is loss from the femur beginning at age 30. But
3 if you actually look at the BMC, and you can see this in the
4 NHANES data, there is no loss of BMC at age 30. The BMC is
5 actually increasing between the ages of 30 and 40 so there
6 is no loss there.

7 There is actually an increase of area that is
8 occurring between 30 and 40 which is causing an artificial
9 decrease of BMD. So I think these kinds of problems are
10 problems that the industry needs to resolve and the
11 committee on standardization needs to resolve in order to
12 try to get uniformity.

13 But they are contributing--under 5 percent of the
14 problem of disparity in T-score is really associated with
15 reference values or standardization. In my view--I have
16 said to Dennis Black that is it is 90 percent and he says,
17 no, it is 75. So we say it is somewhere between 75 and
18 90 percent.

19 DR. GARRA: Any other questions? Thank you.

20 I would like to move on to the next speaker, Dr
21 Eric von Stetten from Hologic talking about reporting of
22 bone densitometry results.

23 **Reporting of Bone Densitometry Results**

24 DR. VON STETTEN: Good afternoon.

25 [Slide.]

1 My name is Eric von Stetten. I am scientific
2 director of Hologic. Those of you who were here a couple of
3 years ago, the FDA and several other panel members may
4 remember us and, perhaps, myself from our panel meeting for
5 the Sahara Heel Ultrasound System which was reviewed that
6 day back in August. Bill tells me it is the 18th. I
7 usually say the 17th, but I guess it was the 18th of August.

8 The panel ought to be congratulated from sitting
9 through quite a bit of data today and I am going to try and
10 keep it short and the concepts very simple because you have
11 had to absorb quite a bit.

12 In addition, in fairness, I think it is right that
13 I tell the panel and those in the audience today that part
14 of the reason that we are all here, and certainly the reason
15 that I am here, is that Hologic has submitted a PMA
16 supplement which actually asks for the approval of ethnic
17 and gender-based databases.

18 [Slide.]

19 As I indicated, the Sahara system was approved
20 eventually on March 12, 1998. In the end of 1998, we
21 submitted a PMA supplement for Caucasian male and African-
22 American female reference ranges for the Sahara system kind
23 of in parallel to what is done for DEXA devices, as you have
24 heard today.

25 The original system had Caucasian female

1 references ranges included with it. And then we were
2 attempting to add the Caucasian male and African-American
3 females.

4 [Slide.]

5 In the course of the review of this submission,
6 the agency raised concerns, many of which we have talked
7 about here today, about the utility of ethnicity and gender-
8 matched databases. Those concerns are quite well taken as
9 you have seen with all the differing opinions that you have
10 had in just a sample of five or six speakers today.

11 There is quite a degree of differing opinions on
12 even what to do with Caucasian female results, let alone
13 black female and Caucasian males. The agency organized this
14 meeting in order to get these opinions aired out and to see
15 what the perspectives of yourselves were after having heard
16 them.

17 Quite explicitly in the agenda, one of the goals
18 is to clarify the question of whether gender and ethnicity-
19 matched referenced databases should continue to be made
20 available to physicians to interpret results.

21 [Slide.]

22 I promised I would only show a little bit of data
23 and so I am just going to show two quick slides with data on
24 them. On the left, here, if you see this dot there, it
25 corresponds to a 75-year-old male who has a lumbar spine

1 bone density measured by DEXA of 0.9 grams per centimeter
2 squared. On the left here he is plotted against male
3 reference ranges, a gender-matched reference database, and
4 you can see that he is a little bit below normal for his
5 age, which would indicate an increase in risk of fracture
6 compared to his peers.

7 If you plot that same male patient versus a
8 universal or white female database on the right, you might
9 conclude that that patient was above normal for their age
10 and might even conclude that they are at reduced risk for
11 fracture compared to their peers but, certainly, you would
12 not be aware that he is actually below normal.

13 I would point out that, in all the talks that we
14 have had today, we have talked a lot about T-scores and not
15 a whole lot about Z-scores, but, in fact, the difference
16 between the patient's result and the mean for the age, which
17 is the solid line, is, in fact, a Z-score.

18 These dashed lines are plus or minus one standard
19 deviation above and below the mean which is plus or minus
20 one Z-score. In fact, all of the fracture studies that we
21 have talked about for the entire day have done age-matched
22 comparisons of patients to their peers, Caucasian females to
23 Caucasian females of the same age. The relative-risk terms
24 that we have talked about are per-population standard
25 deviation.

1 So you could take this dashed line up above and
2 label that risk equals one-half x , because it would be one-
3 half the risk of a patient who had a value on the mean on
4 the line. The dashed line at the bottom, z equals -1 , might
5 be labeled risk equals $2x$ for a doubling of the risk per pop
6 SD.

7 [Slide.]

8 Looking on the right, first, here, I have the same
9 male patient plotted against the universal white female
10 database. On there is the line which is corresponding to T
11 equals -2.5 . As you have heard, there is abundant data for
12 Caucasian females that has established what is the
13 relationship between bone density and fracture risk. So we
14 understand quite well what that T equals -2.5 line means for
15 Caucasian females.

16 If we go over to the left and ask what would we do
17 with a male database, there is quite a bit of disagreement
18 that you have already heard today about where, exactly, we
19 might put an equivalent 2 equals -2.5 line.

20 Dr. Wasnich has suggested that it is absolute BMD
21 and it would have to be in exactly the same spot where I
22 have drawn it here. But others might argue that it is a
23 little higher or a little lower, somewhere probably in that
24 shaded region. But, at this time, the data is not
25 sufficient to be able to say exactly where it should be.

1 I would just like to add that this is exactly the
2 status of Caucasian females evaluated by bone densitometry
3 for at least ten or so years before the WHO criteria were
4 proposed where they were evaluated based on their T-scores
5 and their Z-scores without the definition of a criteria.

6 [Slide.]

7 So if I could say for a moment what the advantages
8 of ethnicity and gender-matched databases might be, clearly
9 they allow comparison of the patient results to those of
10 their peers and it allows you to stratify them and get a
11 picture, are they above or below normal.

12 Secondly, it allows risk-based diagnostic and
13 treatment thresholds to be added as data and consensus does
14 develop. So where Caucasian female thresholds might be
15 determined today, as they get determined, they could be
16 added to the reference dataplot that I just showed you.

17 Thirdly, it provides the physician with more
18 information which can only help in evaluating individual
19 patients and it does not detract from any of the information
20 that we have already talked about. I would also like to
21 point out that virtually all physicians desire this
22 information and we are constantly bombarded with requests,
23 and I would say sometimes, facetiously, with demands from
24 each one of our physicians that use our systems, and other
25 manufacturers are the same.

1 Most physicians very much want this information.
2 They want to know how to stratify their patients versus
3 their peers. Are they high or low or otherwise.

4 Lastly, having ethnic and gender-matched databases
5 is consistent with the historical reporting of densitometry
6 results for the last fifteen or so years, as has been done
7 for DEXA and might also be done for ultrasound.

8 [Slide.]

9 I would be remiss not to mention the limitations
10 of ethnicity and gender-matched databases as the FDA is
11 keenly aware. There are certainly not risk-based diagnostic
12 or treatment thresholds for groups other than Caucasian
13 females established at this point in time. It is also
14 possible that some physicians will inappropriately use
15 ethnic and gender-matched databases.

16 Just as in any other field of medicine, it is
17 possible for the physicians to take the information and use
18 it improperly.

19 [Slide.]

20 Finally, to conclude, ethnicity and gender-matched
21 databases only add important information. The availability
22 of ethnicity and gender-matched databases does not restrict
23 the development or use of risk-based diagnostic information
24 or intervention thresholds as they become available and as
25 the data and consensus develops.

1 The logic is committed to providing relevant
2 information and clinical guidelines to physicians as they
3 become available and we believe that the ethnic and gender-
4 matched databases are relevant information and they can be
5 used effectively by physicians even before the diagnostic
6 thresholds become defined.

7 Finally, Hologic supports the efforts described
8 today by Dr. Black and by Dr. Johnston and others to develop
9 risk-based diagnostic and intervention thresholds and looks
10 forward to being able to implement them on all of our
11 devices so that we can have more uniformity as we all desire
12 in reporting, interpreting and in patient care.

13 Thank you.

14 DR. GARRA: Thank you.

15 Are there questions?

16 DR. MCGOWAN: I'm sorry. I am a little confused.
17 You have no prospective studies in men and ethnic minorities
18 that correlate bone-mineral density with fracture; is that
19 correct?

20 DR. VON STETTEN: There are published studies that
21 show lower bone density is a higher fracture risk for any
22 population. There are no specific studies to show, with an
23 individual device such as ours, what that relationship is.

24 DR. MCGOWAN: So that information is missing. I
25 would be looking for kind of an intrinsic biological reason

1 why bone isn't bone, to go back to an earlier discussion,
2 why the intrinsic--which the bone-mineral density and
3 ultrasound are measuring--intrinsic qualities of bone. I
4 would need a rationale for why the package that that bone is
5 in makes a difference.

6 DR. VON STETTEN: I think that the only answer
7 that I can give you to that question is that if, for
8 example, a female and a male Caucasian, let's say, since we
9 know the answer, have a difference in fracture risk if about
10 a factor of 3, if both of them have exactly the same bone
11 density of, say, the hip to avoid controversy, then you can
12 say the woman has a three-fold higher risk of fracture.

13 However, if I knew that that woman, having the
14 same bone density as the man, also was quite high compared
15 to her age-matched peers and the man was quite low compared
16 to his age-matched peers, it might make a clinical
17 difference in how I treat that patient if I was a physician.

18 I might say, "My goodness, that patient is lower
19 than they ought to be even though their risk is the same as
20 that of a woman."

21 DR. MCGOWAN: I think I have trouble with that.
22 Although I understand that physicians and patients sometimes
23 say, "I don't want to be compared with some twenty-year-
24 old," I think that is a lack on our part of educating
25 physicians about the meaning of things.

1 I have a problem that putting this kind of
2 information in physicians' hands wouldn't be misguided
3 because they would be looking at treating more men and more
4 minorities than seemed justified by the data at this point.

5 DR. GARRA: I had a question of my own here, and
6 then we will let Harry get in. You were talking about
7 ethnicity-match and gender-match, not age matching, on your
8 data; is that correct?

9 DR. VON STETTEN: All three. All of the above.

10 DR. GARRA: You have all three?

11 DR. VON STETTEN: Yes. And that is the standard
12 that has been done in DEXA for many years.

13 DR. GARRA: But, of course, we expect--yet other
14 speakers have told us that the risk will fluctuate all over
15 the place. If you do age matching, you may have the person
16 be normal for their age-matched group but then still have a
17 very high risk of fracture so the correlation is unknown,
18 basically, and that could be a severe problem.

19 Also I think Dr. Looker had mentioned earlier that
20 when they tried to do the gender and ethnicity matching that
21 the correlation with risk also sort of fell apart. If am
22 not mistaken, I believe she said that.

23 So I do have a real concern, also, here that we
24 may be adding some misinformation along with information
25 when we do this sort of gender matching.

1 DR. GENANT: I think that, clearly, down the road,
2 we would like to have more definitive information about
3 risks in different ethnic groups and gender differences.
4 But I would tend to concur with the points that you made,
5 Eric, and I think a number of other presenters made already
6 today that it is not uncommon for clinicians to use
7 normative data in reviewing results of a given patient,
8 particularly if there is an age relationship, it stands to
9 reason that being able to plot a given patient against the
10 normal curve for that patient's peers--that is, gender and
11 ethnicity-matched--seems a reasonable first approximation of
12 kind of where this particular patient stands.

13 As the additional information becomes available in
14 a more definitive fashion for fracture risk, I would think
15 that that could be added, the types of data and analyses
16 that Dennis Black has been talking about. But it may be
17 some time before we have more definitive information.

18 I think, in the interim, that an ability to
19 compare a given patient with his peers or her peers would
20 seem, perhaps, the best approach.

21 DR. VON STETTEN: If I could add for Dr. Garra,
22 when fracture-risk studies are done and the correction is
23 done for ethnicity and age and so on, the relationship to
24 fracture risk does not fall apart. In fact, that is the way
25 the relationship to fractures is determined. When you do a

1 study of males for fracture risk, a case-control study, for
2 example, might be age-matched males versus males with
3 fractures.

4 They are sex and ethnicity compared, by
5 definition. In fact, prospective studies are done the same
6 way so it does not fall apart. That is the way it is
7 established.

8 DR. GARRA: So you are saying you have collected
9 the fracture-risk data for those groups?

10 DR. VON STETTEN: We have not collected specific
11 fracture-risk data for those groups. We have collected the
12 normative data. It is widely accepted that all groups have
13 higher risk of fracture as you decrease relative to your
14 age-matched peers.

15 The question is whether the relative risk for the
16 population, standard deviation or Z-score is 1.5 or 1.7 or
17 2.0. It is just the quantitative question of exactly how
18 steep is that gradient that has not been established. The
19 fact that there is a gradient is established.

20 DR. GARRA: But that is a very important question.
21 However, I do like the idea of having age-matched and
22 ethnicity-matched groups because it was mentioned earlier
23 today that it may tip you off to another process that is
24 causing accelerated bone loss relative to their peers that
25 might be something that is correctable. So I think that is

1 an important feature.

2 DR. FAULKNER: I think that is comment I wanted to
3 make as well. I think the concern, if I can sort of state
4 what I am hearing--we are getting concerns that you are
5 quantifying that this man would be at eight times the
6 fracture risk of somebody else, quantifying it in that way
7 without any data.

8 But, at the same time, we know that, in women--
9 there was a study from Marjorie Lucky a few years ago, that
10 30 percent of them, or so, the women that came through her
11 clinic with low bone density had secondary causes for that.
12 With men, it is probably a lot bigger than that. The only
13 way we are going to identify those is through the use of
14 these gender-specific databases.

15 DR. GARRA: Ny other questions or comments?

16 We are running a little bit behind. We are going
17 to move on to the final speaker of the industry
18 presentations. That is Daniel Michaeli from Schick
19 Technologies talking about giving clinicians useful and
20 simple guidelines without creating confusion. We have
21 certainly had no confusion today.

22 **Giving Clinicians Useful and Simple Guidelines**
23 **Without Creating Confusion**

24 DR. MICHAELI: Good afternoon.

25 [Slide.]

1 Many of the previous presenters here today have
2 talked about some of the scientific and technical aspects of
3 using T-score and prognostic criteria within a clinician's
4 practice. What I would like to focus on are some of the
5 more practical aspects.

6 What we must keep in mind, no matter what criteria
7 we decide to ultimately come up with, is that these criteria
8 must be useful and simple for the clinician and, most
9 importantly, that they don't cause confusion for physicians
10 who are currently using these in their practice.

11 [Slide.]

12 I would just like to put the discussion that we
13 are having today in some sort of context. Bone densitometry
14 has come a long way here in 1999. It is now recognized by
15 physicians that BMD is the most predictive measure they can
16 use in their practice along with other clinical risk factors
17 to assess osteoporotic fracture risk and potentially
18 diagnose osteoporosis.

19 A larger number of individuals are being counseled
20 about osteoporosis within their practice and I believe we
21 owe this to two major advantages; first, peripheral
22 technologies have placed the tools to assessment
23 osteoporosis in the hands of primary-care and OB-GYN
24 physicians, the primary point of care for most patients.

25 There are challenges now that these physicians who

1 may not be experts in the technology and in bone
2 densitometry are using and applying criteria that are, as we
3 have heard, very complicated.

4 The other thing I think we owe to this is the T-
5 score which does place individuals into various categories
6 of disease state. We know it has some limitations but, by
7 and large, individuals who are at increased risk for
8 fracture are being counseled and are potentially being
9 placed on drug therapy and reducing their subsequent risk
10 for fracture.

11 We now have the benefit of experience. Several
12 years have passed since the initial World Health
13 Organization's criteria were introduced to physicians and we
14 now know that there are, indeed, several limitations of the
15 T-scores. I believe what we should do is provide this
16 additional information which we, as a research community,
17 know is available to physicians.

18 [Slide.]

19 I would like to outline two or three of the
20 limitations of T-scores that we have talked about today.
21 Shown first are T-scores for a female with a BMD of her
22 finger of 0.5 grams per centimeter squared. This is on our
23 Acudex bone densitometer. This individual, if she were
24 Caucasian, would be assessed with a T-score of -.3; if she
25 were African-American, a T-score of -1.2.

1 I would like you to note the these are two
2 different categories of disease state as defined by the
3 World Health Organization's criteria. At the very least,
4 the T-score of -1.2 may be a little bit confusing to the
5 primary-care physician that doesn't know much about the
6 technology.

7 Okay; they may realize that African-Americans as a
8 group have lower bone-mineral density, but this information,
9 there is no cutoff value that it can use along with this T-
10 score. At worst, I believe there are certainly physicians
11 out there that are basically using the same cutoff values
12 for Caucasian women and applying it to African-American
13 women.

14 Similarly, I have actually generated this data
15 based on some published information in the Primer for
16 Metabolic Bone Diseases published by the American Society of
17 Bone and Mineral Research. It is based on the hologic QDR.
18 A BMD of 0.8 grams per centimeter squared for a Caucasian
19 female individual would translate to a T-score of -1.6 and,
20 for a male Caucasian, would translate to a T-score of -2.6,
21 again two different categories of disease state as defined
22 by the World Health Organization's criteria.

23 Even though we know, or have some good evidence,
24 that, at a given bone-mineral density, males and females
25 have approximately the same risk for fracture.

1 [Slide.]

2 A further limitation that we have talked about
3 today is that T-scores from device to device definitely, in
4 many cases, give different results. We know that this is
5 due to anatomic body site. It is due to the fact that we
6 have ultrasound and DEXA techniques and even among
7 ultrasound and DEXA technology, themselves, there are
8 differences.

9 Perhaps the most important difference is due to
10 the database. Some manufacturers use 20 to 29-year-olds as
11 the young-healthy normal database. Other manufacturers used
12 peak bone mass, perhaps age 35. And this does cause
13 differences in the ultimate T-scores that we generate.

14 Prognostic information such as fracture-risk
15 information eliminate the database problem pretty much
16 entirely. Certainly, even if we use prognostic information,
17 there will be differences in the risk of fracture as we go
18 from one bone densitometer to the next. However, viewed as
19 a prognostic criteria--in other words, a risk for fracture--
20 it is sort of less problematic.

21 Certainly, if you look at the prognostic criteria
22 for any disease state, no two prognostic criteria are going
23 to give you the same risk for the expression of a disease.
24 These are bone densitometry measurements so, certainly, they
25 are going to be equivalent more often than most risk

1 factors. But, viewed as a risk factor, the discordance
2 problem becomes a little bit less cumbersome.

3 [Slide.]

4 I would like to go over some of our various
5 criteria that we have available to us today. Actually, the
6 initial WHO report did recognize that both diagnostic
7 criteria--that is T-scores and prognostic criteria,
8 estimates of risk of fracture--both had their advantages and
9 disadvantages.

10 Some of the advantages of diagnostic criteria or
11 our current T-scores are that they are simple. They are
12 accepted and well understood, at least partially understood,
13 by physicians today and they break individuals into
14 categories of disease state which are easily interpreted by
15 physicians.

16 Unfortunately, they give inequivalent information
17 for varying race, gender and densitometer. Prognostic
18 criteria are potentially more complicated and prospective
19 information is not available for all densitometers and
20 certainly not all densitometers, genders or ethnicities.

21 However, they do provide more equivalent
22 information for varying race, gender and densitometer and
23 can be easily combined with other risk factors.

24 [Slide.]

25 Better information is now available to us and I

1 believe it is important that we provide it to physicians. I
2 believe that we cannot keep our current T-score the way it
3 stands because we know that there are limitations and we,
4 perhaps, have solutions to offer physicians in assessing
5 some of the individuals who may be male or may be ethnicity
6 other than Caucasian females.

7 Developing a new T-score certainly has its
8 advantages. Creating a common database on all machines also
9 has some advantages. However, doing so would potentially
10 stagnate the industry. I am concerned that creating a new
11 T-score will place, basically, the lump of bone
12 densitometers we have today in a study and, subsequently, in
13 the future, no bone densitometer will be able to be marketed
14 because it will always be claimed that this bone
15 densitometer has an inferior dataset.

16 Removing the T-score, I also don't believe is an
17 option because the T-score is now understood by physicians,
18 or at least somewhat understood by physicians. They are
19 using it in their practice. Removing it would sort of have
20 them wonder whether bone densitometry works at all.

21 We can't take something away from physicians,
22 especially because it does have its advantages. It does
23 break individuals into categories of disease state. And I
24 believe we need to keep it as such. It is unfortunate that
25 this got cut off, but one possible way--and this is one

1 possible way, not necessarily the possible way--but if the
2 FDA decided to include some sort of prognostic information
3 on the patient report, one possible way we could come up
4 with some sort of statement as to how it is to be used is
5 that osteoporosis drug therapy may be warranted in Caucasian
6 females with evidence of osteopenia or osteoporosis or in
7 any individual with an accelerated risk of fracture.

8 Using such a consensus statement like this, it is
9 likely that the National Osteoporosis Foundation's cutoff of
10 -1.5, or the cutoff that one should be starting to think
11 about whether the patient should be on some sort of
12 preventative therapy, would likely still be used for
13 Caucasian females although they would also have prognostic
14 information.

15 For individuals who are not female--in other
16 words, males--or individuals who are not Caucasian, they
17 would at least have prognostic information. We could
18 develop some sort of mutually accepted cutoff beyond which
19 any individual, perhaps, should be considered for some sort
20 of preventative therapy.

21 [Slide.]

22 The fact is, we have predictive information about
23 fracture. Just like other clinical measurements, bone-
24 mineral density is, in fact, as predictive of fracture as
25 blood pressure is of future risk of stroke.

1 What I am concerned about is that if we send a
2 message, a confused message to physicians, if we send a
3 confused message to the insurance companies, for instance,
4 Medicare, or the Health Care Finance Administration, which
5 has recently mandated coverage for bone densitometry, or
6 private insurance companies that are currently considering
7 whether bone densitometry should be reimbursed or the extent
8 to which it should be reimbursed, we may lose our support
9 for this important measure that needs to remain in hands of
10 clinicians.

11 Similarly, Congress is currently considering a
12 bill that would require private insurance companies to
13 reimburse for bone densitometry.

14 [Slide.]

15 My conservative estimate for the Year 2000, or
16 2000 and beyond, is that we at least have clinicians
17 advising individuals with the best information available
18 regardless of age, ethnicity, gender or densitometer and
19 that payers, clinicians and patients realize the importance
20 of bone densitometry in assessing osteoporotic fractures.

21 Thank you.

22 DR. GARRA: Thank you.

23 Are there any questions?

24 DR. FAULKNER: Are you getting inquiries from your
25 customers regarding databases for other genders, for gender

1 and ethnicities?

2 DR. MICHAELI: Absolutely. I get inquiries all
3 the time from customers who want a male, Hispanic or a male-
4 -all sorts of databases that, perhaps, even other bone-
5 densitometry companies don't even have. I am talking for
6 specific parts of Europe, specific parts of Asia. That
7 gives me the concept, or at least idea, that they don't
8 necessarily know how these should be applied.

9 If they are really wanting these so badly, it
10 makes me wonder whether they are just going to be using the
11 same cutoffs with those new databases.

12 DR. FAULKNER: Do you have a sense why they want
13 them? I think Dr. Wasnich pointed this out. When you get
14 to all the combinations, if you live in Northern Ireland,
15 you have to have a Northern Irish database. How far do you
16 segment this down?

17 DR. MICHAELI: I think the first thing is that,
18 obviously, there was a period of time that we didn't have,
19 for instance, an African-American database before we had
20 developed it. African-American individuals don't like being
21 compared to Caucasians. On our report, it says,
22 "Caucasian." That is definitely the first problem.

23 I think that is pretty much primarily the issue.
24 You have to remember that the physicians primarily that have
25 our peripheral devices are, by and large, primary-care and

1 OB-GYN physicians that do not have too much training with
2 bone densitometry.

3 DR. GARRA: Thank you very much.

4 This concludes the section on industry
5 presentations.

6 The next session, which is going to begin right
7 after a short break, a ten-minute break, is a second open
8 public hearing session. The people who are going to be
9 speaking at that, please remember that the same
10 identification processes, disclosure statement requirements
11 and five-minute time limit will be applied.

12 Several individuals have already indicated that
13 they would like to speak. If there are others, please
14 approach Mr. Doyle during the break. We will see you all in
15 ten minutes, no longer, please.

16 [Break.]

17 MR. DOYLE: In order to make our record complete,
18 I would ask those speakers who have not done so, as of yet,
19 to please give me a copy of their slides.

20 Thank you.

21 DR. GARRA: Our first speaker--in fact, we only
22 have one speaker in the afternoon public session, and that
23 is Cindy Pearson, Executive Director of the National Women's
24 Health Network.

25

Open Public Hearing

1 MS. PEARSON: Thank you. As you said, I am Cindy
2 Pearson. I am the Executive Director of the National
3 Women's Health Network which is a non-profit, science-based,
4 women's health advocacy group. We are supported by a
5 national membership of 12,000 individuals and nearly 300
6 local groups.

7 To do our financial disclosure, I am going to do
8 broader than most people have done because not only do we
9 not accept money from any company that is involved in
10 anything to do with bone strength assessment testing, we
11 don't take money from drug companies including those
12 companies involved in making drugs to treat or prevent bone
13 loss, and we don't take money from the dairy industry. We
14 don't take money from exercise-equipment manufacturers. We
15 really believe in staying poor but pure so that we can be an
16 independent voice for women's health issues.

17 That great independence gives us the freedom to
18 talk about the sins of omission and the sins of commission
19 and how they should be righted to make women's health in the
20 United States better.

21 Today, I think the sins of omission which usually,
22 for a group with a 25-year-old history, you would think we
23 would see a sin of omission as leaving women out. It was
24 very interesting that the FDA opened up the day by asking
25 you, "Are we committing a sin of omission by leaving men out

1 of the reference database?"

2 After having been here all day, I can see it is
3 still very contraversial. It looks like, from our
4 perspective, there is at least some data from three studies
5 that appears that leads you to think it might be safe to
6 assume that, at the same bone-mineral density, the risk is
7 the same between men and women.

8 But it is clear that men, certainly, haven't been
9 as well researched on this as women, although given the
10 incidence of the disease of fragility fractures in men, it
11 may not be a real sin that they have been treated in this
12 way.

13 But I would say that the past history of leaving
14 women of color out, although, again, there is the balance
15 that, at least in the United States, this is a more serious
16 and more common problem for white women, it is a problem
17 that some women of color face and it seems obvious, at least
18 to us, although certainly not to the expert researcher who
19 presented from Hawaii--but it seems obvious to use that we
20 certainly cannot say that data show something or other, that
21 he believes you can say that there is no evidence that there
22 is a difference, but I think you could also look at those
23 same data and say, "There is not nearly enough evidence to
24 know what you can and what you can't say about the
25 relationship between BMD and later risk for women of color."

1 The data that we saw earlier were Japanese-
2 American women living in Hawaii. I don't think any of us
3 want to assume those predict or apply to African-American
4 women or Latinas living in the United States.

5 Our belief is that the panel should give some
6 advice to the agency along the lines of that we recognize
7 that it is a research question of interest to determine
8 whether the relationship that exists between BMD and
9 fracture risk in white women is similar in women of other
10 ethnicities.

11 Then to the sins of commission that our group
12 likes to talk about as a watchdog for women's health. Those
13 in the FDA who know us already from testifying over at the
14 drug division or other parts of CDER know that we are often
15 very concerned about actual harm that has been done to
16 women.

17 That is very easy to see when you talk about the
18 harm done from poorly tested or unsafe drugs, the harm done
19 by unnecessary surgery. But how can we be standing up today
20 saying that we want to talk about the sin of commission or
21 actual harm that could be done by a screening test,
22 especially a screening test like bone-strength assessment
23 which is really very benign as tests go?

24 Here we go right back to the public-health
25 definition of what does it take for a test to be shown to be

1 effective as a screening test? It means that there should
2 be an important condition, one that causes death or
3 significant decrement in quality of life, that early
4 detection should be possible and that early detection should
5 enable the patient and clinician to intervene in a way that
6 changes the course of the disease.

7 If all of these criteria are not met, then the
8 "risk," and I put that in quotes in my notes--the "risk" of
9 the tests are not worth it. Just for clarity's sake,
10 because this hasn't been said explicitly, the risks here are
11 the false positives.

12 I will just note that I do feel a little bit like
13 I am saying the emperor has no clothes on. There has only
14 been twice in this day when there has been an explicit
15 mention of the possibility of overtreatment as a risk of
16 either bone-density screening or which reference database is
17 applied to which group of people.

18 But we believe it is important to raise this
19 issue. It is always important to challenge assumptions. I
20 know we are probably the only voice that you are hearing
21 from today that is bringing this up, but we are not alone in
22 our lack of enthusiasm for bone-strength assessment to be
23 considered by the average busy clinician and the average
24 person as a gold-standard-proven screening test.

25 Particularly, we are concerned about this now

1 because bone-density screening tests, as we saw in that very
2 powerful presentation early in the morning, between '95 and
3 '99, there have been tremendous changes in the number of
4 machines, the number of people getting screened. And that
5 has been accompanied by and accomplished with quite intense
6 popularization and promotion of this test.

7 It is beyond radio and magazine ads and public-
8 service announcements. In this area, I can walk into a
9 local grocery-store chain and not just find out about the
10 test, but get it. So what this has led to, in our
11 impression as a consumer group, is that the average woman
12 who is aware of bone-strength testing really believes that
13 it is something like a Pap smear. It is going to take her,
14 with no symptoms, do a pretty simple test and give her a
15 result that is either good, bad--maybe she might get an in-
16 between result--and that, if she has a bad result, that
17 result is enough to spur action.

18 I know I don't need to say to all the experts on
19 the panel that there is so much more to preventing fractures
20 and even just to assessing the risk for fracture than that
21 one result that prints out after a bone-strength assessment
22 test is done.

23 But I think we, and I am speaking in the
24 collective "we" of women concerned about their health--we
25 need the FDA to do something to balance out what feels like

1 an imbalance of information, that, right now, there has been
2 such a need to get osteoporosis, the real suffering caused
3 by osteoporosis in old age, into the consciousness of
4 clinicians and into the consciousness of women as something
5 that could be prevented or that they don't have to just
6 accept with aging.

7 But the pendulum has swung so far now that people
8 wrongly assume that this test and its one-number result can
9 be the red light or green light for a drug intervention. So
10 we know that the FDA doesn't regulate the practice of
11 medicine. It doesn't regulate what tests are promoted to
12 the general population as screening tests, but the FDA does
13 regulate labeling and you are asked to give some advice to
14 FDA today about labeling.

15 So we would ask that, in addition to that
16 incredibly complicated problem you have about absolute value
17 versus T-score versus new T-score, which we won't even go
18 near, we would ask that you recommend, in addition to
19 whatever the numerical value is, that that simple clear
20 report that physicians get at the end of a bone-density test
21 include some additional information, that it include some
22 information about the predictive value of other risk factors
23 than BMD, the need to look at BMD in combination with other
24 factors and the limits of its predictive value both in an
25 older population, 65, 70 years, and particularly in the

1 Kenneth Faulkner, Director of the Osteoporosis Center at
2 Sinarc will serve as lead discussant for these points and we
3 will try to arrive at some conclusions here.

4 MR. DOYLE: I will read the first discussion
5 point. We are asking the panel to do this; "Please discuss
6 and attempt to define the roles of absolute values, BMD,
7 SOS, BUA, et cetera, T-scores and Z-scores in the assessment
8 of fracture risk in patient management for osteoporosis as
9 well as for other secondary conditions leading to bone
10 abnormalities." And then a subquestion under that is, "Are
11 these roles the same or different for DEXA, ultrasound and
12 other bone assessment devices?"

13 DR. FAULKNER: My understanding is that we first
14 have some discussion and if you would like to ask questions
15 of anyone else here, the ultimate goal is to get to some
16 recommendation from each of the panel members about each of
17 these questions.

18 I have been doing a lot of talking, I know, but it
19 has been awful quiet on the other side of the room. I am
20 hoping you can provide some input, at least for this first
21 question, if you have any additional questions or concerns.

22 DR. DESTOUET: I will open my mouth first. I was
23 unaware that the T-score alone, and I think many clinicians
24 are probably unaware, that the T-score alone is fallible and
25 that, basically, we need to bind it with some other

1 measurements or some other evaluation of the patient in
2 order to get a real true assessment of fracture risk.

3 I share the concerns of many of the speakers that
4 if we eliminate T-score, we will have a major rebellion on
5 our hands because the clinicians are now so much in tune
6 with that measurement that whatever the panel recommends, it
7 has to be based on T-score, some kind of new T-score or tied
8 in to other risk analyses to come up with a better
9 measurement of fracture risk.

10 DR. FAULKNER: If I might just comment. I think
11 the concepts we have to deal with here are specifically the
12 measurement of bone density and how it relates to fracture.
13 I don't think it is going to be possible--you can tell me if
14 I am wrong here--for us to require the manufacturers of this
15 equipment to include, in their software, additional risk
16 factors beyond density.

17 That has got to be kind of clearly in the realm of
18 clinical practice. But those have always been important
19 points. I am way too emersed in the field. That has always
20 been stressed. It may not be realized among the primary-
21 care population and that is an education issue, but I think
22 the concepts that we are here trying to provide, how do we
23 convey the information about bone density and specifically
24 for this question; is it absolute values? Is it T-scores,
25 Z-scores? Are all three of them to be used? Is it not only

1 for fracture assessment but also for secondary causes?

2 There are many reasons to measure bone density
3 beyond just for osteoporosis. And are they the same for all
4 these technologies?

5 DR. GARRA: I have been making a lot of comments
6 but I am going to make one here, also. One of the speakers
7 earlier said that there was a feeling that they had to have
8 a single number as an output for the machines. I really
9 think that is unrealistic, especially if they--I think that
10 is what got us into this problem, people took the T-score
11 and tried to make it into a single number that would do all
12 the predictions for them and do their thinking for them.
13 And it has gotten everybody into trouble.

14 It is my feeling that you need the absolute value,
15 you need the bone-mineral density value and I think that can
16 be tied directly to risk as it becomes available, but that
17 we do need a transition and that you need a transitional
18 period of adjusted T-values for people who are used to using
19 T-values.

20 But I think eventually the T-values which are
21 useful in showing where you are with respect to your
22 population, especially if you used an age-matched group, the
23 Z-value, would be used only for specialized situations.

24 For fracture assessment, I think that fracture
25 risk and the corresponding BMD value will eventually replace

1 the T-value and that you will still continue to use the Z-
2 value, the so-called Z-score, for specific things like
3 determining that this patient may have a secondary process
4 going on that is accelerating bone loss.

5 DR. FAULKNER: I would agree. It seems, though,
6 from the data we have seen today, the state that we are left
7 in today, if we stay with T-scores, the current T-scores are
8 different for different technologies which is probably on to
9 question No. 2, more.

10 But I think I had asked the question of our
11 representatives, I mean how they would deal with this--if
12 all of a sudden, T-scores were removed from the equation,
13 this could cause chaos. I thought it was maybe sort of
14 asking indirectly from our NOF and ISCD friends if they
15 could confirm that or deny that.

16 Dr. Miller, I would appreciate an opinion on that.

17 DR. MILLER: I am Paul Miller. You all heard the
18 issues and are increasingly aware of the issues. Even
19 though in the ideal world we would like to be able to tie an
20 absolute BMD to fracture risk, it will take a transition.
21 It has to be an evolution, not a revolution.

22 What we think here in this room may not be exactly
23 what the rest of the world thinks with regard to this
24 process which was set up by the World Health Organization.
25 For example, the scientific membership of the International

1 Osteoporosis Foundation, which is representative of Europe
2 and much of South America, is very resistant to even the
3 idea of a T-score equivalent which, I think, as you
4 mentioned, is probably the way to get into this transition.

5 The other issue is the fact that--and I am a
6 practicing physician--despite the fact that we think we
7 study and are cognitive, we try to do that, there are many,
8 many physicians who are seeing so many patients a day that a
9 single number triggers a whole cognitive process of what
10 they do and how they think about things, even though it may
11 not be the right cutoff. It is the 140 over 90; that
12 triggers a diagnosis.

13 The other thing is that, in this country, in
14 America, unlike Europe and unlike Asia, we make diagnoses
15 and we get reimbursed by diagnoses. We don't get reimbursed
16 by risk assessment. There is no international
17 classification of disease, the ICD9 codes, that pass for
18 risk.

19 So, if we simply went to risk immediately, we
20 would have to change the whole ICD9-code system. I think
21 that is another hurdle. So I would suggest that we think
22 about ultimately changing in an evolutionary process the
23 concepts that Dennis has so hard worked on in terms of the
24 T-score equivalent based on risk and have that linked to
25 prevalence is probably the way to go in the near future.

1 DR. FAULKNER: So what I am hearing is we would
2 have BMD and we have T-scores and we have Z-scores and now a
3 T-score equivalent. We seem to be going backwards at some
4 level. And we want to have risk.

5 DR. GENANT: Clearly, as the information becomes
6 available and Dennis Black had indicated that we are looking
7 at potentially something in the fall at which time this
8 group, representing a number of the organizations, will have
9 some specific recommendations, I think that we would
10 envision that, down the road, the T-score, as we know it
11 now, would go by the boards.

12 The likelihood of the continuation of a Z-score or
13 some ability to look at a patient in relationship to that
14 patient's peers will probably remain, but then some kind of
15 a score or a reading that is going to be either prevalence-
16 based or risk-based that will essentially replace the T-
17 score as we are currently using it is what I would envision.

18 DR. TURNER: May I comment quickly? It seems like
19 there are two issues when it comes to T-scores and Z-scores.
20 The T-scores are what have been used to calculate risk of
21 fracture where the Z-scores typically just put somebody in a
22 general realm with their peers. In one case, with the Z-
23 score, ethnic and gender-based databases might be very
24 appropriate.

25 In another case, with the T-score or risk, it may

1 not be so appropriate as the data is not quite available
2 yet. We need to make this distinction on what either of
3 these scores might be used for and if ethnic and gender-
4 based Z-scores are placed on the screen, that they be used
5 appropriately.

6 The downside is that if a clinician were to use a
7 Z-score based on male young-normal, a T-score based on that
8 same normal would probably give indication for treatment
9 where maybe treatment is not necessary. There is a
10 potential if these get confused of overprescription.

11 DR. FAULKNER: So I guess is the panel more
12 interested in--and we have heard proposals of going
13 completely to risk. We have heard to T-score equivalence.
14 Are there thoughts about which we would may recommend that
15 would be pursued?

16 DR. MCGOWAN: I think we have heard where the NOF
17 committee and the International Densitometry Committee are
18 going. I think we should wait to see that proposal. They
19 are giving very thoughtful consideration that we really
20 can't do in this forum to the best way to present this.
21 There is always--beyond that, other groups have to take
22 over, perhaps the NOF, perhaps the NIH Resource Center, in
23 promulgating that information.

24 But I think we have to wait to see the end of that
25 process before we can really say would risk be better.

1 DR. FAULKNER: But I am hearing a sense that we
2 don't want to pull the rug out from underneath the T-score
3 and that, also, there are conditions that are vital besides
4 fracture-risk prediction for bone density that would require
5 good normal databases and the use of Z-score; is that
6 correct

7 DR. GARRA: Correct.

8 DR. MCGOWAN: No. Actually, I can't see that. I
9 can't see that we have information about fracture, the end
10 disease, that disease scores would really help. I have
11 heard people say that if we put gender and race-specific Z-
12 scores there that it would be useful information.

13 But I don't know how. I don't know how they are
14 going to use it. We have, in the works, a large study of
15 males. Cindy will be happy to know that we are finally
16 going to study males. The Women's Health Initiative has a
17 large cohort of African-American and Hispanic females that
18 they are going to be studying.

19 But, right now, I don't think we have that data.
20 And I think we would do better to add more information to
21 the physician's arsenal, what is the meaning of that T-
22 score.

23 DR. FAULKNER: We are going to get there. I think
24 we have to get there in No. 3. Maybe we should try and move
25 on to that, but it may be representing the gender that

1 suffers a third of the hip fractures that do occur, which is
2 sometimes not recognized--25 percent; excuse me, Dr.
3 McGowan.

4 We will have more data because I am also hopeful
5 to see more. Shall we move on to the second question?

6 MR. DOYLE: If you are ready. For the benefit of
7 those who may not have a copy, "Please discuss and attempt
8 to define the role of the young-normal reference database in
9 assigning appropriate levels of fracture risk to individual
10 patients including various age, gender and ethnicity.
11 Specifically address the pros and cons of using a single
12 young white female database, the pros and cons of using
13 multiple gender and ethnic-related databases, the associated
14 information needed to correctly interpret the various
15 measurements--that is, absolute values, T-scores and Z-
16 scores, based upon these various databases."

17 DR. FAULKNER: So, again, the same idea here. We
18 have the need for other databases and the appropriate use of
19 those given the lack of prospective data and some of these
20 other idea, the ability to relate, as Dr. McGowan said, to
21 relate these things to fracture risk. Is it appropriate to
22 have these different databases?

23 DR. GENANT: Maybe I will take a stab at it. It
24 is somewhat repetitious of some of the information that we
25 have just gone over. I don't know that I would discuss this

1 totally in the context of just the young-normal reference
2 database. I think we need the database across age and that,
3 again, until we know for the other ethnic groups and for
4 males, somewhat better information about specific fracture
5 risk. I think just being able to at least view a patient's
6 value in the context of peers is still useful at this point
7 in time.

8 Down the road, we will have more information we
9 can relate as well to a fracture risk. I don't think we can
10 do it that well at this point.

11 DR. GARRA: I would like to make a comment. I
12 totally agree with Harry on that. I think the problem with
13 the single young white female database is we don't have a
14 single one. The problem is everybody is using a different
15 one. And that is where all the problems lie. So I think,
16 in the sense, it would be great if we had a single one
17 because then it would be just, basically, the bone-mineral
18 values multiplied by the same numbers by everybody.

19 But we have multiple ones and that is introducing
20 a source of variability that is really hurting us in many
21 ways rather than helping. So if there is an alternative to
22 that, and I keep hearing reference to a standardization
23 committee, which should be able to come up with a solution
24 to that because part of the impetus for that single young
25 white female database was to standardize the values across

1 different instruments. I think that is the solution in the
2 end.

3 DR. FAULKNER: Is it appropriate, also, to put
4 information about risk in those populations where we have
5 that prospective data? Is that appropriate to recommend
6 that be included in the reports?

7 DR. GARRA: I think it is appropriate if the
8 information is there.

9 DR. FAULKNER: Specifically, I think I made a
10 comment regarding the fact that the reason that we tend to
11 compare some of these populations to the Caucasian female
12 reference population is because they are the population we
13 know the fractures. That is the high-risk population and if
14 you would tell these other populations that they have a T-
15 score of -2, you don't really have a concept of what that
16 means.

17 But it does mean that you have an underlying
18 belief that bone is bone, as we have talked about before,
19 which may or may not be true. I am not sure I am completely
20 convinced of that effect for men. When I talk to Dr.
21 Orwall, my neighbor in Portland, he will tell me that he is
22 not convinced that that is completely true. But we saw some
23 excellent data today from Dr. Wasnich that would support
24 that it might be true, especially the measurements of the
25 heel.

1 So I think that remains a question. We have also
2 got a bullet point here, the associated information needed
3 to correctly interpret the various measurements. The
4 concept that we don't have standardization is something that
5 we talked about. We really don't have agreement on a
6 standard, what constitutes a normal database, what are the
7 requirements for a normal database.

8 We have heard recommendations that we create some
9 kind of super-normal database if would could. How does the
10 panel feel about those concepts? It is very quiet.

11 DR. DESTOUET: You keep looking at this side of
12 the table and we are all mammographers and other people.

13 DR. FAULKNER: We can make all the choices. It's
14 fine, if you would like us to.

15 DR. DESTOUET: I think, just based on a
16 clinician's standpoint, you absolutely need to have some
17 kind of--you talked about a phantom or some kind of tool
18 with which you can measure and develop a normal reading, I
19 think, across manufacturers.

20 It is interesting that, in mammography, we have to
21 meet certain very rigid guidelines, that a piece of
22 equipment has to show so many particles to show that it can
23 detect cancer. That is uniform across all manufacturers. I
24 wonder why, in the bone-densitometry field, that there could
25 not be development of some equal standard so that we

1 wouldn't have each manufacturer developing his own normal
2 database.

3 Harry, is that impossible?

4 DR. GENANT: I might comment on that a little bit.
5 At UCSF, in conjunction with the International Standards
6 Committee a number of years ago, of course, we undertook the
7 cross-calibration of the major DXA, central DXA, systems at
8 that point in time, at least, using patients and then we
9 also employed some phantoms.

10 But there are some problems with regard to
11 phantoms in this context because the phantoms do not always
12 fit nicely on all of the cross-calibration curves of the
13 patient data. So one has to look at that aspect. But,
14 nevertheless, I think that we have made considerable strides
15 and there generally was acceptance of the cross-calibration
16 formulae that have been applied now for spine and for hip
17 and, currently, there is underway a cross-calibration for
18 some of the forearm and calcaneal, at least, DXA
19 measurements. So I think that we can make some progress
20 along those lines. That would be based upon patient data as
21 well as phantom data to the extent that the phantoms are
22 representative of real people.

23 In the case of ultrasound, it is a bit--
24 substantially more challenging because of the greater
25 variation in the parameters that are measured, the sites

1 that are measured. So that is something that is still on
2 the horizon to be dealt with.

3 DR. FAULKNER: In mammography, you have got the
4 MQSA. Do we have a densitometry QSA? No. I do know that
5 the International Society of Clinical Densitometry, I saw
6 Len Abacilla around. He is the Director of the Site
7 Certification Office. I have been waiting to see something
8 come--I think there is some move there.

9 But it is happening. It is going to take some
10 time but I think it would be a good recommendation to try
11 and pursue because, even getting to point No. 3, when you
12 get one of these done in the local drug store, how do you
13 know that that has any bearing, at all, to reality.

14 So to maybe address those issues and to figure out
15 maybe there are certain requirements that need to be met to
16 insure that these are, indeed, valid and properly done, in
17 addition to the standardization.

18 MS. PETERS: As a consumer, I would expect that no
19 matter where I went, to what facility or what doctor doing
20 whatever tests, whether it was measuring the spine, the hip
21 or the bone, that whatever results would be appropriate for
22 treatment no matter which one was done, so that the results,
23 whatever the number, whether it was a -2.5 or a -3 for one
24 part of the body as opposed to another, that the treatment
25 for me would be the same, that I wouldn't go to one doctor

1 and they say, "No; you don't need treatment. You are fine,"
2 and I would go somewhere else and have another part of my
3 bone tested and, "Oh, yes; you are really at risk for
4 fracture and we need to do this, this and this."

5 So I think there has to be some kind of uniformity
6 across the system.

7 DR. GARRA: I would like to comment that I wish--I
8 would like that, too. But I don't see that happening
9 anywhere in medicine. You can go and get widely disparate
10 opinions on just about everything, blood pressure,
11 fingernail length, anything.

12 MS. PETERS: True, but now we are having, within
13 the profession, a lot of nurse practitioners being trained
14 now who will be primary-care providers and who will be using
15 or recommending some of these things being done. And we
16 have to make sure that their interpretation of the results
17 is equal to other health practitioners.

18 DR. FAULKNER: There is some--I should probably
19 let Len address this question, but, Len, correct me if I am
20 wrong, there are some health HMOs that are requiring
21 certification by the ISCD for reimbursement, in little
22 segments of the U.S. He is shaking his head for the record
23 that's true.

24 So this may evolve. There may be a recommendation
25 we would want to continue to recommend that there is always

1 quality done in these measurements. That probably gets a
2 little afield of the second question here but more addresses
3 the third. So the concepts of pursuing a common normal
4 database; any comments on that?

5 DR. TURNER: Ken, as we have been sitting here, I
6 have been trying to think through the logistics of actually
7 doing that. When you consider that there are, I don't know
8 how many different devices that measure at all the different
9 sites in the body and you want a common database which
10 means, essentially, the same people that have to be measured
11 by all these devices, it would require sites to have 20, 30
12 devices and people are willing to go through all of these
13 measurements to develop it. Is this feasible?

14 DR. GENANT: That might not actually be necessary
15 because we know that among some of the devices there is
16 really comparability. To the extent that one has very high
17 comparability, perhaps one could select one of those
18 instruments for that particular representative measurement;
19 for example, among the DXA systems measuring the spine and,
20 to a large extent, the hip, there is pretty strong
21 comparability and there already are cross-calibration curves
22 that are derived.

23 But it is when you start to get to some of the
24 newer devices where there is less data and they are
25 measuring somewhat less typical sites that it would be more-

1 -

2 DR. TURNER: But there would still be eight or ten
3 measurements, wouldn't there?

4 DR. GENANT: Yes; sure.

5 DR. FAULKNER: At the same time, I know we have
6 been battling this issue for some time and there is a part
7 of me that says we ought to just answer the question and
8 maybe do some kind of a--there are sites that have--at the
9 clinic in Oregon, we have sixteen bone densitometers. And I
10 think Paul's got a few of them. I know, Harry, you have one
11 or two in the clinic.

12 I know there are centers that have capabilities.
13 At some level, I think this question will always remain,
14 until we do address it and take it up up front.

15 MR. SILKAITIS: This is Ray Silkaitis. In terms
16 of helping industry in setting standards and things like
17 that, it would be very helpful if there are standard curves
18 to develop phantoms because if you have many manufacturers
19 out there and to have every single one go out and do a
20 clinical trial, that would be--I don't know--"a huge cost"
21 that could be spent either developing new technologies.

22 I agree that when you have new technologies, yes;
23 they do have to go out to the clinics and to the patients to
24 evaluate that technology but for comparing one
25 manufacturer's device to another that is basically the same

1 technology, there should be a non-clinical means of being
2 able to compare those devices.

3 The other question I had goes back to the
4 databases. Obviously, to generate a database, you have to
5 have a sample size that is based upon a statistical
6 rationale. I am wondering whether there is guidance in
7 terms of the appropriate databases, sample sizes, that are
8 needed to make these estimations.

9 DR. FAULKNER: I know that that has been looked
10 at. I do know that Dr. Miller has convened a meeting with
11 Dennis Black--I think Anne Looker was there--to talk
12 specifically about sample size. Statistics means never
13 having to say you're certain, so I am not sure if they ever
14 came up with--that was discussed and it is reasonable to do.
15 It is not completely unreasonable. You don't need a million
16 people here.

17 DR. GARRA: I was thinking, at the very least--
18 well, we already have a core of instruments that we know are
19 roughly equivalent. If that information is made available
20 and the new players on the field would simply be required to
21 demonstrate the calibration of their instrument relative to
22 one of the existing ones, I think that would get us a long
23 ways there. That is a lot simpler than trying to develop a
24 large database where everybody is included and then having
25 to redo that every several years.

1 DR. FAULKNER: I am hearing the sense that we have
2 got the idea that having comparisons to a single database, a
3 fracture-referenced database, seemed to have some utility
4 but, at the same time, ethnic and gender databases also have
5 utility for definite clinical questions.

6 I am not hearing that we can just eliminate
7 gender, male databases or the need for ethnic databases, but
8 if they are used for fracture-risk prediction that that may
9 not be appropriate, in the absence of prospective data. Is
10 that correct?

11 DR. GARRA: Agree.

12 DR. TURNER: You say it isn't appropriate.

13 DR. FAULKNER: Is not appropriate, however--you
14 know what I mean.

15 DR. MCGOWAN: For the panel, there are two kinds
16 of databases we are talking about. The database of young
17 normals and the database of age-matched people going
18 through, we can have--we do have, we can have tomorrow--for
19 men of all ages, for African-American women, for Hispanic
20 women, that we have.

21 What we don't have is the relationship between
22 different levels of bone-mineral density and fracture in any
23 population except white Caucasian women. I would prefer to
24 say, at this juncture, we have a set of human data. I think
25 if they change their database right now and said, "You are

1 being compared to young humans," that we would be correct,
2 until we have information that confirms that that is
3 appropriate or that changes our opinion and that says, "In
4 men, there are simply different fracture risks at different
5 bone-mineral densities."

6 DR. FAULKNER: There might be some wording that
7 could be created in terms of, "When we compare you to the
8 fracture population," or something that takes the gender,
9 ethnicity, out of it.

10 DR. MCGOWAN: And young normal humans.

11 DR. FAULKNER: At the same time, it sounds as
12 though we would be uncomfortable allowing these things to be
13 used for fracture-risk prediction or in places where we
14 don't have prospective data. Are prospective data necessary
15 in order to make those extrapolations or would case-cohort
16 studies--case-cohort studies very often produce odds ratios
17 similar to prospective trials. And they are much easier to
18 do.

19 DR. GENANT: I think we heard several times today
20 that well-established and well-performed and well-conceived
21 cross-sectional studies or cohort studies could likely give
22 information that would be of comparable, or at least
23 acceptable, standards.

24 DR. FAULKNER: Maybe we should move on to the
25 third question unless there are any issues that we would

1 like to address here.

2 Okay. We will move on to question No. 3.

3 MR. DOYLE: "One of FDA's major roles in the
4 regulation of medical devices is to assure clear and
5 meaningful labeling for health practitioners and patients.
6 Please provide recommendations regarding appropriate
7 labeling of bone-assessment devices.

8 "Specifically address indications for use,
9 warnings and precautions, device description, what
10 information is presented, and instructions for use, how to
11 interpret and use the information provided by these devices
12 to make appropriate patient-management decisions."

13 DR. FAULKNER: I think we have addressed all of
14 these issues in some of our earlier discussions but I do
15 think there is concern, and I think it is rightly stated;
16 are we treating people that don't need to be treated? Are
17 we potentially overtreating? Do we need to put some
18 stricter indications for use and are there people who are
19 not being treated who should be treated due to the fact that
20 we were limited by knowledge or data or what we know.

21 That would go under maybe warnings, precautions.
22 Do we want these things being used in drug stores or using
23 predictions of fracture risk without prospective data?
24 Thoughts?

25 DR. ROMILLY-HARPER: I realize that a lot of these

1 studies are being used by clinicians because we finally have
2 what we call interventions. There are all the multiple
3 drugs that they are willing to give individuals based on
4 information that may not be accurate.

5 But I want to caution the FDA, too. I was very
6 impressed with what is apparently ongoing, and Dennis Black
7 really presented some real solid information. I would be
8 tempted to say let's wait and see what comes out of that
9 before we change the course of what we are currently doing
10 because we can confuse the physicians even more.

11 Right now, I am seeing in our clinical practice
12 where we have a bone densitometer predominantly for breast-
13 cancer patients, and we are seeing treatment interventions
14 that may or may not be appropriate at this time based on the
15 information that they have.

16 I would caution us not to jump the gun at this
17 point in time because I think we need a lot more
18 information. Whether we will be using absolute scores--my
19 problem is that we really don't seem to have a good grasp on
20 what score reflects true fracture risk in a lot of these
21 individuals.

22 I think we could wait. If they are going to be
23 bringing out information in November, I would love to see
24 it. Then we will discuss this issue because I think
25 changing recommendations now--I agree they should be changed

1 but I don't think we have the information necessary to
2 probably change that.

3 DR. FAULKNER: So you would support really
4 answering the first two questions before we can really get
5 into No. 3.

6 DR. ROMILLY-HARPER: Before we could get into No.
7 3, and not confuse the issue.

8 DR. FAULKNER: In fairness, too, I know it was
9 presented--sort of another option was to also ask that risk,
10 actual absolute risk values, be put into some of these
11 reports as well, if that is possible to do. We may have to
12 wait and see. I think we heard some data that indicates
13 that that is possible for some skeletal sites and some
14 devices, but maybe we need more information.

15 MS. PETERS: If we have these machines out in the
16 community and drug stores, and they are giving general
17 information to the consumer, I think that there should be
18 some labeling that lets the consumer know that this may not
19 be accurate for them, that they need to seek their
20 healthcare provider.

21 I don't know what information comes out with that
22 score to them and if that is appropriate.

23 DR. FAULKNER: I will tell you, very little. It
24 really is not, I don't think, well explained but it probably
25 does require answering the first two questions before we can

1 address the third. I think it is a good comment.

2 DR. MCGOWAN: That is a good question that I
3 didn't want to bring up. I thought I had missed previous
4 meetings. How are these questions currently answered?
5 These have been approved so, for the approved devices, how
6 are they currently answering those--

7 DR. FAULKNER: I will tell you that at the drug
8 store below my house, it was a single sheet of paper where
9 they did the measurement and wrote in the T-score value and
10 listed the WHO criteria below and said, "If you fall between
11 -1 and -2.5, you have osteopenia," which everyone thinks is
12 some horrid disease, and they run to their primary-care
13 physician waving their T-score wondering what they need to
14 do.

15 I don't know if any of the other physicians have
16 had anyone come in waving one of these things wondering what
17 to do. Dr. Miller never has that happen, I'm sure.

18 DR. MILLER: May I comment? This has been a
19 serious issue because of the fact that, as you well know,
20 patients can get single-site testing, whether that be hip or
21 wrist. You can have a normal value at one site for all the
22 reasons we have heard and have a low value at another site
23 and get told they don't need an intervention when they may
24 need an intervention or even vice-versa.

25 So in the December issue of the General Clinical

1 Densitometry, we put out some clinical recommendations about
2 which patients that have a normal peripheral test may need
3 additional central testing. That is not very widely
4 distributed, but at least it is out there.

5 In the body of that paper is a single table that
6 would be, in our opinion, one of the ways of approaching
7 this issue of what information should be presented to the
8 patient because it has a message in there that, if you have
9 additional risk factors and your single site is normal, you
10 should consider talking to your doctor about additional
11 testing.

12 It is not perfect, but at least it gives some
13 guidelines in that regard and some kind of implementation of
14 a suggestion on that might be a consideration.

15 DR. ROMILLY-HARPER: There are two other issues--
16 and maybe you can help me on this--that we get from our
17 clinicians. One is, with interventions, how often you
18 should follow these individuals, how often do you do
19 recurrent bone-densitometry tests.

20 Secondly, if you have some other ethnic group, and
21 at the bottom of our reports, we say, "The database is young
22 female, Caucasian," whether the test is even valid. We get
23 those questions all the time and I haven't been able to
24 answer them.

25 DR. FAULKNER: I know Dr. Miller can answer them,

1 but I know he would also take about an hour to do it, if we
2 were lucky. Those are great questions. I get five phone
3 calls a day and it is great because I am Ph.D., I can say
4 whatever I want.

5 It was suggested maybe Dr. Schultz could give us
6 some indication of what the current labeling is on these
7 devices.

8 DR. SCHULTZ: Let me just make a couple of
9 comments. One, I understand the idea that we want to wait
10 to have all the answers before we start making and broad
11 recommendations in terms of additional labeling requirements
12 and things like that.

13 I think that the point that I tried to make
14 earlier this morning was the fact that what we are asking
15 you, basically, for is the state of the art as it exists
16 today. We are not asking you to predict what is going to
17 happen even six months from now in terms of additional
18 studies and additional data.

19 I would like to comment that the labeling, at
20 least in terms of the newer devices, the ultrasound devices
21 that have been approved where we have had much more
22 interaction with companies through the PMA process, I think,
23 in general, we have had very good interactions with
24 companies in terms of having the information clearly and
25 appropriately presented and, in general, outlining what the

1 appropriate indications, contraindications, warnings,
2 precautions are for these types of devices.

3 I think, as Eric mentioned earlier, when we were
4 confronted specifically with this issue of the gender and
5 ethnic databases, we were unable to reach that kind of
6 agreement with respect to how the label should reflect the
7 appropriate use of that information.

8 I think that the discussion that you have had in
9 terms of providing a lot of background in terms of the
10 entire field of osteoporosis has been very valuable. We are
11 not asking, really, for you to come to a final conclusion on
12 all of those questions.

13 I would, however, like to ask you, even given the
14 lack of total understanding of questions No. 1 and 2, to, to
15 the extent possible, specifically address question No. 3
16 with respect to the labeling and, again, specifically with
17 respect to the labeling of if we were to have gender,
18 ethnic-related databases, what labeling should go along with
19 those databases based on our current knowledge,
20 understanding again that that knowledge is incomplete.

21 I know we don't have too much time left, but if I
22 could sort of get you to focus your efforts in that
23 direction, I think we would be most grateful.

24 Thank you.

25 DR. FAULKNER: I think that is a good point.

1 MR. SILKAITIS: Dr. Schultz, in regards to the PMA
2 devices and the labeling for those devices, in terms of
3 providing complete information for physicians, is there a
4 section, like, typically, with other PMS devices, that talks
5 about clinical data.

6 I noted that you highlighted indications for use,
7 warnings, device descriptions, instructions for use. But I
8 know that there are many devices that have a clinical-data
9 section which allows the physician to then interpret the
10 clinical data in his or her own way.

11 Then they can apply their risk factors to the way
12 they interpret the clinical data that is provided in the
13 package insert. My question is, those devices, do they have
14 that clinical data section?

15 DR. SCHULTZ: Again, the more recent approvals do
16 have those data sections. I think you are absolutely right.
17 I think having the data there to look at is very helpful for
18 physicians to be able to put that into perspective. What we
19 would like to see, in addition to the clinical data section,
20 however, is some application of the clinical data to the
21 indications, to the contraindications, warnings,
22 precautions, and specifically to the instructions for use.

23 I think that that would, in addition to having a
24 data section because--again, in part, we are talking about
25 not a clinical data section but a lack of clinical data

1 section. We don't have a lack of clinical data section. So
2 I think there needs to be something more in terms of what we
3 don't understand as well as what we do understand.

4 DR. FAULKNER: We should probably try and move on
5 to our wrap up.

6 DR. GARRA: We are going to move to the wrapup
7 section. Dr. Faulkner, at this point, is then going to go
8 around to each panel member and ask them for recommendations
9 on each of the three points in question.

10 But, as Dr. Schultz has mentioned, if you can't
11 think of things for some of them, you can focus on item No.
12 3 and discuss possible warnings, precautions, indications,
13 in the context of the other two.

14 DR. FAULKNER: Possibly, to try and help things
15 along, I could try and summarize what I have heard and, if
16 you don't agree with it, maybe let us know. Maybe that
17 might help. But I heard clearly that there is definitely a
18 need for the absolute value, that we don't want to pull the
19 rug out from T-scores. We realize that they are imperfect
20 and would like a solution that would maybe transition us
21 away from T-scores.

22 We talked about this T-score equivalent and are
23 interested in seeing that further developed and that there
24 are situations when Z-scores are important as well, not for
25 fracture risk but for other indications and that, indeed,

1 they may be different for some of these different devices
2 and would encourage, again, the ISCD NOF Committee in
3 pursuing those relationships.

4 We also did talk about the young-normal reference
5 database and the need for possibly redefining this into a
6 fracture-risk database, but also there are situations when
7 gender-specific, ethnic-specific, databases would be
8 required. We didn't talk much about what detail we would go
9 into. I made the comment earlier about do we have a
10 Northern Irish ethnicity base. Do we go into it, like,
11 county by county. I think that is something we may have to
12 still consider.

13 But the pros and cons are related to the possible
14 misuse of these particular databases in situations for
15 assessing fracture risk where we don't have prospective or
16 cohort data. The associated information, I think I
17 indicated and it may be a sense of the panel as well, that
18 if we have absolute fracture risk information that that
19 would be very useful and would be nice to see on these bone-
20 density reports.

21 I think Dr. Genant echoed the comment as well
22 that, perhaps, we can use case-control studies to provide
23 some of this fracture risk data and not require these long,
24 expensive prospective trials.

25 Also, we need to look at these indications for use

1 and make sure that we have got proper training, that we have
2 these people properly certified and maybe go through some
3 process that is not yet defined, recommend creation of some
4 minimum standards for performing these measurements and also
5 try and investigate the concepts--we didn't talk too much
6 about the young-normal database as Dr. Miller suggested, but
7 I think there is, at some level, a concern that if we don't
8 do at least at some level these types of measurements that
9 these questions will always remain; a consistent set of
10 patients were scanned on all equipment. We could define
11 what the numbers are exactly and what pieces of equipment,
12 but that question will always remain.

13 That is sort of what I was hearing. Did I get it
14 close?

15 DR. SCHULTZ: Could I ask just one additional
16 question. Those general conclusions, would you say that
17 they apply to all of the different devices irrespective of
18 whether it is DEXA, ultrasound? That is what I was hearing,
19 but I just wanted to make sure that I am hearing that
20 correctly.

21 DR. FAULKNER: I do think that ultrasound can be
22 included. I heard a sensitivity of calling ultrasound a
23 bone densitometry. I actually think for the clinician, it
24 is a bone densitometry. In the real world, that is how it
25 is used. It doesn't spit out density per se, but they do

1 give a density equivalent.

2 In fact, if I understand the approval, it is an
3 estimator of DXA-measured bone density of some kind. It is
4 not strictly a bone densitometry, I know that. But, despite
5 the fact that I do agree that it is measuring some other
6 parameters, for most of what we are doing here, it is maybe
7 a bone-density estimator or a fracture-risk predictor.

8 DR. TURNER: It is a fracture-risk predictor, but
9 it is not a bone-density measuring device, per se.

10 DR. FAULKNER: Long answer. Yes; I think we can
11 include ultrasound.

12 DR. GENANT: I think that I would agree with that.
13 Clearly, the evidence that we have for the DXA measurements,
14 particularly at the spine and hip with regard to the
15 significance and the importance of T-score is much greater
16 than it is at the moment for the ultrasound, but I don't
17 think we want to pull the rug out from under the T-score
18 broadly at this point in time.

19 Hopefully, by mid-fall or so, we will have some of
20 the alternative approaches in place.

21 DR. FAULKNER: I would like to hear from our
22 statisticians, too, maybe when they do this, the
23 appropriateness of using case-control data. If we can get
24 fracture-risk data from those populations, it would go a
25 long way to transition us away from T-scores much more

1 quickly.

2 Dennis, can you shake your head up and down how
3 you feel about that? Are you comfortable?

4 DR. BLACK: It is important that the case-control
5 studies be done in a standardized way, that we have standard
6 instructions for selecting cases, for selecting controls,
7 and then, also, the idea that you do another BMD site in
8 conjunction with the new site that is being tested because,
9 for example, we know the relative risk for hip fracture is
10 2.6, so if you get, in your case-control study, 7.8 you
11 obviously know you have got to calibrate it.

12 DR. FAULKNER: It would just be great to have some
13 guidelines of what is a proper case-control study that would
14 allow us to then use that to produce these fracture-risk
15 estimates. Maybe the NOF ISCD group can help.

16 DR. BLACK: That is one of the things that we were
17 thinking of including would be standards for case-control
18 studies.

19 DR. FAULKNER: That would be very nice.

20 DR. GARRA: I would like to make a few comments.
21 I pretty much agree with what Ken said. With specific
22 reference to question 3, warnings and precautions, and with
23 specific reference to gender and ethnic-related databases, I
24 think there needs to be a warning appended that the use of
25 these databases has not yet been clearly defined and that,

1 at the present state of knowledge, they are not reliable
2 predictors of fracture risk.

3 That has to be very clearly stated if they are
4 going to be allowed to use those types of databases.

5 The other issues, I think as far as question 1,
6 the relationship of the various T-scores and Z-scores, I
7 think that there needs to be a clear-cut migration path
8 established. It looks like it might happen this fall--where
9 I would like to see a transition away from T-scores to the
10 use of Z-scores, absolute values and direct fracture-risk
11 estimates.

12 I think that the advantage of the T-scores was to
13 make a diagnosis. I think you can do that based on
14 fracture-risk estimates directly rather than having this
15 intermediate surrogate value which, I think, adds to
16 confusion for people that are new to the field.

17 But you do need the T-scores, the modified T-
18 scores, perhaps, as a transition but that scheme should be
19 laid out so people are prepared for that process and know
20 what is going to happen. I agree with Ken on the database
21 issues.

22 DR. FAULKNER: But having the ability to do case-
23 control studies will make that happen. Otherwise, we will
24 never get that data.

25 DR. MCGOWAN: Just one thing. On question No. 3,

1 if the indication for use for these instruments is risk
2 assessment, then I still have a problem with using gender
3 and ethnic databases where risk assessment is impossible.

4 DR. GARRA: I think we were proposing not using it
5 for that. They were doing to be used for diagnoses of other
6 medical conditions.

7 DR. MCGOWAN: I wonder about payers paying for
8 information on where you fit in bone density with your
9 peers. I think that they pay for risk assessment. This
10 other information doesn't really bear on your medical
11 condition to the extent that we know it now.

12 DR. GARRA: I think the answer to that question is
13 not known. I think that, as a physician, and I think most
14 patients also feel as if there is going to be useful
15 information in there once we get it.

16 However, it doesn't preclude you from taking the
17 standard database and doing a risk assessment on that and
18 giving this as additional information. I think this is
19 something that you will get as additional information not in
20 place of your standard information.

21 DR. FAULKNER: Any other comments?

22 DR. GARRA: So I guess we are done with the
23 wrapup. Any final comments that the committee members would
24 like to make?

25 I wish to thank the speakers, the members of the

1 panel and the special consultants for their preparation and
2 participation. It was a long day. I think we covered a lot
3 of material. I learned a lot and I am sure everybody else
4 did as well. I would like to extend special thanks to Dr.
5 Faulkner for leading the discussion and wrapup segment of
6 the meeting.

7 Any final administrative issues to deal with?

8 MR. DOYLE: Just, once again, if there are any
9 speakers who did not happen in the room when I made the
10 announcement earlier. Those who haven't given me copies of
11 their slides, I would appreciate it if they would do that
12 before they leave. Thank you.

13 DR. GARRA: Once again, thank you all for
14 attending. Dr. Schultz, would you like to say something?

15 DR. SCHULTZ: I just want to, very quickly, add my
16 thanks for a wonderful discussion. I think we learned a lot
17 and I think we can go home and digest a lot of what you said
18 and, hopefully, use it effectively. Thank you.

19 DR. GARRA: Thank you all. This meeting is
20 adjourned.

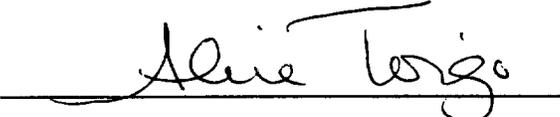
21 [Whereupon, at 5:10 p.m. the meeting was
22 adjourned.]

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C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a solid horizontal line.

ALICE TOIGO