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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OFFICE OF DEVICE EVALUATION

MEETING OF THE RADIOLOGICAL DEVICES PANEL

OPEN SESSION

Monday, May 17, 1999

9:00 a.m.

9200 Corporate Boulevard
Rockville, Maryland

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1 P R O C E E D I N G S

2 **Introductory Remarks**

3 DR. GARRA: I would like to call this meeting of
4 the Radiological Devices Panel to order, and I would like to
5 request everyone in attendance at this meeting to sign in on
6 the attendance sheet that is available outside the door.
7 Please record that the voting members present
8 constitute a quorum as required by 21 CFR Part 14.
9 At this time I would like each panel member and
10 guest at the table to introduce him or herself and state his
11 or her specialty, title, institution, and status on the
12 panel. I will begin with myself.
13 My name is Brian Garra. I am Director of Research
14 and Vice Chairman of Radiology at the University of Vermont
15 and the Chairman of this panel.
16 DR. McGOWAN: I am Joan McGowan. I am the
17 Director of Musculoskeletal Diseases at the National
18 Institute of Arthritis and Musculoskeletal and Skin Diseases
19 at the NIH.
20 DR. TURNER: My name is Charles Turner. I am
21 Associate Professor in Orthopedic Surgery at Indiana
22 University, and I am a temporary member of the panel today.
23 DR. SCHULTZ: My name is Dan Schultz. I am the
24 Acting Director for the Division of Reproductive, Abdominal,
25 ENT, and Radiological Devices at FDA.

1 DR. ROMILLY-HARPER: I am Pat Romilly-Harper. I
2 am a diagnostic radiologist and Director of the Indianapolis
3 Breast Center.
4 DR. DESTOUET: I am Judy Destouet, Chief of
5 Mammography for Advanced Radiology in Baltimore, Maryland.
6 DR. MALCOLM: I am Arnold Malcolm, Director of
7 Radiation Oncology, Provident St. Joseph Medical Center in
8 Burbank, California.
9 DR. SILKAITIS: My name is Raymond Silkaitis. I
10 am the temporary Industry Rep. The panel that I usually am
11 present for is the Orthopedic Panel. I am the Vice
12 President of Regulatory Affairs at Gliatech and have 20
13 years of experience in running clinical trials and dealing
14 with regulatory matters.
15 DR. GARRA: Two additional panel members have
16 shown up. Dr. Faulkner and Dr. Genant, would you like to
17 introduce yourselves, state your title and your position on
18 the panel.
19 DR. FAULKNER: My name is Ken Faulkner. I am the
20 Director of Osteoporosis Research for Sinarc. I am a
21 temporary non-voting member.
22 DR. GENANT: I am Harry Genant, University of
23 California at San Francisco, Director of the Osteoporosis
24 and Arthritis Research Group, and I am a temporary non-
25 voting member.

1 MS. PETERS: I am Marilyn Peters, the Consumer
2 Representative. I am from Los Angeles, California, employed
3 by the Department of Veterans Affairs Medical Center in West
4 Los Angeles.
5 MR. DOYLE: I am Bob Doyle. I am the Executive
6 Secretary of this Radiological Devices Panel.
7 DR. GARRA: Speaking of Mr. Doyle, Mr. Doyle would
8 like to make some introductory remarks including a short
9 listing of the panel members' commercial interests and
10 associations. Mr. Doyle.
11 MR. DOYLE: First, two quick announcements, one
12 very important one. You see in front of you a lunch menu
13 sheet. The point I want to make that just came up, I
14 received a phone call from Alicia Toledano, who is listed on
15 all the lists here as being a member of the panel. She had
16 a medical emergency which prevented her from making it here
17 today.
18 Now, I would like to read the conflict of interest
19 statement.
20 The following announcement addresses conflict of
21 interest issues associated with this meeting and is made
22 part of the record to preclude even the appearance of any
23 impropriety.
24 To determine if any conflict existed, the agency
25 reviewed the submitted agenda and all financial interests

1 reported by the committee participants.

2 The conflict of interest statutes prohibit special
3 government employees from participating in matters that
4 could affect their or their employers' financial interests,
5 however, the agency has determined that participation of
6 certain members and consultants, the need for whose services
7 outweighs the potential conflict of interest involved, is in
8 the best interest of the government.

9 Full waivers have been granted to Drs. Harry
10 Genant, Kenneth Faulkner for their interest in firms that
11 could potentially be affected by the panel's decisions. The
12 waivers permit them to participate in all matters before the
13 panel. Copies of these waivers may be obtained from the
14 agency's Freedom of Information Office, Room 12A-15 of the
15 Parklawn Building.

16 The agency took into consideration matters
17 regarding Drs. Charles Turner, Brian Garra, and Ada Romilly-
18 Harper. These individuals reported financial interests in
19 firms at issue, but in matters not related to topics to be
20 discussed by the panel. The agency has determined therefore
21 that they may participate fully in today's deliberations.

22 The agency would also like to note for the record
23 that Drs. Paul Miller, Alan Tenenhouse, and Dennis Black,
24 who are speakers with us today, have acknowledged financial
25 interests in, or professional relationships with, firms at

1 issue. Dr. Miller has grants, contracts, and speaking
2 engagements, Dr. Tenenhouse has a consulting involvement,
3 and Dr. Black has a contract, a research study, and speaking
4 engagements.
5 In the event that the discussions involve any
6 other products or firms not already on the agenda for which
7 an FDA participant has a financial interest, the participant
8 should excuse him or herself from such involvement and their
9 exclusion will be noted for the record.
10 With respect to all other participants, we ask, in
11 the interest of fairness, that all persons making statements
12 or presentations disclose any current or previous financial
13 involvement with any firm whose product they may wish to
14 comment upon.
15 If anyone has anything to discuss concerning these
16 matters, please advise me now and we can leave the room to
17 discuss them. [Pause.] Seeing no indication, I will
18 proceed.
19 The FDA seeks communication with industry and the
20 clinical community in a number of ways. First, FDA welcomes
21 and encourages pre-meetings with sponsors prior to all IDE
22 and PMA submissions. This affords the sponsor an
23 opportunity to discuss issues that could impact the review
24 process.
25 Second, the FDA communicates through the use of

1 guidance documents. Towards this end, FDA develops two
2 types of guidance documents for manufacturers to follow when
3 submitting a premarket application. One type is simply a
4 summary of the information that has historically been
5 requested on devices that are well understood in order to
6 determine substantial equivalence.
7 The second type of guidance document is one that
8 develops as we learn about new technology. FDA welcomes and
9 encourages the panel and industry to provide comments
10 concerning our guidance documents.
11 I would also like to remind you that the meeting
12 of the Radiological Devices Panel schedule for the remainder
13 of this year are August 16th and November 8th. You may wish
14 to pencil in these dates on your calendars, but please
15 recognize that these dates are tentative at this time.
16 I would also like to take this opportunity to make
17 it known that two premarket approval applications that this
18 panel discussed and made recommendations on have now been
19 approved. Our two technologies Image Checker M-1000 and
20 Image Analysis System for Mammograms was approved in June of
21 last year, and Transcan Medical's T-Scan 2000, a
22 multifrequency impedance breast scanner, was approved in
23 April of this year.
24 Finally, I would like to note for the benefit of
25 all that this meeting will be broadcast live by FDC to

1 selected locations around the country.

2 Dr. Garra.

3 DR. GARRA: Thank you.

4 We are going to now proceed with two short

5 briefings by FDA management. The first concerns the Y2K

6 issue and its impact on medical devices and will be given by

7 Dr. Tom Shope of the Office of Science and Technology.

8 That will be followed by Dr. Larry Kessler,

9 Director of the Office of Surveillance and Biometrics, who

10 will address postmarket surveillance and its role at CDRH.

11 Dr. Shope.

12 **Briefing on the Y2K Issue and the Impact**

13 **on Medical Devices**

14 DR. SHOPE: Good morning. Thank you.

15 [Slide.]

16 What I want to do this morning is just take a

17 brief couple of minutes to review with the panel, as we are

18 doing with each of the advisory panels this year, the issue

19 of the Year 2000 date problem and its potential impact on

20 medical devices, tell you just a very little bit about what

21 we have been doing with regard to this issue, and offer the

22 invitation and the encouragement for the panel to

23 communicate with us about any potential issues or problems

24 that you see in your area of expertise.

25 [Slide.]

1 You have a set of slides that actually include a
2 few more slide than I am going to show here with some of our
3 little background information toward the back of the
4 package. I don't think anybody now who is listening to the
5 news that hasn't heard about this problem unless perhaps you
6 are very astute at avoiding unpleasantness.
7 It has been referred to a lot of different ways,
8 everything from "digital doomsday" to the "millennium bug
9 syndrome." I think the issue here is there are potential
10 problems for medical devices due to this date manipulation
11 problem that can come from using two digits to represent the
12 year. I like the bottom one there, the millennium bug
13 syndrome. I first heard that used by the Director of the
14 Health Administration, I guess, at the Department of
15 Veterans Affairs, Dr. Kaiser talked about how to treat this
16 syndrome at one point, and it was a very good
17 characterization of it, I think.
18 [Slide.]
19 What is the problem? I think we pretty much all
20 know what this is. It is the failure of the computer system
21 to properly process or display dates due to probably
22 representing the year only with two digits or other problems
23 related to dates, such as failure to recognize leap year.
24 The real problem there, shown at the bottom, is
25 how do you distinguish between 2000 and 1900 when the

1 display shows 00. Well, that is probably not a critical
2 problem for use of the date which is only to display or to
3 date a paper record. 00, if it prints clearly, it is pretty
4 clear that is 2000. There weren't any computers writing
5 dates or presenting dates in 1900, so the human interpreter
6 can probably deal with that.
7 However, if those numbers are used in calculations
8 in an algorithm of some sort to do a calculation, you can
9 see the potential for problems there in software that failed
10 to take account of the fact that you get into trouble with
11 using just two digits to represent the year.
12 There are some other issues which will occur in
13 thinking of date representation. Expiration dates dated 01,
14 02, 03 will be kind of problematic depending on what your
15 interpretation of day, month, year - year, month, day -
16 month, day, year is. So I think we have some work to sort
17 that out in the future, but we are not focusing on that
18 issue right now.
19 [Slide.]
20 This is from a couple of years ago when one of the
21 IT journals talked about the problems with PCs, making the
22 point that there were many PCs back a few years ago that
23 were not going to be Year 2000 compliant and therefore
24 needed activities to make them deal with dates correctly,
25 primarily dates associated with file, recordkeeping type

1 activities in the PC.

2 But there are medical devices that are also

3 controlled or use PCs for their control, and so these kinds

4 of problems can reflect over in the actual medical device

5 functionality if not addressed properly.

6 [Slide.]

7 Another quote which I thought was kind of neat

8 back then, and sort of made us start thinking seriously

9 about this, and this was focusing more on the information

10 technology, the hospital recordkeeping systems, the billing

11 systems, the inventory systems, the supply systems, but

12 talking about the kind of work that needed to be done to get

13 all the hospital health information systems and other types

14 of administrative systems squared away, that there were

15 going to be lots of systems that had problems if they

16 weren't remediated.

17 [Slide.]

18 What kind of problems can we have in medical

19 devices that are due to this problem? Well, as I mentioned,

20 microprocessors or PC-controlled devices, if utilizing a PC

21 that is not Year 2000 date compliant, could present problems

22 either in their recordkeeping or they actual functionality.

23 Some of the products may just refuse to operate if they get

24 confused. We all have experience with our PCs freezing up

25 and going astray. The same sort of thing could perhaps

1 happen with the medical device controlled by a PC.

2 There are many software applications where the

3 medical device itself is just a software program. I think

4 the best example of this are radiation treatment planning

5 systems where they are used to plan the radiation therapy

6 treatments.

7 There, in fact, were some of these systems that

8 were used to teletherapy or brachytherapy calculations in

9 which the dates for source decay calculations were done with

10 two digits, and those products definitely have problems and

11 the manufacturers for the most part have identified those,

12 have made software upgrades available, but that is an

13 example of the kind of software algorithm problem that can

14 occur.

15 Of big concern are interfaces between devices,

16 from devices to databases, between devices and some sort of

17 recordkeeping system. Probably the best example of this are

18 clinical laboratory systems where you have a lot of clinical

19 laboratory instruments that may be providing patient related

20 data to a central laboratory system. Perhaps in Radiology,

21 the radiology information systems carrying along the date

22 when an image was made. With the image, there is a

23 potential for problems. And there are many products that

24 use date display embedded chips whose function it is to keep

25 track of the day or the time or the hours and minutes, and a

1 few of these actually keep track of the day of the week and
2 the year.
3 Most of these kinds of products, fortunately, I
4 think, are just involved with display and don't impact the
5 other functionality of the system, but there is a potential
6 for a chip with a date/time function to be incorporated in a
7 device and to lead to problems if not properly assessed by
8 the manufacturer.
9 [Slide.]
10 We have been using a definition here at FDA that
11 comes directly out of the Federal Acquisition regulations,
12 the requirement on the Federal Government when we purchase
13 information technology products these days, and basically,
14 in short, it says, there shouldn't be any problems with
15 regard to dates between, during, before and after the turn
16 of the century including leap years.
17 This is compatible basically with the British
18 Standards Institute definition of Year 2000 compliance.
19 There, they speak in that definition a little bit of
20 implicit and explicit representation of the century.
21 So, we have taken the position that there are many
22 applications where two digits for a display are perfectly
23 appropriate if the human interpreter of that information can
24 make the distinction between Year 2000 or 1900. So, we
25 don't automatically say if you just use two digits, that is

1 noncompliant. It depends on the application. A two-digit
2 usage that gets involved in a calculation that could go
3 astray would certainly be a noncompliant product. A two-
4 digit that just uses the digits for display of a date or
5 information interpreted by the human, we think there are
6 probably ways to deal with that, and I think that implicit
7 representation of the century is probably okay in many
8 situations.
9 [Slide.]
10 With that very brief introduction that there is a
11 problem, I think most people have heard about this problem
12 by now. This was kind of an interesting talk, maybe the
13 first few panels we gave it to, when this was kind of new to
14 us, but the reason for raising this issue is to ask the
15 panel from your areas of expertise and your experience to
16 give us any advice you have on particularly problematic
17 devices that FDA needs to give particular attention to.
18 In particular, we are talking about devices, were
19 there to be a date problem, could result in a significant
20 and immediate risk to the patient. We don't think there are
21 very many of those devices, but there is that possibility.
22 So we are very interested in hearing from you, not here in a
23 verbal exchange, but either through the panel chair or
24 directly to me afterwards, any particular products that you
25 think we need to pay attention to.

1 If you have any other suggestions for actions that
2 CDRH or the FDA might take related to this issue in medical
3 devices, we would be very much interested in hearing those
4 inputs, as well.
5 [Slide.]
6 The next slide shows you the address of our FDA
7 worldwide web site. On this site we have established a Year
8 2000 section. It has recently been changed, so my next
9 slide is a little out of date, but I won't go to that next
10 slide yet. I am going to leave this up for a minute.
11 If you go to this spot and select the Year 2000,
12 you have the option then of selecting which of the device
13 centers' products you are interested in. If you select the
14 medical device section, you will then be given access to our
15 CDRH section on the web site which currently contains a
16 database of information on noncompliant medical devices that
17 have been provided to FDA by the manufacturer, as well as
18 all the letters we have written to manufacturers about this
19 issue, our guidance document that was published in the
20 Federal Register back in June of '98, such things as
21 testimony to Congress and other information related to the
22 Year 2000 problem in medical devices.
23 So, we think we are providing a resource there
24 that will be of use to the medical community in dealing with
25 this problem.

1 The next slide is the one I realize now is out of
2 date because last week or so we reformatted the web site,
3 but this was initially the way the web site looked.
4 [Slide.]
5 What I wanted to point out is the second bullet
6 there. To get a report or search the biomedical equipment
7 database, this has now been replaced by a little icon on the
8 page that you first get to, but what that allows one to do
9 is to search by manufacturer name for any products reported
10 by that manufacturer as having a date problem.
11 We currently have over 4,300 manufacturers listed
12 in the database who have provided information on their
13 product status. Out of that we have about 800 or 900
14 products where the manufacturers have described problems
15 with the products. Most of those problems are minor date-
16 related problems involving date display or date stamping,
17 date printing on a record, but there are some problems in
18 there that unless the health care facility takes advantage
19 of the upgrades offered by the manufacturer, could lead to
20 problems in the delivery of health care if the problem is
21 not addressed.
22 We just recently back in March asked
23 manufacturers, as well, to give us a list of their products
24 that are vulnerable to the Y2K problem, that is, medical
25 devices that use software computer controlled in some way

1 that a hospital would have a question about is this product
2 Y2K compliant or not, and we have asked manufacturers to
3 cooperate with us to provide us an inventory of all their
4 products that they have assessed that are compliant, and we
5 will put that inventory up to allow hospitals, who are sort
6 of late into the game of doing their inventory, to have a
7 useful way to search and get immediate information about
8 products which either have a problem or don't have a
9 problem. If they have a problem, the database contains
10 information on the fix or the solution that is offered by
11 the manufacturer, and these range from free-cost upgrades to
12 upgrades that cost, to descriptions of the problems as being
13 rather minor and something that you can live with, to in
14 some situations products being described as obsolete, that
15 the manufacturer doesn't even plan to assess, and so
16 therefore, the user needs to decide what action they want to
17 take with regard to the obsolete products.
18 With that, I think there may be one more slide.
19 [Slide.]
20 This is just to summarize briefly our activities
21 that we have done to date. We started discussing this issue
22 with manufacturers in the summer of 1997, putting them on
23 notice about this problem and telling them they needed to
24 assess all their products to determine which ones could
25 present a risk to patients, and to provide the appropriate

1 information about those products to the users.

2 This was followed last year by a guidance document

3 published in the Federal Register in June. We have our

4 database. We are continuing a lot of monitoring and

5 assessment activities to monitor the status of what is

6 happening with regard to the industry.

7 We are also concerned about potential Y2K impacts

8 on the manufacturer's ability to continue to produce

9 consumable type medical devices that are needed on a daily

10 basis, and so that is an issue that we are currently

11 exploring. In fact, there is a meeting happening today,

12 sponsored by the White House, dealing with pharmaceutical

13 shortage issues, where they are bringing the industry

14 together, the consumers, the medical groups that are

15 associations associated with this issue to discuss where the

16 industry is and what recommendations could be made to the

17 public.

18 There are discussions for a similar meeting

19 regarding consumable medical supplies, probably to occur in

20 early June, but that is still in the planning stages, so

21 don't quote me as to it is actually going to happen, but I

22 think it will, and this would be an issue to assess for the

23 health care community where the manufacturers are in their

24 preparations, what kind of reasonable action should

25 facilities be taking to deal with this issue of consumable

1 supplies that you need on a regular basis for delivery of
2 health care.
3 We will continue our educational activities to the
4 manufacturers about this issue. We think we will probably
5 need to get some specific messages out to consumers and to
6 clinicians using devices as we get a little further into the
7 year and this become higher up on people's radar screens as
8 opposed to just the manufacturing issue.
9 [Slide.]
10 This last slide is just you can provide Robert
11 Doyle with any comments you have or you can contact me. I
12 would be glad to hear from you and hearing any concerns or
13 suggestions that you have.
14 With that, if there is a brief question or two,
15 Bob, if you have time, I would be glad to address them.
16 DR. GARRA: Any questions from the panel members?
17 [No response.]
18 DR. GARRA: Thank you very much, Tom.
19 The next speaker will be Dr. Larry Kessler, and he
20 is going to be addressing the issue of postmarket
21 surveillance information and its role at CDRH.
22 **Postmarket Surveillance Information and**
23 **its Role in CDRH**
24 DR. KESSLER: My name is Larry Kessler. I am the
25 Director of the Office of Surveillance and Biometrics.

1 [Slide.]

2 About a year and a half or two years ago I was
3 invited by Dr. Alpert to give a talk to the panel chairs.
4 There was one meeting of all the panel chairs, and I
5 discussed postmarket surveillance.

6 At the end of the talk, somebody asked that I come
7 and give talks to the individual panels, so Dr. Gross, who
8 heads their Division of Postmarket Surveillance, and I are
9 trying to make the rounds and hit all the advisory panels to
10 give you a flavor of what we do with postmarket surveillance
11 because it is not always clear to everybody what postmarket
12 evaluation at FDA is all about.

13 The Office of Surveillance is about one-half of
14 the two offices, the other one is Compliance, that are very
15 heavily concentrated in the postmarket arena. We do get
16 excellent help from all the other offices, but OSB and OC
17 spend most of their time in postmarket surveillance.

18 What I am going to do in the next 10 to 12 minutes
19 is try and describe a few of the methods of device
20 postmarket evaluation at CDRH, present the challenges that
21 we face in accomplishing postmarket evaluation, and finally,
22 describe the pivotal role that you, the advisory panel, can
23 plan in postmarket evaluation.

24 [Slide.]

25 The first thing I am going to do is just spend a

1 minute giving you our view of our world and part of yours.
2 This is a time scale from left to right. From the left end,
3 from design modification through lab and bench testing,
4 clinical testing, up through FDA review, most of the
5 lefthand side is handled by the manufacturing and clinical
6 community, and once we get into the testing arena, FDA
7 becomes more heavily involved.
8 The postmarket evaluation phase of this process
9 actually should extend much further than the lefthand side
10 if we had something that was true to scale, but I have too
11 many words to fit on the righthand side of the overhead.
12 The object here of putting the clinical community
13 both above and below is to give you the notion that we hope
14 that we are working with the clinical and the manufacturing
15 community in a continuous loop from design through device
16 evolution, all the way to design obsolescence as
17 appropriate.
18 On the right side of the slide you will see five
19 phrases under postmarket evaluation which describe very
20 briefly some of the programs that we use to evaluate
21 products in the postmarket period.
22 We use the Medical Device Reporting Program, and I
23 will talk about that in some more detail, as I will also the
24 postmarket surveillance section 522 provisions of the Act,
25 and postapproval authority with which you are probably

1 somewhat familiar.

2 I won't talk very much about our epidemiology

3 program or the compliance in ORA field inspection program,

4 but those are critical elements of postmarket evaluation.

5 [Slide.]

6 These are some of the key questions of interest

7 that we find once we approve a device and have it go to

8 market that we are often interested in asking. Long-term

9 safety, of course, performance of device in community

10 practice in contrast to what you might see in clinical

11 trials, effects of changes in user setting.

12 As you are very well aware, although maybe not so

13 much for radiologic products, hospital equipment is leaving

14 the door to the hospital faster than ever. It is winding at

15 the patient's bedside. So, some of those changes can bring

16 use problems that we might not have otherwise anticipated,

17 rapid changes in technology, and unusual patterns of adverse

18 events are also things that remain of interest in the

19 postmarket period.

20 [Slide.]

21 The Medical Device Reporting Program is probably

22 our chief way of figuring out how we approach adverse event

23 reporting and what we do with the kind of signals we see in

24 the postmarket period.

25 Manufacturers must, by law, report deaths and

1 serious injuries if a medical device may have caused or
2 contributed to the event, as well as malfunctions. In the
3 EU, you will hear these referred to as near incidents.
4 All user facilities since the Safe Medical Devices
5 Act of 1990, that means every hospital, nursing home,
6 ambulatory care center, surgery center, ambulances are
7 supposed to report deaths to the FDA and deaths and serious
8 injuries to manufacturers.
9 I will tell you that that provision of the law
10 where we put our regulation into effect in '96, is observed
11 in the breach. Most user facilities in this country have no
12 idea this is their job. Most clinicians in the country have
13 no idea this is their job. They will see a death with
14 someone attached to a medical device, and won't recognize
15 that there is a provision of law that suggests they should,
16 and are supposed to, send us a report.
17 [Slide.]
18 Beginning about 1992, FDA received over 100,000
19 medical device adverse event reports per year, and we were
20 at that time relatively swamped with reporting and not
21 knowing quite what to do about it.
22 The information in those reports should include
23 device specifics, event description, event date, patient
24 characteristics. Unfortunately, the reports that we get
25 often have very limited information. They also provide

1 critical signals to the FDA, and I will talk about a few of
2 those in a minute, but just in case you have a chance to
3 come and peruse the MDR system which in our web, the entire
4 file is on the web with a recently in-place search engine,
5 there are a lot of reports with very limited information,
6 patient death, device, date, that is about it for some of
7 them, and that is not very helpful, but there are some very
8 important informations that leads to signals that we can do
9 things about.
10 [Slide.]
11 So, our analysts, who are primarily nurses, when
12 they review the medical device reporting data, will then
13 turn them into actions that we can take, and we are very
14 proud of the way the system does work when it works
15 correctly.
16 We will often do a directed inspection of the
17 facility or the manufacturer. We are involved in one now
18 relevant to this panel, which resulted in over-
19 administration of therapeutic radiation in some facilities
20 in Indiana.
21 We are occasionally involved in product
22 injunctions and seizures, procedures prompted by the MDR
23 program, although those actions are more often taken by the
24 Office of Compliance.
25 Last year we put out one public health notice and

1 one safety alert in the radiology area. In the public
2 health notice arena, we put out an alert about lead in
3 shielding products. It is kind of interesting that lead ore
4 mined in Brazil and shipped to the United States, no one
5 bothered to detect it happened to be radioactive producing.
6 So, having that in the lead shields was of concern.
7 Now, we did a fairly quick health hazard
8 evaluation, and discovered that the real risk of the amount
9 of radiation from the shield was virtually negligible, but
10 Dr. Burlington at the time felt this was the kind of product
11 or situation that poses a public outrage situation, that
12 even if the health risk is low, people would not enjoy
13 finding out later, guess what, you have been wearing a
14 shield that was giving you a little bit of radiation even if
15 it was negligible, so we had to put out a public health
16 notice and try and get that off the market.
17 The safety alert we put out was very interesting
18 this year. It resulted from a malfunction report. In
19 isocam gamma camera in the United Kingdom has two very large
20 heads, and one of them swooped down and fell, it is about
21 800 pounds I understand, and whacked the table where a
22 patient might have been.
23 Well, the good news is there was no patient there.
24 So, technically, this is not a death or serious injury, and
25 in many cases is not necessarily reportable. In fact, in

1 the European Union, it is not a reportable event, neither is
2 that fall of the paper there, malfunctions happen.
3 Now, it could be important. This is probably not
4 an important malfunction, but that was.
5 This was important because it looked like there
6 might be a problem, this might happen again. We tried to
7 contact the UK Medical Devices Agency, and the company was
8 peculiar about this situation. The company that made the
9 camera, Parke Medical in Canada, was bankrupt, and there was
10 no way to trace them, and the folks in the United Kingdom
11 Parke Medical did an engineering analysis of this.
12 Their lawyers refused to allow that to be shared
13 with us. We were left with no choice but to send out an
14 alert to the 16 places that owned these cameras in this
15 country and say we think you need to take a look at them and
16 shut them down, and we got some very angry and upset calls.
17 This is a very expensive piece of equipment that some of the
18 clinicians felt was important, critical in their practice
19 frankly.
20 We had no choice. We could not get an engineering
21 analysis from the company in Britain, they refused. The
22 company in Canada was defunct. So, this wound up in having
23 these guys shut down fairly fast and new cameras bought.
24 What was interesting is along the way we discovered that a
25 camera in Iowa, I recall, had to have its motor replaced the

1 year before because of funny sounds it was making, which we
2 believe was a precursor to swooping arms down and major
3 catastrophe, but we couldn't get anyone to replace or repair
4 and warranty them, so they went out of service.
5 It is the kind of thing that we see in the MDR
6 program that does prompt interesting and useful public
7 health action.
8 [Slide.]
9 I would like to talk in a little more detail about
10 the two postmarket study authorities which you might have
11 heard about and may get confused. One is postmarket
12 surveillance Section 522 of the Act. The second is the
13 postapproval or condition of approval authority associated
14 with premarket approval.
15 Section 522 was originally mandated in SMDA-90
16 with both a required postmarket surveillance and a
17 discretionary postmarket surveillance provision. The
18 required part of the program was dropped in '97 and replaced
19 with a discretionary postmarket surveillance authority only
20 in FDA in May of 1997. We think, in fact, it was a good
21 piece of the law that was written because the required
22 postmarket surveillance program was problematic, to say the
23 least, and I will talk about that in just a minute.
24 Postapproval refers to PMA products, and they are
25 also called condition of approval studies. 522, the

1 postmarket surveillance authority, covers Class II or III
2 products whose failure may present a public health problem,
3 and there is a lot more statutory language that goes along
4 with this, but this is the basic emphasis here.
5 Both authorities are seen as complements to
6 premarket, and they can help us and help you address primary
7 questions you have in postmarket period.
8 [Slide.]
9 These are the criteria we generally use for
10 postmarket surveillance studies. We need to understand the
11 critical public health question. This can result from "for
12 cause" problems, that is, adverse event reporting that we
13 see or other concerns, new or expanded conditions of use,
14 and evolution of technology.
15 Before we apply either a condition of approval or
16 particularly the 522 authority, we consider other postmarket
17 strategies, such as MDR, does it do what we need it to do,
18 for example.
19 We try and review the practicality or feasibility
20 of conduct--I will talk about that in a minute--and how will
21 data be used. In addition, we have to consider the
22 priority, what is the magnitude of risk and benefit that we
23 see in trying to conduct such a postmarket surveillance
24 study.
25 [Slide.]

1 In the early 1990s, the approaches that were used
2 tended to be at the bottom of this range of study types,
3 randomized trials or case controlled studies or use of
4 product registries, but we have just put out a guidance
5 document about Section 522 studies that suggests we may be
6 more often calling for less intensive, less intrusive, less
7 expensive kinds of approaches to evaluate postmarket
8 concerns.
9 We don't need to always go for the home run. We
10 can sometimes achieve what we need by less intensive
11 methods, so detailed review of complaint history,
12 nonclinical testing of device, or use of existing data sets,
13 say, something from the Medicare system may suffice without
14 having to redo randomized or well-controlled studies in the
15 postmarket period.
16 [Slide.]
17 However, in doing any of these studies, we face
18 particular frustrations especially when it comes to
19 collecting clinical data in the postmarket period.
20 Why? First of all, rapid evolution of technology
21 makes studies obsolete very often. Second, there is a lack
22 of incentive to the industry. Once you all have approved a
23 product, and we have agreed and said let's go to market,
24 industry isn't so interested. They are not likely to get
25 great news in the postmarket period.

1 So, their incentive for pursuing these
2 aggressively and getting them done has not been so dramatic.
3 There is a general lack of interest in the clinical
4 community for doing a postmarket study. It's not new and
5 sexy, that was last year's technology. Why should I be
6 involved? Why should I spend my time, am I going to publish
7 on this? Maybe not so likely.
8 Finally, sometimes--and this happens both in my
9 office, the Office of Surveillance and Biometrics, it
10 happens in ODE, and it happens among panel members--that
11 they ask for a postmarket study, but don't clearly specify
12 the critical public health question that you want answered.
13 [Slide.]
14 So, the challenge for you is when considering
15 postmarket studies, whether postapproval or 522--and you are
16 more than welcome to suggest a 522 study as part of your
17 deliberations--should ensure this is of primary clinical
18 importance, clearly specify the public health question you
19 want us to answer, and if you can, note the clinical or
20 regulatory relevance of answering the question, what will we
21 do with the data, what will you do with the data, will you
22 make a decision, could you withdraw your recommendation to
23 approve the product, would you withdraw certain clinical
24 indications or expand them. Let us know what you plan to do
25 with the data.

1 So, asking for postmarket study per se doesn't get
2 us the whole way there.
3 [Slide.]
4 Finally, I will wrap up with this slide. It is
5 the future of the Medical Device Reporting and Postmarket
6 Surveillance Program. I haven't talked a lot about our
7 international harmonization efforts, but those are part of
8 this.
9 We have been changing the Medical Device Reporting
10 Program in a lot of different ways. I don't have a lot of
11 time to talk about it. We moved into major summary
12 reporting to reduce our paper load.
13 We are moving into a sentinel reporting system
14 based on our pilot study in May of '97. We are trying to do
15 more with electronic interchange, and in the postmarket
16 surveillance area, on the right, we are using a wider
17 variety of design approaches, we are trying to collaborate
18 more with industry and the clinical community, and, in part,
19 through you, and finally, we are hoping to use expanded data
20 resources, particularly registries, which are sprouting up a
21 lot around the world and this country, which we could use
22 for postmarket study.
23 Thank you for your time.
24 DR. GARRA: Questions? Any questions from the
25 panel?

1 [No response.]

2 DR. GARRA: Thank you, Dr. Kessler. That was very
3 helpful to me because I think on some of the recommendations
4 we have made in the past, we haven't always been very
5 specific what we wanted you to do with the data.

6 MR. KESSLER: Sometimes those studies don't get
7 done or done very well. We did a review of ODE studies in
8 the postmarket period, OSB studies, and most of them, have
9 not gotten off the ground, not produced successful results,
10 so the recommendation let's do a postmarket study is not the
11 end of it, and unfortunately, things don't get off the
12 ground very well, it is not very effective, it doesn't
13 address your problems or ours.

14 DR. GARRA: Thank you very much.

15 We are now ready to proceed with the first of two
16 half-hour open public hearing sessions for this meeting.
17 The second half-hour public session will occur after the
18 industry presentations this afternoon.

19 At these times, public attendees are given the
20 opportunity to address the panel, present data or views
21 relevant to the panel activities. Several individuals have
22 already indicated that they would like to address the
23 meeting.

24 Are there any other individuals who have not
25 already indicated they would like to, that would like to

1 address the panel? If so, please raise your hands.

2 I see no hands raised.

3 What we are going to do then, I have got to remind

4 the public observers at this meeting that this portion of

5 the meeting is open to public observations, but that public

6 attendees may not participate unless they are invited to do

7 so by the chairman.

8 I would ask that the persons addressing the panel

9 please come forward to the microphone and speaking clearly

10 as the transcriptionist is dependent on this means for

11 providing an accurate transcript.

12 If you have a hardcopy of your talk available,

13 please provide it to the Executive Secretary for use by the

14 transcriptionist to help provide an accurate record. We

15 also request that all persons making statements either

16 during the open public hearings or during the open committee

17 discussion portions of the meeting disclose if they have

18 financial interests in any medical device company.

19 Before making your presentation to this panel, in

20 addition to stating your name, please state the nature of

21 your financial interest in the organization you represent.

22 If you are an employee of that organization, please state

23 that and no further discussion is necessary.

24 Definition of financial interests in a sponsor

25 company may include compensation for time and services of

1 clinical investigators, their assistants and staff, in
2 conducting the study and in appearing at the panel meeting
3 on behalf of the applicant.
4 Second, a direct stake in the product under
5 review, in other words, the inventor of the product, a
6 patentholder, owner of shares of stock in the company, or an
7 owner or part owner of the company.
8 We are now ready to begin the open public portion
9 of this meeting. Each speaker will be allowed a maximum of
10 five minutes to give their presentation.
11 We are going to start with Dr. Lewis M. Sherwood,
12 Director of Bone Measurement Institute, who is going to be
13 talking about the development of the bone densitometry
14 market from 1995 to 1998.
15 Dr. Sherwood.
16 **Open Public Hearing**
17 DR. SHERWOOD: Thank you very much, Dr. Garra. I
18 am pleased to be here to comment briefly to the advisory
19 panel. I am a full-time employee of Merck and Company. I
20 have no financial interest in any bone measurement device
21 company.
22 [Slide.]
23 I would like to address you as Chief Medical
24 Officer from Merck and Company in the U.S. and as President
25 of the Bone Measurement Institute.

1 The Bone Measurement Institute was something that
2 we created four years ago as a not-for-profit entity to
3 focus on bone density testing and diagnosis only, not
4 treatment, and to be technology neutral.
5 We set up a distinguished external medical and
6 scientific advisory panel, some of those members are here.
7 They include Dr. Robert Lindsay as chairman, and Drs. Sydney
8 Bonnick, Conrad Johnston, Michael Kleerekoper, Paul Miller,
9 and Ethel Siris.
10 [Slide.]
11 The mission of the Bone Measurement Institute was
12 fourfold: One, to make bone measurement more accessible to
13 physicians and to their patients; secondly, the lower the
14 cost of bone measurement tests; thirdly, to educate
15 physicians on the role of bone mineral density testing and
16 available technologies; and fourth, to advance the science
17 of bone measurement technology.
18 [Slide.]
19 What was the state of the field in 1995? Well, it
20 was relatively undeveloped. Imagine a situation in which
21 there are only 750 physicians who had sphygmomanometers and
22 could measure blood pressure. Imagine a situation in which
23 only 750 physicians could measure cholesterol.
24 Well, in 1995, there were only 750 densitometers
25 in the country to deal with 40 million postmenopausal women,

1 an average of 60,000 women per instrument. The average
2 machine was being used two to three times per week for bone
3 density tests. The average cost of those tests was $195,
4 and the average instrument cost, between 80 to $100,000.
5 At the same time that this was true, over 90
6 percent of primary care physicians did not know what the
7 term BMD meant, so, a relatively undeveloped marketplace, to
8 put it mildly.
9 Well, the BMI has worked very hard over the last
10 four years working in association with major organizations,
11 such as the National Osteoporosis Foundation, the
12 International Society for Clinical Densitometry, and both of
13 the presidents of those organizations have been on the
14 Scientific Advisory Board.
15 We have also worked individually with the
16 instrument manufacturers, talked to them, had them visit us
17 and talk to the BMI panel.
18 Well, what is the situation in 1999, four years
19 later? We now estimate somewhere between 8,000 and 10,000
20 instruments, compared to 750, and, of course, this panel has
21 played a key role in recommending approval to the FDA for a
22 variety of new instruments that have been approved.
23 Utilization is up to 20 or more tests per week
24 versus 2 to 3, and we estimate somewhere around three and a
25 half million bone density tests last year.

1 The price range is now much wider. It goes from a
2 low of about $30,000 to a $140,000 for a central axial
3 measurement device, and as low as $11,000 for peripheral
4 devices, and, of course, as you know, low bone mass can be
5 identified at any site and is helpful in predicting future
6 risk of fracture.
7 The average cost of central testing is now $125,
8 peripheral tests are one-third that rate or lower. Working
9 in association with NOF and other organizations, we have
10 seen the Bone Mass Measurement Act implemented in July 1st,
11 1998, which allows women of Medicare age to have
12 reimbursement for bone density testing, and now at least the
13 majority of primary care physicians know what bone density
14 means.
15 [Slide.]
16 Let me say a couple of words about the T-score.
17 We understand that the T-score is not an ideal measurement,
18 but it serves many, many valuable purposes. Even more
19 importantly, it is embedded so thoroughly in many processes
20 that are used widely.
21 First of all, it was central to the diagnostic
22 criteria set out by the World Health Organization several
23 years ago. The output of the devices includes T-score. FDA
24 has used it on the drug approval side in labeling. The
25 National Osteoporosis Foundation treatment guidelines and

1 other treatment guidelines refer to T-score. So, again,
2 while not ideal, it serves many valuable purposes.
3 We believe that many of the issues currently
4 extant and problems with the T-score can be addressed, that
5 is, trying to adjust for differences across different
6 devices and age-related differences, trying to correct for
7 differences in the normative database that is extant in
8 different devices, and trying to link T-score to the
9 ultimate concern of people dealing with osteoporosis, and
10 that is the spine fractures and the hip fractures, and other
11 clinical fractures in women and men with osteoporosis.
12 If you just look at clinical practice and refer to
13 something like cholesterol as a good model, the total
14 cholesterol is useful in identifying patients with
15 hyperlipidemia. The National Cholesterol Education Program
16 has set out guidelines as to when to treat. When any of us
17 get a cholesterol measured, we get back with the report
18 high, moderate, or low risk depending on LDL to HDL ratio.
19 Cholesterol is one of several factors in
20 atherosclerosis as risk factors, just like bone density is
21 one risk factor among others for assessing likelihood of
22 fracture.
23 So, there are many parallels between T-score as a
24 clinical parameter and its use by physicians and
25 understanding by patients.

1 [Slide.]

2 Finally, just to wrap up and to encourage this
3 panel in their deliberations today to focus on the public
4 health problem, as I know you are, and also to try to keep
5 things as simple and straightforward as possible for both
6 the physicians who are caring for these women, as well as
7 the women themselves.

8 Let me emphasize that osteoporotic fractures are
9 more common and frequent in postmenopausal women than the
10 combined incidence of heart attack, stroke, and breast
11 cancer, not that any of those diseases are not important,
12 but the total number of fractures is enormous, and it is an
13 enormous financial and clinical burden.

14 Through your activities, new diagnostic devices
15 have been approved, but only one-fifth of postmenopausal
16 women have even had their bone density tested.

17 In the final analysis, whatever the results and
18 conclusions of this panel, it is important that practicing
19 physicians and their patients have information that they can
20 find clinically useful and is helpful in both the diagnosis
21 and the ultimate care and treatment of their patients.

22 Thank you very much.

23 DR. GARRA: Thank you.

24 At this time, if there are any brief questions
25 directly related to the material that the presenter just

1 made, you may ask them, panel members.

2 [No response.]

3 DR. GARRA: Thank you very much, Dr. Sherwood.

4 The next speaker is Dr. Ethel Siris, Director of

5 the National Osteoporosis Risk Assessment, and she is going

6 to be talking about a clinical perspective of T-scores from

7 the National Osteoporosis Risk Assessment Survey.

8 Dr. Siris, please identify your organization.

9 DR. SIRIS: Yes, sir. Thank you very much. Mr.

10 Chairman, ladies and gentlemen: I am a Professor of

11 Clinical Medicine at Columbia University working in the

12 field of metabolic bone diseases. My research group

13 currently is doing some research with Schick Technologies.

14 I am here this morning, though, as the Medical

15 Director of the National Osteoporosis Risk Assessment, and

16 should comment that two of the folks sitting here with you

17 today, Dr. Faulkner and Dr. Miller, are also colleagues at

18 work on that particular project.

19 [Slide.]

20 The purpose of talking to you today is to convey

21 some new data from the study that pertains to peripheral BMD

22 in fracture risk and also to give you some information about

23 data from ethnic minorities. All of our patients are women,

24 but we have data from ethnic minorities, as well as

25 Caucasian women.

1 [Slide.]

2 NORA has what is called a primary care arm. This
3 is a study that was implemented in those parts of the United
4 States where 80 percent of postmenopausal women are located.
5 The participants in NORA are postmenopausal women not
6 previously evaluated for osteoporosis by their primary care
7 physicians.

8 We utilize peripheral BMD measurements of the
9 heel, forearm, or finger, and questionnaires, and there will
10 be longitudinal questionnaires following the initial BMD
11 measurement dealing with risk factors, behaviors, and
12 attitudes. The questionnaires will extend up to five years.

13 [Slide.]

14 The current enrollment in NORA, which ended March
15 31st, is 204,000 postmenopausal women from across the United
16 States, but the database I will discuss today has to do with
17 the initial grouping of women from the first 12 states
18 studied, including 76,000 postmenopausal women age 50 to 100
19 from 13,086 physician offices.

20 These women had had no previous diagnosis of
21 osteoporosis and no prior BMD test in the past 12 months.
22 The BMD units that are used in NORA are those that measure
23 peripheral sites, and the initial two machines, which were
24 the ones available in 1997, that were FDA-approved, had
25 normative databases, and were portable, include measurements

1 at the heel and the distal radius.

2 Very, very importantly, a decision was made at the
3 beginning of NORA that all measurements would utilize the
4 Caucasian Young Normal database within the machines, in
5 other words, other ethnic groups aside from Caucasians would
6 be compared with Caucasian young normals.

7 [Slide.]

8 The ethnicities are shown here of the first 76,000
9 women. Remember, that we now have over 200,000 women, and
10 we expect an approximate tripling of these numbers. About
11 90 percent were Caucasian, but as you see, there were 2,400
12 African-American women, 2,100 Hispanic women, 1,200 Asian
13 women, and 715 Native American women, and as I said, we
14 expect to approximately triple these numbers.

15 [Slide.]

16 I want to show you a couple of data slides. The
17 first of these has to do with the prevalence of osteoporosis
18 at baseline, in other words, the finding of a T-score of
19 less than minus 2.5 in women who were African-American,
20 Caucasian, Asian, Hispanic, or Native American, showing that
21 very clearly among all of these ethnic groups with advancing
22 age there is a consistent lowering of BMD and a consistent
23 increase in the percentage of patients identified as having
24 osteoporosis.

25 The point of this slide, and remember that over 90

1 percent of these are Caucasians, and the n's are much
2 smaller in the other groups, but it clearly shows that with
3 respect to a diagnosis of osteoporosis, with advancing age,
4 that BMD diagnosis can be made in all ethnic groups, and
5 even though some groups are relatively protected against
6 having a low BMD, percentages of all groups will have this
7 number if they grow to be old enough.
8 [Slide.]
9 This is a slide that shows the incidence of
10 fracture by age and ethnicity. At the six-month
11 questionnaire, there were already enough people in the NORA
12 database of 76,000 who had experienced fractures that we
13 were able to show the incidence of fracture by age and
14 ethnicity, showing that the numbers are similar with
15 advancing age in both Caucasian and pooled non-Caucasian
16 groups.
17 [Slide.]
18 But I think this is the most important slide I
19 will show you, and that is, based upon the six-month follow-
20 up questionnaire, we are able to show that there is an
21 incidence of fracture by both ethnicity and T-score which is
22 very similar between Caucasian and non-Caucasian women, in
23 other words, the low BMD predicted fracture risk whether the
24 subject being measured was a Caucasian or a non-Caucasian
25 subject.

1 The greatest number of fractures were in
2 individuals with T-scores less than minus 2.5. Intermediate
3 were those individuals with osteopenic T-scores, and the
4 smallest number of fractures was seen in individuals who had
5 T-scores that were better than minus 1.
6 This, I think is very significant because these
7 are all statistically significant differences, this group
8 and this group are similar, this group and this group are
9 similar, these two groups are similar. These are all
10 statistically significantly different from each other in
11 both groups.
12 So, using a Caucasian reference population, we are
13 able to show a progressive increase in the risk of having
14 fractures, i.e., the T-score of minus 2.5 with advancing
15 age, and also an increased number of fractures in both
16 Caucasian and non-Caucasian women with T-score.
17 Thank you very much.
18 DR. GARRA: Thank you. Are there any questions
19 for Dr. Siris? One question.
20 DR. FAULKNER: As I recall, the rationale for
21 using the Caucasian database for the study was because that
22 is the fracture population, not because we didn't want to--
23 that was the only population we had good prospective data.
24 DR. SIRIS: That's right, and certainly it was the
25 population of women who have the greatest numbers of

1 fractures as far as we were aware. In other words, if an
2 African-American woman has a T-score that is a standard and
3 a deviation and a half below that of her peers, given that
4 her--excuse me--if a postmenopausal African-American woman
5 has a T-score of minus 2 compared with young normal African-
6 American women, she still has a fairly decent T-score
7 because of the relatively high level of bone density in 30-
8 year-old African-American women, whereas, if she has a T-
9 score that is 2 standard deviations below the young normal
10 Caucasian woman, she has a fairly low T-score, and we
11 believed when we did this, that that was really the relevant
12 population to look at.
13 DR. FAULKNER: But if we are looking at other
14 clinical questions, there could be clinical questions that
15 would require possibly ethnic databases?
16 DR. SIRIS: Absolutely, there might well be, but I
17 think in terms of predicting fracture risk, the NORA data at
18 this point, from a fairly sizable number of people, suggests
19 that the young normal Caucasian population, which was what
20 was in the machines that we utilized, was an effective way
21 of predicting fracture.
22 DR. GARRA: Dr. Genant.
23 DR. GENANT: Ethel, I wonder, have you had an
24 opportunity to look at the impact of adjusting the data for
25 body size, either weight or height or some combination of

1 those?

2 When one looks at the percentage of the various

3 racial groups that were identified as being osteoporotic,

4 there were substantial differences, and perhaps those

5 differences would have been minimized if the data were

6 corrected for body weight.

7 DR. SIRIS: The data were corrected for all of

8 these things. Tom, is that correct, these are adjusted?

9 DR. GARRA: Please identify yourself and your

10 affiliation.

11 DR. SIRIS: Dr. Abbott has dealt with a lot of the

12 data analysis for us.

13 DR. ABBOTT: I am Tom Abbott. I am the Director

14 of Outcomes Research and Management at Merck and Company,

15 and have no financial interest in any of the device

16 manufacturers.

17 DR. GARRA: Thank you.

18 DR. ABBOTT: In terms of answering the specific

19 question, we have looked at and have presented results at

20 last years's ASBMR, looking at the BMD and prevalence issue

21 adjusting for body mass composition, height, et cetera, and

22 in terms of the fracture incidence rates that were presented

23 today, those have not been adjusted. We are in the process

24 of developing logistic risk equations to evaluate whether or

25 not there are significant differences.

1 DR. GENANT: How about the prevalence data that
2 you showed? I assume those were not corrected.
3 DR. ABBOTT: The prevalence data, as presented,
4 were not corrected.
5 DR. GARRA: Thank you very much.
6 Any other questions?
7 [No response.]
8 DR. GARRA: We can proceed then to the third
9 speaker, who is Dr. Conrad Johnston, Vice President of the
10 Board of Trustees of the National Osteoporosis Foundation
11 and President of the National Osteoporosis Foundation
12 Science Advisory Board.
13 He is going to speak to us on several foundation
14 activities and provide some comments on techniques and
15 databases.
16 DR. JOHNSTON: Thank you.
17 I am Professor of Medicine, Indiana University
18 School of Medicine, and an endocrinologist, and I have no
19 holdings in any of the device manufacturers.
20 As I think we all know, osteoporosis and its
21 attendant fractures are a large and growing population with
22 a particular problem particularly as the population ages,
23 and it is our goal at the National Osteoporosis Foundation
24 to reduce those fractures in the future.
25 I think we have made a great deal of progress in

1 the last decade, particularly in diagnosis and treatment, so
2 that more people, especially postmenopausal women, the
3 largest segment at risk, are benefitting, and I believe this
4 is because of the development of new and effective
5 therapeutic interventions, and because of our better ability
6 to identify those at risk.
7 Bone mass measurement is the key to identifying
8 high risk individuals, especially those who have not as yet
9 experienced a fracture. The ability to predict fracture or
10 risk of fracture has been shown in a number of prospective
11 studies where bone mass was measured at a variety of site -
12 the hip, the radius, the spine phalanges, and the calcaneus.
13 The WHO, the World Health Organization, in an
14 effort to provide a definition of osteoporosis, based on
15 quantitative measurement of bone mass, suggested the use of
16 the T-score or the number of standard deviations below the
17 mean of a young normal population, and I was fortunate
18 enough to be on that panel.
19 This could be used to define populations with the
20 disorder, but it was not proposed for cut points for
21 therapeutic interventions, and I think sometimes this is not
22 understood.
23 I think this approach works well for central
24 measurements of the spine and the hip, however, a number of
25 new technologies for peripheral measurements have been

1 developed to provide better access at lower cost. These
2 include ultrasonography.
3 Most have been shown in prospective studies to
4 provide risk assessment for subsequent fracture. The T-
5 score produced by these methodologies in some instances may
6 not provide the same level of risk as central measurements.
7 This is either because of known differences in rates of
8 change in bone mass at different sites, or differences
9 initiative the mean and standard deviation of the young
10 normal participants evaluated.
11 A committee of experts has been formed under the
12 auspices of the National Osteoporosis Foundation and the
13 International Society of Clinical Densitometry to address
14 this problem, and a potential solution will be presented to
15 you later by Dr. Black.
16 The databases used to establish norms have been
17 composed largely of Caucasian females since this is the
18 group at greatest risk in the United States. There, of
19 course, may be gender and ethnic variation in risk, although
20 at present the data is insufficient to reach a consensus.
21 Continued research should address this issue.
22 I must emphasize, at the present time we have a
23 very good approach to identifying those at risk of fracture
24 using bone mass measurements and allowing them to have
25 access to the new and effective treatments.

1 We must learn more as we continue with our
2 assessments in order to provide better outcomes for our
3 patients.
4 Thank you very much.
5 DR. GARRA: Thank you very much.
6 Are there any questions from the panel members?
7 [No response.]
8 DR. GARRA: Thank you.
9 **Open Committee Discussion**
10 **Charge to the Panel**
11 DR. GARRA: Since there are no other speakers, we
12 now conclude the open public portion of the meeting, and we
13 are going to now proceed with the open committee discussion
14 portion of this meeting and consider the issues of bone
15 strength assessment with a focus on the use of gender and
16 race-specific databases in assessing fracture risk and their
17 applicability to bone densitometry and sonometry device
18 labeling.
19 If the panel members could refer to the discussion
20 points, a handout in their packet of materials, the FDA is
21 asking this panel and the experts invited for today's
22 meeting to provide inputs in the roles on three issues.
23 One is the role of various types of measurement
24 for the assessment of fracture risks. That is Item 1 of the
25 discussion points.

1 Item 2 is to define the role of the young normal
2 reference database and determine whether the databases as if
3 it presently described and used is an appropriate one or
4 not.
5 The third issue is to make recommendations for
6 clear and meaningful labeling of bone assessment devices.
7 We will now proceed with the presentations on this
8 topic by the FDA. These will be introduced by Dr. Dan
9 Schultz, the Acting Director of the Division of
10 Reproductive, Abdominal, Ear, Nose, and Throat, and
11 Radiologic Devices Section of the FDA.
12 Dr. Schultz.
13 **Introduction**
14 DR. SCHULTZ: Good morning. Distinguished members
15 of the Radiological Devices Panel, guest speakers,
16 colleagues from industry, sister agencies, and other valued
17 guests: I would like to welcome you on behalf of CDRH to
18 this meeting. This is a somewhat unusual meeting in the
19 sense that we have no specific submissions before you and we
20 are not looking for recommendations with regard to marketing
21 for a specific device, however, I promise you that we will
22 have a lot of work for you to do today and that you will
23 earn every penny of the huge sums of money that we are
24 paying you for being here.
25 Thank you.

1 [Slide.]

2 So, why are we here? I am not going to reiterate
3 what you have already heard. Clearly, the issue of bone
4 fragility assessment and its clinical consequences of low
5 impact fractures is a major public health issue.

6 As a result of that, the FDA is now confronted
7 with a number of new diagnostic and therapeutic products.
8 These two are interrelated I think in both ways in the sense
9 that as the public health concern has grown, companies have
10 taken up the gauntlet and have developed a lot of new and
11 exciting products.

12 As these new and exciting products improve our
13 ability to identify people at risk and treat them, that has
14 focused even more concern with respect to this particular
15 area.

16 So, what is the problem? Well, as we get more
17 answers to questions, as is usual in scientific endeavors,
18 more questions become apparent, and what I would like to
19 propose to you today is that we are now in somewhat of a
20 period of uncertainty with respect to how to use all of the
21 new and exciting information that is being derived from
22 these new technologies.

23 My hope is that this meeting and others like it
24 will be important and useful in bringing some degree of
25 resolution to this uncertainty.

1 [Slide.]

2 Two more comments. One is FDA's role is not to
3 dictate the practice of medicine. Let me repeat that.
4 Maybe I can turn around for the people in the back and just
5 say it one more time. FDA's role here today and in general
6 is not to dictate the practice of medicine. We leave that
7 to you in the clinical community, hospitals, states, et
8 cetera, but we do have a role in this process and I think it
9 is a very important role, and that is to provide reasonable
10 assurance of the safety and effectiveness of the products
11 that you use in your clinical practice.

12 I would break that down into two major components.
13 The one that is probably more clearly understood and
14 recognized is to make sure that the device works, when you
15 turn on the switch, the electricity comes on, the
16 measurements show up, and that the device does what it is
17 purported to do.

18 The other is a little more subtle, and that
19 includes how the device is labeled, that it is labeled
20 appropriately and provides the user with the kind of
21 information that is necessary for he or she to use the
22 information appropriately and treat his or her patients
23 appropriately.

24 Both of these should be based on valid scientific
25 evidence, and that is what is known today. Clearly, we all

1 understand that what was thought to be true yesterday is now
2 not as true today and that what we think is true today
3 probably will change tomorrow.
4 So, what we are asking for is not to have the full
5 answer today, but rather for you, as experts in this field,
6 to tell us what you think is the state-of-the-art, so that
7 we can provide a better regulatory service and assist
8 companies in labeling their products as clearly and as
9 completely as possible.
10 With that, I would like to close. Dr. Sacks will
11 be providing you with some more in-depth discussion of this
12 issue, and I would like to say thank you once again for
13 being here and we look forward to listening to your
14 presentations, your discussions, and your conclusions.
15 Thank you very much.
16 DR. GARRA: Thank you, Dr. Schultz.
17 Dr. Sacks.
18 **The Key Issues for Panel Consideration**
19 DR. SACKS: Good morning.
20 The down side of this is I am going to be a little
21 redundant; the up side is it is going to be mercifully
22 short.
23 [Slide.]
24 The FDA is seeking advice today from the panel
25 with respect to labeling and the form of output of bone

1 diagnostic devices, so that instructions to physician users
2 are clear. The concepts are sufficiently complex that even
3 specialists may have difficulty arriving at a common
4 understanding.
5 Since the new bone ultrasound devices are
6 relatively inexpensive and portable, we face the likelihood
7 that they will be acquired by a significant number of
8 primary care physicians who likely will have little
9 experience in interpreting information from bone assessment
10 devices and in making decisions whether or not to treat to
11 prevent fragility fractures.
12 This makes it incumbent on the FDA to guarantee
13 that device reports to the physicians are expressed in the
14 most accessible way and that labeling educates physicians to
15 help them avoid common confusions insofar as this is
16 possible.
17 The FDA has identified a number of areas of
18 confusion and disagreement which we present to the panel
19 today for clarification. Dr. Garra has outlined these.
20 These are included in the panel discussion points in your
21 handouts, but I want to outline them one more time, so that
22 everyone is listening particularly for these points during
23 the presentations to follow and, indeed, some of the
24 introductory comments have already touched on them.
25 [Slide.]

1 The first point is that there are three primary
2 forms in which bone device outputs can be expressed. One is
3 as an absolute measurement, and the other two are as
4 relative measurements.
5 The absolute measurement, that is, values of
6 either bone mineral density, that is, BMD, or quantitative
7 ultrasound. That is QUS. We have heard today a number of
8 acronyms. Government and medicine are notorious for having
9 tons of initials. Earlier speeches talked about ODE, PMA,
10 FDAMA, SMDA, and so on, and we will try to make sure that
11 everyone today is on the same wavelength.
12 None of the panel here, who are not involved in
13 bone primarily, should hesitate to ask if there was any set
14 of initials that you are not clear on. Believe me, you are
15 in the majority.
16 The first point, though, at the top, which is on
17 the ceiling, is the absolute values, and that is one
18 possible way for all devices, whether they be x-ray, that
19 is, DEXA, or others, quantitative CT, on the one hand, or
20 quantitative ultrasound outputs.
21 The second type, the two below that, T-score and
22 Z-score, are relative measurements. Those will be explained
23 more fully by other speakers, I won't go into them now, but
24 be sure that they are explained to your satisfaction.
25 The two types of relatively measurements, though,

1 I want to say express the absolute measurement through a
2 reference to a population of which your patient is a member,
3 that is, through a reference database, whether that a young
4 normal reference database or an age-matched reference
5 database, T-score and Z-score are those two respectively,
6 that is, T-score relates an individual to a young normal
7 reference database, and Z-score to an age matched. Again,
8 more will be said about that later.
9 Each of these three forms of expressing the device
10 output has its strengths and weaknesses. What we need to
11 decide, "we," the FDA--need to decide which one or ones will
12 lead to minimizing misclassifications of patients by
13 physicians and to minimizing erroneous treatment decisions,
14 that is, treating when not necessary or not treatment when
15 it is necessary.
16 Furthermore, we need to decide this in the
17 contexts of age-related bone loss and, indeed, other medical
18 conditions, as Dr. Faulkner has already referred, other
19 medical conditions leading to bone loss.
20 [Slide.]
21 For the two forms of relative measurement, that
22 is, the T-score and the Z-score, young normal and age-
23 matched reference databases are currently unique to each
24 manufacturer, to each modality, to each gender, and to each
25 socially defined ethnic group.

1 We particularly need to define the best way to
2 deal with specific gender and ethnic databases. I am going
3 to say that again, taking a page out of Dr. Kessler's
4 approach. We particularly need to define the best way to
5 deal with specific gender and ethnic databases. That is one
6 of the two most important questions that we want to get some
7 clarification from the panel today.
8 We need to arrive at a common understanding of
9 which forms of presentation of relative measurements, if
10 any, are invalid and which are the most advantageous. at the
11 other end of that spectrum, for avoiding confusion and
12 misclassifications of patients, and we also need to decide
13 whether or not to require common databases for all
14 manufacturers of each modality.
15 Thank you.
16 DR. GARRA: Thank you very much.
17 Before we proceed, we need to turn in the lunch
18 forms and I think people are ready for a short break. We
19 are going go no more than 10 minutes, take a short break,
20 and please, panel members, turn in your forms to me for
21 lunch.
22 [Recess.]
23 DR. GARRA: Dr. Miller is going to be speaking to
24 us on the history and basis for the World Health
25 Organization osteoporosis paradigm.

1 Dr. Miller.

2 **The History and Basis for the WHO**

3 **Osteoporosis Paradigm**

4 DR. MILLER: Good morning. Thank you for the

5 opportunity to be here and to have hopefully a positive

6 impact on this field that we are all very interested in

7 having resolutions in solving.

8 [Slide.]

9 I was asked to speak about the history and the

10 basis for the World Health Organization paradigm that very

11 importantly established cutoff points for the criteria for

12 the diagnosis of osteoporosis.

13 [Slide.]

14 In 1991, the Consensus Development Conference on

15 Osteoporosis defined osteoporosis in this way - "A systemic

16 skeletal disease characterized by low bone mass, and

17 microarchitectural deterioration of bone tissue, with a

18 consequent increase in bone fragility and susceptibility to

19 fracture."

20 This definition has withstood the critics and the

21 test of time, and is quite valid, but as clinicians in the

22 practice of medicine, we can't measure yet

23 microarchitectural deterioration. We can't measure yet bone

24 fragility in a way that we would apply in pragmatic use of

25 patients. What we can measure is bone mineral density or

1 bone mass, realizing that for the histomorphometrist, those
2 two are not equal terms, but for the purpose of this
3 discussion, they may be interchangeable.
4 So, we, as clinical physicians, can measure bone
5 mineral density to use it as our surrogate marker for the
6 definition of osteoporosis until the time comes that we have
7 ways of defining microarchitectural deterioration.
8 [Slide.]
9 Before the WHO committee came up with the criteria
10 for diagnosing osteoporosis based on bone mass measurement
11 testing devices, we had to rely on routine x-rays and the
12 presence of a fracture in order to have an established
13 diagnosis of osteoporosis.
14 This is the end result of the disease process that
15 we want to prevent, and this is the reason why there has
16 been tremendous impetus in trying to develop quantitative
17 tools for diagnosing low bone mass and applying certain
18 criteria.
19 [Slide.]
20 The justification comes from data that has been
21 published in a number of studies, one of the first ones from
22 Dr. Phil Ross, Dr. Richard Wasnich, and the Hawaiian
23 osteoporosis group, that looked at the relationship between
24 bone mass in postmenopausal women or existing fractures on
25 future fracture risk.

1 In this particular slide, postmenopausal women in
2 the lower tertile of bone mineral density, who have no
3 fracture, had a relative risk for their first fracture of
4 7.4. Independent of bone mass, if you have one prevalent
5 fracture, your relative risk for the second fracture is
6 increased tenfold.
7 But here is the issue and here is the reason why
8 identifying people with low bone mass before the first
9 fracture occurs is important. Individuals who have low bone
10 mass and have already sustained one fracture, have an
11 exceptionally high risk for the second fracture.
12 [Slide.]
13 So, consequently, the World Health Organization
14 met in 1992, a study group that decided with these new tools
15 that can quantitate bone mass and the known relationship
16 between low bone mass and fracture risk, that we needed to
17 define that disease by an objective number, because the
18 machines were becoming increasingly available clinically in
19 order to stratify individuals within a certain reference
20 range and to pick cutoff values for the diagnosis of
21 osteoporosis based on bone mass measurement technologies for
22 any diagnostic assessment that would be set at a level of
23 BMD associated with an unacceptably high risk of fracture in
24 the population.
25 They have recognized that low BMD is a risk factor

1 and that it needs to be diagnosed clinically before their
2 first fracture occurs.
3 [Slide.]
4 The WHO Study Group consisted of these
5 international experts, and I just want to again make the
6 point of the fact that in this country, Professor Joseph
7 Melton, Professor Conrad Johnston were instrumental in this
8 regard.
9 The Chair of the committee, Professor John Kanis,
10 I want to extend my thanks to him for a lot of the work and
11 help that he has provided me over the last few weeks and
12 months and helping to put this particular session together.
13 [Slide.]
14 They picked these cutoff points for the diagnosis
15 of osteoporosis in the postmenopausal Caucasian population,
16 that osteoporosis could be defined if an individual in that
17 group had a bone mineral density that was equal to or lower
18 than 2.5 standard deviations below the young reference
19 population database.
20 Recognizing that the relationship between low bone
21 mass and fracture risk is truly a gradient and not a
22 threshold, they picked a second category, the so-called
23 osteopenic category, so that physicians could be alerted to
24 the issue that postmenopausal women that are not on therapy
25 and are at risk for the silent progress of bone loss needs

1 some kind of a label in order to think about the cognitive
2 process of initiating interventions. So, the second
3 category of minus 1 to minus 2.5.
4 [Slide.]
5 Now, why did the WHO use standard deviations from
6 the mean of a young normal BMD or BMC to define osteoporosis
7 rather than any particular instrument's absolute BMD or BMD?
8 They did it because the calibrations of the
9 absolute BMD or BMC of any individual device are not the
10 same. So, standard deviations help to at least reduce or
11 correct for different manufacturer's instrument
12 calibrations.
13 [Slide.]
14 Well, was the WHO criteria based on prevalence,
15 that is, the number of people that are below certain cut
16 points of minus 2.5 or minus 1, or was it based on risk,
17 that is, the number of people at a particular cut point that
18 may have fractures?
19 [Slide.]
20 It is actually based predominantly on prevalence
21 with initially an approximation of the lifetime fracture
22 risk in Caucasian postmenopausal women.
23 [Slide.]
24 This is some of the data that was used to bring
25 these cut points. If they used this particular cut point of

1 minus 2.5 SD, and looked at the hip alone at femoral neck,
2 and the age group of postmenopausal over 50, it picked up 16
3 percent on a prevalence basis, 16 percent of the population
4 that were below that cut point, and that approximates the
5 lifetime fracture risk for hip fractures from the age of 50
6 in the Caucasian postmenopausal population.
7 If it looked at combining spine, hip, or wrist, it
8 detected about 30 percent, in another study from the UK 38
9 percent, and this approximates the risk of fracture at the
10 spine, the hip, or the wrist in this population from age 50
11 to the end of their lives.
12 [Slide.]
13 This is the lifetime fracture risk data with
14 regard to approximation of the lifetime fracture risk, and
15 you will see that a Caucasian woman at the age of 50, who
16 lives an average life span, can be expected to have a 17
17 percent lifetime fracture risk, and this approximates the
18 prevalence of around 17 or 16 percent in the Caucasian
19 population measuring bone mass at the proximal femur in
20 women over the age of 50.
21 [Slide.]
22 Looking at the combined fractures of the femur or
23 the vertebrae or the forearm, the lifetime risk is about 38
24 to 40 percent, and approximately the prevalence above the
25 age of 50 in the Caucasian population.

1 [Slide.]

2 In addition, in cross-sectional data that was
3 derived predominantly from the Sheffield UK area, it is also
4 from the Rochester, Minnesota area, when they applied these
5 cut points in the postmenopausal population, a bone mineral
6 density T-score of minus 2.5 identified over 50 percent of
7 postmenopausal Caucasian women who have sustained a fracture
8 not only of the hip, vertebrae or wrist, but also now adding
9 the humerus and pelvis, which are known to be fragility
10 fractures, now this cut point identified the majority of
11 people who could be expected to suffer a fracture.

12 [Slide.]

13 And so the World Health Organization cut points
14 were based predominantly on prevalence, also on estimated
15 lifetime risk and cross-sectional fracture risk data was
16 based on British and U.S.A. data.

17 The T-scores were derived from machine-specific
18 manufacturer's reference databases, and minus 2 SD picked up
19 50 percent of the population, and they felt that was too
20 much, minus 3 SD for definition was too small, since it only
21 detected 8 percent of the population, and therefore,
22 arbitrarily, for the reasons also previously stated, minus
23 2.5 was selected.

24 [Slide.]

25 In fact, in 1992, Professor Melton, who was on

1 this committee, wrote an editorial in the JBMR.

2 When they decided to use the cutpoint of minus 2.5

3 standard deviations instead for the cut point for the

4 diagnosis of osteoporosis, he revised his editorial to say

5 how many women have osteoporosis now.

6 [Slide.]

7 In 1994, there were only a few machines that were

8 available, and as you know, there are now approximately

9 worldwide 25 different manufacturers who make some form of

10 bone mass measurement devices.

11 The World Health Organization at that time

12 probably didn't have a clue that there would be so many

13 machines available between 1992 and 1999, but with the

14 development of all the technologies, it has become apparent

15 and clear that a problem exists, and this is a slide that

16 was created by Dr. Eric von Stetten of Hologic Corporation,

17 and will be published as a peer review article in the

18 September issue of the Journal of Clinical Densitometry with

19 Dr. Faulkner being the first author and my being the third,

20 and Dr. von Stetten being the second, that looked at least

21 from the Hologic data that looked at the T-score, which is

22 on the vertical access, across age by measuring ultrasound

23 of the heel with their device, the total hip by DEXA, PA

24 spine by DEXA, forearm by DEXA, lateral spine by DEXA, or

25 spine by CT.

1 For any individual patient, let's just arbitrarily
2 take a patient who is 75 years of age, that singular patient
3 measured on this particular heel device could have a T-score
4 of minus 1, and the same patient measured on lateral DEXA or
5 a CT could have a T-score of minus 4 or 5.
6 Hence, the problem of misclassifications of
7 patients, which has tremendous impacts with regard to the
8 competency of our care of our patients, which has tremendous
9 implications with regard to how we make a diagnosis or miss
10 a diagnosis, or who gets treated, who does not get treated
11 has emerged in the field in part as a result of the success
12 of the increased awareness of osteoporosis.
13 Now, what is responsible for these discrepancies?
14 Well, this is not clear. A major part of this is probably
15 due to the fact that bone is not the same throughout our
16 body, like measuring the cholesterol in a vein of one side
17 of the arm and a cholesterol in the vein of the other side
18 of the arm. Bone is different. It is not homogeneous.
19 In addition, rates of bone loss from the menopause
20 are different at different skeletal sites. You lose faster
21 in the early menopausal years from the spine than the hip.
22 So, there are differences in age-related bone loss, the
23 biology of bone that explains some of these differences.
24 But being asked here today to address the
25 implications of the T-score and how it is established and

1 the WHO criteria, I will also submit and show you data to
2 suggest that a major part of this, potentially major part of
3 this discrepancy is due to the fact that different
4 manufacturers derive their T-score from different dissimilar
5 young normal reference population databases.
6 It is not that the databases in any individual
7 manufacturers are wrong or bad, they are all very good.
8 It's they are not consistent, and that has to do with the
9 fact that the T-score is the point of how classification of
10 the WHO criteria is made. It is dependent upon the young
11 normal reference population database, because the equation
12 for T-score as shown here, it is any individual patient's
13 bone mineral density or ultrasound equivalent minus the
14 average bone mineral density of the young normal reference
15 population database divided by the standard deviation of
16 that young reference population database, and if either the
17 average BMD of the reference population or the standard
18 deviation of the so-called young normals is different, it
19 has a profound effect on the subsequently calculated T-
20 score, therefore, the WHO classification.
21 [Slide.]
22 Let me just give you a couple of models of this.
23 For example, if a patient's bone density were 0.7 grams per
24 square centimeter, and the average BMD of the young
25 reference population database in a manufacturer's machine

1 was 1, but the standard deviation was 0.1, the T-score would
2 be minus 3, but if that same patient on a different machine
3 or with a different manufacturer's young normal database
4 even had the same average BMD of the young normals of 1, but
5 the standard deviation was 25 percent different, the T-score
6 would be minus 2.4.
7 [Slide.]
8 Another slide that was developed by Dr. Faulkner
9 and looking at the bottom panel across here, if the same
10 patient with a BMD of 0.7, but the standard deviation of the
11 reference population was 0.1 or 0.15 or 0.20, which is not
12 uncommon when you look at how population selections are
13 done, the T-score in the same patient could be minus 3 or
14 minus 2 or minus 1.5.
15 [Slide.]
16 Some data that has been published to show this,
17 and this has been published by Joel Finkelstein and the
18 people at Mass. General, has been published by Ahmed, in
19 this slide by Blake, and in Fogelman's group in the UK, and
20 here they measured 2,550 postmenopausal women on the same
21 machine and calculated their T-scores at their spine or at
22 their hip according to the WHO classification shown here,
23 and had their T-score derived from their own study site, SYN
24 is their study site, young normal database, or the
25 manufacturer's young normal database. The parentheses are

1 the percent that were classified according to the WHO
2 criteria.
3 Take a look at the femoral neck, for example.
4 When these 2,550 same women were measured on the same
5 machine at the same skeletal site, but their T-score was
6 calculated from their own institution's database, 3 percent
7 were below minus 2.5; on the manufacturer's database 23
8 percent. Highly different classifications not due to the
9 technology, not due to the patient, not due to the bone
10 site, but because of the T-scores being derived from
11 different young normal databases.
12 [Slide.]
13 The only common young database that we have in our
14 equipment is the NHANES database that Dr. Looker will be
15 talking about this afternoon, the National Health and
16 Nutrition Examination Survey, a common database which is in
17 our central densitometer machines for the hip only. It
18 doesn't exist for the spine, and it doesn't exist for the
19 wrist.
20 When this was realized and published by Dr.
21 Faulkner, before the NHANES common young normal database for
22 the hip was put in the machines, the same patient could be
23 measured on a Hologic and have a T-score of minus 3 and a
24 Lunar to have a T-score of minus 2. This was removed by the
25 institution and the incorporation in all manufacturers'

1 central densitometry machines, the common NHANES database.
2 We don't have the common young normal standardized
3 database for all of these other devices, and I would submit
4 that that is one of the issues in terms of long-term
5 solutions that may help solve some of these differences.
6 [Slide.]
7 To give you one piece of evidence to show you that
8 using the same young normal database can reduce some of the
9 differences in the T-scores shown in this column, as shown
10 by a study by Susan Greenspan and Mary Bucksein in the JBMR
11 1997, when they studied about 100, in this column here,
12 postmenopausal women, and measured them on different devices
13 at different skeletal sites, different ultrasound devices,
14 heel DXA, and hip DXA, and calculated this T-score here from
15 a small, although nonetheless the same young normal
16 database, 55 patients, and when the T-score was calculated,
17 regardless of what technology was used or skeletal site was
18 measured, it all hovered around minus 2.
19 [Slide.]
20 So, the prevalence of osteoporosis is dependent
21 upon a number of factors, but clearly one of them is the
22 young normal database from which the T-score and the WHO
23 criteria are derived.
24 Number two, it has to certainly do with different
25 rates of bone loss from different skeletal sites, the cutoff

1 level that is used to define the condition, and the accuracy
2 errors of the technology, the ability of that technology to
3 measure the bone that is there, they are all very good.
4 This is not so much an accuracy error as it is a pattern of
5 bone loss or reference population problem.
6 [Slide.]
7 So, when you look at the strength limitations of
8 the WHO criteria, I want to make the point that it shifted
9 the field in the right direction. It took a disease that e
10 had to define by fracture to one defined by certain cutoff
11 points of bone mineral density, and it was a major step
12 forward, and it has only been in the last couple of years
13 with different devices that we realized that we have to
14 address some problems.
15 The WHO criteria has strengths for the busy
16 practitioner who is seeing 30 patients a day. It is a
17 straightforward number for diagnosis, and it emphasizes the
18 need to diagnose osteoporosis prior to the fracture, and it
19 finally provided some uniform terminology heretofore not
20 present in the field.
21 There are some limitations clearly. It is misused
22 by many payers to deny reimbursement if you don't have that
23 cutoff point. It is based on data from postmenopausal
24 Caucasian women, another point of discussion of this panel.
25 It is dependent upon the accuracy of the BMD and

1 the standard deviation of the young reference population
2 database. It is often misinterpreted as an intervention
3 threshold, as Dr. Johnston mentioned.
4 It implies a threshold of BMD rather than the
5 gradient of risk, like hypertension and high cholesterol,
6 and there are some people who have low bone mass who don't
7 have osteoporosis, and we don't want to have everybody
8 assume that low bone mass is only osteoporosis, and so
9 therefore education to physicians in this regard are
10 important.
11 [Slide.]
12 Well, what are the potential solutions? These are
13 going to be discussed in great detail this afternoon by Dr.
14 Black, and as Dr. mentioned, the combined committee of the
15 NOF-ISED has been working very, very hard and very
16 diligently to try to bring responsibility here, and some of
17 the suggestions that may emerge out of this, because these
18 are solvable problems, we have a problem, there are
19 solutions.
20 One would seem for the busy physician and since
21 the T-score has been out there now for five years that we
22 ought to do something in some way to retain it. To go back
23 and say tomorrow it is wrong would have them look at us in
24 terms of their perception and say, well, what have you been
25 teaching us for the last five years.

1 It is consistent with the NOF clinical guidelines
2 of who to treat, and there is a new WHO working group in
3 progress to try to address this issue, as well. Dr. Black
4 will suggest some short-term solutions of these different
5 devices of T-score equivalence based on either prevalence or
6 risk, and I would submit that one of the long-term solutions
7 for this is the creation of the NHANES equivalent of all
8 peripheral devices, and that is the standardized common
9 young normal reference population database.
10 So, I think we are here to try to work with you to
11 answer these particular issues, and we will come to the
12 resolution of this to maintain the credibility of bone
13 densitometry in the practice of medicine.
14 Thank you very much.
15 DR. GARRA: Thank you.
16 Dr. Genant.
17 DR. GENANT: Paul, thank you for that informative
18 presentation, and you have emphasized to a large extent the
19 T-score approach. By this, do you mean that the clinicians
20 do not have need for normal age-related databases?
21 Certainly, in the use of T-scores, this gives
22 information as it relates to fracture risk. Do you see
23 other applications of bone density where reference to a
24 normal age-based data set is useful?
25 DR. MILLER: I do in this sense. Particularly in

1 the premenopausal population where we may not have the issue
2 of the postmenopausal population, but certainly for the
3 younger patients who have secondary conditions associated
4 with bone loss, that are on prednisone, that are receiving
5 chronic heparin, that have celiac disease, being able to
6 have a 28-year-old and know what her bone mass is, for
7 example, with those secondary conditions as compared to a
8 28-year-old, age match is important information. That is
9 number one.
10 Number two, there is data to suggest that if you
11 even have in the older population an age-matched Z-score
12 that is more than 2 standard deviations below other women of
13 that particular aged person, that other secondary causes of
14 osteoporosis other than age-related bone loss are more
15 likely to be present, and it may trigger for that physician
16 a more aggressive workup for secondary causes.
17 DR. GARRA: Thank you very much.
18 Let's move on now to the next speaker. That is
19 going to be Dr. Richard Wasnich. He is going to be speaking
20 to us on the possible basis for race and gender measurement
21 differentiation.
22 **Is There a Basis for the Race and Gender**
23 **Measurement Differentiation?**
24 DR. WASNICH: Thank you, Dr. Garra, and thanks to
25 the panel for inviting me to speak here.

1 [Slide.]

2 I have been asked to address the issue of whether
3 there is a basis for the race and gender differentiation of
4 bone density. Dr. Miller has done a good job of pointing
5 out some of the problems.

6 [Slide.]

7 This is a very significant issue in order to
8 answer this issue. The issue really is does the
9 relationship between bone density and fracture risk differ
10 by gender or race.

11 Another way of saying it is does the contribution
12 of bone density to fracture risk remain fairly constant even
13 though other risk factors may vary, such as tendency to
14 fall, for example.

15 [Slide.]

16 This issue is important because if gender and race
17 do no matter, then having normal reference databases are
18 unnecessary, and that is the significance of this issue,
19 and, in fact, fracture risk can be directly calculated from
20 the bone measurement.

21 Also, without normal--I should say, quote, "normal
22 reference" databases and arbitrary T-scores, there is no
23 longer an issue of misclassification or at least it takes on
24 an entirely different meaning than I think has been used so
25 far.

1 [Slide.]

2 I think it is important to address what the issues
3 are not. It is known that bone density varies according to
4 gender, race, and other factors. That is not the issue.

5 It is known that risk factors for fracture differ
6 between men and women, and between different racial groups.
7 That is not the issue we are addressing, and it is also true
8 that risk factors vary according to fracture location. For
9 example, falls play a greater role in hip fractures,
10 whereas, in the case of spine fractures, existing fractures
11 play a great role, and falls don't play as great a role.
12 However, that is also not the issue.

13 [Slide.]

14 To further illustrate this point, let's look at
15 some general trends observed among Japanese and Caucasians.
16 Bone density is generally higher in Caucasians, while
17 vertebral fractures are probably more common in Japanese.
18 However, hip fractures clearly appear to be higher in
19 Caucasians as compared to Japanese. Now, while these data
20 are very interesting, they do not answer the question that
21 we have just been asked.

22 [Slide.]

23 We know, for example, that a higher frequency of
24 falls in Caucasians--and I have represented falls here by
25 pink just arbitrarily--may contribute to the higher fracture

1 incidence of hip fracture among Caucasians. There is also
2 some evidence that a longer hip axis length may contribute
3 to the greater frequency of hip fractures in Caucasians.
4 However, this is not the issue.
5 It is also known that risk factors for hip
6 fracture, for example, and I don't consider these to be the
7 final answer to all of our questions, but a somewhat
8 arbitrary contribution pie chart of where bone density, for
9 example, in this case, falls, age, and other risk factors
10 may contribute to each of the fracture types, and it is
11 known that the risk factors differ for different fracture
12 types.
13 As I mentioned before, falls probably play a
14 greater role in hip fractures, whereas, existing prevalence
15 spine fractures play a greater role than future spine
16 fractures. This is also not the issue.
17 [Slide.]
18 The issue is, I believe, is that when you look at
19 the entire patient and the risk of all fractures, is the
20 contribution of bone density, irrespective of other risk
21 factors, consistent regardless of race or gender? And that
22 is the question that I will try to address.
23 [Slide.]
24 In order to answer this question, I considered two
25 types of evidence. The most conclusive evidence I think,

1 which I have called primary evidence, would be derived from
2 studies in which both genders or both races are studied
3 simultaneously and prospectively, using identical
4 methodology and adjusting for the other risk factors or the
5 covariates. The goal of this kind of study is to determine
6 the independent contribution of bone density to fracture
7 risk in each group.
8 [Slide.]
9 Other evidence which I would consider to be
10 supportive evidence, and I have called secondary evidence,
11 and these data come from prospective studies involving a
12 single race or gender, but an attempt was made to adjust for
13 the independent risk factors. The results of such studies
14 are usually expressed as relative risks per SD decrement in
15 bone density.
16 [Slide.]
17 As a reminder, relative risks are nothing more
18 than ratios of absolute fracture rates derived from these
19 studies. I have heard it said with regard to the clinical
20 use of absolute fracture data that we don't have enough
21 data, and I fail to understand that, because it is actually
22 the same data expressed differently. You can express it
23 either as absolute rates directly from the studies or you
24 can express it as relative risks.
25 I will argue later today that the direct use of

1 absolute fracture rates is more clinically useful than
2 ratios of these rates or comparisons to some hypothetical
3 normal value that probably doesn't exist.
4 [Slide.]
5 I would like to first consider the issue of race.
6 Unfortunately, I was unable to find any studies that would
7 qualify as primary evidence in which both racial groups were
8 studied simultaneously, so the evidence here all comes as
9 secondary evidence.
10 Fortunately, there are a number of studies
11 providing secondary evidence, and most of them have been
12 nicely summarized in this meta-analysis published by
13 Marshall in 1996 in the British Medical Journal, so I am
14 going to use this meta-analysis for most of my presentation
15 on this.
16 [Slide.]
17 These are the prospective studies that Marshall
18 considered, and you see all the usual familiar culprits here
19 and most of the studies. They are clearly a wide diversity
20 of studies including three European studies, two Australian
21 studies, and six U.S. studies.
22 I am going to be showing summary results for the
23 three main fracture sites, namely, wrist, spine, and hip.
24 [Slide.]
25 Without trying to digest everything on this slide,

1 let me ask you to focus on two columns. This is for wrist
2 fractures. Notice that a number of different bone density
3 sites have been used for these studies, and notice here the
4 different locations and ethnicity.
5 I always am a little puzzled when I see the term
6 "Caucasian" used in this country. I understand from the
7 U.S. Census there are supposed to be 33 distinct ethnic
8 groups, so for us to pretend like this is homogeneous race
9 is, of course, a little--and I am not going to try to answer
10 that question, but let's keep that in mind that some
11 diversity is already represented here.
12 [Slide.]
13 Now, this slide is a summary basically of what I
14 have just shown in the previous slide. On the y axis are
15 the relative risks reported after adjustment for other
16 covariates, so this should represent the independent
17 contribution of bone density.
18 Here are the various measurement sites used for
19 these studies. The letter represents the various studies,
20 and the small red cross represents the mean from this site
21 in the case of the distal radius, the case of the hip
22 measurements, or the spine measurements, and this number
23 represents the mean for all of the data.
24 As you can see, there is a pretty tight range
25 between 1.5 and 2.5 except for one outlier. The average

1 relative risk for wrist fractures for all studies, all
2 skeletal measurement site, is 1.95. Keep that number in
3 mind.
4 [Slide.]
5 For hip fractures, we have a number of different
6 Caucasian populations that have been studied, and again a
7 variety of different skeletal measurement sites employed in
8 these studies.
9 [Slide.]
10 The summary slide again shows a fairly tight
11 clustering between 1.5 and 2.5 for relative risks, and this
12 is irrespective of skeletal measurement site. The average
13 relative risk for all studies and all measurement sites is
14 2.06.
15 [Slide.]
16 For vertebral fractures we do have more racial
17 diversity because of our Japanese-American group in Hawaii,
18 and which is Study C. Note again that a variety of
19 different skeletal measurement sites have been used, and
20 technologies, including ultrasound, have been employed to
21 derive these data.
22 [Slide.]
23 For vertebral fractures, there is a very
24 consistent relationship irrespective of measurement site,
25 and the average relative risk of all of these studies for

1 vertebral fracture is 1.9.

2 [Slide.]

3 So, irrespective of fracture site, BMD measurement
4 site, or race, there is an approximate doubling of fracture
5 risk for each SD decrement of bone density. In fact, it is
6 even more consistent than I think most people understand.

7 These data also indicate that the nature of the
8 relationship between BMD and fracture risk is very similar
9 among different races and ethnic groups.

10 [Slide.]

11 This graph illustrates what I think is the core
12 and the crux of the entire matter of interpretation of bone
13 density. This represents absolute fracture incidence rate,
14 in this case vertebral fracture, and this is for a 70-year-
15 old population.

16 So, a 70-year-old, who is average for her age, has
17 an absolute risk of 4.5 percent during the next year. Now,
18 it is clear that this doubling of risk that you hear about
19 is consistent through the entire range of bone density.

20 The data that I have just reviewed indicate that
21 the nature of this relationship and the shape of this curve
22 is very similar for all racial and ethnic groups that have
23 been reported.

24 There is another point that I would like to make
25 from this slide. If you have a patient who is 70 years old,

1 knowing, for example, that she has a 20 percent chance of
2 fracture in the next year, or in five years a 100 percent
3 probability, I find that far more useful than any arbitrary
4 scoring system to make a clinical decision. Keep that
5 patient in mind, and we will come back later to that
6 patient.
7 [Slide.]
8 Now, with regard to gender, we are more fortunate
9 in that there are three studies available that I think
10 provide primary evidence of this relationship between bone
11 density and fracture, and these are located in Hawaii,
12 Australia, and Finland.
13 [Slide.]
14 In our study of Japanese-Americans, these were men
15 and wives, we observed 41 spine fractures among the 1,008
16 men, 151 spine fractures among the 934 women, their wives.
17 [Slide.]
18 This is again the annual fracture risk. The
19 orange represents the women and the red represents the men.
20 In fact, they are so superimposed you can almost miss the
21 fact. So, although the men have on average higher bone
22 density, the relationship between BMD and absolute fracture
23 risk appears identical. What that means is a man and woman
24 with the same bone density have the same absolute fracture
25 risk.

1 [Slide.]

2 The Dubbo study from Australia reported fracture
3 rates for both men and women, but the BMD intervals they
4 reported were not really continuous and were slightly
5 different, but I have plotted the male values, an M, and the
6 women, females here, and on a best fit, you can again see,
7 despite the intervals being a little bit different, there is
8 a fairly consistent relationship between men and women in
9 this group also.

10 [Slide.]

11 For the Finnish study, first of all, let me note
12 their observation that among women they calculated that the
13 BMD contribution to fracture was 61 percent, and for men 70
14 percent. I think those are very similar, and they
15 underscore the fact that bone density is a major risk factor
16 for fractures, but it is not the only risk factor.

17 [Slide.]

18 Here are the male and female data, and you can see
19 the women are here, and the men are here. We are looking at
20 absolute fracture occurrence. Obviously, they are again
21 essentially identical.

22 [Slide.]

23 So, with regard to gender, men and women with
24 identical levels of bone density have the same absolute
25 fracture risk after adjustment for age and other covariates.

1 This is true in three separate studies and three different
2 locations, and in this case, two distinct racial groups.
3 [Slide.]
4 In summary, we have looked here so far at 12
5 different prospective studies around the world, 14 different
6 geographic locations, various ethnicities and races and
7 mixes, and in both men and women, and we find that the
8 independent relationship of bone density to fracture is
9 remarkable consistent, irrespective of fracture type or bone
10 measurement site or technology.
11 [Slide.]
12 I think it is worth noting that in these same 14
13 geographic locations, the mean bone density among "normal"
14 30-year-old women may differ, but this fact has no bearing
15 upon the basic bone density/fracture relationship. In fact,
16 it is not only irrelevant, it is potentially misleading.
17 In other words, any 65-year-old patient's fracture
18 risk will not be changed by changing the 30-year-old
19 reference group, at least it shouldn't.
20 [Slide.]
21 So, from these data of primary and secondary
22 evidence, I would conclude that, number one, men and women
23 with identical levels of bone density have the same absolute
24 fracture risk after adjustment for other independent risk
25 factors, and there is no evidence to suggest that bone

1 densities among women of various ethnicities have any
2 different relationship to fracture incidence.
3 [Slide.]
4 I think this is very good news because if we have
5 to develop a separate reference database for each
6 manufacturer, each skeletal measurement site, each
7 technology, and each ethnic group, for the U.S. alone we
8 will need 4 million reference databases, and, of course, we
9 don't want to ignore men. This number was 8 million if we
10 include men. So, this solves a lot of potential problems
11 for us.
12 [Slide.]
13 Now, if that is not sufficient reason to move away
14 from arbitrary scoring systems and towards the use of
15 absolute fracture risk, let me suggest one more reason.
16 First, recall again that bone density is a risk
17 factor, and not a diagnostic test, and a lot of problems
18 derive from that misunderstanding, and it is one of multiple
19 risk factors which include age, falls, prevalent fractures,
20 probably bone turnover in our data, and probably risk
21 factors that we currently haven't identified.
22 We are already on pretty shaky ground when we
23 choose a single risk factor and attempt to make a
24 "diagnosis" from it, i.e., bone density. However, when we
25 make clinical decisions based upon a single risk factor, and

1 ignore all other risk factors, that is when true
2 misclassification occurs, and the wrong patients may receive
3 the wrong treatment, and that is the misclassification I
4 would like to focus on.
5 [Slide.]
6 To illustrate this--and you will have to read
7 through my amateur Power Point skills here--these are data
8 from the Hawaii study. They have all been published
9 individually, but what I did for this analysis was to put
10 additional risk factors in the model to see how it changed
11 absolute risk.
12 This is absolute risk. This is 20 percent. The
13 time interval is 2.8 years. This is 50 percent. Now, the
14 average age is 74. So, for 74-year-old women, this shows
15 the BMD contribution to absolute fracture rate.
16 If this woman also has high bone turnover, which
17 is defined as osteocalcin in the highest quartile, this
18 would be the curve. If she also has an existing spine
19 fracture, this is the relationship, and if she has both of
20 these risk factors, this is the relationship.
21 Now, let's for the purposes of illustration choose
22 three different patients based on bone density and WHO. The
23 first one is normal, minus 0.9. The second one is
24 osteopenic, minus 1.9, and the third one is osteoporotic,
25 minus 2.5.

1 Now, what we are going to do to interpret these is
2 assume that in the case of this patient we only have bone
3 density, and she is classified as osteoporotic. In the case
4 of the osteopenic patient we also have a history of
5 nonviolent fracture, therefore, we are reading this curve.
6 In the case of the "normal" patient we have a
7 history of nonviolent fracture and high bone turnover.
8 In the next slide, we will summarize what the
9 actual risks to these three patients are.
10 [Slide.]
11 As you can see, based on bone density alone, the
12 "osteoporotic" patient has an 8 percent absolute probability
13 of fracture in the next three years.
14 The osteopenic patient, based on this history, has
15 a 20 percent probability, and the "normal" patient has an
16 absolute probability of 23 percent.
17 Therefore, if we had classified risk based
18 completely upon bone density, we would have been completely
19 wrong about their true absolute fracture risk. The fact
20 that the normal women based upon bone density alone would
21 receive the most benefit from treatment because, in fact,
22 she has the highest risk.
23 So, this is the impact of looking at all risk
24 factors as opposed to looking at a single risk factor.
25 [Slide.]

1 Now, I suppose that any sensible dog would shut up
2 and sit down at this point, but since I am neither, let me
3 risk making one other point.
4 [Slide.]
5 This is the very familiar relationship, and I wish
6 we could get used to seeing the data published in this form,
7 these are years old, but they show vertebral fracture
8 incidence from our study at three skeletal measurement
9 sites: heel, radius, and spine.
10 The respective scales for the measurements are
11 shown here, and I should say that very similar data have
12 been published for hip fractures and for all fractures. In
13 fact, most of the time when you look at all fractures, these
14 curves are pretty much identical.
15 We have looked at a variety of different
16 measurement techniques and have shown the same relationship
17 that includes heel ultrasound, phalangeal density, and
18 metacarpal density. I have yet to evaluate a technique that
19 does not show this relationship.
20 I think that the entire crux of the current debate
21 derives from how these data are interpreted or
22 misinterpreted. I would suggest that the correct way to
23 interpret these data is to, number one, note the absolute
24 measurement level, read up to that curve and read over to
25 the absolute fracture rate.

1 Obviously, if you have measured the spine in this
2 patient, you would read the spine curve; if you have
3 measured the heel, you will read the heel curve. This risk,
4 this absolute risk can be expressed easily as one year or
5 five year or 10 year, or whatever time frame a clinician may
6 desire, but I would submit that this is the information
7 required, and all the information required, to make clinical
8 decisions for osteoporotic patients.
9 I think the problem occurs when this curve is read
10 backwards. What I mean by that is if you start here, and
11 you assume a priori that the spine measurement is the gold
12 standard, and then you read backwards, what you will find is
13 that the radius and heel have different Z-scores and
14 different scales and different T-scores than the spine, and
15 therefore, are considered by some as being not as perfect as
16 the spine, but you can read the same data, and you can make
17 them identical.
18 This same erroneous reasoning, I believe has been
19 applied to hip fracture data. The fact is if these data are
20 correctly interpreted, and expressed as absolute fracture
21 risk, all measurements can be made to produce the same
22 answer by simply referring to the data and reading the
23 fracture rate.
24 So, if you have decided that this is your
25 treatment threshold, there are the three levels that

1 correspond to that treatment threshold.

2 [Slide.]

3 So, my recommendation will be that we stand back,
4 look at the entire patient, consider all risk factors, and
5 assess overall fracture risk, and not risk at any one
6 skeletal site. After all, we don't know which patient will
7 have which fracture.

8 I think we should stop obsessing about T-score
9 discrepancies because I think they mean nothing. Most
10 importantly, we must make our interpretations simple and
11 intuitive, which they currently are not, and I can think of
12 nothing simpler when explaining to a patient, such as the
13 70-year-old I referred to previously, that she has a 100
14 percent probability of fracture in the next five years, and
15 that if I prescribe, and she complies, with Treatment A,
16 that risk will drop by 50 percent.

17 That is the information that I think is so simple
18 that both physicians and patients can understand what they
19 are getting by complying with the treatment.

20 [Slide.]

21 Now, in preparing for this talk, I rummaged
22 through some old slides, and I came across this 1984
23 quotation from Michael Parfitt, which he said, "No useful
24 purpose is served by pretending that subjects whose values
25 fall below the dividing line suffer from a disease that

1 those whose values fall above the dividing line have
2 escaped."
3 As I recall, this is about the year that DPA
4 technology first became commercially available, and it seems
5 odd that our technology has evolved so quickly, but our
6 concepts have probably fallen behind.
7 So, the answer to this dilemma of what we should
8 do next, and there is a proposal that we come up with a
9 modified T-score equivalence or take the big step and go to
10 absolute risk, strangely enough out yesterday in downtown
11 Bethesda, I found the answer in one of your buildings. I
12 forget who said this, but the quote was, "If you are in a
13 hole, stop digging." I would suggest we fix it all the way,
14 and not go halfway.
15 Thank you.
16 DR. GARRA: Thank you very much.
17 Are there any brief questions for Dr. Wasnich?
18 Dr. Genant.
19 DR. GENANT: Yes. A very informative
20 presentation, Dick. I think your emphasis of the importance
21 of other risk factors, as well as the concept of the
22 gradient of risk, is indeed important.
23 Two of our other presenters this morning have
24 indicated that aside from specifically indicating fracture
25 risks, that clinicians also often deal with patients--these

1 could be of different races or male and female gender--
2 wherein there may be disease processes including
3 osteoporosis, and they would like to have some idea of the
4 impact of disease on that patient, not specifically in the
5 context of fracture risk necessarily.
6 Do you think that in going to an approach as you
7 have suggested, that it would be appropriate to eliminate
8 normative databases? I don't mean just young normal, but
9 age related databases. Is there not a role for this
10 material for clinicians?
11 DR. WASNICH: I think the clearest role for
12 knowing what may be "normal" at age 30 is in the younger
13 patient when he is trying to evaluate their skeletal
14 development. Then, that is one of the comparisons, and age-
15 related comparisons would be useful. So, I think that is a
16 very clear area in the young patient where we would use
17 those.
18 For the older patient, I think it is somewhat
19 debatable, because that "2 SD's below the mean," would you
20 really do something about it if it didn't relate to some
21 level of high fracture risk? So, I don't know that your
22 instigation to do a further workup wouldn't be also
23 precipitated by an exceedingly high fracture rate.
24 It may be that these have to coexist for a while
25 to meet the needs, and I think there is no reason why they

1 can't coexist and we can have the scale knowing that it has
2 got problems, but use it for what it is worth, but base our
3 clinical decisions on treatment on real data.
4 What I see in the community, as a real fact, are
5 patients, osteopenic young women whose actual true current
6 and future risks, because they aren't losing bone, is
7 actually very low receiving prescriptions.
8 At the same time I see 75-year-old women who have
9 had a prevalent fracture, who are not getting treatment
10 because their bone density is not low enough.
11 So, I think making better decisions for patients
12 really will fall upon the use of absolute risk.
13 DR. GENANT: I had another issue with regard to
14 you relied heavily upon some of the meta-analysis to show
15 data that indicated that the risk for fracture at various
16 anatomic sites was relatively constant across different
17 measurement techniques and measurement sites.
18 Yet, in some of the large prospective studies,
19 particularly I could say the study of osteoporotic fracture,
20 there were very substantial differences in the ability to
21 predict fractures at specific anatomic sites related to in
22 particular measurements at that site.
23 DR. WASNICH: First of all, the study of
24 osteoporotic fractures is one of the studies included in
25 that summary, so those values were included with other

1 studies.

2 Again, that question of whether a measurement is

3 better comes full circle back to the erroneous

4 interpretation of that curve. If you remember, that curve

5 that we just saw there for spine fracture showed the heel to

6 be in the highest position.

7 Well, I have never heard anyone propose that you

8 had to measure the heel to predict spine fracture risk, but

9 that is exactly what has happened with hip fracture, because

10 the hip occupies a slightly higher relationship, it is being

11 proposed that you have to measure the hip.

12 I don't understand that, I don't believe that. I

13 think you can read the fracture rates as long as you know

14 the shape of that curve and have reliable data.

15 DR. GARRA: One more question here from Dr.

16 Faulkner.

17 DR. FAULKNER: If I understand, the practical

18 solution, though, is this going to require the curves, as

19 you have outlined, be derived for each skeletal site and

20 possibly each technology, there would have to be a separate

21 bone density related to absolute risk for each different

22 device?

23 DR. WASNICH: Well, the data I think are well

24 established for heel, radius, spine, and hip. I think to

25 bring in new technologies, there are easier ways to do it

1 without going through another 15-year study.

2 If a new machine that measures radius comes up, if

3 they can show high predictability to the old radius

4 measurements, in my mind, for example, the pDEXA from

5 Norland relates very closely to the values derived that were

6 used in these studies. So, I have no discomfort converting

7 that value and then going on to do absolute risk.

8 DR. FAULKNER: Given that we know that there is no

9 standardization in ultrasound, there is really no

10 standardization in any of these measurements, we are going

11 to end up having a Lunar hip number, and there will be a

12 Lunar heel number, and Hologic. I mean each of the

13 manufacturers, each of the devices will have a unique

14 number.

15 DR. WASNICH: Well, the output, though, will be

16 the same. The output of the report, no matter what

17 information you plug in, as long as you read absolute

18 fracture risk and have the coefficient, will be the chance

19 that this person will fracture next year. That will never

20 change.

21 DR. FAULKNER: The output would have to be from

22 the devices is not a BMD value or an ultrasound value. It

23 would have to be fracture risk.

24 DR. WASNICH: Yes.

25 DR. FAULKNER: In order for this to be practically