U.S. Department of Health & Human Services

Food and Drug Administration

FOIA RESPONSE

USER:	(ixg)
FOLDER:	K082402 - 270 pages (FOI:11002065)
COMPANY:	IMAGING THERAPEUTICS, INC. (IMAGTHER)
PRODUCT:	DENSITOMETER, BONE (KGI)
SUMMARY:	Product: OSDX HIP BMD SYSTEM
DATE REQUESTED:	Mar 28, 2011
DATE PRINTED:	Apr 20, 2011
Note:	Releasable Version

OCT 1 6 2008

K082402

SECTION 2

510(k) SUMMARY OF SAFETY AND EFFECTIVENESS

This summary of the 510(k) Premarket Notification for the Imaging Therapeutics OsDx Hip BMD System is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

PREDICATE DEVICES

The Imaging Therapeutics OsDx Hip BMD System is substantially equivalent to FDA-approved predicate devices with regard to indications for use and technological characteristics. These predicate devices are:

Technological Characteristics and Indication for Use
• CTXA Hip: K002113 • Pronosco X-Posure System Bone Densitometer: K984178 • Hologic Hip Structural Analysis Software K061561

INTENDED USE

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20 – 39) and age matched normals to compute T-scores and Z-scores respectively.

PRODUCT DESCRIPTION

The OsDx Hip BMD System is a software package that provides an estimate of BMD based on analysis of data derived from scanned hip X-rays. The program utilizes a quantitative bone structural algorithm that measures a composite of weighted cortical and trabecular parameters in proximal femur projection radiographs from which total hip bone mineral density (BMD) is mathematically derived. Image analysis can take place remotely or at the point of care.

The results, expressed as gm/cm^2, can be used for comparison to a reference data base of young normals (T-score) or age-matched controls (Z-Score).

SUBSTANTIAL EQUIVALENCE

Use of the Term "Substantial Equivalence"

The term "Substantial Equivalence" is used in this submission within the confines of the statutory use in the FDA's evaluation of a Pre-Market Notification Submission. Any statement regarding Substantial Equivalence used in this submission relates only to whether the device that is the subject of this submission may be lawfully marketed in the United States without pre-market approval or reclassification, and should not be interpreted as an admission, or any kind or type of evidence, in any patent proceeding, including patent infringement litigation or proceeding before any Patent Office.

The present submission and statements therefore should not be construed as affecting or relating to the scope of any patent or patent application, or to whether the product addressed in the submission, or its use, may be considered indistinct, from a patentability perspective, from any other device referred to in this sub mission.

Technological Characteristics

The technological characteristics (including anatomic site analyzed) of the OsDx Hip BMD System are substantially equivalent to those of the cited predicate devices. Standard x-ray images are scanned and evaluated to provide an estimate of BMD and a comparison to a normative data cohort for interpretation, including T-Score and Z-Score determination.

Indications for Use

Substantial equivalence is also supported for the OsDx Hip BMD System by the predicate devices previously cited and cleared in the treatment for the estimation of BMD.

TESTING IN SUPPORT OF SUBSTANTIAL EQUIVALENCE DETERMINATION

The device design was evaluated using standard methods for evaluation of BMD estimates in patient populations including patients across the spectrum of age. Software validation was performed using standard techniques.

SUMMARY

Based on the similarities in analytical approach, anatomic site evaluated and technological characteristics, the OsDx Hip BMD System is substantially equivalent to the devices currently marketed under the Federal Food, Drug and Cosmetic Act. In addition OsDx Hip BMD System raises no new safety or effectiveness issues.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 16 2008

Patrick Hess, Ph.D.
Chief Executive Officer
Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
REDWOOD CITY CA 94063

Re: K082402
Trade/Device Name: Imaging Therapeutics OsDx Hip BMD System
Regulation Number: 21 CFR 892.1170
Regulation Name: Bone densitometer
Regulatory Class: II
Product Code: KGI
Dated: August 15, 2008
Received: August 20, 2008

Dear Dr. Hess:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

21 CFR 876.xxx	(Gastroenterology/Renal/Urology	240-276-0115
21 CFR 884.xxx	(Obstetrics/Gynecology)	240-276-0115
21 CFR 894.xxx	(Radiology)	240-276-0120
Other		240-276-0100

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometrics' (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Joyce M. Whang, Ph.D.
Acting Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K 082402

Device Name: Imaging Therapeutics OsDx Hip BMD SYSTEM

Indications for Use:

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20 – 39) and age matched normals to compute T-scores and Z-scores respectively.

Prescription Use ___x____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (Part 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-

CONTINUE ON ANOTHER PAGE IF NEEDED)

(Division Sign-Off)
Division of Reproductive, Abdominal and Radiological Devices
510(k) Number K082402

Document Cover Sheet:

Date of Submission	08/15/2008
Description	OSDX HIP BMD SYSTEM
Date of Scan	*AAC4 03/24/2011*
Document Prep	*AAC4 03/24/2011*
Scanner	*AAC4 03/24/2011*
Image Quality Reviewer	

K082402 - K7043

FSR0203-003

--978045-MAR2402031 3

DOCUMENTS EXPECTED	DOCUMENT DATE	PAGE# START	PAGE# END	PAGE IN DOC	INDEXER
Decision Letter	10/16/08	1	2	3	
Indications for Use	10/16/08	3	3	2	
Reviewer Memorandum	10/16/08	4	5	3	
Reviewer Notes	10/14/08	6	9	5	
510K Decision Tree		10	10	2	
Reviewer Notes	10/08/08	11	21	12	
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Cover Letter	08/15/08	27	27	2	
Contents	08/15/08	28	172	146	
Attachments	08/15/08	173	262	91	

PAGE SUMMARY	
Total Documents:	8
Total Document Pages:	262
Total Separator Pages:	11
Total Scan Pages:	273

Document Cover Sheet:

K082402 - K7043

FSR0203-003

Date of Submission	08/15/2008
Description	OSDX HIP BMD SYSTEM
Date of Scan	*Enter Date of Scan Here*
Document Prep	*Enter Document Prep Here*
Scanner	*Enter Scanner Here*
Image Quality Reviewer	

DOCUMENTS EXPECTED	DOCUMENT DATE	PAGE# START	PAGE# END	PAGE IN DOC	INDEXER

QC Signature

QC Bar Code Sticker

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 1 6 2008

Patrick Hess, Ph.D.
Chief Executive Officer
Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
REDWOOD CITY CA 94063

Re: K082402
Trade/Device Name: Imaging Therapeutics OsDx Hip BMD System
Regulation Number: 21 CFR 892.1170
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Received: August 20, 2008

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Sincerely yours,

Joyce M. Whang, Ph.D.
Acting Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K 082402

Device Name: Imaging Therapeutics OsDx Hip BMD SYSTEM

Indications for Use:

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20 – 39) and age matched normals to compute T-scores and Z-scores respectively.

Prescription Use ___x____ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (Part 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-

CONTINUE ON ANOTHER PAGE IF NEEDED)

(Division Sign-Off)
Division of Reproductive, Abdominal and Radiological Devices
510(k) Number K082402

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-40
9200 Corporate Blvd.
Rockville, Maryland 20850

August 21, 2008

IMAGING THERAPEUTICS, INC.
400 SEAPORT COURT, SUITE 250
REDWOOD CITY, CA 94063
ATTN: PATRICK HESS

510(k) Number: K082402
Received: 20-AUG-2008
Product: OSDX HIP BMD SYSTEM

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification, (510(k)), you submitted in accordance with Section 510(k) of the Federa Food, Drug, and Cosmetic Act(Act) for the above referenced product and for the above referenced 510(k) submitter. Please note, if the 510(k) submitter is incorrect, please notify the 510(k) Staff immediately. We have assigned your submission a unique 510(k) number that is cited abov Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. We will notify you whe the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (DMC)(HFZ-401) at the above letterhead address. Correspondence sent to any address other than the one above will not be considered as part of your official 510(k) submission.

On September 27, 2007, the President signed an act reauthorizing medica device user fees for fiscal years 2008 - 2012. The legislation - the Medical Device User Fee Amendments of 2007 is part of a larger bill, th Food and Drug Amendments Act of 2007. Please visit our website at http://www.fda.gov/cdrh/mdufma/index.html for more information regardin fees and FDA review goals. In addition, effective January 2, 2008, any firm that chooses to use a standard in the review of ANY new 510(k) nee to fill out the new standards form (Form 3654) and submit it with their 510(k). The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf.

We remind you that Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the PHS Act by adding new sectio 402(j) (42 U.S.C. ' 282(j)), which expanded the current database known ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Section 402(j) requires that a certification form (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf) accompany 510(k)/HDE/PMA submissions. The agency has issu

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a draft guidance titled: "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Foo and Drug Administration Amendments Act of 2007" (http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html). According to the draft guidance, 510(k) submissions that do not contain clinical data do not need the certification form.

Please note the following documents as they relate to 510(k) review:
1)Guidance for Industry and FDA Staff entitled, "Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs and BLA Supplements". This guidance can be found at http://www.fda.gov/cdrh/ode/guidance/1655.pdf. Please refer to this guidance for information on a formalized interactive review process.
2)Guidance for Industry and FDA Staff entitled, "Format for Traditional and Abbreviated 510(k)s". This guidance can be found at www.fda.gov/cdrh/ode/guidance/1567.html. Please refer to this guidance for assistance on how to format an original submission for a Traditiona or Abbreviated 510(k).

In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, HDE) with an electron copy. For more information about the program, including the formatting requirements, please visit our web site at www.fda.gov/cdrh/elecsub.html.

Lastly, you should be familiar with the regulatory requirements for medical devices available at Device Advice www.fda.gov/cdrh/devadvice/" If you have questions on the status of your submission, please contact DSMICA at (240) 276-3150 or the toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsma/dsmastaf.html. If you have procedural questions, please contact the 510(k) Staff at (240)276-4040.

Sincerely yours,

Marjorie Shulman
Supervisory Consumer Safety Officer
Office of Device Evaluation
Center for Devices and Radiological Heal

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

August 20, 2008

IMAGING THERAPEUTICS, INC.
400 SEAPORT COURT, SUITE 250
REDWOOD CITY, CA 94063
ATTN: PATRICK HESS

510(k) Number: K082402
Received: 20-AUG-2008
User Fee ID Number: 6038069
Product: OSDX HIP BMD SYSTEM

The Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and the FDA Amendments Act of 2007 (FDAAA) (Public Law 110-85), authorizes FDA to collect user fees for certain types of 510(k) submissions. The submission cannot be accepted for review until the fee is paid in full ; therefore, the file has been placed on hold. When your user fee payment has been received , review of the 510(k) will resume as of that date. Alternatively, you may request withdrawal of your submission. Please send a check to one of the addresses listed below:

By Regular Mail	By Private Courier(e.g.,Fed Ex, UPS, etc.)
Food and Drug Administration P.O. Box 956733 St. Louis, MO 63195-6733.	U.S. Bank 956733 1005 Convention Plaza St. Louis, MO 63101 (314) 418-4983

The check should be made out to the Food and Drug Administration referencing the payment identification number, and a copy of the User Fee Cover sheet should be included with the check. A copy of the Medical Device User Fee Cover Sheet should be faxed to CDRH at (240)276-4025 referencing the 510(k) number if you have not already sent it in with your 510(k) submission. After the FDA has been notified of the receipt of your user fee payment, your 510(k) will be filed and the review will begin. If payment has not been received within 30 days, your 510(k) will be deleted from the system. Additional information on user fees and how to submit your user fee payment may be found at www.fda.gov/oc/mdufma.

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In all future premarket submissions, we encourage you to provide an electronic copy of your submission. By doing so, you will save FDA resources and may help reviewers navigate through longer documents more easily. Under CDRH's e-Copy Program, you may replace one paper copy of any premarket submission (e.g., 510(k), IDE, PMA, or HDE) with an electronic copy. For more information about the program, including the formatting requirements, please visit our web site at www.fda.gov/cdrh/elecsub.html.

Please note that since your 510(k) has not been reviewed, additional information may be required during the review process and the file may be placed on hold once again. If you are unsure as to whether or not you need to file a 510k Submission with FDA or what type of submission to submit, you should first telephone the Division of Small Manufacturers, International and Consumer Assistance (DSMICA), for guidance at (240) 276-3150 or its toll-fee number (800)638-2041, or contact them at their Internet address www.fda.gov/cdrh/dsma/dsmastaf.html, or you may submit a 513(g) request for information regarding classification to the Document Mail Center at the address above. If you have any questions concerning receipt of your payment, please contact Christina Zeender at Christina.Zeender@fda.hhs.gov. If you have questions regarding the status of your 510(k) Submission, please contact DSMICA at the numbers or address above.

Sincerely yours,

Diane M. Garcia
Public Affairs Specialist
Office of Device Evaluation
Center for Devices and
Radiological Health

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K082402

Form Approved: OMB No. 0910-511 Expiration Date: January 31, 2010. See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
MEDICAL DEVICE USER FEE COVER SHEET

PAYMENT IDENTIFICATION NUMBER: (b)(4) (b)(4)
Write the Payment Identification number on your check.

A completed cover sheet must accompany each original application or supplement subject to fees. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment and mailing instructions can be found at: http://www.fda.gov/oc/mdufma/coversheet.html

1. COMPANY NAME AND ADDRESS (include name, street address, city state, country, and post office code)

IMAGING THERAPEUTICS INC
400 Seaport Ct.,Suite 250
Redwood City CA 94063
US

1.1 EMPLOYER IDENTIFICATION NUMBER (EIN)
(b)(4) (b)(4)

2. CONTACT NAME
Partick Hess

2.1 E-MAIL ADDRESS
partick.hess@imatx.com

2.2 TELEPHONE NUMBER (include Area code)
949-4669525

2.3 FACSIMILE (FAX) NUMBER (Include Area code)
650-2864160

3. TYPE OF PREMARKET APPLICATION (Select one of the following in each column; if you are unsure, please refer to the application descriptions at the following web site: http://www.fda.gov/dc/mdufma

Select an application type:
[X] Premarket notification(510(k)); except for third party
[ ] 513(g) Request for Information
[ ] Biologics License Application (BLA)
[ ] Premarket Approval Application (PMA)
[ ] Modular PMA
[ ] Product Development Protocol (PDP)
[ ] Premarket Report (PMR)
[ ] Annual Fee for Periodic Reporting (APR)
[ ] 30-Day Notice

3.1 Select one of the types below
[X] Original Application
Supplement Types:
[ ] Efficacy (BLA)
[ ] Panel Track (PMA, PMR, PDP)
[ ] Real-Time (PMA, PMR, PDP)
[ ] 180-day (PMA, PMR, PDP)

4. ARE YOU A SMALL BUSINESS? (See the instructions for more information on determining this status)
[X] YES, I meet the small business criteria and have submitted the required qualifying documents to FDA
NO, I am not a small business

4.1 If Yes, please enter your Small Business Decision Number: SBD087011

5. IS THIS PREMARKET APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCEPTIONS? IF SO, CHECK THE APPLICABLE EXCEPTION.

[ ] This application is the first PMA submitted by a qualified small business, including any affiliates, parents, and partner firms

[ ] This biologics application is submitted under secion 351 of the Public Health Service Act for a product licensed for further manufacturing use only

[ ] The sole purpose of the application is to support conditions of use for a pediatric population

[ ] The application is submitted by a state or federal government entity for a device that is not to be distributed commercially

6. IS THIS A SUPPLEMENT TO A PREMARKET APPLICATION FOR WHICH FEES WERE WAIVED DUE TO SOLE USE IN A PEDIATRIC POPULATION THAT NOW PROPOSES CONDITION OF USE FOR ANY ADULT POPULATION? (If so, the application is subject to the fee that applies for an original premarket approval application (PMA).)

[ ] YES [X] NO

7. USER FEE PAYMENT AMOUNT SUBMITTED FOR THIS PREMARKET APPLICATION
(b)(4) (b)(4)
19-Aug-2008

Form FDA 3601 (01/2007)

"Close Window" Print Cover sheet

K7

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Imaging Therapeutics

August 15, 2008

Food and Drug Administration
Center for Devices and Radiological Health
510(k) Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

FDA CDRH DMC

AUG 20 2008

Received

Dear Reader:

Submitted in duplicate with this letter is a Pre-Market Notification ("510-K") for the Imaging Therapeutics OsDx Hip BMD System.

The following information is provided to identify this submission:

TYPE OF SUBMISSION	Traditional 510(k)
DATE OF APPLICATION	August 15, 2008
DEVICE NAME	OsDx Hip BMD System
CLASSIFIATION NAME	Bone Mineral Densitometer
CLASSIFICATION	Class II
PRODUCT CODE	KGI
CONTACT	Patrick Hess, PhD Chief Executive Officer Imaging Therapeutics, Inc. 400 Seaport Court, Suite 250 Redwood City, CA 94063 Phone: 650.286.4166 Email: Patrick.hess@imatx.com

A copy of the CDRH 510(k) Screening Checklist has been completed and is included as the initial page of the submission. A copy of the Medical Device User Fee Cover Sheet is also attached.

Any questions regarding this submission should be addressed to the undersigned.

Sincerely,

Patrick Hess

Patrick Hess, PhD, MBA

400 Seaport Court, Suite 250
Redwood City, CA 94063
650.286.4151 650.286.4160 fax

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CDRH's 510(k) SCREENING CHECKLIST

Imagining Therapeutics OsDx HIP BMD SYSTEM

	Present or Omission Justified	Inadequate or Missing
Cover letter containing the elements listed on page 3-2 of the Pre-Market Notification Manual	YES	

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Truthful and Accurate Statement	Page	001
Device's trade name, classification name and establishment registration number	Page	004
Device classification regulation number and regulatory status	Page	004
Proposed labeling including the material listed on page 3-4 of the Premarket Notification Manual	Page	010
Statement of Indications for Use, on a separate page	Page	003
Substantial equivalence comparison, including comparisons of the new device with the predicate device(s) in areas that are listed on page 3-4 of the Premarket Notification Manual	Page	068
510(k) Summary or Statement	Summary Page	006
Description of the device including diagrams, engineering drawings, photographs or service manuals	Page	008
Identification of legally marketed predicate device	Pages	069
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Biocompatibility data for all patient-contacting materials OR certification of identical material/formulation	Not Applicable	---
Sterilization and expiration dating information	Page	101
Software Documentation	Page	102

IMAGING THERAPEUTICS, INC

510(k) Premarket Notification

for the

OsDx HIP BMD SYSTEM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	(b)(4) (b)(4)	(b)(4) (b)(4)

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Patrick Hess, PhD	Chief Executive Officer
FIRM/ORGANIZATION Imaging Therapeutics, Inc. 400 Seaport Ct, Suite 250, Redwood City, CA 9406+2	
SIGNATURE Patrick Hess	DATE 8.15.08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

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See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 06-30-2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
Imaging Therapeutics, Inc.

2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
August 15, 2008

3. ADDRESS *(Number, Street, State, and ZIP Code)*
Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
Redwood City, CA 94063

4. TELEPHONE AND FAX NUMBER *(Include Area Code)*
(Tel.) 650.286.4166
(Fax) 650.286.4160

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
(Attach extra pages as necessary)

OsDx Hip BMD System (Bone Mineral Densitometer)

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☒ 510(k) ☐ PDP ☐ Other

7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*

8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

☒ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/ SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

NCT Number(s):

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.
Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)
Patrick Hess, PhD

12. NAME AND TITLE OF THE PERON WHO SIGNED IN NO. 11
(Name) Patrick Hess, PhD
(Title) Chief Executive Officer

13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in No. 11 and 12)*
Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
Redwood City, CA 94063

14. TELEPHONE AND FAX NUMBER *(Include Area Code)*
(Tel.) 650.286.4166
(Fax) 650.286.4160

15. DATE OF CERTIFICATION

FDA-3674 (1/08) (FRONT)

PSC Graphics: (301) 443-1090 EF

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Imaging Therapeutics, Inc.

OsDx Hip BMD System

510(k) Premarket Notification

PREMARKET NOTIFICATION
TRUTHFUL AND ACCURATE STATEMENT
(As required by 21 CFR 807.87(j))

I certify that, in my capacity as Chief Executive Office of Imaging Therapeutics, Inc. to the best of my knowledge, all data and information submitted in this pre-market notification are truthful and accurate and that no material fact has been omitted.

Patrick Hess

Signature

8.15.08

Date

Patrick Hess, PhD
Chief Executive Officer
Imaging Therapeutics, Inc.

Imaging Therapeutics, Inc.

OsDx HIP BMD System

510(k) Premarket Notification

CONFIDENTIALITY STATEMENT

The information contained in this Premarket Notification is trade secret confidential information and should not be disclosed under the Freedom of Information Act, even after the existence of the submission becomes public. Consequently, we respectfully request that you consult with the contact person identified for this submission prior to disclosing any information pertaining to this submission.

510(k) Number: K _____

Device Name: Imaging Therapeutics OsDx Hip BMD SYSTEM

Indications for Use:

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20 – 39) and age matched normals to compute T-scores and Z-scores respectively.

Prescription Use ___x____ (Part 21 CFR 801 Subpart D)	AND/OR	Over-The-Counter Use _____ (Part 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-

CONTINUE ON ANOTHER PAGE IF NEEDED)

SECTION 1

GENERAL INFORMATION

a. Company Contact

Patrick Hess, PhD
Chief Executive Officer
Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
Redwood City, CA 94063
Phone 650-286-4166
FAX 650-286-4160

b. Trade/Proprietary Name

OsDx Hip BMD System

c. Common/Classification Name

Bone Mineral Densitometer

Establishment Registration

Pending

d. Manufacturing and Sterilization Facility Information

The OsDx Hip BMD System is manufactured by

Imaging Therapeutics, Inc.
400 Seaport Court, Suite 250
Redwood City, CA 94063
Phone 650-286-4166
FAX 650-286-4160

The device is not sterilized

e. Device Classification

Class II - 21 CFR §892.1170
Product Code: KGI

f. Reason for Premarket Notification

The purpose of this 510(k) notice is to obtain clearance to market the OsDx Hip BMD System, which is substantially equivalent to other FDA-approved devices currently in commercial distribution.

g. Substantial Equivalence

The OsDx Hip BMD System is substantially equivalent toe the following devices:

Technological Characteristics and Indication for Use
CTXA Hip: K002113 Pronosco X-Posure System Bone Densitometer: K984178 Hologic Hip Structural Analysis Software K061561 Advanced Hip Assessment (AHA) Software for GE Prodigy x-ray bone densitometers: K011917

SECTION 2

510(k) SUMMARY OF SAFETY AND EFFECTIVENESS

This summary of the 510(k) Premarket Notification for the Imaging Therapeutics OsDx Hip BMD System is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

SECTION 2

510(k) SUMMARY OF SAFETY AND EFFECTIVENESS

This summary of the 510(k) Premarket Notification for the Imaging Therapeutics OsDx Hip BMD System is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

PREDICATE DEVICES

The Imaging Therapeutics OsDx Hip BMD System is substantially equivalent to FDA-approved predicate devices with regard to indications for use and technological characteristics. These predicate devices are:

Technological Characteristics and Indication for Use
• CTXA Hip: K002113 • Pronosco X-Posure System Bone Densitometer: K984178 • Hologic Hip Structural Analysis Software K061561

INTENDED USE

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20 – 39) and age matched normals to compute T-scores and Z-scores respectively.

PRODUCT DESCRIPTION

The OsDx Hip BMD System is a software package that provides an estimate of BMD based on analysis of data derived from scanned hip X-rays. The program utilizes a quantitative bone structural algorithm that measures a composite of weighted cortical and trabecular parameters in proximal femur projection radiographs from which total hip bone mineral density (BMD) is mathematically derived. Image analysis can take place remotely or at the point of care.

The results, expressed as gm/cm^2, can be used for comparison to a reference data base of young normals (T-score) or age-matched controls (Z-Score).

SUBSTANTIAL EQUIVALENCE

Use of the Term "Substantial Equivalence"

The term "Substantial Equivalence" is used in this submission within the confines of the statutory use in the FDA's evaluation of a Pre-Market Notification Submission. Any statement regarding Substantial Equivalence used in this submission relates only to whether the device that is the subject of this submission may be lawfully marketed in the United States without pre-market approval or reclassification, and should not be interpreted as an admission, or any kind or type of evidence, in any patent proceeding, including patent infringement litigation or proceeding before any Patent Office.

The present submission and statements therefore should not be construed as affecting or relating to the scope of any patent or patent application, or to whether the product addressed in the submission, or its use, may be considered indistinct, from a patentability perspective, from any other device referred to in this sub mission.

Technological Characteristics

The technological characteristics (including anatomic site analyzed) of the OsDx Hip BMD System are substantially equivalent to those of the cited predicate devices. Standard x-ray images are scanned and evaluated to provide an estimate of BMD and a comparison to a normative data cohort for interpretation, including T-Score and Z-Score determination.

Indications for Use

Substantial equivalence is also supported for the OsDx Hip BMD System by the predicate devices previously cited and cleared in the treatment for the estimation of BMD.

TESTING IN SUPPORT OF SUBSTANTIAL EQUIVALENCE DETERMINATION

The device design was evaluated using standard methods for evaluation of BMD estimates in patient populations including patients across the spectrum of age. Software validation was performed using standard techniques.

SUMMARY

Based on the similarities in analytical approach, anatomic site evaluated and technological characteristics, the OsDx Hip BMD System is substantially equivalent to the devices currently marketed under the Federal Food, Drug and Cosmetic Act. In addition OsDx Hip BMD System raises no new safety or effectiveness issues.

SECTION 3

DEVICE LABELING

(a) Draft Operator Manual, including Instructions for Use
A draft copy of Operator Manual is provided for review

(b) Draft Patient Information Leaflet
A draft copy of the draft Patient Information material to be made available to users of the OsDx System is provided for review.

DRAFT OPERATOR MANUAL/INSTRUCTIONS FOR USE

OsDx Hip BMD System

OsDx

Hip Analysis Module

Version 1.2

User's Manual

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About Imaging Therapeutics ("ImaTx")

ImaTx has developed unique proprietary software to diagnose and monitor osteoporosis and osteoarthritis.

Our image-based biomarkers provide fast, accurate, non-invasive and inexpensive tools to analyze bone and cartilage for supporting pharmacology clinical trials and investigational studies.

Our goal is to cost effectively fill unmet medical needs that permit:

- Large population screening for osteoporosis
- Fracture risk assessment
- Articular cartilage damage assessment
- Therapeutic monitoring of drug treatment

400 Seaport Ct, Suite 250

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General information email: info@imatx.com

Technical support email: techsupport@imatx.com

1. Introduction

This user manual provides reference information for the certified user on the correct use of Imaging Therapeutics' x-ray image assessment system, OsDx, with the Hip Analysis Module installed. This setup is referred to as OsDx Hip BMD System in this document.

1.1. Intended Use

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with referenced populations of young (20 – 39) and aged matched normals to compute T-scores and Z-scores respectively.

1.2. Training Requirements

Users of OsDx Hip BMD System must complete a training and certification process provided by Imaging Therapeutics.

1.3. Service and support

There are no service tasks that can be performed by the user. To obtain support, contact Imaging Therapeutics by email at techsupport@imatx.com or call 650-286-4151.

1.4. Overview

In the normal patient population, the proximal femur is composed of significant proportions of trabecular bone within the interior core. The structural arrangement and density of trabecular bone in conjunction with the cortical shell affects the overall femoral quality and strength. The OsDx Hip BMD System combines measurements of projected trabecular bone pattern, with cortical bone and geometric dimensions to estimate the total hip BMD. The estimation model was built using DXA BMD measurements of non-black women 65 years or older.

The OsDx Hip BMD System utilizes diagnostic quality hip and pelvic radiographs taken in the antero-posterior (AP) view. The next chapter provides details of acceptable image quality and describes recommended protocols that can be used to obtain usable images.

2. X-ray Imaging Protocol and Quality Criteria

The OsDx Hip BMD System can process x-rays from three radiographic views of the proximal femur. These are the standard AP unilateral hip x-ray (section 2.1), the AP bilateral hip x-ray, and AP full pelvis x-ray (section 2.2). In all the acceptable techniques, the femoral neck axis should be as parallel as possible to the imaging plane. To achieve this, the patient's leg is rotated internally 15° to 20° which can most easily be achieved using a positioning aid such as one shown in Figure 1 (described in section 2.1.2). The settings described in section 2.1.1 are specifically used in a screen-film radiography system. Other systems which use phosphorus plate computed radiography or direct digital flat panel require that a calibration and qualification process be conducted by the vendor to assure accurate results.

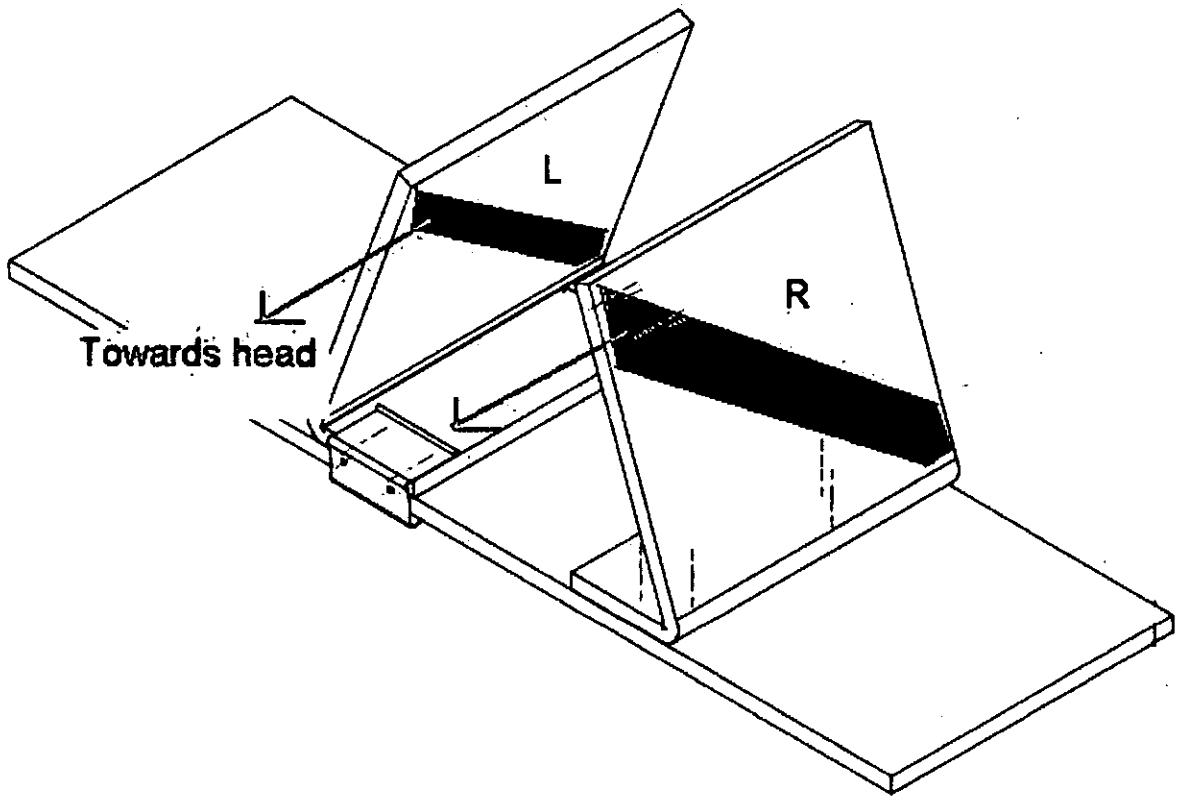

Figure 1. *Bilateral foot holder that aids in positioning both femora in order to achieve and maintain a correct and consistent femora rotation.*

2.1. AP Unilateral Hip X-ray Protocol

The AP hip x-ray protocol is the standard procedure for use with OsDx Hip BMD System. Section 2.1.2 shows a patient position procedure that will produce AP hip radiographs with the correct view of the femur. This protocol is applicable for all table-top x-ray systems.

2.1.1. Imaging Parameters for screen-film radiography

Conventional hip radiographs will be obtained in Antero-posterior (AP) projection with the following radiographic parameters and procedures:

View:	AP Unilateral Hip (Left preferred)
Film-focus distance:	40 inches (102 cm)
Tube voltage:	70-80kVp
Tube current:	150mA
Exposure:	Automatic Exposure Control using the ionizing chamber closest to the central ray.
Image Receptor size:	12" x 14" (30 x 36 cm) or larger film
Film-Screen:	400 speed
Positioning:	Supine, leg extended and rotated internally 15-20 degrees with both feet secured to the positioning aid with Velcro straps (Fig. 1).
Centering:	Center x-ray aiming cross to the center of left femoral neck (Fig. 2). Center image receptor to collimated x-ray field.
Shielding:	Use gonad shield.
Collimation:	12" x 14" (30x 36 cm)

2.1.2. Patient positioning

The use of a femur positioning device (**Fig. 1**) that produces and maintains 15° – 20° internal rotation of the femora is recommended because the OsDx algorithm has been calibration to perform optimally using images taken in this configuration. Rotate the leg such that the femoral neck axis is horizontal to the imaging plane. Figure 2 illustrates the correct positioning procedure. Figure 3 show the x-ray settings used in a screen-film system.

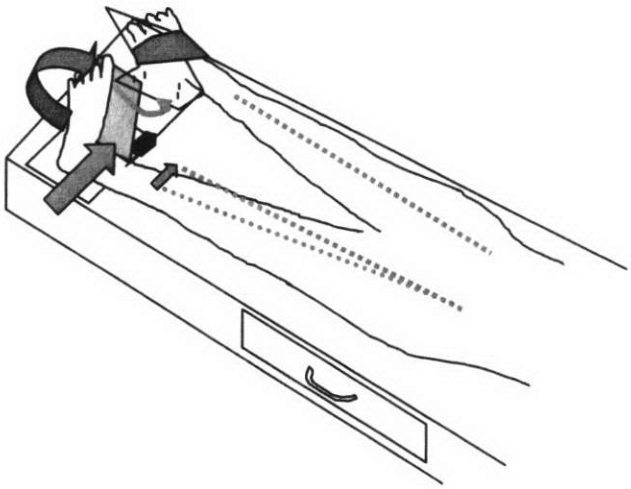

Figure 2. *Strap both feet to the positioning device. Slide the adjustable footrest so that legs are parallel*

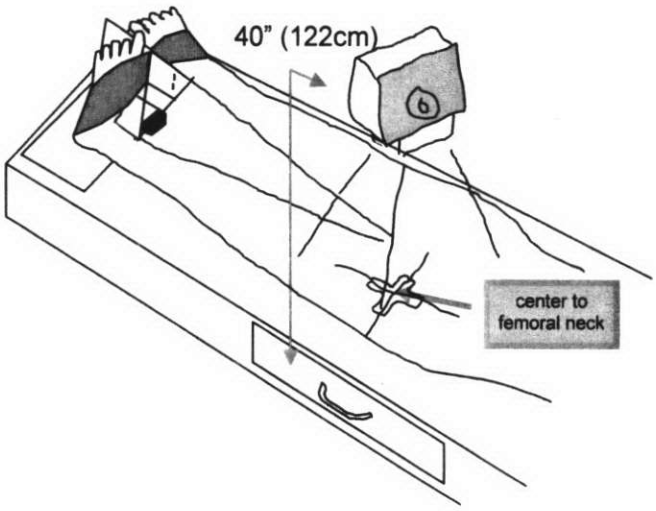

Figure 3. Adjust x-ray source height to 40" from film (in tray). Center x-ray aiming cross to left femoral neck. Shoot at 70 to 80 kVp (depending of subject size), 150 mA, using auto timer.

2.2. AP Bilateral Hip and Pelvic X-ray Protocols

Patient positioning and x-ray source height for the AP bilateral hip view is similar to that for AP unilateral hip except the center ray is midway between the femoral heads. For the AP pelvic view, the central ray is between the Anterior Superior Iliac Spine (ASIS) and symphysis pubis. Use the bilateral ionizing chambers for auto timing.

2.3. Existing image sources

Existing images to be analyzed using OsDx Hip BMD System will need to be qualified using the image quality criteria described in section 2.4. In addition, the vendor will conduct an equipment calibration & qualification process as described in section 2.5.

2.4. Image quality criteria

Images that can be analyzed using OsDx Hip BMD System must meet all the following criteria. Examples showing images that meet and fail to meet these criteria can be found in Chapter 7

Factors	**Criteria**
Resolution	Pixel/detector size 200 um or smaller (5 line /mm or finer)
Contrast	Diagnostic quality
View	Antero-Posterior Unilateral Hip, Bilateral Hip, or Pelvis
Femur Positioning	Inter-trochanteric crest not in the femoral neck region (see Figure 4. The left image shows a femur with acceptable internal rotation. Image on the right shows a femur with unacceptable external rotation. The dotted lines show the femoral neck-trochanteric boundary and arrows point to the ***inter-trochanteric crest.*** Processing done on images with improper femur positioning can produce incorrect measurements.
Phantom objects	Must <u>*not*</u> have phantom objects on or near the proximal femur

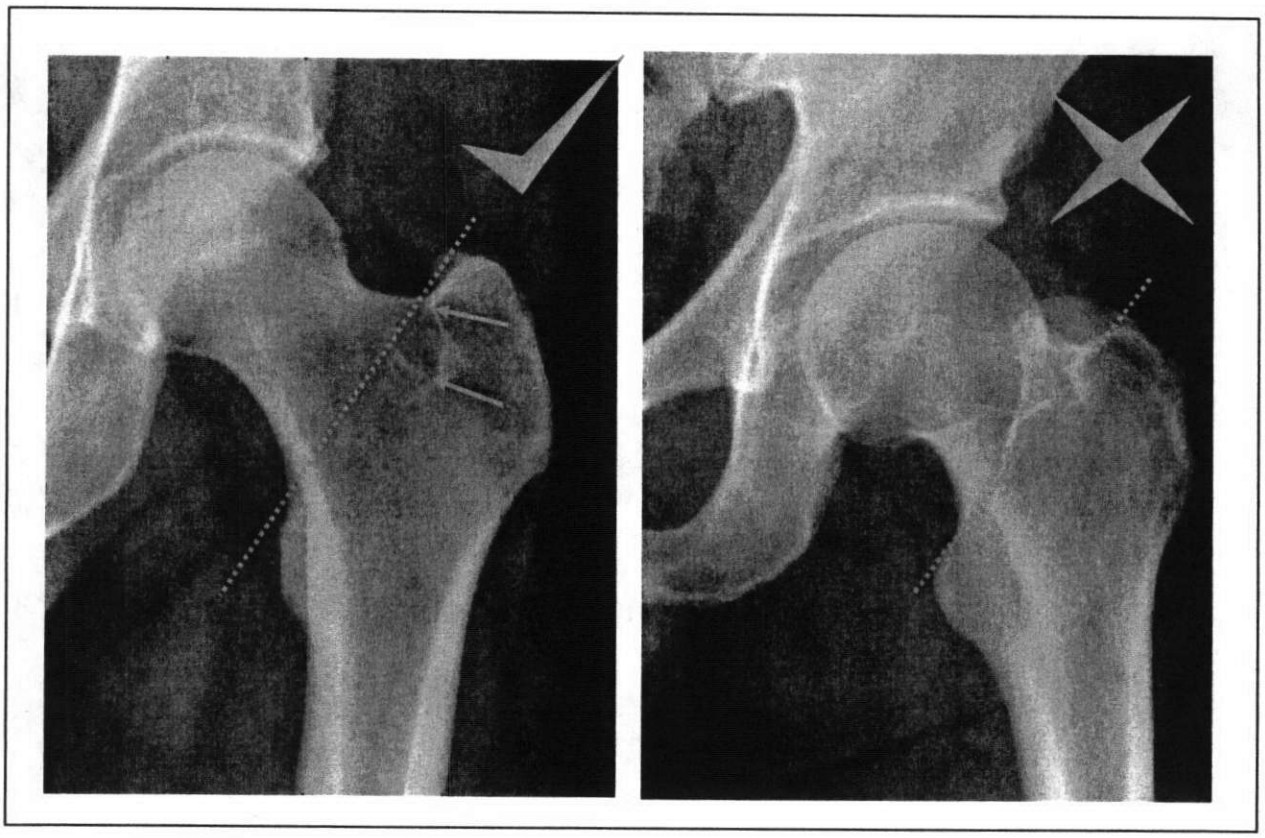

Figure 4. *The left image shows a femur with acceptable internal rotation. Image on the right shows a femur with unacceptable external rotation. The dotted lines show the femoral neck-trochanteric boundary and arrows point to the inter-trochanteric crest. Measurements done on images with improper femur positioning can produce incorrect results.*

2.5. Calibration & Qualification

Before images from an x-ray system can be analyzed, the vendor must first characterize the system. This includes taking images of a calibration phantom and an anthropomorphic phantom at various exposure settings and conditions. A number of in-vivo sample images will also be needed to complete the calibration and qualification process. Completion of this calibration and qualification process prior to use as a diagnostic device is essential to assure accurate diagnostic output.

3. Software Setup

3.1. Minimum system requirements

IBM Compatible PC with Pentium 4 2.8GHz / AMD Athlon 3400+ or better
SXGA Graphics driver capable of displaying 1280 x 1024 pixels
SXGA 17" Monitor capable of displaying 1280 x 1024 pixels
Windows XP
Minimum memory of 768MB
Free hard disk space of 500MB

3.2. Installation

Installation, including system calibration and installation validation, will be performed by an Imaging Therapeutics service engineer.

3.3. Software overview

The OsDx Hip BMD System analyzes digitized hip or pelvic radiographs stored on file systems accessible to the PC on which this software is installed. It currently does not support DICOM connectivity or manages the digitization/acquisition of radiographs. The OsDx Hip BMD System software has the following workflow and is described in detail in the named sections:

3.4 Options setup
3.5 Image loading
4.1 Region selection
4.3 Reference markers positioning
5 Image analysis
6 Reporting

An overview of the user interface functionalities is shown in Figure 5 next.

The following describe the functions of the user interface of OsDx Hip BMD System

A. Patient information display
B. Main image display panel
C. Options tab button displays the options control panel.
D. Process tab button displays the process control panel.
E. Image flipping buttons for vertical and horizontal transformations.
F. Contrast adjustment button for enhancing image visibility when necessary.
G. Help button brings up the user instruction document.
H. Position button starts the automatic region placement algorithm.
I. Analyze button starts the measurement and analysis process.
J. Report button brings up the analysis report page.
K. Manual button starts the manual region placement procedure.
L. Update button updates file list by applying the filtering syntax in K.
M. Image source location text box shows path of image source location.
N. Change directory button sets the image source location.
O. File list box contains file names with the extension or string pattern given in the file source text box. A single click on a file name loads the image for preview while a double-click opens the image onto the main display panel.
P. System status display.
Q. Preview display panel show the selected image (single clicked) in the file list box.

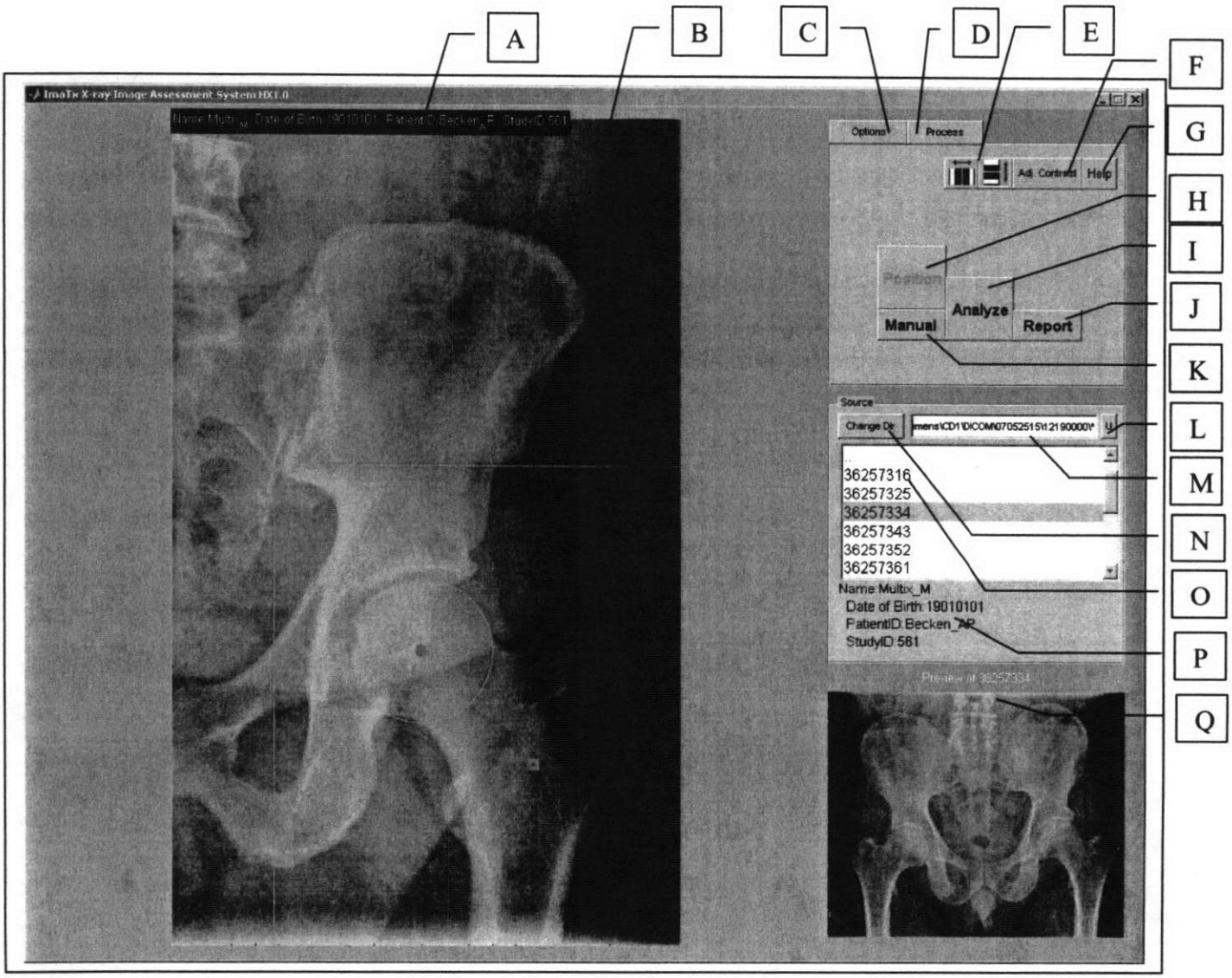

Figure 5. *Overview of software user interface functionalities.*

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3.4. Option settings

When the software starts, the options tab is the default plane on the control panel. If both the image type, and resolution of the images to analyze are known in advance the user can select the appropriate choices before loading the images. Otherwise, the options can be left in their default setting.

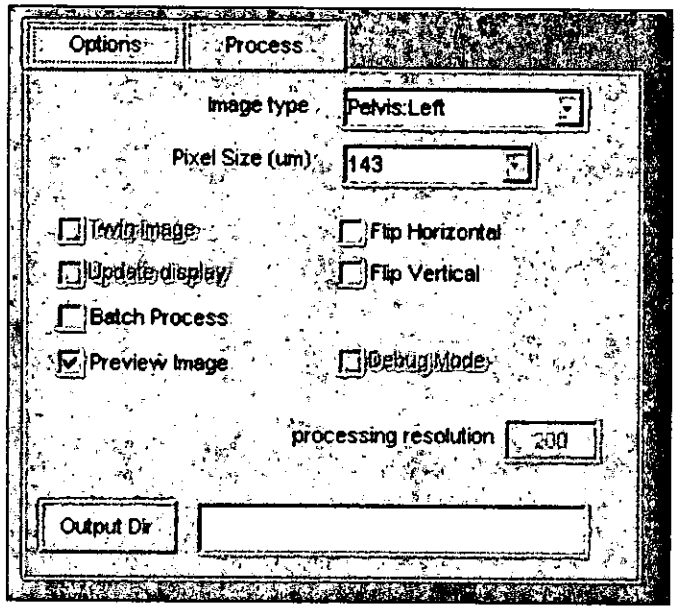

Figure 6. *The option tab allows the user to select image type, image resolution, enable preview, and image flipping.*

3.4.1. Image type selection

Set image type to the appropriate input image type. Select "Hip" for unilateral (single sided) AP images of the femur. When "Hip" is selected, the entire image will be load. Select Pelvis: Left or Pelvis:Right for opening a single side of Pelvis or Bilateral Hip x-rays. The pelvis x-ray will be cropped to only the side selected. This assumes images are in the correct orientation. If image type is not known in advanced, user can leave the setting in default and change as necessary.

3.4.2. Image resolution selection

The choices of image resolution will be customized to what is available at user's facility. If the DICOM header of images contains a valid entry of `DetectorElementPhysicalSize` or `ImagerPixelSpacing`, these parameters will be used as the true resolution of the image which overrides the selected setting. If an image does not have the expected size that is consistent with

the read or selected resolution, an error message will appear and the image cannot be processed until the resolution setting is corrected.

3.4.3. Flip vertical and flip horizontal checkboxes

OsDx Hip BMD System assumes images are stored in the correct orientation for direct viewing and retrieves them as is. However, if image orientation is consistently incorrect, the flip vertical and flip horizontal checkboxes, when checked, enable automatic image flipping as the images load. The flipping operations can also be done after loading through the *Process* control panel.

3.5. Opening image files

Locate image source using the **Source Image** button (**Figure 7**). Select the image file you would like to load first and click open or double click on the file. All the files in the directory with the same extension as the one selected will be listed in the file list box. To open the next file, double click on the file name in the list box. The list box will turn gray to indicate that the selected image is being acquired. *Note. Some images may take longer to open than others due to the image size.*

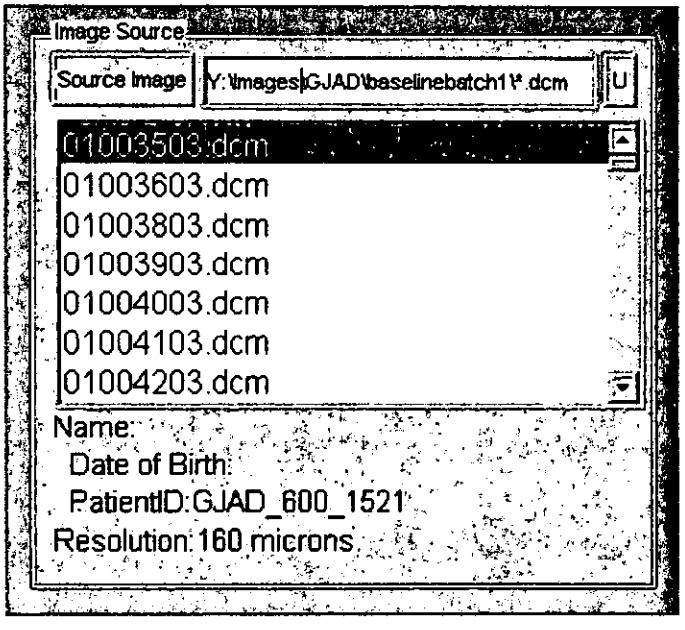

***Figure** 7. Locating image source and opening image file*

3.6. Data Output Directory

The output directory (Output Dir) on the Options control panel is the location where region placement data, processing screenshots, and analysis results are stored. It is automatically set by default to "ImaTxData" on the storage drive where OsDx is installed. A subfolder will be created using the directory names of the image source. For example, if the program is installed on F:\OsDx\ and image source is G:\HipXray\Fracture, the default output directory will be F:\ImaTxData\HipXRay_Fracture. User may edit or select any output directory if the default is not suitable.

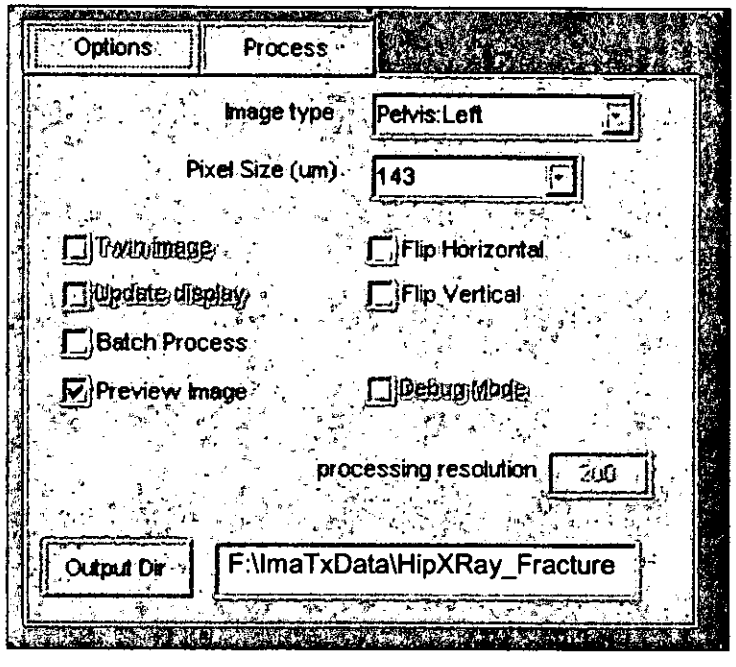

Figure 8. *Output directory is set by default to the program root location drive and using the directory names of image source.*

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4. Region selection

The positioning process in OsDx Hip BMD System is semi-automated and requires user inspection and adjustments. Qualified users must be trained in this process to ensure high measurement reliability and reproducibility. The positioning in general involves two steps: defining the processing window, and adjusting geometric markers. They are described in section **4.2** and section **4.3**.

4.1. Adjusting display contrast

At anytime during the region selection process, the user can adjust image contrast to improve positioning accuracy. The "Contrast Adj." (button F in as shown **Figure 5**) brings up the image histogram where user can move or change the windows of display range (red area in **Figure 9**). Display range is changed by moving the red handles with a held left mouse click, while display window is shifted by moving the red area. This adjustment only changes the display output and does not affect the image data or measurement results. Close the Adjust Contrast window when done.

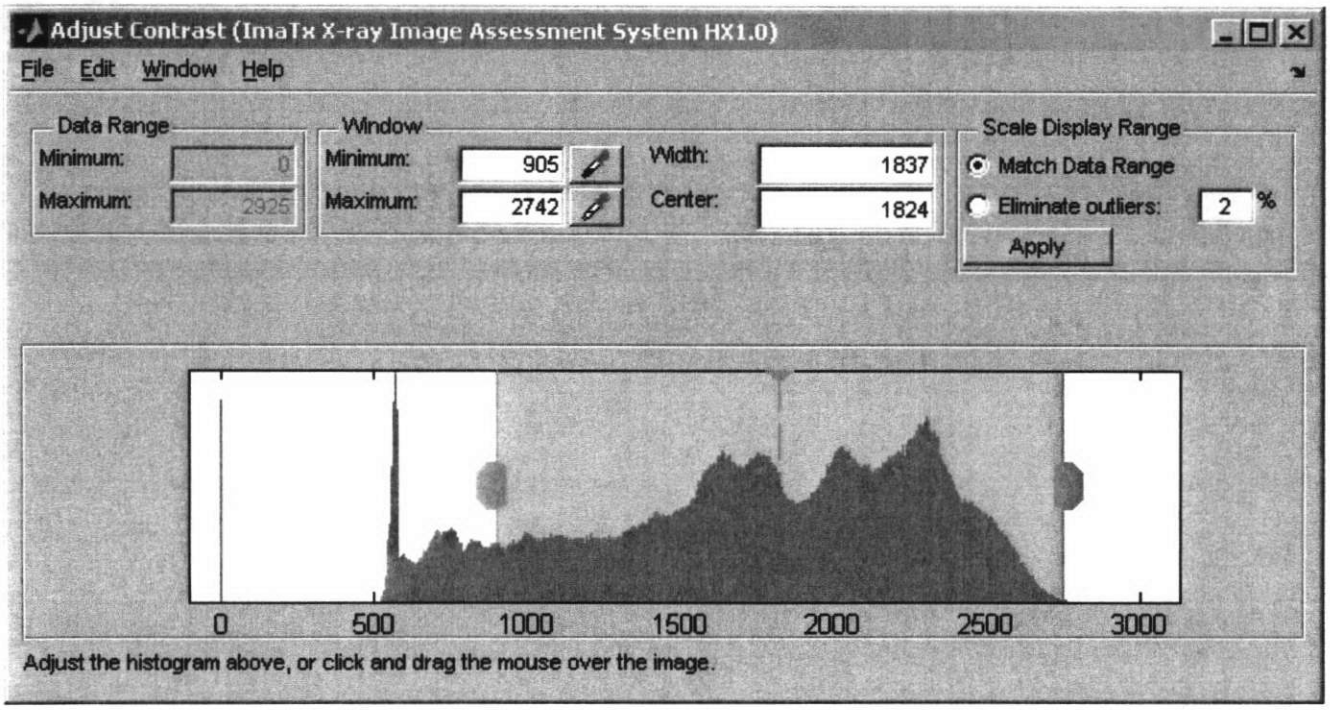

Figure 9. *Image display contrast adjustment using windows and leveling.*

4.2. Defining processing window

The processing window is a cropped rectangular region of the radiograph that includes the proximal femur. When an image is first loaded, a red rectangle should be seen enclosing the proximal femur region. You will also see a red circle (femoral head circle) that should be positioned to tightly enclose the femoral head. To position the femoral head circle, left click and hold the mouse button on circular

green handle as shown in **Figure 10**. Move the femoral head circle so that it outlines the articular surface of the femoral head.

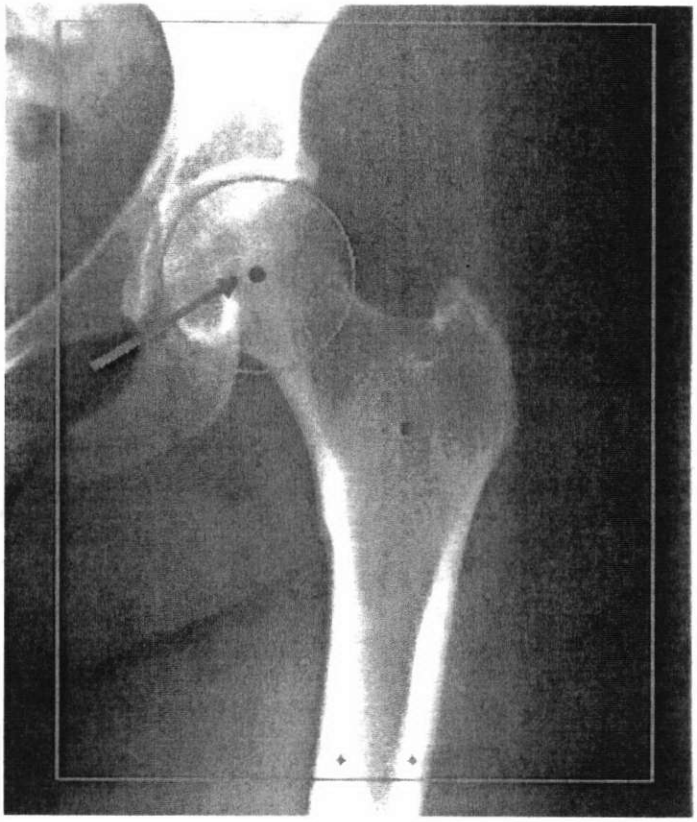

Figure 10. *Position femoral head circle using the circular green handle to enclose the femoral head.*

Next, adjust the size of the femoral head circle using the square green handle so that the circle is enclosing and just inside of the femoral head, **leaving no background region in the circle**. Repeat placement and sizing to improve fit. You will also notice that the processing window rectangle moves and resizes with the femoral head circle. **Figure 11** shows an ideal placement and sizing of the femoral head circle.

***Figure 11**. Adjust the size of the femoral head circle to tightly enclose the femoral head and leaving no background region in the circle. The figure shows an ideal placement and size of the femoral head circle.*

4.3. Adjusting geometric markers

When the femoral head circle is satisfactorily placed, click on the Position button (button H, **Figure 5**) on the Process control panel. This action crops the image as defined by the processing region window. You will now see some geometric markers, the already placed femoral head circle, and another circle in the trochanter region (trochanteric circle). Adjust the trochanteric circle using the circular handle for placement and square handle for sizing to such that it as large as it can be without infringing outside of the bone region. **Figure 12** shows the ideal placement and sizing of the trochanteric circle. Click Position again to update the geometric markers. If there is a need to readjust the trochanteric circle, you can do so and click Position to update markers.

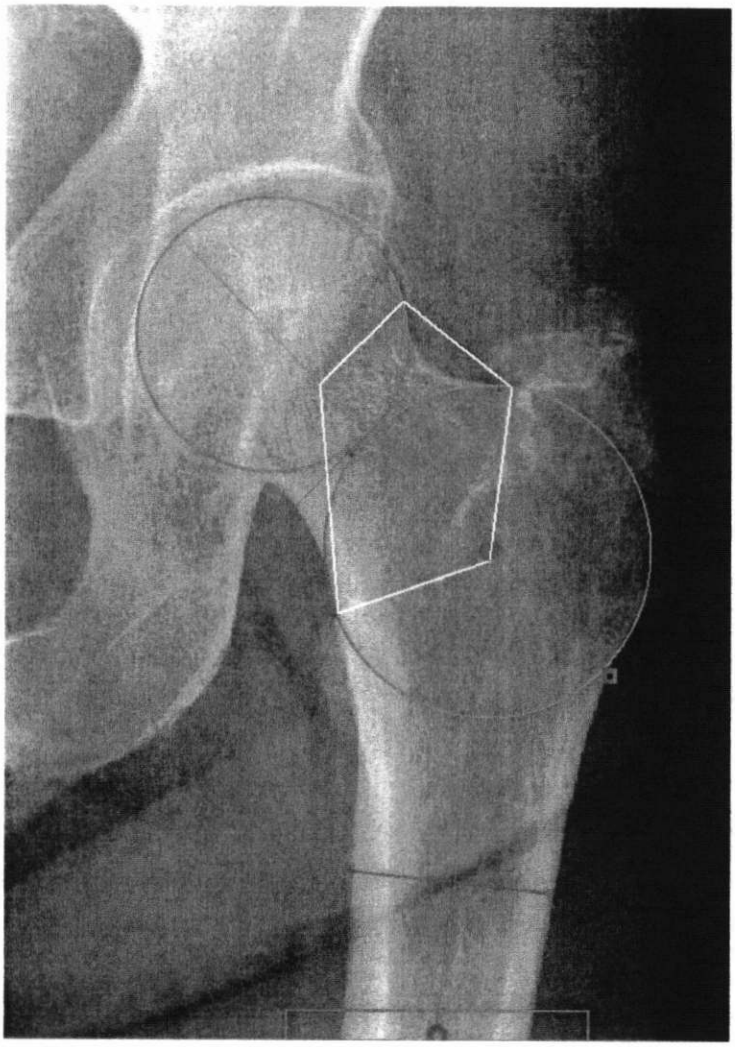

Figure 12. *Place geometric markers by fitting the trochanteric circle tightly within the trochanter region.*

4.4. Manual positioning

In some cases, image conditions prevent the semi-automatic pre-placement of the trochanteric circle. In such a case you will only see the femoral head circle. This can happen if the femur does not have an acceptable rotation angle (see **Figure 4)** which indicates that the image cannot be analyzed. If this is not the case, proceed with geometric marker placement by clicking the Manual button (button K, **Figure 5**). The trochanteric circle, and a rectangle (shaft pivot window) will appear. Place the trochanteric circle and the shaft pivot window as shown in **Figure 13** and click Position to initiate the geometric marker placement. If successful, you will see geometric markers place as seen in **Figure 12.** The shaft pivot window defines the region where the software searches for a pivot point for fitting the femoral shaft axis.

Figure 13 *Manual positioning of trochanteric circle and shaft pivot window.*

5. Image Analysis

Upon successful adjustment of geometric marker placement, start the image analysis by clicking the Analyze button (button I, **Figure 5**). At this point, all measurements are done automatically. When all measurements are complete, you will see a structural overlay and markers of geometric measurement on the femur as shown in **Figure 14** below. The report interface will also appear showing the results of analysis. Chapter 6 provides detail on using the report interface as well as the interpretation guide.

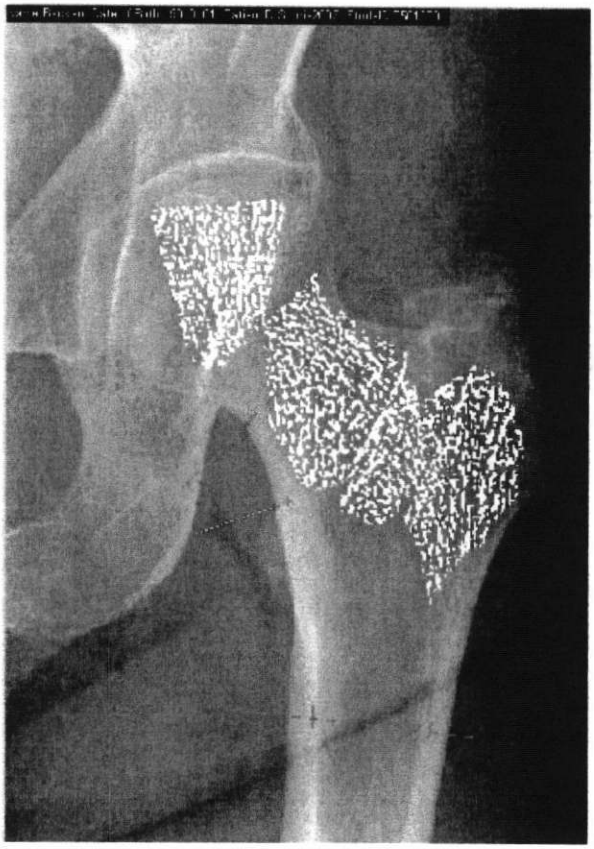

Figure 14. *Structural pattern and geometric measurement markers showing successful analysis.*

5.1. Data and report files

When the report interface appears, all measurements data will have been saved in the specified data output directory (see section 3.6 Data Output Directory). Three folders will be constructed under the data output directory. The data files type in these folders is described in **Table 1** below:

Table 1. Files in subfolders in the data output directory

File content	Filename pattern	Folder
CSV (comma separated values) of information presented on the report for all processing performing on day [date]. Each analysis result is stored in one line of	ImaTxbatch[date]report.csv	csv

the file.		
All raw data for measurements performed for the day [date]. Data from each run data is stored in one line of the file.	ImaTxbatch[date].csv	csv
Marker placement and region of interests data.	[filename]_roi.mat	data
Binary files of saved report. This file will be overwritten if the same image with filename [filename] is reanalyzed. Saved by and used by the report interface.	[filename]report.mat	data
Image files showing placed markers.	[filename]roi.png	img
Image files showing processed structures and measurement markers.	[filename]str.png	img

6. Report & Interpretation

6.1. Report overview

The report interface shown in

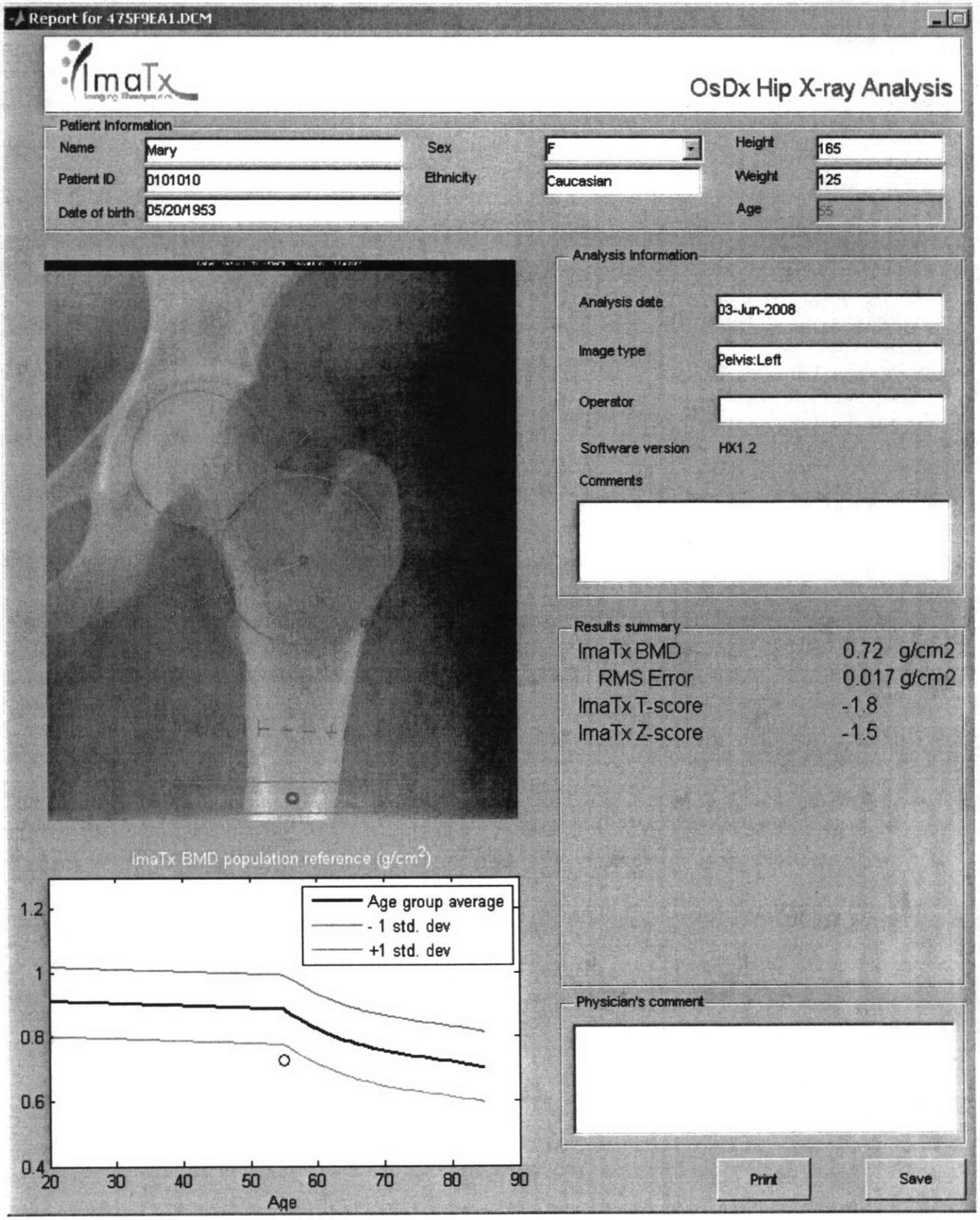

Figure *15* will appear when analysis is completed. It also can be evoked by clicking on the Report button (button J, **Figure 5**). If processing has not been completed when the report interface is invoked, it will not have the results displayed. However user can click on the Load button to open an existing report from the report folder. Clicking the print button generates a PDF file that is displayed using Adobe Reader. User can then print the report through the Adobe Reader interface. The save button will save any information updated by user. The report is automatically saved when it is first displayed and a resave will overwrite the initial save. The report interface is divided into the following sections:

6.2. Patient Information

Patient information that is available in the image header is automatically transferred to the corresponding fields. The user can edit the fields if the information is incorrect or empty.

Age is required for Z-score calculation and display of patient BMD on the reference curve. If age is not available from the image header, user will be prompted to key in the age and hit enter. To enter the age, click on the age field. The age field background will turn white. Enter the age and press the enter key. The report will be updated with the calculated Z-score value and reference curve.

6.3. Analysis Information

The analysis date and image type is automatically displayed. User can fill the operator name or initials and add any comments regarding the analysis or the patient.

6.4. Results summary

The BMD value estimate provided is a fitted approximation of the Total Hip BMD. This approximation model uses several of the parameters measured in hip x-rays and was fitted to available DXA measurements and Hip X-Rays from a group of non-black women 65 years or older selected from the Study of Osteoporotic Fractures.

The recommended interpretation of the BMD value provided is to be used as an estimate of the Total Hip BMD value that approximates a DXA Total Hip BMD measurement, if the patient is a non-black woman 65 years or older.

T-score is defined as the multiples of standard deviation that the BMD estimate is above or below the average BMD of women age 20-39, estimated using OsDx. The standard deviation is that of the BMD values in the said reference group.

Z-score is defined as the multiples of standard deviation that the BMD estimate is above or below the average BMD of women in the same age as the patient, estimated using OsDx. The standard deviation is the average of standard deviation of BMD in each age decade group having ages 20-29, 20-39, 40-49, 50-59, 60-69, 70-79, and 80-89.

6.5. Analysis image

The analysis image provides evidence that the image analyzed meets the quality criteria and the analysis was successful. User should note that the marker placement is correct as described in this manual (section 4.3, **Figure 12**), and cortical thickness markers are within the femoral shaft region as shown in **Figure 15.** The report is not valid if any of the conditions illustrated in Chapter 7 is seen.

6.6. Reference curves chart

The chart shows the reference database curves and assessment value of the patient. The circle represents the Hip Total BMD estimate of the patient (y-axis) given the age (x-axis). The black line represents the average BMD of the reference population across age groups. The green line represents BMD values one standard deviation above the average while the red line represents BMD values one standard deviation below the average across age groups.

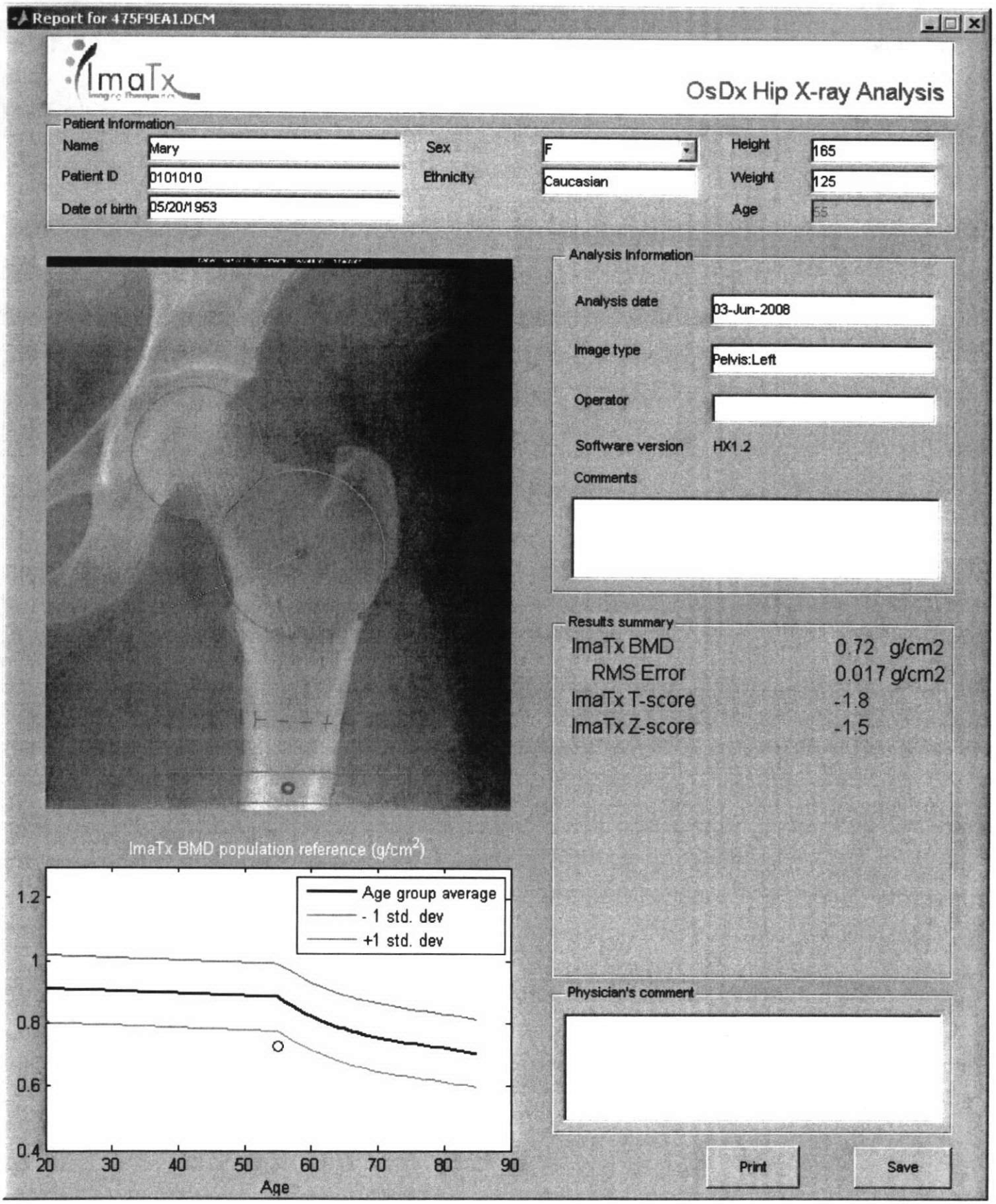

Figure 15 *Report layout of ImaTx OsDx Hip*

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7. Unacceptable image and conditions examples

The OsDx Hip BMD System can analyze most hip or pelvis radiographic images but may not provide meaningful measurements and results if the images do not meet the acceptable image quality criteria as described in section 2.4 Image quality criteria. This chapter provides examples of radiographs commonly encountered that do not meet the quality criteria.

7.1. Incorrect resolution

There could be cases where the image header contains incorrect resolution information for the image. When the software detects that the image size is not consistent with the provided resolution information, an error message will appear and the image cannot be further analyzed.

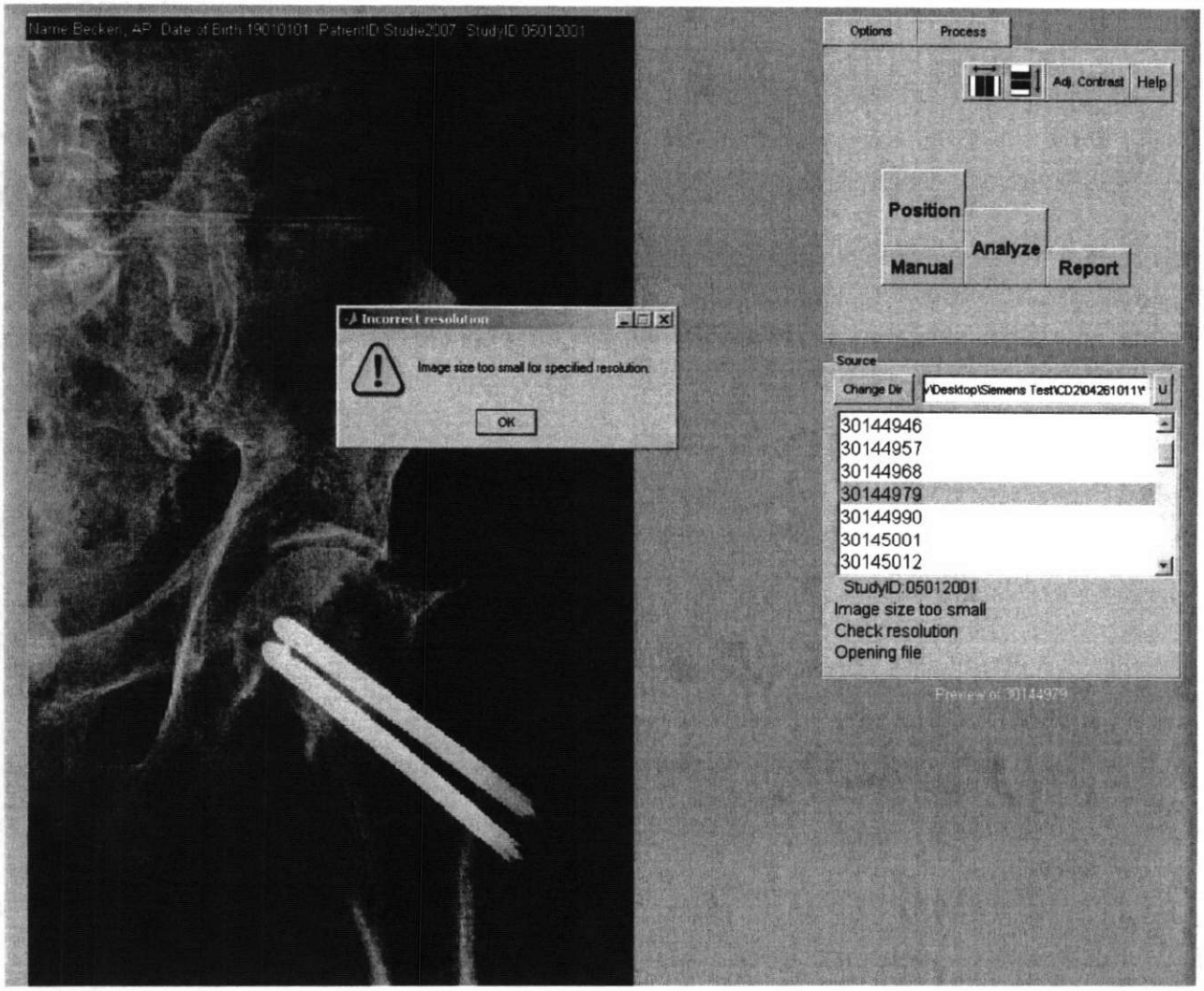

Figure 16. *An error message alerts user when image size is inconsistent with the resolution implied in image header.*

7.2. Objects in X-Ray

Images that show phantoms such as implants, stretcher, coins, labels, etc that are overlaying the proximal femur region cannot be analyzed.

Figure 17. *Images with phantom objects overlaying the proximal femur regions cannot be analyzed.*

7.3. Poor femur positioning

This image show a rotated femur that cannot be analyzed with OsDx Hip BMD System. Refer to section 2 for imaging protocol and guidelines for judging positioning acceptance.

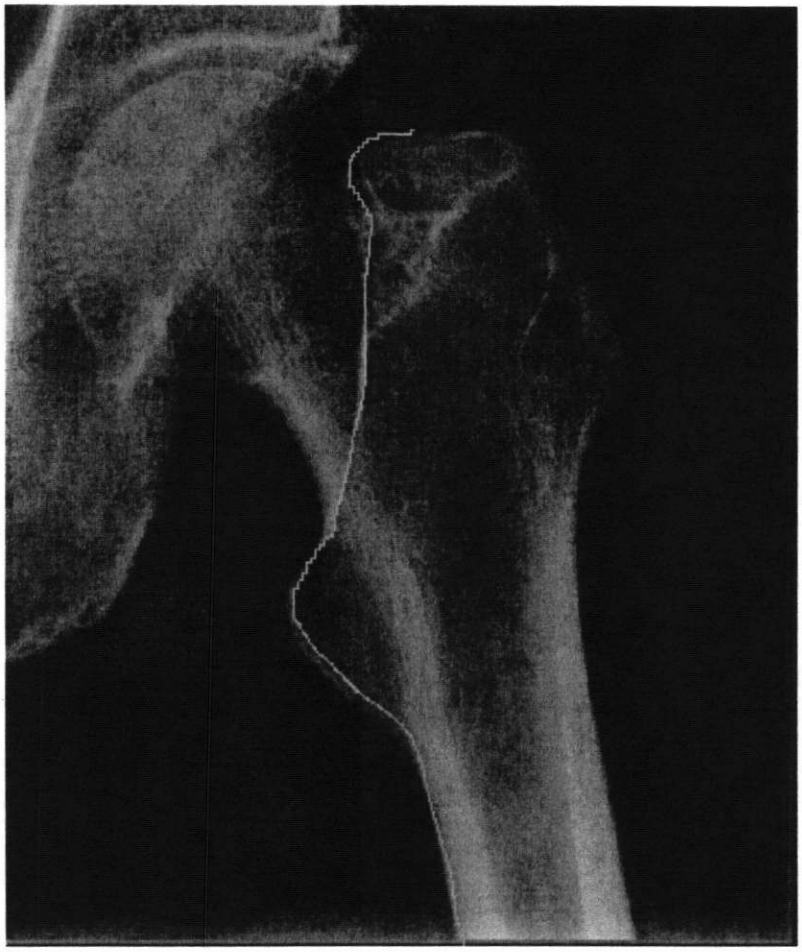

Figure 18. *Image with unacceptable femur positioning.*

7.4. Incorrect view

OsDx Hip BMD System analyzes AP hip and pelvis x-ray only. Figure below show an image taken with frog-leg view protocol that cannot be analyzed with OsDx Hip BMD System at this time.

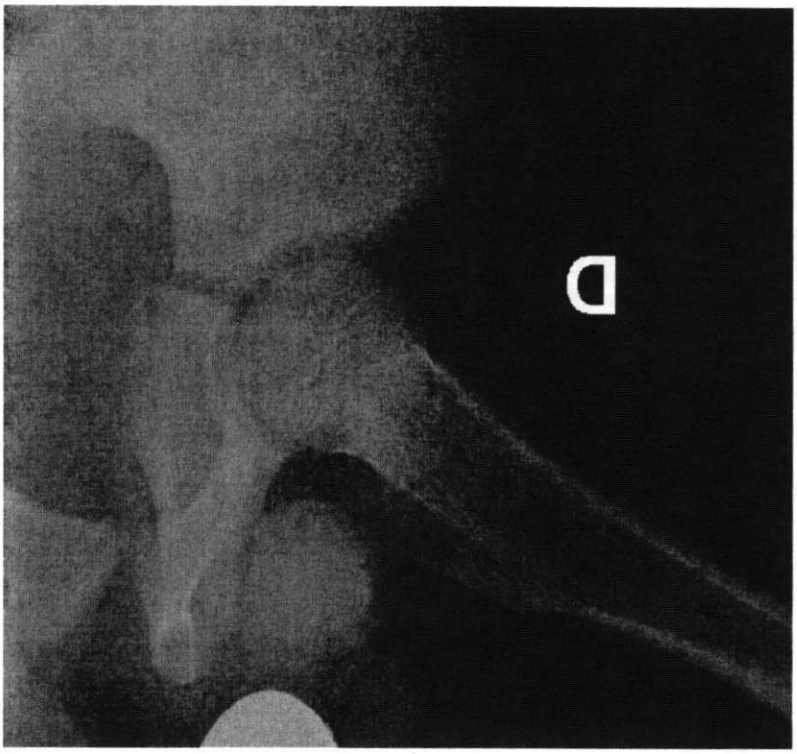

Figure 19. *Images taken with frog-leg protocol are not supported at this time.*

7.5. Fractured and abnormal femur

Fractured femur or femur with developmental anomalies may produce erroneous measurements and assessment results.

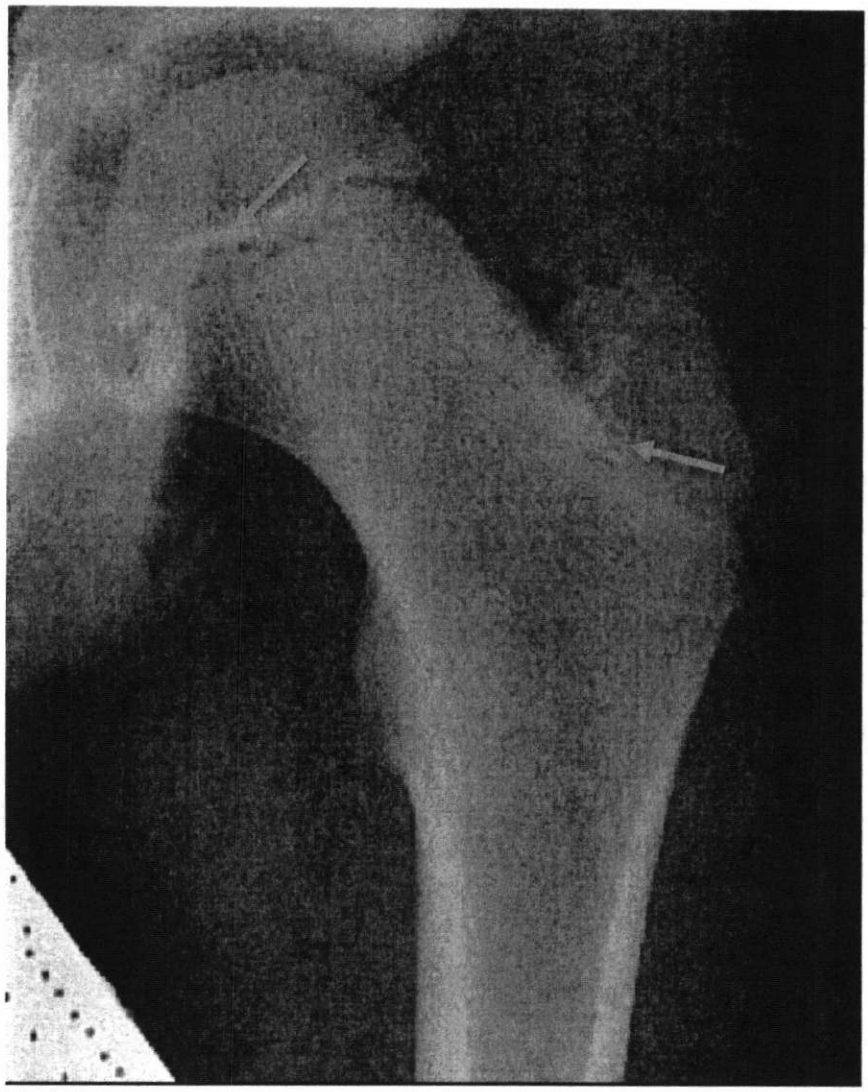

Figure 20. *Fissures across femur may produce erroneous measurements.*

7.6. Abnormal Shaft Measurement

Below is an image that displays incorrect shaft measurement. Notice how the cortical thickness measurement markers are misplaced after analysis. This can occur if there are obstructions on or near measurement regions or if the field of view is too narrow, as shown in image below.

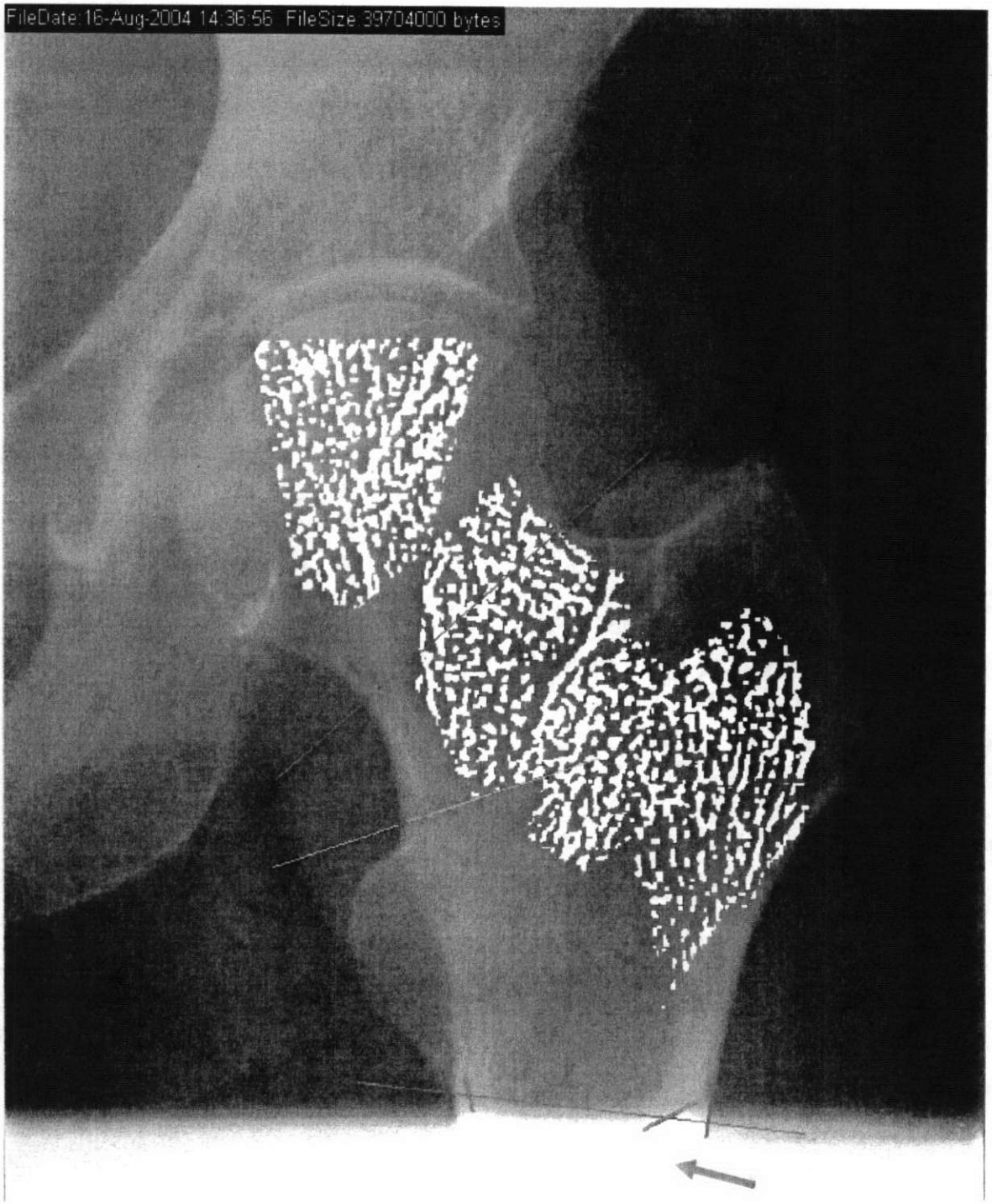

Figure 21. *Image shows incorrect shaft measurements caused by the narrow field of view.*

Draft Patient Information Leaflet

Osteoporosis what is it?
Osteoporosis is a disease in which bones become fragile and more likely to break. If not prevented or if left untreated, osteoporosis can progress painlessly until a bone breaks. These broken bones, also known as fractures, occur typically in the hip, spine, and wrist. (1)

What are the symptoms?
People cannot feel their bones getting weaker. They may not know that they have osteoporosis until they break a bone. A person with osteoporosis can fracture a bone from a minor fall, or in serious cases, from a simple action such as a sneeze or even turning over in bed.

Vertebral (spinal) fractures may initially be felt or seen in the form of severe back pain, loss of height, or spinal deformities such as kyphosis or stooped posture. In many cases, a vertebral fracture can even occur without pain.

Women can lose up to 20 percent of their bone mass in the five to seven years after menopause, making them more susceptible to osteoporosis. (1)

Am I at risk?
Certain people are more likely to develop osteoporosis than others. Factors that increase the likelihood of developing osteoporosis and broken bones are called "risk factors." Many of these risk factors include:

- Being female
- Older age
- Family history of osteoporosis or broken bones
- Being small and thin
- Certain race/ethnicities such as being Caucasian, Asian, or Hispanic/Latino. African Americans are at a lower risk for developing the disease.
- History of broken bones
- Low estrogen levels in women, including menopause
    - Missing periods (amenorrhea)
    - Low levels of testosterone and estrogen in men
- Diet
    - Low calcium intake
    - Low vitamin D intake
    - Excessive intake of protein, sodium and caffeine
- Inactive lifestyle
- Smoking
- Alcohol abuse
- Certain medications such as adrenal steroids, some anticonvulsants, high doses of thyroid hormones, and others
- Certain diseases and conditions such as anorexia nervosa, rheumatoid arthritis, gastrointestinal diseases and others(1)

Are treatments available?

The National Osteoporosis Foundation recommends five steps to take to prevent and/or minimize osteoporosis:

- Get your daily recommended amounts of calcium and vitamin D (3)
- Engage in regular weight-bearing exercise
- Avoid smoking and excessive alcohol
- Talk to your healthcare provider about bone health
- When appropriate, have a bone density test and take medication

How can I find out whether I have osteoporosis?

Bone mineral density (BMD) is used to estimate bone strength and the likelihood of bones to break with simple trauma. (2)

How is BMD tested?

Bone densitometry is a non-surgical method that can be used to assess fracture risk. However, it is only part of an overall assessment of fracture risk that your doctor or healthcare provider can perform. (2)

1. National Osteoporosis Foundation Website (www.nof.org)
2. International Society of Clinical Densitometry website (www.iscd.org)
3. American Bone Health website (www.americanbonehealth.org)

SECTION 4

DEVICE DESCRIPTION

General Functional Description

The OsDx Hip BMD System is a software program that incorporates an algorithm that performs a composite measurement of proximal femur structure from hip or pelvic x-rays that yields a value for the estimated total hip bone mineral density. This value can be used in conjunction with other risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to this disorder and to estimate the likelihood of subsequent_atraumatic fracture in non-black women older than 50 years of age. Output is expressed in terms of gm/cm^2 and T and Z-scores are calculated based on an established normative database.

The operating algorithm upon which the OsDx Hip BMD System is based is a quantitative bone structural analysis algorithm that measures a composite of weighted cortical and trabecular parameters in proximal femur projection radiographs from which total bone mineral density (BMD) is mathematically derived. Image analysis can take place remotely or at the point of care (e.g. physician office, clinic or hospital).

The automated report system provides an estimate of BMD reported as gm/cm^2 calcium. To provide a context for diagnosis and evaluation this value is compared with an average value for young normal Caucasian women based on a normative database of measurements using the system in normal subjects. This comparison is made using an index referred to as a T-Score, which represents the BMD value on a normalized scale. T-Scores less than -1 are indicative of bone that is less dense than normal and a T-Score value below -2.5 is considered diagnostic of osteoporosis (based on the WHO criteria).

The system also provides a measure referred to as the Z-Score, which is derived by comparing the actual BMD value for a particular patient to the average value (developed from the normative database) in a health population matched by gender, age, ethnic origin and age, expressed in terms of the standard deviations of that population, which can be used as an aid to the physician in the detection of conditions associated with non-age-related bone loss.

Detailed Software Design Description

The following documents were produced under the Design Control procedures of the Imaging Therapeutics Quality System as part of the design and development process.

The first document, the Software Design Description, provides an in depth description of the total software system and architecture. The second describes the image assessment module using a flow-chart of the data flow through the software functional systems.

OsDx Hip BMD SYSTEM

Software Design Description

Pages 73 through 90 redacted for the following reasons:
- -
Software Design, b4

SECTION 5

COMPARATIVE INFORMATION

This section focuses on the comparative summary information related to the Imaging Therapeutics OsDx Hip BMD System and the predicate devices with regard to the intended use of the device, the anatomical site used to gather information, technological characteristics, target population, etc.

Comparison To Predicates

There are numerous systems now available to measure and provide estimates of bone mineral density. This information is provided to physicians to assist in the evaluation of patients at risk for osteoporosis. These systems include integrated systems that require the use of specific imaging technology, such as dual energy x-ray absorptiometry (DXA) scans. Other approaches make use of ultrasonic sonometry, while still others, including the subject device, use morphologic information derived from standard plan-film X-rays using specialized software algorithms.

To demonstrate substantial equivalence, predicate devices have been identified based on Technological Characteristics as well as the Intended Use of the devices. This section describes the predicate devices to support this 510(k) submission. No new issues of safety or efficacy have been identified with the OsDx Hip BMD System.

Substantial Equivalence Analysis

Based on regulatory classification, technological characteristics, anatomic site analyzed, target population and intended use, the OsDx Hip BMD System is substantially equivalent to devices currently marketed under the Federal Food, Drug and Cosmetic Act. There are several predicate devices that have similar Technological Characteristics and similar Intended Use.

The Technological Characteristics predicate devices described in this submission support morphologic software technology used in the OsDx Hip BMD system. Predicates also support the use of the hip (i.e. proximal femur) as the site to be analyzed, and the use of scanned X-rays as the data input source for the OsDx Hip BMD System.

The Intended Use of the OsDx system is substantially equivalent to those of the identified predicates. Copies of the 510K Summary provided for each of the predicates may be found in Attachment 1 to this submission.

Regulatory Status

The table below provides a summary of relevant regulatory characteristics:

Regulatory Characteristic	OsDx Hip BMD System	Hologic Hip Structural Analysis Software	Pronosco X-Posure System Bone Densitometer	CTXA Hip
Classification	Class II	Class II	Class II	Class II
Product Code	MGI	MGI	MGI	MGI
Classification Name	Bone Densitometer	Bone Densitometer	Bone Densitometer	Bone Densitometer
Classification Rule	21 CFR 992.1170	21 CFR 992.1170	21 CFR 992.1170	21 CFR 992.1170
510K	Pending	K061561	K984178	K002113

Technological Characteristics

Technological Characteristic	OsDx Hip BMD System	Hologic Hip Structural Analysis Software	Pronosco X-Posure System Bone Densitometer	CTXA Hip
Software only	YES	YES	YES	YES
Data Source	Scanned X-rays	DXA input	Scanned X-rays	CT Scan
Operating Principle	Radiogrammatic	Absorbtiometry	Radiogrammatic	Radiogrammatic
Output measure	BMD in gm/cm^2	BMD in gm/cm^2	BMD in gm/cm^2	BMD in gm/cm^2
Anatomic Site	Hip	Hip	Forearm	Hip
Normative Reference Database?	YES	YES	YES	YES
T-Score Calculated?	YES	YES	YES	YES
Z-Score Calculated?	YES	YES	YES	YES

Intended Use Predicates

The OsDx Hip BMD System is similar in intended use to the following predicate devices:

Imaging Technology OsDx Hip BMD System
The OsDx Hip BMD System stand-alone software is intended to prove an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with referenced populations of young (20 – 39) and aged matched normals to compute T-scores and Z-scores respectively.

Hologic Hip Structural Analysis Software:
The Hip Structural Analysis (HAS) option for QDR X-Ray Bone Densitometers uses data from conventional Dual Energy Absorptiometry (DXA) scans to measure the distribution of bone mineral mass at specific cross-sections of the hip and allows the physician to estimate structural properties of the hip, such as CSA, CSMI, Z and buckling ratio.

Pronosco X-posure System:
The Pronosco X-posure System is intended for use to estimate BMD in the forearm and to assess increased risk of osteoporotic fractures according to World Health Organization ("WHO") criteria. The device is specifically indicated for use to: (1) assist the physician in diagnosing subjects who have already been identified to be at risk of suffering from osteoporosis, together with other known risk factors (i.e. history of fractures, advanced age, low body weight, lack of physical exercise, lack of exposure to sunlight, insufficient dietary intake of calcium and vitamin D, and smoking); and (23) compare the BMD estimate with reference populations of young normals and aged matched normals to compute T-scores and Z-scores respectively.

CTXA Hip Bone Mineral Densitometer Module ("CTXA Hip"):
CTXA Hip Bone Mineral Denistometer Module ("CTXA Hip") is intended to estimate bone mineral content (BMC) and Bone Mineral Density (BMD) in the proximal femur. The BMD estimates can be compared with CTXA Hip-derived reference data. T-Scores are calculated with respect to CTXA Hip young normal female reference data, and the T-Scores can be used by the physician as an aid in determining fracture risk.

Conclusion

The OsDx Hip BMD System substantially equivalent in terms of the technological characteristics of the predicates sited herein. It is also substantially equivalent to the cited predicates in terms of Indications for Use. Imaging Therapeutics believes that the device presented in this submission is substantially equivalent in essential Technological Characteristics to the predicate devices, thus permitting the conclusion that the OsDx Hip BMD system raises no questions for safety or effectiveness.

SECTION 6

PERFORMANCE AND SAFETY TESTING

The OsDx Hip BMD System has been evaluated in a number of studies, both clinical and non-clinical. The following studies are reported in this section:

1. Optimization Study for DXA-BMD Estimation Using Standard Pelvic Radiographs (b)(4) (b)(4)
2. Optimization Study for Failure Load and DXA-BMD Estimation Using Radiographs of Cadaver Femora.
3. Clinical Correlation of DXA and OsDx BMD Estimates and Development of a Normative Reference Data Set for BMD Estimation Using the OsDx Hip BMS System.
4. Precision/Reproducabity Study of the OsDx Hip BMD System

Clinical information regarding the performance of the OsDx Hip BMD System was gathered in three separate, but comparable, studies. These clinical studies were designed after the principles outlined in the "Retrospective Fracture Risk" study in the Final Guideline for Industry and FDA (June 21 pp 9 of 12.) The first study (designated Study 1 in the following reports) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) Institutional Review Board ("IRB") approval was obtained at and for each investigative site. This was designated "Non-Significant Risk" and thus no IDE was required.

A second study (b)(4) (b)(4) (hereafter referred to as Study #2) and was preformed (b)(4) (b)(4) (b)(4) (b)(4) Institutional Review Board review, approval and oversight were provided by (b)(4) (b)(4)

A copy of the protocol used in these studies is included in Attachment 2 to this submission.

The third study (b)(4) (b)(4) (b)(4) (b)(4) (hereafter referred to as Study # 3). (b)(4) (b)(4) (b)(4) (b)(4)

Certifications Related to Clinical Trials

The following required certifications are found in the preliminary section of this submission:

1. Certification of Compliance: Registration of Clinical Trials (FDA-3674)
2. Financial Certification Form

Optimization Study for DXA-BMD Estimation Using Standard Pelvic Radiographs

(b)(4) (b)(4)

Purpose: To compare bone mineral density (BMD) estimates of the proximal femur based on measurements from plain digital radiographs of the pelvis or hip of bone geometry and projected trabecular structure, with BMD measurements performed by dual-energy X-ray absorptiometry (DXA).

Background: The most widely utilized method for measuring bone mineral density (BMD) is DXA. However, the need for relatively expensive equipment, trained personnel and decreasing reimbursement, significantly lessen the accessibility of DXA as a routine screening tool. In contrast, BMD estimation from plain pelvic or hip X-ray radiography offers the potential of a widely available and comparatively inexpensive technique useful in the management and treatment of osteoporosis worldwide.

Methods

Dataset: (b)(4) (b)(4) pelvic X-Ray images were used for this study. The X-Ray images (b)(4) (b)(4)

Image Processing and Parameter Measurement: The general image processing and parameter measurement paradigm followed in this study is illustrated in Figure 1. All pelvic X-Ray images (b)(4) (b)(4) were acquired by standard film projection (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4)

(b)(4)

The digitized images were analyzed with dedicated software for image visualization and processing developed by Imaging Therapeutics (Imatx). For each digitized pelvic X-Ray image, the left proximal femur region was outlined and extracted for further processing with a semi-automatic approach, (user interaction is allowed in case the proximal femur outline requires correction). Once the femur region was extracted, all subsequent image-processing and measurement steps were completely automated. Measurements focused on evaluating the general femur geometry, the characteristics of the cortical bone and the internal structure of the bone from the projected radiographic image of the femur.

(b)(4)

(b)(4) macro-anatomical parameters were defined

(b)(4)

(b)(4)

(b)(4) Micro-anatomical parameters were defined (b)(4)

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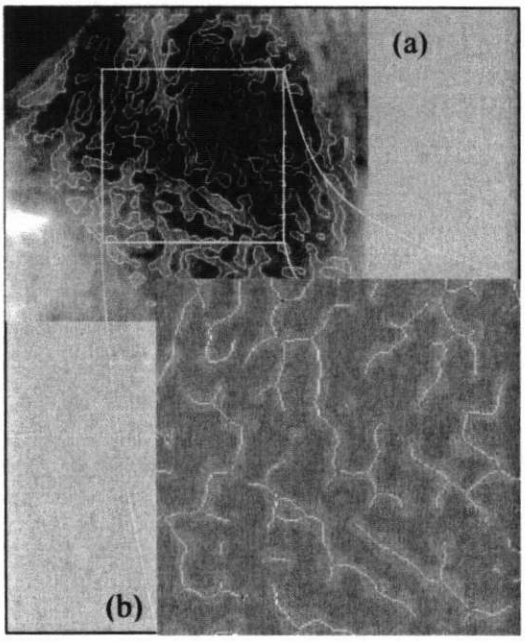

Figure 2. a) Example showing the outlined projected trabecular structure and b) the skeletonization of the structures from which several structural measurements are derived.

(b)(4)

(b)(4)

Parameter selection and optimization: The goal of this step was to select from the (b)(4)

Summary of Results

The parameters selected through optimization-validation for BMD estimation with the (b)(4) x-ray images from the (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

Figure 3. Optimization results from leave-one-out cross-validation testing. (b)(4) (b)(4) (b)(4) (b)(4) each sample is then removed and BMD estimation is made using coefficients generated from the rest of the samples.

Selected micro-structural measurements (b)(4) (b)(4) (b)(4) (b)(4) estimation of BMD. The correlation between the estimated values of BMD and corresponding measurements by DXA was significant and very high, as shown by plot in Figure 3, and with a correlation coefficient of r=071. The correlation coefficient increases to r=0.74 (R^2=0.5436) after removing the apparent outlier data point outlined by the dotted circle in Figure 3. This (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

Interpretation

The present study demonstrates that a strong and significant correlation can be achieved between DXA-BMD measurements of femoral bone in 65 year and older Caucasian American women and a corresponding BMD estimation model based on discrete geometrical and trabecular architecture parameters measured from a radiographic image of the bone. Selection of the (b)(4) (b)(4) and (b)(4) (b)(4) parameters as important parameters for BMD estimation based on model optimization from data also agree with findings from other studies proposing the estimation of BMD based on geometric measurements of bone and a consistent shape definition from radiographs (radiogrammetry). The most basic underlying assumption of this approach is that the (b)(4) (b)(4) can be approximated and assumed constant. Under this assumption, the bone mineral density can thus be estimated from the (b)(4) (b)(4) of bone and (b)(4) (b)(4) as measured from radiographic images. The agreement of BMD estimates obtained following this approach with measurements from dual-energy x-ray absorptiometry (DXA) is very good as demonstrated by the correlation and data distributions shown in Figure 3. These methods are widely applicable and versatile in the sense that they can be changed and optimized

depending upon the selected anatomical region and the X-Ray image application (e.g., film, computed radiography or direct digital radiography), thus offering the potential of a widely available and relatively inexpensive technique useful in the management and treatment of osteoporosis worldwide.

Optimization Study for Failure Load and DXA-BMD Estimation Using Radiographs of Cadaver Femora

Purpose: To compare mechanical failure load measurements from cadaver femora in a sideways fall configuration with estimates of femoral failure load based on bone mineral density (BMD) by dual-energy X-Ray absorptiometry and corresponding estimates obtained from radiograph-based trabecular pattern and geometry analysis.

Measurement of bone mineral density (BMD) by DXA is the current gold standard for diagnosis of osteoporosis and the evaluation of bone quality. However, BMD does not fully account for the changes in hip fracture rates that have been observed in studies monitoring effectiveness of osteoporosis treatments. In this context, bone geometry and trabecular architecture have been proposed as factors contributing to bone strength which together with BMD could provide a better characterization of bone quality.

Methods and Materials: (b)(4) human-cadaver femora (b)(4) (b)(4) (b)(4) 55 to 98 years old were selected as representative of the target population of individuals likely to suffer a hip fracture. DXA BMD and X-Ray images were obtained for all femurs in a water bath following a predefined imaging and positioning protocol (Figure 1). All the X-Ray images were obtained with direct digital (DR) radiography (b)(4) (b)(4) (b)(4) (b)(4) Following imaging assessment, mechanical testing was performed on all femurs in a sideways fall configuration simulating impact to the greater trochanter (Figure2). X-Ray images were analyzed performing measurements of general femoral geometry (macro) and trabecular micro-architecture. (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) Useful/relevant measurements for fracture load estimation were selected (b)(4) (b)(4) (b)(4) (b)(4)

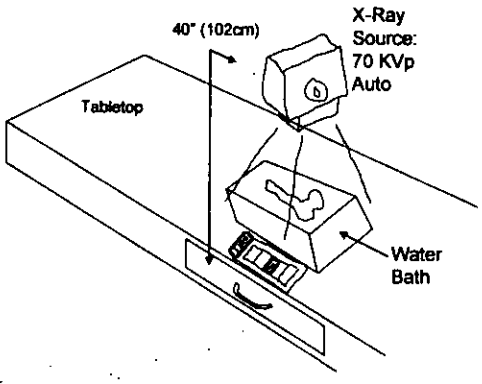

Figure 1. Imaging and positioning protocol used during the study. Each femur was positioned in a water bath with the diaphyseal and neck axes parallel to the film plane.

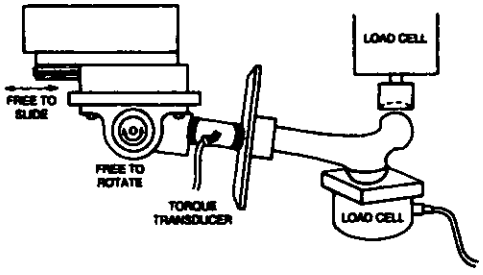

Figure2. Loading configuration simulating a side impact to the greater trochanter.

Fracture load estimation performance was quantified in terms of coefficients of determination (R2) or correlation coefficients (r). Estimation performance was then compared to the corresponding R2 (or r) obtained with DXA-BMD using a linear regression fit between an exponential transformation of DXA-BMD measurements and measured fracture load values. The

relative contribution of X-Ray based measurements to BMD for fracture load prediction was also investigated. For further performance evaluation, all fracture load estimation models were also cross-validated with 1000 repetitions of random selections of (b)(4) (b)(4) (b)(4) (b)(4) (i.e., leave 45% out cross-validation).

Results: The R2=0.76 (r=0.87) for fracture load estimation using (b)(4) (b)(4) (b)(4) (b)(4) (Table I and Figure 3.a). Additional testing with leave-45% out cross-validation resulted in an average coefficient of determination value of R2=0.72 (r=085). DXA by itself correlated with fracture load at R2=0.7 (r=0.84) but improved to R2=0.87 (r=0.93) (b)(4) (b)(4) (b)(4) (b)(4)

(b)(4) (b)(4) ImaTx-maximum breaking force estimation.

(b)(4) (b)(4)

R2 with leave one out cross-validation	0.76 (r=0.87)
R2 with leave 45% out cross-validation	0.72 (r=0.85)

(b)(4) (b)(4) DXA-BMD + ImaTx estimation of maximum breaking force

Parameter	Linear Regression Coefficient
DXA-BMD estimated fxLd using regression with exponential transformation	1.138654
(b)(4) (b)(4)	
R2 with leave one out cross-validation	0.87 (r=0.93)
R2 with leave 45% out cross-validation	0.85 (r=0.92)

(b)(4) (b)(4) ImaTx-BMD estimation.

(b)(4) (b)(4)

R2 with leave one out cross-validation	0.71 (r=0.84)
R2 with leave 45% out cross-validation	0.67 (r=0.82)

(b)(4)

(b)(4)

Interpretation: The present study demonstrates that a strong and significant correlation can be achieved between mechanical fracture load measurements of femoral bone and a corresponding estimation model based on a limited number of geometry and trabecular architecture parameters measured from a radiographic image of the bone. The fracture load estimation performance obtained with radiographic macro and micro parameters is comparable if not better to that obtained with DXA-BMD alone. Although the number of cases analyzed was limited, variation in estimation performance of selected models was very small between the two main cross-validation set-ups (leave-one-out and leave 45% out) suggesting that the obtained figures of fracture load estimation performance can be generalized to additional cases. Furthermore, it was possible to optimize a joint DXA-BMD, macro and micro parameter model to improve significantly the fracture load estimation performance. This suggests that bone composition, as estimated by DXA-BMD, bone geometry and trabecular architecture, as estimated from radiographic images, hold complementary information that could help explaining bone quality issues that are not possible with DXA-BMD alone.

(b)(4)

(b)(4)

Finally, it was also possible to optimize and demonstrate considerable overlap between DXA-BMD and macro and micro parameters, as shown by the correlations in Table III and Figure 4. (b)(4)

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(b)(4)

These parameters and

results confirm findings from other studies proposing the estimation of BMD based on geometric measurements of bone and a consistent shape definition from radiographs (radiogrammetry). (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) as measured from radiographic images. The agreement of BMD estimates obtained following this approach with measurements from dual-energy x-ray absorptiometry (DXA) is very good as demonstrated by the correlation values shown in Table III, but there is room for improvement. Considering the underlying assumptions, and due to natural variability and the effects of age and disease, specifically osteoporosis, the distribution of bone mineral within a bone volume might not be uniform across all cases. (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

In summary, these results indicate that measurement of femoral geometry and projected trabecular bone micro-architecture from X-Ray image analysis has the potential of providing an alternative and a widely accessible approach to the estimation of fracture load and thus provide an evaluation of bone strength. Further optimization and verification of performance for generalization is needed. Testing the possible implementation of fracture load estimates using X-Ray images from in-vivo cases for estimation of fracture load and fracture risk evaluation is also of great importance and interest.

Clinical Correlation of DXA and OsDx BMD Estimates and Development of a Normative Reference Data Set for BMD Estimation Using the OsDx Hip BMS System.

Imaging Therapeutics

Clinical Correlation of DXA and OsDx BMD Estimates and Development of a Normative Reference Data Set for BMD Estimation Using the OsDx Hip BMS System.

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(b)(4)

(b)(4)

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1.0 OBJECTIVES:

The objectives of this study were:

1) Determine the degree of correlation between estimates of Bone Mineral Density ("BMD") derived using a standard method Dual Energy X-Ray Absorptiometry ("DXA") and the method under study (OsDx).
2) Develop a normative Reference Database for use with the OsDx Hip BMD System that would provide reference data for comparison to young normals ("T-Score") and age and gender-matched controls (Z-Score).

2.0 BACKGROUND:

Fractures related to osteoporosis are a significant public health concern. Bone mineral density has been identified as one of the primary risk factors within a multi-factoral range of additional risk factors. The World Health Organization has published diagnostic criteria for osteoporosis based on bone density. The screening for osteoporosis or increased risk using BMD, primarily in post-menopausal women, has become increasingly routine in the United States. Several approaches have been developed for the estimation of BMD, including radiogrammatic, densitometric and absorbtiometric. Many such systems require the use of dedicated, specialized radiographic or other equipment. The cost and complexity of such instrumentation increases the cost of screening and limits its availability. The system being evaluated, the OsDx Hip BMD System, is a free-standing software package that runs on a standard personal computer. The program uses data obtained scanned plain x-ray films of the hip or pelvis. These data are evaluated using measures of structure and morphology to develop an estimate of total hip BMD. If demonstrated to be acceptably precise and reproducible, and well correlated to standard measures of BMD, such a system could make efficient screening more widely available.

3.0 METHODS:

3.1 Clinical Data Acquisition

A protocol was developed for a study to gather data from normal female volunteers who underwent a standard hip x-ray using a standardized technique. When available, BMD measurements previously obtained using DXA were recorded for each subject. The (b)(4) (b)(4) (b)(4) (b)(4) Routine demographic information, including age, weight, and ethnicity was obtained. All subjects were questioned regarding previous osteoporotic fracture of the hip. Patients with such a history were included in the study to provide

information for additional research purposes but were excluded from the normative reference database and correlation of DXA and OsDx derived BMD measurements that were carried out on both the non-fracture cohort and the entire cohort.

Clinical information regarding the correlation of OsDx to DXA derived BMD estimates and the establishment of a normative reference database, which are the subject of this report, was gathered in three separate, but comparable, studies. These clinical studies were designed after the principles outlined in the "Retrospective Fracture Risk" study in the Final Guideline for Industry and FDA (June 21 pp 9 of 12.)

The first study (designated Study 1 in the following reports) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) Institutional Review Board ("IRB") approval was obtained at and for each investigative site.

A second study (b)(4) (b)(4) (hereafter referred to as Study #2) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4) (b)(4)

A copy of the protocol used in these studies is included in Attachment 2 to this submission.

The third study (b)(4) (b)(4) (b)(4) (b)(4)

3.2 Statistical Analysis

(b)(4) (b)(4)

"A regression equation will be used to model the relationship between OsDx BMD to age. The fit of a linear vs. quadratic vs. third-order polynomial will be compared. The addition of second and third order terms will be tested and the simplest model accepted. From this model the peak BMD age and the peak mean will be determined for OsDx BMD. The peak standard deviation will be defined as the standard deviation in the age decade in which the peak BMD occurs. Age-specific correlation of the OsDx and DXA BMD, including n, correlation and p value for the correlation will be calculated."

4.0 RESULTS:

4.1 Enrollment

(b)(4) (b)(4) For purposes of analysis several other cohorts were derived: Non-Fracture Cases, Caucasian Subjects and Subjects for who both a DXA and OsDx BMD estimate were available. The following table provides a summary of the sample size of each cohort.

Table 1: Sample size and distribution of the total and sub-cohorts

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(b)(4)

4.2 Ethnicity of the Study Population

Because published normative data has been based, in general, on information from Caucasian women (cf. Black, et al, J Clin Densitometry, 4(1):5-12, 2001), the distribution of subjects by ethnicity was evaluated. Table 2 shows the distribution of ethnicity.

Table 2: Ethnicity of subjects, fracture and non-fracture With DXA and OsDx BMD Available

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Based on the paucity of data from non-Caucasian subjects and the fact that similar normative databases are derived from a Caucasian population, the decision was made, in consultation with the study statistician (b)(4) (b)(4) to limit the analysis of correlation, and the normative database, to Caucasian subjects.

4.3 Demographic Characteristics of the Study Population

The following tables provide information regarding the baseline characteristics of all non-fracture Caucasian cases (Table 3) and for Caucasian cases with both DXA and OxDx BMD (Table 4).

Table 3: Baseline characteristics of all non-fracture Caucasian cases

Variable Label	Descriptive Characteristic	Study 1	Study 2	Study 3	Total
	Number of cases	(b)(4)	(b)(4)		
Ethnicity	Classification	Caucasian	Caucasian	Caucasian	Caucasian
Weight (kg)	Mean ± 1 Std	64.5 ± 9.6	63.5 ± 9.3	68.1 ± 12.3	65.1 ± 10.4
	Min, Median, Max	45.0, 63.0, 92.7	44.5, 63.0, 88.5	43.8, 67.1, 109.5	43.8, 63.7, 109.5
Height (cm)	Mean ± 1 Std	165.7 ± 6.5	164.9 ± 6.7	158.3 ± 5.2	163.6 ± 7.0
	Min, Median, Max	141.0, 166.0, 186.6	141.0, 165.1, 182.9	147.0, 158.0, 175.3	141.0, 163.6, 186.6
BMI	Mean ± 1 Std	23.5 ± 3.1	23.4 ± 3.2	27.2 ± 4.5	24.4 ± 3.9
	Min, Median, Max	16.5, 23.1, 30.7	17.0, 23.0, 30.8	17.7, 26.9, 40.1	16.5, 23.7, 40.1
Age (years)	Mean ± 1 Std	34.4 ± 12.3	50.4 ± 15.5	74.8 ± 5.8	48.7 ± 20.3
	Min, Median, Max	20.0, 30.0, 77.0	20.0, 54.0, 80.0	65.0, 75.0, 90.0	20.0, 45.0, 90.0
Age 20-29	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	24.8 ± 2.3	24.8 ± 3.0		24.8 ± 2.4
Age 30-39	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	34.2 ± 3.0	35.2 ± 2.7		34.4 ± 2.9
Age 40-49	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	44.5 ± 2.4	42.3 ± 1.8		43.3 ± 2.3
Age 50-59	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	53.8 ± 2.3	55.5 ± 2.6		54.7 ± 2.6
Age 60-69	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	63.3 ± 3.1	63.6 ± 2.9	67.3 ± 1.4	64.8 ± 3.1
Age 70-79	N	(b)(4)	(b)(4)		
	Mean ± 1 Std	75.3 ± 2.1	73.3 ± 2.8	74.5 ± 2.9	74.3 ± 2.9
Age 80+	N	(b)(4)	(b)(4)		
	Mean ± 1 Std		80.0 ± .	83.2 ± 3.2	83.0 ± 3.2
OsDx BMD	Mean ± 1 Std	0.923 ± 0.103	0.893 ± 0.095	0.800 ± 0.113	0.885 ± 0.115
	Min, Median, Max	0.646, 0.925, 1.215	0.656, 0.892, 1.125	0.408, 0.789, 1.080	0.408, 0.890, 1.215
DXA BMD	Mean ± 1 Std	0.912 ± 0.133 [1]	0.864 ± 0.096	0.794 ± 0.134	0.849 ± 0.127
	Min, Median, Max	0.597, 0.910, 1.341	0.628, 0.856, 1.135	0.444, 0.795, 1.083	0.444, 0.850, 1.341

Table 4: Baseline Characteristics of all non-fracture Caucasian cases with both DXA and OsDx BMD available

Variable Label	Descriptive Characteristic	Study 1	Study 2	Study 3	Total
	Number of cases	(b)(4) (b)(4)			
Ethnicity	Classification	Caucasian	Caucasian	Caucasian	Caucasian
Weight (kg)	Mean ± 1 Std	66.6 ± 10.3	63.5 ± 9.3	68.1 ± 12.3	65.9 ± 10.9
	Min, Median, Max	50.0, 65.6, 92.7	44.5, 63.0, 88.5	43.8, 67.1, 109.5	43.8, 65.0, 109.5
Height (cm)	Mean ± 1 Std	166.1 ± 6.5	164.9 ± 6.7	158.3 ± 5.2	162.7 ± 7.0
	Min, Median, Max	153.0, 166.5, 181.7	141.0, 165.1, 182.9	147.0, 158.0, 175.3	141.0, 162.4, 182.9
BMI	Mean ± 1 Std	24.1 ± 3.2	23.4 ± 3.2	27.2 ± 4.5	24.9 ± 4.1
	Min, Median, Max	17.8, 24.3, 30.7	17.0, 23.0, 30.8	17.7, 26.9, 40.1	17.0, 24.4, 40.1
Age (years)	Mean ± 1 Std	48.0 ± 13.3	50.4 ± 15.5	74.8 ± 5.8	58.9 ± 17.3
	Min, Median, Max	22.0, 50.0, 77.0	20.0, 54.0, 80.0	65.0, 75.0, 90.0	20.0, 62.0, 90.0
Age 20-29	N	(b)(4) (b)(4)			
	Mean ± 1 Std	25.2 ± 1.7	24.8 ± 3.0		25.0 ± 2.6
Age 30-39	N	(b)(4) (b)(4)			
	Mean ± 1 Std	33.8 ± 4.0	35.2 ± 2.7		34.9 ± 2.9
Age 40-49	N	(b)(4) (b)(4)			
	Mean ± 1 Std	44.8 ± 2.2	42.3 ± 1.8		43.4 ± 2.3
Age 50-59	N	(b)(4) (b)(4)			
	Mean ± 1 Std	53.8 ± 2.3	55.5 ± 2.6		54.7 ± 2.6
Age 60-69	N	(b)(4) (b)(4)			
	Mean ± 1 Std	63.3 ± 3.1	63.6 ± 2.9	67.3 ± 1.4	64.8 ± 3.1
Age 70-79	N	(b)(4) (b)(4)			
	Mean ± 1 Std	75.3 ± 2.1	73.3 ± 2.8	74.5 ± 2.9	74.3 ± 2.9
Age 80+	N	(b)(4) (b)(4)			
	Mean ± 1 Std		80.0 ± .	83.2 ± 3.2	83.0 ± 3.2
OsDx BMD	Mean ± 1 Std	0.899 ± 0.107	0.893 ± 0.095	0.800 ± 0.113	0.860 ± 0.114
	Min, Median, Max	0.646, 0.904, 1.131	0.656, 0.892, 1.125	0.408, 0.789, 1.080	0.408, 0.864, 1.131
DXA BMD	Mean ± 1 Std	0.912 ± 0.133	0.864 ± 0.096	0.794 ± 0.134	0.849 ± 0.127
	Min, Median, Max	0.597, 0.910, 1.341	0.628, 0.856, 1.135	0.444, 0.795, 1.083	0.444, 0.850, 1.341

4.4 Establishment of the Normative Reference Database

In order to develop a normative reference database, the mean and standard deviation for BMD derived using the OsDx Hip BMD System were calculated. Table 5 provides these values for all non-fracture Caucasian subjects, the cohort which was used to establish the database.

Table 5: Mean BMD by OsDx for all non-fracture Caucasian subjects by decade

Variable Label	Age	Values	Total
OsDx BMD	**20-29**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.929 ± 0.100
		Min, Median, Max	0.656, 0.926, 1.215
OsDx BMD	**30-39**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.933 ± 0.095
		Min, Median, Max	0.679, 0.938, 1.164
OsDx BMD	**40-49**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.899 ± 0.092
		Min, Median, Max	0.707, 0.892, 1.104
OsDx BMD	**50-59**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.884 ± 0.109
		Min, Median, Max	0.674, 0.860, 1.131
OsDx BMD	**60-69**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.875 ± 0.093
		Min, Median, Max	0.674, 0.872, 1.080
OsDx BMD	**70-79**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.812 ± 0.108
		Min, Median, Max	0.581, 0.796, 1.024
OsDx BMD	**80+**	N	(b)(4) (b)(4)
		Mean ± 1 Std	0.744 ± 0.129
		Min, Median, Max	0.408, 0.739, 1.026

Figure 1: Distribution of OsDx BMD with respect to age and associated fitted Normative Reference curve (in blue)

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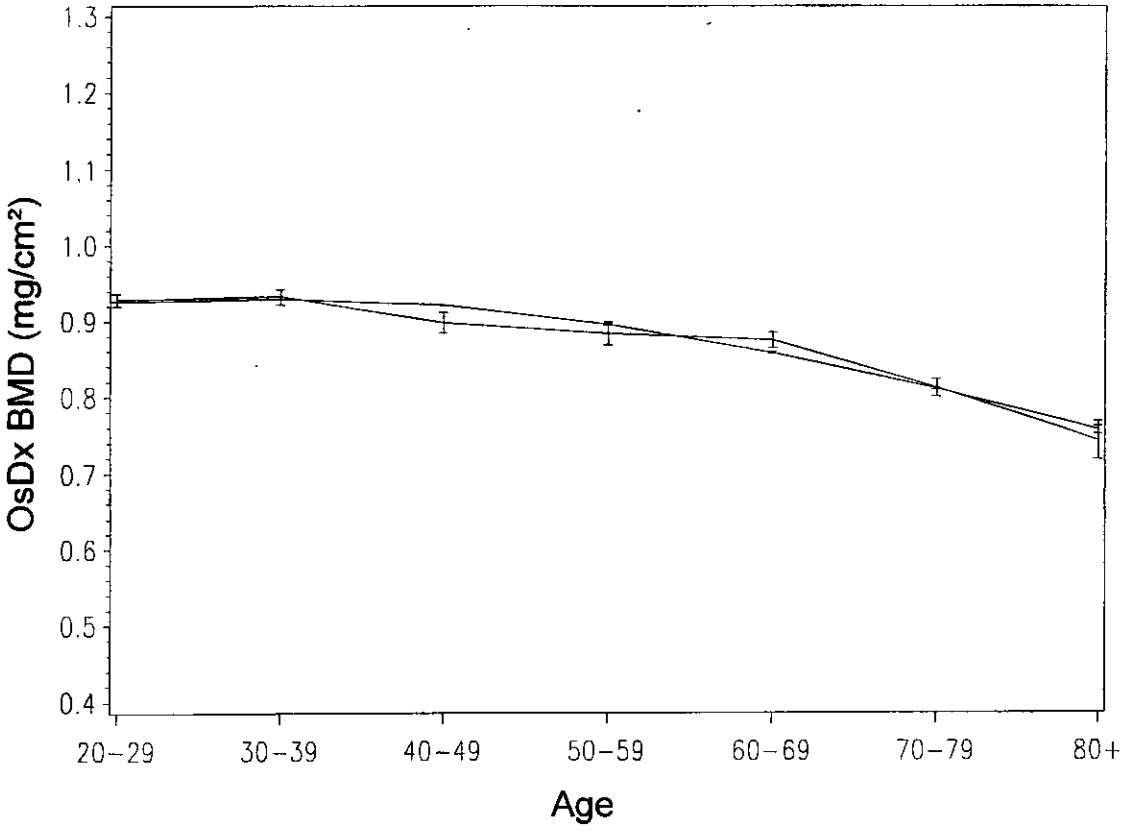
Figure 2: Distribution of OsDx BMD presented as the mean value per decade along with the Standard Deviation (in black). The fitted Normative Reference Data Curve is also shown (in blue)



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095

4.5 Correlation of DXA and OsDx BMD Estimates

The degree of correlation between BMD values for a given patient derived using standard DXA and the OsDx Hip BMD System was evaluated using Pearson's correlation coefficient for the entire cohort being analyzed and by subject age in decades. Table 6 presents these correlations for all subjects for whom both BMD values were available for analysis, which Table 7 provides the same information for the Caucasian non-fracture cohort.

Table 6: Person's coefficient of correlation for all subjects, regardless of ethnicity, with DXA and OsDx BMD values

Age	Number of cases	r (p-value)
All	(b)(4	0.75962 (<.0001)
20-29		0.56988 (<.0001)
30-39		0.63538 (<.0001)
40-49		0.58438 (<.0001)
50-59	(b)(4)	0.65262 (<.0001)
60-69		0.70264 (<.0001)
70-79		0.73093 (<.0001)
80+		0.62883 (<.0001)

Table 7: Pearson's coefficient of correlation for all Caucasian subjects with DX and OsDx Available

Age	Number of cases	r (p-value)
All	(b)(4	0.71146 (<.0001)
20-29		0.54934 (<.0001)
30-39		0.60340 (<.0001)
40-49		0.58411 (<.0001)
50-59	(b)(4)	0.67294 (<.0001)
60-69		0.55983 (<.0001)
70-79		0.73164 (<.0001)
80+		0.69922 (<.0001)

5.0 CONCLUSIONS

5.1 Normative Reference Database

The date generated in this combined study is demonstrated to be sufficient to establish an appropriate Normative Reference Database to permit comparison of OsDx BMD values to a young normal population (T-Score) and to an age and gender-matched population (Z-Score). The techniques which were used are consonant with those described in Black, Plaermo, Sorensen, et al. A Normative Reference Database Study for Pronosco X-posure System. J Clin Densitometry. 2001; 4(100:5-12 and Looker, Orwoll, Johnston, et al. Prevalence of Low Femoral Bone Density in Older U.S.Adults from NHANCE III. J Bone and Mineral Res. 1997; 12(11):1761-17-67. (Copies of these papers may be found in Attachment 4).

(b)(4)

(b)(4)

"These normative data seem quite comparable to other similar data I have seen or worked with for other instruments. The fact that BMD seems to be highest in the years between 20 and 39, that it doesn't change much during that interval and the overall shape of decline with age after age 40 is all very consistent with several other measurements of hip BMD. The fact that the pattern of change with age is so similar between your device and the hip DXA used in this study further supports the consistency with other measurements of hip BMD."

5.2 Correlation of BMD Estimates Derived Using DXA and OsDx

The data presented herein show a consistently high degree of correlation between BMD measurements derived from these two methods. The correlations have a p value of <0.001 across all decades of age. These data demonstrate that the OsDx BMD Hip System is substantially equivalent to DXA in provided an estimate of total hip BMD.

Precision/Reproducabity Study of the OsDx Hip BMD System

STUDY TO EVALUATE THE PRECISION AND REPRODUCABILITY OF THE IMAGING THERAPEUTICS OsDx HIP BMD SYSTEM

OBJECTIVE:

The objective of this study was to obtain and estimation of the in-vivo precision and intra-operative error of total hip BMD measurements made using the OsDx Hip BMD System.

Methods:

a) Estimation of short-term precision of the system: (b)(4) (b)(4) subjects enrolled in the clinical data gathering trials at sites 1 and 2 and ranging in age from 20 – 83 years of age, were recruited to have a second x-ray taken for evaluation. All subjects gave informed consent for this second procedure. Two x-ray images, taken as described in the clinical study protocol and the OsDx Hip BMD Operators Manual, were obtained at the same visit, or if that was not possible, within an approximate two-week window. Both images were processed, scanned and analyzed by the same operator using the OsDx System and the results compared.

b) Estimation of Intra-Operator error was evaluated using a subset of hip x-ray films taken from the Study 3 data set, (b)(4) (b)(4) This data set included (b)(4) (b)(4) subjects aged (b)(4) to (b)(4) years of age. Older patients were specifically selected in order to increase the likelihood that the data set would include BMD values outside of the "normal" range. The films were digitized and processed twice by the same operator using the OsDx System.

Results:

a) Short-term in-vivo precision: Precision was evaluated by calculating the Root-Mean-Squared Standard Deviation (RMS-SD) and the RMS Coefficient of Variation (RMS-CV). The results of this evaluation are presented in the table below.

Evaluation Parameter	Study 1 (b)(4) (b)(4) each repeated twice	Study 2 (b)(4) (b)(4) each repeated twice	Total Cohort (b)(4) (b)(4) each repeated twice
RMS-SD	0.0351 gm/cm2	0.0404 gm/cm2	0.0374 gm/cm2
RMS-CV	4.02%	4.48%	4.22%

b) b) Intra-Operator Error was evaluated by calculating the Root-Mean-Squared Standard Deviation (RMS-SD) and the RMS Coefficient of Variation (RMS-CV) as well as the Root-Mean-Squared Error (RMSE) for the comparison of the (b)(4) paired readings. The results of this evaluation are presented in the table below.

Evaluation Parameter	Value
RMS-SD	0.0256 gm/cm2
RMS-CV	3.69%
RMSE	0.0362 gm/cm2

Conclusion:

These results provide evidence of an acceptable level of precision in the estimation of total hip BMD using the OsDx Hip BMD System.

These results provide evidence of an acceptable level of intra-operator error when a trained operator uses the OsDx Hip BMD System to estimate total hip BMD.

SECTION 7

STERILIZATION INFORMATION

Not applicable: This device consists of software only.

SECTION 8

SOFTWARE VALIDATION AND VERIFICATION

The OsDx Hip BMD System software was evaluated using established principles and methods of software validation and verification. These processes and procedures are established with reference to appropriate standards (See Section 9 of this submission) according to applicable elements of the Imaging Therapeutics Quality System as noted in the report.

The initial aspect of Software validation and verification was the conduct of a Software Risk Analysis, a copy of which follows. As part of the Risk Analysis, a "Level of Concern Analysis" was performed, based upon the FDA's Guidance Document.

Based on this analysis, the Level of Concern for this software was determined to be minor.

A complete report of the software validation and verification performed for the OsDx Hip BMD System, including the completed Software Validation Record, follows the report of the Risk Analysis.

OsDx Hip BMD System

Hip X-Ray Image Assessment Software Risk Analysis

Pages 126 through 131 redacted for the following reasons:
- -
Risk Analysis, b4

OsDx Hip BMD System

Software Validation Report

FOI - Page 131 of 270

Pages 133 through 162 redacted for the following reasons:
- -
Software Validation Report, b4

SECTION 9

SPECIFIC STANDARDS AND GUIDANCES

Standards Met

The Imaging Therapeutics OsDx Hip BMD System has been tested to the following safety standards/guidelines:

1. ISO 14971:207 Medical Device Software : Software Life Cycle Processes
2. EN/ISO 14971:2001, Medical Devices: Application of Risk Management to Medical Devices
3. General Principles of Software Validation; Final Guidance for Industry and FDA Staff. (2002)
4. The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4 (ISPE/GAMP Forum, 2001)

Additionally, the Imaging Therapeutics' OsDx Hip BMD System complies with the requirements of 21 CFR, §820, Quality System Regulations and ISO 13485 Medical Devices – Quality Management Systems.

ATTACHMENT 1

PREDICATE DEVICE INFORMATION

PREDICATE DEVICE 510(K) SUMMARY:

Product:	**CTXA Hip**
510(k) No.	**K002113**
Clearance Date:	**December 04, 2001**
Sponsor:	**Mindways Software, Inc.**

DEC 0 4 2001

K002113

510(k) SUMMARY OF SAFETY AND EFFECTIVENESS

This summary of safety and effectiveness information is submitted in accordance with the requirements of 21 CFR 807.92(c).

Contact Information:

Christopher E. Cann, Ph.D.
CEO and Director of Research and Development
Mindways Software, Inc
282 Second St., 4th Floor
San Francisco, CA 94105
Phone: 415-247-9930
Fax: 415-247-9931
Email: chris@qct.com

Date: September 28, 2001

Device/Trade Name: CTXA Hip

Common/Usual Name: Bone Mineral Densitometer

Classification Name: Bone Densitometer, 21 CFR 892.1170, Class II

Predicate Devices:

K894854: QCT Bone Mineral Density Analysis Software
Intended Use: Estimate bone mineral density within the spine.

K883280: Hologic QDR 1000 X-Ray Bone Densitometer
Intended Use: Estimate bone mineral density and bone mineral content at various anatomical sites, including the proximal femur.

K943505: Hologic QDR 3000 X-Ray Bone Densitometer
Intended Use: Estimate bone mineral density and bone mineral content at various anatomical sites, including the proximal femur.

Preamendment: Norland Model 178 Bone Densitometer
Intended Use: An aid to the physician in determining fracture risk.

Device Description

The CTXA Hip Bone Mineral Densitometer (CTXA Hip) is a software package intended for estimation of bone mineral content (BMC), in grams, and bone mineral density (BMD), in g/cm^2, of the proximal femur. The CTXA Hip uses quantitative computed tomography (QCT) methods to derive bone mass and bone density estimates from 3D CT image data sets. The CTXA Hip is

intended to be used with compatible, whole-body CT scanners and with compatible CT calibration phantoms. BMD estimates are derived in units of g/cm^2 equivalent K_2HPO_4 density.

Intended Use

The CTXA Hip Bone Mineral Densitometer is intended to estimate bone mineral content (BMC) and bone mineral density (BMD) in the proximal femur. The BMD estimates can be compared with CTXA Hip-derived reference data. T-scores are calculated with respect to CTXA Hip young normal female reference data, and the T-scores can be used by the physician as an aid in determining fracture risk.

Summary of Technological Characteristics and Comparison with Predicate Devices

The CTXA Hip Bone Mineral Densitometer Module (CTXA Hip) provides estimates of bone mineral content (BMC) and bone mineral density (BMD) values similar to those obtained from the predicate DXA devices (K883280: Hologic QDR 1000 X-Ray Bone Densitometer; K943505: Hologic QDR 3000 X-Ray Bone Densitometer) for regions of interest in the proximal femur. CTXA Hip uses the same technical procedures to acquire and calibrate CT image data as are used for the predicate device K894854: QCT Bone Mineral Density Analysis Software. CTXA Hip reference data for young normal US Caucasian females were acquired in a clinical study so that patient results obtained using CTXA Hip can be compared to this normal reference population. The CTXA Hip BMD estimates compared to the CTXA Hip reference population are used as an aid to the physician in identifying patients with low bone mineral density. Additionally, normal data comparisons provide a basis for estimating fracture risk, as is done with the predicate preamendment device Norland Model 178 Bone Densitometer.

BMC and BMD estimates are returned by the CTXA Hip for the following proximal femur regions-of-interest (ROIs): (1) femoral neck, (2) trochanter, (3) intertrochanter, (4) Ward's Triangle, and (5) total hip (i.e., superposition of ROIs 1-3).

Summary of Non-Clinical Performance Data

In vitro phantom studies with the CTXA Hip indicate a device precision of approximately 0.007 g/cm^2 across a variety of CT scanners. These tests also indicate that *in vitro* CTXA Hip BMD estimates are unbiased when expressed as equivalent K_2HPO_4 mineral density.

Summary of Clinical Performance Data

CTXA Hip clinical studies indicate a long term *in vivo* device precision of 0.011 g/cm^2 for total hip and 0.012 g/cm^2 for femoral neck regions of interest. Clinical studies were done comparing BMD results from CTXA Hip with results from Hologic QDR1000 and QDR4500 bone densitometers. BMD correlations (Pearson's R) were 0.90-0.97 for the Total Hip region of interest and 0.88-0.95 for the Femoral Neck region of interest. A clinical study was done to collect a set of young normal female reference data for calculation of T-scores for CTXA Hip results.

Conclusions

The CTXA Hip Bone Mineral Densitometer is substantially equivalent to the listed predicate devices. The CTXA Hip *in vitro* and *in vivo* performance is comparable to that associated with the predicate devices. The radiation dose associated with the CT study that provides the data set to be analyzed by the CTXA Hip is well within accepted patient dose guidelines.

Signature

Christopher Cann
Printed Name

CEO and Director of Research and Development
Title

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 0 4 2001

Christopher E. Cann, Ph.D.
CEO and Director of Research
Mindways Software, Inc.
282 Second St., 4th Floor
SAN FRANCISCO CA 94105

Re: K002113
Trade/Device Name: CTXA HIP, CTXA; QCT PRO CTXA HIP
Regulation Number: 21 CFR 892.1170
Regulation Name: Bone densitometer
Regulatory Class: II
Product Code: 90 KGI
Dated: September 28, 2001
Received: October 2, 2001

Dear Dr. Cann:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

8xx.1xxx	(301) 594-4591
876.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4616
884.2xxx, 3xxx, 4xxx, 5xxx, 6xxx	(301) 594-4616
892.2xxx, 3xxx, 4xxx, 5xxx	(301) 594-4654
Other	(301) 594-4692

Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Nancy C. Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K002113/S002

Device Name: CTXA Hip Bone Mineral Densitometer

Indications For Use:

Intended Use

The CTXA Hip Bone Mineral Densitometer is intended to estimate bone mineral content (BMC) and bone mineral density (BMD) in the proximal femur. The BMD estimates can be compared with CTXA Hip-derived reference data. T-scores are calculated with respect to CTXA Hip young normal female reference data, and the T-scores can be used by the physician as an aid in determining fracture risk.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ (Per 21 CFR 801.109) OR Over-The-Counter Use_____

(Optional Format 1-2-96)

Nancy C Brogdon

(Division Sign-Off)
Division of Reproductive, Abdominal, and Radiological Devices
510(k) Number K002113

PREDICATE DEVICE 510(K) SUMMARY

Product:	**Hologic Hip Structural Analysis Software**
510(k) No:	**K061561**
Clearance Date:	**July 28, 2006**

K061561

JUL 28 2006

Section G
510(k) Summary

000081

H. 510(k) Summary

H.1 Manufacturing Establishment and Contact Information

H.1.1 Manufacturer Name and Address:

Hologic, Inc.
35 Crosby Drive
Bedford, MA 01730

H.1.2 Establishment Registration Number:

1221300

H.1.3 Name, Title, and Telephone Number of Contact:

Jeanette Schier-Pugsley
Regulatory Affairs Manager
Phone: (781) 999-7300, ex. 7406
Fax: (781) 999-0614
jschierpugsley@hologic.com

H.2 Device Identification

H.2.1 Device Trade Name:

Hip Structural Analysis (HSA) Software Option for the Hologic QDR X-Ray Bone Densitometers.

H.2.2 Common / Usual Name:

Software option for Bone Densitometers

H.2.3 Intended Use:

The Hip Structural Analysis (HSA) Option for QDR X-Ray Bone Densitometers uses data from conventional Dual Energy X-Ray Absorptiometry (DXA) scans to measure the distribution of bone mineral mass at specific cross sections of the hip and allows the physician to estimate structural properties of the hip, such as CSA, CSMI, Z and Buckling Ratio.

H.3 Device Classification

H.3.1 Classification:

Class II

H.3.2 Classification Name and Rule

Bone Densitometer: 21 CFR 892.1170

H.3.3 Classification Panel

Radiology

H.3.4 Product Code

90 KGI

H.3.5 Predicate Devices

- 510(k) No.: K023398
  Trade Name: Discovery Package for QDR Densitometers
  SE Date: November 8, 2002
  Manufacturer: Hologic, Inc.

- 510(k) No.: K011917
  Trade Name: Advanced Hip Assessment (AHA) Software for GE Prodigy x-ray bone densitometers.
  SE Date: August 3, 2001
  Manufacturer: GE Lunar Corporation

H.4 Conclusion:

Based on the scientific literature and testing supplied in the 510(k) submission, the Structural Analysis (HSA) Option for QDR X-Ray Bone Densitometers is substantially equivalent to the presently marketed Discovery Package for QDR Densitometers software (K023398) and the Advanced Hip Assessment (AHA) Software for GE Prodigy x-ray bone densitometers (K011917). No new safety and efficacy questions are raised with the HSA Software Option.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

JUL 28 2006

Ms. Jeanette Schier-Pugsley, RAC
Regulatory Affairs Manager
HOLOGIC, Inc.
35 Crosby Drive
BEDFORD MA 01730

Re: K061561
Trade/Device Name: Hip Structure Analysis (HAS) Software Option for QDR X-Ray Bone Densitometers
Regulation Number: 21 CFR 892.1170
Regulation Name: Bone densitometer
Regulatory Class: II
Product Code: KGI
Dated: June 2, 2006
Received: June 5, 2006

Dear Ms. Pugsley:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Protecting and Promoting Public Health

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at one of the following numbers, based on the regulation number at the top of this letter:

21 CFR 876.xxx	(Gastroenterology/Renal/Urology	240-276-0115
21 CFR 884.xxx	(Obstetrics/Gynecology)	240-276-0115
21 CFR 894.xxx	(Radiology)	240-276-0120
Other		240-276-0100

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150
or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Nancy C Brogdon

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

A.2 Indications for Use Statement

510(k) Number (if known): 061561

Device Name: Hip Structural Analysis (HSA) Software Option for QDR X-Ray Bone Densitometers

The Hip Structural Analysis (HSA) Option for QDR X-Ray Bone Densitometers uses data from conventional Dual Energy X-Ray Absorptiometry (DXA) scans to measure the distribution of bone mineral mass at specific cross sections of the hip and allows the physician to estimate structural properties of the hip, such as CSA, CSMI, Z and Buckling Ratio.

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-The-Counter-Use

(Per 21 CFR 801.109) (Optional Format 1)

Nancy C Brogdon
(Division Sign-Off)
Division of Reproductive, Abdominal,
and Radiological Devices
510(k) Number K061561

PREDICATE DEVICE 510(K) SUMMARY

Product:	**Pronosco X-Posure System Bone Densitometer**
510(k) No.:	**K984178**
Clearance Date:	**October 23, 2000**
Sponsor:	**Torsana Osteoporosis Diagnostics A/S**

2/18/99

K984178

510(K) SUMMARY
Pronosco X-posure System™

Submitter's Name, Address, Telephone Number, Contact Person, and Date Prepared

Submitter: Pronosco
Torsana Osteoporosis Diagnostics A/S
Torsana Park, Kohavevej 5
DK-2950 Vedbaek
Denmark

Contact Persons: Svenn Poulsen, MD, MBA, MFPM
Managing Director

Telephone number: (011) 45 45 65 06 00
Facsimile: (011) 45 45 65 06 06

Jonathan S. Kahan, Esq.
Hogan & Hartson, L.L.P
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

Telephone number: (202) 637-5794
Facsimile: (202) 637-5910

Date Prepared: November 18, 1998

Name of Device and Name/Address of Sponsor

Pronosco X-posure System™ Bone Densitometer

Sponsor: Pronosco
Torsana Osteoporosis Diagnostics A/S
Torsana Park, Kohavevej 5
DK-2950 Vedbaek
Denmark

Telephone number: (011-45) 45 65 06 00
Facsimile: (011-45) 45 65 06 06

Common or Usual Name

Pronosco X-posure System™

Classification Name

Bone Densitometer

Predicate Devices

1. Hologic, Inc.'s QDR 2000 X-Ray Bone Densitometer (K913321)
2. Norland Medical Systems' Norland 178 Bone Mineral Analyzer (preamendments device)
3. Norland Medical Systems' pDEXA® Bone Densitometer with Fracture Risk Assessment Option (K973104)
4. Compumed, Inc.'s Osteogram (preamendments device)

Intended Use

The Pronosco X-posure System™ is intended for use to estimate BMD in the forearm and to assess increased risk of osteoporotic fractures according to World Health Organization ("WHO") criteria. The device is specifically indicated for use to: (1) assist the physician in diagnosing subjects who have already been identified to be at risk of suffering from osteoporosis, together with other known risk factors (*i.e.*, prior history of fractures, advanced age, low body weight, lack of physical exercise, lack of exposure to sunlight, insufficient dietary intake of calcium and vitamin D, and smoking); and (2) compare the BMD estimate with reference populations of young normals and age matched normals to compute T-scores and Z-scores, respectively. All of the predicate devices are also intended for use in BMD estimation, and several are intended for use to estimate fracture risk. The specific indications for use of the Pronosco X-posure System™ are also substantially similar to the predicates.

Principles of Operation

The Pronosco X-posure System™ estimates BMD based on established principles of radiogrammetry. A standard x-ray is first scanned into the system, then analyzed by computer to assess cortical thickness and textural characteristics in the pre-defined region of interest, which consists of the radius, the ulna, and the second through fourth metacarpals. The BMD estimate may be compared to a reference database of young normals and age matched normals to compute T-scores and Z-scores, respectively.

Technological Characteristics

The Pronosco X-posure System™, the Hologic QDR-2000, the Norland Model 178, the Norland pDEXA®, and the Compumed Osteogram all provide estimates of BMD to aid the physician in diagnosing osteoporosis. While the Pronosco X-posure System™ derives the BMD estimate based on radiogrammetric principles, rather than absorptiometry methods, this approach does not raise any new questions of safety or effectiveness, because the Compumed Osteogram similarly derives BMD estimates from computerized analysis of radiographic images. In addition, all of the devices determine forearm BMD using similarly defined regions of interest, and several of the devices use similar methods to analyze fracture risk. Clinical testing and performance testing have also demonstrated the safety and effectiveness of the Pronosco X-posure System™ for this intended use.

Summary Basis for the Finding of Substantial Equivalence

The Pronosco X-posure System™ has substantially the same intended use and indications for use as the predicate devices. In addition, the minor differences in the technical characteristics of the devices, such as differences in the BMD estimation method or the precise regions of interest used to determine forearm BMD, do not raise new questions of safety or effectiveness, as confirmed by clinical and performance testing. Thus, the devices are substantially equivalent.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 18 1999

Jonathan S. Kahn, Esq
C/o Hogan & Harston, LLP
Torsana Osteoporosis Diagnostics A/S
555 13th Street, N.W.
Washington, DC 20004

Re: K984178.
Pronosco X-posure System™
Dated: Novermber 20, 1998
Received: November 20, 1998
Regulatory class: II
21 CFR 892.1170/Procode: 90 KGI

Dear Mr. Kahn:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4613. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Capt. Daniel G. Schultz, M.D.
Acting Director, Division of Reproductive,
Abdominal, Ear, Nose and Throat,
and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known):_____

Device Name: Pronosco X-posure System™

Indications For Use:

The Pronosco X-posure System™ is intended for use to estimate BMD in the forearm and to assess increased risk of osteoporotic fractures according to World Health Organization ("WHO") criteria. The device is specifically indicated for use to: (1) assist the physician in diagnosing subjects who have already been identified to be at risk of suffering from osteoporosis, together with other known risk factors (*i.e.*, prior history of fractures, advanced age, low body weight, lack of physical exercise, lack of exposure to sunlight, insufficient dietary intake of calcium and vitamin D, and smoking); and (2) compare the BMD estimate with reference populations of young normals and age matched normals to compute T-scores and Z-scores, respectively.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Reproductive, Abdominal, ENT, and Radiological Devices
510(k) Number K984178

Prescription Use ✓ OR Over-The-Counter Use____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

ATTACHMENT 2

CLINICAL PROTOCOL

Pages 187 through 236 redacted for the following reasons:
- -
Protocol, b4

ATTACHMENT 4

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Original Article

A Normative Reference Database Study for Pronosco X-posure System™

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Abstract

Cortical width from radiographs has been used for more than 40 yr as a means of estimating bone strength. In the last 5–10 yr, increased availability of computers and the development of automated algorithms for image assessment have led to an increased interest in radiogrammetry. In this study, we examined a new radiogrammetry device, the Pronosco X-posure System™, which estimates bone mineral density (BMD) from forearm/hand radiographs. We obtained hand and forearm radiographs and performed dual X-ray absorptiometry (DXA) at the wrist and hip on 832 women ages 20–79 at four clinical centers across the United States. We then used the X-posure System to estimate BMD (DXR-BMD). The goal of the study was to establish reference ranges for the method and to compare the measurement to DXA measurements of BMD at the wrist and hip. Using statistical models, we estimated that the peak value for DXR-BMD occurred at age 38 (mean = 0.598 g/cm^2, standard deviation = 0.034 g/cm^2). The correlation between DXR-BMD and DXA was 0.90 at the wrist and 0.61 at the hip. The relationship of DXR-BMD to reported history of fracture was of similar magnitude to that for DXA at the wrist and hip. The strong correlation of DXR-BMD from the X-posure System with DXA at the wrist from the Hologic machine suggests that the X-posure System may be an alternative to DXA at the wrist for the assessment of osteoporosis.

Key Words: Bone density; radiogrammetry; bone mineral density.

Introduction

The use of radiograph-assessed cortical bone width as a measure of bone strength was originally proposed by Barnett and Nordin *(1)* and Virtama and Mahonen *(2)* in 1960 using radiographs of the hand bones. Later refinements in radiogrammetry increased its precision. More recently, measurements of cortical width have been shown to be predictive of fracture *(3,4)*.

The escalating use of other densitometric methods for assessing bone density by single X-ray absorptiometry and dual X-ray absorptiometry (DXA) made radiogrammetry a somewhat neglected technique for many years. However, increased availability of computers and the development of automated algorithms for image assessment in the last 5–10 yr have led to an increased interest in radiogrammetry *(5)*.

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In the present study, we examined a new device for performing radiogrammetry from hand/forearm radiographs. Using the Pronosco X-posure System™, radiographs were obtained on 832 women between the ages of 20 and 79 from four clinical centers in the United States. The goal of the study was to establish reference ranges for the method and to compare the measurement to bone mineral density (BMD) at the wrist and hip as measured by DXA (Hologic).

Materials and Methods

Subjects

Eight hundred thirty-two normal Caucasian women (ages 20–79) were recruited from four geographically diverse sites within the United States (Iowa City, IA [n = 260]; Memphis, TN [n = 258]; Portland, OR [n = 213]; Birmingham, AL [n = 101]). Women using drugs that affect bone, including bisphosphonates, estrogen, calcitonin, steroids, fluoride, tamoxifen, and raloxifene, were excluded. Other exclusion factors included prolonged hospitalization or immobilization and limited use of one or both arms within 6 mos of the study. If women were of childbearing age, a negative pregnancy test was required.

The population was divided by age into the following groups: 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 yrs, with a goal of recruiting approximately equal numbers in each group; the actual number of subjects in each age group ranged from 127 to 141. The recruitment techniques used varied among the four sites but included mass mailings (based on motor vehicle registration lists) and advertisements in local newspapers. Before a woman could be entered into the study, a telephone interview was conducted in order to obtain initial demographic data and to review the inclusion and exclusion criteria.

All subjects signed a written informed consent form. The study was conducted in accordance with the revised Helsinki Declaration (Somerset West 1996), the International Conference on Harmonization's (ICH's) guidelines for good clinical practice, and local regulations. The local institutional review boards approved the protocol, patient information, and informed consent form before the study was initiated. Each participant was given both written and oral information about the study before informed consent was obtained and any study procedures performed.

Measurements

After inclusion in the study, the subject's medical history, including menopausal status, overall health assessment, and medication use, was obtained. Participants were queried about fractures that had occurred since menopause. Each subject had her nondominant hand and forearm radiographed. If the nondominant forearm had been fractured, the dominant hand and forearm were measured. The radiographs were analyzed and the estimated BMD (DXR-BMD) value was calculated using the Pronosco X-posure System. DXA BMD was also measured for the nondominant distal forearm and the femoral neck of the corresponding hip using a Hologic QDR2000 Bone Densitometer. If the subject had a history of previous fracture of the nondominant forearm or hip, the dominant forearm or the nonfractured hip was scanned. The distal forearm DXA BMD in this study was equivalent to the Hologic QDR2000 mean of the radius and ulna.

Estimation of Bone Mineral Density

Having been previously described in great detail by Jørgensen et al. *(5)*, the calculation of DXR-BMD is only briefly summarized here. The X-posure System calculates the cortical width and overall bone width for five bones: the second, third, and fourth metacarpals; the radius (radial side, only cortical width); and ulna (ulnar side, only cortical width) (Fig. 1). For each bone, the cortical volume per area (VPA) is calculated as an approximation to bone density. The DXR-BMD value is corrected for striation and porosity, which are assumed to reflect properties of the cortical bone microarchitecture. Striation is a visual phenomenon in the radiograph that can be seen as longitudinal striping in the endosteal region between the inner cortical bone edges *(6)*. It probably reflects the irregularity of the inner surface of the cortical bone, which may be the result of endosteal resorption. Porosity is the fraction of cortical bone that is not occupied by compact bone. It is derived from the ratio of local intensity minima found in the cortices of a bone, relative to the entire cortical area. A combined porosity measure p is derived by averaging over the five bones and by appropriate scaling to reflect a volumetric ratio rather than a projected ratio *(7)*.

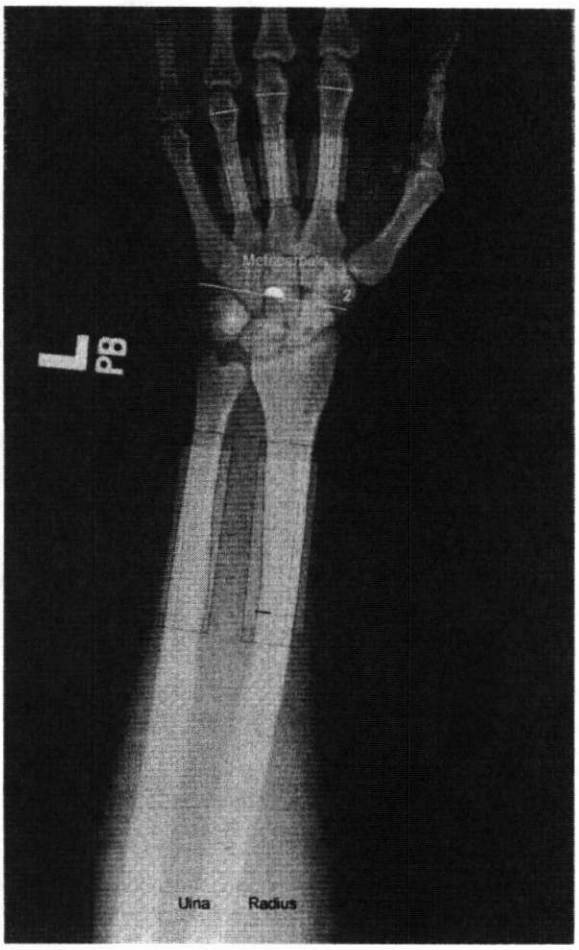

Fig. 1. Regions of interest for calculation of DXR-BMD.

The mean VPA for the two bones in the wrist and a mean for the three metacarpals were calculated. The mean of these two measurements was, in turn, calculated as the DXR-BMD and calibrated to correspond with Hologic DXA at the wrist according to a constant derived from previous studies *(5)*.

The fit of a linear vs quadratic vs third-order polynomial to the DXR-BMD and age relationship was tested. The second-order polynomial fit significantly better than a linear model, but the fit was not significantly improved by adding a third-order term. Therefore, the normal reference curve was calculated based on fitting a second-order polynomial to the DXR-BMD age values:

$$\text{Mean DXR} = a + b\ \text{Age} + \text{Age}^2$$

A similar second-order polynomial was used to model the square of the standard deviation (SD) of DXR as a function of age.

Data Analysis

The relationship of BMD measurements to postmenopausal fracture history (self-reported fracture after age 50) was assessed using logistic regression models restricting the analysis to women age 50 and over. Age-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) are reported.

Results

Eight hundred thirty-two subjects were enrolled and 828 subjects completed the study. Four of the subjects enrolled were discontinued, three of these owing to treatment with a bisphosphonate and one because she was unable to remain still for her DXA forearm scan. Six subjects had X-ray images taken that were rejected by the X-posure System owing primarily to insufficient centering. Table 1 gives the characteristics of the remaining 822 women in the study. The mean age was 49.7 yr, and 52% were premenopausal.

Because of a calibration problem with the DXA device at one study center, data from 258 subjects at this site were excluded from all equivalence tests; their DXR-BMD data were still available. The normative reference database (to be used for T- and Z-scores) was therefore computed from information obtained from 822 subjects, and the equivalence testing was based on information obtained from 564 subjects. The characteristics among the subset of 564 with usable DXA were similar to those in Table 1 (data not shown).

The mean DXR-BMD was highest between ages 30 and 59 (Table 2). The model fit to mean BMD yielded the following equation:

$$\text{Mean DXR} = 0.446417 + 0.008015 \times \text{Age} - 0.0001058 \times \text{Age}^2$$

The equation for the squared SD was as follows:

$$\text{SD}^2\ \text{DXR} = 0.0033 - 1.24 \times 10^{-4} \times \text{Age} + 1.81 \times 10^{-6} \times \text{Age}^2$$

Based on this equation, the peak BMD occurred at age 38 (mean: 0.598 g/cm^2) with an SD at that age of

249

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Table 1
Baseline Characteristics of Study Population[a]

Characteristic	n	%
Age (yr)		
20–39	127	15.5
30–39	140	17.0
40–49	138	16.8
50–59	135	16.4
60–69	141	17.2
70–79	141	17.2
Mean age (SD)	49.7 (16.8)	
Menopausal status		
Postmenopause	390	47.4
Premenopause	429	52.2
Do not know	3	0.4
Years since menopause		
Premenopausal	429	52.2
1–5	57	6.9
5–10	47	5.7
10–20	130	15.8
20+	156	19.0
Do not know	3	0.4
Clinical center		
Iowa City, IA	258	31.4
Memphis, TN	258	31.4
Birmingham, AL	97	11.8
Portland, OR	209	25.4
Weight (kg), mean (SD)	70.8 (15.8)	
Body mass index (g/m^2), mean (SD)	26.5 (5.7)	
Height (cm), mean (SD)	163.6 (6.4)	

[a] n = 822.

Table 2
Mean and SD by Decade (DXR and DXA at Wrist)[a]

	DXR		DXA at wrist	
Age (yr)	Mean	SD	Mean	SD
20–29	0.580	0.033	0.572	0.039
30–39	0.594	0.038	0.590	0.040
40–49	0.594	0.034	0.584	0.044
50–59	0.583	0.041	0.579	0.055
60–69	0.507	0.061	0.510	0.072
70–79	0.470	0.057	0.472	0.074

[a] n = 564.

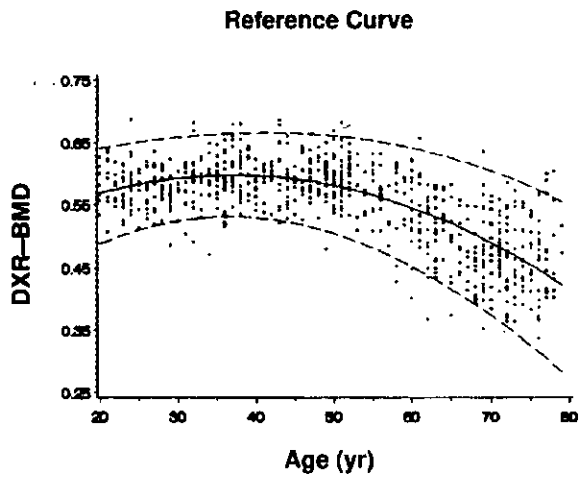

Fig. 2. Calculated reference curve for DXR-BMD. Solid line represents mean, and dashed line represents mean ± 2 SDs.

0.034 g/cm^2. The equations for age-specific means and for age-specific SDs closely approximated the corresponding observed values. There was an increasing SD with age (0.03 g/cm^2 at age 20–29 to 0.06 g/cm^2 at age 60 and above), which is also shown in the model equation. The modeled curve of means and SDs by age are shown in Fig. 2 together with the observed 822 data points.

The means for DXR-BMD and DXA at the wrist (n = 564) by age were similar (Table 2), and there was a strong relationship between the two (Fig. 3). The correlation between DXR-BMD and DXA at the wrist was 0.90 and between DXR-BMD and DXA at the hip was 0.61 (Table 3). There was a suggestion of an increase in correlation with age, but this trend was not statistically significant.

Among the 313 women age 50 and over with DXA measurements, the ORs for DXA at the hip, DXA at the wrist, and retrospective history of fracture were slightly higher than that for DXR-BMD, but, again, the differences were not statistically significant (Table 4).

To explore the relative value of the VPA for each of the bones, as well as for striation and porosity, we examined the decline in each parameter by age, as well as the relationship of each to history of fracture (Table 5). In terms of decrease in SDs with age, the largest

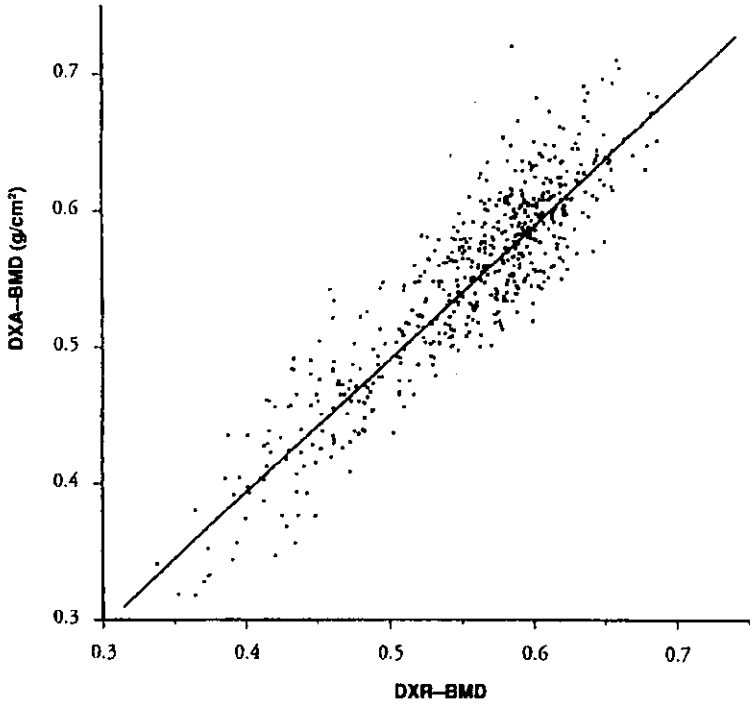

Fig. 3. Scatter plot of DXR-BMD vs DXA-BMD. Line represents linear regression

Table 3
Age-Specific Correlation of DXR with DXA at Wrist and DXA at Hip[a]

Age (yr)	n	DXA at wrist Correlation	DXA at wrist p Value	DXA at hip Correlation	DXA at hip p Value
All	564	0.90	0.0001	0.61	0.0001
20–39	165	0.69	0.0001	0.22	0.0053
40–59	190	0.80	0.0001	0.42	0.0001
60–79	209	0.89	0.0001	0.56	0.0001

[a] The correlation between DXA at wrist and hip was 0.64.

Table 4
Relationship of DXR and DXA to History of Fracture[a]

	OR	95% CI	p Value
DXR	1.81	1.23–2.68	0.0028
DXA at wrist	1.98	1.38–2.85	0.0002
DXA at hip	2.06	1.39–3.07	0.0004

[a] Among 313 women age 50 and over with a DXR and DXA at wrist, adjusted for age. Note that 60 women reported at least one fracture: a total of 83 fractures was reported. Most commonly reported fracture sites were forearm (n = 22), ankle (n = 13), arm (n = 11), and foot (n = 8).

decreases were seen at the wrist (both DXR and DXA). The metacarpals changed less with age, as did porosity and striation. The second metacarpal seemed to decline more rapidly than the fourth. The relationships of the individual bones to fracture history were not significantly different. Both striation and porosity were less strongly related to fracture history. These results for the individual bones are shown for VPA. Results using cortical thickness were similar (data not shown).

Discussion

The overall goal of this study was to establish normal reference ranges for the Pronosco X-posure System and to assess the comparability of digital radiogrammetry at the wrist and hand to BMD at the

Table 5
Relationship of DXR at Individual Bones to Age and Fracture History

Measurement site	Age 20–39, mean (SD) (n = 165)	Age 60–79, mean (SD) (n = 209)	Difference[a] SD	Difference[a] %	OR for fracture history (n = 313)[b]
Metacarpals					
2	0.58 (0.04)	0.49 (0.06)	−2.08	−16	1.71 (1.17–2.50)
3	0.58 (0.05)	0.50 (0.06)	−1.68	−14	1.54 (1.06–2.25)
4	0.57 (0.05)	0.51 (0.06)	−1.13	−10	1.60 (1.11–2.30)
Mean	0.58 (0.04)	0.50 (0.05)	−1.83	−13	1.75 (1.19–2.59)
Radius/ulna					
Radius	0.59 (0.04)	0.49 (0.07)	−2.63	−17	1.60 (1.11–2.31)
Ulna	0.59 (0.05)	0.48 (0.08)	−2.19	−19	1.71 (1.18–2.48)
Mean	0.59 (0.04)	0.48 (0.07)	−2.75	−18	1.73 (1.19–2.53)
DXR	0.59 (0.03)	0.49 (0.06)	−2.89	−16	1.81 (1.23–2.68)
DXA at wrist	0.58 (0.04)	0.49 (0.08)	−2.23	−16	1.98 (1.38–2.85)
DXA at hip	0.86 (0.10)	0.67 (0.12)	−1.78	−21	2.07 (1.39–3.07)
Porosity	3.40 (0.97)	4.30 (1.11)	0.92	26	0.73 (0.54–0.99)
Striation	3.67 (0.80)	4.77 (1.32)	1.38	30	1.29 (0.94–1.77)

[a] From age 20–39 to age 60–79. SD from age 20–39.
[b] Among 313 women age 50 and over with a DXR and DXA at the wrist, age adjusted.

wrist as assessed by DXA. Our results showed that these two forearm measurements were highly correlated in our sample of 20- to 79-yr-old Caucasian women. In addition to a high correlation, the means and SDs for the two measurements were similar within each age group. This suggests that DXR can serve as an alternative to DXA at the wrist. Because it requires a standard hand X-ray and no specific DXA equipment, the use of DXR should broaden the availability of fracture risk assessments to women to whom DXA scans are not available.

We found a correlation coefficient between DXR-BMD and DXA measured at the wrist of 0.90. In other studies in which radiogrammetry of the second metacarpal has been compared to densitometric BMD measurements at the forearm, the same high correlation has not been obtained. Correlation between combined cortical thickness and single photon absorptiometry of the forearm has generally ranged from 0.50 to 0.65 *(3,8,9)*. In other studies, the metacarpal index has been correlated to radiographic absorptiometry at the forearm with correlation coefficients ranging from 0.39 to 0.52 *(10,11)*, and to DXA forearm with a correlation coefficient of 0.51 *(12)*. We attribute the high correlation between DXR-BMD and DXA to the precision of DXR technology, the practice of averaging over five bones, and the fact that the measurement includes regions of interest at both the radius and ulna *(5)*.

We estimated that the peak DXR value occurs at age 38, although the mean changed little between ages 20 and 50. The mean value at peak was estimated to be 0.598 g/cm^2 and the SD at that age was 0.034 g/cm^2. The normative database for the Hologic measurements has a peak value of 0.588 g/cm^2 and an SD of 0.053 g/m^2 at age 20, compared with age 38 for DXR-BMD. However, the mean values change little in the 20–40 age range, and thus this distinction in peak age could be accounted for by small or random differences in the sampling or by variations in the models that are fit to the data.

Another difference between the two reference data sets is that the data we collected suggest a significant increase in the SD with age for both DXR-BMD and DXA at the wrist, but we did not observe an increase in SD with age for DXA at the hip. However, the reference data for Hologic DXA at the wrist include a constant SD (0.053 g/cm^2) with age. A study of Scandinavian women using the Pronosco device reported a similar increase in SD with age:

0.035 at age 20 to 0.051 g/cm^2 at age 79 (T. Sørensen, personal communication). However, no other studies have reported an increased SD at the wrist with age.

The peak SD for DXR-BMD is slightly lower than that for DXA at the wrist. This may be owing to added precision for DXR-BMD associated with averaging five, rather than two (radius and ulna), bones or it may be related to the increase in SD with age (and therefore lower value at peak) whose discussed for DXR-BMD. DXA-BMD and DXR-BMD have similar age-specific mean values, but the SDs were lower for DXR-BMD. This suggests that a higher proportion of women will be diagnosed with osteoporosis using the World Health Organization's definition of osteoporosis as a T-score below –2.5, adding to the growing literature suggesting that fixed T-score cut points do not yield consistent diagnostic categories across devices *(13)*. This supports attempts to develop new diagnostic algorithms for peripheral BMD devices.

We examined the relationship between retrospective report of fracture and the DXR and DXA values. We found that the relationship between DXR and fracture history is of similar magnitude to that of DXA at the wrist and DXA at the hip and fracture history. However, these results are preliminary and should be viewed cautiously because the assessment of fracture was based on self-report and not confirmed; the assessment was retrospective, and, therefore, the occurrence of the fracture potentially changed the measurements; and the types of fractures were mixed, and it is therefore difficult to extrapolate predictions to individual fracture types. Additional studies with confirmation of individual types of fractures are required in order to determine the extent to which DXR-BMD is useful for prediction of future fractures. One of the potential advantages of DXR is that its ability to prospectively assess fracture risk could be ascertained from already completed longitudinal studies in which hand X-rays were obtained at baseline. Such an analysis, using hand X-rays obtained in 1985–1986, is in progress.

DXR measurement was calculated from individual values at five bones using a weighted average of those bones. We compared the performance of each individual bone using the magnitude of bone loss from age 20 and the relationship to reported history of fracture as criteria. Although there were no statistically significant differences, the point estimates suggest that the metacarpals performed almost as well as the forearm. The development of devices to measure bone mass based on the metacarpals (perhaps only the second metacarpal) may lead to new, simpler measurements to assess fracture risk. However, there seemed to be some additional value to averaging the measurements across several bones because the fracture relationship was strongest for the mean of the five bones, although only slightly better than the mean of the three metacarpals. Future prospective studies will be better able to examine the individual bones in more detail and to determine whether there is some other method for optimally combining them or whether fewer bones can be assessed to give similar performance.

A unique aspect of the X-posure System is that it calculates striation and porosity of cortical bone. These values are used to correct the estimate of DXR-BMD. However, the correction made little practical difference: the correlation between the corrected and uncorrected values was >0.99. However, we also tested the measurements of porosity and striation themselves in terms of their decrease with age and association with fracture history. The results, particularly for striation, were intriguing and suggested that these parameters deserve further study. These parameters are calculated using algorithms still under development. Future refinements may yield values that are more precise or more strongly predictive of fracture risk. It may also prove interesting to examine longitudinal changes in porosity and striation. A recent study of changes in porosity with alendronate and with hormone replacement therapy *(14)* found increases in cortical width and decreases in porosity. Two additional studies examined the effect of treatment on cortical porosity using quantitative computed tomography (QCT) *(15,16)*. In the first, QCT at the femur was used to assess cortical bone in a trial of parathyroid hormone (PTH). The results suggested that PTH increases cortical porosity. That study also noted an increase in cortical width. In the second, histomorphometry of a small number of patients suggested similar changes with bisphosphonate therapy. These results imply that measurements of porosity and striation may be use-

ful in understanding changes to bone that occur with antiresorptive therapy. If such changes prove to be germane to predicting the effect of treatment on fracture reduction, the X-posure System may be useful as a simple, inexpensive, and noninvasive method for assessing similar changes in bone structure.

In summary, we have established reference ranges for the DXR measurements in Caucasian women in the United States and have determined that these measurements are highly correlated with DXA at the wrist. Furthermore, preliminary retrospective analyses have suggested that DXR-BMD and DXA at the wrist have similar relationships to fracture history. Taken together, these data support the use of the X-posure System as an alternative to DXA at the wrist in the assessment of osteoporosis.

Acknowledgments

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Prevalence of Low Femoral Bone Density in Older U.S. Adults from NHANES III*

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ABSTRACT

Most estimates of osteoporosis in older U.S. adults have been based on its occurrence in white women, even though it is known to affect men and minority women. In the present study, we used dual-energy X-ray absorptiometry measurements of femoral bone mineral density (BMD) from the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) to estimate the overall scope of the disease in the older U.S. population. Specifically, we estimate prevalences of low femoral BMD in women 50 years and older and explore different approaches for defining low BMD in older men in that age range. Low BMD levels were defined in accordance with an approach proposed by an expert panel of the World Health Organization and used BMD data from 382 non-Hispanic white (NHW) men or 409 NHW women ages 20–29 years from the NHANES III dataset. For women, estimates indicate 13–18%, or 4–6 million, have osteoporosis (i.e., BMD >2.5 standard deviations [SD] below the mean of young NHW women) and 37–50%, or 13–17 million, have osteopenia (BMD between 1 and 2.5 SD below the mean of young NHW women). For men, these numbers depend on the gender of the reference group used to define cutoff values. When based on male cutoffs, 3–6% (1–2 million) of men have osteoporosis and 28–47% (8–13 million) have osteopenia; when based on female cutoffs, 1–4% (280,000–1 million) have osteoporosis and 15–33% (4–9 million) have osteopenia. Most of the older U.S. adults with low femur BMD are women, but, regardless of which cutoffs are used, the number of men is substantial. (J Bone Miner Res 1997;12:1761–1768)

INTRODUCTION

Osteoporotic hip fracture remains a major public health concern in the United States. Although the etiology of osteoporotic fractures is multifactorial, bone mineral density (BMD) has been identified as one of the primary predictive risk factors.[1–3] Based on this fact, an expert panel of the World Health Organization (WHO) recently proposed diagnostic criteria for osteoporosis based on bone density.[4,5] The applicability of these criteria to groups other than white women is not certain; but osteoporosis is not only a disease of white women.[6,7] For example, of the 281,000 hospital discharges for hip fracture among persons age 45 years and older in the U.S in 1994, 74,000, or 26%, were men (personal communication, Dr. W. Edward Bacon). The proportion of men may increase in the future because the hip fracture incidence rate in U.S. men appears to be going up over time, while rates in women may have plateaued.[8,9]

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We recently estimated the prevalence of older U.S. women with low femoral BMD using the WHO diagnostic criteria in conjunction with femoral BMD data collected in the first 3-year national sample of the third National Health and Nutrition Examination Survey (NHANES III).[10] We included estimates for nonwhite women from two minority groups with BMD values that fell below cutoffs based on white women. Since that time, the second 3-year national sample of NHANES III has been completed. In this paper, we update the estimates of osteoporosis in older U.S. women, including minority women, using the full 6 years of NHANES III. In addition, we explore the application of the WHO criteria to older U.S. men.

MATERIALS AND METHODS

Data source

Estimates of low femoral bone density are based on data collected in NHANES III. The NHANES are conducted periodically by the National Center for Health Statistics, Centers for Disease Control and Prevention, to assess the health and nutritional status of the civilian noninstitutionalized population of the United States. NHANES III is a 6-year study (1988–1994) divided into two 3-year national probablity samples: phase 1 (1988–1991) and phase 2 (1991–1994). Both phases were designed to be separate national probability samples. The survey uses a stratified, multistage probability design to select the sample and has been described in detail elsewhere.[11]

All men and nonpregnant women age 20 years and older were eligible for bone densitometry unless they had fractured both hips previously. Bone mineral measurements were performed on 14,646 men and women age 20 years and older in the full survey. This represents 63% of the eligible selected sample, 78% of the eligible interviewed sample, and 88% of the eligible examined sample. The left hip was scanned unless there was a history of previous fracture or surgery; only 1% received a scan of the right femur. Because their inclusion did not alter prevalence estimates, those who received a scan of the right femur were included in the analyses.

Prevalences were estimated for men and women age 50 years and older because the predictive relationship between fracture and femur BMD has been studied exclusively in older persons.[1–3] Bone mineral measurements were performed on 3176 older men in NHANES III, but 86, or 3%, were rejected for technical reasons after review, leaving 3090 with acceptable data. Of the 3379 women age 50 years and older who received scans, 68, or 2%, were rejected, leaving 3311 with acceptable BMD data. The race/ethnic composition of the sample of older persons with acceptable BMD data for men and women, respectively, was 1723 and 1880 non-Hispanic whites (NHW), 647 and 695 non-Hispanic blacks (NHB), and 625 and 600 Mexican Americans (MA). Race and ethnic categories were based on self-reported data using U.S. Census Bureau definitions. There were too few persons of other race and ethnic groups (n = 95 and 136 older men and women, respectively) to report prevalences separately for these groups, although they were included in estimates for the total population.

Bone density measurements

BMD of the proximal femur was measured using dual-energy X-ray absorptiometry (DEXA) at five regions of interest. In this study, we present data on four regions: femoral neck, trochanter, intertrochanter, and total femur. Data for the fifth region, Ward's triangle, was not included because (1) it represents a calculated area of low bone density rather than a true anatomic region; (2) Ward's triangle data from the two phases of NHANES III are not directly comparable due to software changes that allowed the location of Ward's triangle to vary in phase 1, but fixed it midcervically in phase 2; and (3) it had a larger in vivo measurement error (5%) than the other regions (2–3%).[12] Three densitometers (Hologic QDR 1000; Waltham, MA, U.S.A.), located in mobile examination centers, were used to obtain the measurements. A rigorous quality control (QC) program, including use of anthropomorphic phantoms and review of each QC and respondent scan at a central site, was used throughout the study to ensure data quality. QC results for the first phase of NHANES III have been published elsewhere[12]; QC results from the second phase were similar to those for phase 1.

Definition of low bone density

The WHO diagnostic criteria for osteopenia and osteoporosis[4,5] were used to define low bone density among men and women age 50 years and older. This approach defines cutoff values using BMD data from a young adult reference group. The WHO criteria did not specify details about the reference group in terms of age, race, or gender. NHW men or women between 20 and 29 years of age were used as the reference group in the present study because there are prospective data indicating that bone loss occurs at the femur in women during their 30s.[13] In addition, the International Committee for Standards in Bone Densitometry recently chose the 20–29 year age range as the reference range for standardizing cutoffs between different bone densitometry instruments (personal communication, Dr. Peter Steiger). Of the scans performed on the young white men (n = 388) and women (n = 415), all but six scans (1.5%), excluded for technical reasons in each group, were used for the reference group. For each of the four regions of interest, low bone density was defined as: (1) osteopenia: a BMD value between 1 standard deviation (SD) and 2.5 SD below the mean of white men or women age 20–29 years; and (2) osteoporosis: a BMD value >2.5 SD below the young reference mean.

These cutoff points were applied to minority men and women in this study as well as to NHWs because data on the predictive utility of femur BMD for hip fracture in nonwhites is lacking to date. In addition, estimates for men were made using cutoffs derived from both the young male and female reference groups, since currently there are insufficient data to identify clearly the most appropriate approach for men.

TABLE 1. MEAN FEMORAL BONE MINERAL DENSITY (BMD) OF 20–29-YEAR-OLD NONHISPANIC WHITE MEN AND WOMEN, NHANES III 1988–94

Region of interest	Mean (g/cm^2)	Standard deviation (g/cm^2)	Range	BMD cutoff values for: Osteopenia*	Osteoporosis*
Men (n = 382)					
femur neck	0.93	0.137	0.585–1.314	0.59–0.79	<0.59
trochanter	0.78	0.118	0.496–1.258	0.49–0.66	<0.49
intertrochanter	1.21	0.172	0.775–1.794	0.78–1.03	<0.78
total femur	1.04	0.144	0.688–1.538	0.68–0.90	<0.68
Women (n = 409)					
femur neck	0.86	0.12	0.56–1.283	0.56–0.74	<0.56
trochanter	0.71	0.099	0.48–1.051	0.46–0.61	<0.46
intertrochanter	1.09	0.142	0.717–1.588	0.74–0.95	<0.74
total femur	0.94	0.122	0.635–1.379	0.64–0.82	<0.64

* WHO diagnostic criteria[4,5]: Osteopenia, BMD value between 1–2.5 SD below mean of young adult reference group; Osteoporosis, BMD value >2.5 SD below mean of young adult reference group.

Data analysis

Sampling weights were used to calculate prevalence estimates and to account for oversampling and nonresponse to the household interview and physical examination. The sampling weights for phases 1 and 2 were based on the March 1990 and March 1993 Current Population Survey values for the civilian noninstitutionalized population, both adjusted for undercounts.[14] All analyzes were performed using SUDAAN.[15]

Both unadjusted and age-adjusted prevalences of low BMD among men and women age 50 years and older were calculated by race and ethnic group. Unadjusted prevalences were used to calculate the number of men and women with low BMD in the U.S., while age-adjusted prevalences were used for comparison of prevalences between genders and race/ethnic groups, since bone density is related to age[16] and the age structure of the different gender and race/ethnic groups varies in the U.S. population. Prevalences were age-adjusted using the direct method to the age distribution of the 1980 population.

RESULTS

Mean BMD, SDs, range of BMD, and the cut-off values corresponding to the WHO diagnostic criteria for low bone mass in the four regions of interest for the reference group of young white men and women are shown in Table 1.

Updated prevalences of osteopenia and osteoporosis in women in the four femur regions using the WHO diagnostic criteria are shown by population in Table 2. Estimates of osteopenia in older women ranged from 37 to 50%, or 13–17 million women, while osteoporosis ranged from 13 to 18%, or 4–6 million. Prevalences of each condition were higher in the femoral neck region than in the other femoral regions. Age-adjusted prevalences of both osteopenia and osteoporosis were higher in NHWs than in NHBs; prevalences in MAs were similar or slightly lower than in NHWs. The ratio of age-adjusted prevalences in NHWs versus NHBs ranged from 1.5 to 2.8, depending on the femoral region and definition of low BMD used (data not shown). Corresponding ratios of prevalences for NHWs versus MAs ranged from 0.8 to 1.2.

Prevalences of osteopenia and osteoporosis in men of all races based on male versus female cutoff values are shown in Table 3. Prevalences of osteopenia were noticably higher when based on male cutoffs than female cutoffs, ranging from 38 to 47%, compared with 15–33%. However, prevalences of osteoporosis were only slightly higher when based on male versus female cutoffs.

When age-adjusted prevalences in men and women are compared, the female-to-male ratios were 1.1–1.6 for osteopenia when prevalence in men was based on male cutoffs and 1.5–2.8 when based on female cutoffs (data not shown). For osteoporosis, the female-to-male ratios were 2.7–4.3 when using male cutoffs for men and 4–7.5 when using female cutoffs.

Patterns of osteopenia and osteoporosis by race or ethnicity in men using the two sets of cutoffs are compared with the patterns seen in women as shown in Fig. 1. The pattern for osteopenia is similar in men and women regardless of the cutoff used in men, with NHWs of both genders having the highest prevalences, followed by MAs, and NHBs having the lowest prevalences. The prevalences of osteoporosis were also greatest in NHW men regardless of the cutoff used. Prevalences of osteoporosis in men of either minority group were so small that they did not achieve statistical reliability, and so the pattern must be interpreted with caution. It suggests, however, that, unlike women, MA men may have a lower prevalence of osteoporosis than NHB men.

DISCUSSION

A considerable number of noninstitutionalized older citizens in the U.S. have low femoral bone density, as defined

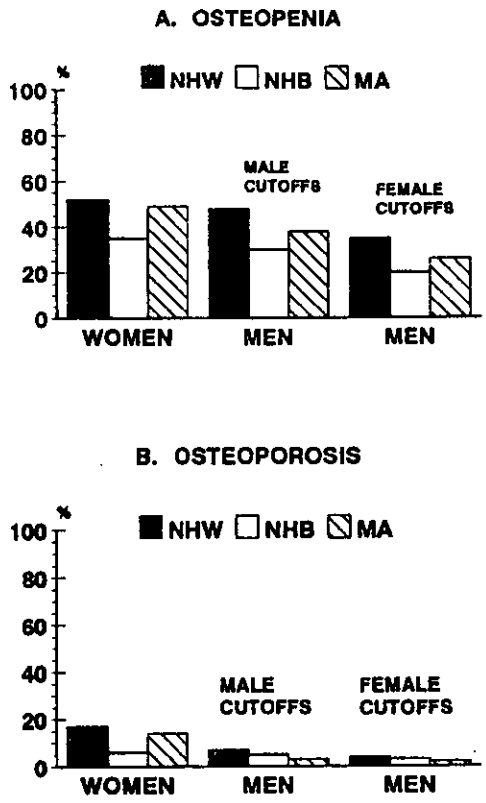

FIG. 1. Age-adjusted prevalence of low femur neck BMD by race or ethnicity, ages 50+ years. NHW = NonHispanic white; NHB = NonHispanic black; MA = Mexican American.

by WHO diagnostic criteria.[4,5] For women, updated estimates indicate 4–6 million have osteoporosis and 13–17 million have osteopenia. For men, these numbers depend on whether male versus female cutoff values are used. When based on male cutoffs, 1–2 million men have osteoporosis and 8–13 million have osteopenia; when based on female cutoffs, 280,000–1 million have osteoporosis and 4–9 million have osteopenia. Regardless of which cutoffs are used for men, the numbers are substantial.

The updated prevalences of osteopenia in women are similar to those published previously using phase 1 data only, while the updated prevalences of osteoporosis are slightly lower.[10] The latter is a result of the larger SDs and concomitantly lower osteoporosis cutoff values when based on the larger reference group of 409 young NHW women. By chance, the representative sample in phase 2 of the survey included a small number of young women with BMD values that exceeded the BMD range observed in phase 1. This wider BMD distribution contributed to the larger SD for the total sample of these young women. Because of the larger sample sizes, we believe the updated prevalence estimates are the most reliable estimates of osteoporosis and osteopenia in women.

The definitions of low BMD used in this study were based on the WHO diagnostic criteria.[4,5] These guidelines represent an important step in describing the extent and characteristics of osteoporosis, but the panel was aware that the guidelines had limitations and would likely change with more experience. A major issue for the current study is the application of the guidelines to men, since they were developed for women. The WHO panel noted that the criteria likely should be modified for men, but there were insufficient data to do so. To firmly resolve the issue, prospective data on the absolute risk of fracture at any given BMD level in men must be obtained. In the absence of such data, the panel suggested either applying female cutoffs to men or using a more stringent criterion of 3–4 SD for osteoporosis if cutoffs were based on a male reference group.

Our cross-sectional study can illustrate some of the issues to be addressed in determining the appropriate definitions of osteopenia and osteoporosis in men. For example, in our sample of older men, 1.5% had BMD values more than 3 SD below the young men's mean, which suggests that this criterion may be too stringent. When we used the 2.5 SD criterion, the prevalence of femoral osteoporosis in older men was similar regardless of the gender of the reference group. This is probably because the osteoporosis cutoff values fell in the tail of the BMD distribution of older men, where small differences in cutoff values will not result in adding or subtracting many individuals. Our estimates of osteoporosis in older men using either male or female cutoffs were similar in magnitude to the estimates of lifetime risk of hip fracture for men from other studies[17]; this type of similarity was cited by the WHO panel to support the validity of the guidelines for women.[4,5] Until the appropriate prospective data on fracture risk in men are available, it seems reasonable to use the 2.5 SD criterion to estimate prevalence of osteoporosis among older men in the population. This approach for defining osteoporosis in a population does not, however, constitute a clinical diagnostic criteria for men.

An interim definition of osteopenia for the male population is not clear though, since prevalences of osteopenia depended on the gender of the reference group used to derive the cutoff values. When based on male cutoffs, the prevalences of osteopenia in older men were almost as high as those in older women, which may seem too high given the lower fracture rate in men. When considering how to define osteopenia in men, it may be pertinent to recall that this category was defined for women primarily to identify those in whom preventing further bone loss would be most useful.[4,5] The gradient of risk between BMD and fracture is continuous,[4,5] so men with osteopenia are likely to be at some increased risk of developing osteoporosis compared with men with higher BMD values. In addition, femoral BMD also declines progressively with age in men.[18] Given this, an osteopenia category in men may be useful to help direct prevention efforts regardless of whether it is defined by male or female cutoffs.

Other issues may be important to consider in defining low bone mass for men. For example, uniform criteria for men and women have been used for other disease risk factors, such as hypercholesterolemia and hypertension. The assumption of similar mechanisms, levels of risk, and response to treatment in men and women is inherently appealing and also provides clinical simplicity. However,

TABLE 2. PREVALENCE OF LOW FEMORAL BONE DENSITY IN NONINSTITUTIONALIZED U.S. WOMEN AGES 50+, NHANES III 1988–94

	Osteopenia			Osteoporosis		
Region of interest	*Prevalence**	*95% CI*†	*Millions*‡	*Prevalence**	*95% CI*†	*Millions*‡
All races						
femur neck	50 (50)	47, 53	17	18 (18)	16, 20	6
trochanter	44 (44)	42, 47	15	13 (12)	11, 14	4
intertrochanter	37 (36)	35, 40	13	14 (13)	13, 16	5
total femur	40 (40)	38, 43	14	16 (15)	14, 18	5
NonHispanic whites						
femur neck	52 (52)	49, 55	15	20 (17)	17, 22	6
trochanter	45 (44)	43, 48	13	13 (12)	11, 15	4
intertrochanter	39 (38)	37, 42	11	15 (13)	13, 17	4
total femur	42 (41)	40, 45	12	17 (15)	15, 19	5
NonHispanic blacks						
femur neck	35 (35)	30, 39	1	5 (6)	4, 7	0.2
trochanter	31 (31)	26, 37	1	7 (7)	5, 8	0.2
intertrochanter	24 (24)	20, 28	0.8	7 (8)	5, 10	0.2
total femur	28 (28)	25, 31	0.9	8 (8)	6, 10	0.3
Mexican Americans						
femur neck	49 (49)	43, 54	0.4	10 (14)	7, 13	0.1
trochanter	42 (42)	37, 47	0.4	12 (15)	7, 16	0.1
intertrochanter	31 (32)	27, 35	0.3	11 (14)	7, 14	0.1
total femur	37 (38)	33, 42	0.3	12 (16)	8, 16	0.1

* Prevalences shown in parenthesis are age-adjusted to the 1980 U.S. census population.
† Pertain to unadjusted prevalences.
‡ Based on the average of undercount-adjusted population estimates from the March 1990 and March 1993 Current Population Surveys.

TABLE 3. PREVALENCE OF LOW FEMORAL BONE DENSITY IN NONINSTITUTIONALIZED U.S. MEN AGES 50+, USING MALE VS. FEMALE CUTOFF VALUES, ALL RACES, NHANES III 1988–94

	Osteopenia				Osteoporosis			
	Female cutoffs		*Male cutoffs*		*Female cutoffs*		*Male cutoffs*	
Region of interest	*Prevalence**	*95% CI*	*Prevalence**	*95% CI*	*Prevalence**	*95% CI*	*Prevalence**	*95% CI*
Femur neck	33	30, 36	47	45, 50	4	3, 5	6	5, 7
Trochanter	16	13, 18	28	25, 31	1†	0.8, 2	3	2, 4
Intertrochanter	15	12, 18	29	26, 32	2†	2, 3	4	3, 5
Total femur	16†	14, 19	33	30, 36	2	2, 3	4	3, 5

* Not age-adjusted. Age-adjusted prevalances equal unadjusted prevalences except where noted with dagger.
† Age-adjusted prevalence is 1% higher.

these considerations must be reconciled with factors that may favor gender-specific cutoffs. For example, male fracture cases have higher BMD levels than female fracture cases[19–22]; it is unclear, however, whether this finding reflects a truly higher fracture risk for a given BMD in men or simply that the entire male BMD distribution is higher than that of women. Fracture risk at a given BMD level might truly differ between genders because of differences in skeletal loads from the larger male body mass or gender differences in structure–resistance relationships.[23]

Alternatively, fracture risk in men could appear to differ because areal bone density, as measured by DEXA, does not completely account for the confounding effect of bone size.[24] Young adult men and women have similar spinal volumetric bone density, as measured by computed tomography, but spinal areal bone density by DEXA is greater in men.[23,24] At the femur, men have approximately 10% higher areal femoral BMD than women before adjusting for body size,[16] but levels are similar after this adjustment, with the possible exception of the femoral neck.[25–27] The current DEXA reports do not adjust BMD for body size, so gender-specific cutoff values may be necessary to account for this artifact even though men and women may have similar true volumetric bone density levels.

Another unresolved issue in using the WHO criteria is the appropriate cutoff values for minority men and women. We applied cutpoints based on young whites to the minority groups in this study, as well as previously,[10] because the relationship between femur BMD and hip fracture risk has been studied exclusively in whites to date.[1,2,3] Prevalences of osteoporosis for whites and blacks in our study are similar to estimated lifetime fracture risks for these groups.[17] We also found a similar ratio of age-adjusted prevalences in whites versus blacks in our study as the white–black fracture ratio reported by others.[7,28–31] Both of these findings provide some indirect support for our approach. The validity of applying white cutoffs to MAs is more difficult to assess, since very little data are available on hip fracture rates in U.S. Hispanics. The few studies done to date suggest that they have lower rates than whites.[31–33] We found lower prevalences of osteopenia in MAs than in NHWs, but prevalences of osteoporosis in women were similar in the two groups (prevalences in men were too small to compare reliably). However, due to their higher mean BMD levels,[16] cutoffs based on young MAs would have resulted in even higher prevalences in this group compared with NHW, which is less consistent with fracture patterns. Finally, fracture risk is also influenced by other, non-BMD factors such as hip axis length, muscle strength, or falls, which may differ among race or ethnic groups.[21,34–39]

Other issues noted previously in our application of the guidelines to older women in the U.S., such as accounting for the individual's age in addition to BMD when considering risk,[40–42] still remain to be resolved. In addition, as noted previously,[10] the young white male and female reference groups in our study had a lower mean BMD and higher SD than the male and female references group provided by the densitometer manufacturer,[43] so that fewer individuals will be identified with low bone mass than if the manufacturer's cutoff values are used. Finally, it should be noted that the absolute BMD values presented in this paper, including the cutoff values, are densitometer-specific and cannot be compared directly with BMD results from other DEXA instruments without a conversion factor for the femur.

Limitations of this study include potential nonresponse bias in the sample and the exclusion of institutionalized people from the NHANES III sample frame. Nonresponse bias in the sample who came to the mobile exam centers in NHANES III is reduced to some extent by a nonresponse adjustment factor included in the calculation of the sample weights.[11,14] After applying these weighting adjustments, differences between examinees and nonexaminees were minor.[14,44,45] However, about 12% of those who came to the mobile exam centers did not have usable BMD data, and this nonresponse is not addressed by the sample weight adjustments. A nonresponse bias study for phase 1 of NHANES III found differences in weight, self-reported health status, and vitamin supplement use between those with bone density data compared with the examined sample as a whole.[45] We explored nonresponse bias among the 20- to 29-year-old NHW women and in individuals age 50+ years to assess the possible impact on means and prevalences. Nonrespondents in the young female reference group weighed more than respondents, but mean total femur BMD did not differ greatly when imputed data for nonrespondents (based on their body weight) were added to the dataset (i.e., 0.941 g/cm^2 based on actual and imputed data vs. 0.937 g/cm^2 based on actual data only). Likewise, differences in weight, self-reported health status, and age between respondents and nonrespondents age 50+ years did not appear to impact greatly the prevalence estimates (e.g., ~16% of women and 2–4% of men had total femur osteoporosis whether based on actual and imputed data or on the actual data alone). Studies to assess the effect of missing BMD data in phase 2 are continuing as more data become available from NHANES III. It is also important to note that the prevalence estimates in this study pertain only to the noninstitutionalized U.S. population. Institutionalized persons may have lower bone mass,[46,47] so the prevalence of low bone mass in the total U.S. population is probably higher than our estimates.

In conclusion, the number of older U.S. adults with low femur BMD using the WHO criteria is substantial. Most of these are women, but the number of older U.S. men with osteopenia or osteoporosis of the femur is not small, regardless of whether these are defined with male or female cutoffs. Much remains to be learned about BMD and fracture risk in men, but it is likely that men with osteopenia and osteoporosis would benefit from taking steps to prevent further bone loss.

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Address reprint requests to:
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6525 Belcrest Road, Room 900
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Received in original form January 13, 1997; in revised form April 11, 1997; accepted June 3, 1997.

Food and Drug Administration
Office of Device Evaluation &
Office of In Vitro Diagnostics

COVER SHEET MEMORANDUM

From: Reviewer Name _Ewa Czerska_____

Subject: 510(k) Number _K082402_____

To: The Record

Please list CTS decision code _SE_____

☐ Refused to accept (Note: this is considered the first review cycle, See Screening Checklist http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)

☐ Hold (Additional Information or Telephone Hold).

√ Final Decision (SE, SE with Limitations, NSE, Withdrawn, etc.).

Please complete the following for a final clearance decision (i.e., SE, SE with Limitations, etc.):		YES	NO
Indications for Use Page	*Attach IFU*	√	
510(k) Summary /510(k) Statement	*Attach Summary*	√	
Truthful and Accurate Statement.	*Must be present for a Final Decision*	√	
Is the device Class III? If yes, does firm include Class III Summary?	*Must be present for a Final Decision*		√
Does firm reference standards? (If yes, please attach form from http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4136/ABBREVIATED STANDARDS DATA FORM.DOC)			√
Is this a combination product? (Please specify category _____, see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_413b/COMBINATION%20PRODUCT%20ALGORITHM%20(REVISED%203-12-03).DOC			√
Is this a reprocessed single use device? (Guidance for Industry and FDA Staff – MDUFMA - Validation Data in 510(k)s for Reprocessed Single-Use Medical Devices, http://www.fda.gov/cdrh/ode/guidance/1216.html)			√
Is this device intended for pediatric use only?			√
Is this a prescription device? (If both prescription & OTC, check both boxes.)		√	
Is clinical data necessary to support the review of this 510(k)?			√
Does this device include an Animal Tissue Source?			√
Is this device subject to Section 522 Postmarket Surveillance? (Postmarket Surveillance Guidance, http://www.fda.gov/cdrh/osb/guidance/316.html)	*Contact OSB.*		√
Is this device subject to the Tracking Regulation? (Medical Device Tracking Guidance, http://www.fda.gov/cdrh/comp/guidance/169.html)	*Contact OC.*		√

Regulation Number	**Class***	**Product Code**
__21CFR 892.1170_____	II_____	KGI_____

(*If unclassified, see 510(k) Staff)

Additional Product Codes: _____

Review: _____ (Branch Chief) RADB (Branch Code) 10/14/08 (Date)

Final Review: _____ (Division Director) 10/16/08 (Date)

4

PRE-REVIEW FORM: COMPANY/DEVICE HISTORY

Please complete the pre-review form prior to beginning the review of this 510(k). This form is designed to be a tool to identify key items that may be important to consider regarding the regulation of the subject device and if you should even begin the review of the 510(k).

If you answer YES to questions 1, 2 or 3; do NOT begin the review of this 510(k):	**YES**	**NO**
1. Are you aware of the submitter being the subject of an integrity investigation? (Please see H:\INTEGRITY LIST\CDRH REVIEWER SCREENING LIST.DOC)		√
2. Is the device exempt from 510(k) by regulation (Please see http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4134/510(K)%20EXEMPT%20%20FORM.DOC or subject to enforcement discretion (No regulation - See 510(k) Staff)?		√
3. Does this device type require a PMA by regulation? (Please see management.)		√
Questions 4-8 are intended to help you start your review:	**YES**	**NO**
4. Is this 510(k) a candidate for "Refuse to Accept"? (If so, please use the Traditional/Abbreviated or Special 510(k) Refuse to Accept Screening Checklist, http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_5631/Screening%20Checklist%207%202%2007.doc)		√
5. a. Did the firm request expedited review? (See management.)		√
b. Was expedited review granted? (See *Guidance for Industry and FDA Staff: Expedited Review of Devices for Premarket Submissions*, http://www.fda.gov/cdrh/mdufma/guidance/108.html)		
6. To the best of your knowledge, was there a pre-IDE, 513(g) or other pre-submission for this type of device? Please list document number and/or date, here:		√
7. To the best of your knowledge, has a 510(k) previously been submitted for this specific device (i.e., previously found NSE or withdrawn)? Please list document number, here:		√
8. Does this device have indications or technology that are cross-cutting and impact the review policy of another branch(es)? (Please contact other branch(es) and see *Guidance for Industry and FDA Staff on Bundling Multiple Devices or Multiple Indications in a Single Submission* http://www.fda.gov/cdrh/mdufma/guidance/1215.html)		√

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

Premarket Notification [510(k)] Review
Traditional/Abbreviated

K082402

Date: 9/26/2008
To: The Record
From: Ewa Czerska

Office: ODE
Division: DRARD

510(k) Holder: Imaging Therapeutics, Inc.

Device Name: OsDx Hip BMD System
Contact: Patrick Hess, PhD
Phone: 650-286-4166
Fax: 650-286-4160
Email: Patrick.hess@imatx.com

I. Purpose and Submission Summary

The Imaging Therapeutics would like to introduce bone mineral density system in commercial distribution.

II. Administrative Requirements

	Yes	No	N/A
Indications for Use page (Indicate if: Prescription or OTC)	√		
Truthful and Accuracy Statement	√		
510(k) Summary or 510(k) Statement	√		
Standards Form			√

III. Device Description

The OsDx Hip BMD System is a software package that provides an estimate of BMD based on scanned x-rays analysis. The program utilizes a quantitative bone structural algorithm that measures a composite of weighted cortical and trabecular parameters in proximal femur projection radiographs from which total hip bone mineral density (BMD) is mathematically derived. Image analysis can take place remotely or at the point of care.
The results, expressed as gm/cm^2, can be used for comparison to a reference data base of young normals (T-score) or age-matched controls (Z-score).

	Yes	No	N/A
Is the device life-supporting or life sustaining?		√	

	Yes	No	N/A
Is the device an implant (implanted longer than 30 days)?		√	
Does the device design use software?	√		
Is the device sterile?		√	
Is the device reusable (not reprocessed single use)?			
Are "cleaning" instructions included for the end user?			√

IV. Indications for Use

The OsDx Hip BMD System stand-alone software is intended to provide an estimate of the bone mineral density (BMD) of the proximal femur using digital antero-posterior hip or pelvis radiographic images. This information may be used by the physician in the assessment of fracture risk in conjunction with the World Health Organization ("WHO") criteria and to compare the derived BMD estimate with reference populations of young (20-39) and age matched normals to compute T-scores and Z-scores respectively.

Comments: The Indication for Use statement is acceptable.

V. Predicate Device Comparison

The subject device is comparable to Hologic Hip Structural Analysis Software, K061561, Pronosco X-Posure System Bone Densitometer, K984178, and CTXA Hip, K002113. Tabular comparison is provided on page 69 of the premarket notification.

Comments: The sponsor provided adequate comparison on the intended use and technology of their device and these two predicate devices, and thus demonstrated substantial equivalence. The Substantial Equivalence demonstration is acceptable.

VI. Labeling

The sponsor provided a draft user's manual and promotional material on page 11 of the document. The labeling is acceptable.

VII. Sterilization/Shelf Life/Reuse: N/A

VIII. Biocompatibility: N/A

IX. Software

Version:		
Level of Concern: **Moderate.**		
	Yes	**No**
Software description:	√	
Device Hazard Analysis:	√	
Software Requirements Specifications:	√	
Architecture Design Chart:	√	
Design Specifications:	√	
Traceability Analysis/Matrix:	√	

Development:	√
Verification & Validation Testing:	√
Revision level history:	√
Unresolved anomalies:	√

X. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety: **N/A**

XI. Performance Testing – Bench:

The company performed optimization Study using standard pelvic Radiographs from the Study of Osteoporotic Fractures and optimization study for failure load and DXA-BMD Estimation using radiographs of cadaver.

XII. Performance Testing – Animal: **N/A**

XIII. Performance Testing – Clinical:

Clinical testing is provided in section 6 of the document. The performance of the device was validated in three separate clinical studies. The IRBs were obtained; IDE was not required, since the studies were NSR. The device was used in retrospective fracture risk studies and is used in ongoing prospective multicenter study entitled the Study of Osteoporotic Fractures.
Precision and reproducibility study was also provided on the page 99.

XIV. Substantial Equivalence Discussion

	Yes	No	
1. Same Indication Statement?	√		If **YES** = Go To 3
2. Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NSE**
3. Same Technological Characteristics?	√		If **YES** = Go To 5
4. Could The New Characteristics Affect Safety Or Effectiveness?			If **YES** = Go To 6
5. Descriptive Characteristics Precise Enough?	√		If **NO** = Go To 8 If **YES** = Stop **SE**
6. New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NSE**
7. Accepted Scientific Methods Exist?			If **NO** = Stop **NSE**
8. Performance Data Available?			If **NO** = Request Data
9. Data Demonstrate Equivalence?			Final Decision: **SE**

Note: See http://eroom.fda.gov/eRoomReq/Files/CDRH3/CDRHPremarketNotification510kProgram/0_4148/FLOWCHART%20DECISION%20TREE%20.DOC for Flowchart to assist in decision-making process. Please complete the following table and answer the corresponding questions. "Yes" responses to questions 2, 4, 6, and 9, and every "no" response requires an explanation.

1. Explain how the new indication differs from the predicate device's indication:

2. Explain why there is or is not a new effect or safety or effectiveness issue:

3. Describe the new technological characteristics:

4. Explain how new characteristics could or could not affect safety or effectiveness:

5. Explain how descriptive characteristics are not precise enough:

   The company provided software documentation adequate for minor level of concern. Moderate level of concern is required. I have contacted the sponsor by e-mail (attached) for adequate software documentation. Dr. Hess agreed to change the level of concern to moderate and provide appropriate documentation.

6. Explain new types of safety or effectiveness question(s) raised or why the question(s) are not new:

7. Explain why existing scientific methods can not be used:

8. Explain what performance data is needed:

9. Explain how the performance data demonstrates that the device is or is not substantially equivalent:

XV. Deficiencies

When developing deficiencies please consider the following "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA" (http://www.fda.gov/cdrh/modact/guidance/1195.html) and "A Suggested Approach to Resolving Least Burdensome Issues" (http://www.fda.gov/cdrh/modact/leastburdensome.html).

XVI. Contact History:

- **E-mail on September 30, 2008 asking for change in software LOC.**
- **E-mail from sponsor on October 2 with the change**
- **Phone conference on October 3, 2008 (Dr. Hess, Dr. Paquerault, and Dr. Czerska) to explain what documentation is needed in order to clear the subject device.**
- **E-mail from sponsor on October 8, copy of software documentation for moderate level of concern included.**

XVII. Recommendation

Regulation Number: 21 CFR 892.1170
Regulation Name: Bone Densitometer
Regulatory Class: Class II,
Product Code: KGI

I recommend the device to be cleared.

Ewa Czerska

Reviewer Ewa Czerska — Date 10/9/2008

Branch Chief — Date 10/14/08

Czerska, Ewa M.

From: Patrick Hess [patrick.hess@conformis.com]
Sent: Wednesday, October 08, 2008 2:48 PM
To: Czerska, Ewa M.
Subject: Response to #K082402
Attachments: OsDx 510K082402_Oct808.doc; 510k082402 Oct808.zip

Dear Dr. Czerska,

Thank you for your review of the documents relating to software in Imaging Therapeutics' 510k application #K082402 for the OsDx Hip BMD System.

We appreciate the opportunity to respond to your request for additional details regarding the software documentation.

We have enclosed the summary of the software section of the 510k.

Additionally, copies of the referenced documents are enclosed in the attached ZIP file.

Please let me know if there are any other questions I can answer during the review cycle.

Best regards,

Pat

Patrick Hess, PhD, MBA, FACB

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President and CEO
400 Seaport Court, Suite 250
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Office: 650.286.4151
Fax: 650.286.4160
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The information contained in this e-mail message, and any attachments, may be confidential and protected from disclosure. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think that you have received this e-mail message in error, please e-mail the sender at patrick.hess@imatx.com

Section 8 Software Verification and Validation

Software for the OsDx Hip BMD System has been developed, verified and validated in accordance with Imaging Therapeutic's Design Control Process (SOP-00003), Software Development, Verification and Validation (SOP-00047), and Software Configuration Management (SOP-00046). In addition, the OsDx Hip BMD System software has been developed in accordance with the *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (issued 5/11/2005), *General Principles of Software Validation* (finalized 1/11/02).

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

The documents described in this section have been provided for reference purposes, for convenience in review of the 510k.

Verification and Validation demonstrate that the OS Dx software meets the requirements of the Software Requirements Specifications and Design Descriptions, performs as intended, and supports the indications for use.

Czerska, Ewa M.

From: Patrick Hess [patrick.hess@conformis.com]
Sent: Thursday, October 02, 2008 2:23 PM
To: Czerska, Ewa M.
Subject: RE: K082402
Attachments: OsDx 510K082402_Oct20.8_response.doc

Dear Dr. Czerska,

Thank you for your response regarding the 510k application #K082402 for the OsDx Hip BMD System. We appreciate the opportunity to respond to your question regarding the level of concern.

We have re-evaluated the Level of Concern questions described in ODE *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidance for Industry and FDA Staff* issued on May 11, 2005.

We agree with the Agency that this device should be a "Moderate" Level of Concern.. Imaging Therapeutics will reconvene a meeting to review the risk analysis and the associated software hazards and revise the documentation to reflect software with a "Moderate" level of concern. The revised risk analysis and LOC analysis is on file and maintained in the Risk Management File in the design history file.

Please note that Imaging Therapeutics has detailed documentation regarding the software, which is described in the attached response. Please let me know if there are any other questions I can answer during the review cycle.

Best regards,

Patrick Hess, PhD, MBA
Imaging Therapeutics, Inc

From: Czerska, Ewa M. [mailto:ewa.czerska@fda.hhs.gov]
Sent: Tuesday, September 30, 2008 9:23 AM
To: Patrick.hess@imatx.com
Cc: Czerska, Ewa M.
Subject: K082402

Dear Dr. Hess,

I am in the process of reviewing your 510K application for OsDx Hip BMD System. The document is still under review however I noticed that you have provided the software documentation for minor level of concern. All imaging devices are at least moderate level of concern since the diagnosis and consequently treatment are based on the image.

Please provide the appropriate software documentation for your device.

Section 8 Software Verification and Validation

Software for the OsDx Hip BMD System has been developed, verified and validated in accordance with Imaging Therapeutic's Design Control Process (SOP-00003), Software Development, Verification and Validation (SOP-00047), and Software Configuration Management (SOP-00046). In addition, the OsDx Hip BMD System software has been developed in accordance with the *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (issued 5/11/2005), *General Principles of Software Validation* (finalized 1/11/02).

(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

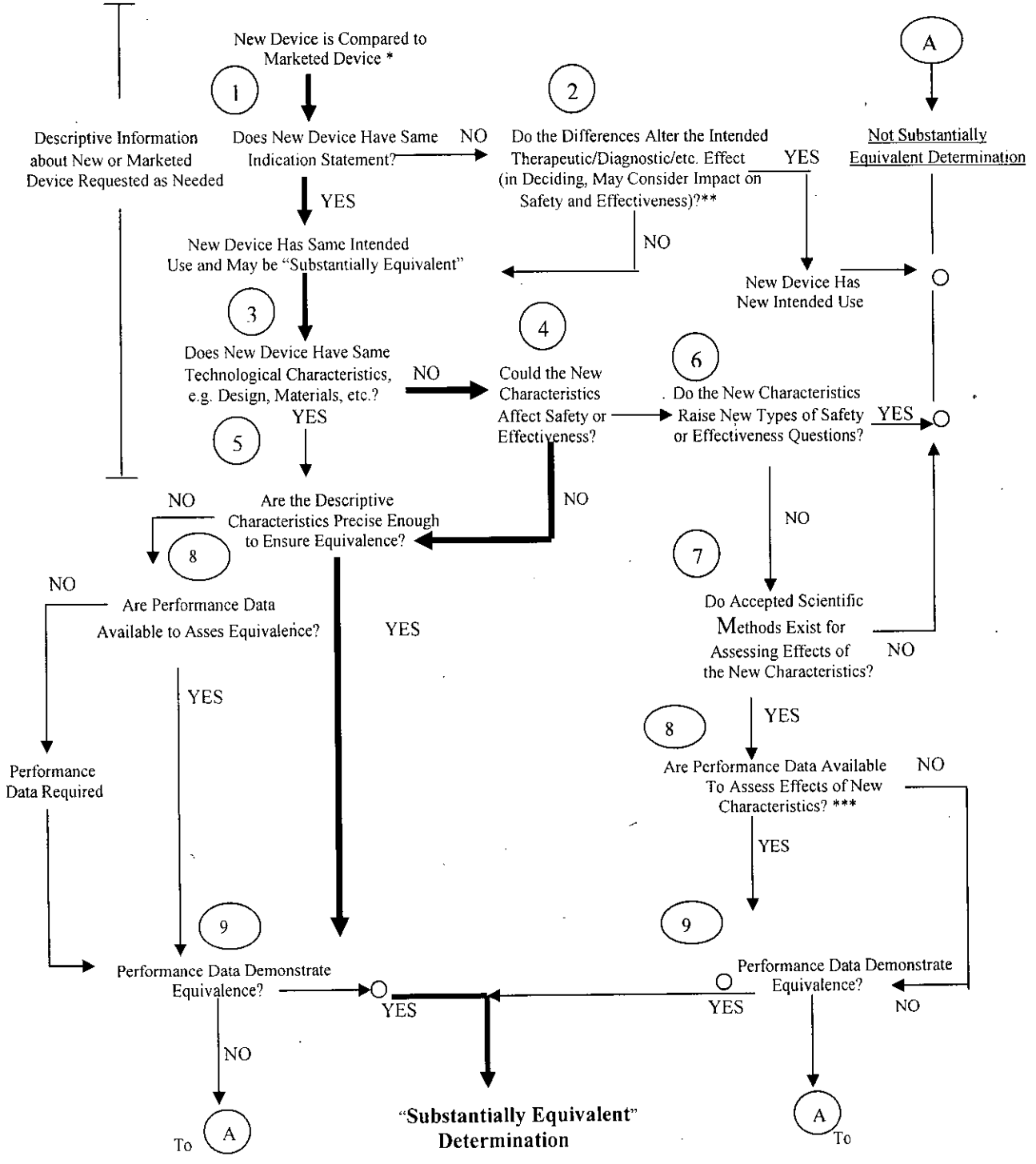
(b)(4), (b)(5)

(b)(4), (b)(5)

(b)(4), (b)(5)

Verification and Validation demonstrate that the OS Dx software meets the requirements of the Software Requirements Specifications and Design Descriptions, performs as intended, and supports the indications for use.

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.