IBEX Bone Health v1.5.0
Instructions For Use
End User Manual

Document Revision 1

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Document approvals:

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Contents

Overview

Instructions for use of the IBEX Bone Health software are separated by topics relevant to the user.

The end users manual (IBX_PRD_SOP_002) provides an overview of the intended use as well as information on the indications for use, contraindications, suggested use cases, and limited troubleshooting advice. All of the information needed by the end user for safe and effective use of the product, including background on the technical basis and clinical validation of the product is provided in this manual.

The service manual (IBX_PRD_SOP_003) provides guidance to the engineer on how to configure the product for use. The instructions include details on licensing, system calibration, settings optimisation, and troubleshooting. Engineers should familiarise themselves with the contents of the end users manual so they have a good understanding of how the product will be used.

The integration manual (IBX_PRD_SOP_004) is intended for developers integrating IBEX BH into OEM systems. Guidance on hardware requirements, API use, and system optimisation is provided. Integrators should familiarise themselves with both the service manual and the end users manual for a complete understanding of the product and its use.

Revision History

Starting from IBEX BH v1.5.0 the instructions for use will be split into three manuals; one each for end users, service engineers, and integrators. To ensure consistency across all versions of the product, vendor-specific IFUs have been merged into a single set of documents describing the configuration and use of IBEX BH. For traceability purposes, the revision histories for previous versions of the manuals are shown below.

Revision	Date	Comment	Initials
1	2024/01/26	First release IFU for IBEX Bone Health v1.1	BL
2	2024/03/08	IFU for IBEX Bone Health v1.2 including customer feedback and error corrections from the first version; clarification of user responsibilities and activities; additional information on errors and warnings; additional information on system configuration including output configuration and licensing; removing the kV offset setting; adding information on deep learning components.	DJ
3	2024/05/22	IFU for IBEX Bone Health v1.3 including calibration workflow simplification; updated default aBMD normative data; new APIs for flushing pipeline and deleting records; new settings for licensing configuration, report configuration, and HTTP request size limit; minor additions to the licensing status API; updated screenshots to the latest interface.	DJ, CS
v1.3rev2	2024/05/29	Corrected information in [Production and Service Engineers] Section 2.2.6.4 on the management of the “calibration QA mode” setting.	CS
v1.3rev3	2024/06/13	Added instructions for native integrations. Added documentation for new settings on report configuration (rotation and clip). Added recommendations on password storage and sharing. Clarify that passwords may only contain ASCII characters.	CS
v1.4rev1	2024/12/11	Added documentation for new settings on report configuration (scaling and version label). Added description of new error code E210. Added details on the training and testing of deep learning elements of the product, and other minor edits.	CS, DJ

Table 1: Instructions for Use IBEX Bone Health, AGF_01_PRD_SOP_004 (DISCONTINUED)

Revision	Date	Comment	Initials
0.1	2024/02/14	First release IFU for IBEX Bone Health v1.1	BL
v1.3rev1	2024/06/13	IFU for IBEX Bone Health v1.3 including customer feedback and error corrections from the first version; clarification of user responsibilities and activities; additional information on errors and warnings; additional information on system configuration including output configuration and licensing; removing the kV offset setting; adding information on deep learning components. Also including calibration workflow simplification; updated default aBMD normative data; new APIs for flushing pipeline and deleting records; new settings for licensing configuration, report configuration, and HTTP request size limit; minor additions to the licensing status API; updated screenshots to the latest interface. Corrected information in [Production and Service Engineers] Section 2.2.6.4 on the management of the "calibration QA mode" setting. Added instructions for native integrations. Added documentation for new settings on report configuration (rotation and clip). Added recommendations on password storage and sharing. Clarify that passwords may only contain ASCII characters.	DJ, CS
v1.3rev2	2024/05/29	Corrected information in [Production and Service Engineers] Section 2.2.6.4 on the management of the "calibration QA mode" setting.	CS
v1.3rev3	2024/06/13	Added instructions for native integrations. Added documentation for new settings on report configuration (rotation and clip). Added recommendations on password storage and sharing. Clarify that passwords may only contain ASCII characters.	CS
v1.4rev1	2024/11/15	Added documentation for new settings on report configuration (scaling and version label). Added details on use of IBEX BH in a mammography setting, details on the training and testing of deep learning elements of the product, and other minor edits.	CS, DJ
v1.4rev2	2024/12/11	Added documentation for new settings on report configuration (bone edges scaling). Added description of new error code E210.	CS

Table 2: Instructions for Use IBEX Bone Health, MET_01_PRD_SOP_001 (DISCONTINUED)

Revision	Date	Comment	Initials
v1.5rev1	2025/03/03	IFU for IBEX Bone Health split into three documents (end users manual, service manual, and integration manual). Document links updated. Added new error/warning codes (new in v1.5.0): W211, E503, E601, E602, E603, E604. Expanded the troubleshooting information in Section 3.2 and made it more relevant to the end user.	CS, DJ, BL

Table 3: Instructions for Use IBEX Bone Health, IBX_PRD_SOP_002

Terms and Definitions

Term	Definition
Central Osteoporosis	An individual with a measured T-score ≤ -2.5 at the femoral neck or lumbar spine is defined as having central osteoporosis.
Customer/End User	Clinical end user or medical physicist — responsible person.
Fingerprint	The set of images used to produce calibration files by IBEX.
Fingerprinting	The process of collecting the set of images used to produce calibration files by IBEX.
IBEX	Engineer or other appropriate personnel appointed by IBEX.
Integrator	Production, service, or other appropriate personnel appointed by the system manufacturer.
T-score	Score created by comparing the patient's bone density to the average bone density of a healthy population of the same sex between 20 and 30 years of age. A score of 0 indicates normal bone health, and a score of -1 indicates bone health lower than the norm by one standard deviation. Osteoporosis is typically indicated by a score lower than -2.5 at the neck of femur.
Working hours	Core working hours are Monday through Friday from 10am - 5pm CET. Response times outside of these hours cannot be guaranteed but special arrangements for out of hours support can be made by prior arrangement if necessary.

Abbreviations

Abbreviation	Meaning
AET	Application Entity Title
AP	Anterior Posterior
API	Application Programming Interface
aBMD	areal Bone Mineral Density
CPU	Central Processing Unit
DICOM	Digital Imaging and Communications in Medicine
DP	Dorsi-Palmar
DR	Digital Radiograph
DXA	Dual-energy X-ray Absorptiometry
FRAX	Fracture Risk Assessment Tool
GPU	Graphics Processing Unit
HTML	HyperText Markup Language
HTTP	HyperText Transfer Protocol
IBEX BH	IBEX Bone Health
IP	Internet Protocol
JSON	JavaScript Object Notation
NHS	National Health Service
NICE	National Institute for Healthcare and Excellence
NoF	Neck of Femur
OEM	Original Equipment Manufacturer
PA	Posterior Anterior
PACS	Picture Archiving and Communication System
PMMA	Polymethyl Methacrylate
QA	Quality Assurance
RAM	Random Access Memory
ROI	Region Of Interest
SCP	Service Class Provider
SCU	Service Class User
SDK	Software Development Kit
SID	Source-to-Image Receptor Distance
SOP	Service Object Pair
TD	Distal-third
UD	Ultra-distal
UDI	Unique Device Identifier
UK	United Kingdom
WHO	World Health Organisation
WSL2	Windows Subsystem for Linux version 2

1 Clinical Use of IBEX BH

1.1 Background to Osteoporosis

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue. The official World Health Organisation (WHO) definition of osteoporosis is a T-score of less than -2.5 at the femoral neck [1] which is determined by conducting a DXA scan of the pelvis.

The consequence is an increase in bone fragility and susceptibility to fracture. Osteoporosis leads to nearly 9 million fractures annually worldwide [2], and over $300,000$ patients present with fragility fractures to hospitals in the UK each year [3].

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or "low-energy") trauma [4]. The WHO has quantified this as forces equivalent to a fall from a standing height or less. Reduced bone density is a major risk factor for fragility fracture. Other factors that may affect the risk of fragility fracture include the use of oral or systemic glucocorticoids, age, sex, previous fractures and family history of osteoporosis [5]. Because of increased bone loss after the menopause in women, and age-related bone loss in both women and men, the prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years in women [6]. As the longevity of the population increases, so will the incidence of osteoporosis and fragility fracture.

Osteoporotic fractures are defined as fractures associated with low BMD and include clinical spine, forearm, hip and shoulder fractures. Osteoporotic fragility fractures can cause substantial pain and severe disability, often leading to a reduced quality of life, and hip and vertebral fractures are associated with decreased life expectancy. Hip fracture nearly always requires hospitalisation, is fatal in 20% of cases and permanently disables 50% of those affected; only 30% of patients fully recover [7]. Direct medical costs due to fractures cost the UK National Health Service (NHS) £4.6 billion per annum [8] .

A number of risk assessment tools are available to predict fracture incidence over a period of time, and these may be used to aid decision making. These tools are limited in that they may not include all risk factors, or may lack details of some risk factors. Tools are dependent on the accuracy of the epidemiological data used to derive them and tools validated in other populations may not apply to the patient demographic. Two tools, Fracture Risk Assessment tool (FRAX) and QFracture, are available for use in the UK and elsewhere [6].

Fracture risk prediction tools are also underutilised, and the Royal Osteoporosis Society Stop at One survey suggested that 1 in 5 women who break a bone will suffer 3 or more fractures before being diagnosed [9].

IBEX BH is designed to help clinicians to find these patients, ideally before a first fracture occurs, by automatically highlighting patients who are at risk. Based on the finding from IBEX BH, clinicians are able to refer patients for further assessment and ultimately treatment to reduce their fracture risk.

1.2 Introduction to IBEX Bone Health

IBEX Bone Health (BH) provides an automated bone health assessment through analysis of standard digital radiographs (DRs). Developed for compatibility with wrist and forearm X-rays, the software provides a measure of areal Bone Mineral Density (aBMD), which is measured in units of grams per square centimetre ($\mathrm{g\,cm^{-2}}$), and T-score (see Section 2.4), which is an indication of bone mass relative to a healthy population. T-score is calculated as the number of standard deviations a patient's bone mass is from a normative population. The measures are provided at the ultra-distal (UD) region and optionally the distal-third (TD) region if it is present in the image. The software is designed to produce measures comparable to a Dual-energy X-ray Absorptiometry (DXA) forearm scan, which is currently the reference standard for measuring aBMD at the UD and TD regions [10].

The general characteristics of the IBEX BH aBMD estimate are as follows:

1. Well correlated to DXA forearm aBMD (see Section 2.1).
2. Insensitive to clinical variations in capture conditions (see Sections 1.6 and 1.7).

3. Reference databases are available (see Section 2.4).

The following steps are performed during an IBEX BH analysis:

1. A wrist or forearm image containing a UD region is acquired.
2. The report Digital Imaging and Communications in Medicine (DICOM) is sent to the Picture Archiving and Communication System (PACS).

A typical output report from the software is shown in Figure 1. The orange numbered sections in the figure are as follows:

1. Standard diagnostic image, which is a copy of the image sent to PACS. Not intended for assessment purposes.
2. Automatic region of interest (ROI) placed at the UD radius if present. The box indicates the ROI, and the inner lines denote the bone/soft tissue boundaries. The enclosed area inside these boundaries is the region where aBMD and T-score are calculated.
3. As 2. but for the TD region. Note that this output will be ignored if the image field of view does not extend to the TD region.
4. Clear indication (see Section 2.3) of the finding is displayed. In this example, “Osteoporosis detected at wrist” is returned if the lowest T-score returned is less than -2.5. The text message and threshold can be changed by your service engineer to meet local needs.
5. aBMD and T-score for the UD region. Where sex is known, this appears in brackets. Where sex is not known, T-score values for both male and female are shown so that the correct value may be selected by the clinician receiving the result. aBMD is the same, regardless of sex, meaning the same value is provided in all cases.
6. As 5. but for the TD region.

Note that your output may differ in appearance from that shown in Figure 1. Please refer to your system vendor’s documentation or contact your system vendor for information on site- or system-specific output formats.

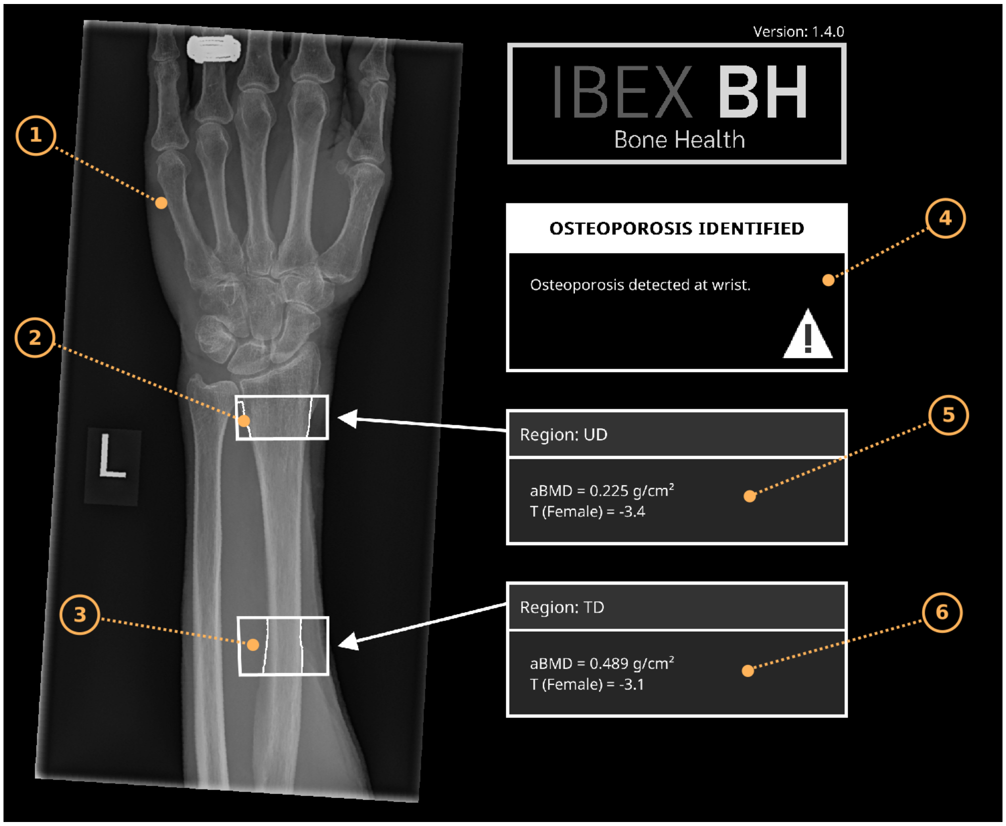

Figure 1: Example IBEX Bone Health output report.

1.3 Intended Use

IBEX BH is intended to provide opportunistic screening for osteoporosis from DRs. The IBEX BH software analyses image data from a DR to generate outputs pertaining to the diagnosis and treatment of osteoporosis, including a measurement of aBMD at the examination site. These measures provide indications which can be used by qualified interpreting clinical professionals to support case finding and diagnosis of osteoporosis.

Its application aims to address the underdiagnosis of osteoporosis, providing clinicians with a decision support to identify patients at risk and potentially improve early intervention strategies.

1.4 Intended Users

The primary intended end user of the deployed device is a radiographer, radiologist, or other qualified clinical professional who will use this software to support case finding and diagnosis of osteoporosis. IBEX BH produces a DICOM output compatible with PACS. Please refer to the system vendor for display options available.

A secondary intended user is a production, field service or support engineer, who needs to access the configuration interface of the device. IBEX BH provides limited functionality to interact with the secondary intended user, namely a HyperText Markup Language (HTML) interface for editing the software configuration. Instructions are provided in the service manual (`IBX_PRD_SOP_003`).

Deployment of the device is managed by a software developer (or "integrator") who is responsible for integrating the IBEX BH device into an X-ray system or clinical workflow. Instructions are provided in the integration manual (`IBX_PRD_SOP_004`).

1.5 Indications for Use

The use of the IBEX BH software is indicated in the following situations:

1. electively for patients at risk of reduced bone density, where an early indicator of bone health would enable more efficient clinical decision making, or
2. opportunistically, for patients who have received a compatible X-ray exposure for another purpose.

The validated population is male or female, 50 years of age or over (see Section 2.1).

1.6 Supported Protocols

IBEX BH is applied to single wrist or hand scans as a post-processing step. The scans must be Posterior Anterior (PA) view, also sometimes referred to as Dorsi-Palmar (DP). Anterior Posterior (AP) images may also be compatible with IBEX BH but validation data is limited so outputs should be used with caution.

The optimal patient presentation for a wrist scan is shown in Figure 1.

In digital radiography (DR) the scan is performed as follows:

- Patient's elbow flexed at 90 degrees with the forearm and palm placed directly on the detector surface.
- Patient's hand relaxed with fingers close, but not tight, and slightly flexed so the radius and ulna are brought closer to the detector surface.
- No wrist rotation — radial and styloid processes equidistant from the detector.
- Vertical central beam centred midway between the radial and styloid processes.
- Image presents the proximal two thirds of the metacarpals, the carpal bones and the TD of the radius and ulna. Note that, if the TD of the radius and ulna is not contained in the image, the software will return only a UD bone health score. If the UD region cannot be identified, no bone health score will be returned and the software will flag an error.

PA or AP hand scans will be processed if the UD radius appears in the field of view with a minimum radial length of 5 cm.

In mammography applications the scan is performed as follows:

- Patient's elbow flexed at 90 degrees with the forearm and palm placed directly on the bucky near the front (by the chest wall edge).
- Patient's hand relaxed with fingers close, but not tight, and slightly flexed so the fingers (distal and middle phalanges) curl over the edge of the bucky and the radius and ulna are brought closer to the detector surface.
- No wrist rotation — radial and styloid processes equidistant from the detector.
- Image presents the proximal two thirds of the metacarpals, the carpal bones and the TD of the radius and ulna. Note that, if the TD of the radius and ulna is not contained in the image, the software will return only a UD bone health score. If the UD region cannot be identified, no bone health score will be returned and the software will flag an error.

All IBEX BH functions require an accurate calibration of the software to the X-ray system. This will be provided by the system vendor. IBEX BH must not be used on a system (or system setup) that falls outside of the calibrated regime.

For DR systems the standard supported protocols are as follows:

- Free exposure without an anti-scatter grid.
- Straight tube without angulation.
- Source-to-image receptor distance (SID) between 100 cm and 115 cm.

- X-ray beam energy between 50 kVp and 60 kVp.
- X-ray exposure setting between 2 mAs and 4 mAs.

For mammography systems a single protocol will generally be provided within a range defined as follows:

- X-ray beam perpendicular to the floor in standard breast screening mode (typical cranio-caudal geometry).
- X-ray beam quality as defined by the system integrator (typically 45 kVp with 0.5 mm aluminium filter but other energies and filters are supported).
- X-ray exposure setting as defined by the system integrator (typically 5 mAs).
- Anti-scatter grids removed.
- Breast compression paddle in the upper (rest) position, typically approximately 15 cm above the bucky.

1.7 Contraindications and Limitations

The software has been validated for use on specific patient demographics (see Section 2.1). Performance on patients outside of this demographic is untested and results should be interpreted with caution.

The use of the IBEX BH software is explicitly not indicated in the following situations:

1. Patients who have sustained a displacement fracture that is visible at the UD radius and TD radius (a fracture at just one site may still provide a usable measure).
2. Images with casts, splints, implants or other radio-opaque objects in the image, with the exception of finger rings.
3. Images taken with an anti-scatter grid.
4. Images that do not contain the UD region and at least 5cm of the radius length.
5. DR images with a non-zero object-to-detector distance (the wrist must be flat on the detector). In mammography the wrist must be flat on the bucky.
6. Images where the ulna overlaps the UD radius (for example, a lateral scan of the forearm or wrist).
7. Images of body parts that are not the arm or hand.

The software performance is untested under the following use cases:

1. Patients under the age of 50.
2. Patients with a non-displaced fracture in the ROI being used for decision support. For example, if the UD contains a non-displaced fracture, the TD region could still be used.
3. Patients with historic forearm fractures, particularly within the ROI being used for decision support. ROIs that include a previous fracture are likely to provide misleading T-score results due to higher local bone density around the previous fracture site [11].
4. Patients with clothing, jewellery or other items that cause an artefact within the image, particularly within the ROI. The performance is acceptable when rings are present.
5. Images where the wrist is not positioned in standard PA view (see Section 1.6) but the ulna does not overlap the UD radius. Particularly, the performance is not confirmed for oblique images or if flexion, extension, ulna deviation or pronation is evident [12].
6. Images with other trauma views where an adapted technique is required.
7. Patient wrist images taken on mammography systems. IBEX BH should be used on mammography systems only as part of a controlled trial and under clinical supervision.

2 Reference Data and Suggested Use Cases

2.1 Performance Compared to Reference Standards

The performance of the IBEX BH software has been published in two papers based on a clinical trial of 261 patients who received PA wrist scans[13], [14]. The performance was compared to the reference standard, DXA. The patient demographic information is presented in Tables 4 and 5.

	μ All (SD)	μ O (SD)	μ Non-O (SD)	T	W	AUC
Age	70.92 (9.03)	73.88 (8.27)	69.75 (9.12)	3.52	8007.5	0.62
Height	167.93 (9.74)	162.16 (8.41)	170.55 (9.17)	-7.20	3509.50	0.75
Weight	72.35 (14.34)	62.57 (11.67)	76.78 (13.21)	-8.68	2713	0.81

Table 4: Table of continuous variables split by i) all and ii) osteoporosis (O) defined as T-score ≤ -2.5 at either left or right ultra-distal region, as measured by DXA with participant's arm length. The total number of participants reported in this table is $n = 261$ (80 in the Osteoporosis Cohort). The mean (μ) of the group and the standard deviation (SD) of the group are reported in the first three columns. The test statistics of a t-test (T) and a Wilcoxon signed rank test (W) for the difference between osteoporosis and non-osteoporotic groups are reported in the fourth and fifth columns. All t-test statistics and Wilcoxon test statistics were statistically significant with a p-value < 0.001. The sixth column reports the area under the receiver operating characteristic curve (AUC) for classifying the osteoporosis group.

	Total	%	n O	% O	n Non-O	% Non-O	p-value
Male (No)	144	56.03	70	87.50	74	41.81	< 0.001
Previous fracture (No)	237	92.22	68	85	169	95.48	0.01
Parental hip fracture (No)	220	85.60	69	86.25	151	85.31	0.99
Smoker (No)	254	98.83	79	98.75	175	98.87	1
Glucocorticoids (No)	237	92.22	71	88.75	166	93.78	0.25
Rheumatoid arthritis (No)	246	95.72	76	95	170	96.05	0.96
Secondary osteoporosis (No)	215	83.66	61	76.25	154	87.01	0.05
High alcohol use (No)	227	88.33	76	95	151	85.31	0.04

Table 5: Demographic factors split by i) all and ii) osteoporosis (O) defined as T-score ≤ -2.5 at either left or right ultra-distal region, as measured by DXA with participant's arm length. The total number of participants reported in this table is n = 261 (80 in the Osteoporosis Cohort). Column one reports the number of participants without that factor. Column two reports the percentage of the entire cohort without that factor. Column three reports the number without that factor in the osteoporotic group. Column four is the percentage without the factor in the osteoporotic group. Column five reports the number without that factor in the non-osteoporotic group. Column six is the percentage without the factor in the non-osteoporotic group. Column seven is the p-value testing whether the percentages are different.

Table 6 shows that IBEX BH returns an aBMD at the wrist which is well correlated to a DXA scan at the same site [14]. Figure 2 shows a number of comparisons of aBMD measured by IBEX BH against aBMD measured by a GE Lunar Prodigy DXA system [14].

	DXA Actual R^2 [LCI, UCI]	DXA 29cm R^2 [LCI, UCI]
IBEX BH Manual UD	0.87 [0.83, 0.89]	0.86 [0.83, 0.89]
IBEX BH Manual TD	0.88 [0.85, 0.90]	0.88 [0.86, 0.91]

Table 6: Table reporting the adjusted R^2 values for linear regression models mapping IBEX BH to DXA with 99% confidence intervals. The first column shows the values matching to DXA reports that used the patient's arm length. The second column shows the values matching to DXA reports with a default 29cm arm length.

When predicting T-score ≤ -2.5 at the TD radius, an area under the receiver operating characteristic curve (AUC) of 0.98 (99% CI $[0.97, 0.99]$) was found when comparing to DXA. The receiver operating characteristic (ROC) curve for the UD and TD regions is shown in Figure 2.

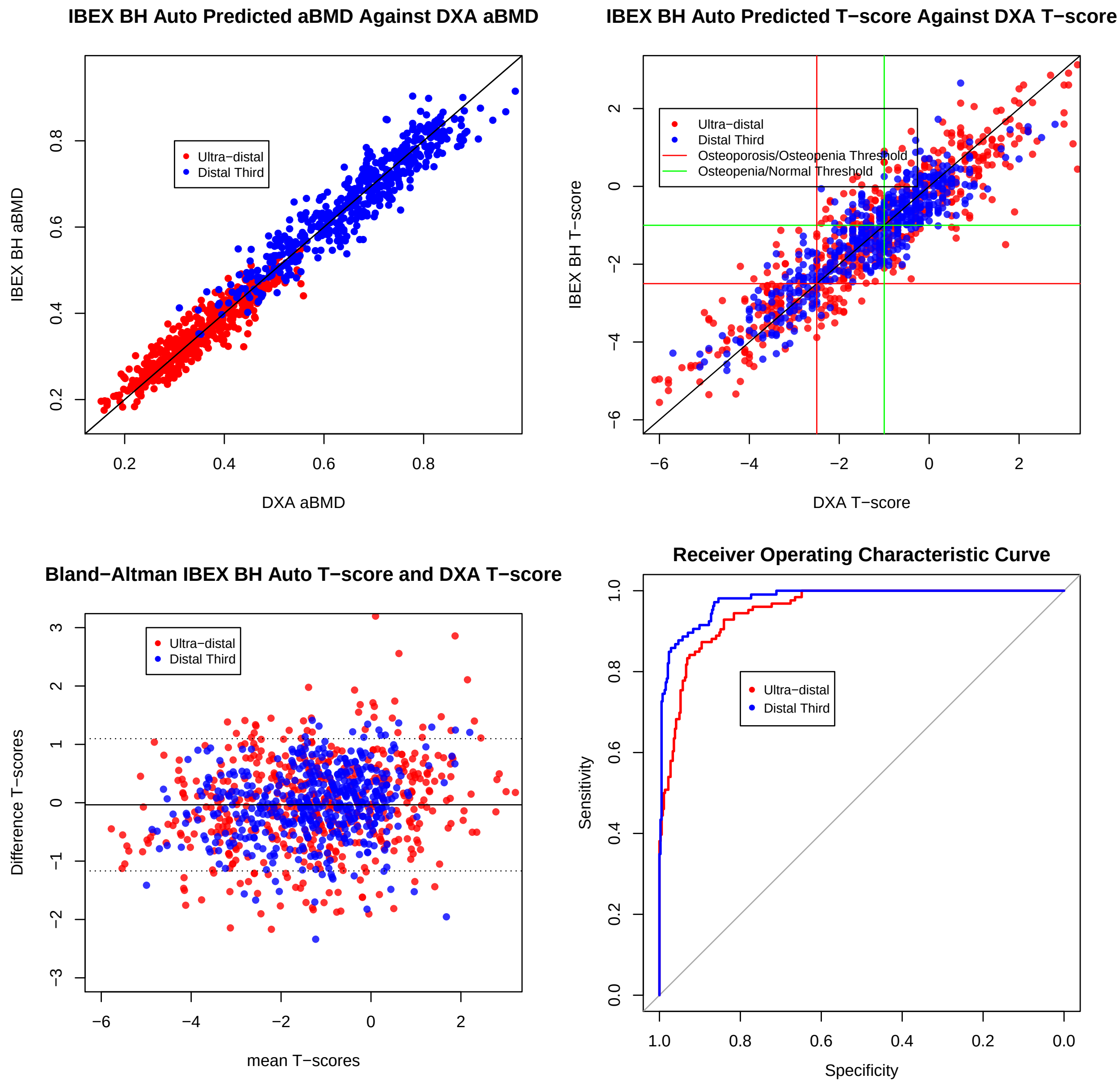

Figure 2: Top left: IBEX Bone Health (IBEX BH) predicted areal Bone Mineral Density (aBMD) using the software, against Dual-energy X-ray Absorptiometry (DXA) aBMD reported using the participant's arm length at the ultra-distal (UD) and distal-third (TD) regions. Top right: IBEX BH predicted T-score using the software, against DXA T-score reported using the participant's arm length at the UD and TD regions. The manufacturer's reference ranges were used to calculate the T-score. Bottom left: Bland-Altman plot depicting the difference between DXA T-scores using a participant's arm length and IBEX BH T-scores using the automated software at the UD and TD regions. Bottom right: Receiver Operating Characteristic curve of the output of the logistic regression model predicting DXA (reported with the patient's arm length) T-score ≤ -2.5 using the IBEX BH outputs.

The risk of osteoporosis at the hip has been shown to increase as the T-score at the UD radius decreases [10]. This was confirmed for IBEX BH, the results of which can be seen in Figure 3 (see also [13]). Taking the example referral threshold of T-score ≤ -3, patients in the clinical study have a 4.75 times greater risk of osteoporosis than the average over 50s population (Figure 4). This risk increases further for lower T-scores, allowing a referral threshold to be selected which optimises for downstream resource availability and minimises false positive results.

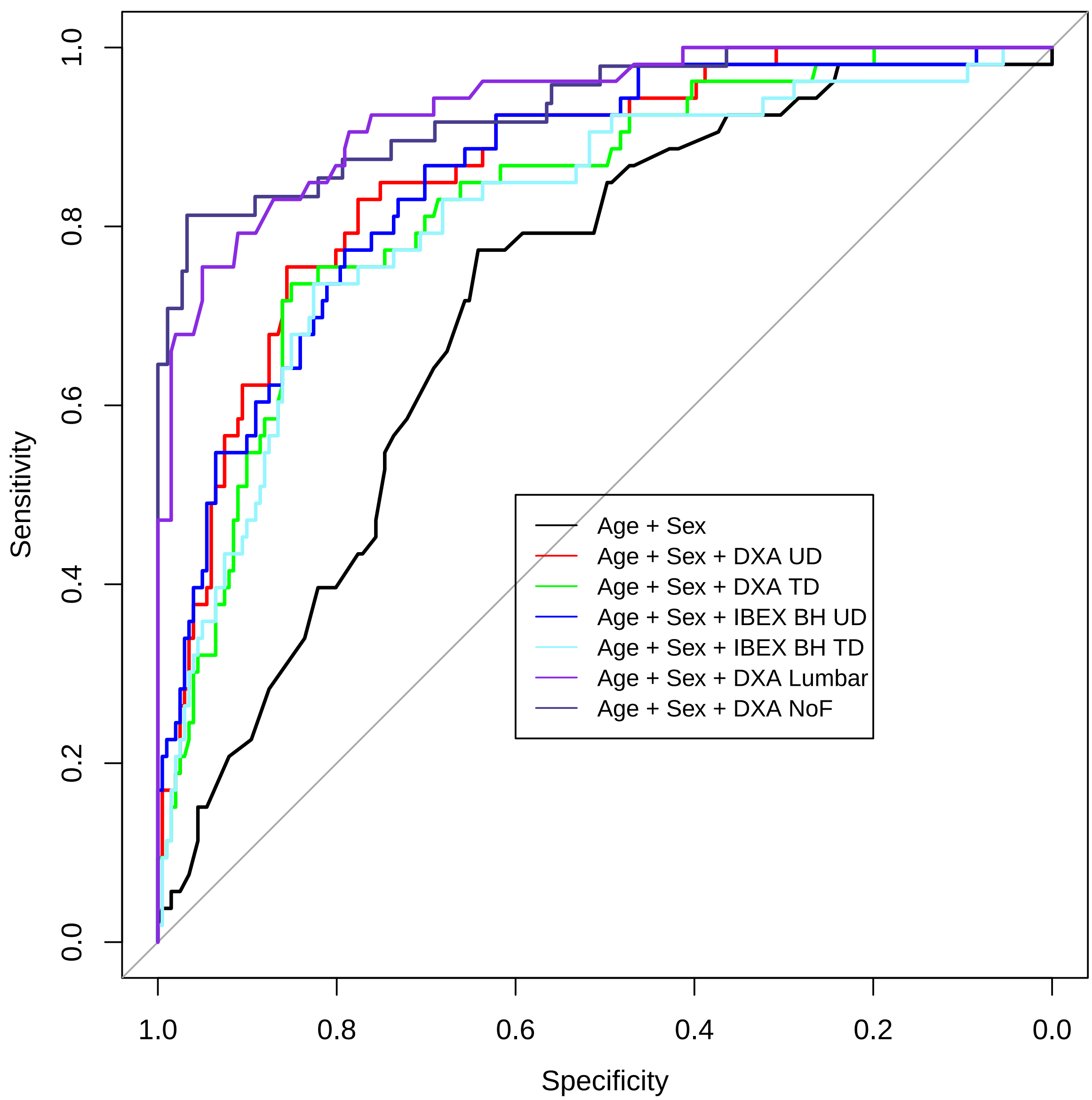

Figure 3: Receiver operating characteristic curves for clinical central osteoporosis prediction, where osteoporosis is defined as the minimum central T-score ≤ -2.5, as measured by Dual-energy X-ray Absorptiometry (DXA).

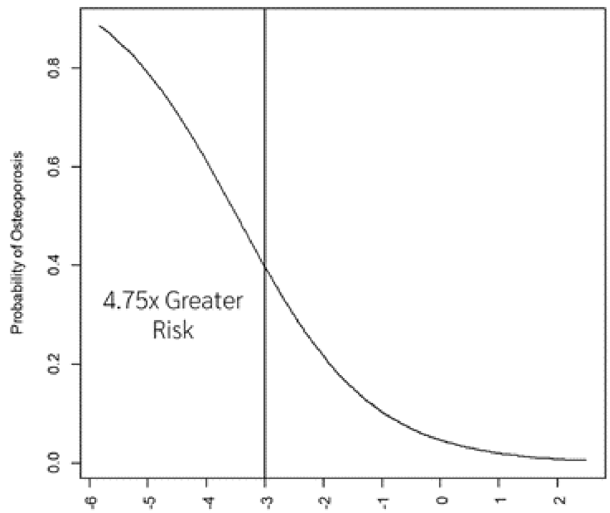

Figure 4: Probability of osteoporosis as a function of T-score at the ultra-distal radius. An example intervention threshold of T-score = −3 is shown, where patients with a T-score less than −3 have a 4.75 times greater chance of osteoporosis at the hip compared to the average for the over 50s population.

2.2 Clinical Application

Clinical use of the IBEX BH finding will depend on local factors. However, an example use case based on general radiography is provided below for illustration purposes. Figure 5 shows an example care pathway where the patient receives their normal X-ray and subsequent follow-up. In parallel, the IBEX BH software analyses key regions in the DR image, in this case the UD and TD regions. If the lowest T-score is less than a predefined threshold (less than −3 in this example) then the patient should be referred for a follow-up assessment. The threshold is configurable by a service engineer.

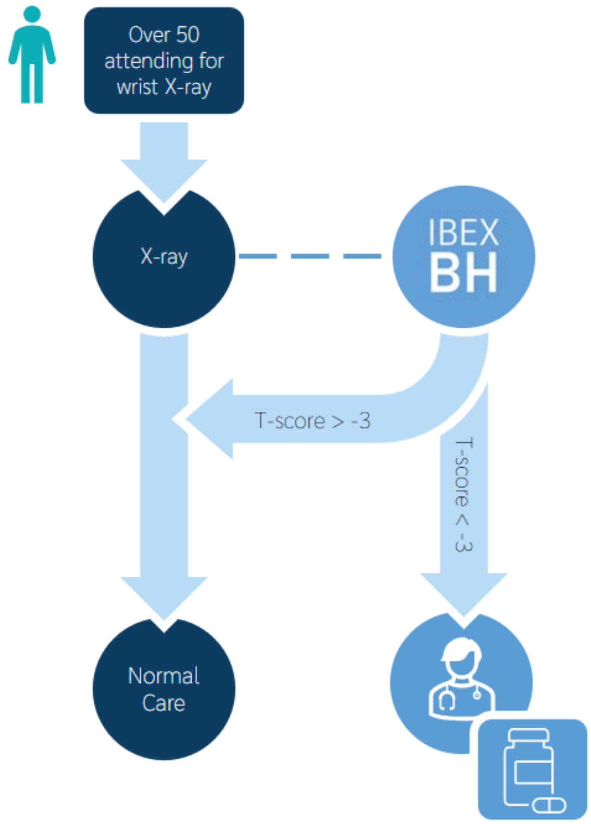

Figure 5: Illustration of the use of IBEX Bone Health as an opportunistic screening tool, used alongside a standard wrist X-ray. In this example, the patient is referred for follow-up assessment if the lowest T-score measured by the software is less than −3.

The indication provided by IBEX BH should be considered as a risk factor for osteoporosis and local clinical guidelines should be followed in relation to the necessary course of action for patients who are suspected of having osteoporosis. Taking the United Kingdom (UK) National Institute for Healthcare and Excellence (NICE) guidelines, CG146 [15], as an example, an illustration of a potential referral pathway is given in Figure 6. The example follows the NICE guidelines which state that women aged under 65 years and men aged under 75 years should be assessed for fracture risk in the presence of risk factors. These risk factors may not be evident when a patient presents for an X-ray, but should be considered when considering referral after an IBEX BH assessment.

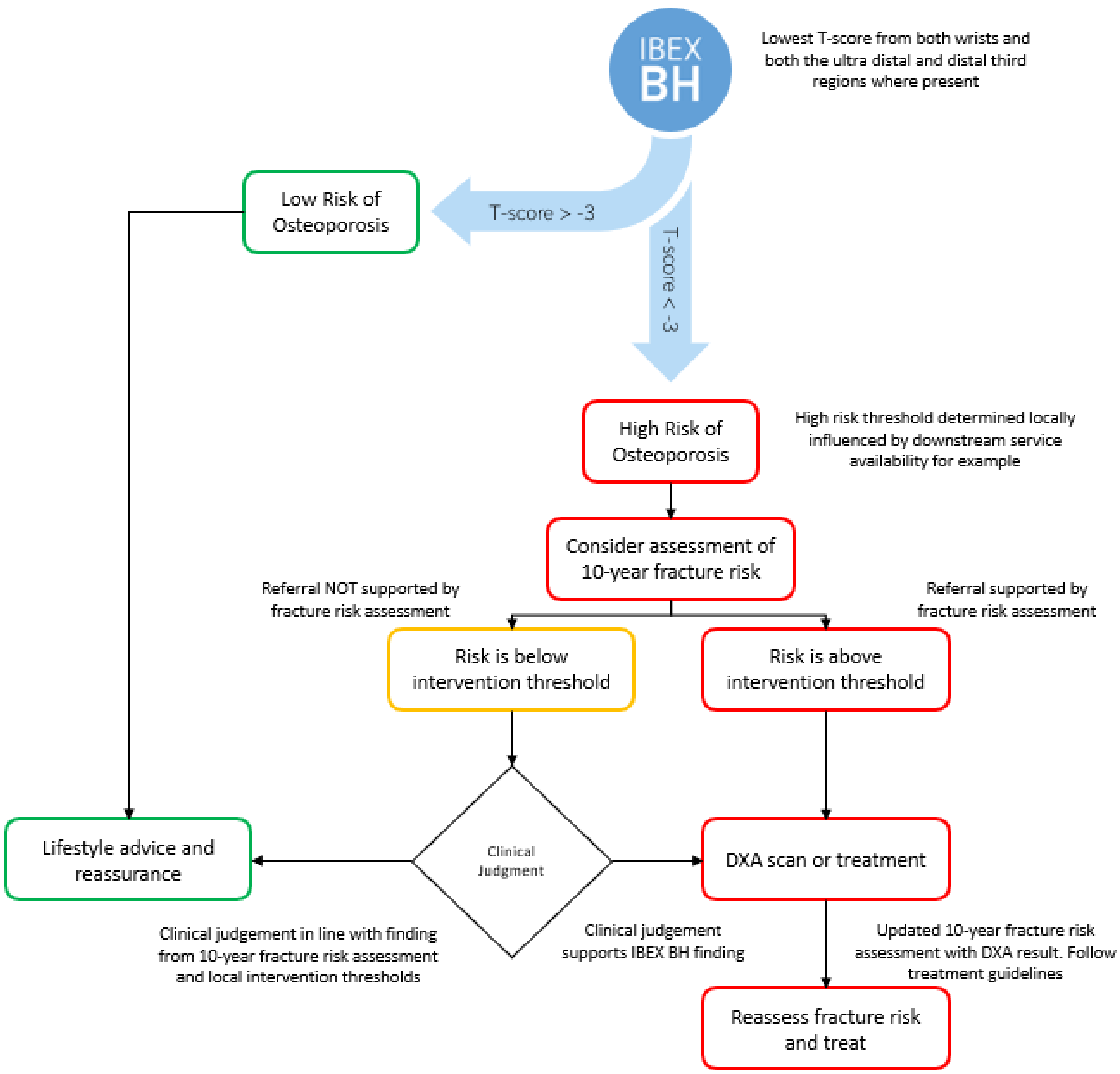

Figure 6: Illustration of a potential referral pathway for a patient found to have a T-score less than −3 (locally defined) from the IBEX Bone Health software. The actual pathway will depend on local guidelines for assessment of patients identified to be at risk of osteoporosis.

As a screening test, the purpose of IBEX BH is to raise awareness of the likelihood of the disease and ensure that the patient receives the correct follow-up assessment. For this reason, the standard clinical guidelines should be followed when a patient is identified as being at risk.

2.3 Intervention Threshold

A T-score intervention threshold of less than −3 is shown in Figures 5 and 6. This is chosen as an example and may be configured by a service engineer. The graph in Figure 4 in Section 2.1 shows data from a clinical study (see Section 2.1) which indicates a 4.75 times increase in risk of central osteoporosis for patients with a T-score of −3 or lower.

Selecting a lower T-score as the intervention threshold will result in a smaller cohort having a relative risk of osteoporosis higher than 4.75. This in turn leads to fewer referrals for follow-up assessment and, of these, fewer false positive cases. This has a beneficial impact on downstream resources but comes at the expense of more patients having osteoporosis not being referred.

Selecting a higher T-score for the intervention threshold increases the size of the cohort identified as high risk, resulting in more patients with osteoporosis being referred but also more patients without osteoporosis being referred. This has a beneficial impact on diagnosis rate but higher downstream costs, for example, more DXA scans not resulting in a recommendation to treat.

The selection of a referral threshold is therefore likely to depend on local factors. In areas with a high prevalence of osteoporosis and sufficient downstream capacity, a more sensitive approach may be advisable and hence a lower referral threshold may be chosen. Conversely, in an area of either low prevalence or low downstream capacity, a more specific criteria would be advisable to avoid large numbers of false positives overwhelming downstream services.

These decisions require local clinical judgement and the result from IBEX BH should be used to support, rather than replace, clinical decision making. In doing so, other patient-specific factors should be taken into account prior to making a referral decision.

2.4 Normative Data

Normative data is a set of summary statistics of a sample of the sex-matched healthy population. "Healthy normal" is any individual between 20–30 years of age without any clinical risk factors for osteoporosis or fracture. The summary statistics are the sample mean:

$$\mu = \frac{1}{n}\sum_{i=1}^{n} x_i, \tag{1}$$

and sample standard deviation

$$\sigma^2 = \frac{1}{n-1}\sum_{i=1}^{n} \left(x_i - \mu\right)^2. \tag{2}$$

Here n is the number of individuals sampled from the healthy normal population and x_i is the aBMD in an ROI. The normative DXA is sex-matched meaning that males and females have separate summary statistics. Each ROI also needs a distinct set of summary statistics.

A T-score is calculated using the following formula:

$$T = \frac{x_j - \mu}{\sigma}, \tag{3}$$

where x_j is a measure of aBMD from an individual in the test population. Therefore, a T-score is how far an individual's T-score is from the healthy normal population measured in standard deviations of the healthy normal population.

Normative data has been gathered by IBEX Innovations from 131 females and 76 male volunteers between the ages of 20 and 30. Updates may be provided in the future if additional normative data sets become available (ethnic background-adjusted, for example). These limitations should be considered when interpreting the T-score provided by IBEX BH and patient-specific adjustments should be made: the result may appear normal relative to the normative population, but does it look normal for this patient?

2.5 Deep Learning Components

There are two components of the algorithm that are deep learning neural networks and are therefore considered black box algorithms. As such, the mechanism by which they come to a decision is non-interpretable. All other components of IBEX BH are considered interpretable or explainable.

The two components are a segmentation algorithm that identifies the tissue regions and bone regions within the image, and an ROI identification algorithm that identifies the radius and the ulna, and then uses these bones to draw the UD and TD ROIs. Non-interpretable methods were considered acceptable for these models as they automate time-consuming tasks that a clinician would otherwise be unable to perform. The clinician acting upon an IBEX BH report can supervise the algorithms and check that they have performed the task correctly.

Figure 1 items (2) and (3) show the two regions a clinician should check. The white lines within the boxes should demarcate the bone from the tissue. The boxes should be aligned with the scanning axis of the wrist. The UD region (2) should be 1.58 cm below the styloid process. The TD region (3) should be 9.62 cm below the styloid process.

If any of these criteria are not met, the result from that ROI should be treated with caution.

2.5.1 Deep Learning Methodology - Semantic Segmentation

A proprietary CNN (convolutional neural network) architecture designed for the task of semantic segmentation is used within the IBEX BH software to segment the bone and tissue of the sample. The CNN assigns values to each pixel within the image, providing each pixel within the images with a class index representing the material in the pixel. These classes determine if the pixel contains any bone, contains soft tissue, is illuminated by x-rays, or is not illuminated due to the position of the collimator vanes. The architecture developed for the IBEX BH algorithm is XNet, a close relation to the UNet architecture which is widely used within medical image segmentation applications. A description of the XNet architecture may be found here: `https://arxiv.org/pdf/1812.00548.pdf`.

2.5.1.1 Semantic segmentation algorithm training methods

- Criteria for training dataset
  - Digitised x-ray images (digital or computed radiography)
- Application to patient target groups
  - The target group is patients over 50 presenting for a posterior-anterior (PA) wrist radiograph.
  - The algorithm was tested on a random sample 261 participants from the over 50s population.
  - Recruitment was performed with the target population between February and October 2022.
  - Participants meeting the following criteria were considered eligible for the study:
    1. Male or female, 50 years of age or over.
    2. Either:
       (a) a member of the group of 10,000 individuals pre-consented by Exeter University to for participation in clinical research
       (b) attending radiology department for plain radiograph of PA forearm or wrist showing UD radius
       (c) outpatients with a scheduled DXA assessment
       (d) other members of the public who wished to participate.
    3. Able to comprehend and sign the informed consent prior to enrolment in the study.

- Participants meeting the following criteria were not eligible for the study:
  1. women who are pregnant or are breastfeeding
  2. participants who have previously sustained a fracture that affects the UD radius on both arms
  3. participants who have sustained fractures in both hips
  4. have implants or other radio-opaque objects in the region of study
  5. unwilling or unable to provide informed consent.
- Participants received two AP Long Wrist X-rays (both left and right wrists) using an AGFA DR100s mobile DR system. The following exposure parameters were fixed for all acquisitions: field of view = 24cm×12cm, source voltage = 60kVp and current = 2mAs. Four independent qualified radiographers of varying experience carried out measurements.
- Participants completed a questionnaire to record aspects of their medical history. The patient's age, sex, height, weight and clinical fracture risk factors were recorded. The clinical risk factors were whether: i) the patient had a previous fracture, ii) their parent had a fractured hip, iii) they are a current smoker, iv) they are taking glucocorticoids, v) they have rheumatoid arthritis, vi) they have secondary osteoporosis and vii) they drink 3 or more units of alcohol per day.

- Pre-processing of Training data
  - A limited number of pre-processing steps were applied before the data was used for training the CNN model, or before inference is performed on a patient image. The pipeline is set out below:
    1. Min-max normalisation of the input image
    2. Resample of the image to 256x256 pixels
    3. Ensure correct photometric interpretation of the image (bone is black)
  - As a supervised learning approach is used for training of the semantic segmentation model, each image was labelled by IBEX's in-house annotation team. A labelling specification was devised for the tissue-bone task. Each label undergoes an annotation team peer review and moderation was performed by a team lead.
  - An augmentation pipeline was applied to the training data and multiple training samples were generated from each image. The augmentation pipeline included the following transformations:
    1. Translation
    2. Rotation
    3. Shear
    4. Flip
  - The body part imaged was tracked, and training samples per image were adjusted accordingly to ensure no over-sampling of a single body part.
- Training methodology
  - Data was randomly sampled into training and validation sets, with a 95% (train) and 5% (validation) split. Model selection was performed by training multiple models with varying architecture and hyperparameters (such as loss functions, optimisers, learning rate schedulers, reqularisation techniques) with the training set and evaluating performance on the validation set.
  - The model with the best performance on the validation set was selected, and then trained on the combined training and validation set. Performance of this model was then checked on the out-of-sample test set to ensure overfitting had not occurred.
- Dataset version control

  - A dataset consisting of 1158 images was used in the training of the semantic segmentation model; the images are stored in a github repository with the git large file storage enabled. The commit hash of the repository is stored when training is performed. Image details are stored in a comma separated variable file, including a cryptographic hash derived from the image file to allow for checking of data integrity.

2.5.1.2 Semantic segmentation algorithm testing

- Test methodology
  - For model selection and assessment of the final model, multiple metrics evaluating different aspects of the segmentation performance are considered. Key metrics are the pixel accuracy and intersection over union (IoU) of the bone and tissue classes, misclassification of tissue as other classes and metrics considering the accuracy and IoU of the pixels at class boundaries. Outputs for these metrics are aggregated and weighted according to perceived importance to prior generation for the IBEX BH algorithm. Visual assessment of the segmentation output is also considered. With the metric information and the visual assessment, a final qualitative assessment is undertaken.
  - The semantic segmentation algorithm has been evaluated for the initial hold-out set and was monitored for the data collected as part of the OFFER 1 clinical study [13].
- Test Results
  - Performance of the semantic segmentation model was assessed quantitatively with a series of metrics. The model shows high overall pixel accuracy and intersection over union (IoU) close to 1, demonstrating that the model classifies almost all pixels correctly. The key segmentation classes of bone and tissue have high overlap with the hand labelled mask and thus high IoU. Similarly, in the typically more difficult border regions (defined as a 5-pixel neighbourhood around the line where the class changes) of the class there is relatively high overlap between the hand labelled mask and the model prediction. Additionally, misclassification of bone and tissue as different classes as proportion of the class is small, with less than 5% of the bone or tissue typically misclassified.
- To assess whether the performance of the algorithm was sufficient, a comparison was made between IBEX BH and DXA using both hand labelled images and the outputs of the algorithm. The R^2 between IBEX BH and DXA using hand labelled images was 0.87 (99% confidence interval (CI) $[0.83, 0.89]$) for the UD region and $0.88[0.85, 0.90]$ for the TD region. The R^2 between IBEX BH and DXA using the algorithm was 0.87 (99% confidence interval (CI) $[0.84, 0.89]$) for the UD region and 0.87 (99% CI $[0.85, 0.90]$) for the TD region. As the confidence intervals overlap, there is no evidence to suggest that the performance is degraded by using automated segmentation over hand labelling.

2.5.2 Deep Learning Methodology - Region of Interest Definition

The Mask Region-based Convolutional Neural Networks (R-CNN) framework for object detection, consisting of several convolutional neural network (CNN) components is used within the IBEX BH software to segment the individual radius and ulna bones of the forearm within the sample. The framework produces multiple binary masks with an associated class label representing each instance of each bone found within the sample image. Mask R-CNN is a widely used framework for object detection. A description of Mask R-CNN may be found here: `https://arxiv.org/abs/1703.06870`.

2.5.2.1 ROI algorithm training methods

- Criteria for training dataset
  - Inclusion

  1. Digitised x-ray images of anthropomorphic samples (digital or computed radiography)
  2. Wrist, forearm or hand patient series
  3. Aged 18+ patients
  4. PA, AP and oblique views
- Exclusion
  1. Presence of orthopaedic cast

- Application to patient target groups
  - The target group is patients over 50 presenting for a posterior-anterior (PA) wrist radiograph. The algorithm was tested on a random sample 261 participants from the over 50s population.
  - Recruitment was performed with the target population between February and October 2022. Participants meeting the following criteria were considered eligible for the study:
    1. Male or female, 50 years of age or over.
    2. Either:
       (a) a member of the group of 10,000 individuals pre-consented by Exeter University to for participation in clinical research
       (b) attending radiology department for plain radiograph of PA forearm or wrist showing UD radius
       (c) outpatients with a scheduled DXA assessment
       (d) other members of the public who wished to participate.
    3. Able to comprehend and sign the Informed Consent prior to enrolment in the study.
  - Participants meeting the following criteria were not eligible for the study:
    1. women who are pregnant or are breastfeeding
    2. participants who have previously sustained a fracture that affects the UD radius on both arms
    3. participants who have sustained fractures in both hips
    4. have implants or other radio-opaque objects in the region of study
    5. unwilling or unable to provide informed consent.
  - Participants received two AP Long Wrist X-rays (both left and right wrists) using an AGFA DR100s mobile DR system. The following exposure parameters were fixed for all acquisitions: field of view = 24cm×12cm, source voltage = 60kVp and current = 2mAs. Four independent qualified radiographers of varying experience carried out measurements.
  - Participants completed a questionnaire to record aspects of their medical history. The patient's age, sex, height, weight and clinical fracture risk factors were recorded. The clinical risk factors were whether: i) the patient had a previous fracture, ii) their parent had a fractured hip, iii) they are a current smoker, iv) they are taking glucocorticoids, v) they have rheumatoid arthritis, vi) they have secondary osteoporosis and vii) they drink 3 or more units of alcohol per day.
- Pre-processing of Training data
  - A number of pre-processing steps were applied before the data was used for training the CNN model, or before inference is performed on a patient image. The pipeline is set out below:
    1. Min-max normalisation of the input image
    2. Resample of the image so that its smallest dimension is 800 pixels

3. Ensure correct photometric interpretation of the image (bone is black)

- As a supervised learning approach is used for training of the model, each image was labelled by IBEX's in-house annotation team. Each label undergoes an annotation team peer review and moderation was performed by a team lead.
- An augmentation pipeline was applied to the training data and multiple training samples were generated from each image. The following augmentations were applied:
  1. Rotation
  2. Horizontal and vertical flips
  3. Addition of gaussian noise
  4. Addition of multiplicative noise
  5. Gaussian blur
  6. Power law transforms
  7. Contrast and brightness adjustment

- Training methodology
  - Data was randomly sampled into training, validation sets. Model selection was performed by training multiple models with varying architecture and hyperparameters (for example loss functions, optimisers, learning rate schedulers, reqularisation techniques) with the training set and evaluating performance on the validation set. The data from the OFFER 1 trial was used as the test or hold-out set.
  - Transfer learning was used, with weights from Imagenet [16] used to train the ResNet-50 backbone, and weights from the COCO Train 2017 dataset used for all additional subsystems of the Mask R-CNN framework.
  - The model with the best performance on the validation set was selected, and then trained on the combined training and validation set. Performance of this model was then checked on the test set to ensure overfitting had not occurred.
- Dataset version control
  - A dataset consisting of 1622 images was used in the training of the Mask R-CNN model. Data was stored within files containing singular datasets which have not been updated, with backups created. Datasets were produced from version-controlled code which accessed these folders. After the initial training process, version control was implemented in which each dataset is described by a csv file, with cryptographic hashes stored for each image. The csv files are also stored in a backed-up drive.

2.5.2.2 ROI algorithm testing

- Test methodology
  - For model selection and assessment of the final model, multiple metrics evaluating different aspects of the segmentation performance are considered. Key metrics are the pixel accuracy and IoU for the radius and ulna classes. Additionally mean average recall and mean average precision are calculated for various IoU thresholds. Visual assessment of the segmentation output is also considered. With the metric information and the visual assessment, a final qualitative assessment is undertaken.
  - The algorithm has been evaluated for the data collected as part of the OFFER 1 clinical study [13].

- Test results
  - High IoU with ground truth was demonstrated for both the radius and bone masks detected for the OFFER 1 clinical study dataset. High IoU signifies large overlap between the ground truth and detected mask, therefore detected masks closely match the ground truth.
  - The average precision and recall results show that the object detection model produces high quality masks (large overlap of ground truth and detected mask) with very few false positive (detection of a mask that should not exist) and false negative (low overlap with ground truth or non-existent) masks. Therefore, the ROI algorithm reliably produces masks that are suitable for determining key points and direction vectors for determining the ROI position across the OFFER 1 clinical study dataset.
  - To assess whether the performance of the algorithm was sufficient, a comparison was made between IBEX BH and DXA using both hand labelled images and the outputs of the algorithm. The R^2 between IBEX BH and DXA using hand labelled images was 0.87 (99% confidence interval (CI) $[0.83, 0.89]$) for the UD region and $0.88[0.85, 0.90]$ for the TD region. The R^2 between IBEX BH and DXA using the algorithm was 0.87 (99% confidence interval (CI) $[0.84, 0.89]$) for the UD region and 0.87 (99% CI $[0.85, 0.90]$) for the TD region. As the confidence intervals overlap, there is no evidence to suggest that the performance is degraded by using automated ROI selection over hand labelling.

3 Hazards and Troubleshooting

3.1 Hazard Summary

There are no hazards related to the diagnostic image quality or dose to the patient of this device due to the following:

- Essential performance of the X-ray system does not depend on this device.
- The device does not control the X-ray equipment.
- The output DICOM image is not used for diagnostic purposes.
- If the device fails to process a given input for any reason, an error message will be generated and no useable bone health output will be returned.

There is a risk that the software could provide a wrong indication in that either:

1. a patient without osteoporosis is identified as high risk or
2. a patient with osteoporosis is not identified as high risk.

The first could make the patient unduly concerned and lead to an unnecessary follow-up, most likely a DXA scan. DXA scans are low dose and, as any indication will be confirmed on the reference standard DXA, there is no additional risk of incorrectly treating patients. The second would mean no change to the patient's current care.

3.2 User Troubleshooting Guide

Warning and error messages are automatically generated by IBEX BH in the event of image presentation, data processing, or other software issues. The more clinically relevant messages are displayed in the Secondary Capture DICOM output image, either as a list of warning and error codes (codes start with "W" for warnings and "E" for errors), or as a watermark for the most important messages. The system integrator may also choose to display messages on the user interface. All messages are saved and available to view within a private tag in the DICOM output. Note that, in the event of an error, no bone health outputs will be returned. The output will be a DICOM containing the errors and warning messages only. Bone health output DICOMs labelled with one or more warnings should be reviewed carefully.

Warnings and errors will generally be resolved by contacting a service engineer or your system vendor. The list of warnings, errors, and probable causes that are actionable by an end user is provided in Table 7, along with recommended actions. Causes will typically fall into the following categories:

- Protocol-related errors. This includes: incompatible view or orientation (E201, E210), incompatible body part (E201), poor positioning of the body part (W202, E301, W302), non-standard protocol (W211), or no calibration available for the selected protocol (E201, E203, E210).
- Patient-related errors. This includes: patient falling under one of the contraindications or limitations of the software (W202), or bone health assessment not indicated (W206).
- System-related errors. This includes: calibration is out-of-date (W205), or license has expired (E401).

If any other warning or error is produced, or if none of the probable causes listed in Table 7 apply, or if the issue persists after attempting the proposed corrective action, please contact customer support. The complete list of warnings and errors is provided for completeness in Table 8.

Table 7: Error and warning codes actionable by end user

Code	Meaning	Cause	Action
E201	DICOM tag value unsupported or out-of-range	Wrong protocol selected.	Please select an appropriately configured protocol.
W202	Similarity check failed	Incorrect body part or positioning.	Please ensure the wrist is positioned as expected. Output should not be used.
		Patient falls under one of the contraindication and limitations of the software.	Output should not be used.
		Incorrect tagging of input data.	Please correct the selected protocol, or contact customer support. Output should not be used.
		Any other cause.	Use output with caution.
E203	Protocol out of calibrated range	Wrong protocol selected.	Please select an appropriately configured protocol.
W205	Calibration out-of-date	Calibration is too old.	Please contact customer support to renew the calibration, and use output with caution.
W206	Bone health assessment not indicated	Patient is too young.	Product intended and tested for use on patients over 50 years of age. Discretion advised if used on younger patients.
E210	Invalid input property	Wrong protocol selected.	Please select an appropriately configured protocol.
W211	Experimental protocol	Software configured to accept non-standard protocol (see Section 1.6) and exposure from such protocol is received.	Exercise caution when interpreting the results.
E301	Required ROI was not detected	Incorrect body part in image.	Please only send images of wrists or hands containing the ultra distal radius region.
		Field of view too narrow.	Ensure the field of view covers relevant parts of the wrist and ultra distal radius.
W302	Optional ROI was not detected	Field of view too narrow, does not include third distal radius region.	Ensure the field of view covers the third distal radius region, or ignore the warning.

Continued on next page

Table 7: Error and warning codes actionable by end user (Continued)

Code	Meaning	Cause	Action
E401	Invalid license	License has expired.	End user software licensing is provided by the system vendor or service engineer. All end user queries relating to software licensing should be referred to the software licensor.

Table 8: Error and warning codes (full list)

Code	Meaning
E101	Required DICOM tag unavailable
W102	Optional DICOM tag unavailable
E201	DICOM tag value unsupported or out-of-range
W202	Similarity check failed
E203	Protocol out of calibrated range
W204	Protocol out of explicitly calibrated range
W205	Calibration out-of-date
W206	Bone health assessment not indicated
E207	Ambiguous protocol calibration
W208	Unused system property
E209	Calibration awaiting QA
E210	Invalid input property
W211	Experimental protocol
E301	Required ROI was not detected
W302	Optional ROI was not detected
E303	Bone health calculation failed
E304	Exhausted resource
E305	Unexpected internal error
E306	Processing cancelled
E307	Calibration QA failed
E401	Invalid license
E402	No calibration data available
E403	Corrupted calibration data
E404	No normative population data available
E405	Calibration is invalid
E501	Inbound request refused
E502	Invalid inbound request
E503	Inbound connection aborted
E601	Output connection failed
E602	Output connection aborted
E603	Invalid outbound request
E604	Outbound request refused

3.3 Emergency Situations

In the event of a serious incident (leading to death or serious deterioration of health) involving this device, the user must inform IBEX (the manufacturer), and the competent authority of the member state in which the user is established as soon as possible. When in doubt, report. A list of contact points of the competent authorities for EU member states can be found here: `https://health.ec.europa.eu/system/files/2022-10/tse_bse_contact_points.pdf`.

4 Appendix

4.1 Medical Device Label

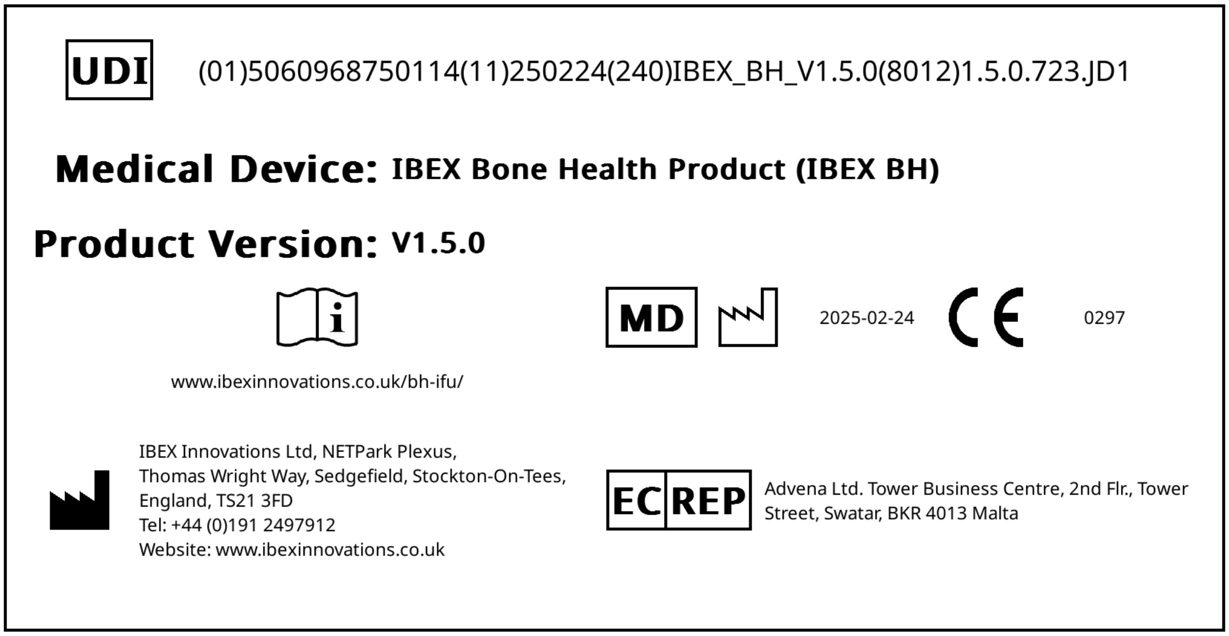

Figure 7: Product label for integration on Nvidia Jetson Xavier NX (Docker, Linux).

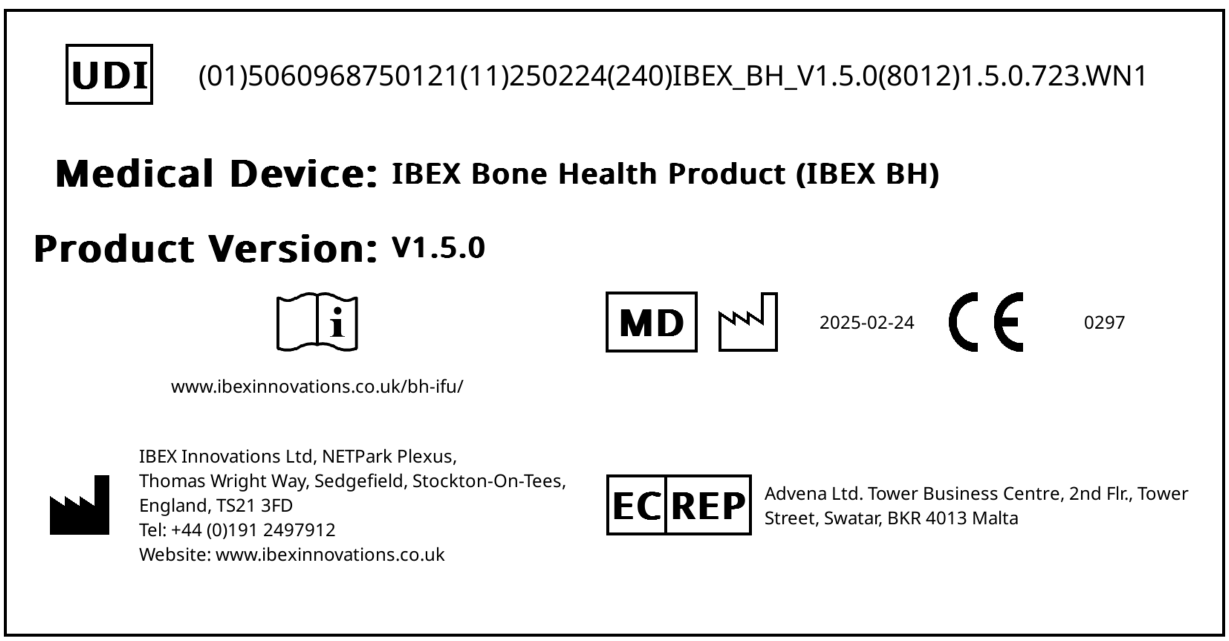

Figure 8: Product label for integration on generic desktop PC (Native, Windows).

4.2 Regulatory Clearance

IBEX BH is a CE marked class IIa according to Regulation (EU) 2017/745 (EU MDR) and approved for use in applicable jurisdictions.

- 2017/745 — Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 concerning Medical Devices.
- EN ISO 13485:2016+A11:2021 — Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes.
- EN ISO 14971:2019+A11:2021 — Medical Devices — Application of Risk Management to Medical Devices.
- EN ISO 15223-1:2021 — Medical devices. Symbols to be used with information to be supplied by the manufacturer — General requirements.
- EN ISO 20417:2021 — Medical devices. Information to be supplied by the manufacturer.

4.3 Patents

The IBEX BH software is protected by following patents: JP6598087, US10588592, GB2576772, GB2608900, GB2611231, GB2589643, GB2563115, US 10820878 (Japan, South Korea Pending, EU, China Pending).

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Instructions For Use - End User Manual - IBEX BH v1.5.0

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