Optellum Ltd.
% Mr. David Arrowsmith
RA/QA Manager
Oxford Centre for Innovation, New Road
Oxford, Oxfordshire OX1 1BY
UNITED KINGDOM

March 5, 2021

Re: K202300
Trade/Device Name: Optellum™ Virtual Nodule Clinic, Optellum™ Software, Optellum™ Platform
Regulation Number: 21 CFR 892.2060
Regulation Name: Radiological computer-assisted diagnostic software for lesions suspicious of cancer
Regulatory Class: Class II
Product Code: POK
Dated: January 25, 2021
Received: January 27, 2021

Dear Mr. Arrowsmith:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

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); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

For

Thalia T. Mills, Ph.D.
Director
Division of Radiological Health
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K202300

Device Name

Optellum™ Virtual Nodule Clinic, Optellum™ Software, Optellum™ Platform

Indications for Use *(Describe)*

Virtual Nodule Clinic (VNC) is a software device used in the tracking, assessment and characterization of incidentally detected pulmonary nodules.

VNC includes a computer-aided diagnosis (CADx) function, available only to pulmonologists and radiologists. This automatically analyzes user-selected regions of interest (ROI) within lung CT data to provide volumetric and computer analysis based on morphological characteristics. Using only imaging features extracted from the CT image data, an artificial intelligence algorithm calculates a single value, the LCP-CNN score, which is displayed to the user. The LCP-CNN score is analyzed relative to LCP-CNN scores generated on a database of cases with known ground-truth using a histogram display format. The LCP-CNN score may be useful in the characterization of pulmonary nodules during image interpretation and may be used as one input to clinical decision making when following published clinical guidelines.

VNC's LCP-CNN score is indicated for the evaluation of incidentally detected solid and semi-solid pulmonary nodules of diameter 5-30mm in patients aged 35 years or above. In cases where multiple abnormalities are present, VNC's LCP-CNN score can be used to assess each abnormality independently.

Note that LCP-CNN is not indicated for lung cancer screening nor is it indicated for nodules of pure ground glass opacity. In addition, high contrast CT images were not used in clinical validation (as measured as >300HU median attenuation in the aortic arch) and the validation data also excluded CT images with only calcified nodules (since these are typically considered to be benign), with implants, motion artifacts, missing slices, or cases with greater than 5 nodules. Finally, the validation data excluded patients with history of cancer of less than 5 years to avoid the presence of metastatic lesions.

Users other than radiologists and pulmonologists, e.g. clinicians, nurses, nurse practitioners and navigators, may use VNC to view CT images and reports, organize patient management workflow, track patients, record management decisions and organize nodule clinics. For these users, the LCP-CNN score is unavailable.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

5 510(K) SUMMARY

This 510(k) Summary of safety and effectiveness information is submitted as part of the Pre-Market Notification in accordance with the requirements of 21 CFR Part 807, Subpart E, Section 807.92.

5.1 Submitter information

Submitter organization:	Optellum Ltd.
Submitter address:	Oxford Centre for Innovation New Road Oxford OX1 1BY United Kingdom
Submitter telephone:	+44 1865 261400
Sponsor:	Dr. Timor Kadir, Chief Science and Technology Officer timor.kadir@optellum.com
Correspondence contact:	David Arrowsmith, RA/QA Manager david.arrowsmith@optellum.com

5.2 Date of Summary

March 4, 2021.

5.3 Device

Device 510(k) number:	K202300
Device trade names:	Optellum™ Virtual Nodule Clinic Optellum™ Software Optellum™ Platform
Device common names:	Computer-aided diagnosis (CADx) software
Device classification:	Computer-Assisted Diagnostic Software For Lesions Suspicious For Cancer (21 CFR §892.2060, Product Code POK)
Safety classification:	Class 2 (Special Controls)

5.4 Predicate device

This section identifies the legally marketed device (predicate) to which Optellum claims equivalence.

Predicate device name:	QuantX
Predicate device manufacturer:	Quantitative Insights, Inc
Predicate device PMA Number:	DEN170022
Device classification name:	Computer-Assisted Diagnostic Software For Lesions Suspicious For Cancer (21 CFR §892.2060, Product Code POK)
Safety classification:	Class 2 (Special Controls)

5.5 Device description

5.5.1 Device identification

The device may have any of the following trade names:

- Optellum™ Virtual Nodule Clinic
- Optellum™ Software
- Optellum™ Platform

For clarity, the rest of this document refers to the device as Virtual Nodule Clinic or VNC.

VNC is a software only device which consists of two main components: a web application accessed via standard desktop web browsers and the LCP-CNN machine learning model. These are further described in the following sections.

5.5.2 Device characteristics

Virtual Nodule Clinic (VNC) is a software application designed for trained medical professionals in the clinical management of patients with pulmonary nodules. VNC includes a computer-aided diagnosis (CADx) function to assist pulmonologists and radiologists in the assessment and characterization of incidentally detected pulmonary nodules using CT image data.

VNC has two main functions:

- A CADx function to assist radiologists and pulmonologists in clinical decision making by providing a score using machine learning (namely the LCP-CNN algorithm, Lung Cancer Prediction Convolutional Neural Network). Also note that the output of the CADx function is referred to synonymously in this document as either “Optellum LCP Score” or “LCP-CNN score”, depending on context.
- A management function to allow users to easily track patients that need to be under management follow-up for indeterminate pulmonary nodules (IPNs).

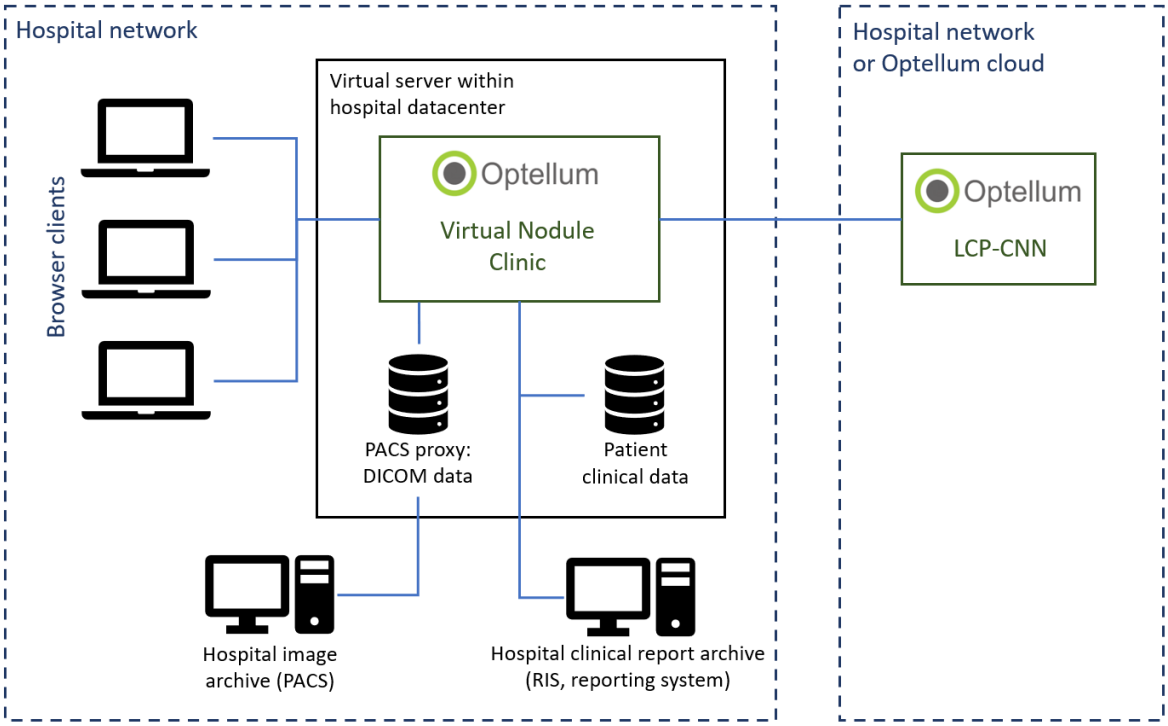
These functions are further described below.

VNC consists of two main software components:

- A web application deployed on a virtual server within a hospital datacenter;
- The LCP-CNN module deployed on a GPU-equipped server on hospital premises or in the cloud.

VNC is connected to two other IT systems in the hospital (see Figure 1): a DICOM-compatible Picture Archiving and Communication System (PACS) for accessing images and to the Radiology Information System (RIS) or reporting system for accessing the clinical reports.

Figure 1: Virtual Nodule Clinic and connectivity to other hospital IT systems



5.5.3 Use environment

The pulmonary nodule management process typically includes setting up pulmonary nodule clinics in hospitals, so that nodules can be followed up or clinical investigations can be prescribed to confirm the diagnosis associated with the presence of pulmonary nodules. A nodule clinic is typically led by a pulmonologist and includes a multi-disciplinary team of radiologists, thoracic surgeon and sometimes pathologist and oncologist. Virtual Nodule Clinic is intended for use in hospitals to support these clinics.

5.5.4 Description of main functions

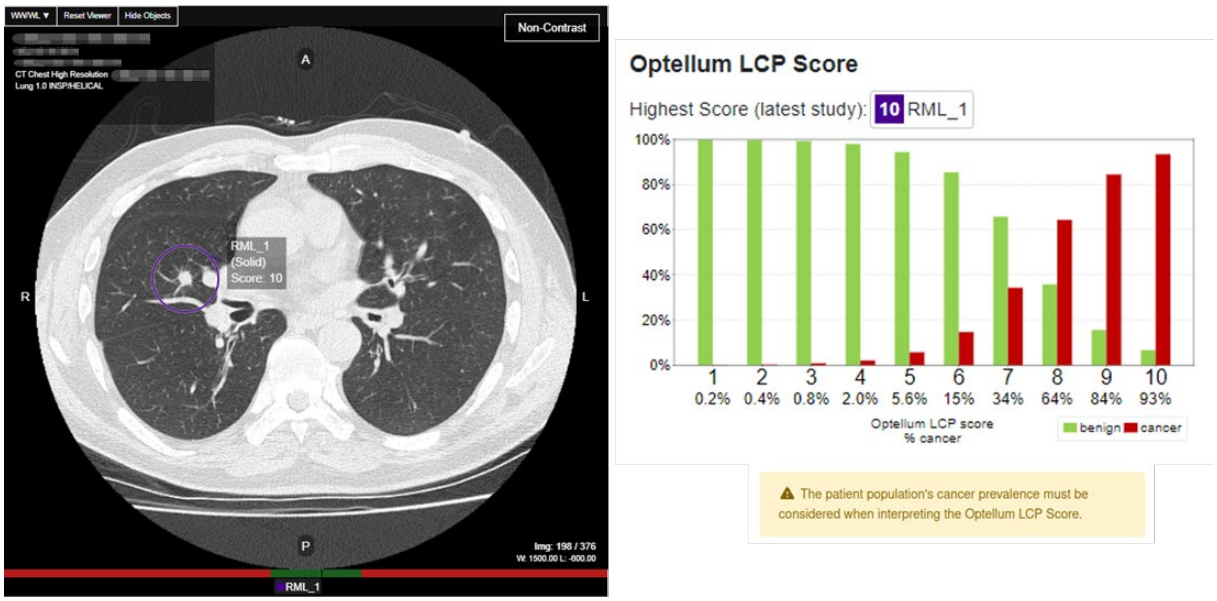
This section explains, for each of the intended functions listed in section 5.5.2, how the device functions and related scientific concepts.

5.5.4.1 Computer-aided diagnosis

The software's computer-aided diagnosis (CADx) function, only available to pulmonologists and radiologists, automatically analyzes user-selected regions of interest (ROI) from lung CT data. This function extracts image data from the ROI to provide 3D analysis and computer analytics based on morphological characteristics. These imaging (or radiomic) features are computed solely from the image extract and then synthesized by an artificial intelligence algorithm into a single value, the LCP-CNN score, which is displayed to the user. The score displayed is an integer between 1 and 10 where 1 means very likely benign and 10 means very likely malignant. The LCP-CNN score is not a probability of malignancy but is intended to be analyzed relative to LCP-CNN scores generated on a database of cases with known ground-truth, using a histogram display format. See Figure 2.

The LCP-CNN score, in combination with other information may be used in the characterization of incidentally detected pulmonary nodules and may be used as one input to clinical decision making when following published clinical guidelines.

Figure 2: a CT image with a user-selected region of interest, RML_1 (left) and the histogram of scores from a database of malignant and benign nodules where the ground-truth is known (right).



Images courtesy of Oxford University Hospitals NHS Foundation Trust, Oxford, UK

5.5.4.2 Nodule clinic management

The software is connected to the Picture Archiving and Communication System (PACS) for accessing images and to the Radiology Information System (RIS) or reporting system for accessing reports. Medical CT images of the patient can be displayed within the software, used to track nodules over time, and for radiologist and pulmonologist users provide access to the CADx function described in the previous section. Both access to the PACS and the RIS or reporting system is read-only: VNC does not modify, manipulate, or push any data back to these systems.

During patient enrollment, the user accesses the nodule history of a patient with pulmonary nodules by looking at existing reports and images of the patient. With this information, the user can enroll the patient if clinically indicated.

Enrollment can be assisted through automated identification of key words ("#nodule", a value that can be configured) in the reports. Key words are included by the radiologists themselves in reports at the time of the image interpretation (reading). Automatic identification of this key word produces a filtered list of patients proposed to the user for enrollment. The user will then need to confirm the enrollment of the patient. If not present in the list, a patient can be searched by the user (from their medical record number or name) and then reviewed for enrollment.

Once enrolled, the user can make certain decisions about the clinical management of the patient, according to pulmonary nodule management guidelines, for instance, requesting a follow-up scan, or a clinical investigation (biopsy), refer to a lung cancer team or discharge. The booking of these examinations is done separately through the hospital booking system, and the actual date of the follow-up can be entered by the user once the booking is confirmed.

When a new CT study is found for a patient in the PACS, the user is automatically informed about it in the software. The user can then take appropriate decision regarding this new study for the patient.

Patients missing their follow-up examinations are automatically flagged to the user, allowing patient rescheduling or discharge if indicated.

The patient management ends when the user discharges this patient from the nodule clinic once clinical diagnosis has been confirmed or for other indicated reasons (e.g. patient death, refusal to continue follow-up).

5.5.5 Materials of use

VNC is a software only device.

5.5.6 Key performance characteristics

VNC is a software only device, so design, validation and verification were planned, executed and documented according to FDA guidance, including the following:

- FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.
- 21 CFR §892.2060 special controls.
- FDA's Guidance for Applying Human Factors and Usability Engineering to Medical Devices.
- FDA's Guidance for Content of Premarket Submissions for Management of Cybersecurity in Medical Devices.

See sections 5.8 and 5.9.

5.6 Intended use

This section describes Virtual Nodule Clinic's intended use, including a general description of the diseases or conditions that the device will diagnose and of the patient population for which the device is intended. It also compares VNC's intended use to that of the predicate device.

5.6.1 Indications for Use statement

Virtual Nodule Clinic (VNC) is a software device used in the tracking, assessment and characterization of incidentally detected pulmonary nodules.

VNC includes a computer-aided diagnosis (CADx) function, available only to pulmonologists and radiologists. This automatically analyzes user-selected regions of interest (ROI) within lung CT data to provide volumetric and computer analysis based on morphological characteristics. Using only imaging features extracted from the CT image data, an artificial intelligence algorithm calculates a single value, the LCP-CNN score, which is displayed to the user. The LCP-CNN score is analyzed relative to LCP-CNN scores generated on a database of cases with known ground-truth using a histogram display format. The LCP-CNN score may be useful in the characterization of pulmonary nodules during image interpretation and may be used as one input to clinical decision making when following published clinical guidelines.

VNC's LCP-CNN score is indicated for the evaluation of incidentally detected solid and semi-solid pulmonary nodules of diameter 5-30mm in patients aged 35 years or above. In cases where multiple abnormalities are present, VNC's LCP-CNN score can be used to assess each abnormality independently.

Note that LCP-CNN is not indicated for lung cancer screening nor is it indicated for nodules of pure ground glass opacity. In addition, high contrast CT images were not used in clinical validation (as measured as >300HU median attenuation in the aortic arch) and the validation data also excluded CT images with only calcified nodules (since these are typically considered to be benign), with implants, motion artifacts, missing slices, or cases with greater than 5 nodules. Finally, the validation data excluded patients with history of cancer of less than 5 years to avoid the presence of metastatic lesions.

Users other than radiologists and pulmonologists, e.g. clinicians, nurses, nurse practitioners and navigators, may use VNC to view CT images and reports, organize patient management workflow, track patients, record management decisions and organize nodule clinics. For these users, the LCP-CNN score is unavailable.

5.6.2 Contraindications

The Optellum LCP Score is not indicated for pure Ground-Glass Opacities (GGO) or for calcified nodules.

The Optellum LCP Score is not indicated for patients with a history of cancer less than 5 years.

The Optellum LCP Score is not indicated for nodules detected by lung cancer screening studies.

The Optellum LCP Score is not indicated for patients with more than five pulmonary nodules.

The Optellum LCP Score is not indicated for patients with thoracic implants that impact the image appearance of the nodule.

The Optellum LCP Score is not indicated for patients younger than 35 years.

5.6.3 Intended patient population

Virtual Nodule Clinic's Optellum LCP Score is intended to be used for patients meeting all of the following criteria:

- aged 35 or older
- have between one and five incidentally detected solid and/or semi-solid pulmonary nodules 5-30mm in diameter
- no other history of cancer in the past five years
- no thoracic implants that impact the image appearance of the nodule.

VNC's Optellum LCP Score can be used for male and female patients who are smokers, non-smokers or ex-smokers.

5.6.4 Comparison with predicate

This subsection explains the similarities with and differences between VNC and the predicate device in relation to intended use, including their respective Indications for Use statements, and explains why the differences are not critical to the intended diagnostic use of the device.

5.6.4.1 Similarities

Both QuantX and Virtual Nodule Clinic (VNC) are computer-aided diagnosis (CADx) software devices used to assist clinicians in the assessment and characterization of abnormalities using image data. Both devices extract image data from user-selected ROIs to provide volumetric and computer analysis based on morphological characteristics. Both devices use an artificial intelligence algorithm to synthesize these imaging (or radiomic) features into a single value represented as a score which is analyzed relative to scores generated on a database of cases with a known ground truth.

For both devices, device failure could lead to an absence of results, delay to diagnosis or incorrect results.

Similar to the QuantX device, efficacy of VNC is determined following the same special controls for design, validation, verification and labeling; both use reader studies to validate the impact on reader performance.

Both devices provide the user with information to aid in the interpretation of medical images and both devices provide a machine learning based score derived from the patient's image to aid the reader in interpreting the image and making recommendations and patient decisions. The QuantX

device provides the QI score whereas the VNC device provides the LCP-CNN score. In both cases, the score is not a probability of malignancy but provides a likelihood function, to be interpreted using a display of information derived from a database of cases with known ground-truth.

In cases where multiple abnormalities are present, both devices can be used to assess each abnormality independently.

Both devices provide a histogram of the score distribution over malignant and benign cases from a database where the ground-truth is known. In both devices, the histogram is provided as a reference to aid in the use of the score in image interpretation.

In both devices, the user makes the final determination and decision on patient management.

Both devices are able to display DICOM-compliant medical images.

Both devices provide a means for the user to select images to load from a database of patient images. In the case of VNC this comes in the form of a convenient timeline. VNC also provides access to the patient's previous images and radiology reports as a convenient feature to save time for the user. While it is not clear whether the QuantX device provides such features, it is to be used in the context of radiology workflow and access to prior images and reports is readily available via the electronic medical record, PACS and RIS systems.

VNC provides a convenient means by which the user can record the recommended management decision or next steps. In QuantX this is likely to be recorded in the reporting system rather than in an integrated way.

Both devices provide information regarding the patient demographics.

5.6.4.2 Differences

The QuantX device is intended to be used in the case of patients undergoing imaging for breast cancer whereas VNC is to be used in the context of lung cancer. While these are different sets of patients and diseases, both devices are being used in the same clinical context, i.e. diagnostic image interpretation as an input to patient management decision making. Risks relating to input (image appropriateness and quality), human factors (ROI selection) and output (reliance on the user to make management decision) are the same in both devices.

QuantX can automatically register and segment user-selected regions of interest (ROI) and provides measurement tools. This allows QuantX to provide additional information over VNC, based on radiomics and quantitative features. VNC's LCP-CNN score, also derived from user-selected ROIs encapsulates all information necessary to aid the user for our use-case. This difference does not result in increased risk or reduced efficacy of VNC over QuantX.

QuantX is indicated for high-risk screening, diagnostic workup or evaluation of extent of known disease. VNC is indicated to assist users in diagnosis of patients with incidentally detected pulmonary nodules, i.e. diagnostic workup. This apparent difference is a function of the differing methods of identification of the respective diseases. Breast abnormalities are not routinely discovered incidentally but lung ones are. Each device is indicated for its expected suitable method of abnormality identification and management. Therefore, this difference does not indicate a difference in risk or efficacy.

VNC's intended users are split into two groups by the functionality available to them. All functions, including the CADx function, are available to pulmonologists and radiologists. Other intended medical users (e.g., nurses, nurse practitioners and nurse navigators) do not have access to the CADx function or its output. QuantX is intended for radiologists only. Roles in VNC are clearly defined in the system and the functionality associated to each role is clearly differentiated when they need to

be, and only the radiologist or pulmonologist can use the CADx function. The functionality available to the nurse or nodule clinic administrator is restricted to the management of patients. This difference does not indicate a difference in risk or efficacy.

The QuantX device provides examples from the database that score similarly to that of the current patient. VNC does not provide this feature. However, we do not believe that this additional feature changes the device risk and merely provides additional information that may be useful to the user. Efficacy is determined in the reader study clinical validation.

The QuantX device provides additional information based on radiomics and quantitative features. VNC does not provide any such information. The LCP-CNN score encapsulates information necessary to aid the user for our use-case and we have confirmed this by performing a reader study.

The QuantX device processes MRI images to arrive at the QI score whereas VNC processes CT images to arrive at the LCP-CNN score. Both are taking voxel data from the images to arrive at the score and both are using supervised machine learning algorithms to produce the score. Moreover, both are to be used as an aid to interpretation of the images as part of oncology workflow. We do not believe the difference in modality is a substantial difference in the devices.

5.7 Technological characteristics

This section summarizes Virtual Nodule Clinic's technological characteristics and explains the similarities and differences with those of the predicate device, including explanation of why the differences are not critical to the intended diagnostic use of the device.

5.7.1 Principles of operation

VNC is accessed via a web browser on any PC or Apple workstation in the hospital. The software is validated with web browsers Google Chrome, Mozilla Firefox, Microsoft Edge, Microsoft Internet Explorer and Apple Safari.

5.7.1.1 Image analysis algorithm

Image analysis algorithms behind VNC's CADx function, LCP-CNN, are described in detail in this submission, according to 21 CFR §892.2060 special control 1(i), and summarized here.

CNN and input: The LCP-CNN system is based on the Dense Convolutional Network, a widely used type of deep learning CNN architecture that was designed for computer vision tasks. LCP-CNN's ensemble of convolutional neural network models ends with a fully connected binary classification layer (malignant or benign). Input to LCP-CNN is a 3-dimentional crop of a CT image, centered on a lung nodule.

Training dataset: The LCP-CNN network was trained using solid and semi-solid nodules of at least 5mm in diameter. The training data consisted of 8% malignant nodules and 92% benign nodules, and included both screening (95%) and incidentally detected (5%) nodules. The median age of the subjects was 62 (20-90) and included a mix of US (95%) and EU data (5%). The data included females (38%) and males (62%). Only nodules that were confidently matched to a definitive diagnosis, as provided with the data, were used for training.

CNN output: LCP-CNN's output is a continuous value between 0 and 1; this is mapped to an integer score between 1 and 10. This mapping was constructed by computing the raw LCP score on a dataset consisting of malignant (10%) and benign nodules (90%) but which were not used during the model training. The mapped integer score is shown to the user alongside a plot detailing the cancer prevalence in each of 10 bins for a population with a 30% cancer prevalence.

5.7.1.2 PACS connectivity

VNC can display DICOM-compatible images of the patient. For load performance reasons, this DICOM data is pulled from the hospital's PACS and copied locally in a PACS proxy. VNC can query the hospital PACS for a patient's images, for example when a patient is considered for enrollment into the nodule clinic or when an enrolled patient has a new image in the PACS. This results in the local storage being synchronized with the PACS data used by VNC.

Access to the hospital's PACS is read-only: VNC does not modify, manipulate or push any data back to the hospital PACS.

VNC displays DICOM data as-is, without performing any modifications to the data. No reconstruction, resampling, interpolation or compression is performed in order to display DICOM data. VNC does not provide any facility to export DICOM data.

VNC provides standard DICOM viewing tools such as pan, zoom, Window/Level and slice scrolling.

5.7.1.3 Reporting archive connectivity

VNC can display clinical reports from a supported RIS or reporting system. Where the report is associated with a DICOM image the report is displayed in VNC alongside that image. Access to the hospital's RIS or reporting system is read-only: VNC does not modify, manipulate, or push any data back to the RIS or reporting system.

5.7.2 Comparison with predicate

Similarities: Both devices use an artificial intelligence algorithm to synthesize imaging features into a single value represented as a score which is analyzed relative to scores generated on a database of cases with a known ground truth.

Both devices are software only (software as a medical device). Both devices have a graphical user interface. Both devices comply with DICOM 3.0, with differences in modality discussed above. Both can import DICOM images from connected third party DICOM-compatible devices.

Differences: VNC is installed on Linux server(s), while QuantX is installed in Windows. Both are state-of-the-art operating systems capable of supporting secure, safe and effective use of the device. Safety and effectiveness have been demonstrated by performance testing. Therefore, this difference is not substantial.

5.8 Nonclinical performance

This section includes discussion the nonclinical tests used to establish substantial equivalence of Virtual Nodule Clinic to the predicate device.

5.8.1 Design, verification and validation

Like the predicate device, VNC is a software only device, so design, validation and verification were planned, executed and documented according to the following, and summarized in the rest of this subsection:

- FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices. Based on this guidance, VNC was assessed to represent a Moderate Level of Concern, the same as the predicate device.
- 21 CFR §892.2060 special control 1(v) Appropriate software documentation.

As a software-only device, all requirements are software requirements. User requirements (those relating directly to the intended users) and product requirements (e.g. environmental and regulatory requirements) were identified without reference to design; they are design inputs.

Device hazard analysis and risk management, based on ISO 14971:2019 Application of Risk Management to Medical Devices, was used to identify and control hazards associated with the device. This consists of:

- Device Characteristics Analysis, including intended use, reasonably foreseeable misuse, identification of characteristics related to safety.
- Risk analysis, including identification of hazards and estimation of the associated risks.
- Risk control, including identification and analysis of risk control measures (design specifications and architectural design), implementation and verification of risk control measures; traceability; residual risk analysis to determine acceptability.
- Risk review, including the overall residual risk compared to benefits of using the device.

Implementation of requirements is documented in detailed architectural design and design specifications, including acceptance criteria.

Planned and pre-defined testing included:

- Validation that VNC's user and product requirements are met (acceptance testing) – test results are included in this submission.
- Verification of correct implementation of design specifications, including risk control measures (system testing) – test results are included in this submission.
- Verification of correct implementation of architectural and detailed software design (unit and integration testing).

A series of traceability tables link enumerated requirements, risks, design specifications and tests.

Unresolved software anomalies known at the time of manufacture are listed in this submission. None affect or create any identified hazards, nor do they affect the device's safety and effectiveness.

In summary, VNC is successfully validated against user and product requirements and successfully verified against design specifications. All risk control measures, including those related to usability, are verified to be performing as designed.

5.8.2 Usability evaluation

The following types of usability evaluation were performed as part of validation and verification, using FDA guidance Applying Human Factors and Usability Engineering to Medical Devices.

- Formative usability evaluation: activities to identify potential usability issues and risks and otherwise inform design.
- Summative usability evaluation: activities for the purpose of establishing whether usability-related safety risks have been successfully mitigated.

Usability engineering activities included identification and assessment of usability-related hazards and risk control measures. Test scenarios were designed to validate VNC's usability. Test subjects selected included representatives from the intended user groups.

In summary, usability testing using VNC was performed and confirmed that usability-related risk control measures were successful. Subsequent residual risk analysis determined that all associated usability risks have been reduced to an acceptable level. Accordingly, no further device development or re-validation work was deemed to be required: usability evaluation has shown that Virtual Nodule Clinic is safe and effective for the intended users, uses and use environments.

5.8.3 Cybersecurity

Cybersecurity activities were performed using FDA's Guidance for Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (2014). The following activities were performed:

- Identification of assets, threats, and vulnerabilities.
- For each threat and vulnerability, assessment of:
  - the impact on device functionality and end users/patients
  - the likelihood of a threat and of a vulnerability being exploited
  - risk levels and suitable mitigation strategies
  - residual risk and risk acceptance criteria.
- Planning activities for post-market surveillance of cybersecurity.

Identified cybersecurity risks, their control measures and verifications were managed along with other device risks. VNC's installation guide includes description of requirements and activities related to cybersecurity at installation locations.

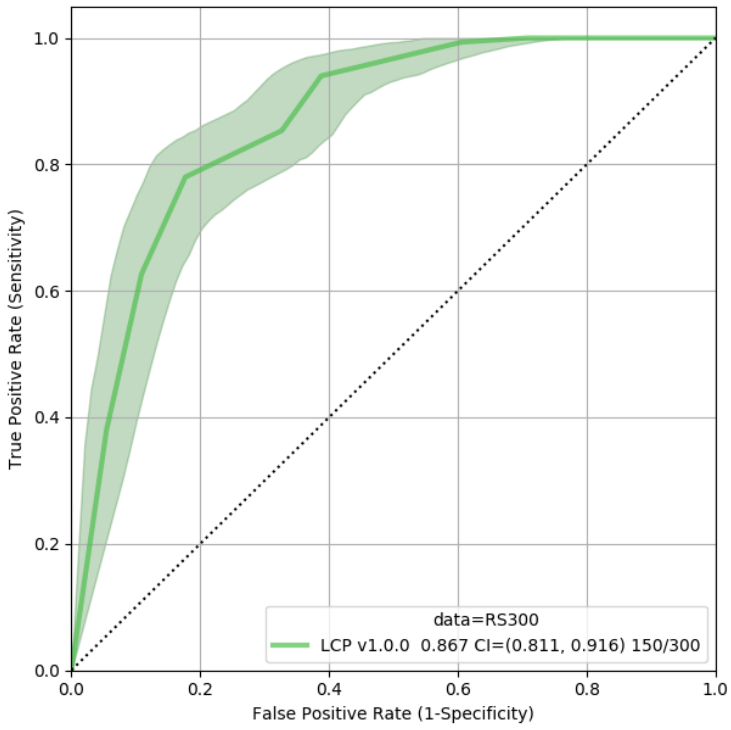
5.8.4 CADx standalone testing

Like the predicate device, standalone testing of the LCP-CNN model (the CADx function) of VNC was planned and performed in accordance with 21 CFR §892.2060 special control 1(iv).

This testing was designed to measure performance of VNC's LCP-CNN model in discriminating between benign and malignant nodules before the model's incorporation into the device for further testing, including clinical testing. For the purpose of this test, a minimum area under curve (AUC) on a receiver operator characteristic (ROC) plot of 0.8 was selected.

The LCP-CNN model achieved an AUC of 0.867, meaning that the LCP-CNN model is performing as expected and therefore accepted as the model to be incorporated into the device for further testing. See Figure 3.

Figure 3: Receiver Operating Characteristics (ROC) for standalone testing of LCP-CNN.



5.8.5 Testing not included in submission

Non-clinical bench performance testing, as defined in section I of Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Pre-Market Submissions (2019), was not performed so is not included in this submission.

Animal testing was not performed for VNC so is not included in this submission.

5.9 Clinical performance

5.9.1 Summary

Like the predicate device, clinical performance of VNC's CADx function was assessed and documented according to 21 CFR §892.2060 special controls 1(ii) and 1(iii).

Clinical performance of the LCP-CNN feature in the VNC software was evaluated in a fully-crossed, multiple-reader multiple-case (MRMC) study. This study evaluated the performance of twelve readers, six radiologists and six pulmonologists, in stratifying incidentally detected pulmonary nodules in CT scans from 300 subjects. Subject dataset comprised 136 females and 164 males between the ages 38 to 88 with a median age of 65. Half of the cases comprised malignant nodules. Data was collected from a variety of scanners and centers from across the US and EU and includes both academic and community centers.

The readers were required to specify the likelihood of malignancy blinded to the LCP-CNN score and then again unblinded to the score. Efficacy was measured by calculating the area-under-the-curve (AUC) of the receiver-operating-characteristic (ROC) curve.

The results showed that the average performance of the readers improved by 6.85 AUC points, that every reader's average accuracy improved, and readers became more consistent with each other.

5.9.2 Clinical endpoints

Primary: The primary endpoint compared the ability of the readers to discriminate between malignant and benign pulmonary nodules from CT images only, with and without the aid of the LCP-CNN. For a given reader, discrimination was measured using the area under the receiver operating characteristic curve (AUC) across all cases. The effect size of the LCP-CNN intervention was measured as the difference in AUC before and after consulting the malignancy score provided by the LCP-CNN (i.e. unaided and aided reads).

Sub-analysis: The following sub-analyses were performed:

- Between data collected from US centers and non-US centers
- Between data collected from academic and non-academic (e.g. community) centers
- Between screening and non-screening (i.e. incidentally detected) pathways
- Nodule sizes (5-9mm, 10-15mm, >15mm)
- Per nodule attenuation: solid, semi-solid
- Per scanner manufacturer (GE, Siemens, Philips, Canon/Toshiba)
- Volume CT dose
- Reconstruction slice thickness
- Reconstruction algorithm/kernels
- Per reader specialty (radiologist vs chest physician)
- Per reader's experience (experienced vs inexperienced)
- Patient sex
- Hospital for data collection
- Patient age range.

Secondary: A number of secondary endpoints were also evaluated including change of Likelihood of Malignancy (LoM) and recommended next management action, consistency of readers and sensitivity and specificity at 5% and 65% risk (ACCP thresholds) for blinded and unblinded evaluations.

5.9.3 Test methods

Reader selection: Table 1 lists the readers recruited for the study. They all satisfied minimum qualifications and experience as follows:

1. Current medical license
2. American Board of Radiology or equivalent specialty certification
3. At least 1 year of chest CT interpretation experience
4. Fellowship-trained in thoracic/chest imaging or 2 years' experience in thoracic imaging
5. Successful training on the use of study software.

Table 1: Reader experience summary

Reader	Category	Years of relevant experience
Reader 1	Pulmonologist	19
Reader 2	Pulmonologist	7
Reader 3	Radiologist	15
Reader 4	Radiologist	10
Reader 5	Pulmonologist	3
Reader 6	Pulmonologist	1
Reader 7	Pulmonologist	4
Reader 8	Pulmonologist	4
Reader 9	Radiologist	11
Reader 10	Radiologist	2
Reader 11	Radiologist	3
Reader 12	Radiologist	2

Reader training: Prior to performing study reads, readers were trained on LCP-CNN operating principles and asked to perform 3 example patient reads in the presence of an Optellum trainer (training was performed remotely), then 17 further cases on their own. After each of these reads, the reader was provided with ground truth diagnosis. This is typical of the training users are recommended to receive for clinical use of the device.

Reading: Readers used image data and the LCP-CNN score only to assess the study's cases – no other data such as smoking history, age, etc. were known to the reader. For each of the 300 cases (presented in a pseudo-random order for each reader), the reader created a region of interest by clicking at the centroid of the patient's indeterminate pulmonary nodule (IPN), then, blinded to the LCP-CNN score, estimated its likelihood of malignancy (LoM – 0 to 100, with 100 meaning definitely cancer) and selected the next appropriate action for the patient (no action, long term CT follow-up, short term CT follow-up, immediate imaging follow-up, biopsy, surgical resection/other destructive techniques). LoM1 and the follow-up action were then locked, and the reader shown the LCP-CNN score. The likelihood of malignancy was then re-estimated (LoM2), and follow-up action based on this recorded and locked.

5.9.4 Validation dataset

The study was performed using three hundred patients with solid and semi-solid indeterminate pulmonary nodules retrospectively collected from 9 academic and community hospitals. The data comprised 174 cases from the USA and 126 from the EU. The data was collected from both academic and non-academic, i.e. community (in the USA) or district general (in the UK) hospitals. For all datasets, the ground-truth was known either by biopsy, resection, or in the case of benign nodules from 2-year follow-up (or nodule disappearance). The following tables summarize the validation dataset. In these studies (other than for NLST data), patient consent had been waived.

Note that although VNC is indicated only for incidentally detected lung nodules, scarcity of such data from community datasets meant that some community screening-detected nodules were included in the validation dataset. Sub-analysis included comparison between incidental and screening datasets (see section 5.9.6). The diagnosis of all nodules used in the study, whether screening or incidental, were established using the same common protocol that was used for the training dataset.

Table 2: Patient characteristics for the Validation Set.

	Study Validation Set
Patients	
Number (cancers)	300 (150)
Age	
Median	65
Range	38-88
Sex	
Female (Male)	136 (164)
Cancer Histology	
Adenocarcinoma	96
Other	54
Total	150

Table 3: Nodule characteristics for the Validation Set, broken down by malignancy status. For the "Malignant" and "Benign" columns, the percentage given is the within-category percentage (e.g. 42% of the Male patients in the validation set have a malignancy), and for the "Total" column, the percentage is the row total as a percentage of the dataset, e.g. 55% of the validation patients are male.

Study Validation Set						
	Malignant		**Benign**		**Total**	
Sex	**N**	**%**	**N**	**%**	**N**	**%**
Male	69	42	95	58	164	55
Female	81	60	55	40	136	45
Total	150	50	150	50	300	100
Data Source						
Academic	113	65	62	35	175	58
Community	37	30	88	70	125	42
Total	150	50	150	50	300	100
Case Pathway						
Incidental	130	63	76	37	206	69

Screening	20	21	74	79	94	31
Total	150	50	150	50	300	100
Data Origin						
USA	73	42	101	58	174	58
EU	77	61	49	39	126	42
Total	150	50	150	50	300	100
Nodule diameter						
0 to ≤6mm	5	11	39	89	44	15
>6 to ≤8mm	18	33	36	67	54	18
>8 to ≤15mm	76	58	56	42	132	44
>15mm	51	73	19	27	70	23
Total	150	50	150	50	300	100
Nodule Margin						
Non-spiculated	38	27	105	73	143	48
Spiculated	75	73	28	27	103	34
Unreported	37	69	17	31	54	18
Total	150	50	150	50	300	100
Nodule Type						
Solid	123	51	120	49	243	81
Semi-Solid	27	49	30	51	57	19
Total	150	50	150	50	300	100

Table 4: Scan-wise summary of the validation data, broken down by nodule malignancy status. All four major vendors are represented, and a variety of slice spacings up to 2.5mm.

Pilot Study Validation Set						
	Malignant		**Benign**		**Total**	
Scanner Manufacturer	**N**	**%**	**N**	**%**	**N**	**%**
GE	60	67	30	33	90	30
Philips	27	55	22	45	49	16
Siemens	41	47	46	53	87	29
Canon/Toshiba	22	30	52	70	74	25
Total	150	50	150	50	300	100
Reconstructed Slice Spacing (mm)						
<1.0	32	64	18	36	50	17
1.0 - <1.5	69	68	33	32	102	34
1.5 - <2.0	1	33	2	67	3	1
2.0 - <=2.5	48	33	97	67	145	48
Total	150	50	150	50	300	100

Table 5: Validation dataset breakdown by scan dose. 20 patients have no usable data in either mAs or CTDIvol fields. Values of mAs over 1000 were assumed to be recorded in incorrect units, and have been divided by 1000 for the tables presented in this document. Within the "N" columns are two numbers: the first represents the number over which the median and range

values were calculated (because of the missing dose information), and the second represents the total number of patients in the category.

Pilot Study Validation Set							
	Malignant			Benign			
Dose Information	**N**	**Median**	**Range**	**N**	**Median**	**Range**	**N Total**
kVp <=100							
CTDIvol	5/12	4.9	3.3-6.8	3/3	8.2	4.5-10.6	8/15
Exposure (mAs)	9/12	69	1.0-108.0	3/3	98	56.0-126.0	12/15
kVp 101-120							
CTDIvol	64/138	7.4	1.6-32.8	39/144	7.3	1.6-32.8	103/282
Exposure (mAs)	129/138	44	1.0-375.0	136/144	42.5	1.0-266.0	265/282
kVp >120							
CTDIvol	0/0	-	-	1/3	12.6	12.6-12.6	1/3
Exposure (mAs)	0/0	-	-	3/3	76	2.0-165.5	3/3

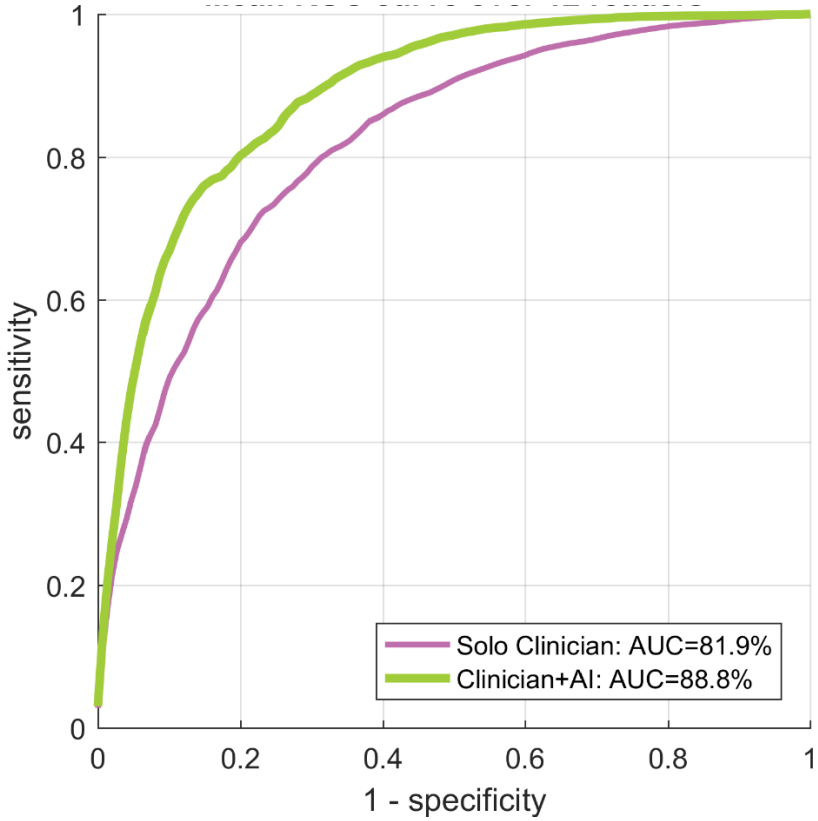
5.9.5 Test results

Primary endpoint: The mean effect size of the LCP-CNN intervention across all readers was 6.85 AUC points, 95%CI [4.29, 9.41], indicating a significant improvement in the discriminability of the readers ($p < .001$). Table 6 provides the per reader results. Figure 4 shows the mean ROCs for all 12 readers' performance unaided and aided by the LCP-CNN.

Table 6: Reader performance summary

Reader	LoM1 AUC	LoM1 AUC 95%CI	LoM2 AUC	LoM2 AUC 95% CI	Delta AUC	Delta AUC 95%CI
1	75.3	69.6-80.5	85.2	80.8-89.2	9.88	6.22-13.66
2	80.0	75.0-84.8	88.2	84.2-91.9	8.25	5.74-10.97
3	79.2	74.0-84.1	89.4	85.7-92.7	10.20	6.52-14.01
4	76.5	70.8-81.7	88.6	84.6-92.1	12.14	8.11-16.40
5	87.5	83.5-91.2	89.9	86.2-93.1	2.42	1.18-3.68
6	82.5	77.6-86.9	89.4	85.7-92.7	6.93	4.01-10.10
7	85.7	81.3-89.7	89.5	85.7-92.8	3.78	1.62-6.14
8	80.5	75.5-85.1	88.0	84.1-91.6	7.52	5.02-10.13
9	85.4	80.8-89.5	90.2	86.6-93.5	4.79	2.67-7.02
10	82.1	77.0-86.6	89.6	85.9-92.8	7.52	4.16-11.08
11	83.8	79.2-88.1	89.2	85.4-92.6	5.37	2.36-8.50
12	84.6	80.1-88.8	88.0	83.9-91.6	3.42	1.58-5.34

Figure 4: MRMC reader study ROC performance: mean ROC curves (unaided and aided by LCP-CNN) over 12 readers.



Secondary endpoint: The results of the secondary endpoints show that the benefit of the LCP-CNN support is captured by a range of performance metrics with statistical significance: net reclassification improvement (NRI), sensitivity and specificity. The secondary results also indicate that, when a reader decided to change their likelihood of malignancy and/or clinical recommendation following a consultation of the LCP-CNN score, the direction of change was predominantly the correct one. Finally, the secondary endpoints showed that the spread of the estimates, as measured by standard deviation, of nodule malignancy across readers was reduced significantly when the readers were aided by the LCP-CNN.

5.9.6 Summary of sub-analyses

The sub-analysis of the primary endpoint indicates that the effect of the LCP-CNN score was positive across a wide range of relevant sub-groups. Notably, we observed no significant differences between academic vs. community centers, screening vs. incidental, CT energy, slice thickness, reconstruction types, radiologists vs. pulmonologists, age groups and sex.

There were some moderate differences between the US and non-US data and reader experience, and one manufacturer showed much greater change in AUC than the others. However, such differences were due to the mixture of cases in each sub-group rather than inherent performance differences in the algorithm.

There were some differences in performance of readers between different nodule appearances and sizes as to be expected. Readers generally performed better on larger nodules (>15mm) and with solid nodules.

We observed no significant differences between 5 of the 6 sites/data sources. On the data from one UK site, the use of the LCP-CNN output resulted in an improvement in reader performance which

was greater than for the other sites. This seems to be caused by lower than average reader accuracy on this dataset when blinded to the LCP-CNN score.

5.10 Conclusions

5.10.1 Nonclinical performance testing

Standalone testing of the LCP-CNN model demonstrated that it performed as expected in discriminating between benign and malignant nodules, prior to incorporation into VNC for further testing.

Software verification and validation demonstrated that VNC is validated against user and product requirements and successfully verified against design specifications. All risk control measures, including those related to usability, are verified to be performing as designed.

5.10.2 Clinical performance testing

The described clinical performance study concluded that:

- Concurrent use of the LCP-CNN feature in Optellum Virtual Nodule Clinic software to read CT exams improves radiologists' and pulmonologists' accuracy for the diagnosis of pulmonary nodules by an average of 6.85 AUC points ($p < .001$) (from 81.9 to 88.8 AUC)
- Every radiologist and pulmonologist improved their accuracy when using the Optellum LCP-CNN feature to assist their read.

5.10.3 Benefit-risk assessment

Risk management based on ISO 14971:2019 was performed in the design and development of this device.

Benefits of use of the Optellum LCP Score are assessed primarily by analysis of primary and secondary endpoints of the clinical study described above. In this study, every radiologist and pulmonologist improved their accuracy when using the score to assist their read (primary endpoint). Secondary endpoints showed that the score improved the consistency of readers' estimates of the likelihood of malignancy, and a significant proportion of patients could have a more appropriate follow-up, either reducing time to diagnosis for patients with malignant nodules or reducing follow-up scans for those with benign nodules.

The data used in the validation study were a majority of incidentally detected nodules and a minority (ca. 30%) of screening detected nodules, whereas intended use is for incidentally detected nodules. While we observed no significant difference in the effect of the LCP-CNN between screening and incidentally detected nodules, there remains the possibility that differences may be present between these populations. Consequently, overdiagnosis in intended use could result, because screening populations can be expected to have higher cancer prevalence than the device's intended incidental population.

The risk of overdiagnosis is controlled by a specific warning in the device labeling, repeated in relevant sections of the device's user guide, and reinforced by a similar warning in the user interface. The warning states that the cancer prevalence in the intended use patient population must be considered in comparison to the prevalence in data used to train and validate the LCP-CNN model. The warning in the device labeling includes a reference to details of the training and validation data, also included in the labeling.

With the risk control measures provided, the risk of decisions being affected by over- or under-estimation of malignancy by the LCP-CNN score is small and outweighed by the score's benefit.

More generally, there are risks of non-indicated use of the device, including where the device's indications are limited by validation data used in the study. These risks are controlled by specific warnings and contraindications in the device labeling. For example, validation data did not include Ground Glass Opacities, patient history of cancer less than 5 years, patients with greater than five nodules, patients with implants, and patients younger than 35 years; each of these has a specific contraindication and warning listed in the device labeling, including in the user guide. Risks associated with other limitations (e.g. irregular slice spacing and non-axial orientation) are additionally controlled by design in the device itself, by disabling the score function.

Overall risk control, together with the intended users' knowledge that the score is not to be used in isolation (also reinforced by device labeling), mean all identified risks have been reduced as much as possible within the confines of retaining the associated benefits. In all cases, the individual residual risks are outweighed by the associated benefits. Therefore, the total residual risk associated with use of Virtual Nodule Clinic is outweighed by the benefit of its use.

5.11 Substantial Equivalence Statement

Virtual Nodule Clinic (VNC) has the same or similar intended use as the predicate device; technological differences between VNC and the predicate device do not raise any questions regarding VNC's safety and effectiveness. Clinical and non-clinical performance testing has demonstrated that VNC performs at least as safely and effectively as the predicate device in the context of its intended use and with the proposed labeling. VNC meets requirements for safety and effectiveness and does not introduce any new potential safety risks.

The information provided in this submission supports our claim that VNC is as safe, as effective, and performs as well as or better than the legally marketed predicate device.