CINA

User Guide

Caution: Federal law restricts this device to sale by or on the order of a physician.

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Content

OVERALL

Introduction

This user guide is intended to provide assistance to the User of CINA, developed, marketed, and owned by Avicenna.AI. It provides information for a better understanding and thus a better use of the ICH and LVO image processing applications when integrated, deployed and used with compatible medical image communications devices (3rd-party Platforms).

Document overview

This document is composed of five main parts:

- Intended use and indications for use
- General caution and safety message
- Image acquisition protocol
- Integration of CINA within 3rd-party Platform
- Summary of the Performance testing

Acronyms and glossary

- Acronyms

DICOM	Digital Imaging and COmmunication in Medicine
GSPS	Grayscale Softcopy Presentation State
ICA	Internal Carotid Artery
ICH	Intracranial Hemorrhage
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
PACS	Picture Archiving and Communication System

Glossary

Image Processing Application	Independent CINA Image Processing Application (such as ICH and LVO) integrated and deployed through a 3rd party Platform to be used by the USER.
User	The CINA principal user. The end-user is a trained radiologist.

About this user's guide

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Screen captures

This guide uses screen captures to help illustrate various steps and procedures. The screen captures are used as examples only and may differ somewhat from what you actually see on your monitor.

Feedback

Despite careful review, this manual may contain errors. Should further information be necessary or particular problems arise which are not covered sufficiently in this document, please contact us at support@avicenna.ai.

Conventions

Caution messages indicate procedures which, if not observed, could result in possible problems with the device. Such problems include device malfunctions, device failure, damage to device or damage to property. Do not proceed beyond a Caution message until the indicated conditions are fully understood and met.

Warning messages indicates procedures or practices which, if not observed, could result in potential harm to the patient or user (or environment). Do not proceed beyond a WARNING message until all of the indicated conditions are fully understood and met

Notes are used to indicate information which may be helpful or of special interest to the reader.

Tips messages are used to give very useful information.

INTENDED USE AND INDICATIONS FOR USE

CINA is a radiological computer aided triage and notification software indicated for use in the analysis of (1) non-enhanced head CT images and (2) CT angiographies of the head.

The device is intended to assist hospital networks and trained radiologists in workflow triage by flagging and communicating suspected positive findings of (1) head CT images for Intracranial Hemorrhage (ICH) and (2) CT angiographies of the head for large vessel occlusion (LVO).

CINA uses an artificial intelligence algorithm to analyze images and highlight cases with detected (1) ICH or (2) LVO on a standalone Web application in parallel to the ongoing standard of care image interpretation. The user is presented with notifications for cases with suspected ICH or LVO findings.

Notifications include compressed preview images that are meant for informational purposes only, and are not intended for diagnostic use beyond notification. The device does not alter the original medical image, and it is not intended to be used as a diagnostic device.

The results of CINA are intended to be used in conjunction with other patient information and based on professional judgment to assist with triage/prioritization of medical images. Notified clinicians are ultimately responsible for reviewing full images per the standard of care.

GENERAL CAUTION AND SAFETY MESSAGES

- **Potential Adverse Effects of Device on Health**

There are no known direct safety or health risks caused by or related to use of the CINA device. The device has no direct contact with the patient. Indirect risks are that the device may fail to flag and communicate suspected positive findings (false negative) of non-enhanced head CT images for Intracranial Hemorrhage (ICH) or CT angiographies of the head for large vessel occlusion (LVO); or may flag and communicate some negative cases (false positive). Proper use of the information generated by the CINA device is explained in this manual. The CINA output is intended to be used in conjunction with other patient information and based on professional judgment to assist with triage/prioritization of medical images.

- **Contraindications**

There are no contraindications for this device.

- **Limitations**

CINA may fail to flag and communicate suspected positive findings of non-enhanced head CT images for Intracranial Hemorrhage (ICH) in the situations below:

- not acute ICH,
- small hemorrhage volume (< 3mL),
- post-contrast series,
- inadequate field of view,
- notable image noise,
- motion artifacts,
- severe metal artifacts,

CINA may fail to flag and communicate suspected positive findings of CT angiographies of the head for large vessel occlusion (LVO) in the situations below:

- occlusion located outside the MCA M1, proximal MCA M2 or distal ICA,
- small MCA occlusions (clot length <1.5 mm), particularly in presence of important collaterals,

- series displaying no visible contrast due to bad bolus timing during the series acquisition process,
- series containing improperly ordered slices (e.g. as a result of manual correction by an Imaging technician),
- inadequate field of view,
- motions artifacts,
- severe metal artifacts,

Warnings

Notifications include compressed preview images that are meant for informational purposes only, and are neither intended for primary image interpretation nor diagnostic use beyond notification.

Cautions

Before use, please make sure that you have thoroughly read and fully understood all the caution and safety considerations outlined in this section.

To prevent incorrect use, the operator must know and apply the contents of the User Guide. Make sure that the correct version of the user guide is constantly at hand. Ensure periodically reviewing the procedures as well as the safety precautions.

The device is not intended to be used as a diagnostic device. The use of CINA can by no means replace a diagnosis by a licensed and competent physician nor constitute medical advice or diagnosis which can only be obtained from a physician. The physician bears the sole responsibility for the diagnosis.

The results of CINA are intended to be used in conjunction with other patient information and based on professional judgment to assist with triage/prioritization of medical images. Notified clinicians are ultimately responsible for reviewing full images per the standard of care.

This medical software in no way replaces the competence and judgement of a qualified medical practitioner. It should only be used by qualified and trained personnel who are fully aware of the software potential and limitations.

Avicenna.AI does not guarantee the quality, the accuracy or the legality of images acquired with CT scanners based on which the software provides triage and notification. The user must, therefore, use caution when using the software.

CINA is compatible with the DICOM 3.0 standard, a format that allows the interchange of medical images. DICOM is a standard format for encoding and transmitting medical images. CINA is

interoperable with CT scanners or PACS systems that meet this standard. The performance characteristics of CINA software have been assessed using the four main medical imaging equipment manufacturers (Canon Medical Systems Corporation, GE Healthcare, Philips Healthcare, Siemens Healthineers).

Users must make sure that image series are complete and organized into properly ordered slices. For example, users should make sure the number of images in each series matches what is expected.

It is the user's responsibility to ensure that the input image datasets are complete and that no image or information is missing as results may not be reliable.

The modality operator is responsible for the input data's quality and the correctness of the patient information. Suboptimal data may induce suboptimal results.

CINA performs a quality check of the input data to make sure that each slice of a same DICOM series is consistent with the other ones (e.g. same series instance UID, modality, orientation, pixel spacing, slice thickness, number of rows and columns). Inconsistent DICOM series are rejected.

Effective use of CINA device requires adherence to CT imaging protocol requirements and the imaging manufacturer's instructions regarding maintenance and calibration of the CT scanner.

Although CINA software is subjected to very thorough and intensive testing by Avicenna.AI, it is nevertheless possible unforeseen errors may arise during use of this software. Users should at all times be aware and warned of such a possibility. Should the user notice any dysfunctions or faulty behavior of the software liable to put the patient at risk, we strongly recommend that the user contacts Avicenna.AI without delay to the following email address: support@avicenna.ai

This product should only be used with compatible medical image communications devices (3rd-party Platforms) responsible for transferring suitable series to CINA device, storing, converting formats, notifying of suspected findings and display medical device data such as radiological data.

IMAGE ACQUISITION PROTOCOL

Acquisition protocol requirements for an optimal use

Intracranial Hemorrhage (ICH) image processing application

The ICH image processing application is intended to be used on DICOM data that complies with the following acquisition protocol:

- Non-enhanced (non-contrast) head CT images:
  - DICOM CT Image Storage or Enhanced CT Image Storage SOP Class UID[1]
  - DICOM Implicit VR Endian or Explicit VR Little Endian Transfer Syntax UID[1]
- Scans performed on adults ≥ 18 years of age[2],
- Matrix size ≥512 x 512 (rectangular matrix accepted)[1],
- Axial acquisition only[1],
- Slice thickness ≤ 5 mm[1],
- Radiation dose parameters: 100 kVp to 160 kVp[1], recommended: 120 To 140 kVp[2], 150 to 400 mAs,
- Reconstruction diameter above 170 mm[2],
- Soft tissue reconstruction kernel.

Large Vessel Occlusion (LVO) image processing application

The LVO image processing application is intended to be used on DICOM data that complies with the following acquisition protocol:

- CT angiography of the head:
  - DICOM CT Image Storage or Enhanced CT Image Storage SOP Class UID[1]
  - DICOM Implicit VR Endian or Explicit VR Little Endian Transfer Syntax UID[1]
- Scans performed on adults ≥ 18 years of age[2],
- Matrix size ≥512 x 512 (rectangular matrix accepted)[1],
- Axial acquisition only[1],
- Head First-Supine (HFS) or Feet First-Supine (FFS) patient position[1]
- Slice thickness ≤ 1.25 mm[1],
- Radiation dose parameters: 80 kVp to 140 kVp[1], recommended: 100 to 120 kVp[2], 100 to 400 mAs,
- Reconstruction diameter above 170 mm[2],
- Arterial phase timing of contrast bolus as confirmed by mini test bolus or automatic bolus tracking software,

- Arterial (or other sharp) reconstruction kernel.

[1] Mandatory protocol items
[2] Recommended protocol items

CINA performs data quality checks on DICOM data. For both the ICH and LVO image processing applications, if the DICOM data does not comply with the *mandatory* protocol requirements ([1]) the image processing application will not be executed, and no result will be issued from the non-compliant data. If the DICOM data does not comply with the *recommended* protocol ([2]), the image processing application will be executed but the user will be notified in the generated results.

INTEGRATION OF CINA WITHIN 3RD PARTY PLATFORM

CINA image processing applications are intended to be integrated, deployed and used with compatible medical image communications devices (3rd-party Platforms). CINA receives CT scans identified by the 3rd-party Platforms, processes them using algorithmic methods involving execution of multiple computational steps to identify suspected presence of ICH or LVO and generates results files to be transferred by the 3rd-party Platforms for output to a PACS system or workstation for worklist prioritization.

It is the responsibility of the medical image communications device's manufacturer to integrate CINA image processing applications, package the system and verify that they are compatible with the Platform and able to work together as assembled in order to ensure the safe and proper use of the system.

Two image processing applications are available: Intracranial Hemorrhage (ICH) and Large Vessel Occlusion (LVO). Depending on your configuration, one of the two applications or both may be available.

Resource requirements

The CINA image processing applications have been designed to be used with the following minimal system configuration:

- CPU: 8 threads at 3.0+ GHz (supporting SSE4.2 and AVX2 instructions)
- Memory: 16 GB

Input data format

The CINA image processing applications take DICOM series provided by the 3rd party Platform in which they are integrated.

In general terms, the platform is responsible for dispatching the relevant series to the CINA image processing applications. But depending on the application integration within the 3rd party Platform, applications can be featured with the MasterMind component making them possible to receive one to several DICOM series (e.g. series belonging to a same DICOM study) and select the most appropriate one to be used by the applications. Avicenna.AI collaborate in either way with the Platform's manufacturer to ensure that the Platform is able to efficiently fetch and dispatch patient data to CINA image processing applications.

CINA image processing application execution

CINA image processing applications are instantiated by the Platform. They do not require any kind of user interaction.

Depending on their integration within the 3rd party Platform, execution status or textual logs may be provided to the user.

CINA image processing applications generate outputs and notifications which are made accessible to the user through the Platform.

CINA image processing application outputs

- **Notifications for cases with suspected ICH or LVO findings**

CINA image processing applications provide a case-level notification in case of suspected positive findings. This notification can be used by the 3rd party Platform to flag series in the Platform's Worklist *(Figure 1)* to assist trained radiologists in workflow triage by flagging and communicating suspected positive findings of Intracranial Hemorrhage (ICH) and large vessel occlusion (LVO).

Figure 1: Illustrative example of a 3rd party Platform's Worklist with flagged series for cases with suspected ICH or LVO findings and Image processing application execution status

CINA image processing applications also provide a textual description of the findings that can be used by the 3rd party Platform.

■ Intracranial Hemorrhage (ICH) application generated results

The ICH image processing application analyzes non-enhanced head CT images, flags and communicates suspected positive findings of Intracranial Hemorrhage (ICH).

The ICH image processing application is dependent on series provided as input data. In general terms, the platform is responsible for providing only suitable series to the application. But depending on the application integration within the 3rd party Platform, the application can be featured with the MasterMind component making it possible to receive one to several DICOM series (e.g. series belonging to a same DICOM study) and select the most appropriate one to be used. This image series identification stands on DICOM tags but also on a smart categorization algorithm. In case of application inexecution on expected series

or application execution on irrelevant series, please refer to the Platform's manufacturer user guide and support.

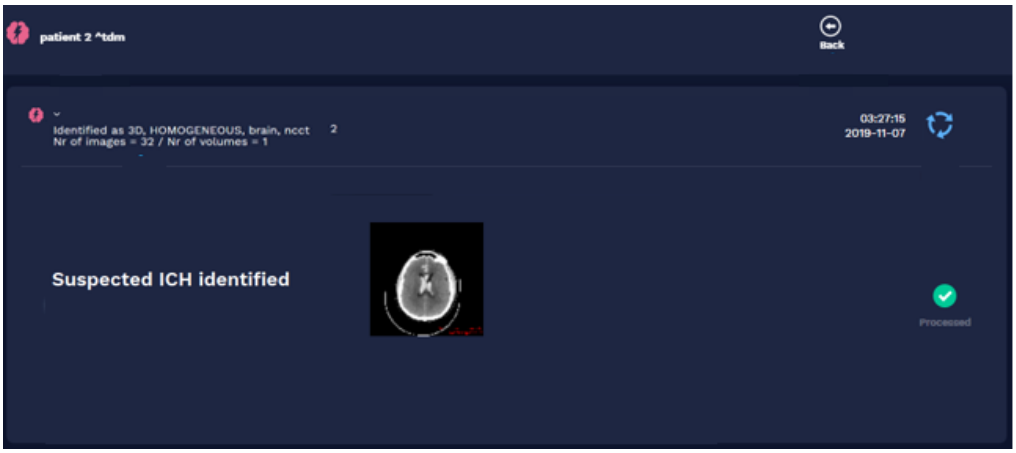
In case of positive findings of ICH, the image processing application provides the user with a preview image of the series in which suspected positive findings of Intracranial Hemorrhage have been detected.

A preview image is provided into different formats:

- PNG
- DICOM Secondary Capture
- DICOM GSPS

It is intended to be used by the 3rd party Platform so that the user has the possibility to verify the series sent to the image processing application.

In the illustrative example below *(Figures 2a and 2b),* a Platform user interface displays a preview image of the series where the suspected Intracranial Hemorrhage has been found.



Figures 2a and 2b: Illustrative examples of a 3rd party Platform user interface displaying results provided by the ICH image processing application

Warning: Notifications may include a compressed preview image that is meant for informational purposes only, does not contain any marking of the finding, and is neither intended for primary image interpretation nor diagnostic use beyond notification.

- **Large Vessel Occlusion (LVO) application generated results**

The LVO image processing application analyzes CT angiographies of the head (CTA) images, flags and communicates suspected positive findings of Large Vessel Occlusion (LVO).

The LVO image processing application is dependent on series provided as input data. In general terms, the platform is responsible for providing only suitable series to the application. But depending on the application integration within the 3rd party Platform, the application can be featured with the MasterMind component making it possible to receive one to several DICOM series (e.g. series belonging to a same DICOM study) and select the most appropriate one to be used. This image series identification stands on DICOM tags but also on a smart categorization algorithm. In case of application inexecution on expected series or application execution on irrelevant series, please refer to the Platform's manufacturer user guide and support..

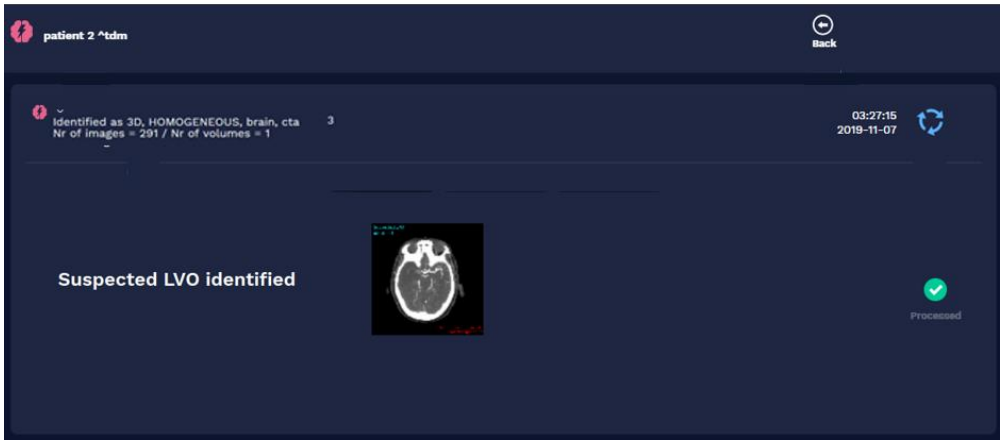
In case of positive findings of LVO, the image processing application provides the user with a preview image (axial MIP reconstruction) of the series in which positive findings of Large Vessel Occlusion have been detected.

A preview images is provided into different formats:

- PNG
- DICOM Secondary Capture
- DICOM GSPS

It is intended to be used by the 3rd party Platform so that the user has the possibility to verify the series sent to the image processing application.

In the illustrative example below *(Figure 3a and 3b)*, a Platform user interface displays a preview image (axial MIP reconstruction) of the series where the suspected large vessel occlusion has been found.



Figures 3a and 3b: Illustrative examples of a 3rd party Platform user interface displaying results provided by the LVO image processing application

Warning: Notifications may include a compressed preview image that is meant for informational purposes only, does not contain any marking of the finding, and is neither intended for primary image interpretation nor diagnostic use beyond notification

DATA PROTECTION AND DATA SECURITY

CINA device is designed to manage and analyze data that contains sensitive patient information. Oblige to all HIPAA (Health Insurance Portability and Accountability Act) standards and GDPR (Regulation (EU) 2016/679) requirements in safeguarding all patient information and allow access to authorized users only.

Please refer to the Platform's manufacturer user guide for recommendations about data protection and data security.

LEGAL INFORMATION

Copyright

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Integrated 3rd-Party Software

All integrated 3rd-party Software are provided under Free and Open-Source Software (FOSS) licenses. For a detailed list please refer to the Platform's manufacturer.

CE Label

CE	• The CE label indicates that the CINA software complies with the essential requirements of European Council Directive 93/42/EEC, the Medical Device Directive ("MDD"). • According to the rules established by the MDD, CINA software is a Class I device. • Avicenna.AI is ISO 13485:2016 certified. *NOTE: The validity of the CE label can only be confirmed for products manufactured by Avicenna.AI.*

CONTACT

You can obtain a printed version of this user guide by contacting Avicenna.AI at this address: contact@avicenna.ai

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Support and safety contact	support@avicenna.ai
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APPENDIX - SUMMARY OF THE PERFORMANCE TESTING

A retrospective, multileader, blinded, multicenter, multinational study with the CINA software was conducted with the primary endpoint to evaluate the software's standalone performance in 1/ non-enhanced head CT images (NCCT) head images pertaining to patients with suspected intracranial hemorrhage (ICH) findings and 2/ CT angiographies of the head (CTA) pertaining to patients with suspected large vessel occlusion (LVO) findings, in 814 and 476 clinical anonymized cases, respectively. A secondary endpoint aimed to evaluate the time-to-notification (per-case processing time) effectiveness, for both applications. The data was provided from 3 clinical sources (2 US and 1 OUS). There were 255 (31.3%) positive ICH (images with ICH) and 188 (39.5%) positive LVO (images with LVO) cases included in the analysis.

EVALUATED DATA

Both tested datasets (for ICH and LVO) contained a sufficient numbers of cases from important cohorts in terms of imaging acquisitions (e.g. scanner makes, number of detector rows, slices thickness), patient groups (e.g., age, sex and US regions) and ICH characteristics (e.g., ICH subtypes and ICH volumes). Statistical distribution of cases among the categories was deemed to be suitable for the representativeness of the data used in the performance testing study. Moreover, the distribution of positive and negatives ICH and LVO cases among all presented above categories was judged satisfactory.

Five types of ICH were included:

- IPH – INTRAPARENCHYMAL
- IVH – INTRAVENTRICULAR
- SAH – SUBARACHNOID
- SDH – SUBDURAL
- EDH – EPIDURAL

The validation datasets were separate from the ones used for the image processing application training.

ANALYSIS

Two US board-certified expert neuroradiologists proceeded to the visual assessment of all datasets to determine whether there is (or not): 1) a suspected hemorrhage on NCCT data; 2) a suspected Middle Cerebral Artery (MCA) and/or Internal Carotid Artery (ICA) occlusion on the CTA ones. In case of discrepancy between the two US board-certified radiologists, a third US board-certified radiologist reviewed the cases and the final ground truth was established by majority consensus.

All readers were blinded to each other. Visual assessments were performed separately: either NCCT or CTA data were randomly presented to each observer in two separate reading sessions. Neither of the radiologists had access to CINA device results.

Separately, the same NCCT and CTA databases were processed with CINA device. The results were automatically computed and collected for further analysis. For each tested case, the time-to-notification (time between receiving each DICOM case into the Platform and the positive/negative notification) was also recorded.

The comparison between the results provided by the US board-certified neuroradiologists (ground truth) and the ones automatically computed by the CINA device, was performed according to a Confusion Matrix which provided the number of true positive, true negative, false positive and false negative values. Sensitivity, Specificity, ROC curves (AUC), Accuracy, Positive Predictive and Negative Predictive values - computed with varying prevalence values from 10% to 50% (range of 5%), were computed for the both (ICH and LVO) overall cohorts. Additionally, stratified statistical analyses on imaging acquisitions parameters (scanner makes, number of detector rows, slices thickness), patient group (age, sex and US regions) and ICH characteristics (ICH subtypes and ICH volumes) were also calculated.

RESULTS

For both applications, Sensitivity and Specificity exceeded 90% performance.

Sensitivity and Specificity for the “ICH” prioritization and triage application were observed to be 91.4% (95% CI: 87.2% – 94.5%) and 97.5% (95% CI: 95.8% – 98.6%), respectively. The ROC curve for ICH detection showed an AUC of 0.94.

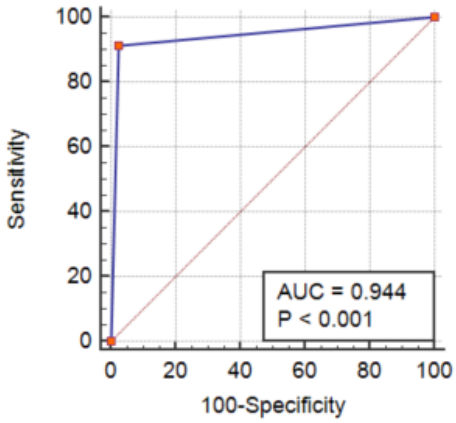

Figure 4: The ROC curve for the ICH detection shows an AUC of 0.94

Regarding the stratified statistical analysis for the ICH types, the True Positive Rates (TPR) were about 90% and more, for all ICH types. For the ICH volumes' sizes, the TPR was lower (71.8%) for "Small" volumes (<5 mL), in comparison to the "Medium" and "Large" ones (100% for both).

For the "LVO" prioritization and triage application, Sensitivity and Specificity were 97.9% (95% CI: 94.6% – 99.4%) and 97.6% (95% CI: 95.1% – 99%), respectively. The ROC curve for LVO detection showed an AUC of 0.98.

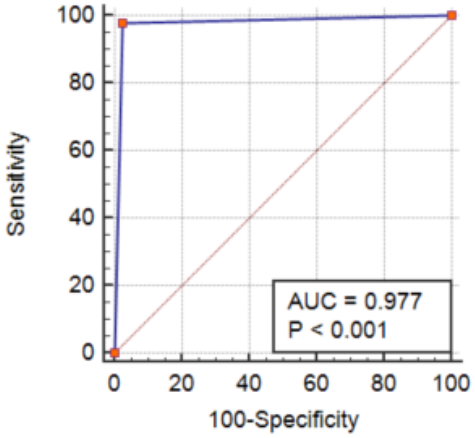

Figure 5: The ROC curve for the LVO detection shows an AUC of 0.98

The results of the current performance testing study demonstrated an overall agreement (Accuracy) of 95.6% and 97.7% for the "ICH" and "LVO" tested cases, respectively, when compared to the ground truth (operators' visual assessments).

Positive predictive value (PPV) and negative predictive value (NPV) with varying prevalence, for both applications, are presented in the table below:

Prevalence	"ICH" image processing application		"LVO" image processing application	
	PPV (%)	**NPV (%)**	**PPV (%)**	**NPV (%)**
10%	80.2	99.0	81.7	99.8
15%	86.6	98.5	87.7	99.6
20%	90.1	97.8	91.0	99.5
25%	92.4	97.1	93.1	99.3
30%	94.0	96.3	94.5	99.1
35%	95.2	95.5	95.6	98.8
40%	96.1	94.4	96.4	98.6
45%	96.8	93.2	97.1	98.2
50%	97.3	91.9	97.6	97.9

Per-case processing time (time-to-notification) of "ICH" and "LVO" image processing applications are presented in the table below:

Time-to-Notification	MEAN ± SD (seconds)	MEDIAN (seconds)	MIN (seconds)	MAX (seconds)
"ICH" image processing application	21.6 ± 4.4	20.4	14.4	53.3
"LVO" image processing application	34.7 ± 10.7	33.4	14.3	63.3