AIRAscore 3.0.1

Instructions for Use

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Dear customers,

The software AIRAscore is a certified medical device with CE mark according to the Regulation (EU) 2017/745. AIRAmed has a certified quality management system according to ISO 13485.

This customer information applies as instructions for use, describes the basic features of our evaluation reports and provides information on the correct use of AIRAscore. It describes the correct indication, characterizes the patients, and provides basic warnings that must be followed. The customer information is intended for all physicians with knowledge of MR anatomy of the brain who use the AIRAscore reports to check segmentations and place the output measurements in the clinical context (primary users).

All users and administrators of the software who use the software or install and maintain it must have access to these instructions for use and be familiar with their contents.

If you have any questions beyond this customer information, please do not hesitate to contact us:

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1 General Specifications

It is your responsibility as the user to inform the patient of the service and the associated transfer of image data to AIRAmed, and to take appropriate local protective measures to prevent unauthorized third parties from accessing AIRAmed's service and patient data.

1.1 Intended Purpose

AIRAscore is intended for automatic labeling, visualization and volumetric quantification of segmentable brain structures from a set of MR images. This software is intended to automate the current manual process of identifying, labeling and quantifying the volume of segmentable brain structures identified on MR images.

1.2 Indication

The software AIRAscore is intended to be used for MR image data of patients for which a physician requires a volume quantification of brain structures.

1.3 Contraindications

The device is not intended to be used for segmentation of brains with structural abnormalities (e.g., tumor, arachnoid cyst, postoperative-, posttraumatic-, postischemic-, or posthemorrhagic defects, brain development disorders and neuronal migration disorders) or on patients with an age younger than 18 years.

1.4 Availability

AIRAscore is intended to be available 24 hours a day and operates fully automated.

Scheduled maintenance is usually performed Monday through Friday from 0:00 to 4:00 (CET) or all day on weekends. Scheduled maintenance is announced at least 24 hours in advance. Unscheduled maintenance can be performed at any time without notice, for example, if the security of the system is affected. Downtime is kept as low as possible.

If you have any questions, our support is available Monday through Friday from 9:00am to 4:00pm (CET) by phone or email.

1.5 Avoidable Misuse and Abnormal Use

⚠
- AIRAscore is not suitable for evaluating image data that is not based on a T1 data set.
- Image datasets after administration of contrast agents are not suitable for evaluation and may lead to erroneous findings.
- Any mass lesion (e.g., tumor, hemorrhage, arachnoid cyst) or any lesion that is characterized by a defect of the brain tissue (e.g., defects after trauma, ischemia) may lead to severe missegmentation and also cannot be evaluated against the reference set.

Corresponding patient image data must NOT be evaluated with AIRAscore!

⚠ Age and natural sex of the patients are essential for a correct classification of the volumes. Changes to the DICOM metadata should therefore be avoided, since AIRAmed has no possibility to check the correctness of the DICOM data. In the case of anonymized data or research data, it is therefore essential to ensure that age, sex and the interval between examination date and date of birth are correctly preserved in the DICOM data.

⚠ Reports of the same patient are only comparable with regards to the progression if they were acquired with the same scanner and the same sequence. Even minor changes in scan parameters can lead to strong contrast changes and discrete shifts in the gray-white boundary, which make segmentation comparability impossible.

⚠ The automated quantitative evaluation of brain structures can only support the assessment by a qualified physician (specialist), and by no means replaces it.

1.6 Clinical Benefit

The automated labeling, visualization and quantification of segmentable brain structures replaces time-consuming manual segmentation by the attending physicians.

2 AIRAscore Report Types

AIRAscore provides the following types of reports.

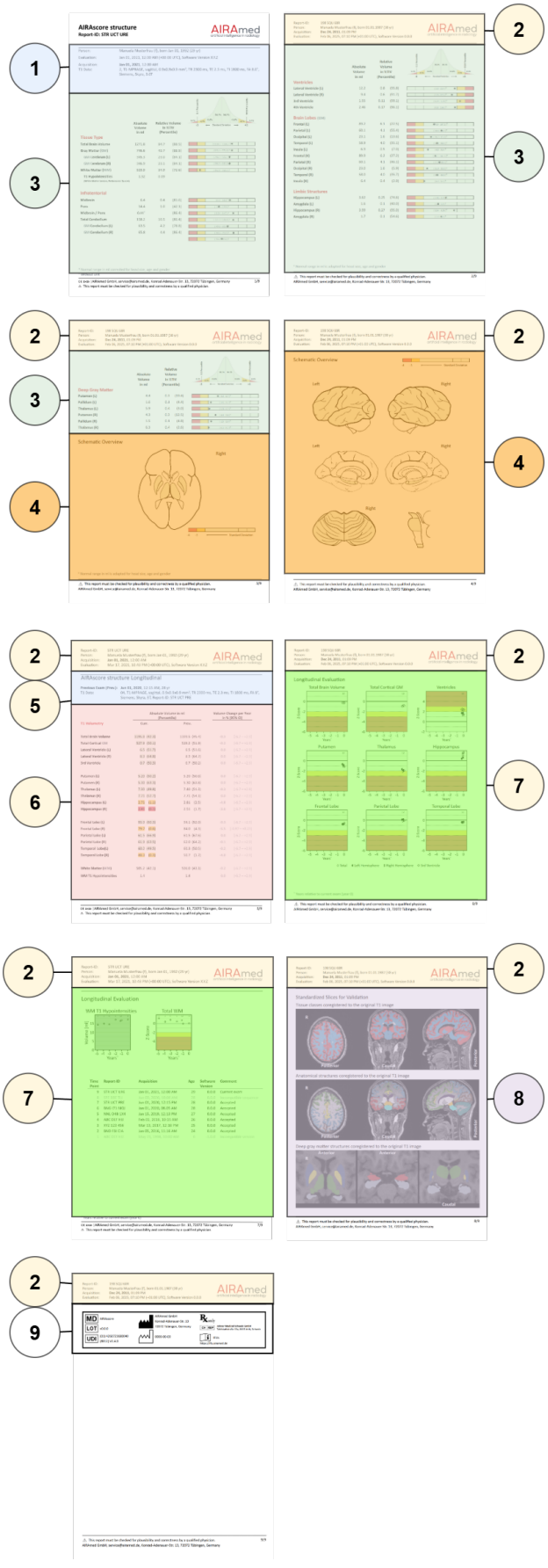
2.1 AIRAscore structure Report

The AIRAscore structure report contains volumetric evaluations of anatomical brain structures based on T1 images. Volumes are compared to an age- and sex-matched reference collective.

If previous data of the same patient is available the report also includes longitudinal information. Page 5, 6 and 7 of the report are only included if longitudinal information is available.

The longitudinal part of the report contains longitudinal comparison of volumes to previous AIRAscore evaluations of the same patient. Displayed are volumetric evaluations of anatomical brain structures based on T1 images that are also displayed in the AIRAscore structure report.

2.1.1 Structure of the Report



The AIRAscore structure report has 9 pages. The respective page number is listed on the bottom right.

The individual sections of the report are described below:

① Examination Summary:
Contains the unique order ID*, personal data of the patient and the sequence on which the report is based.

② Header:
The headers also list the most important identification parameters and relevant data again.

③ Volume Report:
Contains the volumetric evaluation for each segmented anatomical structure - the absolute volume in ml, the relative volume (absolute volume normalized by the total intracranial volume), and the percentile for the patient compared to the reference set**.

④ Schematic Overview of Reference Comparison:
Quick overview of z-scores for brain areas. For values smaller than two or three standard deviations compared to the reference set, areas are shown in yellow or red, respectively**.

⑤ Summary of previous order:
Contains previous sequences on which the report is based.

⑥ Longitudinal Volume Report:
Contains the longitudinal volumetric comparison of anatomical structures - the absolute volume in ml and the percentile of reference comparison** for the current and previous evaluation, as well as the difference.

⑦ Longitudinal Evaluation:
Overview of z-scores** and T1 hypointensity volumes for the current evaluation and all previous AIRAscore evaluations.

⑧ Quality Control Images:
Excerpt from the overlay sets provided as separate DICOM series for validation of the segmentation results (for more information see section *Color Overlays*). The overlays must always be checked for plausibility.

⑨ Label:
The label contains information to identify the device and its manufacturer and other information relevant to the device.

For a detailed description of the elements in the report, refer to section *AIRAscore Components*.

* The individual order ID allows us to make a reliable assignment if required.
** If the patient age is not between 18 and 100, no comparison to the reference set will be performed and the percentile and z-score will not be shown in the report. Furthermore, a watermark “Not approved for clinical use in your country“ will be shown in the report, if the patient is younger than 18 years.

2.1.2 Reported Elements

The AIRAscore structure report provides evaluations for the following elements. The referenced Anatomy, Tissue and DGM maps are color overlay sets described in detail in section *Color Overlays.*

Reported Element		Definition
Tissue Type		
Total brain volume		Summed volume of white matter, gray matter and T1 hypointensities based on the Tissue map
Gray matter (GM)		Volume of gray matter based on the Tissue map
	GM cerebrum (L)/(R)	Summed GM volume of left or right hemisphere of temporal, frontal, occipital, parietal, and insula lobes, cingulate gyrus, and hippocampus based on the Anatomy map
White matter (WM)		Volume of white matter based on the Tissue map
	T1 Hypointensities	Volume of T1 hypointensities based on the Tissue map
Infratentorial		
Midbrain		WM volume of midbrain based on the Anatomy map
Pons		WM volume of pons based on the Anatomy map
Midbrain / Pons		Ratio of midbrain to pons
Total cerebellum		Summed GM and WM volumes of left and right hemisphere cerebellum based on the Anatomy map
	GM cerebellum (L)/(R)	GM volume of left or right hemisphere cerebellum based on the Anatomy map
Ventricles		
Lateral ventricle (L)/(R)		Cerebrospinal fluid (CSF) volume of left or right hemisphere lateral ventricle based on the Anatomy map
Third ventricle		CSF volume of third ventricle based on the Anatomy map
Fourth ventricle		CSF volume of fourth ventricle based on the Anatomy map
Brain Lobes (Gray Matter)		
Frontal (L)/(R) *		GM volume of left or right hemisphere frontal lobe based on the Anatomy map
Parietal (L)/(R) *		GM volume of left or right hemisphere parietal lobe based on the Anatomy map
Occipital (L)/(R)		GM volume of left or right hemisphere occipital lobe based on the Anatomy map

Reported Element	Definition
Temporal (L)/(R)	GM volume of left or right hemisphere temporal lobe based on the Anatomy map
Insula (L)/(R)	GM volume of left or right hemisphere insula lobe based on the Anatomy map
Limbic Structures	
Hippocampus (L)/(R) *	GM volume of left or right hemisphere hippocampus based on the DGM map
Amygdala (L)/(R)	GM volume of left or right hemisphere amygdala based on the DGM map
Deep Gray Matter	
Putamen (L)/(R)	GM volume of left or right hemisphere putamen based on the DGM map
Pallidum (L)/(R)	GM volume of left or right hemisphere pallidum based on the DGM map
Thalamus (L)/(R)	GM volume of left or right hemisphere thalamus based on the DGM map

* The hippocampus is not included in the volume of the temporal lobe. The cingulate gyrus is not included in the volume of the frontal lobe or parietal lobe.

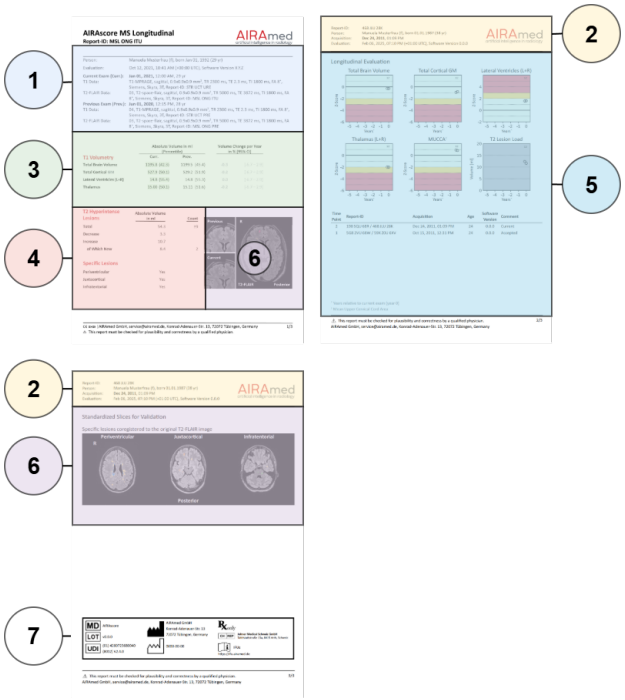
2.2 AIRAscore MS longitudinal Report

The AIRAscore MS longitudinal report contains volumetric evaluations of T2 lesions based on T2-FLAIR images and volumetric evaluation of anatomical brain structures based on T1 images. Lesions are categorized based on their location. The longitudinal T2 lesion comparison provides information about the presence of new lesions and the volume changes of preexisting lesions. T1-based volumes are compared to an age- and sex- matched reference collective.

If no previous AIRAscore evaluations of the same patient are available, no longitudinal comparison information is displayed.

> AIRAscore MS longitudinal is not intended for diagnosis of multiple sclerosis, but rather is a tool for quantitative analysis of MR images in patients with existing diagnosis of MS.

2.2.1 Structure of the Report



The AIRAscore MS longitudinal report has 3 pages. The respective page number is listed on the bottom right.

The individual sections of the report are described below:

① Examination Summary:
Contains the unique order ID*, personal data of the patient and the current and previous sequences on which the report is based.

② Header:
The headers also list the most important identification parameters and relevant data again.

③ Longitudinal Volume Report:
Contains the longitudinal volumetric comparison of anatomical structures - the absolute volume in ml and the percentile of reference comparison** for the current and previous evaluations, as well as the difference.

④ T2 Hyperintense Lesion Report
This page shows the number and volume of lesions and their categorization for the current evaluation. If a previous AIRAscore MS longitudinal evaluation exists, the volumes of new, decreased and increased T2 lesions are displayed.

⑤ Longitudinal Evaluation:
Overview of z-scores** and lesion volumes for the current order and all previous AIRAscore evaluations.

⑥ Quality Control Images:
Excerpt from the overlay sets provided as separate DICOM series for validation of the segmentation results (for more information see section *Color Overlays*). The overlays must always be checked for plausibility.

⑦ Label:
The label contains information to identify the device and its manufacturer and other information relevant to the device.

For a detailed description of the elements in the report, refer to section *AIRAscore Components*.

2.2.2 Reported Elements

The AIRAscore MS longitudinal report provides evaluations for the following elements. The referenced Tissue map is a color overlay set described in detail in section *Color Overlays.*

Reported Element	Definition
T1 Volumetry	
Total brain volume	Summed volume of white matter, gray matter and hypointensities based on the Tissue map
Total cortical GM	Summed volume of GM cerebrum (L) and GM cerebrum (R)
Lateral ventricles (L+R)	Summed volume of lateral ventricle (L) and lateral ventricle (R)
Thalamus	Summed volume of thalamus (L) and thalamus (R)
T2 Hyperintense Lesions	
Total absolute volume and count	Summed volume of voxels segmented as lesions independent of their location in the brain. Only lesions ≥5 µl are taken into account in the total absolute volume and count. A minimum distance of 1 mm applies to all individual lesions. The total lesion count is set to “>=9” if the lesion count is 9 or higher (according to one of the Barkhof MRI criterias)
Periventricular lesion	Is there a lesion that borders the ventricles?
Juxtacortical lesion	Is there a lesion that borders the cerebral cortex?
Infratentorial lesion	Is there a lesion with an infratentorial position?
T2 Lesions Longitudinal Comparison	
New or increased lesion	Voxels belonging to a new lesion or voxels showing where a lesion has increased in volume
Decreased or vanished lesion	Voxels showing where a lesion has decreased in volume or a vanished lesion

3 Ordering AIRAscore Reports

After installation of the AIRAscore client (see *AIRAscore Client Installation Instructions*), different PACS nodes are available, depending on whether a single or a multi node configuration has been selected. The names of the nodes can be defined during the installation. If not changed, the default Application Entity Titles (AETs) of the multi node configuration are `AIRASCORE_STRUCT` and `AIRASCORE_MS`, and `AIRASCORE` of the single node configuration. The nodes accept the following datasets:

- The `AIRASCORE_STRUCT` node accepts only T1 datasets. The returned report is an AIRAscore structure report.
- The `AIRASCORE_MS` node accepts a set of a T1 and a T2-FLAIR dataset. The returned report is an AIRAscore MS report.
- The `AIRASCORE` node accepts T1 and T2-FLAIR datasets. The returned report is AIRAscore MS if matching T1 and T2-FLAIR datasets are found. The AIRAscore structure report is returned, if only a T1 dataset is found.

For a detailed description of the dataset requirements, refer to section *Technical Requirements for the Dataset*.

3.1 Ordering AIRAscore structure Report

To receive an AIRAscore structure report, choose one of the following options based on your node configuration:

- Multi node: Send a valid T1 dataset to PACS node `AIRASCORE_STRUCT`.
- Single node: Send a valid T1 dataset without an accompanying T2-FLAIR to `AIRASCORE`.

3.2 Ordering AIRAscore structure Report with Longitudinal Data

To receive longitudinal data in an AIRAscore structure report, two or more T1 datasets from different time points of the same patient are required.

- Send in the older T1 datasets to PACS node `AIRASCORE` (single node) or `AIRASCORE_STRUCT` (multi node).
- After the older orders are accepted send in the newest T1 dataset for the patient.
- If all datasets for a longitudinal comparison are send in the same association, AIRAscore identifies the newest dataset automatically.

The report for the latest dataset includes longitudinal data from all datasets associated with this patient. Datasets already processed with an AIRAscore of version 3.0.0 or higher do not need to be resent.

3.3 Ordering AIRAscore MS Report

To receive an AIRAscore MS report, choose one of the following options based on your node configuration:

- Multi node: Send a valid T1 dataset with a corresponding T2-FLAIR dataset for the same patient and studyID to PACS node `AIRASCORE_MS`.
- Single node: Send a valid T1 dataset with an accompanying T2-FLAIR dataset for the same patient and studyID to PACS node `AIRASCORE`.

The report design mirrors an AIRAscore MS longitudinal report but omits the longitudinal comparison parameters.

3.4 Ordering AIRAscore MS longitudinal Report

To obtain an AIRAscore MS longitudinal report, at least two T1 datasets paired with accompanying T2-FLAIR datasets from different time points of the same patient are required.

- Send the older T1 datasets of a patient with their accompanying T2-FLAIR datasets with the same studyID to the PACS node `AIRASCORE_MS` (multi node) or `AIRASCORE` (single node).
- After the older orders are accepted send the newest T1 dataset with its accompanying T2-FLAIR dataset.
- If all datasets for a longitudinal lesion comparison are send in the same association, AIRAscore identifies the newest dataset automatically.

The report for the latest dataset includes longitudinal data from all datasets associated with this patient. Datasets processed with AIRAscore version 3.0.0 or higher do not need to be resent. The AIRAmed Database automatically identifies these datasets for longitudinal comparison.

For more information regarding the technical requirements for the longitudinal comparison datasets, please refer to the section *Longitudinal Comparison Requirements*.

You will additionally receive an AIRAscore structure report for every processed T1 dataset.

> Every placed order will be billed separately.

4 AIRAscore Components

This section describes all elements provided by AIRAscore.

4.1 Metrics

4.1.1 General Metrics

AIRAscore provides the following metrics:

Metric	Definition
Absolute volume	Volume in ml.
Relative volume	Absolute volume normalized to the total intracranial volume (TIV). Values range from 0 to 100 %TIV.
Delta	The difference between two measured values.
Volume Change per Year	The percental absolute volume change between a previous and current evaluation scaled to one year.
Total absolute T2 lesion volume	The sum of all T2 lesions in milliliter. Only lesions ≥5 µl are taken into account.
Total T2 lesion count	The number all of T2 lesions. Only lesions with a minimum distance of 1 mm to other lesions and a volume of ≥5µl are counted. The total lesion count is set to “>=9” if the lesion count is 9 or higher (according to one of the Barkhof MRI criterias)
T2 lesion decrease	Brain volume that was categorized as T2 lesion in the previous evaluation, but not in the current evaluation. Lesion volume changes are reported only for lesions larger than 40µl that have an increase or decrease of at least 25% and that are at least 5 mm large in each direction.
T2 lesion increase	Brain volume that was categorized as T2 lesion in the current evaluation, but not in the previous evaluation. Lesion volume changes are reported only for lesions larger than 40µl that have an increase or decrease of at least 25% and that are at least 5 mm large in each direction.
Absolute volume of new T2 lesions	The sum of new T2 lesions in milliliter. Subcategory of *T2 lesion increase*.
Count of new T2 lesions	The number of new T2 lesions. Only lesions with a minimum distance of 1 mm to other lesions are counted. Subcategory of *T2 lesion increase*.

4.1.2 Reference Comparison Metrics

If the patient age is between 18 and 100, a comparison to an age- and sex-specific reference set is performed. AIRAscore provides the following metrics for the reported structures:

Metric	Definition
Z-score	A value that represents how many standard deviations the computed relative volume falls below or above the reference mean.
Normal range lower limit	The 2.5th percentile of the reference set volume converted to absolute volume in ml using the patient’s total intracranial volume.
Normal range upper limit	The 97.5th percentile of the reference set volume converted to absolute volume in ml using the patient’s total intracranial volume.

Metric	Definition
Percentile	Percentage of values from the reference set that fall below the computed z-score assuming a normal distribution.

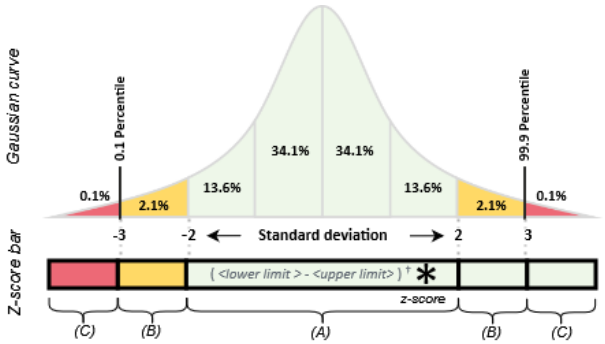
Metrics from the reference comparison in evaluation reports from version 3.0.0 or higher cannot be compared with older versions of AIRAscore.

4.2 Z-score Bars and Gaussian Curve

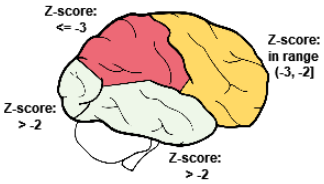
The z-score bar visualizes the reference comparison z-score as an asterisk. Measured brain volumes of the patient are compared against the mean volume of the reference collective. The central segment (*A*) represents the range of -2 to +2 standard deviations from the reference mean. The neighboring segments (*B*) represent the intervals of -3 to -2 and +2 to +3 standard deviations from the reference mean. The outermost segments (*C*) represent the interval of -4 to -3 and +3 to +4 standard deviations from the reference mean.

The z-score bars additionally display the upper and lower limit of normal range (*A*). See section *Reference Comparison Metrics.*

The Gaussian curve visualizes the standard deviations compared to the reference mean.



4.3 Schematic Overview of Reference Comparison



Each anatomical structure is colored in green, yellow or red based on the reference comparison z-score (see section *Reference Collective Colors*).

4.4 Reference Collective Colors

AIRAscore uses the colors green, yellow and red to visualize the outcome of the reference comparison. The colors indicate the distance of a measurement to the reference collective mean.

Color	Description
	Z-score > -2 standard deviations from the mean of the reference collective*
	Z-score in the intervals of -3 to -2 standard deviations from the mean of the reference collective*
	Z-score < -3 standard deviations from the mean of the reference collective*

* For ventricles green color is used for z-scores < +2 standard deviations. Yellow color is used for z-scores in the interval of +2 to +3 standard deviations. Red color is used for z-scores > +3 standard deviations from the mean of the reference collective.

4.5 Quality Control Images

The quality control images are a set of anatomical standardized slices at predefined positions that are intended to provide a first impression of the segmentation. These slices are taken from the color overlays described in section *Color Overlays*. Nevertheless, the full set of colored overlays must still be checked.

4.5.1 Anatomy Segmentation and Tissue Segmentation

The segmentation of anatomical structures and brain tissues is displayed with a sagittal, a coronal and an axial slice. The sagittal slice is the slice that separates the left and right hemisphere, 1cm to the right of the midsagittal plane. The axial slice is orthogonal to the mid-sagittal plane and 4cm cranial to the most cranial section of *Pons*. The coronal slice location is orthogonal to the mid-sagittal plane and axial plane, and slices through the center of mass of the left and right *Hippocampus*.

4.5.2 Deep Gray Matter Segmentation

The segmentation of anatomical structures in the deep gray matter is displayed with two axial slices and one coronal slice: One axial slice displays the center slice of the deep gray matter area. The other axial slice displays the *Hippocampus.* The coronal slice is positioned 1 cm posterior to the center of the deep gray matter area.

4.5.3 T2-FLAIR Lesions

The segmentation of lesions is displayed with three axial slices, one for each lesion category (juxtacortical, periventricular and infratentorial). Each slice is positioned to display the lesion with largest volume of the respective category.

An axial slice of the largest new or increased lesion is created, supplemented with the zoomed-in location of the lesion from the previous scan and the current scan. In case of no longitudinal comparison, the axial slice shows the largest lesion.

4.6 Longitudinal T1 Volumetry Comparison Table

	Absolute Volume in ml (Percentile)				Volume Change per Year in % [95% CI]	
T1 Volumetry	**Curr.**		**Prev.**			
Total Brain Volume	1097.0	(13.6)	1095.5	(13.6)	0.2	[-7.2 – +7.6]

The table provides a comparison of the T1 volumetry between the previous and the current evaluation. The absolute volume and percentile for the current and previous evaluations are shown, as well as the difference metric “Volume Change per Year” described in the following section.

4.6.1 Volume Change per Year

“Volume Change per Year” indicates the percentage change in absolute volume between the previous and current evaluation, relative to the previous evaluation and extrapolated to an annual rate.

Values in brackets denote the upper and lower bounds of the 95% confidence interval. This error metric is based on general volumetric precision, which is also extrapolated to one year according to the time interval between evaluations.

The font weight and color of the reported “Volume Change per Year” metrics indicates the probability that the rate of change is distinct based on the confidence intervals of the volumetry measurements.

- **Bold black** – Indicates a distinct annual change in volume between assessments.
  The 99% confidence interval for the annual volume change is all positive or negative. This means there is a 99% level of confidence that the observed change is real and not due to random variation.
- **Black** – Indicates a likely annual change in volume between assessments.
  The 90% confidence interval for the annual volume change is all positive or negative. This means there is a 90% level of confidence that the observed change is real, suggesting a potential trend.
- **Gray** – Indicates that no distinct annual volume change can be inferred from the data, meaning there is no statistically reliable indication of a change in either direction.

> ⚠ **Interpretation Guidance**
> 1. **Grayed-out %Delta/Year values** indicate that no clear increase or decrease in volume was detected between assessments.
> 2. **Reported annual volume changes** do not inherently indicate a pathology and should not be interpreted as evidence for a pathology on their own.
> 3. **Statistical classification:** The confidence intervals used to classify annual volume changes are based on test–retest datasets and represent expected measurement variability. As with any statistical method, false-positive and false-negative results are possible.
>
> A qualified physician must review these findings to make any definitive clinical interpretation.

If “Volume Change per Year” is marked as “N/A” (not available), the values could not be calculated – possibly because the patient’s age falls outside the reference cohort.

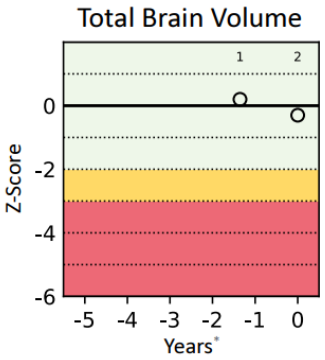
4.7 T2 Hyperintense Lesions Table

The table provides information about the presence of lesions and a comparison to the previous evaluation.

For the current evaluation, absolute volume and lesion count are displayed. The longitudinal comparison displays the decrease and increase of T2 lesion absolute volume, as well as the absolute volume and count of new T2 lesions. See section *General Metrics* for metric description.

T2 Hyperintense Lesions	Absolute Volume in ml	Count
Total	45.3	>=9
Decrease	-9.4	
Increase	18.1	
of Which New	23.4	4

4.8 Longitudinal Z-Score Plot



The plot visualizes all available reference comparison z-scores of a patient. It shows the z-scores on the y-axis and the time points of the included evaluations in years relative to the current evaluation on the x-axis.

The volume of an anatomical brain structure is compared to the reference collective mean. If the difference to that mean is stable between evaluations, the z-score is similar and therefore the data points lie on a flat line.

All displayed evaluations are labeled with numbers. The current evaluation is labeled with “1”. Information about all evaluations is provided in the table underneath. Evaluations that are not included in the plot are grayed out.

Time Point	Report-ID	Acquisition	Age	Software Version	Comment
2	59X Z0U 6XV	Aug 14, 2013, 12:32 PM	43	0.0.0	Current
1	5G8 2VU 68W	Dec 24, 2011, 12:32 PM	39	0.0.0	Accepted

4.9 Color Overlays

For visual control the segmentation results are returned as separate DICOM series. These segmentation results are displayed as colors overlaid on top of the original input image. The overlays can be found in the study of the input

images. Each overlay can be identified by the DICOM attribute SeriesDescription. For the used colors, see section *Color Legend for Segmentation Results*.

AIRAscore returns the following segmentation overlays:

- Anatomy regions (DICOM SeriesDescription *Anatomy Map*)
- Tissue classes (DICOM SeriesDescription *Tissue Map*)
- Deep gray matter structures (DICOM SeriesDescription *DGM Map*)

Optionally, the following overlays are provided:

- T2 lesion categories (DICOM SeriesDescription *T2-Lesion Map*)
- T2 lesion changes (DICOM SeriesDescription *T2-Lesion Longitudinal Map*)
- Comparison with second most recent and Lesion Map. (DICOM SeriesDescription *Lesion comparison with second most recent study. (Se 9))*

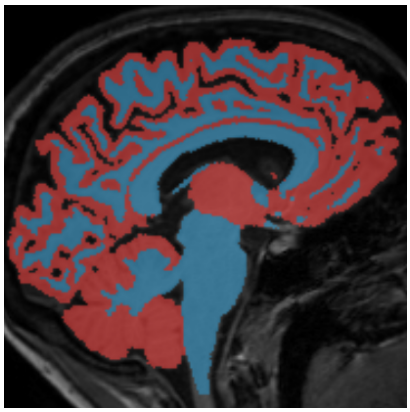


Figure 1: Exemplary Tissue Map

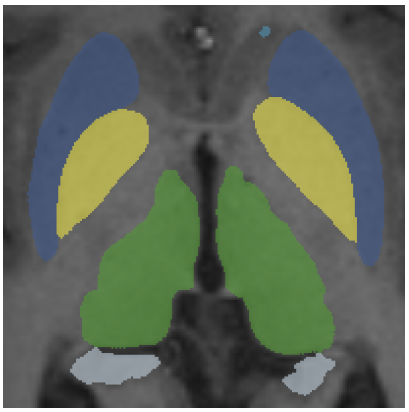


Figure 2: Exemplary DGM Map

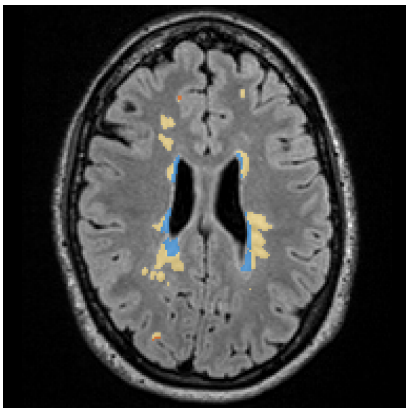


Figure 3: Exemplary T2 Lesion Map

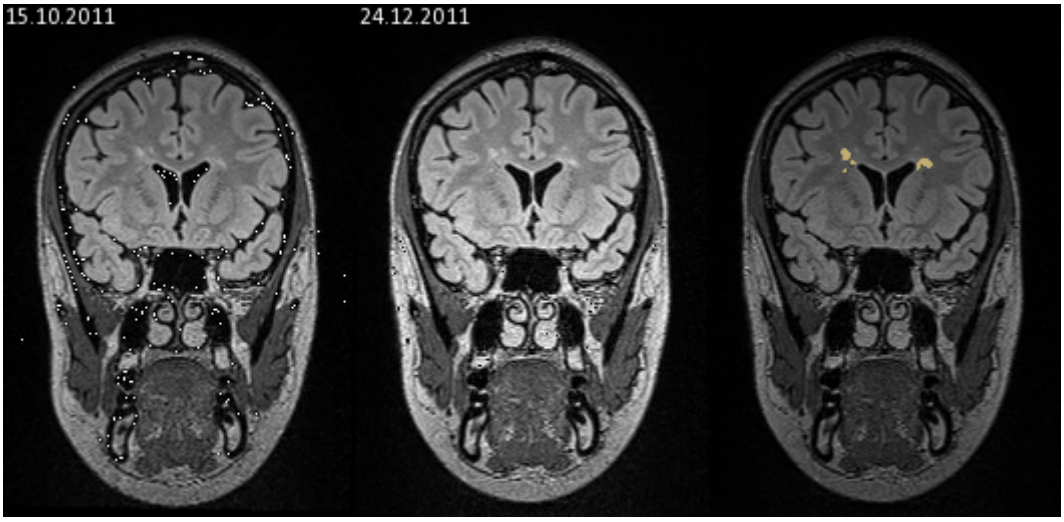
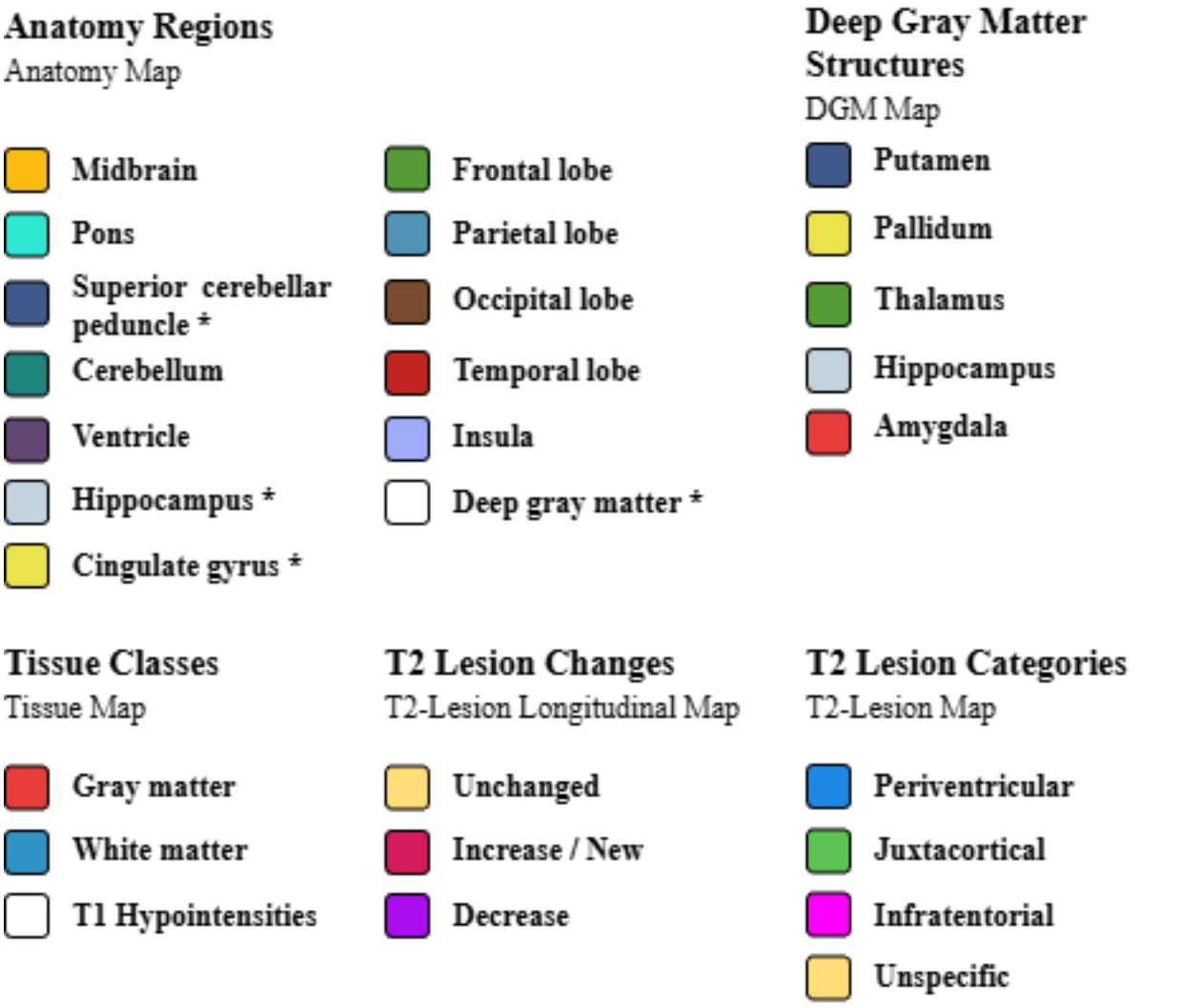


Figure 4: Exemplary Second Most Recent Comparison

5 Color Legend for Segmentation Results

Color overlays (see section *Color Overlays*) and quality control images (see section *Quality Control Images*) use colors to display the segmentation results. Below is the legend of all used colors.



* Volume of this structure is not reported.

6 Technical Requirements for the Dataset

AIRAscore processes T1 and T2-FLAIR datasets that conform to the following requirements.

For a detailed list of all requirements for DICOM data, please refer to the separate (v3.0.1) DICOM Conformance Statement.

6.1 T1 Dataset Requirements

- T1 dataset, native, DICOM format: *MR Image IOD*
- Clear gray-white contrast between gray and white matter and, if possible, hypointense representation of cerebrospinal fluid (CSF)
- 3D dataset
- Device manufacturer: GE, Philips or Siemens
- Field strength: 1.5 or 3 Tesla
- Voxel size must be < 2mm in each dimension
- Range of voxel volume: 0.1 mm^3 ≤ voxel volume ≤ 2.4 mm^3
- In the slice selection direction, the number of slices x (slice thickness including gap) must be at least 140 mm and no more than 260 mm.
- The field of view must be no more than 260 mm in both the phase and gradient encoding directions.
- The head must be completely captured
- The head should not be captured tilted
- No pronounced artifacts should be visible in the image (motion, folding, etc.)

6.2 T2-FLAIR Dataset Requirements

- T2-FLAIR dataset, DICOM format: *MR Image IOD*
- 2D or 3D dataset
- Device manufacturer: GE, Philips or Siemens
- Field strength: 1.5 or 3 Tesla
- Resolution of image data ≤ 1.5 mm in x and y direction and ≤ 6 mm in slice direction
- In the slice selection direction, the number of slices x (slice thickness including gap) must be at least 140 mm and no more than 260 mm
- The field of view must be no more than 260 mm in both the phase and gradient encoding directions
- The head must be completely captured
- The head should not be captured tilted
- No pronounced artifacts should be visible in the image (motion, folding, etc.)

6.3 Longitudinal Comparison Requirements

For a longitudinal comparison the same requirements apply for the input data. A separate data set that was recorded with the same scanners and compatible sequences is required for each timepoint.

The following DICOM attributes need to be identical or within a tolerance in order for a sequence to be compatible:

Identical values required:

- Manufacturer
- SliceThickness
- PixelSpacing
- ScanningSequence
- MRAcquisitionType
- ImagedNucleus
- EchoTrainLength
- FlipAngle

Differences within tolerance are accepted:

- RepetitionTime within +/- 5 ms
- EchoTime within +/- 1 ms

- InversionTime within +/- 10ms
- MagneticFieldStrength within +/- 0.1 T
- PixelBandwidth within +/- 10Hz

For technical reasons, only data from evaluations of version v3.0.0 or higher can be considered for the longitudinal comparison. This is independent of other information, such as the date of the scan.

⚠ The DICOM attribute PatientID must be set to a non-empty value and must be unique for each patient. This is required for the correct assignment during the longitudinal comparison, as the patient is identified by the PatientID in the DICOM metadata.

7 Automated Control of Image Data and Accountability of the Requesting Physician

All image data is automatically checked after being received by AIRAscore. The technical data of the sequence is checked for compatibility with AIRAscore (see section *Technical Requirements for the Dataset*).

While this allows the detection of the majority of possible technical errors, there remains the residual risk that datasets that do not meet the technical requirements or datasets of patients with contraindications are nevertheless processed. Therefore, despite all due care, incorrect segmentation may occur in rare cases. To verify the correctness of the segmentation results, the requesting physician is required to ensure correct segmentation using the provided colored overlays (see section *Colored Overlays*).

⚠ All AIRAscore reports must be checked for plausibility and accuracy by a qualified physician (specialist) with sufficient knowledge of neuroanatomy and MR imaging of the head.

⚠ It is the responsibility of the requesting physician to check the identity of the patient.

ⓘ AIRAmed does not assume any warranty for assessments or diagnoses derived from the evaluation results of the evaluation reports and cannot be held liable for this.

For viewing you need a DICOM viewer and a monitor that can display the DICOM formats *Encapsulated PDF IOD* as well as *Secondary Capture Image IOD* in color. For reporting you need an approved monitor in appropriate illumination in order to control the gray-white boundary (typically room class 2).

8 Obligation to Report

If you are of the opinion that there is a safety-relevant malfunction in the product, please contact our customer service immediately.

8.1 Obligation to Report in EU-Countries

If you are located in an EU country, please report all serious incidents (harms, injuries, etc) related to this medical device to the manufacturer and the responsible authority of the EU member state that you are established in.
In Germany the responsible authority is the BfArM. The latest contact information can be obtained from the BfArM website at: https://www.bfarm.de.

9 Expected Processing Times

You will receive the results within a few minutes. However, the actual time depends on your internet connection. In rare cases, data transfer or processing errors can occur. Therefore, if you do not receive a report within one hour after sending the data, please contact us directly.

10 Handling of Personal Data

Only image data, as well as age and sex, which are required for the reference collective comparison, are stored on AIRAmed servers. This data is encrypted during data transfer. All other personal data (e.g., patient name and date of birth) of the patient remains encrypted on the customer system.

11 Precision and Accuracy

Metrics used for the precision and accuracy calculations include the intraclass correlation coefficient (ICC), 95% confidence interval (CI95%), median, sensitivity, and precision.

11.1 Precision

The precision of anatomical structure segmentations was calculated through the evaluation of a test-retest dataset consisting of 398 samples. The precision of lesion segmentations was calculated using a dataset of 19 test-retest samples. The precision of the longitudinal comparison of lesion segmentation was evaluated on 20 tests of three different T2-FLAIR scans for 11 multiple sclerosis patients in total.

Precision metrics are the median difference between absolute segmentation volumes in paired test-retest scans and the ICC between the absolute volumes.

Label	Median [ml]	Median CI95% [ml]	ICC(2,1)	ICC(2,1) CI95%
Tissue				
Total brain volume	1.13	[0.96, 1.30]	0.999	[0.999, 0.999]
Gray matter (GM)	1.5	[1.2, 1.8]	0.999	[0.998, 0.999]
White matter (WM)	1.01	[0.67, 1.27]	0.999	[0.999, 0.999]
GM cerebrum (L)	0.62	[0.53, 0.77]	0.998	[0.997, 0.998]
GM cerebrum (R)	0.71	[0.59, 0.93]	0.998	[0.997, 0.998]
WM T1 Hypointensities	0.052	[0.046, 0.060]	0.999	[0.999, 0.999]
Infratentorial				
Midbrain	0.033	[0.028, 0.039]	0.995	[0.993, 0.996]
Pons	0.043	[0.036, 0.054]	0.999	[0.999, 0.999]
Total cerebellum	0.23	[0.21, 0.27]	0.999	[0.998, 0.999]
GM cerebellum (L)	0.13	[0.11, 0.16]	0.998	[0.997, 0.999]
GM cerebellum (R)	0.17	[0.15, 0.20]	0.997	[0.997, 0.998]
Ventricles				
Lateral ventricle (L)	0.052	[0.044, 0.059]	0.999	[0.999, 0.999]
Lateral ventricle (R)	0.047	[0.041, 0.055]	0.999	[0.999, 0.999]
3rd ventricle	0.020	[0.016, 0.023]	0.999	[0.999, 0.999]
4th ventricle	0.022	[0.020, 0.025]	0.998	[0.997, 0.998]
Brain lobes (gray matter)				
Frontal (L)	0.33	[0.28, 0.40]	0.996	[0.994, 0.997]
Frontal (R)	0.37	[0.30, 0.46]	0.995	[0.993, 0.996]
Parietal (L)	0.23	[0.20, 0.30]	0.996	[0.995, 0.997]
Parietal (R)	0.30	[0.24, 0.33]	0.995	[0.994, 0.996]

Occipital (L)	0.13	[0.11, 0.16]	0.997	[0.996, 0.997]
Occipital (R)	0.15	[0.12, 0.18]	0.998	[0.997, 0.998]
Temporal (L)	0.16	[0.14, 0.19]	0.998	[0.997, 0.998]
Temporal (R)	0.21	[0.18, 0.24]	0.998	[0.997, 0.998]
Insula (L)	0.053	[0.045, 0.060]	0.995	[0.993, 0.996]
Insula (R)	0.060	[0.048, 0.066]	0.993	[0.991, 0.995]
Deep gray matter				
Amygdala (L)	0.015	[0.012, 0.018]	0.993	[0.991, 0.995]
Amygdala (R)	0.015	[0.013, 0.020]	0.992	[0.990, 0.994]
Hippocampus (L)	0.019	[0.017, 0.023]	0.995	[0.993, 0.996]
Hippocampus (R)	0.021	[0.016, 0.025]	0.996	[0.994, 0.997]
Pallidum (L)	0.015	[0.012, 0.018]	0.991	[0.988, 0.993]
Pallidum (R)	0.016	[0.013, 0.020]	0.989	[0.985, 0.991]
Putamen (L)	0.027	[0.022, 0.032]	0.997	[0.997, 0.998]
Putamen (R)	0.025	[0.020, 0.029]	0.997	[0.996, 0.998]
Thalamus	0.062	[0.050, 0.072]	0.997	[0.996, 0.998]
Thalamus (L)	0.040	[0.036, 0.049]	0.995	[0.993, 0.996]
Thalamus (R)	0.035	[0.028, 0.043]	0.995	[0.993, 0.996]
T2 lesions				
Total lesion volume	0.083	[0.064, 0.153]	0.999	[0.999, 0.999]
Total lesion count	2†	[1, 2]†	0.996	[0.984, 0.998]
T2 lesions longitudinal comparison				
Total lesion volume change	0.0078	[0.0000, 0.1989]	0.999	[0.999, 0.999]

† These values represent counts, rather than volumes. They show the absolute difference of detected lesions between segmentations of paired test-retest scans.

GPU-induced (graphics processing unit) random effects can lead to minor differences in volumes for the same image. These differences are smaller or equal to the 10th percentile of test-retest differences for all regions.

11.2 Accuracy

The accuracy of the anatomical structures segmentation was evaluated by comparison with 20 samples that were manually segmented by experts. Across all anatomical structures located in the deep gray matter the mean ICC(3,1) is 0.85 with a CI95% of [0.76, 0.86]. Across all remaining anatomical structures the mean ICC(3,1) is 0.86 with a CI95% of [0.75, 0.92].

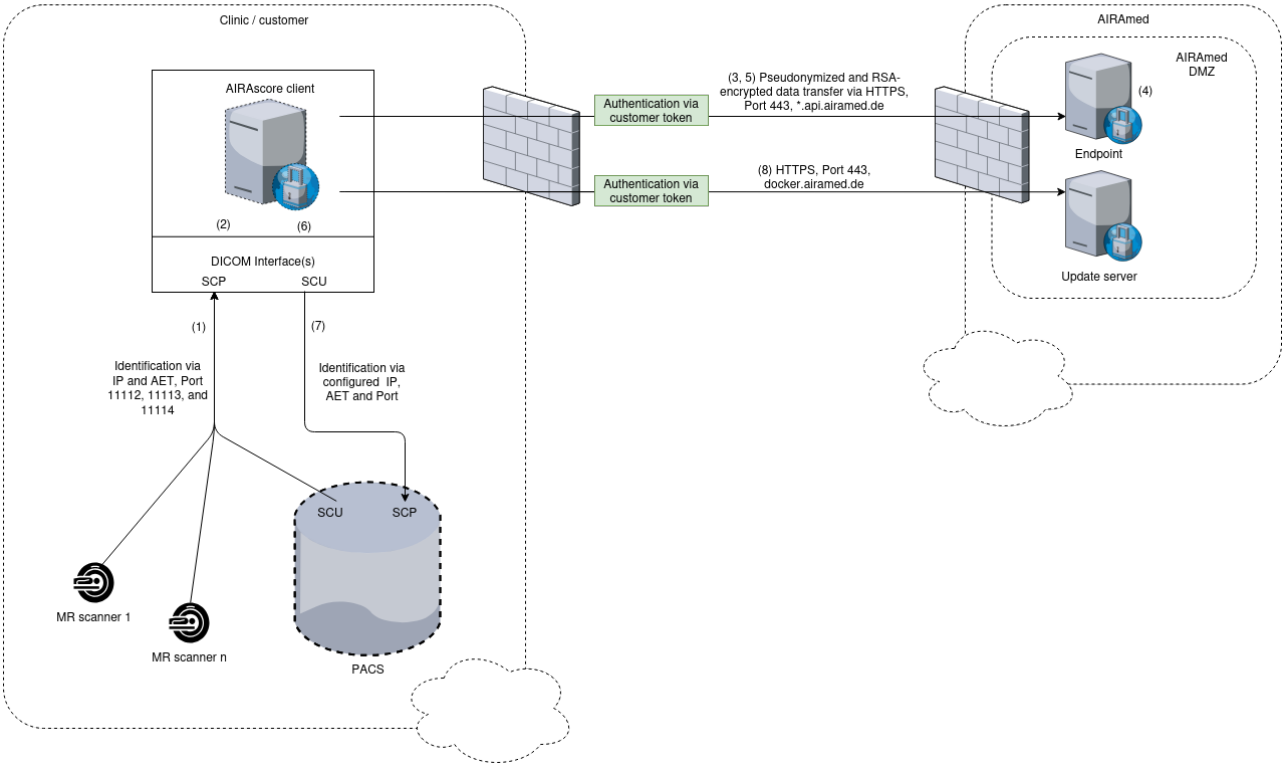
The accuracy of the lesion segmentation was evaluated by comparison with 10 samples of multiple sclerosis patients that were manually segmented by experts. The sensitivity and precision of the total lesion count is 70% and 72%, respectively. The ICC(2,1) for the total lesion volume is 0.964 with a CI95% of [0.745, 0.989]. The accuracy of the longitudinal lesion segmentation was evaluated by comparison with 15 samples of multiple sclerosis patients

that were manually segmented by experts. The ICC(2,1) for the total lesion volume change is 0.92 with a CI95% of [0.63, 0.94].

12 AIRAscore Client

AIRAmed provides the AIRAscore Client software. The AIRAscore Client operates as the interface to AIRAmed servers.

System Architecture Sketch for AIRAscore



General information

- Arrows indicate the direction of communication structure.
- Access to the DICOM interface of the AIRAscore client from IPs outside the customer network shall be prevented by appropriate firewall rules on the customer side.
- The front end has no dedicated graphical user interface. Instead, AIRAscore integrates into the customer's software. The process of sending data from the customer to AIRAmed is comparable to selecting a printer.

12.1 Data Flow

The dataflow of the medical device begins with selected imaging data being transmitted from the customer's DICOM storage SCU or scanner to the AIRAscore client's DICOM storage SCP. Subsequently, the data undergoes pseudonymization and RSA encryption, with the encrypted patient data being stored locally on the customer's side. This encryption key is then transmitted via HTTPS Port 443 to *.api.airamed.de, with customer authorization facilitated through a customer token.

Upon arrival at AIRAmed, the order is processed accordingly. Following this, the AIRAscore client periodically initiates requests to check the order status. Once the order is ready, the client retrieves the pseudonymized and RSA-encrypted results via HTTPS. These results are then depseudonymized on the customer side.

After depseudonymization, the results are transmitted back from the AIRAscore client's DICOM storage SCU to the PACS DICOM storage SCP. Additionally, AIRAscore initiates periodically checks for available updates, with any updates being fetched and installed accordingly to ensure the system remains up to date.

12.2 Installation

For instructions how to install AIRAscore Client, please refer to the *AIRAscore Client Installation Instructions*, which is provided by AIRAmed.

12.3 Configuration

The AIRAscore Client can be configured as follows.

12.3.1 Report Language

The reports can be returned in one of the languages listed below. To change the configured language, please refer to *AIRAscore Client Installation Instructions*, section *Country Code*.

The formatting of the following information in the reports is affected by the configured country code:

Country Code	Language	Patient Name Format	Date Format	Time Format
en_US	English	First_Name Last_Name	Mon dd, yyyy	AM/PM
de_DE	German	Last_Name, First_Name	dd.mm.yyyy	24-hour clock (military time)
es_ES	Spanish	First_Name Last_Name	dd.mm.yyyy	AM/PM
pt_PT	Portuguese	First_Name Last_Name	dd.mm.yyyy	AM/PM

12.3.2 Error Reports

Problems may occur during processing of datasets by AIRAmed. In such a case, a DICOM Secondary Capture image containing the error reason will be sent to your PACS. If you do not wish to receive error reports, please contact the AIRAmed support to deactivate this feature.

12.3.3 DICOM Structured Reports

AIRAscore can create DICOM Structured Reports (*Comprehensive SR CIOD*). The following DICOM Structured Reports can be enabled:

- Order confirmations
- AIRAscore imaging measurement reports
- Error reports

By default, the DICOM Structured Reports are disabled. If you wish to receive DICOM Structured Reports, please contact the AIRAmed support to activate this feature.

⚠ The DICOM Structured Report is only an add-on to the AIRAscore report and must not be used on its own.

13 Known Problems

The DICOM PatientOrientation field is set as an empty field for the segmentation results. However, the ImageOrientation (Patient) [0020,0037] and ImagePosition (Patient) [0020,0032] fields contain the relevant information.

The DICOM field IssuerOfPatientID contains the value *None* if it was not set in the input data.

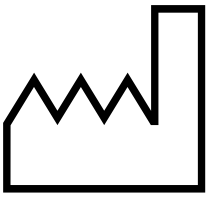
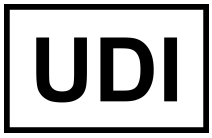
14 Querying the UDI

The Unique Device Identification (UDI) for AIRAscore can be obtained by accessing the following URL: https://api.airamed.de/v1/udi. The response will include the UDI-DI (Device Identifier) as well as the UDI-PI (Production Identifier).

15 Information about eIFU

Please contact service@airamed.de, to receive a printed copy of the instructions for use within 7 days.

16 Glossary

Symbol	Symbol Title	Explanatory Text
	CE-Marking	This product complies with the applicable requirements set out in the European Union harmonization legislation on their affixing.
	Manufacturer	Indicates the medical device manufacturer.
	Manufacture Date	Indicates the date the medical device was manufactured.
	Consult instructions for use	Indicates the need for the user to consult the instructions for use.
	Prescription only	Caution: US federal law restricts this device to sale by or on the order of a physician.
	Caution	Indicates that the current situation requires the user's attention to avoid undesirable consequences.
	Medical Device	Indicates that the item is a medical device.
	Batch code/Lot number	Indicates the manufacturer’s batch code or lot number.
	Unique Device Identification	Indicates the Unique Device Identification information.

Symbol	Symbol Title	Explanatory Text
	Indication	Alerts the user to helpful information.
	Swiss Authorized Representative	Indicates the authorized representative in Switzerland.

17 About AIRAscore Client

AIRAscore Client is used to connect to the AIRAscore software and is developed by AIRAmed GmbH. All rights reserved.

AIRAscore Client uses the Requests library, Copyright 2019 Kenneth Reitz, in version 2.26.0.

AIRAscore Client uses Watchtower, Copyright 2021 Simon Aronsson, in version 1.3.0.

AIRAscore Client uses the fpdf2 library, Copyright 2013 Lucas Cimon, in version 2.5.1.