Hepatogram *plus*+ User Manual

For Software Version 3

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Section 1 – Introduction

It is recommended that you read this instruction manual carefully before use.

Hepatogram plus+ is a software tool designed by Resoundant to help draw reproducible regions-of-interest (ROIs) for the stiffness measurement from Magnetic Resonance Elastography (MRE) and multi-point Dixon fat/water (F/W) images by providing preliminary automated ROIs in the liver of these images. The preliminary ROIs should be verified and, if necessary, modified by an experienced MRE and F/W reader before being used as an element for clinical care.

Please carefully read the precautions with  symbols, to ensure that the device is used in best conditions and in complete safety.

1-1 Contents

Hepatogram plus+ software. Configuration and available options may vary based on the service or method of installation. Options include:

- Hepatogram plus+ server, which generates MRE inversion results, automated ROIs, and Summaries with images and statistics.
- Hepatogram plus+ viewer, which allows review and manual editing of exams processed by Hepatogram plus+ server, as well as generation of Summaries.

1-2 System Description

Hepatogram plus+ software is a tool for assisted MRE and multi-point F/W image analysis which calculates preliminary automated ROIs. The Hepatogram plus+ viewer may be available to facilitate the review, approval, and modification of the ROIs by trained readers. All ROIs, regardless of their source –automated or manual—must be reviewed and approved by a trained reader before the stiffness reported in the summaries can be used clinically.

The inputs for Hepatogram plus+ are the MRE and F/W images. In the case of MRE, this includes magnitude images (showing anatomy) and phase images. Inputs for F/W images include fat, water, fat fraction, and, optionally, R2*.

From these images, Hepatogram Plus+ calculates automated ROIs which must be reviewed by an authorized trained reader. For MRE data, Hepatogram plus+ outputs wave images (showing wave propagation with multiple time points across the wave cycle), elasticity images and confidence images calculated by an inversion algorithm packaged with Hepatogram plus+. No secondary images are created from F/W inputs. Hepatogram plus+ additionally outputs ROIs and a summary image containing calculated stiffness and/or PDFF/R2* values, all in a DICOM archive compatible format.

1-2-1 Non-diagnostic

Hepatogram plus+ is an automated ROI assistance and analysis tool, it is not a diagnostic tool. All outputs are intended for review by a trained reader or physician and used as an element of clinical care.

1-2-2 Users of the software

Users of the software must understand the images being analyzed to effectively determine if the automated output is acceptable or requires manual modification.

1-2-3 Input data sources

Only certain data sources—pulse sequences from specific MRI manufacturers—are supported.

Hepatogram plus+ only supports display and calculation from a maximum of four slices. More slices may be available in the input data, but only four will be displayed in reports and used in composite calculations of quantitative output.

1-2-4 Patient population and anatomy

The software is intended for use in patients with approximately normal liver anatomy. If tumors are present, these may need to be removed from the ROI during manual review. The MRE or F/W exam should be of a quality that would be considered acceptable by a trained reader. The intended use does not cover images with significant artifacts, such as respiratory ghosting, signal dropout due to implant, or a lack of signal (no MRE waves, severe iron overload).

1-2-5 Use cases and effectiveness

MRE:

In MRE analysis, 95% of cases processed by Hepatogram plus+ produced results that were equivalent to expert human readers without modification.

In 2.5% of MRE cases studied, Hepatogram plus+ produced automated ROIs that expert readers deemed inaccurate. These ROIs often contained non-liver tissue that, when removed from ROIs, produced stiffness measurements different by 20% or more from the automated result. For this reason, it is necessary that all ROIs are reviewed by trained readers to confirm the validity of quantitative results and, when necessary, manually modify the ROI or discard the automated result and perform a manual analysis.

In another 2.5% of MRE cases, Hepatogram plus+ failed to produce sufficient ROI area to yield a result, whereas an expert reader was able to manually produce sufficient-size ROIs in the same data. When the automated system produces no ROIs or small ROIs, such that the composite ROI data is deemed too small, Hepatogram plus+ will not automatically report composite stiffness value (or report the stiffness as 0). Manual analysis from an alternative tool will be necessary.

Though only a total of 5% of cases require manual modification, expert users have been observed to electively modify ROIs in one or more slice in 20% of all cases. These elective

modifications have a non-significant impact (less than 20% change in stiffness). Examples include when a small portion of an ROI is in non-liver tissue, or when the ROI includes non-liver tissue of similar stiffness to the liver.

Fat/Water:

In F/W analysis, Hepatogram plus+ has produced optimal ROIs in >99% of cases studied. The two possible modes of failure are having an ROI include non-liver tissue which has the same fat-fraction as the liver, and having an ROI include tissue of different fat fraction. The first mode can occur in patients with low fat-fraction (<5%) if the acquired slices are prescribed too high or too low in the body to include the heart, lung, or kidneys. The inclusion of these tissues would not affect the liver PDFF/R2* in such a patient. The issue can be identified by reviewing anatomy in the water image in the Hepatogram plus+ viewer, or another DICOM viewer. The second failure mode is the inclusion of blood vessels, abdominal fat, or the noise in the visceral space. These structures may have a very different PDFF/R2* value than the liver but these structures are typically small and do not significantly affect the composite liver PDFF/R2* values. In these cases, the trained reader may modify the ROIs or discard the automated result and perform a manual analysis.

1-3 Operator Manual Information

Operator manual is available:

- Under the Help menu of Hepatogram plus+
- On the Resoundant website, www.resoundant.com
- Via email request to software-support@resoundant.com
- Via written request to:

  Resoundant, Inc.
  421 First Avenue SW STE 204W
  Rochester, Minnesota 55902 USA

1-4 Use of Symbols

Installation and information technology professionals should understand the following symbols used for caution and warning explanations:

	Manufacturer
	Authorized Representative in the European Community
	Authorized Representative for Swiss Community
	General Warning

	eIFU Indicator
	Medical Device
	Caution: Federal law restricts this device to sale by or on the order of a physician

Note: Other symbols used in device labeling that are NOT accompanied by adjacent text are defined in FDA recognized standard ISO 15223, latest version.

1-5 Safety

U.S. federal law restricts use of this device by or on the order of a physician.

1-5-1 System Operating Safety

There are no operator safety concerns associated with the operation of this software.

1-5-2 Patient Safety

There are no patient safety concerns associated with the operation of this software.

1-5-3 Modifications

Other than configuration settings, changes or modifications to the Hepatogram plus+ software application are not permitted.

1-5-4 Reporting of Incidents

Users should contact Resoundant immediately to report an incident and/or injury to an individual, operator or maintenance employee that occurred as a result of system operation.

For reporting of incident and/or injury, contact:

Resoundant, Inc.
421 First Avenue SW STE 204W
Rochester, Minnesota 55902 USA
Phone: 507.322.0011
Email: quality@resoundant.com

If an accident occurs because of system malfunction, do not operate the application until an authorized investigation is conducted.

1-5-5 Residual Risks

Appropriate control measures have been applied to all known risks associated with Hepatogram plus+. The benefit/risk comparison is overwhelmingly favorable and residual

risks are defined to be low. Residual risks are further communicated and addressed within general warnings and cautionary statements.

1-6 Environmental Requirements

There are no environmental requirements associated with this software.

1-7 Installation and Troubleshooting

Technical support for the Hepatogram plus+ application may be obtained through the following sources:

Email: software-support@resoundant.com

Please have the following information ready when contacting Resoundant:

- Hepatogram plus+ version information
- Source(s) of the images (MR scanner make and model, software level)
- Detailed description of the problem experienced
- Your contact information

1-8 External Standards

ISO 13485:2016: The development and manufacturing processes associated with this product conform to the requirements of ISO 13485:2016.

1-9 Quality Assurance

Prior to using Hepatogram plus+, follow all installation instructions, and confirm that datasets are complete and have undergone appropriate processing prior to use.

Section 2 – Indications for Use and Setup

2-1 Indications for Use

Hepatogram plus+ is an assisted ROI drawing tool for liver MRE and Fat/Water images and is used for receiving, displaying, ROI selection, and summary generation. It displays to a trained reader MRE and Fat/Water images, preliminary ROIs that it calculates from these images, and statistical analysis calculated from the ROIs and images. ROIs and images are presented for review and, optionally, modification by the trained reader.

2-1-1 Contraindications

Hepatogram plus+ is contraindicated to situs inversus, where major visceral organs are mirrored from their normal positions and may produce automated ROI in the right side of the body in a non-liver organ. This does not preclude use of the tool to manually correct the ROI.

Hepatogram plus+ is contraindicated to conditions that lead to heterogenous liver stiffness. In this case, the automated ROI may only include tissue with homogenous stiffness. An example of this is Primary Sclerosing Cholangitis (PSC), where heterogenous fibrosis results in the liver exterior being stiffer than the interior. The automated ROI may only be in the soft tissue, excluding the stiffer exterior. This does not preclude use of the tool to manually correct the ROI.

2-1-2 Intended users

Hepatogram plus+ must only be used by medical image readers trained with MRE and F/W. Users with suitable training may be image analysis techs, radiologists, radiology residents, researchers, or other qualified individuals who have received training from experienced MRE and F/W readers and have experience calculating stiffness from liver MRE and parameters from F/W, or are under the supervision of trained readers.

Any use by non-trained, inexperienced unsupervised readers, or use for purposes other than calculation of stiffness from liver MRE images and PDFF/R2* from liver F/W images is contraindicated.

The User must:

Be specially trained and qualified to analyze MRE and F/W images.

Carefully review each automatically generated ROI provided by Hepatogram plus+ for accuracy and modify or reject when necessary. This includes ensuring that the ROIs include only liver tissue and avoid areas with artifact.

Check that the input images displayed by Hepatogram plus+ look reasonable for contrast and SNR, appear in appropriate order, and that the final ROIs are acceptable to an experienced reader's best standard.

Consider patient history and patient-specific factors when appropriate to ROI selection or interpretation of the stiffness value.

Only use Hepatogram plus+ for measurements in liver data from acquisitions for which it has been validated.

2-2 Installation and Setup

See "Hepatogram Plus – Server Integration" for details.

2-3 Conditions for Normal Use

Hepatogram Plus is a backend post-processing tool. Multiple options exist to submit data to the tool, which will cause results to be generated, or an error summary for incomplete data, or no result for badly formed data.

See "Hepatogram Plus – Server Integration" for details on version control and traceability.

Section 3 – Maintenance

3-1 Software Updates

See “Hepatogram Plus – Server Integration” for details.

3-2 Cybersecurity updates

See “Hepatogram Plus – Server Integration” for details.

3-3 Use and Operation

3-3-1 Runtime parameters

See “Hepatogram Plus – Server Integration” for details.

3-3-2 Supported acquisitions

Hepatogram plus+ processes MRE and multi-point Dixon F/W images. Hepatogram plus+ is designed to receive an entire liver MR exam dataset. DICOM header information of all data provided is used to discover which series contain MRE or F/W datasets that can be processed. Any pulse sequences that it does not recognize will be ignored.

If Hepatogram plus+ discovers multiple datasets of any supported type, all datasets will be processed and result in one or more output series, depending on server-side configuration and can be a single series of all results, or one output series per input series.

Supported acquisition types:

	MRE	F/W
GE	MR-Touch	IDEAL/IQ
Philips	FFE MRE, SE-EPI MRE	mDixon-quant
Siemens	greMRE, epseMRE	qDixon

NOTE: Supported sequences are identified by DICOM metadata. Unrecognized DICOM headers cannot be processed by Hepatogram plus+. See Revision History for a list of vendors and software versions supported.

If you believe your pulse sequence should be recognized but Hepatogram plus+ is not producing results, contact Resoundant for support.

3-3-3 MRE: Required Images

A complete set of MRE Magnitude and Phase images are the required input to Hepatogram Plus: this means acquired slices with multiple timepoints per slice.

Hepatogram plus+ will derive stiffness, wave, and confidence images for MRE exams from the MRE magnitude and phase images using MMDI (multi-model direct inversion); it Hepatogram Plus does not accept these contrasts from the MRI scanner and ignores them if provided. This can yield results that look different from those processed on the scanner, particularly in the cases of colorized images, but are quantitatively equivalent.

3-3-4 F/W: Required images

Proton density fat fraction (PDFF) and Water contrasts are required. R2* contrast is optional and will be used to calculate R2* measurements if this image set is present.

3-3-5 Automated ROI generation

Automated ROI generation algorithms within Hepatogram plus+ will attempt to find and segment the liver then produce an ROI within that boundary avoiding artifact, tumors, and blood vessels. Automated ROIs are shown to be as effective as human drawn ROIs for finding quantitative values of liver stiffness and fat fraction in >95% of cases. In the remaining 5% of cases, modification of ROIs or manual re-draw is required. In all cases, for the quantitative results to be valid, a trained reader must verify that ROIs are acceptable.

Hepatogram plus+ processing takes 2-4 minutes per dataset. For example, a study containing one MRE series and one F/W series will take 4-8 minutes.

3-3-6 Reviewing results

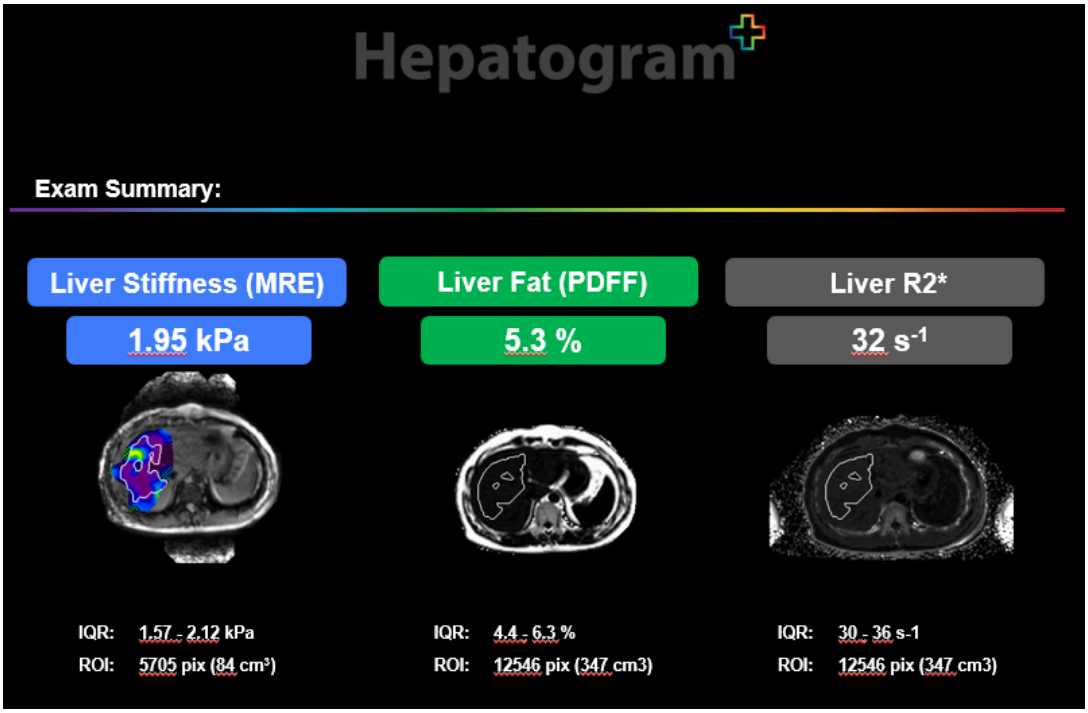
In some situations, a compatible graphical interface may be available for review and modification. See that tool's manual for instructions.

Hepatogram plus+ output series can be configured to create the following outputs:

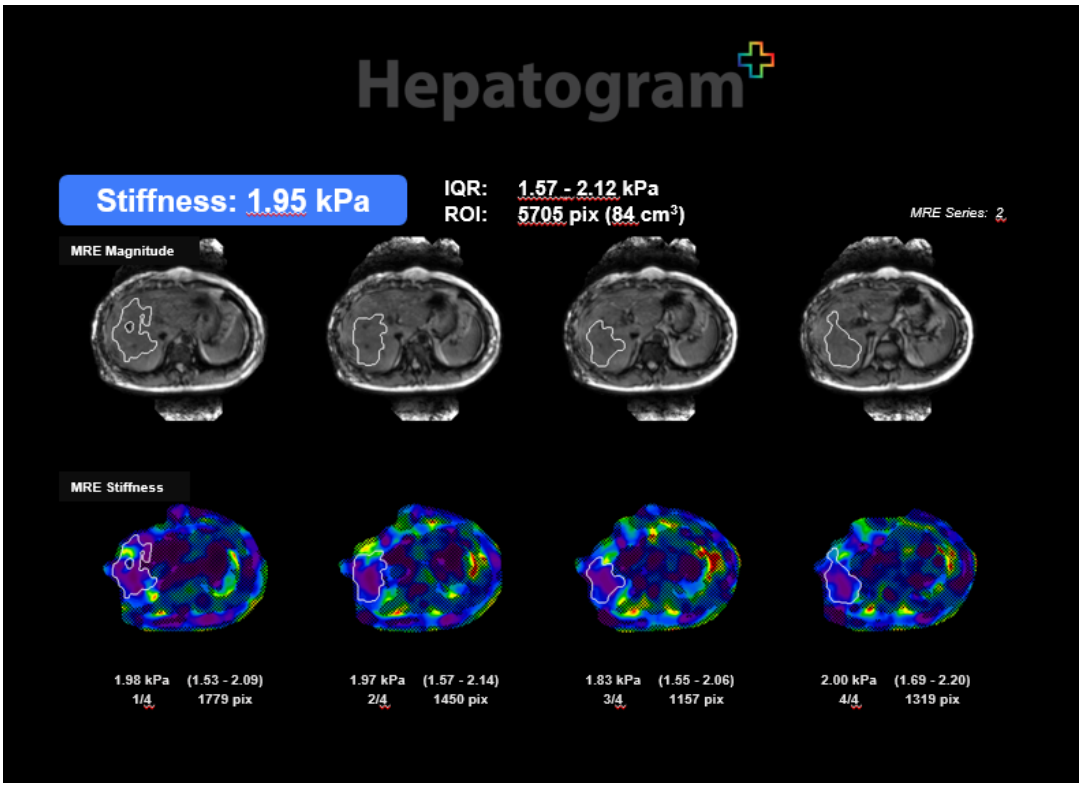
- Exam summary – one example thumbnail of Stiffness, PDFF, and R2*, including composite results.
- MRE Summary and F/W Summary – a series of thumbnail images with ROI overlay, composite quantitative values, and per-slice values. This is useful for at-a-glance qualitative evaluation of the ROI and related quantitative results.
- Images - Full size images of the thumbnails in the Summaries, including ROI overlay. This can include MRE magnitude, stiffness, F/W water, PDFF, and R2* contrasts. No quantitative values are present. Useful for features that may not be obvious in thumbnails.
- Label – copy of the Hepatogram Plus device label.

	**Caution – Review all data**

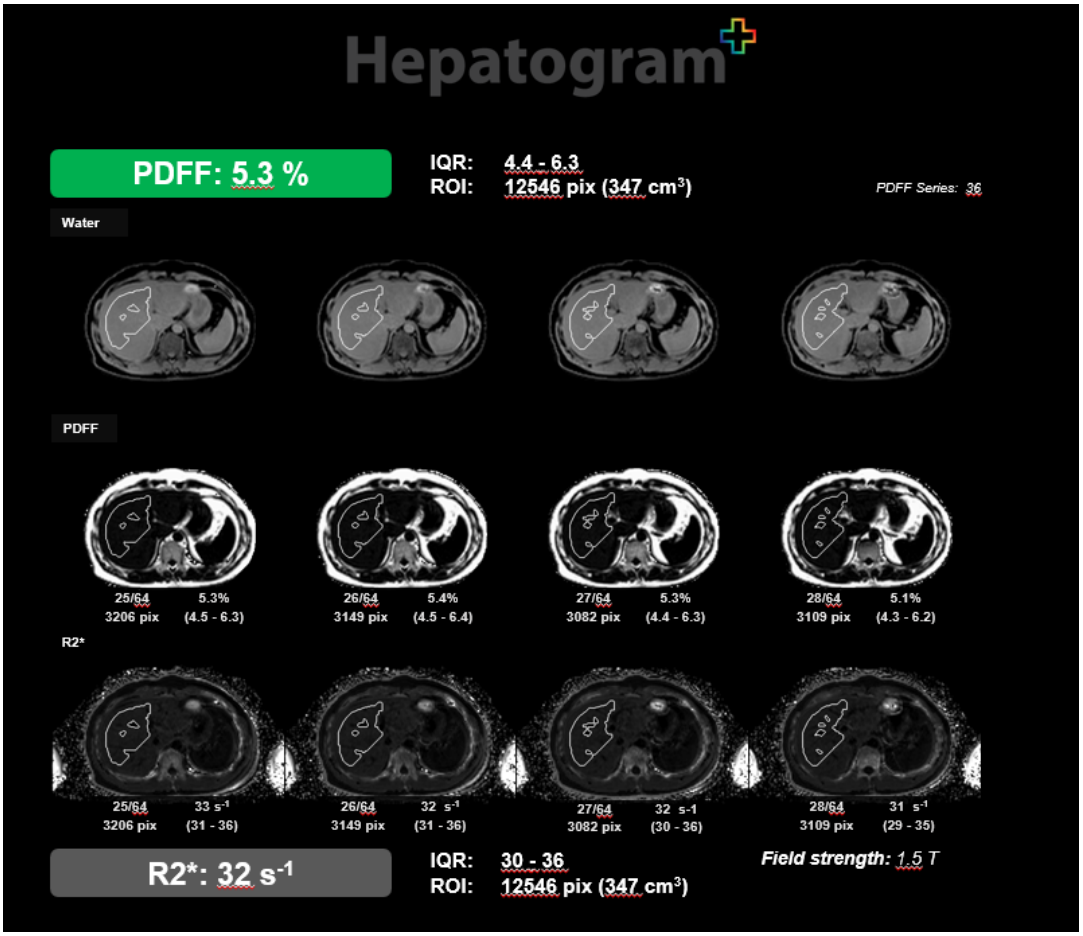
Example: Exam Summary



Example: MRE Summary

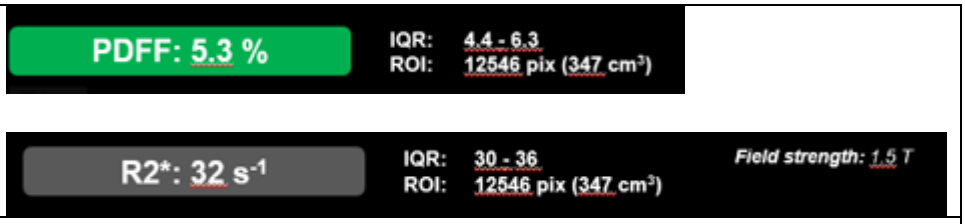
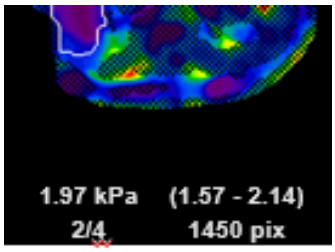


Example: F/W Summary



Annotations in summaries:

Source Series	Notes the image source for the summary  F/W will preferentially refer to the PDFF series number, with fallback to the first series in the F/W data. MRE will refer to the lowest series number of MRE magnitude or phase.
Composite values	Area weighted statistics of all data in all ROIs. These are listed in colored text boxes and adjacent tables: 

	
Per-slice values	Statistics applicable to ROI(s) in a single slice. These are located immediately below the associated slice. 
IQR	**Inter Quartile Range:** The values representing 25% - 75%
ROI	**Region of interest (size):** Reported as Pixels (pix) and cubic centimeters (cm^3)

3-3-7 ROI Size

A composite ROI area of 500 pixels is the minimum recommended size for MRE data, and 500 pixels for F/W data. If the composite ROI size is beneath this threshold, no composite result will be reported, but per-slice values will be reported.

3-3-8 Data quality

High data quality is required to produce meaningful results.

Indicators of poor MRE data quality include:

- Low signal-to-noise (SNR) or low magnitude signal (dark liver).
- Absence of waves - flat wave image that shows no wave propagation.
- Noisy wave images - patchy, aberrantly changing wave images.
- Motion artifact - ghosting in the magnitude image, patchy confidence map, unclear wave pattern
- Chemical shift artifact – presence of fat signal shifted relative to water, particularly in SE-EPI acquisitions. Also indicative for poor fat suppression.
- Low confidence - most of the Elastogram is masked out with the confidence mask
- checkerboard.

Indicators of poor F/W data quality include:

- Fat/water swap
- Motion artifact – excessive blurring or presence of ghosting

3-3-9 Measurements

Measurements that are made and reported for the calculated ROI include:

- Area
- Mean
- Range

The Mean and Range measurements apply to the contrasts on which the ROI is applied, such as stiffness, fat fraction, and R2*. Measurements are provided for individual slices and composite values.

3-3-10 Degree of Accuracy

Precision of measurements is +/- 1 of the least significant digit.

Accuracy of mean, range, and area measurements are equal to the specified precision. Hepatogram plus^{+} acts upon the quantitative values that were input and makes no claim to the accuracy of these inputs.

Section 4 - Troubleshooting and Support

4-1 Troubleshooting

Exam failed to process: Consult the error log for additional information. Exam may not be recognized due to insufficient detail in the DICOM header, the DICOM header may have been changed, or the data may have been transferred incompletely.

Exam processed successfully, but there are no ROIs or data: Hepatogram plus+ may not have found any areas that meet its selection criteria for automated ROIs. Review case manually to determine if viable data is present.

4-2 Support

4-2-1 User Manual

A current copy of this User Manual can be found under the Help icon of Hepatogram plus+ or online:

World Wide Web: http://www.resoundant.com

4-2-2 Contact Resoundant Technical Support

Questions regarding the installation and use of Hepatogram plus+ software may be obtained by utilizing any of the following sources:

World Wide Web: http://www.resoundant.com

Email: software-support@resoundant.com

When contacting Resoundant Technical Support, please have the following information ready:

- License Key (or product number – however it is defined in the software)
- Version of software being used
- Scanner model and software version
- Your Contact information (email, telephone)

4-2-3 Contact Manufacturer

For other questions, contact:

Resoundant, Inc.
421 First Avenue SW STE204W
Rochester, Minnesota 55902 USA
Phone: 507.322.0011
Email: mreinfo@resoundant.com

4-2-4 Authorized Representatives

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