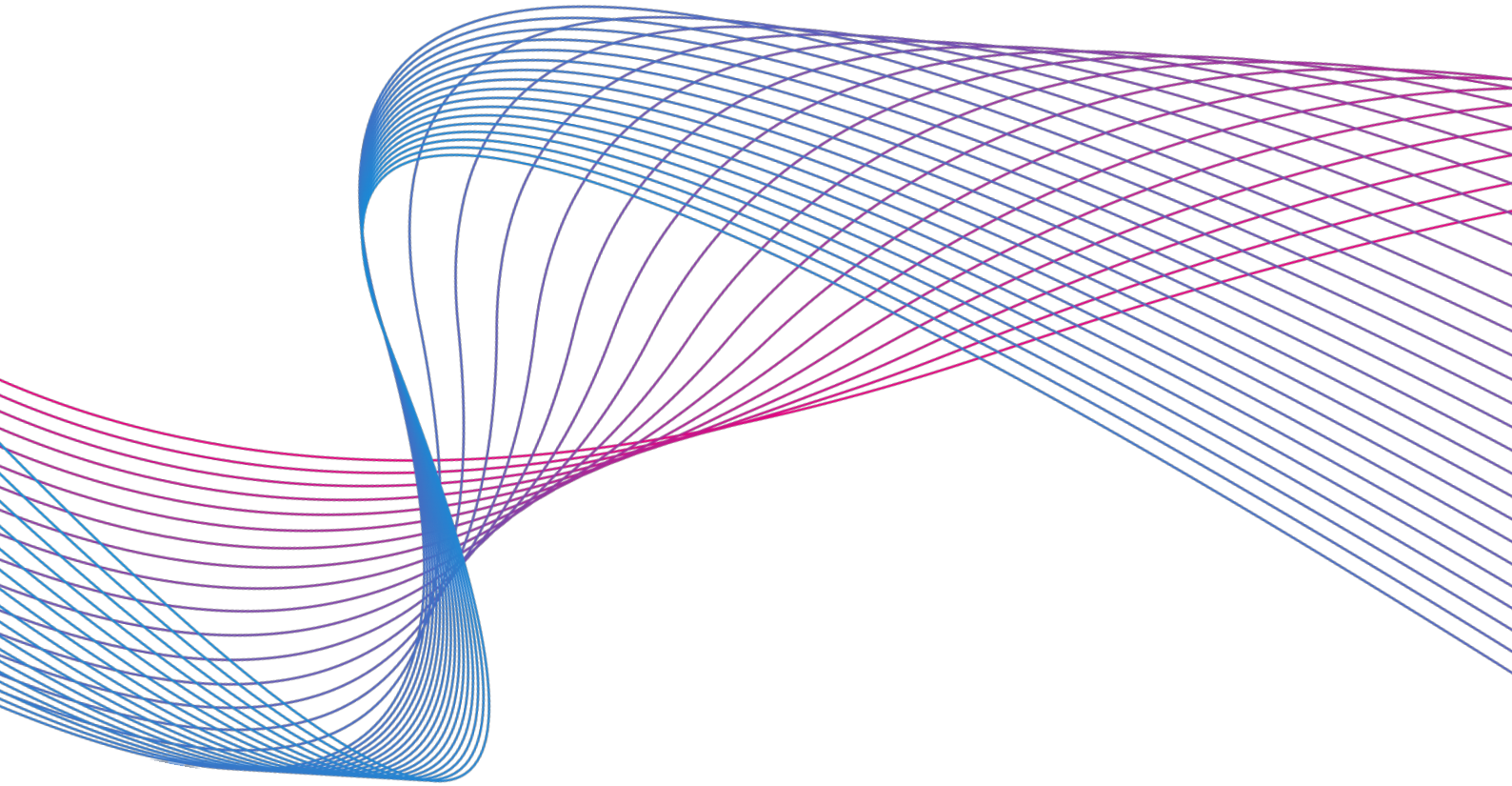
Perspectum



LiverMultiScan v5

Guide to Interpreting Liver Tissue Characterization for Physicians

TABLE OF CONTENTS

Disclaimer: The explanation of LiverMultiScan's metrics in this guide is intended exclusively for use by physicians.

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1. Symbols Key

Symbol	Meaning
	**Caution:** indicates a hazardous situation which, if not avoided, could result in minor or moderate injury or material damage.
	**EC Rep:** indicates the Authorized Representative in the European Community/ European Union
	**Date:** denotes date of manufacture of the device.
	**eIFU (electronic Instructions for Use):** denotes that the instructions for use for this device is made available electronically.
	**Manufacturer:** denotes the legal manufacture of the device.
	**Notice:** is used to provide information on how to avoid operating errors or information emphasizing important details.

2. Definitions and Abbreviations

Term	Description
cT1	Corrected T1
DICOM	Digital Imaging and Communications in Medicine
eIFU	Electronic instructions for use
FDA	U.S. Food and Drug Administration
GRE	Gradient echo
IDEAL	Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation
IQR	Interquartile range
LIC	Liver iron concentration
LMSv5	LiverMultiScan version 5

Term	Description
MAGO	MAGnitude-only
mg Fe/g	Milligrams of iron per gram of dry weight liver
MOLLI	Modified Look-Locker Inversion Recovery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
ms	Milliseconds
OEM	Original equipment manufacturer
PDFF	Proton density fat fraction
QAS	Qualitative analysis service
QC	Quality control
ROI	Region of interest
RR Interval	The time elapsing between two consecutive R waves in the electrocardiogram (ECG)
SNR	Signal to noise ratio
UDI	Unique device identifier
V1.2.3	Software Version including major, minor and patch information. In this example, the Major version is 1, Minor version is 2 and Patch version is 3.

3. Copyright

4. Use and Limitations

This document is intended to be used as a guide for licensed physicians interpreting LiverMultiScan version 5 reports. It is expressly not intended to be relied upon by the reader for instruction to practice medicine. Any physician reading this guide must use their own education, training, and expertise when dealing with individual patients. This material is not a substitute for that duty of care and is not intended by Perspectum Ltd. to be used for any purpose in that regard. The physicians bear the sole responsibility for the care of their patients.

LiverMultiScan does not make diagnostic recommendations. LiverMultiScan provides measurements derived from magnetic resonance (MR) data which can be used for tissue quantification which may be used as part of a wider diagnostic process. Physicians must take into consideration the modality, in this case MR, and LiverMultiScan's limitations when integrating the information from MR data, as presented by LiverMultiScan, into a wider diagnostic process.

4.1. Diagnostic and therapeutic restrictions

The following diagnostic and therapeutic restrictions apply. LiverMultiScan or reports produced by LiverMultiScan are not intended to be used in any of the following circumstances and any such use is expressly forbidden by Perspectum Ltd.

- The LiverMultiScan report should not be used as the sole basis for forming a diagnosis. To do so would constitute a misuse of the device.

Caution: All metrics reported by LiverMultiScan should be interpreted only by a licensed physician who can interpret MR examinations and the reported metrics, considering the totality of the information available on the patient, including the patient's medical history.

Caution: Measurements reported by LiverMultiScan should supplement and not replace a radiologist's image interpretation and associated reports.

- The LiverMultiScan report should not be used for interpreting anything outside the liver. To do so would constitute a misuse of the device.

Caution: The LiverMultiScan colormaps are designed for maximum contrast on corrected T1 (cT1) values of the liver parenchyma. The colormap is simply a range of all possible abdominal values mapped onto a color scale, and not representative of any disease state or suggestive of a diagnostic decision. The LiverMultiScan

colormap serves purely as a visual aid, which should in no way be considered indicative of a diagnostic decision. The physician must consider this when interpreting a cT1 image and, in particular, be aware of the non-meaning of the colors generated.

- The LiverMultiScan report should not be used as a control mechanism for biopsy guidance. To do so would constitute a misuse of the device.
- The LiverMultiScan report should not be used as the basis for surgical planning, the preparation, execution or post-operative assessment of surgical practices. To do so would constitute a misuse of the device.
- The LiverMultiScan report should not be used as the sole basis for deciding on a control mechanism for the delivery of treatment. To do so would constitute a misuse of the device.

Caution: LiverMultiScan processes MRI data to produce quantitative metrics of disease activity, iron, and fat. Individual datasets may not be assessed by a radiologist, and this report is not intended for the morphological, anatomical, structural, or radiological assessment of images. LiverMultiScan is not intended to be used for the assessment of incidental findings in patients.

- The LiverMultiScan report should not be used as the sole basis for evaluating the success or therapeutic response to treatment. To do so would constitute a misuse of the device.

Caution: Routine magnetic resonance imaging (MRI) safety screening must be carried out to ensure patients do not have a contraindication for MRI scanning.

4.2. Residual risks and safety

After a thorough analysis of all mitigated risks and residual risks pertaining to LiverMultiScan v5, it has been determined that the benefits significantly outweigh the potential risks. Any safety cautions pertaining to the use of LiverMultiScan v5 and interpretation of its metrics are provided throughout this guide.

4.3. Intended use

LiverMultiScan v5 (LMSv5) is intended for use as a magnetic resonance diagnostic device software application for non-invasive liver evaluation that enables the generation, display and review of 2D magnetic resonance medical image data and pixel maps for quantification of MR relaxation times.

LMSv5 is designed to utilise DICOM 3.0 compliant magnetic resonance image datasets, acquired from compatible MR Systems, to display the internal structure of the abdomen including the liver and quantify liver health metrics. Other physical parameters derived from the images may also be produced.

LMSv5 provides several tools, including automated liver segmentation and region of interest (ROI) placements, to be used for the assessment of selected regions of an MR image. Quantitative assessment of selected regions includes the determination of triglyceride fat fraction in the liver

(PDFF), T2*, LIC (Liver Iron Concentration) and iron corrected T1 (cT1) measurements.

The LMSv5 report output, including images and the quantitative metrics derived from the images, when interpreted by a trained physician, yield information that may assist in diagnosis.

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

5. The LiverMultiScan Device

LiverMultiScan v5 provides three quantitative metrics of liver health in one short scan, namely cT1, PDFF and LIC, which correlate with histological measures of fibro-inflammatory disease activity, liver fat fraction, and liver iron content, respectively. Unlike conventional MRI, LiverMultiScan v5 is a multiparametric MRI software application that uses a series of images to calculate quantitative parametric maps.

5.1. The LiverMultiScan report

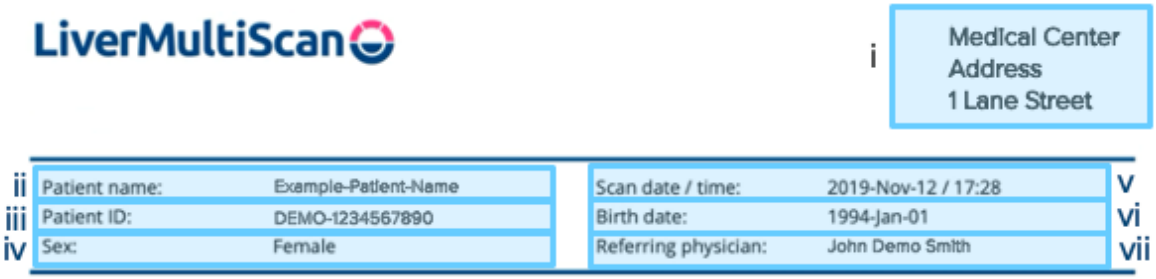
LiverMultiScan v5 results are delivered to the physician as a quantitative report similar to a report from a blood test. It provides summary metrics for cT1, PDFF, and LIC, as well as images of the generated parametric maps. The LiverMultiScan v5 report typically consists of four pages (for a single-slice analysis) and can be longer for a multi-slice analysis.

5.1.1. Header

The report header is consistent across all the pages of the report. It provides the following information:

i. Scanning center address
ii. Patient name
iii. Patient ID
iv. Patient sex
v. MRI scan date and time
vi. Patient birth date
vii. Referring physician name

An example is shown below.



Date and time of scan acquisition, patient identifiers, and referring physician's details which are noneditable. This data is automatically generated from DICOM (if available). If not available, these are populated with "Not recorded".

5.1.2. Footer

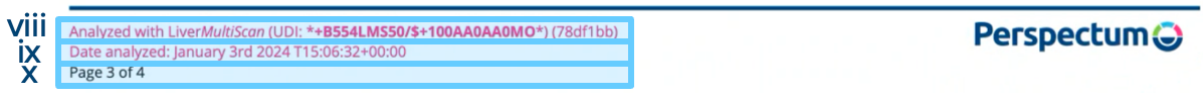
The report footer is also consistent across all the pages of the report. It provides the following information:

viii. Medical device UDI for LiverMultiScan.

ix. Date analyzed by LiverMultiScan.

x. Page number.

An example is shown below. This example does not have supplementary materials so is 4 pages long.



5.1.3. Page 1 – Results Page

The first page of the report is the results page, this reports the quantitative metrics and a visual scale of the values, together with the parametric maps and scan acquisition details.

The features on the page are, when available:

xi. Liver cT1 values, measured in milliseconds (ms), including whole-liver median and inter-quartile range (IQR) for obtained cT1 parametric maps. This is also provided with a plot with the upper limit of normal value for cT1 (values above this indicate the likely presence of disease activity) provided to aid interpretation of reported values.

xii. Patient's cT1 parametric map image, produced and used in the analysis.

xiii. Liver PDFF values, expressed as a percentage (%), including whole-liver median and IQR for obtained PDFF parametric maps. This is also provided with a plot with the upper limit of normal value for PDFF (values above this indicate the likely presence of steatosis) provided to aid interpretation of the reported values.

xiv. Patient's PDFF parametric map image, produced and used in the analysis.

xv. LIC values, expressed as mg Fe/g dry tissue, including whole-liver median and IQR for obtained LIC parametric maps. This is also provided with a plot with the upper limit of normal for LIC (values above this indicate elevated iron content) provided to aid interpretation of reported values.

xvi. Patient's LIC parametric map image, produced and used in the analysis.

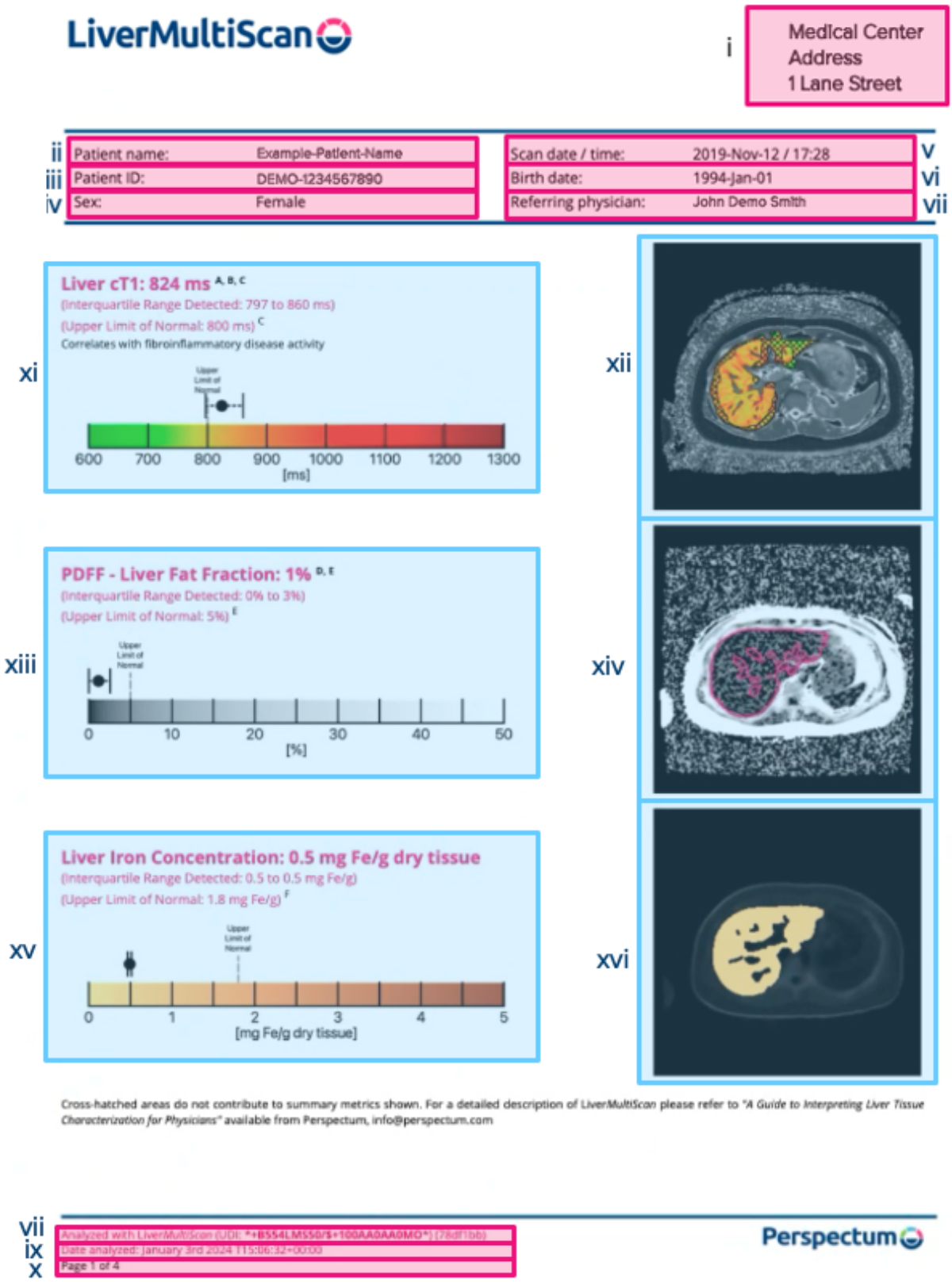
Notice: The responsibility for entering correct patient identifiers lies with the MRI acquisition center.

Notice: In some cases, there may not be a single 'representative' value. Heterogeneous patterns of liver fat fraction and cT1 can occur in patients with liver disease. If parametric maps appear heterogeneous and acquisition problems have been ruled out, it can be concluded that local elevations in parameters may reflect regional heterogeneity of signal changes.

Caution: Variations in reference values can be observed between some populations or demographics.

Caution: The physician remains responsible for the proper clinical evaluation of the patient and/or consideration of medical history. The reference values provided in the report should not be used solely to make a diagnostic decision. Liver function tests, blood tests, ultrasound scanning, or liver biopsy should be used at the discretion of a qualified physician, in addition to information obtained from the use of the LiverMultiScan report to reach a diagnostic decision.

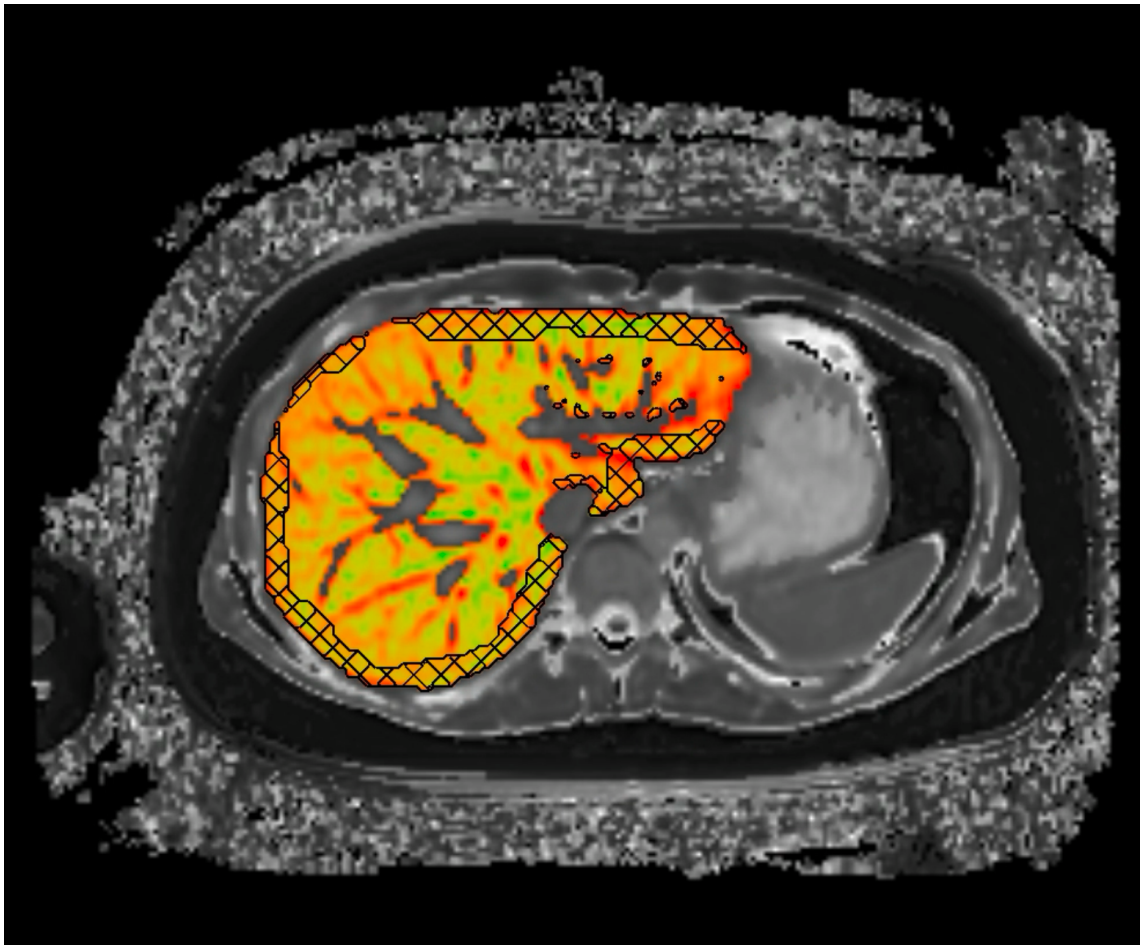
Caution: The physician remains responsible for the complete clinical evaluation of the patient. The reference values provided in the LiverMultiScan report should not be used in isolation to make a diagnostic decision. Metrics within reference values do not rule out disease. Measurements of tissue characteristics outside the reference range may not always reflect disease and should be considered only as part of the full clinical assessment of the patient.



5.1.4. Parametric maps

LiverMultiScan v5 uses segmentation to define the outer contour of the liver, excluding any vasculature of the parametric maps. The segmented liver is presented in color, while the rest of the image is presented in greyscale, as per the image below.

When analyzing using segmentation, all voxels within the contour of the segmentation count towards the outputted metric, excluding any regions with detected artifacts (indicated with cross-hatching in the parametric map).



5.1.5. cT1 metric

The cT1 metric relates to the amount of extracellular fluid present in the liver parenchyma and is derived from T1 and T2* maps. T1 is a measure of the longitudinal (spin-lattice) relaxation time of a given tissue, measured in ms. The T1 value of a tissue depends on its free water content, which relates to the proportion of extracellular fluid in the tissue.

Protein-dense tissues with a low free water content (e.g., tendon, healthy liver) have short T1 values, while tissues with high free water content (e.g., spleen, kidney) have longer T1 values. Inflammation and/or scarring (fibrosis) change the structural organization of a tissue, and lead to longer T1 values.

The application of T1 as a biomarker for inflammation and fibrosis in the liver is impeded by elevated liver iron levels in patients with chronic liver disease[1]. In a conventional T1 map, the local magnetic

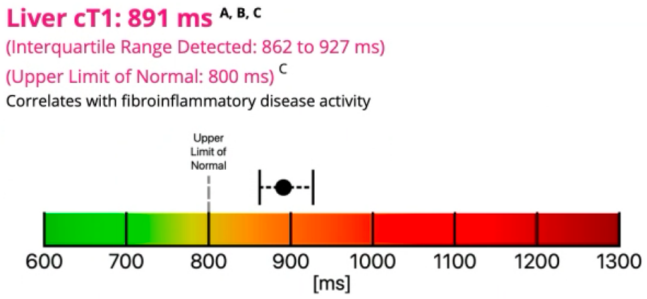
1. Hoad, C., et al. (2015). A study of T1 relaxation time as a measure of liver fibrosis and the influence of confounding histological factors. NMR Biomed, 28(6), 706–714. https://doi.org/10.1002/nbm.3299.

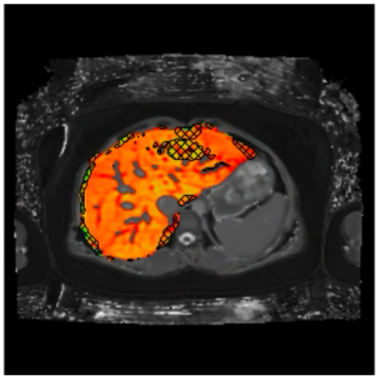
effects exerted by the iron shorten the T1 measurement, leading to the potential underestimation of disease.

LiverMultiScan v5 uses the T2* map to correct signal changes related to iron deposits, producing a T1 map that is corrected, or cT1. This corrected T1 map compensates for the effects of elevated iron on T1 measurements.[2] cT1 is also corrected for variations in MRI scanner field strengths so that 1.5T and 3T scanners give similar values in subjects with healthy livers (i.e., normal liver fat fraction and cT1 values). Additionally, cT1 is standardized for scanners from different MRI vendors.

LiverMultiScan's cT1 strongly depends on the T1 of free water, which in turn can be affected by inflammation and fibrosis in the liver. The presence of liver fat also increases cT1, due to the fast-imaging methods that are needed to capture the liver in a short breath-hold.

The LiverMultiScan report presents cT1 as the median and IQR of all the pixels within the contour of the parametric map(s) generated by automatic liver segmentation. LiverMultiScan can report cT1 values between 600 ms to 1300 ms as per the image below.





5.1.6. cT1 reference values

A cT1 value of 800 ms has been calculated as the upper limit of normal; cT1 values above this value indicate the likely presence of disease activity. This was derived from a cohort of 2874 asymptomatic individuals from the UK Biobank and performance testing studies (age [mean ± SD] = 52 ± 6 years; gender = 34 % male; race = 100 % White population; BMI = 23 ± 2 kg/m^2; nondiabetic; nonhypertensive) analyzed with LiverMultiScan, from the 95 % confidence interval (1.96 SD [SD = 51 ms]) of the mean (695 ms), adjusted for the coefficient of variance (CoV [2.8 %]) and rounded[3]. Furthermore, a cT1 of 800 ms represents the intersect in the distribution of cT1 data between those with NAFLD (n = 543) and healthy individuals (n = 100)[4].

Caution: cT1 increases with increasing amounts of fat on all the different models of scanners supported by LiverMultiScan. cT1 is not reported when fat levels exceed 35 % as in that range cT1 behaves in a way that is difficult to interpret.

2. Banerjee, R., et al. (2014). Multi-parametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatology, 60(1), 69–77. https://doi.org/10.1016/j.jhep.2013.09.002.
3. Mojtahed, A., et al. (2019). Reference range of liver corrected T1 values in a population at low risk for fatty liver disease—a UK Biobank sub-study, with an appendix of interesting cases. Abdom Radiol, 44:72–84. https://doi.org/10.1007/s00261-018-1701-2.
4. Andersson, A., et al. (2021). Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis. Clin Gastroenterol Hepatol, 20(11), 2451–2461.e3. https://doi.org/10.1016/j.cgh.2021.09.041.

Caution: As cT1 is a measure of liver disease activity this biomarker might be below the upper limit of normal value in patients with cryptogenic and/or burnt-out cirrhosis where histopathological features of inflammation, ballooning, or steatosis may no longer be present, depicting the absence of inflammatory disease activity.

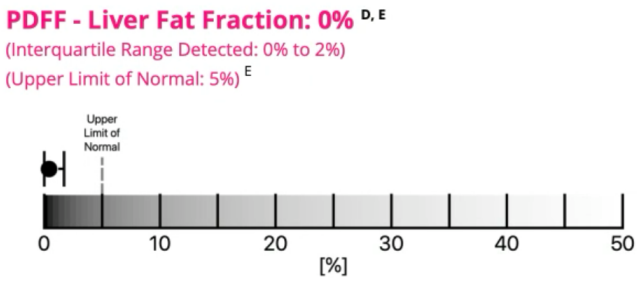
Caution: Measurements of T1 by LiverMultiScan demonstrate a proportional bias relative to the ground truth (inversion recovery spin echo relaxometry determined T1). This should be considered when reviewing results produced by LiverMultiScan.

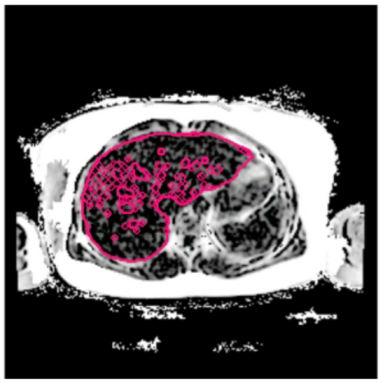
Caution: Variations in reference values can be observed between some populations/demographics.

5.1.7. PDFF metric

PDFF is an estimate of the fat fraction (fat / [fat + free water]) within the liver tissue, expressed as a percentage (%). It is defined as the proportion of the mobile protons in the liver attributable to fat. PDFF is quantified using Perspectum's post-processing MAGnitude-Only (MAGO)[5] methodology.

The PDFF metric is displayed as the median and IQR of all the pixels within the contour of the parametric maps generated by automatic liver segmentation. LiverMultiScan can report PDFF values between 0 % to 100 % as per the image below.





5.1.8. PDFF reference values

A PDFF value of ≥ 5 % is a clinically accepted threshold indicating liver fat levels are above normal. This threshold has been confirmed in a large meta-analysis, including 667 patients from six studies evaluating the diagnostic accuracy of MRI for hepatic steatosis detection against histology as the gold standard in NAFLD[5]. Szczepaniak et al.[6] reported a magnetic resonance spectroscopy (MRS)-PDFF of 5.6 % as the "upper limit of the reference range" in 345 subjects with no identifiable risk factors for hepatic steatosis (nonobese, nondiabetic subjects with minimal alcohol consumption, normal liver function tests, and no known liver disease). MRS-PDFF and MRI-PDFF are substantially

5 Gu, Q., et al. (2020). A meta-analysis on the diagnostic performance of magnetic resonance imaging and transient elastography in nonalcoholic fatty liver disease. Eur J Clin Invest, 51(2), e13446. https://doi.org/10.1111/eci.13446.
6 Szczepaniak, L. S., et al. (2004). Magnetic Resonance Spectroscopy to Measure Hepatic Triglyceride Content: Prevalence of Hepatic Steatosis in The General Population. Am J Physiol Endocrinol Metab, 288(2), E462–E468. https://doi.org/10.1152/ajpendo.00064.2004.

equivalent, with a slight bias towards lower MRI-PDFF.[7]

Caution: PDFF imaging methods can be susceptible to fat and water components being erroneously swapped, which may lead to incorrect liver tissue fat percentage being reported. LiverMultiScan uses the MAGO method for PDFF quantification, which is robust against fat/water swaps, but in some cases, this may still occur.

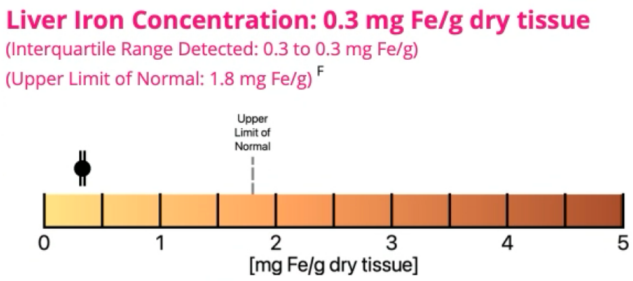
Caution: Variations in reference ranges can be observed between some populations/demographics.

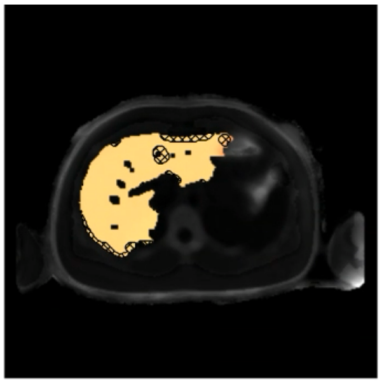
5.1.9. LIC metric

LIC, expressed in mg Fe/g dry tissue weight of the liver, provides the concentration of iron in hepatic tissues. LIC is derived from T2*, which is a measure of the transverse (spin-spin) relaxation of a given tissue in the presence of magnetic field inhomogeneities.

The T2* of a tissue is affected by local magnetic susceptibility effects, including those caused by iron deposits, typically ferritin and hemosiderin. Hepatic tissues with high iron content have short T2* values, and tissues with low iron content have long T2* values. While T2* is field strength dependent, LIC is not affected by field strength.

The LIC metric is displayed as the median and IQR of all the pixels within the contour of the parametric maps generated by automatic liver segmentation. LiverMultiScan can report LIC values between 0 mg Fe / g dry tissue to 5 mg Fe / g dry tissue as per the image below.





5.1.10. LIC reference values

A LIC value of 1.8 mg Fe/g dry tissue weight of the liver has been calculated as the upper limit of normal; LIC values above this indicate the likely presence of high liver iron content. This reference value was derived from a cohort of 129 individuals, of which 51 had alcoholic liver disease, 40 were healthy controls, and 38 were first-degree relatives of previously diagnosed patients with hemochromatosis. The diagnosis of hemochromatosis was based on the histological demonstration of parenchymal cell iron overload from biopsy in the absence of other known causes of iron

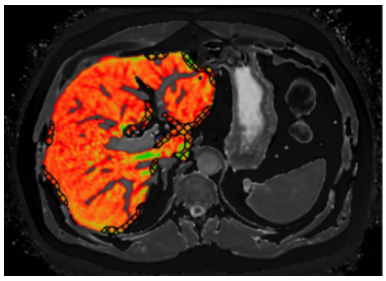
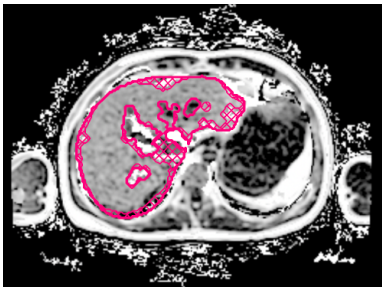
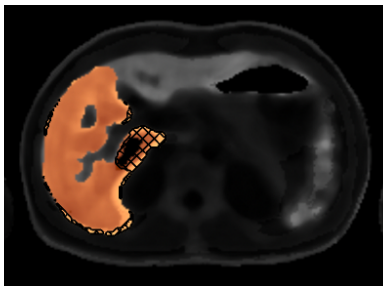
7 Yokoo, T., et al. (2017). Linearity, Bias, and Precision of Hepatic Proton Density Fat Fraction Measurements by Using MR Imaging: A Meta-Analysis. Radiology, 286(2), 486–498. https://doi.org/10.1148/radiol.2017170550.

overload.[8]

Caution: Variation in reference ranges can be observed between some populations / demographics.

5.1.11. Artifact detection

LiverMultiScan v5 automatically detects and highlights any artifacts that may appear on the parametric maps. Any detected artifacts will appear as cross-hatched areas on the parametric map, see images below. Cross-hatched areas will be in black on cT1 and LIC maps and pink on the PDFF map.

LiverMultiScan automatically detects and alerts the analyst to the following map artifacts:

- Within-slice heterogeneity.
- Fat-water swaps are characterized by high PDFF values where fat is not expected to be the dominant component.
- Low dynamic range – images should have as large a dynamic range as possible.

Furthermore, LiverMultiScan automatically selects the best slice for analysis, considering the following:

- Segmentation quality
- Inter-slice variability
- Mis-triggering
- Shim box location – ensuring that slices fall within the shimmed volume.
- The presence of distortion correction on the image.

All automation is reviewed by a human operator, who may amend the analysis. When calculating the metrics for the map, the cross-hatched areas do not count towards the outputted metrics.

8 Bassett, M. L., et al. (1986). Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. *Hepatology*, *6*, 24–29. https://doi.org/10.1002/hep.1840060106.

5.1.12. ROI and Segmentation

Quantification of images using segmentation is achieved by computing a median value from all the voxels within the outer contours of the segmented liver. Areas of artifacts or cross-hatched images within the segmented contour are not included in the calculation. In contrast, an ROI analysis computes a median value from all the voxels within the placed ROIs; typically, three ROIs are placed per map.

Notice: If ROIs are used to analyze a metric, then the median from a segmented region will not be displayed for that metric.

Notice: It is not possible to directly compare the metrics generated by the ROI method and the segmentation method for either the cT1, LIC or the PDFF maps. When using the ROI method, only the voxels within the placed ROI are quantified to give the median and IQR metrics displayed on the summary page and the per-slice pages following in the report. When the whole-liver segmentation method is used, a contour of the liver slice is drawn and all voxels within this contoured boundary are quantified to give the 'Whole liver' median and IQR metrics, as well as a histogram of the distribution of voxels within the contour.

5.1.13. Partial Reports

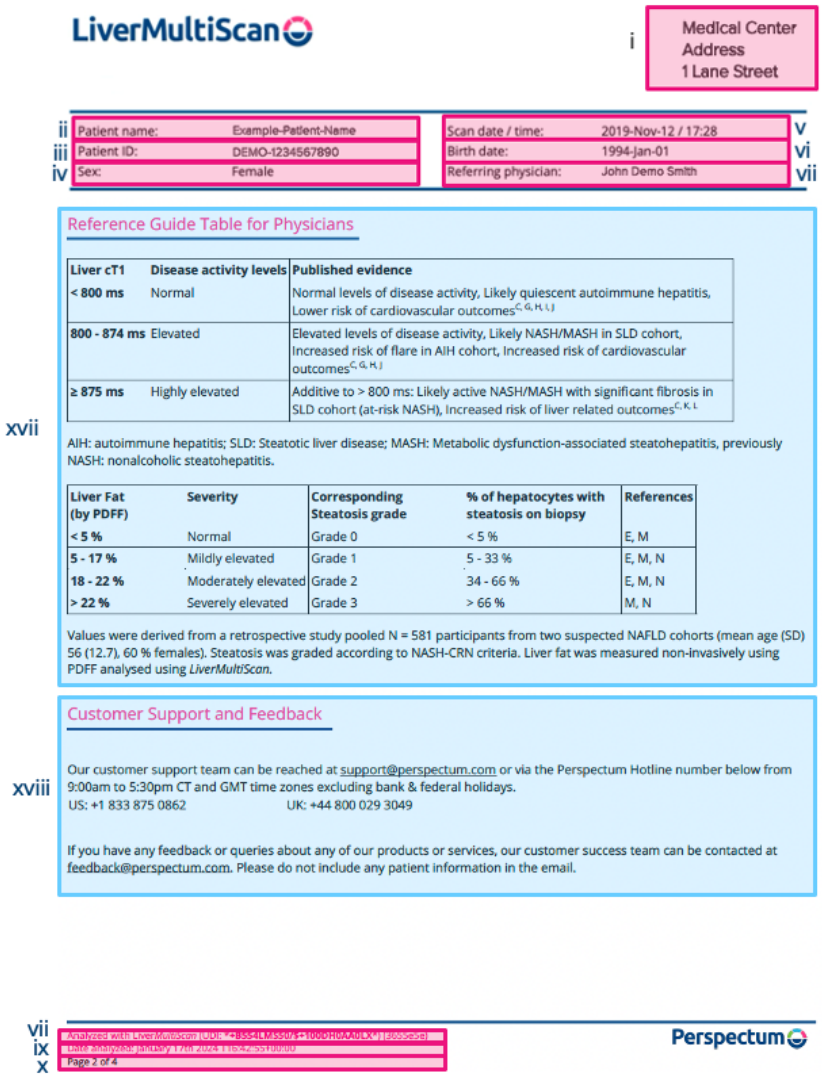
In a small percentage of cases (~2 %), it may be possible to return a partial LiverMultiScan report containing only one or two of the available metrics (e.g., PDFF or LIC only). This may occur due to a severely high liver fat fraction (PDFF > 35 %) or elevated liver iron in the patient, low-quality acquisition data, patient movement, and other artifacts. These factors may hinder the delivery of a report in less than 2 % of analyzed cases.

5.1.14. Page 2 – Guidance and support page

The second page of the report is the guidance and support page, this provides a guidance information for interpreting the report and information on how to reach out for support if required. It provides the following information:

xvii. Reference guide table for physicians section

xviii. Customer support and feedback section



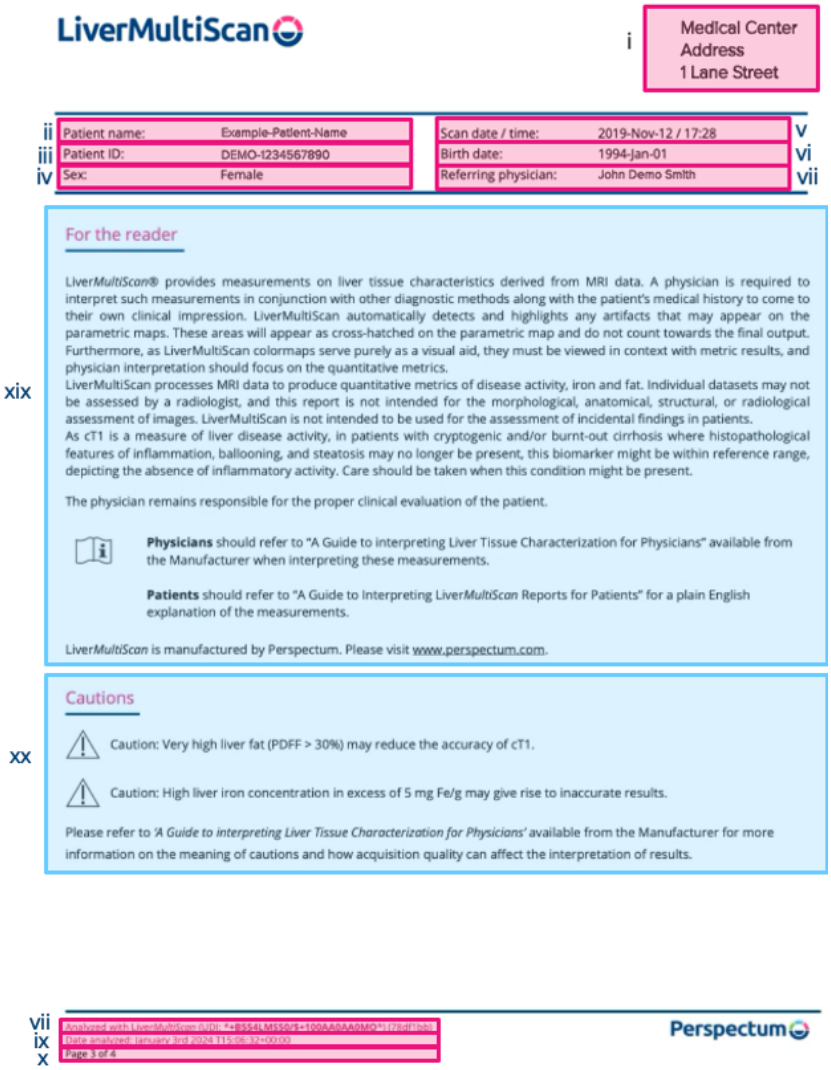
5.1.15. Page 3 – Information and Cautions Page

The third page of the report is the information and cautions page, this provides information on the device and cautions from the device that were identified during analysis. It provides the following information:

xix. For the reader section

xx. Cautions section

If the software does not detect any cautions, this section will be blank. Otherwise, it will provide cautions related to the analysis completed such as atypical RR intervals (the time elapsed between two successive R waves of the QRS signal on the electrocardiogram or heartbeats) or poor shimming.

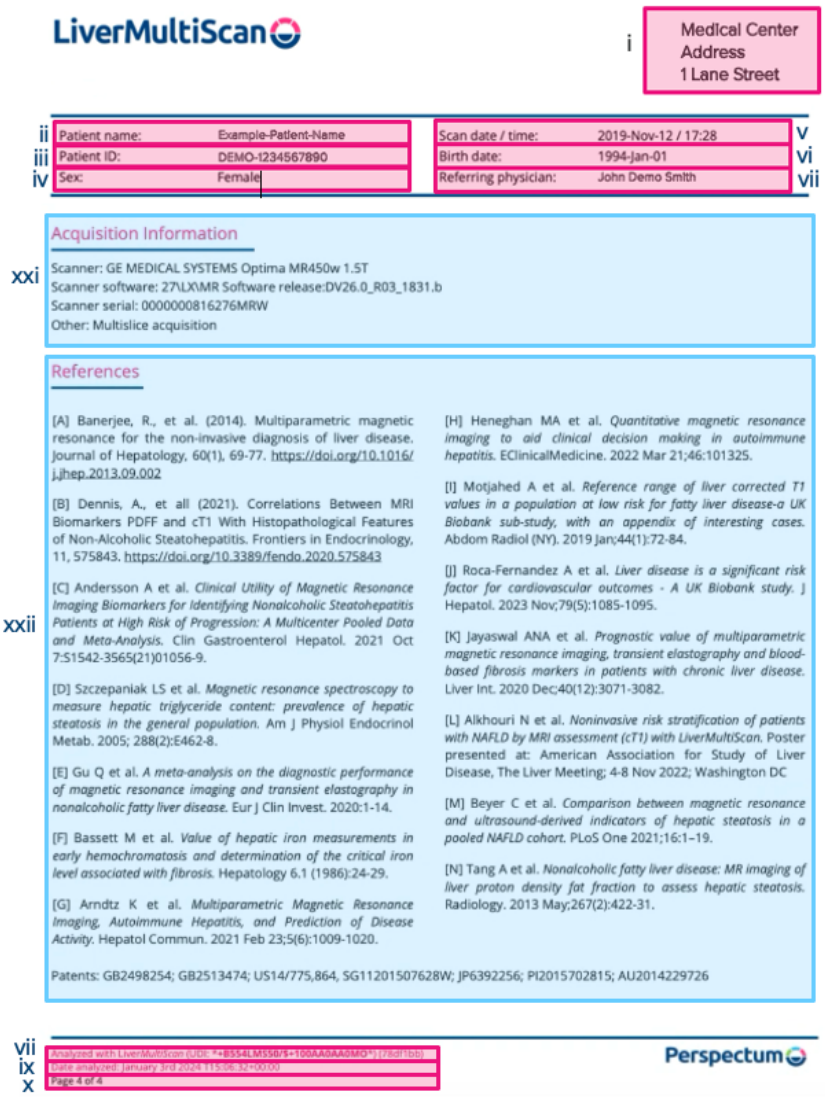


5.1.16. Page 4 – Acquisition and references page

The fourth page of the report is the acquisition and reference page, this provides the acquisition information for the MRI data analyzed and the references used in the report, including the literature references for reference/upper limit of normal values. It provides the following information:

xxi. Acquisition information section

xxii. References section



5.2. Reported metric variation

It is important to understand the performance limitations of LiverMultiScan. This section provides a summary of its performance characteristics.

5.2.1. Accuracy

Accuracy shown in Table 1 was tested by calculating the difference between the ground truth values in phantoms and their corresponding LiverMultiScan metrics (cT1, PDFF, and T2*).

The phantom ground truth measurements used by LiverMultiScan were:

- T1: Using a series of inversion recovery turbo spin echo acquisitions with long repetition time and fitting the T1 from MR images.
- PDFF: Destructive testing and measurement in a rapid fat analysis nuclear magnetic resonance machine.
- T2*: Measured using even echoes of an 8-echo GRE protocol and then fitting the T2* from MR images.

Table 1. Performance testing for accuracy. Results are reported in the percentage space for cT1 and the native space for T2* and PDFF.

Accuracy of LiverMultiScan v5 derived from bench testing		
Metric	Limits of agreement (bias)	
	1.5T	3T
cT1	-16 % to -6.1 % (-11.0 %) Lower than ground truth	-15 % to -8.66 % (-12 %) Lower than ground truth
T2*	-0.59 ms to -0.27 ms (-0.43 ms)	-0.78 ms to 0.30 ms (-0.24 ms)
PDFF	-2.6 % to 4.2 % (0.79 %)	-2.1 % to 4.2 % (1.1 %)

NB: Limits of agreement are calculated as bias (mean difference ± 1.96 * standard deviation of differences).

5.2.2. Metric variability

The performance of LiverMultiScan has been validated in a performance study to assess its 'worst case' variability in the tested population. These include the mean difference (reported as maximum absolute bias), widest Limits of Agreement (LoA; reported as the range of minimum observed lower and the maximum observed upper LoA across all comparisons), and maximum variability (reported as maximum standard deviation [SD]). These comparisons are representative of 'worst case' variability (i.e., different operators, different scanner original equipment manufacturer (OEM; e.g., GE, Siemens and Philips), and different field strengths).

Data was used from a retrospective cohort of thirty datasets (mean age 41.7 years; mean BMI 26.0 kg/m^2; 50 % females) including a subset with NAFLD (n = 8) and other liver diseases (AIH, PBC, PSC; n=3).

NB: The results below are all of the 'worst case' variability in the tested population, independently

found across tests — the LoA will not necessarily be related to the bias and standard deviation. These comparisons do not include inter-/intra-operator variability. Larger absolute biases might be observed in populations with high liver fat (PDFF > 20 %). The reported performance of LiverMultiScan v5 is derived from segmentation analysis. Analysis using ROIs may lead to greater variability in the reported metrics.

Table 2: Observed 'worst case' performance testing results using segmentation analysis. Results are reported in the percentage space for cT1 and the native space for LIC and PDFF.

Metric	Maximum absolute bias	Widest LoA	Maximum SD
cT1	-4.53 %	-11.38 % to 7.098 %	4.14 %
LIC	0.142 mg Fe/g dry weight	-0.352 to 0.346 mg Fe/g dry weight	0.126 mg Fe/g dry weight
PDFF	-1.175 %	-3.03 % to 2.73 %	1.467 %

5.2.3. Variability across scanners at high PDFF

The process by which cT1 is determined means that it is standardized between different MRI scanners, both field strengths (1.5 and 3T), and OEMs (presently GE, Siemens and Philips). That means that approximately the same values should be reported for the same patient across different scanners.

In addition to the influence of water T1 (representing the T1 of liver tissue without the influence of fat) and iron, the cT1 parameter also depends on the level of liver fat. This effect is due to the specific imaging acquisition technique which is used, which collects signals from both fat and water but does not differentiate between them. The sensitivity of cT1 to liver fat can differ depending on the specific image acquisition on a given MRI scanner. This is managed by adapting the image acquisition upon scanner set-up. However, some differences cannot be adjusted for, consequently cT1 values from different scanner models depend differently on the level of liver fat. These cross-scanner differences in cT1 are small for low levels of fat (PDFF < approx. 10 %), but become larger at higher levels of fat exemplified with simulated values in Figure 1.

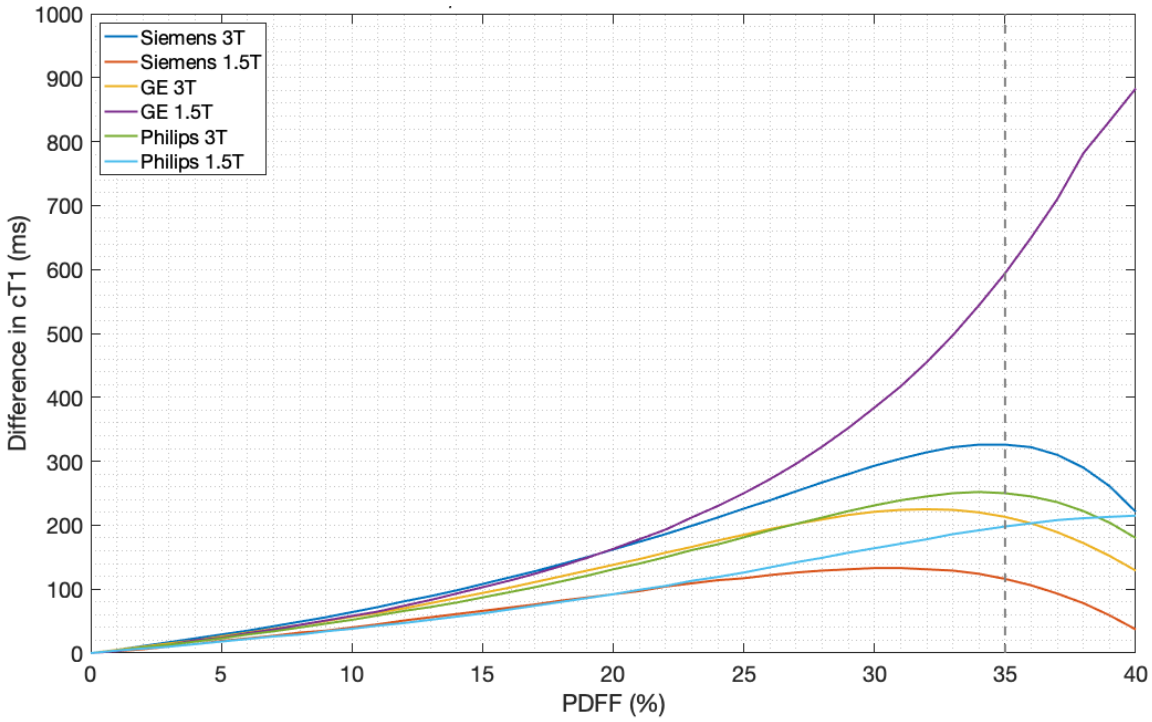


Figure 1. Simulated differences in cT1 values across scanner models with increasing liver fat. Differences in cT1 for each scanner is relative to cT1 value at PDFF = 0 %, assuming normal water T1 and normal liver iron concentration.

5.2.4. Inter-reader

The performance of LiverMultiScan v5 has been validated in a study using a cohort of 60 clinical cases across two field strengths (1.5T and 3T) and three OEMs (GE, Siemens and Philips). Participants included those with mixed liver disease etiology to represent a wide range of reportable metrics. The ground truth for the validation data set was based on independent analyzes by three blinded expert radiologists. Although experiment design, blinding, data access, and custody of data and analysis were chosen to minimize potential sources of bias, performance statistics may be affected by numerous sources of analysis bias that cannot be eliminated.

Table 3: Inter-reader performance.

Inter-Reader analysis derived from clinical testing					
Metric	IEC	ANOVA p-Value	ICC	Mean CV	Pooled performance testing LoA (bias)
cT1	6.8	0.89	0.99	0.18 to 0.48	-25 % to 31 % (-1.7 to 4.8)
LIC	9.2	0.83	0.99	0.089 to 0.49	-0.0056 mg Fe / g dry weight to 0.0061 mg Fe / g dry weight (-0.0003 mg Fe/g dry weight to 0.0008 mg Fe / g dry weight)
PDFF	1.9	0.72	0.99	1.7 to 3.2	-1.7 % to 1.2 % (-0.13 to 0.20)

NB: Pooled performance testing Limits of Agreement for inter-reader using segmentation-based analysis. Summary results are all reported as the minimum and maximum Limits of Agreement with bias in the percentage space for cT1 and the native space for LIC and PDFF. (IEC, individual equivalence coefficient; ICC, inter-class coefficient; CV, coefficient of variation).

5.2.5. LIC reporting

LiverMultiScan v5 was deemed substantially equivalent to FerriScan (K043271) at reporting a LIC value of up to 5 mg Fe / g dry tissue. If the calculated median iron is higher than 5 mg Fe/g dry weight, the LiverMultiScan report states, “Liver iron concentration: > 5 mg Fe/g dry tissue.”

Inhomogeneity of iron within the liver leads to variability in LIC values estimated by liver biopsy and results reported by LiverMultiScan v5. The reported LIC coefficient of variation is approximately 19 % by needle biopsy for non-diseased liver and may increase to more than 40 % for cirrhotic livers.[9,10] Unlike biopsy, LiverMultiScan provides images of cross-sections of the whole liver and the distribution of iron throughout the liver slices.

The average standard error of LIC by FerriScan on a single LIC measurement was approximately 15 %, and the average standard error for LIC reported by LiverMultiScan (over the supported range) was approximately 14 %. Thus, demonstrating the robustness of LiverMultiScan-derived LIC in comparison to liver biopsy.

9 Emond, M. J., et al. (1999). Quantitative study of the variability of hepatic iron concentrations. Clin Chem, 45(3):340-6. https://doi.org/10.1093/clinchem/45.3.340.
10 Kreeftenberg, H. G., et al. (1984). Measurement of iron in liver biopsies—a comparison of three analytical methods. Clin Chem Acta, 144(2-3):255-62. https://doi.org/10.1016/0009-8981(84)90061-5.

6. Perspectum's Quantitative Analysis Service

Patients are prescribed a quick, non-contrast MR abdominal scan at a Perspectum-cleared scanning center. The MR scan will capture an abdominal image, including the liver, which is quality-checked and analyzed using LiverMultiScan at Perspectum's dedicated image analysis center.

Quantitative results derived from the analysis are subsequently returned to a physician for interpretation in the form of a report via a secure interface. The physician uses the information in the report, along with other diagnostic tests or procedures, to make a diagnosis and decide the clinical management for the patient. Figure 2 illustrates the Quantitative Analysis Service (QAS) workflow incorporating the Perspectum Portal.

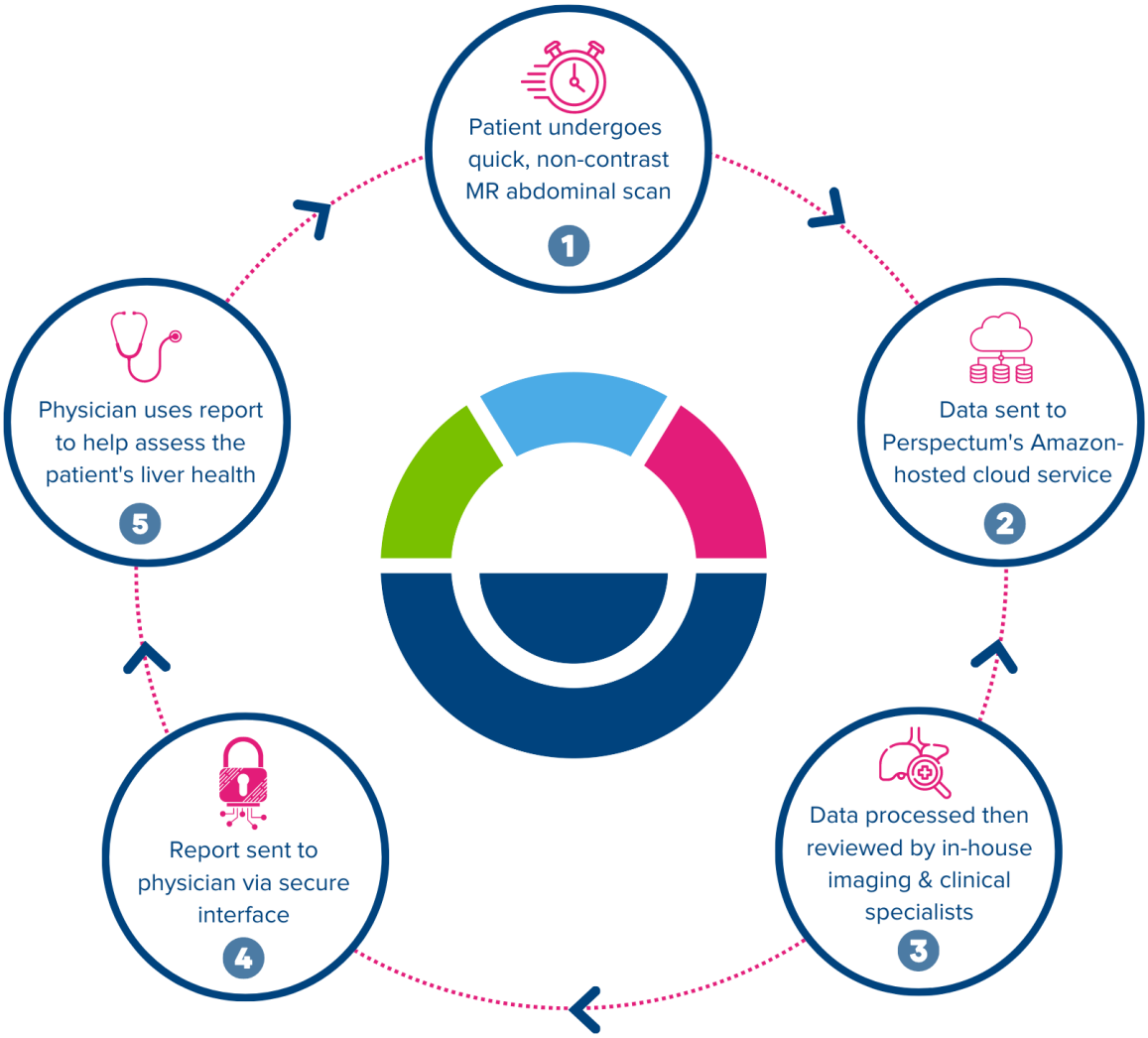


Figure 2. Perspectum's Quantitative Analysis Service (QAS) facilitated by the Perspectum Portal Secure Data Transfer.

The Perspectum Portal, Perspectum's data transfer system, transfers data from scanning sites to Perspectum's image analysis center. The data security infrastructure is supported by an ISO 27001 and ISO 13485 compliant quality management system designed around a defense-in-depth approach with multiple layers of redundancy, surveillance, physical access controls, and audit logs. Access to the portal is controlled and secured by SSL encryption mandating a HTTPS protocol for web-based

data transmissions to prevent eavesdropping, tampering, and forgery. All data are encrypted while in storage and routinely backed-up to an alternative secondary physical location to ensure service continuity.

The Perspectum Portal is hosted by Amazon Web Services (AWS), a market-leading cloud platform solutions provider that employs rigorous and sophisticated security processes to guard data privacy against malicious or accidental incidents.

6.1. Comprehensive data quality checks

The use of LiverMultiScan is contingent on data acquisition of sufficient quality. Therefore, once the datasets are received, these are checked for quality and acquisition errors that may affect analyzes.

As part of the QAS, image quality is assessed both automatically and manually. Typical acquisition problems are detailed in Annexure 1, together with exemplar report comments. Each check can result in one of three outcomes:

- Quality Control (QC) passed: Checks did not indicate any problems.
- Quantification could be affected: Checks indicated a potential problem, but the analysis will continue considering the findings.
- Fatal failure: The checks have raised issues, meaning the data cannot be processed.

Notice: The only check that results in a “fatal failure” is the protocol acquisition parameter check; all other failures will be reported as “quantification could be affected”.

Notice: If a check cannot be executed successfully for any reason (e.g., missing data), it is considered a “fatal failure”.

6.2. Help and assistance

If you have any questions regarding LiverMultiScan, the QAS or interpretation of the LiverMultiScan v5 report, our customer support team can be reached at support@perspectum.com or via the Perspectum hotline number below from 9:00 am to 5:50 pm CT and GMT time zones excluding bank & federal holidays.

US: +1 833 875 0862 UK: +44 800 029 3049

This information is repeated on page 2 of the LiverMultiScan v5 report.

7. LiverMultiScan Frequently Asked Questions

7.1. Before my patient has a LiverMultiScan, what preparation is needed?

Preparation for a LiverMultiScan includes the following:

- Patients should have no food or drink, for four hours before the MRI scan.
- Patients can take any medication or have had any treatment, considering the diagnostic and therapeutic restrictions, before the MRI scan.

It is not necessary to abstain from alcohol in the days prior to a scan.

7.2. Is LiverMultiScan done with a contrast agent?

No. LiverMultiScan images must always be acquired before administering a contrast agent. If a contrast agent has been administered prior to undergoing a LiverMultiScan, no quantification can be made.

7.3. Is LiverMultiScan covered in any clinical guidelines?

Yes. As of 03/13/2022, Carelon (former AIM Specialty Health) Clinical Guidelines deem LiverMultiScan medically appropriate for managing chronic liver disease.

Additionally, LiverMultiScan is recognized in clinical guidelines by American Association for the Study of Liver Diseases (AASLD) American Association of Clinical Endocrinology (AACE) and American Gastroenterological Association (AGA), for assessment in NAFLD.

7.4. How can a physician use LiverMultiScan to aid the diagnosis of liver disease?

LiverMultiScan provides measurements derived from MR data which can be used for tissue quantification and may be used as part of a wider diagnostic process. When interpreted by a trained physician, these images and the physical parameters derived from the images yield information that may assist in the diagnosis of liver disease.

Inflammation and fibrosis are increasingly believed to be part of a continuum of disease progression. Injury to the liver parenchyma, such as deposition of liver fat resulting from a poor diet, hereditary or acquired iron overload, or viral infection, can all lead to an inflammatory response. If the injury persists, collagen, the major component of scar tissue, is deposited in the liver. In advanced stages of fibrosis, the collagen fibers cross-link (known as bridging fibrosis), eventually resulting in the nodular phenotype that is the hallmark of cirrhosis.

7.5. Can a physician use the analysis metrics in isolation to form a diagnosis?

No. LiverMultiScan is an aid to diagnosis and the diagnosis and clinical decision-making remains the sole responsibility of the physician. The metrics on liver tissue characterization provided by LiverMultiScan are exclusively intended for interpretation by a trained physician as additional inputs forming part of a wider diagnostic process.

Caution: The physician remains responsible for the proper clinical evaluation of the patient and consideration of medical history. Liver function tests, blood tests, ultrasound scanning, as well as liver biopsy are all expected to be used, at the discretion of a qualified physician, in addition to information obtained from the use of the LiverMultiScan report, to reach a diagnostic decision.

7.6. What are the cybersecurity recommendations for viewing reports produced by LiverMultiScan?

- Keep your operating system and applications up to date.
- Protect your device with a strong and unique password.
- Use a secure network connection.
- Report suspected incidents to your administrator immediately.
- Protect your device with an up to date, reliable antivirus package.

8. Reporting an incident

8.1. Device incident

If you have reason to suspect an incident has occurred where there has been a deterioration in the characteristics or performance of the device or if the information supplied with the device by Perspectum is inadequate, please immediately email us at safety@perspectum.com and the competent authority in your country.

8.2. Cybersecurity incident

If you believe a cybersecurity incident has occurred, please contact Perspectum's Information Security Team by immediately sending us an email at and report the suspected incident at incidents@perspectum.com.

9. Cybersecurity

Ensuring cybersecurity is vital in the development and use of medical devices. This ensures not only compliance with regulatory standards and privacy laws, but also safeguards patient health and information. Precautions must be taken to create secure usage scenarios and environments, with adequate security measures in place.

The recommendations provided below are not a comprehensive list but rather a sampling of issues that may help in alleviate cybersecurity concerns:

- Keep your operating system and applications up to date with latest patches.
- Protect your device with a strong and unique passwords.
- Use a secure network connection with firewalls. Usage of virtual private networks, should also be appropriate.
- Protect your device with an up-to-date, reliable antivirus software which runs routine scans.
- Be wary of suspicious emails that may include malicious links to gather personal data.
- Report suspected incidents immediately.

The above recommendations should be taken into considerations on all computer systems dealing with LiverMultiScan data. These help protect your systems from potential threats such as but not limited to:

- Virus: Harmful software that replicates itself and spreads itself to other devices.
- Adware and spyware: Embedded in free software, such as weather trackers and screensavers; this type of malware generates ads and tracks user behavior.
- Ransomware: When downloaded, ransomware blocks access to files and programs until users pay a set fee.
- Phishing: Seemingly safe links take users to malicious sites that gather personal data and login credentials, and can be found within websites, emails or ads

Notice: The physician should follow cybersecurity best practices when viewing LiverMultiScan reports.

10. Manufacturer Information

LiverMultiScan v5 and subsequent version iterations are manufactured by Perspectum © 2024 Perspectum.

Website: https://www.perspectum.com/our-products/

Basic UDI-DI for LiverMultiScan: ++B554LMSST

Owner/Operator Number: 10056574

Establishment Registration Number: 3014232555

Premarket Notification Number: K213960

Address: Gemini One, 5520 John Smith Drive, Oxford, Oxfordshire, United Kingdom, OX4 2LL.

Date of manufacture: 2024-02.

Authorized Representative: Perspectum Unipessoal Lda, Avenida Antonio Augusto de Aguiar, no 19, 4th Floor right, Room B, 1050-012, Lisbon, Portugal authrep@perspectum.com.

Electronic Instructions for Use:

This Instructions for Use document is available electronically at https://www.perspectum.com/our-company/pdf-library.

The Perspectum website supports all browser types but an appropriate plug-in for viewing pdf documents must be installed. If this guidance is required in a paper format, please contact support@perspectum.com to request it.

11. ANNEXURE 1

Table 4. Potential acquisition issues

Issue	Cause	Impact on quantification	Mitigation
Protocol acquisition parameter check	MR images are acquired with sequence parameters that do not conform to the LiverMultiScan protocols.	Metrics are potentially biased, which invalidates the established reference ranges.	LiverMultiScan checks DICOM metadata against the expected values, and alerts the operator if deviations are detected.
Atypical R-R interval check	LiverMultiScan MOLLI data acquired on a subject who does not have a heart rate of approximately 60 bpm. This can cause the MOLLI inversion times to be sub-optimal.	cT1 metric is biased, or has a high degree of uncertainty.	A check on MOLLI inversion times is performed, and the operator is cautioned if the inversion times do not satisfy the established criteria.
Dynamic range	Data is saved with low dynamic range (i.e., the data is compressed into a small number of bits).	Low dynamic range can cause inaccuracies in metrics, and may render the metric unquantifiable.	LiverMultiScan cautions the operator if low dynamic range is detected.
Centre frequency check	Data is acquired with a center frequency that is different from that expected from water protons, often due to poor shim or large amounts of fat present.	Parametric maps and metrics are affected. In LiverMultiScan MOLLI data, this often manifests as a reduction in cT1. In LiverMultiScan IDEAL and MOST, fat-water swaps will be more likely.	LiverMultiScan cautions the operator if the spread of center frequencies is outside of the expected range.
Shim box location check (field homogeneity)	The patient acquisition manual stresses the importance of proper magnetic field optimization (shimming) prior to acquisition. Poor shimming can occur due to human error or mechanical issues. This can result in images being acquired in regions that have not been shimmed.	Where inhomogeneity is severe, it may not be possible to perform quantitation.	If a slice is reported that is found to lie outside the shimmed region, then a caution will appear in report listing all such images.
Patient motion	The patient acquisition manual stresses the	Regular motion is typified by band of high	LiverMultiScan acquisitions are

Issue	Cause	Impact on quantification	Mitigation
	importance of controlled breathing and breath holding to minimize the likelihood of motion affecting LiverMultiScan image acquisition.	and low intensity signal through the anterior/posterior direction. Motion typically results in poor parametric fitting and high variability. Where motion is severe, it may not be possible to perform quantitation.	designed to be robust against motion. Automatic processing considers fitting quality and regional variability.
Magnetic susceptibility artifacts	Different tissues and materials have different magnetic susceptibilities, which produce signal inhomogeneity, particularly at air-tissue interfaces (e.g. breasts) and around stents and other metal implants.	Magnetic susceptibility artifacts appear as obvious regions of geometric distortion accompanied by focal areas of very dark and very bright appearance. These artifacts result in poor parametric fitting and high variability.	Automatic processing considers fitting quality and regional variability.
Fat/water swap	The method of generating PDFF from IDEAL data can occasionally fail, causing areas of high PDFF to appear uncharacteristically low (e.g., a PDFF of 10 % for subcutaneous fat) and areas of relatively low PDFF to appear high (e.g. a PDFF of 95 % for liver).	Fat/water swaps may cause an unusually high value for fat in the liver.	Automatic processing detects regions of unusually high PDFF so that these are avoided.
Presence of contrast agent	Contrast agent significantly affect metrics provided by LiverMultiScan.	If contrast agent has been administered prior to LiverMultiScan scanning, no quantification can be made.	Radiographer and operator training
Low SNR (signal to noise)	Reduced signal can be caused by mechanical issues, e.g., incorrect coil selection or biological issues, e.g. high iron, very small or large patients. Images affected by low SNR can appears noisy or ‘grainy’. In some cases, abdominal	Reduced signal can compromise quantification.	Automatic processing detects regions of low signal so that they can be excluded from quantification.

Issue	Cause	Impact on quantification	Mitigation
	structures can be masked by the noise.		

12. Annexure 2

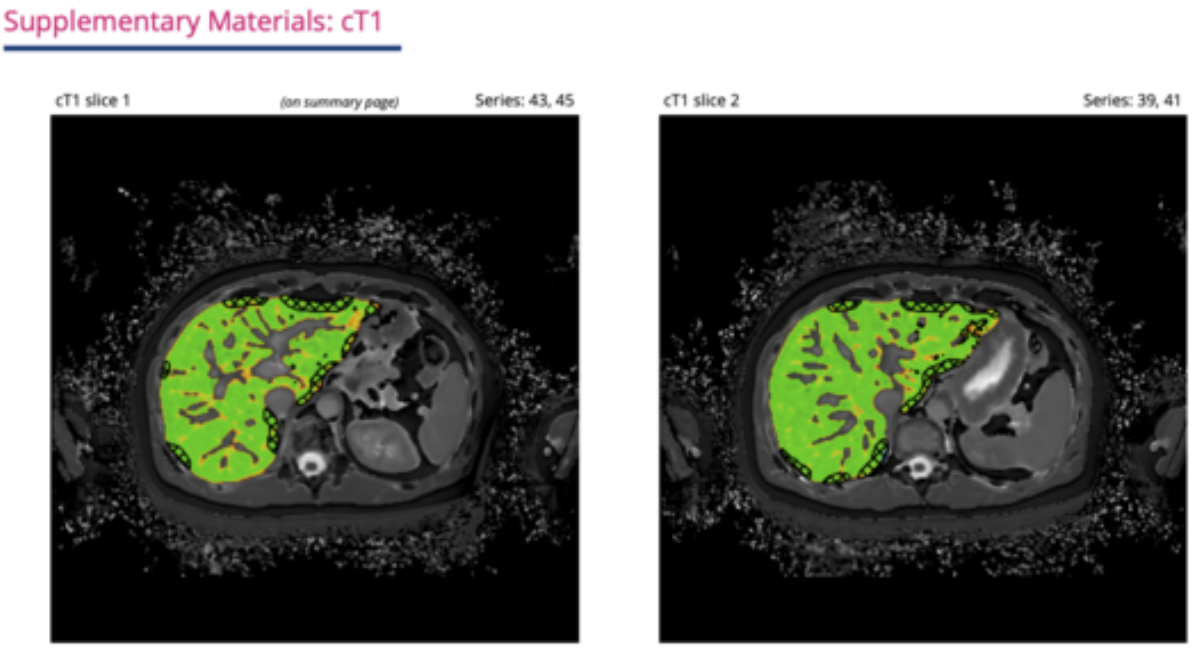
12.1. Supplementary materials page(s)

The default LiverMultiScan report contains all the pages as detailed in the previous sections. If additional information is requested, then additional results can be made available in the LiverMultiScan Report if either a multi-slice analysis has been performed, and/or whole liver statistics are provided.

Notice: The Supplementary Materials pages will appear at the end of the standard 4 pages.

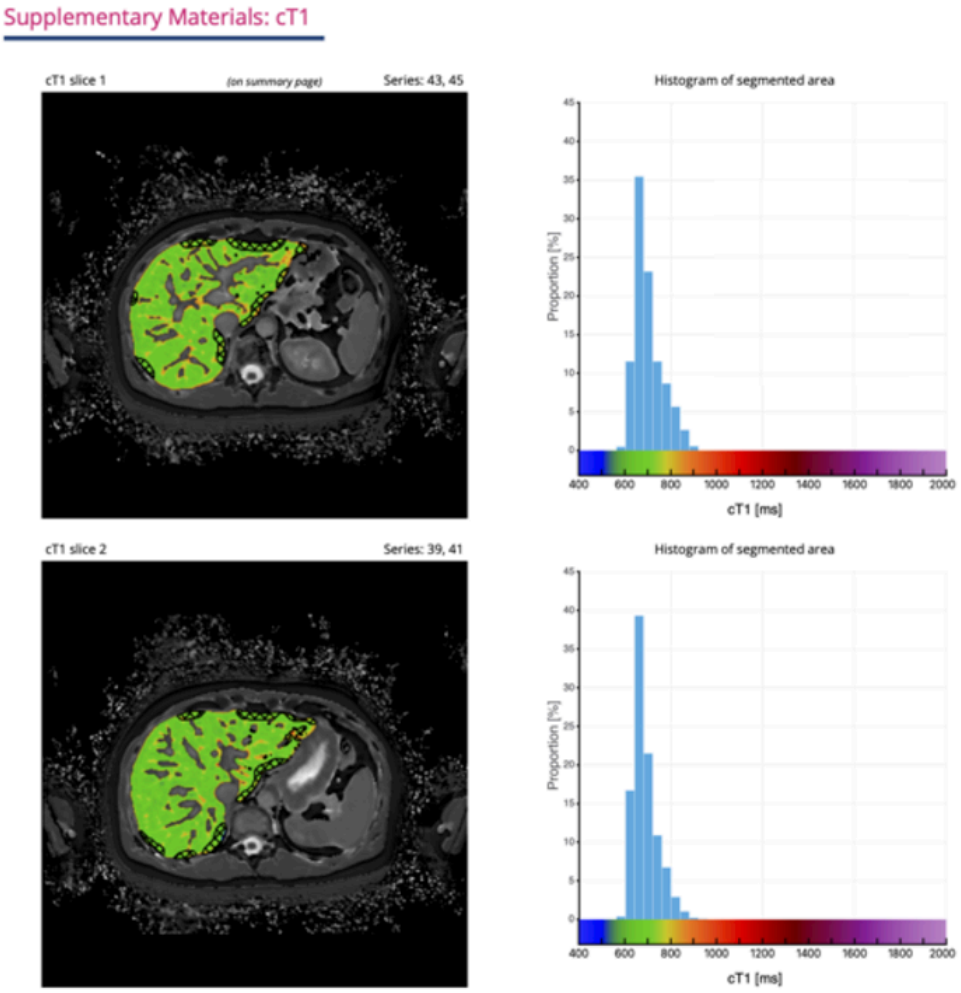
12.1.1. Multi-slice analysis

The contents of the Supplementary Materials page when multiple slices of cT1, PDFF, or LIC are analyzed, is as below. This example shows a multi slice cT1 analysis, however, equivalent LIC and PDFF supplementary materials are available in the event of a multi-slice analysis for LIC and/or PDFF.



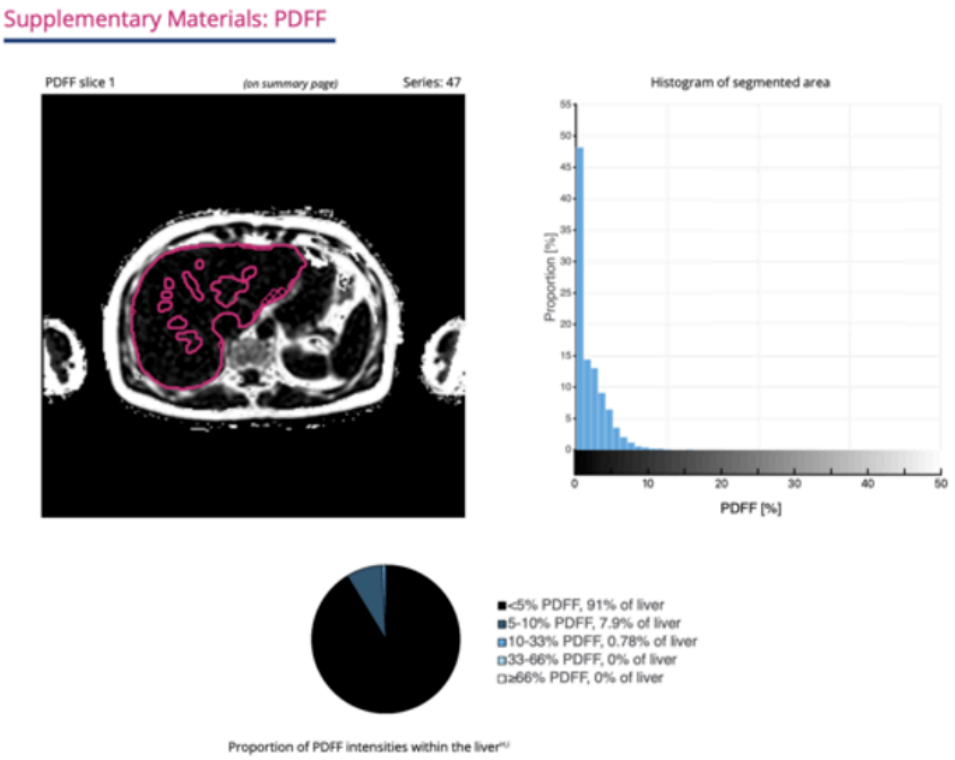
12.1.2. cT1 whole-liver statistics

The contents of the supplementary materials cT1 page when whole liver statistics are provided, is as below. It additionally provides histograms of segmented area, showing the cT1 mode.



12.1.3. **PDFF whole liver statistics**

The contents of the supplementary materials PDFF page when whole liver statistics are provided, is as below. Whole-liver PDFF results are presented as one page per slice analyzed. It additionally provides histograms of segmented area, showing the PDFF mode and a pie chart of the segmented area showing the liver fat percentage in pre-defined sections.[11,12].



11 Brunt, E.M., et al., (2011). The NAS and the histopathologic diagnosis in NAFLD: Distinct opathologic Meanings. Hepatology 53(3):810-820
12 Satkunasingham, J. et al., (2017). Can negligible hepatic steatosis determined by MRI-Proton density fat fraction obviate the need for liver biopsy in potential liver donors? Liver Transplantation 'Accepted Article', doi: 10.1002/lt.24965.

13. ISSUE CONTROL

Issue	Details	Date / Initial
0.1	New document.	20 Oct 2021 / AB
1.0	Ready for signing.	15 Nov 2021 / AB
2.0	Updated language and precision tables.	14 Dec 2021 / AB
3.0	Additional review of new performance testing.	25 Jul 2022 / IW
4.0	IFU Update – IFU to be identical to FDA form 3881.	15 Aug 2022 / DV
5.0	Addition of worst-case variability data for LIC.	30 Aug 2022 / JB
6.0	Amendments and changes post-FDA review.	12 Sep 2022 / IW
7.0	Amendments on variability and minor updates.	04 May 2023 / AA
8.0	Amendment – addition of residual risks and safety section.	24 May 2023 / JB
9.0	Amendment – update to Intended Use.	11 Sep 2023 / DS
10.0	Amendment for LiverMultiScan v5.1.0 changes.	22 Jan 2024 / EA

Distribution: Documents and Records are distributed as per the **Control of Documents and Records Process - IMS0113**.