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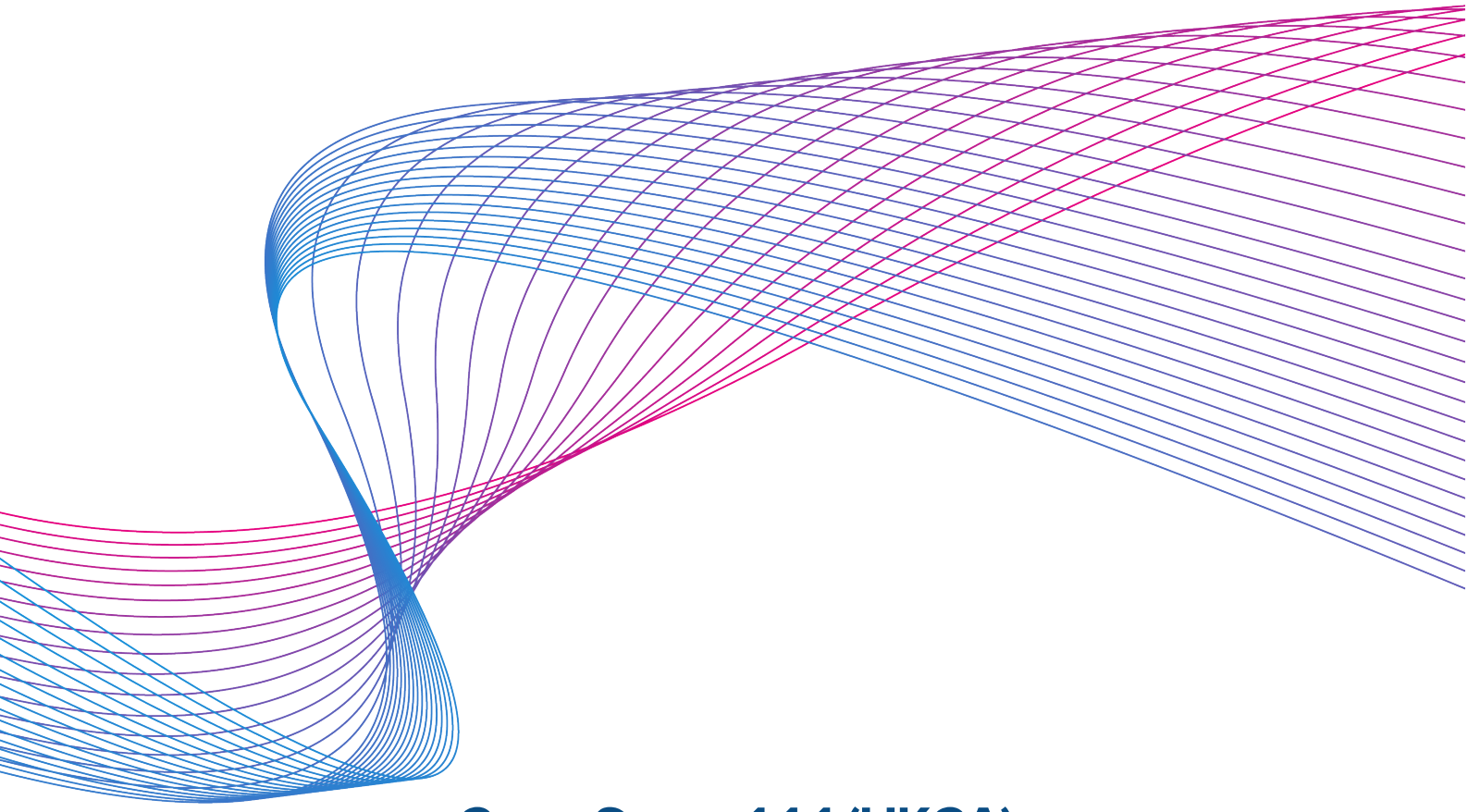

CoverScan v1.1.1 (UKCA)

A Guide to Interpreting Multi-Organ Morphological Characteristics for Physicians

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USE AND LIMITATIONS

This guidance is intended to be used as a reference guide for the interpretation of CoverScan reports by physicians. It is expressly not intended to be relied upon by the reader for instruction as to the practice of medicine. Any physician reading this information is reminded that they must use their own education, training and expertise when advising individual patients. This material does not substitute for that duty and is not intended by Perspectum Ltd to be used for any purpose in that regard. Physicians bear the sole responsibility for the diagnosis and treatment of patients.

CoverScan does not make diagnostic recommendations. CoverScan provides measurements derived from MR data which may be used as part of a wider diagnostic process. Any conclusions arrived at can only be made by a licensed physician interpreting such measurements. In this sense, the physician needs to take into consideration the modality, in this case magnetic resonance (MR), and CoverScan's limitations and accuracy when integrating the information from MR data, as presented by CoverScan, into a wider diagnostic process.

FOR THE READER

All metrics reported by CoverScan should be interpreted only by a physician who can interpret MR examinations and the subsequently produced metrics

CoverScan reported measurements should supplement and not replace a radiologist's image interpretation and review

All users must be cognizant of state and local requirements regarding the use of the imaging system.

CoverScan results should only be interpreted by a physician considering the totality of the information available on the patient, including a medical history of the patient.

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

Variation in reference ranges can be observed between some population/demographics. A description of the population and demographics used for each reference range can be found on pages 15-22 in 'CoverScan – A guide to Interpreting Multi-Organ Morphological Characteristics for Physicians'.

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INTRODUCTION

CoverScan is a post-processing software system comprising several software modules. It uses acquired MR data to produce metrics of quantified tissue characteristics and function of the heart, liver, pancreas, kidneys, lungs, and spleen.
Each software module is used within its intended use: no data manipulation performed to the outputted data prior to inclusion of metrics in report apart from number rounding of raw data when inputted into the collated CoverScan report, for ease of interpretation.

Measurements produced by CoverScan can be used by physicians in a clinical setting.

CoverScan is comprised of the following software modules:

Organ	Quantification Device
Heart	**CVI42 5.13** (510(k) number: K141480) manufactured by Circle Cardiovascular Imaging Inc and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO).
Liver	**LiverMultiScan v3.5.0 ("LMS")** (510(k) number: K190017) manufactured by Perspectum Ltd and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO).
Pancreas	**MultiScan v1.2.0 ("MS")** (510(k) number: K230294) manufactured by Perspectum Ltd and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO)
Kidney	**MultiScan v1.2.0 ("MS")** (510(k) number: K230294) manufactured by Perspectum Ltd and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO).
Lung	**OsiriX MD v13.0** (510(k) number: K101342) manufactured by Pixmeo SARL and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO).
Spleen	**OsiriX MD v13.0** (510(k) number: K101342) manufactured by Pixmeo SARL and compiled by CoverScan v1.1 manufactured by Perspectum Ltd (B554CSMD10/$+000AAO).

Table 1: Medical devices used to calculate metrics reported by CoverScan and their regulatory status

A detailed list of metrics is provided below.

INTENDED USE

CoverScan is a medical image management and processing software package that allows the display, analysis and post-processing of DICOM compliant medical images and MR data.

CoverScan provides both viewing and analysis capabilities to ascertain the tissue characteristics and organ function of multiple organs such as the heart, lungs, liver, spleen, pancreas and kidney.

CoverScan provides measurements in different organs to be used for the assessment of fibrosis and/or inflammation of an organ (T1, srT1, cT1, T2), fat content (proton density fat fraction or PDFF) and/or organ function (e.g. left ventricular ejection fraction; lung fractional area change on deep inspiration).

These metrics derived from the images, when interpreted by a physician, yield information that may assist in diagnosis, clinical management and monitoring of patients.

Caution: CoverScan is clinically validated for the intended use above only

Is CoverScan a Medical Device?

Yes. CoverScan is manufactured in compliance with the Council Directive 93/42/EEC. CoverScan is classified as a class IIa device using rule 10 in Annex IX of the Council Directive 93/42/EEC.

CoverScan is a Medical Imaging Management and Processing System with reference to Section 21 CFR 892.2050 of the United States Code of Federal Regulations. As such, it is a class II device with product code LLZ.

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

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June, 2021

UK CA 0086

CoverScan is manufactured in compliance with the Council Directive 93/42/EEC. CoverScan is classified as a class IIa device using rule 10 in Annex IX of the Council Directive 93/42/EEC.

Basic UDI-DI for CoverScan: ++B554CSMDBQ

Owner/Operator Number:	10056574
Establishment Registration Number:	3014232555
Premarket Notification Number:	K212565

UKCA 752965

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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.

What does CoverScan measure?

CoverScan data are processed by a trained internal operator located at one of Perspectum's image analysis centers. Data analysis is performed under an ISO 13485 compliant QMS. The following metrics are reported by CoverScan:

Liver Metrics

Metric	Comment
Liver cT1 (ms)	Corrected T1 (cT1) relates to the amount of extracellular fluid present in the liver parenchyma. cT1 is derived from T1 and T2* maps. T1 is a measure of the longitudinal (spin-lattice) relaxation time, measured in milliseconds (ms). The T1 of a tissue depends on its free water content, which relates to the proportion of the extracellular fluid in the tissue. Proton-dense tissues with a low water content, such as fat, have very short T1 values, while tissues with a high-water content, such as muscle and the spleen have much longer T1 values. When tissue is inflamed or scarred (fibrotic), the water content increases, leading to longer T1 values. The application of T1 as a biomarker for inflammation and fibrosis in the liver is impeded by the liver iron. In a conventional T1 map, the local magnetic effects exerted by the iron artificially shorten the T1 measurement, leading to potential underestimation. CoverScan uses the T2* map to correct for signal changes related to iron deposits, producing a corrected T1 map, referred to as cT1. This iron-corrected T1 map compensates for the effects of elevated iron from T1 measurements. cT1 is sensitive to inflammation, fibrosis, and liver fat (PDFF). cT1 has been shown to correlate with liver parenchymal fibrosis, inflammation, and ballooning (14–17). ⚠ **Caution**: High levels of hepatic fat can confound the accuracy of cT1. ⚠ **Caution**: In cases of very high levels of hepatic fat (>35%), Liver cT1 will not be reported. ⚠ **Caution**: CoverScan reports a MOLLI-T1 value; the MOLLI method consistently underestimates T1 values, very high T1 values (>1500ms) may be underestimated by more than 20%.
Liver Fat (PDFF) (%)	Liver fat or Proton Density Fat Fraction (PDFF) is a ratio, expressed as a percentage, of the fraction of the MRI-detectable protons attributable to fat divided by all MRI-detectable protons in that region of the liver attributable to fat and water. The PDFF metric is an average of all the pixels within the contour generated by automatic liver segmentation. ⚠ **Caution**: PDFF imaging methods can be susceptible to fat and water components being erroneously swapped, leading to the water percentage reported as the fat percentage. CoverScan is robust against fat/water swaps, but in some cases this may still occur.

Table 2: Liver metrics reported by CoverScan

CARDIAC METRICS

Metric	Comment
Left Ventricular Ejection Fraction (%)	LVEF (Left Ventricular Ejection Fraction) is a measurement, expressed in percentage, of how much blood is pumped out of the left ventricle by each heartbeat and it is used to assess global heart function. It is calculated by dividing the volume of blood pumped from the left ventricle per beat (stroke volume) by the volume of blood collected in the left ventricle at the end of diastolic filling (end-diastolic volume).
Cardiac T1 segments (ms)	T1 is a time constant representing the recovery of longitudinal magnetization after a radiofrequency inversion pulse and provides a measure of the intrinsic properties of the myocardial tissue that can be shortened or prolonged by disease. For T1 mapping acquisition methods, T1 values are estimated by fitting a T1 recovery curve to each pixel in a series of images with different degrees of T1 recovery using a three-parameter fit (1,2). T1 values are measured in 16 of the heart segments according to the 17 AHA segment model over three T1 short-axis slices (basal, mid, apical). Cardiac T1 has good discriminatory ability to detect myocardial pathology, whether without or with pre-existing cardiovascular disease (3)(4)(5)(6)(7)(8). ⚠ **Caution:** CoverScan reports using the MOLLI-T1 value commonly used in cardiac MRI, the MOLLI method consistently underestimates T1 values, very high T1 values (>1500ms) may be underestimated by more than 20%. ⚠ **Caution:** CoverScan cannot report cardiac T1 metrics if contrast agent has been used. **NOTE**: Cardiac T1 in apical segments is susceptible to partial volume artefact, thus these measures may not be available for quantification in all instances.
Cardiac T2 segments (ms)	T2 is a time representing the decay of transverse magnetization following a 90-degree radiofrequency pulse and it is used to measure the T2 relaxation time. T2 values are estimated by fitting a T2 decay curve to each pixel in a series of images with different degrees of T2 value according to the 17 AHA-segment model requiring three T2 short-axis slices (basal, mid, apical). Cardiac T2 has good discriminatory ability to detect myocardial pathology in patients, whether without or with pre-existing cardiovascular disease (9)(10) (11–13). ⚠ **Caution:** CoverScan cannot report cardiac T2 metrics if contrast agent has been used. **NOTE**: Cardiac T2 in apical segments is susceptible to partial volume artefact, thus these measures may not be available for quantification in all instances.
End Diastolic Volume (Left Ventricle) (mL)	A measurement of the maximum amount of blood present in the left ventricle before the beginning of contraction.
End Systolic Volume (Left Ventricle) (mL)	A measurement of the amount of blood present in the left ventricle at the contraction.
Stroke Volume (Left Ventricle) (mL)	The measure of the amount of blood pumped out of the left ventricle at each heartbeat. This is calculated by the difference between the end diastolic volume and the end systolic volume.
Muscle Mass (Left Ventricle) (g)	Based on the volume of tissue between the endocardial and epicardial contours multiplied by the density of myocardial tissue (1.05g/mL).
Maximum Wall Thickness (Left Ventricle) (mm)	Wall thickness is the distance between endocardial and epicardial contours at the end diastole. LV Wall Thickness is defined as the highest value of wall thickness measured at various location.

Table 3: Cardiac metrics reported by CoverScan

PANCREAS METRICS

Metric	Comment
Pancreas srT1 (ms)	As with cardiac T1, the T1 of the pancreatic tissue depends on its free water content, which relates to the proportion of extracellular fluid in the tissue. Increased T1 can be used in the diagnosis of edema (increased tissue water) or increased interstitial space due to fibrosis. Scanner make and field strength can introduce potential bias to the T1 measurement. The srT1 (scanner referenced T1) map relies on a modified look-locker inversion recovery (MOLLI) acquisition, enabling T1 maps from a single breath-hold acquisition to be generated. The T1 maps built from different scanner models and manufacturers may produce slightly different T1 values depending on the software implementation and hardware. The calculation of pancreas T1 maps using the MultiScan module uses the signal from supported scanners and MRI field strengths to simulate the data as it would be acquired on the reference scanner, providing improved reproducibility. The srT1 pipeline maps MRI-system dependent T1 images to MRI-system independent srT1 images and that allows comparison of srT1 values over a wide variety of MRI systems. srT1 is standardized to the MOLLI T1 measurement that would be made on a Siemens 3T scanner. It does not correct for any other potential confounders e.g. iron or fat. ⚠ **Caution:** CoverScan reports a MOLLI-T1 value; the MOLLI method consistently underestimates T1 values, very high T1 values (>1500ms) may be underestimated by more than 20%
Pancreas fat (PDFF) (%)	Pancreatic fat or Proton Density Fat Fraction (PDFF) is a ratio, expressed as a percentage, of the fraction of the MRI-detectable protons attributable to fat divided by all MRI-detectable protons in that region of the liver attributable to fat and water. The PDFF metric is a summarized metric from the individual pixels within all of the ROIs (Region of Interest) placed on the PDFF parametric map (18). ⚠ **Caution**: PDFF imaging methods can be susceptible to fat and water components being erroneously swapped, leading to the water percentage reported as the fat percentage. CoverScan is robust against fat/water swaps, but in some cases this may still occur.

Table 4: Pancreas metrics reported by CoverScan

KIDNEY METRICS

METRIC	COMMENT
Kidney cortical T1 (ms)	As with cardiac T1, the T1 of the kidney tissue depends on its free water content, which relates to the proportion of extracellular fluid in the tissue. Increased T1 can be diagnostic of edema (increased tissue water) or increased interstitial space due to fibrosis. ⚠ **Caution:** CoverScan reports a MOLLI-T1 value; the MOLLI method consistently underestimates T1 values, very high T1 values (>1500ms) may be underestimated by more than 20%.
Kidney length (cm)	Kidney length (size) is a measure of the point-to-point length of each kidney and has been found to serve as surrogate for renal functional reserve (19).

Table 5: Kidney metrics reported by CoverScan

LUNG METRICS

Metric	Comment
Lung fractional change (%)	Lung fractional change for deep breathing is an MRI-derived proxy measure of relaxed vital capacity. This is calculated by the difference between the lung area, measured from images acquired in the coronal view, at maximum inspiration and expiration, which is divided by the maximum area at inspiration for normalisation of patient size. The change in lung area with deep breathing correlates with forced vital capacity measured from spirometry (20).

Table 6: Lung metrics reported by CoverScan

SPLENIC METRICS

Metric	Comment
Spleen Length (cm)	The point-to-point length (size) of the spleen in the inferior to superior direction.

Table 7: Splenic metrics reported by CoverScan

The CoverScan Report

Metrics derived from CoverScan are provided to the licensed physician as a quantitative report. It contains a summary page, analysis pages and an acquisition details page. The report is typically 6 pages.

Summary page

The summary page provides a summary of the quantitative analysis conducted.

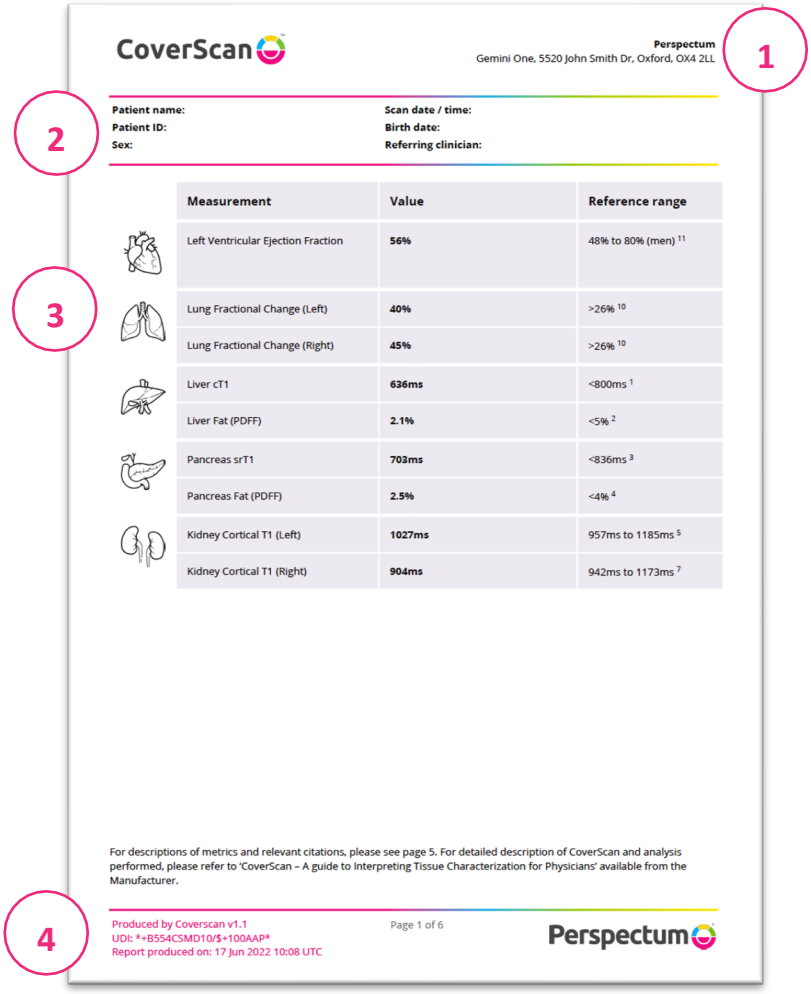

Figure 1: Summary page of CoverScan report

1. **Scanning center details.** Center name and address
2. **Scan date, patient identifiers and referring clinicians.** Date of Acquisition is automatically generated from DICOM if available. If not present in the DICOM file it is left blank
3. **Summary values for metrics** and reference ranges
4. Date of analysis, UDI and Software version

Information: Responsibility for entering the correct patient identifiers lies with the MRI acquisition center.

ANALYSIS PAGES

Those pages report additional measurements acquired with CoverScan: cardiac T1 and T2, cardiac function and organ length (spleen and each kidney).

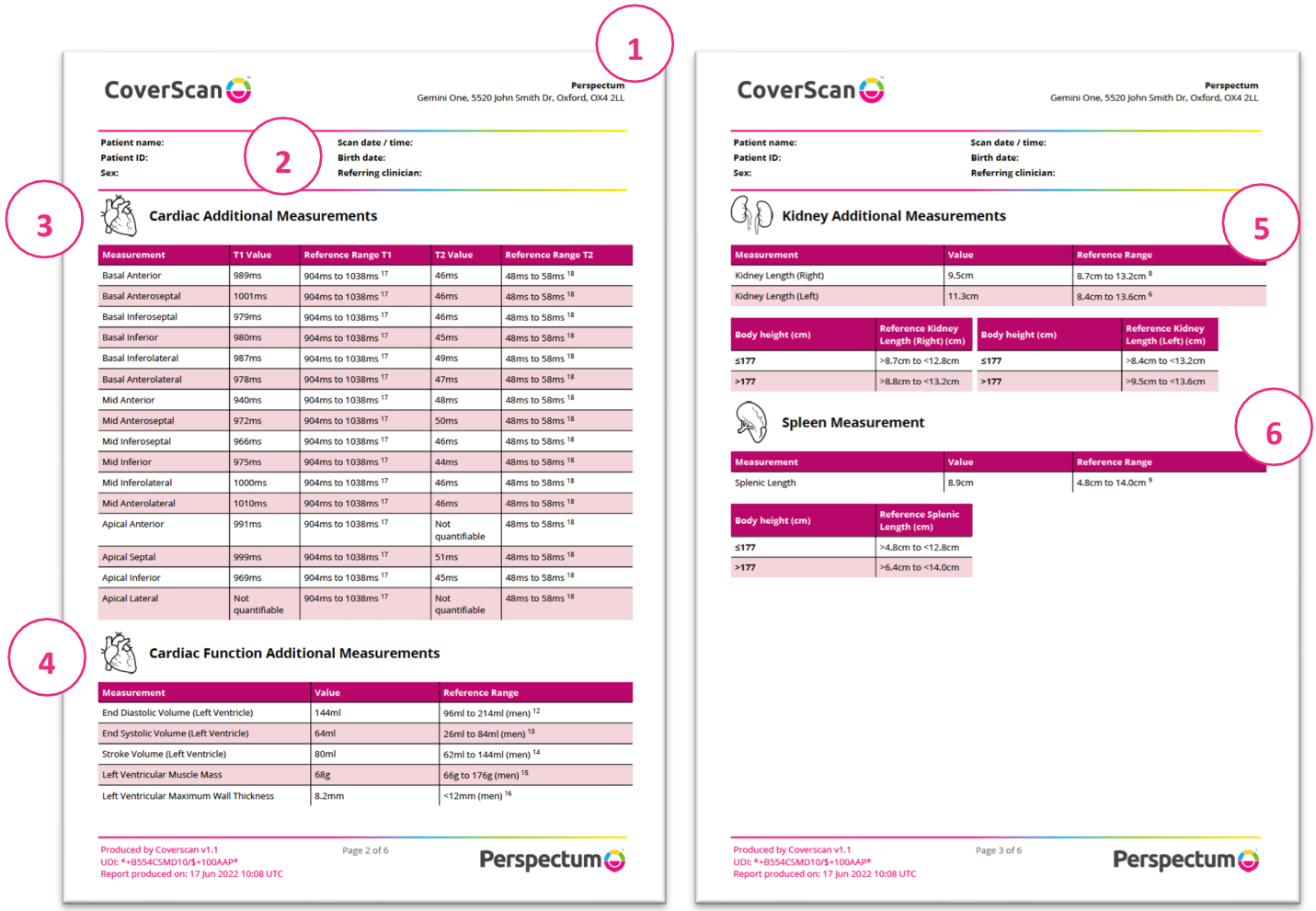

Figure 2: Analysis pages of CoverScan report

1. **Scanning center details**. Center name and address
2. **Scan date, patient identifiers and referring clinicians**. Date of Acquisition is automatically generated from DICOM if available. If not present in the DICOM file it is left blank
3. Cardiac T1 and T2 additional metrics, reference ranges
4. Cardiac Function additional metrics, reference ranges based on patient sex
5. Kidney size, reference ranges based on patient sex and height
6. Spleen size, reference ranges based on patient sex and height

Information: The Additional Measures pages will appear after the Summary page.

ACQUISITION DETAILS PAGE

The Acquisition details pages provide details of the acquisition, including the metric information and any cautions, relevant literature for established reference ranges.

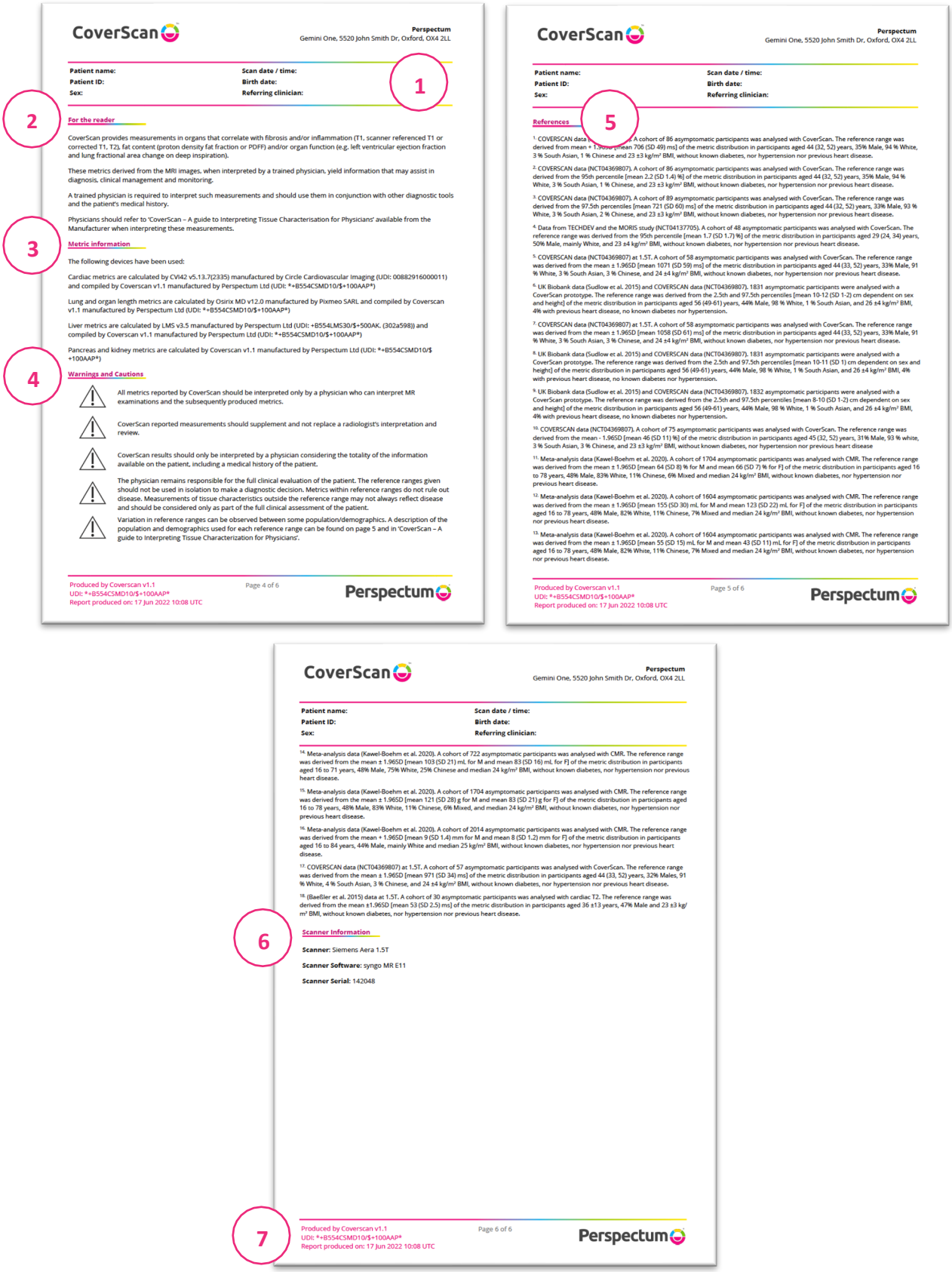

Figure 3: Acquisition details pages of CoverScan report

1. **Scan date, patient identifiers and referring clinician**. Date of Acquisition is automatically generated from DICOM if available. If not, left blank
2. **For the reader**
3. **Metric Information**, devices used to analyze each of the metric
4. **Warning and Cautions**
5. **References** to published literature containing reference ranges for quantified metrics
6. **Scanner details**
7. **Date of analysis and Software version**

WHAT ARE THE REFERENCE RANGES FOR COVERSCAN METRICS?

The reference ranges presented in Table 8 should be used as a guideline when interpreting the CoverScan report.

Variation in reference ranges can be observed between some population/demographics.

The physician remains responsible for the full clinical evaluation of the patient. The reference ranges given should not be used in isolation to make a diagnostic decision. Metrics within reference ranges do not rule out disease.

CoverScan reference ranges can be found below:

Metric (Unit)	Reference Range	Scanner	Demographics*
Liver cT1 (ms)	<800ms	Siemens 1.5T Siemens 3T GE 1.5T	COVERSCAN data (NCT04369807). A cohort of 86 asymptomatic participants was analysed with CoverScan. The reference range was derived from mean + 1.96SD [mean 706 (SD 49) ms] of the metric distribution in participants aged 44 (32-52) years, 35% Male, 94 % White, 3 % South Asian, 1 % Chinese and 23 ±3 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.
Liver PDFF (%)	<5%	Siemens 1.5T Siemens 3T GE 1.5T	COVERSCAN data (NCT04369807). A cohort of 86 asymptomatic participants was analysed with CoverScan. The reference range was derived from the 95th percentile [mean 2.2 (SD 1.4) %] of the metric distribution in participants aged 44 (32-52) years, 35% Male, 94 % White, 3 % South Asian, 1 % Chinese, and 23 ±3 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.

Metric (Unit)	Reference Range	Scanner	Demographics*
Pancreas srT1 (ms)	<836ms	Siemens 1.5T Siemens 3T GE 1.5T	COVERSCAN data (NCT04369807). A cohort of 89 asymptomatic participants was analysed with CoverScan. The reference range was derived from the 97.5th percentiles [mean 721 (SD 60) ms] of the metric distribution in participants aged 44 (32-52) years, 33% Male, 93 % White, 3 % South Asian, 2 % Chinese, and 23 ±3 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.
Pancreas PDFF (%)	<4%	Siemens 1.5T Siemens 3T GE 1.5T	Data from TECHDEV and the MORIS study (NCT04137705). A cohort of 48 asymptomatic participants was analysed with CoverScan. The reference range was derived from the 95th percentile [mean 1.7 (SD 1.7) %] of the metric distribution in participants aged 29 (24-34) years, 50% Male, mainly White, and 23 ±4 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.
Kidney length Left (cm)	- 8.8 cm to 12.4 cm (F up to 164 cm height); - 9.2 cm to 13.2 cm (F >164cm height); - 8.4 cm to 13.2 cm (M up to 177 cm height); - 9.5 cm to 13.6 cm (M >177cm height)	Siemens 1.5T Siemens 3T GE 1.5T	UK Biobank data (Sudlow et al. 2015) and COVERSCAN data (NCT04369807). 1831 asymptomatic participants were analysed with a CoverScan prototype. The reference range was derived from the 2.5th and 97.5th percentiles [mean 10-12 (SD 1-2) cm dependent on sex and height] of the metric distribution in participants aged 56 (49-61) years, 44% Male, 98 % White, 1 % South Asian, and 26 ±4 kg/m2 BMI, 4% with previous heart disease, no known diabetes nor hypertension.
Kidney length Right (cm)	- 8.0 cm to 12.0 cm (F up to 164 cm height); - 8.0 cm to 12.4 cm (F >164cm height); - 8.7 cm to 12.8 cm (M up to 177 cm height); - 8.8 cm to 13.2 cm (M >177cm height)	Siemens 1.5T Siemens 3T GE 1.5T	UK Biobank data (Sudlow et al. 2015) and COVERSCAN data (NCT04369807). 1831 asymptomatic participants were analysed with a CoverScan prototype. The reference range was derived from the 2.5th and 97.5th percentiles [mean 10-11 (SD 1) cm dependent on sex and height] of the metric distribution in participants aged 56 (49-61) years, 44% Male, 98 % White, 1 % South Asian, and 26 ±4 kg/m2 BMI, 4% with previous heart disease, no known diabetes nor hypertension.

Metric (Unit)	Reference Range	Scanner	Demographics*
Kidney cortical T1 Left (ms)	957ms to 1185ms	Siemens 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 58 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1071 (SD 59) ms] of the metric distribution in participants aged 44 (33-52) years, 33% Male, 91 % White, 3 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
	1288ms to 1527ms	Siemens 3T	COVERSCAN data (NCT04369807) at 3T. A cohort of 29 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1408 (SD 63) ms] of the metric distribution in participants aged 42 (32, 53) years, 31% Male, 93 % White, 7 % South Asian, and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
	957ms to 1185ms	GE 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 58 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1071 (SD 59) ms] of the metric distribution in participants aged 44 (33, 52) years, 33% Male, 91 % White, 3 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
Kidney cortical T1 Right (ms)	942ms to 1173ms	Siemens 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 58 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1058 (SD 61) ms] of the metric distribution in participants aged 44 (33-52) years, 33% Male, 91 % White, 3 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.

Metric (Unit)	Reference Range	Scanner	Demographics*
Kidney cortical T1 Right (ms)	1278ms to 1516ms	Siemens 3T	COVERSCAN data (NCT04369807) at 3T. A cohort of 29 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1397 (SD 64) ms] of the metric distribution in participants aged 42 (32, 53) years, 31% Male, 93 % White, 7 % South Asian, and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
	942ms to 1173ms	GE 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 58 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1058 (SD 61) ms] of the metric distribution in participants aged 44 (33, 52) years, 33% Male, 91 % White, 3 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
Lung fractional change: **- Left (%)** **- Right (%)**	>26%	Siemens 1.5T Siemens 3T GE 1.5T	COVERSCAN data (NCT04369807). A cohort of 75 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean - 1.96SD [mean 46 (SD 11) %] of the metric distribution in participants aged 45 (32-52) years, 31% Male, 93 % white, 3 % South Asian, 3 % Chinese, and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
Spleen length (cm)	- 5.2 cm to 11.1 cm (F up to 164 cm height); - 5.7 cm to 12 cm (F >164cm height); - 4.8 cm to 12.8 cm (M up to 177 cm height) - 6.4 cm to 14 cm (M >177cm height)	Siemens 1.5T Siemens 3T GE 1.5T	UK Biobank data (Sudlow et al. 2015) and COVERSCAN data (NCT04369807). 1832 asymptomatic participants were analysed with a CoverScan prototype. The reference range was derived from the 2.5th and 97.5th percentiles [mean 8-10 (SD 1-2) cm dependent on sex and height] of the metric distribution in participants aged 56 (49-61) years, 44% Male, 98 % White, 1 % South Asian, and 26 ±4 kg/m2 BMI, 4% with previous heart disease, no known diabetes nor hypertension.

Metric (Unit)	Reference Range	Scanner	Demographics*
Ejection fraction (Left Ventricle) (%)	48% to 80% (M) 52% to 80% (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 1704 asymptomatic participants was analysed with CMR. LVEF was normally distributed, thus the reference range was derived from the mean ± 1.96 SD [mean 64 (SD 8)% for M and mean 66 (SD 7)% for F] of the metric distribution in participants aged 16 to 78 years, 48% Male, 83% White, 11% Chinese, 6% Mixed and median 24 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
End diastolic volume (Left Ventricle) (mL)	96 to 214 mL (M) 80 to 166 mL (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 1604 asymptomatic participants was analysed with CMR. The reference range was derived from the mean ± 1.96SD [mean 155 (SD 30) mL for M and mean 123 (SD 22) mL for F] of the metric distribution in participants aged 16 to 78 years, 48% Male, 82% White, 11% Chinese, 7% Mixed and median 24 kg/m^2 BMI without known diabetes, nor hypertension nor previous heart disease.
End systolic volume (Left Ventricle) (mL)	26 to 84 mL (M) 21 to 65 mL (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 1604 asymptomatic participants was analysed with CMR. The reference range was derived from the mean ± 1.96SD [mean 55 (SD 15) mL for M and mean 43 (SD 11) mL for F] of the metric distribution in participants aged 16 to 78 years, 48% Male, 82% White, 11% Chinese, 7% Mixed and median 24 kg/m^2 BMI without known diabetes, nor hypertension nor previous heart disease.
Stroke volume (Left Ventricle) (mL)	62 to 144 mL (M) 52 to 114 mL (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 722 asymptomatic participants was analysed with CMR. The reference range was derived from the mean ± 1.96SD [mean 103 (SD 21) mL for M and mean 83 (SD 16) mL for F] of the metric distribution in participants aged 16 to 71 years, 48% Male, 75% White, 25% Chinese and median 24 kg/m^2 BMI without known diabetes, nor hypertension nor previous heart disease.

Metric (Unit)	Reference Range	Scanner	Demographics*
Muscle mass (Left Ventricle) (g)	66 to 176g (M) 42 to 124g (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 1704 asymptomatic participants was analysed with CMR. The reference range was derived from the mean ± 1.96SD [mean 121 (SD 28) g for M and mean 83 (SD 21) g for F] of the metric distribution in participants aged 16 to 78 years, 48% Male, 83% White, 11% Chinese, 6% Mixed, and median 24 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.
Wall thickness (Left Ventricle) (mm)	<12 mm (M) <10 mm (F)	Siemens 1.5T Siemens 3T GE 1.5T	Meta-analysis data: Kawel-Boehm, A et al. 2020. A cohort of 2014 asymptomatic participants was analysed with CMR. The reference range was derived from the mean ± 1.96SD [mean 9 (SD 1.4) mm for M and mean 8 (SD 1.2) mm for F] of the metric distribution in participants aged 16 to 84 years, 44% Male, mainly White and median 25 kg/m2 BMI without known diabetes, nor hypertension nor previous heart disease.
Cardiac T1 (ms): **basal anterior** **basal anteroseptal** **basal inferoseptal** **basal inferior** **basal inferolateral** **basal anterolateral** **mid anterior** **mid anteroseptal** **mid inferoseptal** **mid inferior** **mid inferolateral** **mid anterolateral** **apical anterior** **apical septal** **apical inferior** **apical lateral**	904ms to 1038ms	Siemens 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 57 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 971 (SD 34) ms] of the metric distribution in participants aged 44 (33, 52) years, 32% Males, 91 % White, 4 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
	1086ms to 1269ms	Siemens 3T	COVERSCAN (NCT04369807) and RADIUS (NCT05110248) data at 3T. A cohort of 50 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 1177 (SD 46) ms] of the metric distribution in participants aged 33 (29, 49) years, 40% Males, and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.

Metric (Unit)	Reference Range	Scanner	Demographics*
Cardiac T1 (ms): **basal anterior** **basal anteroseptal** **basal inferoseptal** **basal inferior** **basal inferolateral** **basal anterolateral** **mid anterior** **mid anteroseptal** **mid inferoseptal** **mid inferior** **mid inferolateral** **mid anterolateral** **apical anterior** **apical septal** **apical inferior** **apical lateral**	904ms to 1038ms	GE 1.5T	COVERSCAN data (NCT04369807) at 1.5T. A cohort of 57 asymptomatic participants was analysed with CoverScan. The reference range was derived from the mean ± 1.96SD [mean 971 (SD 34) ms] of the metric distribution in participants aged 44 (33, 52) years, 32% Males, 91 % White, 4 % South Asian, 3 % Chinese, and 24 ±4 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
Cardiac T2 (ms): **basal anterior** **basal anteroseptal** **basal inferoseptal** **basal inferior** **basal inferolateral** **basal anterolateral** **mid anterior** **mid anteroseptal** **mid inferoseptal** **mid inferior** **mid inferolateral** **mid anterolateral** **apical anterior** **apical septal** **apical inferior** **apical lateral**	48ms to 58ms	Siemens 1.5T	(Baeßler et al. 2015) data at 1.5T. A cohort of 30 asymptomatic participants was analysed with cardiac T2. The reference range was derived by addition of a 5ms scanner bias to the mean ±1.96SD [mean 53 (SD 2.5) ms] of the metric distribution on Siemens in participants aged 36 ±13 years, 47% Male and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.
	35ms to 46ms	Siemens 3T	COVERSCAN (NCT04369807) data at 3T. A cohort of 28 asymptomatic participants was analysed with cardiac T2. The reference range was derived from the mean ±1.96SD [mean 40 (SD 2.8) ms] of the metric distribution in participants aged 42 (32, 52) years, 32% Male, 97 % White, 3 % South Asian and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.

Metric (Unit)	Reference Range	Scanner	Demographics*
Cardiac T2 (ms): **basal anterior** **basal anteroseptal** **basal inferoseptal** **basal inferior** **basal inferolateral** **basal anterolateral** **mid anterior** **mid anteroseptal** **mid inferoseptal** **mid inferior** **mid inferolateral** **mid anterolateral** **apical anterior** **apical septal** **apical inferior** **apical lateral**	53ms to 63ms	GE 1.5T	(Baeßler et al. 2015) data at 1.5T. A cohort of 30 asymptomatic participants was analysed with cardiac T2. The reference range was derived by addition of a 5ms scanner bias to the mean ±1.96SD [mean 53 (SD 2.5) ms] of the metric distribution on Siemens in participants aged 36 ±13 years, 47% Male and 23 ±3 kg/m2 BMI, without known diabetes, nor hypertension nor previous heart disease.

Table 8: Reference range for organ metrics produced by CoverScan.

*Age presented as mean ± SD median (IQR) or just range, BMI as mean± SD.

Accuracy and Precision of CoverScan

When interpreting the report, especially for monitoring over time, it is important to understand the limitations in the performance of CoverScan. Table 10 and Table 11 below provide a summary of performance characteristics.

Accuracy

Accuracy represents the degree of closeness of a given measurement of a quantity to that quantity's true value (the ground truth) and is tested using phantoms. The phantom ground truth measurements used by CoverScan were:

- T1: Inversion recovery spin echo in each scanner.
- PDFF: Destructive testing and measurement in an Oracle Rapid Fat Analysis nuclear magnetic resonance machine.

MultiScan accuracy was tested in-vitro on Siemens 1.5T and 3T. MultiScan sequences were run on this scanner and compared to the gold standard value. The results of the statistical test are displayed in Table 11. Table 12 contains the true characterisation between the gold standard and MOLLI T1 (i.e., IR-based T1 vs MOLLI T1).

Accuracy in bench testing		
Metric (unit)	Pooled performance testing Limits of Agreement (Bias)	
	1.5T	3T
T1 (ms)	-8.4ms to 9.0ms	-9.0ms to 7.2ms
PDFF (%)	-5.6% to 1.9%	-1.4% to 0.38%

Table 9: Results of the accuracy tests on Siemens relative to gold standard with an applied bias and to pre-defined acceptance criteria

*T1 analysed in percentage difference space and PDFF analysed in native space

Note: Liver T1 and Liver PDFF accuracy measurements taken from LiverMultiScan (K190017).

Repeatability

Repeatability is a measurement of precision that occurs with identical or near-identical conditions and reflects the degree of agreement between repeated measurements under identical or near-identical conditions. Scan-rescan repeatability was performed with the subject being scanned then being removed from the scanner and then rescanned all within a ~1 hour interval. The same scanner is used on both occasions and the same operator analyses the data. The 95% limits of agreement (the interval within which we expect 95% of future differences between 2 measurements to lie and includes both systematic and random error) and repeatability coefficient (the least significant difference between 2 repeated measurements under identical conditions at a two-sided-significance of a=0.05) are particularly useful for evaluating change in a metric over time (23). The limits of agreements given in percentage space are in bold, otherwise they are given in native space.

Repeatability in clinical testing		
Metric (unit)	Pooled performance testing Limits of Agreement	
	1.5T	3T
Liver cT1 (ms)	-16ms to +42ms	-53ms to +77ms
Liver PDFF (%)	-0.5% to +0.4%	-1% to +1%
Pancreas srT1 (ms)	**-4.9% to +7.7%**	**-8% to +10%**
Pancreas PDFF (%)	-3% to +3%	-3% to +3%
Kidney length Left (cm)	**-7% to +8%**	**-7% to +8%**
Kidney length Right (cm)	**-6% to +8%**	**-5% to +6%**
Kidney cortical T1 Left (ms)	**-4.4% to +6.3%**	**-3% to +6%**
Kidney cortical T1 Right (ms)	**-2.9% to +6.4%**	**-5% to +7%**
Lung fractional change Left (%)	-23% to +16%	-14% to +14%
Lung fractional change Right (%)	-25% to +18%	-10% to +11%
Spleen length (cm)	**-16% to +13%**	**-9% to +16%**
LV Ejection fraction (%)	-8% to +6%	-6% to +9%
LV End diastolic volume (mL)	**-10% to +9%**	**-12% to +11%**
LV End systolic volume (mL)	-10mL to +13mL	-16mL to +10mL
LV Stroke volume (mL)	-24mL to +19mL	-16mL to +22mL
LV Muscle mass (g)	-15g to +6g	-9g to +14g
LV Max wall thickness (mm)	-1.7mm to +1.0mm	-2mm to +3mm
Cardiac T1 segments (ms)	**-7% to +6%**	**-9% to +10%**
Cardiac T2 segments (ms)	**-18% to +15%**	**-16% to +15%**

Table 10: Performance Testing based on in vivo data – Repeatability. Repeatability values expressed as % of the metric value are in **bold**.

Reproducibility

Reproducibility is a measurement of precision that occurs under different sets of conditions and reflects the degree of agreement between measurements under different conditions. Reproducibility was performed scanning the same subject on different scanners all within a ~2 hour interval and analyzing the data using the same operator. The 95% limits of agreement (the interval within which we expect 95% of future differences between 2 measurements to lie and includes both systematic and random error) are particularly useful for evaluating field strength differences in performance (23). Limits of agreement are reported as percentage of the metric value.

Reproducibility in clinical testing	
Metric (unit)	Pooled performance testing Limits of Agreement
Pancreas srT1 (ms)	-7% to +3%

Table 11: Performance Testing based on in vivo data – Reproducibility. Limits of agreement are reported as percentage of the metric value.

CoverScan Workflow

Patients undergo an MRI scan at a Perspectum-cleared scanning center, and the images are then uploaded to our secure Perspectum Portal (https://portal.perspectum.com/). Data are analyzed by trained operators in Perspectum's dedicated image analysis center, and the results are subsequently returned to the Portal as a report. The physicians will be able to access the report and interpret the results. Figure 4 shows a representation of CoverScan workflow.

Figure 4: Representation of CoverScan workflow, from data acquisition to results delivery

CoverScan Acquisition & Analysis

Patients are scanned by highly qualified and well-trained imaging centers following Perspectum standardized protocol. The MRI scan will capture images of the abdomen and chest that includes the liver, pancreas, spleen, kidneys, lungs, and heart. Descriptions of sequences and how data are acquired on the scanner can be found in the CoverScan **Patient Acquisition Manual for Siemens Scanners - MRA1253.**

The physician remains responsible for the full clinical evaluation of the patient. The reference ranges given should not be used in isolation to make a diagnostic decision. Metrics within reference ranges do not rule out disease.

Factors associated with image acquisition that can affect the quality of measurements

The use of CoverScan is contingent on the acquisition of data of sufficient quality to conduct processing. As part of the Quantitative Analysis Service, image quality is assessed both automatically and manually. Typical or common acquisition problems are detailed in the table below.

Problem	Reason?	Impact on quantification
Acquisition outside of the shim box	Whilst the patient acquisition manual stresses the importance of proper shimming prior to acquisition, poor shimming can occur due to human error or mechanical issues. This can lead to regions of inhomogeneity in the parametric maps.	Where inhomogeneity is severe, it may not be possible to perform quantitation.
Atypical RR interval	T1 data acquisition is cardiac-gated. There are a number of causes for an atypical RR interval: • Patient has a high heart rate. • Patient has a low heart rate, or individual beats are not detected. • Patient has variable heart rate, or beats are not detected.	Where missed heartbeats cannot be ruled out, it may not be possible to perform T1 quantification in that slice.

Problem	Reason?	Impact on quantification
Evidence of motion	Whilst the patient acquisition manual stresses the importance of controlled breathing to minimize the likelihood of motion, breathing and moving to get comfortable may occur. Patient motion corrupts the images and makes quantitation difficult or impossible.	Where motion is severe, it may not be possible to perform quantification.
Susceptibility artefact	Different tissues and materials have different magnetic susceptibilities, which produce signal inhomogeneity, particularly at air-tissue interfaces (e.g., lungs) and around stents and other metal implants. Susceptibility artefacts can appear as geometric distortion, with focal areas of very dark and very bright appearance.	Where a suitable region cannot be found, it may not be possible to perform quantitation.
Fat/water swap	The method of generating PDFF from 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).	Quantification can be performed in parts of the liver or pancreas that remain unaffected by the fat/water swap
Low SNR (signal to noise ratio)	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 appear noisy or 'grainy.' In some cases, abdominal or chest structures can be masked.	Quantification can be performed in regions where it is possible to provide accurate parametric mapping and low image noise, if such regions exist. If noise is too severe, it may not be possible to perform quantitation.
Suboptimal anatomical location	Incorrect positioning of the patient prior to scanning, suboptimal planning of acquisitions or motion during scanning can result in the relevant organ not being imaged.	Quantification can be performed if a sufficient area of the relevant organ is captured within the parametric map. If no relevant tissue is visible, no quantification can be made.
Presence of MRI contrast agent	Caution: Contrast agents must not be administered prior to acquiring data. Where imaging contrast agents have been administered, T1, T2, and T2* will be shortened. CoverScan processing is mitigated against post-contrast reporting with MRI contrast agents, but it remains possible that post-contrast results will be reported.	If contrast agent has been administered, typically no quantification can be made, erroneous measurements may result.
Presence of CT contrast agent	Caution: CT contrast agents must not be administered prior to acquiring data. Where imaging contrast agents have been administered, T1, T2, and T2* may be affected. CoverScan processing is not mitigated against post-contrast reporting with CT contrast agents.	If CT contrast agent has been administered, erroneous measurements may result.

Table 12: Factors associated with image acquisition that affect quality of measurements from parametric maps

In addition to the measurements from parametric maps (i.e., those of PDFF, T1, T2, and T2*) CoverScan provides measurements of lengths and volumes. The following table describes typical problems that can occur with those acquisitions.

Problem	Reasons?	Impact on quantification
Variation in breathing instructions	The Lung Fractional Change will only be repeatable if the patient attempts to breathe to the same depth. The solution is to have consistent instructions in the center and to rehearse with the patient prior to scanning.	Lung Fractional Changes will be returned but may not be consistent.
Cardiac slice positioning	Cardiac function requires very precise positioning of the basal slice for accurate cardiac function measurements.	Additional variance in the metrics that relate to blood volumes of the heart, potentially no cardiac metrics can be reported.
Cardiac slice coverage	Cardiac function requires the slices to be accurately axial and to span from the apex to the basal slice as described in the operator's manual.	Poorly positioned slices and failures of cardiac gating can add variance to the quantitation of cardiac parameters or even make quantitation impossible.

Table 13: Factors associated with image acquisition that affect quality of measurements for lengths and volumes

PERSPECTUM PORTAL

All images are uploaded to our secure, ISO 27001 and 21 CFR Part 11 compliant Perspectum Portal (https://portal.perspectum.com/) making data and results available on a single platform. Images are checked for quality, and then processed and reviewed by our imaging and clinical specialists in Perspectum's dedicated image analysis centers. The results are then summarized in CoverScan report which is delivered to the physician through the Portal. The physician then uses the information, as well as other diagnostic tests or procedures, to make a diagnosis.

Cybersecurity

Cybersecurity is a critical part of ensuring that patient safety, patient information, healthcare networks, as well as your own devices are not compromised. The recommendations provided below are not a comprehensive list, but rather a sampling of issues that may be helpful in alleviating cybersecurity vulnerabilities. Keeping your operating system, as well as the viewer used to view the pdf report produced by CoverScan up to date is strongly recommended. Other controls, such as firewalls or virtual private networks may also be appropriate. Please contact your system administrator if you believe this to be the case. The use of antivirus software is recommended. It is important that your antivirus software is kept up to date and routine scans are performed at appropriate intervals. This may aid in protecting your device from malware, as well as other devices on your network.

Malware is a general term that refers to many types of threats, such as the following:

- 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
- Phishing: Seemingly safe links take users to malicious sites that gather personal data and login credentials, and can be found within websites, emails or even ads
- Pharming: Similar to phishing attacks, pharming attacks redirect users from a legitimate site to a malicious one
- Ransomware: When downloaded, ransomware blocks access to files and programs until users pay a set fee

Antivirus software may be useful in identifying and blocking incoming threats and scanning your device for existing malware. Reliable, tested malware protection aims to get to the root of an infection and completely remove it.

What are the Cybersecurity recommendations for viewing reports produced by CoverScan?

- 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

Reporting an Incident

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 safety@Perspectum.com and the competent authority in your country.

Cybersecurity Incident

If you believe a cybersecurity incident has occurred, please contact Information Technology or Information Security immediately by emailing it@perspectum.com or is@perspectum.com and report the suspected incident at incidents@perspectum.com.

Frequently Asked Questions

Who performs the quantitative analysis on the acquired data?

Perspectum employ trained operators based in our dedicated data analysis centers.

How is the quality of the data acquired assessed?

All data goes through both automated and manual Quality Control (QC) checks. Once a dataset passes the automated QC checks, our operators are trained to identify potential problems (image artefacts), as detailed in **Error! Reference source not found.**. If a dataset appears severely affected by acquisition artefacts, the case is escalated to specialist teams within Perspectum who may be able to characterize acquisition issues and recommend the best ways to salvage poor quality data. In some cases, the recommendation will be to reject the acquisition or even the entire study.

How is the physician informed of the quality of the acquired data and confidence in the reported metrics?

Operators are trained to report on the quality of the data acquired, carefully considering potential problems outlined in **Error! Reference source not found.** and **Error! Reference source not found.**. This information is communicated as comments to the interpreting physician in order to consider the quality comments in conjunction with the reported metrics. Repeated issues with image quality may lead to a remedial QC visit from Perspectum to identify the root cause of the problems, and retrain the MR technician, if required.

How is quality assured?

The CoverScan device was designed and developed in a controlled environment in compliance with ISO 13485 and IEC 62304 using modern practices and the CoverScan code was peer-reviewed prior to undergoing rigorous performance testing. Performance testing constituted of in-vivo acquired scans of volunteers and phantom acquired scans, analyzed with the CoverScan device to gain accuracy and precision metrics. Perspectum's teams install the CoverScan MRI protocols and provide tailored training to the MR Radiographers at scanning centers. Sites are then cleared to ensure that both the MR scanner and MR radiographer(s) are able to produce images that meet quality standards. The data undergo automated quality checks prior to analysis by trained operators at Perspectum's dedicated analysis center. Results are re-checked prior to returning the analyzed metrics to the scanning center. Perspectum's in-house analysts are highly trained with expert knowledge of the device, anatomical areas of interest, and radiological imaging. Prior to commencing analysis of clinical cases, analysts are thoroughly examined against strict acceptance criteria and their ongoing performance is periodically checked.

How secure is the service?

Perspectum is in compliance with the UK Data Protection Act of 1998, and as such, is a registered data controller with the Information Commissioner's Office. In addition, our QAS (Quantitative Analysis Service) infrastructure is compliant with the US Health Insurance Portability and Accountability Act (HIPAA) and the US Health Information Technology for Economic and Clinical Health Act (HITECH). Perspectum's 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 Perspectum 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 is encrypted while in storage in the Perspectum Portal 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 provider of cloud platform solutions that employs rigorous and sophisticated security processes to guard data privacy from malicious or accidental incidents.

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