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# Issue Control

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# Approval

|  |  |  |
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# General

## Acronyms and Abbreviations

|  |  |
| --- | --- |
| Term | Description |
| MRCP | Magnetic Resonance Cholangiopancreatography |
| GIT | Gastrointestinal tract |
| PJ | Pineapple Juice |
| cT1 | Corrected T1 |
| PDFF | Proton Density Fat Fraction |
| LMS | LiverMultiScan |
| ROI | Region of Interest |
| LoA | Limits of Agreement |
| AC | Acceptance Criteria |

## Internal References

|  |  |
| --- | --- |
| Ref | Description |
| RA0302 | MRCP+v1 In-Vivo Performance Testing Report |
| RA0457 | MRCP+v1 Performance Literature Review |
| RTD0555 | Image-based Automatic Processing Algorithmic Specification |
| IIP105 | LiverMultiScan v3 In Vivo Performance Testing Report |
| RA0673 | LiverMultiScan v4 In Vivo Performance Testing Report |

# Purpose

The purpose of this report is to determine whether pineapple juice’s effect impact on participant’s cT1, Iron and PDFF for device (LiverMultiScan) reporting.

# Introduction

In Magnetic Resonance Cholangiopancreatography (MRCP) examination, the aim is to visualise the biliary tree structure. The bile, due to its fluid property, can provide intrinsic signal intensity in T2 weighted sequences. However, the fluid from the surrounding gastrointestinal tracts (GIT) also provides high signal intensity and, in this case, cause noise to the region of interest, i.e., biliary tree. To mitigate this issue, negative contrast agent is provided to patient prior to the MRCP scan. The contrast agent contains iron dioxide and effect by shortening T2 relaxation time on heavily T2 weighted sequences [1]. However, those contrast agents are unpalatable for patient with existing digestion/ingestion issues and are not widely available due to the requirement of storage and associated costs. Scientists thus directed focus on using various fruit juices with high manganese concentration as alternatives [2]. Pineapple juice, with manganese concentration of 27.6 mg/L is found to provide comparable effect of reducing T2 signal as commercial contrast agent ferumoxsil [1]. We therefore recommended imaging sites to provide pineapple juice about 20 min prior to image acquisition. However, the effect of pineapple juice on the biomarkers cT1, PDFF, T2\* (or Iron) on another Perspectum product, LiverMultiScan, was not exhaustively investigated. **This analysis report aims to investigate whether there is difference between the pre- and post- pineapple juice (PJ) administration on participant’s cT1, Iron and PDFF values with existing dataset acquired during 2018 performance testing for MRCP+ v1.**

# Material and Methods

During 2018 performance testing for MRCP+v1, 40 volunteers (20 healthy volunteers, 10 with hepatobiliary conditions and 10 with liver diseases), apart from undergoing MRCP+ image acquisition, were also scanned twice with LiverMultiScan protocol (before and after pineapple juice ingestion) on Siemens Avantofit 1.5T and Siemens Prisma 3T scanners. (Patient demographic can be found at MRCP+v1 In-Vivo Performance Testing Report – RA0303.)

In total 80 DICOM datasets were collected through the Perspectum Portal where historic data were stored. The LiverMultiScan images then underwent automatic processing of segmentation and multi-parametric quantification with LMS Discover v5 function loadAndProcessWithAutomation.m over one night. (Details can be found at Image-based Automatic Processing Algorithmic Specification – RTD0555). LMS reports were completed and uploaded to the corresponding records on the Perspectum Portal. Those retrieved DICOM datasets along with analysed json data(.json) map images(.png), report file(.pdf) and session file(.mat) can be found at NAS Drive (/Volumes/Image Analysis/Joao/pineapple\_results).

Among the 80 patients’ LMS reports, 14 of the patients’ reports were incomplete (some lack cT1 and Iron values) and therefore were excluded from further analysis. After matching, there were in total 60 LMS reports (30 pre-PJ and 30 post-PJ), the segmented cT1, Iron and PDFF median values and interquartile range values were organised to proceed with cross comparison against LMSv3 performance testing experiment. (Please see Appendix 1 for organised datasets of the pineapple juice experiment). In order to facilitate interpretation of the findings, the acceptance criteria established during LMSv4 performance testing were recruited to from conclusion. Figure 1 shows the schematic summary of the comparison of pineapple juice experiment with performance testing experiment. Both of these experiments had two scans each. The difference between these two experiments is the introduction of pineapple juice.

Shape

Description automatically generated

Figure Schematic presentation of data comparison between Pineapple Juice Experiment (left) and Performance Testing Experiment (right)

# Results

### Comparison within Pineapple Juice Experiment

From both histograms and boxplots (Figure 2 to Figure 4), the distributions of the data collected do not follow Gaussian distribution. This is expected because the participants scanned include both healthy and unhealthy individuals. The sample sizes of 13 in the Avantofit group and 17 in the Prisma group are also not considered large.A picture containing graphical user interface

Description automatically generated

Figure Box plot to show distribution of data collected with Siemens Avantofit 1.5T scanner

Text

Description automatically generated with low confidence

Figure 2 Box plot to show distribution of data collected with Siemens Prisma 3T scanner

Graphical user interface

Description automatically generated with medium confidence

Figure Histograms to show distribution of data collected with Siemens Avantofit 1.5T scanner

Graphical user interface, chart

Description automatically generated

Figure Histograms to show distribution of data collected with Siemens Prisma 3T scanner

Further analysis aims to visualise if the values are different across the 2 timepoints. Line plots (Figure 5) below show the trend of the biomarkers after PJ administration with the red lines connecting the medians for both datasets. Median was chosen due to the skewness of the measurements resulted from healthy and unhealthy participants. From Figure 5 and Figure 6, the medians of the collected data do not visually represent an obvious trend of the biomarkers after PJ ingestion. Another type of graph is therefore used.

Graphical user interface

Description automatically generated

Figure Line trends of data collected with Siemens Avantofit 1.5T scanner. Blue dots are pre-PJ values. Orange dots are post-PJ values

Graphical user interface

Description automatically generated

Figure Line trends of data collected with Siemens Prisma 3T scanner. Blue dots are pre-PJ values. Orange dots are post-PJ values

The bar plots below (Figure 7 and Figure 8) show the difference between post-PJ values and pre-PJ values for each biomarker with red lines indicating the medians of the differences. The bar above 0 shows the positive outcome after the subtraction: (post-PJ) - (pre-PJ) and vice versa. These graphs showed a positive change in the cT1 after PJ ingestion, collectively no change in the Iron values, and a slight decrease in the PDFF value on both Avantofit and Prisma groups.

Chart, waterfall chart

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Figure Bar charts to show the differences after subtraction of data collected with Siemens Avantofit 1.5T scanner. Red lines indicate the median of the difference (Post-PJ values – Pre-PJ values)

Chart, waterfall chart

Description automatically generated

Figure Bar charts to show the differences after subtraction of data collected with Siemens Prisma 3T scanner. Red lines indicate the median of the difference (Post-PJ values – Pre-PJ values)

### Comparison between Pineapple Juice Experiment and Performance Testing Experiment

The above results can potentially conclude pineapple juice’s effect on the biomarkers, especially on cT1 and PDFF. However, the question we would like to answer is whether the change caused by the pineapple juice is more than a repeatability scan without any pineapple juice. We therefore compare the pre-PJ and post-PJ scans results with the LMSv3 performance testing results to determine whether the differences seen on pineapple juice data is bigger than the measurement bias. Subsequently, we should use acceptance criteria of measurement bias to determine whether the differences cause by pineapple juice will be concerning to us. Bland-Atman plots are used for this purpose.

#### cT1 Comparison on 1.5T

Chart, scatter chart

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Figure Bland-Altman plot of pineapple juice cT1 values with difference (Pre-PJ values – Post-PJ values) plotted against mean of the cT1 values from Siemens Avantofit 1.5T

Chart, scatter chart

Description automatically generated

Figure Bland-Altman plot of LMSv3 performance testing cT1 values with difference (Scan1- Scan2) plotted against mean of the cT1 values from Siemens Avantofit 1.5T

Bland-Altman plots (Figure 9 and Figure 10) for cT1 comparison on 1.5T showed the measurement bias of the pineapple dataset (-9.38 ms) is smaller than the performance testing dataset (-13 ms). To interpret the results, one should understand that Bland-Altman analysis performed for LMS device performance testing is to investigate repeatability and reproducibility, meaning 2 identical scans were consecutively performed. In the context of pineapple juice data, pre-PJ and post-PJ scans were considered as scan 1 and scan 2. Therefore, if the measurement bias fall within accepted measurement bias will address that the effect of pineapple juice on measured biomarkers will be neglectable because during normal measurement procedure which do not introduce pineapple juice as intervention, measurement bias effect has larger impact on the precision of measurement.

#### cT1 Comparison on 3T

Chart, scatter chart

Description automatically generated

Figure Bland-Altman plot of pineapple juice cT1 values with difference (Pre-PJ values – Post-PJ values) plotted against mean of the cT1 values from Siemens Prisma 3T

Chart, scatter chart

Description automatically generated

Figure Bland-Altman plot of LMSv3 performance testing cT1 values with difference (Scan1 -Scan2) plotted against mean of the cT1 values from Siemens Prisma 3T

Figure 11 and Figure 12 for cT1 comparison on Prisma 3T showed the measurement bias of the pineapple dataset is about 7.3 ms higher. However, the Limits of agreement (LoA), which is represented as ± 1.96\* Standard Deviation (SD), is larger in the LMS v3 performance testing data (-76.9 ms to 52.9 ms) than those in the pineapple juice data (-60.72 to 22.14). In practice, when setting out the acceptance criteria for measurement precision based on Bland-Altman analysis, one would set the acceptance criteria (AC) region larger than the LoA, i.e., outside the dash lines in Figure 12 left. Therefore, if the LoA in LMS device performance testing cover the LoA in pineapple juice dataset, one can conclude that the **extend of the measurement bias** will be acceptable. This also imply that the measurement bias effect has larger impact on the precision of measurement than pineapple juice’s effect.

#### PDFF Comparison on 1.5T

Chart

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Figure Bland-Altman plot of pineapple juice PDFF values with difference (Pre-PJ values – Post-PJ values) plotted against mean of the PDFF values from Siemens Avantofit 1.5T

Chart, scatter chart

Description automatically generated

Figure Bland-Altman plot of LMSv3 performance testing PDFF values with difference (Scan1- Scan2) plotted against mean of the PDFF values from Siemens Avantofit 1.5T

#### PDFF Comparison on 3T

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Figure Bland-Altman plot of pineapple juice PDFF values with difference (Pre-PJ values – Post-PJ values) plotted against mean of the PDFF values from Siemens Prisma 3T

Chart, scatter chart

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Figure Bland-Altman plot of LMSv3 performance testing PDFF values with difference (Scan1 -Scan2) plotted against mean of the PDFF values from Siemens Prisma 3T

Figure 13 to Figure 16 show the Bland-Altman plots for PDFF quantifications on Avantofit 1.5 and Prisma 3T data. Although the measurement biases are higher in the pineapple juice datasets than those from LMSv3 performance testing data for both 1.5T and 3T arms, PDFF is a metric represented in the fashion of percentage and all the bias are no bigger than 1% PDFF. In LMSv3 performance testing, the acceptance criteria for segmented PDFF were set out as **Limits of agreement ± 4%.** With the bias and LoA of the data acquired for pineapple juice effect investigation all fall within this criterion, we therefore do not worry about whether pineapple juice cause reporting issue on PDFF in LMS.

# Discussion & Future Work

For cT1 and PDFF, the pineapple juice used for MRCP+ image acquisition does not affect the reporting of cT1 and PDFF on LiverMultiScan. Strictly speaking, the values of cT1 and PDFF obtained from pineapple juice data should be transformed to log-space due the data were not normally distributed. However, for better comparison with the performance testing data, we did not conduct the transformation and back-transformation. The observation with the acquired Bland-Altman plots showed that there is no proportional relationship between the differences and mean of the measurements[3].

The comparison of T2\* and iron between the pineapple juice datasets and LMS v3 performance testing results was not conducted because during LMS v3, we reported ROI T2\* values but not segmented T2\* values and we did not directly report iron. However, Figure 7 and Figure 8 showed no difference after pineapple juice ingestion on segmented iron. These observations allow us enough confidence to flexibly change order in the image acquisition protocol for future studies.

There are some future experiments can be conducted to further validate the conclusion of this analysis report. A bigger sample size and choose of appropriate statistical test is also suggested to be determined.

### Impact from Various Nutrients other than Manganese

The element of focus for the current analysis is manganese. Research done by Hiraishi et al. showed that manganese from orally administered fruit juices are poorly absorbed and do not significantly elevate serum concentrations up until 6 hours after pineapple juice ingestion [4]. The time interval from the moment before pineapple juice administration to image acquisition is roughly up to 20 min. The effect of manganese on the biomarkers are therefore neglectable.

According to United State Department of Agriculture, a bottle of 100 ml unsweetened pineapple juice contains nutrients such as fat (0.08 g), sugar (14.5 g), dietary fibre (0.8 g), protein (0.42 g), and minerals including Calcium (14mg), Copper (0.09 mg), **Iron (0.28 mg),** Magnesium (14mg), **Manganese (1.12 mg**), Phosphorus (6 mg), Potassium (122 mg), Sodium (1mg), and Zinc (0.01 mg) [5]. To work out exactly which element cause T1 and T2 relaxation times change in the patients’ liver requires extensive understanding of magnetic properties of minerals and expertise in nutrition absorption and pharmacodynamics.

### Impact of Hydration

The fluctuation of T1 and T2 relaxation times can be due to pure hydration. In this case, designing in-vivo experiment with fluids having various viscosity will be essential.

# Conclusions

It can be concluded that the pineapple juice used for MRCP+ image acquisition does not affect Perspectum’s reporting of cT1 and PDFF for LiverMultiScan. The differences are not statistically significant, and the differences are within the measurement bias acceptance criteria.

# Reference

[1] R. D. Riordan, M. Khonsari, J. Jeffries, G. F. Maskell, and P. G. Cook, ‘Pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography: a preliminary evaluation’, *Br. J. Radiol.*, vol. 77, no. 924, pp. 991–999, Dec. 2004, doi: 10.1259/bjr/36674326.

[2] S. Mohabir, R. D. Pitcher, R. Perumal, and M. D. M. Goodier, ‘The efficacy of pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography’, *SA J. Radiol.*, vol. 24, no. 1, Jul. 2020, doi: 10.4102/sajr.v24i1.1875.

[3] J. M. Bland and D. G. Altman, ‘Statistical methods for assessing agreement between two methods of clinical measurement’, *Lancet Lond. Engl.*, vol. 1, no. 8476, pp. 307–310, Feb. 1986.

[4] K. Hiraishi *et al.*, ‘Blueberry juice: preliminary evaluation as an oral contrast agent in gastrointestinal MR imaging.’, *Radiology*, vol. 194, no. 1, pp. 119–123, Jan. 1995, doi: 10.1148/radiology.194.1.7997537.

[5] ‘FoodData Central’. https://fdc.nal.usda.gov/ (accessed May 28, 2021).

# Appendix 1

## Collected Dataset for Pre and Post Pineapple Juice Ingestion

Spreadsheet in excel format along with graphs and scripts can be found at **IMSOL Controlled Register > Working > Pineapple Juice Investigation**

