LiMAx®

Simply analyzing liver function capacity

Erwin de Buijzer, COO

June 2017

Humedics

The LiMAx test is the only commercially available real-time and non-invasive *in vivo* liver function capacity test

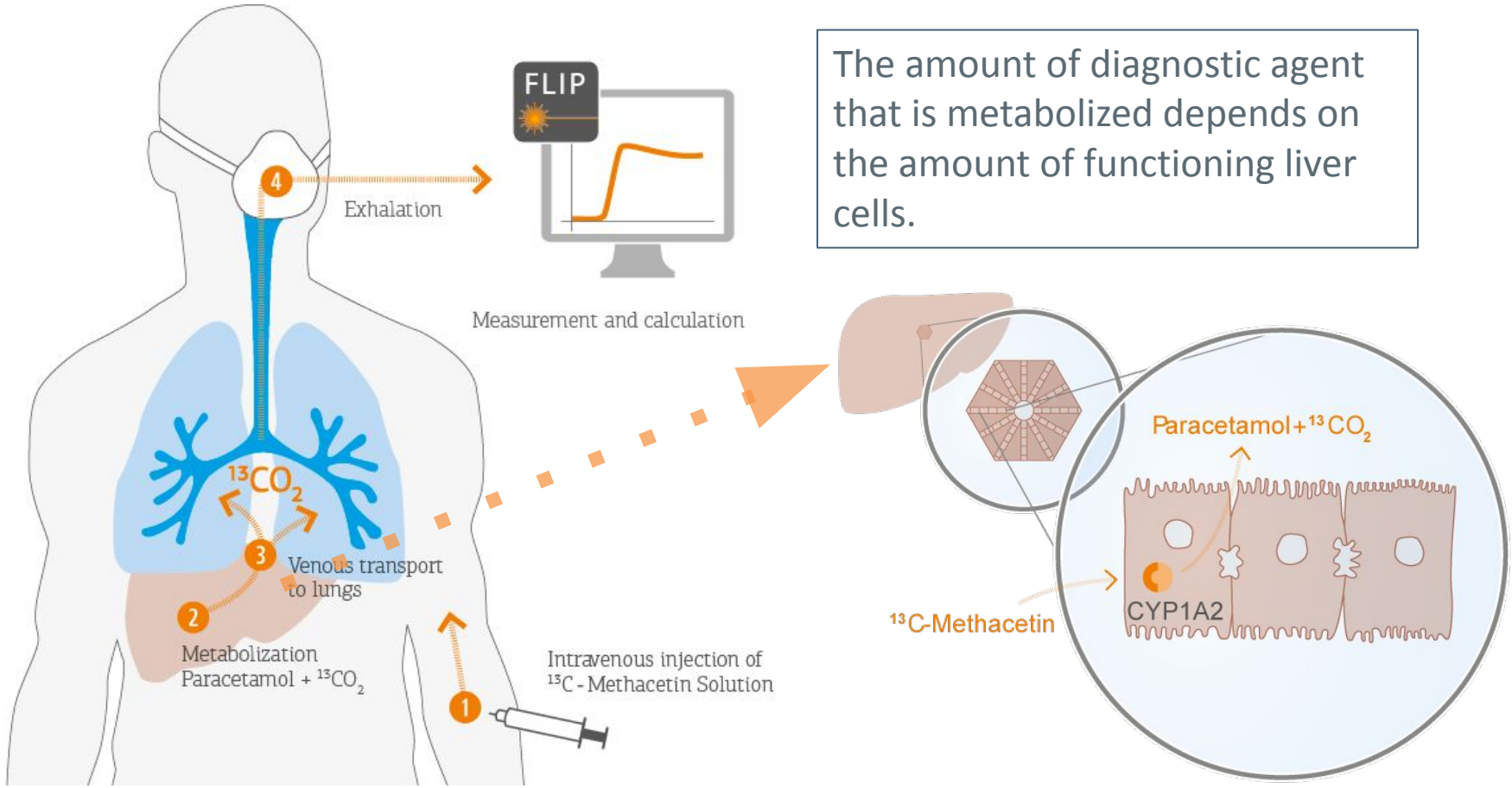
❶ Inject the diagnostic agent

❷ The diagnostic agent is exclusively metabolized by liver enzyme CYP1A2 into $^{13}CO_2$

❸ The patient exhales $^{13}CO_2$

❹ The LiMAx test device measures the amount of exhaled $^{13}CO_2$ in real time

❺ Result is shown instantaneously on the display



The amount of diagnostic agent that is metabolized depends on the amount of functioning liver cells.

The LiMAx system is a unique combination of state of the art technology and an approved diagnostic agent

+

LiMAx

The medical device has several advantages over other existing technologies

- Instant on
- No calibration needed
- Highly accurate
- Accurate over time

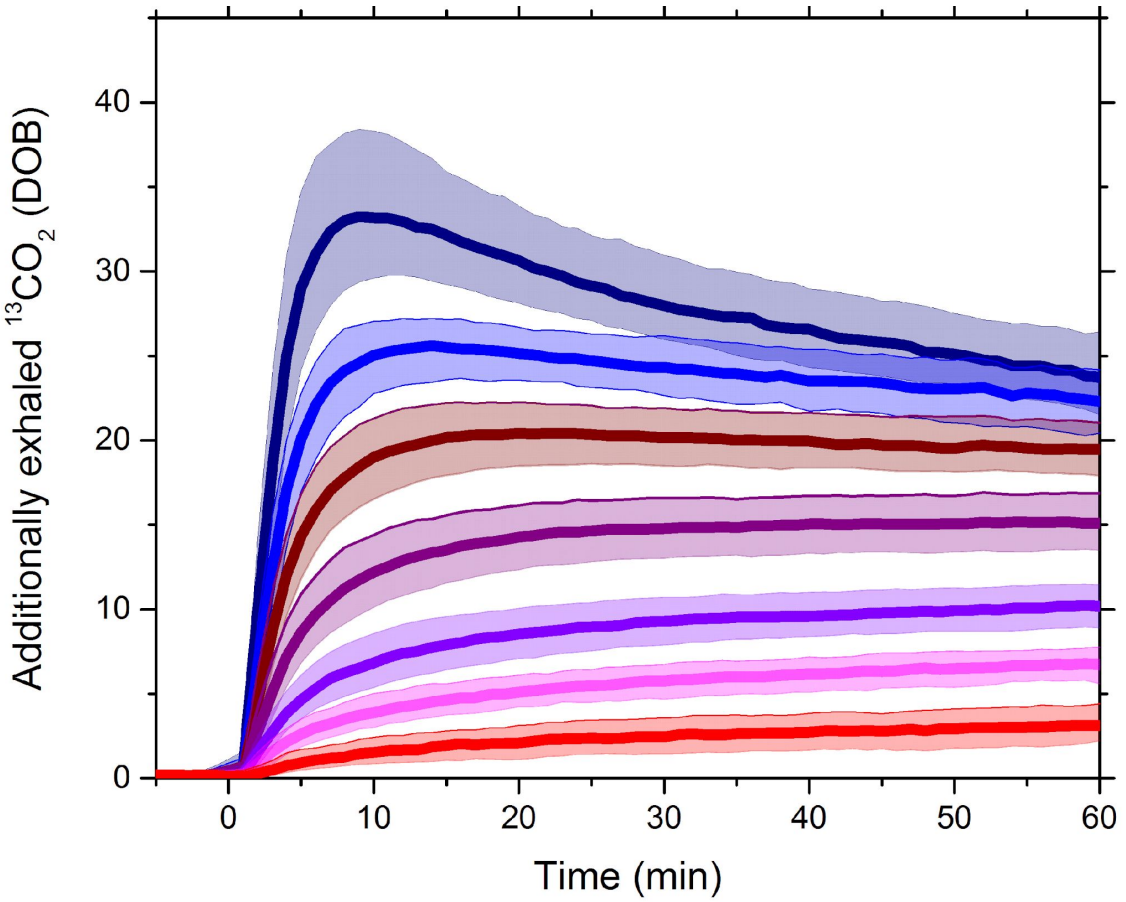
The test kit with diagnostic agent and breathing mask is unique

- Pharma dossier approved in Europe
- Shelf life of 2 years
- Bundled with class IIa medical device

A LiMAx measurement has a characteristic shape that indicates the liver function –10. 000 measurements in humans have been analyzed

+

LiMAx

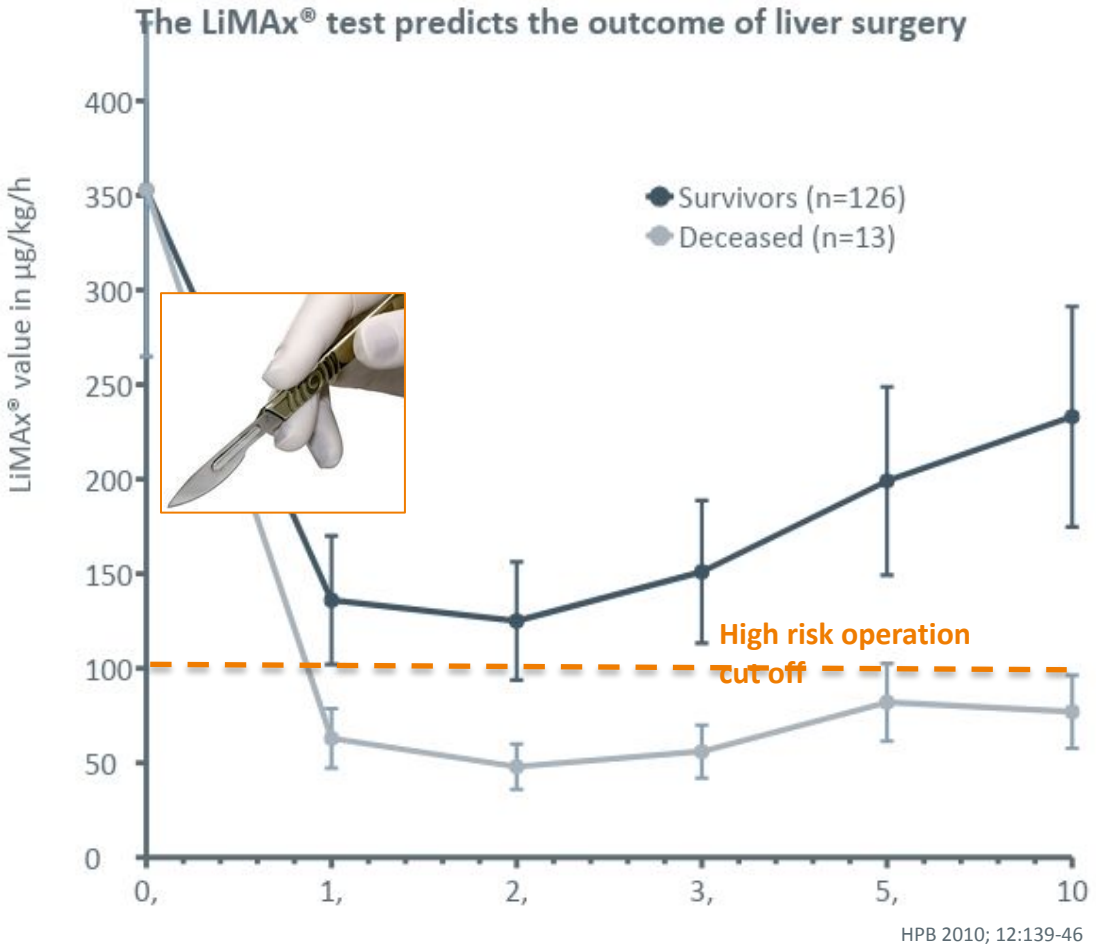


J Breath Res. 2017 Jul 25.

In Liver Surgery the LiMAx® test accurately predicts the post-operative risk of Acute Liver Failure (ALF)

- The LiMAx® test has demonstrated unprecedented prognostic value in determining the risk of post-operative acute liver failure (ALF)

- Pre-operative LiMAx® testing resulted in a 60% reduction in post-hepatectomy ALF



HPB 2010; 12:139-46

The LiMAx® test drives decision making in liver surgery

① Preoperative LiMAx measurement

② Planning of surgery

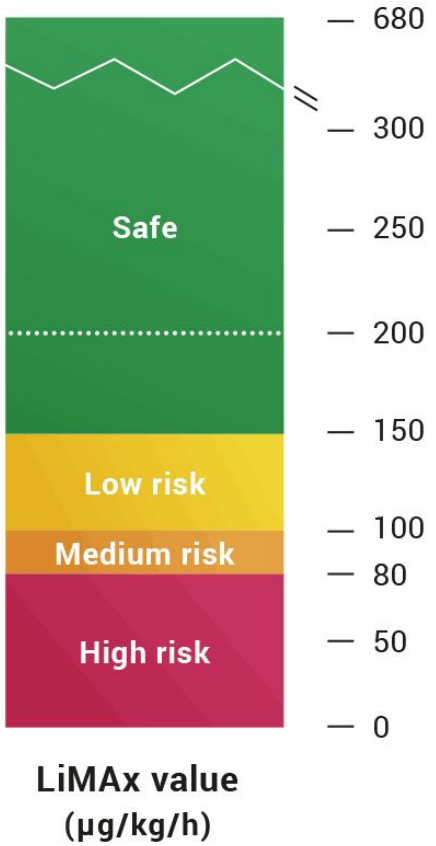
Preoperative LiMAx value: 500

Total liver volume: 1200 ml
Tumor volume: 200 ml
Functional liver volume: 1000 ml
Resected liver volume: 800 ml
Remnant liver volume: 400 ml

Calculated* residual LiMAx value: 200

$$* \frac{\textit{Remnant liver volume}}{\textit{Functional liver volume}} \times \textit{Preoperative LiMAx value}$$

$$\frac{400}{1000} \times 500 = 200\ \mu g/kg/h$$



③ Postoperative LiMAx measurement

Postoperative LiMAx value: 200

max. resection volume: 1000 ml

The LiMAx® test has proven health economic benefits in the registration trial

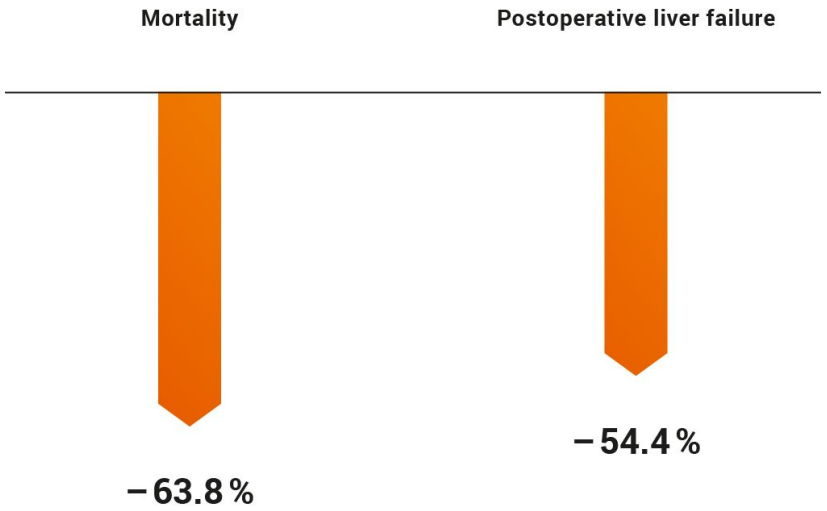
The LiMAx® test demonstrated in the clinical registration trial that based on a post-operative LiMAx® cut off value of 150 a decision on transfer to the normal ward or ICU could be made

- Of all patients that were transferred to the normal ward, none had to be transferred to the ICU later on
  - Specificity 100%

- 90% of the patients that were recommended to be transferred to the ICU, were confirmed by a team of ICU doctors
  - Sensitivity 90%

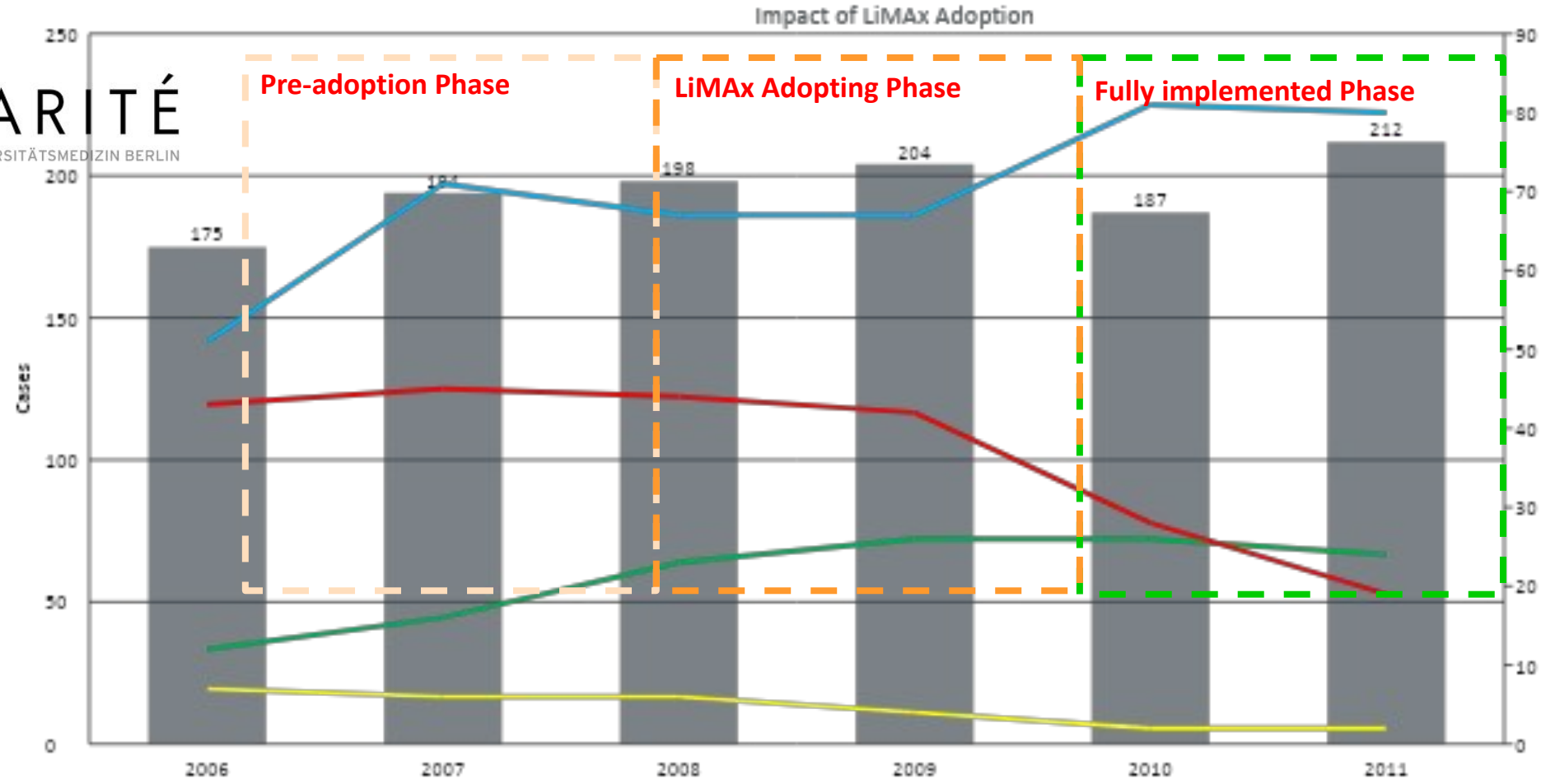
Use of the LiMAx® test in liver surgery results in

- 3 days shorter overall length of stay (LoS) in the hospital
- 1,5 days reduction in LoS in the ICU
- 62% less patients sent to the ICU
- This translates in roughly €2500 savings per patient per liver surgery operation



Article accepted for publication 2018

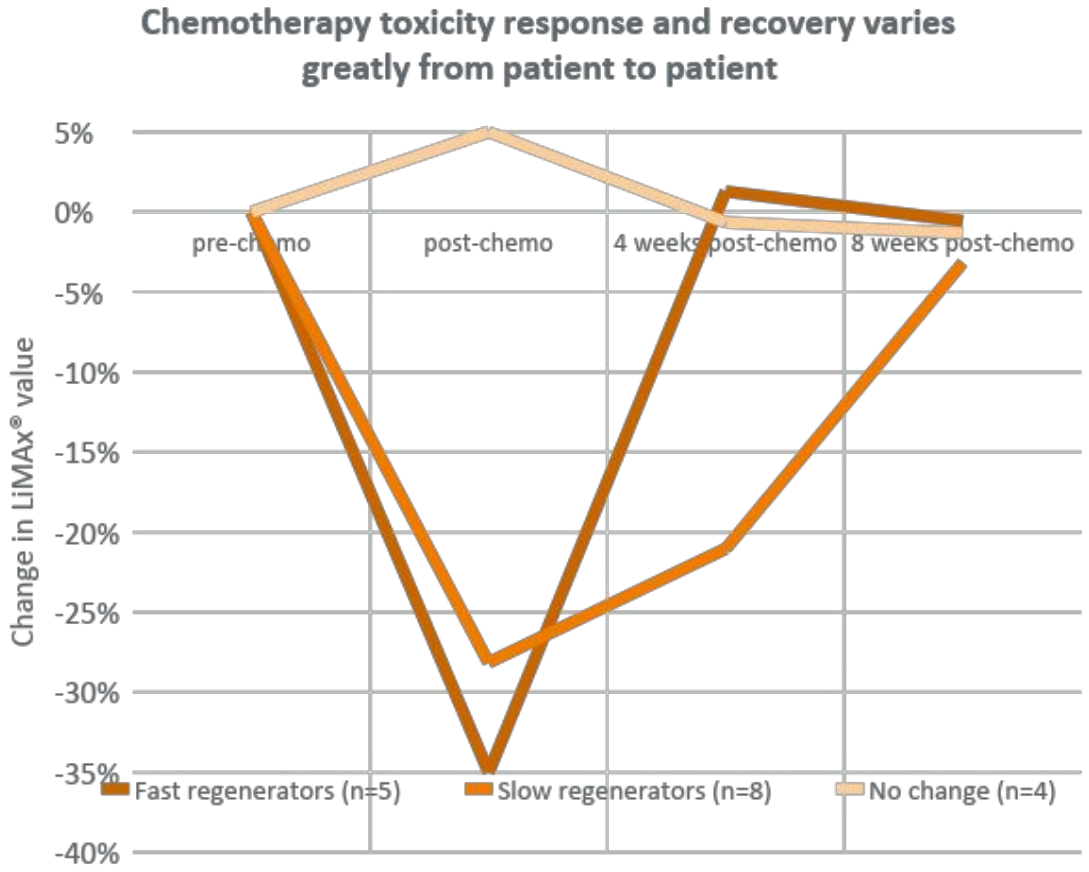
LiMAx® adoption results in treating more complex cases in real life



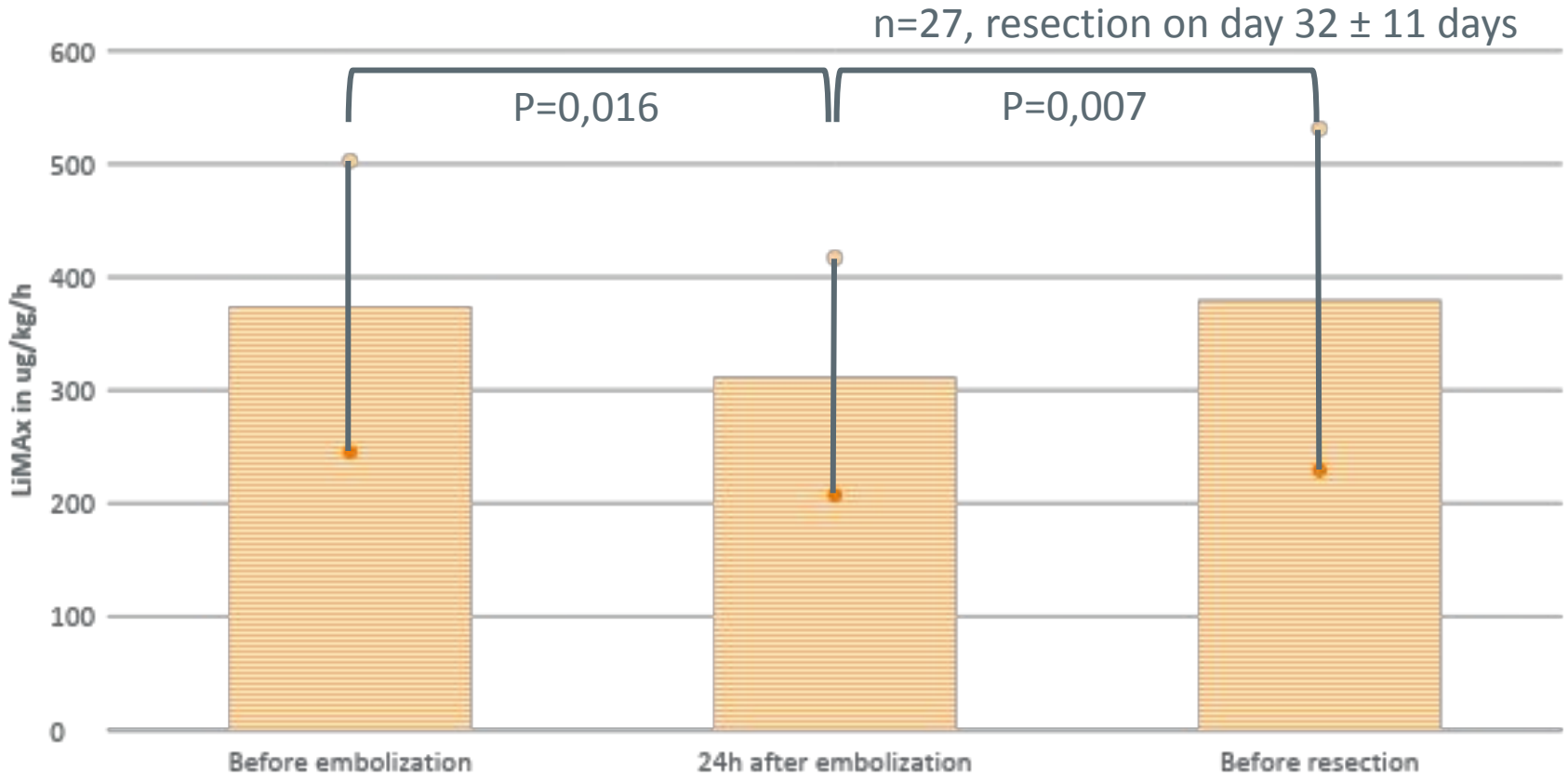
Maximillian J et al, HPB-2015-0024.R2

The LiMAx® test allows effective monitoring and management of chemotherapy toxicity

- The LiMAx® test is the ideal tool for monitoring the toxicity response to chemotherapy
- The LiMAx® test can measure the impact of chemotherapy, including dose adjustments, termination of therapy and monitoring of the time needed for recovery
- Following neoadjuvant chemotherapy, use of the LiMAx® test allows better, safer and more cost-effective patient management



The LiMAx® test is able to measure even small changes in liver function, for example in portal vein embolization

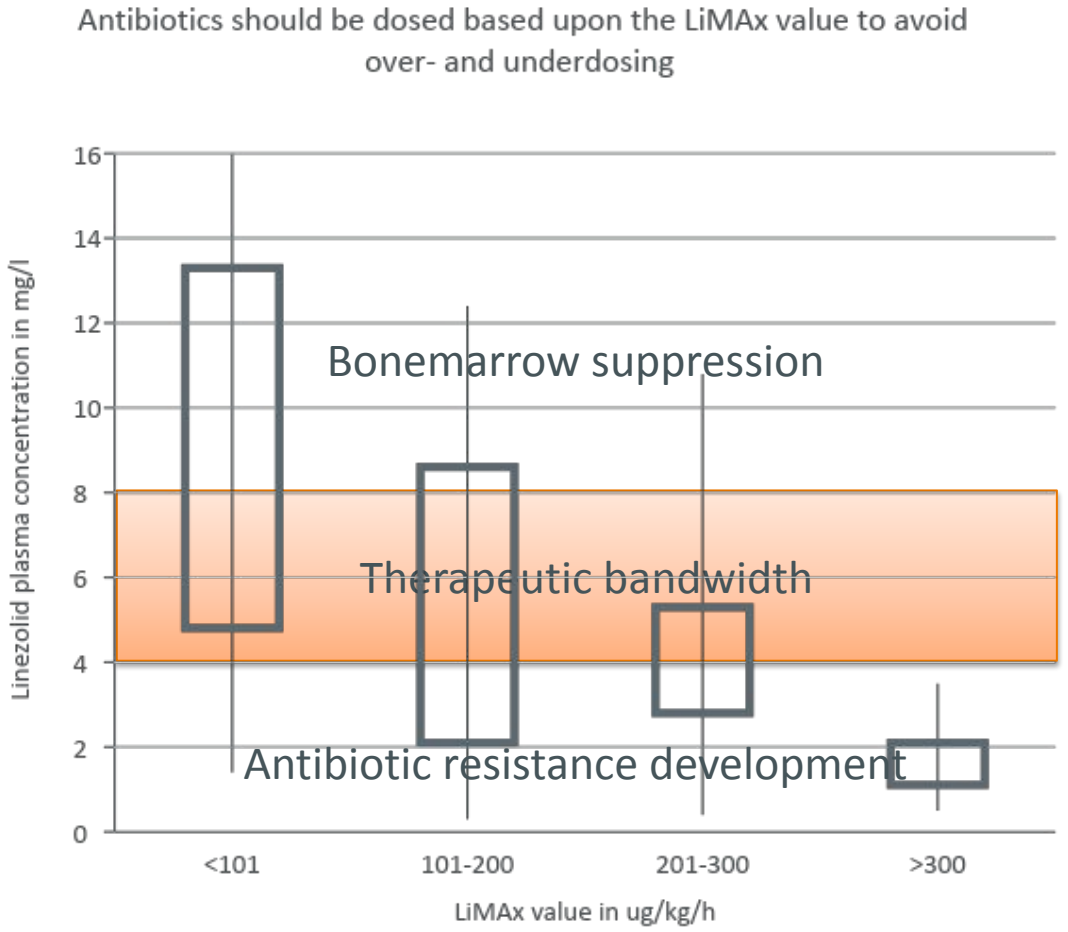


Röth, Alizai, UK Aachen, DGCH 2012

Dose optimization of drugs using LiMAx® can prevent toxicity or lack of efficacy

- Overdosing of drugs can lead to intoxications resulting in complications
- Complications of inadequate dosing of an antibiotics like linezolid:
  - Immunosuppression if overdosed
  - Lack of effect/Death or
  - Bacterial resistance development if the dosing is too low

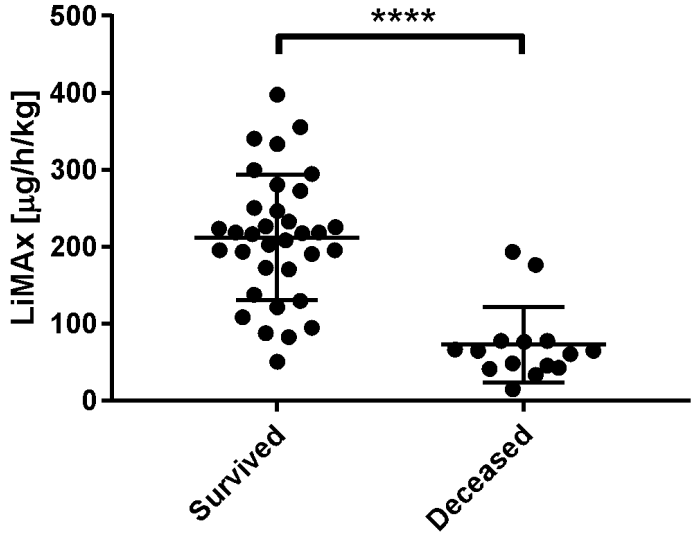
- Inadequate dosing of immunosuppressants after liver transplantation leads to
  - Renal toxicity / neurotoxicity in overdosing
  - Transplant rejection if the dose is too low
    - » Clin Transplant 2011; 25:436-443



ECCMID 2016; P1193

The LiMAx® test has the highest predictive value for the outcome of Acute Liver Failure (ALF)

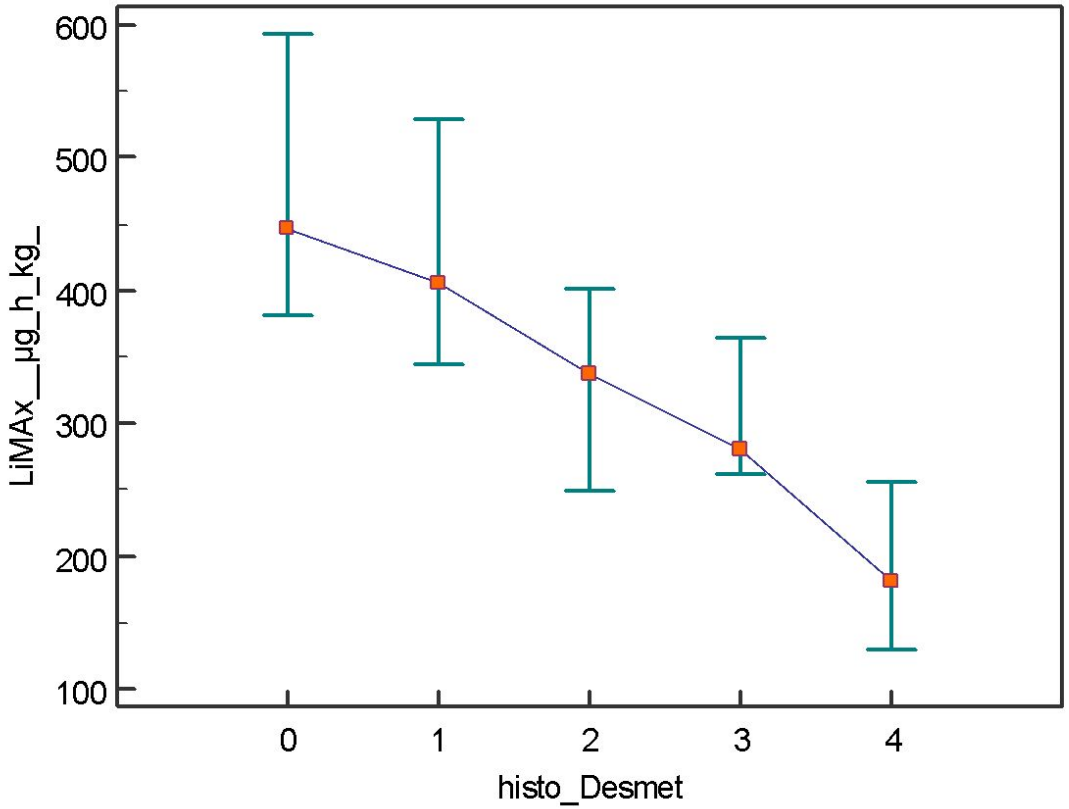
- The LiMAx® test may be a helpful additional prognostic tool in patients with acute- and acute-on-chronic liver failure achieving the highest statistical significance.
- This is a typical finding confirmed by several centers
- And is changing the diagnostic decision making to request high urgent liver transplants



characteristic	group I (survivors)	Outcome group II (non-survivors, LT)	p-value
LiMAx, µg/kg/h	213 ± 78 [51-356]	85 ± 65 [15-194]	< 0.0001
bilirubin, mg/dl	13.47 ± 9.38 [0.6-32.9]	14.23 ± 8.87 [1.1-30.1]	n.s.
INR	1.49 ± 0.71 [1.00-4.30]	2.17 ± 0.8 [1.67-4.07]	< 0.05
creatinine, mg/dl	0.72 ± 0.21 [0.41-1.12]	1.28 ± 0.59 [0.49-2.16]	< 0.001
AST, U/l	948.08 ± 940.81 [51-3983]	1056.38 ± 1692.93 [43-4878]	n.s.
ALT, U/l	1384.73 ± 1660.86 [20-7351]	846.13 ± 1508.77 [12-4375]	n.s.
MELD	18.77 ± 5.69 [6-31]	26.38 ± 2.92 [24-33]	< 0.01

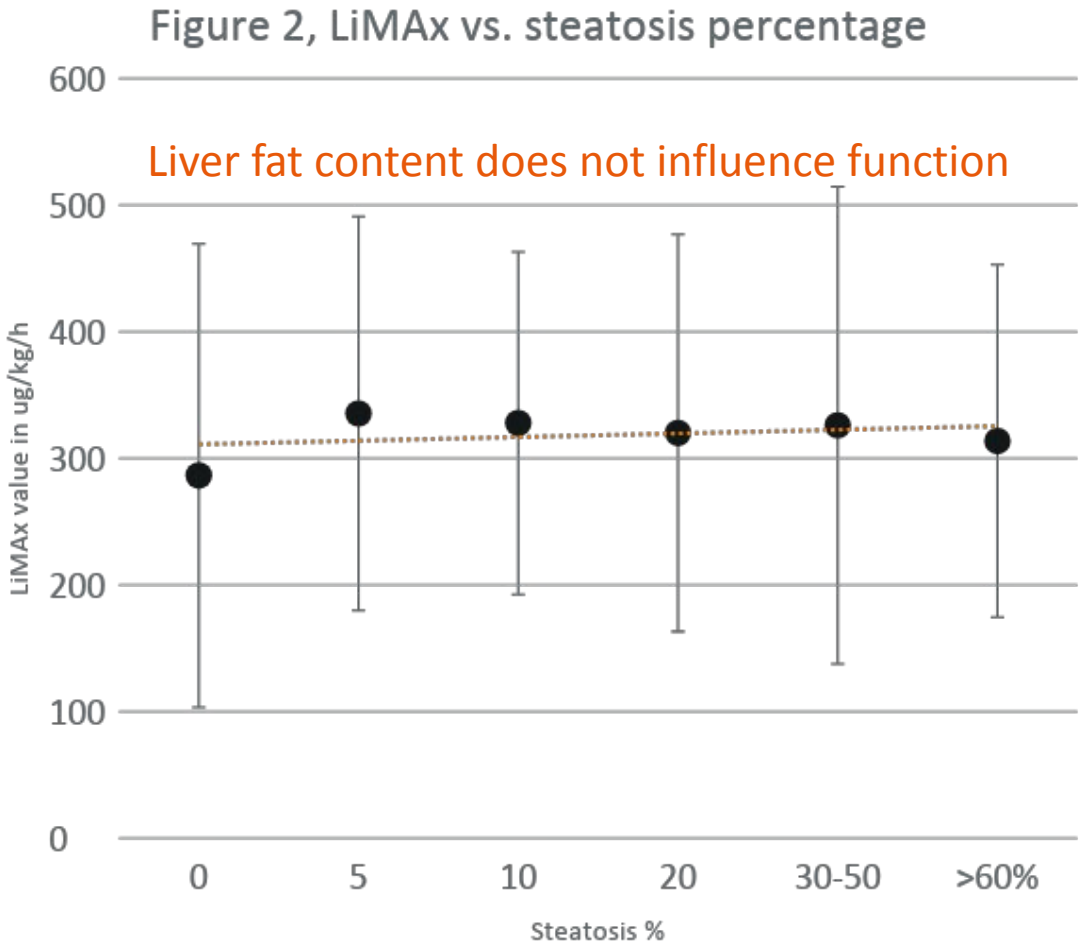
GASL 2018

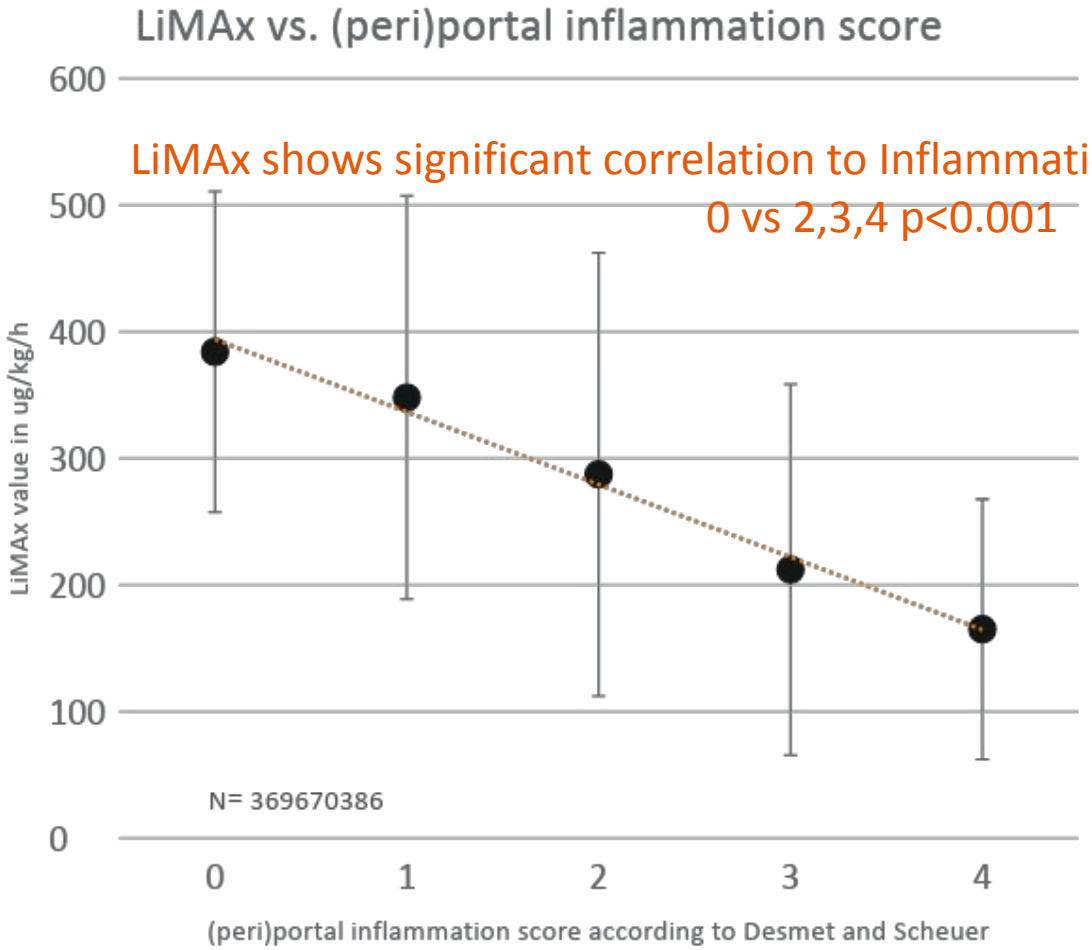
LiMAx® reliably stages chronic liver disease non-invasively
This makes it optimal liver test for a patient stratification



- The LiMAx test demonstrated excellent correlation to histological analysis of liver tissue
- Based on this analysis cut off values have been determined for cirrhosis
  - Sensitivity 90%, specificity 95%
  - +Likelihood ratio 14,5, -LH ratio 0,13
- This makes the LiMAx test the preferred tool for non-invasive staging of chronic liver failure
  - Replacing biopsy as the ‘best available’ gold standard

LiMAx® measures accurately inflammation in a fatty liver which is a key characteristic of NASH (n=246)





Inflamm Intest Dis 2017;2:35

LiMAx® is the first non-invasive function test to monitor the recovery of the liver function capacity after obesity surgery

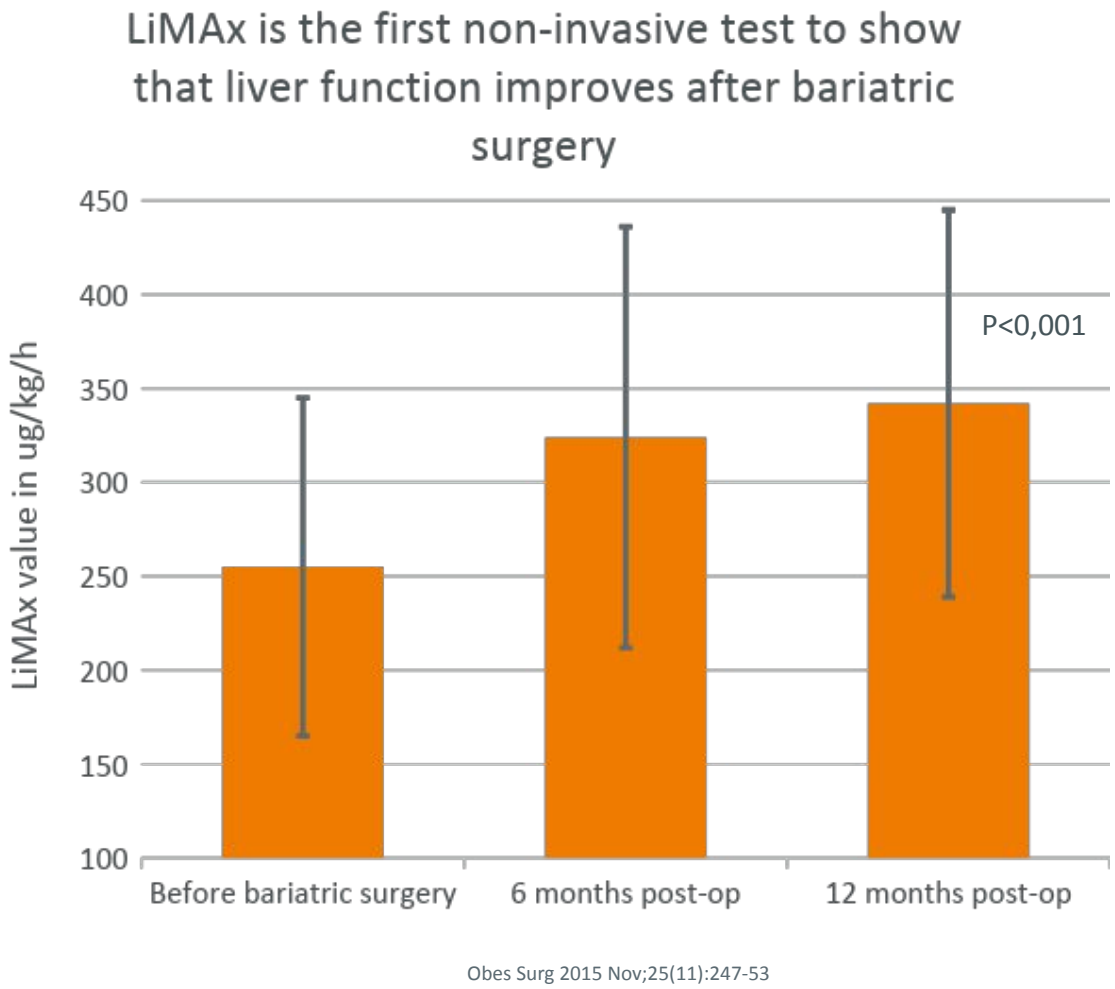
- The LiMAx® test is the first test to demonstrate non-invasively that the liver function capacity recovers after bariatric surgery
- LiMAx® value showed good correlation to the NAS score of per-operative biopsies
- A follow up study including 200 patients receiving bariatric surgery is ongoing

- Obese patients have larger livers; however the liver function capacity (LiMAx®) is impaired

» Sarcopenia Muscle. 2015 Jun;6(2):155-63

- Obese patients showed impaired recovery of the liver function capacity after liver resection surgery

» J Invest Surg 2015 Feb;28(1):24-31



Obes Surg 2015 Nov;25(11):247-53

„The LiMAx test is for the liver…. what GFR is for the kidney“

Prof. Peter Galle, University of Mainz – past president International Liver Cancer Association

- Non-invasive evaluation of chronic liver disease like HCV, NASH
  - Ideal for stratification of patient cohorts
- Monitoring of therapy effect on the liver
  - Hepatic toxicity of chemotherapy can be measured and has therapeutic consequences
  - Pre-operative determination of post-operative risk of acute liver failure
  - Post-transplantation monitoring of liver function
- Dosing optimization of drugs according to liver function
  - Dose adjustment of antibiotics, immunosuppressants and other drugs that are eliminated via the liver, can be based on LiMAx value
- Health Economic advantages
  - Shorter hospital stay
  - Avoiding ICU stay, since complications can be predicted and avoided