AXINON® renalTX-SCORE®*

Metabolomics-Based, Non-Invasive Detection of Kidney Allograft Rejection

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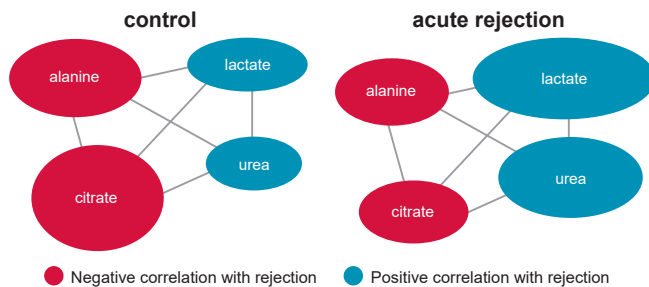## AXINON® renalTX-SCORE® for Diagnosis of Renal Allograft Rejection

- Non-invasive urine test to identify kidney rejection
- Indication of kidney injury based on a metabolite biomarker constellation
- Outpatient follow-up care even before biopsy is performed

Kidney transplantation is the treatment of choice for end stage renal disease. Approximately 10% of all kidney transplant recipients experience an episode of acute rejection within the first year post-transplant [1-3]. Patients with episodes of acute rejection have an increased risk of late graft failure, underlining the importance of timely detection and therapy of acute rejection [4-6].

AXINON® renalTX-SCORE® is a non-invasive test intended to support the diagnosis of a kidney allograft rejection in conjunction with other measurements and clinical evaluations.

The urine test is not based on a single marker, but on multi-parametric metabolomics analysis. It evaluates a metabolite constellation of the four metabolites alanine, citrate, lactate and urea, which have been shown to be correlated with renal allograft rejection. The concentrations of single metabolites are not meaningful in the context of acute kidney rejection. Only the combination of all four metabolites into a metabolite constellation, allows to predict kidney rejection with sufficient reliability.

The AXINON® renalTX-SCORE® analyzes this metabolite constellation by Magnetic Group Signaling™ (MGS®) empowered NMR spectroscopy and calculates a score for acute graft rejection.

control | **acute rejection**

alanine, lactate, citrate, urea

- ● Negative correlation with rejection
- ● Positive correlation with rejection

Performance Data

AXINON® renalTX-SCORE® can detect renal allograft rejection. Combination of the AXINON® renalTX-SCORE® with eGFR results in the following performance:

| CUT-OFF	SENS [%]	SPEC [%]
0.007	83.3%	72.0%
0.037	59.5%	92.3%

Interpretation

AXINON® renalTX-SCORE® is a score, ranging from 0 to 100. A higher score indicates a higher probability of acute allograft rejection. Patients with a score below 3 have a probability of only 2.2% of an acute rejection. Only 11.2% of patients without an acute rejection have a score above 13.

We recommend to use the score in combination with eGFR and classify patients according to the AXINON® renalTX-SCORE® interpretation scheme (see below). With this scheme patients can be classified in three different risk categories for acute kidney rejection ranging from low to high.

RISK CATEGORY

renalTX-SCORE/eGFR^2	≤ 0.007	Low risk
renalTX-SCORE/eGFR^2	> 0.007	Intermediate risk
renalTX-SCORE/eGFR^2	≥ 0.037	High risk

- ● Acute rejection (cases)
- ● No rejection (controls)
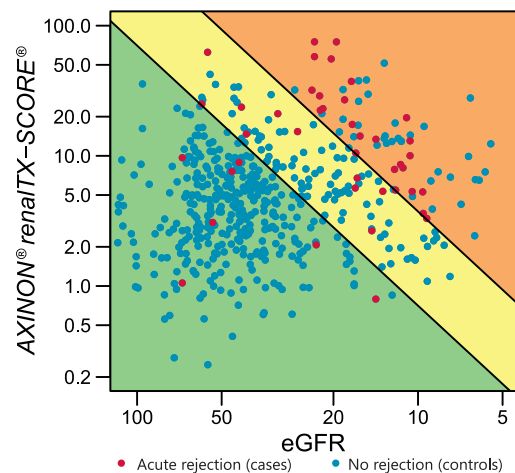
In the low risk category the risk of an acute rejection is very small (1 in 50), while it is increased in the intermediate (1 in 10) and in the high risk category (1 in 3). For the patient that means being classified in the intermediate or high risk range increases the probability of an acute rejection by the factor 5 or 20, respectively.
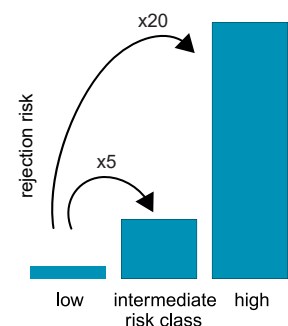
AXINON® renalTX-SCORE® is based on the four metabolites alanine, citrate, lactate and urea, whose concentrations are normalized to creatinine and then used in a non-linear model to calculate the score. For all metabolites an association with (patho)physiological conditions has been shown:

Substance	Pathophysiology	References
Citrate	↓ urinary citrate indicates renal tubular acidosis; hypocritraturia after ischemic reperfusion injury; ↓ urinary citrate indicates chronic kidney disease	[7-10]
Alanine	tubulitis-induced aminoaciduria before clinical manifestons of acute rejection; ↑ urinary alanine in patients with graft dysfunction; ↓ urinary alanine in patients with acute rejection	[11-13]
Lactate	↑ urinary lactate excretion in renal Fanconi syndrome patients due to reduced lactate co-transport in proximal tubule; ↑ urinary lactate in graft dysfunction	[12, 14]
Urea	↑ serum urea indicates decreased glomerular filtration rate; elevated urinary urea might increase serum levels described to be predictive for kidney transplant failure	[15]

Table: Substances delivered by AXINON® renalTX-SCORE®

Clinical Utility

- *AXINON® renalTX-SCORE®* can be used to monitor kidney transplant recipients starting 2 weeks after transplantation.

- *AXINON® renalTX-SCORE®* can indicate a renal rejection even without any clinical symptoms.

- *AXINON® renalTX-SCORE®* can indicate a renal rejection 1 to 7 days before a documented rejection.

- *AXINON® renalTX-SCORE®* is a non-invasive test, that can be performed from spot urine. Urine collection is even possible at home.

- *AXINON® renalTX-SCORE®* is a further application of the multi-testing capable *AXINON® System.*

The *AXINON® renalTX-SCORE®* test is especially useful in the following scenarios:

Use Cases

Support of decision for/against a biopsy: When symptoms are unclear, *AXINON® renalTX-SCORE®* can help to decide if a biopsy is necessary to check for acute rejection.

Initiation of therapy: In order to timely start medication, it is critical to detect acute rejection as soon as possible. *AXINON® renalTX-SCORE®* can help to see rejection on the metabolic level very early and give confidence in diagnosis/therapy decision.

Evaluation of success of therapy against acute graft rejection: *AXINON® renalTX-SCORE®* can be used to monitor response to rejection therapy against acute renal rejection.

Interpretation of unclear biopsy results: Sometimes, the result of a biopsy leaves space for interpretation to diagnose acute kidney rejection. *AXINON® renalTX-SCORE®* can be used as an additional source of information to decide on further measures.

Patients not eligible for biopsy: Due to conditions, such as anticoagulant therapy, some patients are not eligible for biopsy. In these cases *AXINON® renalTX-SCORE®* can be used to get a first impression of the patient's renal "status" and to decide how to proceed.

Support of communication with patients of needed biopsy or as source of information, if the patient denies biopsy: When patients are concerned about getting a biopsy for negative experiences in the past or other reasons, *AXINON® renalTX-SCORE®* can deliver an additional argument for or against a biopsy in order to support communication with the patient and find a joint decision.

How to Use the Test

Specimen Collection, Storage and Transport
The *AXINON® renalTX-SCORE®* test is performed on human urine samples collected according to standard techniques for laboratory testing. Standard clean specimen collection cups must be used. Urine specimens can be stored or transported at room temperature (20-30°C) for up to 24 hours before proceeding to sample preparation. The specimens are stable for further 48 hours at 2-8°C. For prolonged storage, freeze urine specimens at -20°C or below. Specimens are stable at -20°C for up to one month.

Test Principle
Samples are prepared with the *AXINON®* urine kit 1.0 and measured using a qualified *AXINON®* 600 MHz NMR system. The NMR measurement is controlled by the *AXINON® Software* and produces standardized NMR spectra which are interpreted by the *AXINON® renalTX-SCORE®* test. The calculated score is determined by a multiparametric assay of a metabolite constellation of biomarkers associated with kidney allograft rejection.

Literature

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