

## A Urinary Metabolite Constellation to Detect Acute Rejection in Kidney Allografts

Banas MC<sup>1</sup>, Neumann S<sup>2</sup>, Pagel P<sup>2</sup>, Putz FJ<sup>1</sup>, Krämer BK<sup>3</sup>, Rümmele P<sup>4</sup>, Eiglsperger J<sup>2</sup>, Schiffer E<sup>2</sup>, Banas B<sup>1</sup>  
<sup>1</sup> Dept. of Nephrology, University Hospital Regensburg, Germany, <sup>2</sup> numares AG, Regensburg, Germany, <sup>3</sup> Fifth Department of Medicine, University Medical Center Mannheim, Germany, <sup>4</sup> Dept. of Pathology, University Hospital Erlangen, Germany

### Background

#### Kidney transplant rejection

##### Routine diagnostics

- (clinical symptoms)
- GFR ↓
- urine production ↓

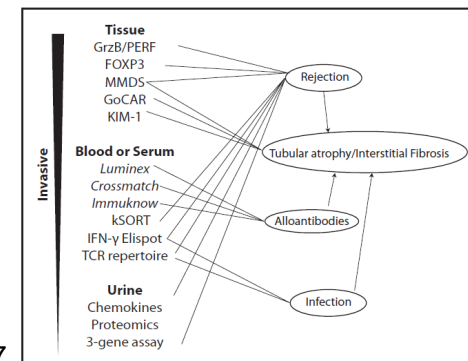
#### Confirmation by Transplant biopsy

Actual gold standard, but

- invasive
- risk of bleeding and organ damage
- maybe not representative

#### Requirements for an ideal biomarker

- appropriate sensitivity and specificity
- non-invasive
- quick diagnosis
- inexpensive



Safa K. et al, Curr Opin Nephrol Hypertens, 2017

### Material Methods

#### Discovery cohort (n=1883)

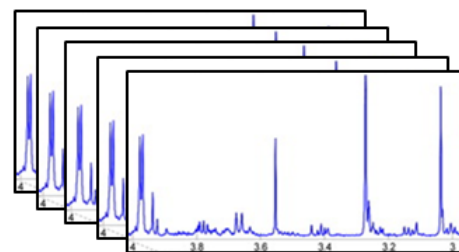
- urine samples with biopsy-proven acute rejection and controls



Urine samples



NMR analysis



NMR spectra

**Alanine**  
**Glucose**  
**Urea**  
**Creatinine**  
**Lactate**  
**Hippurate**

**2-Ketobutyric acid**  
**Citrate**  
**Biotine**  
**Carnosine**  
**Deoxyinosine**  
 ...

*Detected metabolite concentrations and constellations associated with rejection*

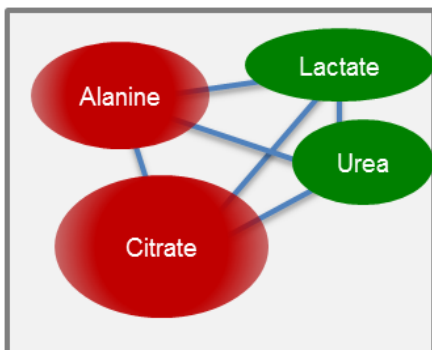
Banas M et al. Metabolomics 2018

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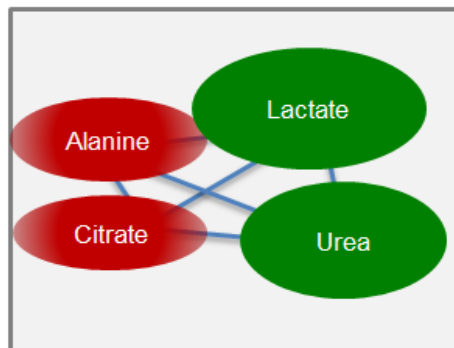
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### Results

- Negative correlation with rejection
- Positive correlation with rejection



Controls



Rejection

#### Clinical validation study:

Urine-based *metabonomic* fingerprinting for assessment of the rejection risk after renal transplantation – *UMBRELLA*

- Prospective observational study
- 109 patients after kidney transplantation have been included (January 2011 - October 2013, University Hospital Regensburg)
- 1 year follow-up starting with kidney transplantation
- Study visits were identical with regular visits
- 2,479 urine samples
- 296 transplant biopsies have been performed

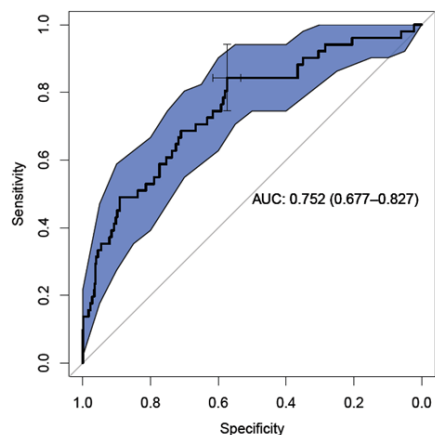
$$\text{renalTX-SCORE} = 100 / (1 + e^{-\omega}) \text{ with } \omega = 0.95 * C_{\text{Lactate}} + 0.25 * C_{\text{Urea}} - 0.25 * C_{\text{Alanine}} - 0.82 * C_{\text{Citrate}} - 3.00$$

and  $C_i$  as the creatinine-normalized urine concentration of metabolite  $i$

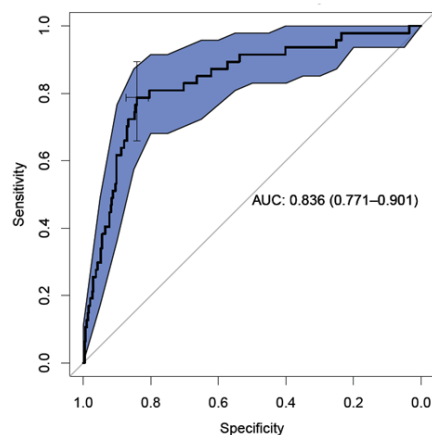
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## Results, Discussion and Outlook

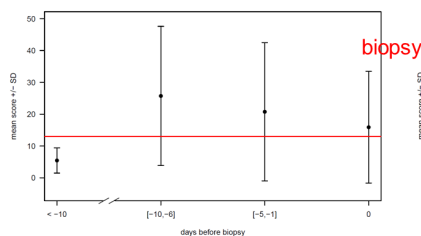


**Score alone**  
> 14 days after Tx

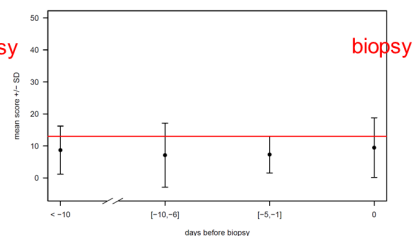


**Score / eGFR**  
> 14 days after Tx

Retrospective time course before positive biopsy



Retrospective time course before negative biopsy



Marked increase above threshold associated with high risk of acute rejection already 6 to 10 days before positive biopsy

### Summary

- Fast, precise and non-invasive detection of kidney transplant rejection from urine samples by NMR-Spectroscopy
- Successful prospective validation (UMBRELLA study) at the University Hospital in Regensburg
- The test showed an AUC of 0,75, which could be increased to an AUC of 0,83 by consideration of GFR
- Early detection of acute rejection 6 to 10 days before positive biopsy

### Outlook

#### The Parasol Study

- participating centers: Regensburg, Vienna, Prague, Grenoble, Barcelona