UNIVERSITÄTS-
KINDERSPITAL
ZÜRICH

ERNDIM
QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

Common sample 2019 – DPT CH
Adenine phosphoribosyltransferase (APRT) deficiency

Rotterdam, 3rd September 2019

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Case overview

Clinical information provided to the participants:

The female was admitted to hospital due to a history of pain on passing urine. Had been treated but urine collected off treatment.

Diagnosis:

Adenine phosphoribosyltransferase (APRT) deficiency

Kantonsspital Baden
KSB

Sample provided by Dr. Hans-Rudolf Räz and Dr. Hans-Ruedi Schmid (Kantonsspital Baden, Switzerland)

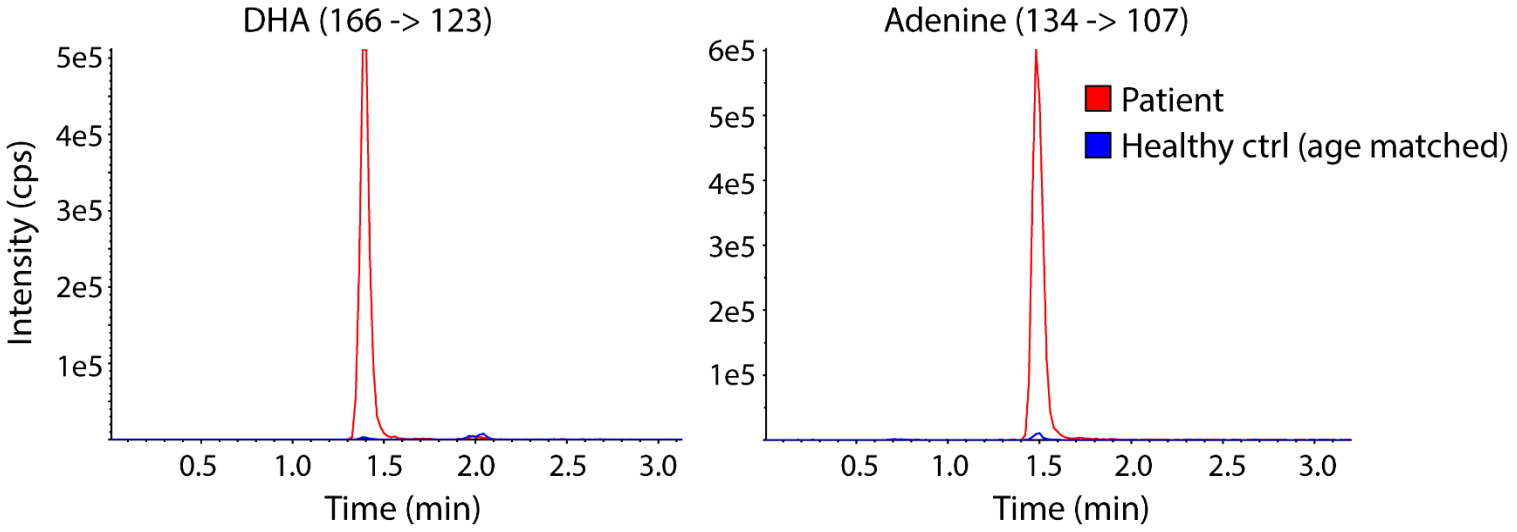
Initial presentation and investigations

- 28-year-old healthy Caucasian woman
- Right side abdominal pain
- Macro-hematuria
- No fever
- No dysuria
- No urinary tract infections
- CT scan reveals a Ø 2 cm concrement in the right renal pelvis

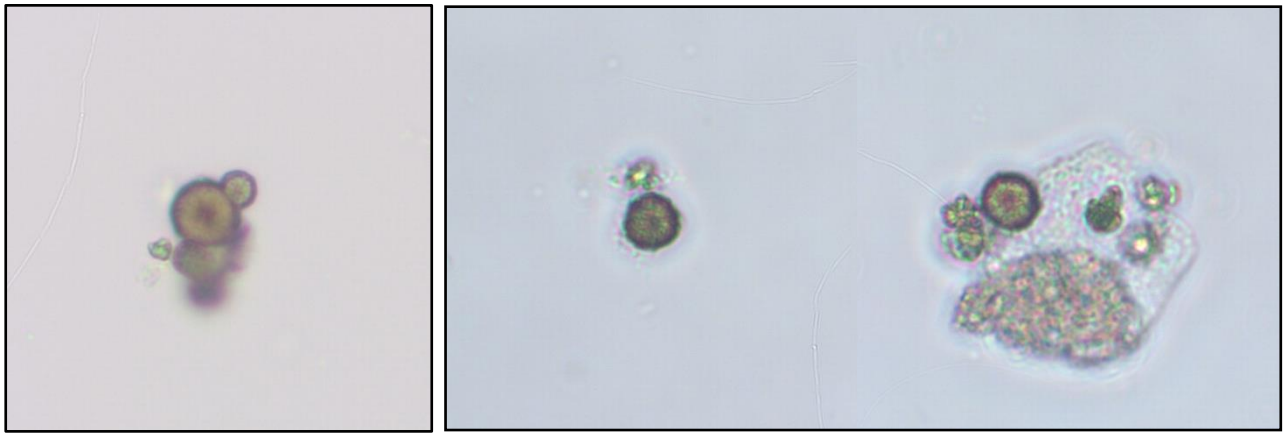
First metabolic workup in Zürich

Analysis	Metabolite	mmol/mol creat	Ref. range (mmol/mol creat)
Amino acids	Cystine	4	<19
	Lysine	18	12 – 52
	Arginine	<3	<7
	Ornithine	<3	<9
Organic acids	Oxalic acid	<50	<200
Purines/Pyrimidines (Pu/Py)	Uric acid	233	129 – 536
	Xanthine	3.4	<5
	2,8-Dihydroxyadenine (DHA)	110	<3
	Adenine	15	<1

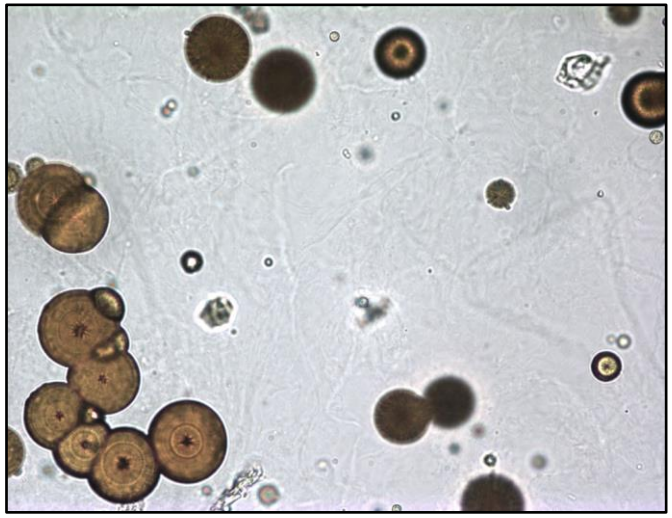
LC-MS/MS



Urinalysis

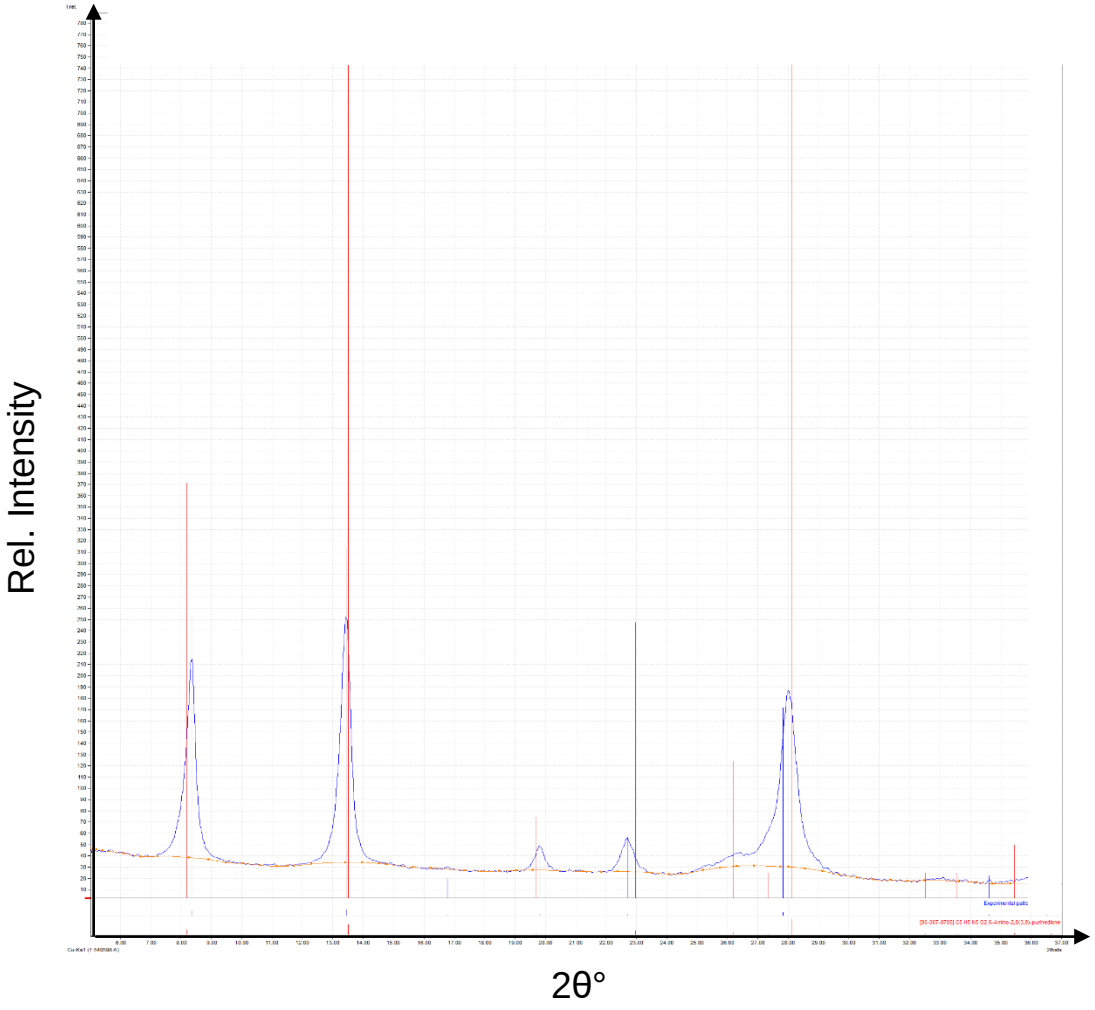


Bright field (400x), no centrifugation



From rarekidneystones.org

Stone analysis by X-ray crystallography



Extracorporeal shockwave therapy (ESWT) followed by analysis of the extracted stone by X-ray

Diffraction pattern consistent with the presence of DHA in the stone

Measurement

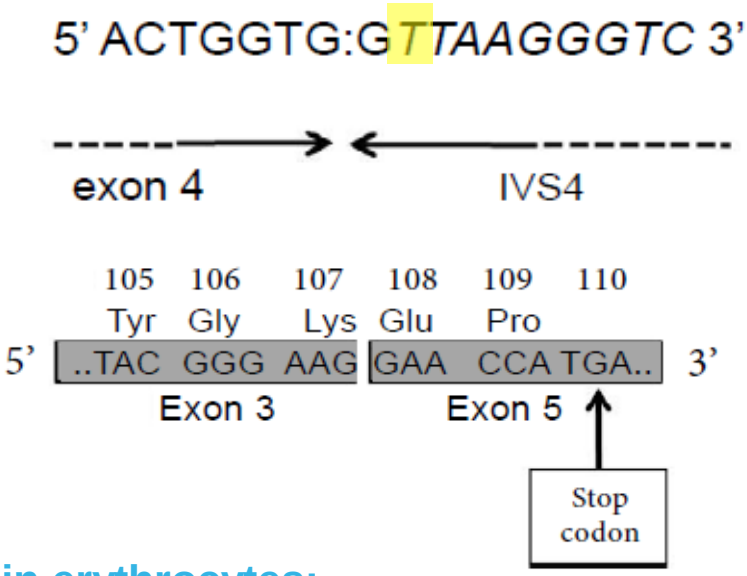
Reflex maxima according to library

Analysis performed at the department of Clinical Chemistry of the University Hospital Zürich, Zürich, Switzerland (Dr. D.M. Müller)

Additional confirmatory tests

- **APRT gene sequencing:**

  Homozygous IVS4+2insT of the APRT gene (chromosome 16q24.3)



Picot IC et al, J Nephrol Ther 2014

- **Enzymatic activity in erythrocytes:**

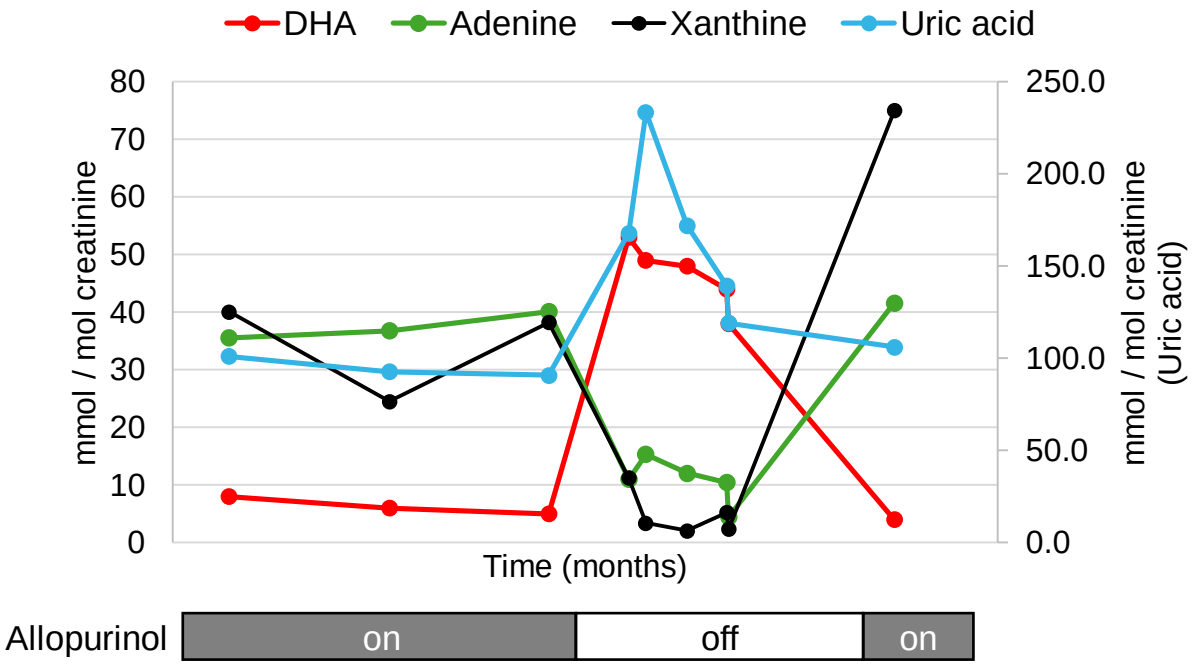
Enzyme	nmol/min/mg	Ref. Range (nmol/min/mg)
APRT	n.d.	0.4 – 0.6
HPRT	2.4	2.0 – 2.9

Tests performed at Necker Hospital, Paris, France (Dr. I. Ceballos-Picot)

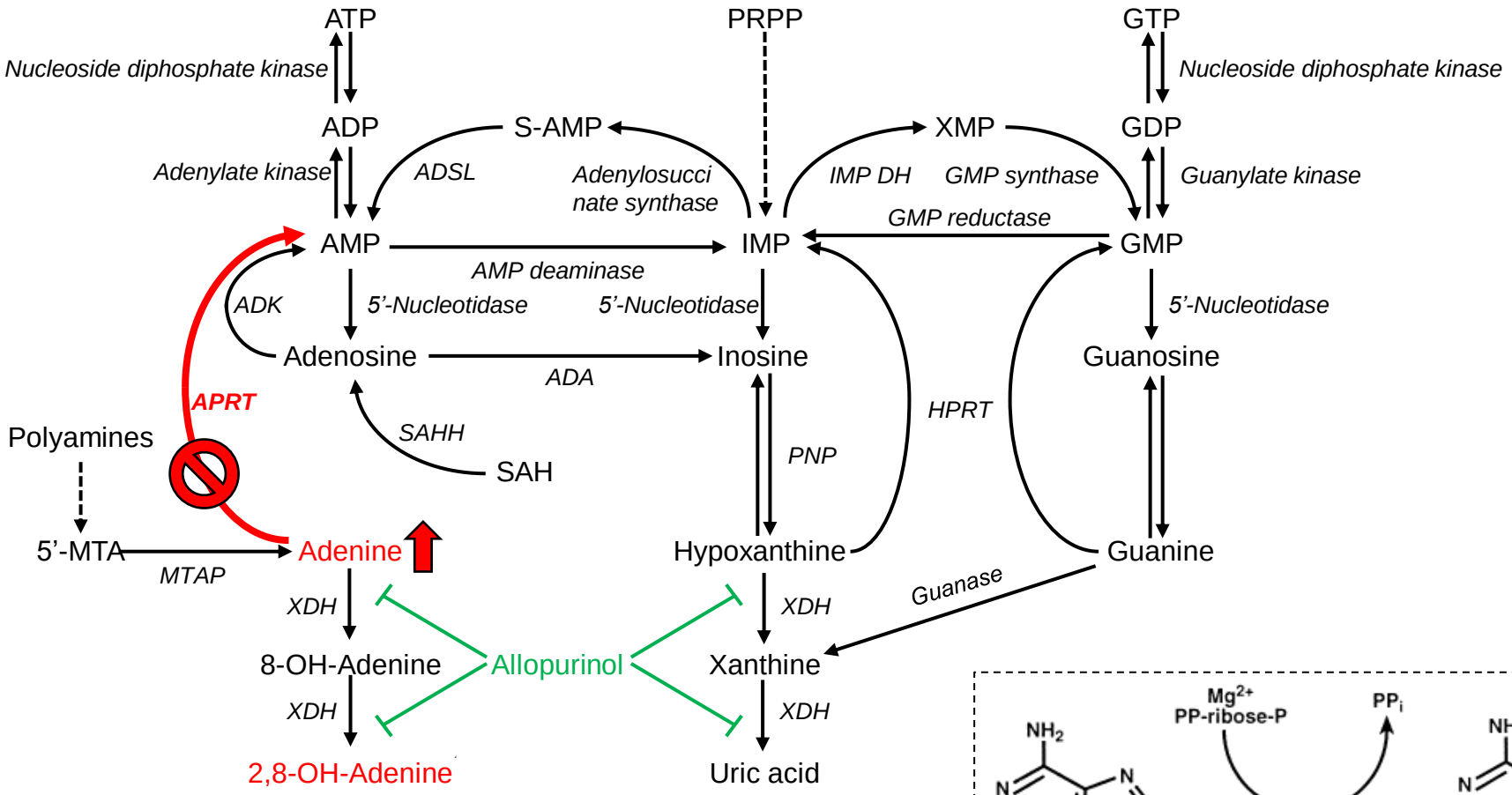
Treatment

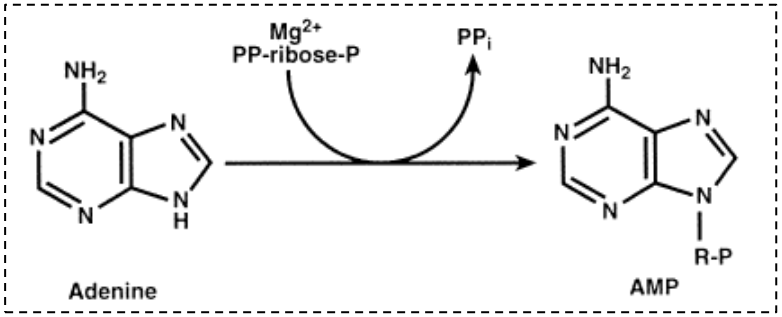
Metaphylactic measures:

- Increased fluid intake to dilute urine to specific gravity ≤ 1.010 g/cm^3
- Reduced dietary purine intake
- Regular intake of Allopurinol (alternatively Febuxostat)
- Urinary alkalinization is not recommended, as DHA remains very insoluble at any pH



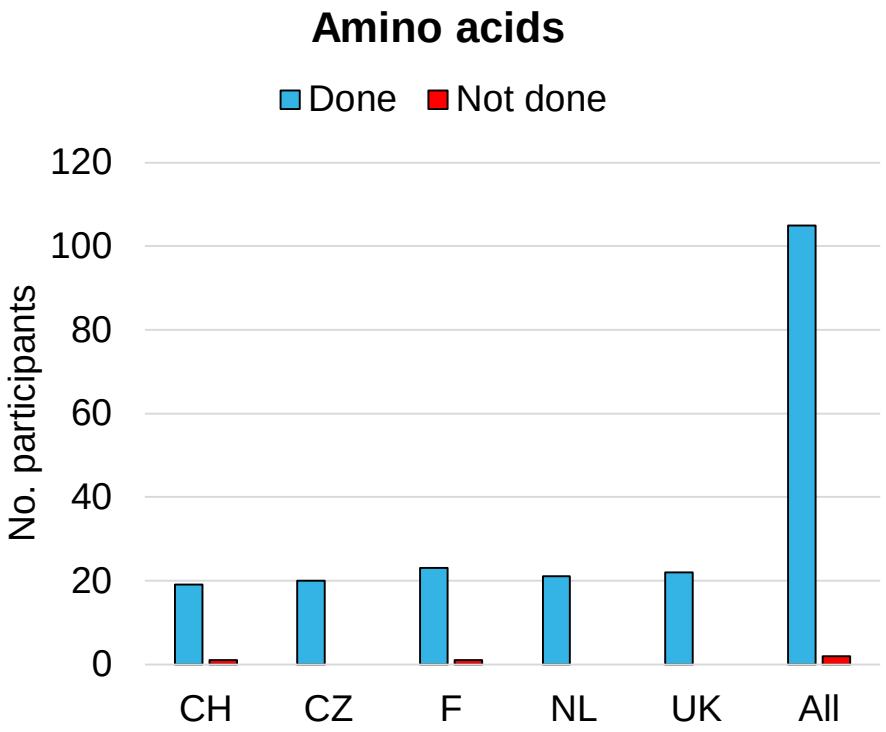
Biochemistry of APRT deficiency



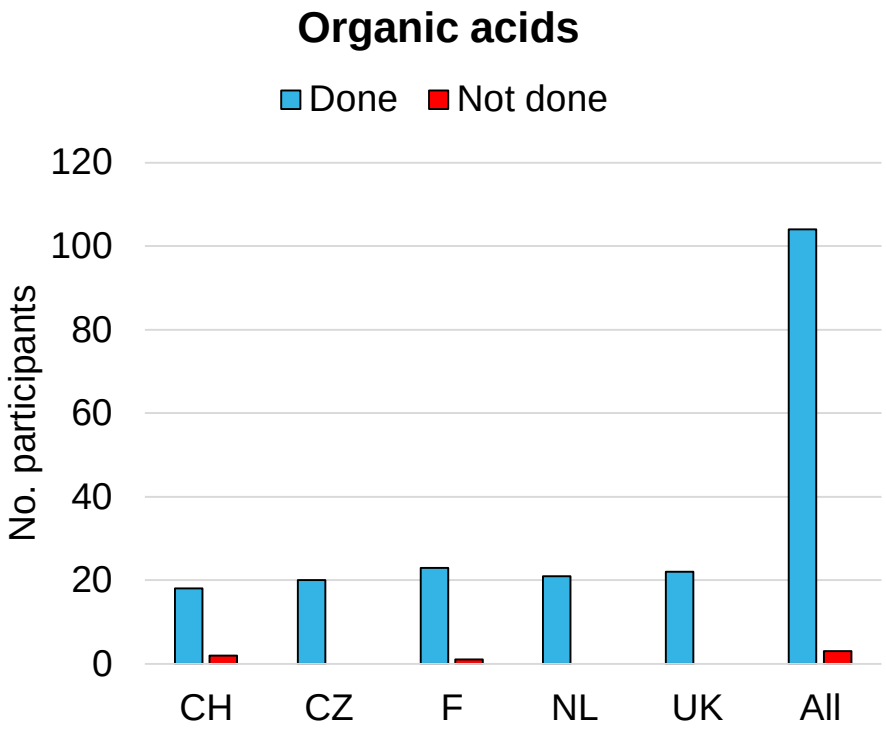


DPT Scheme Results

Type of analysis performed



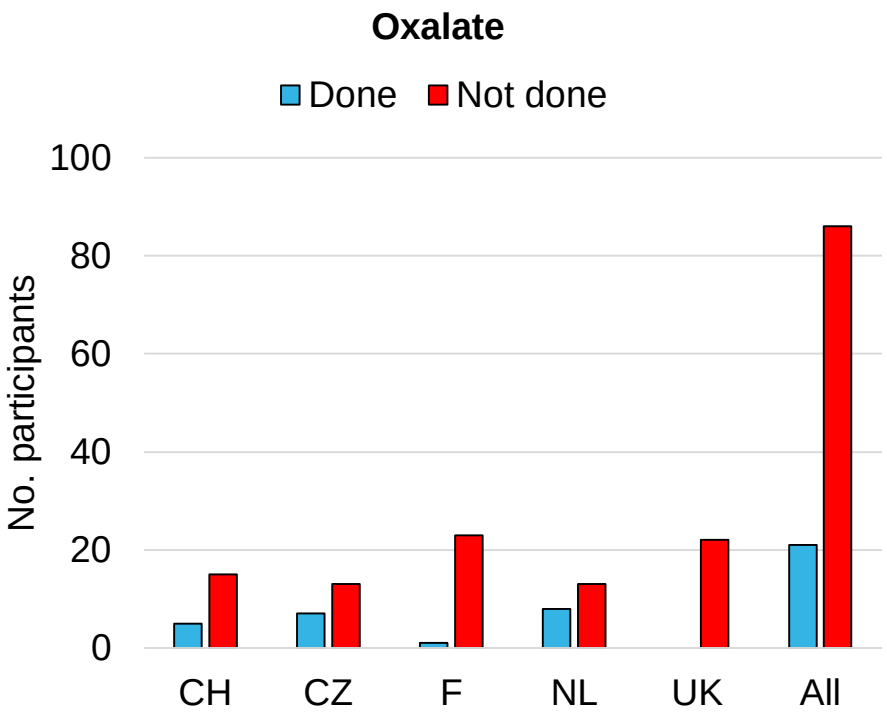
All labs except 2 measured amino acids



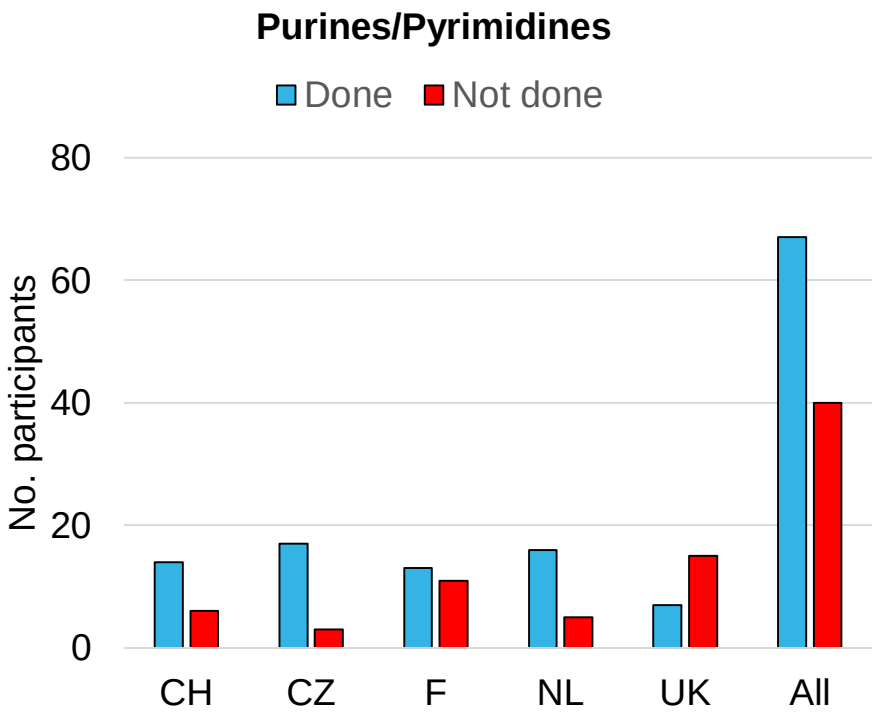
All labs except 3 measured organic acids

Number of labs in each DPT center:
CH: 20 CZ: 20 F: 24 NL: 21 UK: 22 All: 107

Type of analysis performed

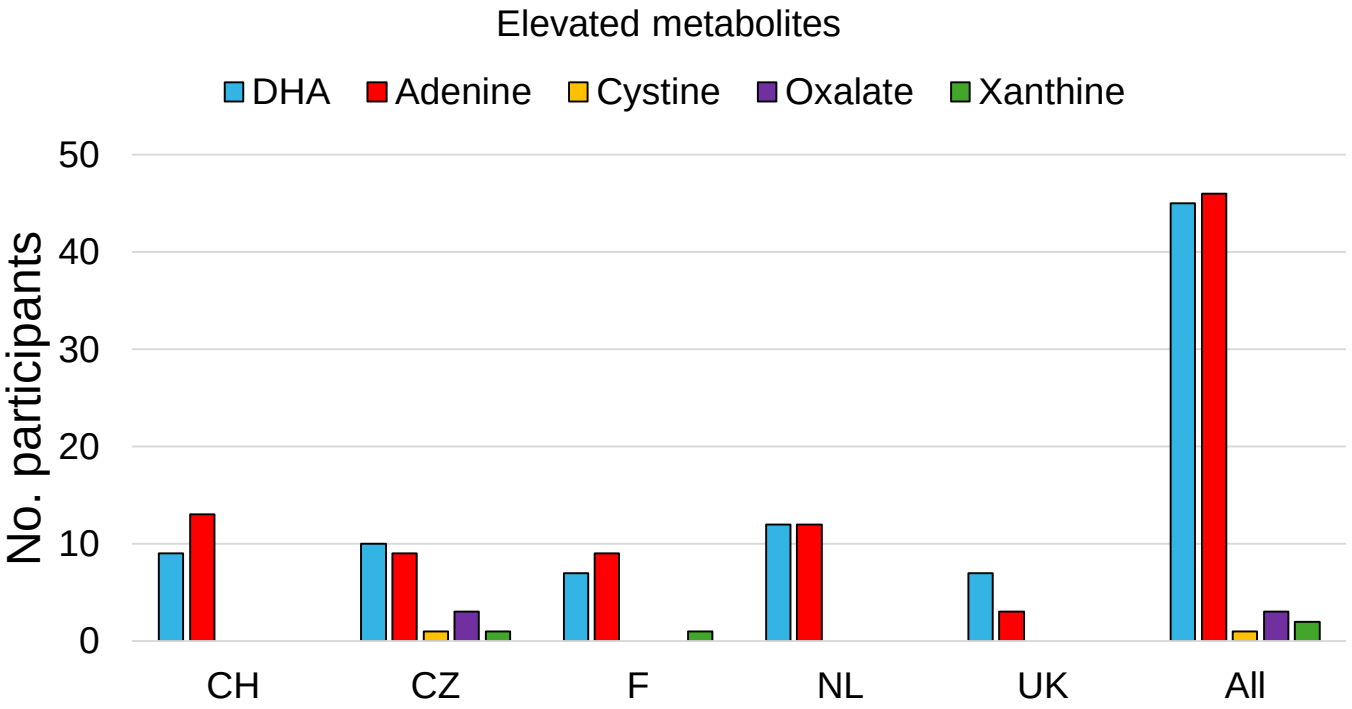


The majority of labs didn't consider it necessary to measure specifically oxalate



67/107 labs performed the analysis of Pu/Py and 19 labs recommended this analysis. (Note: not all Pu/Py methods include DHA)

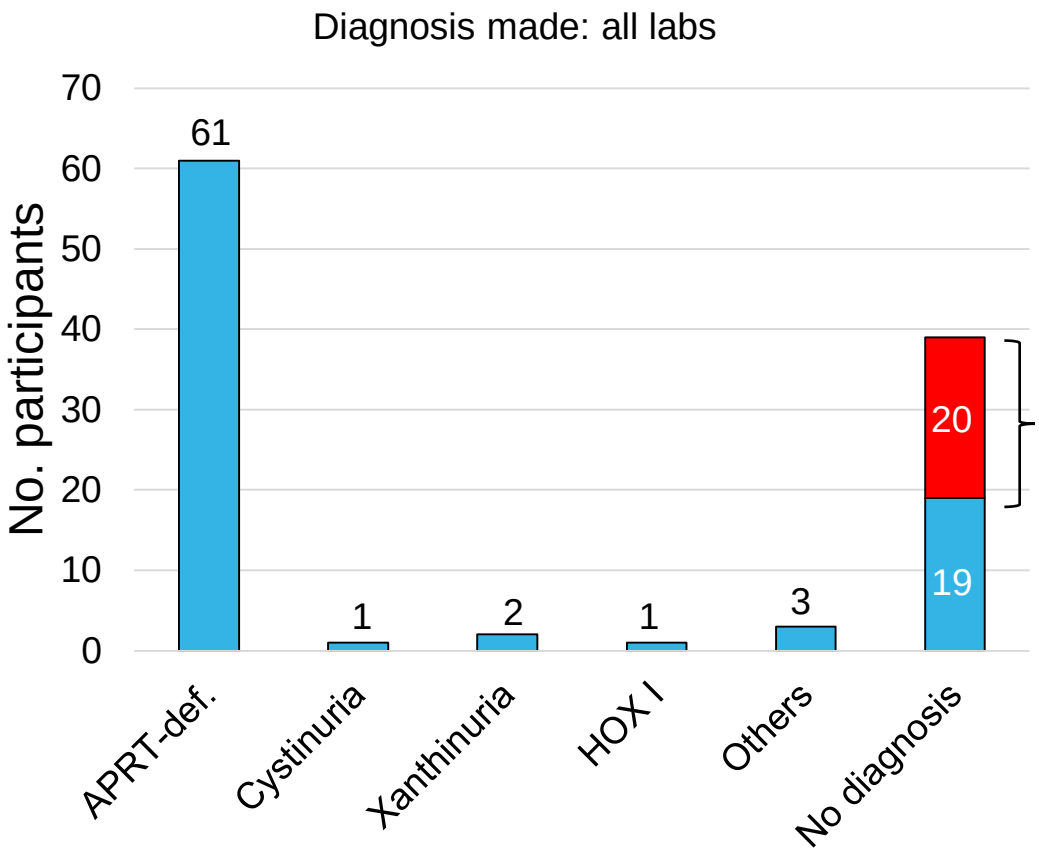
Results interpretation (*qualitative*)



Analytical scores:
DHA: 2 points
Only adenine: 1 point

- Many labs reported increased concentrations of DHA and adenine
- Some labs found slightly increased lactate and slightly decreased uric acid in the urine but didn't consider this relevant for the final diagnosis
- Some labs found elevated concentrations of oxalate (3), xanthine (2) and cystine (1). This led to the incorrect diagnosis of HOX I (1), xanthinuria (2) and cystinuria (1)

Most likely diagnosis



57% of labs made the correct diagnosis. In most of the cases this was based on abnormally elevated DHA and/or adenine. In a few cases the diagnosis was done based on clinical signs and the presence of DHA crystals in the urine

~50% of labs with no diagnosis recommend the measurement of purines and pyrimidines

Interpretative scores:
APRT def.: 2 points
Recommend Pu/Py analysis: 1 point
Tentative diagnosis according to symptoms: 1 point

Results interpretation (*quantitative*)

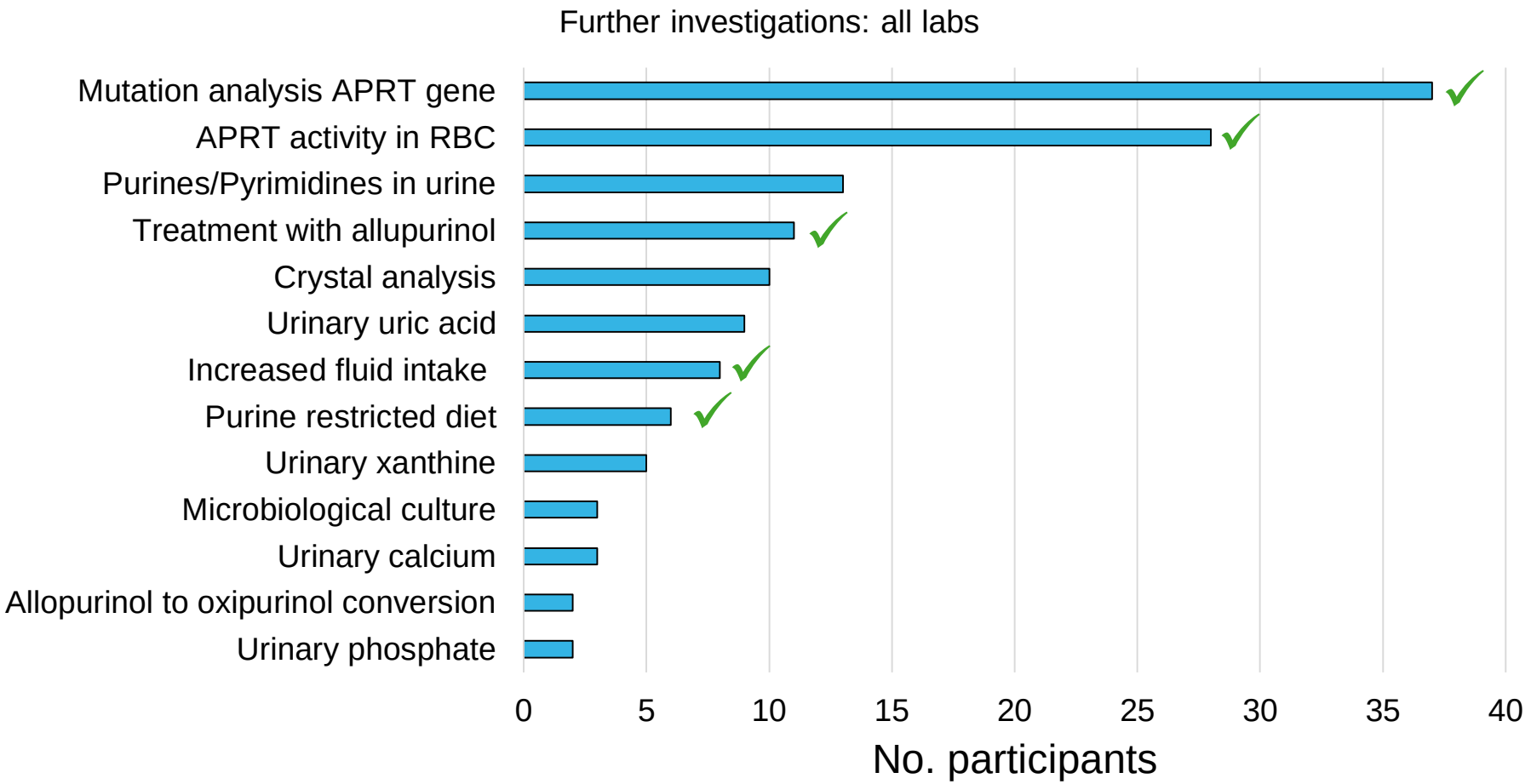
DPT Center	n	Creatinine	
		Range (mmol/L)	CV (%)
CH	20	2.8 – 3.8	6.8
CZ	20	3.2 – 3.7	4.4
F	24	1.2 – 4.1	16.2 (8.8*)
NL	21	3.0 – 4.0	7.0
UK	22	2.8 – 3.6	5.4

* Outlier removed

DPT Center	DHA			Adenine		
	n	Range (mmol/mol crea)	CV (%)	n	Range (mmol/mol crea)	CV (%)
CH	4	19 - 76	77.8	10	6.0 - 10	14.3
CZ	4	30 – 116	52.1	8	5.0 – 51	113.0
F	2	15 – 19	15.2	7	8.5 – 11	9.2
NL	7	13 – 83	48.8	11	6.6 – 24	48.7
UK	4	24 – 25	2.7	0	-	

- Only 21 and 35 quantitative results provided for DHA and adenine, resp.
- The range is particularly large for DHA → Calibration? Internal standard? Solubility? Etc.
- Low accuracy of adenine measurement even though present in external quality controls

Advice for further investigations and/or treatments



Conclusions and recommendations

- In patients with urolithiasis measure:
  - Amino acids
  - Organic acids (+/- oxalate)
  - Purines and pyrimidines – Note: large variation in measurement of Pu/Py metabolites
    - Increased DHA and/or adenine → APRT deficiency

- Qualitative interpretation:
  - 61 labs (~57%) came to the correct diagnosis

- Quantitative interpretation:
  - Large inter-lab variation of DHA measurement → Harmonization of Pu/Py measurement (e.g. ERNDIM PuPy scheme)

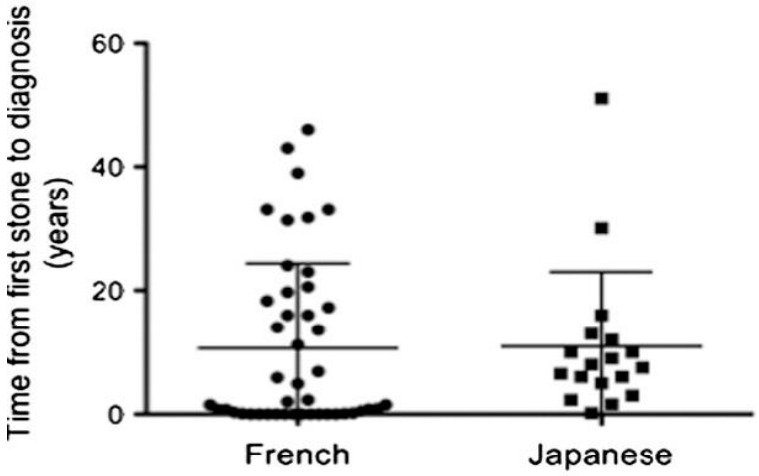
- Don’t forget alternative techniques like urine microscopy (best: polarized microscopy), or stone analysis (IR spectrophotometry or X-ray crystallography)

Why is it so important to not miss this diagnosis?

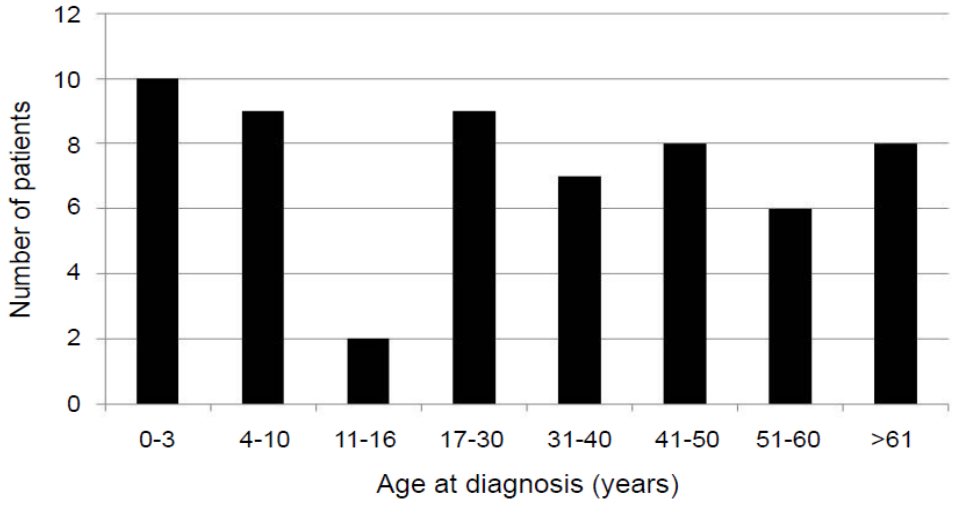
Because of its catastrophic consequences!

- APRT deficiency may lead to chronic kidney disease and may lead to end-stage renal disease
- Invasive procedures such as renal biopsy can be avoided
- In some cases, APRT deficiency remains unrecognized and untreated after renal transplantation leading to ultimate loss of allograft function (one patient was reported to have received 4 renal transplants!)

Because a treatment exists!



Bollée G et al, Clin J Am Soc Nephrol 2012



Picot IC et al, J Nephrol Ther 2014

Picot et al., J Nephrol Ther 2014, 4:4
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Review Article Open Access

Adenine Phosphoribosyltransferase Deficiency: An Under-Recognized Cause of Urolithiasis and Renal Failure

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