Analytical Evaluation of Point of Care Uric Acid Tests

The Goal: Improving the Monitoring of Gout Treatment and Associated Hyperuricemia

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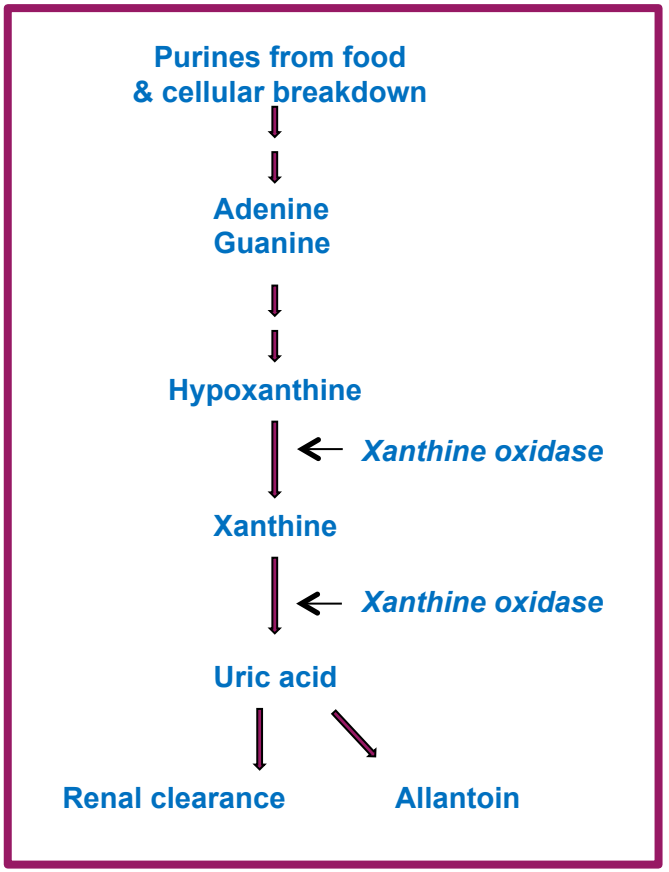
DISCLOSURES:
Z. Berke, J. Paraskos, J. Cook, and A. Platt are employees of AstraZeneca PLC. J. Miner is an employee of Ardea Biosciences, a wholly-owned subsidiary of AstraZeneca PLC, and an Advisory Board member of ARTA Bioscience.

Uric Acid (UA)
Metabolite and Disease Markers

- UA is the product of purine catabolism[1]
- Detectable in circulation in healthy and disease conditions such as gout[1]
  - Levels may vary due to food intake (purine content), circadian rhythm, gender, age
- Hyperuricemia defined as >6.8 mg/dL (>400 μmol/L) UA in circulation[1]
  - Primarily due to inefficient renal excretion of UA[2,3]
  - Overproduction of UA also contributes in some patients[2,3]
  - Potential association with several disease conditions[2] (gout, cardiovascular diseases, nephropathies, cancers)
- Current UA-lowering therapies for treatment of gout
  - Xanthine oxidase inhibitors blocking UA production (e.g., allopurinol and febuxostat)
  - Uricuretic agents/URAT-1 inhibitors increasing UA excretion (e.g., benzbromarone, probenecid)
  - Uricases that degrade UA (e.g., pegloticase)
  - Lowering serum and joint UA levels facilitates dissolution of crystals

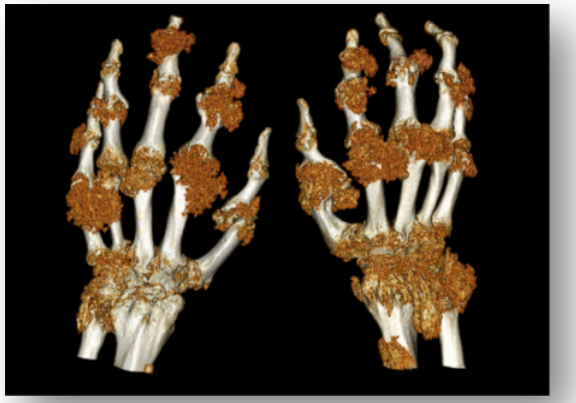


1. Terkeltaub R, Edwards NL (eds). Gout: Diagnosis and Management of Gouty Arthritis and Hyperuricemia (3rd edition), 2013.
2.Firestein GS, *et al*. (eds). Kelley's Textbook of Rheumatology (9th edition), 2013.
3.Boss. *N Engl J Med*. 1979;300:1459-68.

Gout and Uric Acid

Pathophysiology and Diagnostic Biomarkers

- Gout is a urate crystal deposition (UCD) disease and the most common inflammatory arthritis in men and postmenopausal women[1]
- Results from chronic hyperuricemia[2]
  - Over time, uric acid crystals form and deposit in joints and other tissues
  - UCD causes chronic inflammation, leading to acute gout flares and painful, disfiguring tophi
- Criteria for clinical diagnosis[3]
  - Acute arthritis (pain, swelling, inflammation of joints)
  - Demonstration of monosodium urate crystals (MSU) in joint fluid
  - Serum UA levels
- Serum UA levels[3]
  - Hyperuricemia defined as >6.8 mg/dL (>400 μmol/L)
  - Recommended target level for disease control <6 mg/dL (<360 μmol/L)
    - <5 mg/dL (<300 μmol/L) in certain populations, e.g., for tophaceous gout, per EULAR and ACR guidelines



Extensive articular deposition of monosodium urate crystals

(With permission from Nicola Dalbeth). Dalbeth et al. *Arthritis Rheum.* 2007:56(1):29.

1. Zhu Y, Pandya BJ, Choi HK. *Arthritis Rheum*. 2011:63(10):3136-3141.
2. Girardet JL and Miner JN. *Ann Rep Medicinal Chem*. 2014;49:151-164.
3. Hamburger M, et al. *Postgrad Med*. 2011 Nov;123(6 Suppl 1):3-36

Interest in Point of Care Tests (PoCTs)

Potential Longitudinal Assessment of Disease Progression and Efficacy of Treatment in Gout

- Hyperuricemia
  - For treating gout, target UA levels are defined in guidelines → **But is an occasional test sufficient?**
- Clinical diagnosis
  - Symptoms, crystals in joint fluid (via needle biopsy), and possibly a separate serum UA laboratory test needed
  - UA data rarely available at physician visit – blood sample and Clinical Chemistry analysis needed
  - In US, UA level determination is not part of standard blood chemistry panel
- Efficacy of treatment
  - Clinical / symptomatic measures are not sufficient; often, there is no confirmation of UA levels
  - Confounded by the fact that urate-lowering treatments can cause *temporary increase* in flares, while flares cause a *temporary decrease* in UA levels
- Novel aspects of PoCT
  - Accessible to both patient and physician
  - Ease of use by finger-prick test – amenable to home testing and at physician's office
  - Regular monitoring of blood UA levels – generation of longitudinal data

Measurement of Serum UA

Laboratory Analyses and PoCTs

- UA standards available from NIST (909b and 913)
- Clinical chemistry analyzers
  - Available in-hospital and diagnostic laboratories (e.g., Roche Cobas, Abbott Architect, and Beckman-Coulter Synchron)
- LC-MS
  - Used as reference method – available at CROs
  - Method development and validation performed in house
- PoCTs
  - Available over Internet or OTC
  - Limited QA (analytical performance) data
  - CE marking in Europe, but no 510k cleared tests available in US

NIST, National Institute of Standards and Technology
LC-MS, Liquid chromatography–mass spectrometry
CRO, contract research organization
OTC, over the counter

PoCTs

Commercially Available Tests

- Many different commercial kits available over the Internet or OTC
- Some look identical and originate from the same manufacturer, but may be branded under different names or offered by different suppliers
- Four tests chosen – different appearance, different manufacturers, and different suppliers

EasyTouch® GU
BiopTik Technology

UAsure
Apex Biotechnology

BeneCheck™ Plus
General Life Biotechnology Company Ltd

HumaSens plus
Human

PoCTs

Kit Components and Technical Specifications

- *EasyTouch® GU*
  - Meter, batteries, test strips, lancing device and 10 needles, user guide, patient diary
  - Glucose and UA testing (designated test strips), requires 4 µL blood, reading in 20 sec, UA range 3-20 mg/dL, memory capacity for 100 tests
- *UAsure*
  - Meter, batteries, test strips, lancing device and needles, user guide, and patient diary
  - UA testing only, requires 4-6 µL blood, reading in 30 sec, UA range 3-20 mg/dL, memory capacity 50 tests
- *BeneCheck™ Plus*
  - Meter, batteries, test strips, lancing device and needles, user guide, and quick starter guide
  - Cholesterol, glucose, and UA testing (designated test strips), requires 1.0-1.5 µL blood, reading in 15 sec, UA range 3-20 mg/dL, memory capacity 50 tests
- *HumaSens^plus*
  - Meter, batteries, test strips (glucose only), user guide, and quick starter guide (lancing device and needles not supplied)
  - Cholesterol, glucose, and UA testing (designated test strips), requires 1 µL blood, reading in 15 sec, UA range 3-20 mg/dL, memory capacity 50 tests

PoCTs

Basis of Evaluation and Comparison of Four Tests

- *Precision*
  - Variability of test results between individual test occasions (CV<17% recommended by CAP)
- *Accuracy*
  - Agreement between experimental and known data
- *Comparison to "gold standard LC-MS*
  - Comparing results form testing specific samples by PoCTs and LC-MS
- *Ease of use*
  - Instructions for end user / Tutorial
    - How well the supplied information describes the procedure and the use of the test result
  - Hurdle to actually start self-testing
    - How well the packaging and inserts help patients to actually start using the kit
  - Ease of start
    - How confident the end user can be that all required kit pieces and instructions are in place

CAP, College of American Pathologists
CV, coefficient of variation (imprecision)

Precision Testing of PoCTs and LC-MS

EasyTouch, UASure, BeneCheck, HumaSens

		EasyTouch® GU			UA*Sure*			Benecheck™ Plus			HumaSens-Pro			Mass Spectrometry		
	Replicate	Concentration (mg/dL)			Concentration (mg/dL)			Concentration (mg/dL)			Concentration (mg/dL)			Concentration (mg/dL)		
	Number	Determined	Mean	CV (%)	Determined	Mean	CV (%)	Determined	Mean	CV (%)	Determined	Mean	CV (%)	Determined	Mean	CV (%)
HV1	1	HI	6.3	**8.6**	9.3	6.2	**26.4**	5.5	5.6	**3.1**	5.6	5.4	**4.6**	5.7	6.1	**4.4**
	2	6.9			5.6			5.6			5.3			6.3		
	3	6.7			5.6			5.5			5.1			6.1		
	4	5.9			6.1			5.5			5.4			6.4		
	5	6.3			6.0			5.9			5.8			6.0		
	6	5.6			4.5			5.4			5.3			6.3		
HV2	1	8.7	7.0	**22.1**	7.2	7.0	**9.5**	5.0	4.5	**6.3**	4.4	4.2	**7.9**	4.4	4.1	**6.0**
	2	8.3			7.7			4.3			3.9			3.9		
	3	6.9			6.9			4.7			3.6			4.2		
	4	4.4			7.1			4.3			4.3			3.9		
	5	6.3			5.8			4.5			4.4			4.3		
	6	7.2			7.5			4.3			4.3			3.8		
HV3	1	6.9	9.3	**26.3**	7.7	6.0	**25.5**	6.3	6.7	**5.8**	6.1	6.7	**7.4**	6.5	6.4	**5.8**
	2	10.6			6.3			6.4			6.7			6.2		
	3	13.4			4.0			6.8			6.6			6.2		
	4	9.5			Lo			7.3			6.9			7.1		
	5	7.2			4.9			7.0			7.5			6.1		
	6	8.2			7.1			6.5			6.3			6.2		
HV4	1	Lo	7.2	**25.5**	5.4	6.3	**28.4**	4.7	4.8	**6.9**	5.0	4.5	**8.0**	4.1	4.1	**2.5**
	2	8.0			7.2			4.9			4.8			4.1		
	3	6.9			3.2			5.2			4.2			4.2		
	4	6.0			6.2			4.8			4.6			4.2		
	5	5.2			7.6			4.9			4.3			3.9		
	6	9.9			8.0			4.2			4.1			4.2		
HV5	1	10.6	8.4	**24.6**	6.4	6.8	**31.2**	6.9	6.5	**5.3**	6.1	6.2	**4.5**	5.4	5.9	**5.5**
	2	8.5			7.3			6.2			6.0			6.0		
	3	8.5			5.3			6.0			6.6			5.8		
	4	10.6			6.2			6.5			5.8			5.7		
	5	6.0			4.9			6.8			6.3			6.2		
	6	6.0			10.8			6.4			6.1			6.2		

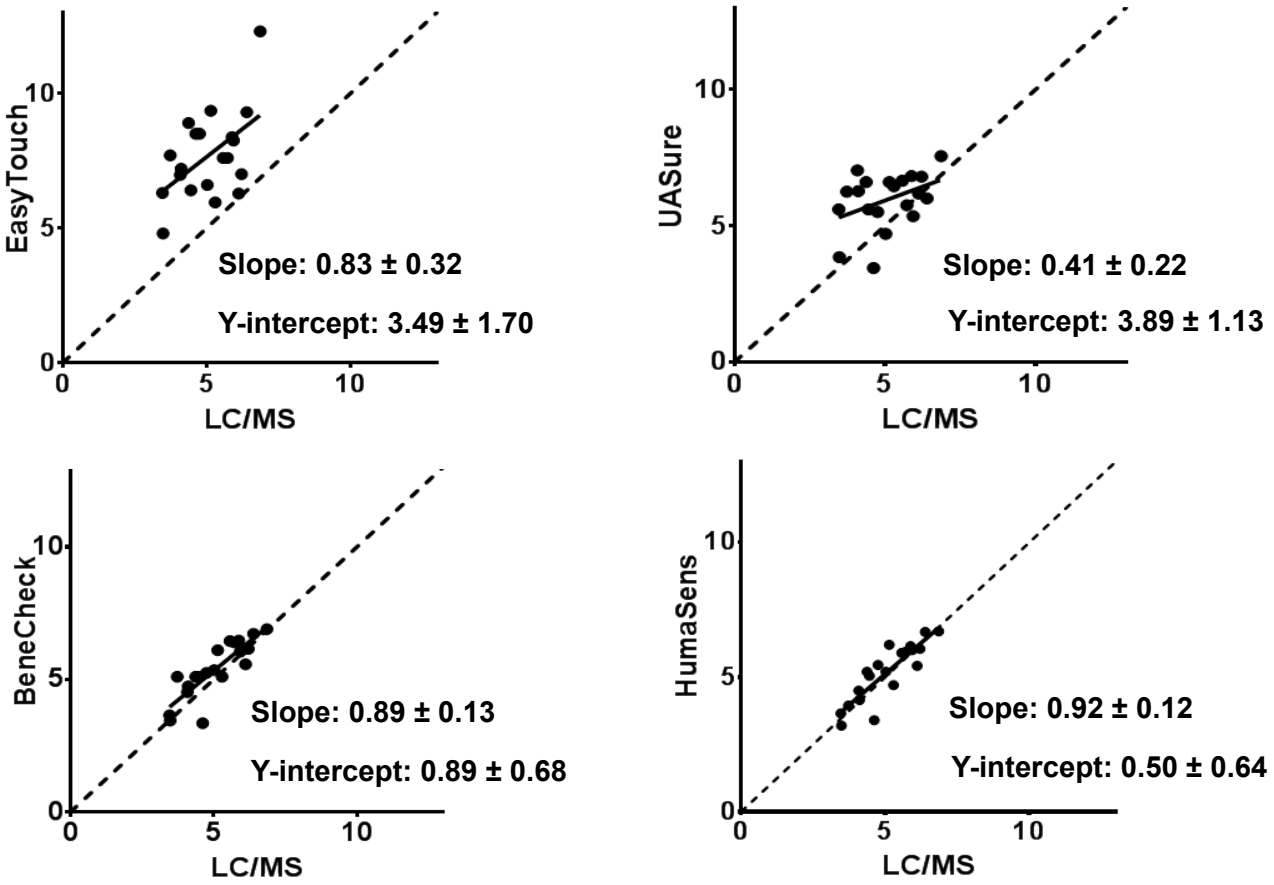
- Acceptable precision (**<17%** CV): *BeneCheck Plus* and *HumaSens-Pro*
- Non-acceptable precision (**≥17%** CV): *EasyTouch* GU and *UAsure*
- LC-MS assay performed with acceptable precision

HV, Healthy Volunteer, CV %, Coefficient of variation

Accuracy Testing of PoCTs and LC-MS

EasyTouch, UAsure, BeneCheck, HumaSens

UA levels (mg/dL), individual samples



- Non-acceptable accuracy: *EasyTouch* GU and *UAsure*
- Acceptable accuracy of meters: *BeneCheck Plus* and *HumaSens-Pro*

Analytical evaluation of PoCTs

Results and Conclusions

- Four different PoCTs were evaluated with respect to precision and accuracy
- Two of these (*BeneCheck* and *HumaSens*) had both acceptable precision and accuracy
- The other two PoCTs (*UAsure* and *EasyTouch*) did not meet both the precision and accuracy criteria

Ease of use evaluation of PoCTs

Results and conclusions

- Quality of tutorial and user friendly instructions are key
- Quality of lancing device is critical
- Ease of applying the test strips onto the reader is critical
- Supply of lancing device(s) and test strips are important
- BeneCheck and Humasens kits gave a more "professional" impression and gave a more user-friendly performance

Our Vision

PoCTs Transforming Disease Management

- Reliable and fast measurement of UA levels
  - Proven precision and accuracy of meters
  - Availability of meters, test strips, lancets, instructions, note books
- Patient involvement
  - Ability to participate in disease management
  - Ability to observe progress/achievement of treatment goal
  - Understanding disease, compliance to treatment
- Physician involvement
  - Monitoring patients “at a distance”
  - Improved ability to monitor and measure if target sUA goals are met
  - Adjusting therapy (e.g., dosing or choice of drug)
- Glucose testing in diabetes is an excellent example