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The promise of microsampling, delivered

microsampling

Introducing Quantitative, Drop-of-blood Testing

CEDARS-SINAI®

agenda for today

1. Background and Introductions
2. Mitra Overview
3. Q+A
4. Logical next steps

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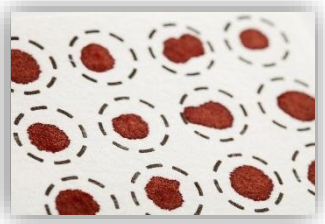
microsampling devices

	DBS card	Capillary tube
		
No hematocrit (HCT) bias		x
Automatable extractions		
Quantitative volume collection		x
User-friendly sampling		
No freeze/thaw cycle	x	
No cold chain/biohazard shipping	x	
No sub-punching required		x

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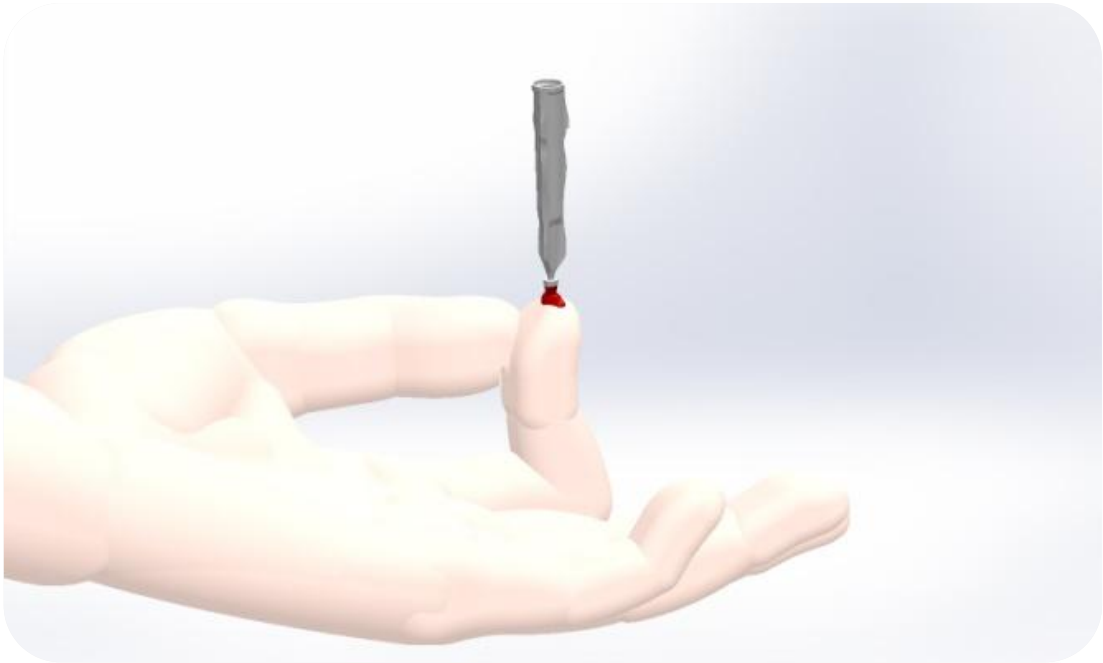
the Mitra™ microsampler

- Based on **V**olumetric **A**bsorptive **M**icrosampling (VAMS) technology
- Accurate 10 or 20 µL collection



CE IVD

The Mitra Microsampling Device is a FDA listed Class 1 device (D254956). Neoteryx complies with FDA good manufacturing practices, CFR 820 regulations, and ISO 13485.

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the Mitra™ microsampler

- Fixed, highly reproducible internal volume
- Hydrophilic porous material
- Rapid wicking (< 6 sec)
- Accurate (10 or 20 µL volume)
- Precise (< 4% RSD)
- Automation-friendly

CE IVD

The Mitra Microsampling Device is a FDA listed Class 1 device (D254956). Neoteryx complies with FDA good manufacturing practices, CFR 820 regulations, and ISO 13485.

The Mitra Microsampler class I medical device is for direct specimen collection of blood and other biological fluids. It is not specific to any clinical test, and is not for use in diagnostic procedures. Use of the Mitra Microsampler in Laboratory Developed Tests (LDTs) requires further processing including the establishment of performance characteristics and successful validation by the laboratory in a manner consistent with CLIA requirements. The Mitra microsampler is patent pending.

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video of rapid, simple sample collection

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effect of HCT on dried blood spot (DBS) area

Hematocrit (HCT) % inversely related to blood spot area

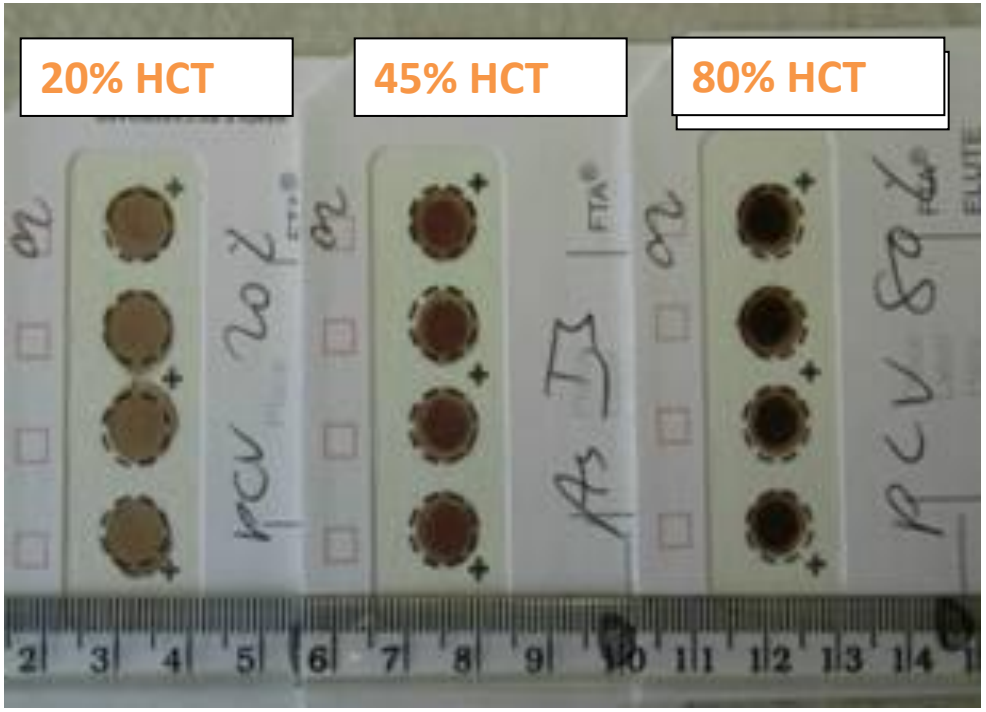
Low HCT

- Larger, light spots

High HCT

- Smaller, dark spots

Whatman™ FTA™ Elute Card



Area change = 41%

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DBS spot uniformity

1. Specimen quantity insufficient for testing.

2. Specimen appears scratched or abraded.

3. Specimen not dry before mailing.

4. Specimen appears supersaturated.

5. Specimen appears diluted, discolored or contaminated.

6. Specimen exhibits serum rings.

7. Specimen appears clotted or layered.

8. No blood.

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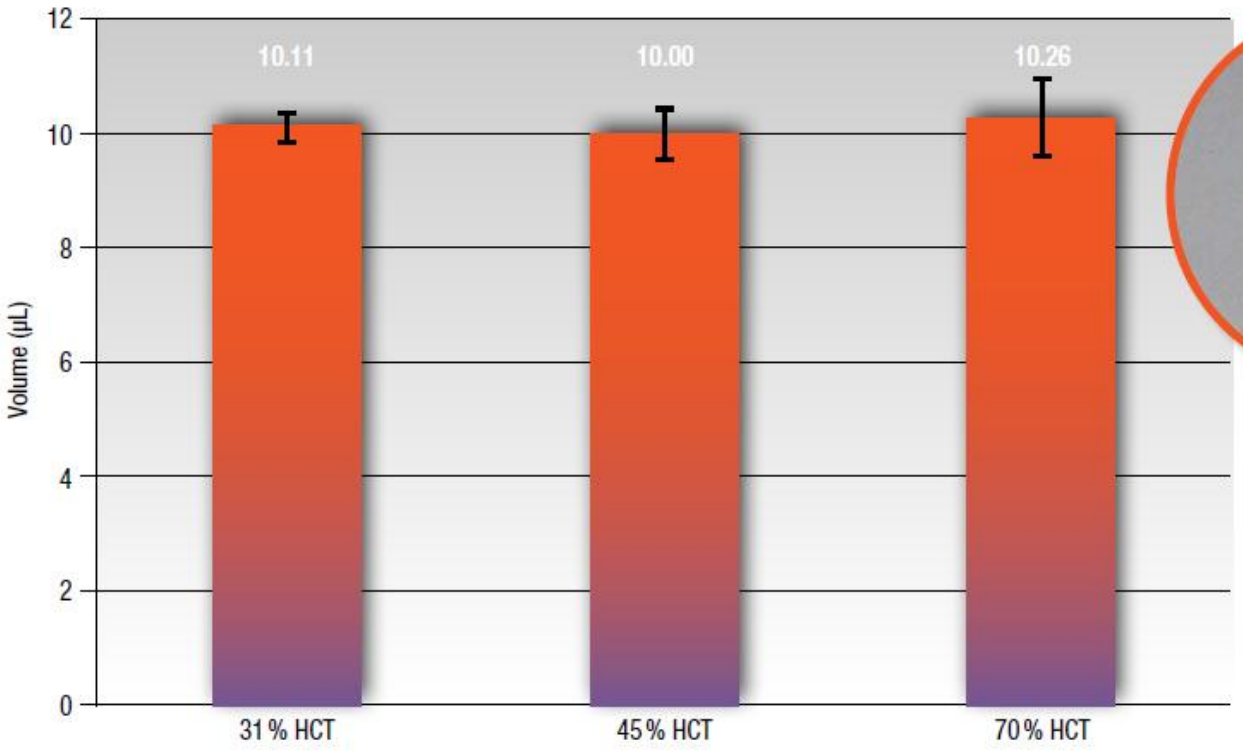
HCT independent collections (10 µL)



Overall average = 10.1 µL
Overall RSD = 3.5 %

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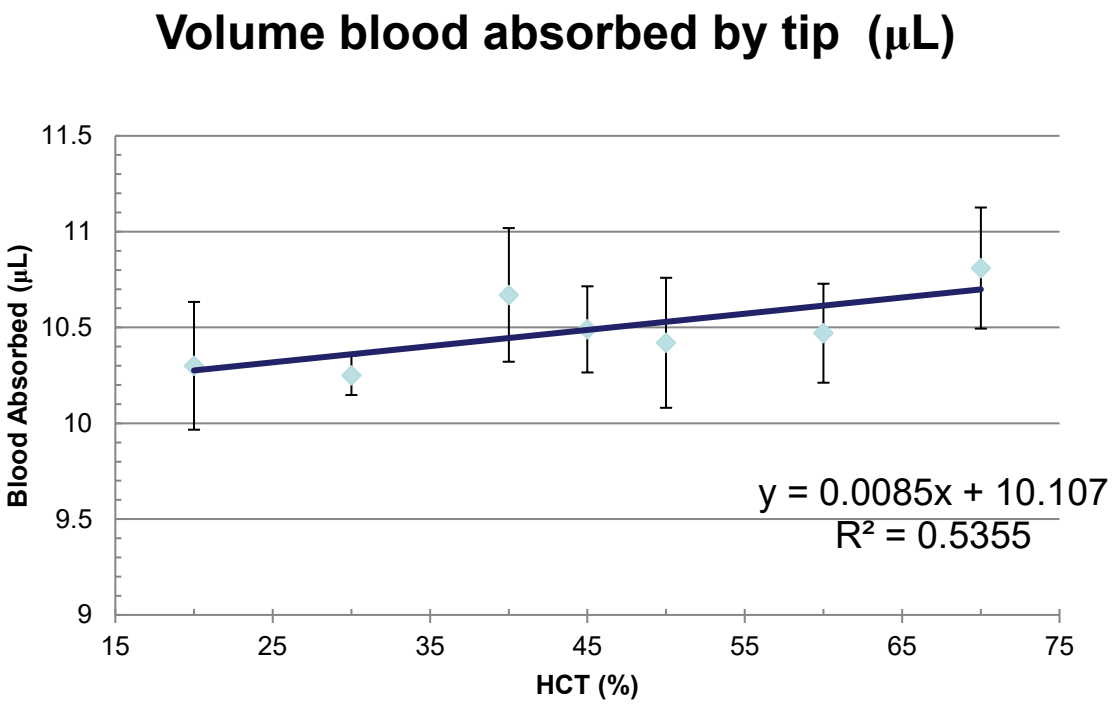
HCT effect on blood volume absorbed

- Max volume bias from 45% HCT is 3%
- 5% max volume deviation over HCT ranges 20% to 70%



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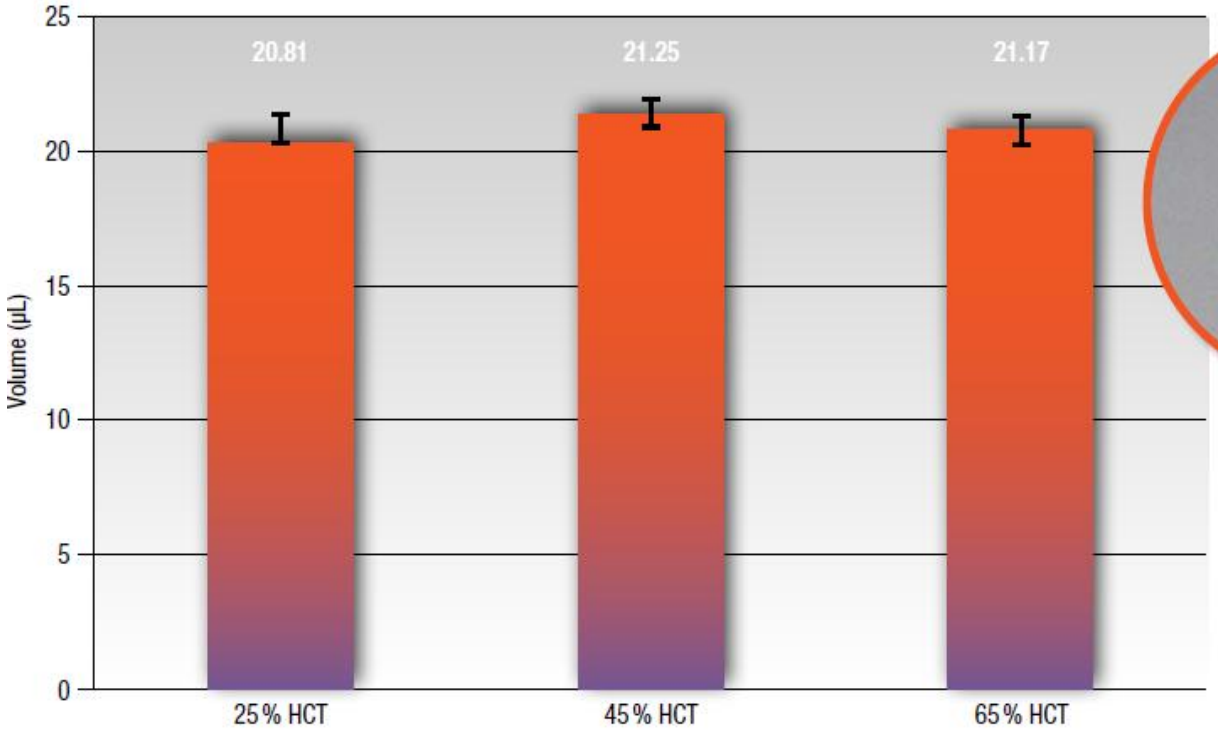
Data Courtesy of Neil Spooner and Phil Denniff, GSK (Anal. Chem., 2014, 86 (16), pp 8489–8495)

HCT independent collections (20 µL)



Overall average = 21.08 µL
Overall RSD = 2.5 %

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accuracy and precision

Penicillins have a linear (R2>0.995) range from 0.15 µg/mL-200 µg/mL in plasma using Mitra devices. Accuracy and precision were tested (n=5) in low (0.15 µg/mL), medium (20 µg/mL) and high (80 µg/mL) concentrations.

Compound	Within-day accuracy		Within-day precision (CV%)	
	Mitra sampling	10 µL blood plasma pipetting	Mitra sampling	10 µL blood plasma pipetting
Amoxicillin	2-5%	4-9%	2-4%	5-12%
Ampicillin	3-6%	4-8%	1-3%	4-7%
PenicillinG	1-5%	6-11%	2-6%	5-10%
Piperacillin	2-6%	4-10%	2-5%	5-11%
Flucloxacillin	2-7%	5-9%	3-6%	5-9%

St George's University of London

Evaluation of the Mitra microsampling device for dry sample processing in a pharmacokinetic/pharmacodynamic study of beta-lactams

Karin Kipper[1,2,], Charlotte Barker[1], Dagan Lonsdale[1], Mike Sharland[1], Atholl Johnston[3]*

[1]Institute for Infection and Immunity, St. George's, University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom
[2]Institute of Chemistry, University of Tartu, Ravila 14A, Tartu, Estonia, 50411
[3]Analytical Services International, St George's University of London Cranmer Terrace, London, SW17 0RE, United Kingdom
*kkipper@sgul.ac.uk

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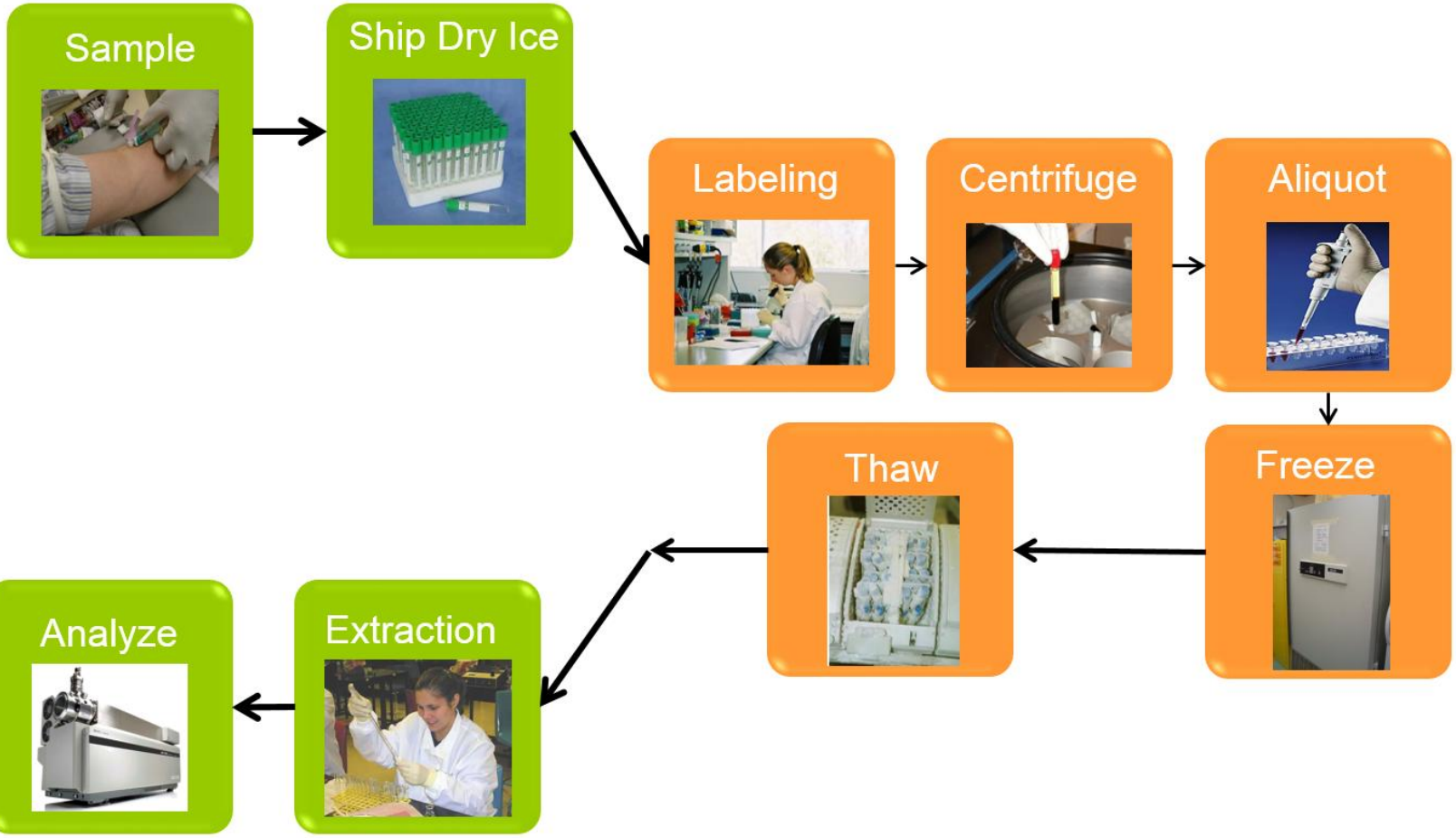
traditional blood-plasma workflow



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streamlined Mitra workflow

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microsampling devices

	DBS card	Capillary tube	Mitra® device
			
No hematocrit (HCT) bias by spot migration		x	x
Automatable extractions			x
Quantitative volume collection		x	x
User-friendly sampling			x
No freeze/thaw cycle	x		x
No cold chain/biohazard shipping	x		x
No sub-punching required		x	x

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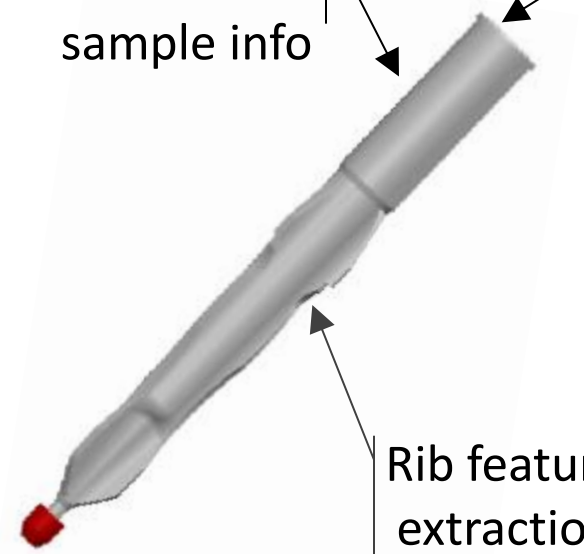
the sampler & sampling tool

Barrel easily labeled or written on for sample info

Distal end fits to 20-200 µL pipette head and fits a custom tool for moving individual samplers



Rib features aids alignment in extraction well/plate, provides slight friction and easy finger grip

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Mitra® device formats

- Direct sampling cartridges and clamshells

- Automatable 96-racks

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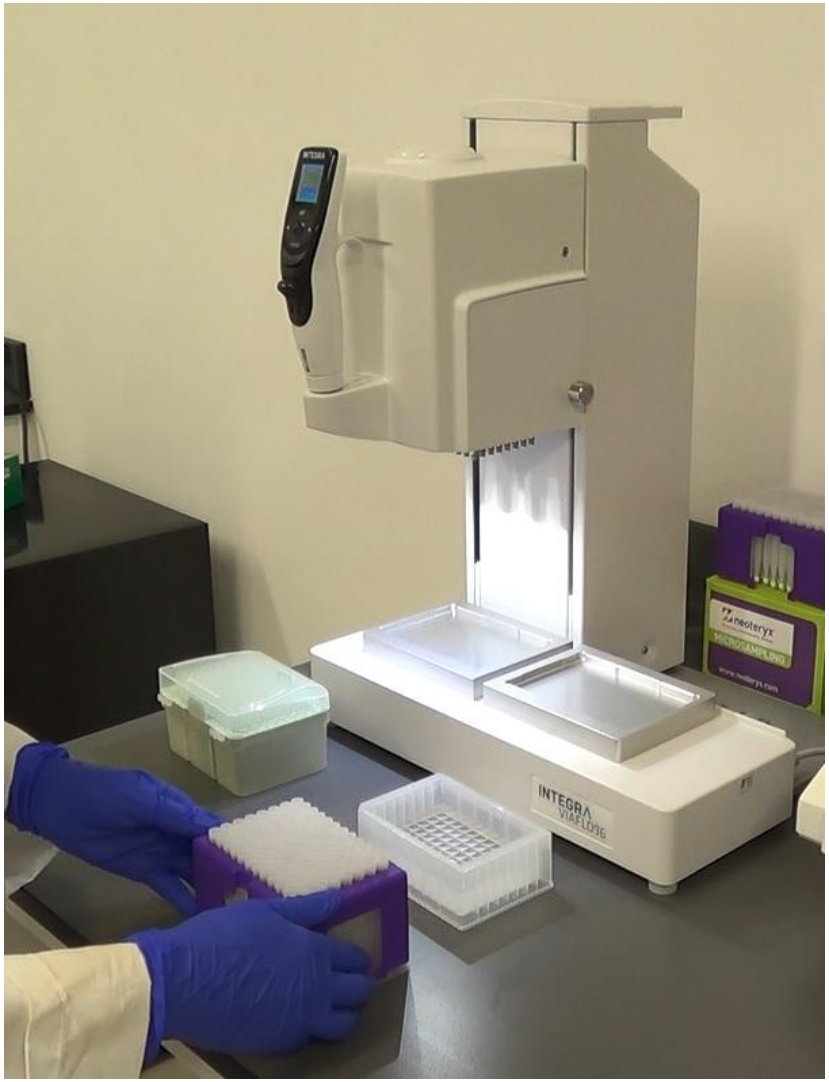
semi-automation of Mitra® device



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secure sample packaging

Ventilated enclosure allows immediate bagging for drying and shipment

Secure fitting of each sampler within the clamshell prevents cross-contamination during drying and shipment

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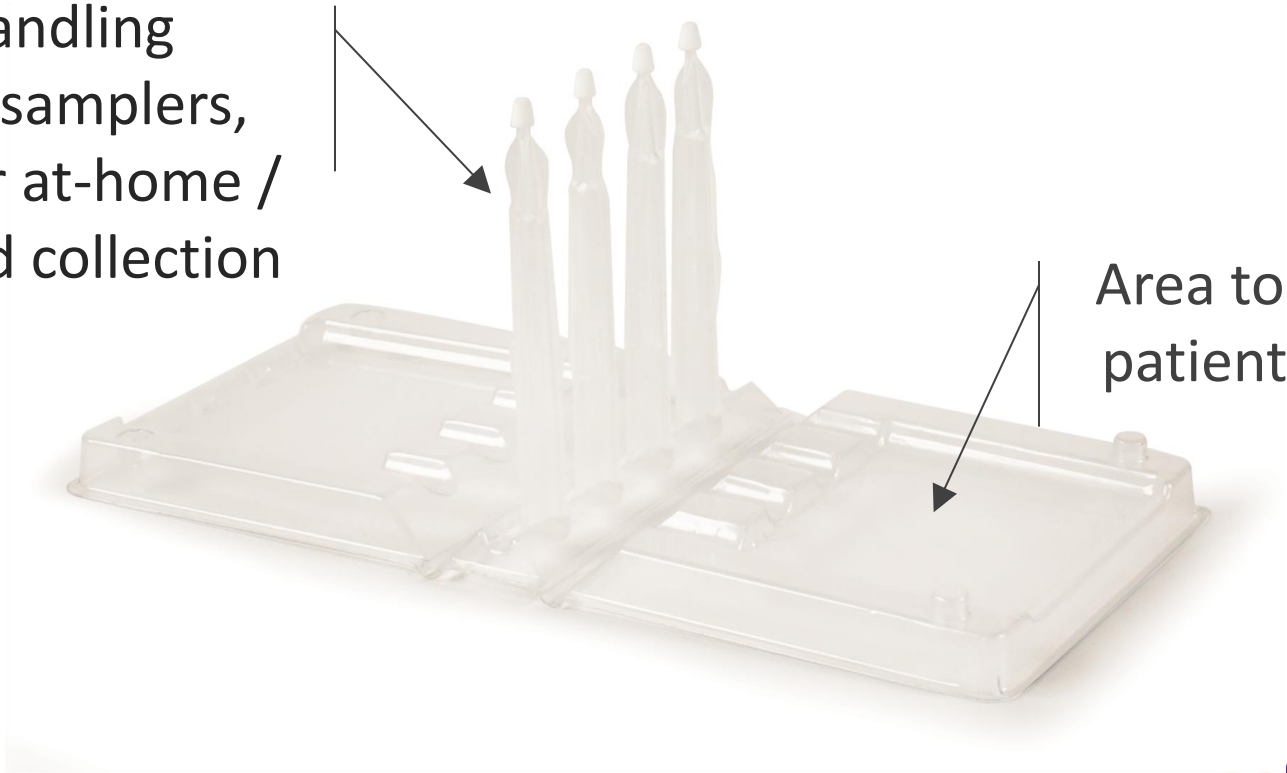
clamshell format for patient use

Easy replicate sampling without handling individual samplers, perfect for at-home / non-skilled collection



Area to apply patient label

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96-rack format for lab use

Storage Box
- Storing and transporting deck of samples

Removable Deck
- Holds 96 indexed samplers
- Rapid, open air drying
- Easy handling

Deck Adapter Plate
- Mounting 96-rack on deck of liquid handlers

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suitable applications

- Therapeutic drug monitoring (TDM)
  - Immunosuppressants, antiretrovirals
- Clinical trials
  - Pediatric studies
  - Remote location sampling
- At-home sampling
- Genetics
  - DNA testing
  - Pharmacogenomics

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Mitra benefits for the patient

- Improved patient experience
  - Less painful than venipuncture
  - Easier and better compliance
  - Minimizes patient needle and blood anxiety
  - Convenience of at-home testing

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Mitra benefits for the lab

- Happy patients

- Streamlined lab operations
  - No freezing/thaw cycle or centrifugation
  - Elimination of cold chain and b
  - Minimal training required

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Mitra benefits for the lab

- Happy patients
- Streamlined lab operations
- Broad range assay & patient compatibility
  - Clinical chemistry, immunoassay, pharmacology, LC-MS/MS
  - Easer access to patients with low blood flow (e.g neonatal, pediatrics, geriatrics)

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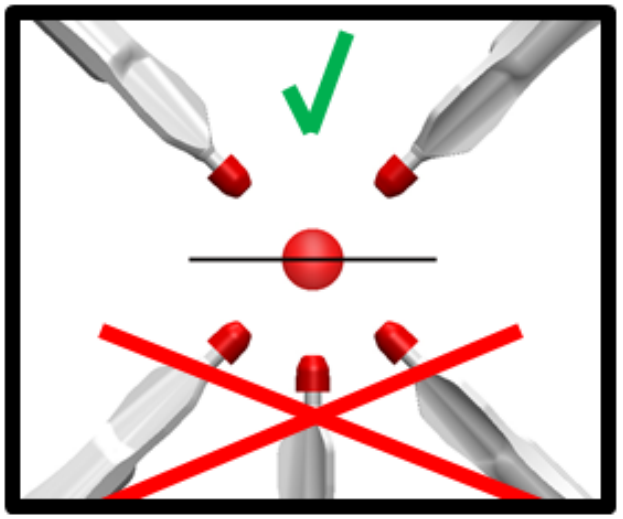
properties & techniques

sampling environment does not affect Mitra

- Excess contact time with samples
- Limited blood sample
- Temperature variation
- Humidity
- High or Low hematocrit*
- Minimal training required to ensure sampling from a positive angle
- Oversampling can occur if:
  - Full submersion of tip
  - Sample from negative angle



* With optimized extraction

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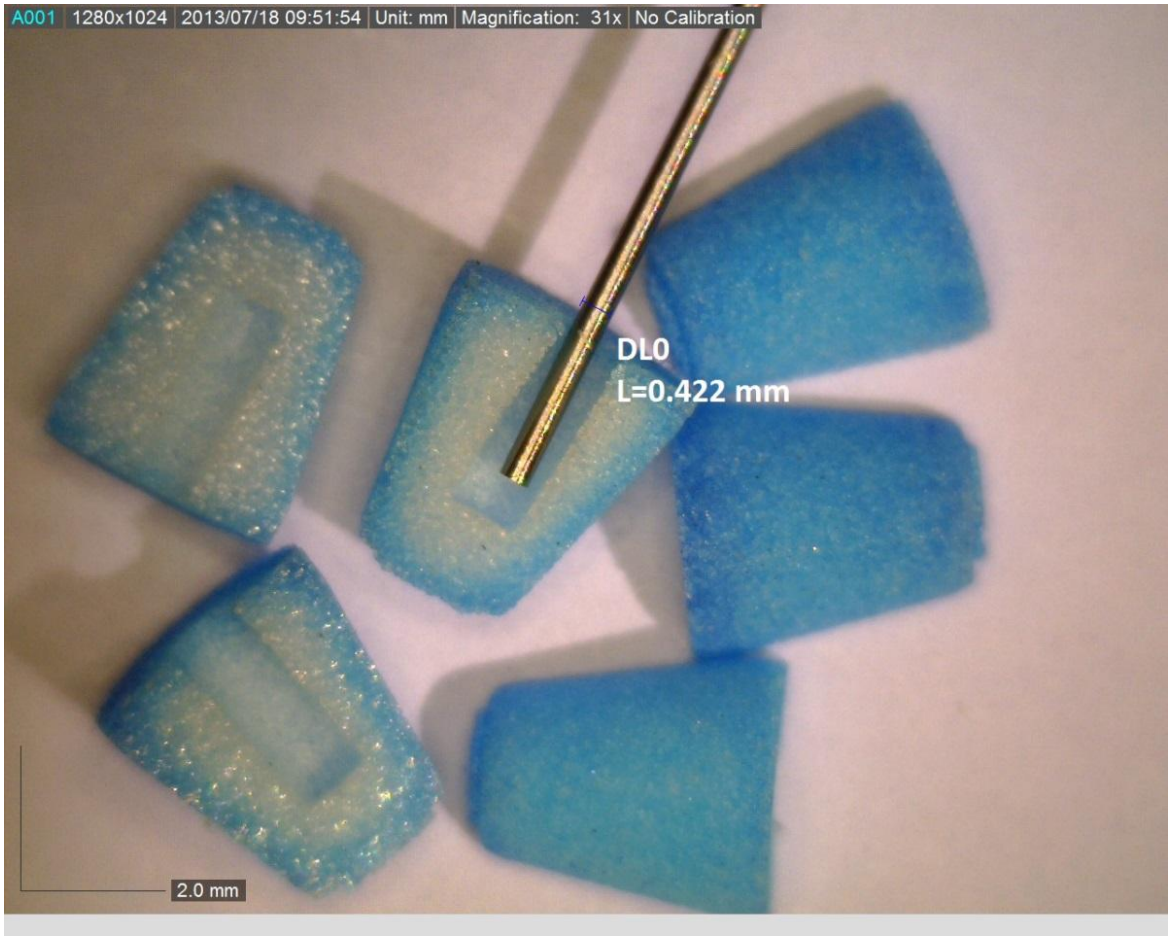
dye dried on the tips



The dye dries at the periphery of the tip.

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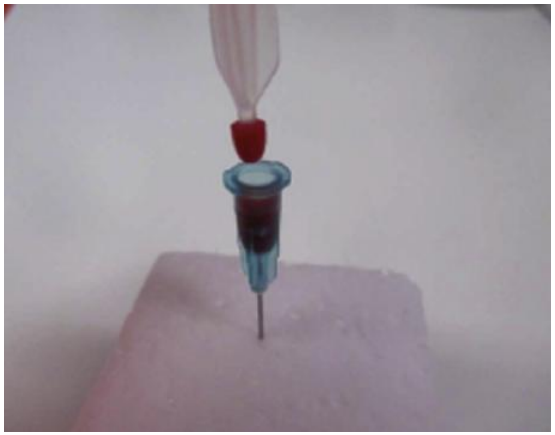
sampling technique examples

Modified Butterfly Canula

Need Hub Approach

Fill



Collect

P. Denniff, S.Parrya, W. Dopson, N. Spooner; Quantitative bioanalysis of paracetamol in rats using volumetric absorptive microsampling (VAMS); J Pharma Biomed Analysis Bioanalysis 108 (2015) 61–69.

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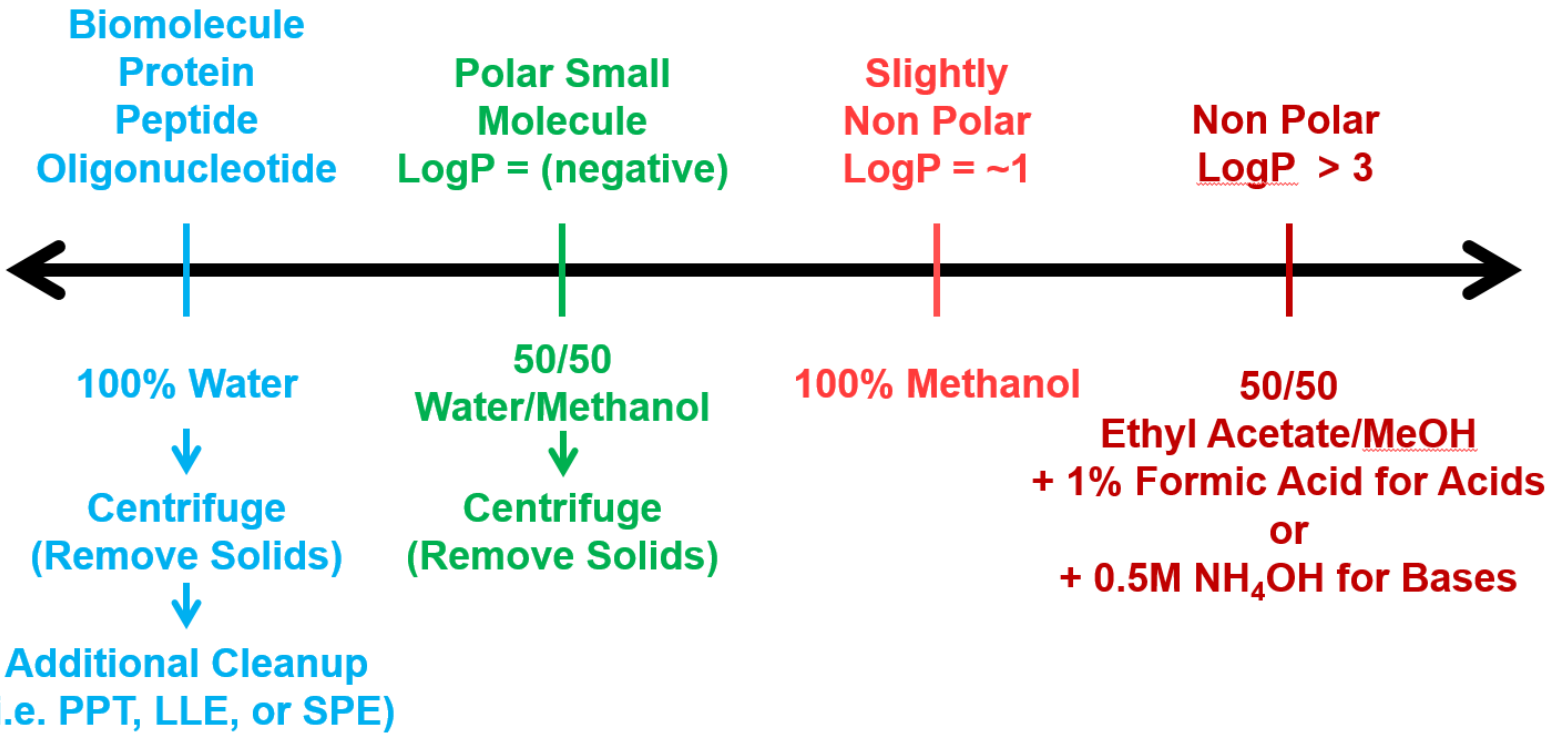
extractions by analyte chemotype



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molecular diagnostics

molecular diagnostics

- Study by Norgen Biotek Corp for total RNA/DNA purification and detection from blood preserved on Mitra® device
  - Aims to validate if dry blood microsampling can be used as a collection device for various downstream applications
  - Is microsampling a viable solution for genotyping and biomarker identification

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study design

- DNA purification, quantitation and detection
- RNA purification, quantitation, and detection
- SNP detection
- RNA expression analysis by Next Generation Sequencing

Data courtesy Dr. Bernard Lam, et. al. Norgen Biotek Corp., Canada.

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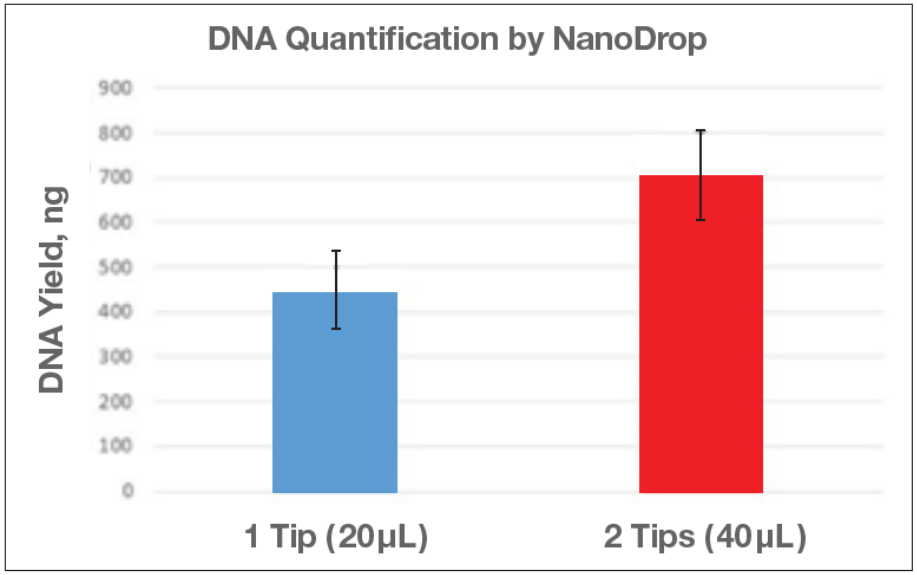
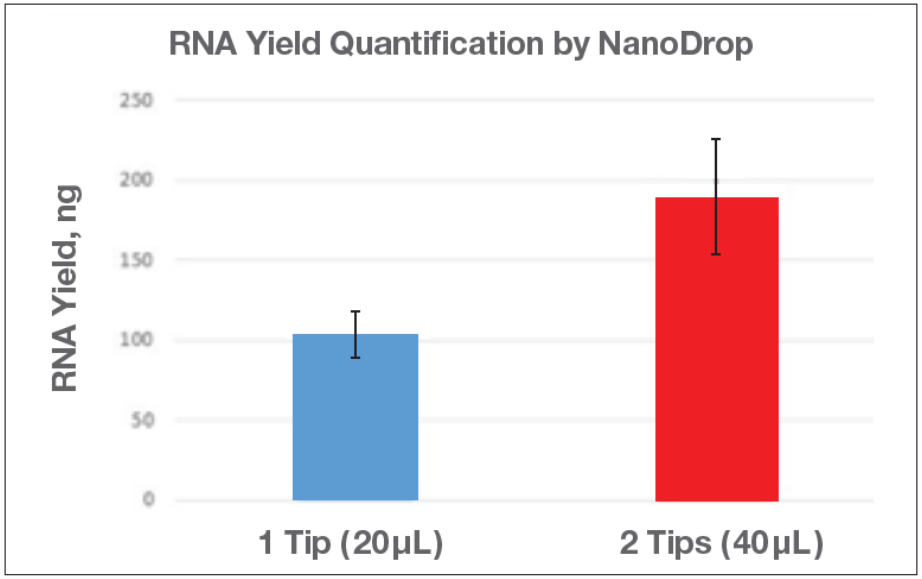
DNA and RNA quantification by NanoDrop™





Data courtesy Dr. Bernard Lam, et. al. Norgen Biotek Corp., Canada.

NanoDrop is a trademark of Thermo Fisher Scientific.

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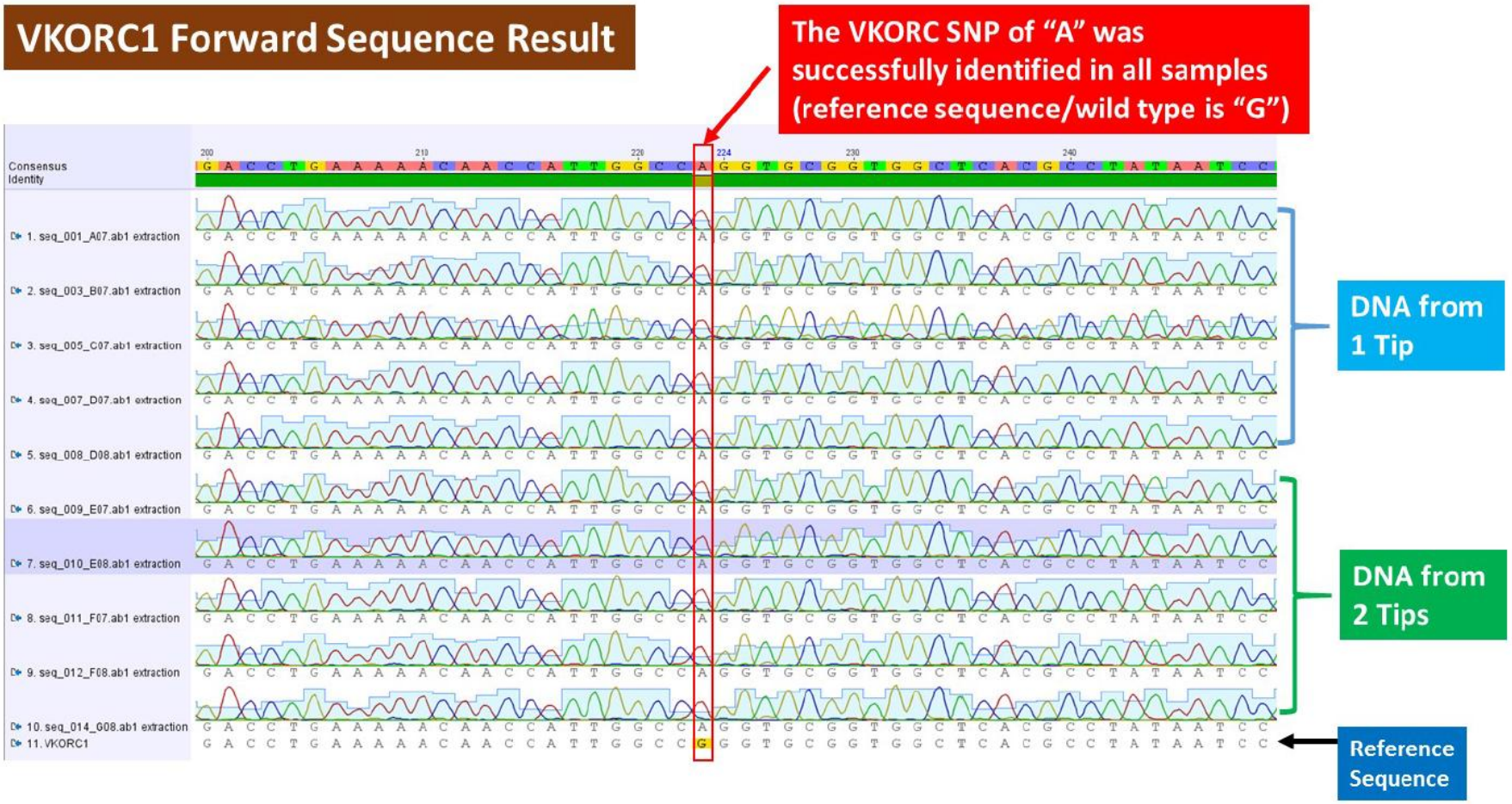
SNP identification



Data courtesy Dr. Bernard Lam, et. al. Norgen Biotek Corp., Canada.

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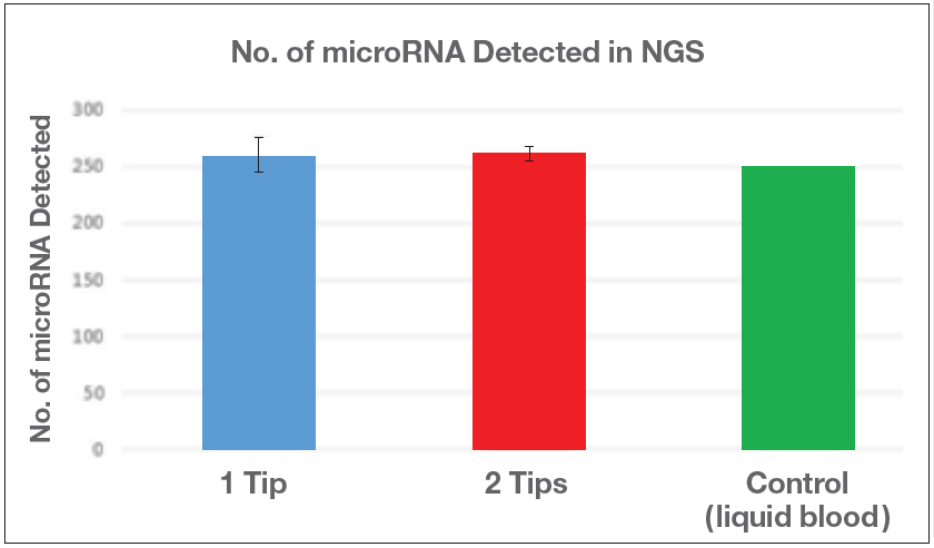
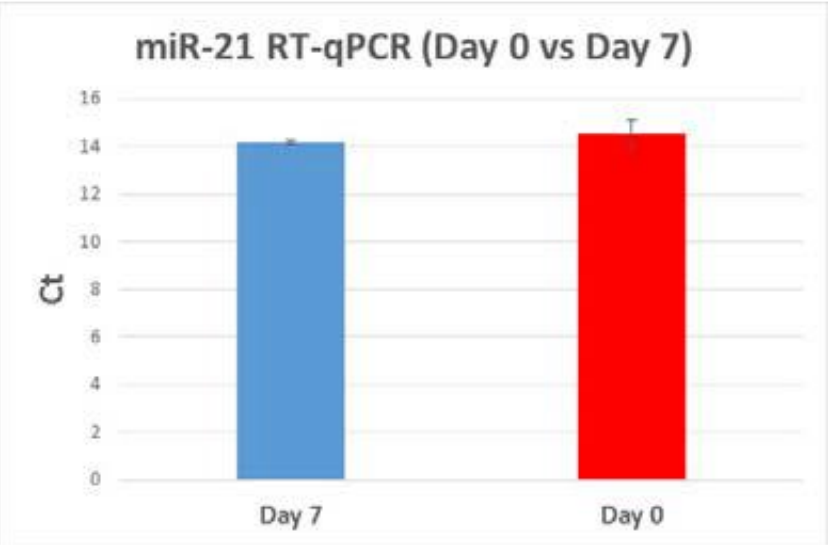
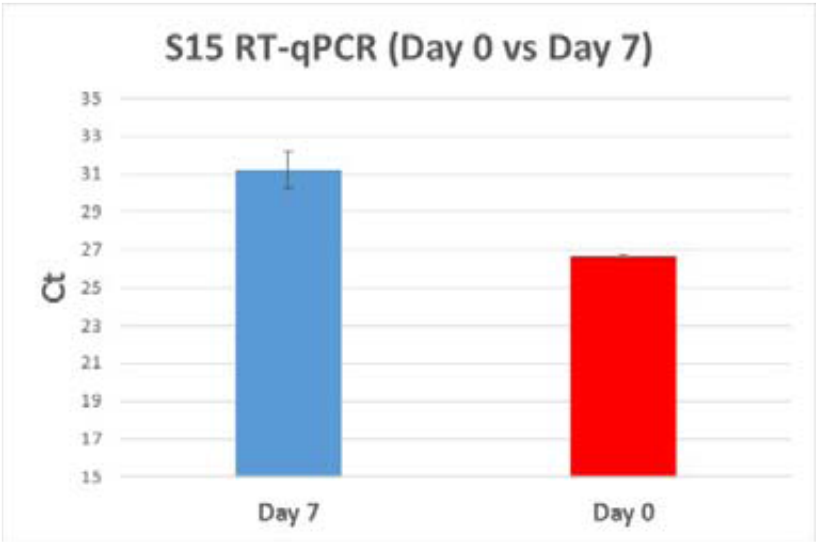
microRNA detection by NGS







Data courtesy Dr. Bernard Lam, et. al. Norgen Biotek Corp., Canada.

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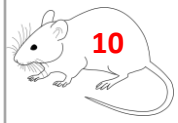
mouse PK study

original PK protocol: 3 mice

Time Points

1st	2nd	3rd	4th	5th	6th	7th	8th	9th
								
								
								

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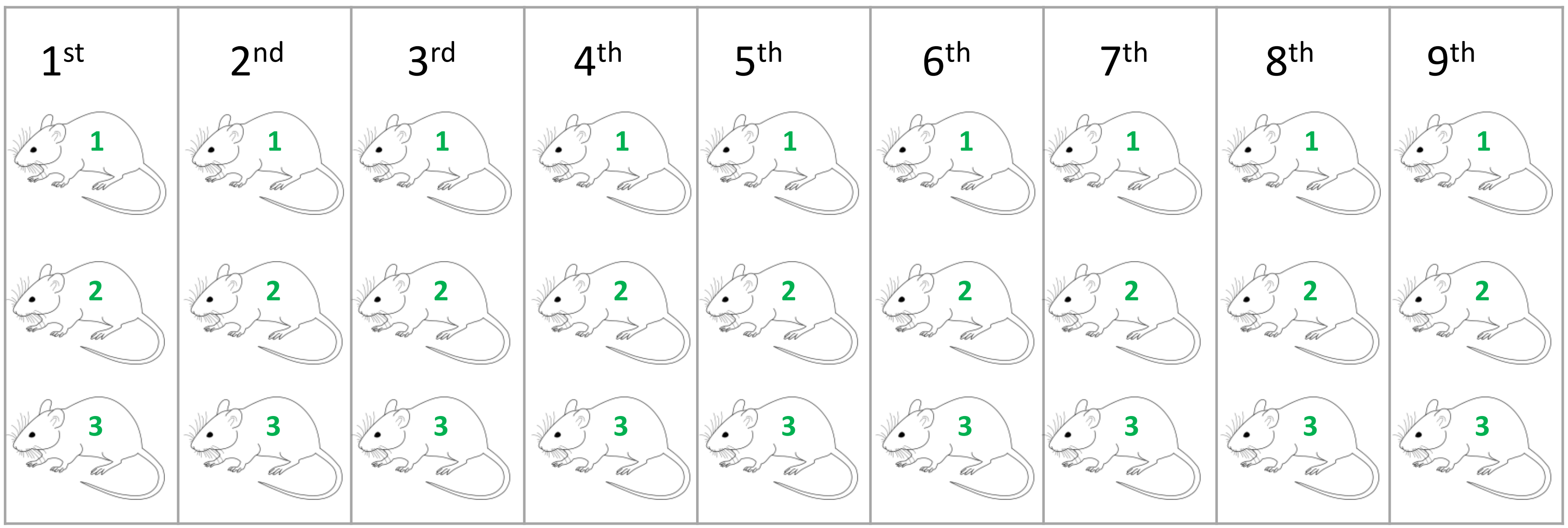
microsampling goal:
reduce pk protocol to 3 mice

Time Points



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mouse PK study design

- IV Dosing Route
  - (acetaminophen 2 mg/kg into tail vein)
- 6 Time points (0.08, 0.25, 0.5, 1, 2, and 4 hours) + predose
- Cardiac Puncture collected into tubes
  - 21 Mice Sacrificed
  - Compared:
    - Whole Blood → Plasma
    - Mitra Microsampling → Dried Whole Blood

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Data Courtesy of SciAnalytical Strategies, Inc.

mouse PK extractions

- Whole Blood → Plasma Approach
  - 9:1 Protein Precipitation with MeOH

- Mitra → Dried Blood Approach
  - Add Tips to 100µL of Water + 1% Formic Acid; Vortex 30 mins
  - Add to Tips 100µL of MeOH; Vortex 30 mins
  - Remove Tips, and add 600µL Cold Acetonitrile; Vortex 10 mins

- The For both approaches.
  - Centrifuge, Remove Supernate
  - Evaporate, and reconstitute for injection.

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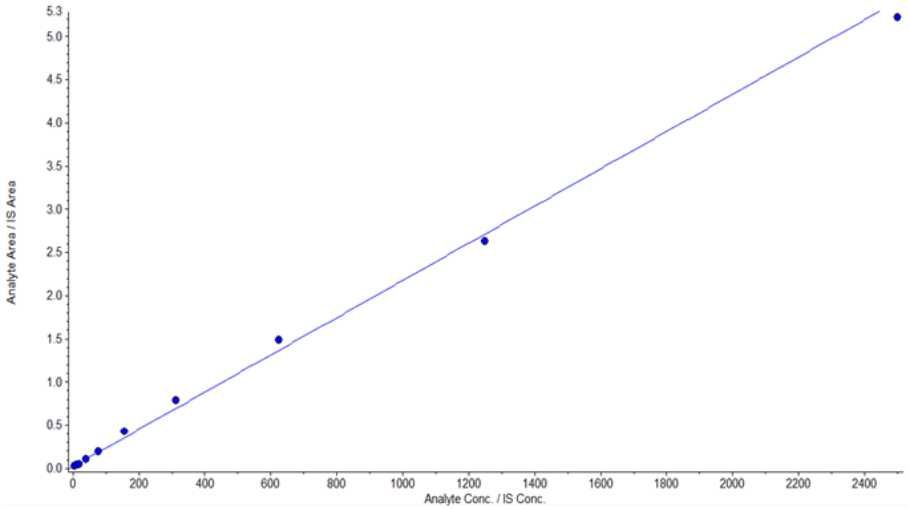
Data Courtesy of SciAnalytical Strategies, Inc.

mouse PK standard curves

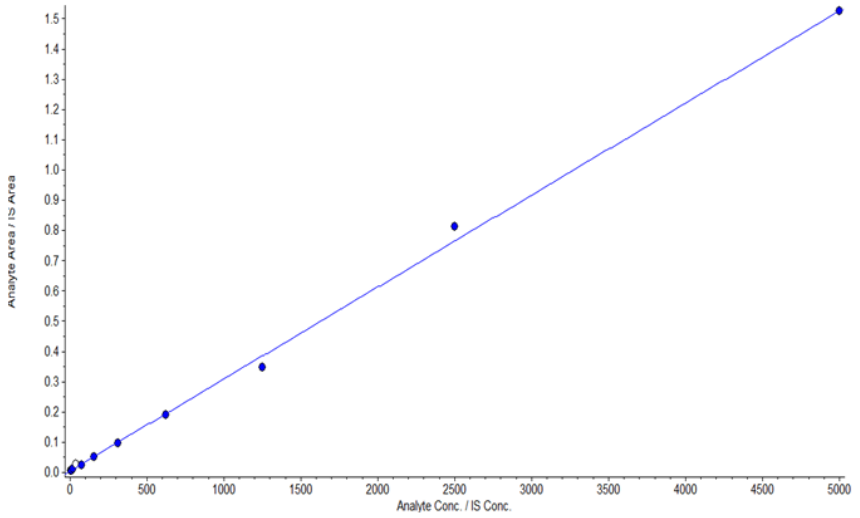
Standard curve for acetaminophen (mouse plasma)

Mouse plasma results – linear regression, 1/x weighting, y=0.00216+ 0.0183 (r=0.9975)



Standard curve for acetaminophen (mouse whole blood)

Mouse whole blood results, linear regression, 1/x weighting, y=0.00216+ 0.0183 (r=0.9986)



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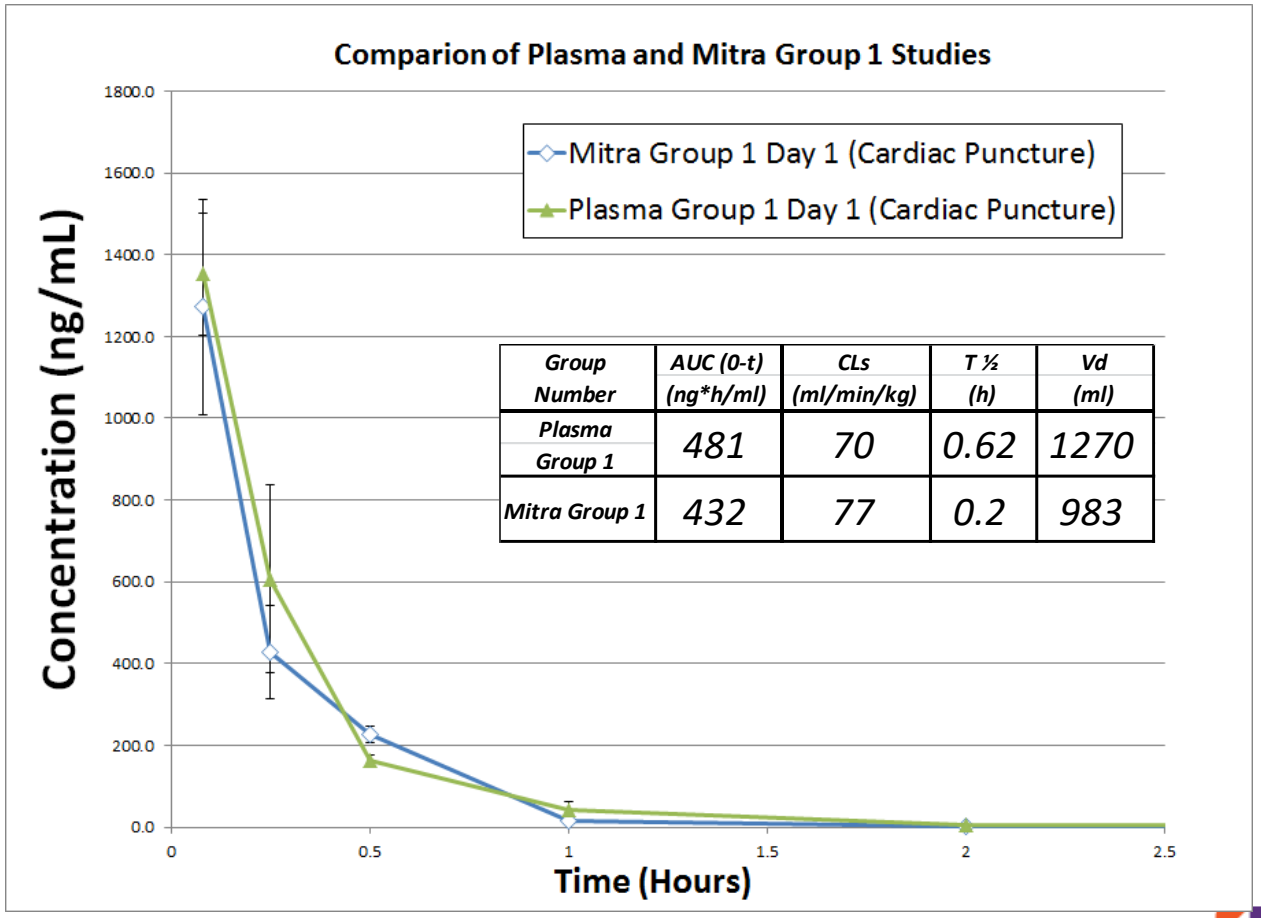
Data Courtesy of SciAnalytical Strategies, Inc.

acetaminophen PK parameters



Group Number	AUC (0-t) (ng*h/ml)	CLs (ml/min/kg)	T ½ (h)	Vd (ml)
Plasma Group 1	481	70	0.62	1270
Mitra Group 1	432	77	0.2	983

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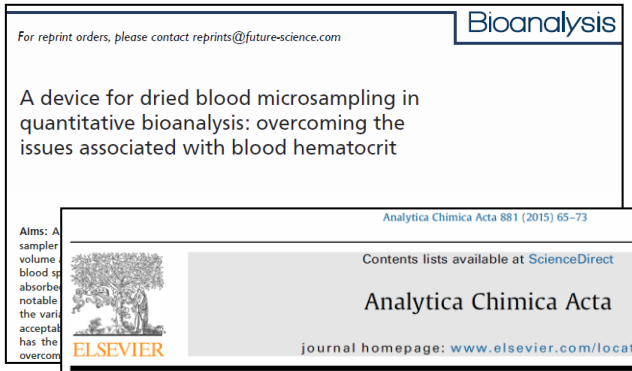
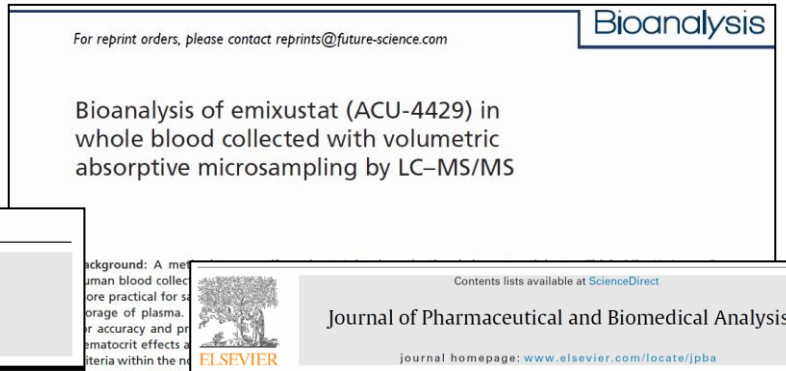
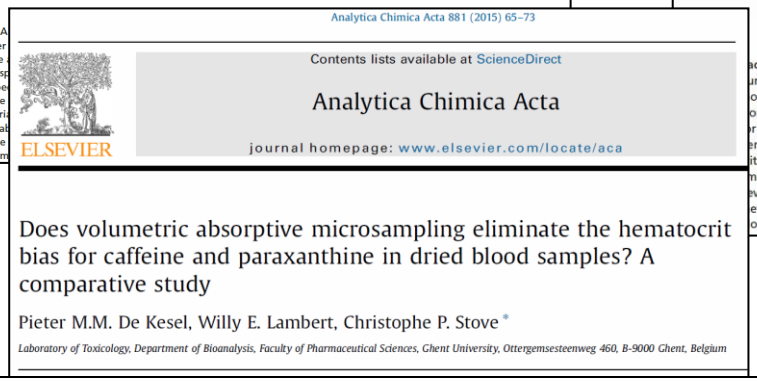
Data Courtesy of SciAnalytical Strategies, Inc.

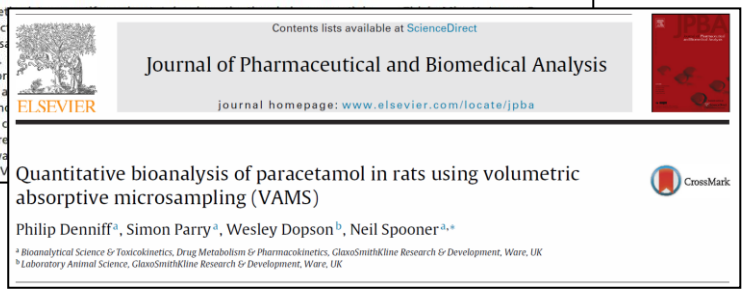
from July 2014 to now

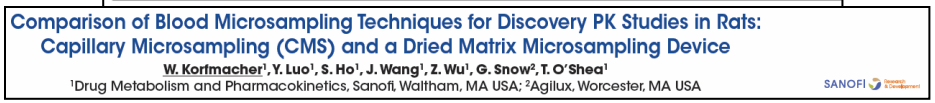
- Over 10 Posters and ~10 publications.

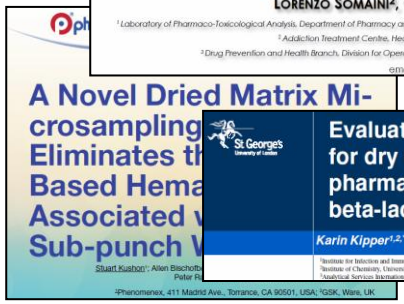


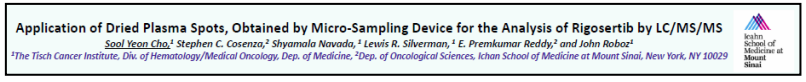












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resources

VAMS™ publications

general

De Kesel, P.M.M., Lambert, W. E., Stove, C. P. (2015). **Does volumetric absorptive microsampling eliminate the hematocrit bias for caffeine and paraxanthine in dried blood samples? A comparative study.** *Anal. Chim. Acta., 881,* 65–75.

Mano, Y.; Kita, K.; Kusano, K. (2015). **Hematocrit-independent recovery is a key for bioanalysis using volumetric absorptive microsampling devices, Mitra.** *Bioanalysis, 7(15)* , 1821–1829.

Kushon, S., Bischofberger, A., Carpenter, A., Denniff, P., & Guo, Y. (2014). **A Novel Dried Matrix Microsampling Device that Eliminates the Volume Based Hematocrit Bias Associated with DBS Sub-Punch Workflows,** 62nd ASMS Conference on Mass Spectrometry and Allied Topics.

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pharmaceutical

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continued on other side

The Mitra Microsampler class I medical device is for direct specimen collection of blood and other biological fluids. It is not specific to any clinical test, and is not for use in diagnostic procedures. Use of the Mitra Microsampler in Laboratory Developed Tests (LDTs) requires further processing including the establishment of performance characteristics and successful validation by the laboratory in a manner consistent with CLIA requirements.

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VAMS™ publications

clinical research & diagnostics

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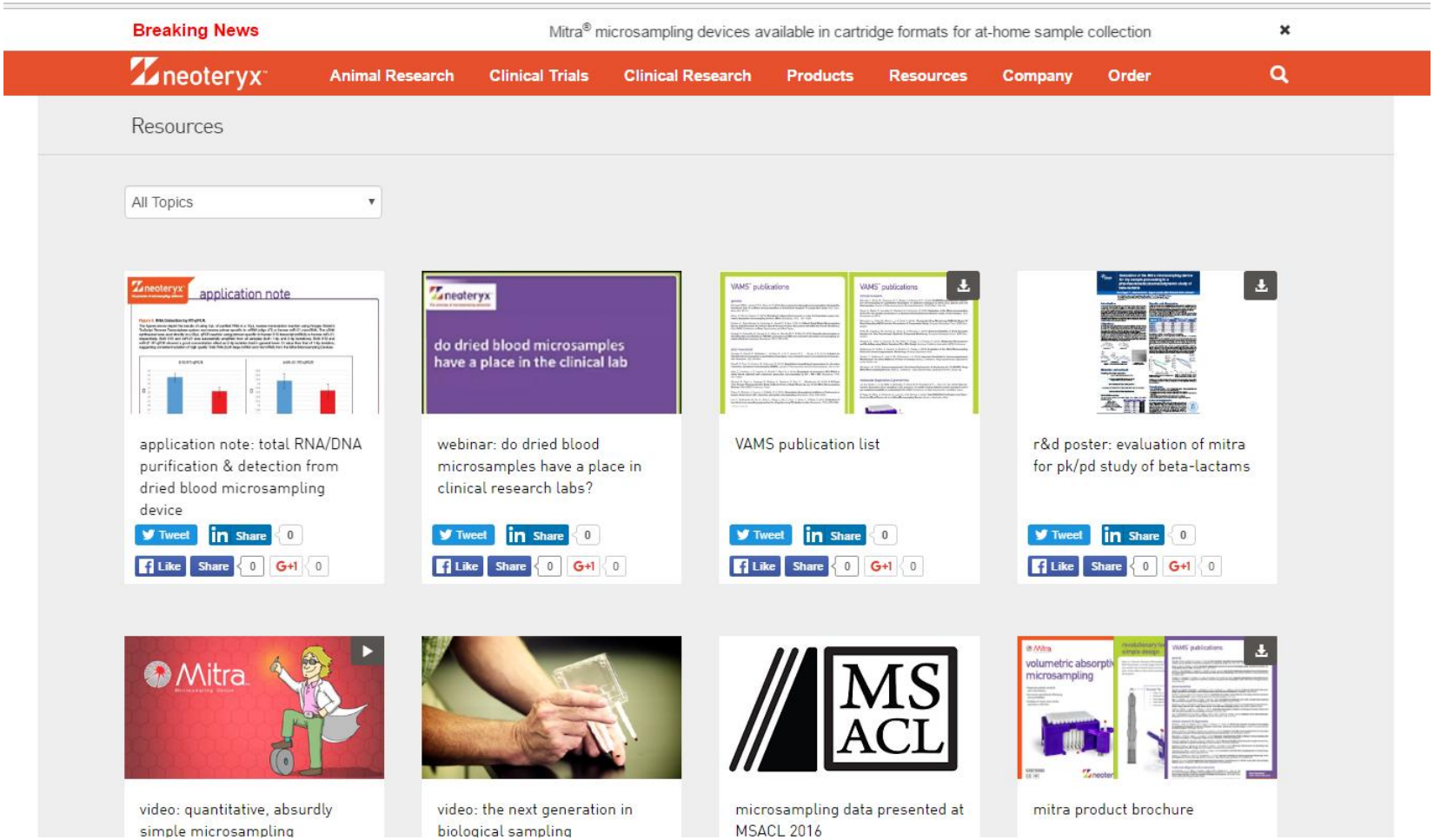
resources



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conclusions

- High quality biological fluid collections **with minimal training**
- Improved **patient experience**
- **High degree of convenience** for nurses, patients, and physicians
- Replaces existing sampling avenues or supplements them with **additional sample inflow**
- Standard methods and Mitra methods **strongly correlate** using simple (or identical) extraction methodology
- Enables **at-home or remote sampling** for increased compliance and adherence

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thank you!

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