neoteryx®

Microsampling Solutions by TRAJAN

Use of Patient Centric Sampling in Clinical Trials & Public Health

James Rudge, PhD, Microsampling Technical Director

TRAJAN

Trajan Scientific and Medical

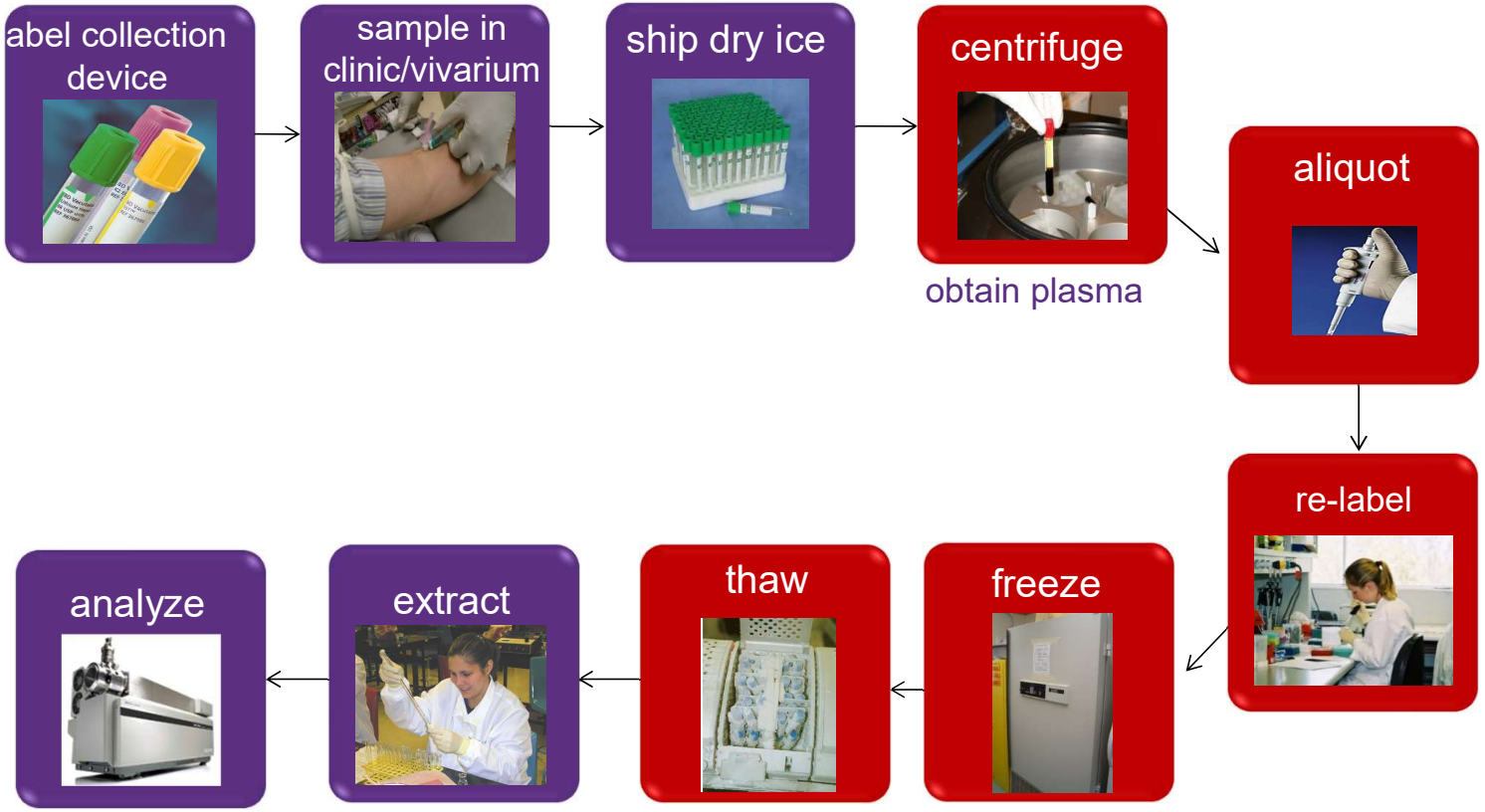
disclaimer

Mitra® devices are CE-IVD (IVDR) devices intended as specimen collectors and for the storage and transport of dried blood. They are available as registered IVD Devices in the European Union and United Kingdom, Australia, Brazil, China, and Canada, as well as multiple Health Ministries worldwide. In the USA, Mitra devices are supplied as a research use only (RUO) product to assist in method development, other research-related and non-diagnostic activities. Mitra has not been validated for use with any diagnostic testing.

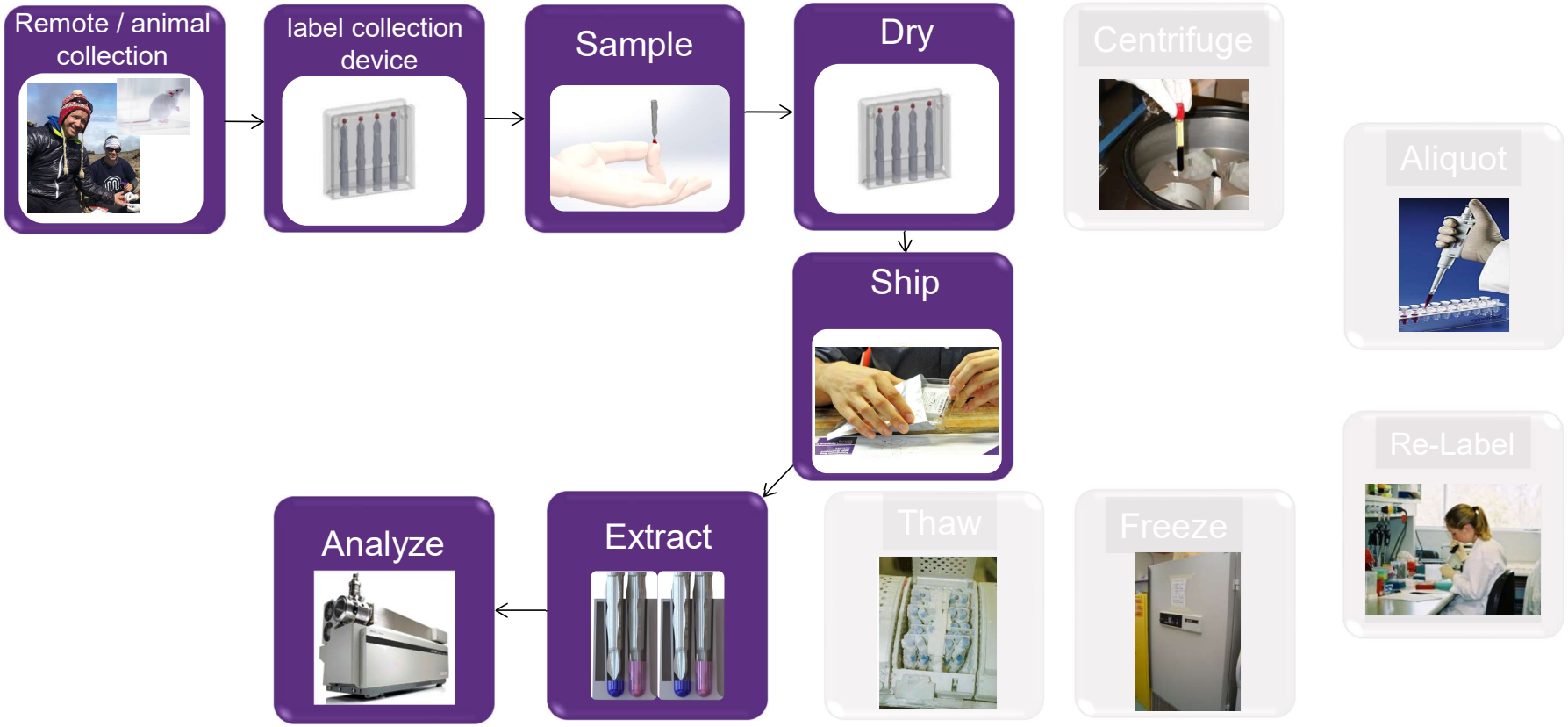
hemaPEN® variants are CE-IVD (IVDR) devices intended as specimen collectors, for the storage and transport of dried blood specimens and are available as registered IVD Devices in the European Union and United Kingdom, Australia/New Zealand, and the USA. Outside of these territories, the hemaPEN is supplied for research use only (RUO).

The Harpera™ skin microbiopsy tool is currently supplied as an investigational use only (IUO) product globally.

traditional wet sampling workflow



remote & dry sampling workflow



remote blood sampling approaches

< 100 µL fluid vs ~ 5 mL for traditional collection

wet microsampling (e.g., nanotainer, capillary tube)

Image Credit: https://www.hensomed.com/products/micro-capillary-blood-collection-tubes/

Image Credit: https://www.kentscientific.com/products/microvette-200-capillary-blood-collection-with-round-bottom-inner-tube-edta/

dried microsampling (e.g., DBS, VAMS®, HemaPEN®)

What are the concerns about remote sampling in clinical trials?

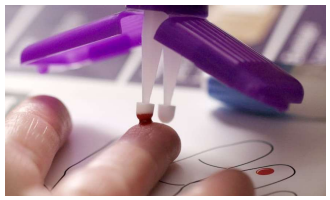
- less patient contact with clinical team
- less control over quality of samples collected
- less patient involvement
- possible increased anxiety risk for some
- less control of identity of sample collection
- less control over time sample taken
- less control over temperature of sample at collection
- transportation temperature control
- bridging studies needed
  - Capillary vs Venous
  - EDTA plasma vs Capillary blood
- some labs experienced in processing microsamples
- regulatory acceptance

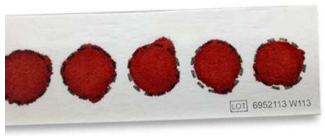
What are the concerns about remote sampling in clinical trials - microsamples?

wet microsampling (e.g., nanotainer, capillary tube)

- poor stability (often needs cryostorage)
- cold chain shipping
- difficult to collect
- hazardous
- messy

dried blood microsampling (e.g., VAMS®, DBS, HemaPEN®)





- hemolysis
- HCT biases
- no access to plasma / serum
- bridging studies needed

What are the benefits of remote patient monitoring in clinical trial design?

- significant reduction in clinical trial costs
- remote option improves patient enrolment
- fewer or no visits to clinic
- potential for improved compliance
- greater patient involvement
- reduced patient anxiety
- wider & more diverse recruitment area
- access to vulnerable patients/samples
- reduced blood volume collected (microsamples)
- dried blood samples show high stability for many analytes

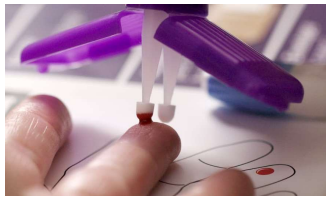
What are the benefits of remote patient monitoring in clinical trial design - microsamples?

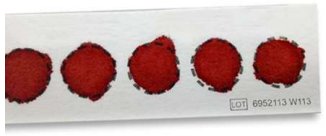
wet microsampling (e.g., nanotainer, capillary tube)

- self-sample collection
- eliminates phlebotomist
- intact blood
- access to plasma / serum
- concordant data – no bias*
- most bio-fluids

* for the majority of analytes

dried blood microsampling (e.g., VAMS®, DBS, HemaPEN®)





- self-sample collection
- eliminates phlebotomist
- stability (RT) – most samples
- no cold chain shipping for many analytes
- concordant data **
- ease of collection
- most bio-fluids

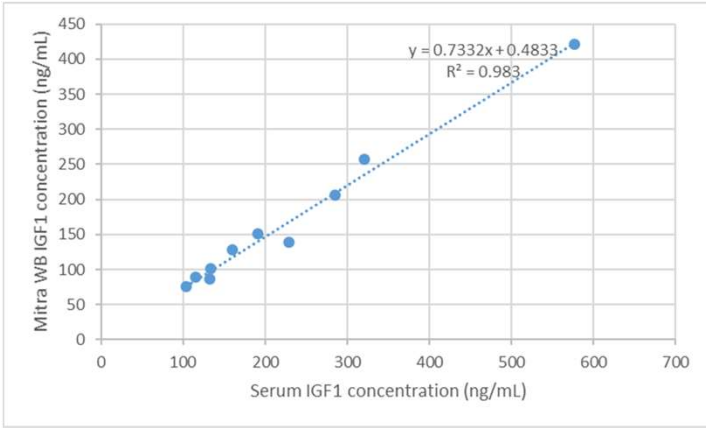
** Biases seen for some analytes

What can be reliably measured from dried blood microsamples?

A wide range of analytes including

- **Biomarkers:** such as hormones and creatinine
- **Drugs:** large and small (e.g., MAbs)
- **Antibodies:** serology for example
- **Viral antigens:** such as SARS-CoV-2 nucleocapsid
- **DNA / RNA:** such as transgene detection
- **Heavy Metals:** for example, mercury
- **Environmental contaminants:** such as PFAS
- **Toxins:** such as Saxitoxin and aflatoxin
- **Proteomic markers:** such as cardiovascular risk factors
- **Metabolomic markers:** such as amino acids

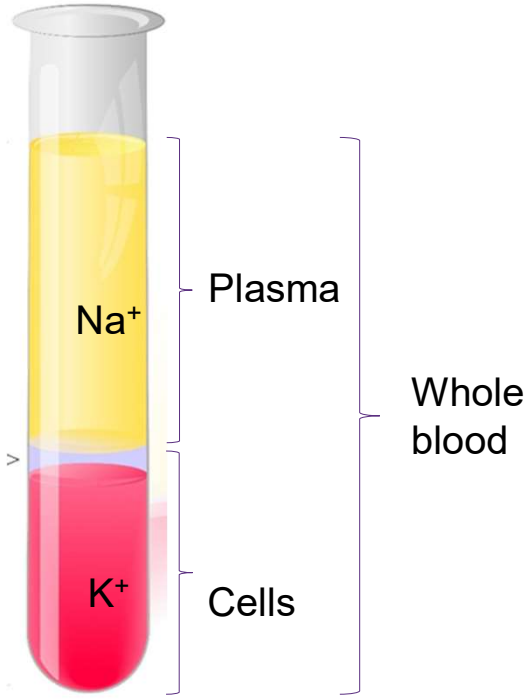
Comparison of IGF-1 result in serum vs VAMS extracted with whole blood



What can't be reliably measured from dried blood microsamples?

1. **Physiological incompatibility**: Where the drying and processing of blood damages the analytes in the matrix (or damages the matrix itself) in such a way that they are not measurable in any meaningful way (or even at all) - such as measurement of potassium

2. **Analytical incompatibility:** Where current / popular instrumentation is incompatible with microsamples and or dried blood extracts. An example of this is common blood tests such as liver function enzymes and lipids, which are measured using clinical chemistry analyzers.



Dried Blood Extract

Fully Lysed

offering remote sampling in clinical trials

Understanding Bridging

Pharmacol Res Perspect. 2019 Feb; 7(1): e00459.
Published online 2019 Jan 28. doi: 10.1002/prp2.459
PMCID: PMC6349788
PMID: 30705758

Pharmacol Res Pers

A pharmacokinetic study of radiprodil oral suspension in healthy adults comparing conventional venous blood sampling with two microsampling techniques

David Sciberras,[1] Christian Otoul,[1] Françoise Lurquin,[1] John Smeraglia,[1] Aurélia Lappert,[1] Steven De Bruyn,[1] and Jan Jaap van Lier[2]

"This [result in the study] confirms that either technique is fit for purpose for use in future clinical studies with radiprodil. These less invasive microsampling techniques have great potential to facilitate and add value to any paediatric programme."

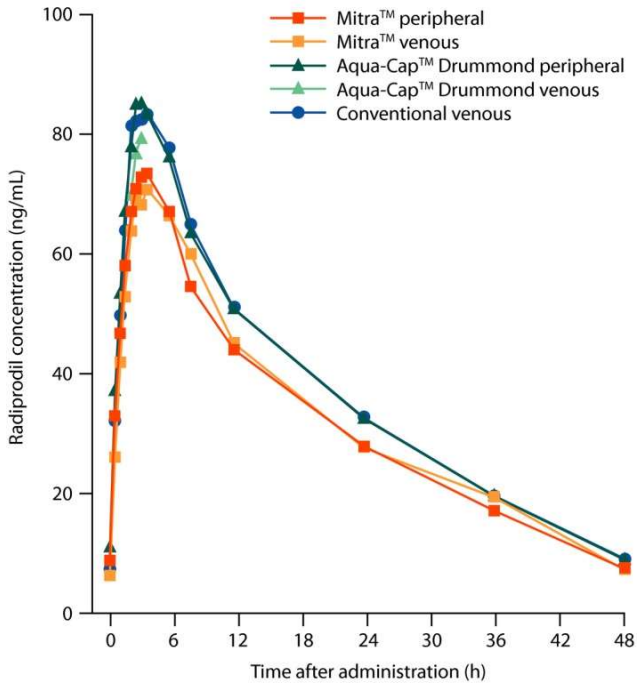


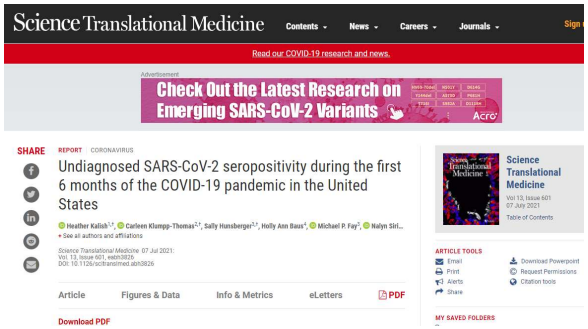
Image: D Sciberras et al, UCB Biopharma & PRA Health sciences, Jan. 2019, Pharmac Res & Perspect.

NIH announces large serological survey using remote sample collection

Credit: https://www.niaid.nih.gov/news-events/nih-begins-study-quantify-undetected-cases-coronavirus-infection

NIH serosurveillance survey results (2021)

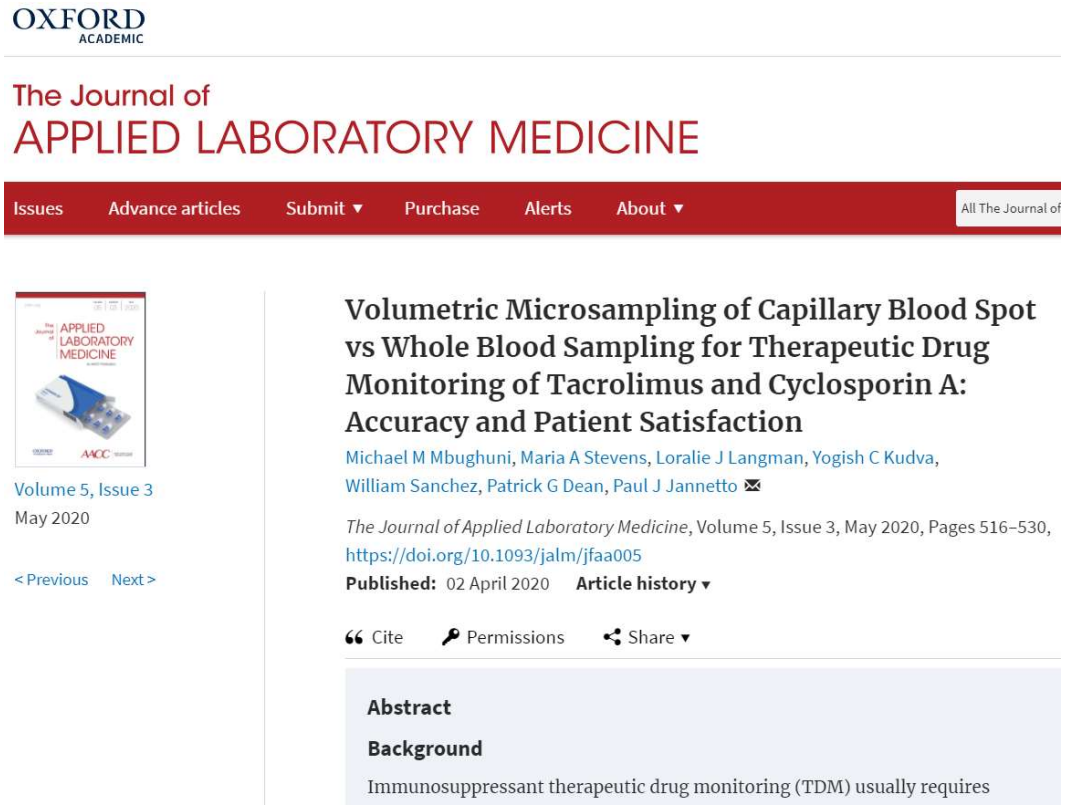
- Remote participants submitted **9,028 self-collected** Mitra with VAMS microsamples
- Only **61** of the remote samples **rejected**
- 88.7% of samples were **collected** between **May 10 - July 31**, 2020
- Samples were analyzed via **ELISA** for anti-**Spike** and anti-**RBD** antibodies
- **Seroprevalence** was estimated with **weighted** analysis to **reflect** the **US** population
- An **undiagnosed seropositivity** rate of **4.6%** (95% CI: 2.6 – 6.5%) was detected
- For every **1 Dx case** of COVID-19 in the US during this period, there were **4.8** (95% CI: 2.8-6.8) **undiagnosed** cases
- **~16.8 million undiagnosed** cases by mid-July 2020



Credit: NIBIB, NIH: https://stm.sciencemag.org/content/13/601/eabh3826/tab-pdf

patient experience

- **Total cohort 100**
- 81 % - Capillary collection is better (n=48)
- 85 % - Capillary collection was easy to perform (n = 48)
- 85 % - Lancet easy to use (n = 48)
- 73% - Less painful than venous (n = 48)
- 90% - Would try now seen (n = 52)
- 82 % - Prefer self-collection (100 %)
- 0 - No samples rejected



OXFORD ACADEMIC

The Journal of APPLIED LABORATORY MEDICINE

Issues | Advance articles | Submit | Purchase | Alerts | About | All The Journal of

Volume 5, Issue 3
May 2020

< Previous Next >

Volumetric Microsampling of Capillary Blood Spot vs Whole Blood Sampling for Therapeutic Drug Monitoring of Tacrolimus and Cyclosporin A: Accuracy and Patient Satisfaction

Michael M Mbughuni, Maria A Stevens, Loralie J Langman, Yogish C Kudva, William Sanchez, Patrick G Dean, Paul J Jannetto

The Journal of Applied Laboratory Medicine, Volume 5, Issue 3, May 2020, Pages 516–530, https://doi.org/10.1093/jalm/jfaa005

Published: 02 April 2020 **Article history**

Cite | Permissions | Share

Abstract

Background

Immunosuppressant therapeutic drug monitoring (TDM) usually requires

Credit: https://academic.oup.com/jalm/article-abstract/5/3/516/5815223

MAYO CLINIC

giving patients a choice

SPECIAL FOCUS ISSUE I Patient-centric sampling

Perspective

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Giving patients choices: AstraZeneca's evolving approach to patient-centric sampling

Christopher Bailey*,[1], Cecilia Arfvidsson[2], Lynsey Woodford[3] & Miné de Kock[1]

[1]Clinical Pharmacology & Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, AstraZeneca, Cambridge, UK

[2]Clinical Pharmacology & Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, AstraZeneca, Gothenburg, Sweden

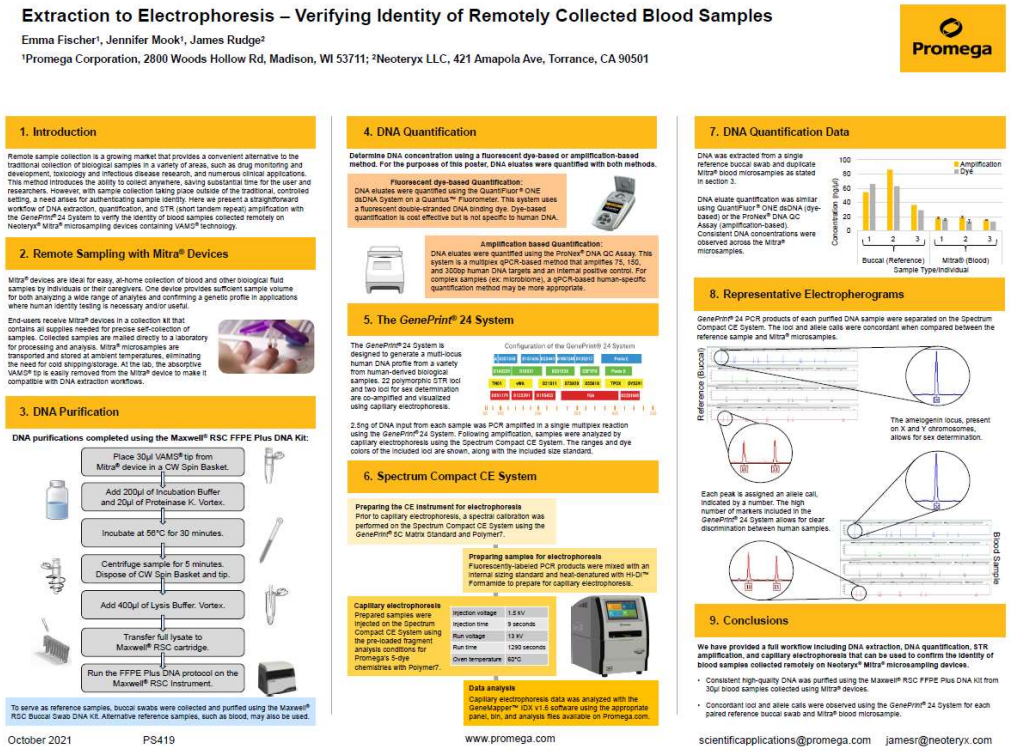
[3]Clinical Sampling & Alliances, AstraZeneca, Cambridge, UK

https://www.future-science.com/doi/abs/10.4155/bio-2020-0105

"continuous patient engagement throughout the study life cycle and accepting that if the aim is to give patient choice, then one solution (device, procedure and design) will not fit all."

the future

Verifying Identity of Remotely Collected Blood Samples using DNA



Extraction to Electrophoresis – Verifying Identity of Remotely Collected Blood Samples

Emma Fischer[1], Jennifer Mook[1], James Rudge[2]
[1]Promega Corporation, 2800 Woods Hollow Rd, Madison, WI 53711; [2]Neoteryx LLC, 421 Amapola Ave, Torrance, CA 90501

Promega

1. Introduction

Remote sample collection is a growing market that provides a convenient alternative to the traditional collection of biological samples in a variety of areas, such as drug monitoring and development, toxicology and infectious disease research, and numerous clinical applications. This method introduces the ability to collect anywhere, saving substantial time for the user and researchers. However, with sample collection taking place outside of the traditional, controlled setting, a need arises for authenticating sample identity. Here we present a straightforward workflow of DNA extraction, quantification, and STR (short tandem repeat) amplification with the *GenePrint*® 24 System to verify the identity of blood samples collected remotely on Neoteryx® Mitra® microsampling devices containing vAMS® technology.

2. Remote Sampling with Mitra® Devices

Mitra® devices are ideal for easy, at-home collection of blood and other biological fluid samples by individuals or their caregivers. One device provides sufficient sample volume for both analyzing a wide range of analytes and confirming a genetic profile in applications where human identity testing is necessary and/or useful.

End-users receive Mitra® devices in a collection kit that contains all supplies needed for precise self-collection of samples. Collected samples are mailed directly to a laboratory for processing and analysis. Mitra® microsamples are transported and stored at ambient temperatures, eliminating the need for cold shipping/storage. At the lab, the absorptive VAMS® tip is easily removed from the Mitra® device to make it compatible with DNA extraction workflows.

3. DNA Purification

DNA purifications completed using the Maxwell® RSC FFPE Plus DNA Kit:

- Place 30µl VAMS® tip from Mitra® device in a CW Spin Basket.
- Add 200µl of Incubation Buffer and 20µl of Proteinase K. Vortex.
- Incubate at 56°C for 30 minutes.
- Centrifuge sample for 5 minutes. Dispose of CW Spin Basket and tip.
- Add 400µl of Lysis Buffer. Vortex.
- Transfer full lysate to Maxwell® RSC cartridge.
- Run the FFPE Plus DNA protocol on the Maxwell® RSC Instrument.

To serve as reference samples, buccal swabs were collected and purified using the Maxwell® RSC Buccal Swab DNA Kit. Alternative reference samples, such as blood, may also be used.

4. DNA Quantification

Determine DNA concentration using a fluorescent dye-based or amplification-based method. For the purposes of this poster, DNA eluates were quantified with both methods.

Fluorescent dye-based Quantification:
DNA eluates were quantified using the QuantiFluor® ONE dsDNA System on a Quantus™ Fluorometer. This system uses a fluorescent double-stranded DNA binding dye. Dye-based quantification is cost effective but is not specific to human DNA.

Amplification based Quantification:
DNA eluates were quantified using the ProNex® DNA QC Assay. This system is a multiplex qPCR-based method that amplifies 75, 150, and 300bp human DNA targets and an internal positive control. For complex samples (ex: microbiome), a qPCR-based human-specific quantification method may be more appropriate.

5. The *GenePrint*® 24 System

The *GenePrint*® 24 System is designed to generate a multi-locus human DNA profile from a variety from human-derived biological samples. 22 polymorphic STR loci and two loci for sex determination are co-amplified and visualized using capillary electrophoresis.

Configuration of the GenePrint® 24 System

2.5ng of DNA input from each sample was PCR amplified in a single multiplex reaction using the *GenePrint*® 24 System. Following amplification, samples were analyzed by capillary electrophoresis using the Spectrum Compact CE System. The ranges and dye colors of the included loci are shown, along with the included size standard.

6. Spectrum Compact CE System

Preparing the CE instrument for electrophoresis
Prior to capillary electrophoresis, a spectral calibration was performed on the Spectrum Compact CE System using the GenePrint® SC Matrix Standard and Polymer7.

Preparing samples for electrophoresis
Fluorescently-labeled PCR products were mixed with an internal sizing standard and heat-denatured with Hi-Di™ Formamide to prepare for capillary electrophoresis.

Capillary electrophoresis
Prepared samples were injected on the Spectrum Compact CE System using the pre-loaded fragment analysis conditions for Promega's 5-dye chemistries with Polymer7.

Injection voltage	1.5 kV
Injection time	9 seconds
Run voltage	13 kV
Run time	1290 seconds
Oven temperature	62°C

Data analysis
Capillary electrophoresis data was analyzed with the GeneMapper™ IDX v1.6 software using the appropriate panel, bin, and analysis files available on Promega.com.

7. DNA Quantification Data

DNA was extracted from a single reference buccal swab and duplicate Mitra® blood microsamples as stated in section 3.

DNA eluate quantification was similar using QuantiFluor® ONE dsDNA (dye-based) or the ProNex® DNA QC Assay (amplification-based). Consistent DNA concentrations were observed across the Mitra® microsamples.

8. Representative Electropherograms

GenePrint® 24 PCR products of each purified DNA sample were separated on the Spectrum Compact CE System. The loci and allele calls were concordant when compared between the reference sample and Mitra® microsamples.

9. Conclusions

We have provided a full workflow including DNA extraction, DNA quantification, STR amplification, and capillary electrophoresis that can be used to confirm the identity of blood samples collected remotely on Neoteryx® Mitra® microsampling devices.

- Consistent high-quality DNA was purified using the Maxwell® RSC FFPE Plus DNA Kit from 30µl blood samples collected using Mitra® devices.
- Concordant loci and allele calls were observed using the *GenePrint*® 24 System for each paired reference buccal swab and Mitra® blood microsample.

October 2021 PS419

www.promega.com
scientificapplications@promega.com jamesr@neoteryx.com

"We have provided a full workflow including DNA extraction, DNA quantification, STR amplification, and capillary electrophoresis that can be used to confirm the identity of blood samples collected remotely on Neoteryx® Mitra® microsampling devices."

Thank you!

www.neoteryx.com