FACULTY OF
PHARMACEUTICAL SCIENCES

DEPARTMENT OF BIOANALYSIS
LABORATORY OF TOXICOLOGY

WORKSHOP

"MICROSAMPLING/DBS IN TDM AND TOXICOLOGY"

NVKFAZ SYMPOSIUM 8 APRIL 2022

Sigrid Deprez, Christophe Stove

GHENT UNIVERSITY

fwo Research Foundation Flanders
Opening new horizons

BACKGROUND INFORMATION

Ghent University

Laboratory of Toxicology

Prof. C. Stove

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PRESENTATION OUTLINE

- Dried blood spots: advantages and challenges
- Non-volumetric *vs.* volumetric dried blood sampling
- Automated DBS-analysis
- Key factors to success
- Toxicological & clinical implementation

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HEBT U ERVARING MET DRIED BLOOD SAMPLES (DBS) VOOR THERAPEUTIC DRUG MONITORING OF TOXICOLOGIE?

1. Nee, ik ben niet bekend met DBS.

   0%

2. Ja, maar enkel voor onderzoeksdoeleinden.

   0%

3. Ja, we gebruiken het in de klinische praktijk.

   0%

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PRESENTATION OUTLINE

- Dried blood spots: advantages and challenges
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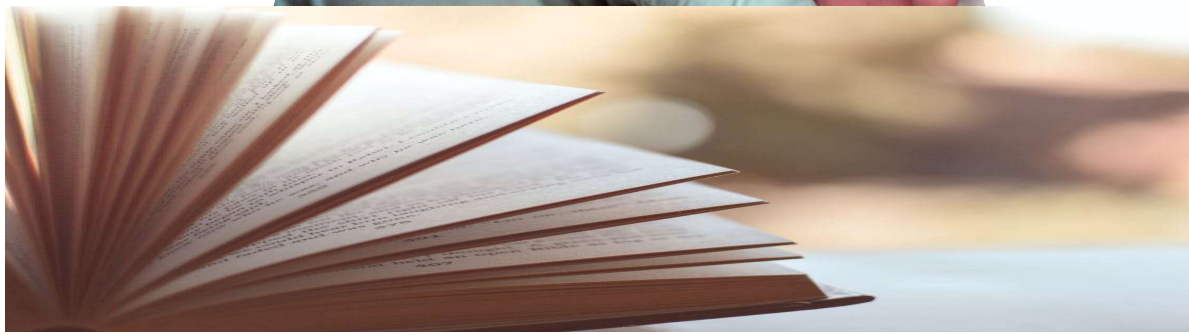
THE JOURNEY OF MICROSAMPLING

Robert Guthrie

Heel prick

Use of capillary, dried blood on filter paper for the TDM of immunosuppressants (Cyclosporin A)

Lampe et al. 1987. Clinical Chemistry



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DRIED BLOOD SPOTS: ADVANTAGES AND CHALLENGES

- Small volume
- Minimally invasive
- Ease of sampling
- Economic
- Amenable to automation
- Sample preparation simplification
- Convenient storage and transport
- Often stabilizing effect
- Ethical (3R)

- Limited amount
- Capillary-venous differences
- Interpretation (blood vs. plasma)
- Stability issues
- Sample quality
- Specific DBS issues: Recovery issues
  - Hematocrit effect
  - Volume issues (saturation)
  - Spot inhomogeneity

DRIED BLOOD SPOTS: ADVANTAGES AND CHALLENGES

Small volume

Minimally invasive

Ease of sampling

Economic

Amenable to automation

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Often stabilizing effect

Ethical (3R)

Limited amount

Capillary-venous differences

Interpretation (blood vs. plasma)

Stability issues

Sample quality

Specific DBS issues: Recovery issues

Hematocrit effect

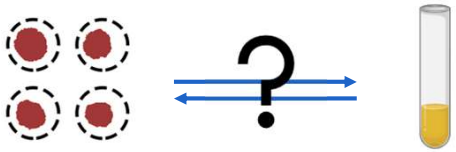
Volume issues (saturation)

Spot inhomogeneity

DRIED BLOOD SPOTS: ADVANTAGES AND CHALLENGES

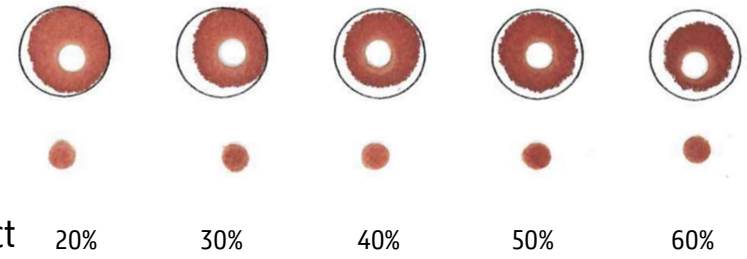
THE HEMATOCRIT EFFECT

Physiological aspect



Analytical aspect

- Area bias
- Recovery bias
- Matrix bias



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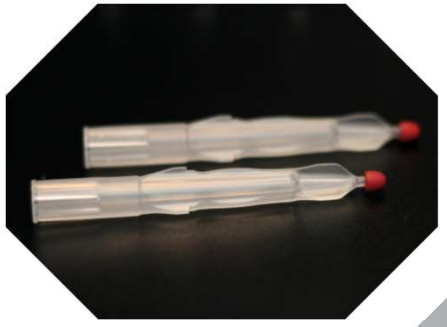
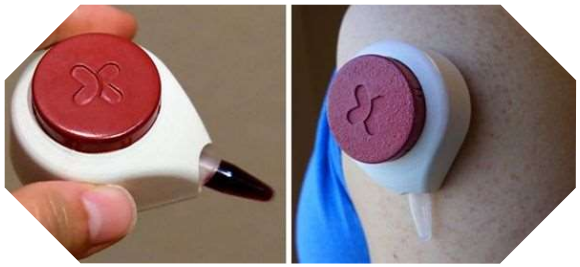
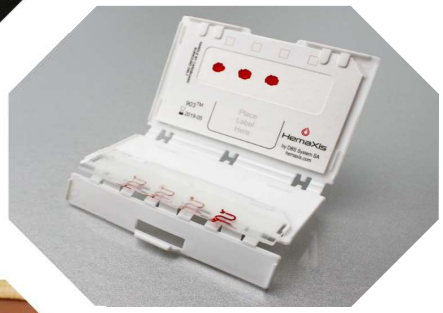
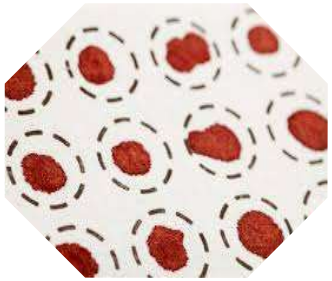
NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING









Delahaye et al. 2020. TDM

FOCUS SERIES: ALTERNATIVE SAMPLING STRATEGIES

Alternative Sampling Devices to Collect Dried Blood Microsamples: State-of-the-Art

Lisa Delahaye, PharmD, Herman Veenhof, PhD,† Birgit C. P. Koch, PhD,‡ Jan-Willem C. Alffenaar, PhD,§¶|| Rafael Linden, PhD,** and Christophe Stove, PhD**

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

DBS

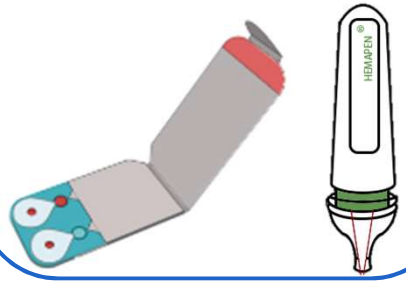
- Whole spot
- Partial spot
- Hemaspot HF

Volumetric devices

- Mitra™ device (VAMS)
- Capitainer qDBS

(Follow-up for Capitainer-B)

- HemaPEN®
- Hemaxis™ DB10



(Micro)needle based

- Tasso device (Tasso Inc.)
- Touch activated phlebotomy (TAP) device (YourBio Health)

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

DBS

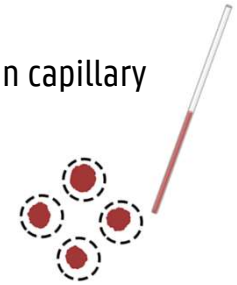
- Whole spot
- Partial spot
- Hemaspot HF

Volumetric application via pipetting

DBS punch (3-6mm)

⊖ Hematocrit prediction and correction

Precision capillary

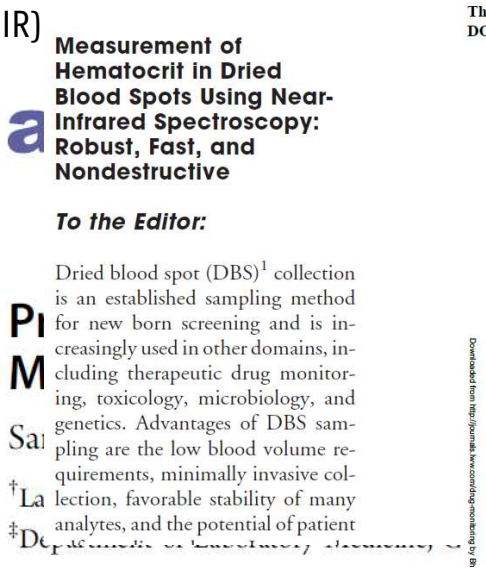


⊖

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

Hct-prediction of DBS

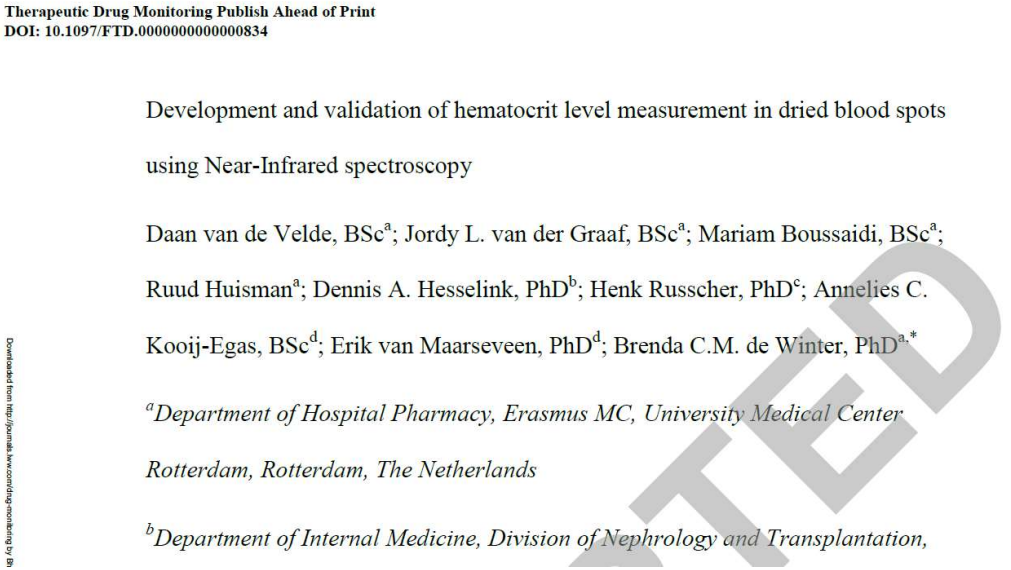
- Quantification of the potassium concentration in DBS
- Quantification of hemoglobin levels with ultraviolet-visible spectroscopy (reflectance spectroscopy)
- Near-Infrared spectroscopy (NIR)



Measurement of Hematocrit in Dried Blood Spots Using Near-Infrared Spectroscopy: Robust, Fast, and Nondestructive

To the Editor:

Dried blood spot (DBS)[1] collection is an established sampling method for new born screening and is increasingly used in other domains, including therapeutic drug monitoring, toxicology, microbiology, and genetics. Advantages of DBS sampling are the low blood volume requirements, minimally invasive collection, favorable stability of many analytes, and the potential of patient



Therapeutic Drug Monitoring Publish Ahead of Print
DOI: 10.1097/FTD.0000000000000834

Development and validation of hematocrit level measurement in dried blood spots using Near-Infrared spectroscopy

Daan van de Velde, BSc[a]; Jordy L. van der Graaf, BSc[a]; Mariam Boussaidi, BSc[a]; Ruud Huisman[a]; Dennis A. Hesselink, PhD[b]; Henk Russcher, PhD[c]; Annelies C. Kooij-Egas, BSc[d]; Erik van Maarseveen, PhD[d]; Brenda C.M. de Winter, PhD[a,*]

[a]*Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

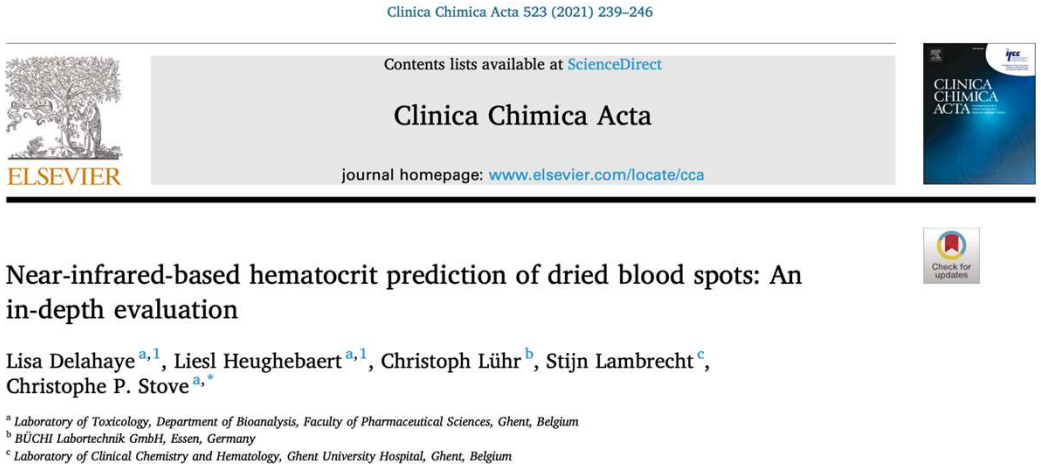
[b]*Department of Internal Medicine, Division of Nephrology and Transplantation,*

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

Hct-prediction of DBS

- Quantification of the potassium concentration in DBS
- Quantification of hemoglobin levels with ultraviolet-visible spectroscopy (reflectance spectroscopy)
- Near-Infrared spectroscopy (NIR)

Delahaye and Heughebaert *et al.*
Extensive evaluation of a commercially available NIR set-up
- Performance of the calibration model
- Method validation and stability
- Robustness
- Method comparison and application



Clinica Chimica Acta 523 (2021) 239–246

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Near-infrared-based hematocrit prediction of dried blood spots: An in-depth evaluation

Lisa Delahaye [a,1], Liesl Heughebaert [a,1], Christoph Lühr [b], Stijn Lambrecht [c], Christophe P. Stove [a,*]

[a] Laboratory of Toxicology, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent, Belgium
[b] BÜCHI Labortechnik GmbH, Essen, Germany
[c] Laboratory of Clinical Chemistry and Hematology, Ghent University Hospital, Ghent, Belgium

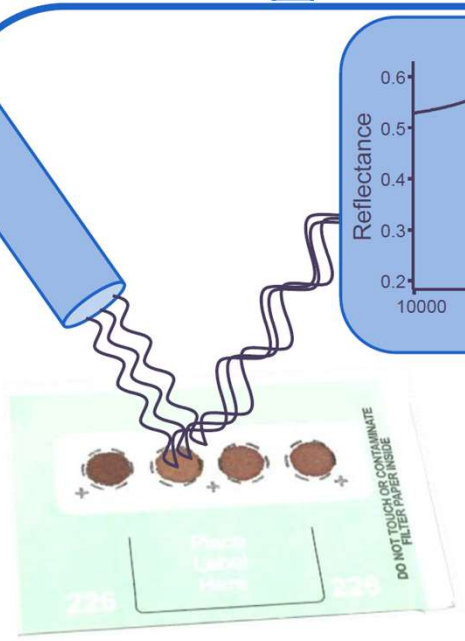
NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

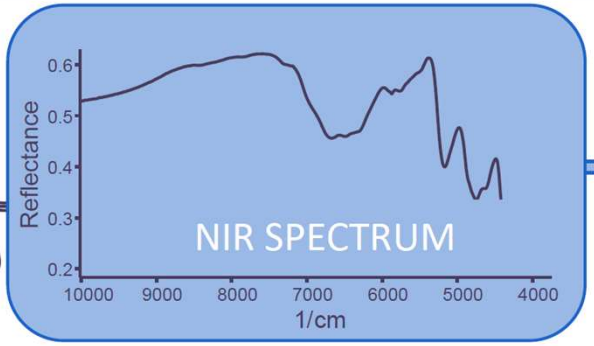
1. Performance of the initial calibration model

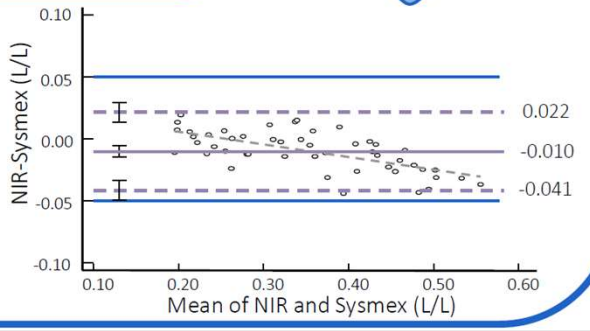
2. Method validation

3. Robustness

4. Method comparison and application







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NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

DBS

- Whole spot
- Partial spot
- Hemaspot HF

Eight replicate ‘blades’ per device

Non-volumetric sample collection

Suitability for quantitative purposes not demonstrated

Hirshfield et al. 2018. JMIR Public Heath Surveill.
Hall et al. 2020. Diabet Med.
Yamamoto et al. 2020. Sci Rep.
Lingani et al. 2020. BMC

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

DBS

- Whole spot
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Volumetric devices

- Mitra™ device (VAMS)
- Capitainer qDBS

(Follow-up for Capitainer-B)

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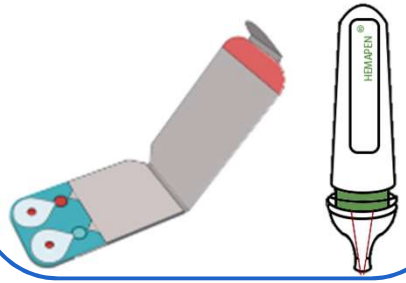
- Hemaxis™ DB10



(Micro)needle based

- Tasso device (Tasso Inc.)
- Touch activated phlebotomy (TAP) device (YourBio Health)

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BENT U BEKEND MET VOLUMETRISCHE GEDROOGDE BLOODSPOT DEVICES?

1. Nee, dit is nieuw voor mij.

2. Al eens van gehoord, maar ik weet er niet zoveel over.

3. Ja.

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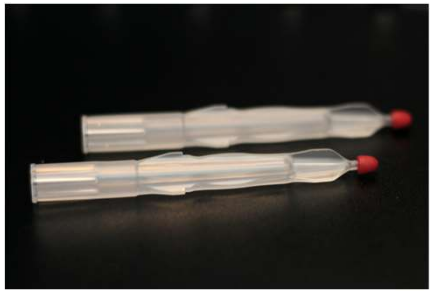
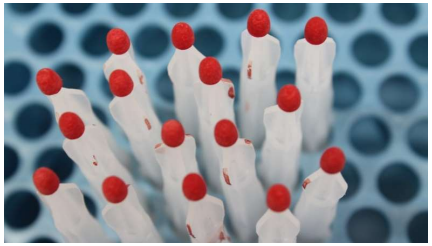
NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING





Extensive analytical evaluation

Visual evaluation of sample quality

Automated analysis under development

Volumetric devices

- Mitra™ device (VAMS)
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(Follow-up for Capitainer-B)

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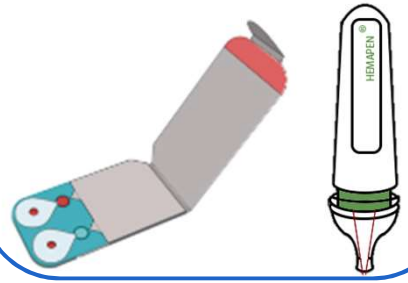
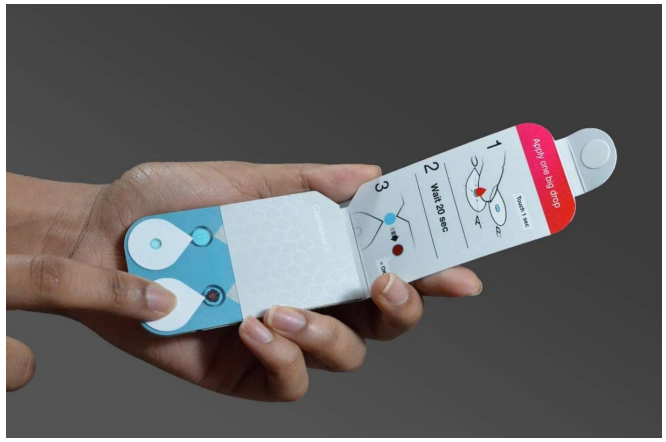


Hct-based effect on recovery

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING



Visual indicator for sample volume

Volumetric devices

- Mitra™ device (VAMS)
- Capitainer qDBS

(Follow-up for Capitainer-B)

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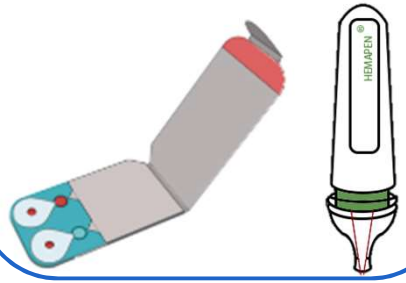
- Hemaxis™ DB10



Manual steps required in sample processing

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

Four replicate DBS per blood drop

Little risk of external contamination

Visual evaluation of sample quality

Volumetric devices

- Mitra™ device (VAMS)
- Capitainer qDBS

(Follow-up for Capitainer-B)

- HemaPEN®
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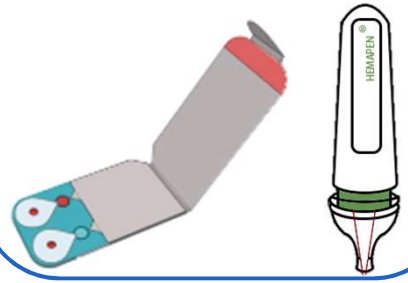
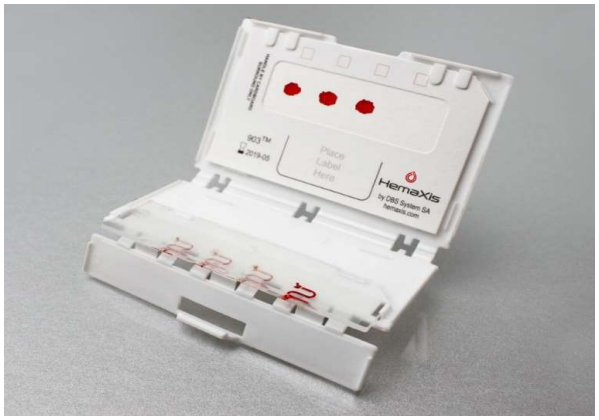


Small sample volume (2.74 µL)

Manual steps required in sample processing

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING



Visual indicator for sample volume

DBS-card format (automation)

Volumetric devices

- Mitra™ device (VAMS)
- Capitainer qDBS

(Follow-up for Capitainer-B)

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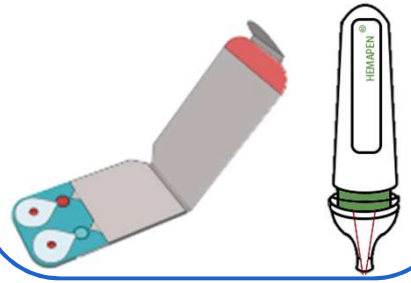
- Hemaxis™ DB10



Higher risk of external contamination

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

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- Partial spot
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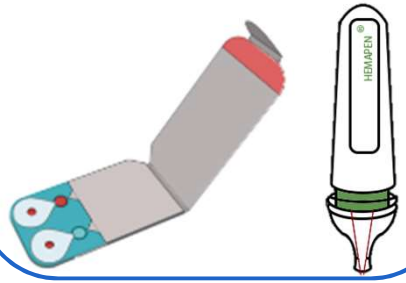
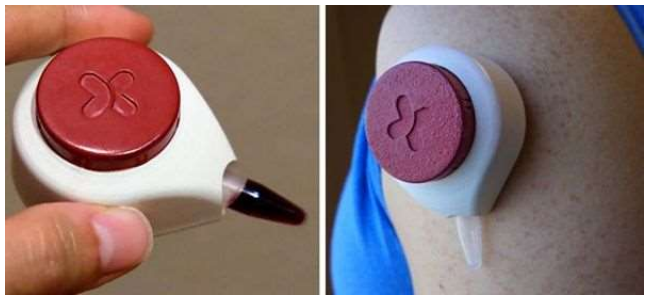
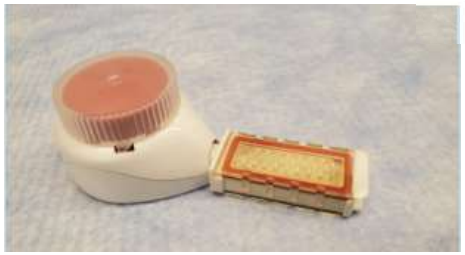


(Micro)needle based

- Tasso device (Tasso Inc.)
- Touch activated phlebotomy (TAP) device (Seventh Sense Biosystems)

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING





a lancet to puncture the skin, leading to the withdrawal of blood from the capillaries in the skin, under vacuum

Virtually painless

Sometimes no sample is generated

Tasso M-20 & Tasso-SST/+

(Micro)needle based

- Tasso device (Tasso Inc.)
- Touch activated phlebotomy (TAP) device (YourBio Health)

NON-VOLUMETRIC VERSUS VOLUMETRIC DRIED BLOOD SAMPLING

collect blood through vacuum pressure via microneedles

Virtually painless via use of microneedles

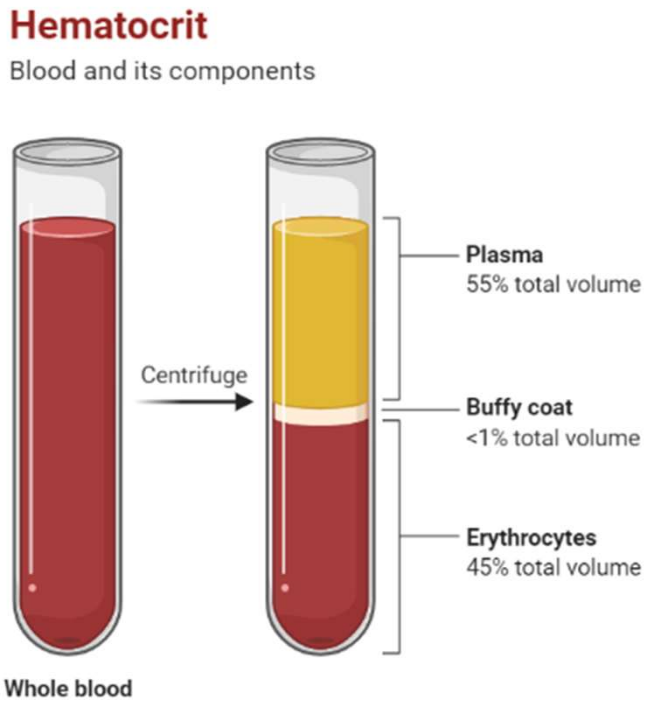
Experimental

Collection of liquid blood

(Micro)needle based

- Tasso device (Tasso Inc.)
- Touch activated phlebotomy (TAP) device (YourBio Health)

DRIED PLASMA SAMPLING



- TDM analytes often determined in plasma

→ Disadvantage of DBS: conversion to plasma? Hct needed!

- Now: Dried Plasma Devices available/under development

→ Dried plasma based on membrane filtration

→ Dried Plasma = Plasma?

"….average protein recovery of filtered plasma relative to centrifuged plasma of 73%, with a significant amount of blood proteins retained by the filtration device." (Hauser, Anal Chem, 2018)

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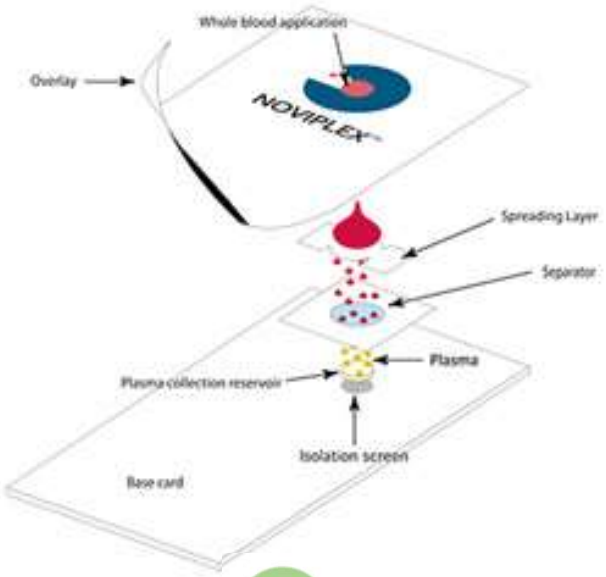
DRIED PLASMA SAMPLING



Collection of dried plasma

Visual indicator for sample volume

DPS devices

- Noviplex plasma Prep cards
- HemaSpot SE
- HemaXis DX
- Book-Type Dried Plasma Spot Collection
- Autonomous Microfluidic DPS Device (Capitainer)

Large blood drop volume required per spot

Small sample volume (2.5 or 3.8 µL)

Unclear to what extent the 'dried plasma' is equivalent to conventional plasma

DRIED PLASMA SAMPLING

DPS devices

- Noviplex plasma Prep cards
- HemaSpot SE
- HemaXis DX
- Book-Type Dried Plasma Spot Collection
- Autonomous Microfluidic DPS Device (Capitainer)

Other DPS devices are under development

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- **Automated DBS-analysis**
- Key factors to success
- Toxicological & clinical implementation

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KENT U OPLOSSINGEN OM DBS ANALYSE TE AUTOMATISEREN EN GEBRUIKT U DIT BIJ U OP HET LABO?

1. Nee, ik heb hier geen weet van. Wij doen geen DBS analyses.
   0%
2. Ja, ik weet dat dergelijke oplossingen bestaan, maar heb deze nog nooit gebruikt.
   0%
3. Ja, en wij maken hier gebruik van.
   0%

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AUTOMATED DBS-ANALYSIS

- Semi-automated solution
  - Automated DBS spotting
  - Automated DBS punching
  - Automated DBS extraction

- Fully Automated DBS solutions

FIGURE 5.1. Commercially available (semi-)automated punching and pipetting instruments. From top-left to bottom-right: the DBS Pneumatic Card Punch (Analytical Sales and Services), the BSD GalaxyA9 (BSD Robotics) and the Freedom EVO Robotic Handler (Tecan). Reproduced with permission of Analytical Sales and Services, BSD Robotics and Tecan.

AUTOMATED DBS-ANALYSIS

↑ Throughput

↑ Safety

↓ Hands-on time

↓ Risk on human mistakes

Different fully automated DBS-extraction systems available

No commercial systems (yet) for volumetric devices

In the laboratory of Toxicology

DBS Autosampler, Spark Holland

Transcend DSX-1 System, Thermo Fisher

SCAP system, Prolab

DBS-MS 500, CAMAG

Journal of Chromatography A, 1601 (2019) 95–103

Journal of Chromatography A 1653 (2021) 462430

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Full length article

Fully Automated Dried Blood Spot Extraction coupled to Liquid Chromatography-tandem Mass Spectrometry for Therapeutic Drug Monitoring of Immunosuppressants

Sigrid Deprez, Christophe P Stove*

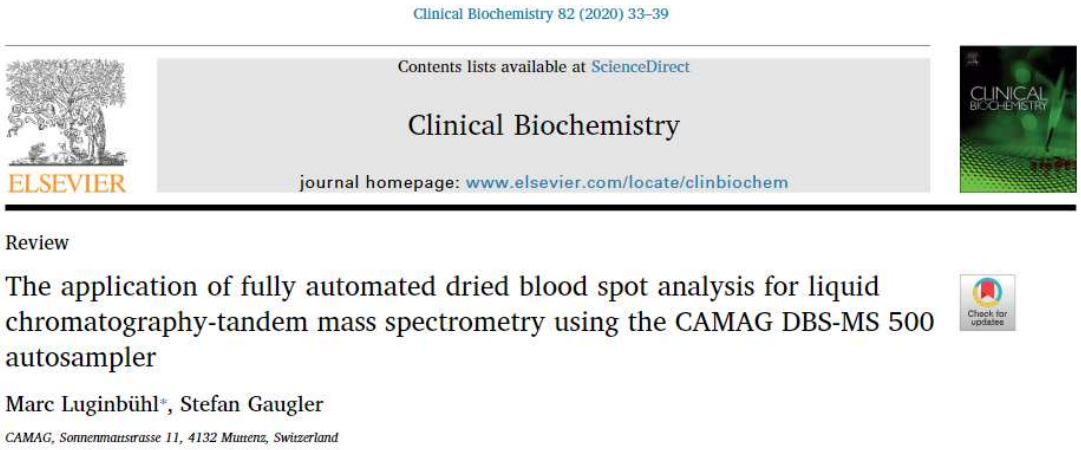
Laboratory of Toxicology, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, Ghent 9000, Belgium

AUTOMATED DBS-ANALYSIS

Recent overview of microsampling methods using the DBS-MS 500 *(Luginbühl et al.)*

Used for different applications:

- TDM: anti-epileptic drugs, anti-retroviral drugs, ivermectin and immunosuppressants
- Toxicology: drug screening, quantification of tramadol and phospatidylethanol (PEth)
- Newborn screening
- Vitamin analysis
- Diagnostic field: detect SARS-CoV-2 antibodies



Clinical Biochemistry 82 (2020) 33–39

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

The application of fully automated dried blood spot analysis for liquid chromatography-tandem mass spectrometry using the CAMAG DBS-MS 500 autosampler

Marc Luginbühl*, Stefan Gaugler

CAMAG, Sonnenmattstrasse 11, 4132 Muttenz, Switzerland

GHENT UNIVERSITY

Join: **vevox.app** ID: **158-747-646**

WAT ZIJN VOLGENS U DE ANALIETEN WAARBIJ DBS DE GROOTSTE MEERWAARDE KUNNEN BETEKENEN VOOR DE PATIËNT?

1. Immunosuppressiva (tacrolimus, sirolimus, everolimus, cyclosporine A en mycofenolaat)
   0%
2. Anti-epileptica
   0%
3. Antibiotica
   0%
4. Tricyclische anti-depressiva
   0%
5. andere geneesmiddelen
   0%

Vote for up to 5 choices

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AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS

Application of a fully validated LC-MS/MS method, utilizing a fully automated extraction module CAMAG DBS-MS-500, for TDM of four immunosuppressants.

https://www.youtube.com/watch?v=7s6SpMRP77U&t=7s

AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS

Calibration model

Homoscedasticity

Carry-over

Accuracy

Precision

Selectivity

Stability

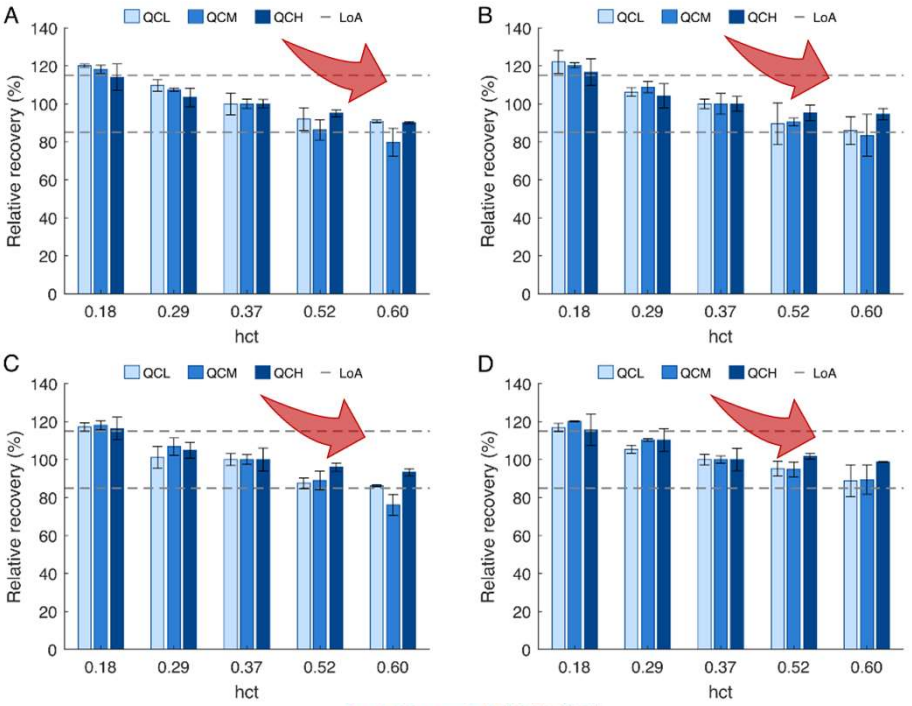
Matrix effect

A tacrolimus

B sirolimus

C everolimus

D cyclosporin A



Journal of Chromatography A 1653 (2021) 462430

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Full length article

Fully Automated Dried Blood Spot Extraction coupled to Liquid Chromatography-tandem Mass Spectrometry for Therapeutic Drug Monitoring of Immunosuppressants

Sigrid Deprez, Christophe P Stove*

Laboratory of Toxicology, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, Ghent 9000, Belgium

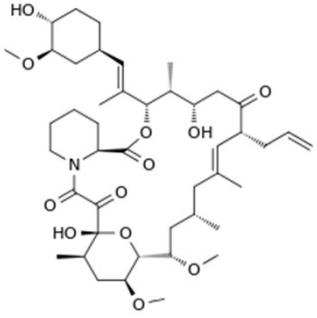
Recovery and impact of Hct on recovery

GHENT UNIVERSITY

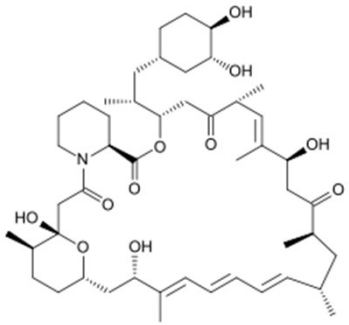
AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS

Application of a fully validated LC-MS/MS method, utilizing a fully automated extraction module CAMAG DBS-MS-500, for TDM of four immunosuppressants.

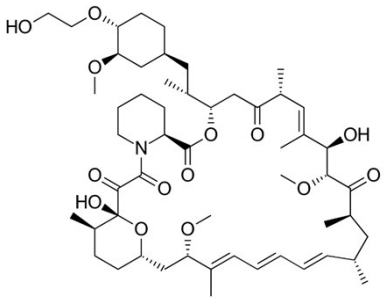
- Paired venous-DBS patient samples and venous whole blood samples
- Set-up of hct correction model for DBS results
- Clinical validation: agreement between both matrices after correction of DBS concentration



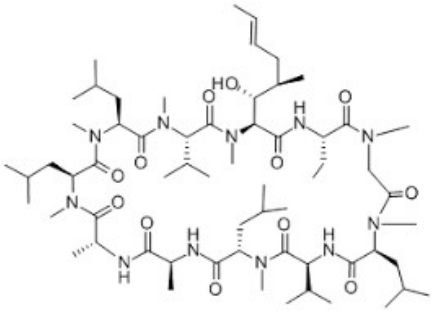
Tacrolimus



Sirolimus



Everolimus



Cyclosporin A

GHENT UNIVERSITY

AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS

Application of a fully validated LC-MS/MS method, utilizing a fully automated extraction module CAMAG DBS-MS-500, for TDM of four immunosuppressants.

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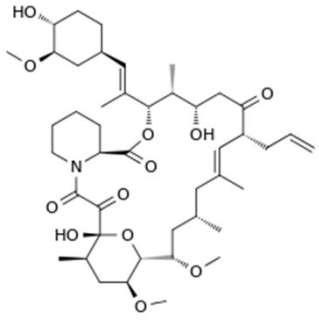
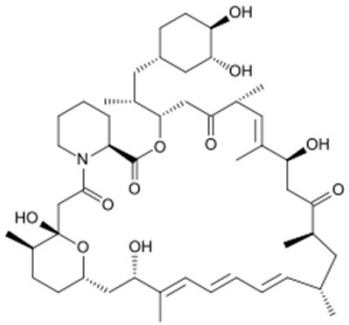
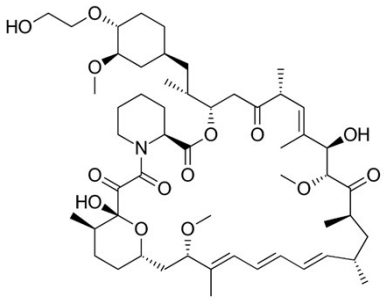


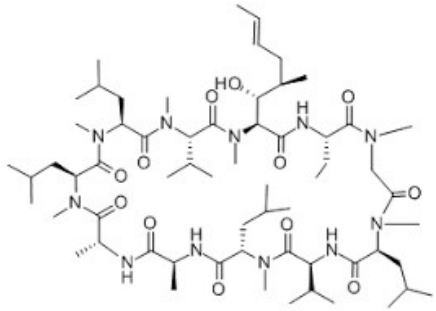
Tacrolimus



Sirolimus



Everolimus



Cyclosporin A

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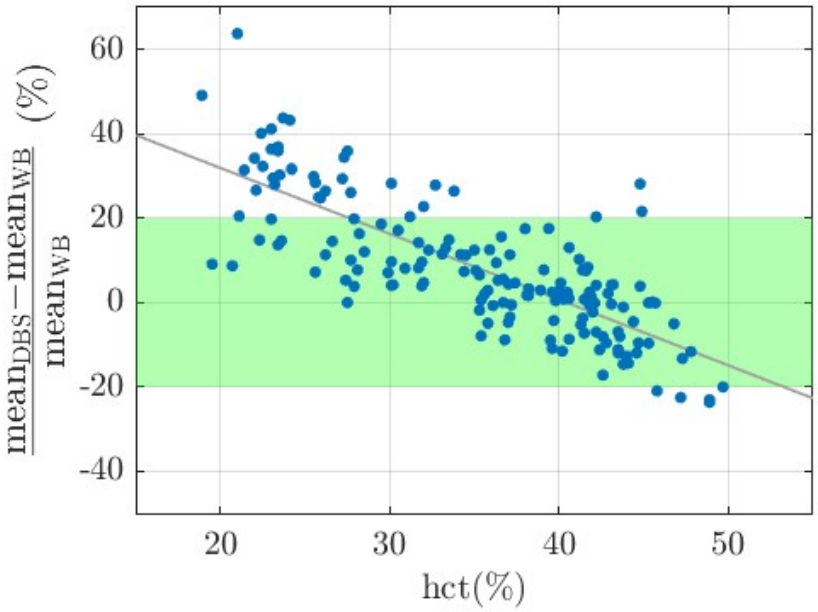
AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS HCT CORRECTION



Application on 162 venous DBS samples for Tacrolimus

→ % difference between DBS and whole blood as a function of the hct.

→ Clear effect of the hct on DBS quantitation

→ Set-up of correction formula

$$Y = -1{,}56\,X + 0{,}6305$$

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AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS HCT CORRECTION

Application of a fully validated LC-MS/MS method, utilizing a fully automated extraction module CAMAG DBS-MS-500, for TDM of four immunosuppressants.

- Paired venous-DBS patient samples and venous whole blood samples
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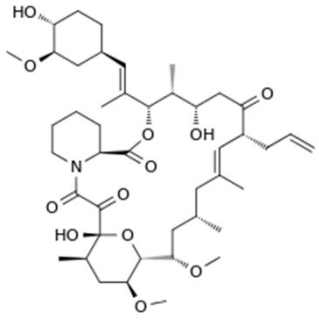
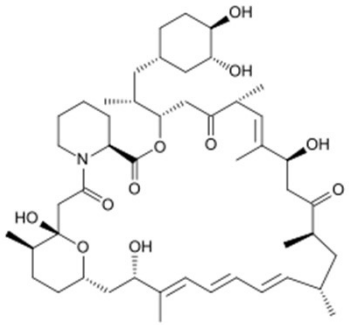
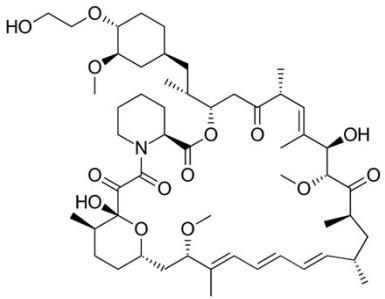


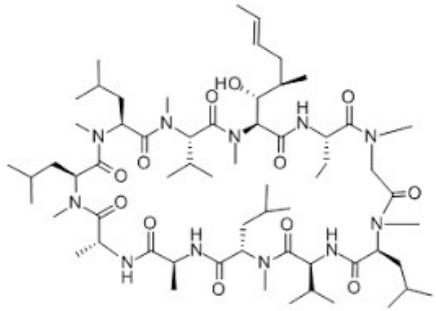
Tacrolimus



Sirolimus



Everolimus



Cyclosporin A

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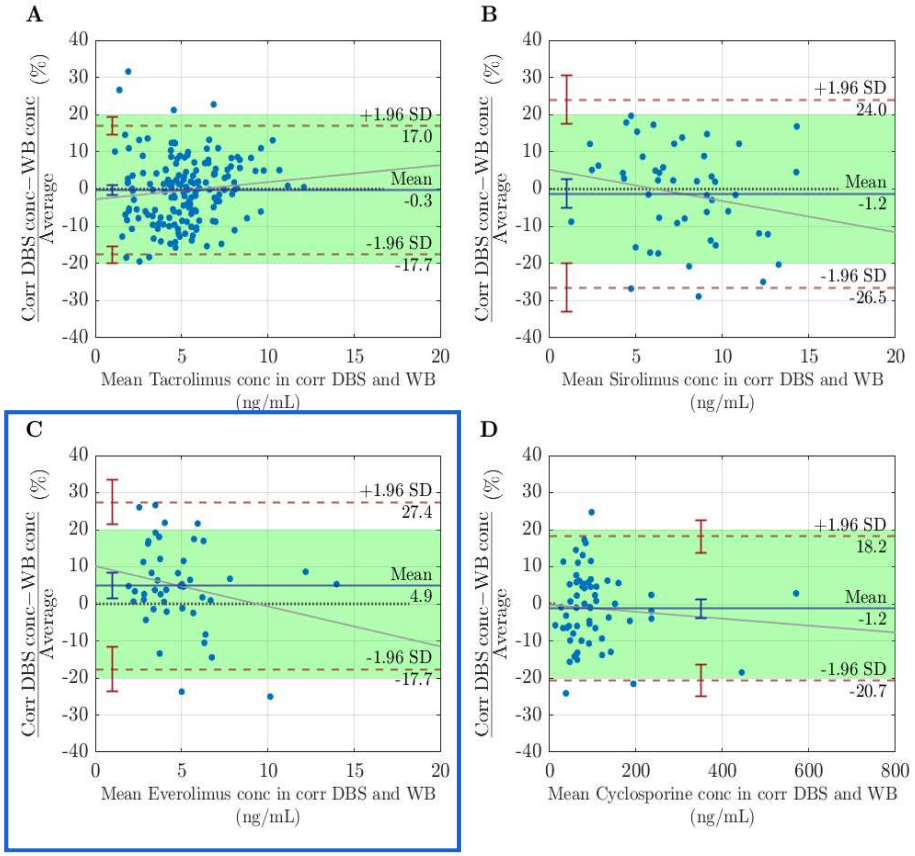
AUTOMATED DBS-ANALYSIS: IMMUNOSUPPRESSANTS APPLICATION



Bland-Altman analysis

→ Agreement between corrected DBS and whole blood

→ No significant bias for Tacrolimus, Sirolimus and Cyclosporin A

→ Everolimus: remaining bias after correction

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Join: **vevox.app** ID: **158-747-646**

BENT U OVERTUIGD VAN HET POTENTIEEL VAN VOLLEDIG AUTOMATISCHE DBS EXTRACTIE UNITS?

1. Nee, de kostprijs is te hoog.

   0%

2. Nee, omwille van andere nadelen.

   0%

3. Ja, ik denk dat dit belangrijk is om meer DBS analyses te integreren in het labo in de toekomst.

   0%

4. Ja, omwille van andere redenen.

   0%

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PRESENTATION OUTLINE

- Dried blood spots: advantages and challenges
- Non-volumetric *vs.* volumetric dried blood sampling
- Automated DBS-analysis
- **Key factors to success**
- Toxicological & clinical implementation

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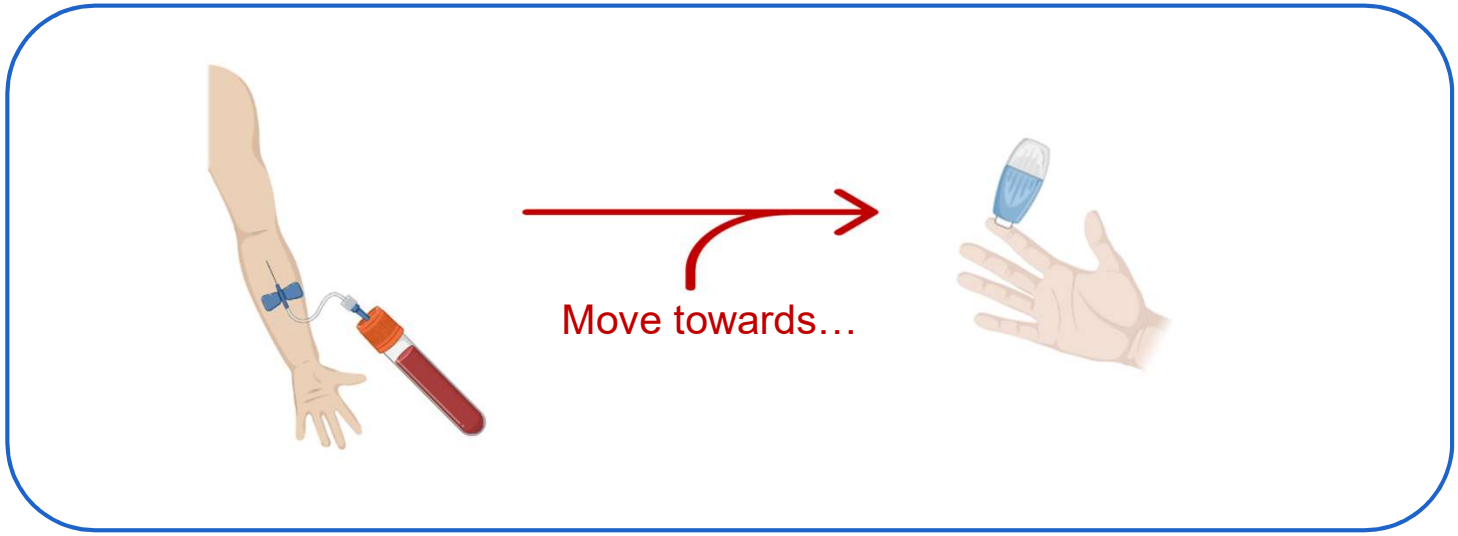
KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.

In different studies patients' experience was found positive.



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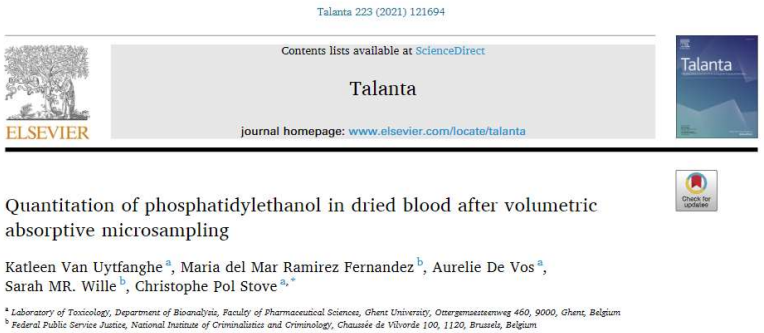
Follow-up of historic alcohol consumption via the direct alcohol marker phosphatidylethanol

PEth Case study: Feasibility of sampling @ home: large-scale study using non-supervised VAMS @ home, completed by n=687

Positive assessment via questionnaire


Talanta 223 (2021) 121694

Contents lists available at ScienceDirect

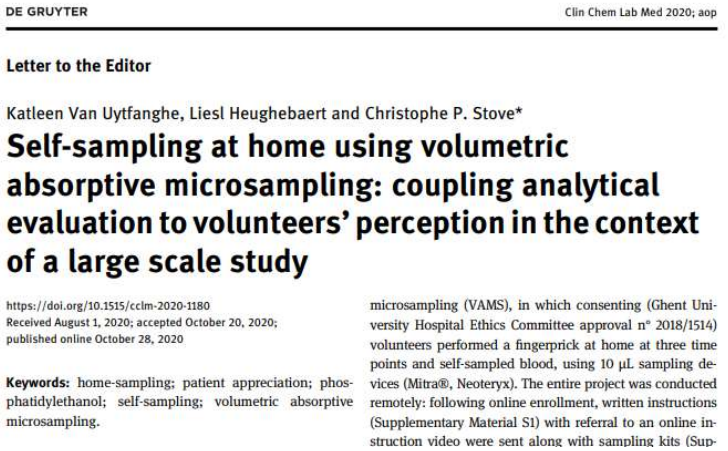
Talanta

journal homepage: www.elsevier.com/locate/talanta

Quantitation of phosphatidylethanol in dried blood after volumetric absorptive microsampling

Katleen Van Uytfanghe [a], Maria del Mar Ramirez Fernandez [b], Aurelie De Vos [a], Sarah MR. Wille [b], Christophe Pol Stove [a,*]

[a] Laboratory of Toxicology, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000, Ghent, Belgium
[b] Federal Public Service Justice, National Institute of Criminalistics and Criminology, Chaussée de Vilvorde 100, 1120, Brussels, Belgium


DE GRUYTER Clin Chem Lab Med 2020; aop

Letter to the Editor

Katleen Van Uytfanghe, Liesl Heughebaert and Christophe P. Stove*

Self-sampling at home using volumetric absorptive microsampling: coupling analytical evaluation to volunteers' perception in the context of a large scale study

https://doi.org/10.1515/cclm-2020-1180
Received August 1, 2020; accepted October 20, 2020; published online October 28, 2020

Keywords: home-sampling; patient appreciation; phosphatidylethanol; self-sampling; volumetric absorptive microsampling.

microsampling (VAMS), in which consenting (Ghent University Hospital Ethics Committee approval n° 2018/1514) volunteers performed a fingerprick at home at three time points and self-sampled blood, using 10 µL sampling devices (Mitra®, Neoteryx). The entire project was conducted remotely: following online enrollment, written instructions (Supplementary Material S1) with referral to an online instruction video were sent along with sampling kits (Sup-

KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.

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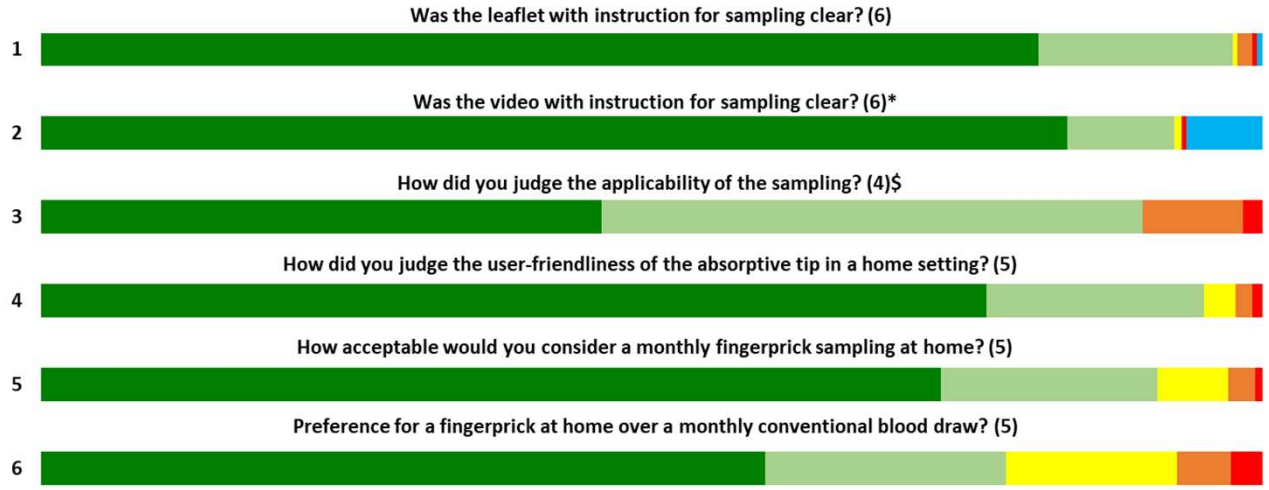

Source: Van Uytfanghe et al. 2020. CCLM.

KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.
  In different studies patients' experience was found positive.
- Pre-analytical considerations are very important: sampling, transportation of the samples, analysis

KEY FACTORS TO SUCCESS

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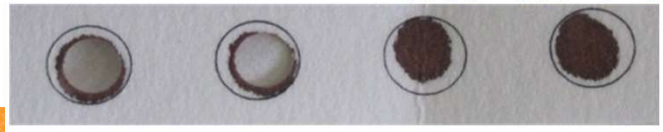
"Good results require good samples"

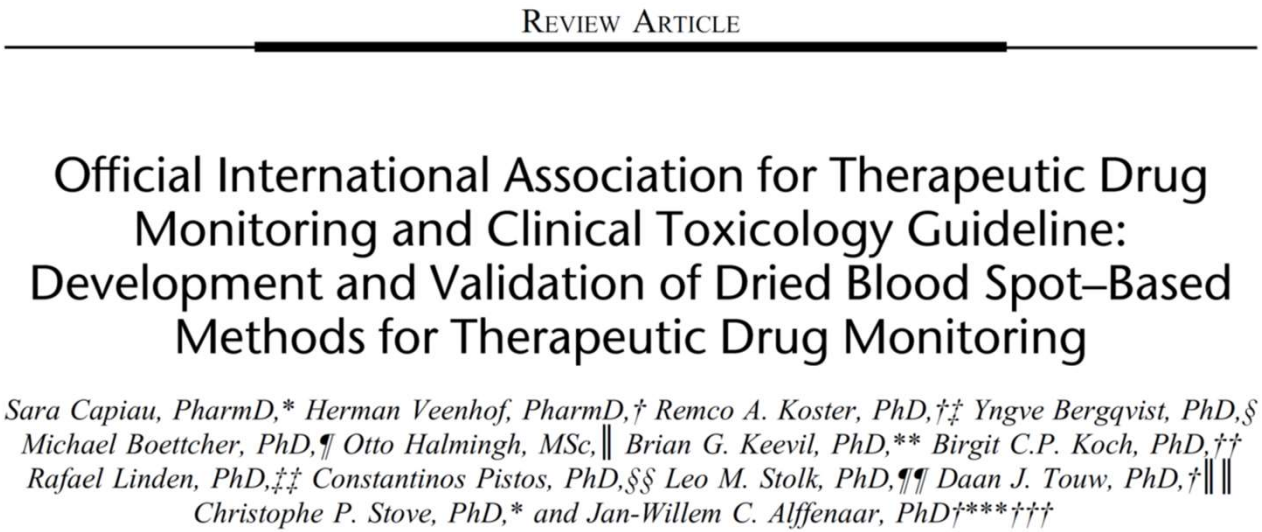


1. Make use of instruction folders or an instruction video
   https://www.umcg.nl/NL/ZORG/VOLWASSENEN/ZOB2/VINGERPRIK/Pages/default.aspx
2. Verify sample quality by patients at home (and in the lab) via App

KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.
  In different studies patients' experience was found positive.
- Pre-analytical considerations are very important: sampling, transportation of the samples, analysis

Some Guidance…



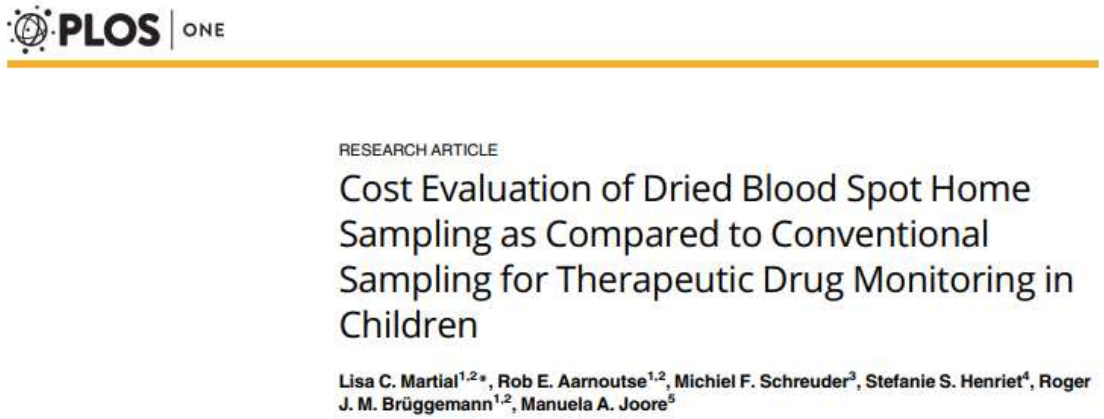
REVIEW ARTICLE

Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology Guideline: Development and Validation of Dried Blood Spot–Based Methods for Therapeutic Drug Monitoring

Sara Capiau, PharmD, Herman Veenhof, PharmD,† Remco A. Koster, PhD,†‡ Yngve Bergqvist, PhD,§ Michael Boettcher, PhD,¶ Otto Halmingh, MSc,‖ Brian G. Keevil, PhD,** Birgit C.P. Koch, PhD,†† Rafael Linden, PhD,‡‡ Constantinos Pistos, PhD,§§ Leo M. Stolk, PhD,¶¶ Daan J. Touw, PhD,†‖‖ Christophe P. Stove, PhD,* and Jan-Willem C. Alffenaar, PhD†***†††*

KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.
  In different studies patients' experience was found positive.
- Pre-analytical considerations are very important: sampling, transportation of the samples, analysis
- Cost-effectiveness of home sampling approach in TDM (Martial *et al., 2016, Plos One*) has been found positive for DBS.
  …Other device costs???


PLOS ONE

RESEARCH ARTICLE

Cost Evaluation of Dried Blood Spot Home Sampling as Compared to Conventional Sampling for Therapeutic Drug Monitoring in Children

Lisa C. Martial[1,2]*, Rob E. Aarnoutse[1,2], Michiel F. Schreuder[3], Stefanie S. Henriet[4], Roger J. M. Brüggemann[1,2], Manuela A. Joore[5]

KEY FACTORS TO SUCCESS

- Patient population: for selected applications, dried blood microsampling (with sampling @ home) may be a viable option. New devices may be of help to increase the ease of & reliance in self-sampling @ home.

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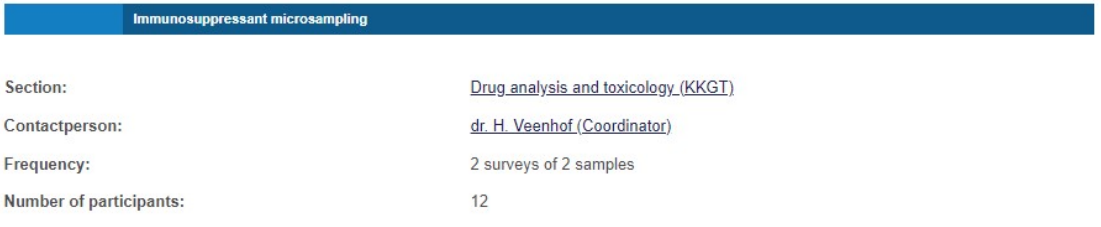
- Pre-analytical considerations are very important: sampling, transportation of the samples, analysis
- Cost-effectiveness of home sampling approach in TDM (Martial *et al., 2016, Plos One*) has been found positive for DBS.

  …Other device costs???
- From a Laboratory/analytical point of view: a dedicated preanalytical (incl. sampling) and analytical workflow is required. The introduction of automation may lead to more implementation in clinical labs.

  Another requirement is proficiency testing.



PRESENTATION OUTLINE

- Dried blood spots: advantages and challenges
- Non-volumetric *vs.* volumetric dried blood sampling
- Automated DBS-analysis
- Key factors to success
- Toxicological & clinical implementation

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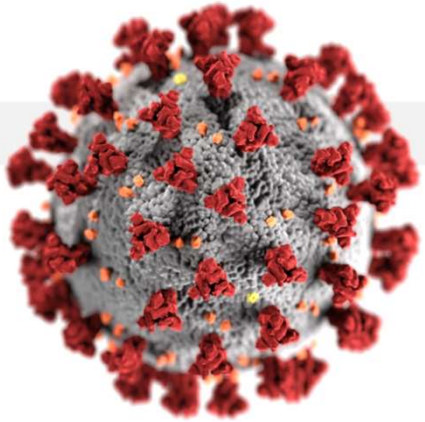
TOXICOLOGICAL & CLINICAL IMPLEMENTATION OF DBS

- Toxicology: PEth
- TDM: Immunosuppressants
- Health and diagnosis: testing for measles, HIV, hepatitis and Covid-19



EBioMedicine 70 (2021) 103502

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Research paper

A dried blood spot protocol for high throughput analysis of SARS-CoV-2 serology based on the Roche Elecsys anti-N assay

Jessica Beyerl[a,#], Raquel Rubio-Acero[a,#], Noemi Castelletti[a], Ivana Paunovic[a], Inge Kroidl[a], Zohaib N. Khan[a], Abhishek Bakuli[a], Andreas Tautz[d], Judith Oft[c], Michael Hoelscher[a,b,c], Andreas Wieser[a,b,*], on behalf of the KoCo19 Study group (members listed in the supplementary material)

[a] Division of Infectious Diseases and Tropical Medicine, University Hospital, Ludwig-Maximilians-Universität (LMU) Munich, Munich 80802, Germany
[b] German Center for Infection Research (DZIF), Partner Site Munich, Germany
[c] Center for International Health (CIH), University Hospital, LMU Munich, Munich 80336, Germany
[d] Corporate Health Management / Department Occupational Health; DPDHL Group, Bonn 53113, Germany

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-23893-4 OPEN

Multianalyte serology in home-sampled blood enables an unbiased assessment of the immune response against SARS-CoV-2

Niclas Roxhed[1,2✉], Annika Bendes[3,11], Matilda Dale[3,11], Cecilia Mattsson[3,11], Leo Hanke[4], Tea Dodig-Crnković[3], Murray Christian[4], Birthe Meineke[5,6], Simon Elsässer[5,6], Juni Andréll[7], Sebastian Havervall[8], Charlotte Thålin[8], Carina Eklund[9], Joakim Dillner[9], Olof Beck[10], Cecilia E. Thomas[3], Gerald McInerney[4], Mun-Gwan Hong[3], Ben Murrell[4], Claudia Fredolini[3] & Jochen M. Schwenk[3✉]

Review

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Bioanalysis

Volumetric absorptive microsampling: its use in COVID-19 research and testing

James Rudge*,[1] & Stuart Kushon[1]
[1]Neoteryx LLC, 421 Amapola Ave., Torrance, CA 90501, USA
*Author for correspondence: Tel.: +44 7584126116; jamesr@neoteryx.com

RESEARCH ARTICLE

At-home self-collection of saliva, oropharyngeal swabs and dried blood spots for SARS-CoV-2 diagnosis and serology: Post-collection acceptability of specimen collection process and patient confidence in specimens

Mariah Valentine-Graves[1], Eric Hall[1], Jodie Lynn Guest[1], Elizabeth Adam[1], Rachel Valencia[1], Kaitlin Shinn[2], Isabel Hardee[2], Travis Sanchez[1], Aaron J. Siegler[3], Patrick Sean Sullivan[1]*

1 Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, United States of America, **2** Emory University School of Medicine, Atlanta, Georgia, United States of America, **3** Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, Georgia, United States of America

GHENT UNIVERSITY

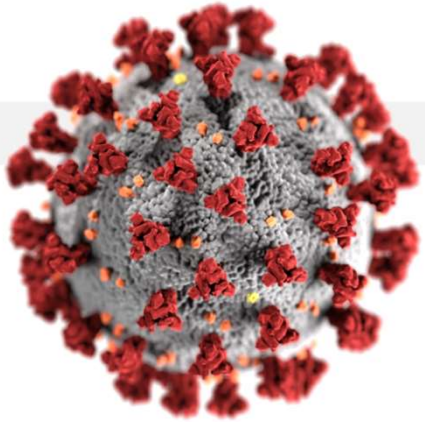
TOXICOLOGICAL & CLINICAL IMPLEMENTATION OF DBS

- Toxicology: PEth
- TDM: Immunosuppressants
- Health and diagnosis: testing for measles, HIV, hepatitis and Covid-19

  Diagnosis and surveillance

  Serological testing of SARS-CoV-2 IgG antibodies (ELISA or lateral flow)

  Regular DBS, Mitra and Capitainer q-DBS



Received: 9 April 2021 | Revised: 29 May 2021 | Accepted: 1 June 2021
DOI: 10.1002/dta.3107

REVIEW

WILEY

Microsampling: A role to play in Covid-19 diagnosis, surveillance, treatment and clinical trials

Madhura Rajadhyaksha[1,2] | Vaishali Londhe[1]

remote, contactless, small volume & self-sampling

TOXICOLOGICAL & CLINICAL IMPLEMENTATION OF DBS

- Toxicology: PEth
- TDM: Immunosuppressants
- Health and diagnosis: testing for measles, HIV, hepatitis and Covid-19

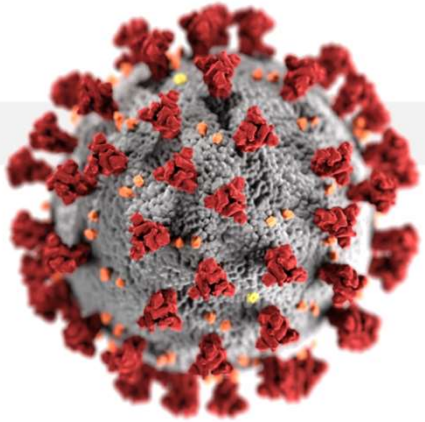


TABLE 2 Summary of microsampling applications in Covid-19 diagnostics and surveillance

Country	Purpose	Sampling technique	Antibody	Assay format	Reference
Germany	Proof-of-principle pilot study	DBS VAMS	IgG and IgM	ELISA	30
USA	Seroprevalence	DBS	IgG	Serological assay, ELISA	26
USA	At-home sample collection and acceptability of specimen	DBS	–	–	24
USA	Serosurvey protocol	DBS	–	–	59,60
USA	Seroprevalence (at-home sample collection)	VAMS	IgG and IgM	Serological assay, ELISA	61
USA	At-home sample collection kit	DBS	Antibody	Serological assay	62
USA	Antibody profiling and prevalence	DBS	IgG, IgA and IgM	Multiplex testing	63
USA	Population-wide serological testing	DBS	IgG, IgA and IgM	Serological assay, ELISA	64
Switzerland	Large population antibody testing	DBS	IgG	ELISA	65
USA	At home-remote sampling	VAMS	IgG and IgM	Electrochemiluminescence	66
USA	Validation of DBS samples	DBS	IgG	ELISA	22
New Zealand	Feasibility of using finger prick sampling	VAMS	IgG	Multiplex testing	21
Germany	Feasibility and utility of automated DBS extraction	DBS, VAMS, Tasso-kit	Antibody	ECLIA	23

Source: Rajadhyaksha et al. 2021. DTA

OPPORTUNITIES

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CHALLENGES AND OPPORTUNITIES

Potential advantages and hurdles for implementation of (automated) DBS analysis	
Advantages	**Comments**
Availability of clinical MS[1] analysers	No more specialized training needed and only very limited intervention of a laboratory technician. Currently, these systems are only compatible with conventional liquid blood/plasma methods.

Cost-savings	Depending on the stakeholder, (automation of) DBS analysis will result in a cost-saving:
	- The patient: Costs related to transportation and parking at the hospital versus home-sampled DBS sent to the lab via postal services.
	- Clinical laboratory:
	  o The total cost of a sampling (using either microsampling devices or a regular blood draw) is comparable (situation in Belgium).
	  o The costs related to the laboratory technicians will be saved using automated DBS extraction.

Decreased hands-on time and increased throughput	Implementation will depend on the throughput of the samples and the priorities of the local hospital laboratory.
Patient centricity	The use of DBS has proven to be beneficial in terms of patient experience.

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CHALLENGES AND OPPORTUNITIES

Hurdles	Comments
Administrative practicalities	- Arrival of DBS samples via postal or courier services would result in additional cost for personnel. However, this can easily be overcome by the use of pre-barcoded microsampling devices. - Microsampling devices are currently not compatible with pre-analytical automated systems present in clinical laboratories.
Batch analysis versus random access	An LC-MS/MS system coupled to an automated DBS extraction unit is partially limited to DBS analysis, as switching from automated DBS extraction to conventional LC has to be performed manually. However, since DBS samples will mostly arrive via postal services, batch analysis may be preferred hereby overcoming the former issue.
Determination of regular TDM parameters	In routine follow-up of patients, often multiple TDM parameters are determined from a single blood sample. To maintain the benefit associated with the use of DBS for TDM purposes, these standard parameters should also be determined in DBS.
Extensive method validation	Guidelines have become available for the validation of DBS-based methods to facilitate the validation process.
Investments	Depending on the stakeholder, (automation of) DBS analysis will result in additional costs: - The patient: The use of microsampling devices is currently not reimbursed by the public healthcare system (situation in Belgium). - Clinical laboratory: A significant investment is needed to purchase an automated DBS extraction unit and a (clinical) MS analyser.
IVD Regulation (EU) 2017/746	More complicated to maintain lab-developed tests.
PT programs specific for microsampling applications	E.g. the PT program set up by the KKGT for immunosuppressant quantification from dried microsamples.
Specialized training needed when using LC-MS/MS	This also holds true for conventional LC-MS/MS-based TDM on whole blood/plasma.
The Hct effect	Hct prediction technologies and/or volumetric collection of DBS can be used to overcome this effect.

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WAT ZIJN VOLGENS U DE BELANGRIJKSTE UITDAGINGEN OM MEER DBS ANALYSES TE IMPLEMENTEREN IN DE KLINISCHE PRAKTIJK?

1. Andere manier van werken ten opzichte van klassieke bepalingen

   0%

2. Regulatoire beperkingen (IVD regulatie)

   0%

3. Nog andere bepalingen nodig buiten spiegels

   0%

4. Extensieve validatie

   0%

5. Resultaten zijn minder betrouwbaar

   0%

6. Andere redenen

   0%

Vote for up to 6 choices

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DENKT U DAT HET BELANGRIJK IS OM OOK ANDERE KLINISCHE PARAMETERS IN DBS TE BEPALEN, OM OPTIMALE MEERWAARDE TE CREËREN? INDIEN WEL, WELKE ANDERE KLINISCHE PARAMETERS VINDT U BELANGRIJK OM OOK IN DBS TE BEPALEN? VB. ER ZIJN METHODES OM SIMULTAAN IMMUNOSUPPRESSIVA EN CREATININE TE BEPALEN VOOR NIERTRANSPLANTEN.

1. Nee, dit is niet belangrijk. De TDM bepalingen via home-sampling bieden voldoende meerwaarde.

   0%

2. Ja, het is nodig om zoveel mogelijk parameters te bepalen. Belangrijke parameters zijn leverparameters (vb. SGOT, SGLP, bilirubine) voor lever transplanten.

   0%

3. Ja, het is nodig om zoveel mogelijk parameters te bepalen. Belangrijke parameters zijn hartparameters voor harttransplanten.

   0%

4. Ja, het is nodig om zoveel mogelijk parameters te bepalen. Belangrijke parameters zijn andere parameters dan voorgaande.

   0%

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TAKE HOME MESSAGES

- Hct related issues of DBS can be overcome by
  - Hct prediction strategies
  - The use of volumetric alternative devices
- Automated DBS-analysis is available, facilitating its implementation into a clinical lab context
- The use of DBS for home sampling in a TDM context has proven to be preferred by patients and to be cost-effective
- Covid-19 pandemic: opportunities for microsampling

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EN NU IS HET AAN U!

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