Patient Centricity: One Blood Draw at a Time

October 23, 2023
Enaksha Wickremsinhe Ph.D.
Keynote Speaker
Bill and Melinda Gates Medical Research Institute
Session Description and Objectives

• Over the past decade, microsampling techniques have been adopted to collect small volumes of blood (without the need for venipuncture) to support PK analysis during drug development.
• This presentation will focus on the broader adoption of such techniques across clinical trials and in healthcare practice, globally.

Learning objectives:
• Why and how we collect blood
• What types of analyses are conducted using blood
• Is blood = blood?
• Why we should collect smaller volumes of blood and how
• What are the challenges
Overview

• Why do we collect blood
• How much blood is collected vs needed
• Challenges conducting clinical trials
• Technologies available for blood sampling
• What can we measure (using a small sample)
• Making patient centricity a reality
Biography and Contact Information

• Enaksha has over 20 years of bioanalytical experience in quantitative LC/MS/MS supporting all phases of drug development (discovery through clinical development).

• His expertise also includes microsampling (preclinical and clinical studies), patient centric sampling, pediatric studies, and blood sampling for decentralized clinical trials.

• He is also an experienced ADME project leader and been responsible for both preclinical and clinical development of several oncology assets including abemaciclib (Verzenio®), baricitinib (Olumiant®) and selpercatinib (Retevmo™).

• He is the past co-chair of the AAPS Bioanalytical community and current co-chair of the AAPS Microsampling and Patient Centric Sampling subgroup.

• He is a member of the ICH M10 Expert Working Group, representing PhRMA.

Contact Info: enaksha.wickremsinhe@gatesmri.org
Trivia

How many vacutainers are sold globally

Source: BD - Plymouth Makes
Trivia: How much water does an Olympic-size pool hold?

Take a guess
Blood testing is a cornerstone of the medical diagnostic process ➔ provides important information about countless aspects of health.
Blood samples used to:

• Assess general state of health
• Check if you have an infection
• Cholesterol levels
• Liver and kidney function
• Monitor the activity and severity of certain conditions
• Help diagnose a variety of health conditions, including HIV, cancer, diabetes, etc.
• Screen for certain genetic conditions
• Therapeutic drug monitoring, drug testing

• CLINICAL TRIALS
Clinical trials:

**Pharmacokinetics**
- Drugs & metabolites
- mAbs
- Peptides, SiRNAs
- ADCs, AOCs
- Combination drugs
- ADA

**Safety Labs**
- Chemistry
- Hematology
- Liver panel
- Lipid panel

**Special labs**
- Biomarkers
- Disease specific
- Cytokines
- PGX, Omics
- Exploratory

Healthy volunteers, Patients, Pediatric
Blood collected via **venipuncture**

- Requires trained phlebotomist
- Inconvenient (requires travel)
- Distressing for many patients
- Painful
- Can exacerbate anemia
- Waste (extra blood >90%)
- People with trypanophobia

- Majority of children
- 20-50% adolescents
- 20-30% young adults

*The fear of needles: A systematic review and meta-analysis - PubMed (nih.gov)*
## Volumes of blood collected

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Total volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tests</td>
<td>45</td>
</tr>
<tr>
<td>Clinical laboratory tests</td>
<td>256</td>
</tr>
<tr>
<td>PK drug</td>
<td>189</td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>500</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Total volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tests</td>
<td>40</td>
</tr>
<tr>
<td>Clinical laboratory tests</td>
<td>256</td>
</tr>
<tr>
<td>Other lab tests</td>
<td>40</td>
</tr>
<tr>
<td>PK Drug (vacutainer A)</td>
<td>144</td>
</tr>
<tr>
<td>PK Drug (vacutainer B)</td>
<td>68</td>
</tr>
<tr>
<td>PK Drug (vacutainer C)</td>
<td>180</td>
</tr>
<tr>
<td>Biomarker</td>
<td>120</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>848</strong></td>
</tr>
</tbody>
</table>

Multiple number of vacutainers are collected during a single clinic visit
Multiple visits for blood collection

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 16</th>
<th>Day 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinanalysis</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Clinic visits scheduled just for PK blood collection
Recruitment (and retaining) patients is challenging

Approximately 30% patients drop out of clinical trials

Inconvenience
- Site is far from patient’s home or workplace
- Multiple visits
- Scheduling conflicts – work, family

Studies with higher levels of difficulty – study procedures

Financial costs
- Missed work, single parents, childcare

Travel challenges
- Elderly, non-urban areas
Recruitment (and retaining) is expensive

Cost of Patient Recruitment

- $7 billion spent on clinical trials
- 27% related to patient recruitment
- ~$6,500 to recruit one patient
- ~$20,000 to replace one during a trial

Understanding Why Patients Drop Out of Clinical Trials (patientcentra.com)
The True Cost Of Patient Drop-outs In Clinical Trials - mdgroup
Cater to patient’s needs (listen to the patient)

Design trials to be “patient centric”

- “Visits” – fewer, more convenient
- Blood sampling – convenient, less invasive
- Digital technologies – eDiaries, PROs
Advancements in analytical technologies

High sensitive, high throughput, low volume

PK analyses
Safety panels
Hematology
Biomarkers
qPCR
Flow cytometry
Special assays

LC-MS
HRMS
MSD
Gyrolab
Quanterix Simoa®
Clinical analyzers
Volume of blood used for analysis

<table>
<thead>
<tr>
<th>Assay</th>
<th>Volume used for analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK assays (LC-MS/MS)</td>
<td>10 - 50 µL</td>
</tr>
<tr>
<td>Hematology, Chemistry</td>
<td>200-300 µL</td>
</tr>
</tbody>
</table>

- Draw 3-5 mL blood - by nurse/phlebotomist at clinic
- Blood sampling technology has not kept up with advances in analytical technology
Trivia

How many vacutainers are sold globally: 10,300,000,000

If each vacutainer draws 3 mL of blood, how much blood is collected? 30,000,000 Liters

Source: BD - Plymouth Makes
Vacutainers

- **Vacutainer** technology: developed in 1947 by Joseph Kleiner
- Marketed by Becton Dickinson (B-D)

Vacutainer PLUS - developed by B-D in the early 1990s
Innovation…
BLOOD

- Liquid blood
- Dried blood

PLASMA/SERUM

- Liquid plasma/serum
- Dried plasma/serum
“Patient-centric” blood collection options

1. At home - by trained professional (mRn)
2. At a local pharmacy or local clinic
3. Self sampling using a novel device
Key questions....

• How much blood is needed for the test?
• Does it need to be collected via venipuncture?
• Does it have to be collected at the clinic?
• Can it be collected at home and sent to the lab?
• When does it need to be collected?
• How many samples are needed?
• *Does it have to be blood?*
Why Patient Centric Sampling (microsampling)

Reduce patient burden – especially in vulnerable patients
• Oncology patients, elderly,
• Pediatric – birth to 18 years
• Privacy*

Collect samples without visiting a clinic/phlebotomist
• At home or local pharmacy

Access to a more diverse patient population
• Conduct trials in resource limited locations
• Better popPK

Collect samples during a “clinical event”
• Episodic events - migraine, heart failure patients,

Better compliance, fewer drop-outs, faster trial completion

Can this be the future?

Graphic is an example – not an endorsement.
Trivia: How much is 30 million liters of blood

How much of this do we use/need?
Time for Change
Dried Blood Spot (DBS)

- Technique introduced in 1960's by Dr. Guthrie for neonatal screening
- Subsequently adopted to quantify drug concentrations – non-clinical (especially rodents) and human clinical trials

DBS study n = 4
Traditional n = 24
Adoption of microsampling - Pharma

- Survey conducted in 2017 (AAPS Microsampling)
- Multiple techniques used (liquid and dried)
- Dried blood used in clinical development
- Broader implementation across drug development

Figure 1. Utilization of different microsampling approaches for studies at various stages of drug development. The data represents responses from 39 different pharmaceutical companies and contract research organizations.

Microsampling in clinical trials

Numerous publications on validating methods

Fewer publications with clinical data

Merck: Publications and presentations
Eli Lilly: Publications and presentations
Pfizer: Publications & presentations


Wed RapidFire VAMs for mAb and NAB assay
Microsampling in clinical trials

Studies on ClinicalTrials.gov that has the words “dried blood” in the Study Title

- Dried blood spot (DBS)
- VAMS (Mitra®)
- Tasso M20 : dried capillary blood
- Tasso+ : capillary blood

Note: this list may not be current
Microsampling Liquid Blood

Dried blood suitable for most PK assays

But ... can we collect liquid blood (serum, plasma)

The new “vacutainers”
Is Blood = Blood?

• Is IV blood = finger stick blood?
• How do you establish concordance?
• Does the sampling site matter?
• What would the FDA say?

• ICH M10 Guidelines on Bioanalytical Method Validations
• CLSI guideline EP09c
What else can you do with microsampling

PK ✔

Routinely used clinical tests:
• Chemistry (Chem 14)
• Hematology (CBC)
• Other panels – liver, lipids
• Inflammation markers (CRP)
• Cardiac markers (NTproBNP)
• A1C
• Thyroid function
• Immunosuppressant drugs
Using a small volume (microsample)

Can we conduct routine blood tests with a microsample using the same analytical method/technique/instrument?

300 µL blood

3 mL blood
Monitoring patients with abnormal liver chemistry

Serum

15 analyte panel

Monitoring patients with abnormal liver chemistry

Refrigerated Blood


Approx upper limit of normal

15 analyte panel
Monitoring patients conveniently (and frequently)

One blood draw at a time ....blood drawn at home
Vendors / Manufacturer / Service Providers

• Approval of devices (FDA, CE mark, etc.) – available/approved globally?
• Approval of specific tests/panels – FDA, CAP/CLIA labs
• Provide Kits and Training info
• Seamless **integration with established workflows**
• Sample ordering & tracking: collection time/date
# Devices and uses

## Blood Samplers | PCSIG

<table>
<thead>
<tr>
<th>Vendor</th>
<th>Brand Name</th>
<th>Matrix</th>
<th>Volume (mL)</th>
<th>Precise Volume Collection</th>
<th>Sampling Type</th>
<th>Available for Purchase</th>
<th>Web</th>
</tr>
</thead>
<tbody>
<tr>
<td>An strom</td>
<td>Biokap</td>
<td>dried blood</td>
<td>70.0</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.anstrom.com">Link</a></td>
</tr>
<tr>
<td>An strom</td>
<td>123</td>
<td>dried blood</td>
<td>123.0</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.anstrom.com">Link</a></td>
</tr>
<tr>
<td>An strom</td>
<td>HemaSed</td>
<td>dried plasma</td>
<td>105.0</td>
<td>N</td>
<td>stick</td>
<td>N</td>
<td><a href="https://www.anstrom.com">Link</a></td>
</tr>
<tr>
<td>BD</td>
<td>Vacutainer Blood Collection Tubes</td>
<td>liquid (Hep, EDTA, serum)</td>
<td>250-500.0</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.bd.com">Link</a></td>
</tr>
<tr>
<td>Capitainer</td>
<td>Capitainer/BD</td>
<td>dried blood</td>
<td>2 or 10 x 0.2, 2 or 80 x 0.5</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.capitainer.com">Link</a></td>
</tr>
<tr>
<td>Drawbridge Health</td>
<td>OneDraw</td>
<td>dried blood</td>
<td>2 or 75 x 0.5</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.drawbridgehealth.com">Link</a></td>
</tr>
<tr>
<td>Greiner Bio-One</td>
<td>Minicollect Blood Collection Tubes</td>
<td>liquid (Hep, EDTA, serum)</td>
<td>0.25 - 1.0</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.greinerbio-one.com">Link</a></td>
</tr>
<tr>
<td>Health ID</td>
<td>Health ID PCD</td>
<td>dried plasma</td>
<td>4-6 drops of blood</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.healthid.com">Link</a></td>
</tr>
<tr>
<td>Hemaxis</td>
<td>Hemaxis DB10</td>
<td>dried blood</td>
<td>0.15 x 0.5</td>
<td>N</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.hemaxis.com">Link</a></td>
</tr>
<tr>
<td>Hemaxis</td>
<td>Hemaxis DX</td>
<td>dried blood</td>
<td>0.1 x 0.5</td>
<td>Y</td>
<td>stick</td>
<td>N</td>
<td><a href="https://www.hemaxis.com">Link</a></td>
</tr>
<tr>
<td>Loop Medical</td>
<td>Orinon</td>
<td>liquid blood (Hep, EDTA, serum)</td>
<td>up to 1.4 mL</td>
<td>N</td>
<td>stick</td>
<td>N</td>
<td><a href="https://www.loopmedical.com">Link</a></td>
</tr>
<tr>
<td>Neverlyx, brand of Tassign Scientific</td>
<td>Nima</td>
<td>dried blood</td>
<td>2 or 4 x 10, 5 x 30</td>
<td>N</td>
<td>stick</td>
<td>N</td>
<td><a href="https://www.neverlyx.com">Link</a></td>
</tr>
<tr>
<td>Neverlyx, brand of Tassign Scientific</td>
<td>hemPack</td>
<td>dried blood</td>
<td>3 x 2.7 mL</td>
<td>Y</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.neverlyx.com">Link</a></td>
</tr>
<tr>
<td>Prevo Health</td>
<td>PBS-1000</td>
<td>liquid blood</td>
<td>180 x 2 mL</td>
<td>N</td>
<td>upper arm</td>
<td>Y</td>
<td><a href="https://www.prevohealth.com">Link</a></td>
</tr>
<tr>
<td>QiaGen</td>
<td>QiAcard Bloodstain</td>
<td>dried blood</td>
<td>1 x 20-125 μL</td>
<td>Y</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.qiagen.com">Link</a></td>
</tr>
<tr>
<td>QiaGen</td>
<td>QiAcard FTA DNA kits 5</td>
<td>dried blood</td>
<td>1 x 30-125 μL</td>
<td>Y</td>
<td>stick</td>
<td>Y</td>
<td><a href="https://www.qiagen.com">Link</a></td>
</tr>
<tr>
<td>RedDrop DX</td>
<td>RedDrop DX</td>
<td>liquid blood and plasma</td>
<td>600 μL</td>
<td>N</td>
<td>microneedle upper arm</td>
<td>Y</td>
<td><a href="https://www.reddropdx.com">Link</a></td>
</tr>
</tbody>
</table>

## Blood Samplers

- **QiAcard FTA DNA kits 5**: dried blood, 1 x 30-125 μL, Y, stick, Y, [Link](https://www.qiagen.com)
- **RedDrop DX**: liquid blood and plasma, 600 μL, N, microneedle upper arm, Y, [Link](https://www.reddropdx.com)
- **QiAcard FTA DNA kits 5**: dried blood, 1 x 30-125 μL, Y, stick, Y, [Link](https://www.qiagen.com)

---

**Source**: Blood Samplers | PCSIG
Technologies “needed” for Home Sampling

**Collection, processing and shipping**
- Refrigerated shipping (savENRG COOL Pack)
- Home centrifuge
- Centrifuge shipper

**Electronic data capture (on device)**
- Patient ID
- Time & Date
- Sample tracking (chain of custody)
- Shipping temp & humidity
- “smart technologies”

*Pics provided by Tasso*
Bioanalytical challenges (for PK)

**Preparation of Std curves and QCs**
- Fresh blood (refrigerated?)
- Anticoagulant
- Manual effort
- Select/validate appropriate Hct range
- Addition of stabilizers (enzyme inhibitors, pH)

**Addition of IS** – in extraction solvent, pretreated

**Interferences** – due to device/collection matrix

**More time and effort needed in BioA lab**
- Not in 96-well format

*Overall BioA cost higher?*
Issues with small volumes

Assay sensitivity

Losses due to “device/capillary”
  • Adsorption, evaporation

Accuracy of sample volume
  • Lot-to-lot variability

Contamination
  • Cross-contamination
Stability Experiments

Additional stability experiments

• Drying time/conditions
• Storage at home
• Storage at clinic
• Shipping – local, international
Patient centricity – why has it taken so long

- Acceptance by stakeholders
  - health authorities, healthcare providers, laboratories, etc.
- Acceptance by patients – testing by self and/or at home
- Logistics – available commercially, globally
- Integration with established workflows
- Skepticism
- Resistance to change
- Cost
- Privacy concerns
- First followers?
Disruptive innovation

Clinical site  Central Lab  Kits  Sampling  Analysis  Reporting
Its going to take a village…..

...and one BLOOD draw at a time

• Multiple stakeholders

• Patient Centric Sampling Interest Group (not-for-profit organization that brings together a variety of interested parties who wish to develop and promote the use of patient centric sampling technologies for blood, plasma and other human matrices to better facilitate the advancement of human healthcare and well-being).

Home Sampling | Patient Centric Sampling Interest Group (pcsig.org)

• AAPS microsampling and patient centric sampling working group

• IHI (EC): Patient-centric blood sample collection to enable decentralised clinical trials and improve access to healthcare

Funding & tenders (europa.eu)
What COVID did (for home sampling)

- Remote health monitoring became a necessity during the COVID-19 pandemic
- Increased patient demand for “remote applications”

Home blood testing (its already here)
Patient centricity....

Point-of-care devices
Home diagnostics
Non-invasive (bloodless)
  • Video based AI (vital signs, Hb, A1C, cholesterol, etc.)
  • Imaging for WBC
  • Etc.

Abaxis | Better at Point of Care
HemoScreen - Complete Blood Count (CBC) Diagnostic Analyzer (pixcell-medical.com)
Sight OLO | Sight Diagnostics (sightdx.com)
Video-based Vital Signs Monitoring – Binah Leuko
Make patient centricity a reality….

.... because we are all patients at some point in time
Trivia: How much blood is collected by the Red Cross

Red Cross collects annually = 13.6 million units = **7.1 million Liters**

*Source: American Red Cross web site*
Acknowledgments

• Tony Fantana, PhD (Eli Lilly)
• AAPS Microsampling & PCS group
• Erwin Berthier, PhD (Tasso)
• Neil Spooner, PhD (Spooner Bioanalytical)
• Joleen White, PhD (Gates MRI)
• Brian Booth, PhD (FDA)
• Colleagues and Management at Eli Lilly

All images from royalty free sites or from the product website

Other company and product names are trademarks of their respective owners
Questions

enaksha.wickremsinhe@gatesmri.org