Are clinical facilities ready for POC beyond HCT?

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Representing the Grand Challenges Canada funded team
Unmet needs for POC
(Peeling, R, Clin Microbial Infect 2010)

Infectious diseases in the developing world:
- Appropriate clinical management of sick patients presenting at PHC is a global health challenge.
- Lack of accessibility to services and poor integration (HIV/TB) is one reason why health services fail.

<table>
<thead>
<tr>
<th>Unmet needs for POC</th>
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<tbody>
<tr>
<td>Acute lower respiratory infectious</td>
</tr>
<tr>
<td>Febrile illness in children</td>
</tr>
<tr>
<td>STI (incl HIV)</td>
</tr>
<tr>
<td>Antenatal care</td>
</tr>
<tr>
<td>Diseases (malaria, TB, Human African Trypanosomiasis, Visceral leishmaniasis)</td>
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</table>
Laboratory systems and services are critical in global health: *time to end the neglect* (Nkengasong, J, Am J Clin Pathol 2010)

- Frameworks exist for strengthening laboratory core elements
- Point of Care has a place and should follow this framework....
A test performed that has immediate impact on patient outcome

**The purpose** of POC is to provide timely test results that clinically and cost effectively contribute to immediate patient management decisions. *Clinical Laboratory Standards Institute*

**The description** is outpatient clinic, ER, theatre, mobile clinics, PHC clinics, or even small laboratories:

- Small bench top analysers (blood gas machines or full blood count analyzers), portable hand held devices (glucometers, strip based assays). *(Warsinke, 2009; Plebani, 2009)*
**POCT requirements**

- **Quality, quality, quality!!!**

<table>
<thead>
<tr>
<th>POC checklist</th>
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<tbody>
<tr>
<td>Clinical need</td>
</tr>
<tr>
<td>Type of test and equipment</td>
</tr>
<tr>
<td>Testing infrastructure</td>
</tr>
<tr>
<td>Personnel</td>
</tr>
<tr>
<td>Connectivity</td>
</tr>
<tr>
<td>Impact and cost benefit</td>
</tr>
</tbody>
</table>

*ISO/FDIS 22870: Point-of-care testing (POCT) — Requirements for quality and competence; NIH guidelines; National Academy of Clinical; Biochemistry (Clinica Chimica Acta, 2007); British Society of Haematology (BJH, 2008)*
### POC implementation checklist
*(snapshot Gous, N, 2012)*

<table>
<thead>
<tr>
<th>Requirements for POC implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Space requirements</strong></td>
</tr>
<tr>
<td>POCl instrument space and room requirements</td>
</tr>
<tr>
<td>POCl equipment</td>
</tr>
<tr>
<td>Safety requirements</td>
</tr>
<tr>
<td>POCl reagents and consumables</td>
</tr>
<tr>
<td>Miscellaneous items needed</td>
</tr>
</tbody>
</table>

- Workspace with allocated areas for sample receiving, sample preparation and incubation
  - Work area: H 50cm W 40cm D 40cm
  - Draft area: H 60cm W 23cm L 22cm
  - Refrigerator: H 21cm W 50cm D 65cm
  - Hemocue: H 4.9cm W 5.5cm D 10.6cm
  - Storage space (cupboards)
  - Power outlet

- POCl instruments
  - GeneXpert instrument, computer, barcodes reader, UPS, printer
  - Printer and scanner
  - Refrigerator and freezer
  - Blood glucose instrument and power adapter

- POCl accessories
  - Multiplug Adapter
  - Fridge (4°C)
  - Keyless lock (optional)
  - Medication tray (Med-Cart)

- Safety requirements
  - Secure room that can be locked
  - Limited access
  - Good ventilation - windows/aircon
  - Desk with running water and soap dispenser

- POCl reagents and consumables
  - GeneXpert
    - Primers, enzymes, template, master mix
    - Containing: assay cartridges, sterile disposable transfer pipettes, sample reagent SR1 buffer
    - Sputum sputum- capped specimen collection containers
    - Stop watch
    - (BP 700 ultraspeed)
    - Urine, CSF, blood

- Miscellaneous
  - 13. NaOH, wash bottles or equivalent
  - 1 hemip permanent marker pens
  - 1 printer, 1 printer paper

- Training
  - Standard operating procedures
Quality in POCT

- Site-neutral philosophy of CLIA* “control over the entire process”
  - **Pre-analytical** (patient ID, sample quality, aseptic technique, collection devise/tube, draw, label)
  - **Analytical** (device operation, ID, mix, analysis, maintenance, operator competency)
  - **Post-analytical** (sample disposal, result interpretation, audit trail, EQA, reporting)
- CLSI# for standardised best practices of patient testing

### CAP (College of American Pathologists) POCT requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform under direction of doctor/scientist</td>
<td></td>
</tr>
<tr>
<td>Site enrolled in proficiency program</td>
<td></td>
</tr>
<tr>
<td>Quality control and quality improvement program</td>
<td></td>
</tr>
<tr>
<td>Written procedures manual (patient identification – result reporting – action errors)</td>
<td></td>
</tr>
<tr>
<td>Personnel are trained</td>
<td></td>
</tr>
<tr>
<td>Results are reported with normal ranges</td>
<td></td>
</tr>
<tr>
<td>Critical test limits established</td>
<td></td>
</tr>
<tr>
<td>Appropriate person available for troubleshooting</td>
<td></td>
</tr>
<tr>
<td>Procedures and records maintained ~2yrs</td>
<td></td>
</tr>
<tr>
<td>Reagents, calibrations expiry dates recorded</td>
<td></td>
</tr>
<tr>
<td>New lots verified</td>
<td></td>
</tr>
<tr>
<td>Two levels of controls evaluated daily and corrective action documented</td>
<td></td>
</tr>
<tr>
<td>A system to regularly check maintenance</td>
<td></td>
</tr>
</tbody>
</table>

*clinical improvement amendments
#clinical and laboratory standards institute
So are we ready for POC post HCT?

Feasibility study:
Implementing multi-disciplinary POCT in an active HIV treatment clinic in South Africa

- Develop a Combined Clinical POC Laboratory Platform (CCPLP) model.
- Determine whether multi-disciplinary POC testing for HIV and TB can be performed in remote settings and is feasible, by non-laboratory personnel.
- Evaluate: cost effectiveness
- Recommend policy (including appropriate model of POCT placement in SA’s health care)
Clinic workflow and POCT options

HCT
- HIV Negative
- HIV Positive

CD4
- CD4> 350
  - Creatinine
  - ALT
  - Hemoglobin
- CD4< 350
  - TB screening (questionnaire)
    - Positive
      - GeneXpert
    - Negative
      - GeneXpert

Adherence counseling
- ART start (same day)

Follow up for 6 or 12 months
- Creatinine
- ALT
- Hemoglobin
- Viral load
- GeneXpert
CD4 count: PIMA (Alere)

- Portable bench-top flow cytometer
- A disposable test cartridge and PIMA analyzer
- Capillary or Venous whole blood
- Critical range is 350 cells/μl
- Time to result: 20 minutes
ALT, Creatinine: Reflotron (Roche)

- Uses disposable test trips
- Enzymatic reaction measured by photometry
  - ALT - 5.00 – ~ 2000 U/l
  - Creatinine – 44.2 -884umol/l
- Direct from whole blood, serum or plasma
- Time to result: 3 minutes
Hemoglobin Hb: Hemocue Hb201

- Hand-held device
- Disposable cuvettes
- Quantitative determination of Hb
- Enzymatic reaction measured by photometery
- Capillary, venous or arterial blood
- The measuring range is 0-25.6 g/dL.
- Time to result: <1 minute
TB with Rif resistance: GeneXpert (Cepheid)

- Closed platform for extraction, amplification and detection of *Mycobacterium tuberculosis* (*Mtb*) complex and Rif resistance
- Direct from unprocessed sputum (0.5 – 4ml)
- Time to result: 2 hours

1. Add 2:1 Sample Buffer to sample
2. Shake then stand 10 minutes
3. Shake then stand further 5 minutes
4. Transfer 2ml to cartridge

Begin Test…
Findings: Space in clinics

- Multiple POC requires space (POC work flow: specimen, testing, reporting, disposal) security and place for computer for connectivity.
- Clinic space varied
During the RCT the number of incidents in the clinic which affected patient recruitment and testing were noted:

- **Flooding**
- **Clinic kit shortages**
- **Clinic staff shortages** (no counselors/nurses on duty to initiate) and high turnover
- **Disruption in the clinic workflow**: No eligible patients to recruit (patients being referred from other areas due to trials and community programs)

**Incidents experienced by clinic which affected patient recruitment**

<table>
<thead>
<tr>
<th>Category of incident</th>
<th>Number of incidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>No eligible patients</td>
<td>2</td>
</tr>
<tr>
<td>No water/electricity</td>
<td>2</td>
</tr>
<tr>
<td>POC instrument breakdown</td>
<td>2</td>
</tr>
<tr>
<td>Flooding</td>
<td>1</td>
</tr>
<tr>
<td>Clinic kit shortages</td>
<td>1</td>
</tr>
<tr>
<td>Clinic staff shortages</td>
<td>1</td>
</tr>
</tbody>
</table>

**Majority of incidents were due to:**

- VCT kit shortages at the clinic,
Training for POCT in Australia: (Shephard et al 2009, rural and remote health)

- Remote POCT users had a greater need for training and support to urban counterparts.
- Remote training requires flexible options to cater for much higher staff turnover.

South Africa (SEAD report on assessment of POC HIV rapid testing, 2010)

- Overall process compliance: 3.4% nationally: rural facilities (6.9%) performed better than urban (1.7%), higher workflow clinics performed better

- Recommendations: A system’s approach is essential to address training, mentoring, responsibilities, on-going monitoring, effective and efficient procurement, on-going quality assurance,
Training: our experience

- Developed **SOP manuals** in POC-GCLP format
  - quick reference charts more effective
- Training: Centralised training
  - ½ day per platform (Pima, Hemocue, Reflotron, Accutrend)
  - Xpert MTB/RIF required 1 full day due to computer and software operation.
- On-site test witnessing
  - Xpert MTB/RIF required more intensified on-site training.
  - Measured also by QC testing
- Made use of pre and post training questionnaires
  - N=18 trainees (mostly for Xpert MTB/RIF)
  - Training yielded 8.3% increase in knowledge
Assay performance:
Can nurses perform multiple POC as well as lab?

- Site 1: (HJH) n=160; site 2: TAH, n= 320
- Venepuncture POCT compared well with laboratory results:
  - mean differences: 24cells/µl CD4; 0.5g/dl Hb; 1.27µmol/l creatinine; 8.4IU/l ALT
  - 5.8% (9/155) CD4 tests required repeat testing

![Graphs showing correlation between Hb, Creatinine, and ALT with reference values.](image)
Sample collection: open tube vs finger-stick

- Increased variability with finger stick for CD4 PIMA testing (Glencross et al, J int AIDS soc, 2012).
- Alternative to finger-stick using a Vacuette VacuDop

Ref: Pooled data re-analysis from 30 studies published on CD4 PIMA
QC and EQA

- QC (Levy Jenning plots): good QC performance
- NHLS QAD can provide: EQA for CD4, Hb, (chemistry needs matrix validation)
- New “kid” = GeneXpert?
  - Novel verification and EQA developed.
  - DCS: *M. tb* single cell organisms, inactivated, quantified by flow cytometry, spotted onto filter cards, distributed to sites, tested.
  - Good performance on ~1500 DCS for verification
  - Good performance of DCS for EQA
Who will perform POCT?

Task Shifting – management of task shifting from lab staff to clinical staff

Regulation and certification around scope of work?

Phlebotomy training need for non-clinical staff!

Nurse = phlebotomy

Technical POC officer = finger-stick
Numbers of tests requested at any one time: HJH (site 1)
- 34% = 4 tests at one visit
- 25% = 3 tests
- 21% = 2 tests
- 17.8% = 1 test
- n=1 patient had 5 tests requested

69% required >3 tests at one visit
Time taken to perform POCT

- HJH study:
- Earliest **blood draw** 8:15 (median time 9:55).
- Earliest **time a POCT performed** was **09:30**, (median **11:00** and the latest **12:24**).
- Median time taken from the time the nurse started the first POCT to the time taken to start the last POCT varied depending on the number and type of tests requested.
  - When **CD4 requested**, tests took ~1hr47min,
  - **CD4 not requested**, ~6min - 14minutes. These time measurements did not include acting on result or any connectivity.
GeneXpert at POC >2hrs

- Gx placement (phased approach) currently at moderate to advanced infrastructure NHLS sites
- Collaboration with clinical partners to assess feasibility and impact of Gx at POC.
  - Concerns: Expanding Xpert to POC could result in important patient benefits but requires substantial strengthening of primary care facilities and investment in human resources (a minimum of two full-time staff required to supervise sputum collection, process sputum, perform assays, document and communicate results for an average of 15 TB suspects daily). Some patients did not receive same day treatment due to specimen preparation times. (Clouse, K et al, SAMJ 2012)
Study: Hospital POC placement of Hemocue (Hb201 DM)

Aim: to assess value of POC HB in wards where rapid result may alter care

- Lab Role
  - Training – 370 health care workers and laboratory staff trained
  - Quality control, maintenance of Hemocue instrument
  - Data management and stock control

- First outcome: No change in lab based FBC and Hb testing volumes before or after POC HB placed in specific wards
  - 12% increase in lab testing?
  - Awaiting clinical evaluation for impact.

<table>
<thead>
<tr>
<th>Ward Type</th>
<th>Number</th>
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<tbody>
<tr>
<td>Casualty</td>
<td>165</td>
</tr>
<tr>
<td>Paeds ICU</td>
<td>276</td>
</tr>
<tr>
<td>Paeds Renal</td>
<td>296</td>
</tr>
<tr>
<td>Trauma ICU</td>
<td>376</td>
</tr>
<tr>
<td>Trauma high care</td>
<td>377</td>
</tr>
<tr>
<td>General surgery</td>
<td>396</td>
</tr>
<tr>
<td>General surgery</td>
<td>394</td>
</tr>
<tr>
<td>Adult renal transplant</td>
<td>561</td>
</tr>
<tr>
<td>General ICU</td>
<td>576</td>
</tr>
<tr>
<td>General high care</td>
<td>577</td>
</tr>
</tbody>
</table>

Average test volume per month

- Chart showing testing volume per month.
Duties

**CLINIC DUTIES**
- Patient registration
- History taking
- Physical exam
- Counselling
- Rapid testing (HIV, pregnancy)
- Phlebotomy – lab tests
- Treatment
- Return visit booking

**POC DUTIES** (pre-analytical, analytical, post-analytical)
- Additional finger stick/venepuncture
- Sample labelling
- Instrument QC testing
- Instrument maintenance
- Testing:
  - ALT, Creat, Hb: <2 minutes
  - PIMA = 20 minutes
  - Xpert MTB/RIF = 2 hours
- Result recording/printing/reporting
- External quality assessment (EQA)
- Infection control
- Spill cleaning
- Waste disposal
- Additional skills:
  - Phlebotomy
  - Testing performed from blood tubes (pipetting skills)
- Additional duties:
  - Operator certification and on-going monitoring
  - Managing test failures, instrument downtime
  - Stock control
  - Specimen storage

Automation through information technology
Manual result entry…..

<10% POCT managed by central LIS.
Billing and data management often handled manually
(Blick, K, Clin Chem Acta 2001)

Our experience:

Manual entry transcription errors

- Both clinic sites had transcription errors (1%; n=5/480):
  - Incorrect assay result recorded
  - Assay result recorded under incorrect test.
Solution is connectivity?

- **Level III and IV**
  - tertiary referral and reference laboratory: provincial hospitals

- **Level II**
  - laboratory: district hospital

- **Level I laboratory**: health post/health center

NHLS LIS* and links to HIS* extends to here

Solutions beyond: sms printers, wireless networks

*Laboratory information system
*Hospital information system
Connectivity standards \textit{(Nichols Expert Rev Mol Diagn 2003)}

Results must be passed onto LIS and/or HIS:
- Permanent record of medical history
- Billing/reimbursement purposes
- Future reference

- CIC (Connectivity Industry Consortium) 1999: "The vision: to expeditiously develop, pilot and transfer the foundation for set of seamless ‘plug-and-play’ POC communication standards: bidirectionality, device connection commonality, commercial software interoperability, security, and QC / regulatory compliance."

- The result was the \textit{POCT1-A international standard}
What is the situation with connectivity?

Ideal is a universal management system

Host LIS/HIS

COBAS IT

GENEXPERT SOFTWARE

3rd PARTY APPLICATION

REFLotron

ACCUTRENd

GENEXPERT

PIMA

HEMOcUE

HL7/ASTM

HL7/ASTM

HL7/POCT1-A

Proprietary

HL7/ASTM

N/A

POCT1-A

The good the bad and the non-connected
....off the shelf options don’t satisfy all requirements

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<tbody>
<tr>
<td>AegisPOC</td>
<td>Extensive</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>POCcelerator</td>
<td>Extensive</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cobas IT</td>
<td>Limited</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Identicare</td>
<td>Development</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapy Edge</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>eKAPA</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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</table>

**Instrument and Data Management**

**Patient Management**
Are we ready?

<table>
<thead>
<tr>
<th>Checklist</th>
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<tbody>
<tr>
<td>Clinic infrastructure for dedicated POC space</td>
<td><strong>Limited</strong>: needs reorganisation</td>
</tr>
<tr>
<td></td>
<td>Follow pharmacy (dedicated space, well organised, security gate, some temperature controlled)</td>
</tr>
<tr>
<td>Instrument availability</td>
<td><strong>Yes</strong>: CD4, ALT, Creat, Hb₄ Xpert, Viral load</td>
</tr>
<tr>
<td>Nurse operated POC accuracy</td>
<td><strong>Yes</strong>: nurses as good as lab (venepuncture useful for multiple POCT)</td>
</tr>
<tr>
<td>Quality systems</td>
<td><strong>Yes</strong>: for QC, not all for EQA (some need cold storage)</td>
</tr>
<tr>
<td>Staff</td>
<td>Nurses <strong>yes</strong>: time and workflow?</td>
</tr>
<tr>
<td></td>
<td>Technical <strong>no</strong>: new cadre dedicated to POC? but need for phlebotomy!!!!! Also useful if want to reflect blood specimen for lab re-testing or POC repeat test.</td>
</tr>
<tr>
<td>Training and SOP</td>
<td><strong>Yes</strong>: quick reference charts are effective, need large scale training (success story Xpert)</td>
</tr>
<tr>
<td>Data management and instrument connectivity</td>
<td><strong>No</strong>: lose national data (no program performance or measure of interventions), reimbursement?, billing?</td>
</tr>
<tr>
<td></td>
<td>Solution: (1) extend the LIS, (2) off the shelf products (included operator certification, EQA/QC, stock control etc</td>
</tr>
<tr>
<td></td>
<td>Issue: instrument connectivity “the good, the bad and the not connectable”, <strong>national coverage</strong> via wireless routers?</td>
</tr>
<tr>
<td>Questions</td>
<td>Answers</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Does POC have a place post HCT?</td>
<td>Yes</td>
</tr>
<tr>
<td>Does it flow with clinic care</td>
<td>Reengineer</td>
</tr>
<tr>
<td>Who takes responsibility for the test?</td>
<td>A partnership</td>
</tr>
<tr>
<td>Who performs the POCT?</td>
<td>New cadre of technical POC officers?</td>
</tr>
<tr>
<td>Is a solution better logistics?</td>
<td>&lt;4hr specimen transport to the lab (POC lab)</td>
</tr>
<tr>
<td>Is a solution better specimen preservation &gt;6hrs?</td>
<td>DBS, ppt, Primestore (preservative material)</td>
</tr>
<tr>
<td>Is a solution faster TAT on reported result?</td>
<td>SMS printers, lab LIS terminals in each clinic – electronic era</td>
</tr>
</tbody>
</table>
Acknowledgements

- The National Health Laboratory Service and the NHLS POC working group and NPP
- The GCC team:
  - Wendy Stevens, Johan Potgieter, Lumka Ntabeni, Natasha Gous, Brad Cunningham, Elizabeth Prentice, Sebaka Molapo, Matilda Nduna, Regina Osih, Charlotte Jansen van Rensburg, nurses and counsellors
- Funders (USAID, GCC, CDC, Pepfar)
- Clinical Partners (WRHI, CHRU/RTC, PHRU)

- Patients and participants
- Suppliers forum/working group (hardware and software suppliers) for technical support, platforms and reagents.
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Quality and efficiency of care can be improved in certain scenarios</td>
<td>• Difficulties with quality control/documentation</td>
</tr>
<tr>
<td>• Improved accessibility</td>
<td>• Greater personnel requirements at clinic</td>
</tr>
<tr>
<td>• Improve patient compliance and LTFU</td>
<td>• Longer patient wait times</td>
</tr>
<tr>
<td>• Improved turnaround time</td>
<td>• Data management/audit issues</td>
</tr>
<tr>
<td>• Smaller sample volumes</td>
<td>• Slower sequential processing time/throughput in high clinics</td>
</tr>
<tr>
<td>• Economic benefits –</td>
<td>• Over-servicing</td>
</tr>
<tr>
<td>◦ reduced length of stay</td>
<td>• Higher unit of cost/reagent</td>
</tr>
<tr>
<td>◦ reduced complications and readmission</td>
<td>• Poor regulatory control</td>
</tr>
<tr>
<td>• Improved patient and clinician satisfaction</td>
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</tbody>
</table>