Opportunities Created by Diagnostic HCV and HIV Nucleic Acid Tests

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Improved HCV RNA Testing Rates in New York City Following Health Code Change

2019 HIV Diagnostics Conference
March 26, 2019

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Bureau of Communicable Disease
Viral Hepatitis Program
Hepatitis C Reporting Required Through Electronic Clinical Reporting System, New York City

Reportable

- Positive antibody
- Positive and negative RNA results, genotype
- ALTs reported if on the same accession as a reportable lab

Not reportable

- Negative antibody tests
- Positive rapid antibody tests
In 2016, in New York City
- 60% had reflex RNA testing
- 77% patient had any RNA test
- 23% --2684 patients—had NO RNA testing
Percentage of Patients Receiving Hepatitis C RNA Test Within 3 Months of Positive Hepatitis C Antibody, New York City Hospitals, 2017

- Hospitals with no reflex testing (n=14): 49.4%
- Hospitals with reflex testing (n=25): 93.2%
New York City Health Code Amendment to Require Confirmatory RNA Testing

• Amend Health Code to require laboratories to routinely perform a confirmatory RNA HCV test when there is a positive HCV antibody test result
  • Similar to how HIV testing is performed

• Help ensure that patients infected with HCV are aware of their status, linked to appropriate medical care and treatment, and cured, improving their health and reducing the risk of transmission
Board of Health Rule Making Process and Adoption of Health Code Requiring Mandatory Reflex RNA Testing

- Board of Health approved publication of proposed rule on June 13, 2017
  - Public hearing held on July 27, 2017
  - 10 comments received (3 oral; 7 written)
  - No changes to the amendment proposal were made
- September 12, 2017 Board of Health adopted Health Code amendment
- Starting October 20, 2017, laboratories were required to perform a reflex RNA test if an antibody test is positive
Evaluating the Impact of the Health Code Amendment

• Use surveillance data to identify 20 highest volume reporting labs

• Outreach and technical support to laboratory directors
  • Reiterate details of Health Code Amendment
  • Share lab-specific surveillance data to show the pre and post Health Code Amendment rates of reflex testing
  • Provide random sample of accession numbers if requested to understand reasons RNA testing not performed

• No outreach at this time to
  • Labs that have reflexed at least 80% of antibody tests post health code change
  • Labs that have shown improvement in percentage of tests reflexed
Number of Hepatitis C Antibody Tests by Top 20 New York City Laboratories, 2017

Data as of 5/25/2018
Proportion of Positive Antibody Tests Reflexed to RNA Tests by Top 20 High Volume Laboratories, May 1, 2017–April 30, 2018

Data as of 5/25/2018
Larger commercial lab with no option for ordering stand-alone HCV antibody testing.

Reflex RNA testing pre health code (May 2017-Oct 2017)
Reflex RNA testing post health code (Nov 2017-Apr 2018)
RNA reflex testing (May 2017-Apr 2018)

<table>
<thead>
<tr>
<th>Lab name</th>
<th># antibody tests reflexed</th>
<th>Total antibody tests</th>
<th>% reflex RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMERCIAL LAB A</td>
<td>2888</td>
<td>4859</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>2565</td>
<td>4755</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>5453</td>
<td>9614</td>
<td>57%</td>
</tr>
</tbody>
</table>

Lab Response: “We reflex all positive antibody results. Please send examples.”

Lab Response: “We randomly checked 10 and all had quantity insufficient. Most only included 1 Corvac/serum tube with multiple submissions on same accession number.”

Health Department outreach to largest client: a “detox” facility with more than 1000 positive antibody results from May 2017-2018 and only 7% RNA confirmation: “We send five tubes of blood.”
Challenges

• Providers default to ordering HCV antibody only if the option exists
• Even for large commercial labs that only offer option for HCV antibody to reflex RNA, we observed many QNS results
  ➢ Client PROVIDER education about specimen collection
• Use of assays FDA approved for monitoring but not for diagnostic testing
  ➢ Labs can perform their own validation but have expressed that this is resource intensive
  ➢ Labs have included statements on the report that results should not be used for diagnostic testing
  ➢ Dual claim
• Workflow challenges
  ➢ Number of specimens, serology and virology labs, RT-PCR contamination
• Limited Heath Department resources to conduct outreach
Proportion of Positive Antibody Tests Reflexed to RNA Tests by Month

Oct 20, 2017
Laboratories required to perform reflex RNA testing

Data as of 3/23/2019
Conclusion

• Hepatitis C antibody test with confirmatory RNA is standard of care for all patients, and is the first step in developing treatment plan and curing a patient of hepatitis C

• Surveillance data can be used to advocate for policy change and for evaluating the impact of the change

• Systems change is required
  • Hospitals and commercial labs must remove option for providers to order a stand-alone HCV antibody test

• Next steps:
  • Monitor reflex RNA uptake
  • Continue outreach out to laboratory directors, clinical providers and facility leadership to advocate for systems change
  • Offer assistance to providers with implementing reflex RNA testing, including referral to peer laboratories
Acknowledgements

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    • Jennifer Baumgartner
  • Division of Disease Control Policy Staff
    • Rima Oken

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Validation of HIV-1 Quant Dx Assay on the Hologic Panther for Diagnostic Use

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Introduction

1. Summarize results of the Panther assay evaluation for both HIV-1 diagnosis and monitoring in a pediatric patient population

2. Recapitulate performance on samples from patients under 2 years of age

3. Review impact on laboratory workflow and efficiencies gained and turnaround-time
HIV diagnosis in infants and children

• Antibody tests, (including Ag/Ab combo IA) do not establish HIV infection in infants because of transfer of maternal Ab

• The sensitivity of p24 antigen in the first months of life is <HIV NAT

• HIV exposed children 18 - 24 months old may have residual maternal HIV Ab; confirmation should be based on a NAT

• HIV RNA or DNA NAT must be used to diagnose HIV infection in children <18 months old
HIV diagnosis in infants and children

- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>2-3 weeks</th>
<th>4-8 weeks</th>
<th>8-10 weeks</th>
<th>4-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
<td></td>
<td>NAT</td>
</tr>
<tr>
<td>Higher risk</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
<td>NAT</td>
</tr>
</tbody>
</table>

Laboratory impact

There are no FDA-approved assays with a dual claim for diagnosis and monitoring of HIV-1

1. Laboratories end up getting two instruments, one for HIV viral loads and a qualitative NAT for diagnosis

2. Laboratories end up having to validate their viral load test to use as a diagnostic assay and not just for monitoring
Previous workflow

**Architect**
Sample Volume: 1.5 mL
Serum or Plasma
Run Daily

**Geenius**
Sample Volume: 5µL
Serum or Plasma
Run Daily

**Aptima (qual)**
Sample Volume: 600µL
Serum or Plasma
Run 2 x week

**m2000 (quant)**
Sample Volume: 1.1mL
Plasma
Run 1 x week
Aptima HIV-1 Quant Dx Assay

• Hologic’s TMA-based Aptima HIV-1 Quant Dx Assay
  • First commercially available automated NAT that has CE certification for both HIV-1 diagnosis and monitoring
  • Feb. 14, 2019 – two new CE marks for early infant diagnosis and dried blood spots
  • FDA-approved for HIV-1 monitoring only
  • Workflow

Viral load Comparison

96% Agreement

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.28</td>
<td>0.64 and -0.45</td>
</tr>
</tbody>
</table>
As a diagnostic test:

- 185 plasma samples (25 reactive and 160 non-reactive) previously tested on the Aptima Qual were tested on the Panther platform.
- The median patient age was 11.4 months.
- Panther showed 100% agreement with Aptima Qual.
Our current workflow:

**Architect**
- Sample Volume: 1.5 mL
- Serum or Plasma
- Run Daily (STAT)

**Geenius**
- Sample Volume: 5µL
- Serum or Plasma
- Run Daily (non-STAT)

**Panther (Quant)**
- Sample Volume: 700µL
- Plasma
- Run 1 x week (ASAP)
Implementing the Panther system allowed for repurposing 600 sq ft (13%) of our laboratory space.

Using a single platform decreased hands-on-time and saved 0.4 FTE.
CHOP patient population

• 27% of all samples tested on the HIV-1 Quantitative assay are from infants and children <2 years old

• 24% of samples are from patients 2-17 years of age

• 49% of samples are from patients older than 18
CHOP data

• In patients younger than 2 years of age:
  • Tested 268 samples from 134 patients
  • We have had 2 positive patients (4 samples)
    1. International adoption – suspected HIV
    2. Mother diagnosed after delivery
  • No false-positives or false negatives
Summary

- The Panther platform is a viable option for both HIV-1 diagnosis and monitoring in the pediatric population, including patients <2 years of age
- Bland-Altman analysis demonstrated excellent agreement between the m2000 and the Panther
- Repurposed 600 sq ft (13%) of laboratory space, decrease hands-on-time by 70% and saved 0.4 FTE
- The Panther assay has performed as expected
Opportunities Created by POC HIV NAT

Joanne Stekler, MD MPH
Associate Professor
University of Washington
Current state of HIV screening and diagnostic tests in the U.S.

**Laboratory-based Tests**
- Antibody screening
- Antibody-antigen screening
- Supplemental testing
  - Geenius
  - Western Blot
- p24 assays
- Qualitative RNA
- Quantitative RNA (viral load)

**Point-of-Care Tests**
- Oral fluid antibody
- Fingerstick antibody
- Fingerstick antigen-antigen-antibody

**Home collection/self-tests**
Current state of HIV screening and diagnostic tests in the U.S.

Laboratory-based Tests

More accurate testing

Point-of-Care Tests

More people get results
## Product characteristics of POC NAT

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>VOLUME (uL)</th>
<th>RNA/TNA</th>
<th>QUANTITATIVE? QUALITATIVE?</th>
<th>LIMIT OF DETECTION</th>
<th>TURN-AROUND TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlereQ HIV-1/2 Detect (m-PIMA)</td>
<td>WB</td>
<td>25</td>
<td>TNA</td>
<td>Qualitative</td>
<td>1759</td>
<td>60</td>
</tr>
<tr>
<td>AlereQ NAT</td>
<td>WB</td>
<td>25</td>
<td>Total RNA</td>
<td>Quantitative</td>
<td>1000*</td>
<td>60</td>
</tr>
<tr>
<td>Xpert HIV-1 Qual (Cepheid)</td>
<td>WB, DBS</td>
<td>100 (WB)</td>
<td>RNA</td>
<td>Qualitative</td>
<td>WB 350 DBS 634</td>
<td>90</td>
</tr>
<tr>
<td>Xpert HIV-1 Viral Load (Cepheid)</td>
<td>Plasma</td>
<td>1000</td>
<td>RNA</td>
<td>Quantitative</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>SAMBA II Qual (DRW)</td>
<td>WB, DBS</td>
<td>100</td>
<td>TNA</td>
<td>Qualitative</td>
<td>400</td>
<td>120-135</td>
</tr>
<tr>
<td>SAMBA II Semi-Q WB (DRW)</td>
<td>WB</td>
<td>100</td>
<td>RNA</td>
<td>Semi-quant</td>
<td>1000*</td>
<td>85-100</td>
</tr>
<tr>
<td>SAMBA II Semi-Q plasma (DRW)</td>
<td>Plasma</td>
<td>200</td>
<td>RNA</td>
<td>Semi-quant</td>
<td>1000*</td>
<td>80-95</td>
</tr>
</tbody>
</table>
Opportunities created by POC HIV NAT

- Provide resolution following positive screening test
  - Supplemental testing – since Geenius not (yet?) CLIA-waived
    - HIV screening settings
    - L+D
    - Discordance in rapid-rapid algorithms
- POC diagnosis of acute HIV infection
  - Symptomatic persons
  - PrEP starts? Follow-up visits?
- Infant diagnosis/MTCT
- Real-time evaluation of antiretroviral treatment response
- Cure research: monitor viral rebound following treatment d/c
# SAMBA II Qual in Project DETECT

Presentation by Lauren Violette

<table>
<thead>
<tr>
<th>HIV-1 viral load threshold</th>
<th>Finger stick whole blood</th>
<th>Venipuncture whole blood</th>
<th>Previously frozen plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 copies/mL</td>
<td>22/23 = 96%</td>
<td>42/43 = 98%</td>
<td>13/25 = 52%</td>
</tr>
<tr>
<td>≥400 copies/mL</td>
<td>20/21 = 95%</td>
<td>35/36 = 97%</td>
<td>13/18 = 72%</td>
</tr>
<tr>
<td>≥700 copies/mL</td>
<td>18/19 = 95%</td>
<td>32/33 = 97%</td>
<td>12/15 = 80%</td>
</tr>
<tr>
<td>≥1,000 copies/mL</td>
<td>18/18 = 100%</td>
<td>29/29 = 100%</td>
<td>9/11 = 82%</td>
</tr>
<tr>
<td>≥2,000 copies/mL</td>
<td>16/16 = 100%</td>
<td>26/26 = 100%</td>
<td>7/8 = 88%</td>
</tr>
<tr>
<td>≥3,000 copies/mL</td>
<td>15/15 = 100%</td>
<td>25/25 = 100%</td>
<td>7/7 = 100%</td>
</tr>
</tbody>
</table>
“Point-of-care viral load testing improves HIV viral suppression and retention in care”

Xpert HIV-1 Viral load
Randomized at Month 6 HIV test
Outcomes measured at 12 months

<table>
<thead>
<tr>
<th></th>
<th>Intervention N=195</th>
<th>Standard-of-care N=195</th>
<th>Absolute risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint (composite)</td>
<td>89.7%</td>
<td>75.9%</td>
<td>13.9% (95% CI 6.4-21.2%)</td>
</tr>
<tr>
<td>HIV RNA &lt;200</td>
<td>93.3%</td>
<td>83.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Receipt of ART at research clinic</td>
<td>92.3%</td>
<td>84.6%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Drain et al., Abstract #53, CROI 2019
“Point-of-care viral load testing improves HIV viral suppression and retention in care”

Questions –

What should be done with a positive result?
Would results be similar in the U.S.?
How do we integrate other novel POC testing
   POC tenofovir tests
POC HIV NAT
Other remaining questions

- What significance do the cases of discrepant results using SAMBA, including one with 10,000,000 copies/mL, have for implementation of POC NAT?
- Can the LOD be lowered for whole blood quant tests?
- Can turnaround times be shortened?
- Can assays respond to high throughput needs?
Questions for Discussion

• **HCV**
  - For programs using HCV NAT, how has it improved the identification of current HCV infection and what lessons have been learned?
  - What steps could be taken to improve the number of people with an antibody positive test that get a NAT?

• **HIV**
  - What barriers and opportunities do you see with using a qualitative or quantitative NAT as the 2nd step in the HIV laboratory testing algorithm?
  - What are adequate levels of detection for qualitative HIV NATs in the U.S. and what sample types would be most beneficial for increasing NAT utilization?