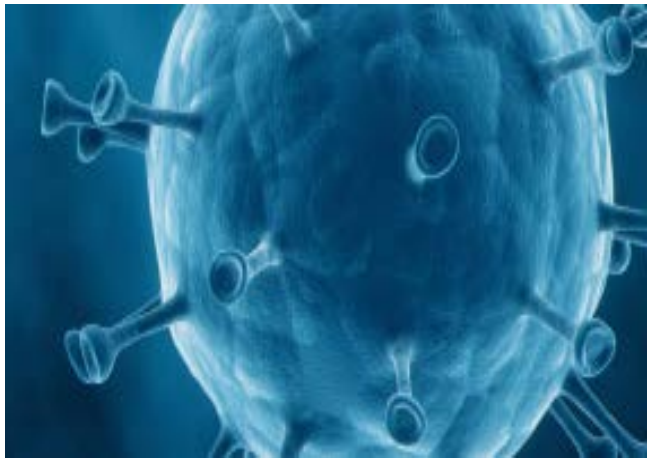
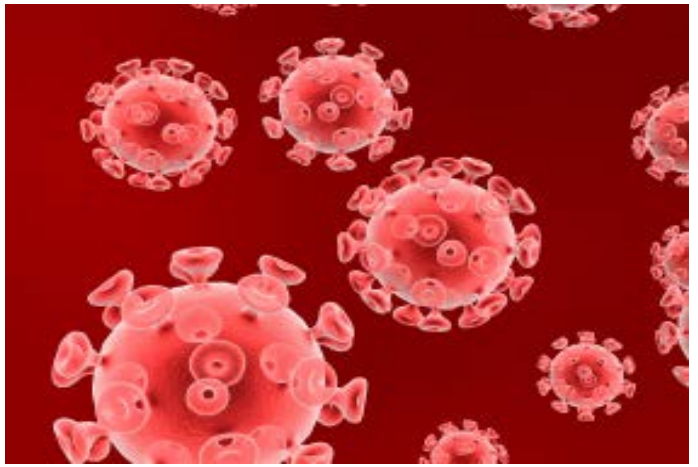
Opportunities Created by Diagnostic HCV and HIV Nucleic Acid Tests





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

2019 HIV Diagnostics Conference

March 26, 2019

Ann Winters, MD

New York City Department of Health and Mental Hygiene

Bureau of Communicable Disease

Viral Hepatitis Program

Hepatitis C Reporting Required Through Electronic Clinical Reporting System, New York City

Reportable

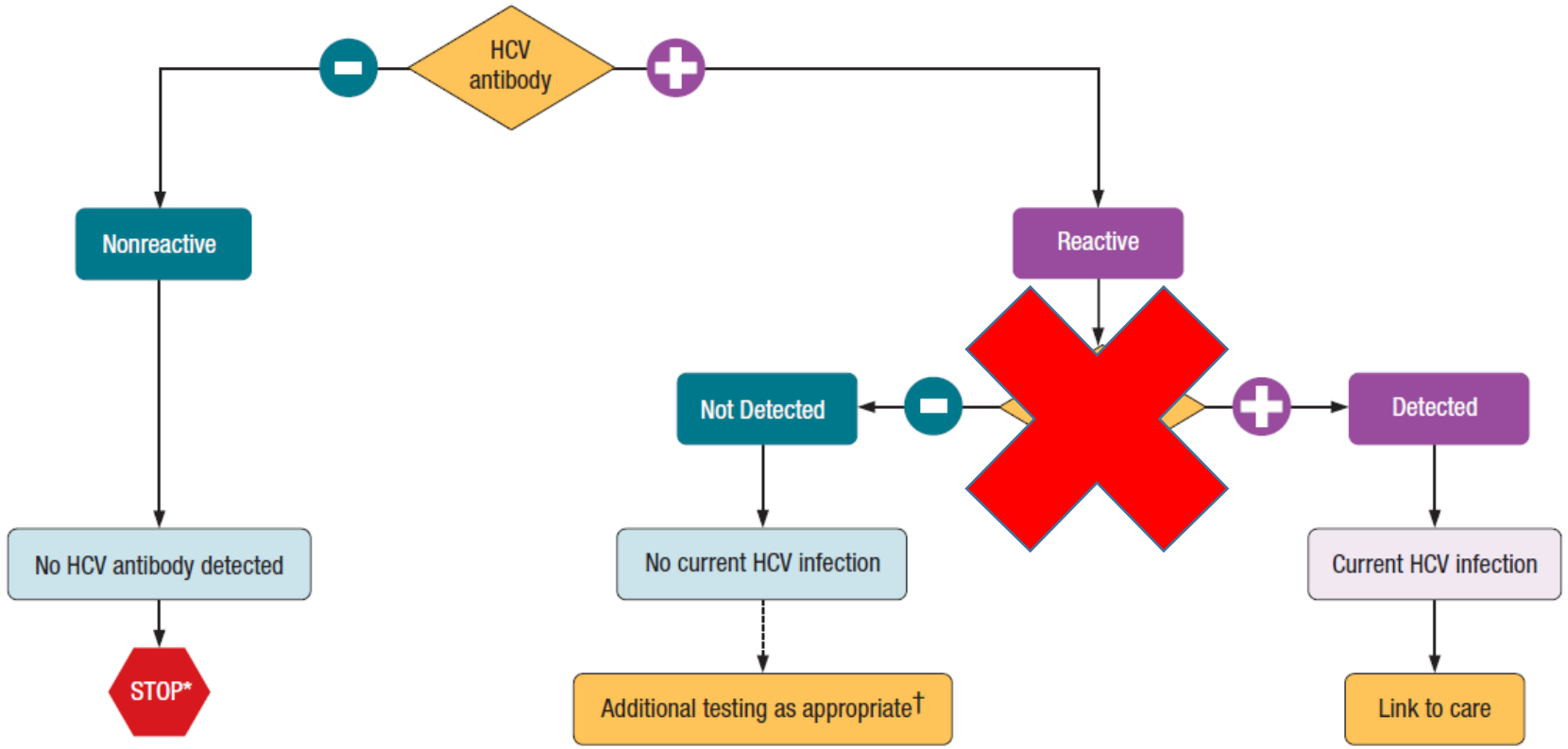
- Positive antibody
- Positive and negative RNA results, genotype
- ALTs reported if on the same accession as a reportable lab

Not reportable

- Negative antibody tests
- Positive rapid antibody tests

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

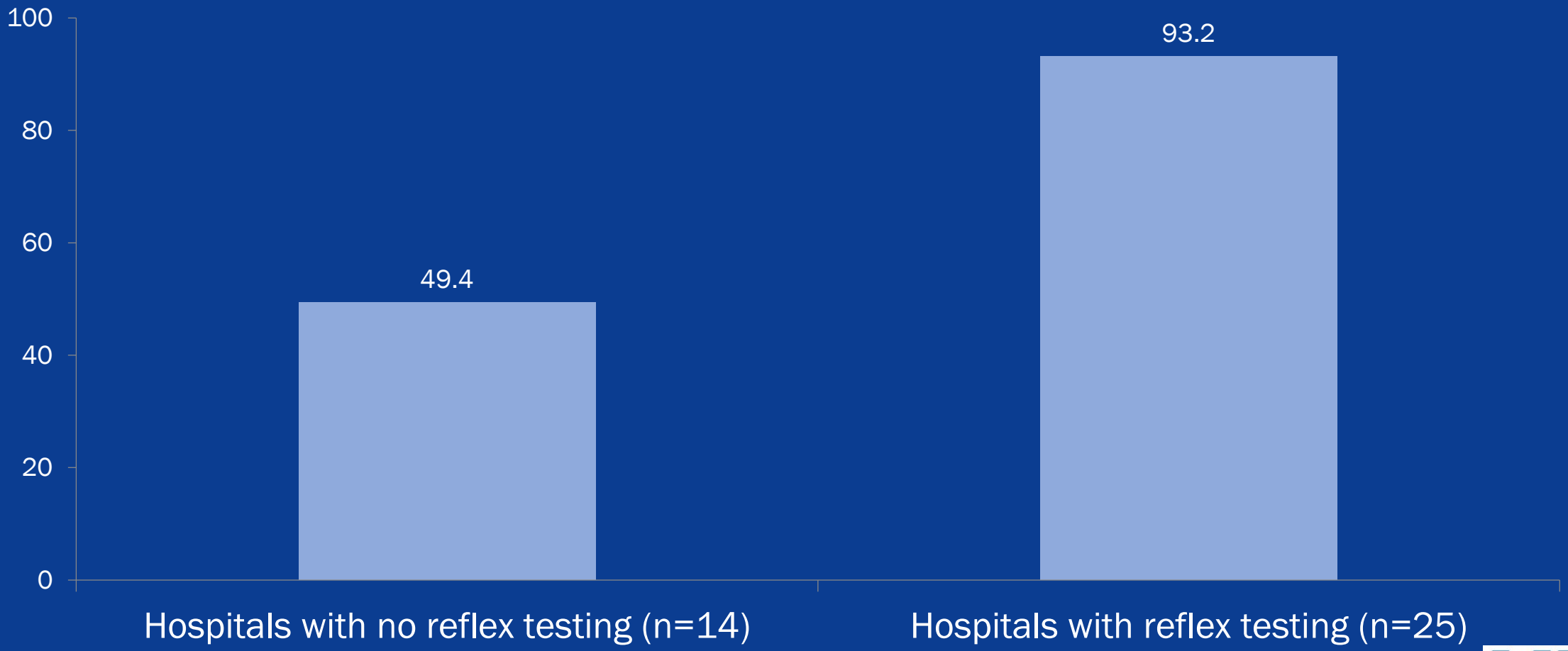
Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

In 2016, in New York City

- 60% had reflex RNA testing
- 77% patient had any RNA test
- **23% --2684 patients—had NO RNA testing**

NYC Health

Percentage of Patients Receiving Hepatitis C RNA Test Within 3 Months of Positive Hepatitis C Antibody, New York City Hospitals, 2017



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

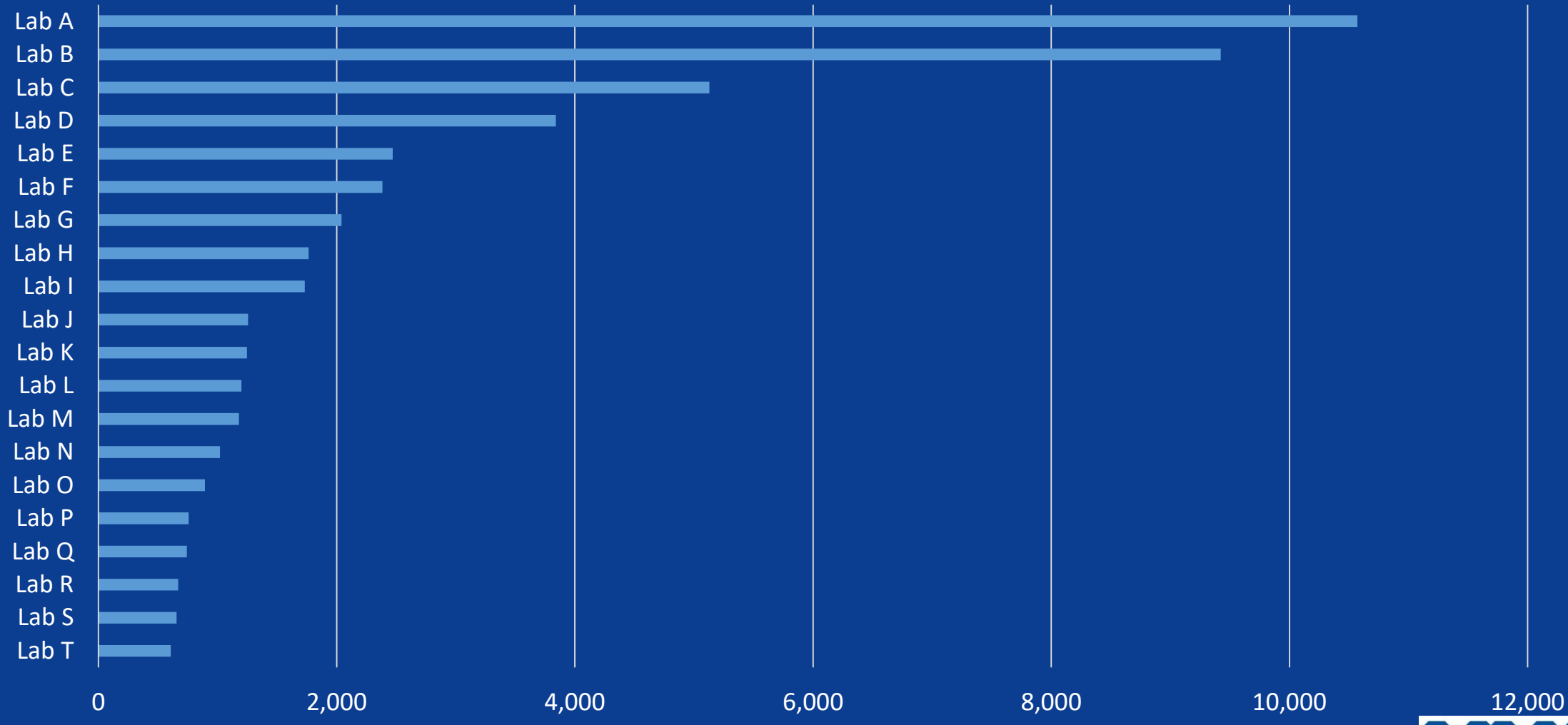
Board of Health Rule Making Process and Adoption of Health Code Requiring Mandatory Reflex RNA Testing

- 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
  - http://www1.nyc.gov/assets/doh/downloads/pdf/notice/2017/noa-article13.pdf
- 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

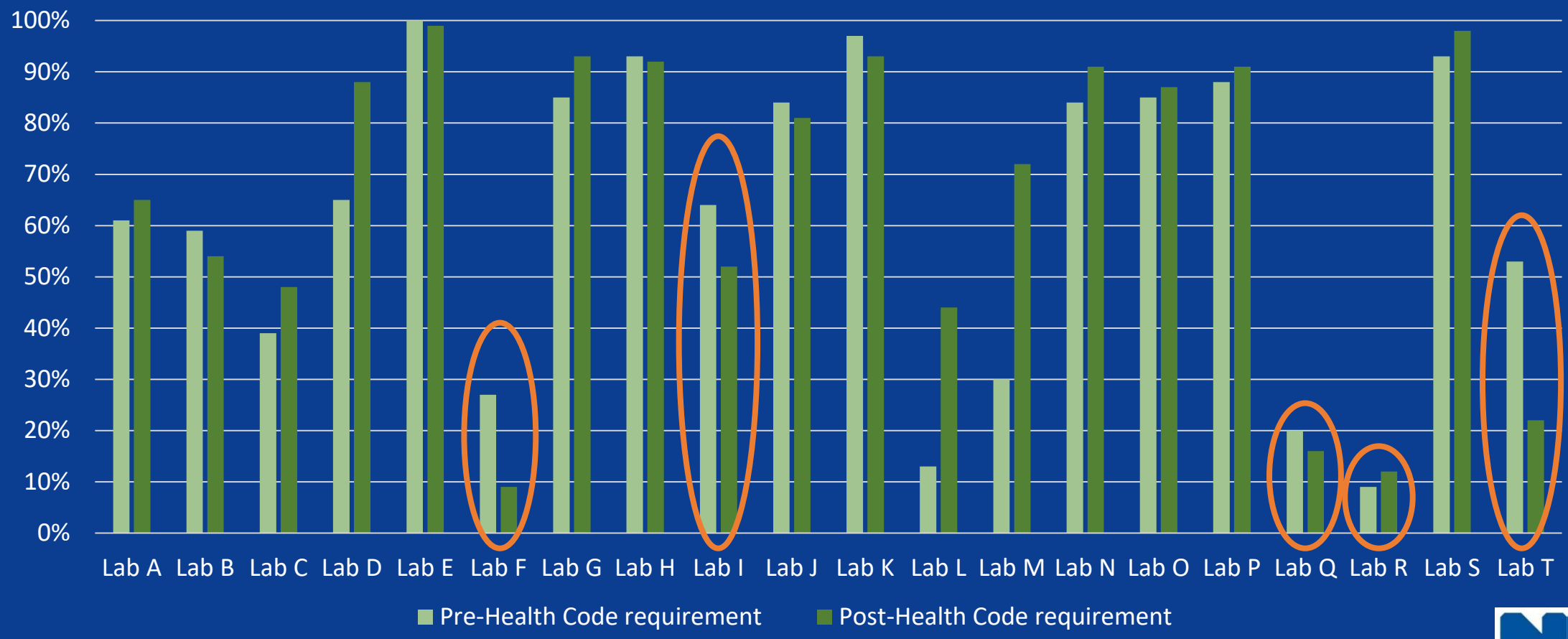
Number of Hepatitis C Antibody Tests by Top 20 New York City Laboratories, 2017



Data as of 5/25/2018

NYC Health

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

NYC Health

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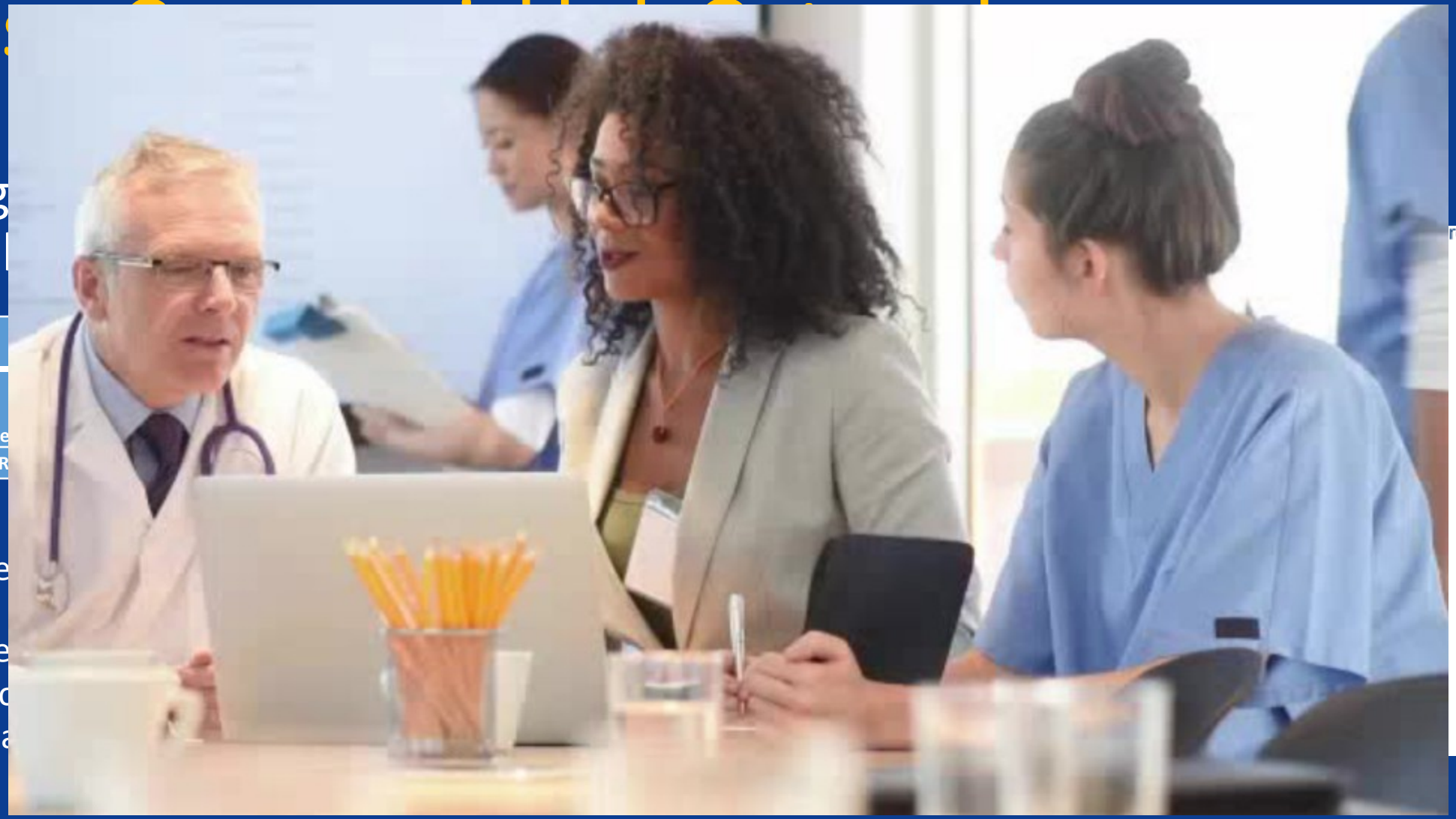
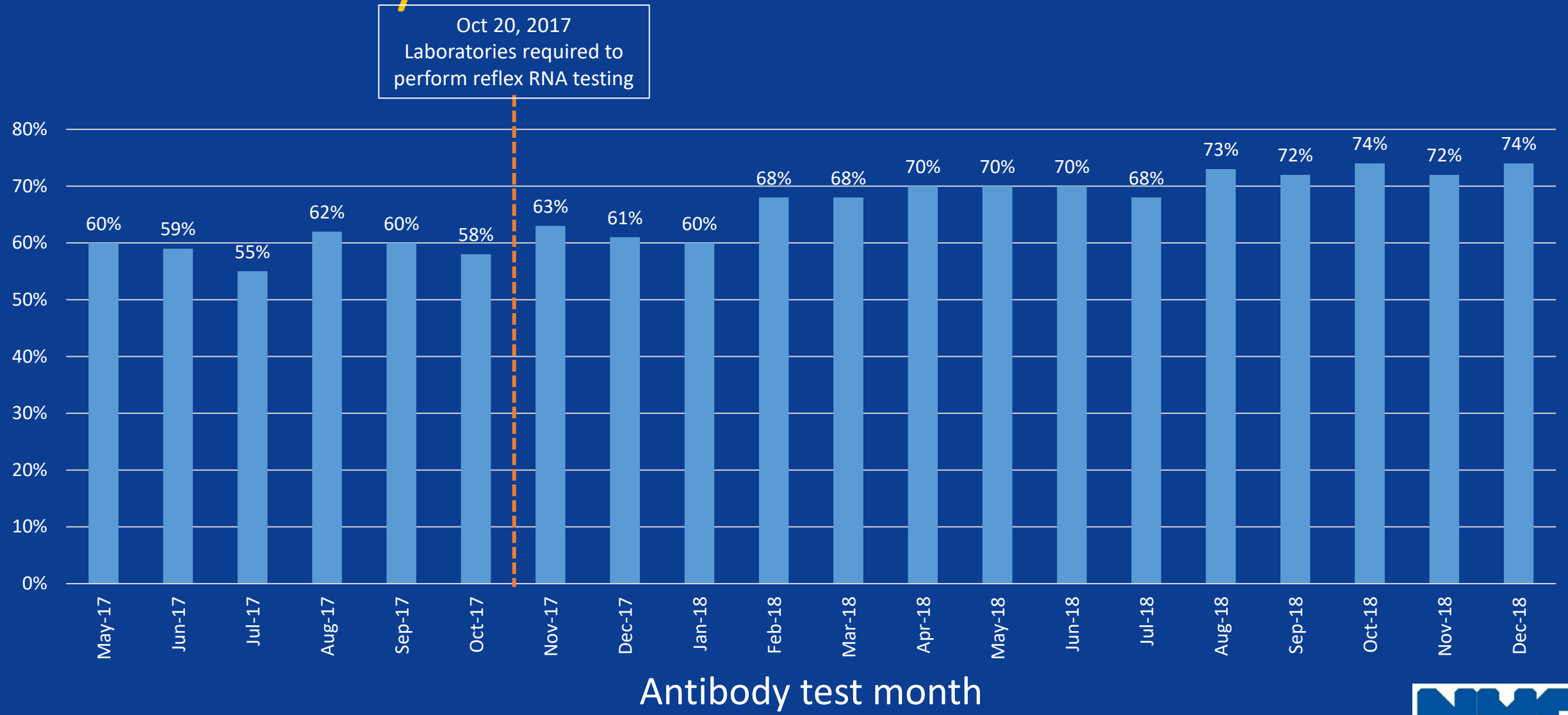


Health Department outreach to largest client: a “detox” facility with more than 1000 positive antibody results from May 2017-2018 and only 7% RNA confirmation: “We send five tubes of blood .”

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



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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  - Division of Disease Control Policy Staff
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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

American academy of Pediatrics Red Book 31st Edition 2018-2021
https://aidsinfo.nih.gov/guidelines/html/3/perinatal/509/diagnosis-of-hiv-infection-in-infants-and-children (Nov. 2017)

HIV diagnosis in infants and children

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

	Birth	2-3 weeks	4-8 weeks	8-10 weeks	4-6 months
Low risk		NAT	NAT		NAT
Higher risk	NAT	NAT	NAT	NAT	NAT

American academy of Pediatrics Red Book 31st Edition 2018-2021
https://aidsinfo.nih.gov/guidelines/html/3/perinatal/509/diagnosis-of-hiv-infection-in-infants-and-children (Nov. 2017)

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

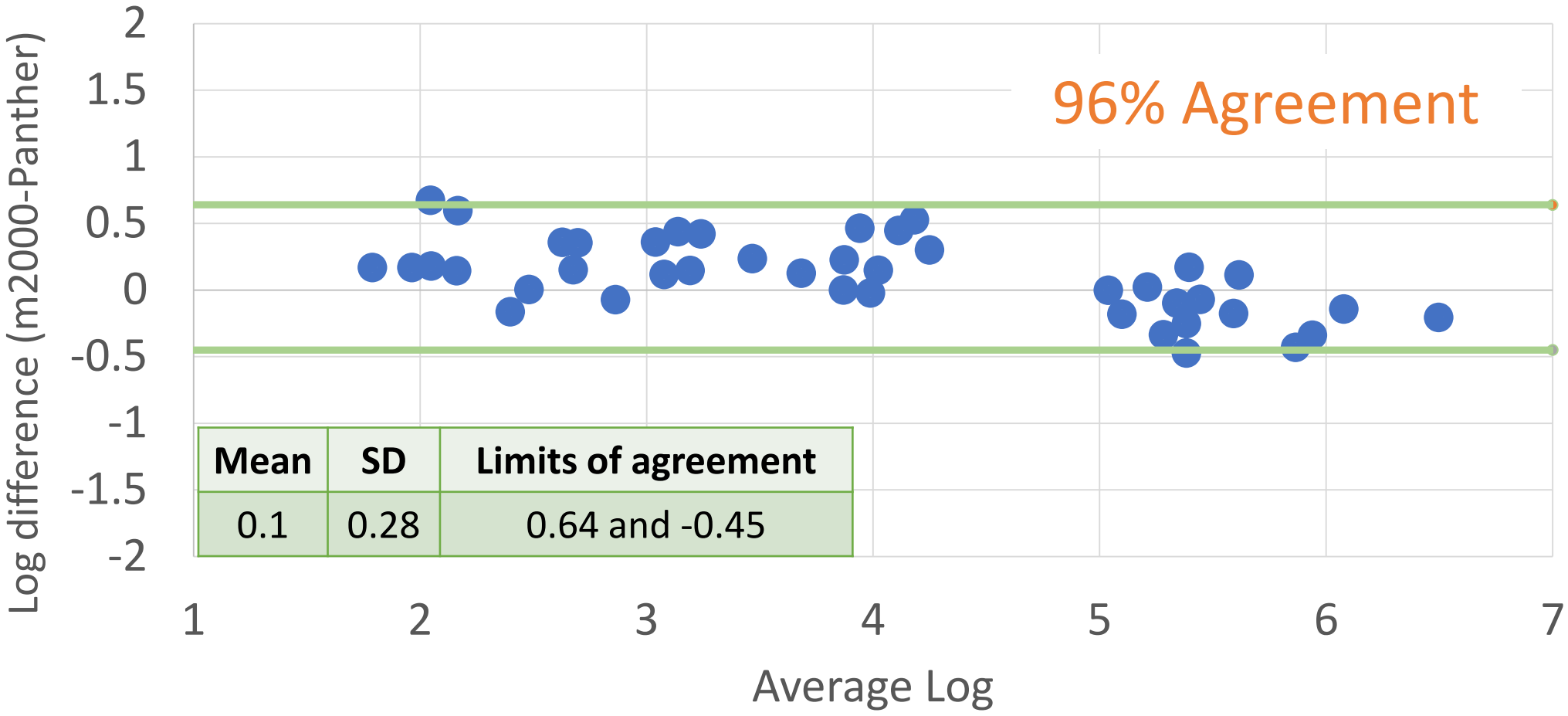
Run 1 x week

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

https://www.businesswire.com/news/home/20190214005129/en/

Viral load Comparison



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

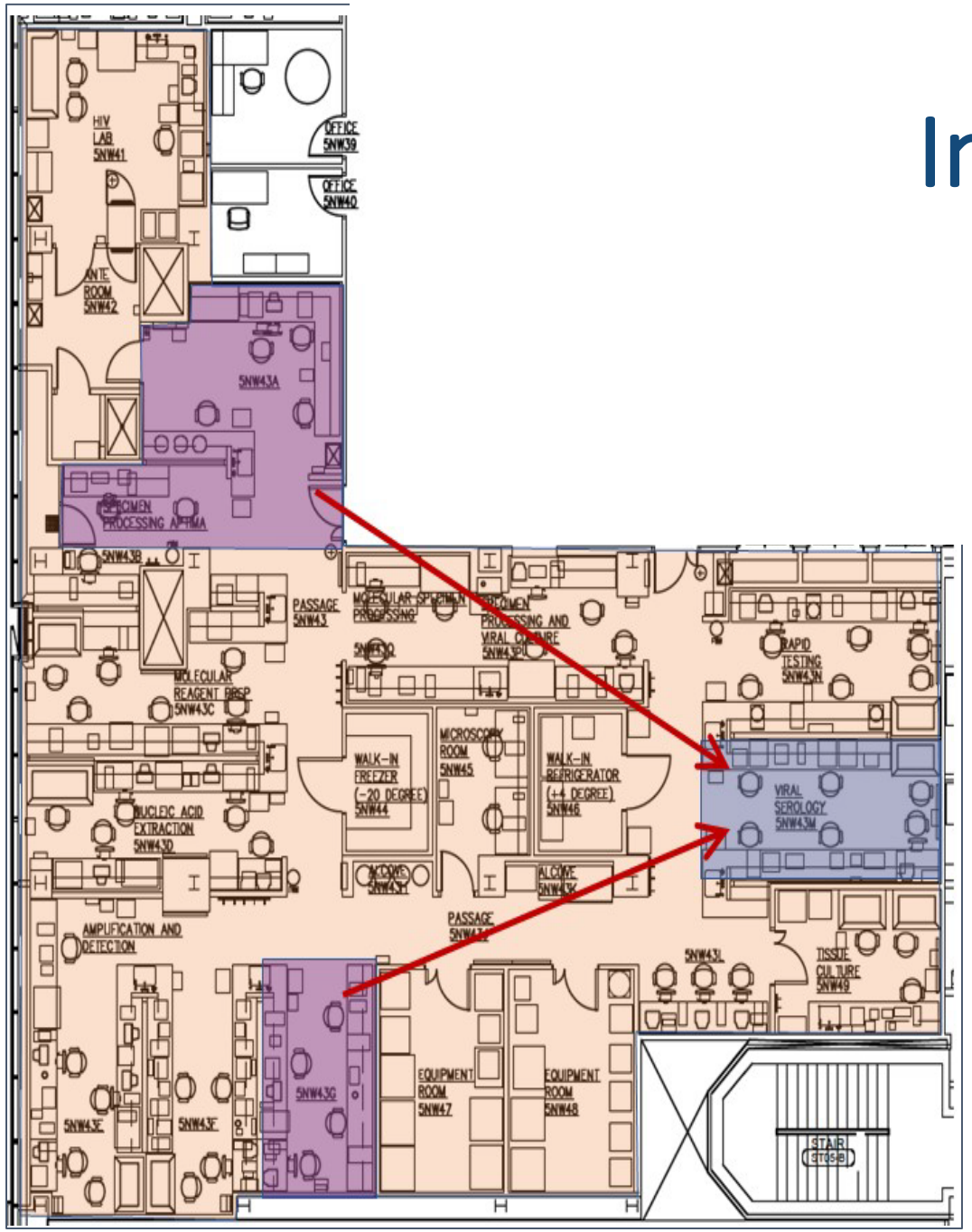
Run Daily (non-STAT)

Panther (Quant)

Sample Volume: 700µL

Plasma

Run 1 x week (ASAP)



Impact

- 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.

<u>Laboratory-based Tests</u>

Antibody screening

Antibody-antigen screening

Supplemental testing

- Geenius
- Western Blot

p24 assays

Qualitative RNA

Quantitative RNA (viral load)

<u>Point-of-Care Tests</u>

Oral fluid antibody

Fingerstick antibody

Fingerstick antigen-antibody

<u>Home collection/self-tests</u>

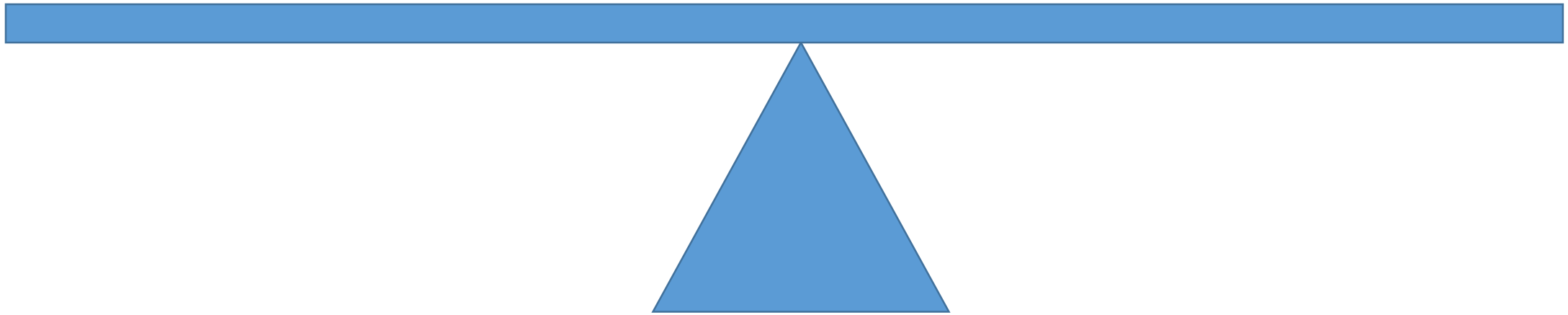
Current state of HIV screening and diagnostic tests in the U.S.

Laboratory-based Tests

More accurate testing

Point-of-Care Tests

More people get results



Product characteristics of POC NAT

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

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

HIV-1 viral load threshold	Finger stick whole blood	Venipuncture whole blood	Previously frozen plasma
≥50 copies/mL	22/23 = **96%**	42/43 = **98%**	13/25 = **52%**
≥400 copies/mL	20/21 = **95%**	35/36 = **97%**	13/18 = **72%**
≥700 copies/mL	18/19 = **95%**	32/33 = **97%**	12/15 = **80%**
≥1,000 copies/mL	18/18 = **100%**	29/29 = **100%**	9/11 = **82%**
≥2,000 copies/mL	16/16 = **100%**	26/26 = **100%**	7/8 = **88%**
≥3,000 copies/mL	15/15 = **100%**	25/25 = **100%**	7/7 = **100%**

“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

	Intervention N=195	**Standard-of-care N=195**	**Absolute risk difference**	
Primary endpoint (composite)	89.7%	75.9%	13.9% (95% CI 6.4-21.2%)	p<.001
HIV RNA <200	93.3%	83.1%	10.3%	p=.003
Receipt of ART at research clinic	92.3%	84.6%	7.7%	p=.03

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?

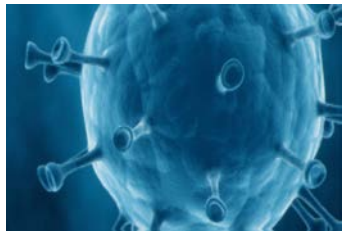
Would results be similar in the U.S.?

How do we integrate other novel POC testing

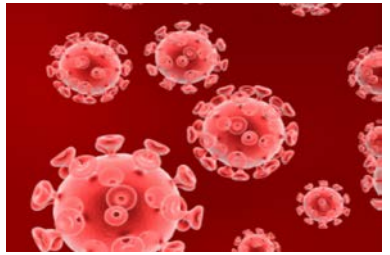
POC tenofovir tests

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?