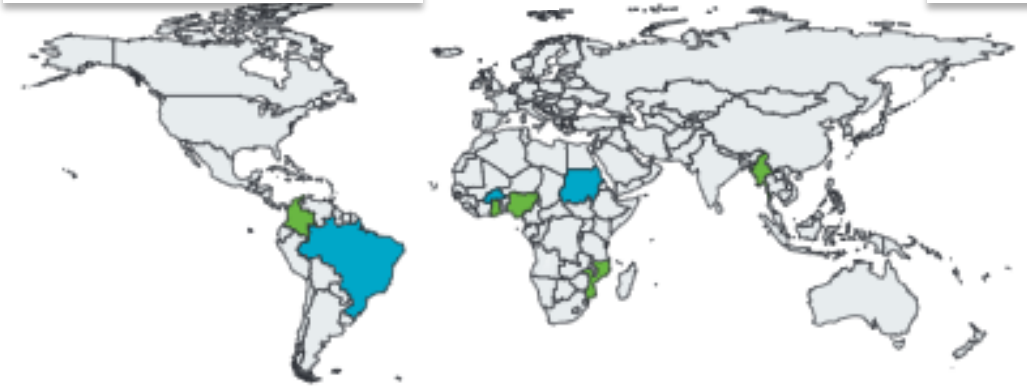
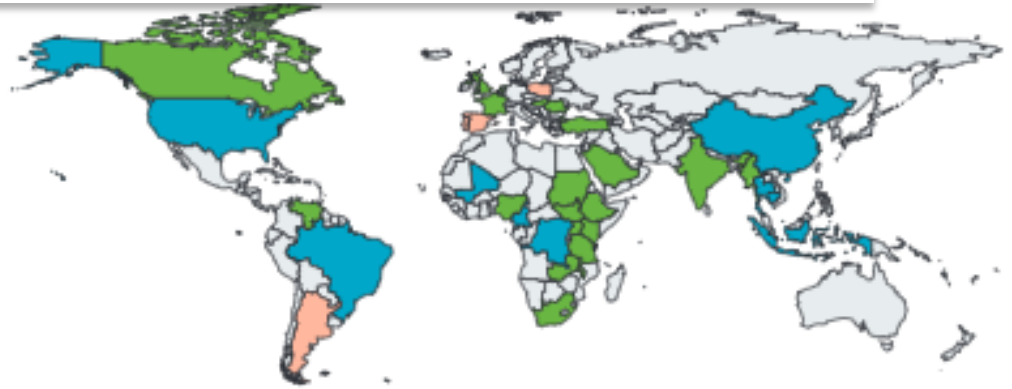
Global Prevalence of HIV-HCV Coinfections

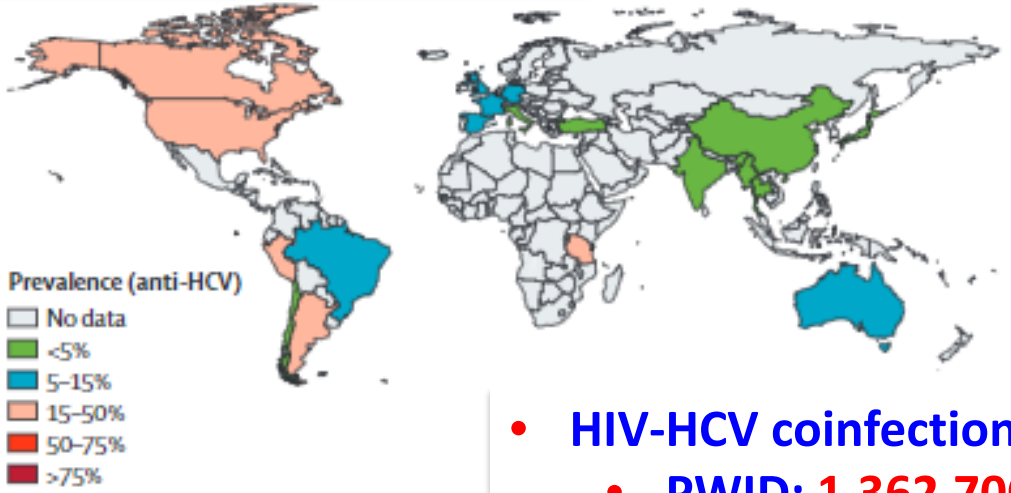
General population **2.4%**



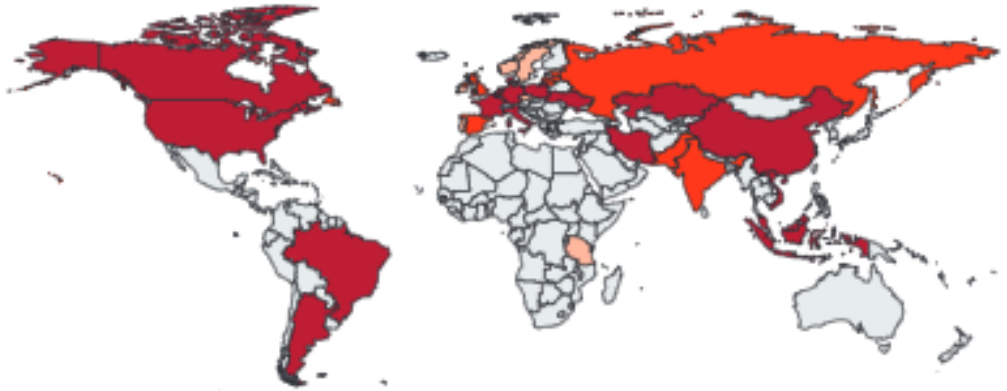
People living with HIV (heterosexual exposure & pregnant women) **4.0%**



Men who have sex with men **6.4%**



People who inject drugs **82.4%**



- **HIV-HCV coinfection: 2,278,400**
  - **PWID: 1,362,700**

Lancet Infect Dis 2016; 16: 797–808

HIV-HCV Coinfection in United States

- Of people with HIV about 25% are coinfected with HCV
- Nearly 75% of PWID with HIV are infected with HCV
- HIV/HCV coinfection more than triples the risk for liver disease, liver failure, and liver-related death

https://www.cdc.gov/hiv/pdf/library/factsheets/hiv-viral-hepatitis.pdf

Page updated June 2017

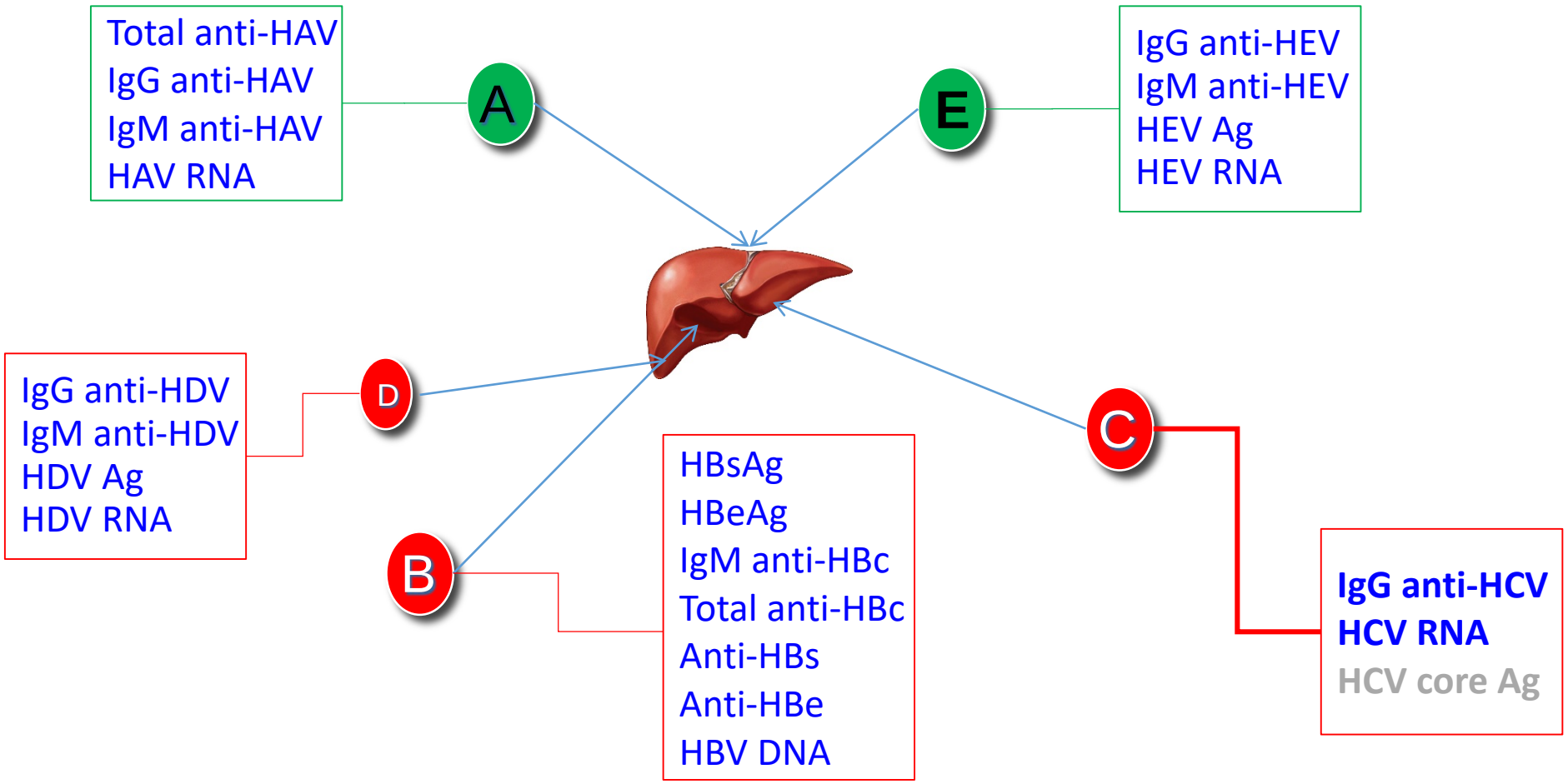
Hepatitis C Virus Infection: Diagnostic Methodologies

Saleem Kamili, PhD

Division of Viral Hepatitis
Centers for Disease Control and Prevention, Atlanta, GA

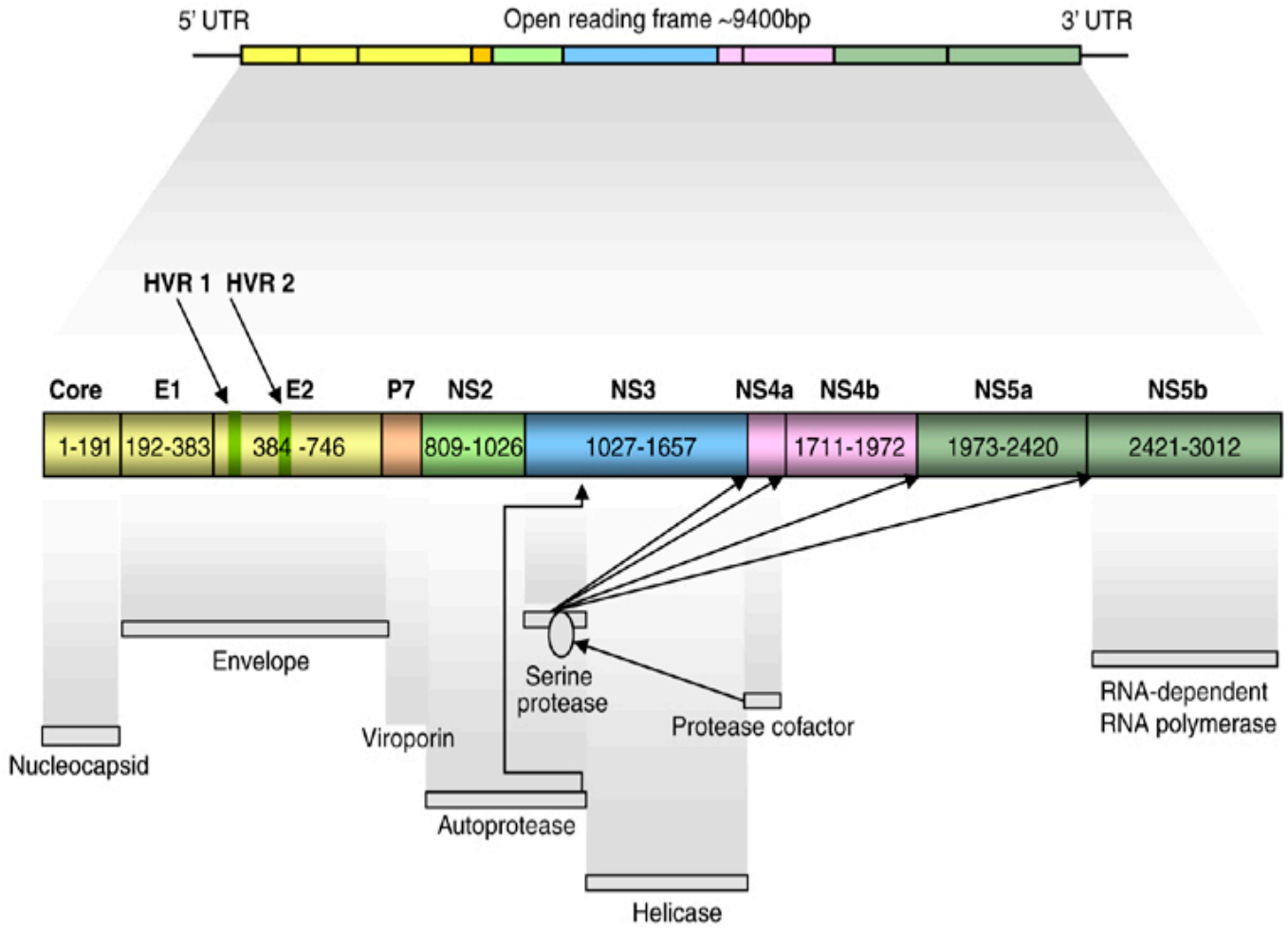
HIV Diagnostic Conference
25 March 2019

Viral Hepatitis: Diagnostic Landscape

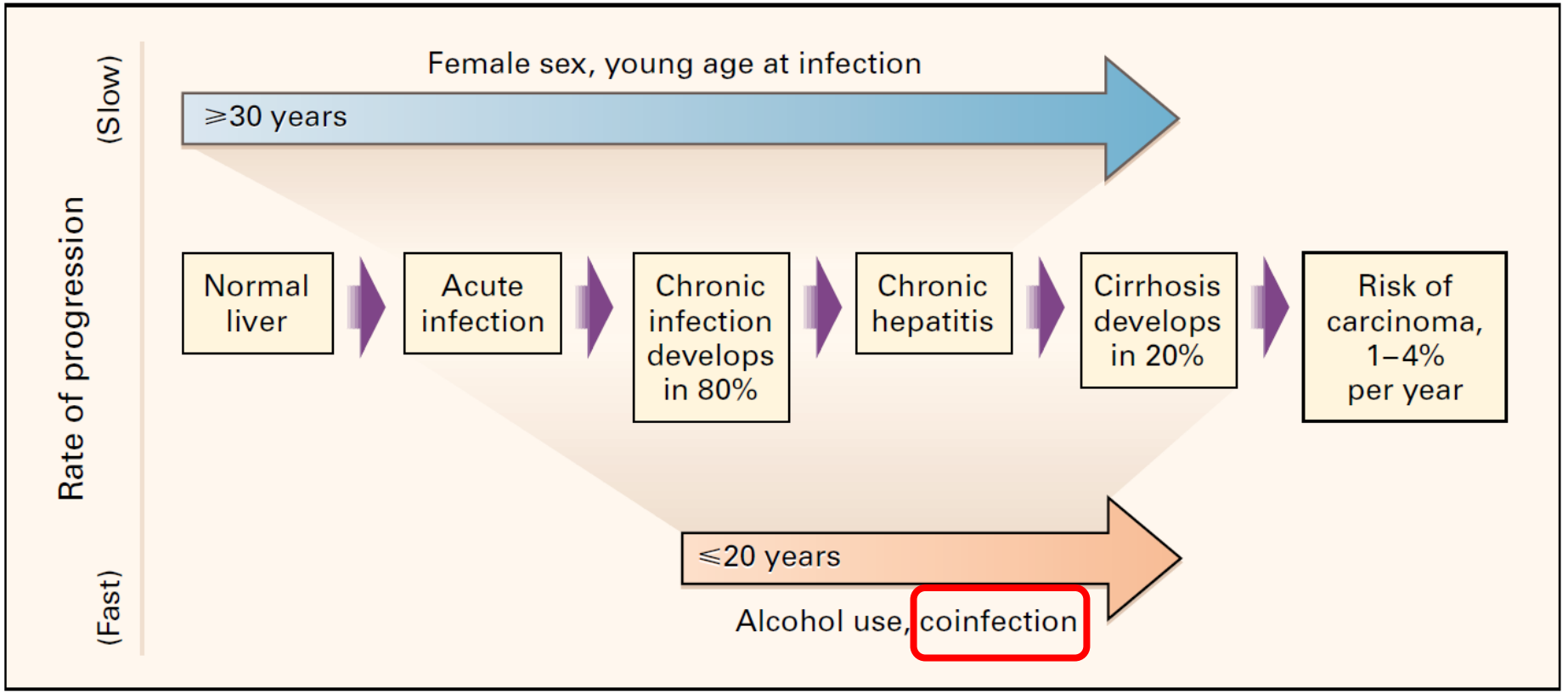


Hepatitis C Virus

- Identified in 1989
- Single, positive-stranded RNA virus
- Family *Flaviviridae*
- Seven genotypes
  - >60 subtypes

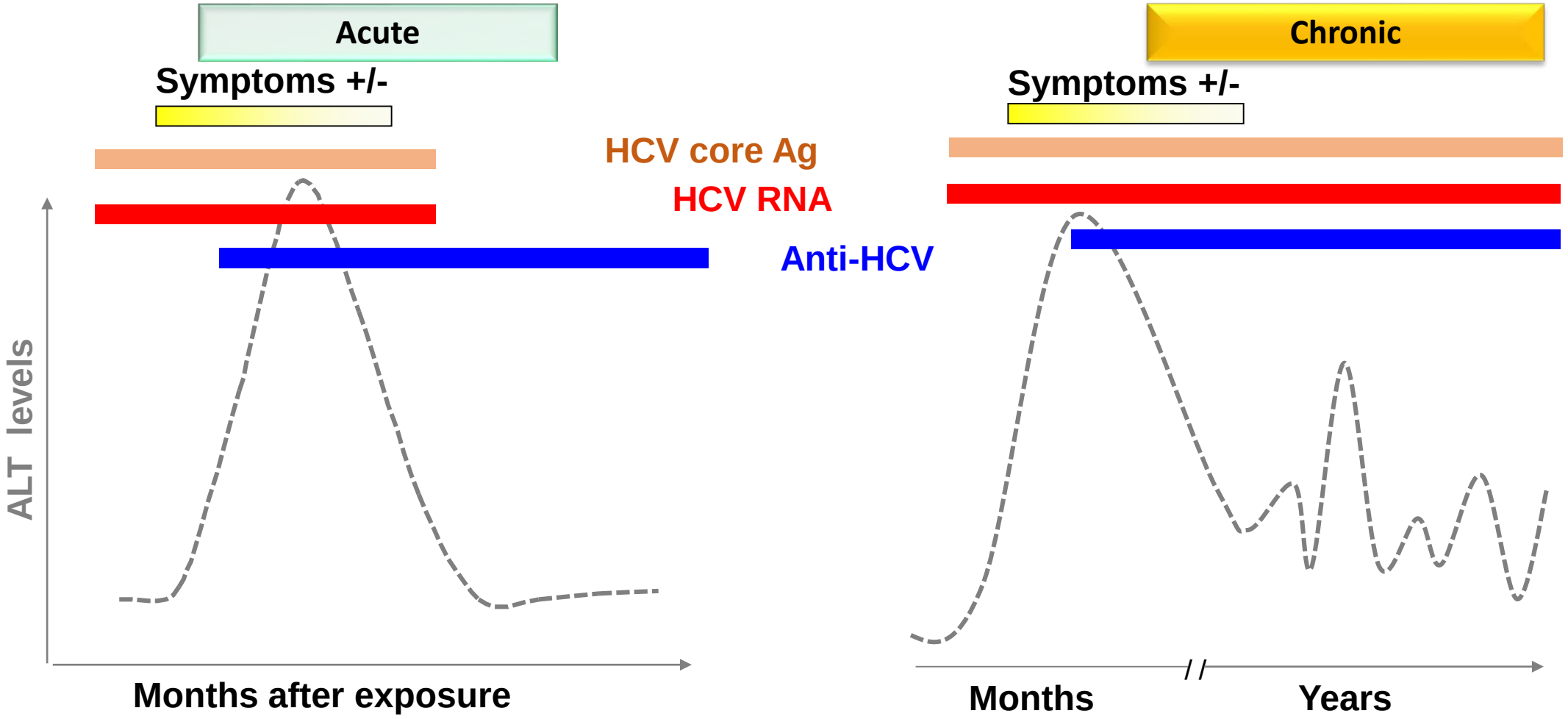


Natural History of HCV Infection

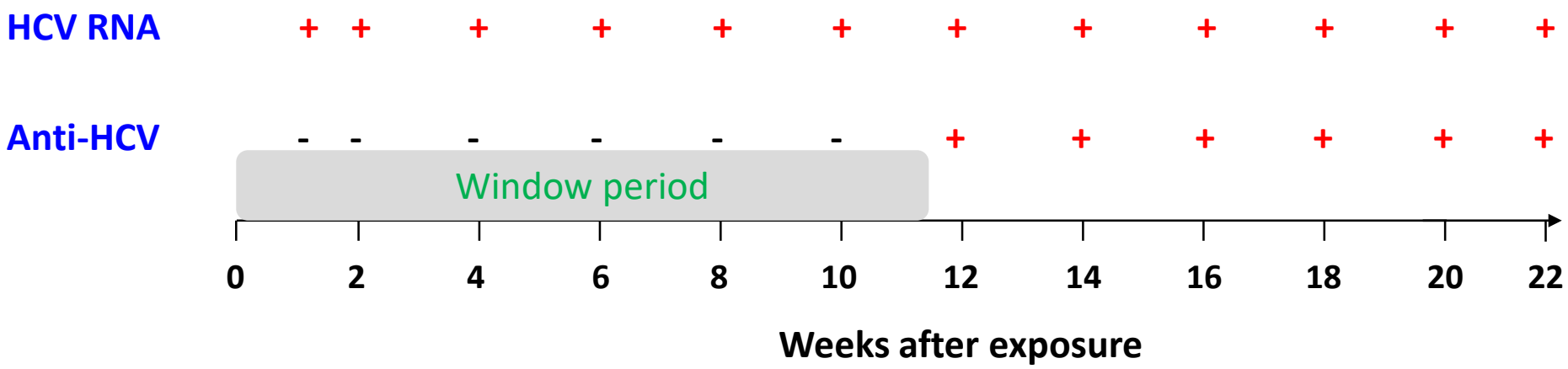


New Engl J Med 2001; 345: 41-52

Clinical and Serologic Course of HCV Infection



Diagnostic Markers of HCV Infection



Anti-HCV IgG Assays: Antigenic Composition

Screening Assays

Confirmatory Assays

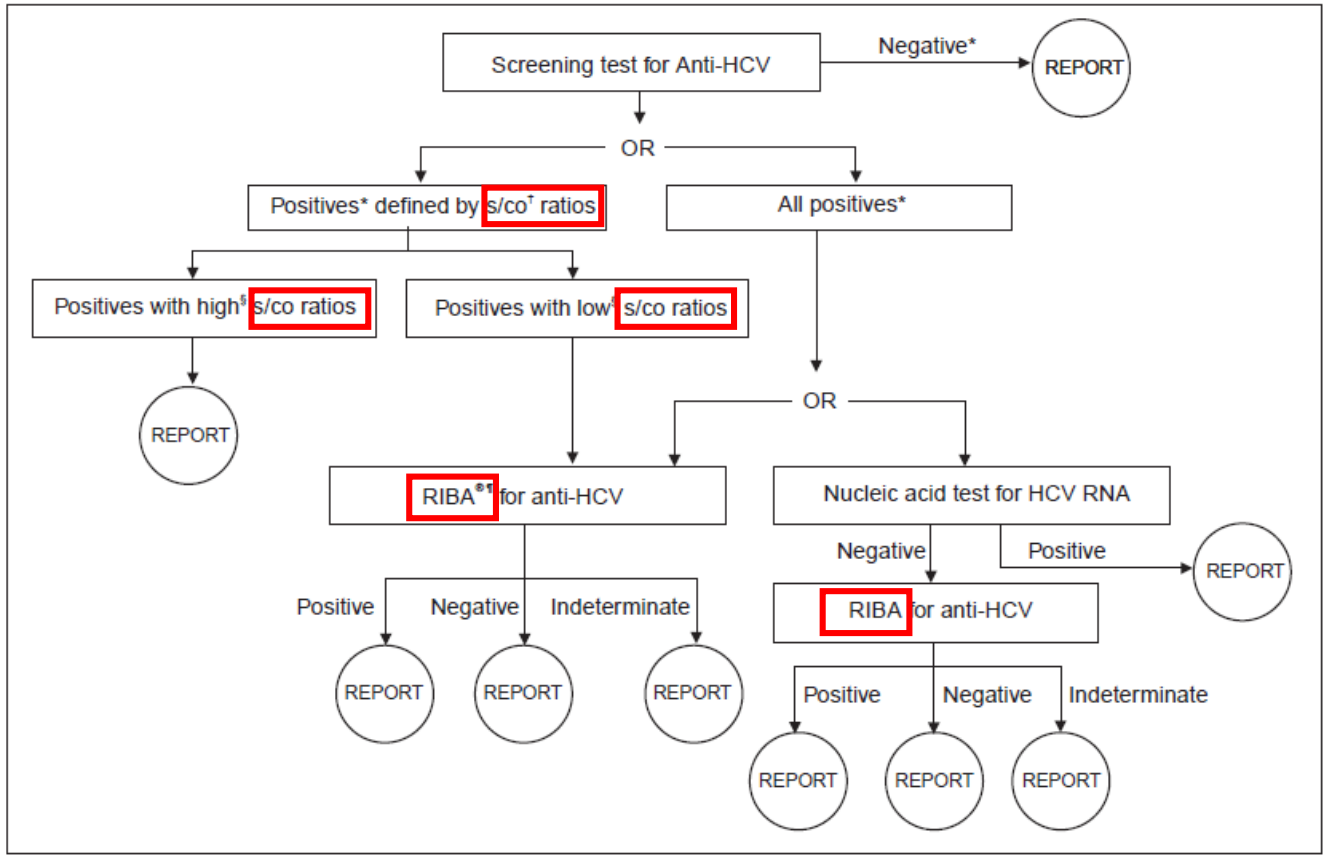
		Window period
EIA 1.0	c-100-3	22 wks
EIA 2.0	c22-3 c33-c c-100-3	13 wks
EIA 3.0	c22-c c33-c c-100-3 NS5	11 wks
RIBA 2.0	c22-3 c33-c c-100-3 5-1-1	
RIBA 3.0	c22-p c33-c c-100-p NS5	
INNO-LIA	C1 C2 E2 HVR1 NS3 NS4A NS4B NS5A	

Anti-HCV Assays

Manuf.	Device	PPA (Sensitivity) [95% CI]	NPA (Specificity) [95% CI]
Roche Diagnostics	Elecsys Anti-HCV II	**99.6%** [98.7%-99.96%]	98.8% [98.2%-99.3%]
OraSure Technologies	OraQuick HCV Rapid Antibody Test	**99.5%** [98.4%-99.9%]	99.0% [98.0%-99.6%]
		97.9% [96.9%-98.8%]	98.5% [97.5%-99.2%]
Roche Diagnostics	Elecsys Anti-HCV	**99.6%** [98.5%-99.5%]	96.9% [95.9%-97.7%]
Roche Diagnostics	Elecsys Anti-HCV	**99.6%** [98.5%-99.95%]	97.1% [96.2%-97.9%]
Roche Diagnostics	Elecsys Anti-HCV	**99.4%** [98.1%-99.9%]	97.2% [96.3%-98.0%]
Abbott Laboratories	ARCHITECT Anti-HCV	**99.53%** [97.4%-99.99%]	97.6% [96.5%-99.8%]
Siemens Healthcare	ADVIA Centaur HCV	**99.9%** [99.5%-100%]	97.5% [96.4%-98.3%]
Ortho-Clinical Diagnostics	VITROS Anti-HCV	**99.5%** [98.7%-99.9%]	98.2% [97.5%-98.8%]

Courtesy: Maria Garcia (FDA)

CDC's Guidelines for Hepatitis C Testing -2003



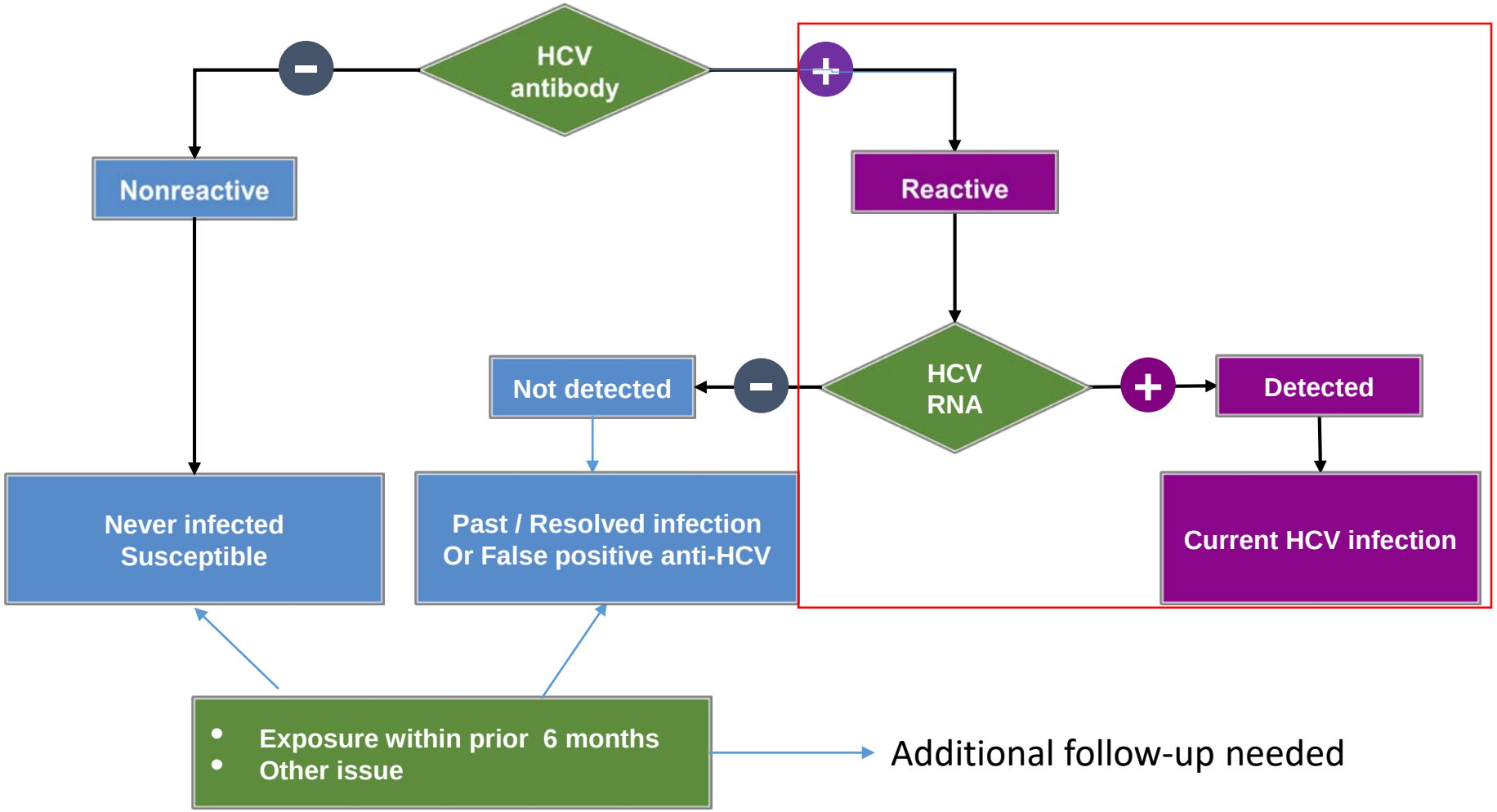
Manuf.	Device
Roche Diagnostics	Elecsys Anti-HCV II
OraSure Technologies	OraQuick HCV Rapid Antibody Test
Roche Diagnostics	Elecsys Anti-HCV
Roche Diagnostics	Elecsys Anti-HCV
Roche Diagnostics	Elecsys Anti-HCV
Abbott Laboratories	ARCHITECT Anti-HCV
Siemens Healthcare	ADVIA Centaur HCV
Ortho-Clinical Diagnostics	VITROS Anti-HCV

MMWR. 2003 /52 / RR-33

Updating HCV Testing Guidelines

- Identify actively infected HCV cases for referral to care
- New antivirals achieve >90% SVR
- Discontinuation of RIBA
- Availability of an FDA-approved rapid test for anti-HCV

Updated HCV Testing Guidelines - 2013



MMWR. 2013;62(18)

Challenges in Implementation of Updated Testing Guidelines

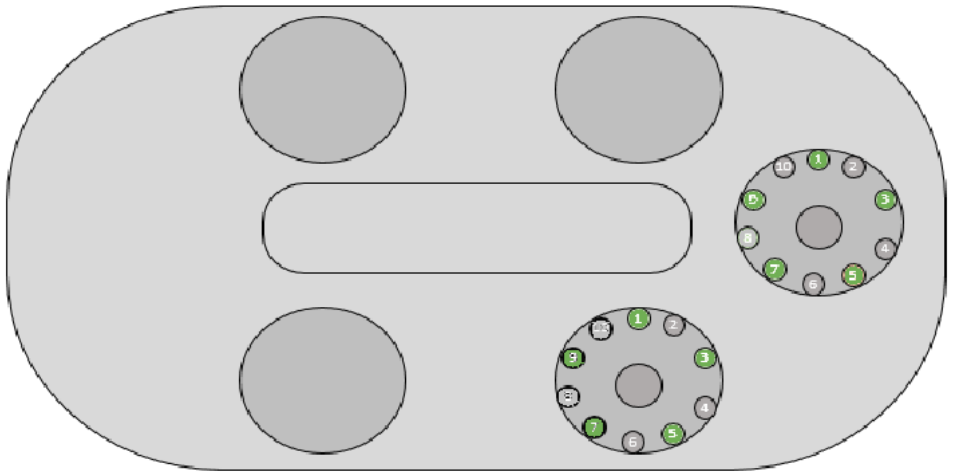
- All quantitative HCV RNA assays not approved for diagnostics
  - Logistics of reflex testing
    - Potential of contamination if same sample used for NAT?
  - Cost
  - Not all states have implemented reflex testing
- Requires expert technical staff, expensive kits
- Dedicated procedure areas
- Requires pristine serum/plasma samples
- *Not routinely performed in many clinical laboratories*

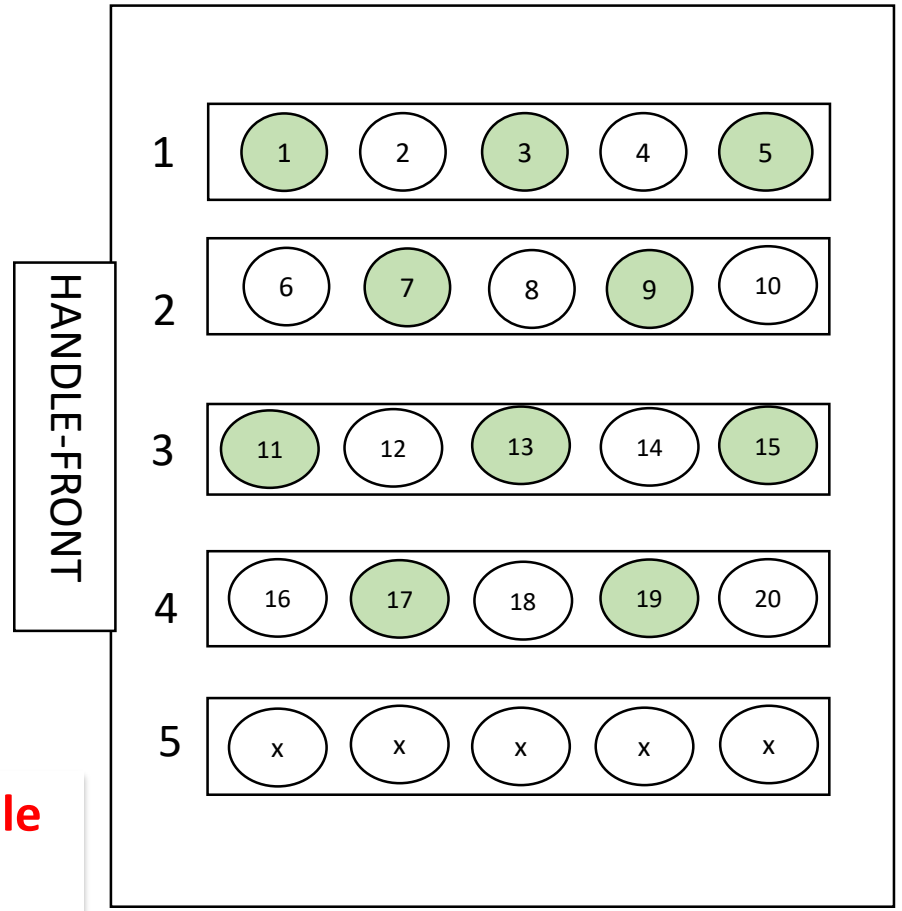
Reflex Testing to HCV RNA
Evaluation of Potential of Contamination

- Assessed potential to test same serum sample for HCV RNA used on various serology platforms
  - Ortho-Clinical Vitros Eci
  - Advia Centaur
  - Abbott ARCHITECT
  - Roche Elecsys
- HCV negative serum interspersed with low, mid and high positive specimens

CDC, unpublished data

Reflex Testing to HCV RNA
Evaluation of Potential of Contamination





Low level contamination in a system with fixed probe, while systems with disposable tips had no cross contamination

CDC, unpublished data

Performance of Currently Marketed HCV RNA Tests (Qualitative & Quantitative)

Manufacturer	Device	LoD[a] serum (IU/mL)	PPA (Sensitivity) [95% CI]	NPA (Specificity) [95% CI]
Hologic	Aptima HCV Quant Dx Assay	**3.4 IU/mL**	**98.8%** [96.7-99.6]	**100%** [95.4-100]
Roche Molecular	cobas-HCV	**13.7 IU/mL**	**100.0%** [97.5-100]	**98.8 %** [93.3-99.8]
Abbott Molecular	Abbott RealTime HCV[b]	**12 IU/mL**	**N/A[b]**	**N/A[b]**
Roche Molecular	COBAS AmpliPrep/ COBAS TaqMan HCV Test	**18 IU/mL**	**100.0%** [97.3-100]	**100.0%** [95.5-100]
Hologic (Gen-Probe)	VERSANT TM HCV RNA Qualitative Assay	**7.5 IU/mL**	**99.7% [d]**	**97.9% [d]**

[a] LoD as assessed with the WHO IS for HCV RNA (Genotype 1a); LoDs can vary by genotype
[b] Performance metrics were related to the ability of the test result to predict SRV (PPV/NPV)
[c] Diagnostic claim added to P060030 per PMA supplement
[d] Performance against another PCR assay

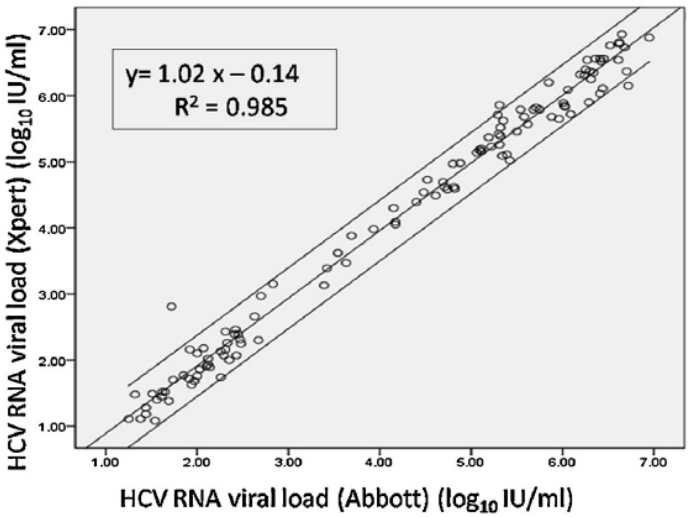
Courtesy: Silke Schlottmann (FDA)

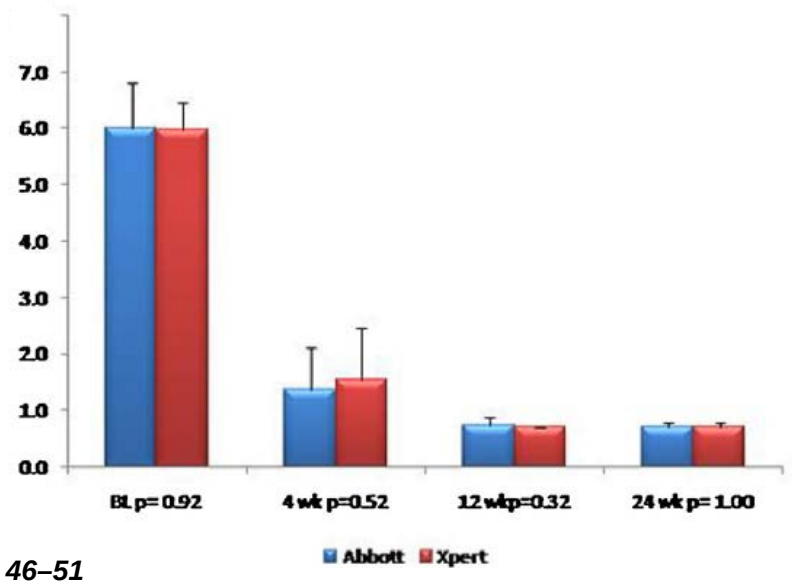
Sequencing of HCV Genome

- Genotyping
- Outbreak investigations
- Transmission studies
- Resistance-associated variants
- Recombinants
- Evolutionary studies
- Phylodynamics/phylogeography

- Technologies
  - Sanger
    - Whole genome
    - Amplicon
    - clones
  - NGS
    - Ion Torrent
    - MiSeq
    - PacBio

Point-of-care HCV RNA Test – the Xpert System





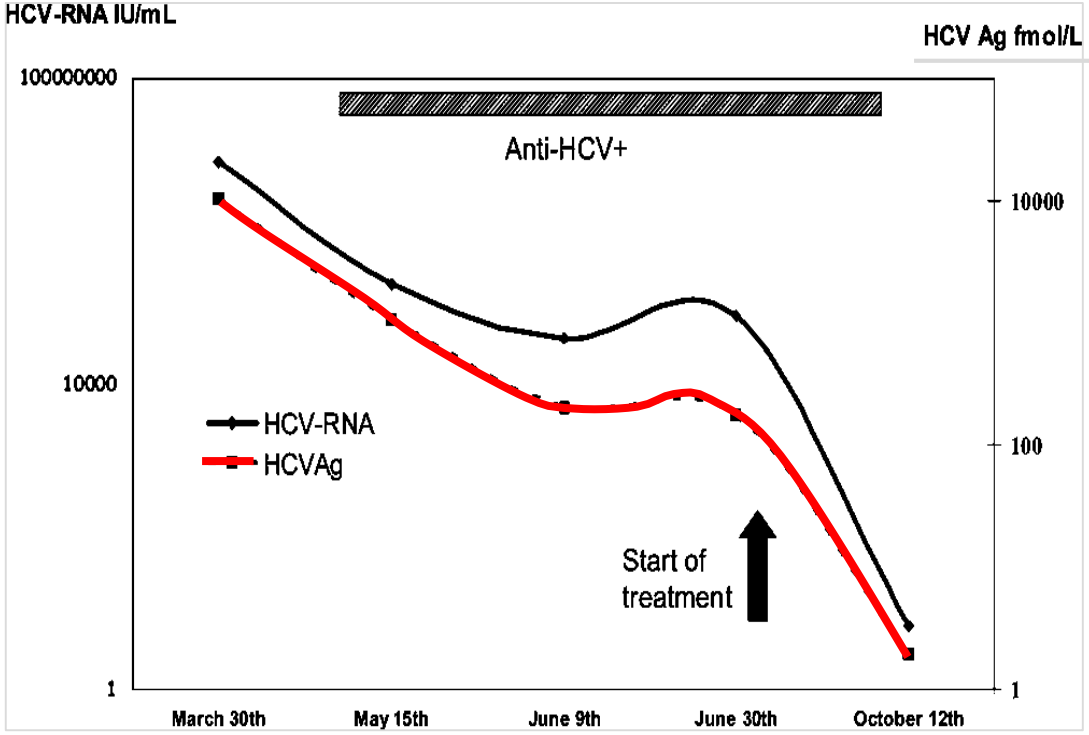
Journal of Clinical Virology 88 (2017) 46–51

Lancet Gastroenterol Hepatol. 2017 Jul;2(7):514-520. doi: 10.1016/S2468-1253(17)30075-4. Epub 2017 Apr 22.

Evaluation of the Xpert HCV Viral Load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study.

Grebely J[1], Lamoury FMJ[2], Hajarizadeh B[2], Mowat Y[2], Marshall AD[2], Bajis S[2], Marks P[2], Amin J[3], Smith J[4], Edwards M[5], Gorton C[6], Ezard N[7], Persing D[8], Kleman M[9], Cunningham P[10], Catlett B[10], Dore GJ[2], Applegate TL[2]; LiveRLife Study Group.

HCV Core Antigen



Medici MC et al. J Clin Virol 2011; 51: 264-269

Eval. panel: 551 serum samples

- **Pre-seroconversion: Anti-HCV - / HCV RNA +**
  - **Sensitivity 100%**
- **Post-seroconversion: Anti-HCV and HCV RNA +**
  - **Sensitivity ~ 94%**

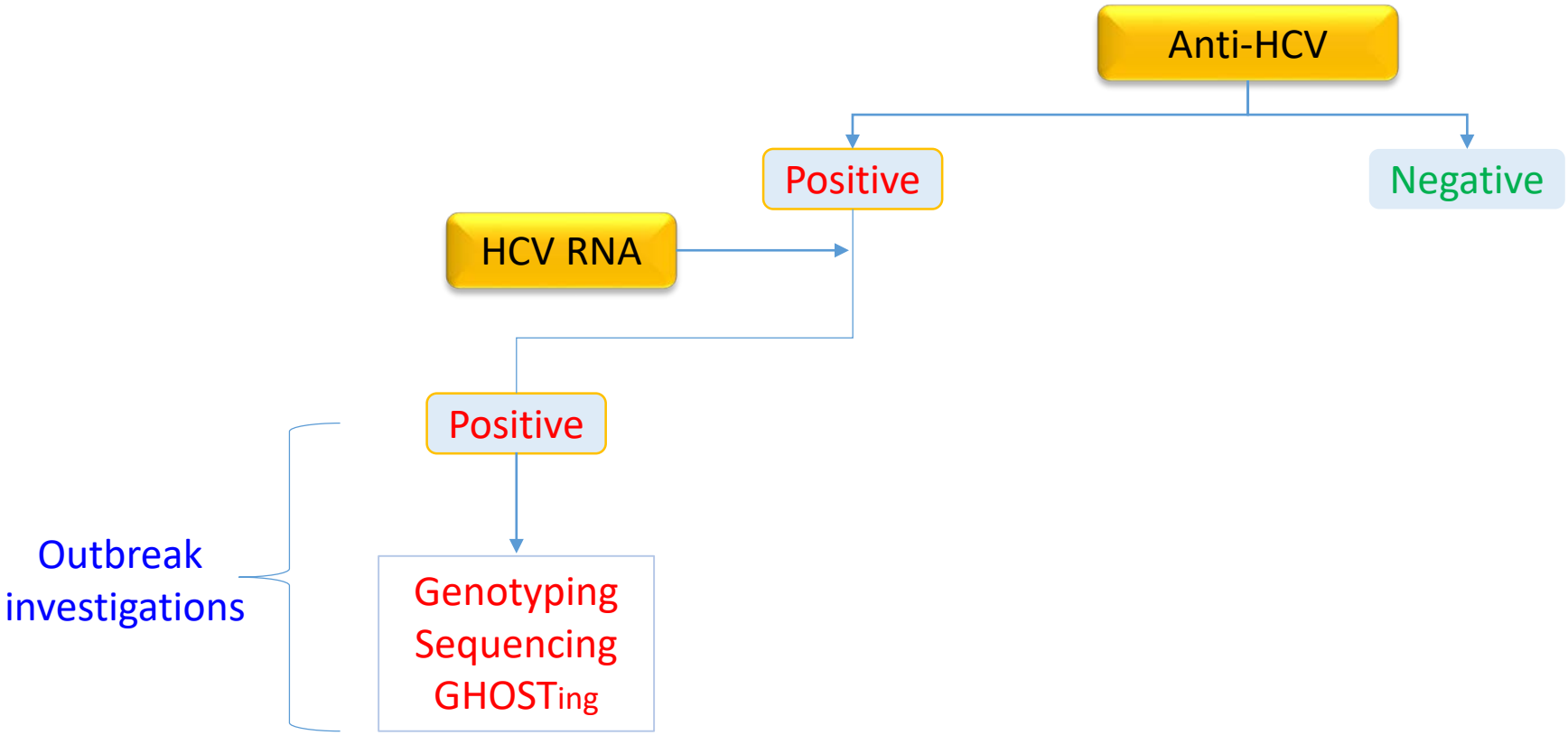
Hayden et al. J Clin Virol 2015;66:15-18

HCV Core Antigen

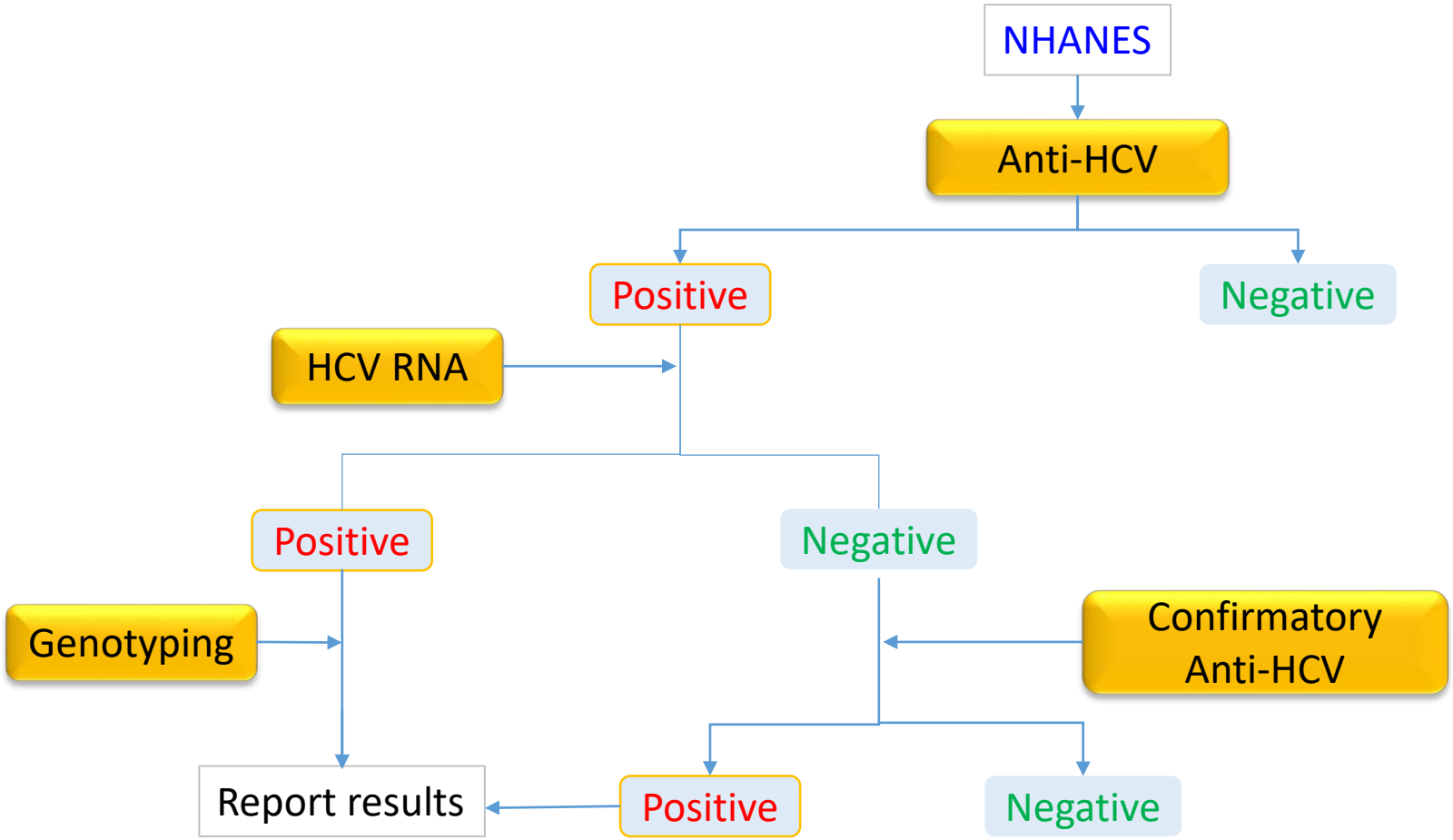
- Detectable within 1-2 weeks after exposure to HCV
- Broad linear range of detection by serologic assays
- Test samples
  - Serum, plasma, dried blood spots, urine
  - Lower sample volume than NAT
  - No pristine sample needed

- Undetectable when HCV RNA <2000 IU/ml
- Requires Abbott ARCHITECT i2000 platform

HCV Testing Algorithm for Diagnosis



HCV Testing Algorithm for Surveillance



Summary

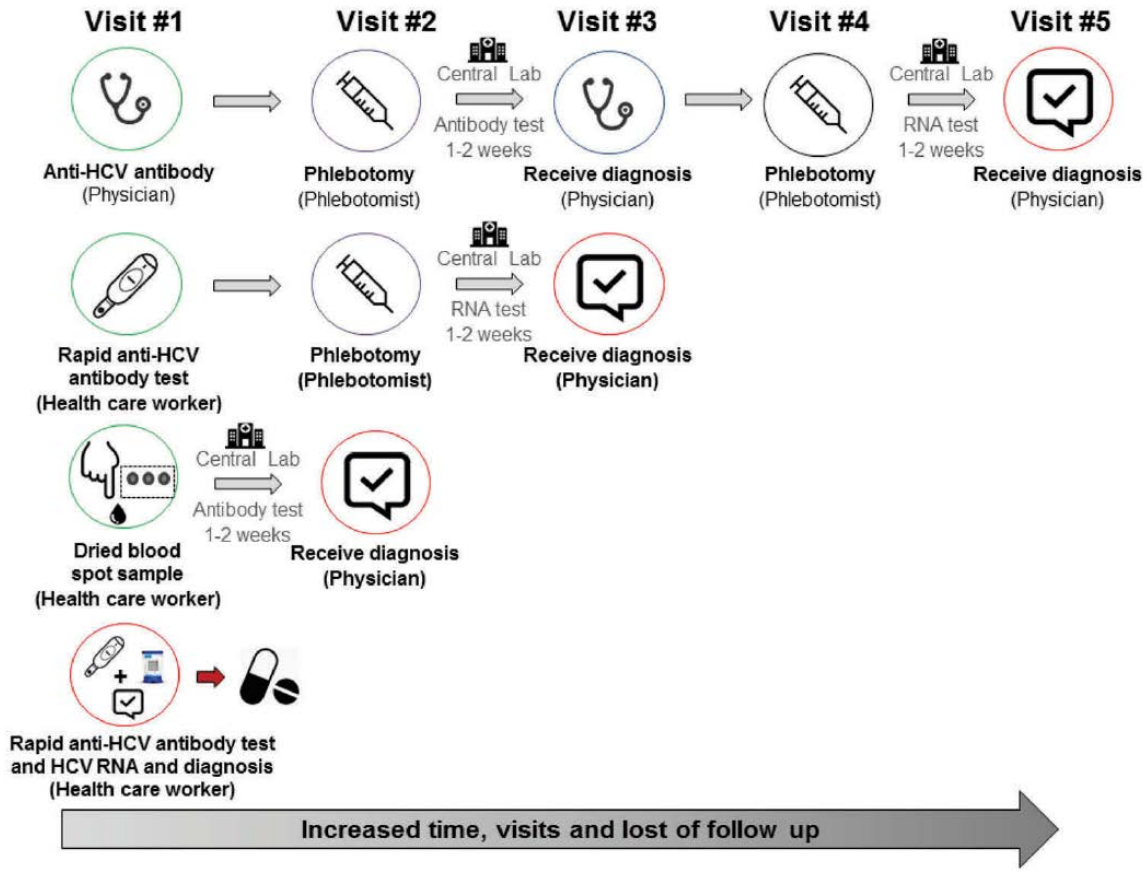
- The diagnostic landscape of hepatitis C is limited to just anti-HCV and HCV RNA; HCV core antigen
- Anti-HCV antibodies are present through acute, chronic, and resolved phases of infection
- HCV RNA (and HCV core antigen) remain(s) the only marker/s for diagnosing active infection
- NGS technologies provide unique opportunities for outbreak investigations, transmission studies, and molecular surveillance of HCV
- **A**ccurate, **A**ffordable and **A**ccessible assays for diagnosing current infections key to any elimination programs

Thank you!

Saleem Kamili, PhD

SKAMILI@CDC.GOV

In Pursuit of Single visit for hepatitis C Diagnosis



Expert Reviews of Mol Diag 2017;17: 1109–1115

"Diagnostic burn-out"

Country	HCV Epidemic	Diagnosed Before 2016	New HCV Diagnoses	Cures in 2016	Outcome Dx Burn-out
Brazil	1.8M	235,000 (13%)	10,000 (0.6%)	43,000 (2.4%)	2025
Spain	328,000	140,000 (43%)	5500 (1.7%)	25,000 (8%)	2022
Portugal	96,000	37,000 (39%)	1300 (1.3%)	4400 (4.6%)	2026

potential outcomes, based on 2016 data

AASLD 2017, Abstract #205
Andrew Hill, University of Liverpool