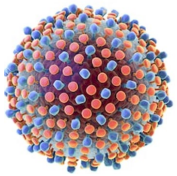
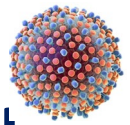
CHAC Viral Hepatitis Workgroup Approved Terms of Reference



This Workgroup will engage in evaluation activities & consult with experts in the field. The Workgroup will inform CHAC of findings & propose recommendations for CHAC to consider.

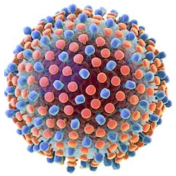
1. Objective: To help develop feasible guidance related to enhanced hepatitis C virus infection (HCV) diagnostics based on the following priorities:
    a. How can CDC best provide national leadership to accelerate the development, registration and implementation of rapid, point-of-care HCV RNA diagnostic testing?
    b. What partnerships should CDC strengthen to better guide the US in diagnosing our HCV-undiagnosed populations as quickly as possible to avert liver-related morbidity and mortality and stem rising HCV incidence?

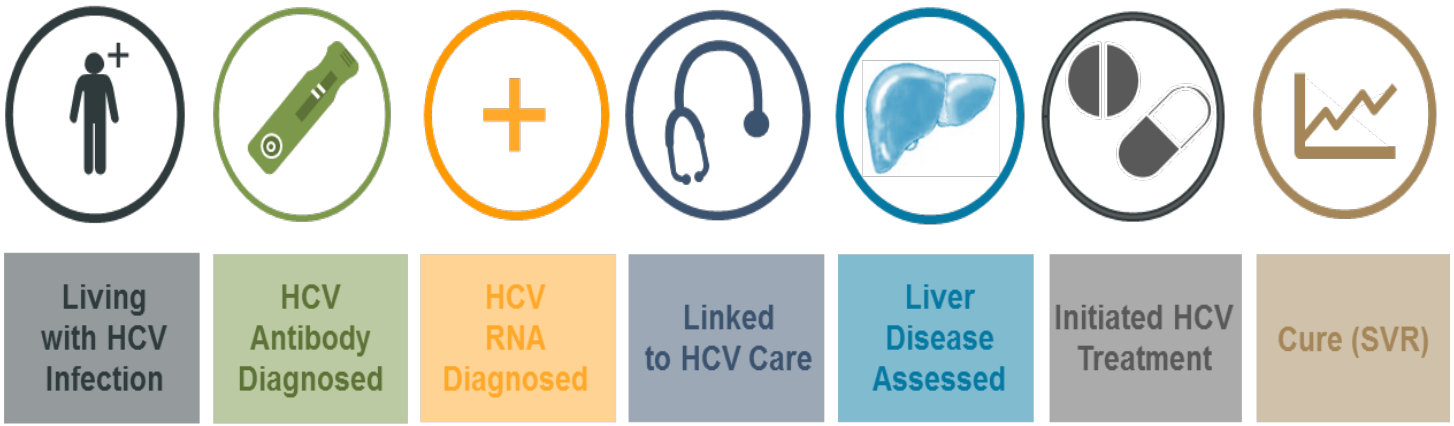
Next Steps in HCV Diagnostics: Background

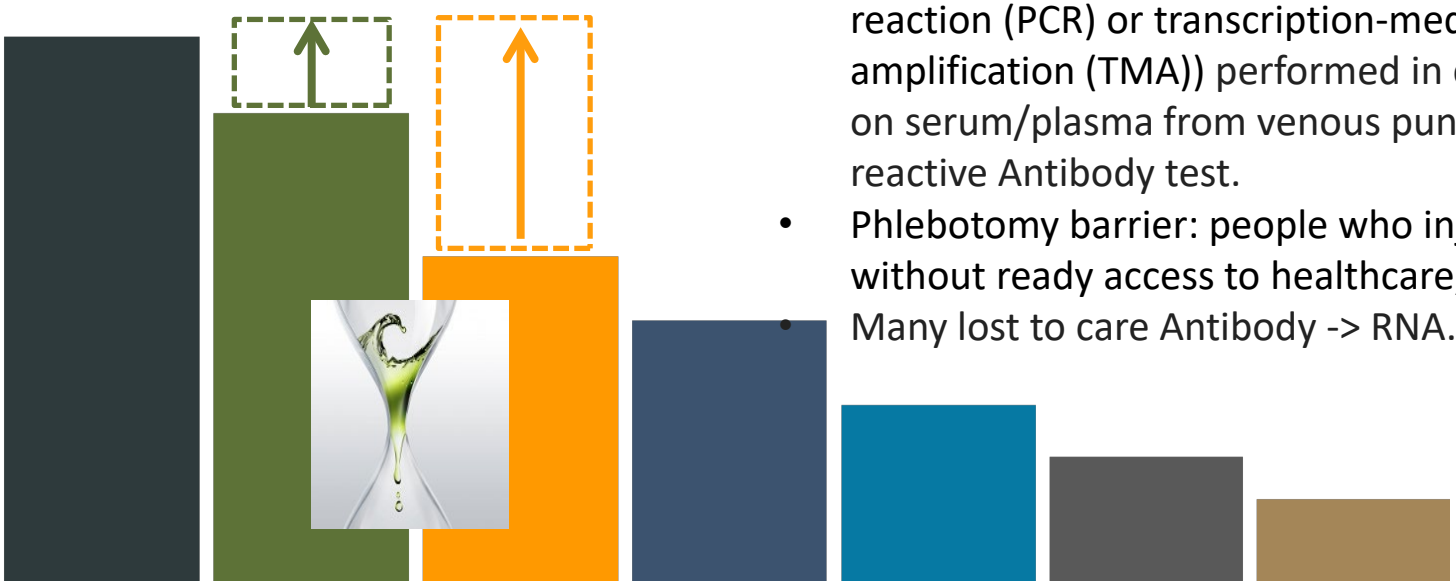


- HCV 2nd biggest infectious disease killer in US.
- 2014: Development of oral, well-tolerated, short duration, pan-genotypic direct-acting antivirals (DAAs) with high cure rates (>95%) paved the way to cure those with HCV.
  - 2019: Universal treatment (American Association for the Study of Liver Diseases/Infectious Diseases Society of America)
  - 2020: Universal screening (CDC, USPSTF)
- Impact of DAAs in decreasing HCV burden at population level contingent on level of testing and diagnosis.

2-step Diagnostic Process: Bottleneck in HCV Cascade to Cure







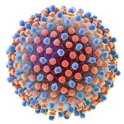
- HCV RNA testing (via real-time polymerase chain reaction (PCR) or transcription-mediated amplification (TMA)) performed in centralized lab on serum/plasma from venous puncture following reactive Antibody test.
- Phlebotomy barrier: people who inject drugs, people without ready access to healthcare, COVID-19.
- Many lost to care Antibody -> RNA.

Graphics adapted from Grebely J *Int J Drug Policy* 2015

Simplified HCV care delivery

- Other countries eliminate this barrier by providing rapid, point-of-care (POC), finger-prick RNA testing.
  - Molecular (HCV RNA) POC tests now available allow diagnosis at site of patient care using fingerstick capillary whole blood.
- 1-step diagnosis:
  - enables “test & treat” model of care.
  - enables self-testing: person collects her/his/their own specimen, interprets the result.

Applegate TL. *Infect Dis Clin North Am* 2018 Chevaliez S. *Expert Review Anti-Infective Therapy* 2019 Kpokiri EE. *OFID* 2020



Next step:
Make HCV RNA POC diagnostic testing available for wide-scale treatment

Diagnostic testing should be:

- Rapid: results in 1 hour or less
- Simple: require minimal equipment, training to perform
- Cost-effective
- Have same or better sensitivity and specificity characteristics as similar FDA-approved diagnostic tests currently available for HCV
- Utilize sample types that are minimally invasive (capillary whole blood)

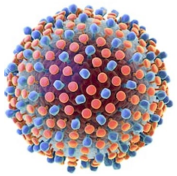
Chevaliez S. *Expert Review Anti-Infective Therapy* 2019

1st molecular POC test available

- Xpert® HCV Viral Load Fingerstick (Cepheid, Sunnyvale, CA).
- Detects and quantifies HCV RNA from 100 µL of capillary whole blood within 1 hour.
  - Utilizes single-use cartridge to extract, amplify and detect HCV by fluorescent reverse transcriptase PCR
- Performance comparable to that of other available HCV RNA assays, with a limit of quantification 100 IU/mL, limit of detection 35 IU/mL.

https://www.cepheid.com/uk/cepheid-solutions/clinical-ivd-tests/virology/xpert-hcv-viral-load

Point of Care HCV RNA testing: Xpert®

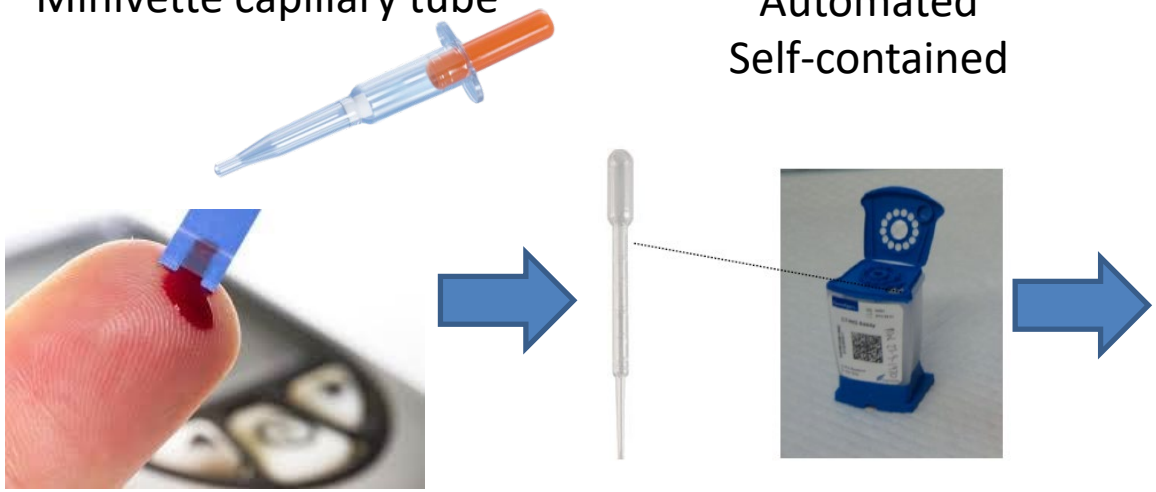


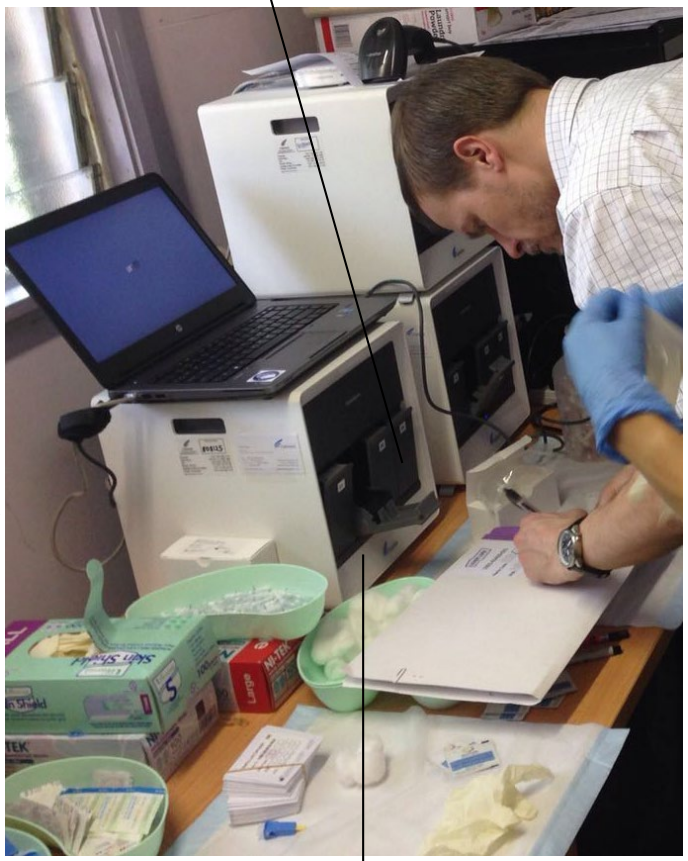
- Portable system, minimal training
- Test results in 60 min
- Specificity & Sensitivity ~100% for HCV quantification

Xpert machine

Finger-prick
Minivette capillary tube

Single-use test Cartridge
Automated
Self-contained





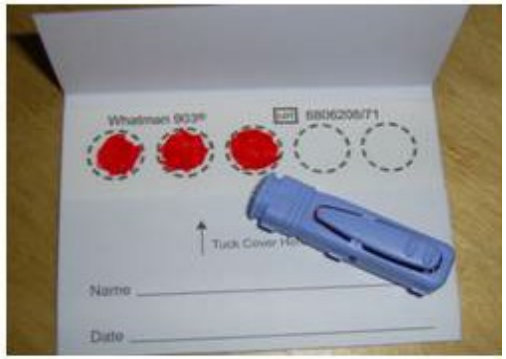
- Single platform for integration (HIV, HPV)
- Instrument costs ~ $17,000 (+ Service $4000/yr)
- Assays price range ~ $15 - $40

Xpert cartridge

2nd platform: Genedrive HCV IVD kit (Gene-drive Diagnostics, Manchester, UK)

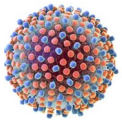
Lamoury FMJ. *J Infect Dis*. 2018

Alternative pathway: Dried Blood Spot (DBS) testing



+ Specimens collected by placing few drops of blood onto a filter paper which is desiccated at room temperature.
+ DBS can be then shipped (as non-hazardous materials using regular mail) to reference laboratories.
+ Easy to collect, painless, inexpensive.
- Results not immediate/loss to follow-up.

Asking CHAC to consider recommending:



1. National HCV testing strategy

   - Systematic 1-step HCV RNA-based testing strategy as a pillar of US national HCV elimination effort.

2. National, coordinated, efficient approach to development of optimal HCV diagnostics

   - Development, validation and regulatory approval of POC molecular fingerstick and DBS must be a priority to facilitate access and rapidly scale up diagnosis.

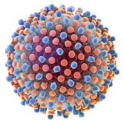
The NEW ENGLAND JOURNAL of MEDICINE

Covid-19 Molecular Diagnostic Testing — Lessons Learned

- When a public health threat warrants large-scale testing, it is more effective to authorize a small number of well-designed and validated tests manufactured in large quantities, than to simultaneously develop and authorize scores of diagnostics. Such diffuse efforts are an inefficient use of resources.
- A handful of test designs could be developed or identified by the US government alone or in collaboration with the testing community, then manufactured by the CDC, preset contract manufacturers, commercial manufacturers, and laboratories, which would speed up development, validation, authorization, production, launch, and testing.
- We need common approaches to validating test design and performance, regardless of whether there is an emergency. Our experience with Covid-19 highlights the need for a common legislative framework to ensure that all clinical tests are accurate and reliable.

Shuren J. and Stenzel T. *NEJM* 2020

Breakthrough HCV diagnostics should not be priced so that they cannot meet public health need

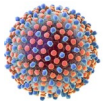


- Some things are simply too important to public health to leave their distribution to the private interests vying against each other in the US healthcare system.
- Transparent collaborations are required to understand relationships and costs/mark-ups associated with diagnostic companies, distributors, service providers and government, and to help develop mechanisms to control end-prices/volume pricing.
- Precedent: Government action on medicines – legislation
  - Allow subset payers join together, commit to broad strategy, lower prices (Ryan White ADAP)
  - Government purchases the meds (Vaccines for Children program)
  - Government manufactures without regard to pharma patents (anthrax/cipro)

Conti R. *JAMA* 2016

2. Continued. National approach to development HCV diagnostics

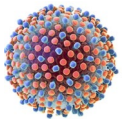
Workgroup considerations for CHAC



- Encourage CDC to take leadership role regarding steps to streamline transparent processes to expedite assay approval.
- Ask FDA to update CHAC on progress of HCV diagnostics, down-classification from Class III to Class II, what is needed to approve self-administered rapid RNA testing.
- Invite manufacturers to CHAC meeting to present on their technologies -- may encourage them to pursue FDA-approval.
- Encourage inter-agency collaboration between CDC, FDA, HHS
  - Regarding down-classification of HCV molecular tests and need for manufacturers to pursue FDA-approval.
  - As inaccurate results pose a high risk to public safety:
    - Ensure that diagnostic assays rigorously assessed during review.
    - Support visibility into accuracy to consolidate market around handful of high-performing diagnostic tests.
    - Promote quality assurance programs and processes for oversight of POC testing at federal level to ensure high, sustainable performance.

Nuzzo J. *JAMA* 2020

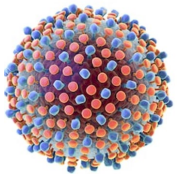
3. Do not delay this process due to the COVID-19 pandemic



- Self-testing for HCV outside clinical settings is particularly advantageous in situations with restricted movement, as seen under COVID-19, where access to health care services and diagnostic testing become more limited.

Kpokiri EE. *OFID* 2020

Acknowledgements
Viral Hepatitis Workgroup Members



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