



Reflex RNA testing on hepatitis C antibody positive samples: is it being adopted?

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INTRODUCTION

Hepatitis C (HCV) is a blood-borne virus with an estimated 214,000 individuals chronically infected in the UK¹. Persons with chronic HCV infection are at increased risk of HCV related end stage liver disease and primary liver cancer, the mortality rates of which have doubled over the last 10 years¹.

Hepatitis C virus antibody testing (anti-HCV), the first-line diagnostic test, does not differentiate between current and past HCV infections. As a result, RNA testing is required for assigning current HCV status, so they may be appropriately linked to, and engaged in, care. UK public health guidelines on HCV-testing, by the National Institute for Health and Care Excellence (NICE) in 2012, state that commissioners should ensure that laboratories automatically test anti-HCV positive samples for the presence of HCV RNA (reflex testing), or refer the sample to a laboratory which can perform this test². However, as an RNA test is more expensive than an anti-HCV test, current contracts often prohibit automatic RNA testing unless there is a specific clinical request. We investigated the distribution of RNA testing within the Sentinel Surveillance of Blood Borne Virus Testing (SSBBV) in England.

METHODS

All anti-HCV and RNA tests between 2008 and 2014 were extracted from SSBBV. Persons testing anti-HCV positive were identified, along with their first subsequent RNA test. A reflex test was defined as an RNA test within seven days of a positive anti-HCV test. Reflex testing on dried blood spot (DBS) samples and venous blood samples were compared.

Persons were linked to a treatment algorithm, which identifies persons with 3 sequential RNA tests within 390 days, indicative of treatment monitoring, to ascertain treatment rates and outcomes³.

A cost analysis of testing strategies was conducted on testing data from 2013, where the reflex testing pathway assumed anti-HCV testing in primary care and RNA testing on the same sample if anti-HCV positive, with subsequent referral to secondary care if RNA positive. The non-reflex pathway assumed anti-HCV testing in primary care, then referral to specialist secondary care services for assessment if anti-HCV positive, followed by HCV RNA testing on a second sample taken in secondary care.

RESULTS

RNA Testing

- Between 2008 and 2013, 3.8% (41,730/1,112,603) of individuals tested for anti-HCV were positive. Of whom 73.8% (30,792) had an RNA test within 12 months:
 - 71.4% (21,996) of whom were reflex tested, 24.8% (7,638) were RNA tested between one week and six months, and 3.8% (1,158) between six and 12 months.
- Among the 8,796 persons RNA tested between one week and 12 months:
 - 37.5% (1,332/3,553) of those RNA tested between one week and one month, 40.4% (1,763/4,085) of those RNA tested between one and six months and 46.7% (541/1,158) of those RNA tested between six and 12 months had additional anti-HCV tests before an RNA test.
 - Most subsequent tests (70.9%; 2,873) occurred in the same category of healthcare service as the first recorded positive anti-HCV.

Venous blood samples VS Dried Blood Spot (DBS) samples

- One laboratory provided both dried blood spot (DBS) testing and venous blood sample testing to SSBBV.
 - In those testing anti-HCV positive by DBS (2,378), 50.5% (1,201) were reflex tested, 3.2% (77) were RNA tested between one week and six months after their positive anti-HCV test, 1.3% (31) between six and 12 months and 45.0% (1,069) had no RNA test within 12 months.
 - Whereas, 47.1% (4,701/9,972) of persons tested with venous blood sample were reflex tested, 17.6% (1,760) were RNA tested between one week and six months after their positive anti-HCV test, 2.8% (284) between six and 12 months and 32.4% (3,227) had no RNA test within 12 months.

Predictors of Reflex Testing

- In a multivariate model, laboratory of test was the most important independent predictor of reflex RNA testing.
- Furthermore, reflex testing was more likely in specialist liver services (OR 3.4; 95% CI 3.0-3.8), prisons (OR 2.3; 95% CI 2.1-2.6), drug (OR 2.3; 95% CI 2.1-2.5) and specialist HIV services (OR 1.86; 95% CI 1.43-2.40) when compared to GP services, and
- Less likely in older persons (10 year increase: OR 0.96; 95% CI 0.94-0.98), females (OR 0.92; 95% CI 0.88-0.97) and in GUM services (OR 0.83; 95% CI 0.71-0.97).

Treatment and Outcomes

- Persons reflex tested received treatment more quickly than those persons RNA tested between one week and six months (167.5 days vs 282.5 days, $p < 0.0001$)
- However, a lower proportion of persons reflex tested received treatment (20.6% vs 31.1%, $p < 0.001$) and subsequently achieved SVR (65.4% vs 74.9%; $p < 0.001$).

Cost Comparison

- Table 1 shows the cost comparison if all persons were tested according to a reflex testing pathway or a non-reflex testing pathway in 2013.
 - The estimated annual savings gained from automatically RNA testing an anti-HCV positive sample was £166,500.
 - The savings are due to the reduction in the number of people being referred: from 6,001 in the non-reflex pathway, to 3,781 in the reflex pathway.

Table 1. Cost comparison of reflex and non-reflex pathway for persons diagnosed in 2013 England and reported to SSBBV

Non-reflex pathway	Unit cost (£)	Number of persons	Total Cost (£)
Anti-HCV test	7.4	236,185	1,747,769
Referral of Anti-HCV positives	75	6,001	450,075
HCV-RNA test	64.2	6,001	385,264
Total			2,583,108
Reflex pathway	Unit cost (£)	Number of persons	Total Cost (£)
Anti-HCV test	7.4	236,185	1,747,769
HCV-RNA test on Anti-HCV positives	64.2	6,001	385,264
Referral of HCV-RNA positives	75	3,781	283,575
Total			2,416,608

DISCUSSION

Overall, half of persons were RNA reflex tested, with the majority (71%) of persons having an RNA test within six months.

DBS samples had a lower proportion of persons having an RNA test within 12 months, which may be related to the setting of the test or insufficient information of protocols with regards RNA testing on anti-HCV positive DBS samples.

Wide variations in laboratory testing practices remain, and a significant proportion still do not reflex test samples. For example, reflex testing was less likely to occur in GP services. Persons reflex tested had shorter period to receiving treatment.

Significant efficiencies could be gained with the widespread adoption of reflex testing, by ensuring only those with a current HCV infection are referred to specialist care. Variation in reflex testing provision appears to follow the individual laboratory's contract. National guidance encourages commissioning for a clinically-relevant diagnosis, rather than a single test, and should inform contracts between healthcare providers and laboratories.

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