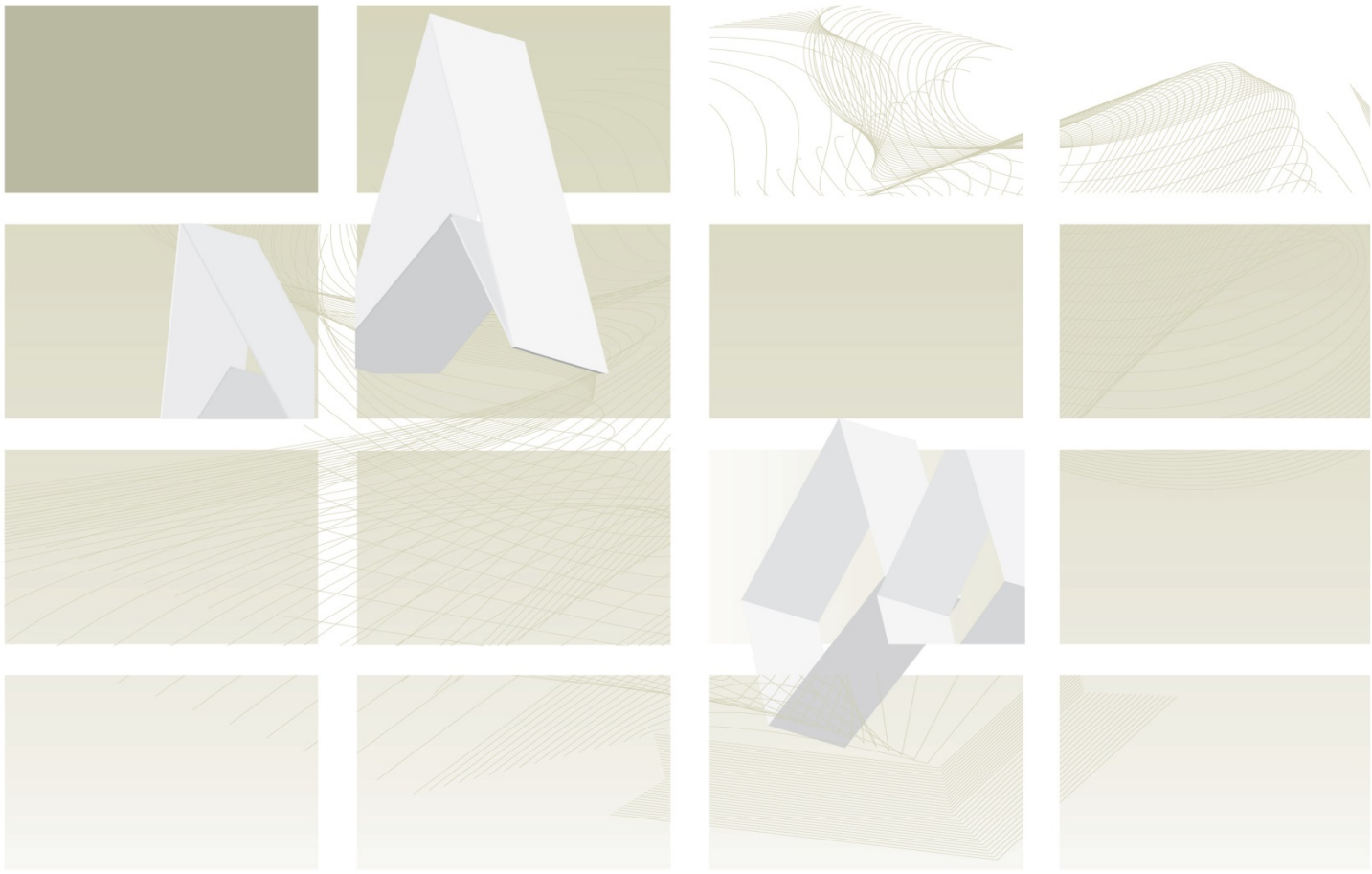
Public Health England

NHS

UK Standards for Microbiology Investigations

Review of users' comments received by Working group for microbiology standards in clinical virology/serology

V 5 Screening for hepatitis C infection



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"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

First consultation: 02/08/2013 – 30/08/2013

Version of document consulted on: V 5df+

Proposal for changes

Comment number	1		
Date received	07/08/2013	**Lab name**	Southampton PHE
Section	Algorithm page 8		
Comment			
a. For reactive PCR/antigen it would be better to state - ensure hepatitis A and B 'serostatus' are known NOT 'immunity'. b. For unreactive PCR/antigen suggest report only as 'No evidence of active HCV infection' is it necessary to do second antibody test? c. Also suggest following comment if antibody reactive/PCR negative 'Evidence of HCV infection at some time. There is no evidence of active infection as HCV RNA has not been detected. Please repeat to confirm the negative HCV RNA status. Please note HCV RNA can become intermittently undetectable, particularly early after infection.' d. If antibody equivocal/low level and PCR negative suggest 'Unable to differentiate between false EIA reaction or past HCV infection. Importantly, the negative HCV RNA result shows the infection is not active. Please repeat to confirm.'			
Financial barriers			
No.			
Recommended action	a. **NONE** The group agreed with the sentiment of this comment; however they felt that the term 'immunity' is sufficiently well understood. This wording was agreed by the UK virology community through the CVN. b. **NONE** It is necessary to do the second antibody test to check that the result is not a false negative. The patient may have had HCV infection at some point previously, and there is also the possibility of fluctuating viraemia. c. **NONE** This is a well written comment, but does not give advice on what to do. The group agreed to keep the comment as it was. d. **PARTIAL ACCEPT** Add 'No evidence of current activity' and 'Please send a repeat sample in 3-6 months' to the report box on the far right of the algorithm.		

Comment number	2		
Date received	09/08/2013	**Lab name**	Bristol PHL
Section	First section		
Comment			
a. A reactive combined antigen antibody assay sample is next tested for antigen or nucleic acid, and if latter negative report is issued as no evidence of active infection - that doesn't work if the original test was antigen reactive - then you have a discrepancy. b. Also, in footnote d the term 'less sensitive PCR' is used- needs defining as there is a minimum threshold for diagnostics.			
Evidence			
None.			
Recommended action	a. **ACCEPT** If antigen reactive in the combined Ag/Ab screening test followed by unreactive Ag, the result is discordant. The algorithm assumes the reactivity is Ab positive initially. Add a footnote to report box 'if antigen activity is unconfirmed (that is Ag +ve, followed by Ag – ve) investigate why'. b. **NONE** PCR sensitivity was discussed, but no minimum level was agreed.		

Comment number	3		
Date received	11/08/2013	**Lab name**	Nottingham
Section			
Comment			
Where do I start? a. I don't agree with the flowchart. I guess there are a number of ways of doing things, but it seems to me that, by not attempting to confirm the initial Ab reactivity, the flow chart becomes unnecessarily complicated. There are also some errors of detail. b. Testing for anti-HCV and testing for HCV RNA are 2 distinct processes, revealing different things about the relationship between the virus and the host. I would therefore favour testing for antibody, confirming antibody reactivity, testing for HCV RNA and confirming HCV RNA, which is much simpler than the chart. The 2 activities can proceed at the same time, on the same sample more or less. c. The right hand side of the chart is the tricky one. Antibody reactivity followed by PCR negativity leads to reporting of the PCR result before confirmation of the Ab			

result. Is this helpful? Necessary?

d. If the second Ab assay is positive, then I don't agree with the comment box 'suggest an immediate sample to confirm Ab and a further sample in 6-12 months for PCR'.

   i. Firstly, this doesn't help the clinician interpret the result - the footnote k should be here ie tell the clinician there is no evidence of active infection.

   ii. If you are going to ask for an immediate repeat sample (and I agree you should) then why not test it for HCV RNA?

   iii. And why wait for 6-12 months before repeating the RNA? The clinical need is to be sure this patient does not have chronic infection now due to a cock-up in your HCV RNA result, so I ask for a repeat sample to confirm absence of viraemia. I don't specify a time - this is an inherently difficult patient group who are well known to default from their clinic appointments, so I take what I can get.

   iv. If you are worried that there may be a fluctuating RNA positivity due to recent acute HCV infection, then it doesn't make sense to wait 6 months for the repeat test - by which time any possible benefit of early antiviral therapy will have been lost!

e. I think it would also be helpful for this group to add a comment along the lines of 'If the patient is still exposed to risk of HCV infection, then please re-test for HCV RNA annually.'

f. If you now go down the extreme left hand side, you have Ab +ve in one assay, PCR neg, and Ab neg in a second assay. You recommend what to me seems like a completely pointless comment, indicating that the lab cannot interpret the results, and asking for, what seems to me, a pointless repeat sample.

   i. Surely it is of no interest AT ALL to the clinician to be told that the Ab result is a bit tricky. The key fact here, which is essentially lost - or rather, not mentioned AT ALL, is that the patient has no evidence of active infection.

   ii. The lab then needs to ask for a repeat sample to confirm absence of viraemia. I would suggest for discordant Ab results an appropriate comment would be 'Ab reactivity indeterminate, but RNA testing shows no evidence of current infection. Please send repeat sample to confirm absence of viraemia.'

Health benefits

If the prevarication asking for a further sample for 6 -12 months for PCR testing is because of a worry about missing acute infection, then this is clinically dangerous, as it will negate the benefits of early treatment. If it isn't because of a worry about fluctuating viraemia at acute infection, then I cannot see any point in delaying this second sample by 6 -12 months, which will result in a significant non-compliance rate, given the well-known characteristics of this patient group.

Recommended action	a. **ACCEPT** Footnote a updated to clarify that initial Antibody result should be confirmed. *'Initially reactive samples which on repeat screening are reproducibly negative can be reported as negative without further NAAT testing. Initially reactive samples*

	which on repeat screening are reproducibly positive require confirmation; request confirmatory repeat sample if this is the first reactive result.' b. **ACCEPT** Flow charts split into two. c. **ACCEPT** The algorithm has been split in to two confirmatory pathways. This will take into account the way that different laboratories work; once separated the algorithms can run at their own pace and be reported independently. Scope updated to advise which algorithm is preferable and how to choose the appropriate one. d. **ACCEPT** It was agreed that a repeat test should be done straight away as there is no point in waiting for 6-12 months. If negative, then repeat in 6 months. e. **ACCEPT** Footnote added 'If the patient is still exposed to risk of HCV infection or has an increase in ALT, please test for HCV RNA annually.' f. **PARTIAL ACCEPT** The group agreed that there is no evidence of active infection. Update final report to: 'No evidence of active HCV infection. Indeterminate HCV antibody status. Unable to differentiate false EIA reactivity or past HCV infection. Cannot exclude past infection. If recent risk factors, or if abnormal LFT or ALT are observed, please send repeat sample for antibody and PCR testing.'

Comment number	4		
Date received	13/08/2013	**Lab name**	Abbott Diagnostics Division UK
Section	Footnote C		
Comment			
If an acute infection is suspected or the patient is immunocompromised and may have a delayed antibody response, in addition to the comments already in footnote C it may be appropriate to screen the sample immediately with a HCV RNA test or HCV Antigen to look for the presence of Hepatitis C virus. As the footnote suggests screening later with a HCV RNA, at six weeks, to check no infection has been missed is vital.			
Evidence			
A new sensitive and automated chemiluminescent microparticle immunoassay for			

quantitative determination of hepatitis C virus core antigen Morota et al Journal of Virological Methods 157 (2009) 8-14 Performance and clinical utility of a novel fully automated quantitative HCV-core antigen assay Mederacke et al Journal of Clinical Virology 46 (2009) 210-215 Analytical Performance Characteristics and Clinical Utility of Novel assay for Total Hepatitis C Virus Core Antigen Quantification Ross et al. Journal of Clinical Microbiology, April 2010, Vol 48, Number 4, 1161-1168. Highly Sensitive Assay For Hepatitis C Virus Core Antigen: Report of an expert meeting on its evaluation and clinical significance Wolfram Gerlich and Angela Vockel Gastroenterology and Hepatology Insights	
Recommended action	**ACCEPT** The comment refers to patients with acute infection (that is abnormal LFTs) and is not covered by footnote C. Add to scope and cross reference to syndromic algorithm S1 – Acute infective hepatitis. Footnote c is for a defined known single contact, not ongoing vague exposure risk.

Comment number	5		
Date received	14/08/2013	**Lab name**	Dundee
Section	Algorithm and footnote H and Notification section		
Comment			
a. It is not made explicit what the comment should be on the Ab report when PCR or Ag is shown to be positive, or whether or not a second Ab assay is still indicated. Could this be added to a footnote? b. In labs that perform PCR / Ag testing less frequently than their second antibody test do they have to wait for the PCR / Ag result before completing the rest of the reporting? It might have implications for the reporting of samples from acute cases where PCR may be positive but only 1 of 2 ab tests is positive. c. Footnote H and the Notification appendix seem like duplication, perhaps the detail in H would be better transferred into the Notification appendix. d. Do we know what the relevant legislation is in Northern Ireland? e. The Scottish equivalent of CoSurv is called Ecoss.			
Recommended action	a. **PARTIAL ACCEPT** Footnote b details interim report comment. Footnote a strengthened to include repeat and confirmation Ab tests. b. **ACCEPT** Addressed by the split algorithm. c. **ACCEPT** Footnote c moved to Notification section.		

	d. **ACCEPT** Reference for legislation and link to Northern Ireland's Public Health Agency website added. e. **NONE** It was discussed whether Scotland, Wales and Northern Ireland should have a footnote or separate paragraph regarding devolved nation reporting. Devolved nation equivalents for reporting systems are mentioned in the referenced devolved nation guidance. Link to appropriate websites have been included.

Comment number	6		
Date received	16/08/2013	**Lab name**	South London Specialist Virology Centre King's College Hospital NHS Foundation Trust, London
Section	Page 8 flowchart		
Comment			
The algorithm and notes are clear and well written. I just wondered why the report after the unreactive PCR/antigen on the far right is where it is. We test for RNA and if below the limit of detection the second antibody/antigen assay is carried out at that stage and then reported. That way we have 2 EIAs and the PCR result reported together. In addition, we would report 2 indeterminate EIAs and a PCR that is below the limit of detection as possibly consistent with previous HCV exposure and waning antibody or low level reactivity that is difficult to interpret. Further specimen requested.			
Financial barriers			
No.			
Health benefits			
No.			
Recommended action	**ACCEPT** Algorithm updated.		

Comments received outside of consultation

Comment number	1		
Date received	31/08/2013	**Lab name**	Cardiff
Section			
Comment			
We have one comment from Cardiff which relates to the footnote ‘e’. You state that ‘The HCV antigen test is reported to have a 100% positive predictive value in confirming HCV infection, but a lower negative predictive value (90%) than PCR. HCV antigen testing therefore should not be used to confirm infection in sera with low levels of antibody as false positives are more likely.’ Should this actually read that false NEGATIVES are more likely?			
Recommended action	**ACCEPT** Document updated. False negatives (rather than positives) are more likely if using HCV antigen testing to confirm infection in sera with low levels of antibody.		

Comment number	2		
Date received	30/11/2015	**Lab name**	Royal Preston Hospital
Section			
Comment			

We fully respect that the aim of this SMI is to expedite the diagnosis of hepatitis C infection and help patient management but we - as a diagnostic laboratory in a busy teaching hospital - would like to raise a few points regarding the suggested test algorithm.

Test availability

a. HCV antigen tests, and combined HCV antibody and antigen tests, are not currently available for all test platforms.

Further testing, confirmatory samples and reporting

b. The algorithm suggests that samples which are reactive on screening be then tested by PCR or HCV antigen test. The disadvantage for ourselves (who have Roche PCR, but not HCV antigen testing, available) is that the sample volume left after screening is often inadequate for PCR, especially if a number of screening tests have been done (for example for different hepatitis viruses). We would typically do a second antibody test at this point and then report and seek further samples accordingly.

c. The algorithm invites a confirmatory sample after a first reactive result and also again after further testing of a reactive specimen whatever the final outcome. Is this really necessary? Why not wait until further testing has been done when a fuller report can be issued and a further sample(s) requested then?

d. Reporting – how necessary is the interim report on a reactive screening sample which is PCR/antigen unreactive? Why not wait for the further antibody test result? **Sample types** e. While our HCV PCR platform (Roche) allows serum or plasma samples to be tested, other HCV platforms allow only plasma samples which would be a problem for reflex HCV testing of reactive serum screening samples.	
Recommended action	a. **ACCEPT** Algorithms have been amended to allow for initial HCV antibody screen. b. **PARTIAL ACCEPT** The need for optimal volume for NAAT is acknowledged in footnote d *'if less than the recommended volume is used (perhaps diluted) this must be reported and a repeat sample requested'.* However, confirmation with antibody is not recommended as *'management is dependent on whether active hepatitis C infection is present and therefore a positive HCV antigen or NAAT result, which indicates active infection, is required'* in *addition 'where infections are common in groups who may be difficult to re-bleed, requesting an additional repeat sample to confirm active infection is not ideal*'. c. **ACCEPT** The algorithms have been updated. Confirmation after the second reactive result is no longer included. d. **NONE** If insufficient sample to perform additional tests on original sample, results may be delayed. Interim reports should be issued where the result may have immediate significance for patient management. e. **ACCEPT** Plasma samples are recommended for reflex testing. However test has been added to the introduction regarding the use of serum. *'Therefore, if serum samples are used for routine viral hepatitis screening, negative NAAT results for hepatitis A, B, C and E may not exclude infection'.*

Second consultation: 30/11/2016 – 15/12/2016

Version of document consulted on: V 5dzze+

Proposal for changes

Comment number	1		
Date received	01/12/2016	**Lab name**	Imperial College Healthcare NHS Trust
Section	All		
Comment			
I am disappointed to see that this document recommends NAT testing for HCV on serum. This carries a risk of false negative results (as experienced by the Bristol lab several years ago), and we are always very careful to restrict NAT testing for HCV to EDTA plasma samples only.			
Evidence			
Bristol HCV lookback study following SUI of missed HCV infections. Reported by David Carrington.			
Health benefits			
Risks: false negative NAT results.			
Recommended action	**NONE** The Bristol HCV lookback was centred on lack of an inhibition control and not the use of serum. Reflex testing of the serum sample for viral RNA is recommended for the benefits to the patient care pathway and the reduction to loss to follow up. Laboratories should use assays which have been validated for serum HCV RNA, commercial assays provide validation data on the use of serum versus plasma and laboratories should be cognisant of this when applying this HCV screening algorithm.		

Comment number	2		
Date received	02/12/2016	**Lab name**	Dundee
Section	lab diagnosis page 10		
Comment			
a. Sensitivity of antigen test compared to PCR is dealt with in 2 separate paragraphs and different figures and references are given in each (97%, ref 35 and 96.3%, refs 36 and 37) suggest this should be dealt with only once and a single figure or a range given. Word positive in the second paragraph should be deleted. b. Someone just pointed out to me that the SIGN guideline on HCV and (apparently, I haven't checked) national occupation health guidance suggest that after a needle stick from a HCV positive source there should be PCR testing of recipients			

at 6, 12 and 24 weeks. I think V5 draft is correct in saying otherwise. In fact I think we should be more explicit in saying 6 week PCR and 12 week antibody test is enough.	
Recommended action	a. **ACCEPT** This has been updated accordingly and the word 'positive' has been deleted from the second paragraph. b. **NONE** Many thanks for the information. The group have decided to adhere to the Department of Health guidelines.

Comment number	3		
Date received	07/12/2016	**Lab name**	Bristol PHL
Section	Multiple-see edited version		
Comment			
Overall, I like the structure and the detail included, this evolution is an improvement in style and content. I found it easiest to edit a version and attach. In addition to those edits, I have a comment about the algorithm confirming antibody by antigen, page 14. First, technically it is not confirming by antigen as NAAT is included. If antibody is reactive or equivocal and antigen is equivocal, the interim report is no evidence of active infection by antigen as an equivocal result is not interpretable that clearly, the report is incorrect; better as HCV status inconclusive, further results to follow. The only screening result that does not trigger a NAAT is negative antibody this makes the antigen test redundant other than to provide an interim report; I doubt this was the intention. I can't upload the edit, so will try and send separately.			
Evidence			
None, just my opinion.			
Financial barriers			
Locally determined.			
Health benefits			
Clear benefit to widening HCV testing.			
Recommended action	**ACCEPT** Most comments were accepted and updated accordingly.		

Comment number	4		
Date received	10/12/2016	**Lab name**	PHE, Colindale; King's College Hospital, London
Section	a. Scope of document b. Report comments		

Comment

a. The SMI does not include Dried Blood Spot testing (DBS), in the 'Type of Specimen'. A suggested text: This UK SMI covers the screening of blood, plasma and serum samples for hepatitis C (HCV) using HCV antibody EIA screening assays as well as confirmation using Nucleic Acid Amplification Tests (NAAT)/immunoblots and HCV antigen EIA screening assays. This SMI recognises that Dried Blood Spot (DBS) samples are increasingly employed in hard to access populations and is widely employed as a public health tool in such as prison services, people who inject drugs (PWID), with serum eluate from Dried Blood Spot samples tested using standard CE marked HCV EIA and NAAT assays after verification and validation by accredited testing laboratories.

b. Investigation of hepatitis C infection by antibody testing confirmed by antigen: The scenarios Row numbers 8, 11, 12 should explicitly recommend HCV RNA testing, in addition to the advice for HCV genotype testing.

Evidence

This is relevant as DBS is widely employed in laboratory testing in prison services, people who inject drugs (PWID) and various outreach and community health services.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/565459/Hepatitis_C_in_the_UK_2016_report.pdf

Financial barriers

No.

Health benefits

a. The emphasis on getting HCV RNA status on the very first sample will be a great boost for HCV care pathway as that will address the 20-30% dropout rate for second samples. With new HCV DAAs available, this will greatly improve early treatment taking advantage of the excellent SVRs from the new DAAs.

b. This is crucial to ascertain status of HCV infection as HCV antigen assays are less sensitive than NAAT as mentioned earlier in the document. NAAT has to be standard baseline HCV assessment in these scenarios.

Recommended action

a. **ACCEPT**

This has been updated accordingly in the scope of the document.

b. **ACCEPT**

The row numbers (8, 11 and 12) have been updated

	accordingly.

Comment number	5		
Date received	13/12/2016	**Lab name**	University of Nottingham
Section	Introduction, Lab diagnosis, footnotes for algorithms, 1st algorithm, Report comments		
Comment			
a. Introduction: Lines 1-2 - HCV is not the only member of the hepacivirus genus (eg non-primate hepacivirus). It may not even be the only member of the hepacivirus genus that infects humans - depends on whether you classify GBV-B as a human virus or not. b. Introduction 2nd para - g4 doesn't appear to be prevalent in N Africa - it is prevalent. c. Lab diagnosis - last para (page 11) - knowledge of the genotype may be relevant in treatment selection - there is no may be about it, it is relevant. d. Pages 13 and 14 - I think the letters referring to the footnotes are out of step with the footnotes themselves eg there is an a in the very top box on page 13 (which simply says HCV antibody) but footnote a clearly does not apply to this box. e. Page 13. If you go down the route HCV antibody - Reactive - HCV RNA NAAT - not detected, the report states No evidence of active HCV infection. However, you cannot rule out recent infection with a dip in HCV RNA, so I would always ask for a repeat sample if recent infection might be suspected. You may or may not cover this in a footnote - as the footnotes are incorrectly labelled, I can't be sure. f. Report comments page 16. The first sentence states that the final result should be able to distinguish active infection from resolved infection (I agree) and acute infection - which is simply not possible using a combination of HCV Ab and NAAT tests. There is no way to tell whether a patient who is anti-HCV pos, HCV RNA pos has had a recent infection or not. g. Report comments pages 16-19 - genotyping should be reflex in any newly diagnosed HCV RNA positive patient, not considered. This will enable clinicians to make decisions about likely course of therapy. h. Report comments item 12, page 19. In the notes there is a statement - If negative, request a further sample. ??!!?? If what is negative??		
Evidence			
Mostly common sense.			
Financial barriers			
There is a cost element to reflex genotyping, but this will be more than offset by saving of time and out-patient appointments for patients in whom the genotype is not known.			
Recommended action	a. **NONE** HCV is a member of the genus *hepacivirus*. The GBV-B		

	has been proposed to be a member of the genus within the family *Flaviviridae* but so far has not been officially assigned. b. **ACCEPT** This sentence has been amended accordingly; the word phrase "*appears to be*" has been removed and replaced with "*is*". c. **ACCEPT** This sentence has been amended accordingly; the word phrase "*may be*" has been removed and replaced with "*is*". d. **ACCEPT** The footnotes have been arranged in alphabetical order accordingly. e. **ACCEPT** This is already covered in the footnotes and the footnotes have been arranged in alphabetical order. f. **ACCEPT** This has been addressed and updated accordingly in the reporting comments section. g. **ACCEPT** This has been addressed and updated accordingly in the reporting comments section pages 16-19. h. **ACCEPT** This comment has been removed in the reporting comments section.

Comment number	6		
Date received	14/12/2016	**Lab name**	Cardiff
Section	Lab diagnosis, footnotes for both algorithms, table comments		
Comment			
a. 'Assays that detect free HCV antigen are about 97% as sensitive as HCV NAAT'. You also have a similar statement in the next paragraph 'The HCV antigen test is reported to have a 100% positive specificity and 96.3% sensitivity in con confirming HCV infection, when compared with the HCV NAAT tests' Suggest to amalgamate as: 'The HCV antigen test is reported to have a 100% positive specificity (ref 36) and 96-97% sensitivity (ref 35 and 36) in confirming HCV infection, when compared with the HCV NAAT tests' b. All the footnotes are incorrect! Footnote a should be under HCV antibody reactive. Footnote b should be under HCV antibody not reactive. Footnote c should under HCV RNA NAAT (from the original tube).There is no footnote e on			

the algorithm - this should be in the bullet 'HCV antibody reactive or equivocal, HCV RNA not detected' (and take out footnote g from this bullet) Footnotes f and g should be under the bullet 'Evidence of active infection with HCV' There is no footnote h comment anywhere...what is this? We would suggest an extra footnote under the bullet 'HCV antibody reactive or equivocal, HCV RNA not detected' to state 'Request further sample if not split within the correct time frame for the assay' c. 4. Take out of notes 'some laboratories may like to do a second antibody test to confirm' A second antibody test has already been performed! d. 12. Take out 'If negative, request a further sample'. What result is negative? Suggest to have instead 'Please send a repeat sample to confirm including by NAAT'.	
Financial barriers	
No.	
Health benefits	
No.	
Recommended action	a. **ACCEPT** The two sentences have been amalgamated and updated accordingly. b. **PARTIAL ACCEPT** The footnotes have been arranged and updated in alphabetical order accordingly. Footnote e includes the following “manufacturers’ recommendations should be followed where sample preparation protocols or assays are being utilised “off label” local validation should be performed prior to use. c. **ACCEPT** The sentence mentioned has been removed from the comments table 4. d. **PARTIAL ACCEPT** The report comment 12 has been removed from the reporting comments section and document updated accordingly.

Comment number	7		
Date received	14/12/2016	**Lab name**	Newcastle
Section	Pages 14/15		
Comment			
a. Page 15. The numbering of the footnotes is out of sync with the numbering in the			

flow charts. b. Page 14. (Ag confirmation algorithm) and footnote d) (as numbered on page 15) This algorithm suggests reflex testing by PCR on the original sample after Ag testing regardless of results. If Ag is to be offered as a potential confirmation route, then there is limited value in requiring PCR on the same sample as this will further delay a final result. The footnote does not reflect the algorithm as it says NAAT should be 'considered'. Likewise the table gives the option of asking for a further sample for PCR where Ag testing is negative. This is the practice in our laboratory. We use the comment 'HCV infection at some time. Results are likely to represent past/cleared HCV infection although a low level of HCV replication cannot be excluded. Please send an EDTA sample for HCV PCR to confirm status'.	
Recommended action	a. **ACCEPT** The footnotes have been arranged and updated in alphabetical order accordingly. b. **ACCEPT** This has been updated accordingly in the document.

Comment number	8		
Date received	15/12/2016	**Lab name**	Cepheid
Section	Page 9		
Comment			
Page 9 a. Qualitative HCV PCR or quantitative PCR, ideally with a lower limit of sensitivity of less than 50 IU/ml (as used in treatment monitoring). Note that these levels of sensitivity are only achieved with optimal sample volumes; if less than recommended volume is used (perhaps diluted) this must be reported and a repeat sample requested. Assays should include appropriate controls including inhibition control. The limit of sensitivity needs to be in line with the EASL recommendations of 15 IU/ml. http://www.easl.eu/medias/cpg/HCV2016/Summary.pdf http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf Ideally should be removed from the sentence as they should reference guidelines. In addition the note regarding that these levels of sensitivity are only achieved with optimal sample volumes should be removed. The recommendation should be kits with performance of 15 IU/ml, if that level can be obtained with a dilution then this is sufficient. A SMI should not encourage poor practices. b. Specific HCV antigen EIA assays substantially reduce the serological 'window' period between infection and seroconversion, and may offer a cost-effective alternative to PCR. However, note that PCR is more sensitive than antigen testing and will be positive before antigen appears. This guidance should be in line with EASL recommendations: HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic			

infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication) c. Nucleic acid amplification is optimal at this point; so that patients who have circulating HCV, and who may be difficult to bleed again, are given an early opportunity to enter the care pathway. Patients with detectable hepatitis C antibodies always need HCV PCR before treatment. Where delaying testing by HCV PCR to a later time is seen as a more cost-effective approach, then confirmation of antibody status should be done at this point using a second antibody test, as outlined in this algorithm, for those who are PCR or antigen negative. We don't understand the statement regarding delaying HCV PCR to a later time if seen as more cost effective. Decisions regarding delay should not be based upon testing alone but in conjunction with the clinical picture. Liver disease severity should be assessed prior to any decision to delay and confirmation of antibody status by a second antibody test. d. If EIA antibody reactivity is low, consider checking specificity with HCV immunoblot. A low reactivity is not granular and very subjective. In addition there are few HCV immunoblots still commercially available. We don't see this point as being helpful or constructive in the management of Hepatitis C patients.	
Recommended action	a. **NONE** This UK SMI discusses diagnosis of HCV infection and not the treatment. UK SMIs encourage good laboratory practices that staff should follow. b. **NONE** The Virology Working Group has addressed this comment in the algorithms. c. **NONE** This UK SMI does not state that HCV PCR should be delayed in diagnosis. d. **NONE** This UK SMI does not recommend the use of immunoblots but it has been mentioned within the document that it can be used for detection of antibodies to HCV.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 2			
Date received	15/12/2016	**Professional body**	Institute of Biomedical Science
Date received	15/12/2016	**Professional body**	British Infection Association