Web Appendix

Table 1. Search Strategy- Literature Review

1. CT.ti,ab.
2. tomodensitometry.ti,ab.
3. PET.ti,ab.
4. MRI.ti,ab.
5. NMRI.ti,ab.
6. zeugmatogra*.ti,ab.
7. ((computed or computeri?ed or magneti* or proton or "Acoustic Radiation Force Impulse" or ARF) adj5 (tomogra* or scan or scans or imaging)).ti,ab.
8. Tomography, X-Ray Computed/
9. Magnetic Resonance Imaging/
10. elastography.ti,ab.
11. elastographies.ti,ab.
12. sonoelastography.ti,ab.
13. sonoelastographies.ti,ab.
14. sono-elastography.ti,ab.
15. sono-elastographies.ti,ab.
16. elastogram.ti,ab.
17. elastograms.ti,ab.
18. vibroacoustography.ti,ab.
19. vibroacoustographies.ti,ab.
20. vibro-acoustography.ti,ab.
21. vibro-acoustographies.ti,ab.
22. fibroscan.ti,ab.
23. elastometry.ti,ab.
24. elasticity.ti,ab.
25. "liver stiffness".ti,ab.
26. elastogra*.ti,ab.
27. echogra*.ti,ab.
28. ultrason*.ti,ab.
29. ultrasound.ti,ab.
30. Ultrasonography/
31. Elasticity Imaging Techniques/
32. Elasticity.ti,ab.
33. ((alanine* or aspartate* or glutamic*) and (transaminase or aminotransferase*)).ti,ab.
34. SGOT.ti,ab.
35. SGPT.ti,ab.
36. AST.ti,ab.
37. ALT.ti,ab.
38. Aspartate Aminotransferases/
39. Alanine Transaminase/
40. platelet.ti,ab.
41. platelets.ti,ab.
42. thrombocyte.ti,ab.
43. thrombocytes.ti,ab.
44. APRI.ti,ab.
45. Blood Platelets/
46. Biological Markers/
47. ELF.ti,ab.
48. "enhanced liver fibrosis".ti,ab.
49. Fibrotest.ti,ab.
50. Fibrosure.ti,ab.
51. Fibrometer.ti,ab.
52. FIB4.ti,ab.
53. FIB-4.ti,ab.
54. BARD.ti,ab.
55. Fibrospect.ti,ab.

56. Hepascore.ti,ab.
57. "Hyaluronic acid".ti,ab.
58. hyaluronate.ti,ab.
59. Hyaluronic Acid/
60. "Forns index".ti,ab.
61. laminin.ti,ab.
62. Laminin/
63. YKL-40.ti,ab.
64. "YKL 40".ti,ab.
65. "Type IV collagen".ti,ab.
66. Collagen Type IV/
67. "Procollagen III N-peptide".ti,ab.
68. "Lok index".ti,ab.
69. MP3.ti,ab.
70. MP-3.ti,ab.
71. "Fibrosis probability index".mp. or "sydney index".ti,ab.
72. FPI.ti,ab.
73. Fibroindex.ti,ab.
74. "Virahep-C index".ti,ab.
75. "Virahep C index".ti,ab.
76. "Goteborg University Cirrhosis Index".ti,ab.
77. GUCI.ti,ab.
78. SHASTA.ti,ab.
79. Glycocirrhotest.ti,ab.
80. Glycofibrotest.ti,ab.
81. BAAT.ti,ab.
82. "NAFLD fibrosis score".ti,ab.
83. Cytokeratin-18.ti,ab.
84. "Cytokeratin 18".ti,ab.
85. M30.ti,ab.
86. M-30.ti,ab.
87. "NASJH test".ti,ab.
88. "NAFIC score".ti,ab.
89. PGA.ti,ab.
90. "PGAA index".ti,ab.
91. "Bonancini score".ti,ab.
92. "Pohl score".ti,ab.
93. "Cirrhosis discriminant score".ti,ab.
94. "Age-platelet index".ti,ab.
95. TIMP-1.ti,ab.
96. "tissue inhibitory metalloprotease".ti,ab.
97. MBT.ti,ab.
98. "C-methacetin breath test".ti,ab.
99. "Phosphoproteomic biomarker".ti,ab.
100. "Phosphoproteomic biomarkers".ti,ab.
101. PICP.ti,ab.
102. PIIINP.ti,ab.
103. PON-I.ti,ab.
104. "paraoxonase I".ti,ab.
105. MFAP-4.ti,ab.
106. "MFAP 4".ti,ab.
107. MFAP4.ti,ab.
108. "microfibril associated glycoprotein 4".ti,ab.
109. or/1-9,27-30,33-39
110. limit 109 to yr="1988 -Current"
111. or/10-26,30-32,40-108
112. limit 111 to yr="2001 -Current"
113. 110 or 112
114. cirrhosis.ti,ab.
115. cirrhoses.ti,ab.

116. fibrosis.ti,ab.
117. fibroses.ti,ab.
118. "liver disease".ti,ab.
119. (hepatitis or hepatic).ti,ab.
120. steatohepatitis.ti,ab.
121. Liver Cirrhosis/
122. Fibrosis/
123. Liver Diseases/
124. Hepatitis/
125. or/114-124
126. 113 and 125
127. exp "sensitivity and specificity"/
128. "reproducibility of results"/
129. diagnos*.ti. or diagnostic.ab.
130. di.fs.
131. sensitivit*.ab.
132. specificit*.ab.
133. (ROC or "receiver operat*").ab.
134. Area under curve/
135. ("Area under curve" or AUC).ab.
136. (sROC or "optimal cut-off").ab.
137. (accura* or ((gold* or reference) adj2 standard)).ti,ab.
138. (likelihood adj3 (ratio* or function*)).ab.
139. ((true or false) adj3 (positive* or negative*)).ab.
140. ((positive* or negative* or false or true) adj3 (rate* or predictive)).ti,ab.
141. or/127-140
142. 126 and 141
143. *liver cirrhosis/di
144. *hepatitis/
145. *fibrosis/
146. (liver or hepatitis or hepatic or fibrosis).ab.
147. di.fs.
148. 146 and 147
149. or/143-145,148
150. 113 and 149
151. 113 and 149
152. 142 or 151

Search narrative: This search strategy has been kept deliberately very broad – utilizing only two main search concepts: index test/s (concept A) - lines 1-108 and the disease of interest (concept B)/location of disease of interest (concept B) – lines 110-120. A methodological filter (concept C) is included but does not act as a filter to all search results (it is used in parallel: ((A AND B AND C) OR (A AND B-focussed)).
Potential studies for inclusion were initially identified from published non-Cochrane reviews and background literature. This generated a reference set of 70 potential (and probable) studies for inclusion to use to test the search strategy detailed above. The strategy was designed without knowledge of the 70 potential studies or of the search strategies used to identify the 70 from their original publications. All 70 studies were identified by the above strategy.
The yield from the above strategy was high. However, due the large number of tests within the scope of the review, a large yield could not be avoided.

Validation string:
("19196449" or "18448567" or "16823833" or "15685546" or "19013661" or "18673426" or "18410556" or "18672413" or "16394849" or "16020491" or "17255218" or "18192914" or "17258346" or "17530363" or "18987556" or "19413672" or "17663420" or "18568136" or "18637064" or "18818788" or "18930329" or "18705692" or "19261000" or "21904476" or "17608672" or "18218676" or "19030204" or "19104699" or "18544945" or "19308312" or "18832522" or "18083083" or "12883497" or "20493576" or "20180868" or "19060630" or "19013661" or "18672413" or "19758273" or "19171202" or "18339075" or "18285716" or "18339592" or "19999223" or "18796094" or "18706734" or "18482283" or "18553008" or

"18692034" or "17156890" or "17321634" or "17634962" or "17914968" or "16970597" or "16538110" or "16487951" or "16863553" or "17032409" or "16118349" or "17032410" or "16737415" or "16620291" or "16825937" or "16268817" or "16109665" or "15894397" or "15915455" or "16284529" or "15122779" or "17393509" or "18390575" or "19291784").ui.

EMBASE

1. exp *Liver Cirrhosis/ or exp *Liver Fibrosis/ or exp *Liver Disease/ or exp *Hepatitis/
2. (liver or hepatic).ti,ab.
3. exp *Liver/
4. 3 or 2
5. (cirrhosis or cirrhoses or fibrosis or fibroses or liver disease or hepatitis or steatohepatitis).ti,ab.
6. 4 and 5
7. 1 or 6
8. (CT or tomodensitometry or MRI or NMRI or zeugmatogra*).ti,ab.
9. ((computed or computerised or computerized or CT or magneti* or MR or NMR or proton) and (tomogra* or scan or scans or imaging)).ti,ab.
10. exp *computer assisted tomography/
11. exp *nuclear magnetic resonance imaging/
12. (elastography or elastographies or sonoelastography or sonoelastographies or sono-elastography or sono-elastographies or elastogram or elastograms or vibroacoustography or vibroacoustographies or vibro-acoustography or vibro-acoustographies or fibroscan or elastometry or elasticity or liver stiffness or echogra* or ultrason* or ultrasound).ti,ab.
13. exp *ultrasound/
14. exp *elastography/
15. ((alanine* or aspartate* or glutamic*) and (transaminase or aminotransferase*)).ti,ab.
16. (platelet or platelets or thrombocyte or thrombocytes or APRI or ELF or enhanced liver fibrosis or Fibrotest or Fibrosure or Fibrometer or FIB4 or FIB-4 or BARD or Fibrospect or Hepascore or Hyaluronic acid or hyaluronate or Forns index or laminin or YKL-40 or YKL 40 or Type IV collagen or Procollagen III N-peptide or Lok index or MP3 or MP-3 or Fibrosis probability index or FPI or Fibroindex or Virahep-C index or Virahep C index or Goteborg University Cirrhosis Index or GUCI or SHASTA or Glycocirrhotest or Glycofibrotest or BAAT or NAFLD fibrosis score or Cytokeratin-18 or Cytokeratin 18 or M30 or M-30 or NASJH test or NAFIC score or PGA or PGAA index or Bonancini score or Pohl score or Cirrhosis discriminant score or Age-platelet index or TIMP-1 or tissue inhibitory metalloprotease or MBT or C-methacetin breath test or Phosphoproteomic biomarker or Phosphoproteomic biomarkers or PICP or PIIINP or PON-I or paraoxonase I or MFAP-4 or MFAP 4 or MFAP4 or microfibril associated glycoprotein 4).ti,ab.
17. (SGOT or SGPT or AST or ALT).ti,ab.
18. exp *alanine aminotransferase/
19. exp *aspartate aminotransferase/
20. exp *thrombocyte/
21. exp *biological marker/
22. (2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012*).em.
23. 12 or 14 or 16 or 20 or 21
24. 22 and 23
25. 8 or 9 or 10 or 11 or 13 or 15 or 17 or 18 or 19
26. limit 25 to yr="1988 -Current"
27. 24 or 26
28. 7 and 27

Science Citation Index expanded
Search: 1988 – April 2012
#1 TS=(cirrhosis OR cirrhoses OR fibrosis OR fibroses or liver disease or hepatitis or steatohepatitis)
#2 TS=(liver or hepatic)
#3 TS=(CT OR tomodensitometry OR PET OR MRI OR NMRI OR zeugmatogra*)
#4 TS=((Acoustic Radiation Force Impulse or ARFI OR computed OR computerised OR computerized OR CT OR magneti* OR MR OR NMR OR proton) AND (tomogra* OR scan OR scans OR imaging))
#5 TS=(elastography or elastographies or sonoelastography or sonoelastographies or sono-elastography or sono-elastographies or elastogram or elastograms or vibroacoustography or vibroacoustographies or vibro-acoustography or vibro-acoustographies or fibroscan or elastometry or elasticity or liver stiffness

OR echogra* OR ultrason* OR ultrasound)
#6 TS=((alanine* OR aspartate* OR glutamic*) AND (transaminase OR aminotransferase*))
#7 TS=(SGOT OR SGPT OR AST OR ALT OR platelet OR platelets OR thrombocyte OR thrombocytes OR APRI OR ELF OR enhanced liver fibrosis OR Fibrotest OR Fibrosure OR Fibrometer OR FIB4 OR FIB-4 OR BARD OR Fibrospect OR Hepascore OR Hyaluronic acid OR hyaluronate OR Forns index OR laminin OR YKL-40 OR YKL 40 OR Type IV collagen OR Procollagen III N-peptide OR Lok index OR MP3 OR MP-3 OR Fibrosis probability index OR FPI OR Fibroindex OR Virahep-C index OR Virahep C index OR Goteborg University Cirrhosis Index OR GUCI OR SHASTA OR Glycocirrhotest OR Glycofibrotest OR BAAT OR NAFLD fibrosis score OR Cytokeratin-18 OR Cytokeratin 18 OR M30 OR M-30 OR NASJH test OR NAFIC score OR PGA OR PGAA index OR Bonancini score OR Pohl score OR Cirrhosis discriminant score OR Age-platelet index OR TIMP-1 OR tissue inhibitory metalloprotease OR MBT OR C-methacetin breath test OR Phosphoproteomic biomarker OR Phosphoproteomic biomarkers OR PICP OR PIIINP OR PON-I OR paraoxonase I OR MFAP-4 OR MFAP 4 OR MFAP4 OR microfibril associated glycoprotein 4)
#8 (#3 OR #4 OR #5 OR #6 OR #7)
#9 (#1 AND #2 AND #8)

Figure 1– Flowchart of Selection of Studies for review

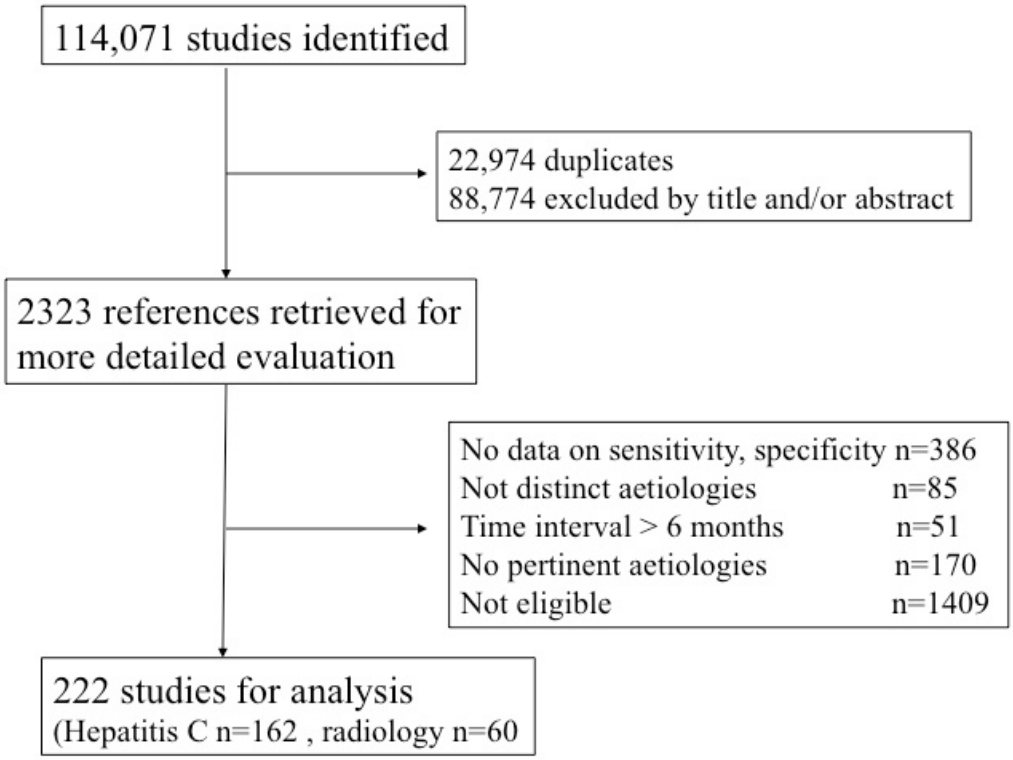

Table 2. Assessment of methodological quality using the QUADAS-2 tool

Quality assessed	Description	Choice	Comment
Domain 1: Patient sampling	Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	
	Was a case-control design avoided?	Yes/No/Unclear	
	Did the study avoid inappropriate exclusions?	Yes/No/Unclear	For example exclusion of patients with severe or low fibrosis, obese etc.
Risk of bias	**Could the selection of patients have introduced bias?**	Low risk/high risk/unclear	Summarizes previous questions: if any has no as answer then high risk, if any has unclear then unclear
Concerns about applicability	**Are there concerns that the included patients and setting do not match the review**	High/Low concern/Unclear	Tertiary centres, selected difficult cases

	question?		
Domain 2: index test	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear	Relevant only in US, CT, MRI
	If a threshold was used, was it pre-specified?	Yes/No/Unclear	
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	Low risk/ High risk/Unclear	Summarizes previous questions: if any has no as answer then high risk, if any has unclear then unclear
Concerns about applicability	**Are there concerns that the index test, its conduct, or interpretation differs from the review question?**	High/Low concern/Unclear	Index test not conducted according to manufacturer reccomendations
Domain 3: Reference standard	Is the reference standard likely to correctly classify	Yes/No/Unclear	Yes if biopsy length >15 mm and/or >6 portal tracts

	the target condition?		
	Was the reference standard results interpreted without knowledge of the results of the index tests?	Yes/No/Unclear	
Risk of bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	Low risk/ High risk/Unclear	Summarizes previous questions: if any has no as answer then high risk, if any has unclear then unclear
Concerns about applicability	**Are there concerns that the target condition as defined by the reference standard does not match the question?**	High Concern/Low concern/Unclear	Always low concern
Domain 4: Flow and timing	Was there an appropriate interval	Yes/No/Unclear	Yes if interval between biopsy and

	between index test and reference standard?		index test < 3 months, no if interval >3 but < 6 months, excluded study if interval > 6 months
	Did all patients receive the same reference standard?	Yes/No/Unclear	
	Were all patients included in the analysis?	Yes/No/Unclear	No if patients with uninterpretable results were not included in the analysis or if there were patients with indeterminate results
Risk of bias	**Could the patient flow have introduced bias?**	Low risk/ High risk/Unclear	Summarizes previous questions: if any has no as answer then high risk, if any has unclear then unclear

Table 3 – Quality assessment of studies included in the meta-analysis for chronic hepatitis C. Quality assessment was done using the QUADAS-2 tool

	Domain 1: Patient sampling		Domain 2: Index test		Domain 3: Reference standard		Domain 4: Flow and timing
Study ID	Risk of bias	Concerns about applicability	Risk of bias	Concerns about applicability	Risk of bias	Concerns about applicability	Risk of bias
Adams 2005 (1)	✔	✔	✖	✔	✖	✔	✔
Ahmad 2011 (2)	?	✔	✔	✔	?	✔	✔
Al Mohri (3)	?	?	✔	✔	?	✔	✔
Anaparthy 2009 (4)	✖	✖	✔	✔	?	✔	?
Arena 2008 (5)	✔	✖	✖	✔	✔	✔	✔
Beckebaum 2010 (6)	✖	✖	✖	✔	✖	✔	✔
Bejarano 2009(7)	✔	✔	✖	✔	?	✔	✔
Berg 2004 (8)	?	?	?	?	?	✔	?
Borroni 2002 (9)	?	?	?	?	?	✔	?

Bourliere 2006 (10)	✔	✖	✖	✔	✖	✔	✖
Boursier 2009 (11)	✔	✔	✖	✔	✖	✔	✖
Boursier 2012 (12)	✔	✔	✔	✖	✖	✔	✔
Burton 2010 (13)	✖	✖	✔	✔	?	✔	?
Cales 2010a (14)	✖	✖	✔	✔	?	✔	✖
Cales 2010b (15)	?	?	✖	✔	?	✔	✔
Calvaruso 2010 (16)	✔	✔	✔	✔	✔	✔	✔
Cardoso 2012 (17)	✔	✔	✔	✔	✖	✔	✖
Carrion 2006 (18)	✔	✔	✖	✖	?	✔	✔
Carvalho 2008 (19)	✖	✖	✖	✔	✖	✔	✔
Castera 2005 (20)	✔	✔	✖	✔	✖	✔	✔
Castera 2007 (21)	?	?	✔	✔	?	✔	?
Castera 2009 (22)	✔	✔	✔	✔	✖	✔	✔
Ceriani 2001 (23)	?	?	✔	?	?	✔	?
Chen 2008 (24)	?	?	✖	✔	?	✔	?
Cheung 2008 (25)	✖	✖	✔	✖	✖	✔	✔

Cho 2011(26)	✔	✔	✔	✔	✖	✔	✔
Christensen 2006 (27)	?	✖	✖	✔	?	✔	✖
Chrysanthos 2006 (28)	✔	✔	✔	✔	✖	✔	✔
Cobbold 2010 (29)	✔	✔	✖	✔	✖	✔	✖
Colletta 2005 (30)	✖	✖	✔	?	✖	✔	✖
Corradi 2009 (31)	✖	✖	✔	✔	?	✔	✔
Crespo 2010 (32)	?	?	✖	✔	?	✔	✔
Cross 2010 (33)	✔	✔	✖	✖	✖	✔	✖
da Silva 2008 (34)	?	✖	✖	✔	?	✔	✔
Danila 2011 (35)	?	?	✖	?	?	✔	✔
De Ledinghen 2006 (36)	✔	✔	✖	✖	✖	✔	✔
Degos 2010 (37)	✔	✔	✔	✔	?	✔	✔
Dinesen 2008 (38)	✖	✖	✖	✔	?	✔	?
Esmat 2007 (39)	✔	✔	✖	✔	✖	✔	✖
Fabris 2006 (40)	✖	✖	✔	✔	✖	✔	✔
Fahmy 2011 (41)	✔	✔	?	✔	✔	✔	✔

Fontaine 2009 (42)	✖	✖	✖	✔	?	✔	?
Fontana 2008 (43)	✖	✖	✖	✖	✔	✔	?
Fontanges 2008 (44)	✖	✖	✖	✖	✖	✔	✔
Forestier 2010 (45)	✖	✖	✖	✖	?	?	✖
Forns 2002 (46)	✖	✖	✖	✖	✔	✔	✔
Fraquelli 2011 (47)	✖	✖	✖	✔	✔	✔	✖
Fujii 2009 (48)	✖	✖	✔	✔	✔	✔	✔
Fujimoto 2011 (49)	✖	✔	✖	✔	?	✔	✔
Gaia 2011 (50)	✖	✔	✔	✔	✔	✔	✖
Ganne-Carrie 2006 (51)	✔	✔	✖	✖	✖	✔	✔
Gara 2011 (52)	✖	✖	✖	✔	?	✔	✖
Giannini 2006 (53)	✔	✔	✖	✔	?	✔	✔
Gobel 2006 (54)	✖	✖	✖	✔	?	✔	✔
Guechot 2010 (55)	✔	✔	✖	✔	✔	✔	✔
Guechot 1996 (56)	✔	✔	✖	✖	?	✔	✔
Guzelbulut 2011 (57)	✔	✔	✖	✔	?	✔	✔

Halfon 2006 (58)	✔	✔	✖	✔	✖	✔	✔
Halfon 2005 (59)	✔	✔	✖	✔	✔	✔	✖
Halfon 2007 (60)	✔	✔	✔	✔	✔	✔	✔
Harada 2008 (61)	✖	✖	✖	✔	?	✔	✖
Hsieh 2012 (62)	✖	✖	✖	✔	?	✔	✔
Iacobellis 2005 (63)	✔	✔	✔	✔	✖	✔	✔
Imbert-Bismut 2001 (64)	✖	✔	✖	✔	✖	✔	✖
Imperiale 2000 (65)	✔	✔	✔	✔	?	✔	✖
Islam 2005 (66)	✖	✖	✔	✔	✖	✔	✖
Iushchuk 2005 (67)	?	?	?	?	?	?	?
Jazia 2009 (68)	✖	✖	✖	✔	?	✔	✔
Kalantari 2011 (69)	✔	✔	✖	✔	✖	✔	✔
Kamphues 2010 (70)	✖	✖	✖	✔	✔	✔	✖
Kandemir 2009 (71)	✖	✖	✖	✔	?	✔	✔
Kelleher 2005 (72)	✖	✔	✖	✔	✖	✔	✔
Khan 2008 (73)	?	✔	✖	✔	?	✔	✔

Kim 2011 (74)	✔	✔	✖	✔	✔	✔	✔
Koda 2007 (75)	✔	✔	✖	✔	✖	✔	✔
Koizumi 2011 (76)	✔	✔	✖	✔	✖	✔	✔
Lackner 2005 (77)	✔	✔	✔	✔	✔	✔	✔
Ladero 2010 (78)	✔	✔	✔	✔	✖	✔	✔
Lee 2011 (79)	✔	✖	✖	✔	✖	✔	✔
Leroy 2004 (80)	✔	✔	✖	✔	?	✔	✔
Leroy 2007 (81)	✔	✔	✔	✔	✖	✔	✔
Leroy 2011 (82)	?	?	?	✔	?	✔	✔
Lewin 2007 (83)	✔	✔	✖	✔	✖	✔	✔
Lieber 2006 (84)	✖	✖	✔	✔	✖	✔	✖
Liu 2006 (85)	✔	✔	✖	✔	?	✔	✔
Liu 2011 (86)	✔	✔	✖	✔	✔	✔	✔
Liu 2007 (87)	✔	✔	✖	✔	?	✔	✔
Loko 2008 (88)	✔	✔	✔	✔	✖	✔	✔
Lupsor 2008 (89)	✔	✔	✖	✔	✖	✔	✔

Lupsor 2009 (90)	✔	✔	✖	✔	✖	✔	✔
Macias 2006 (91)	✔	✔	✔	✔	✖	✔	✔
Macias 2011 (92)	?	?	✔	✔	✖	✔	?
Martinez 2011 (93)	✔	✔	✖	✔	✖	✔	?
Morikawa 2011 (94)	?	✔	✖	✔	?	✔	✔
Murawaki 2001 (95)	✖	✖	✖	✔	?	✔	?
Myers 2002 (96)	?	✔	✔	✔	✖	✔	✔
Nitta 2009 (97)	✔	✔	✖	✔	?	✔	✔
Nojiri 2010 (98)	?	✔	✖	✔	?	✔	?
Nunes 2005 (99)	✔	✔	✖	✔	?	✔	✖
Obara 2008 (100)	✖	✔	✖	✔	✖	✔	✖
Oliveira 2005 (101)	?	?	?	✔	?	✔	?
Orrlachio 2011 (102)	✖	?	✖	✔	✖	✔	✖
Paggi 2008 (103)	✔	✔	✔	✔	?	✔	✖
Parise 2006 (104)	✔	✔	✖	✔	?	✔	✔
Park 2000 (105)	✖	✔	✔	✔	?	✔	✖

Parkes 2011 (106)	✖	✔	✖	✔	?	✔	✖
Patel 2009 (107)	?	✔	✔	✔	✖	✔	?
Patel 2011 (108)	?	✔	✖	✔	✖	✔	?
Pohl 2001 (109)	✖	✔	✔	✔	✖	✔	?
Poynard 2012 (110)	✖	✔	✔	✔	?	✔	✖
Prati 2011 (111)	?	✔	?	✔	?	✔	✖
Qiu 2004 (112)	✔	✔	✖	✔	?	✔	✔
Reedy 1998 (113)	✖	✔	✔	✔	?	✔	✔
Ronot 2010 (114)	✔	✔	✖	✔	✖	✔	✔
Rossi 2003 (115)	✔	✔	✖	✔	?	✔	?
Rossini 2010 (116)	?	?	✖	✔	?	✔	?
Said 2010 (117)	✔	✔	✖	✔	✖	✔	?
Saitou 2005 (118)	?	✖	✖	✔	?	✔	?
Sanvisens 2009 (119)	✔	✔	✖	✔	?	✔	✖
Schiavon 2007 (120)	✖	✔	✖	✔	✖	✔	✖
Schiavon 2008 (121)	✖	✔	✖	✔	?	✔	✖

Schneider 2006 (122)	?	?	✖	✔	?	✔	?
Scneider 2005 (123)	✔	✔	✖	✔	?	✔	✔
Sebastiani 2012 (124)	✔	✔	✔	✔	✖	✔	✔
Sebastiani 2009 (125)	✖	✔	✔	✔	✖	✔	✔
Sebastiani 2006 (126)	✔	✔	✖	✔	✔	✔	✔
Sebastiani 2008 (127)	✔	✔	✔	✔	✔	✔	✔
Sene 2006 (128)	✖	✖	✖	✔	✖	✔	?
Sharabash 2009 (129)	✖	✔	?	✔	?	✔	?
Shastry 2007 (130)	?	?	✖	✔	?	✔	✔
Sheth 1997 (131)	✖	✔	✔	✔	?	✔	✖
Singal 2011 (132)	✔	✔	✔	✔	✖	✔	✖
Sirli 2010 (133)	✖	✔	✔	✔	✔	✔	✔
Snyder 2007 (134)	✔	✔	✖	✔	?	✔	✔
Snyder 2006 (135)	✖	✔	✖	✔	✖	✔	✖
Sohn 2010 (136)	?	✔	?	✔	?	✔	?
Sporea 2008 (137)	✔	✔	?	✔	?	✔	✖

Sporea 2010 (138)	✔	✔	✖	✔	?	✔	✔
Sporea 2011 (139)	?	✔	?	✔	?	✔	✔
Sporea 2011 (140)	?	✔	?	✔	?	✔	?
Sterling 2006 (141)	✔	✖	✖	✔	?	✔	✖
Stibbe 2011 (142)	?	✔	✔	✔	?	✔	✖
Sud 2009 (143)	✔	✔	✖	✔	?	✔	✔
Testa 2006 (144)	?	✔	✖	✔	✖	✔	✖
Thompson 2009 (145)	?	✔	?	✔	?	✔	?
Thompson 2009 (146)	?	✔	?	✔	?	✔	?
Thompson 2010 (147)	?	✔	?	✔	?	✔	?
Toniutto 2007 (148)	✖	✖	✖	✔	?	✔	✔
Trang 2008 (149)	?	✔	✖	✔	?	✔	✖
Trifan 2009 (150)	✔	✔	?	✔	?	✔	✔
Trocme 2006 (151)	?	✔	✖	✔	?	✔	✖
Vallet-Pichard 2007 (152)	✔	✔	✔	✔	?	✔	✔
Tural 2007 (153)	✔	✖	✔	✔	?	✔	✔

Valva 2011 (154)	?	✔	✔	✔	?	✔	✔
Varaut 2005 (155)	✖	✖	✔	✔	✖	✔	✖
Wai 2003 (156)	✔	✖	✖	✔	?	✔	✖
Westin 2008 (157)	✔	✔	?	✔	✖	✔	?
Wilson 2006 (158)	✖	✖	✔	✔	✖	✔	?
Wong 1998 (159)	✔	✔	?	✔	?	✔	?
Zaman 2004 (160)	✔	✔	✔	✔	✔	✔	✔
Zarski 2012 (161)	✔	✖	✔	✔	✔	✔	✖
Ziol 2005 (162)	✖	✔	✖	✔	✖	✔	✖

Red color ☒: High risk of bias

Green color ☑: Low risk of bias

Orange color ?: Unclear risk of bias

Figure 2: Illustration of the reduction in the 'Treat all' ICER when the SVR rate for F0-1 patients is varied

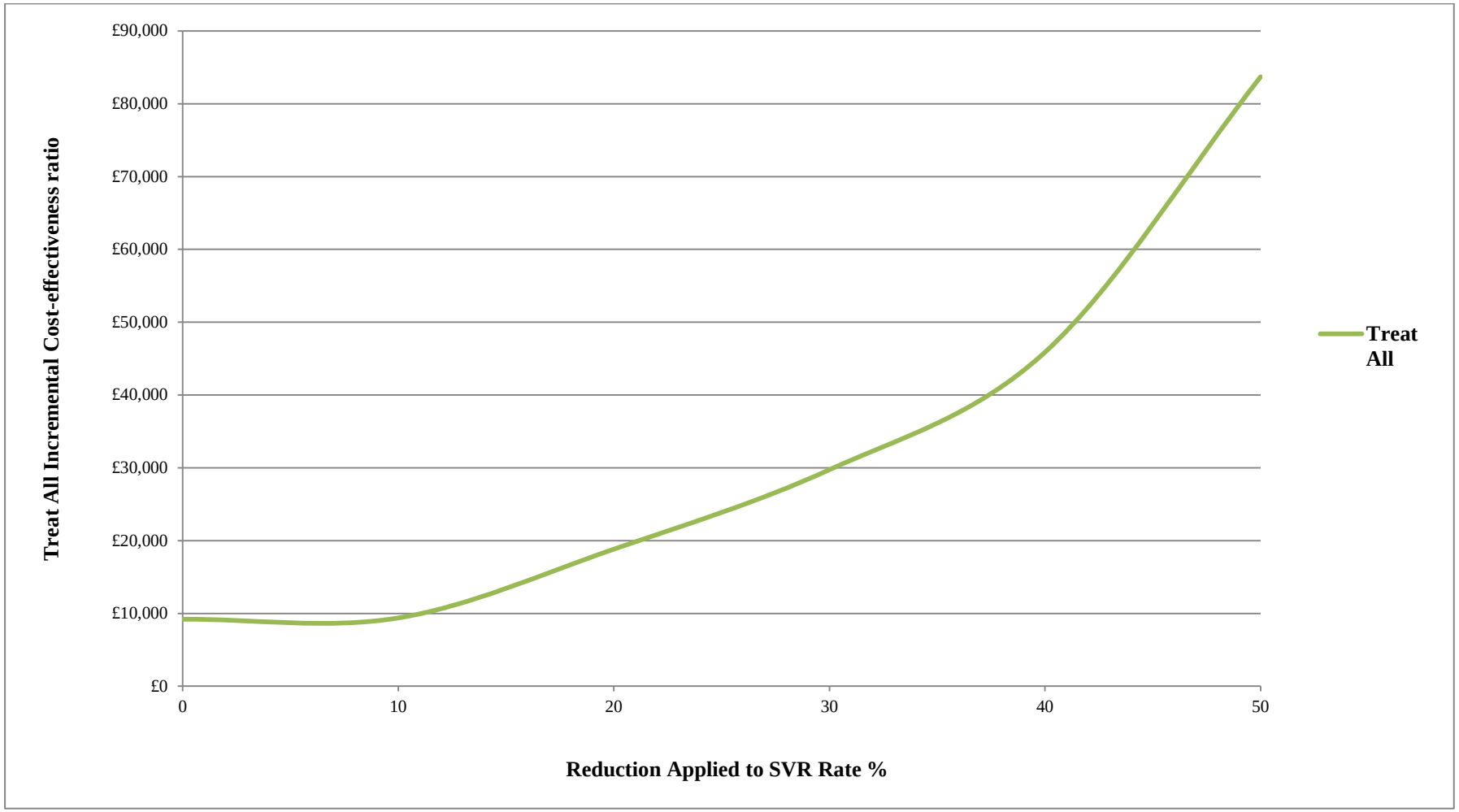

Table 4: Unit Cost of NILTs and Liver Biopsy (2012-13)

Test	Unit Cost £	Source
AAR	0.90	Personal Communication Royal Free (12.12.12)
Age-PLT Ratio (API)	3.50	Personal Communication Royal Free (12.12.12)
APRI	4.05	Personal Communication Royal Free (12.12.12)
ARFI	51.00	As Per personal communication Royal Free- costed at same cost as Fibroscan
AST-ALT ratio (AAR)	0.90	Personal Communication Royal Free (12.12.12)
Bordeaux	94.60	Costed as combination Strategy (Fibrotest and Fibroscan)
CDS	7.19	Personal Communication Royal Free 30.01.13
CEUS	113.70	Department of Health Reference costs 2011-12 (US >20 minutes) plus contrast (SonoVue) cost- £48.70 (Royal Free personal communication)
CT	105.00	Department of Health reference costs 2011-12 (CT with contrast pre and post scan) - Diagnostic Imaging Outpatients
DWMRI	199.00	Cost as per MRI with contrast (as per personal communication Royal Free 04.12.12)
ELF	108.00	From personal communication-Wiktoria Jonasson, Royal Free (09.05.2012)- cost of ELF is £90 + VAT
EOB-MRI	199.00	Cost as per MRI with contrast (as per Royal Free)
Fib 4	4.40	Personal Communication Royal Free (12.12.12)

Fibroindex	48.00	Personal Communication Royal Free (14.01.13)
Fibrometer	44.00	Personal communication - Anne Laure Gilles, BioLiveScale, (22.05.12)- quoted approximate price €50 (converted to UK cost using OECD indices)
Fibropaca-algorithm	509.89	Tests: APRI, Forns, Liver biopsy, Fibrotest: proportion calculated using Sebastiani *et al*. (124)
FibroQ	7.19	Personal Communication Royal Free (30.01.13)
Fibroscan (TE)	51.00	DH Reference Costs 2011/12 - Ultrasound less than 20 minutes (From Diagnostic Imaging, Outpatients (DIAGIM-OP) code RA23Z- As per advice from Royal Free
Fibrosis Index (FI)	4.40	Personal Communication Royal Free (12.12.12)
Fibrospect	35.34	Personal Communication Royal Free (14.01.13)
Fibrotest	43.60	Personal Communication (31.05.12)- Jean marie Castille-Directeur General (Biopredictive) - Converted to GBP Sterling (OECD PPP & Exchange rates data- rate 0.871929)
Fontana_F4	31.50	Personal Communication Royal Free (24.07.13)
Forns Index	4.26	Personal Communication Royal Free (22.01.13)
FPI high	8.58	Personal Communication Royal Free (22.01.13)
FPI low	8.58	Personal Communication Royal Free (22.01.13)
Fibrotest_Fibroscan (FT_TE)	94.60	Costed as Fibrotest & Fibroscan
GUCI	6.84	Personal Communication Royal Free (22.01.13)
HA	8.00	Personal Communication Royal Free (22.01.13)
Hepascore	16.24	Personal communication Royal Free 22.01.13

HUI	4.60	Personal Communication Royal Free (22.01.13)
Kings	6.84	Personal Communication Royal Free (22.01.13)
Leroy-algorithm	724.74	Tests: APRI, Liver biopsy, Fibrotest: proportion calculated using Sebastiani *et al*. (124)
Liver Biopsy	956.61	Stevenson *et al*. (163)
Lok (HALTC)	7.19	Personal Communication Royal Free (30.01.13)
MP3	20.00	Personal Communication Royal Free (30.01.13)
MRE	199.00	Department of Health Reference Costs 2011/12 - Diagnostic Imaging Outpatients, MRI one area pre and post contrast- (code RA23Z)
MRI	199.00	Cost as per MRI with contrast (as per Royal Free)
PGAA	9.07	Royal Free Personal Communication (24.07.13)
PIIINP/MMP-1 index	48.00	Personal Communication Royal Free (14.01.13)
PIINP	28.00	Personal Communication Royal Free (12.12.12)
PLT	3.50	Personal Communication Royal Free (29.05.12)
PLT_Spleen (SPRI)	54.50	Personal Communication Royal Free (04.12.12)
Pohl	4.40	Personal Communication Royal Free (30.01.13)
SAFE	743.22	Tests: APRI, Liver biopsy, Fibrotest: proportion calculated using Sebastiani *et al* (124)
TE	51.00	DH Reference Costs 2011/12 - Ultrasound less than 20 minutes (From Diagnostic Imaging, Outpatients (DIAGIM-OP) code RA23Z (as advised by Royal Free)

Type IV Collagen	20.00	Personal communication Royal Free (30.01.13)
Ultrasound (US)	51.00	DH Reference Costs 2011/12 - Ultrasound less than 20 minutes (From Diagnostic Imaging, Outpatients (DIAGIM-OP) code RA23Z
US SAPI	65.00	DH Reference Costs 2011/12- Ultrasound greater than 20 minutes
YKL-40	20.00	Personal Communication Royal Free (08.02.13)

Table 5: Base Case Analysis: (1st Stage of the analysis- comparison of NITs, liver biopsy, and the 'treat all' and 'no treatment' comparators)

Test Strategy	Costs £	QALYs	Incremental Cost £	Incremental QALY	ICER £
Treat None	54,878	12.45	-	-	Dominated
Liver Biopsy	48,710	14.03	-	-	Dominated
Pohl	47,727	14.04	-	-	Dominated
Fibroindex ((high cut off) cut off)	47,769	14.08	-	-	Dominated
Forns Index (high cut off)	47,426	14.12	-	-	Dominated
Hepascore (high cut off)	47,897	14.13	-	-	Dominated
FPI (high cut off)	47,335	14.14	-	-	Dominated
APRI (high cut off)	47,525	14.14	-	-	Dominated
Fib 4	47,900	14.15	-	-	Dominated
Ultrasound	48,090	14.17	-	-	Dominated
ELF (high cut off)	47,846	14.17	-	-	Dominated
HA (high cut off)	48,969	14.18	-	-	Dominated
PLT	47,742	14.18	-	-	Dominated
US SAPI (high cut off)	47,073	14.18	-	-	Dominated
YKL 40 (high cut off)	48,536	14.19	-	-	Dominated
FT (high cut off)	47,896	14.22	-	-	Dominated
PIIINP/MMP-1 index	47,724	14.24	-	-	Dominated
Kings (low cut off) Cut Off	47,743	14.24	-	-	Dominated
Kings (high cut off)	47,963	14.25	-	-	Dominated
Fibrosis Index	47,423	14.25	-	-	Dominated
ARFI	47,126	14.25	-	-	Dominated
GUCI	47,791	14.25	-	-	Dominated
AST-ALT	48,629	14.26	-	-	Dominated
AST-PLT	47,847	14.26	-	-	Dominated
MR	47,101	14.26	-	-	Dominated
EOB-MRI	48,054	14.26	-	-	Dominated
MR elastography	46,896	14.27	-	-	-
FIB-4 (high cut off)	48,158	14.27	-	-	Dominated
CEUS	47,215	14.28	-	-	Extendedly Dominated
APRI	47,522	14.28	-	-	Extendedly Dominated
Fibroscan	47,449	14.28	-	-	Extendedly Dominated
US SAPI	47,763	14.29	-	-	Extendedly Dominated
DWMRI	47,890	14.30	-	-	Dominated
Fibrotest	48,327	14.30	-	-	Dominated
Hyaluronic Acid (HA)	48,013	14.30	-	-	Dominated

PIINP	47,921	14.30	-	-	Dominated
Hepascore	48,189	14.31	-	-	Dominated
Fibrometer	48,104	14.32	-	-	Dominated
MP3	48,008	14.33	-	-	Dominated
FibrospectII	48,210	14.33	-	-	Dominated
Type IV collagen	47,888	14.34	-	-	Dominated
Hyaluronic Acid (low cut off)	48,824	14.34	-	-	Dominated
Kings	47,990	14.34	-	-	Dominated
ELF	48,232	14.34	-	-	Dominated
CT	48,727	14.35	-	-	Dominated
FibroQ	48,372	14.35	-	-	Dominated
PLT Spleen	47,803	14.35	-	-	Extendedly Dominated
Forns Index	50,555	14.37	-	-	Dominated
Lok	49,077	14.38	-	-	Dominated
APRI (low cut off)	48,713	14.40	-	-	Extendedly Dominated
CDS	49,429	14.40	-	-	Dominated
Fibroindex (low cut off)	48,872	14.40	-	-	Extendedly Dominated
ELF (low cut off)	49,041	14.44	-	-	Extendedly Dominated
FPI (low cut off)	49,232	14.47	-	-	Extendedly Dominated
FIB-4 (low cut off)	49,407	14.48	-	-	Extendedly Dominated
Forns Index (low cut off)	49,571	14.49	-	-	Dominated
FT (low cut off)	49,534	14.49	-	-	Extendedly Dominated
YKL 40 (low cut off)	50,156	14.50	-	-	Dominated
US SAPI (low cut off)	49,561	14.51	-	-	Extendedly Dominated
Treat All	51,241	14.73	4,345	0.46	9,351

Table 6: Base Case Analysis: (2nd Stage of the analysis- comparison of sequential testing strategies, most cost-effective tests from 1st stage of the analysis, liver biopsy, published algorithms, NIT with a combined cut off diagnostic threshold and the 'treat all' and 'no treatment' comparators)

Test Strategy	Costs £	QALYs	Incremental Cost £	Incremental QALY	ICER £
Treat None	54,878	12.45	-	-	Dominated
Liver Biopsy	48,710	14.03	-	-	Dominated
(S3) Type IV Collagen & PLT Spleen	47,099	14.16	-	-	Dominated
(S3) Kings & PLT Spleen	47,139	14.16	-	-	Dominated
(S3) Kings & Type IV collagen	47,113	14.16	-	-	Dominated
Hepascore & Fibroscan	47,675	14.19	-	-	Dominated
(S3) FPI Low & Type IV Collagen	47,417	14.21	-	-	Dominated
(S3) FPI Low & PLT Spleen	47,461	14.21	-	-	Dominated
(S2) Kings & Type IV collagen	47,001	14.21	-	-	Dominated
(S2) Kings & PLT Spleen	46,999	14.21	-	-	Dominated
Fibroindex & Fibroscan	47,368	14.21	-	-	Dominated
(S3) FT Low & PLT Spleen	47,548	14.21	-	-	Dominated
(S4) Kings & Type IV collagen	46,978	14.21	-	-	Dominated
(S4) Kings & PLT Spleen	46,965	14.22	-	-	Dominated
(S3) Kings & FT Low	47,579	14.22	-	-	Dominated
(S3) Type IV Collagen & US SAPI Low	47,516	14.22	-	-	Dominated
(S4) Type IV Collagen & PLT Spleen	46,911	14.22	-	-	-
(S2) Type IV Collagen & PLT Spleen	46,994	14.22	-	-	Dominated
(S3) Kings & US SAPI Low	47,606	14.22	-	-	Dominated
Leroy	47,248	14.23	-	-	Dominated
(S4) FPI Low & Type IV Collagen	47,328	14.24	-	-	Dominated
(S2) FPI Low & Type IV Collagen	47,328	14.24	-	-	Dominated
(S2) FPI Low & PLT Spleen	47,359	14.24	-	-	Dominated
(S4) FPI Low & PLT Spleen	47,347	14.24	-	-	Dominated
(S2) FT Low & PLT	47,519	14.24	-	-	Dominated

Spleen					
(S4) FT Low & PLT Spleen	47,446	14.24	-	-	Dominated
(S4) Kings & FT Low	47,521	14.25	-	-	Dominated
(S4) Type IV Collagen & US SAPI Low	47,427	14.25	-	-	Dominated
Forns & TE	47,233	14.25	-	-	Dominated
(S4) Kings & US SAPI Low	47,525	14.25	-	-	Dominated
(S1) Type IV Collagen	48,155	14.25	-	-	Dominated
(S1) PLT Spleen	48,233	14.26	-	-	Dominated
(S1) Kings	48,375	14.26	-	-	Dominated
Fibropaca	47,545	14.26	-	-	Dominated
APRI & TE	47,355	14.26	-	-	Dominated
(S2) Kings & FT Low	47,467	14.26	-	-	Dominated
Fibrospect & TE	46,954	14.27	43	0.05	928
(S2) Kings & US SAPI Low	47,466	14.27	-	-	Dominated
Bordeaux	47,026	14.27	-	-	Extendedly Dominated
ELF & TE	47,533	14.28	-	-	Dominated
(S2) Type IV Collagen & US SAPI Low	47,411	14.28	-	-	Extendedly Dominated
HA & TE	47,770	14.29	-	-	Dominated
YKL 40 & TE	48,251	14.31	-	-	Dominated
FIB 4 & TE	47,739	14.31	-	-	Dominated
FT & TE	47,748	14.31	-	-	Extendedly Dominated
SAFE	47,985	14.33	-	-	Dominated
Type IV Collagen	47,882	14.34	-	-	Dominated
Kings	47,976	14.34	-	-	Dominated
PLT Spleen	47,874	14.35	-	-	Extendedly Dominated
(S1) FPI Low	49,467	14.42	-	-	Dominated
(S1) FTL	49,699	14.44	-	-	Dominated
(S1) US SAPI Low	49,746	14.46	-	-	Dominated
FPI Low	49,218	14.47	-	-	Extendedly Dominated
FTL	49,536	14.49	-	-	Dominated
US SAPI Low	49,549	14.51	-	-	Extendedly Dominated
Treat All	51,241	14.73	4,287	0.47	9,204

Table 7. Exploratory analysis for treatment with sofosbuvir, peg-IFN and ribavirin: comparison of NITs, liver biopsy, and the 'treat all' and 'no treatment' comparators

Test	Costs £	QALYs	Incremental Cost £	Incremental QALY	ICER £
Treat None	54,836	12.439	-	-	Dominated
Liver Biopsy	53,087	14.508	-	-	Dominated
Pohl score	52,226	14.534	-	-	Dominated
Fibroindex (high cut off)	52,245	14.595	-	-	Dominated
Forns Index (high cut off)	52,224	14.631	-	-	Dominated
Hepascore (high cut off)	52,729	14.656	-	-	Dominated
FPI (high cut off)	52,204	14.656	-	-	-
APRI (high cut off)	52,543	14.666	-	-	Dominated
US	53,754	14.688	-	-	Dominated
Fib 4	53,264	14.689	-	-	Dominated
US SAPI (high cut off)	52,344	14.704	-	-	Extendedly Dominated
ELF (high cut off)	52,885	14.708	-	-	Dominated
PLT	52,885	14.724	-	-	Dominated
YKL 40 (high cut off)	54,051	14.730	-	-	Dominated
HA (high cut off)	54,630	14.732	-	-	Dominated
FT (high cut off)	53,324	14.768	-	-	Dominated
PIIINP/MMP-1 index	53,210	14.791	-	-	Dominated
ARFI	52,817	14.794	-	-	Dominated
Kings Low Cut Off	53,456	14.795	-	-	Dominated
Kings (high cut off)	53,814	14.803	-	-	Dominated
MR	52,809	14.803	-	-	Dominated
Fibrosis Index	52,964	14.805	-	-	Dominated
EOB-MRI	54,137	14.807	-	-	Dominated
AST-PLT	53,674	14.811	-	-	Dominated
AST-ALT	54,799	14.811	-	-	Dominated
MR elastography	52,529	14.814	325	0.16	2,057
GUCI	53,731	14.818	-	-	Dominated
CEUS	52,847	14.826	-	-	Extendedly Dominated
FIB-4 (high cut off)	54,208	14.827	-	-	Dominated
Fibroscan	53,470	14.830	-	-	Dominated
APRI	53,305	14.838	-	-	Extendedly Dominated

US SAPI	53,947	14.841	-	-	Dominated
DWMRI	54,148	14.857	-	-	Dominated
Fibrotest	54,498	14.873	-	-	Dominated
HA	54,050	14.873	-	-	Dominated
PIINP	53,930	14.876	-	-	Extendedly Dominated
Hepascore	54,352	14.883	-	-	Dominated
Fibrometer	54,315	14.898	-	-	Dominated
MP3	54,230	14.908	-	-	Dominated
FibrospectII	54,538	14.910	-	-	Dominated
PLT Spleen	54,356	14.911	-	-	Dominated
Type IV collagen	54,144	14.920	1,615	0.11	15,286
CT	55,641	14.922	-	-	Dominated
Kings	54,410	14.925	-	-	Extendedly Dominated
HA(low cut off)	55,448	14.925	-	-	Extendedly Dominated
FibroQ	54,977	14.929	-	-	Dominated
ELF	54,630	14.932	-	-	Extendedly Dominated
Forns Index	58,351	14.956	-	-	Dominated
Lok	56,139	14.960	-	-	Dominated
APRI (low cut off)	55,837	14.995	-	-	Dominated
CDS	56,871	15.000	-	-	Dominated
Fibroindex (low cut off)	55,934	15.013	-	-	Dominated
ELF (low cut off)	56,424	15.051	-	-	Extendedly Dominated
FPI (low cut off)	57,019	15.091	-	-	Extendedly Dominated
FIB-4 (low cut off)	57,413	15.105	-	-	Dominated
Forns Index (low cut off)	57,600	15.112	-	-	Dominated
FT (low cut off)	57,520	15.118	-	-	Extendedly Dominated
US SAPI (low cut off)	57,828	15.134	-	-	Extendedly Dominated
YKL 40 (low cut off)	58,494	15.137	-	-	Extendedly Dominated
Treat All	61,745	15.394	7,600	0.47	16,028

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