APPENDIX 1

Penetrance-2015 Jun 4-5

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2015 Week 22>
Search Strategy:
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1 (HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D).tw,kw. (6702)
2 ("p.C282Y" or "p.Cys282Tyr" or "p.His63Asp").tw,kw. (106)
3 1 or 2 (6703)
4 Hemochromatosis/ (18128)
5 h?emochromatos#s.tw,kw. (16689)
6 (HHC or HFE-HHC).tw,kw. (987)
7 iron storage disorder$1.tw,kw. (66)
8 (bronze$1 adj1 (diabetes or cirrhos#s)).tw,kw. (119)
9 pigmentary cirrhos#s.tw,kw. (67)
10 (Troisier-Hanot-Chauffard Syndrome or Von Recklenhausen-Applebaum Disease).tw,kw. (0)
11 or/3-10 (23820)
12 Genotype/ (426017)
13 (allel* or gene or genes or genetic* or genotyp* or mutation*).tw,kw. (4808549)
14 Heterozygote/ (87987)
15 Heterozygote Detection/ (13873)
16 (heterozygo* or hetero-zygo*).tw,kw. (185191)
17 Homozygote/ (44539)
18 (homozygo* or homo-zygo*).tw,kw. (161272)
19 exp Mutation/ (1427004)
20 or/12-19 (5297788)
21 11 and 20 (10560)
22 3 or 21 (11344)
23 exp Phenotype/ (593631)
24 (phenotyp* or chromosome marker* or DNA marker* or genetic marker* or penetrance).tw,kw. (939540)
25 exp Gene Expression/ (1388679)
26 exp Gene Frequency/ (153552)
27 Genetic Load/ (447)
28 exp disease progression/ (2328935)
29 (express* or progress*).tw,kw. (5670046)
30 or/23-29 (8438093)
31 22 and 30 (5549)
32 limit 31 to systematic reviews [Limit not valid in Embase; records were retained] (3503)
33 meta analysis.pt. (56502)
34 exp meta-analysis as topic/ (34107)

35 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (181104)
36 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (215242)
37 exp Technology assessment, biomedical/ (21010)
38 (cochrane or health technology assessment or evidence report).jw. (26934)
39 or/33-38 (401321)
40 31 and 39 (75)
41 32 or 40 (3511)
42 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (482025)
43 clinical trials as topic.sh. (173212)
44 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1548482)
45 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (305626)
46 trial.ti. (317019)
47 or/42-46 (1958775)
48 31 and 47 (121)
49 controlled clinical trial.pt. (89663)
50 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (489522)
51 (control* adj2 trial*).tw. (364021)
52 Non-Randomized Controlled Trials as Topic/ (4296)
53 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (80135)
54 (nRCT or nRCTs or non-RCT$1).tw. (835)
55 Controlled Before-After Studies/ (164510)
56 (control* adj3 ("before and after" or "before after")).tw. (6460)
57 Interrupted Time Series Analysis/ (147353)
58 (time series adj3 interrupt*).tw. (2677)
59 (pre- adj3 post-).tw. (124595)
60 (pretest adj3 posttest).tw. (6880)
61 Historically Controlled Study/ (164483)
62 (control* adj2 stud$3).tw. (372615)
63 Control Groups/ (76849)
64 (control$ adj2 group$1).tw. (803589)
65 trial.ti. (317019)
66 or/49-65 (2265509)
67 31 and 66 (285)
68 exp Cohort Studies/ (1645088)
69 cohort$1.tw. (792940)
70 Retrospective Studies/ (938058)
71 (longitudinal or prospective or retrospective).tw. (1908103)
72 ((followup or follow-up) adj (study or studies)).tw. (87298)
73 Observational study.pt. (11384)
74 (observation$2 adj (study or studies)).tw. (131823)
75 ((population or population-based) adj (study or studies or analys#s)).tw. (27532)
76 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (181)
77 Comparative Study.pt. (1711749)
78 ((comparative or comparison) adj (study or studies)).tw. (179788)

79 exp Case-Control Studies/ (821073)
80 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (159007)
81 Cross-Sectional Studies/ (340233)
82 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (268334)
83 or/68-82 (5618988)
84 31 and 83 (836)
85 41 or 48 or 67 or 84 (3996)
86 exp Animals/ not (exp Animals/ and Humans/) (8160413)
87 85 not 86 (3607)
88 (comment or editorial or interview or news).pt. (1545675)
89 (letter not (letter and randomized controlled trial)).pt. (1760438)
90 87 not (88 or 89) (3403)
91 limit 90 to yr="2009-current" (1408)
92 91 use prmz (149) [MEDLINE RECORDS]
93 (HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D).tw,kw. (6702)
94 ("p.C282Y" or "p.Cys282Tyr" or "p.His63Asp").tw,kw. (106)
95 93 or 94 (6703)
96 Hemochromatosis/ (18128)
97 h?emochromatos#s.tw,kw. (16689)
98 (HHC or HFE-HHC).tw,kw. (987)
99 iron storage disorder$1.tw,kw. (66)
100 (bronze$1 adj1 (diabetes or cirrhos#s)).tw,kw. (119)
101 pigmentary cirrhos#s.tw,kw. (67)
102 (Troisier-Hanot-Chauffard Syndrome or Von Recklenhausen-Applebaum Disease).tw,kw. (0)
103 or/95-102 (23820)
104 genotype/ (426017)
105 (allel* or gene or genes or genetic* or genotyp* or mutation*).tw,kw. (4808549)
106 exp heterozygosity/ (89801)
107 heterozygote detection/ (13873)
108 (heterozygo* or hetero-zygo*).tw,kw. (185191)
109 exp homozygosity/ (48338)
110 (homozygo* or homo-zygo*).tw,kw. (161272)
111 exp gene mutation/ (463242)
112 or/104-111 (4985669)
113 103 and 112 (10340)
114 95 or 113 (11177)
115 exp phenotype/ (593631)
116 penetrance/ (7967)
117 genotype phenotype correlation/ (24590)
118 genotype environment interaction/ (7161)
119 exp genetic marker/ (107782)
120 (phenotyp* or chromosome marker* or DNA marker* or genetic marker* or penetrance).tw,kw. (939540)
121 exp gene expression/ (1388679)
122 gene frequency/ (149520)
123 genetic load/ (447)
124 exp disease course/ (2202348)

125 or/115-124 (4545157)
126 114 and 125 (4065)
127 meta-analysis/ (150155)
128 "systematic review"/ (89739)
129 "meta analysis (topic)"/ (19797)
130 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (181104)
131 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (215242)
132 biomedical technology assessment/ (19906)
133 (cochrane or health technology assessment or evidence report).jw. (26934)
134 or/127-133 (437042)
135 126 and 134 (86)
136 randomized controlled trial/ or controlled clinical trial/ (990692)
137 exp "clinical trial (topic)"/ (147485)
138 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1548482)
139 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (305626)
140 trial.ti. (317019)
141 or/136-140 (2123096)
142 126 and 141 (119)
143 controlled clinical trial/ (480502)
144 "controlled clinical trial (topic)"/ (4279)
145 (control* adj2 trial*).tw. (364021)
146 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (80135)
147 (nRCT or nRCTs or non-RCT$1).tw. (835)
148 (control* adj3 ("before and after" or "before after")).tw. (6460)
149 time series analysis/ (15393)
150 (time series adj3 interrupt*).tw. (2677)
151 pretest posttest control group design/ (229)
152 (pre- adj3 post-).tw. (124595)
153 (pretest adj3 posttest).tw. (6880)
154 controlled study/ (4605820)
155 (control* adj2 stud$3).tw. (372615)
156 control group/ (76849)
157 (control$ adj2 group$1).tw. (803589)
158 trial.ti. (317019)
159 or/143-158 (5994002)
160 126 and 159 (998)
161 cohort analysis/ (383322)
162 cohort$1.tw. (792940)
163 retrospective study/ (938058)
164 longitudinal study/ (170268)
165 prospective study/ (682938)
166 (longitudinal or prospective or retrospective).tw. (1908103)
167 follow up/ (916615)
168 ((followup or follow-up) adj (study or studies)).tw. (87298)

169 observational study/ (83204)
170 (observation$2 adj (study or studies)).tw. (131823)
171 population research/ (71808)
172 ((population or population-based) adj (study or studies or analys#s)).tw. (27532)
173 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (181)
174 exp comparative study/ (2725847)
175 ((comparative or comparison) adj (study or studies)).tw. (179788)
176 exp case control study/ (821073)
177 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (159007)
178 cross-sectional study/ (340233)
179 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (268334)
180 or/161-179 (6871944)
181 126 and 180 (817)
182 135 or 142 or 160 or 181 (1617)
183 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38380742)
184 exp humans/ or exp human experimentation/ or exp human experiment/ (29852537)
185 183 not 184 (8529791)
186 182 not 185 (1469)
187 editorial.pt. (854147)
188 letter.pt. not (letter.pt. and randomized controlled trial/) (1756039)
189 186 not (187 or 188) (1412)
190 limit 189 to yr="2009-current" (558)
191 190 use emez (432) [EMBASE RECORDS]
192 92 or 191 (581)
193 remove duplicates from 192 (482) [UNIQUE RECORDS – BOTH DATABASES]
194 193 use prmz (143) [MEDLINE UNIQUE RECORDS]
195 193 use emez (339) [EMBASE UNIQUE RECORDS]

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Cochrane Library

Search Name: Hemochromatosis - Penetrance
Date Run: 04/06/15 19:26:39.883
Description: OHRI 2015 Jun 4

ID	Search	Hits
#1	(HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D):ti,ab,kw	44
#2	("p.C282Y" or "p.Cys282Tyr" or "p.His63Asp"):ti,ab,kw	0
#3	#1 or #2	44
#4	[mh Hemochromatosis]	48
#5	(hemochromatos* or haemochromatos*):ti,ab,kw	89
#6	(HHC or "HFE-HHC"):ti,ab,kw	10
#7	"iron storage" next disorder*:ti,ab,kw	0
#8	(bronze* near/2 (diabetes or cirrhos*)):ti,ab,kw	0
#9	pigmentary next cirrhos*:ti,ab,kw	0

#10 ("(Troisier-Hanot-Chauffard Syndrome" or "Von Recklenhausen-Applebaum Disease"):ti,ab,kw 0
#11 {or #3-#10} 118
#12 [mh ^Genotype] 2731
#13 (allel* or gene or genes or genetic* or genotyp* or mutation*):ti,ab,kw 19703
#14 [mh Heterozygote] 292
#15 [mh "Heterozygote Detection"] 65
#16 (heterozygo* or (hetero next zygo*)):ti,ab,kw 1025
#17 [mh Homozygote] 226
#18 (homozygo* or (homo next zygo*)):ti,ab,kw 1138
#19 [mh Mutation] 1832
#20 {or #12-#19} 20350
#21 #11 and #20 66
#22 #3 or #21 77
#23 [mh Phenotype] 1037
#24 (phenotyp* or (chromosome next marker*) or (DNA next marker*) or (genetic next marker*) or penetrance):ti,ab,kw 3251
#25 [mh "Gene Expression"] 661
#26 [mh "Gene Frequency"] 459
#27 [mh "Genetic Load"] 1
#28 [mh "Disease Progression"] 5455
#29 (express* or progress*):ti,ab,kw 52945
#30 {or #23-#29} 56338
#31 #22 and #30 Publication Year from 2009 to 2015 7

DARE – 1
CENTRAL – 5
NHS EED – 1 (*Did not download*)

Diagnostic Screening-2015 Jun 4-5

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2015 Week 22>
Search Strategy:
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1 Hemochromatosis/ (18128)
2 h?emochromatos#s.tw,kw. (16689)
3 (HHC or HFE-HHC).tw,kw. (987)
4 iron storage disorder$1.tw,kw. (66)
5 (bronze$1 adj1 (diabetes or cirrhos#s)).tw,kw. (119)
6 pigmentary cirrhos#s.tw,kw. (67)
7 (Troisier-Hanot-Chauffard Syndrome or Von Recklenhausen-Applebaum Disease).tw,kw. (0)
8 or/1-7 (22256)
9 Genetic Testing/ (63615)
10 DNA Mutational Analysis/ (493728)
11 ((DNA or gene or genes or genetic* or mutation*) adj3 (analy* or screen* or test*)).tw,kw. (604984)
12 (genotyping or phenotyping).tw,kw. (106555)
13 ((genotyp* or homozygo* or homo-zygo* or heterozygo* or hetero-zygo* or phenotyp*) adj3 (analy* or screen* or test*)).tw,kw. (87411)
14 (HFE adj3 (analy* or screen* or test*)).tw,kw. (682)
15 ((ferritin$1 or isoferritin$1 or iso-ferritin$1 or SF or isotransferrin$1 or iso-transferrin$1 or serotransferrin$1 or sero-transferrin$1 or transferrin$1 or TS) adj3 (analy* or screen* or test*)).tw,kw. (8165)
16 ((iron or iron-binding or UIBC) adj3 (analy* or screen* or test*)).tw,kw. (6533)
17 ((test or tests or testing) adj3 (concordan* or consistent* or agreement*)).tw,kw. (12013)
18 or/9-17 (1224445)
19 Hemochromatosis/ge (3186)
20 exp Genotype/ (618592)
21 Genetic Marker/ (78478)
22 Genetic Techniques/ (30125)
23 Genotyping Techniques/ (5771)
24 exp Genetic Predisposition to Disease/ (185568)
25 (gene or genes or genetic* or genotyp* or mutation*).tw,kw. (4756231)
26 (homozygo* or homo-zygo* or heterozygo* or hetero-zygo*).tw,kw. (284887)
27 exp Phenotype/ (593631)
28 (phenotyp* or chromosome marker* or DNA marker* or genetic marker* or penetrance).tw,kw. (939540)
29 exp Histocompatibility Antigens Class I/ (70539)
30 (Class I adj3 antigen*).tw,kw. (15046)
31 (HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D).tw,kw. (6702)
32 Iron/ (195886)
33 Iron Overload/ (14211)
34 (iron or iron-binding or UIBC).tw,kw. (296802)
35 exp Ferritins/ (46805)
36 (ferritin$1 or isoferritin$1 or iso-ferritin$1).tw,kw. (50298)

37 Transferrin/ (39219)
38 (isotransferrin$1 or iso-transferrin$1 or serotransferrin$1 or sero-transferrin$1 or transferrin$1).tw,kw. (80224)
39 or/19-38 (5780969)
40 Hemochromatosis/di, pc (3908)
41 "Diagnostic Techniques and Procedures"/ (76934)
42 (diagnos* adj3 (method or methods or technique* or technic or technics or procedure*)).tw,kw. (235473)
43 ((diagnos* or routine* or initial* or preliminary or mass or standard* or universal*) adj3 test*).tw,kw. (265370)
44 Iron/an, bl (18919)
45 Iron Overload/an, bl (430)
46 Ferritins/an, bl (9408)
47 Transferrin/an, bl (4354)
48 exp Hematologic Tests/ (406998)
49 ((blood or h?ematologic* or serum) adj3 (analy* or index* or indices or level* or test*)).tw,kw. (893677)
50 exp Mass Screening/ (270889)
51 (screen* or detect*).tw,kw. (4647244)
52 Early Diagnosis/ (90791)
53 (early adj3 (diagnos* or identif* or recogni*)).tw,kw. (252908)
54 or/40-53 (6356313)
55 39 and 54 (1309531)
56 18 or 55 (2175869)
57 8 and 56 (8370)
58 limit 57 to systematic reviews [Limit not valid in Embase; records were retained] (4518)
59 meta analysis.pt. (56502)
60 exp meta-analysis as topic/ (34107)
61 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (181104)
62 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (215242)
63 exp Technology assessment, biomedical/ (21010)
64 (cochrane or health technology assessment or evidence report).jw. (26934)
65 or/59-64 (401321)
66 57 and 65 (86)
67 58 or 66 (4530)
68 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (482025)
69 clinical trials as topic.sh. (173212)
70 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1548482)
71 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (305626)
72 trial.ti. (317019)
73 or/68-72 (1958775)
74 57 and 73 (181)
75 controlled clinical trial.pt. (89663)
76 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (489522)

77 (control* adj2 trial*).tw. (364021)
78 Non-Randomized Controlled Trials as Topic/ (4296)
79 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (80135)
80 (nRCT or nRCTs or non-RCT$1).tw. (835)
81 Controlled Before-After Studies/ (164510)
82 (control* adj3 ("before and after" or "before after")).tw. (6460)
83 Interrupted Time Series Analysis/ (147353)
84 (time series adj3 interrupt*).tw. (2677)
85 (pre- adj3 post-).tw. (124595)
86 (pretest adj3 posttest).tw. (6880)
87 Historically Controlled Study/ (164483)
88 (control* adj2 stud$3).tw. (372615)
89 Control Groups/ (76849)
90 (control$ adj2 group$1).tw. (803589)
91 trial.ti. (317019)
92 or/75-91 (2265509)
93 57 and 92 (382)
94 exp Cohort Studies/ (1645088)
95 cohort$1.tw. (792940)
96 Retrospective Studies/ (938058)
97 (longitudinal or prospective or retrospective).tw. (1908103)
98 ((followup or follow-up) adj (study or studies)).tw. (87298)
99 Observational study.pt. (11384)
100 (observation$2 adj (study or studies)).tw. (131823)
101 ((population or population-based) adj (study or studies or analys#s)).tw. (27532)
102 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (181)
103 Comparative Study.pt. (1711749)
104 ((comparative or comparison) adj (study or studies)).tw. (179788)
105 exp Case-Control Studies/ (821073)
106 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (159007)
107 Cross-Sectional Studies/ (340233)
108 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (268334)
109 or/94-108 (5618988)
110 57 and 109 (1260)
111 67 or 74 or 93 or 110 (5384)
112 exp Animals/ not (exp Animals/ and Humans/) (8160413)
113 111 not 112 (5133)
114 (comment or editorial or interview or news).pt. (1545675)
115 (letter not (letter and randomized controlled trial)).pt. (1760438)
116 113 not (114 or 115) (4875)
117 limit 116 to yr="2009-current" (1573)
118 117 use prmz (208) [MEDLINE RECORDS]
119 hemochromatosis/ (18128)
120 h?emochromatos#s.tw,kw. (16689)
121 (HHC or HFE-HHC).tw,kw. (987)
122 iron storage disorder$1.tw,kw. (66)
123 (bronze$1 adj1 (diabetes or cirrhos#s)).tw,kw. (119)

124 pigmentary cirrhos#s.tw,kw. (67)
125 (Troisier-Hanot-Chauffard Syndrome or Von Recklenhausen-Applebaum Disease).tw,kw. (0)
126 or/119-125 (22256)
127 genetic screening/ (78980)
128 ((DNA or gene or genes or genetic* or mutation*) adj3 (analy* or screen* or test*)).tw,kw. (604984)
129 (genotyping or phenotyping).tw,kw. (106555)
130 ((genotyp* or homozygo* or homo-zygo* or heterozygo* or hetero-zygo* or phenotyp*) adj3 (analy* or screen* or test*)).tw,kw. (87411)
131 (HFE adj3 (analy* or screen* or test*)).tw,kw. (682)
132 ((ferritin$1 or isoferritin$1 or iso-ferritin$1 or SF or isotransferrin$1 or iso-transferrin$1 or serotransferrin$1 or sero-transferrin$1 or transferrin$1 or TS) adj3 (analy* or screen* or test*)).tw,kw. (8165)
133 ((iron or iron-binding or UIBC) adj3 (analy* or screen* or test*)).tw,kw. (6533)
134 ((test or tests or testing) adj3 (concordan* or consistent* or agreement*)).tw,kw. (12013)
135 or/127-134 (818887)
136 exp genotype/ (618592)
137 exp genetic marker/ (107782)
138 genetic procedures/ (19219)
139 genotyping technique/ (5771)
140 exp genetic predisposition/ (185568)
141 (gene or genes or genetic* or genotyp* or mutation*).tw,kw. (4756231)
142 (homozygo* or homo-zygo* or heterozygo* or hetero-zygo*).tw,kw. (284887)
143 exp phenotype/ (593631)
144 (phenotyp* or chromosome marker* or DNA marker* or genetic marker* or penetrance).tw,kw. (939540)
145 major histocompatibility antigen class 1/ (19263)
146 (Class I adj3 antigen*).tw,kw. (15046)
147 HFE protein/ (1078)
148 gene mutation/ (279747)
149 (HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D).tw,kw. (6702)
150 iron overload/ (14211)
151 iron binding capacity/ (2621)
152 (iron or iron-binding or UIBC).tw,kw. (296802)
153 ferritin/ (46343)
154 (ferritin$1 or isoferritin$1 or iso-ferritin$1).tw,kw. (50298)
155 transferrin/ (39219)
156 (isotransferrin$1 or iso-transferrin$1 or serotransferrin$1 or sero-transferrin$1 or transferrin$1).tw,kw. (80224)
157 or/136-156 (5735307)
158 hemochromatosis/di, pc (3908)
159 diagnostic procedure/ (74557)
160 (diagnos* adj3 (method or methods or technique* or technic or technics or procedure*)).tw,kw. (235473)
161 ((diagnos* or routine* or initial* or preliminary or mass or standard* or universal*) adj3 test*).tw,kw. (265370)
162 iron blood level/ (7499)
163 ferritin blood level/ (11523)

164 exp blood analysis/ (121807)
165 ((blood or h?ematologic* or serum) adj3 (analy* or index* or indices or level* or test*)).tw,kw. (893677)
166 mass screening/ or screening/ (256204)
167 (screen* or detect*).tw,kw. (4647244)
168 early diagnosis/ (90791)
169 (early adj3 (diagnos* or identif* or recogni*)).tw,kw. (252908)
170 or/158-169 (6087316)
171 157 and 170 (1254235)
172 135 or 171 (1794152)
173 126 and 172 (7715)
174 meta-analysis/ (150155)
175 "systematic review"/ (89739)
176 "meta analysis (topic)"/ (19797)
177 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (181104)
178 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (215242)
179 biomedical technology assessment/ (19906)
180 (cochrane or health technology assessment or evidence report).jw. (26934)
181 or/174-180 (437042)
182 173 and 181 (97)
183 randomized controlled trial/ or controlled clinical trial/ (990692)
184 exp "clinical trial (topic)"/ (147485)
185 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1548482)
186 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (305626)
187 trial.ti. (317019)
188 or/183-187 (2123096)
189 173 and 188 (219)
190 controlled clinical trial/ (480502)
191 "controlled clinical trial (topic)"/ (4279)
192 (control* adj2 trial*).tw. (364021)
193 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (80135)
194 (nRCT or nRCTs or non-RCT$1).tw. (835)
195 (control* adj3 ("before and after" or "before after")).tw. (6460)
196 time series analysis/ (15393)
197 (time series adj3 interrupt*).tw. (2677)
198 pretest posttest control group design/ (229)
199 (pre- adj3 post-).tw. (124595)
200 (pretest adj3 posttest).tw. (6880)
201 controlled study/ (4605820)
202 (control* adj2 stud$3).tw. (372615)
203 control group/ (76849)
204 (control$ adj2 group$1).tw. (803589)
205 trial.ti. (317019)
206 or/190-205 (5994002)

207 173 and 206 (1322)
208 cohort analysis/ (383322)
209 cohort$1.tw. (792940)
210 retrospective study/ (938058)
211 longitudinal study/ (170268)
212 prospective study/ (682938)
213 (longitudinal or prospective or retrospective).tw. (1908103)
214 follow up/ (916615)
215 ((followup or follow-up) adj (study or studies)).tw. (87298)
216 observational study/ (83204)
217 (observation$2 adj (study or studies)).tw. (131823)
218 population research/ (71808)
219 ((population or population-based) adj (study or studies or analys#s)).tw. (27532)
220 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (181)
221 exp comparative study/ (2725847)
222 ((comparative or comparison) adj (study or studies)).tw. (179788)
223 exp case control study/ (821073)
224 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (159007)
225 cross-sectional study/ (340233)
226 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (268334)
227 or/208-226 (6871944)
228 173 and 227 (1389)
229 182 or 189 or 207 or 228 (2461)
230 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38380742)
231 exp humans/ or exp human experimentation/ or exp human experiment/ (29852537)
232 230 not 231 (8529791)
233 229 not 232 (2315)
234 editorial.pt. (854147)
235 letter.pt. not (letter.pt. and randomized controlled trial/) (1756039)
236 233 not (234 or 235) (2258)
237 limit 236 to yr="2009-current" (767)
238 237 use emez (609) [EMBASE RECORDS]
239 118 or 238 (817)
240 remove duplicates from 239 (669) [UNIQUE RECORDS – BOTH DATABASES]
241 240 use prmz (200) [MEDLINE UNIQUE RECORDS]
242 240 use emez (469) [EMBASE UNIQUE RECORDS]

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Cochrane Library

Search Name: Hemochromatosis - Genotypic or Phenotypic Screening
Date Run: 04/06/15 19:35:53.319
Description: OHRI 2015 Jun 4

ID Search Hits

#1 [mh Hemochromatosis] 48
#2 (hemochromatos* or haemochromatos*):ti,ab,kw 89
#3 (HHC or "HFE-HHC"):ti,ab,kw 10
#4 "iron storage" next disorder*:ti,ab,kw 0
#5 (bronze* near/2 (diabetes or cirrhos*)):ti,ab,kw 0
#6 pigmentary next cirrhos*:ti,ab,kw 0
#7 ("(Troisier-Hanot-Chauffard Syndrome" or "Von Recklenhausen-Applebaum Disease"):ti,ab,kw 0
#8 {or #1-#7} 98
#9 [mh "Genetic Testing"] 531
#10 [mh "DNA Mutational Analysis"] 247
#11 ((DNA or gene or genes or genetic* or mutation*) near/4 (analy* or screen* or test*)):ti,ab,kw 4076
#12 (genotyping or phenotyping):ti,ab,kw 919
#13 ((genotyp* or homozygo* or (homo next zygo*) or heterozygo* or (hetero next zygo*) or phenotyp*) near/4 (analy* or screen* or test*)):ti,ab,kw 1183
#14 (HFE near/4 (analy* or screen* or test*)):ti,ab,kw 7
#15 ((ferritin* or isoferritin* or (iso next ferritin*) or SF or isotransferrin* or (iso next transferrin*) or serotransferrin* or (sero next transferrin*) or transferrin* or TS) near/4 (analy* or screen* or test*)):ti,ab,kw 443
#16 ((iron or "iron-binding" or UIBC) near/4 (analy* or screen* or test*)):ti,ab,kw 426
#17 ((test or tests or testing) near/4 (concordan* or consistent* or agreement*)):ti,ab,kw 399
#18 {or #9-#17} 6743
#19 [mh Hemochromatosis/ge] 32
#20 [mh Genotype] 4295
#21 [mh "Genetic Marker"] 231
#22 [mh ^"Genetic Techniques"] 15
#23 [mh "Genotyping Techniques"] 16
#24 [mh "Genetic Predisposition to Disease"] 1498
#25 (gene or genes or genetic* or genotyp* or mutation*):ti,ab,kw 19509
#26 (homozygo* or (homo next zygo*) or heterozygo* or (hetero next zygo*)):ti,ab,kw 1741
#27 [mh Phenotype] 1037
#28 (phenotyp* or (chromosome next marker*) or (DNA next marker*) or (genetic next marker*) or penetrance):ti,ab,kw 3251
#29 [mh "Histocompatibility Antigens Class I"] 167
#30 ("Class I" next antigen*):ti,ab,kw 20
#31 (HFE or C282Y or HFEC282Y or "C282Y/H63D" or H63D):ti,ab,kw 44
#32 [mh Iron] 1672
#33 [mh "Iron Overload"] 144
#34 (iron or iron-binding or UIBC):ti,ab,kw 5028
#35 [mh Ferritins] 787
#36 (ferritin* or isoferritin* or (iso next ferritin*)):ti,ab,kw 1840
#37 [mh Transferrin] 322
#38 (isotransferrin* or (iso next transferrin*) or serotransferrin* or (sero next transferrin*) or transferrin*):ti,ab,kw 1496
#39 {or #19-#38} 27593
#40 [mh Hemochromatosis/di,pc] 23
#41 [mh ^"Diagnostic Techniques and Procedures"] 115

#42 (diagnos* near/4 (method or methods or technique* or technic or technics or procedure*)):ti,ab,kw 5693
#43 ((diagnos* or routine* or initial* or preliminary or mass or standard* or universal*) near/4 test*):ti,ab,kw 10997
#44 [mh Iron/an,bl] 636
#45 [mh "Iron Overload"/an,bl] 24
#46 [mh Ferritins/an,bl] 728
#47 [mh Transferrin/an,bl] 131
#48 [mh "Hematologic Tests"] 10382
#49 ((blood or hematologic* or haematologic* or serum) near/4 (analy* or index* or indices or level* or test*)):ti,ab,kw 58582
#50 [mh "Mass Screening"] 5188
#51 (screen* or detect*):ti,ab,kw 62414
#52 [mh ^"Early Diagnosis"] 449
#53 (early near/4 (diagnos* or identif* or recogni*)):ti,ab,kw 2541
#54 {or #40-#53} 134835
#55 #39 and #54 9363
#56 #18 or #55 13672
#57 #8 and #56 Publication Year from 2009 to 2015 23

DARE – 1
CENTRAL – 19
HTA – 1
NHS EED – 2 (*Did not download*)

APPENDIX 2

Modified New-Castle Ottawa Scale (NOS) for Cohort Studies

*Items in *italics* have been modified from the original scale to reflect penetrance data*

Selection

1) **Representative of the exposed cohort**
   a) *Is an inception cohort (those who present without symptoms at baseline or those who present with early symptoms of the disease)**
   b) *Is a sub-set of an inception cohort study, and clearly representative of that study**
   c) *Unclear*
   d) *Not an inception cohort*
2) **Selection of non-exposed cohort**
   This question was removed since we were only interested in exposed (genotyped) patients
3) **Ascertainment of exposure**
   a) *Reported that genotype was derived from blood work**
   b) *No description of how it was derived.*
4) **Demonstration that outcome of interest was not present at start of study**
   a) Yes*
   b) No
   c) *Not applicable*

Comparability

This question was removed since we were only interested in exposed (genotyped) patients, and not assessing non-genotyped patients (wild-type

Outcome

1) **Assessment of outcome**
   a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc)*
   b) Record linkage (e.g. identified through ICD codes on database records)*
   c) Self-report
   d) No description
2) **Was follow-up long enough for outcomes to occur?**
   a) *SF & TS- SF should be elevated by 60yrs (women), and 40-50yrs (men). The amount of follow up plus age of inclusion for study exceeds 60yrs (women) and 40-50yrs (men), and 60yrs (if sexes not reported separately)*.*
   b) *SF & TS- The amount of follow up plus age of inclusion does not exceed 60yrs (women) and 40-50yrs (men), and 60yrs (if sexes not reported separately).*
   c) *All other outcomes- Not applicable.*
3) **Adequacy of follow up of cohorts**
   a) Complete follow up- all subjects accounted for*
   b) Subjects lost to follow up unlikely to introduce bias- small number lost >80% follow up[A], or description provided of those lost*
   c) Follow up rate <80% and no description of those lost
   d) No statement.

TOTAL STARS: 6* for TS and SF outcomes; 5* or all other outcomes

***Adapted from:** Wells GA, Shea BJ, O'Connnell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2007. Ref Type: Online Source.

[A] % follow-up used for prognosis (inception cohort) studies for the Annal of Internal Medicine's ACP Journal Club published by the Health Information Unit at McMaster University, CANADA-http://hiru.mcmaster.ca/hiru/InclusionCriteria.html

APPENDIX 3
QUADAS 2

Domain 1: Patient Selection

A. **<u>Risk of Bias</u>**

Signalling Questions:

- 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)

Could the selection of patients have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. **<u>Concerns regarding applicability</u>**

Is there concern that the included patients do not match the review question? CONCERN: LOW/HIGH/UNCLEAR

Domain 2: Index Test(s) *If more than one index test was used, please complete for each test.*

A. **<u>Risk of Bias</u>**

Signalling Questions:

- Were the index test results interpreted without knowledge of the results of the reference standard? (Yes/No/Unclear)
- If a threshold was used, was it pre-specified? (Yes/No/Unclear)

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. **<u>Concerns regarding applicability</u>**

Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW/HIGH/UNCLEAR

Domain 3: Reference Standard or 'Other Test(s)'

A. **<u>Risk of Bias</u>**

Signalling Questions:

- Is the reference standard likely to correctly classify the target condition? (Yes/No/Unclear) ***←*Will be omitted for test concordance studies**
- Was the reference standard or 'other test(s)' results interpreted without knowledge of the results of the index test? (Yes/No/Unclear)

Could the reference standard or 'other test(s)', its conduct, or its interpretation have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. **<u>Concerns regarding applicability</u>**

Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW/HIGH/UNCLEAR
Will be omitted for test concordance studies

Domain 4: Flow and Timing

A. <u>Risk of Bias</u>

Signalling Questions:

- Was there an appropriate interval between index test(s) and reference standard? (Yes/No/Unclear)
- Did all patients receive a reference standard? (Yes/No/Unclear)
- Did patients receive the same reference standard (Yes/No/Unclear)
- Were all patients included in the analysis? (Yes/No/Unclear)

Could the patient flow have introduced bias? RISK: LOW/HIGH/UNCLEAR

***Adapted from:** Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine 2011;155(8):529-36.

APPENDIX 4

Relevant studies with less robust study designs for evidence synthesis

Authors' labeled the study as cohort; however no follow-up reported and study design was unclear (n=5)
Castiella A, Zapata E, Zubiaurre L, Alustiza JM, De Juan MD, Iribarren A, et al. Impact of H63D mutations, magnetic resonance and metabolic syndrome among outpatient referrals for elevated serum ferritin in the Basque Country. Annals of Hepatology: Official Journal of the Mexican Association of Hepatology 2015; 14(3).
Cheng R, Barton JC, Morrison ED, Phatak PD, Krawitt EL, Gordon SC, et al. Differences in hepatic phenotype between hemochromatosis patients with HFE C282Y homozygosity and other HFE genotypes. Journal of clinical gastroenterology 2009; 43(6):569.
Constantine CC, Anderson GJ, Vulpe CD, McLaren CE, Bahlo M, Yeap HL, et al. A novel association between a SNP in CYBRD1 and serum ferritin levels in a cohort study of HFE hereditary haemochromatosis. British journal of haematology 2009; 147(1): 140-9.
Krayenbuehl PA, Hersberger M, Truninger K, Mullhaupt B, Maly FE, Bargetzi M, et al. Toll-like receptor 4 gene polymorphism modulates phenotypic expression in patients with hereditary hemochromatosis. European journal of gastroenterology & hepatology 2010; 22(7):835-41.
Olynyk JK, Gan E, Tan T. Predicting iron overload in hyperferritinemia. Clinical Gastroenterology and Hepatology 2009; 7(3):359-62.
Cross-sectional Studies (n=13)
Aranda N, Viteri FE, Montserrat C, Arija V. Effects of C282Y, H63D, and S65C HFE gene mutations, diet, and life-style factors on iron status in a general Mediterranean population from Tarragona, Spain. Annals of hematology 2010; 89(8):767-73.
Benyamin B, McRae AF, Zhu G, Gordon S, Henders AK, Palotie A, et al. Variants in TF and HFE explain ~40% of genetic variation in serum-transferrin levels. The American Journal of Human Genetics 2009; 84(1):60-5.
Blanco-Rojo R, Toxqui L, Lopez-Parra AM, Baeza-Richer C, Perez-Granados AM, Arroyo-Pardo E, et al. Influence of diet, menstruation and genetic factors on iron status: A cross-sectional study in Spanish women of childbearing age. International journal of molecular sciences 2014; 15(3):4077-87.
Mahfouz RA, Sarieddine DS, Charafeddine KM, Khalik RNA, Cortas NK, Daher RT. Should we screen for hereditary hemochromatosis in healthy Lebanese: a pilot study. Molecular biology reports 2012; 39(1):753-9.
Mariani R, Pelucchi S, Arosio C, Coletti S, Pozzi M, Paolini V, et al. Genetic and metabolic factors are associated with increased hepatic iron stores in a selected population of p.Cys282Tyr heterozygotes. Blood Cells, Molecules, and Diseases 2010; 44(3):159-63.
Park SK, Hu H, Wright RO, Schwartz J, Cheng Y, Sparrow D, et al. Iron metabolism genes, low-level lead exposure and QT interval. Environmental Health Perspectives 2009; 117(1):80-85.
Pedersen P, Milman N. Extrinsic factors modifying expressivity of the HFE variant C282Y, H63D, S65C phenotypes in 1,294 Danish men. Annals of hematology 2009; 88(10):957-65.
Pedersen P, Milman N. Genetic screening for HFE hemochromatosis in 6,020 Danish men: penetrance of C282Y, H63D, and S65C variants. Annals of hematology 2009; 88(8):775-84.
Sanchez-Pablo MA, Gonzalez-Garcia V, del Castillo-Rueda A. Study of total stimulated saliva flow and hyperpigmentation in the oral mucosa of patients diagnosed with hereditary hemochromatosis. Series of 25 cases. Medicina oral, patologia oral y cirugia bucal 2012; 17(1):e45.
Romanowski T, Sikorska K, Bielawski KP. UGT1A1 gene polymorphism as a potential factor inducing iron overload in the pathogenesis of type 1 hereditary hemochromatosis. Hepatology Research 2009; 39(5):469-78.
Santos PC, Pereira AC, Cancado RD, Schettert IT, Sobreira TJ, Oliveira PS, et al. HFE gene mutations in patients with primary iron overload: Is there a significant improvement in molecular diagnosis yield with HFE sequencing? Blood Cells, Molecules, and Diseases 2010; 45(4):302-7.
Thorstensen K, Kvitland MA, Irgens WO, Hveem K, Asberg A. Screening for C282Y homozygosity in a Norwegian population (HUNT2): The sensitivity and specificity of transferrin saturation. Scandinavian journal of clinical and laboratory investigation 2010; 70(2):92-7.
Traglia M, Girelli D, Biino G, Campostrini N, Corbella M, Sala C, et al. Association of HFE and TMPRSS6 genetic variants with iron and erythrocyte parameters is only in part dependent on serum hepcidin concentrations. Journal of medical genetics 2011; 48(9):629-34.
Case-Control Studies (n=19)
Abbas MA, Abraham D, Kushner JP, McClain DA. Anti-obesity and pro-diabetic effects of hemochromatosis. Obesity 2014; 22(10):2120-2.
Acton RT, Barton JC, Leiendecker-Foster C, Zaun C, McLaren CE, Eckfeldt JH. Tumor necrosis factor-alpha promoter variants and iron phenotypes in 785 Hemochromatosis and Iron Overload Screening (HEIRS) Study participants. Blood Cells, Molecules, and Diseases 2010; 44(4):252-6.

Castiella A, Zapata E, De Juan MD, Otazua P, Fernandez J, Zubiaurre L, et al. Signficance of H63D homozygosity in a Basque population with hemochromatosis. Journal of gastroenterology and hepatology 2010; 25(7):1295-8.
De Souza GF, Riberio HL, De Sousa JC, Heredia FoF, De Freitas RM, Martins MRA, et al. HFE gene mutation and oxidative damage biomarkers in patients with myelodysplastic syndromes and its relation to transfusional iron overload: an observational cross-sectional study. BMJ Open 2015; 5(4):e006048.
Desgrippes R, Lanie F, Morcet J, Perrin MI, Manet G, Jezequel C, et al. Decreased iron burden in overweight C282Y homozygous women: Putative role of increased hepcidin production. Hepatology 2013; 57(5):1784-92.
Dostalikova-Cimburova M, Kratka K, Stransky J, Putova I, Cieslarova B, Horak J. Iron overload and HFE gene mutations in Czech patients with chronic liver diseases. Disease markers 2012; 32(1):65-72.
Jain S, Agarwal S, Tamhanker P, Verma P, Choudhuri G. Lack of association of primary iron overload and common HFE gene mutations with liver cirrhosis in adult Indian population. Indian Journal of Gastroenterology 2011; 30(4):161-5.
Leao GDR, Freire JM, Cunha Fernandes ALA, Moura De Oliveira TM, Leao ND, Gil EA, et al. Analysis of HFE genes C282Y, H63D, and S65D in patients with hyperferritinemia from northeastern Brazil. Journal of clinical laboratory analysis 2014; 28(3):178-85.
McLaren CE, McLachlan S, Garner CP, Vulpe CD, Gordeuk VR, Eckfeldt JH, et al. Associations between single nucleotide polymorphisms in iron-related genes and iron status in multiethnic populations. PLoS One 2012; 7(6):e38339.
Merono T, Brites F, Dauteuille C, Lhomme M, Menafra M, Arteaga A, et al. Metabolic alterations, HFE gene mutations and artherogenic lipoprotein modifications in patients with primary iron overload. Clinical Science 2015; 128)9):609-18.
Milic S, Ristic S, Starcevic-Cizmarevic N, Brajenovic-Milic B, Crnic-Martinovic M, Kapovic M, et al. Low frequency of HFE gene mutations in Croatian patients suspected of having hereditary hemochromatosis. American journal of Case Reports 2011; 17(10):CR552-CR556.
Ramakrishna R, Gupta S, Sarathy K, Bowen A. Phenotypic and clinical manifestations of compound heterozygous genetic hemochromatosis (CHGH): a non-invasive approach to clinical management. Internal medicine journal 2013; 43(3):254-61.
Rodriguez-Lopez R, Donoso M, Fernandez-Cavada M, Gonzalez-LM, Margallo A, Corral C, et al. Diagnostic utility of HFE variants in Spanish patients: association with HLA alleles and role in susceptibility to acute lymphoblastic leukemia. Gene 2013; 514(1):31-5.
Ryan JD, Ryan E, Fabre A, Lawless MW, Crowe J. Defective bone morphogenic protein signalling underlies hepcidin deficiency in HFE hereditary hemochromatosis. Hepatology 2010; 52(4):1266-73.
Santos PC, Cancado RD, Pereira AC, Schettert IT, Soares RA, Pagliusi RA, et al. Hereditary hemochromatosis: mutations in genes involved in iron homeostasis in Brazilian patients. Blood Cells, Molecules, and Diseases 2011;46(4):302-7.
Sikorska K, Romanowski T, Stalke P, Izycka-Swieszewska E, Piotr-Bielawski K. Iron overload and HFE gene mutations in Polish patients with liver cirrhosis. Hepatobiliary & Pancreatic Diseases International 2011; 10(3):270-5.
Valenti L, Fracanzani AL, Rametta R, Fraquelli M, Soverini G, Pelusi S, et al. Effect of the A736V TMPRSS6 polymorphism on the penetrance and clinical expression of hereditary hemochromatosis. Journal of hepatology 2012; 57(6):1319-25.
Wood MJ, Powell LW, Dixon JL, Subramaniam VN, Ramm GA. Transforming growth factor –ß and toll-like receptor-4 polymorphisms are not associated with fibrosis in haemochromatosis. World journal of gastroenterology: WJG 2013; 19(48):9366.
Yang Y, Ferec C, Mura C. SNP and halotype analysis reveals new HFE variants associated with iron overload trait. Human mutation 2011; 32(4):E2104-E2117.

APPENDIX 5

'Penetrance' Key Question- List of Excluded Studies at Full-Text Screening

Non-English articles

Drastikova, M.. [The importance of DNA analysis of C282Y, H63D and S65C mutations in the HFE gene]. [Czech]. Casopis Lekaru Ceskych 2012. 151 (9) 428-431.

Ivanoshchuk DE, Mikhailova SV, Kulikov IV, Maksimov VN, Voevoda MI, and Romashchenko AG.. [CCR5, CCR2, apoe, p53, ITGB3 and HFE gene polymorphism in Western Siberia long-livers]. [Russian]. Advances in Gerontology = Uspekhi Gerontologii/Rossiiskaia Akademiia Nauk, Gerontologicheskoe Obshchestvo 2012. 25 (3) 394-397.

Jouanolle, A. M.. [Molecular diagnosis of HFE mutations in routine laboratories. Results of a survey from reference laboratories in France]. [French]. Annales de Biologie Clinique 2012. 70 (3) 305-313.

Full-text not available

Adams, P. C.. The natural history of untreated HFE-related hemochromatosis. Acta Haematologica 2009. 122 (2-3) 134-139.

Dine, G., Hermine, O., Genty, V., Escolano, S., Fumagalli, G., Tafflet, M., Van, Lierde F., El, Helou N., Rousseaux, Blanchi M., Palierne, C., Frey, A., Lapostolle, J., Cervetti, J., Jouven, X., and Toussaint, J.. HFE mutations associated with high level sport performance. Haematologica 2011. 96 (#Issue#) 229-230.

Osterweil, N.. Genotyping predicts toxicity risk in acute myeloid leukemia. Oncology Report 2013. #volume# (MAR) 16-#End Page#.

Wickenhauser, C., Hoeppner, M., Krahl, R., Jaekel, N., Niederwieser, D., and Al-Ali, H. K.. Iron distribution in pre-transplant bone marrow biopsies and outcome after allogeneic hematopoietic cell transplantation. Onkologie 2011. 34 (#Issue#) 274-#End Page#.

Yavarian, M., SaberFiroozi, M., Mehrabani, D., Amirizadeh, S., and Karimi, M.. Prevalence of the HFE gene mutation in the liver transplanted and primary hemochromatosis patients in the Southern Iran. Iranian Red Crescent Medical Journal 2010. 12 (1) 22-26.

Abstracts

Adams, P.. Do hemochromatosis patients have an increased risk of all types of cancer?. Hepatology 2010. 52 (#Issue#) 497A-498A.

Adams, P., Barton, J., McLaren, G., Acton, R., Speechley, M., McLaren, C., Reboussin, D., Leiendecker-Foster, C., Snively, B., Harris, E., Vogt, T., Sholinsky, P., Thomson, E., Dawkins, F., Gordeuk, V., and Eckfeldt, J.. Screening for IRon overload: Lessons from the HEIRS study. American Journal of Hematology 2009. 84 (8) E361-E362.

Aguilar-Martinez, P., Bismuth, M., Blanc, F., Blanc, P., Cunat, S., Dereure, O., Dujols, P., Giansily-Blaizot, M., Jorgensen, C., Konate, A., Larrey, D., Le, Quellec A., Mura, T., Raingeard, I., Ramos, J., Renard, E., Rousseau, F., Schved, J.-F., and Picot, M. C.. The southern french registry of genetic hemochromatosis, a tool for determination of clinical prevalence and genotype penetrance of the disorder. Blood 2009. 114 (22) -#End Page#.

Allen, K.. Lecture 15: Hemochromatosis - Screening and penetrance. American Journal of Hematology 2009. 84 (8) E249-#End Page#.

Athiyarath, R., Shaktivel, K., Singh, D., Abraham, V. J., Srivastava, A., and Edison, E. S.. Association of single nucleotide polymorphisms with TIBC and erythrocyte count in iron deficiency anemia of pregnancy in Indian population. American Journal of Hematology 2013. 88 (5) E81-E82.

Bardou-Jacquet, E., Morcet, J., Perrin, M., Manet, G., Guyader, D., Moirand, R., and Deugnier, Y.. Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients. American Journal of Hematology 2013. 88 (5) E38-#End Page#.

Bardou-Jacquet, E., Morcet, J., Perrin, M., Manet, G., Guyader, D., Moirand, R., and Deugnier, Y. M.. Survival and causes of death in a cohort of 1086 treated C282Y HFE homozygous patients. Hepatology 2012. 56 (#Issue#) 288A-#End Page#.

Bardou-Jacquet, E., Philip, J., Ropert, M., Latournerie, M., Houssel-Debry, P., Guyader, D., Loreal, O., Boudjema, K., and Brissot, P.. Liver transplantation normalizes serum hepcidin level and cures iron metabolism alteration in HFE P.CYS282TYR hemochromatosis. American Journal

of Hematology 2013. 88 (5) E212-#End Page#.

Bardou-Jacquet, E., Philip, J., Ropert, M., Latournerie, M., Houssel-Debry, P., Guyader, D., Loreal, O., Boudjema, K., and Brissot, P.. Liver transplantation normalizes serum hepcidin level and cures Iron metabolism alteration in HFE P.CYS282TYR hemochromatosis. Hepatology 2012. 56 (#Issue#) 287A-#End Page#.

Barton, J., Barton, C., and Acton, R.. Survival and morbidity associated with serum ferritin >1000 mug/L in hemochromatosis probands with HFE C282Y/C282Y in a referral practice. American Journal of Hematology 2011. 86 (9) E23-#End Page#.

Barton, J., Delrio-Lafreniere, S., Leiendecker-Foster, C., Li, H., Acton, R., Press, R., and Eckfeldt, J.. HFE, SLC40A1, HAMP, HJV, TFR2, and FTL mutatons detected by denaturing high-performance liquid chromatography after iron phenotyping and HFE C282Y and H63D genotyping in 785 HEIRS study participants. American Journal of Hematology 2009. 84 (8) E367-E368.

Bignell, P., Schuh, A., and Robson, K.. Juvenile haemochromatosis mutations are not that simple. American Journal of Hematology 2013. 88 (5) E213-#End Page#.

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APPENDIX 6

'Penetrance' Key Question- AMSTAR

Article: European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. Journal of hepatology 2010; 53(1):3-22.	
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review	No (0 point)
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place	No (0 point)
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources: a grey literature search counts as supplementary)	No (0 point)
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.	No (0 point)
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. Note: Acceptable if excluded studies are referenced. If there is an electronic link to the list, but the link is dead, select "no"	No (0 point)
6. Was the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The range of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes (1 point)
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be reported (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc. or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high", a summary score/range for all studies is not acceptable).	No (0 point) *GRADE used, but QA not provided for EACH study.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies". Cannot score "yes" for this question if scored "no" for question 7.	Yes (1 point) *GRADE used.
9. Were the methods used to combine the findings of the studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?)	Yes (1 point)
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken)	No (0 point)

Note: If no test values of funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.	
11. Was conflict of interest included? Potential sources of support should be clearly acknowledged in both systematic review AND for each of the included studies. Note: To get a “yes”, must indicate source of funding or support for the systematic review AND for each of the included studies.	No (0 point)
Overall Score of Quality	**3 (Low Quality)**
Citation: Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of clinical epidemiology 2009; 62(10): 1013-20.	

APPENDIX 7

Population Characteristics								
'PENETRANCE' Key Question								
Authors; (1) Conflicts of Interests; (2) Funding Support	**Country & Ethnicity (E)**	**Inclusion & Exclusion Criteria**	**(1)Method of Cohort Derivation; (2) Length of Follow-Up**	**Inception Cohort?**	**(1)Total N (n=x genotyped and included in study); (2) % Male**	**Age (years)**	**Stages of Disease Progression (Baseline→ Duration/End of study)**	**(1)Receiving Treatment? (2) Co-morbidities?**
Penetrance Data								
Åsberg et al., 2013 (22) (1) No; (2) Unclear	Norway E- 'mostly Caucasian'	**Inclusion:** -C282Y/C282Y who participated in the HUNT 2 study **Exclusion:** -Patients dx with cancer and other events (not described) before participating in HUNT 2.	(1) HUNT 2 screening population; (2) Followed from screening (15 Dec 2009) or until date of cancer dx, death, or emigration	No	(1) 62,860 **(n=292)**; (2) 47%	Mean: ♂: C282Y/C282Y: 48.3; Others: 48.1 ♀: C282Y/C282Y: 50.7; Others: 48.0	Unclear→Unclear	(1) Treatment offered to all newly detected HH; (2) NR
Bardou-Jacquet et al., 2014 (18) (1)Yes; (2) Govn't, Academia	France E-NR	**Inclusion:** -Patients undergoing first single-organ liver transplant from 1Jan99-31Dec2008. -Patients included in HH group only if C282Y/C282Y.	(1) List of patients with first liver transplant at author's study center; (2) Median: 57 months	No	(1)736; **(n=18)** (2) NR	Mean ± SD at dx: 48.7 ± 7 (HH group)	Unclear→Unclear	(1) In HH group, all were receiving liver transplants to treat HH. Most were also given phlebotomy before transplant; (2) NR
Barton et al., 2012 (13) (1)No; (2) Unclear	Canada, The United States E- 100% Caucasian	**Inclusion:** -White and a proband – C282Y/C282Y(first in family to be dx with HH) -treated by phlebotomy if SF levels at dx were elevated -Resides in central Alabama or Ontario.	(1) Searches of medical records to identify patients evaluated for HH because of elevated TS or SF; (2) Start date NR (used age at dx). End of follow up was 1 July 2011.	Unclear	(1) Alabama cohort=294; Ontario cohort=128 **(n=294, 128)** (2) A: 63.9%; O: 68.8%	Mean ± SD: Alabama: SF≤ 1000ug/L= 48±14; SF>1000 ug/L= 50±13 Ontario: SF≤ 1000ug/L= 44±18; SF>1000 ug/L=	Mixed→Mixed	(1) Phlebotomy attempted in each proband with elevated SF. Liver transplant performed in those with cirrhosis or primary liver cancer (as appropriate); (2) NR

						53±13		
Wood et al., 2012 (14) (1)NR; (2) Non-Profit	Australia E-NR	**Inclusion:** -C282Y/C282Y undergone liver biopsy and had hepatic iron concentration measured. **Exclusion:** -Patients with hepatitis. -<16yrs at biopsy	(1) Subjects identified from prospective clinical database of HH patients seen at single institution between 1964-2007; (2) NR	No	(1) 291 **(n=291)**; (2) 67.4%	Mean ± SD: 42.5 ± 13.8	Unclear→Mixed	(1) No; (2) NR
Penetrance Data & Penetrance Data of Limited Utility								
Gurrin et al., 2009 (21) (1)No; (2) Govn't, Unclear	Australia E-NR	**Inclusion:** -Those from Monitoring Project on Cardiovascular Disease Risk Factors who were N. European Descent (born in Australia, UK, Ireland, or New Zealand)	(1)Derived from the Melbourne Collaborative Cohort Study; (2) Mean: 12 yrs	Yes	(1) 1,438 **(n=180)**; (2) 46.7%	Range: 40-69 (Baseline); 54-83 (follow-up)	Unclear→Mixed	(1) Three males underwent vensection during follow-up; (2) NR
Penetrance Data of Limited Utility								
Adams et al., 2014 (16) (1) No; (2) Govn't	Canada E-NR[A]	**Inclusion:** -<u>HEIRS:</u> ≥25 yrs & can provide consent. -<u>Sub-study:</u> Canadians without HFE C282Y/C282Y.	(1) Subjects recruited from HEIRS screening study; (2) Mean: 9 years after initial screening.	Unclear	(1) 19,159 **(n=682)**; (2) 40%	Mean:49	Unclear→Mixed[B]	(1) Subjects who had iron overload during screening underwent weekly phlebotomy; (2) NR
Aguilar-Martinez et al., 2010 (24) (1) No; (2) Govn't	France E- NR	**Inclusion:** -C282Y/C282Y ≥20 yrs with clinical, biological signs of HH **Exclusion:** -Asymptomatic and those whose clinical severity could not be determined.	(1) Registry of patients with HH; (2) Patients included in registry over 6 year period. Duration of follow-up NR.	No	(1) 249 (+ 103 not in registry) **(n=352)**; (2) 54.8%	Mean ± SD: 54.0 ± 13.2	Author defined stages: Stages 2,3,4[C]→Stages 2,3,4	(1) 70% receiving phlebotomies at inclusion; (2) NR
Aleman et al., 2011 (17) (1) No; (2) Govn't, Industry	Sweden E-NR	**Inclusion:** -Patients with HH **Exclusion**: -Patients with porphyria cutanea tarda or secondary iron overload	(1)Patients dx with HH recruited from nine university hospitals; (2) Mean ± SD: 11.9 yrs ± 5.8 yrs	No	(1) 373; **(n=259)** (2) 71%	Mean ± SD at dx[D]: 48 ± 14	Mixed→Mixed	(1) No; (2) NR

Carpenter et al., 2013 (23) (1) Yes; (2) Govn't, Academia	United Kingdom E- 100% Caucasian	**Inclusion:** -Patients with first presentation of clinical dx of HH	(1) Unclear; (2) NR	No	(1) 41 **(n=31)**; (2) 73.1%	Mean ± SD: 58.9 ± 14.1	Mixed→ Mixed	(1) Vensection; (2) NR
Cobbaert et al., 2012 (19) (1) No; (2) Govn't, Non-Profit	The Netherla-nds E: 95% Caucasian	**Inclusion:** -Subjects participating in the Monitoring Project on Cardiovascular Disease Risk Factors	(1) CVD cases and the random sample obtained from the Monitoring Project on Cardiovascular Disease Risk Factors; (2) Mortality follow-up until 1 Jan 2000. Followed for 9-13 yrs (364,917 person years)	Unclear	(1) 1,376 **(n=unclear)**; (2) NR	Range: 20-59 (total cohort)	Unclear→ Unclear	(1) No; (2) NR
Manet et al., 2012 (15) (1) No; (2) Govn't, Non-Profit	France E- NR	**Inclusion:** -Documented follow-up maintenance of phlebotomies for at least 12 consecutive months. -Four determinations of SF levels <100mg/L **-Exclusion:** Unavailability or nonfulfillment of treatment diary -Cannot determine SF -Noncompliance to therapy -Too short of duration for follow-up	(1) Patients recruited from the LOGIFER cohort; (2) At least 12 months	No	(1) 316 **(n=316)**; (2) 60.4%	Median (range) at dx: ♂: 41 (19-69) ♀: 45 (16-75)	Mixed→ Mixed	(1) Phlebotomies; (2) NR
Penetrance Data- Combined genotypes without providing results separately								
Fracanzani et al., 2010 (20) (1)No; (2) Govn't, Academia	Italy E-NR	**Inclusion:** -Subjects with clinical, biochemical and/or histological evidence of HH phenotype	(1) Three reference centers for HH; (2) Median: 112 months.	Unclear	(1) 452; **(n=338)** (2) 74.6%	Mean ± SD: HFE related: 47±13; Non-HFE related; 49±11	Mixed→Mixed	(1) All patients underwent weekly phlebotomy up to iron depletion and thereafter to maintenance phlebotomy; (2) HBC, HCV

'Diagnostic Screening' Key Question							
Authors; (1) Conflicts of Interests; (2) Funding Support	**Country & Ethnicity (E)**	**Inclusion & Exclusion Criteria**	**Method of Cohort Derivation;**	**(1)Index; (2)Reference Test; (3) Type of study**	**(1)Total N; (2) % Male**	**Age (years)**	**(1)Receiving Treatment? (2) Co-morbidities?**
Aleman et al., 2011 (17) (1) No; (2) Govn't, Industry	Sweden E-NR	**Inclusion:** -Patients with HH **Exclusion**: -Patients with porphyria cutanea tarda or secondary iron overload	Patients dx with HH recruited from nine university hospitals;	(1)Phenotypic→Genetic; (2)Liver biopsy (3) Diagnostic Accuracy-Cohort type	(1) 153 (2)79%	Mean ± SD at dx: 45±13	1) No; (2) NR

[A] NR=Not Reported;

[B] Mixed= Includes patients who are different stages along HH progression;

[C] Stage 2= Increased TS and SF (no clinical manifestations); Stage 3= Increased TS and SF with clinical manifestations with no direct impact on survival; Stage 4= Increased TS and SF with life threatening clinical manifestations with impact on survival;

[d] dx=diagnosis

APPENDIX 8

Evidence table for C282Y/C282Y genotype: Penetrance outcomes					
Outcomes (Follow-up)	**Definition**	**Studies (Patients)**	**Disease Progression**	**Results (n/N)**	**Quality score** (6 points for TS and SF outcomes; 5 points for all other)** **Satisfied Criteria¶:**
PENETRANCE OUTCOME- Genotype denominator reported					
BIOCHEMICAL					
*No studies address this domain of outcomes in regards to providing a **proportion**.*					
SF (median 60 mo)(18)	After liver transplant	1 (13)	Unclear→Unclear	Range: 10.7 µg/L -588.7 µg/L	4 (B, D, E, F)
TS (median 60 mo)(18)	After liver transplant	1 (13)	Unclear→Unclear	Median±SD: 28% ± 8.5% vs. 68% ± 30%‡, p=0.021	4 (B, D, E, F)
Serum Iron (median 60 mo)(18)	After liver transplant	1 (13)	Unclear→Unclear	Range: 6.14 µmol/L-22.2 µmol/L	3 (B, D, F)
CLINICAL					
No studies address this domain of outcomes.					
END STAGE ORGAN DISEASE					
Hepatic Fibrosis (NR) (14)	After liver biopsy	1 (291)	Unclear→Mixed	44% (128/291)	2 (B, D)
LIVER RELATED DISEASE OUTCOMES					
Hepcidin (median 60 mo)(18)	NR	1 (13)	Unclear→Unclear	Median±SD: 13.2 nmol/L ± 8.1 nmol/L vs. 1.61 nmol/L ± 3.6 nmol/L‡, p=0.006	3 (B, D, F)
Hepcidin/Ferritin Ratio (median 60 mo)(18)	NR	1 (13)	Unclear→Unclear	Median±SD: 6.93 ± 8.75 vs. 0.35 ± 3.6‡, p=0.015	3 (B, D, F)
Hepatic Iron Overload (median 60 mo)(18)	NR	1 (11)	Unclear→Unclear	18.2% (2/11)	3 (B, D, F)
Liver cancer Screening→date of cancer dx, death or emigration)(22)	NR	1 ♀:122 ♂: 170	Unclear→Unclear	♀: 0% (0/122) ♂: 1.2% (2/170)	4 (B, C, D, F)
Cause-specific death: Iron overload (Age of dx→ End of follow up-1Jul2011)(13)	Deaths including cirrhosis (hepatic failure and primary liver cancer) and cardiomyopathy	1 Alabama (294) Ontario (128)	Mixed→Mixed	*Alabama (SF>1000* µg/L*)*: 17.9% (20/112) vs. 3.3 % (6/182)* *Ontario (SF>1000* µg/L*):* 14.8% (9/61) vs. 3.0% (2/67) § RR (95%CI): *Alabama (SF>1000* µg/L*)*: 5.4	3 (C, D, F)

				(2.2-13.1)*, p=0.0002 *Ontario(SF>1000* µg/L*)*: 4.9 (1.1-22.0) §, p=0.0359	
Cause-specific death: cirrhosis (Age of dx→ End of follow up-1Jul2011)(13)	Deaths including cirrhosis (hepatic failure and primary liver cancer)	1 Alabama (294) Ontario (128)	Mixed→Mixed	*Alabama (SF>1000* µg/L*)*: 17.0% (19/112) vs. 3.3 % (6/182)* *Ontario (SF>1000* µg/L*)*: 13.1% (8/61) vs. 3.0% (2/67) §	3 (C, D, F)
OTHER OUTCOMES					
Cancer (Screening→date of cancer dx, death or emigration)(22)	All	1: ♀:122 ♂: 170	Unclear→Unclear	♀: 11.5% (14/122) ♂: 12.9% (22/170)	4 (B, C, D, F)
	Colorectal Cancer	1: ♀:122 ♂: 170	Unclear→Unclear	♀: 2.45% (3/122) ♂: 3.5% (6/170)	4 (B, C, D, F)
	Lung Cancer	1 ♀:122 ♂: 170	Unclear→Unclear	♀: 1.6% (2/122) ♂: 1.8% (3/170)	4 (B, C, D, F)
	Breast Cancer	1 ♀:122	Unclear→Unclear	2.45% (3/122)	4 (B, C, D, F)
	Prostate Cancer	1 ♂: 170	Unclear→Unclear	4.7% (8/170)	4 (B, C, D, F)
Survival (median 57 mo)(18)	N/A	1 (18)	Unclear→Unclear	*Survival at 1yr after LT:* 83% (15/18) *Survival at 5yr after LT:* 67% (12/18)	4 (B, C, D, F)
Survival (Age of dx→ End of follow up-1Jul2011)(13)	After diagnosis	1 Alabama (294) Ontario (128)	Mixed→Mixed	Mean ± SD: *Alabama:* 13.2yrs ± 7.3yrs *Ontario:* 12.5yrs ± 8.3yrs	3 (C, D, F)
Cause-specific death: cardiomyopathy (Age of dx→ End of follow up-1Jul2011)(13)	Death caused by myocardial siderosis	1 Alabama (294) Ontario (128)	Mixed→Mixed	*Alabama (SF>1000* µg/L*)*: 0.9% (1/112) vs. 0 % (0/182)* *Ontario (SF>1000* µg/L: 1.6% (1/61) vs. 0% (0/67) §	3 (C, D, F)

See **Appendix 7 for detailed NOS quality assessments

‡ Compared to before liver transplant

*Compared to Alabama probands SF≤1000 µg/L

§ Compared to Ontario probands SF≤1000 µg/L

¶ Modified New-Castle Ottawa Scale criteria:

A- Representativeness of the exposed cohort
B- Ascertainment of exposure
C- Demonstration that outcome of interest was not present at start of study
D- Assessment of outcome
E- Was follow-up long enough for outcomes to occur?-TS and SF only
F- Adequacy of follow up of cohorts

Evidence table for C282Y/H63D genotype: Penetrance outcomes					
Outcomes (Follow-up)	**Definition**	**Studies (Patients)**	**Disease Progression**	**Results (n/N)**	**Quality score** (6 points for TS and SF outcomes; 5 points for all other)** **Satisfied Criteria¶:**
PENETRANCE OUTCOME- Genotype denominator reported					
BIOCHEMICAL- Did not provide proportion data					
SF (mean 12yrs)(21) INCEPTION COHORT	SF at follow-up	1 ♀ post-menopausal at follow-up: 91 ♂: 78	Unclear→Mixed	Mean (95%CI): ♀: 120.4 µg/L (100.6-144.0 µg/L) ♂: 186.5 µg/L (148.9-233.6 µg/L)	4 (A, B, D, E)
TS (mean 12yrs)(21) INCEPTION COHORT	TS at follow-up	1 ♀ post-menopausal at follow-up: N=91 ♂: 78	Unclear→Mixed	Mean (95%CI): ♀: 38.9% (36.5-41.3%) ♂: 40.1% (37.1-43.0%)	4 (A, B, D, E)
BIOCHEMICAL- proportion provided					
SF (mean 12yrs)(21) INCEPTION COHORT	SF (>300 µg/L) at follow-up	1 (♀ post-menopausal at follow-up: N=90) (♂: N=78)	Unclear→Mixed	♀: 11% (10/90) ♂: 37% (29/78)	4 (A, B, D, E)
TS (mean 12yrs)(21) INCEPTION COHORT	TS (>45%) at follow-up	1 (♀ post-menopausal at follow-up: N=91) (♂: N=78)	Unclear→Mixed	♀: 22% (20/91) ♂: 8% (6/78)	4 (A, B, D, E)
CLINICAL					
Fatigue (mean 12yrs)(21) INCEPTION COHORT	Sought medical attention (self-report)	1 (♀:N=93) (♂: N=83)	Unclear→Mixed	♀: 15% (14/93) ♂: 11% (9/83)	2 (A, B)
	Sought medical attention (self-report). Stratified by SF levels (>300ug/L)	1 (♀:N=15) (♂: N=38)	Unclear→Mixed	♀: 13% (12/15) vs. 22%‡, p=0.45 ♂: 11% (4/38) vs. 12%‡, p=0.87	2 (A, B)
END STAGE ORGAN DISEASE					
No studies address this outcome domain.					
LIVER-RELATED DISEASE OUTCOMES					
Liver Disease (mean 12yrs)(21) INCEPTION COHORT	Physician diagnosed (self-report)	1 ♀:92 ♂: 83	Unclear→Mixed	♀: 4% (4/92) ♂: 7% (6/83)	2 (A, B)
	Physician diagnosed (self-	1 ♀:15	Unclear→Mixed	♀: 7% (1/15) vs. 6%‡, p=0.88 ♂: 8% (3/38) vs. 6%‡, p=0.74	2 (A, B)

	report) Stratified by SF levels (>300 µg/L)	♂: 38			
Hepatomegaly (mean 12yrs)(21) INCEPTION COHORT	Liver enlargement (span of ≥ 13cm)	1 ♀:77 ♂: 62	Unclear→Mixed	♀: 1% (1/77) ♂: 8% (5/62)	2 (A, B)
	Liver enlargement (span of ≥ 13cm) Stratified by SF levels (>300 µg/L)	1 ♀:12 ♂: 10	Unclear→Mixed	♀: 0% (0/12) vs. 3%‡, p=0.61 ♂: 10% (3/10) vs. 3%‡, p=0.31	2 (A, B)
AST/ALT (mean 12yrs)(21) INCEPTION COHORT	AST>45IU/L or ALT>40IU/L	1 ♀:91 ♂: 78	Unclear→Mixed	♀: 1% (1/91) ♂: 8% (6/78)	3 (A, B, D)
	AST>45IU/L or ALT>40IU/L Stratified by SF levels (>300 µg/L)	1 ♀:15 ♂: 36	Unclear→Mixed	♀: 0% (0/15) vs. 2%‡, p=0.60 ♂: 14% (5/36) vs. 0%‡, p=0.02	3 (A, B, D)
OTHER OUTCOMES					
Abnormal metacarpophalangeal joints (MCP2/3) (mean 12yrs)(21) INCEPTION COHORT	Bony spur, tenderness or effusion on either hand	1 ♀:80 ♂: 64	Unclear→Mixed	♀: 20% (16/80) ♂: 20% (13/64)	3 (A, B, D)
	Bony spur, tenderness or effusion on either hand Stratified by SF levels (>300 µg/L)	1 ♀:13 ♂: 31	Unclear→Mixed	♀: 15% (2/13) vs. 19%‡, p=0.76 ♂: 16% (5/31) vs. 23%‡, p=0.48	3 (A, B, D)
Arthritis (mean 12yrs)(21) INCEPTION COHORT	Physician diagnosed arthritis or rheumatism, taking aspirin	1 ♀:96 ♂: 84	Unclear→Mixed	♀: 7% (7/96) ♂: 2% (2/84)	2 (A, B)
	Physician diagnosed arthritis or rheumatism, taking aspirin	1 ♀:15 ♂: 38	Unclear→Mixed	♀: 7% (1/15) vs. 9%‡, p=0.77 ♂: 3% (1/38) vs. 3%‡, p=0.98	2 (A, B)

‡Normal SF levels (<300ug/L)

¶ Modified New-Castle Ottawa Scale criteria:

- A- Representativeness of the exposed cohort
- B- Ascertainment of exposure
- C- Demonstration that outcome of interest was not present at start of study
- D- Assessment of outcome
- E- Was follow-up long enough for outcomes to occur?-TS and SF only
- F- Adequacy of follow up of cohorts

** See **Appendix 7** for detailed NOS quality assessments

APPENDIX 9

DETAILED QUALITY ASSESSMENT OF INCLUDED STUDIES (MODIFIED NEWCASTLE-OTTAWA SCALE)					
	Åsberg et al., 2013 (22)	Bardou-Jacquet et al., 2014 (18)	Barton et al., 2012 (13)	Gurrin et al., 2009 (21)	Wood et al., 2012 (14)
SELECTION					
Representativeness of cohort					
Inception Cohort*				x	
Sub-set of an inception cohort (representative of original cohort)					
Sub-set of an inception cohort (not representative of original cohort)					
Unclear					
Not an inception cohort	x	x	x		x
Ascertainment of Exposure					
Genotype derived from blood work*	x	x		x	x
No description			x		
Demonstration Outcome was not present at start of study					
Yes*	Overall Incidence cancer, colorectal cancer, lung cancer, breast cancer, prostate, primary liver cancer	Survival	Survival, Iron overload deaths, cirrhosis deaths, cardiomyopathy deaths		
No				Fatigue, liver disease, hepatomegaly, abnormal MCP2/3 joints, arthritis	Hepatic fibrosis
N/A		SF, TS, serum Iron, hepcidin levels, hepcidin /ferritin ratio, HIC	Predictor outcome: SF	SF, TS, AST/ALT	
OUTCOMES					
Assessment of outcomes					
Independent or blind assessment or by reference to secure record.*		SF, TS, serum iron, hepcidin levels, hepcidin/ferritin ratio, HIC, survival	Predictor outcome: SF	SF, TS, AST/ALT, Abnormal MCP2/3 joints	Hepatic fibrosis
Record linkage*	Overall Incidence cancer, colorectal cancer, lung cancer, breast cancer, prostate, primary liver cancer		Survival, Iron overload deaths, cirrhosis deaths, cardiomyopathy deaths		
Self-Report				Fatigue, liver disease, hepatomegaly, arthritis	
No description					
Follow-Up long enough for outcomes to occur					
SF&TS: Enough time has lapsed*		SF, TS		SF, TS	
SF&TS: Insufficient time has lapsed			Predictor outcome: SF (cross-sectional)		
Other outcomes: N/A	Overall Incidence cancer, colorectal	Serum iron, hepcidin levels,	Survival, Iron overload deaths,	Fatigue, liver disease,	Hepatic fibrosis

	cancer, lung cancer, breast cancer, prostate, primary liver cancer	hepcidin-ferritin ratio, HIC, survival	cirrhosis deaths, cardiomyopathy deaths	hepatomegaly, AST/ALT, abnormal MCP2/3 joints, arthritis	
Adequacy of follow-up					
All subjects accounted for*		x	x		
>80% follow up or description provided of those lost*	x				
<80% follow up, and no description of those lost				x	
No statement					x
TOTAL SCORE PER OUTCOME **Penetrance:** **(6 points for TS and SF outcomes; 5 points for all other)**	**Penetrance** Overall cancer:4 Colorectal cancer:4 Lung cancer: 4 Breast cancer:4 Prostate cancer:4 Primary liver cancer:4	**Penetrance** SF: 4 TS: 4 Serum Iron: 3 Hepcidin: 3 Hepcidin/Ferritin Ratio: 3 Hepatic Iron Overload:3 Survival: 4	**Penetrance** Survival:3 Iron overload deaths:3 Cirrhosis deaths:3 Cardiomyopathy deaths:3	**Penetrance** SF:4 TS: 4 AST/ALT:3 Fatigue:2 Liver disease:2 Hepatomegaly: 2 Abnormal MCP2/3 joints:3 Arthritis:2	**Penetrance** Hepatic Fibrosis: 2

APPENDIX 10

'Diagnostic Screening' Key Question- List of Excluded Studies at Full-Text Screening

Non-English articles

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Study does not include an exclusive adult population

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APPENDIX 11

'Diagnostic Screening' Key Question- QUADAS-2

Article: Aleman S, Endalib S, Stal P, Loof L, Lindgren S, Sandberg-Gertzen H, et al. Health check-ups and family screening allow detection of hereditary hemochromatosis with less advanced liver fibrosis and survival comparable with the general population. Scandinavian journal of gastroenterology 2011; 46(9):1118-26.		
Domain#1: Patient Selection		
A. Risk of Bias	Was a consecutive or random sample of patients enrolled? (YES/NO/UNCLEAR)	No
	Was a case-control design avoided? (YES/NO/UNCLEAR)	Yes
	Did the study avoid inappropriate exclusions? Note: Test should be applied to all patients.	No
	Overall assessment of RoB. Any No- 'High Risk'; All Yes- 'Low Risk'; Not enough information- 'Unclear'	High Risk of Bias
B. Applicability	Is there concern that the included patients do not match the review question? (LOW/HIGH/UNCLEAR)	Low Risk of Bias
Domain #2: Index Test #1- Genetic		
A. Risk of Bias	Were the index test results interpreted without knowledge of the results of the reference standard? (YES/NO/UNCLEAR)	Unclear
	If a threshold was used, was it pre-specified? (YES/NO/UNCLEAR)	Yes
	Overall assessment of RoB. Any No- 'High Risk'; All Yes- 'Low Risk'; Not enough information- 'Unclear	Unclear Risk of Bias
B. Applicability	Is there concern that the index test, its conduct, or interpretation differ from the review question? (LOW/HIGH/UNCLEAR)	Low Risk of Bias
Domain #2: Index Test #1- Phenotypic		
A. Risk of Bias	Were the index test results interpreted without knowledge of the results of the reference standard? (YES/NO/UNCLEAR)	Yes
	If a threshold was used, was it pre-specified? (YES/NO/UNCLEAR)	No
	Overall assessment of RoB. Any No- 'High Risk'; All Yes- 'Low Risk'; Not enough information- 'Unclear	High Risk of Bias
B. Applicability	Is there concern that the index test, its conduct, or interpretation differ from the review question? (LOW/HIGH/UNCLEAR)	Low Risk of Bias
Domain#3: Reference Standard		
A. Risk of Bias	Is the reference standard likely to correctly classify the target condition? (YES/NO/UNCLEAR)	Yes
	Was the reference test results interpreted without knowledge of the results of the index test? (YES/NO/UNCLEAR)	Unclear
	Overall assessment of RoB. Any No- 'High Risk'; All Yes- 'Low Risk'; Not enough information- 'Unclear	Unclear Risk of Bias
B. Applicability	Is there concern that the target condition as defined by the reference standard does not match the review question? (LOW/HIGH/UNCLEAR)	Low Risk of Bias
Domain#4: Flow and Timing		
A. Risk of Bias	Was there an appropriate interval between index test(s) and reference standard? Note: Ideally should be done at the same time, but a 12h lag is	Yes

	appropriate (YES/NO/UNCLEAR)	
	Did all patients receive a reference standard? (YES/NO/UNCLEAR)	No
	Did patients receive the same reference standard? (YES/NO/UNCLEAR)	Yes
	Were all patients included in the analysis? (YES/NO/UNCLEAR)	No
Overall Assessment of RoB- Could the patient flow have introduced bias? Any No- 'High Risk'; All Yes- 'Low Risk'; Not enough information- 'Unclear		High Risk of Bias
Citation: Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine 2011; 155(8):529-36.		