

1 Informant-based screening tools for 2 dementia: an overview of systematic reviews

3 Martin Taylor-Rowan¹; Sara Nafisi¹; Rhiannon Owen²; Robyn Duffy³; Amit Patel²; Jennifer K
4 Burton¹; Terence J Quinn¹

5 1. Institute of Cardiovascular and Medical Sciences; University of Glasgow, 126
6 University Place, Glasgow, G12 8TA, United Kingdom.

7 2. Swansea University Medical School, Swansea University, Singleton Park, Swansea,
8 SA2 8PP, United Kingdom.

9 3. Older People's Psychology Service, NHS Greater Glasgow and Clyde, United
10 Kingdom.

11

12

13

14 Martin.taylor-rowan@glasgow.ac.uk (corresponding author)

15 Terry.quinn@glasgow.ac.uk

16 Sara.nafisi@istinye.edu.tr

17 Jenni.burton@glasgow.ac.uk

18 A.patel.13@bham.ac.uk

19 r.k.owen@swansea.ac.uk

20 Robyn.duffy@ggc.scot.nhs.uk

21

22 **Word Count:** 3740

23 **Figures:** 1

24 **Tables:** 4

25 **Supp materials:** Figures 3, Tables 11

26

65 **Abstract**

66 **Background:** Informant-based questionnaires may have utility for cognitive impairment or
67 dementia screening. Reviews describing accuracy of respective questionnaires are available,
68 but their focus on individual questionnaires precludes comparisons across tools. We
69 conducted an overview of systematic reviews to assess comparative accuracy of informant
70 questionnaires and identify areas where evidence is lacking.

71 **Methods:** We searched 6 databases to identify systematic reviews describing diagnostic test
72 accuracy of informant questionnaires for cognitive impairment or dementia. We pooled
73 sensitivity and specificity data for each questionnaire and used network approaches to
74 compare accuracy estimates across the differing tests. We used Grading of
75 Recommendations, Assessment, Development and Evaluation (GRADE) to evaluate overall
76 certainty of evidence. Finally, we created an evidence 'heat-map', describing availability of
77 accuracy data for individual tests in differing populations and settings.

78 **Results:** We identified 25 reviews, consisting of 93 studies and 13 informant questionnaires.
79 Pooled analysis (37 studies; 11,052 participants) ranked the 8-item interview to Ascertain
80 Dementia (AD8) highest for sensitivity (90%; 95%CrI=82%-95%; 'best-test' probability=36%);
81 while the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) was most
82 specific (81%; 95%CrI=66%-90%; 'best-test' probability=29%). GRADE-based evaluation of
83 evidence suggested certainty was 'low' overall. Our heat-map indicated only AD8 and
84 IQCODE have been extensively evaluated and most studies have been in the secondary care
85 setting.

86 **Conclusions:**AD8 and IQCODE appear to be valid questionnaires for cognitive impairment or
87 dementia assessment. Other available informant-based cognitive screening questionnaires
88 lack evidence to justify their use at present. Evidence on accuracy of available tools in
89 primary care settings and with specific populations is required.

90

91 **Key words:** Cognitive impairment; dementia; informant; screening; systematic review;
92 overview; informant

93

94 **Background**

95 Various assessment tools are available for screening of cognitive impairment or dementia.
96 The most commonly used tests directly assess cognition via questions or ‘pencil and paper’
97 tasks. (Harrison, Noel-Storr, Demeyere, Reyish, & Quinn, 2016) These direct assessments
98 provide a ‘snapshot’ of cognitive function that does not capture change in cognition, yet
99 cognitive deterioration is a fundamental component of dementia diagnosis. In addition,
100 direct assessments are often compromised, or not possible, in various acute secondary care
101 settings. (Elliott et al., 2019) There is a need, therefore, to identify measures that can
102 provide an alternative to traditional ‘direct’ cognitive screening methods.

103 An attractive approach is to assess cognition using informant-based interview tools.
104 Through this method, a patient’s close relative or friend (i.e. informant) is used to indirectly
105 identify temporal change in patients’ cognition and related function.

106 There are several informant tools available that are used in practice, such as the Informant
107 Questionnaire on Cognitive Decline in the Elderly (IQCODE), (Jorm and Jacomb, 1989) the 8-
108 item interview to Ascertain Dementia (AD8), (Galvin et al., 2005) and the General
109 Practitioner Assessment of Cognition (GPCOG). (Brodaty et al., 2002) Current guidelines
110 recommend use of structured informant interviews for cognitive assessment, but do not
111 recommend a particular tool in preference to others. (NICE, 2020)

112 A number of systematic reviews have attempted to establish the diagnostic accuracy of
113 informant-based tools in order to inform best tool selection. (Quinn et al., 2014; Harrison et
114 al., 2014; Harrison et al., 2015; Harrison et al., 2016) However, this rapidly growing literature

115 may be overwhelming for clinicians and decision-makers, and to date has only considered
116 available tools in isolation, precluding an answer to the question: which tool is best?

117 Novel evidence synthesis techniques (Owen RK, Cooper NJ, Quinn TJ, Lees R, & Sutton,
118 2018) allow for comparative assessment and are well suited to analysis of the accuracy of
119 the various informant tools. A synthesis of published systematic reviews, i.e. an overview of
120 systematic reviews, combined with a comparative summary could help to concisely
121 summarise the broader evidence-base, improving clinicians' and policy makers' ability to
122 select or recommend tools for cognitive assessment.

123 **Aims and objectives**

124 We performed an overview of systematic reviews to draw together results from systematic
125 reviews of the diagnostic properties of informant-based cognitive screening tools.

126 Our primary question was: what is the comparative accuracy of informant-based screening
127 tools for identifying cognitive impairment or dementia?

128 **Secondary objectives**

129 Where possible, we used this overview of systematic reviews to inform a number of
130 secondary objectives:

131 To determine variability in informant tool diagnostic test accuracy across various settings
132 and cognitive syndromes.

133 To evaluate the quality of systematic reviews of diagnostic test accuracy research such that
134 common methodological issues can be highlighted, and standards improved.

135 To produce an 'evidence map' that reveals gaps in the evidence-base where new primary
136 research is needed.

137

138 **Methods**

139 **Design**

140 We used the PRISMA (preferred reporting for systematic review and meta-analysis) checklist
141 for reporting in this overview of systematic reviews. (see supplemental materials e-1)

142 Design, conduct and interpretation of overviews of systematic reviews is evolving; we
143 followed recent best practice guidance. (Higgins et al., 2019; McKenzie & Brennan, 2017)

144 All aspects of searching, data extraction and review assessment were performed by two
145 reviewers independently, with recourse to a third arbitrator where disagreement could not
146 be resolved.

147 A detailed description of our methodology can be seen in the previously published protocol.
148 (Taylor-Rowan, Nafisi, Patel, Burton & Quinn, 2020) A summary of our methodology is
149 provided in the sections below.

150 **Inclusion and exclusion criteria**

151 We included systematic reviews that investigated the diagnostic properties (test accuracy)
152 of an informant-based cognitive screening tool. We included reviews conducted in any
153 setting or patient population. We operationalised the settings in which informant tools are
154 used as: secondary care, primary care, and community. We made no exclusions on the basis
155 of methodological quality, use of best practice methods, or approach to data synthesis.

156 Reviews were excluded if they exclusively reported on the diagnostic test accuracy of
157 telephone-based assessment, prognostic accuracy, or ‘functional’ informant tools that
158 measure ability to perform activities of daily living, rather than cognition *per se*. We also
159 excluded non-English language reviews.

160 **Search methods for identification of reviews**

161 We searched EMBASE (OVID); Health and Psychosocial Instruments (OVID); Medline (OVID);
162 CINAHL (EBSCO); PSYCHinfo (EBSCO) and the PROSPERO registry of review protocols. All
163 databases were searched from inception to December 2019. Search syntax can be seen in
164 supplementary materials (e-2).

165 We additionally contacted authors working in the field of dementia test accuracy to identify
166 other relevant systematic reviews, and studied reference lists of all included reviews in
167 order to identify additional titles not found by our search. (Greenhalgh & Peacock, 2005)

168

169 **Data collection and analysis**

170 **Title selection and data extraction**

171 Titles were screened using Covidence systematic review software, Veritas Health
172 Innovation, Melbourne, Australia, available at www.covidence.org. Data was extracted on
173 to a data collection proforma that was specifically designed by the author team (see
174 supplementary materials; e-3)

175 **Assessment of methodological and reporting quality of included reviews**

176 Methodological quality of included reviews was evaluated using a modified version of the
177 AMSTAR-2 (assessment of multiple systematic reviews) measurement tool (Shea et al.,
178 2017) which considered the following key domains: clarity of review objective; description
179 of study eligibility criteria; extent of searching undertaken; transparency of assessment
180 process; assessment of publication bias; assessment of heterogeneity. Overall study quality
181 conclusions were established based on guidance from Shea et al. (2017). However, as this
182 guidance is based on reviews of healthcare interventions, we modified the critical domains
183 to include only: adequacy of the literature search (item 4); risk of bias from individual
184 studies included in the review (item 9); appropriateness of meta-analytical methods (item
185 11); and consideration of risk of bias when interpreting the results of the review (item 13).
186 (see supplementary materials; e-4)

187 AMSTAR-2 assessment was complimented with an evaluation of reporting standards of
188 included reviews, utilising the PRISMA-DTA (Preferred Reporting Items for a Systematic
189 Review and Meta-analysis of Diagnostic Test Accuracy Studies) checklist. (McInnes et al.,
190 2018)

191 **Data synthesis**

192 We extracted data for analyses directly from original papers identified within respective
193 reviews. We calculated summary estimates for each informant questionnaire using the
194 bivariate approach (Reitsma, Glas, Scholten, Bossuyt & Zwinderman, 2005). Where suitable
195 data (defined below) were available, we then conducted comparative analyses, creating a
196 network where each questionnaire at a particular threshold score is a node and inferences
197 around relative test performance can be made through indirect comparison and ranking.
198 We used a bivariate network meta-analysis model accounting for the correlations between
199 multiple test accuracy measures from the same study. (Owen et al., 2018; O’Sullivan, 2019)
200 All models were estimated in a Bayesian framework using Markov Chain Monte Carlo
201 (MCMC) simulation and implemented in the WinBUGS 1.4.3 software. (Lunn, Thomas, Best,
202 & Spiegelhalter., 2000) Non-informative prior distributions were specified for test and
203 threshold-specific accuracy parameters. Informant-based screening tools with the highest
204 sensitivity and specificity were ranked in first place at each MCMC iteration. The estimated
205 rankings overall were calculated as a summary of the individual ranks at each iteration. The
206 probability that each screening tool was the best overall was calculated as the proportion of
207 MCMC iterations that each informant tool ranked in first place. Further details on the
208 analyses used are available in the original paper describing the method. (Owen et al., 2018)

209 We only included studies that evaluated informant tool test accuracy against a diagnostic
210 standard consistent with recognised criteria for diagnosis of dementia or MCI (e.g. ICD-10,
211 DSM III-V). We attempted meta-analysis where informant tools were assessed in at least
212 two studies. Case-control studies were excluded due to the potential to over inflate test
213 accuracy. For our primary analysis, we restricted analysis to the cut-points that were most
214 regularly used and of most clinical relevance (3.3. and 3.6 for IQCODE; 2 & 3 for AD8). As

215 our primary question was to evaluate the accuracy of tools as measures of cognitive
216 impairment or dementia (all inclusive), we did not discriminate between forms of cognitive
217 impairment evaluated in included studies. However, where single studies provided
218 sensitivity and specificity data for multiple forms of cognitive screening (e.g.
219 sensitivity/specificity values for screening of dementia vs no dementia and
220 sensitivity/specificity values for screening 'any cognitive impairment' vs normal cognition),
221 we selected one reported sensitivity and specificity figure based on the following hierarchy:
222 'any cognitive impairment vs normal cognition' > 'dementia vs no dementia' > 'Mild Cognitive
223 Impairment' (MCI) vs normal cognition'.

224 We employed GRADE (Grading of Recommendations Assessment, Development, and
225 Evaluation) (Guyatt et al., 2008) to evaluate overall strength of sensitivity and specificity
226 evidence for each tool in our meta-analysis, following recommended guidelines on
227 application of GRADE to diagnostic test accuracy evidence. (Singh, Chang, Matchar & Bass.,
228 2012)

229 **Subgroup analysis**

230 In addition to our primary analysis, we conducted a subgroup analyses designed to provide
231 specific data on performance of tools when used to screen for cognitive syndromes of
232 differing severity and when used in particular settings. Specifically, we evaluated
233 performance of respective informant tools when used to differentiate between people with
234 and without dementia (dementia vs no dementia) and between people with MCI and
235 normal cognition (MCI vs normal cognition). For each analysis, we sub-grouped by setting
236 (primary care, secondary care and community care), where possible.

237 **Sensitivity analysis**

238 We conducted a sensitivity analysis restricting to studies that had no high risk of bias
239 categories and at least 50% low risk of bias categories (based on individual study level data
240 within the included review).

241

242 **Method for generation of evidence map**

243 In addition to our search for relevant reviews, we identified individual (i.e. non-review)
244 informant-based diagnostic test accuracy studies to generate an 'evidence heat-map'.

245 **Search strategy for evidence map**

246 We accessed referenced studies in included reviews and supplemented this with a search of
247 study reference lists and, where provided, review exclusion lists for further available
248 studies.

249 **Inclusion/exclusion criteria for evidence map**

250 To be included in the evidence heat-map, individual studies could be either cohort or case-
251 control, but were required to be published in a peer-reviewed scientific journal and report
252 on the diagnostic test accuracy (i.e. sensitivity and specificity) of an informant tool. We
253 included non-English language papers in our evidence heat-map, but studies were excluded
254 if they reported participant numbers <20; were abstracts; were repeat data sets; assessed
255 prognostic diagnostic test accuracy; described a 'functional' informant measure only (e.g.

256 Independent activities of daily living scale); or if the informant tool was completed by
257 patients rather than informants.

258 Extent of available evidence was depicted via a shading scheme ranging from dark (0-10
259 studies; limited evidence), to light (>40 studies; substantial evidence).

260

261 **Results**

262

263 Our search identified 4865 titles. After screening, we found 25 reviews (including 93
264 studies) that met our inclusion criteria. (see Table 1) Details of the screening process and
265 reasons for each exclusion can be seen in supplementary materials (e-5).

266 [insert Table 1]

267 **Summary of reviews' findings**

268 Thirteen informant-based assessment tools were discussed in included reviews. The
269 diagnostic test accuracy properties of 11 of these tools were described. Each reviewed tool
270 is presented below.

271 **IQCODE**

272 The most comprehensively assessed informant tool was the IQCODE, which was included in
273 18 reviews and 52 original studies. Five distinct versions of the IQCODE were described
274 based on the number of component question items (IQCODE-32, IQCODE-26, IQCODE-16,
275 IQCODE-17, IQCODE-7); the most commonly used versions were the 26-item and the 16-
276 item adaptation.

277 Pooled estimates of IQCODE accuracy for dementia diagnosis ranged from sensitivity 80-
278 91% and specificity 66-85%. Review evaluations of IQCODE diagnostic test accuracy studies
279 suggested study quality was generally poor. In Cochrane reviews, (Quinn et al., 2014;
280 Harrison et al., 2014; Harrison et al., 2015) just 2/25 IQCODE studies were judged to have no
281 high risk of bias categories. Typical issues were around lack of blinding and unnecessary
282 patient exclusions—particularly removal of those who may benefit most from an informant-
283 based assessment (e.g. patients with comorbidities that make traditional cognitive
284 assessments challenging).

285 **AD8**

286 The AD8 was assessed in 5 reviews (20 studies). Pooled sensitivity rates for dementia
287 diagnosis ranged from 88-97% and pooled specificity rates ranged from 64-81%. Cochrane
288 review evaluations (Hendry et al., 2019) determined that 4/10 AD8 studies had no high risk
289 of bias categories. Areas of study limitation were around inadequate reporting,
290 inappropriate exclusions of participants, and high participant drop-out rates due to inability
291 to complete tests.

292 **GPCOG**

293 The GPCOG was evaluated in 6 reviews, describing 5 distinct studies.

294 All but two reviews evaluated the diagnostic test accuracy of the GPCOG based on the
295 evidence of just 1 'fair quality' (Lin, O'Connor, Rossom, Perdu & Eckstrom., 2013) study. A
296 more recent review (Tsoi, Chan, Hirai, Wong & Kwok., 2015) evaluated 5 GPCOG studies and
297 reported a pooled sensitivity of 92% and specificity of 87%. However, risk of bias was
298 substantial (25% of studies rated high risk of bias in 3 out of 4 domains). Unlike most other

299 informant tools, the GPCOG has a combined patient and informant assessment. When the
300 informant component of the GPCOG was used in isolation, it appeared to have poor
301 specificity (49-66%). (Kansagara & Freeman., 2010)

302 **Other informant-based assessment tools**

303 Ten additional informant tools were described in at least one included review. A summary
304 of the diagnostic test accuracy evidence for each can be seen in Table 2.

305 [insert Table 2]

306 **Network meta-analysis**

307 From each review, we identified a total of 37 suitable studies (11,052 participants) to
308 evaluate comparative performance of respective tools. One study (Jorm et al., 1996)
309 provided direct (within study) comparative data on the IQCODE-26 and IQCODE-16; 2
310 studies (Jackson, MacLulich, Gladman, Lord & Sheehan, 2016; Razavi et al., 2014) provided
311 direct comparative data on IQCODE-16 and AD8. All other studies provided test accuracy
312 properties of single informant tools in isolation, meaning indirect (between study)
313 comparisons were predominant in our network meta-analyses.

314 **Primary analysis**

315 Our primary network meta-analysis examined performance of informant tools as measures
316 of cognitive impairment or dementia (all inclusive). Only 3 informant tools had sufficient
317 data for comparative analysis (IQCODE-26; IQCODE-16 & AD8).

318 Results suggest AD8 at cut-point 2 may have the highest sensitivity (90%; 95% credible
319 intervals [CrI]=82%-95%; 'best test' probability=36%) for detecting cognitive impairment or
320 dementia, although there was little difference between AD8 at cut point 2, AD8 at cut point

321 3 and IQCODE-16 at cut point 3.6 with probability best of 36%, 23%, and 22% respectively.
322 IQCODE-26 at cut-point 3.6 may have the highest specificity (81%; 95%CrI=66%-90%; 'best
323 test' probability= 29%), though again there was little difference between IQCODE-26 at cut-
324 point 3.6, IQCODE-16 at cut point 3.6, and IQCODE-16 at cut point 3.3 with probability best
325 of 29%. 26% and 17%, respectively. We noted that two studies (Jackson, MacLulich,
326 Gladman, Lord & Sheehan, 2016; de Jonghe, 1997) were conducted in distinct populations
327 (delirious and depressed, respectively) that could alter diagnostic test accuracy properties.
328 We therefore conducted an additional sensitivity analysis, removing these 2 studies. Results
329 were unchanged. (see supplementary materials; e-6)

330 Comparative performance for each tool at respective cut-points can be seen in Table 3.

331 [insert Table 3]

332 **Subgroup analysis**

333 We evaluated the performance of tools when screening for a specific cognitive syndrome in
334 a particular setting. Sufficient data for pooling in this subgroup analysis was only available
335 for respective tools at certain cut-points. (see Table 4)

336 Comparative data on tool performance for 'dementia vs no dementia' screening suggests
337 that the AD8 at cut-point 2 may have the highest sensitivity for dementia in both secondary
338 care (96%; 95%CrI=72-99%; 'best test' probability= 76%) and community settings (86%;
339 95%CrI=64-95%; 'best test' probability=48%). IQCODE-16 at cut point 3.3 had the greatest
340 specificity for dementia assessment in secondary care (71%; 95%CrI=35-93%; 'best test'
341 probability=73%) while IQCODE-26 at cut-point 3.6 had the highest specificity (93%;
342 95%CrI=81-98%; 'best test' probability=90%) in the community.

343 Comparisons of general tool performance across settings suggest sensitivity of each tool is
344 consistently higher when used in the secondary care setting than when used in the
345 community (secondary care sensitivity range: 82-96%; community care sensitivity range: 68-
346 86%), whereas specificity is comparatively reduced (secondary care specificity range: 39-
347 71%; community care specificity range:71-93%).

348 [insert Table 4]

349 There were insufficient studies to compare tool performance when used in primary care or
350 for assessing MCI vs normal cognition.

351

352 **Risk of Bias sensitivity analysis**

353 We evaluated reported rates when restricted to studies deemed to be at lower risk of bias.
354 Seven studies were available in total; however, there was too much heterogeneity to pool
355 data, hence individual study findings were assessed. (Supplementary materials, e-6) The
356 general trend of informant tool performance was consistent with our pooled analyses.

357 **Strength of overall evidence**

358 Our GRADE rating of the strength of the IQCODE and AD8 diagnostic test accuracy evidence
359 was 'low' for sensitivity and specificity of both tools, primarily due to the risk of bias present
360 in included studies and the imprecision apparent in our pooled rates. (see supplementary
361 materials, e-7)

362

363 **Overview of systematic reviews—evaluation of review methodological and reporting**
364 **quality**

365 Our AMSTAR-2 evaluations highlighted a number of methodological issues in included
366 reviews. Overall review quality was mixed: 8/25 (32%) reviews were ‘critically low’ quality;
367 6/25 (24%) reviews were rated moderate and 3/25 (12%) were high methodological quality.
368 All reviews rated moderate or above were conducted from 2010 onwards (see supplemental
369 materials for AMSTAR-2 evaluation, e-8). All reviews performed a comprehensive search
370 and study inclusion criteria was generally adequately explained. However, a number of
371 reviews did not perform the systematic search and/or conduct data-extraction in duplicate
372 via 2 independent investigators (9/25; 36%); errors in data extraction were frequent, and
373 very few reviews pre-registered a protocol (5/25; 20%).

374 Meta-analyses were performed in 11/25 (44%) reviews and appropriate statistical methods
375 were used in each—though it was common for reviews to include case-control studies in
376 pooled analyses, potentially exaggerating diagnostic test accuracy. (Higgins et al, 2019)

377 Risk of bias was not adequately investigated in 9/25 (36%) reviews. Where risk of bias
378 assessment was conducted, conclusions regarding individual studies were often contrasting.
379 For instance, Chen et al. (2017) rated all seven included AD8 studies to be ‘high quality’,
380 identifying no high risk of bias domains in any study; Hendry et al. (2019) rated 4/7 of the
381 same studies to have at least 1 high risk of bias domain. No reviews conducted a sensitivity
382 analysis gauging the impact of high risk of bias studies upon reported pooled results, and
383 only 1 review (Chen et al., 2017) investigated possible publication bias.

384 Evaluation of reporting standards via PRISMA-DTA revealed main issues around explicit
385 statements of objectives (12/25 [48%] studies), describing information sources in adequate

386 detail (12/25 [48%] studies) and reporting sufficient details of test accuracy from individual
387 included studies (11/25 [44%] studies).

388

389 **Evidence Map findings**

390 A total of 93 distinct informant tool studies were identified and diagnostic test accuracy
391 properties were described across a range of settings and populations. (Figure 1) Our findings
392 suggests that IQCODE and AD8 have a greater evidence-base than other available tools, but
393 there are a lack of diagnostic test accuracy evaluations in primary care and specialised
394 populations (e.g. stroke). References of included papers, along with risk of bias judgements
395 for each included study can be seen in supplementary materials (e-9).

396 [insert Figure 1: evidence map]

397

398

399 **Discussion**

400 **Comparative evidence for available tools**

401 At least 13 informant tools for cognitive assessment are available, though there is a lack of
402 evidence to justify use of all but two of these tools: the IQCODE and the AD8. The reviewed
403 literature suggests that both tools have reasonable diagnostic test accuracy for assessment
404 of cognitive impairment or dementia, comparable with other popular cognitive screening
405 tools such as the Mini Mental State Examination and Montreal Cognitive Assessment. (Tsoi,

406 et al., 2015) Our network meta-analysis indicates the AD8 may be the more sensitive of the
407 two tools, and the IQCODE the more specific; however, the credible intervals (CrI) were
408 overlapping and estimates of 'best test' probability were close for both sensitivity and
409 specificity, implying little performance difference between respective tools. The overall
410 strength of the available evidence was also low according to our GRADE evaluation,
411 tempering conclusions.

412 Our findings highlight that the general performance of each tool is variable and typically
413 lower than originally suggested by the developers. (Jorm & Jacomb, 1989; Galvin et al.,
414 2005) Moreover, while both tools appear capable of screening for dementia, test
415 performance may vary by setting. When used in specialised secondary care settings, where
416 specificity may be the preferred property, at traditional clinical thresholds neither tool
417 appears well-suited to differentiating patients with dementia from those with mild or age-
418 related cognitive changes. Though the IQCODE-16 demonstrated a reasonable specificity of
419 73% in secondary care at cut point 3.3, this value was inconsistent with the suggested
420 performance (57%) of the longer IQCODE-26 at a cut point (3.6) that prioritises specificity;
421 thus, this may be an example of study bias exaggerating tool performance. Specificity may
422 be comparatively higher in community settings. However, in this setting, sensitivity may be
423 the preferred property.

424 We therefore suggest that neither informant tool is well suited for use as a solitary cognitive
425 screening tool. However, these tools can still be useful as solitary assessments in instances
426 where patients are unable or unwilling to complete a more direct test; thus, where clinicians
427 seek to employ an informant tool, selection of the IQCODE or AD8 should be guided by

428 desire for sensitivity or specificity. The AD8 at cut point 2 will likely provide the greatest
429 sensitivity, while the IQCODE-26 at cut point 3.6 will provide the greatest specificity.

430 It is important to emphasise that our analyses were designed to assess test accuracy only.
431 Other properties are also important for consideration when selecting an appropriate tool for
432 cognitive screening. Feasibility, inter-rater reliability, responsiveness to change, and
433 suitability for use in specialist populations are all important test characteristics that may
434 influence the selection of one test over another in clinical practice. While it is beyond the
435 scope of this review to discuss each respective tool in these terms, we encourage further
436 work on this topic to supplement the test accuracy finding we present here.

437

438 **The state of diagnostic test accuracy literature**

439 Previous overviews of systematic reviews have highlighted significant issues with regards to
440 review methodological quality. (Arevalo-Rodriguez et al., 2014) We similarly found prevalent
441 methodological issues, but also some promising signs.

442 In contrast to previous diagnostic test accuracy overviews of systematic reviews, the
443 majority of our included reviews conducted formal risk of bias assessments and the higher
444 quality reviews were all conducted within the previous decade, suggesting increasing
445 standards.

446 However, that risk of bias assessments were inconsistent across reviews indicates a poor
447 understanding of the ways in which a diagnostic test accuracy study design can introduce
448 bias. Existing risk of bias assessment tools typically require investigators to tailor presented
449 questions to the topic of interest. The robustness of this modification process is heavily

450 impacted by the amount of experience investigators have in the topic area; thus,
451 subjectivity influences the process of assessing risk of bias even when formal rating tools are
452 operationalised. Furthermore, study bias is generally under-considered when results are
453 discussed: conclusions and recommendations are frequently made in reviews without full
454 exploration of the potential impact biased studies may have had on pooled results.
455 Clinicians should be mindful of these limitations when consuming the evidence provided in a
456 review.

457

458 **Gaps in the evidence-base**

459 Our evidence map highlights the main areas in which informant tool test accuracy studies
460 are a priority. Primary care has comparatively little evidence to other healthcare settings
461 despite being arguably the most important location for cognitive screening or triage. (Quinn
462 et al., 2014) Similarly, informant tool diagnostic test accuracy evaluations are lacking in
463 specialised populations that typically struggle with more traditional cognitive tests (e.g.
464 stroke populations). We would therefore encourage further work to determine the accuracy
465 of available informant tools in these populations.

466

467 **Future directions**

468 While our data suggest that informant tools may not generally be suitable as solitary
469 screening tools, they may have utility when combined with direct screening tests. Most
470 available evidence suggests that direct and informant tools perform better when used

471 together. (e.g. Tew, Ng, Cheong, & Yap, 2015; Srikanth et al., 2006; Narasimhalu, Lee,
472 Auchus, & Chen, 2008) Thus, informant tools may make ideal supplements to the standard
473 cognitive assessment, yet no reviews exist on this topic.

474 This type of evaluation is very much needed if we are to confirm the value of a dual (i.e.
475 direct and informant) approach to assessment. It is important to note that available tests
476 (both direct and informant) typically cover varying cognitive domains; (Cullen et al., 2007)
477 hence, the best combinations of tests may change dependent upon the types of cognitive
478 problems that are present in a given population.

479

480 **Strengths and limitations**

481 We have conducted a comprehensive overview of systematic reviews that brings together
482 the findings of 25 distinct reviews, depicts an extensive evidence map, and employs new
483 statistical techniques that allow formal statistical comparisons, ranking, and ‘best test’
484 probability estimates between informant tools—addressing a major limitation of this
485 literature.

486 However, our overview of systematic reviews has some limitations. Firstly, the credible
487 intervals in our network meta-analysis are wide for our specificity estimates and most
488 included studies are at risk of bias; hence, resultant rankings should not be viewed as
489 definitive and uncertainty in these estimates should be considered.

490 Secondly, our comparisons between tools are overwhelmingly based on indirect
491 comparisons, reliant upon statistical control for random variations in populations—although
492 our findings are strengthened by a consistency with those studies that directly compared

493 the IQCODE and AD8 within the same participant pool. (Jackson, et al., 2016; Razavi et al.,
494 2014).

495 Thirdly, due to limited study numbers, we were unable to conduct some of our pre-specified
496 analyses, such as evaluations of tool performance in primary care settings.

497 Lastly, our evidence map is restricted to studies referenced in published systematic reviews;
498 thus, there are some recently published studies and informant tools which have not been
499 reviewed, such as the recently developed Quick Dementia Rating System (Galvin, 2015), that
500 do not feature.

501

502 **Conclusion**

503 Our findings suggest that only the IQCODE and AD8 have had their diagnostic test accuracy
504 properties widely evaluated. Based on available data, the AD8 at cut point 2 may be the
505 most sensitive available tool for detecting cognitive impairment or dementia, while the
506 IQCODE-26 at cut point 3.6 is the most specific. However, there is little evidence to suggest
507 an important difference in tool performance overall, and neither tool performs well enough
508 to be used alone for dementia assessment. Further evaluations of test accuracy in primary
509 care and specialised populations are a priority.

510 **Required Statements**

511 **Ethical approval:** Ethics approval and consent to participate not required.

512 **Consent for publication:** All authors have seen the materials and consent.

513 **Conflict of interests:** Dr Owen is a member of the NICE Technology Appraisals Committee
514 and the NICE Decision Support Unit (DSU). Dr Owen has served as a paid consultant to the
515 pharmaceutical industry, not in relation to this research.

516 **Funding:** This work is funded by the National Institute of Health Research. The funders
517 played no part in the conduct of this review.

518 **Authors' contributions:** TQ conceived the idea. MT and TQ designed the study and drafted
519 the manuscript. SN and RD were the 2nd and 3rd reviewers on the paper. JB dealt with
520 disagreements between reviewers. RO performed statistical analysis for the review. AP
521 contributed to data interpretation and writing. MT is the Guarantor and all authors have
522 read and commented on the final draft.

523 **Acknowledgements:** Thanks to Cochrane Test Accuracy Methods Group; and contributors to
524 CRSU workshops.

525 **References**

- 526 Arevalo-Rodriguez I., Segura O., Sola I., Bonfill X., Sanchez E., & Alonso-Coello P. (2014) Diagnostic
527 tools for alzheimer's disease dementia and other dementias: an overview of diagnostic test accuracy
528 (DTA) systematic reviews. *BMC Neurology*, 14. doi: 10.1186/s12883-014-0183-2.
- 529 Breton A., Casey D., & Arnaoutoglou N.A. (2019) Cognitive tests for the detection of mild cognitive
530 impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies.
531 *International Journal of Geriatric Psychiatry*, 34(2), 233-242. doi: 10.1002/gps.5016.
- 532 Brodaty H., Pond D., Kemp N.M., Luscombe G., Harding L., Berman K., & Huppert F.A. (2002) The
533 GPCOG: a new screening test for dementia designed for general practice. *Journal of the American*
534 *Geriatrics Society*, 50(3), 530-534. doi: 10.1046/j.1532-5415.2002.50122.x.
- 535 Burton L., & Tyson S.F. (2015) Screening for cognitive impairment after stroke: a systematic review
536 of psychometric properties and clinical utility. *Journal of Rehabilitation Medicine*, 47(3), 193–203.
537 doi: 10.2340/16501977-1930.
- 538 Carpenter C.R., Banerjee J., Keyes D., Eagles D., Schnitker L., Barbic D., ... LaMantia MA. (2019)
539 Accuracy of Dementia Screening Instruments in Emergency Medicine: A Diagnostic Meta-analysis.
540 *Academic Emergency Medicine*, 26(2), 226-245. doi: 10.1111/acem.13573.
- 541 Chen H.H., Sun F.J., Yeh T.L., Liu H.E., Huang H.L., Kuo B.I.T., & Huang H.Y. (2017) The diagnostic
542 accuracy of the Ascertain Dementia 8 questionnaire for detecting cognitive impairment in primary
543 care in the community, clinics and hospitals: a systematic review and meta-analysis. *Family Practice*,
544 35(3), 239-246. doi:10.1093/fampra/cmz098.
- 545 Cherbuin N., Antsey K.J., & Lipnicki D.M. (2008) Screening for dementia: a review of self- and
546 informant-assessment instruments. *International Psychogeriatrics*, 20(3), 431–458.
547 doi:10.1017/S104161020800673X.
- 548 Cullen B., O'Neill B., Evans J.J., Coen R.F., & Lawlor B.A. (2007) A review of screening tests for
549 cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry*, 78(8), 790–799. doi:
550 10.1136/jnnp.2006.095414.
- 551 American Psychiatric Association. (2000) Diagnostic and statistical manual of mental disorders: DSM-
552 IV-TR. Washington, DC.
553
- 554 de Jonghe, J.F.M. (1997) Differentiating between demented and psychiatric patients with the Dutch
555 version of the IQCODE. *International Journal of Geriatric Psychiatry*, 12(4), 462–465. doi:
556 10.1002/(sici)1099-1166(199704)12:4<462::aid-gps510>3.0.co;2-q.
- 557 Elliott, E., Drozdowska, B. A., Taylor-Rowan M., Shaw R. C., Cuthbertson G., & Quinn T. J. (2019).
558 Who Is Classified as Untestable on Brief Cognitive Screens in an Acute Stroke
559 Setting? *Diagnostics*, 9(3), 95. doi.org/10.3390/diagnostics9030095
- 560 Galvin J.E., Roe C.M., Powlisha K.K., Coats M.A., Much S.J., Grant E., ... Morris J.C. (2005) The AD8: a
561 brief informant interview to detect dementia. *Neurology*, 65(4), 559-564. doi:
562 10.1212/01.wnl.0000172958.95282.2a.

563 Galvin J.E. (2015). The Quick Dementia Rating System (QDRS): A rapid dementia staging tool.
564 *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 1(2), 249-259. doi:
565 10.1016/j.dadm.2015.03.003.

566 Greenhalgh T., & Peacock R. (2005) Effectiveness and efficiency of search methods in systematic
567 reviews of complex evidence: audit of primary sources. *BMJ*, 331(7524), 1064-1065. doi:
568 10.1136/bmj.38636.593461.68.

569 Guyatt G.H., Oxman A.D., Vist G.E., Kunz R., Falck-Ytter Y., Alonso-Coello P., Schunemann H.J. (2008)
570 GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*
571 (Clinical research ed), 336(7650), 924-926. doi: 10.1136/bmj.39489.470347.AD

572 Harrison J.K., Noel-Storr A.H., Demeyere N., Reyish E.L., & Quinn T.J. (2016) Outcomes measures in a
573 decade of dementia and mild cognitive impairment trials. *Alzheimer's Research & Therapy*, 8(48).
574 Doi: 10.1186/s13195-016-0216-8

575 Harrison J.K., Stott D.J., McShane R., Noel-Storr A.H., Swann-Price R.S., & Quinn T.J. (2016) Informant
576 Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early diagnosis of dementia
577 across a variety of healthcare settings. *Cochrane Database of Systematic Reviews*. doi:
578 10.1002/14651858.CD011333

579 Harrison J.K., Fearon P., Noel-Storr A.H., McShane R., Stott D.J., & Quinn T.J. (2014) Informant
580 Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a
581 general practice (primary care) setting. *Cochrane Database of Systematic Reviews*. doi:
582 10.1002/14651858.CD010771

583 Harrison J.K., Fearon P., Noel-Storr A.H., McShane R., Stott D.J., & Quinn T.J. (2015) Informant
584 Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a
585 secondary care setting. *Cochrane Database of Systematic Reviews*. doi:
586 10.1002/14651858.CD010772

587 Harvan J.R., & Cotter V.T. An evaluation of dementia screening in the primary care setting. (2006)
588 *Journal of the American Academy of Nurse Practitioners*, 18(8):351-60. doi: 10.1111/j.1745-
589 7599.2006.00137.x

590 Hendry K., Green C., McShane R., Noel-Storr A.H., Stott D.J., Anwer S., ... Quinn T.J. (2019) AD-8 for
591 detection of dementia across a variety of healthcare settings. *Cochrane Database of Systematic*
592 *Reviews*. doi: 10.1002/14651858.CD011121.pub2.

593 Hendry K., Hill E., Quinn T.J., Evans J., & Stott D.J. (2015) Single screening questions for cognitive
594 impairment in older people: a systematic review. *Age and Ageing*, 44(2), 322–326. doi:
595 10.1093/ageing/afu167.

596 Higgins J.P.T., Thomas J., Chandler J., Cumpston M. Li T., Page M.J., & Welch V.A. (2019) Cochrane
597 Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). *Cochrane*
598 *Database of Systematic Reviews*. doi:10.1002/9781119536604

599 Jackson T.A., MacLulich A.M., Gladman J.R., Lord J.M., & Sheehan B. (2016) Diagnostic test accuracy
600 of informant-based tools to diagnose dementia in older hospital patients with delirium: a
601 prospective cohort study. *Age and Ageing*, 45(4), 505-511. doi: 10.1093/ageing/afw065

602 Jackson T.A., & Naqvi S.H., Sheehan B. (2013) Screening for dementia in general hospital inpatients:
603 a systematic review and meta-analysis of available instruments. *Age and Ageing*, 42(6), 689–695.
604 doi: 10.1093/ageing/aft145.

605 Jorm A.F., & Jacomb P.A. (1989) The Informant Questionnaire on Cognitive Decline in the Elderly
606 (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychological*
607 *Medicine, 19(4)*, 1015-1022. doi: 10.1017/s0033291700005742

608 Jorm A.F., Broe G.A., Creasey H., Sulway M.R., Dent O., Fairley M.J., ...Tennant C. (1996) Further data
609 on the validity of the informant questionnaire on cognitive decline in the elderly (IQCODE).
610 *International Journal of Geriatric Psychiatry, 11(2)*, 131-139.

611 Jorm A.F. (1997) Methods of screening for dementia: a meta-analysis of studies comparing an
612 informant questionnaire with a brief cognitive test. *Alzheimer Disease and Associated Disorders,*
613 *11(3)*, 158-162.

614 Jorm A.F. (2004) The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): a
615 review. *International Psychogeriatrics, 16(3)*, 1–19. doi: 10.1017/S1041610204000390.

616 Kansagara D., & Freeman, M.A. (2010) Systematic Evidence Review of the Signs and Symptoms of
617 Dementia and Brief Cognitive Tests Available in VA [Internet]. *Washington (DC): Department of*
618 *Veterans Affairs (US)*. Retrieved from [https://www.hsrd.research.va.gov/publications/esp/dementia-](https://www.hsrd.research.va.gov/publications/esp/dementia-REPORT.pdf)
619 [REPORT.pdf](https://www.hsrd.research.va.gov/publications/esp/dementia-REPORT.pdf)

620 Kosgallana A., Cordato D., Chan D.K.Y., & Yong J. (2019) Use of Cognitive Screening Tools to Detect
621 Cognitive Impairment After an Ischaemic Stroke: a Systematic Review. *SN Comprehensive Clinical*
622 *Medicine 1*, 255–262. <https://doi.org/10.1007/s42399-018-0035-2>

623 Lin J.S., O’Connor E., Rossom R.C., Perdu L.A., & Eckstrom E. (2013) Screening for Cognitive
624 Impairment in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. *Annals*
625 *of Internal Medicine, 159(9)*, 601-612.

626 Lischka A.R., Mendlesohn M., Overend T., & Forbes D. (2012) A Systematic Review of Screening
627 Tools for Predicting the Development of Dementia. *Canadian Journal on Aging, 31(3)*, 295– 311.
628 doi:10.1017/S0714980812000220.

629 Lunn D.J., Thomas A., Best N., & Spiegelhalter D. (2000) WinBUGS-a Bayesian modelling framework:
630 concepts, structure, and extensibility. *Statistics and Computing, 10*, 325-337.
631 doi.org/10.1023/A:1008929526011

632 McGovern A., Pendlebury S.T., Mishra N.K., Fan Y., & Quinn T.J. (2016) Test Accuracy of Informant-
633 Based Cognitive Screening Tests for Diagnosis of Dementia and Multidomain Cognitive Impairment in
634 Stroke. *Stroke. 47(2)*, 329-335. doi: 10.1161/ STROKEAHA.115.011218.

635 McInnes M.D.F., Moher D., Thombs B.D., McGrath T.A., Bossuyt P.M., & Grp P.D. (2018) Preferred
636 Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies The
637 PRISMA-DTA Statement. *Journal of the American Medical Association. 319(4)*, 388-396. doi:
638 10.1001/jama.2017.19163

639 McKenzie J.E., Brennan S.E. (2017) Overviews of systematic reviews: great promise, greater
640 challenge. *Systematic Reviews, 6*, 185. doi.org/10.1186/s13643-017-0582-8

641 Narasimhalu K., Lee J., Auchus A.P., & Chen C.P. (2008) Improving detection of dementia in Asian
642 patients with low education: combining the Mini-Mental State Examination and the Informant
643 Questionnaire on Cognitive Decline in the Elderly. *Dementia and Geriatric Cognitive Disorders. 25(1)*,
644 17–22 . doi: 10.1159/000111128.

645 NICE. (2020). Retrieved from <http://pathways.nice.org.uk/pathways/dementia>

646 O’Sullivan J.W. (2019) Network meta-analysis for diagnostic tests. *BMJ Evidence-Based Medicine*, 24,
647 192-193. Retrieved from <https://ebm.bmj.com/content/24/5/192>.

648 Owen R.K., Cooper N.J., Quinn T.J., Lees R., & Sutton A.J. (2018) Network meta-analysis of diagnostic
649 test accuracy studies identifies and ranks the optimal diagnostic tests and thresholds for healthcare
650 policy and decision making. *Journal of Clinical Epidemiology*, 99, 64-74. doi:
651 10.1016/j.jclinepi.2018.03.005

652 Quinn T.J., Fearon P., Noel-Storr A.H., Young C., McShane R., & Stott D.J. (2014) Informant
653 Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within
654 community dwelling populations. *Cochrane Database of Systematic Reviews*. doi:
655 10.1002/14651858.CD010079

656 Razack M.A.A, Ahmad N.A., Chan Y.Y., Kasim N.M., Yusof M., Abdul Ghani M.K.A. ... Jamaluddin R.
657 (2019) Validity of Screening Tools for Dementia and Mild Cognitive Impairment Among the Elderly in
658 Primary Health Care: A Systematic Review. *Public Health*, 169, 84-92. doi:
659 10.1016/j.puhe.2019.01.001.

660 Razavi M., Tolea M.I., Margrett J., Martin P., Oakland A., Tscholl D.W., ... Galvin J.E. (2014)
661 Comparison of 2 Informant Questionnaire Screening Tools for Dementia and Mild Cognitive
662 Impairment AD8 and IQCODE. *Alzheimer Disease & Associated Disorders*, 28, 156-161. doi:
663 10.1097/WAD.0000000000000008.

664 Reitsma J.B., Glas A.S., Rutjes A.W., Scholten R.J., Bossuyt P.M., Zwinderman A.H. (2005) Bivariate
665 analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews.
666 *Journal of Clinical Epidemiology*, 58(10), 982-990. doi: 10.1016/j.jclinepi.2005.02.022.

667 Rosli R., Tan M.P., Gray W.K., Subramanian P., & Chin A.V. (2016) Cognitive assessment tools in Asia:
668 a systematic review. *International Psychogeriatrics*, 28(2), 189–210.
669 doi:10.1017/S1041610215001635.

670 Shea B.J., Reeves B.C., Wells G., Thuku M., Hamel C., Moran J., ... Henry D.A. (2017) AMSTAR 2: a
671 critical appraisal tool for systematic reviews that include randomised or non-randomised studies of
672 healthcare interventions, or both. *BMJ*, 358. doi: 10.1136/bmj.j4008.

673 Singh S., Chang S.M., Matchar S.M., & Bass E.B. (2012) Chapter 7: Grading a Body of Evidence on
674 Diagnostic Tests. *Journal of General Internal Medicine*, 27, S47-55. doi: 10.1007/s11606-012-2021-9.

675 Srikanth V., Thrift A.G., Fryer J.L., Saling M.M., Dewey H.M., Sturm J.W., & Donnan G.A. (2006) The
676 validity of brief screening cognitive instruments in the diagnosis of cognitive impairment and
677 dementia after first-ever stroke. *International Psychogeriatrics*, 18, 295–305. doi:
678 10.1017/S1041610205002711.

679 Taylor-Rowan M., Nafisi S., Patel A., Burton J.K., & Quinn T.J. (2020) Informant based screening tools
680 for diagnosis of dementia, an overview of systematic reviews of test accuracy studies- Protocol.
681 *Systematic Reviews*, 9, 271. doi: 10.1186/s13643-020-01530-3

682 Tew C.W., Ng T.P., Cheong C.Y., & Yap P. (2015) A brief dementia test with subjective and objective
683 measures. *Dementia and Geriatric Cognitive Disorders Extra*, 5(3), 341–349. doi:
684 10.1159/000438455

685 Tsoi K.K.F, Chan J.Y.C., Hirai H.W., Wong SYS, & Kwok TCY. (2015) Cognitive Tests to Detect
686 Dementia A Systematic Review and Meta-analysis. *JAMA Internal Medicine*, 175(9), 1450-1458.
687 doi:10.1001/jamainternmed.2015.2152.

688 Tsoi K.K.F., Chan J.Y.C., Hirai H.W., Wong A., Mok V.C.T., Lam LCW, ... Wong S.Y.S. (2017) Recall Tests
689 Are Effective to Detect Mild Cognitive Impairment: A Systematic Review and Meta-analysis of 108
690 Diagnostic Studies. *JAMDA* 18(9), 807. doi: 10.1016/j.jamda.2017.05.016

691 Woodford H.J., & George J. (2007) Cognitive Assessment in the Elderly: A Review of Clinical Method.
692 *Quarterly Journal of Medicine*, 100(8), 469–484. doi:10.1093/qjmed/hcm051.

693 World Health Organization. (2004) ICD-10: international statistical classification of diseases and
694 related health problems: tenth revision, 2nd ed. Retrieved from
695 [https://www.cdc.gov/nchs/icd/icd10.htm#:~:text=The%20International%20Classification%20of%20D](https://www.cdc.gov/nchs/icd/icd10.htm#:~:text=The%20International%20Classification%20of%20Diseases,death%20on%20the%20death%20certificate.)
696 [iseases,death%20on%20the%20death%20certificate.](https://www.cdc.gov/nchs/icd/icd10.htm#:~:text=The%20International%20Classification%20of%20Diseases,death%20on%20the%20death%20certificate.)
697