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1 **Title**

2 A diagnostic test accuracy study investigating GP clinical impression and brief cognitive assessments for
3 dementia in primary care, compared to specialised assessment.

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13 **Keywords: Alzheimer's disease; dementia; General Practice; Sensitivity and Specificity; Symptom**

14 **Assessment**

15

1 **Abstract**

2 *Background:* Many health systems are interested in increasing the number of uncomplicated and typical
3 dementia diagnoses that are made in primary care, but the comparative accuracy of tests is unknown.

4 *Objective:* Calculate diagnostic accuracy of brief cognitive tests in primary care

5 *Design:* We did a diagnostic test accuracy study in general practice, in people over 70 years who had
6 consulted their GP with cognitive symptoms but had no prior diagnosis of dementia. The reference
7 standard was specialist assessment, adjudicated for difficult cases, according to ICD-10. We assessed 16
8 index tests at a research clinic, and additionally analysed referring GPs clinical judgement.

9 *Results:* 240 participants had a median age of 80 years, of whom 126 were men and 132 had dementia.

10 Sensitivity of individual tests at the recommended thresholds ranged from 56% for GP judgement
11 (specificity 89%) to 100% for MoCA (specificity 16%). Specificity of individual tests ranged from 4% for
12 Sniffin' sticks (sensitivity 100%) to 91% for TUG (sensitivity 23%). The 95% centile of test duration in
13 people with dementia ranged from 3 minutes for 6CIT and TAC, to 16 minutes for MoCA. Combining tests
14 with GP judgement increased test specificity and decreased sensitivity: e.g., MoCA with GP Judgement
15 had specificity 87% and sensitivity 55%.

16 *Conclusions* Using GP judgement to inform selection of tests was an efficient strategy. Using IQCODE in
17 people who GPs judge as having dementia and 6CIT in people who GPs judge as having no dementia,
18 would be a time-efficient and accurate diagnostic assessment.

19 The **original protocol** for the study is available at

20 <https://bmcfampract.biomedcentral.com/articles/10.1186/s12875-016-0475-2>

21 **Keywords**

22 Alzheimer's disease; Dementia, General Practice, Sensitivity and Specificity, Symptom Assessment

23

1 **Main Text**

2 **Background**

3 Enhancing the role of general practitioners in making a diagnosis of dementia in uncomplicated cases is a
4 priority in the UK [1], but a barrier for General Practitioners (GPs) is choosing between the wide variety of
5 brief cognitive assessments (BCAs) that are available [2,3]. There is little evidence to help GPs choose
6 between tests; indeed, national guidelines recommend different tests [4].

7 GPs use time as a diagnostic test [5], and dementia is a progressive disorder which can be difficult to
8 diagnose early in the disease process. However, some people wait a long time for a diagnosis after
9 presenting with symptoms largely due to practical and logistical difficulties in accessing specialist
10 expertise [6]. GPs making a formal diagnosis of dementia in uncomplicated cases can reduce anxiety,
11 avoid unnecessary waiting and investigations for alternative diagnosis [7], and is often needed to access
12 additional social care and support (albeit this being an aspect of system design rather than necessity).
13 Most people who are consulting about memory problems would want to know if they had dementia [8].
14 There may also be benefits to explicitly recognising more advanced dementia in people who have lost
15 capacity and insight, as this can prompt a holistic re-evaluation of care-goals and avoid unnecessary tests
16 and treatments [9]. There are currently no widely available disease modifying treatments for dementia,
17 and a focus on highly sensitive tests that does not “miss” any cases of dementia in primary care may
18 result in an overwhelmed secondary care service with unclear benefits for individual patients and families
19 [10].

20 The available evidence typically has limited applicability for GPs evaluating people with possible dementia
21 in primary care. Firstly, current studies often report diagnostic accuracy in an asymptomatic population
22 and therefore are more applicable to screening or case finding [11–13] than helping to support a
23 diagnosis in those presenting with clinical symptoms, who have higher pre-test probability of disease.
24 Secondly, studies often investigate accuracy for the target condition of all cognitive impairment [14],
25 rather than specifically dementia, typically with the implicit assumption that all people with cognitive

1 impairment including both those with dementia and those with mild cognitive impairment (MCI) require
2 specialist referral. Thirdly, studies typically investigate a single test in isolation, rather than making direct
3 comparisons between tests in the same study [15], allowing only indirect comparisons. Fourthly, studies
4 often investigate the accuracy of tests in (high prevalence) specialist settings rather than in the (relatively
5 low prevalence) general practice population, and test accuracy is related to prevalence and the spectrum
6 of disease severity [16]. Finally, existing studies tend to evaluate the accuracy of tests alone rather than
7 when combined with GP judgement which is what happens in “real world” clinical practice.

8 To address the limited applicability of existing studies to primary care, we conducted a study in people
9 with symptoms of possible dementia who had consulted about these with their GP. The aim of this study
10 was to quantify the test accuracy of a range of non-specialist candidate tests, suitable for use in a GP
11 clinic for the evaluation of cognitive symptoms, alone and in combination with GP judgement, compared
12 to a reference standard specialist assessment according to ICD-10 criteria.

13 **Method**

14 *Population*

15 We recruited participants consecutively from 21 participating GP clinics from a total 82 practices in the
16 Bristol, North Somerset, and South Gloucestershire (BNSSG) area between March 2015 and May 2017.
17 Research clinics took place in four participating GP clinics. A minimum sample size of 200 was needed,
18 based on a specificity of 95% in prior studies and a 75% prevalence of dementia in local memory clinic
19 data [17].

20 Participants were people with cognitive symptoms but no prior diagnosis of dementia, who were aged at
21 least 70 years and had been referred by their GP to this research study. Cognitive symptoms were not
22 specified but generally include disturbance in memory, language, executive function, behaviour, or
23 visuospatial skills [18]. Symptoms were required to be present for at least six months, and could be
24 reported by the person themselves, a family member, a professional, or another person; there was no
25 severity threshold. Symptom duration was determined from the clinical history. Cognitive symptoms did

1 not need to be the main focus of the consultation with the GP: an enquiry about cognition could be
2 initiated if there was a perception of a problem.

3 People were excluded if they had a known neurological disorder (i.e. Parkinson's disease, Multiple
4 Sclerosis, learning disability, Huntington's disease), were registered blind, or profoundly deaf (i.e. unable
5 to use a telephone), had a psychiatric disorder requiring current secondary care input, or if cognitive
6 symptoms were either rapidly progressive or co-incident with neurological disturbance. People with
7 cognitive problems that were so advanced that they were unable to consent were excluded.

8 GPs were encouraged to refer a consecutive series of eligible patients with cognitive symptoms. The
9 research team took written consent from all participants. An accompanying informant was mandatory
10 and informants also gave written informed consent to participate. All participants were offered free
11 accessible transport and translation services. All methods were carried out in accordance with relevant
12 guidelines and regulations including Declaration of Helsinki. The National Research Ethics Service
13 Committee London – Bromley (reference 14/LO/2025) gave a favourable ethical opinion on 25 November
14 2014. NHS Research and Development approvals were granted by Avon Primary Care Research
15 Collaboration on behalf of Bristol, North Somerset and South Gloucestershire clinical commissioning
16 groups. The University of Bristol acted as Sponsor.

17 *GP Judgement*

18 The referring GP recorded their clinical judgement using an electronic referral form during a consultation
19 with their patient. GP judgement was operationalised as normal, cognitive impairment not dementia
20 (CIND), or dementia as options for response to the question "Is your gut feeling that this person has...".

21 GPs were not specially trained, were not required to arrange any test, and could refer people
22 simultaneously or subsequently to NHS services. We specifically instructed GPs that they did not need to
23 use any prior cognitive test (we did not mention the index tests by name as we judged on balance this
24 could increase the risk they may be used). The study team contacted the practice at least three times to
25 obtain any missing referral data.

1 *Index tests*

2 The index test battery was selected following a review of the literature and on the basis of the following
3 criteria: not copyright and either previously evaluated in primary care or not previously evaluated in
4 primary care but of interest [19]. The index assessment included eight brief cognitive assessments, three
5 physical tests, and five informant evaluations. Index tests were all performed by the same examiner
6 (STC), a medical doctor undertaking postgraduate training in general practice and a PhD in diagnostic
7 tests. We conducted index tests as instructed by the original authors and followed instructions of the
8 original test authors for clock scoring. We used prespecified test thresholds which are provided in
9 Supplementary Table 1. We calculated time taken for each test in minutes from the start to end time of
10 each test. The eight brief cognitive assessments were the memory alteration test, M@T [11]; Eurotest
11 [20]; Phototest [21]; Scenery Picture Memory Test, SPMT [22]; Six item cognitive impairment test, 6CIT
12 [16]; general practitioner assessment of cognition, GPCOG [23]; Mini-cog [24]; Time and Change, T&C
13 [25]. The three physical tests were Timed Up and Go (TUG) [26,27]; extra-pyramidal signs scale, EPSS
14 [28]; and Sniffin' sticks [29]. The five informant questionnaires were the Pfeffer FAQ [30]; Lawton IADL
15 [31]; Katz ADL [32]; 8-item AD8 [33]; and short form IQCODE [34]. Where possible, items were not
16 repeated, e.g. the 6CIT [16] and the GPCOG [23] both require the recall of a 5-item name and address,
17 and to avoid burdening and potentially confusing participants this item was done once and then scored
18 separately for each test.

19 The Montreal Cognitive Assessment, MoCA [14] was initially not included in the index battery as it was
20 originally designed to diagnose or identify MCI, had been advocated for use in secondary care [35] and
21 had not been investigated in primary care [36]. We revised the protocol in light of subsequent policy
22 changes in 2015 that encouraged GPs to diagnose dementia in typical situations without referring to a
23 specialist [7] using the MoCA as the preferred instrument. We replaced the M@T with the MoCA because
24 we judged that including both the MoCA and the M@T would be overly burdensome for participants and
25 have little added value. We imported Sniffin' sticks on special order and so we added these at a later
26 stage to avoid delaying the start of recruitment while waiting for this single test.

1 Excluding Sniffin' Sticks, we randomly assigned the order of the index tests in the battery for each
2 participant to avoid the effect of order influencing test accuracy. The examiner offered each participant
3 the chance to undertake every test in the battery but was responsive to the participants if they appeared
4 to be becoming tired or distressed.

5 *Reference standard*

6 At the research clinic, a single specialist physician (JH) with more than 20 years' experience in the field of
7 dementia conducted a standardised assessment, including the Addenbrooke's Cognitive Examination
8 (ACE) III [37], Brief Assessment Schedule Depression Cards (BASDEC) [38] and the informant-completed
9 Bristol Activities of Daily Living (BADL) Questionnaire [39], lasting approximately 60 minutes. The
10 specialist was not aware of other test results such as clinical judgement of the referring GP, research
11 clinic index tests, or any investigations. We randomly allocated participants to see the specialist before or
12 after the index tests. All participants were offered, and encouraged, to have a gentle break of 10-20
13 minutes for a drink and snack between sessions. A second specialist, who had access to the primary care
14 medical record for six months after the research clinic follow-up, as well as all information available to
15 the primary specialist, adjudicated borderline cases. The reference standard was an integrated expert
16 assessment according to ICD-10 criteria [40] for each individual patient, and specific test thresholds were
17 not used; people with CIND were included in the "normal" group for evaluation of test accuracy since we
18 were specifically interested in the test accuracy for dementia. We used the term CIND in the reference
19 standard, while also classifying MCI, for consistency with GP judgement who classified against CIND (GPs
20 being generally unfamiliar with MCI criteria). Study data were electronically entered and managed using
21 REDCap (Research Electronic Data Capture) hosted at the University of Bristol [41].

22 *Statistical methods*

23 We calculated a potentially eligible population by indirectly standardising the population at risk of
24 dementia in recruiting practices based on age specific incidence of dementia [42] and GP list size [43]. We
25 used a regression model with total ACE-III score as the dependent variable and categorical randomly

1 allocated assessment order (index battery first or specialist assessment) to investigate a possible effect of
2 assessment order on test scores. We calculated the median and range ACE-III total scores for people who
3 were classified by GPs as being normal but in fact had dementia, compared to people who were correctly
4 classified as having dementia. We classified test duration by the 95th centile of test duration, the time
5 which clinicians could expect 95% of people to complete the test. We calculated measures of test
6 accuracy (sensitivity, specificity, likelihood ratios, predictive values) together with 95% confidence
7 intervals. To determine the effect of combining tests with GP judgement we calculated the accuracy of
8 each test combined with GP judgement so that the combined test positive was taken as being both GP
9 judgement positive and the other test positive; and the combined test negative was taken as either both
10 or one of judgement/test negative. We also calculated the diagnostic accuracy when using an approach
11 of “stratified sequential testing”, where clinical judgement determines what further test should be done,
12 by calculating the diagnostic accuracy in cross-tabulations that were restricted based on GP Judgement.
13 We evaluated how GP judgement influenced the discrimination of the index tests by calculating the
14 AUROC (area under the ROC curve) stratified by GP judgement.

15 In an exploratory analysis we used a bootstrapping procedure with 1000 replications to compare the
16 numbers misclassified, either as false positives or false negatives, from different combinations of
17 cognitive tests, using either an unstratified approach (one cognitive test) or a stratified approach
18 depending on GP judgment. Test combinations for the exploratory bootstrap procedure were chosen on
19 the basis of the three tests with the greatest number of true positives and true negatives for each
20 stratum (unstratified by GP Judgement, GP judgement dementia, GP judgement not dementia).

21 In practice there is a finite amount of resource available to assess people with symptoms of dementia,
22 and longer assessments mean that fewer people can be evaluated. To account for the trade-offs between
23 test duration and accuracy we derived the numbers of people that a full time (37.5 hours a week) NHS
24 Memory clinician could classify in a population of up to 1000 people, using the (simplified but
25 implausible) assumption that all working time was spent administering cognitive assessments. To derive
26 these figures, we used sensitivity and specificity of each index test stratified by GP judgement, together

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- 1 with 95th centile of test duration also stratified by GP judgement (to account for test duration being
- 2 longer in people who GPs suspected of having dementia). For informant completed tests which can be
- 3 completed independently of a clinician we used the time for the shortest duration brief cognitive
- 4 assessment, since a practical implementation would be for an informant to complete their questions
- 5 while a clinician evaluated the patient.

- 6 All analysis was done using Stata Version 15.

1 **Results**

2 *Participants*

3 Recruitment is described in detail in a separate paper [19]. Figure 1 shows that GPs referred 456 people,
 4 of whom 240 (53%) participated and had available data, 45 were ineligible (10%) and 155 declined (34%).
 5 Of 240 participants, 47 were normal, 61 had CIND (59 of whom had Petersen MCI) and 132 had
 6 dementia. The median age overall was 80 years (IQR 75 to 85 years), and the median ACE-III total score
 7 was 75 (IQR 65 to 87); the median age of leaving education was 15 years (IQR 15 to 16 years) and the
 8 median months since symptom onset was 24 months (IQR 12 to 36 months). Using indirectly
 9 standardised rates in the recruiting practices we estimate that during the recruitment period around
 10 1,735 people would have been potentially eligible, of whom GPs referred 456 and we saw 241.
 11 GPs judged 34 people as being normal, 120 as having CIND, and 86 as having dementia. People that GPs
 12 judged as having dementia had a total ACE-III score IQR of 60 to 74 with a 90th centile of 81/100 and a
 13 highest score of 95/100, compared to published ACE-III thresholds of ≤ 82 for dementia. Six people with
 14 dementia were classified as normal by their referring GP, these people had a median ACE-III total score of
 15 72 (range 69 to 82 points) and had a median age of 82 years (range 79 to 86 years). In contrast the 73
 16 people with dementia who were classified as such by their GPs had a median ACE-III total score of 65
 17 (range 26 to 92 points) and had a median age of 82 years (range 71 years to 94 years).

18 Table 1. Characteristics of participants by cognitive category by reference standard

| | Dementia | CIND | Normal |
|--------------------------------|------------|------------|------------|
| | n=132 | n=61 | n=47 |
| <i>Sex n (column %)</i> | | | |
| Male | 68 (51) | 35 (57) | 23 (49) |
| Female | 64 (49) | 26 (43) | 24 (51) |
| <i>Age</i> | | | |
| At clinic (years) Median (IQR) | 82 (77-86) | 80 (75-83) | 75 (72-80) |

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| | | | |
|--|------------|------------|------------|
| Age of leaving education (years) Median (IQR) | 15 (15-16) | 15 (15-16) | 16 (15-16) |
| <i>Symptom onset Median (IQR) (months)</i> | | | |
| Time ago | 24 (12-36) | 18 (12-24) | 21 (12-36) |
| <i>ACE-III Score median (IQR)</i> | | | |
| Total (max 100) | 69 (61-74) | 82 (76-87) | 93 (90-95) |
| <i>GP Judgement n (row %)</i> | | | |
| Normal | 6 (18) | 9 (26) | 19 (56) |
| CIND | 52 (43) | 41 (34) | 27 (23) |
| Dementia | 74 (86) | 11 (13) | 1(1) |

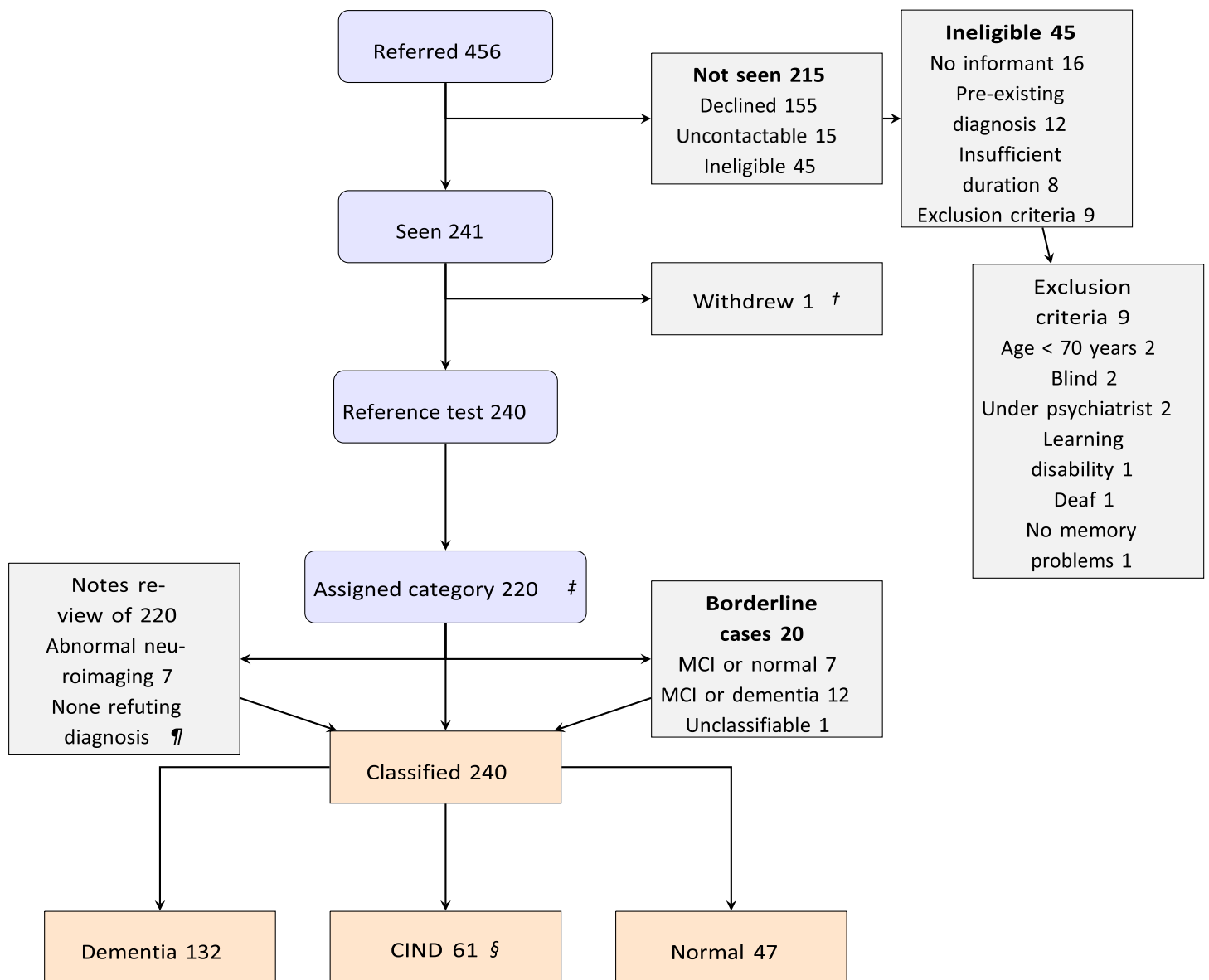
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Dementia according to ICD-10 [40]

ACE-III Addenbrooke's' Cognitive Examination III; CIND Cognitive impairment, not dementia.

1 Fig. 1. STARDdem flowchart for inclusion of participants in the study

2



3

† one person had to withdraw part way through the reference test as they were acutely ill
 ‡ Dementia according to ICD-10 [40]
 § of 61 with CIND 59 met criteria for Petersen MCI [44], 1 affective disorder, 1 brain injury) ¶
 One person met criteria for ICD-10 dementia and also had features of normal pressure hydrocephalus. Expert review endorsed a reference standard diagnosis of dementia.
 People with advanced cognitive problems who could not consent were not eligible and were not referred by GPs.

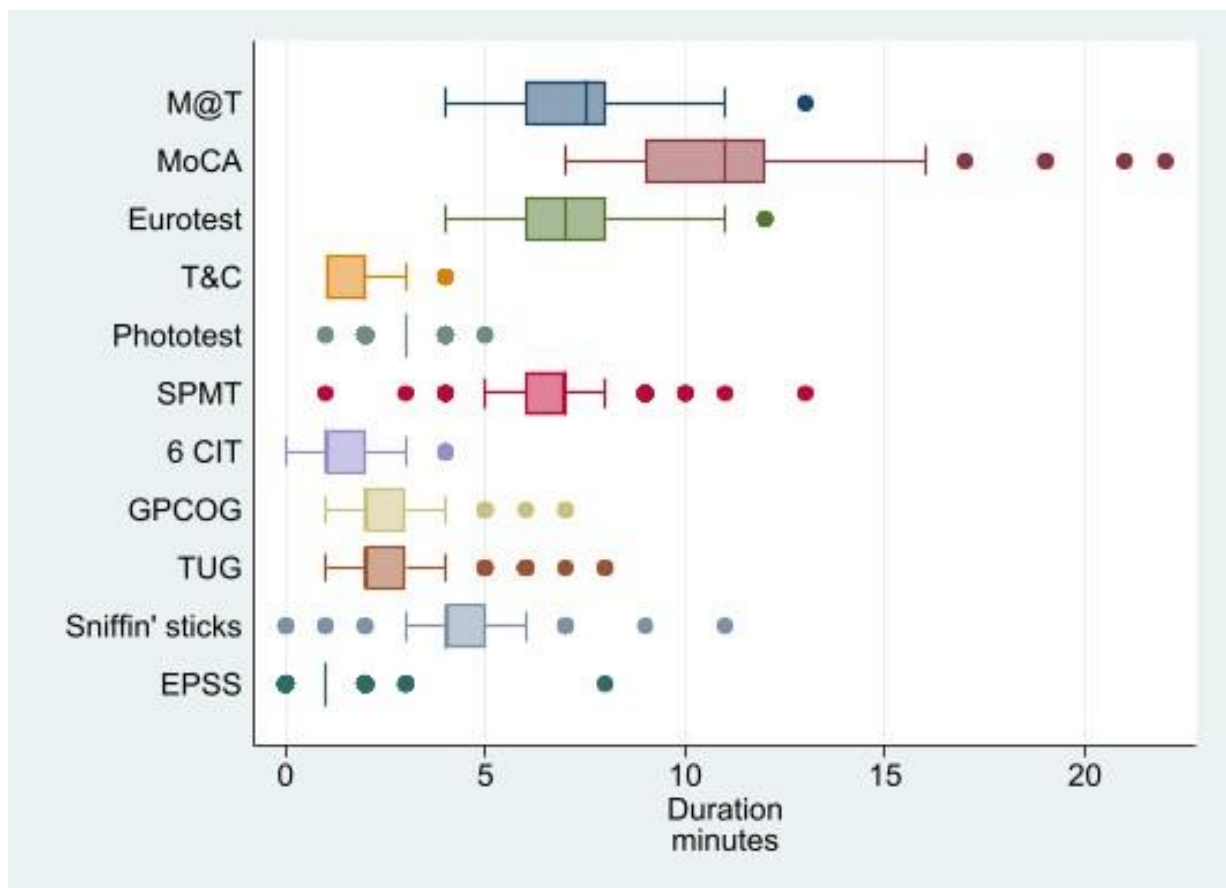
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5

1 Table 1 presents the characteristics of participants. Of 240 participants, 53% were men, median age was
2 80 years, median symptom duration was 24 months and the median ACE-III score was 70 out of 100,
3 compared to published ACE-III thresholds of <82 for dementia and < 88 for MCI. Median age of leaving
4 education age was 15 years (range 13 years to 19 years). Table 1 also provides a 3x3 cross tabulation of
5 GP judgement against the reference standard, showing that referring GPs judged that 86 patients (36%)
6 had dementia. In a regression model with total ACE-III score as the dependent variable and test order
7 (index test / reference test first or second) as the independent variable, people who the specialist
8 assessed first scored 2.4 points more on ACE-III (95% CI -1.3 to 6.1) points than those who underwent the
9 index test battery first, after adjusting for age, sex and cognition category they scored 1.9 points more
10 (95% CI -0.8 to 4.5) than those who underwent the index battery first.

11 *Test characteristics*

12 Fig. 2. Duration of index tests, all cognition categories



13

1 *The box plots the median (darker middle line) and the quartiles (box edges), the whiskers enclose the lower*
 2 *(quartile 1 - 1.5 × interquartile range) and upper (quartile 3 + 1.5 × interquartile range) adjacent values, and*
 3 *the dots mark the outlying values.*

4
 5 There was wide variability in test duration (Figure 2) with the 6CIT having the shortest median duration (1
 6 minute) whereas MoCA had the longest median duration (11 minutes). There was also variation in the
 7 range of times taken to complete tests, which differed between tests, for example being much greater
 8 for MoCA (range 7 minutes to 22 minutes) than Phototest (range 1 minute to 5 minutes). Classified by the
 9 95th centile of test duration (C95), the short duration (<5 minutes) tests were: EPSS (C95 2 minutes), T&C
 10 (C95 3 minutes), 6CIT (C95 3 minutes), Phototest (C95 4 minutes), and GPCOG (C95 4 minutes). The
 11 medium duration (≥5 minutes but ≤10 minutes) tests were: TUG (C95 5 minutes), Sniffin’ sticks (C95 6
 12 minutes), SPMT (C95 9 minutes), and Eurotest (C95 10 minutes). The long duration (> 10 minutes) tests
 13 were: M@T (C95 11 minutes) and MoCA (C95 15 minutes).

14 Supplementary Table 1 shows the characteristics of the brief cognitive assessments and physical tests in
 15 terms of differential performance by cognitive status and test duration. We observed that performance
 16 on every test was worse for people with dementia than people who were cognitively normal, except for
 17 the Sniffin’ sticks, and that tests took longer for people with dementia or CIND than people who were
 18 normal, though for many tests this could have been due to chance (that is confidence intervals
 19 overlapped).

20 *Diagnostic accuracy*

21 Table 2. Accuracy of brief cognitive tests for the diagnosis of dementia

22

23

| | Alone | | With GP Judgement* | |
|---|-------------------------|-------------------------|-------------------------|-------------------------|
| | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
| Cognitive or physical tests | | | | |
| <i>Brief tests, 95%. Completed within less than 5 minutes</i> | | | | |
| EPSS | 85 (78 to 90) | 30 (21 to 39) | 44 (35 to 53) | 91 (84 to 95) |
| T&C | 27 (20 to 36) | 96 (91 to 99) | 17 (11 to 24) | 100 (97 to 100) |

| | | | | |
|---|-----------------|---------------|---------------|-----------------|
| Phototest | 57 (48 to 66) | 82 (74 to 89) | 37 (29 to 46) | 94 (88 to 98) |
| 6CIT | 76 (67 to 83) | 70 (60 to 79) | 46 (37 to 55) | 93 (86 to 97) |
| GPCOG | 93 (87 to 97) | 52 (42 to 62) | 55 (46 to 64) | 91 (84 to 95) |
| Mini-cog | 70 (61 to 77) | 73 (64 to 81) | 42 (34 to 51) | 94 (87 to 97) |
| <i>Medium tests, 95% completed within ≥5 but ≤10 minutes</i> | | | | |
| Eurotest | 70 (62 to 78) | 81 (72 to 88) | 44 (35 to 53) | 97 (92 to 99) |
| SPMT | 77 (69 to 84) | 78 (69 to 85) | 49 (40 to 58) | 96 (91 to 99) |
| TUG | 23 (16 to 31) | 91 (84 to 95) | 14 (9 to 21) | 98 (93 to 100) |
| Sniffin' Sticks | 100 (96 to 100) | 4 (1 to 11) | 51 (41 to 61) | 88 (80 to 94) |
| <i>Longer tests 95% completed within more than 10 minutes</i> | | | | |
| M@T | 63 (41 to 81) | 80 (44 to 97) | 54 (33 to 74) | 100 (69 to 100) |
| MoCA | 100 (97 to 100) | 16 (10 to 25) | 55 (45 to 64) | 87 (77 to 93) |
| GP Judgement | 56 (47 to 65) | 89 (81 to 94) | - | - |
| Informant data | | | | |
| FAQ | 27 (19 to 35) | 97 (92 to 99) | 19 (13 to 27) | 98 (93 to 100) |
| Katz ADL | 26 (19 to 34) | 95 (90 to 98) | 15 (9 to 22) | 99 (95 to 100) |
| Lawton IADL | 37 (29 to 46) | 87 (79 to 93) | 26 (19 to 34) | 96 (91 to 99) |
| AD8 | 96 (91 to 99) | 32 (24 to 42) | 55 (46 to 63) | 92 (85 to 96) |
| IQCODE | 95 (90 to 98) | 38 (28 to 48) | 56 (47 to 64) | 91 (84 to 96) |

1 *Combined test positive was taken as being both GP judgement positive and the other test positive; and
 2 the combined test negative was taken as either both or one of judgement/test negative.

3 See Supplementary Table 1 for test abbreviations. CI confidence interval

4

5

6 Table 2 indicates that some tests with high sensitivity are better for ruling out dementia whilst others

7 with high specificity are better for ruling in the diagnosis. The tests with the highest sensitivity were

8 MoCA at a threshold of 26 (sensitivity 100%; 95% CI 97% to 100%) and Sniffin' sticks at a threshold of 11

9 (sensitivity 100%; 95% CI 96% to 100%). In contrast the tests with the highest specificities were FAQ

10 (specificity 97%; 95% CI 92% to 99%), T&C (specificity 97%; 95% 91% to 99%) and Katz ADL (specificity 95;

11 95% CI 90% to 98%). GP judgement had modest sensitivity (56%; 95% CI 47% to 65%) but was the third

12 most specific test (89%; 95% CI 81% to 94%).

1 For many brief cognitive assessments, using tests in combination with GP judgement led to a reduction in
2 sensitivity and increase in specificity. In contrast, informant measures were less affected by combining
3 with GP judgement, although the sensitivity of both AD8 and IQCODE combined with GP judgement were
4 much lower than when these two tests were used alone. When combined with GP judgement the
5 combined test with the highest sensitivity was GP+IQCODE with sensitivity 56% (47% to 64%), and the
6 combined test with the highest specificity was T&C with specificity 100% (97% to 100%).

7

1 *Impact of GP Judgement on test performance*

2 Table 3. Discrimination of tests, by GP judgement

| TEST | AREA UNDER ROC CURVE (AUROC) (95% confidence interval) Results 10 ⁻² | | | PPV FOR DEMENTIA (95% confidence interval) Results 10 ⁻² | | NPV FOR DEMENTIA (95% confidence interval) Results 10 ⁻² | |
|-----------|---|--------------------|-------------------------|---|-------------------------|---|-------------------------|
| | Overall (n=240) | GP dementia (n=86) | GP not dementia (n=154) | GP dementia (n=86) | GP not dementia (n=154) | GP dementia (n=86) | GP not dementia (n=154) |
| EPSS | 57 (52 to 63) | 48 (36 to 60) | 62 (56 to 68) | 85 (75 to 93) | 45 (36 to 54) | 11 (1 to 35) | 88 (73 to 97) |
| TAC | 62 (58 to 66) | 65 (60 to 70) | 60 (54 to 66) | 100 (85 to 100) | 78 (52 to 94) | 19 (10 to 31) | 68 (59 to 75) |
| 6CIT | 73 (67 to 79) | 58 (43 to 72) | 71 (63 to 78) | 88 (78 to 95) | 62 (49 to 74) | 24 (7 to 50) | 79 (69 to 87) |
| GPCOG | 73 (67 to 78) | 58 (47 to 69) | 71 (65 to 78) | 88 (79 to 94) | 54 (44 to 65) | 67 (9 to 99) | 87 (76 to 94) |
| SPMT | 78 (72 to 83) | 77 (63 to 92) | 71 (64 to 79) | 94 (86 to 98) | 65 (51 to 77) | 47 (23 to 72) | 78 (69 to 86) |
| TUG | 57 (52 to 61) | 54 (42 to 66) | 56 (50 to 62) | 90 (68 to 99) | 58 (34 to 80) | 15 (8 to 27) | 67 (58 to 75) |
| M@T | 71 (53 to 88) | 93 (. to 100) | 50 (30 to 70) | 100 (75 to 100) | 50 (7 to 93) | 33 (1 to 91) | 50 (23 to 77) |
| MOCA | 58 (55 to 62) | . (. to .) | 59 (55 to 63) | . (. to .) | 41 (32 to 50) | . (. to .) | 100 (79 to 100) |
| PHOTOTEST | 70 (64 to 75) | 58 (42 to 74) | 66 (59 to 73) | 89 (78 to 96) | 67 (50 to 81) | 19 (7 to 36) | 73 (63 to 81) |
| MINICOG | 71 (66 to 77) | 59 (43 to 74) | 70 (62 to 77) | 89 (78 to 95) | 62 (48 to 75) | 22 (7 to 44) | 77 (67 to 85) |
| EUROTEST | 76 (71 to 81) | 77 (63 to 90) | 71 (63 to 78) | 95 (86 to 99) | 66 (52 to 79) | 36 (18 to 58) | 77 (68 to 85) |
| SNIFFIN' | 52 (50 to 54) | . (. to .) | 53 (50 to 55) | . (. to .) | 39 (30 to 48) | . (. to .) | 100 (40 to 100) |
| FAQ | 62 (58 to 66) | 59 (46 to 71) | 58 (53 to 63) | 93 (76 to 99) | 91 (59 to 100) | 17 (8 to 29) | 66 (58 to 74) |
| ADL | 61 (56 to 65) | 59 (49 to 68) | 61 (55 to 67) | 95 (75 to 100) | 79 (54 to 94) | 17 (9 to 28) | 69 (60 to 76) |
| IADL | 62 (57 to 67) | 56 (41 to 71) | 58 (51 to 64) | 90 (75 to 97) | 60 (39 to 79) | 17 (7 to 30) | 67 (58 to 75) |
| AD8 | 64 (60 to 69) | 61 (48 to 74) | 64 (59 to 70) | 89 (80 to 95) | 46 (37 to 56) | 60 (15 to 95) | 91 (77 to 98) |
| IQCODE | 67 (62 to 72) | 55 (45 to 65) | 65 (59 to 72) | 89 (80 to 95) | 50 (40 to 60) | 100 (3 to 100) | 86 (72 to 95) |

3 PPV positive predictive value NPV negative predictive value See Supplementary Table 1 for test
 4 abbreviations . Missing data (.) are where the value is not computable. e.g., for example no cases
 5 where GPs judged a diagnosis of dementia were test-normal on MoCA

6
 7
 8 Table 3 shows how GP judgement impacts the discrimination of the index tests quantified using the
 9 AUROC. SPMT was the test with the highest AUROC overall (AUROC 0.7753 95% CI 0.7220 to 0.8285), and
 10 the AUROC was similar regardless of GP judgement for dementia (AUROC 0.7725 95% CI 0.6283 to
 11 0.9168) or not dementia (AUROC 0.7148 95% CI 0.6402 to 0.7894). AUROC was generally higher in people
 12 classified as not having dementia than those classified as having dementia. However, the converse was
 13 true for TAC, SPMT, M@T, and Eurotest, suggesting that these tests may be more useful in people who
 14 GPs judge as having dementia than in people who GPs think do not have dementia.

1 Table 3 also shows the PPV (positive predictive value) and NPV (negative predictive value) for each test
2 stratified by GP judgement. The predictive values are dependent on GP judgement because this
3 influences the prevalence of disease. PPVs were higher when tests were restricted to GP dementia +, and
4 NPVs were higher when restricted GP dementia -, probably attributable to prevalence effects. PPV for
5 M@T was 100% (95% CI 75% to 100%) in people classified by GPs as having dementia, but only 50% (95%
6 CI 7% to 93%) in people classified as not dementia. In contrast NPV for a normal Eurotest was 77% (95%
7 CI 68% to 85%) in people classed as not dementia, but only 36% (95% CI 18% to 58%) in people who GPs
8 thought had dementia.

9 *Natural frequency classification*

10 Supplementary Table 2 shows the natural frequency classification of people in a hypothetical population
11 of 1000 people. Based on our data 550 of the 1000 people have dementia, GPs would classify 358 of the
12 1000 as having dementia, being correct in 308 of the 358. Without taking GP judgement into account
13 SPMT is the test with best classification, leading to half (526) testing positive and potentially needing
14 referral, of these 426 would be true positives (TP) with 100 false positives (FP); there would also be 351
15 true negatives (TN), and 125 false negatives (FN). Taking GP judgement into account then in the 358
16 people GPs classify as having dementia M@T is the test with best classification, whereas Eurotest has
17 best classification in the 642 people classified as not having dementia. Combining M@T in the 358 classed
18 by GPs as having dementia and Eurotest in 642 classed by GPs no dementia results in a total of 414 TP
19 and 75 FP, with 376 TN and 138 FN.

20 Supplementary Table 3 gives the results of the exploratory bootstrapping procedure and indicates that
21 for the tests under evaluation, there is a general trend that the stratified approach has fewer false
22 classifications, though these differences could still be consistent with chance. For SPMT and CIT as the
23 unstratified test, the reduction in false classifications is attributable to fewer false negatives, whereas for
24 GPCOG there are fewer false positives with the stratified approach. With GPCOG (and to a lesser extend
25 SPMT) as the unstratified comparison, the stratified approach has a trade-off between FP and FN
26 whereas with CIT the trade-off is less clear, and stratification typically leads to fewer FP and FN.

1 Supplementary Table 4 presents a STARD checklist. Supplementary Table 6 presents a cross tabulation
2 for each patient-index test against cognitive category.

3 **Discussion**

4 This is the most comprehensive evaluation of a wide variety of tests for the diagnosis of dementia in
5 people aged at least 70 years presenting to their GP with cognitive symptoms. We investigated the
6 accuracy of eight BCAs, three physical tests and five informant measures, both alone and combined with
7 GP judgement. Combining tests with GP judgement altered test accuracy.

8 There are several methodological strengths: patient selection is applicable to clinical practice, we verified
9 all cases against the same reference standard, and there was adjudication of the reference standard for
10 uncertain cases. We randomised the order of the index battery to minimise order effect. However, there
11 are important limitations. We did not include people who were unable to attend with an informant, or
12 people with severe cognitive impairment who were unable to consent, and so our findings cannot easily
13 be generalised to them, especially regarding test duration and informant tests. There was no evidence of
14 bias due to selective recruitment by GPs, or due to selective participation by cognitive status, but any
15 systematic bias in recruitment would limit the generalisability of our findings to the people who were
16 excluded [19]. We do not know whether GPs used any index tests prior to referral but based on previous
17 studies, clinical judgement is likely to be based on rules of thumb [45], not formal tests [46], and
18 information on referral forms indicated that judgement was informed by "face to face presentation".
19 There is insufficient power to detect statistically significant differences between test accuracy and the
20 confidence intervals for tests overlap. Test accuracy may vary between generations, for example when
21 using prime ministers, or currency, which are subject to change. A further important limitation is that
22 despite providing translation services the population were largely white, native English speakers.

23 Most comparable studies have reported the accuracy of single tests. For example, MoCA at a threshold of
24 26 was reported to have a sensitivity of around 94% and specificity of at most 60%, but this was based on
25 studies in secondary care which are likely to have a more severe spectrum of disease [36]. IQCODE at a

1 threshold of 3.2 has been reported to have sensitivity 100% specificity 76% [47] and Eurotest at a
2 threshold of 21 has been reported to have sensitivity 91% specificity 82% [20]. These results are
3 comparable with ours. In a multi-test primary-care based study that included 47 people with dementia
4 out of a total of 141 people, Eurotest took an average 7 minutes and Phototest an average 3 minutes in
5 someone with dementia, and both tests had comparable accuracy [48], which compares well with our
6 findings.

7 While we have only tested a few comparisons with our exploratory bootstrapping procedure, our data
8 suggest that stratification by GP Judgement may help to reduce incorrect diagnostic classifications, but
9 the interplay between judgement and the test will determine the impact. Although it is not possible to
10 make firm recommendations about tests, we believe that BCAs such as M@T, Eurotest, and 6CIT and
11 GPCOG may be particularly useful to consider for further investigation or use in practice; the last two
12 tests may be particularly useful if time is highly valued in practice. These four tests have high predictive
13 values in this setting, and our results suggest that these tests may be particularly useful when GP
14 judgement is used to stratify people for further testing, but this requires confirmation in a future study.

15 One important implication is that there is substantial variation in duration of brief cognitive assessments
16 when performed in this setting. Clinicians who are short of time may prefer to be familiar with the use of
17 (and limitations of) a test which they can reliably do in less than 5 minutes in 95% of people, such as
18 GPCOG, which when combined with clinical judgment has high specificity but only modest sensitivity. A
19 second implication is that GP judgement could inform the selection of future tests because GP judgement
20 has an important impact on prevalence and therefore predictive values (and diagnostic accuracy) of tests.
21 The most time efficient diagnostic procedure while retaining high accuracy would be to stratify by GP
22 judgement and use IQCODE in people who GPs judge as having dementia and 6CIT in people who GPs
23 judge as having no dementia.

24 Further research in primary care to investigate the accuracy of tests for dementia in combination with GP
25 judgement and each other is important to help refine our results and reduce the uncertainty in the
26 estimates. Future research should attempt to identify the most discriminative tests to distinguish

1 dementia and normal from MCI in people who in the clinical judgement of a GP have cognitive
2 impairment but not having dementia, and also investigate the effect of GP stratification of particular tests
3 on diagnostic accuracy, with particular attention given to the time taken to complete tests. We believe
4 that it may be helpful to focus future research on tests such as M@T, Eurotest, 6CIT and GPCOG for
5 reasons discussed above.

6 **Declarations**

7 *Ethics approval and consent to participate*

8 The National Research Ethics Service Committee London – Bromley (reference 14/LO/2025) gave a
9 favourable ethical opinion on 25 November 2014. NHS Research and Development approvals were
10 granted by Avon Primary Care Research Collaboration on behalf of Bristol, North Somerset and South
11 Gloucestershire clinical commissioning groups. The University of Bristol acted as Sponsor.

12

13 *Consent for publication*

14 Not applicable

15

16 *Data availability*

17 The datasets generated and analysed during the current study are not yet publicly available as the funder
18 approved pre-specified data management plan stated we would embargo access for five years, but are
19 available from the corresponding author on reasonable request. Data will be available from the data.Bris
20 repository after an embargo period of five years. Statistical code is available on request from the authors.

21

22 *Competing interests*

23 STC None

24 MF None

1 SC None

2 ML None

3 AB None

4 SP None

5 YBS None

6 The authors have no conflict of interest to report

7

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18

19 *Authors' contributions*

20 STC: conception, design, data acquisition analysis and interpretation, drafting manuscript, final approval
21 of manuscript

22 MF: data acquisition, critical revision of manuscript for important intellectual content, final approval of
23 manuscript

24 SC: design, critical revision of manuscript for important intellectual content, final approval of manuscript

- 1 AB: critical revision of manuscript for important intellectual content, final approval of manuscript
2 SP: conception, design, data interpretation, critical revision of manuscript for important intellectual
3 content, final approval of manuscript
4 ML: analysis and interpretation, critical revision of manuscript for important intellectual content, final
5 approval of manuscript
6 YBS: conception, design, data interpretation, critical revision of manuscript for important intellectual
7 content, final approval of manuscript

8

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