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Featured Article

Economic impacts of introducing diagnostics for mild cognitive impairment Alzheimer's disease patients

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Abstract

Introduction: Disease-modifying treatments for Alzheimer's disease (AD) are likely to be offered only to patients with molecular evidence for Alzheimer pathology and expanded to patients with prodromal AD. We calculated the potential future costs of expanding the number of positron emission tomography (PET) and cerebrospinal fluid (CSF) tests in the United Kingdom.
Methods: We conducted a focused literature review and consulted experts to obtain information on the current use of PET and CSF to diagnose prodromal AD, staffing and equipment requirements for these tests, and associated costs.
Results: We estimate annual costs of 100,000 extra amyloid PET scans and 100,000 extra CSF tests at £113 million and £48 million, respectively; these costs are likely to be higher in the first year.
Discussion: The budgetary impacts are not insignificant but are small in comparison to the likely market price of any disease-modifying treatments or to the probable costs of missed or inaccurate diagnosis.

Keywords: Alzheimer's disease; Dementia; Screening; Molecular tests; Positron emission tomography; Cerebrospinal fluid tests; Costs

1. Background

Considerable work is underway to find disease-modifying treatments for Alzheimer's disease (AD). Treatments targeting the specific molecular pathologies underpinning AD are likely to be effective only in individuals for whom that pathology is present; moreover, it is inappropriate to expose individuals without evidence for AD to potentially harmful medications. It is also likely that disease-modifying treatments will have maximum effects when given early in the disease process. The emergence of disease-specific biomarkers, and the methods to demonstrate amyloid β (Aβ) pathology, in particular, provides a means for improving diagnostic specificity. There is also now clear evidence that biomarkers reflecting aspects of the disease process become abnormal before onset of clinical symptoms [1–3]. This has paved the way for new diagnostic criteria and a new research framework [4]. New criteria allow for diagnosis of AD before the onset of dementia, for example, when patients have mild cognitive impairment (MCI), which in the presence of amyloid biomarkers has variously been termed prodromal AD [5] or MCI-AD [6].

While in due course, blood-based biomarkers may have utility in prescreening or identifying individuals with brain

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Aβ, the two principle methods for demonstrating brain Aβ deposition today are amyloid positron emission tomography (PET) scanning and cerebrospinal fluid (CSF) analysis [7]. Substantial studies are being conducted on the value of amyloid imaging in diagnosis of AD. In the United States, the Imaging Dementia - Evidence for Amyloid Scanning study is assessing whether amyloid PET helps clinicians diagnose the cause of cognitive impairment in diagnostically uncertain cases. In Europe, the Amyloid Imaging to Prevent Alzheimer's Disease study aims to determine the value of Aβ imaging as a diagnostic and therapeutic marker.

As/when a disease-modifying therapy for AD is licensed and evidence of brain Aβ accumulation is required for prescription, demand for amyloid PET/CSF will expand considerably, with implications for health-care provision. We assessed the current costs of PET scans and CSF analyses for AD in the United Kingdom (UK) and estimated potential future costs of expanding the requirement for such diagnostic tests.

There are currently around 800,000 older people living with dementia in the UK and around 200,000 new cases of dementia annually [8]. AD accounts for around 72% of dementia cases when mixed dementia is included in the AD figures [9]. Extrapolating from US age-specific data [10], prevalence of MCI in the UK may be 1.2 million, with annual incidence of 480,000. The study by Vos et al. [11] implies an annual transition rate of 16% from all-cause MCI to AD, with rates higher in those with prodromal AD (27%) than in other forms (7%).

2. Methods

We conducted a focused rapid literature review to find studies of the current costs of amyloid PET and CSF testing and their effectiveness and cost-effectiveness in diagnosis of early stages of AD. We identified 55 articles published between January 2000 and December 2017 that included economic modeling of treatment for MCI or AD. Six of these studies had a specific focus on PET or CSF. We use these previous studies to help us locate and interpret our new cost estimates. We consulted UK experts to obtain information on current use of PET and CSF to diagnose early stages of AD, staffing and equipment requirements for conducting these tests, and associated costs. We estimated how those costs might change if the number of tests increased substantially.

3. Results

3.1. PET scanning

PET scanning is a nuclear imaging technique involving injection of a radiotracer; imaging using a PET/CT or occasionally PET/magnetic resonance imaging unit; and, for clinical purposes, a visual read to determine positivity/negativity using predefined criteria. PET ligands approved for detection of fibrillar Aβ include florbetaben (Neuraceq®), florbetapir (Amyvid®), and flutemetamol (Vizamyl®). Although licensed, no amyloid PET tracer is currently reimbursed in the UK (or US); florbetapir is not clinically available in the UK.

Table 1
PET scan cost per year under three scenarios—additional 10,000, 100,000, or 250,000 scans

	Number of tests per year and related hypothetical costs		
PET scans	10,000	100,000	250,000
Tracer	£9,000,000	£90,000,000	£225,000,000
Radiographer	£666,500	£6,665,000	£16,662,500
Radiologist	£345,000	£3,450,000	£8,625,000
Purchase of scanner	£0	£8,750,000	£20,000,000
Servicing of scanner	£0	£2,975,000	£6,800,000
Workstation and software	£0	£280,000	£6,400,000
Hospital room	£0	£875,000	£2,000,000
Total costs	£10,011,500	£112,995,000	£285,487,500

PET, positron emission tomography.

3.2. Costs of increasing capacity for PET scanning

We estimated costs to the UK National Health Service (NHS) of conducting an additional 10,000, 100,000, or 250,000 PET scans per year for the diagnosis of AD at the MCI stage.

Each of the 50 existing PET scanners in the UK supports between 2000 and 4000 scans per year, most for oncology. There are currently no data on current use for dementia diagnosis but this is clearly only a minority. An additional 10,000 scans per year would be unlikely to require purchase of further scanners or other infrastructure and could be conducted at marginal cost. However, an additional 100,000 scans or 250,000 scans per year would, we assume, require around 35 or 80 extra scanners, respectively.

The marginal resources required for one scan comprise around 80 minutes of radiographer time preparing the patient and conducting the scan, 15 minutes of consultant time reporting the scan, the tracer, and administrative and other support costs. The cost of radiographer (Band 6) time, including salary on-costs, administrative support, and annuitized cost of training, is £50 per hour [12]. The cost of consultant radiologist time is £138 per hour.

The cost of the various amyloid tracers varies but is approximately £900 excluding VAT. This cost might fall if there is a large increase in the number of amyloid scans because of economies of scale, but here we assume that cost would not fall significantly with expansion. However, in the case of 100,000 or more extra scans per year, we conducted sensitivity analysis assuming that cost falls to £500.

The estimated overall cost of 10,000 extra PET scans for AD annually is £10.0 million (Table 1). This includes costs of staff time (£1 million) and the tracer (£9 million) but does not allow for increase in any other resources on the assumption that these scans could be undertaken at marginal cost.

The purchase price of a new PET/CT scanner is around £1.3-£1.9 million excluding VAT. We assume an average

cost of £1.6 million: this sum annuitized over 7 years (the average lifetime of a scanner) at an interest rate of 3.5% is around £250,000. The annual cost of servicing a PET scanner is around £85,000. The annual opportunity cost of 35 scanners is, therefore, around £11.7 million and of 85 scanners is £26.8 million.

The cost of a workstation required for reporting PET scans is around £30,000 and the cost of the software is around £10,000. If these have a lifetime of 5 years, their annual cost is around £8000. A hospital room will be required for the scanner and a room for preparation of patients for scanning, for which we assume £25,000 per year.

We estimated that each scanner needs two to three full-time radiographers to provide the service. The annual cost for an average of 2.5 full-time equivalent radiographers is around £200,000.

The overall annual cost per 3000 additional PET scans (the assumed annual output of one scanner) is estimated at £3.2 million or £1130 per scan. These figures would be £2.1 million or £730 per scan if the price of the tracer fell to £500. This includes the costs of purchasing and servicing the scanner, the tracer, staff (including annuitized training costs), premises, and IT and administrative support.

The overall cost of 100,000 extra PET scans is estimated at £113 million per year. The equivalent annual estimate for 250,000 extra PET scans is £285 million (Table 1). If the cost of the tracer fell to £500, overall annual costs would be £73 million for 100,000 extra PET scans and £185 million for 250,000 extra scans.

3.3. CSF testing

CSF provides a means for evaluating several of the hallmark proteins involved in AD, in particular, Aβ1-42 and tau/p-tau. A meta-analysis by Olsson et al. [13] shows that Aβ1-42 is depressed and tau is elevated in AD. CSF measures are now included in both new diagnostic criteria and research frameworks. CSF sampling involves lumbar puncture (LP) by a suitably trained professional (physician assistant or nurse); collection and storage of CSF in a standardized manner; and quantification of proteins of interest in an accredited laboratory.

3.4. Costs of increasing capacity for CSF testing

We estimated costs to the NHS of providing an additional 10,000, 100,000, and 250,000 CSF tests per year for diagnosis of AD. While we have not found firm data on how many CSF tests are currently conducted for dementia, fewer than 2000 are conducted in the UK annually.

LP could be undertaken by a physician assistant or specially trained nurse (Band 6 or 7). We estimate that each nurse could undertake two LPs per day (450 per year). This means that 22.25 full-time equivalent nurses would be required to conduct 10,000 LPs per year. The annual cost of a Band 7 nurse is £93,364 at 2016/7 prices [12], including salary, salary on-costs, overheads, and annuitized costs of basic training. We assume that a Band 7 salary may be necessary to recruit and retain nurses to conduct LPs. We include annuitized costs of basic training because an increase would be required in the total number of NHS nurses. Annual cost of 22.25 full-time equivalent nurses would be £2,077,350 for 10,000 CSFs (Table 2). Costs for other scales of activity are given in Table 2.

Table 2
CSF first-year cost per year under three scenarios—additional 10,000, 100,000, or 250,000 tests per year (including the first-year cost of specialist nurse training)

	Number of tests per year and related hypothetical costs		
CSF process	10,000	100,000	250,000
Nurses	£2,077,350	£20,773,500	£51,933,750
Equipment	£350,000	£3,500,000	£8,750,000
Hospital room	£250,000	£2,500,000	£6,250,000
CSF analysis	£2,000,000	£20,000,000	£50,000,000
Nurses training	£1,654,550	£16,545,500	£41,363,750
Total costs	£6,331,900	£63,319,000	£158,297,500

CSF, cerebrospinal fluid.

Equipment required for LP (needles, sample collection tubes) costs around £35. The opportunity cost of the hospital room used for LP is arguably included in the overall cost per nurse since it includes capital overheads, but since the amount included may be insufficient, an extra £25 is assumed. The total for room and equipment amounts to £0.6 million for 10,000 patients, £6.0 million for 100,000 patients, and £15.0 million for 250,000 patients.

Analysis of the CSF is estimated to cost £200 per case, including annuitized cost of training for analysts. Hence, total cost for 10,000 CSF samples is £2,000,000; for 100,000 CSF samples, £20,000,000; and for £250,000 CSF samples, £50,000,000. New analysis machines may be needed, but we expect that deployment of new machines would be cost neutral since they would reduce operator time.

We assume that, at the outset, 50 nurses would be offered specialist training to undertake LPs. This allows for some nurses working part-time and for a reasonable distribution of additional LP staff across the country. Specialist training would take 3 months. Salary costs of the nurses would be £1,167,050. If the training cost including travel costs is £150 per day, the direct cost would be £487,500 for 50 nurses. Total training cost for 50 nurses for conducting an additional 10,000 CSFs per year would therefore be £1,654,550. Total cost of training for 500 nurses for 100,000 additional CSFs would be £16.6 million; for 1250 nurses (for 250,000 additional CSFs), it would be £41.4 million.

Total first-year costs for 10,000 CSF tests would be £6.3 million including specialist training for nurses conducting LPs (Table 2). Total first-year costs for 100,000 CSF tests would be £63.3 million including specialist training or £158.3 million for 250,000 tests. These estimates do not

Table 3
CSF cost per year under three scenarios—additional 10,000, 100,000, or 250,000 tests per year (including the second and subsequent year cost of specialist nurse training)

	Number of tests per year and related hypothetical costs		
CSF process	10,000	100,000	250,000
Nurses	£2,077,350	£20,773,500	£51,933,750
Equipment	£350,000	£3,500,000	£8,750,000
Hospital room	£250,000	£2,500,000	£6,250,000
CSF analysis	£2,000,000	£20,000,000	£50,000,000
Nurses training	£165,455	£1,654,550	£4,136,375
Total costs	£4,842,805	£48,428,050	£121,070,125

CSF, cerebrospinal fluid.

allow for training of more technicians to conduct CSF analysis.

If the average period during which each nurse conducts LPs is 10 years, five additional nurses would need to be trained each year for additional 10,000 LPs, and overall cost per year after the first year would be £4.8 million. For larger increases in LPs, overall cost would multiply (see Table 3). This does not allow for any real increase in nurses' salaries, which may be expected.

4. Discussion

4.1. Context

Supporting people with dementia is costly. Total cost in England in 2015 is estimated to be £24.2 billion, 16% of which was for health care, 42% social care, and 42% unpaid care by families and friends [8]. New projections to 2040 suggest that the number of older people in England with dementia will more than double by 2040 and costs more than treble in real terms [14].

Currently available pharmaceutical treatments and standard care can improve the overall health and well-being for people with AD and their carers [3,15]. However, disease-modifying treatments—of which none are currently marketed—offer the possibility of achieving greater improvements in health and well-being, while reducing the costs of support. This is especially important given projections of rapidly escalating costs as the population ages. For new compounds to be most effective, there is a need for early and accurate identification of people most at risk of developing AD to provide prompt access to treatment.

4.2. Summary of findings

We estimated the current UK costs of two molecular diagnostic tests currently available for AD—PET scans and CSF analyses—and the costs of expanding the number of such tests.

Estimated overall costs of 100,000 extra PET scans, requiring an additional 35 scanners, is £113 million per year, which equates to approximately £1000 per scan.

Total first-year costs for 100,000 CSF tests would be £63.3 million, including cost of specialist training for nurses conducting the LPs but not the cost of training more technicians to conduct CSF analyses. Cost in subsequent years would be lower since fewer nurses would require specialist training. Overall, cost in subsequent years would be around £500 per test.

4.3. Previous economic studies

A systematic review of economic evaluations of interventions for early diagnosis of AD and related disorders by Handels et al. [16] found few such studies: only eight decision-analytic modeling studies and one trial-based evaluation. Although there have been a few subsequent studies, the evidence base in this area remains sparse.

Handels et al. [17] modeled potential economic gains from a "perfect" CSF biomarker allied to a hypothetical disease-modifying treatment: the biomarker had greater benefit when used to rule out AD (to prevent undertreatment) than when confirming diagnosis (prevent overtreatment). Cost per CSF test (£211 in the Netherlands) was based on expert opinion, but no details were given of what this cost covers. Handels et al. [18] used data merged from cohort studies to examine the cost-effectiveness of adding CSF testing to standard diagnostic procedures. CSF testing was found to improve the accuracy of prognosis from MCI to AD by 11% and was cost-effective. The additional cost of adding LP to the usual diagnostic process was £432 per patient (based on figures from Sweden, 2015 prices).

Valcarcel-Nazco et al. [19] concluded from a modeling study that use of CSF biomarkers was more cost-effective than standard clinical diagnostic criteria in patients with MCI and probably more cost-effective in patients with dementia. However, from the information provided in the paper, it is not possible to identify the cost per CSF test used in the modeling.

Lee et al. [20] found that the sensitivity and dependency of CSF biomarker analysis are affected by the prevalence of AD in the population tested. Where AD prevalence after clinical assessment and standard neuroimaging is low, analysis is unlikely to be cost-effective, but when it is higher than 15%, it is likely to be cost-saving. This result is therefore linked to the extent of pre-CSF testing, with implications for targeting of diagnostic tests.

4.4. Implications

Given expected rapid growth in the number of people at risk of developing AD and other dementias and the prospect that there may soon be available new medications with potential to prevent, delay, or slow down progression of these conditions, it is highly likely that there will be a need for substantial increases in PET and/or CSF diagnostic testing. While the costs of each test may look modest in comparison to other inputs to the care pathway, serious consideration

will need to be given to possible resource supply constraints and their effects on costs.

A large increase in diagnostic testing will require substantial increases in supply of key inputs to diagnostic testing processes, particularly equipment and laboratory facilities, tracers, skilled nursing, radiology staff, and premises. A key question, therefore, is whether the supply of those resources can be increased. There are already shortages of both nurses and radiologists in the UK [21,22]; increasing supply would take at least a few years given the training required and the low likelihood of recruiting sufficiently from abroad. The supply of radiotracers may not be able to respond to demand, which could push up prices at least initially, although in time the price could fall due to economies of scale. Our cost estimates do not allow for effects of possible supply constraints.

A related consideration is whether the accuracy of testing would be maintained at its present level after substantial expansion in the number of tests. Would greater scale improve accuracy through accumulation of experience or would it make it harder to assure quality if the number of centers carrying out tests multiplied? The finding by Lee et al. [20] that the cost-effectiveness of diagnostic testing is linked to underlying prevalence of AD in the group tested suggests a need to consider offering tests only to people who screen positive on initial screening (e.g., mini-mental state examination). This would not be an issue if testing was offered only to people with MCI, as assumed here, since they have a high probability of having underlying AD. However, with a wider screening approach, a two-step diagnostic process could be considered in which initial screening was an integral part of the care pathway.

Budgetary impacts of a substantially expanded number of PET and CSF tests are not insignificant. However, it needs to be recognized that the costs of these diagnostic tests are small in comparison to the likely market price of any new disease-modifying treatments or to the probable costs of missed or inaccurate diagnosis [23].

Our cost estimates are necessarily specific to the UK and reflect the costs of labor, equipment, and laboratory testing in the NHS. These costs are likely to differ substantially across health-care settings and countries. Nonetheless, the relative costs of CSF and PET imaging are likely to be broadly similar, suggesting that CSF screening may be more cost-effective, noting that LPs are contraindicated in certain settings (e.g., anticoagulation), may be unacceptable to some individuals, and thus, provision of both modalities will be needed. Availability of blood tests to prescreen individuals at low risk of Aβ pathology may also reduce numbers of CSF/PET scans required.

A crucial question is whether there are cost-effectiveness gains or better still actual cost savings, from increasing PET scans or CSF tests. This obviously depends on assumptions made about treatments offered following the tests: are those symptomatic (as currently available) or disease-modifying (as currently under development)? We have not attempted any such modeling here. The few previous studies which have explored those wider economic questions have generally concluded that there is an economic case for diagnostic testing, given what is known and observed today but have not factored in the possibility of unit cost increases or input supply constraints.

The availability of disease-modifying drugs for AD will require major changes in how we approach the investigation of patients with memory complaints, including significant increased provision of molecular diagnostics. Our estimates of the associated costs can inform discussion and planning of future services.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., MEDLINE, EMBASE, OpenGrey) sources and relevant search terms (e.g., dementia, cost analysis, positron emission tomography [PET], cerebrospinal fluid [CSF]). A few articles examined the costs and cost-effectiveness of CSF and PET in diagnosing Alzheimer's disease. Those most relevant are cited.
2. Interpretation: The estimated annual cost of 100,000 extra amyloid PET scans is £113 million per year and of 100,000 extra CSF tests is £48 million (more in first year).
3. Future directions: The prospect of new disease-modifying treatments offered at the mild cognitive impairment stage means that health services should prepare for substantially increased diagnostic testing. Key questions include whether the supply of key resources required for PET or CSF can be increased sufficiently; whether the accuracy of testing would be maintained if there was substantial expansion in testing; and whether PET or CSF should be offered only to those screening positive on an initial screen.

References

[1] Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2009;9:19–28.

[2] Holtzman D, John M, Alison M. Alzheimer's disease: the challenge of the second century. Sci Translational Med 2011;3:77sr1.

[3] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15:455–532.

[4] Jack CR, Bennett DA, Blennow, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimer's Demen 2018;14:535–62.

[5] Dubois B, Feldman H, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–29.

[6] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270.

[7] Frisoni GB, Boccardi M, Barkhof F, Blennow K, Cappa S, Chiotis K, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol 2017;16:661–76.

[8] Wittenberg R, Knapp M, Hu B, Comas-Herrera A, King D, Rehill A, et al. The costs of dementia in England. Int J Geriatr Psychiatry 2019; 34:1095–103.

[9] Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, et al. Dementia UK: Update. London: Alzheimer's Society; 2014.

[10] Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology 2010; 75:889–97.

[11] Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol 2013;12:957–65.

[12] Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury: Personal Social Services Research Unit, University of Kent; 2017.

[13] Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016; 15:673–84.

[14] Wittenberg R, Hu B, Jagger C, Kingston A, Knapp M, Comas-Herrera A, et al. Projections of Care for Older People with Dementia in England: 2015 to 2040. forthcoming. Oxford, UK: Oxford University Press.

[15] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673–734.

[16] Handels R, Wolfs C, Aalten P, Joore MA, Verhey FR, Severens JL. Diagnosing Alzheimer's disease: a systematic review of economic evaluations. Alzheimers Demen 2014;10:225–37.

[17] Handels R, Joore M, Tran-Duy A, Wimo A, Wolfs CA, Verhey FR, et al. Early cost-utility analysis of general and cerebrospinal fluid-specific Alzheimer's disease biomarkers for hypothetical disease-modifying treatment decision in mild cognitive impairment. Alzheimer's Demen 2015;11:896–905.

[18] Handels R, Wimo A, Dodel R, Kramberger MG, Visser PJ, Molinuevo JL, et al. Cost-utility of using Alzheimer's disease biomarkers in cerebrospinal fluid to predict progression from mild cognitive impairment to dementia. J Alzheimer's Dis 2017;60:1477–87.

[19] Valcarcel-Nazco C, Perestelo-Perez L, Molinuevo J, Mar J, Castilla I, Serrano-Aguilar P. Cost-effectiveness of the use of biomarkers in cerebrospinal fluid for Alzheimer's disease. J Alzheimer's Dis 2014; 42:777–88.

[20] Lee S, Sposato L, Hachinski V, Cipriano LE. Cost-effectiveness of cerebrospinal biomarkers for the diagnosis of Alzheimer's disease. Alzheimer's Res Ther 2017;9:18.

[21] Marangozov R, Williams M, Buchan J. The Labour Market for Nurses in the UK and its Relationship to the Demand for, and Supply of, International Nurses in the NHS. Brighton: Institute for Employment Studies; 2016.

[22] Rimmer A. Radiologist shortage leaves patient care at risk, warns royal college. BMJ 2017;359:j4683.

[23] Dixon J, Ferdinand M, D'Amico F, Knapp M. Exploring the cost-effectiveness of a one-off screen for dementia (for people aged 75 years in England and Wales). Int J Geriatr Psychiatry 2014;30:446–52.