Psychiatria Danubina, 2018; Vol. 30, Suppl. 7, pp 463-468 *Conference paper*

ETHICAL AND ORGANISATIONAL CONSIDERATIONS IN SCREENING FOR DEMENTIA

Thomas J. M. Weatherby[1] & Mark Agius[2,3]

[1]*University of Cambridge School of Clinical Medicine, Cambridge, UK*
[2]*Department of Psychiatry, University of Cambridge, Cambridge, UK*
[3]*Clare College, University of Cambridge, Cambridge, UK*

SUMMARY

The United Kingdom National Screening Committee (UKNSC) defines screening as "the process of identifying individuals who may be at higher risk of a disease or condition amongst large populations of healthy people". Building on foundations laid by Wilson and Jungner in the landmark paper in 1968, the UKNSC states that "Once identified, those individuals can consider further tests, and healthcare providers can offer them interventions of benefit. A screening programme needs to offer more benefit than harm, at a reasonable cost to the NHS" (gov.uk 2014).

We will consider the ethical issues surrounding some of the UK's screening programmes and other methods used to assess and communicate patients' risk of disease. We will discuss the appropriateness of candidate dementia biomarkers in order to inform research into developing such a biomarker or series of biomarkers.

Key words: *Alzheimer's disease – dementia – screening - ethics*

* * * * *

INTRODUCTION

Dementia, renamed "Major Cognitive Disorder" in DSM-V is a syndrome characterised by impairment in one or more cognitive domains, that is recognised by the patient, a clinician, objective cognitive assessment or by adverse effect on activities of daily living (Hugo 2014). Dementia is associated with an increasingly significant socio-economic burden in the UK. The total number of people with dementia in the UK is predicted to increase to over 1 million by 2025 and over 2 million by 2051 with increases driven by demographic ageing (Prince 2014). Therefore, the possibility of introducing a screening programme for dementia and reduce the incidence of disease is very attractive, to policy makers and the public. Early detection of a disease process causing dementia or detection of subtle cognitive changes may allow intervention before the onset of frank symptoms to improve patient outcomes and to reduce disease burden.

In 1968, at the request of the WHO, Wilson and Jungner produced their famous criteria for an ethical screening programme (Wilson 1968). Although some other criteria have been proposed and are increasingly widely accepted (Andermann 2008), these remain the gold standard for considering the ethical issues around screening programmes (see Table 1). In this article we will consider the ethical issues surrounding some of the UK's current screening programmes, and then consider how these may apply to dementia screening.

THE AIM OF SCREENING - SAVING MORBIDITY, MORTALITY OR MONEY?

The aim of screening is to reduce incidence of disease, but what is the motivation behind reducing incidence of disease? We will spare individuals from suffering but also reduce the economic burden associated with disease. Does the economic or humanitarian gain weigh more heavily in an argument for screening? If patients can choose to accept or decline screening, how does the healthcare provider treat patients who declined screening and subsequently develop the disease? More importantly, how do we determine the level of morbidity spared as "a reasonable cost to the NHS"? An effective treatment or means of risk reduction should be available for participants identified as being at high risk of developing the disease. It would be unacceptable to identify and inform persons, presently healthy, that they are risk of developing a serious condition without offering an intervention to reduce the risk. A third ethical consideration linked with finance; should healthcare professionals receive a financial incentive to screen? In the UK, GPs have a financial incentive screen all women of the appropriate age group for cervical cancer, as it is paid for as an item of service. All other UK adult screening programmes are delivered centrally, so this financial incentive does not exist. In the aging population, dementia presents an increasing challenge to primary care, secondary care, care in the community and to families. Current treatments for Alzheimer's disease and other causes of dementia rarely provide adequate symptom relief and do not slow disease progression (Buckley 2015). Detection of persons at high risk of future dementia may facilitate early intervention with lifestyle modification or pharmacological agents. If such interventions were shown to be effective, a reduction in cognitive decline in this population would serve the individual, their family, communities and healthcare systems.

Table 1. The Wilson and Jungner Screening Criteria (Wilson & Jungner 1968)

- The condition sought should be an important halth problem.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for Diagnosis and treatment should be available.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural History of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a declared policy on whom to treat as patients.
- The cost of Case-Finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-Finding should be a continuing process and not a ''once and for all'' project.

TESTING AND DELIVERING INFORMATION TO A "HEALTHY" POPULATION

Participants invited to screening programmes view themselves as being free from the disease in question. Usually, screening is carried out in two stages. Screening often involves an initial test which by itself is not diagnostic, but indicates whether further investigation is warranted. The initial test is offered to the population determined to be sufficiently at risk of disease. Thus the test should be acceptable to the population – safe and non-invasive. Patients' ability to identify as "healthy" should be respected. Diagnostic labels should not be administered to asymptomatic persons unless the loss of their "healthy identity" is justified by being able to deliver an effective and acceptable intervention. Furthermore, the ethics of screening large populations for a condition such as dementia, with the implication of assessing person's cognition and thence competence in decision making, long term or short term, and keeping record of such data, has yet to be considered.

PRESENT ADULT UK SCREENING PROGRAMMES

We will examine the various adult screening programmes at present available in the UK and to draw lessons from them, so as to see whether similar screening programmes could be applied to Dementia.

Cervical Screening

Cervical cancer can be detected in an early but latent stage, when it can be treated by large loop excision of the transformation zone as an outpatient procedure much less invasive than that which would be required if it were at a later stage. The facilities to do this exist widely in the UK, and the natural history of the disease if left untreated are well understood. Acceptability of the test is the only one of the Wilson criteria which could be debated. However, with a participation rate of above 70% most women seem to weigh the invasive nature of a cervical smear against the benefits of the programme and consider it worthwhile enough to take part (Jo's Cervical Cancer Trust 2017).

Breast Screening

Although it is estimated to prevent 1300 deaths per year in the UK, breast cancer screening has been controversial in recent years (Public Health England 2017). The areas of particular concern are over-diagnosis, radiation exposure and additional anxiety (Marmot 2012). The screening programme aims to detect lesions which are at an early stage, will go on to cause morbidity and mortality, and could be treated more effectively earlier than they could if they were identified at a later stage. However, it is not clear that for the lesions picked up by breast cancer screening this is always the case. In some groups of women at lower risk, such as women in the 40-49 age group the benefits are particularly difficult to demonstrate as outweighing the harms (Health Quality Ontario 2007). Overall, it does seem that the benefits outweigh the harms, but it is important to communicate to patients that some women across the population will be harmed in this screening programme (Myers 2015, Elmore 2016).

Bowel Cancer Screening

Bowel cancer screening is conducted by way of guaiac faecal occult blood tests followed by a colonoscopy if the test was abnormal (Logan 2012). This aims to reduce mortality in colorectal cancer. One-off flexible sigmoidoscopy is being introduced to all men and women aged 55 following a recent successful pilot (Atkin 2017). The ethical issues involved in bowel cancer screening are to do with health inequalities. Due to difference in uptake of the screening by different socio-economic groups there is a risk that healthcare resources spent on this screening programme will exacerbate inequalities in colorectal cancer outcomes across different groups (von Wagner 2011). While significant efforts have been dedicated to identifying a way to better reach these underserved communities, good solutions are lacking (Wardle 2016). It has however

been argued that the continued low participation rates could be the result of genuine informed choices, thus making the well-intentioned continued attempts to persuade groups who currently choose not to participate ethically questionable (Essink-Bot 2016).

Abdominal Aortic Aneurysm (AAA) Screening

The Wilson's criterion which is most notable in the context of abdominal aortic aneurysm (AAA) screening is that of an acceptable treatment, with preventative surgery carrying a 3-5% mortality risk and a 32% complication rate (Stather 2013). While many AAAs can be managed endovascularly, the screening does not detect only those aneurysms for which an endovascular repair would be appropriate. Is it ethical to screen for AAA in a man for whom open repair would not performed (Lath 2011)? While open repair has been performed in people much older than the current screening time point of 65 (Huber 2001), the invasiveness of a potential treatment is so great that considerable counselling would need to be conducted prior to screening to ensure truly informed consent for many.

Additionally, over diagnosis is a significant risk. For every death prevented by the scheme, four people are diagnosed with an aneurysm which would never have caused a problem in their lifetime (Johansson 2015). This then leaves the patient with the agonising knowledge that they have this problem, and the difficult decision of whether it is worth the risk of preventative surgery.

Hypertension

It has long been advocated that patients on UK general practitioners' lists should be screened for hypertension and that those found to suffer from hypertension should be treated in order to prevent stroke (Hart 1970, 1975, 1980). This idea eventually developed into the idea of screening for all cardiovascular risk factors (Hart 1988) and is now a part of routine UK General Practice, within the routine assessments when a new patient registers.

In 2006, the UKNSC did not recommend routine screening but did recommend the introduction of a Vascular Risk Management Program as a result of the Diabetes, Heart Disease and Stroke (DHDS) prevention project. A Handbook of Vascular Risk Assessment, Risk Reduction, and Risk Management was published in 2008 and an NHS Health Check has been rolled out (UKNSC 2006). This programme covers screening of adults with early intervention for all cardiovascular risk factors including Hypertension, Diabetes Mellitus, and Hypercholesterolemia, as well as educational interventions regarding obesity and smoking. In a subsequent paper, we will later discuss the potential contribution such a programme could have to reducing the risk of dementia (Mackeever 2018)

LESSONS FROM PRESENT SCREENING PROGRAMMES

In summary, present screening programmes cervical screening, bowel Cancer screening and Cardiovascular risk assessment programmes involve simple non-invasive tests carried out in Primary care with patients referred on to secondary care if high risk or serious disease is found. However, in Breast Screening and Abdominal Aaortic Aneurysm Screening procedures, the initial tests are more sophisticated and expert opinion is required to interpret the screening test. In both Breast Screening and Abdominal Aaortic Aneurysm screening, the, treatment offered to high-risk individuals is more invasive, and there is a greater risk of over diagnosis and over treatment. These programmes set a precedent for the degree of risk that is likely to be accepted as other programmes are introduced.

APPLICATIONS OF SCREENING FOR DEMENTIA

Thus far, no formal screening programs have been recommended for mental health conditions. The Wilson and Jungner criteria state that facilities for diagnosis and treatment should be available before initiating any screening programme. This is a very important hurdle in the UK. There is a huge shortfall in mental health staff with 10% of posts vacant; this is over 20 000 unstaffed positions (Nuffield Trust 2017, Health Education England 2017). It is unlikely, then, that even if a suitable test for a suitable condition were available that it would be possible to mount a screening programme, as at risk patients would not be able to be managed.

Dementia is not a single entity, but a syndrome associated with several diseases. Alzheimer's disease, vascular dementia, and Lewy body dementia are three examples, each with a separate pathology. Hence we have the potential to screen for dementia or for the onset of a particular disease process such as Alzheimer's disease or Vascular dementia. To screen for dementia in general, is conceptually different to the above screening programmes, which look for evidence of the beginning of or a latent stage of a disease process.

Focusing on Alzheimer's disease, it seems there is a pathological early latent phase, but there at present is no treatment available that modifies disease trajectory. Therefore, screening is ethically unjustifiable. However, in order to conduct the research necessary to produce disease modifying drugs it is likely to be necessary to find groups of these individuals who are likely to go on to develop Alzheimer's disease but haven't yet manifested any signs. These people would need to be well informed volunteers, as they would be suffering the distress of an early diagnosis of a currently incurable degenerative disease, with no guarantee the research they are participating in will bear fruit quickly enough for them to benefit from it (Vandershaeghe 2018).

The UKNSC does not recommend screening for dementia. (UKNSC 2015) The UKNSC highlights the poor sensitivity and specificity available from neurocognitive test batteries that have been used to test for dementia and MCI. (UKNSC 2015) The difficulties relating to false positives make the use of present tests unethical, despite several papers (Robert 2003, (Solomon 1998, Ijuin 2008) which report good results in terms of rater to rater reliability. The UKNSC also states; 'In order to offer enough information to allow anyone invited to screening to make an informed choice, we would first need to understand how dementia develops and be confident that early treatment will slow the progression or even prevent the disease". However, there is emerging evidence that reduction of cardiovascular risk through lifestyle modification reduces cognitive decline and incidence of dementia in later life (Christie 2017, Solomon 2018).

Therefore, considering other UK screening programmes as a model, a screening program for dementia might be a stepwise process, with testing of cognition (using a battery of cognitive tests) at a first stage (Sindi 2015), followed if necessary by specific tests, e.g. for amyloid beta or cerebral microbleeds. Alternatively, rather than a single test, a panel of biomarkers may offer increased sensitivity and specificity, depending on the selected component tests (Tan 2014). Indeed, if we are testing for dementia, which has clinical diversity and many causes, a panel of tests would be essential. If we are testing for an early stage of Alzheimer's disease, a panel of tests e.g. amyloid-PET, CSF amyloid beta and MRI might be used to provide optimum sensitivity to very early stages of disease (Tan 2014). However, cost and/or invasiveness of the tests listed here make them inappropriate for screening, and hence other tests need to be found. It is clear from the above that other biomarkers or methods of predicting patients risk of disease are required if dementia screening is to be considered.

In a separate paper we will suggest that there is potential in screening for risk factors for dementia rather than dementia itself (Makeever 2018).

FURTHER PROBLEMS WITH SCREENING FOR DEMENTIA

There are a number of issues which arise if screening is carried out for conditions which cannot be treated and which have important implications for the future health of patients. It is not therefore surprising that the Wilson criteria do not recommend screening in these circumstances. However, in the context of Dementia, genetic testing for the apolipoprotein E (APOE) ε4 allele has been suggested. Such genetic testing not only reveals the risk to an individual, but it also reveals the risk to other family members. Also, the recording of the results of Genetic Testing and even information about Mild Cognitive Impairment in the Patient's Notes, while the patient is still well can have major implications for the patient, for example when the patient applies for life insurance or employment. Early biomarkers of dementia are not definitive, that is they indicate an increased risk but they will not say when and whether the person will be disabled. This can be disturbing for people because this information is confusing and it is not clear what action one should take when receiving this information. This is why there should be proper counselling and professional support before and after the test. Another issue is that if the person tested now knows that they may develop dementia, how will this impact on their behaviour towards friends, family and others, including himself? This might even include ideas of suicide. The person tested may feel that other people will be less likely to trust them because of the test result.

CONCLUSION

Because of the potential problems mentioned above, the following points are recommended regarding any form of genetic testing (Arribas-Ayllon 2011). In our view these points should be relevant to every person who might be screened for any form of cognitive impairment or dementia, whether the technique is genetic testing or not; it is recommended that the decision to take the test should be voluntary, free of coercion and based on informed consent (Arribas-Ayllon 2011). Each person screened should receive proper counselling and professional support (Arribas-Ayllon 2011). Only persons who have reached the age of majority should be offered any form of screening for future dementia (Arribas-Ayllon 2011). Full confidentiality, including confidentiality regarding all forms of note-keeping should be maintained so as to avoid any form of discrimination as a result of screening (Arribas-Ayllon 2011). This means that the results of a screening procedure are confidential and the property of the individual and under no circumstances shall any professional communicate this information to third parties (Arribas-Ayllon 2011). Any screening for a potential dementing process should be delayed if there is evidence that the results will lead to psychosocial harm (Arribas-Ayllon 2011). Adhering to these rules will enable useful advice to be given to individual patients while avoiding harm to the patient as a consequence of the screening, information storing, and councelling process.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Thomas J. M. Weatherby - review of lessons from current screening and applications of screening for dementia;

Mark Agius - supervision and significant contributions to redrafting manuscript.

References

1. *Andermann A, Blancquaert I, Beauchamp S, Déry V: Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years Bull World Health Organ 2008; 86:317-319*
2. *Arribas-Ayllon M: The ethics of disclosing genetic diagnosis for Alzheimer's disease: do we need a new paradigm? Br Med Bull 2011; 100:7-21*
3. *Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, Duffy S, Cross AJ: Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017; 389:1299-1311*
4. *Buckley JS, Sapleter SR: A Risk-Benefit Assessment of Dementia Medications: Systematic Review of the Evidence. Drugs Aging 2015; 32:453-67*
5. *Christie G, Hamilton T, Manor B, Farb N, Farzanak F, Sixsmith A, Temprado J, Moreno S: Do Lifestyle Activities Protect Against Cognitive Decline in Aging? A Review. Frontiers in aging neuroscience 2017; 9:38*
6. *Elmore JG: Review: Mammography screening reduces breast cancer mortality in women at average risk. Ann Intern Med 2016; 164:JC26*
7. *Essink-Bot ML, Dekker E: Equal access to colorectal cancer screening. Lancet 2016; 387:724-6*
8. *gov.uk, Evidence and recommendations: NHS population screening https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening Published 1 January 2014 Last updated 30 November 2015*
9. *Hart JT: Semi-continuous screening of a whole community for hypertension. Lancet 1970; 2:223–6*
10. *Hart JT: Management of high blood pressure in general practice. Butterworth Gold Medal essay. Journal of the Royal College of General Practitioners 1975; 25:160–92*
11. *Hart JT:Hypertension: community control of high blood pressure. First edition, 1980*
12. *Hart JT, Stilwell B, Gray M: Prevention of coronary heart disease and stroke: a workbook for primary care teams. Faber, 1988*
13. *Health Education England: Stepping forward to 2020/21: The mental health workforce plan for England. Health Education England, 2017*
14. *Health Quality Ontario: Screening mammography for women aged 40 to 49 years at average risk for breast cancer: an evidence-based analysis. Ont Health Technol Assess Ser 2007; 7:1-32*
15. *Huber TS, Wang JG, Derrow AE, et al.: Experience in the United States with intact abdominal aortic aneurysm repair. J Vasc Surg 2001; 33:304-10*
16. *Hugo J, Ganguli M: Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment Clin Geriatr Med 2014; 30:421-442*
17. *Ijuin M, Homma A, Mimura M, Kitamura S, Kawai Y, Imai Y, Gondo Y: Validation of the 7-Minute Screen for the detection of early-stage Alzheimer's disease. Dement Geriatr Cogn Disord 2008; 25:248-55*
18. *Johansson M, Hansson A, Brodersen J: Estimating overdiagnosis in screening for abdominal aortic aneurysm: could a change in smoking habits and lowered aortic diameter tip the balance of screening towards harm? BMJ 2015; 350:h825*
19. *Jo's Cervical Cancer Trust: Cervical Screening in the Spotlight, 2017. http://www.content.digital.nhs.uk/catalogue/PUB22414*
20. *Lath NR, Rai K, Alshafie T: Open repair of abdominal aortic aneurysm in a centenarian. J Vasc Surg 2011; 53:216-8*
21. *Logan RFA, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C: Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests Gut 2012; 61:1439-1446*
22. *McKeever A & Agius M: Dementia risk assessment and risk reduction using cardiovascular risk factors. Psychiatr Danub 2018; 30(Suppl 7):S469-74*
23. *Marmot M, Altman D, Cameron D, Dewar J, Thompson S, Wilcox M: The Benefits and Harms of Breast Cancer Screening: An Independent Review Cancer Research UK and the Department of Health (England), 2012*
24. *Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, Davidson B, Mongtomery RC, Crowley MJ, McCrory DC, Kendrick A, Sanders GD: Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA 2015; 314:1615-34*
25. *Nuffield Trust: The NHS Workforce in Numbers https://www.nuffieldtrust.org.uk/resource/the-nhs-workforce-in-numbers#references Published 2017*
26. *Prince et al.: Dementia UK: Update Second Edition report produced by King's College London and the London School of Economics for the Alzheimer's Society, 2014*
27. *Public Health England: National Cancer Registration and Analysis Service Cancer statistics: availability and location. Public Health England, 2017. http://www.ncin.org.uk/view?rid=3375*
28. *Robert PH, Schuck S, Dubois B, Lépine JP, Gallarda T, Olié JP, Goni S, Troy S: Validation of the Short Cognitive Battery (B2C). Value in screening for Alzheimer's disease and depressive disorders in psychiatric practice. Encephale 2003; 29:266-72*
29. *Sindi S, Calov E, Fokkens J, Ngandu T, Soininen H, Tuomilehto J, Kivipelto M: The CAIDE Dementia Risk Score App: The development of an evidence-based mobile application to predict the risk of dementia. Alzheimers Dement (Amst) 2015; 1:328-33*
30. *Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW: A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998; 55:349-55*
31. *Solomon A; Turunen H, Ngandu T et.al.: Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention A Subgroup Analysis of a Randomized Clinical Trial JAMA Neurol 2018; 75:462-470*
32. *Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD: Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg 2013; 100:863–72*

33. Tan C, Yu C, Tan L: Biomarkers for Preclinical Alzheimer's Disease. J Alzheimers Dis 2014; 42:1051-69
34. UKNSC 2006. https://legacyscreening.phe.org.uk/hypertension-adult
35. UKNSC 2015. https://legacyscreening.phe.org.uk/dementia
36. Vanderschaeghe G, Schaeverbeke J, Bruffaerts R, Vandenberghe R, Dierickx K: From information to follow-up: Ethical recommendations to facilitate the disclosure of amyloid PET scan results in a research setting. Alzheimers Dement (N Y) 2018; 4:243-251
37. von Wagner C, Baio G, Raine R, Snowball J, Morris S, Atkin W, Obichere A, Handley G, Logan RF, Rainbow S, Smith S, Halloran S, Wardle J: Inequalities in participation in an organized national colorectal cancer screening programme: results from the first 2.6 million invitations in England. Int J Epidemiol 2011; 40:712-8
38. Wardle J, von Wagner C, Kralj-Hans I, Halloran SP, Smith SG, McGregor LM, Vart G, Howe R, Snowball J, Handley G, Logan RF, Rainbow S, Smith S, Thomas MC, Counsell N, Morris S, Duffy SW, Hackshaw A, Moss S, Atkin W, Raine R: Effects of evidence-based strategies to reduce the socioeconomic gradient of uptake in the English NHS Bowel Cancer Screening Programme (ASCEND): four cluster-randomised controlled trials. Lancet 2016; 387:751-9
39. Wilson JMG & Jungner G: Principles and practice of screening for disease. Geneva: WHO, 1968. Available from: http://www.who.int/bulletin/ volumes/86/4/07-050112BP.pdf

Correspondence:
Thomas J. M. Weatherby, BA (Cantab)
University of Cambridge School of Clinical Medicine
Cambridge, UK
E-mail: tw418@cam.ac.uk