

Screening for neurodegenerative disorders

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‘All screening programmes do harm. Some do good as well. Those that are justified must do more good than harm’

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Popularity paradox

The greater the harm through overdiagnosis and overtreatment from screening, the more people there are who believe they owe their health or even their life to the programme

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Outline

- Context
- Definition of screening
- A little history
- Avoiding the mistakes of history – learning from other disorders
- Briefly worked case example with criteria using dementia
- Key questions

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Context

- Dementia Strategy
- Darzi Review – care pathways
- Local work e.g. Joint Strategic Needs and Local Area Agreements (PCT/LA)
- National Service Framework
- NICHE

NB ‘early detection’, ‘enhanced awareness’ mentioned in most but not screening

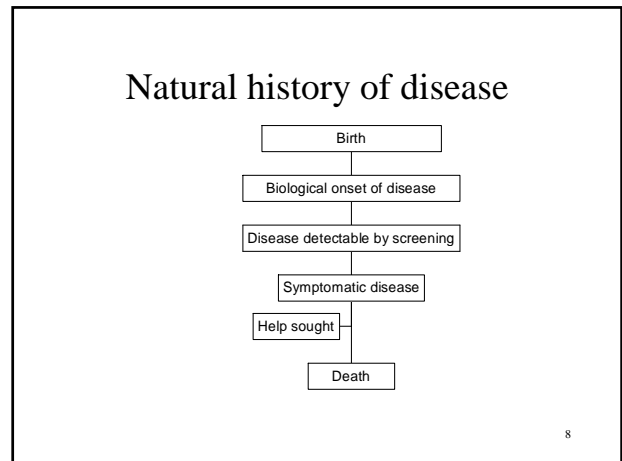
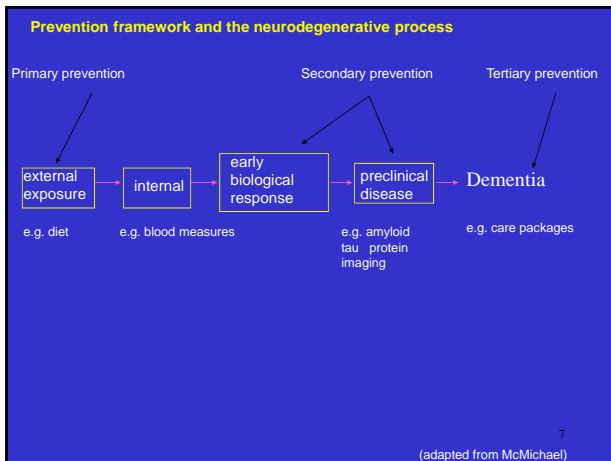


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Prevention framework

- Primary – true prevention
- Secondary – early detection, screening
- Tertiary – doing the best possible in established disease

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What is screening?

- ‘screening is a sieve’ OED definition
- ‘People being screened who either do not have or have not recognised the signs and symptoms of the condition being screened for’
- Full definition from National Screening Committee

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Formal definition of screening (NSC)

- public health service
- defined population
- not necessarily perceive they are at risk of, or are already affected by, a disease or its complications
- asked a question or offered a test
- to identify those individuals who are more likely to be helped than harmed by further tests and treatments to reduce the risk of disease or its complications

UK National Screening Committee

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As opposed to...

- Case finding, which is prevention through early detection of people using health services for other reasons (e.g. testing for diabetes in outpatient clinics)
- Enhanced awareness of problems which should alert knowledgeable professionals /others to presence of dementia

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Why stress the difference?

- different from clinical practice, targets apparently healthy people
- properly organised population screening is not a marginal extra to clinical service if it is to be done properly

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Why screen?

- To reduce future ill health (utilitarian aim)
- To give full information even though risk cannot be changed (humanitarian aim)

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- Public health opinion seems at odds with commonly stated view that screening for dementia (and possibly other neurodegenerative conditions) should be advocated
- Why?

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A little history starting with United States

- 1900 Gould advocated general screening regularly from cradle to grave, but for research
- Life insurers took up idea but those who took part in regular examinations were low risk i.e. good commercial sense
- Work place screening started up to address employer concerns about litigation
- Top executive screening 'stitch in time saves nine approach'



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So screening became widely advocated in US and was conducted by physicians

Why? Because they faced the prospect of the public system conducting screening

By actively taking part they averted governmental interference

(Also influencing compulsory health insurance, school and municipal health programmes)

In the US the public are tested comprehensively and often in the complete certainty that it is in their own interest.



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What about the UK?

- Prevailing attitude was 'best to steer clear of doctors and potentially meddlesome investigations' ..i.e. a much cooler attitude
- 1968 WHO assessed growth of screening, presumption of benefits 'public funds can be, and it seems may already have been, directed from fields of certain benefit to procedures which are not proved and possibly harmful'



Walter Holland 1974

- ..[need] systematic, stringent, unemotional evaluation of..screening..essential for unequivocal evidence to be presented before an experimental project is introduced into routine medical practice...

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The problem for public health

There is an assumption that screening will identify abnormality if present, and that those affected will derive benefit from subsequent treatment or care

BUT

Well conducted trials of generalised screening showed NO benefit both in US and UK (1964, 1984) ...although indications that for specific disorders there may be some benefit

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Learning from other disorders - Cervical cancer screening

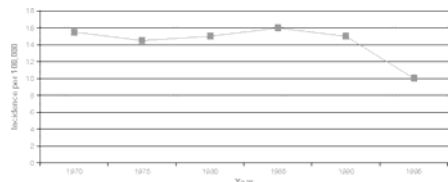
- Disorganised and fragmented up to 80s
- Much false negative i.e. missed cancers
- And much false positive i.e. overdiagnosis
- Mostly low risk women taking up screening
- Increasing cost to NHS of tests and treatment
- No change in mortality from cancer of cervix



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What did we do about that?

- Looked at Nordic countries with carefully organised screening programmes and declining mortality
- Realised that screening involves a system not just a test
- Followed suit – worked out systematic programme, careful attention to all aspects of programme
- Mortality came down



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but

- massive overdiagnosis, since 95% of treated 'early' cancer probably would have reverted to normal
- 'neither wonderful nor useless' but pretty costly

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Does overtreatment matter?

- Depends on consequences of screening
- Is cone biopsy of the cervix acceptable for a 'cancer' that would not have progressed?...



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Learning from cervical cancer screening

Breast cancer screening was introduced following careful accrual of evidence justifying all elements of a screening programme

National Screening Committee in UK seen as world leader

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What evidence is required?

- NSC modification of WHO approved criteria (Wilson and Jungner)
 - the condition
 - the test
 - the treatment
 - the screening programme

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The condition

- Important health problem
 - Natural history well understood
 - latent to declared disease
 - detectable risk factor, disease marker, latent period or early symptomatic stage
- AND
- All cost effective primary care interventions should have been implemented as far as possible

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First, what is it the condition we are screening for?



Dementia as a syndrome – combination of history, examination - investigations assist subtyping:

- Neuropsychological : semantic, early and earlier (MCI) 'changes'
- Imaging : vascular changes, white matter lesions, regional patterns
- Biomarker including Molecular & gene from CSF, Imaging, blood..

BUT none of these define the dementia syndrome



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What is the screening test detecting?

- Simple, safe, precise, validated for particular condition or risk
- Distribution of test values in target population should be known
- The test should be acceptable to the population
- There should be an agreed policy on further diagnostic investigation of individuals with positive test results and on the choices available to those individuals
- [additional issues not raised in NSC criteria are age group and frequency]

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What is the test testing for? How close is the relationship of this to the condition we want to detect?

- 'early detection' - the meaning of biomarkers in screening

Imaging

Vascular changes), white matter lesions (seen in large proportion of older people), protein expression in the brain (new imaging techniques)..not known but also likely to be seen in many older people who would not necessarily develop dementia
expensive

Molecular

biomarkers: lumbar puncture (too invasive), bloods (not proven to be closely associated enough)

Gene

specific genes – even with apoE4 can die without dementia

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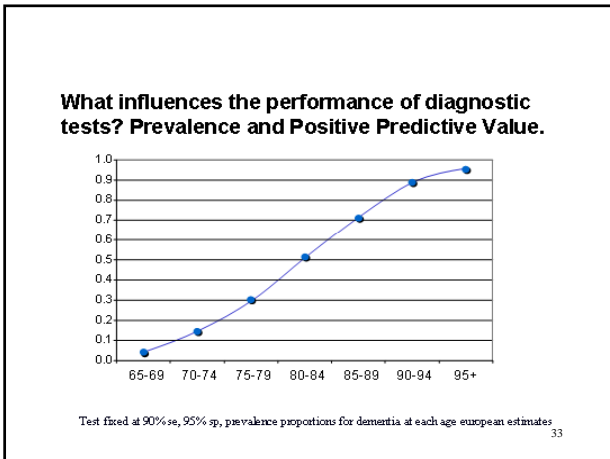
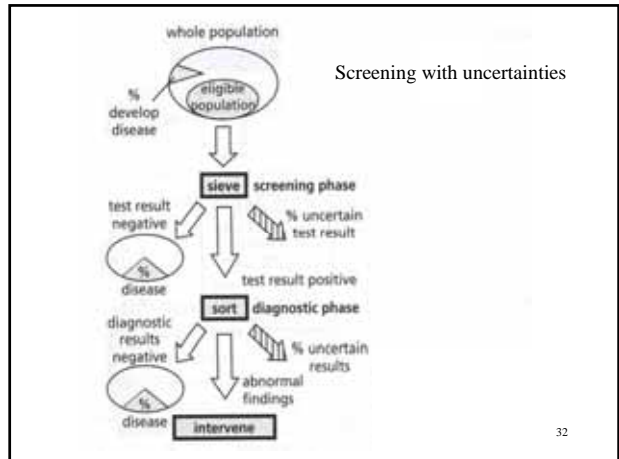
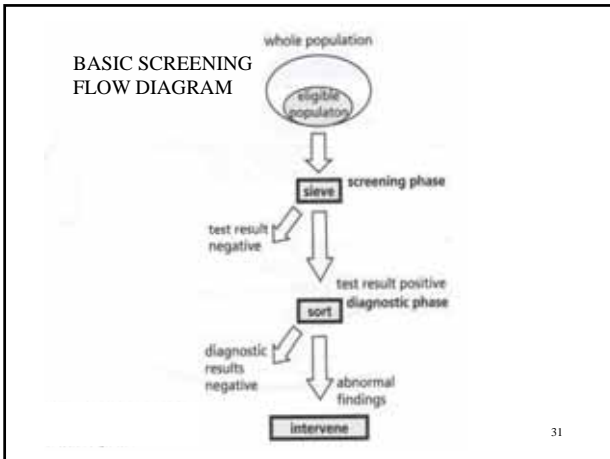
But...if these novel aspects are the target what is the disorder, what exactly are we treating?

What would have been the outcome if untreated?

Do we really know yet, do we have research in place to fill the knowledge gap?

i.e. we need to know much more about natural history than we do...

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- ### Potential bias in screening
- Healthy screenees come forward
 - Slow disease picked up, better prognosis
 - Survival longer in individuals with disease who are screen detected because they are picked up earlier, not because of change in natural history
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- ### The treatment..
- effective treatment or intervention for people identified through early detection **with evidence of early treatment leading to better outcomes than late treatment**
 - agreed evidence based policies covering which individuals should be offered treatment and appropriate treatment to be offered
 - clinical management the condition and patient outcomes already optimised by all health care providers prior to participation in a screening programme
(do we really have the trial evidence to argue this in population screened settings?)
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Outcomes from intervention, not always positive

some suffer complications/ side effects	intervene
	outcome better because of early intervention
	outcome good but early detection made no difference
	outcome poor and early detection made no difference
	condition would have no impact, intervention was unnecessary

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Maximise benefit, minimise harm

High uptake
 High sensitivity/detection rate for both sieving and sorting
 High acceptance rates for intervention

and...

High specificity/low false positive rate for sieving and sorting
 Individuals must understand what is on offer and think carefully about whether participation is right for them

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What further evidence do we need in order to assess whether a population screening programme is desirable?

nb from policy point of view we will be taking resources from other potential uses of the same investment

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The screening programme

- evidence from high quality randomised controlled screening trials that the screening programme is effective in reducing mortality and morbidity
- evidence that the complete screening programme (test, diagnostic procedures, treatment, intervention) is clinically, socially and ethically acceptable to health professionals and the public

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The screening programme

- benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)
- opportunity cost of the screening programme (including testing, diagnosis and treatment, call recall, counselling) should be economically balanced in relation to expenditure on medical care as a whole
- plan for managing and monitoring the screening programme exists and an agreed set of quality assurance standards

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The screening programme

- adequate staffing and facilities for testing, diagnosis, treatment and programme management available before starting the programme
- all other options for managing the condition already considered such as improving treatment, providing other services

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Map of a screening programme



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Summary of just some of the evidence needed for population programmes

- RCTs
- Time trends
- Qualitative studies
- Modelling
- Pilot/demonstrations
- Systematic reviews of existing evidence
- Economic evaluations

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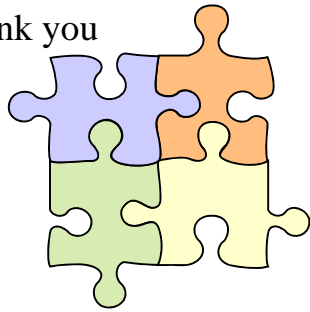
Key questions (just a stab...you'll have many more for discussion)

- Define research to provide the jigsaw pieces of evidence needed – incumbent on us to work to test and generate the necessary evidence (whether it be pro or con)
- i.e. define the specific gaps e.g. natural history of what (beta amyloid deposition in brain), who (are we looking for different disorders at different ages and different stages), work out what we are aiming to prevent – dementia during life, or beta amyloid deposition in the brain...
- How do we set up trials to establish evidence for widely perceived benefit of 'early' diagnosis?
- Are other neurodegenerative disorders too rare to even think about screening?
- How do we really test better case awareness in the clinical setting?
- We need to understand who stands to gain from screening (see BMJ 4th October 2008)

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Thank you

- Over to you....



- Acknowledgement of key resource: Muir Gray and Angela Raffle - Screening, OUP 2007

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NSC Criteria for screening - consider four elements: condition, test, treatment, programme

- | | |
|--|---|
| <p>A</p> <ul style="list-style-type: none"> ▪ Effective intervention and evidence of early treatment producing better outcomes ▪ Facilities available ▪ Policies covering treatment ▪ Management of condition optimised prior to participation <p>C</p> <ul style="list-style-type: none"> ▪ Simple, safe, precise and validated screening test ▪ Distribution of test values in target population known, and cut-off value agreed ▪ Acceptable to population ▪ Agreed policy on further investigation | <p>B</p> <ul style="list-style-type: none"> ▪ Important health problem ▪ Epidemiology and natural history understood ▪ Recognisable early stage ▪ Cost-effective primary prevention implemented <p>D</p> <ul style="list-style-type: none"> • Evidence from RCTs that screening programme is effective • Evidence that complete programme is acceptable to public and professionals • Benefits should outweigh costs • Structures for quality assurance • All other management options should have been considered • Evidence-based information should be supplied to potential participants to allow informed decision-making • Decisions about eligibility criteria for screening should be scientifically justifiable to the public |
|--|---|