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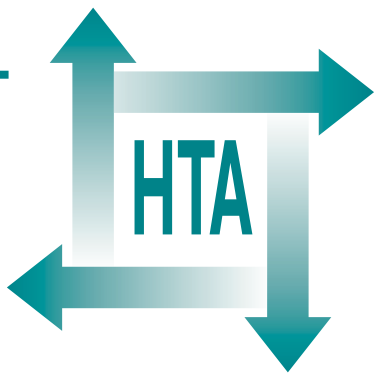
Review

False-negative results in screening programmes: systematic review of impact and implications

MP Petticrew
AJ Sowden
D Lister-Sharp
K Wright

Health Technology Assessment
NHS R&D HTA Programme



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False-negative results in screening programmes: systematic review of impact and implications

MP Petticrew[1*]
AJ Sowden[2]
D Lister-Sharp[2]
K Wright[2]

[1] MRC Social and Public Health Sciences Unit, University of Glasgow, UK
[2] NHS Centre for Reviews and Dissemination, University of York, UK

[*] Corresponding author

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The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Mailpoint 728, Boldrewood,
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List of abbreviations

FN	false-negative*
FP	false-positive*
GP	general practitioner
NCN	National Coordinating Network
NHSCSP	National Health Service Cervical Screening Programme
NRBSRAG	Northern Region Breast Screening Radiology Audit Group
PKU	phenylketonuria
PSA	prostate-specific antigen
SEM	school entry medical
TN	true-negative*
TP	true-positive*
WTP	willingness to pay: method used to assess the strength of people's preferences for some choice (e.g. a type of treatment)

*Used only in tables and appendices

Executive summary

Background

When assessing whether a screening programme is appropriate, there is a particular obligation to ensure that the harms as well as the benefits are considered. Among these harms is the likelihood that false-negative results will occur. In some cases, the consequences of these can be difficult to assess, although false reassurance leading to diagnostic delay and subsequent treatment has been suggested. However, no test is totally accurate (with 100% sensitivity and specificity), and false-negative results are inherent in any screening programme that does not have 100% sensitivity.

This review was carried out to assess the medical, psychological, economic and legal consequences of false-negative results that occur in national screening programmes.

Objectives

- to determine the consequences of false-negative findings
- to investigate how their adverse effects can be minimised
- to assess their implications for the NHS, including the impact of false-negatives on public confidence in screening programmes
- to identify relevant theoretical perspectives that may be potentially useful when considering the implications of false-negative results.

Methods

A systematic literature review was carried out. This included a search of 18 electronic databases, various bibliographies and contact with experts to identify relevant literature and perspectives. Outcomes included in the review fell into four categories:

- medical outcomes (morbidity and mortality)
- psychological outcomes (distress, false reassurance, loss of confidence in services)
- economic outcomes (such as costs to the NHS)
- legal outcomes (such as litigation).

Other outcomes, such as the impact of false-negatives on public confidence in screening programmes, were also included.

The participants included individuals taking part in screening programmes, healthcare professionals and organisations responsible for screening programmes.

Methodological details of the review are provided in the full report.

Results

A total of 6660 abstracts were screened, and 420 potentially relevant papers were identified. Most of the studies that were identified presented only anecdotal evidence.

- Medical outcomes: In all, 13 papers presented quantitative information relevant to the medical consequences of false-negative results; seven of these were primary studies, and the remaining studies were literature reviews or models examining the likely impact of false-negative results.
- Psychological outcomes: A total of eight published studies presented information on the psychological consequences of negative results in general; only one study, on antenatal screening, provided direct evidence of the psychological consequences of false-negative results, where they were associated with lower parental acceptance of the affected child and with blaming others for this outcome.
- Economic outcomes: Only two studies presented information on the economic consequences.

The strength of evidence from most of the primary studies was low. There is some evidence that false-negative results may have a large legal impact. For example, in cervical screening they have led to legal action and its associated costs, including payment of compensation; this is based on reports of events in both the UK and US health systems. There also seems to be a consensus in the literature that false-negatives may have a negative impact on public confidence in screening; evidence is again limited however.

Conclusions

False-negatives are evident in all screening programmes, even when the quality of the service provided is high. They may have the potential to delay the detection of breast and cervical cancer, but there is little evidence to help assess their psychological consequences in these or other screening programmes. False-negatives are likely to lead to legal action being taken by those individuals affected, and potentially may reduce public confidence in screening. Their impact may be reduced by the provision of full information to participants about the benefits and harms of screening programmes, and by increasing public education on these issues.

Implications for policy

New screening programmes need to 'start starting correctly'. In the context of false-negative results, this means that it is desirable that participants in screening programmes are provided with full information on the meaning of negative results. Screening programmes might also include evaluation of the impact of false-negatives. Greater public and professional education on the meaning and limitations of screening is also needed. The wider provision of public education materials that include clear information about the limitations and benefits of screening, and the meaning of all types of test result, may be particularly helpful in this regard. This will help participants to make informed decisions about whether to participate or not in screening programmes.

Recommendations for research

Research is now required that prospectively investigates the long-term medical, psychological and other consequences of false-negative results in a range of screening programmes. Research on the most effective means of presenting information on residual risks to those individuals undergoing screening is also needed. The development of sensitive economic models, which include a full evaluation of the benefits and harms of screening, will also be helpful. These will aid in assessing the appropriateness of screening programmes before their introduction.

Chapter 1
Introduction

Background

The most widely quoted description of the theory and principles of screening is that set out in the WHO report by Wilson and Junger (1968) in which they point out that the purpose of screening is to identify unrecognised disease or defects.[1] This type of screening activity has been usefully characterised as an exercise in sorting those individuals screened into two groups: those at low risk of having or developing a disease, and those at high risk. The low-risk group will always contain some people with the condition, and the high-risk group will contain some of those without it, and so evaluating a screening programme involves assessing how well it performs these sorting procedures.[2]

Screening therefore aims to identify asymptomatic individuals at high risk of developing a specific adverse outcome in order to intervene and reduce the risk of that outcome. This requires further investigations and cost-effective treatments. By identifying a condition at an early enough stage, an effective intervention can be offered. Thus, screening for early manifestations of a disease can reduce subsequent mortality and morbidity, and screening for risk factors can result in action to prevent or limit the impact of subsequent illness. The process of screening involves more than just the screening test: a screening programme should be considered to involve all relevant activities from identification of the population at risk to diagnosis and treatment.[3]

Screening can also be differentiated from other similar procedures for identifying health problems. In particular, it has been differentiated from healthy lifestyle checks because these do not require specific screening tests to recognise unhealthy behaviours or lifestyle factors; it is differentiated from case finding, where opportunistic testing may be carried out as part of a general examination or other health check; and is differentiated from 'spontaneous presentation', where individuals themselves seek out further investigations, such as breast self-examination.[2]

Evaluation of the performance of a screening test requires consideration of the outcomes of a cohort of people who received the screening test, both those who were screened positive and those who were screened negative. This allows calculation of sensitivity (the proportion of those individuals in the screened population with the disease who are classified accurately as diseased) and specificity (the proportion of those individuals without the disease who are classified accurately as non-diseased). Evaluation of a screening programme's performance requires knowledge of sensitivity and specificity, as well as the false-negative rate (the proportion of cases with the disease who are incorrectly identified as not having the disease).[2]

In the NHS, new screening programmes are no longer promoted or introduced until they have been evaluated and proved effective,[4] and in order to evaluate the worth of a programme properly, it is necessary to consider its potential consequences. To do this requires a comprehensive assessment to determine whether evidence exists that the benefits outweigh the harms, and an assessment of whether resources are being used cost-effectively. This judgement of the balance of benefits and harms is likely to be made difficult by the fact that the costs and benefits are qualitatively different, and may include, for example, anxiety, morbidity and increased survival; costs (apart from the opportunity costs of running the screening programme) and benefits are also experienced in different ways by different individuals.[5] However, if screening is effective, the population benefit (e.g. reduction in mortality) is usually expected to outweigh the costs (e.g. increased anxiety and further investigations in healthy people). To support such an argument, not only must the benefits and costs of both true-positive and true-negative findings be quantified, but also the consequences of false-positive and false-negative results. When assessing the effects of false-positives, for example, the implications of 'unnecessary' investigations and procedures must be taken into account, as well as their psychological effects.

The consequences of false-positive results, in particular the anxiety, morbidity and possible mortality associated with investigations in individuals without the condition being screened for, have been the subject of extensive research. It is now

widely recognised and accepted that their impact must be assessed when weighing up the benefits of screening.[6–8]

The implications of false-negative results and their associated consequences have been relatively under-investigated, partly because they are often less easily identified, but also because any harms deriving from them are perhaps assumed to be small in comparison with the overall benefits of screening. Nonetheless, false-negatives are likely to carry some consequences for the individual. For example, in the context of screening for cancers, the main medical consequence of a missed diagnosis is likely to be the additional delay in detection (if any) compared with what would have happened in the absence of screening. When the cancer becomes symptomatic, it may be at a more advanced stage, and more invasive treatment may be required, which may also be less successful. The treatment may also be more costly. The patient may then also seek legal redress for the distress that has been caused. The consequences of false-negatives vary widely according to the screening programme: the birth of a baby with Down's syndrome, missed cases of hip dysplasia, or late detection of vision impairment in preschool children could all be considered as false-negatives with very different consequences.

Estimating and detecting false-negatives in screening

Part of the evaluation of screening programmes involves an assessment of their sensitivity and specificity. Sensitivity refers to the likelihood that the test will detect the condition of interest when it is present. If all cases were identified, the sensitivity of the test would be 100%. However, tests may fail to identify individuals with the condition of interest and these represent false-negative results. Specificity refers to the likelihood that the test will give a negative result when the condition being screened for is absent. Those individuals that are wrongly identified as either having the condition or requiring further diagnostic tests are considered false-positives (*Table 1*). In addition, a number are categorised as 'true-positives' but have borderline disease that would never have led to health problems during the person's lifetime.

No test is totally accurate (i.e. with 100% sensitivity and specificity), and there is always a trade-off between sensitivity and specificity for any given test. The optimal balance depends on the relative costs and benefits of high sensitivity and high specificity. This means that a proportion of those screened will be wrongly categorised.

Specificity and sensitivity are interrelated, and changing the threshold for further investigations will affect both of these parameters. A low threshold increases sensitivity, reducing the number of false-negatives, but at the expense of decreasing specificity. A high threshold will increase specificity, but decreasing sensitivity will increase the number of false-negative results. False-negative results are inherent in any screening programme that does not have 100% sensitivity. In short, there is a trade-off between sensitivity and specificity: a sensitive test misses few diseases but causes more false alarms, and so results in more unnecessary investigations (i.e. false-positives); a specific test causes few false alarms but misses treatable disease (i.e. false-negatives).[9]

False-negative results therefore occur when a screening test cannot, for whatever reason, detect the presence of indicators of the condition or disease of interest. The most obvious consequence of this is that further investigations will not be carried out and the condition or its risk indicators will remain unidentified until either the condition manifests itself (e.g. the birth of a baby with Down's syndrome), or is picked up in further screening cycles. In the latter case, for example, cancers may arise between screens (interval cancers).

TABLE 1 *Distribution of those individuals screened by screening status and disease or condition status*

	Disease or condition status		
Screening status	**Positive**	**Negative**	**Total**
Positive	TP	FP	TP + FP
Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	TP + FP + TN + FN

TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative

In general, there is a risk of under-ascertainment of false-negatives, for reasons pointed out by Stewart-Brown (1997).[2] In particular, because in any screened cohort the proportion of negative results will be very large, following up all of these will be difficult and costly. Where routinely collected data (e.g. from cancer registries) are used, variability in the quality of the information collected may result in underestimates of false-negative rates, and the use of other data sources, such as hospital admission data, similarly will be subject to biases such that the false-negative rate will be underestimated, and consequently the sensitivity and specificity of the screening test will be overestimated.[2]

It should be noted at this point that not all interval cancers represent failures of screening; that is, those that could have been detected at screening, but were missed. 'True' interval cancers may have arisen since the screen, and their numbers can be reduced by reducing the screening interval, while other cancers may have been missed because they were radiographically undetectable. One study of the initial round of screening in the UK in the South East Thames breast screening programme found that of the interval cancers, 30% were false-negative and 8% were mammographically occult.[10] These rates are very similar to those found by the Northern Region Breast Screening Radiology Audit Group (NRBSRAG) study, which classified a cancer as 'false-negative' only when it was identified on the previous screening film by at least two assessors. This avoided classifying cancers as false-negative when the only evidence was based on retrospective searching for a trace of a tumour which may otherwise have been undetected. Their analysis of 167 interval cancers showed 46% 'true intervals', 26% 'false-negatives', 11% 'occult', and 16% 'not classifiable'.[11] A review of screening mammograms from the Nottingham Breast Screening Unit also found similar rates (22% false-negative, 8% occult, 57% true interval cancers, out of 90 interval cancers found). In short, these studies emphasise that not all missed diagnoses are 'screening mistakes', and not every cancer diagnosed between screening tests is a 'false-negative'. Undetectable cancers are unavoidable false-negatives, and missed cancers are avoidable false-negatives; true interval cancers, however, are not false-negatives. Harms are likely to be greatest for avoidable false-negatives, while the harms for unavoidable false-negatives will be the same as those for true interval cancers, and for the true-negatives who later develop the condition screened for.

Although in the previous example the consequences of a false-negative result are easily understood – progression of a cancer in the interval before the next screen – the consequences of a false-negative are sometimes less clear. In general, the impact of a false-negative result may be conceived as 'false reassurance', which refers to the possibility that a negative screening result is interpreted as (for example) preventative of cancer, or that the remaining risk is lower than it actually is. This may result in delay in reporting subsequent symptoms (compared with what would have happened in the absence of screening). The risk of false reassurance, however, applies to all negatives, not just false-negatives. This possibility has been recognised and cautioned against: the Faculty of Public Health Medicine guidelines on screening for health promotion have pointed out that a negative result does not rule out the subsequent development of cancer, and advised that women receiving a negative screen should be told to continue to report problems.[12] However, the potential harms of false-negatives are likely to be varied (apart from medical consequences) and often not widely appreciated, and there is a risk that they may not be considered when a new population screening programme is introduced. Indeed, this review was carried out to identify evidence of the impact of false-negative results in order to help in assessing their implications, and to help ensure that they are assessed when new population screening programmes are established.

This review has not assessed technological interventions, which may reduce false-negative rates, such as automated rescreening and double reading of slides, neural network processing, or organisational changes such as aspects of improvements in quality control in cytopathology laboratories. Nor does it consider in detail the impact of false-negative results in individual diagnostic tests, although such tests are part of the entire screening programme. Rather, it considers the consequences of false-negatives arising from the screening programme as a whole.

Chapter 2

Research questions

The main terms of reference for the review highlighted two key issues: (1) the need to examine the implications of individuals being found to be a false-negative in existing screening programmes, as the size of their disbenefit is largely unknown; and (2) the need to highlight opportunities for incorporating further research into the evaluation of new programmes. It was also emphasised that research on the meaning and interpretation of risk may help in interpreting how false-negative results are understood by the participants in screening programmes.

The review includes four broad categories of information:

- the prevalence of false-negative results in screening programmes
- the consequences of false-negative results in screening programmes
- the implications of such false-negative results for the NHS
- theoretical perspectives that may increase understanding of the implications of false-negatives in screening programmes.

A brief rationale for each of these categories is given below.

How prevalent are false-negative results in current screening programmes, and how can these be assessed?

Prevalence rates for false-negative results in screening are available from reviews of studies on the efficacy of screening, and from the primary studies themselves. Other information on the rates and on the reasons for false-negatives can be derived from studies reporting on false-negative rates identified as a result of rescreening exercises. A background search and comments from the expert panel (see page 9) suggested that this literature is potentially very large. Much of it simply reports sensitivities for various tests, rather than exploring the implications of these rates. This part of the review therefore contains background information on the prevalence of false-negative results derived from relevant literature reviews.

What theoretical perspectives have been used, or are potentially useful, when considering the implications of false-negatives?

Given the paucity of evidence on the implications of false-negatives identified during preliminary searches of the literature, it was felt that it may be useful to include studies suggesting useful theoretical frameworks that may help in understanding the potential implications of false-negative results. Economic evaluation is one potentially useful tool in this respect, and has been widely used in evaluating screening programmes. This requires measurement of all the relevant benefits and costs involved for all screening outcomes, including false-negatives. For example, mortality, morbidity, financial, psychological and legal costs would be assessed. This also requires the development of a system for quantifying these, to allow (for example) false reassurance to be entered into the model. Decision analysis provides a possible structure for incorporating these outcomes, and is therefore discussed below.

Other theoretical models may help elucidate individual parts of the screening process, and in particular psychological models of risk perception and decision-making may help to clarify how people 'understand' the results of screening tests, and thus inform health professionals' practice when delivering results. Theories of blame, adjustment and regret may also become useful in understanding responses to misdiagnosis. Regret theory, for example, suggests that people take up offers of medical interventions partly to reduce the regret they would later feel if they rejected the offer, and this 'regret aversion' may also involve feelings of remorse and self-blame.[13–15] Literature relating to these theoretical perspectives was therefore included if it specifically discussed false-negative results in screening.

What are the consequences of false-negative findings?

It was decided to summarise the evidence for the implications of false-negatives in the following broad categories:

- medical implications
- psychological implications
- economic and legal implications.

Medical implications

Evidence of the consequences of a missed diagnosis is available from primary studies and literature reviews, and the consequences are likely to vary widely according to the condition screened for. While a synthesis of the sensitivities reported in all primary screening studies relating to each of the existing NHS screening programmes was not possible, relevant information is available from primary studies and literature reviews on the likely medical implications of false-negatives for a range of conditions. Therefore, primary and secondary literature was sought that investigated how the associated delay in diagnosis and treatment may affect morbidity and mortality.

Psychological implications

Several psychological implications of false-negatives have been suggested. From preliminary searches of the literature it was clear that 'false reassurance' has often been stated as a consequence,[16–18] although often without any further supporting evidence or exploration of the concept. The review therefore sought to identify studies that presented evidence on the actual consequences of false reassurance; for example, whether this might alter people's subsequent health-related behaviour, and whether there may be adverse psychological consequences resulting from making decisions based on 'wrong' information.

Economic and legal implications

It was also clear from the outset that the consequences of a missed opportunity for diagnosis and treatment are also likely to be financial. While some of this is due to the greater cost of treatment of an illness at a more advanced stage, other anticipated costs may derive from litigation from patients as a result of perceived screening failures, or from the unanticipated birth of a disabled child following antenatal screening.

What are the implications to the NHS?

Some of the implications of false-negatives for the NHS are implicit in the categories laid out above; for example, where litigation results in compensation claims against health authorities, or where a change in health-related behaviour might mean a reduced intention to participate in screening. Other broader aspects of this question that were considered are as follows:

- If false-negatives are an inherent part of even effective screening programmes, how can their adverse effects be minimised?
- Is public knowledge of the extent of false-negatives likely to undermine confidence in screening programmes and, if so, how can this be overcome?

The first question was considered to be worth examining because a programme may be able to increase its net benefits if the harms (such as false-negatives) can be reduced. However, the full range of benefits and harms still need to be assessed; in some programmes stopping screening may be more appropriate than simply attempting to limit the negative consequences.

From a background literature search it was expected that much of the evidence would be derived from studies of antenatal, cervical and breast screening.

Chapter 3
Methods

Objectives of the review

The purpose of the review was to provide the NHS R&D Health Technology Assessment Programme with a review of the implications of being found to be a false-negative in existing screening programmes, and to identify opportunities for further assessment of their impact. The specific objectives were to identify the adverse effects of false-negative results in terms of their medical, psychological, economic and legal impact. In addition, issues that required further research, and the extent to which current research could contribute to the understanding of the broader implications of false-negatives, were identified.

Sources of studies and literature searches

A systematic review was undertaken, which followed the guidelines of the NHS Centre for Reviews and Dissemination (CRD) (Undertaking systematic reviews of research on effectiveness. Report 4. York: University of York, 1996), involving an extensive literature search to obtain both published and unpublished information, and to make a formal assessment of the methodological quality of the identified studies. Screening of studies for inclusion, quality assessment of included studies and data extraction was carried out by one reviewer and checked by a second.

Electronic databases

A range of computerised databases were searched to uncover the relevant medical, psychological, economic, sociological and methodological literature:

- MEDLINE (search strategy: appendix 1)
- PsycLIT
- EMBASE
- SOCIOFILE
- DARE (Database of Abstracts of Reviews of Effectiveness at NHS CRD)
- NHS Economic Evaluations Database
- The Cochrane Library
- ASSIA (social sciences database)
- BIOSIS
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- Dissertation Abstracts
- EconLit
- SIGLE
- Conference Papers Index
- Science Citation Index
- National Research Register
- IAC legal database.

Specific search strategies for the other databases were also developed from the above search terms.

As the objectives of the review were broad, with the need to assess 'implications', it was not appropriate to pre-exclude studies on study design alone. In addition, a range of broad theoretical questions relating to public confidence in screening, and public understanding and expectations of screening, were identified as relevant, and the importance of identifying papers describing relevant theoretical perspectives was emphasised by members of the expert panel (see page 9). The initial literature trawl was designed to be wide-ranging, and the inclusion criteria broad enough to allow any studies that identified implications to be considered for inclusion.

Inclusion and exclusion criteria

The review sought to identify reviews and primary studies documenting the impact of false-negatives in screening programmes. The following outcomes of a false-negative result were included.

Included outcomes:

- medical: morbidity and mortality
- psychological: for example, distress, false reassurance, loss of confidence in services
- economic: for example, changes in costs to the NHS
- legal: for example, litigation and costs arising out of litigation
- other: papers reporting on the broader societal consequences (such as public confidence) of false-negatives or screening failures were also included at this stage.

Included participants:

- medical and psychological consequences: individuals taking part in screening programmes
- economic and legal consequences: individual participants in screening programmes; also health care professionals and organisations responsible for screening programmes.

Two reviewers, working independently, read the abstracts of the 6660 identified papers. All papers that appeared potentially useful were discussed and copies were obtained. In cases of disagreement, the paper was obtained. A total of 420 papers or reports were read and assessed for inclusion independently by two reviewers. Studies in any language were eligible. All papers that identified actual implications or consequences, or highlighted any potential consequences, were read and coded independently by two reviewers. The coding scheme was entered onto a database to allow easy identification of papers addressing specific themes (see *Box 1*). Papers reporting specific information on the consequences of false-negatives (such quantitative information on the outcomes is described above) were then data extracted by one reviewer and checked by a second, and then tabulated. Other papers reporting general or anecdotal information were not tabulated, but where they are discussed in the review, the source of the information and any methodological shortcomings are described in order to highlight the quality of evidence presented. ('Anecdotal' papers were defined as opinion pieces pointing out the possible consequences of false-negative results, but which did not report the results of primary research.) Qualitative research studies on the impact of false-negatives were included.

BOX 1: Coding system

Excx	No relevant information/only brief mention of false-negatives with no discussion of consequences
Backx	Papers without specific information on the impact of false-negatives, but providing background information
Ratesx	Papers quoting rates of false-negatives from screening, which do not report implications
Reasonsx	Papers outlining reasons why false-negatives occur
Qualx	Papers on the relationship between quality of screening and false-negative rates
Medx	Medical implications of false-negatives
Psychx	Psychological implications of false-negatives
Legalx	Legal implications
Costx	Cost/financial implications of false-negatives, or economic perspectives on screening
Commx	Studies on communication with patients with a perspective or results of relevance to false-negatives, e.g. studies on communication of risk, or of screening results
Mediax	Reporting of screening failures, or false-negatives in the media
Theorx	Relevant theoretical perspectives (e.g. regret theory, false reassurance, other)
Publicx	Papers on public perceptions of screening/false-negatives/screening errors

Details of the coding system

Studies reporting only the performance of individual screening tests were excluded, unless they also discussed the impact of false-negatives because this review was not intended to be a systematic review of the sensitivity of all available screening tests. Comments from some members of the expert panel on the protocol for this review also indicated that this would extend the review significantly beyond what was necessary. Data on the prevalence of false-negative results and their assessment was therefore obtained from existing reviews of screening programmes. Studies of screening for drug abuse, employment screening and psychiatric or psychological screening were not included. The review did not include studies examining the impact of false-negative results in specific diagnostic tests. Many studies presented very limited information on false-negatives; for example, a comment to the effect that false-negatives exist and may contribute to false reassurance. Studies that did not present any further supporting information were excluded at this stage.

Studies that presented further quantitative information on consequences were data extracted and are presented in chapter 4 and appendices 2–5, and represent the main summaries of evidence of adverse consequences of false-negatives.

Supplementary literature

An understanding of relevant theoretical perspectives may be of use in helping to anticipate the likely psychological consequences of false-negatives. For example, literature on regret theory, false reassurance and studies examining the impact of a 'clean bill of health' were highlighted by expert panel members, and this was sought via supplementary searches. Where this evidence took the form of primary studies, it is included in the 'Results' section of this review. In cases where it simply involved general discussion of the issues, it was integrated into the general introduction to the review.

In addition, both the Medical Defence Union and the Medical Protection Society were approached to solicit information on the legal implications of false-negative results in order to aid in estimating the size of the problem in the UK; in particular, the number of such claims and the approximate costs involved in settling claims arising from 'false-negatives'. Apart from the occasional 'high profile' case, such information is rarely reported and is difficult to find through searches of the usual sources, such as biomedical databases. The NHS Litigation Authority was therefore also approached for information on cases arising from false-negatives.

Expert panel

An expert panel was recruited to help refine the review questions, identify relevant literature and theoretical perspectives, and to referee the draft report (see 'Acknowledgements'). The panel included individuals involved in primary research in this field.

Quality assessment and synthesis of evidence

A wide range of study designs contributed information on false-negatives. The quality of reviews was assessed before inclusion, according to the following criteria:

- Does the review answer a well-defined question?
- Was a substantial effort made to search for all relevant literature?
- Are the inclusion/exclusion criteria reported and appropriate?
- Is the validity of included studies adequately assessed?
- Is sufficient detail on individual studies presented?
- Have the primary studies been combined or summarised appropriately?

Where a review met all of these criteria it is described in the text as a systematic review. All the systematic reviews described in the text are of good quality. Other literature reviews contributed information but did not meet one or more of these criteria. However, they were included if it was felt that they presented useful information on the adverse effects of false-negatives, included useful background information, or contributed a useful theoretical perspective. These are described in the text as 'literature reviews' or 'reviews'.

Other evidence was derived from a range of study designs, including observational studies and economic evaluations. These were assessed in a standardised manner using existing quality assessment scales. Where methodological problems were identified in this way they are highlighted in the text or relevant table, and summary conclusions were based on the most methodologically sound studies.

Chapter 4

Extent of false-negatives in existing screening programmes

The identification of false-negative results is not always straightforward. While those suspected of having the relevant condition go on to have further investigations, thus revealing any false-positives, this is not always the case with false-negatives. These may be located in further cycles of a screening programme, may manifest themselves in a relatively short time (e.g. through the birth of a baby with Down's syndrome), be picked up in quality assurance exercises, remain undetected and manifest themselves only when the condition becomes symptomatic, or, indeed, remain latent until death from some other cause occurs. In practice, an unbiased estimate of the sensitivity of screening for conditions where compulsory registration of cases is not carried out cannot be made because accurate information on the size of the denominator 'TP + FN' in *Table 1* is unavailable.[19]

The picture is further complicated by the fact that some conditions may develop between successive screening cycles (such as interval cancers). However, estimates of the false-negative rates from various screening programmes are available from a range of sources, including literature reviews. In the case of cancers arising since a previous screen, it is not always easy to differentiate between interval cancers that have arisen since the initial screen and cancers that were missed at the initial screen. The rates in *Table 2* are derived from recent reviews summarising primary studies. The reported false-negative rates are clearly variable between screening tests, ranging from 1% in some forms of neonatal screening to > 30% in some studies of cervical screening.

Causes of false-negative results

It is worth noting some of the causes of false-negative results to emphasise that they cannot always be simply interpreted as screening errors. These causes have been most extensively described in cervical cancer screening. Apart from rapidly growing invasive cancers that have arisen since the screen (true interval cases), there are also a proportion of false-negatives that appear to be due to screening and interpretive errors. These are more likely to arise from errors in sampling than errors in screening.[27] Errors in sampling may be due to cells being taken from the wrong place, or to cells not being picked up on the spatula; slides may also be unreadable because they contain too few cells to allow the smear to be interpreted, or contain cells that are inherently difficult to interpret for morphological reasons, or to a combination of these and other cytologic factors.[28]

There are also a range of psychological and physiological factors from boredom to overwork that make a contribution.[28] In addition, intra- and interobserver variation in slide inspection is unavoidable and some abnormalities will inevitably be missed due to the inherent difficulty of visually inspecting smears containing 50,000–300,000 cells in an attempt to find evidence of pathology.[27–30] Although 100% rapid rescreening of all negative slides may compensate for lapses in performance and may detect more than 50% of missed abnormalities,[27] a small percentage of false-negatives will still occur.

Overall, a wide range of sources of error are possible, any of which may lead to a false-negative diagnosis. To those listed above, can be added: variability in the proficiency of medical professionals at all parts of the screening process, from sampling to laboratory processing; and variability in management procedures for taking further action, as well as other host factors that increase the likelihood of an incorrect diagnosis (such as confounding pathological factors in the person being screened).[31] In addition, 'atypical' cases may result in a false-negative diagnosis in any screening programme, and these should not necessarily be considered as false-negatives for litigation purposes or for comparisons between laboratories because the diagnosis of atypia may not be reproducible.[32]

For example, the National Audit Office 1992 review of cervical and breast screening identified variations in the quality of the cervical

TABLE 2 *False-negative rates identified in recent reviews*

Screening test or programme	Study/review	Source of data	Sensitivity/false-negative rate	Other comments
Neonatal hearing screening	Davis, *et al.*, 1997[20]	Systematic literature review	FN rates up to 20% (screening sensitivity for moderate or worse PCHI = 80–100%; all methods)	Programme sensitivity (as opposed to a particular method, such as HVDT) may be near to 80%
Phenylketonuria	Pollitt, *et al.*, 1997[21]	Systematic literature review	≤ 2% approximately	FN are rare; most cases are due to human or technical error
Neonatal screening for congenital hypothyroidism	Pollitt, *et al.*, 1997[21]	Systematic literature review	< 5%	Usual concept of FN may be difficult to apply because of aspects of the condition such as transient or late-developing hypothyroidism
Down's syndrome	Wald, *et al.*, 1998[22]	Systematic literature review	Mean detection rate (proportion of affected pregnancies with positive results): triple test = 70%; double test = 66%	Results are based on maternal age with two or three serum markers in demonstration projects
Preschool vision screening	Snowdon and Stewart-Brown, 1997[2]	Systematic literature review	Two studies identified, suggesting FN rates of 1–2%	Authors note that eye hospital records rarely record enough detail on those individuals who are screened negative to allow accurate estimation of FN rates
Cervical screening	Mango, 1996[23]; Bosch, *et al.*, 1992[24]	Literature reviews	FN rates range from 5% to 50% and 10% to 58%	Methods of calculation of FN rate vary between studies. Studies are usually carried out in situations involving some foreknowledge of testing by screeners[24]
Breast cancer	Jones, *et al.*, 1996[25]	Brief review of range of previous primary studies on detectability of cancer at incident screen	FN rates range from 6% to 34%	Blinded review of mammograms previously reported normal
Elderly general assessment	Bulpitt, *et al.*, 1990[26]	Review of impact of FN results	Wide variety of screening tests offered to the elderly; FN rates vary accordingly from < 10% to > 40%	See also *Table 3* for range of possible screening tests in elderly patients

PCHI, permanent childhood hearing impairment; HVDT, health visitor distraction test (hearing screening test)

screening programmes, lack of consensus regarding interpretation of smears, lack of acceptance of guidance and lack of performance standards against which authorities could compare their performance; all of which are likely to contribute to false-negative results.[33] The National Coordinating Network (NCN) of the NHS Cervical Screening Programme (NHSCSP) subsequently carried out a range of projects aiming to improve education and the quality of cervical screening, and the NHSCSP issued guidance in 1996 aimed at improving the service offered. Improvements in training those individuals who take and read smears, and the development of an external quality assurance scheme has resulted in yearly reductions in the rate of unacceptable smears that are related to false-negative results.[34] Nonetheless, it is becoming widely accepted that there is an irreducible false-negative fraction of at least 5%,[30] and pursuing these can only be done at the cost of reducing specificity. False-negative results will therefore remain a feature of even good quality screening programmes, and their consequences will need to be dealt with.

Chapter 5

Medical, psychological, economic and legal consequences of false-negatives

This chapter summarises the evidence that was identified relating to the medical, psychological, economic and legal impact of false-negatives for the UK screening programmes for which UK national policy exists.

Societal implications are also described at the end of chapter 4. This last category of evidence includes the broader implications such as the impact of widespread media coverage of false-negatives on public confidence in screening. This chapter is not intended to be an exhaustive list of all papers mentioning false-negative results – it is unlikely that these could be identified by a systematic review because false-negatives are often not identified or discussed in abstracts of papers and are difficult to locate using computerised searches.

Even those papers that consider the impact of false-negatives generally do not present any further information on the medical, psychological or other consequences, beyond highlighting the fact that false reassurance or delayed diagnosis may occur. These studies therefore represent those identified that presented detailed, quantitative information on the impact of false-negatives. Therefore, this chapter represents the main evidence for the various consequences of false-negatives, based on the primary studies that were identified through the literature searches. Other more general implications are drawn out later in the report (see chapter 6).

Medical consequences of false-negatives

Most of the evidence relating to the medical consequences of false-negatives in UK screening programmes derives from studies of neonatal screening, and from studies reporting on the performance of breast and cervical screening programmes.

False-negatives in neonatal screening: screening for phenylketonuria and congenital hypothyroidism

Phenylketonuria (PKU) and congenital hypothyroidism are detected by heel prick blood collected at 6–14 days of age. The outcomes of screening for these conditions have recently been reviewed in a good quality systematic review that emphasised the impact of a delayed diagnosis.[21] Untreated PKU leads to severe mental handicap, and behavioural and neuropsychological problems, while early PKU is treatable and dietary management to control plasma levels of phenylanine results in IQ gains.[21] However, only treatment starting in the first few weeks of life is likely to result in near normal IQ, and outcome is poor when treatment is begun after 2 months.

Untreated congenital hypothyroidism also results in mental retardation and growth retardation. As with PKU, early detection is important in limiting the effects on mental development: the longer the delay in starting treatment with thyroxine, the worse the eventual outcome.[21]

Neonatal child health screening

The medical consequences of false-negatives in child health screening have been suggested by several reviews and studies. A recent good quality systematic review has highlighted some of the potential consequences of a missed diagnosis of congenital hearing impairment.[20] Earlier identification may be associated with improved communication outcomes, and timing of detec-tion is important because most studies show that interventions initiated before 12 months of age have advantages over those initiated at 2 years. Other outcomes are also likely to be affected: management of hearing impairment is easier at an earlier age, for example, because hearing-aid acceptance is greater.

False-negative results in screening for hip dysplasia have also been reported: one-fifth of children presenting late with congenital dislocation of the hip had abnormalities noted at birth, and those diagnosed late were reported to have had lengthy histories of limping and pain.[35] However, it is unclear whether the sample is representative of other late presenting

cases. A comparison of the prevalence of surgery for complete or partial dislocation of the hip in unscreened populations, and in screened populations who had not been splinted as neonates (i.e. false-negatives), shows little difference: 0.8–1.3 per 1000 live births in unscreened, versus 0.1–1.6 in screened populations.[36] However, the rates are difficult to compare directly because the authors point out that the false-negatives may include cases not preceded by instability by 6 weeks of age, reflecting variability in the natural history of congenital dislocation of the hip. There is therefore little clear evidence relating to the impact of missed or delayed diagnosis in neonatal screening other than the evidence relating to congenital hearing impairment.

Breast cancer screening

Studies that were identified in this area are summarised in appendices 2–5. These tables are a summary of those papers that contained an explicit analysis of the medical consequences of false-negative results and contained substantive, quantitative or qualitative information. Anecdotal reports (such as an author's unsupported opinion about what the consequences might be) are not included.

One UK study reported no difference in prognosis associated with false-negative diagnosis. However, the study was small, and the blinded retrospective nature of the study is unlikely to reflect actual screening practice.[25] Other studies reported that delays in seeking further investigations for breast cancer result from the false reassurance that negative results give.[37,38] One of these was a literature review that included results of a small (n = 36) retrospective study. This reported on a series of women with palpable breast cancers whose biopsies had been delayed as a result of negative mammograms. These women were more likely to have positive axillary nodes at surgery than those whose biopsies had not been delayed.[39]

It has been suggested that in some screening programmes, interval cancers (which may include false-negatives) have a worse survival than those arising in an unscreened population, although the results of analysis of breast cancers arising in the East Anglian breast screening programme and in another UK dataset do not confirm this finding.[40,41]

Other reviews and discussion papers give a clearer picture of the potential medical consequences of a missed diagnosis in breast cancer screening. In particular, a general discussion paper on breast cancer screening reviewed reports on the impact on mortality rates of a false-negative result, and describes the potential consequences of a false-negative result.[42] Delay in seeking treatment in women with a palpable lump but with a negative mammogram may lead to a significantly higher rate of more advanced disease compared with those who were operated on despite the initial negative mammogram. In an institution with a high threshold for biopsy and where the tumour has a 2-month doubling time, a patient who has a 1-cm lump undetected at screening which becomes palpable at 2 cm will seek treatment if not falsely reassured. She will then survive for 3.5 years. In the presence of false reassurance, she will delay seeking further evaluation because she has been screened negative; the tumour will then double in size before being detected at the next screen, and she would die about 1 year earlier. False reassurance has therefore brought forward her death by 1 year. This effect would be greatest in rapidly growing tumours; it would be less, but still pronounced, in those with intermediate growth rates; and it would probably be unnoticed in slow growing tumours.

This model would need to be tested empirically, and does not provide direct evidence of the actual consequence of a false-negative result, but confirms that in some circumstances false-negative results could result in outcomes that are worse than no screening.[43] This is also suggested by data from the Canadian National Breast Screening Study, where 5200 breast cancer cases were reviewed and it was found that screening error may have delayed diagnosis by 1–11 months in 35% of interval cancers.[44]

A 1983 review also highlighted the general problem that certain breast cancers are difficult to detect early, and as a result may be overlooked. It was suggested that the result of this would be delayed treatment, which would be more difficult, more costly, more disfiguring and less effective.[45] Overall, the evidence is limited at best, deriving mainly from small studies using a retrospective review of mammograms, which may not represent actual practice. Although the evidence does not consistently suggest that false-negatives result in a more advanced stage of cancer at detection, this may be due to 'absence of evidence' rather than 'evidence of absence'.

Cervical cancer screening

Several studies have investigated false-negatives in cervical cancer in detail. One early review summarised a range of studies where slides of cervical smears initially categorised as negative were re-examined, and reported that 27–58% of slides required reclassification.[46] A more recent brief review of pap smear error rates reported false-negative rates of 15–22% in retrospective studies.[47] However, the general problem with these studies is that they cannot be used to estimate sensitivity because the number of true-positive results is not known, and they may not reflect screening practice in real life because screeners examining the slides are likely to be aware that they are involved in a review exercise.[48] There may also be foreknowledge of an adverse patient outcome, or the reviewer may be aware that the rescreening is taking place because of litigation, and more time is available for review than would normally be the case.[49] This is likely to result in an overestimate of the proportion of slides that 'should' have been reported as abnormal. Moreover, not all of the 'missed' positive smears would eventually have progressed to invasive cancer. Such studies, however, do support the theory that false-negative results commonly occur, and may be a factor underlying the progression of some cellular abnormalities to invasive cervical cancer. The impact of this is highlighted in a Danish case–control study, which reviewed the history of negative smears for women with invasive cervical cancer and a set of matched controls.[50] It concluded that the proportion of preventable cases of invasive cervical cancer could be increased from 62–72% to 83–86% if misclassification of smears could be avoided.

Lapses in performance of the NHSCSP have also provided some evidence of the medical consequences of false-negatives, although they do not necessarily represent 'typical' false-negative cases. At the Kent and Canterbury Hospitals NHS Trust, where rescreening of 91,000 smears identified 2200 slides showing some form of abnormality (2.4%).[51] Eight deaths and 30 hysterectomies for cancerous or precancerous changes in the cervix also occurred. The independent review that was established concluded that a loss of public confidence and unnecessary suffering and anguish had been caused. Other similar cases have involved the need for repeat smears or in some cases colposcopy, with consequent anxiety to the women involved. In one case, the rescreening exercise resulted in a loss of screeners' confidence and produced high rates of abnormal and inadequate smears in the year following the exercise, although by the following year the results were within the acceptable national range.

Again, the evidence relating to the medical consequences of false-negative results in cervical screening is limited because neither the formal retrospective studies nor rescreening exercises arising out of lapses in performance are likely to reflect routine screening practice.

General assessment of elderly patients

In the UK, elderly patients are invited by their general practitioner (GP) to receive a 'health check'. The most common types of screening offered in general practice are visual, hearing, dementia, depression, anaemia, diabetes and glaucoma.[52] One review has summarised the impact of false-negative results arising from this type of screening in the elderly.[26] This covers some of the aforementioned conditions and a range of others of varying severity (*Table 3*). The importance of the false-negative rates shown depends on whether the condition is treatable, whether there are subsequent opportunities for detection and whether delay in detection is likely to impact on the effectiveness of treatment. The authors incorporate categorical scores derived in this manner, with scores relating to the prevalence, severity and acceptability of the test, the false-positive rate and its consequences, the effectiveness of treatment, the cost of the test and the burden on services. This produces an overall model for determining whether a condition should be considered for screening. Although this can be used to highlight the problem that the conditions with the most severe potential consequences of false-negatives also have a high prevalence of false-negative rates, and the consequences are based on the authors' opinion, the authors themselves point out that the scoring system needs further validation (*Table 3*).

False-negatives in antenatal screening

The literature on the consequences of false-negative results in other screening programmes is sparse, although a summary is available from a recent good quality systematic review of antenatal screening for Down's syndrome.[22] In this case the consequence of a false-negative result may include an affected pregnancy, with the associated shock, and the costs of a lifetime of care. The timing of the false-negative result is also relevant to its impact: if a termination is chosen, a termination early in pregnancy may be less distressing than one performed later.

TABLE 3 *Impact of false-negatives in screening tests in the elderly (adapted from reference 26)*

Condition	FN rate*	Consequence of FNs†
Cervical cancer	3	1
Breast cancer	2	1
Colorectal cancer	4	1
Hypothyroidism	4	1
Hypertension	4	2
Diabetes	4	2
Anaemia	1	3
Dementia	4	3
Hearing loss	3	4
Visual impairment	3	4
Varicose veins/ulcer	5	4
Obesity	5	4
Need for chiropody	4	5

*FN rate of test	†Consequence of FNs
5: < 10%	*1: Life-threatening in short term*
4: 10 to < 20%	*2: Shortening of survival*
3: 20 to < 30%	*3: Severe reduction in functioning*
2: 30 to < 40%	*4: Moderate reduction in functioning*
1: = 40%	*5: Minimal reduction in functioning*

With infectious diseases, one of the main considerations may be that the probability of increasing the transmission of disease to others is increased, and in the case of antenatal HIV screening there is the opportunity to reduce the risk of mother-to-child transmission by AZT* administration, Caesarean section and avoidance of breastfeeding. This opportunity is likely to be lost if the diagnosis of HIV is missed.

In addition to the above studies, a recent systematic review reported on the effectiveness and efficiency of the school entry medical (SEM) examination as a screening procedure.[53] This review employed a comprehensive search for studies, and identified 16 for inclusion, none of which presented data on the consequences of false-negative cases resulting from either routine or selective SEM examination. This was due to the absence of follow-up data on the entire cohort of patients who were screened.

Overall, while several studies exist that highlight the potential medical impact of false-negatives, no good evidence was found relating to the actual medical consequences in practice. In the cited studies, it is not clear whether the adverse medical effects are worse than they would be in the absence of screening.

Psychological consequences

False reassurance

It has been suggested that people with a negative result from screening could interpret this as a 'certificate of health' and alter their behaviour accordingly.[54] This may be particularly likely in screening where the medical and lay perspectives of its purpose may be very different. It has been suggested that the medical aims are to seek out, diagnose and treat, while the lay aim is to be reassured about the present and the future.[55] If people are predisposed to seek reassurance, then false reassurance may indeed be a potential outcome of screening. Other psychological consequences of false-negatives may include the feeling that one has been wrongly treated, leading to loss of faith in the medical profession. Surprise and anger have also been offered as possible responses.[56] Overall, however, there is less information on the psychological consequences of false-negative results than on the medical consequences, and the only aspect of screening that has attracted specific research appears to be antenatal screening. Here the consequences were found to be poorer parental adjustment, including blaming others for the birth, and poorer acceptance of the child. For most other screening programmes little or no evidence exists.

A demonstration of false reassurance in practice may have been given in a survey among 133 elderly (75 years old) people in Scotland.[57] A domiciliary visit was made by health visitors to carry out a formal medical and functional assessment. Half of those assessed as being in the medium-risk group and over two-thirds of those in the high-risk group became less worried after their assessment. The result of the assessment was therefore to falsely reassure most of those at risk. Other explanations are possible: the authors suggest for example that the 'false reassurance' may really have been due to patients being assured that something would now be done about their health problems.

Antenatal screening

Some evidence on the potential psychological impact of false-negatives derives from studies of women's experiences of antenatal screening. Some of these studies are primarily concerned with the communication of test results in antenatal care, and are discussed later.[58–60] However, a recent systematic review of antenatal screening for Down's syndrome raises several issues relating

*AZT (zidovudine) is a compound used to prevent vertical transmission of HIV from mother to fetus.

to the psychological implications of false-negative results.[22] First, it is emphasised that the fact that screening is often seen as a means of reassurance leads to the expectation that a negative result rules out an affected pregnancy, and this should be guarded against. This may be difficult to achieve in practice because the provision of counselling and support are not always adequate, and health professionals themselves may not always be fully informed.[61] Specialist training and appropriate communication are seen as two useful approaches to dealing with these problems of inappropriate reassurance.

The possibility has also been raised that a child with Down's syndrome born after no screening may be better accepted than a child born after a false-negative result.[62,63] One study confirms that this may indeed be the case in antenatal screening for Down's syndrome.[64] This compared parents of children with Down's syndrome (mean age 4.1 years) with one of three antenatal serum screening histories: false-negative result; not offered screening; and declined screening. Mothers of children in the false-negative group were more likely to blame others for this outcome, and this was associated with poorer acceptance of the child and higher parenting stress. Mothers of children in the false-negative group had a lower acceptance of their children than those mothers who had declined screening. The authors concluded that a false-negative result has a small adverse effect on parental adjustment. The results are supported by a pilot study of parents' attributions of blame for the birth of a child with Down's syndrome. This reported that blaming others was associated with poorer parental adjustment, and implies that false-negative results may adversely affect parental adjustment if they result in blaming others for the birth of an affected child.[65]

Neonatal screening

The psychological consequences of neonatal screening have been explored in a recent systematic review.[21] Psychological responses to diagnosis through screening appear similar to those outside of screening, with no evidence reported on parental responses to the birth of an affected child after a negative test result. The authors, however, suggest that a false sense of security in doctors may be one consequence, so that there is a delay in the diagnosis of clinical signs and symptoms. The child may then receive inappropriate treatment or no treatment in the interim.

Breast screening

In breast screening, the fact that many women do not return for a repeat screen[12] might suggest that the reassurance offered by a negative screen can result in non-attendance. However, this is probably not generally the case because the first bulletin on breast cancer screening in England (1994–95) reported that uptake rates vary greatly by type of invitation; while 75% of women receiving their first invitation were screened, this rose to 90% among women who had already been screened in a previous round, and were in receipt of their second invitation. As the large majority of those previously screened will have received a negative result, this does not suggest that a negative screen is a major disincentive to re-attendance (*Table 4*; Department of Health Statistical Bulletin, 1996/9).[66] It has also been suggested that interval cancers have a similar stage and prognosis to those detected clinically, and that false reassurance may not be a major problem in breast screening, but there is too little evidence to be sure whether this is the case.[67] This conclusion is supported by the results of a recently published good quality systematic review of factors predicting delayed presentation of symptomatic breast cancer.[68] This reviewed case–control and cohort studies reporting on factors leading to delayed presentation of symptomatic breast cancer and found that no studies met the inclusion criteria relating to the impact of previous false-negative results on delay by providers. The review concluded that there

TABLE 4 *Consequences of a false-negative result*[17]

Consequence	Benefits
False reassurance (the 'unworried ill')	Spared anxiety if treatment of no benefit
The possibility of legitimising an unhealthy lifestyle	
A delay in treatment, which may be more unpleasant, more expensive and have a worse prognosis than treatment at an earlier stage of the illness	
An increased cost per desired outcome	

was insufficient evidence on the issue, and recommended a programme of primary research into patient-specific factors that increase the risk of delay.

Changes in health-related behaviour

Concern is raised in several studies that changes in risk behaviour follow from negative screening results. One study found that a negative HIV test was followed by a rise in the risk of gonorrhoea, which was interpreted as being due to an increase in risky behaviour (a 'rebound effect').[69] However, there was no control group and there are other criticisms of the study that do not support the theory that increased risk behaviour is the most likely explanation of the increase in sexually transmitted disease rates.[70] Other studies raise the prospect that a negative HIV test result may constitute permission to continue engaging in 'risky' behaviour, but evidence appears limited and contradictory, and the studies themselves have many biases.[71–74] An additional limitation from the perspective of the current review is that behaviour change is compared in those individuals tested negative with those tested positive, or those untested, which makes it impossible to isolate the impact of a false-negative result. A negative test in this context, however, does not automatically result in an increase in risky behaviour, but may even serve to reinforce safe behaviour by confirming HIV-negative status.[75]

Another brief review of the issue of changes in risk-related behaviour suggests that false-negatives may lead to the individual neglecting various aspects of self-care, so, for example, a smoker with a normal cholesterol level may feel justified in continuing smoking, or a post-menopausal woman may ignore minor vaginal bleeding because a previous pap test result was normal.[76] The 'optimistic bias' – the tendency to assess one's own risk as less than that of others – may further impair one's perception of the meaning of a negative result.[77] In one study of screening for cardiovascular risk factors, men who were found to have normal test results did not lead healthier lives in terms of exercise, smoking and diet as a result of having participated in mass screening. It was suggested that this may have been because they interpreted their results as a 'certificate of health', which justified any unhealthy practices they may have had.[54] The generalisability of the study is likely to be limited because the participants were healthy young men, and the study was not intended to examine the specific impact of false-negative results.

In summary, while some authors have suggested that a false-negative result may result in false reassurance, the published literature is of limited value in assessing the psychological impact of false-negatives because it is largely theoretical and anecdotal in nature, or relates to negative results in general rather than false-negative results. Only one study appears to have specifically assessed the psychological impacts of false-negative results (antenatal screening for Down's syndrome), and this found that false-negative results are associated with blaming others and with lower acceptance of the child.[64]

Economic and financial consequences or perspectives

The financial consequences associated with some of these scenarios should also be considered. These are related, in the example of cancer screening services, to the costs of treating a more advanced cancer. Other potential costs include those incurred by the health authorities when rescreening tens of thousands of tests, recalling a proportion of those rescreened, establishing helplines and dealing with any litigation that may arise.

Hard evidence on these issues is again limited, although several theoretical approaches to assessing the costs from the health economics literature may provide some stimulus for future research in this area. One review provides an explicit statement of the potential costs of false-negative results, contrasting them with the consequences of the other possible results (*Table 4*).[17] The only benefit of a false-negative identified in this schema is that the recipient is spared anxiety if the treatment is of no benefit.

While the general utilitarian approach of balancing these costs against the benefits of screening may be useful in theory, it has been criticised on the grounds that in screening it emphasises positive outcomes at the expense of the false-positive, false-negative and true-negative outcomes.[78] However, valuing the consequences of false-negatives may often be difficult; for example, in the case of prenatal screening when the intention is to terminate a pregnancy to avert the birth of a handicapped child. The additional cost of a false-negative in the case of Down's syndrome screening may be in the region of £100–£120,000 (equal to the lifetime additional cost of care estimated in 1993 and 1987).[79,80] Other intangible costs and benefits also exist

in antenatal screening, including psychological costs and benefits,[81] and the process of assessing these involves making many value judgements.[78]

Nonetheless, several studies have explored methods of incorporating the costs of false-negatives when comparing antenatal screening programmes. One such study used an economic appraisal of screening for Down's syndrome to compare the cost-effectiveness of the triple test[†] relative to screening based on maternal age, where the outcome was the average cost per Down's syndrome birth avoided. A range of potential additional costs of Down's syndrome were also included: lost parental output, special consumption, housing and educational needs associated with mental handicap, additional medical care needs (e.g. premature ageing, longer stays on paediatric wards), adoption and fostering costs, and lost individual output. In all, the excess lifetime costs of an individual with Down's syndrome were put at £100,500 (discounted at 6%). Adjusting for differences in survival rates produced a final lifetime excess cost of £79,500. The triple test was found to be more cost-effective than screening based on maternal age alone. The authors point out, however, that such a cost-effectiveness analysis using an 'avoided cost' approach is restricted to births avoided, and a range of other intangible effects of screening may not be included, such as the value of information from screening and reassurance from a true-negative result. The impact of the omission of these outcomes is unclear. Several other studies have also assessed false-negatives in Down's syndrome screening by calculating the cost of an avoided birth, while emphasising the other personal preferences, values and emotional factors that need to be considered.[79,82,83] These additional perspectives are clearly important because the aim of the antenatal screening programme is to offer parents choice and not simply to avoid a Down's syndrome birth and any associated costs. It has also been proposed that 'ethical values' should be considered for incorporation into economic assessments of screening programmes, and, should methods be found for including these, the results of such economic evaluations may be very different.[63]

Another analysis, comparing protocols for screening for neural tube defects, has taken into account patient preferences by assuming a false-negative cost of $500,000 as an estimate of undiscounted additional lifetime medical costs.[84] For some parents, it was estimated that the cost of a false-negative could be higher as a result of additional psychological costs related to restrictions on family members and observing suffering, and for some parents lower if an affected child were to be welcomed as much as an unaffected child. These different values were addressed by sensitivity analyses, which used values 50% lower and 100% higher than the $500,000 base cost (equal to $250,000 and $1,000,000). Relative costs were also assigned to false-positives and fetal losses, and the balance between false-positives and false-negatives was struck by calculating these costs under a range of different screening strategies. This was used to derive optimum screening strategies for different levels of maternal serum alpha-fetoprotein. The model is sensitive to parents' preferences about the trade-off between false-positive and false-negative results (termination of unaffected pregnancy versus allowing an affected child to be born). This implies that models need to include a full range of costs and benefits relating to false-negatives. The inclusion of other perspectives, such as the family and the fetus, may also be necessary.[85] The development of more complex models than those published to date may therefore be valuable in evaluating the impact of false-negatives in screening programmes.

A more general description of the clinical use of decision analysis to analyse benefits and harms has been proposed to help guide medical management decisions.[59] This involves assessing individual utilities relating to different aspects of screening, so that, for instance, the disutilities of different outcomes are assessed on a scale ranging from 0 (live healthy birth) to 1 (Down's syndrome birth). Anxiety related to screening is also allotted a disutility value on the same scale, and other disutilities can be incorporated.

One of the major remaining problems for the development of such analyses is the lack of data on many relevant societal and other costs of screening, and the lack of formal data on many of the relevant outcomes. However, decision analysis is likely to be valuable in demonstrating how false-negatives may be incorporated in screening decisions. Explicitly incorporating values associated with false-negative results may show how they affect decisions about the appropriateness of screening. The approach

[†]A screening test for Down's syndrome using three biochemical markers.

can also be applied to individuals, as well as groups, taking account of individual preferences and values to increase the overall utility of a screening programme.[59,83,86]

Finally, one economic perspective on screening suggests that it could be viewed as an investment in acquiring information.[78] In this case, the value of the information given should also be appraised. This perspective is considered in chapter 6.

In summary, evidence on the economic implications of false-negative results is largely theoretical, highlighting ways in which their consequences may be valued and included in analyses of screening. While this literature has limited value as hard evidence of the costs of false-negatives, it may provide useful pointers to how these consequences may be assessed in future screening programmes.

Legal implications

The legal consequences of false-negatives have also been highlighted in the UK where cases of cervical cancer arising after screening have resulted in the women involved seeking to claim compensation from hospitals through the courts. In one example, 12 women who were affected as a result of wrong reporting of cervical smear results in the Kent and Canterbury Hospitals NHS Trust have taken out legal proceedings against the hospital. One woman, who had a hysterectomy following failure to detect a cancer during screening, is asking that the Trust fund a surrogate pregnancy.[87] Individual settlements have ranged from £2500 to £250,000, with the wide range being due to differences between cases in the likely causes of the error.[‡] Other cases in the UK need not be seen as failures of screening, however, because interval cancers lead to legal proceedings and out-of-court settlements irrespective of whether quality standards are being met or not (Raffle A, Avon Health Authority, Bristol, personal communication, 1999). To succeed, these cases would have to prove medical negligence, which would require that a breach of duty had occurred. Although there is no actual legal clarification on what constitutes negligence in screening, there is no requirement in law for performance to be perfect.[30] In practice, these cases tend to be settled out of court to avoid the expense of fighting a legal case.

In the UK, the Medical Defence Union currently has 82 claims files involving false-negatives between 1990 and March 1998, most of which relate to mammograms, cervical smears, ultrasound examinations and antenatal testing.[§] Indemnity payments to date amount to £63,000 and reserves on the active files (to cover estimated damages and legal costs arising from as yet unsettled cases) amount to £1.1 million. This covers payments for damages to patients and/or relatives, and includes the legal costs of plaintiffs. Most cases relate to false-negative results in testing for malignancy (*Figures 1* and *2*).

Although there may be fewer cases arising out of antenatal screening, the costs can be considerable. In one case in Scotland in 1998 where a Down's syndrome child was born following a missed diagnosis, £300,000 was awarded to the parents against their health board. This included £5000 for distress caused to the father.[88]

More generally, high-profile cases such as those recently covered in the media may result in pressure to increase the sensitivity of screening at any cost. One possible consequence is 'defensive' reporting of minor abnormalities.[27] The dangers of this have been emphasised in practice, where in a review of detection rates for cervical smear abnormalities it was concluded that despite good organisation of the service, much effort was currently being devoted to limiting the harm done to healthy women and to protecting staff from litigation.[89] One consequence of this is that health authority expenditure on technology may rise in an attempt to detect any form of abnormality. This will then increase false-positive rates in the process, which can be both harmful and costly. This emphasises the need to consider the cost-effectiveness of screening technologies before they are introduced.

Most of the limited literature in this area relates to the US experience, where it appears that the risk of a lawsuit relating to false-negative reporting is high. In all, 15% of pathologists are currently involved in a malpractice lawsuit, 10% of which relate to false-negative cervical smears,[90,91] and delay in the diagnosis of breast cancer is one of the most common reasons for malpractice claims against doctors.[92] The knock-on effects of litigation resulting from false-negative pap smears may be considerable: this has been

[‡]Based on data supplied by the NHS Litigation Authority, 22 October 1998.
[§] Based on data supplied by the Medical Defence Union, 8 October 1998.

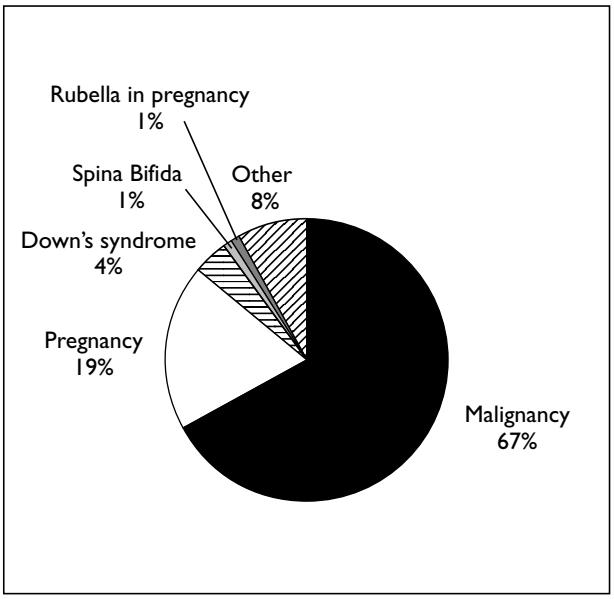

FIGURE 1 *Cases relating to false-negative test results (Medical Defence Union data; see text)*

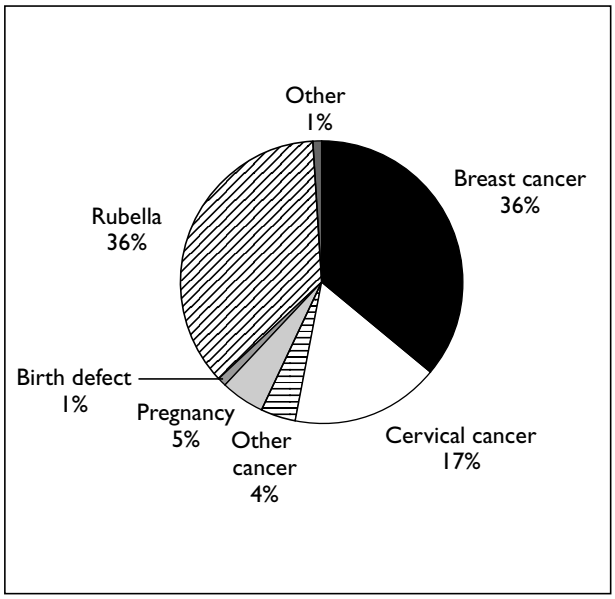

FIGURE 2 *Costs associated with false-negative reporting: percentage of total reserves and indemnity (Medical Defence Union data; see text)*

cited as a threat to the use and availability of the test.[47,93] One particular problem which has been raised is that, as in the UK, cases are settled on a case-by-case basis, and there is no consideration within the context of the overall performance of the cervical screening test. As the public expectation is of a zero error rate, and as no laboratory can meet this expectation, allegations of malpractice are likely to result.[93] Finally, a US review paper has attempted to summarise data on false-negatives but found only information on litigation arising out of negative mammograms. This review reported that the Physician Insurers Association of America found that 35% of claimants with breast cancer had previously had a negative mammogram.[94]

Summary of consequences

Overall, there is insufficient research to help in quantifying the consequences of a false-negative result, although it is widely reported that the main impact of false-negative results is false reassurance, leading to delay in diagnosis and treatment. This observation has been made in the context of screening for breast, cervical, ovarian, testicular, prostatic, skin and other cancers, as well as other conditions.[42,95–99]

Based on the studies described previously it is possible to draw up a table of consequences of false-negative results for current NHS population screening programmes (*Table 5*). The evidence regarding the medical impact of the problem is structured here chronologically, summarising the consequences of false-negative findings in order, from the antenatal period to adulthood. It should be noted, however, that the overall strength of the evidence presented is low, though this does not necessarily mean that the consequences do not exist.

In short, little robust evidence was found relating to the medical, psychological and economic consequences of false-negative results, although they have demonstrable legal and financial consequences. There is also a strong consensus in the literature that they have a powerful impact on public confidence in screening, and this impact is considered below.

The toll of false-negatives on public confidence in screening

It has been pointed out that the outcomes of screening are broader than most other types of health care and are not limited to health gain, but may extend to investment in knowledge and reassurance.[100] For the public these benefits of screening may be compromised by recurring scares about false-negatives. Other consequences are less obvious, such as a loss of morale among staff involved.[51] While these types of outcomes are often not reported in traditional medical literature, and are not easily amenable to grading according to the hierarchy of evidence approach, they are nonetheless important.

TABLE 5 *Inventory of NHS screening programmes where guidance currently exists[3] and the potential consequences of false-negative results*

Screening programme	Coverage	Medical	Psychological	Legal	Economic	Other
HIV antibody	Women at high risk receiving antenatal care	Loss of opportunity to prevent transmission to child	Risk behaviour may be increased but no clear evidence	–	Treatment more costly	–
PKU	All neonates	Delay in diagnosis and possible loss of opportunity for early intervention	–	–	–	–
Congenital hypothyroidism	All neonates	Birth of affected child; possible loss of opportunity for early intervention	–	–	–	–
Physical examination	All neonates	Unclear because there may be later opportunities to detect condition; no evidence	–	–	–	–
Child health screening	GMS regulations	Unclear because there may be later opportunities to detect condition; insufficient evidence	–	–	–	–
Breast cancer	All women aged 50–64 invited once every 3 years; women over 65 on request	Treatment may be less successful, more invasive at more advanced stage	Anxiety and distress among all those involved in initial screening and their families when FN result discovered	Missed cancers may lead to legal action	Treatment more costly; costs arising out of legal action or settling out of court	Loss of public confidence in programme; loss of morale among screening staff
Cervical cancer	All women aged 20–64 invited once every 5 years; every 3 years in Scotland	Treatment less successful, more invasive at more advanced stage	Anxiety and distress among all those involved in initial screening and their families when FN results discovered	Missed cancers may lead to legal action	Treatment more costly; costs arising out of legal action or settling out of court	Loss of public confidence in programme; loss of morale among screening staff
Cardiovascular risk factor screening	Newly registered patients and patients not seen within 3 years	Missed opportunity to treat, or to lower risk, though may be other opportunities later	–	–	–	–
Elderly general assessment*	Patients aged 75 years plus assessed every 12 months	Missed opportunity to treat, or to lower risk; for some conditions impact may be low because there may be other opportunities later	Possible change in risk behaviour for some conditions; for cancer screening services, anxiety and distress	–	–	–

* *May not necessarily be considered as a screening programme, though has some elements of one; it is a contractual requirement of GPs to ensure that those over 75 are offered assessment every 12 months*

–, no clear evidence; GMS, General Medical Services

One such example illustrates the knock-on effects of false-negatives due to screening errors. At the James Paget Healthcare NHS Trust in Great Yarmouth, a rescreening exercise in 1995 identified one substandard screener; levels of inadequate smears and mild and borderline smears rose above the accepted ranges in subsequent years, which was considered to be a consequence of loss of confidence among the other screeners.[33] There are, however, steps that can be taken to limit the damage to public confidence caused by rescreening, and these have been outlined by the chief executive involved.[101] The advice covers dealing with the media, maintaining staff morale and maintaining the confidence of the community in the hospital concerned.

A US report also offers some advice on the management of high-profile lapses in screening performance. This suggests using the issue as an opportunity to educate the public about irreducible false-negative rates and related issues.[102] One US study also reported that media coverage of screening errors had a devastating effect on staff, and attempts at public education about the fact that error rates were not unusual were lost

in an atmosphere of fear and anger generated by tabloid reports.[103,104] A key role in this case was played by the *Wall Street Journal*, which ran a series describing 'Pap mills' with overworked, under-supervised screeners. This contributed to the widespread belief that a false-negative always implied negligence,[105] whereas a good screening programme may actually have a high false-negative rate if the specificity is high.

In the UK, it is hoped that the introduction of quality control indicators, guidance and monitoring procedures, for cervical cytology services, and the introduction of accreditation procedures, whose results will be made publicly available on the Internet, will help to restore public confidence in the NHSCSP, which has been dented in the wake of several well-publicised lapses.[106] However, while maintaining public confidence is important, not least to maintain population coverage of screening at a high level, it is not an end in itself. High public confidence in the efficacy of screening and perhaps falsely high expectations may have created a situation in which all deaths from cervical cancer following screening are perceived as screening 'failures'.[107] This is not necessarily a case of the public 'getting it wrong', but may have been due to the public having been misinformed by providers about the limitations of screening in order to ensure high population coverage by screening programmes. A more realistic picture of the limitations and the benefits of all types of screening is therefore now likely to be useful. This is in accord with the NHS Executive's aim of achieving 'patient partnership', which includes addressing social expectations for openness and accountability, and communicating information about effectiveness of services.[108] In the current context, this could include provision of information on what can be reasonably expected from screening programmes, and in particular, advice that false-negative results are likely to remain even after all possible cost-effective organisational and technological steps have been taken to try to eliminate them.

Given that this 'irreducible fraction' of false-negatives may exist even in effective screening programmes where the benefits outweigh the harms, it may be worth considering how the impact of false-negative results could be limited. The next chapter considers this issue in more detail.

Chapter 6

Minimising the adverse effects of false-negatives

Given the circumstances outlined in the previous section, limiting the impact of false-negatives may perhaps most usefully focus on improvements in the public's (and health professionals') understanding of screening as well as its limitations. Such improvements in education may reduce the likelihood of false reassurance, improve the quality of informed consent to screening, and aid patient decision making. In addition to procedural information, however, education about screening also involves the communication of information about risks and benefits.

Ideally, participants in screening should be fully informed about the nature of the screening test and the meaning of the results. If this is ensured then the impact of false-negatives may be minimised in several ways.

First, the medical impact of false-negatives may be lessened because the person would not interpret a negative result as a clean bill of health, and so may not delay seeking professional help when symptoms of the medical condition eventually arise. Secondly, any psychological impact such as shock or distress may be lessened if the condition subsequently develops ('forewarned is forearmed'). However, it is not clear whether this shock or distress is greater among those individuals in receipt of a false-negative result after screening for a disease condition compared with those unscreened. Thirdly, there may be less incentive on the part of the patient to seek legal redress for what is perceived as a clinical error, and this will limit the financial and legal consequences of false-negatives.

Full provision of information regarding the purpose of screening, and the meaning of screening results, could also help ensure that public confidence in existing NHS screening programmes is not undermined by high-profile cases where errors do occur. The current public and professional perceptions of screening and screening results therefore have a key role to play in limiting the consequences of false-negatives, and these are considered next.

Perceptions of screening

> "There should be evidence that the complete screening programme is clinically, socially and ethically acceptable to health professionals and the public."[3]

This comment from a National Screening Committee document recognises the broader social context of screening, and suggests that the complete programme should be acceptable to the two groups directly involved. It therefore constitutes a clear requirement that both groups have a sufficient understanding of the various components of screening. In practice, however, knowledge of screening may be incomplete, and evidence that this is the case comes from several sources.

Public perceptions of screening

The public does have some misconceptions about the purpose of screening and the accuracy of screening tests, as highlighted by an Australian survey of public understanding of screening carried out by telephone interview on a national quota sample of 835 18 to 70-year-old individuals.[109] About two-thirds of the sample had heard of screening tests, but only 21% understood that screening was directed at asymptomatic people. About 50% of respondents thought that a good test should detect 95% or more of cases, and 66% thought that a good screening test should detect over 90% of cases, with women expecting higher sensitivity than men. With respect to an absolute minimum level of sensitivity, 21% considered 90% detection worthwhile, and 24% saw 87–89% as a worthwhile detection rate. The survey also questioned respondents on their views of compensation for missed cases: 33% favoured compensation, 58% were against, and 9% were unsure. Women and the young were more in favour. The most common reason for not supporting compensation was that people being screened had been warned beforehand (32%). In all, 19% understood that there was no such thing as a perfect test and 15% saw it was a matter of bad luck rather than anyone's fault. This survey suggests that although the public may have misconceptions about screening they do accept that screening

tests are not perfect, that cases will be missed, and that compensation does not automatically follow, providing that people have been adequately informed beforehand.

A more recent survey about women's expectations of the accuracy of screening mammography and compensation for missed cancers reported similar findings regarding compensation.[110] Slightly less than half of the 115 women surveyed thought that financial compensation should be awarded for a cancer missed by screening. About 30% of the women also had extremely high expectations of the sensitivity of the test and about 40% thought that screening should pick up all cancers. The expectations of the British public about screening and compensation for false-negative results are, however, unknown.

Greater public understanding of the organisation of screening programmes is therefore in order: it may not be widely perceived that screening of individual samples is difficult, that it is always likely to involve a human element even with highly trained and motivated staff, and that this should not always be interpreted as medical negligence. It has also been suggested that the term 'false-negative' itself may be seen as inappropriate in the case of cytologic detection of carcinoma because it is true only in reference to the patients and clinician; from the point of view of the laboratory, the slide may have been accurately reported as negative, with no detectable abnormal cells.[19]

However, although the potential benefits of improved public knowledge of the limitations of screening have been emphasised, there may also be costs. For example, there is the risk that it may simply reduce public confidence in screening. Belief in the efficacy of screening is also related to adherence, so emphasising the limitations may also result in reduced coverage,[111–113] and what has been referred to as 'mass informed consent' may even limit the actual effectiveness of screening.[114] Care would therefore need to be taken that any message about the limits of screening does not reduce uptake of effective screening tests among those most likely to benefit, or that it becomes simply a further barrier to access for some segments of the population. An alternative argument is that, above all, patients' autonomy should be respected, which includes their right to decide not to undergo screening, even when refusal may result in harm to themselves.[115]

Perceptions of those individuals invited for screening

One of the key objectives of the NHSCSP was to give women information about the benefits and limitations of the cervical smear test. However, the report of the first 5 years of its operation suggests that women are less aware of the limitations than the benefits.[34] One of the reasons for this has been suggested in a National Audit Office survey[33] of guidance provided to women participating in the NHSCSP. This survey found that although the benefits of screening and a description of the process were well covered, with nearly 90% of invitation letters issued by health authorities including information on the importance and preventive nature of the test, there was less information on the other areas of screening, including limitations; details of these were included in just over 30% of invitation letters. Information provision has been improving, however, as a result of guidance issued in 1997. It was also suggested that unscheduled smear taking, which is reducing but still accounted for 454,000 smears in 1996/97,[33] may be less likely to involve the full, accurate information highlighted as important by the NHSCSP. The fact that information provision was lacking was also suggested by the finding that, of the letters to women with normal and inadequate results prepared by health authorities, only 69% explained the meaning of the result.

A recent review supports this view of the limited information currently provided in the NHSCSP. It was reported that the only information on the limitations of cervical screening currently available to women amounts to two lines in a health education authority leaflet, which points out that cervical screening is not 100% perfect. The author of the review suggested that the Department of Health and the NHSCSP raise public awareness of this issue.[30] It has also been pointed out that a detailed information sheet and the need for signed consent to confirm that women have been fully informed about the nature and limitations of the test may play an important role in education, if not actually providing a defence against negligence.[30]

A recent study assessing the psychological aspects of attendance at breast cancer screening has reported similar findings.[116] Of the 572 respondents who answered the question 'I would have confidence that the result of my mammogram would be accurate', 82% reported being confident

that their test result would be accurate. The authors suggest that women may be unaware of the margin of error in screening programmes and therefore assume that every result is automatically correct.

A lack of adequate information is not confined to cancer screening programmes. Women involved in antenatal screening have a limited knowledge of several important aspects, including the meaning of positive and negative test results.[58,60,117–119] This is perhaps not surprising because little information is actually given about the meaning of negative results.[58] A review of informed decision making in this context concluded that improved provision of information was necessary to reduce the likely consequences of false-negative results and to protect individual autonomy.[60] A recent systematic review of neonatal screening for inborn errors of metabolism similarly concluded that parents' knowledge of the purpose, process and likely outcomes of screening was limited, and found that in Britain informed consent was often not obtained. Moreover, information provision was such that patients could not always make informed decisions about neonatal screening.[21]

These studies provide evidence that the knowledge of participants in screening programmes is often limited.

Perceptions of screening among health professionals

In specific settings, accurate information about screening is likely to come from health professionals, and if they themselves do not fully understand the meaning of the screening test or its results then fully informed consent may be compromised. There is evidence that health professionals' knowledge of screening is imperfect. A recent survey of UK health professionals involved in antenatal care reported that 59% correctly answered only half or less of factual questions relating to serum screening for Down's syndrome.[61] Among this group of GPs, hospital and community midwives, and obstetricians it was found that questions relating to the sensitivity, specificity and positive predictive values of tests were poorly answered. The number of correct responses from GPs was significantly less than from the other groups. This may not be surprising given the large number of screening tests and the formidable task of understanding and presenting such information. A survey of 169 NHS antenatal clinics offering serum screening for Down's syndrome also found that presentation of negative results was very variable; specific arrangements were in place for the communication of negative screening results in less than one-third of programmes surveyed.[120]

Opportunistic screening – offering a test for an unsuspected disorder at a time when a person presents to a doctor for another reason[121] – seems to offer particular opportunities for best screening practice to be ignored. It is more likely to be done without explicit consideration of wider screening issues and so there is likely to be a lack of adherence to national standards and a lack of consideration of harms to those screened.[121] In seeking to limit the adverse effects of false-negatives, calls for opportunistic screening may therefore need to be particularly closely examined.

Causes of limitations in understanding

One obvious cause of limited understanding is the lack of accurate information currently available about screening programmes, as emphasised in the previous chapter. For example, a recent survey of available mammography information leaflets in Australia found that information about the accuracy of screening tests was provided only occasionally: sensitivity was given in 26% of leaflets and specificity was not considered in any of the leaflets.[122]

Simply providing information, however, does not necessarily imply understanding. Misunderstanding may occur for several reasons, including forgetting. Recall of information is known to decline over time. Further misunderstanding may arise when recall is such that the essence of the information is retained but not the complex detail. Also, people are more likely to recall information in a way that underplays risk, often referred to as a self-serving bias. Emotional factors are also likely to influence the processing of information; for example, anxiety about undergoing screening.

Health professionals may fail to provide adequate information to their patients or an understanding of why screening is important. One reason is that they lack the knowledge to discuss the issues relating to screening in any detail, which has been highlighted in the previous chapter. Lack of knowledge may not, however, be the only factor that influences professionals' decisions to communicate information about screening. Their beliefs about the importance of information for decision making and attitudes towards giving

accurate information to patients are likely to be important. A study assessing knowledge in obstetricians and midwives in six UK hospitals found that whilst obstetricians who knew less about prenatal screening tests were less likely to give information about uncertainty, this was not the case for midwives.[123] This finding emphasises that simply providing professionals with more information will not automatically improve the communication of risk to patients.

Professional beliefs about the purpose of screening are also important. Health professionals and those being screened are likely to hold different beliefs and expectations about the purpose of screening. One of the reasons for people opting into screening is to be reassured. This supports the theory that a negative result is perceived differently from professional and lay perspectives: the former see it as indicating reduced risk as opposed to a clean bill of health. Avoidance of regret is another potential motivation for screening.[78,124] Tymstra, for example, suggests that people do not turn down the offer of therapeutic or diagnostic possibilities because refusal increases the risk of missing a positive result, which is something that may be regretted later.[124] This has been suggested as one explanation of why people regularly violate the assumptions of expected utility theory – a theory of decision making under uncertainty that suggests individual decision making can be predicted on the basis of their preferences.[125] Regret theory suggests that when individuals are uncertain about which course of action to take and have no clear preferences to guide them, they may be guided by the need to avoid future self-recrimination and self-blame.[15] In theory, this has the result of forcing their choice towards the safe, risk-averse option (e.g. accepting the offer of screening).[126] However, while the role of anticipated regret has been examined in several medical contexts, for example in relation to physician decision making about treatment for dementia[127] and in theoretical decisions about medical treatment, fetal testing and vaccination,[128] there has been little examination of its contribution to how people assess the benefits of screening in real life.

What is clear is that people do see the reassurance from a negative result as one of the benefits of screening. Negative information can be valuable to those screened because studies using willingness to pay (WTP) as a measure of benefit in cystic fibrosis carrier screening have shown. Here, the reassurance provided by a negative test result had a strong influence on WTP.[100] A reduction in the value of the negative information (by informing participants that a negative result means that a residual risk remains) may therefore alter participants' beliefs about the costs and benefits of screening. Public perceptions of the value of screening may therefore be radically changed by greater public education on the limitations of screening.

These theoretical perspectives suggest that there is a possibility that the negative results from screening will overshadow any information about remaining risk. There is also evidence that misunderstandings about receiving a negative result can occur.[129] In one study of cystic fibrosis carrier testing, 3 months after testing 17% of those receiving a negative result believed that they were at no risk of having a child with cystic fibrosis, despite written and verbal information informing them about the meaning of all test results. Misunderstanding in this group decreased significantly from receipt of the result to the 3-month follow-up period. In individuals who received a positive test result, there was no change in understanding during the same 3-month period. The authors suggested several psychological explanations for their findings, including a decline in information recall over time and the tendency for results to be misremembered in a direction that underplays risk (a self-serving bias).

Some of the problems with information provision may relate to a lack of resources. A 1994 survey of the experience of obstetricians in England and Wales found that they felt they had inadequate counselling resources, and lack of understanding among participants in screening was seen as a problem by over 80%.[130] Clearly, lapses from best practice in information provision are common, and there is evidence that the communication of negative results can be impaired.

Even where resources are available there may be resistance to provide information to patients. One study reported that ultrasonographers were concerned about the provision of evidence to pregnant women, and the study highlighted several key issues in providing 'evidence-informed choice': professional ownership of knowledge, conflicts with professional autonomy, concerns that information provision would provoke anxiety, and professional and organisational barriers to allowing informed choice.[131]

An additional consideration is the issue of target payments, for example in cervical screening, which

some have argued goes against the spirit of enabling women to make an informed choice of whether or not they wish to be screened.[132] If the present system continues to pay for the number of women screened, then the threat of financial penalties may deter discussion about the pros and cons of screening in case uptake is affected.

Potential solutions

General Medical Council guidance on improving informed consent in screening programmes has recently been published.[133] This guidance may help to improve the current situation regarding the lack of understanding that exists around screening. The guidance states that the purpose of screening; the likelihood of positive/negative findings and the possibility of false-positive/negative results; the uncertainties and risks attached to the screening process; any significant medical, social or financial implications of screening and follow-up plans, including the availability of counselling and support services, should be clearly explained.

One approach to improving understanding and informed consent is to develop high-quality information leaflets paying attention to content, readability and presentation. A series of such leaflets has been developed for use in the NHSCSP: 'Your smear test', 'What your abnormal result means' and 'The colposcopy examination'.[134] The authors of the paper in which the process of developing the leaflets is outlined argue, however, that information should not replace the need for direct communication, and that high-quality written information should be matched with effective communication skills.[134]

One option to encourage effective communication is the use of paired sets of information leaflets: one for the patient and one for the health professional. This approach has already been adopted in some areas of screening; for example, in screening for prostate cancer and in antenatal screening tests.[135] The use of the paired information leaflets in antenatal screening is currently being formally evaluated using quantitative and qualitative methods.

Effective communication will probably require that health professionals become proficient in the 'language of risk'.[136] That is, they must know about how best to classify and communicate information about risk to the people undergoing screening. This might involve offering training to health professionals. Health professionals are rarely given any training before or after qualifying in how to present complex information effectively.[60] One study has shown that brief training with midwives and obstetricians can produce modest improvements in the communication of information about prenatal tests. However, in practice, such training may be difficult to implement because a very small proportion (27%) of obstetricians and midwives were willing or able to receive training to improve their information-giving skills.[137]

There is a lack of evidence from research based in clinical settings about the impact of presenting probabilistic information in different ways. Preliminary analyses from one study that has compared verbal and probabilistic risk information to women receiving negative tests results following serum screening for Down's syndrome suggest that numerical presentation of risk information may be better understood than qualitative information (e.g. 'low risk') (Marteau TM and colleagues, unpublished observations, 2000).

A survey of healthy individuals in Wellington, New Zealand has shown that an individual's decision to undergo screening for cancer is affected by the way the benefits are framed. Screening was most likely to be accepted when the benefits were presented as a relative risk reduction and most likely to be rejected when presented as the number needed to screen to save one life.[138]

In addition to providing information to both health professionals and those undergoing screening, health professionals may need to identify and use specific interventions that will improve the participant's understanding of screening. One approach is through the use of decision aids. A recent systematic review has evaluated the use of decision aids in terms of improving decision making and other outcomes for people facing either treatment or screening decisions.[139] Of the 17 studies that met the inclusion criteria, six were concerned with screening, three with prostate-specific antigen (PSA) testing, two with prenatal screening and one with *BRCA1* gene testing. Decision aids were found to reduce preferences for PSA testing by 21–48% in two studies, but had no effect in the other study. The use of decision aids did not have any effect on preferences for screening for breast cancer genes or on prenatal testing. In those studies that assessed knowledge for options and outcomes, increased scores for the intervention group were found. Therefore, decision aids can improve

knowledge and stimulate more active involvement in decisions to undergo screening.

A recent systematic review (currently 'in press') will provide guidance on how to improve the effectiveness of risk communication between health professionals and patients on issues such as risk status and risks involved with screening.[140] Another systematic review from the same research team has reviewed the outcomes used in communicating risk information to individuals.[141] The emphasis was on treatment decisions, but the authors do consider screening and report that in studies of screening behavioural outcomes feature prominently, particularly compliance with the utilisation of screening tests. They go on to conclude, however, that other outcomes (used mainly in studies of treatment choices), such as patient evaluation of the risk information or certainty about making the right choice, would be appropriate to measure in relation to screening. They also argue that further development and validation of measurement scales are needed.

Another review that aims to assess the effects of any informational, educational, behavioural or organisational intervention on people's anxiety, understanding and experience of screening is yet to be completed. Details can be found in the review protocol registered with the Cochrane Consumers and Communication Group entitled 'Interventions for influencing people's experience of screening'.[142]

Finally, Austoker and colleagues have provided evidence-based criteria for the content of letters and leaflets sent to women undergoing cervical screening, which provide the basis for guidelines for best practice in this area.[143] In the case of negative results, the evidence is suggestive that a 'normal result' letter should state that this means low risk rather than no risk of developing cervical cancer. Taken together, the findings from these recent and ongoing reviews should provide options for the development and evaluation of interventions for informed decision making in screening.

Chapter 7

Overall summary and conclusions

In summary, false-negative results are evident in all screening programmes, even when the quality of the screening service provided is high, and for qualitative tests in particular (such as the interpretation of cervical smears or mammograms), where a degree of interobserver variability is common (and normal) and it may be difficult to determine whether the false-negative is 'avoidable' or 'inevitable'. This review has been able only to comment on the implications of false-negative results, rather than their actual impact, owing to the lack of primary research. Although the evidence for the consequences of false-negative results is limited, they have the potential to delay the detection of breast and cervical cancer, but there is little good evidence to determine what effect this may have on mortality. There is little good quality evidence relating to the psychological implications of false-negatives. There is, however, good evidence that false-negatives have legal and related economic implications. There also seems to be a consensus in the literature that there are consequences for public confidence in screening, although, again, clear evidence is lacking.

One approach to addressing the major consequences of false-negatives may involve improving informed consent to screening. The results of screening are not widely understood. This particularly applies to negative results, which tend to be interpreted as reassurance that the condition is not present.[60] This finding has led to calls for the provision of clear and accurate information to be given higher priority, in particular when screening for Down's syndrome, HIV and other conditions,[21,144–147] but also in other screening settings including breast and cervical screening.[51,122] Interventions to reduce the adverse effects of false-negatives should therefore concentrate on effective communication of information, and there is good quality evidence that individualised information about the meaning of results may be helpful in communicating information about risk. The relevance of this to communication about the remaining risk after screening (i.e. to limit the impact of a false-negative) will need to be explored further when the results of a systematic review currently 'in press' become available.[140]

There is still a need, however, for primary research directed at effective communication of the results of screening in specific contexts. This should aim to assess the impact of a false-negative diagnosis on the individual, and to evaluate the specific methods of achieving informed decision making in screening. At a societal level, consideration also needs to be given to how to increase the wider public understanding of screening. In particular, the message that a small percentage of false-negative results is not incompatible with a high-quality service needs to be widely conveyed.

The establishment or consideration of new screening programmes, such as colon cancer screening, provide an opportunity for best practice to be established, and for research into the most effective methods of shared decision making in screening. Demonstration projects*, for example, might seek to monitor and evaluate the medical, psychological and other consequences of false-negative results arising from screening; the opportunity will also exist for qualitative and quantitative research into participants' understanding of screening, and of the meaning of negative results. The full range of benefits and harms might therefore be considered for this and other programmes under consideration, including screening for hepatitis B in pregnancy and *Chlamydia trachomatis*. In the case of chlamydia, the planned pilot schemes might evaluate the impacts of false-negative results as well as systematically investigating the understanding of screening, and the meaning and the value of the information provided to women targeted by this programme. The need for rigorous evaluation of educational interventions as part of a chlamydia screening programme has also been emphasised.[148] Similarly, the colorectal cancer screening pilots in England and Scotland may provide an opportunity to incorporate research into the consequences of false-negative results, and into effective methods of achieving informed decision making by

*Comprises studies used to assess the performance of various screening strategies in practice.

participants.[149] In particular, they provide the opportunity for a wide range of possible effects of colorectal screening to be examined outside of the context of a research setting. For example, an assessment of the impact of the colorectal screening pilots on wider public perceptions and knowledge of the risk of colorectal cancer (i.e. do the screening pilots themselves affect the public understanding of screening?) could be carried out, together with qualitative and quantitative research into the process of colorectal screening (including participants' experiences, their understanding of benefits and limitations, and barriers to informed consent in colorectal screening). The effects of providing full information on the meaning of negative results might also be explored. Relevant outcomes for investigation may include reductions in delays in diagnosis and a reduction in cases of 'false reassurance'. Negative consequences could also be assessed, including a reduction in the perceived value of a negative screen.

Health authorities may decide to introduce other screening programmes where no UK national policy exists as part of research programmes: these too could include provision for assessing the impact of false-negative results as part of an overall assessment of the effectiveness of the programme. This also applies to other screening programmes that may be considered in future, including genetic screening.

In conclusion, the introduction of screening tests into the NHS has been described as piecemeal, uncoordinated and without adequate quality assurance.[150] Ensuring that this does not happen in future is likely to be the most effective way of reducing the impact of false-negatives. If the introduction of a new screening programme also involves full public and professional education, so that the individuals screened understand the process and are clear about the meaning of the results they receive, the negative consequences of false-negatives might be mitigated. It has also been emphasised that 'a properly informed public is a vital but often forgotten ingredient in any analysis of screening'.[150] Without considering the public education aspects of screening, public confidence may be damaged, the value of true-negative results may be reduced, and perhaps the coverage of screening programmes reduced. There is a case for increasing public understanding and encouraging more realistic public expectations of screening by disseminating clear, frank information about the benefits and limitations of screening services as part of both existing and planned NHS screening programmes.

Chapter 8

Implications and recommendations

Based on evidence from the literature, the following implications for policy and recommendations for research are proposed.

Implications for policy

- New screening programmes ideally need to 'start starting correctly'.[3] In particular, this means providing participants with information about the meaning of a negative result.
- New screening programmes might include an explicit evaluation of the impact of false-negatives – considered as part of the overall evaluation of any proposed screening programme (including pilots of screening).
- Participants in screening programmes need access to full, accurate information about all relevant outcomes (including limitations) of screening to allow them to make an informed decision about participation. As with any other type of intervention, it is desirable that the effects of information provision are evaluated.
- There is a case for ensuring that those individuals organising and running screening programmes are fully trained in all aspects of screening, including the meaning of negative test results.
- There is a case for making available both support and education on the presentation and framing of information on risk, and support with counselling resources to all health professionals who act as the public point of contact for screening services.
- Greater public and professional education on the meaning and limitations of screening is desirable. The wider provision of public education materials that include clear information about the limitations of screening (and the meaning of all types of test result) may be particularly helpful.

Recommendations for research

- Research into the most effective means of informing participants of the benefits and limitations of screening is required, which should include randomised, controlled trials of shared decision making in screening.
- Primary research is needed into the long-term consequences of false-negative results across a range of screening programmes, including long-term changes in risk behaviour. Formal standardised instruments for assessing the psychological impact of screening results may also need to be developed to aid this process.
- Primary research into participants' perceptions of the meaning of screening results is needed. This should involve both qualitative and quantitative research to examine participants' motivations, experiences and beliefs about the screening programme in which they are involved.
- Little is known about public perceptions of acceptable levels of sensitivity, or the acceptability of compensation. Primary research into these issues is a priority. This might take the form of surveys to explore public attitudes, and qualitative and quantitative research among those individuals undergoing screening.
- The development of sensitive economic models that include a full evaluation of the benefits and limitations of screening is required. These will aid in assessing the appropriateness of screening programmes, and will allow the explicit consideration of false-negative results in conjunction with other screening outcomes. However, the development of such models will require further information on the harms arising from false-negatives.

In the longer term, as the results of further primary studies become available, an update of this present review will be needed, and should be considered approximately 3 years after publication of this report. This should allow any relevant results from the colorectal cancer screening pilots to be included. A future update of the review should not rely on electronic searches alone to identify relevant literature because of the difficulty of identifying relevant studies in this area from titles and abstracts alone; a panel of screening and health promotion experts should also be consulted to help develop search strategies and locate relevant articles.

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Appendix 1

MEDLINE search strategy

001 exp genetic screening/
002 (genetic adj2 screen$).tw.
003 (genetic adj2 test$).tw.
004 exp heterozygote detection/
005 exp neonatal screening/
006 (neonatal adj2 screen$).tw.
007 (neonatal adj2 test$).tw.
008 (antenatal adj2 screen$).tw.
009 (antenatal adj2 test$).tw.
010 exp mandatory testing/
011 (mandatory adj2 test$).tw.
012 (mandatory adj2 screen$).tw.
013 exp mass screening/
014 (mass adj2 screen$).tw.
015 exp multiphasic screening/
016 exp mass chest x ray/
017 (routine adj2 screen$).tw.
018 (health adj2 screen$).tw.
019 (screening adj2 test$).tw.
020 (screening adj2 program$).tw.
021 (medical adj screen$).tw.
022 (detection adj program$).tw.
023 (interval adj2 cancer$).tw.
024 (interval adj2 neoplasm$).tw.
025 or/1–24
026 exp false negative reactions/
027 (false adj3 negative$).tw.
028 (negative adj2 result$).tw.
029 exp predictive value of tests/
030 exp "sensitivity and specificity"/
031 sensitivity.tw.
032 rescreening.tw.
033 exp quality assurance,health care/
034 exp quality control/
035 exp diagnostic errors/
036 exp observer variation/
037 (screen$ adj2 error$).tw.
038 (negative adj predictive adj value).tw.
039 or/26–38
040 25 and 39

Appendix 2

Primary studies and reviews contributing information on the medical consequences of false-negative results in established programmes

Study	Screening programme/ type	Design*	Results	Conclusions of author(s)	Methodological validity and/or level of evidence
Baines, *et al.*, 1990[44] Canada	Breast screening	Retrospective review of 575 SBC cases; 102 IBC cases; review of 5200 mammograms obtained over the course of the NBSS trial	Observer error and technical problems led to delayed detection in 22% of SBCs and 35% of IBCs. In all, 11% of SBCs and 58% of IBCs were probably mammographically occult	Observer error may have delayed diagnosis by 1 year in 17% of all screening cancers, and by 1–11 months in 35% of all interval cancers	If the study is considered a nested case–control study within a cohort, it appears to be methodologically sound
Bassett and Butler, 1991[38] USA	Breast screening	Short literature review, including brief review of incidence of FN mammograms and prognosis	A 2-month delay of biopsy in one small (n = 28) study was due to FN mammograms. Presence of disease in axillary lymph nodes: 58% in cases with delay, 18% in non-delayed cases	Adverse effects associated with delay of biopsy	Traditional literature review
Buchanan, *et al.*, 1983[45] USA	Breast screening	Literature review assessing the impact of rates of growth and tumour doubling times on prognosis	Variation in the 'cancer control window' (when it reaches threshold of detection but before dissemination) is large	Some cancers are difficult to prevent or detect and this accounts for the inability of the radiologist to detect some breast cancers	Traditional literature review
Bulpitt, *et al.*, 1990[26] UK	Elderly annual screening	Literature review, used as general background to estimation of appropriateness of a range of screening tests	Range of FN rates and their consequences are presented. These are reported in *Table 3*	Impact of FN results varies widely and must be considered in relation to whether the condition is treatable	Traditional literature review. Authors consider that the conclusions are only tentative, given the problems relating to the scoring system, and the weighting given to the scores used to assess impact
Burrell, *et al.*, 1996[41] UK	Breast screening	Review of screening mammograms in individuals with interval cancers (n = 89), and screening-detected and unscreened symptomatic cancers	Of 90 interval cancers, 51 (57%) were TP, 20 (22%) were FN, seven (8%) were mammographically occult, and 12 (13%) were unclassified. Comparisons of interval, symptomatic and screening-detected cancers in relation to size, grade, lymph node involvement, special histologic subtype, and Nottingham Prognostic Index are presented	Prognosis in interval cancers is similar to that in symptomatic, unscreened tumours, and statistically worse than in screening-detected cancers	Nested case–control study

* *The reviews described as simply a 'review' or a 'traditional literature review' lack one or more of the following criteria: comprehensive literature search, inclusion and exclusion criteria, assessment of or details of the included primary studies. However, they are included because they may have contributed to an assessment of the implications of FN results*

SBC, screening-detected breast cancer; IBC, interval breast cancer; NBSS, (Canadian) National Breast Screening Study

continued

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Study	Screening programme/ type	Design*	Results	Conclusions of author(s)	Methodological validity and/or level of evidence
Chamberlain, 1986[46] UK	Cervical screening	Literature review that includes discussion of sensitivity of screening	FN rates are reported from a small number of primary studies; sensitivity varies from 55% to 85%	FN reports are a factor in the progression of some cases to invasive cancer, but as they occur in < 10% of patients with invasive cancer they play a fairly small role among the other failures of the system	Traditional literature review. Primary purpose of review was to address why cervical screening fails, rather than to review FN rates
Day, *et al.*, 1995[40] UK	Breast screening	Comparison of interval cancer rates in East Anglia with Swedish two-county study	Four out of five radiologists recommended recall for approximately 70% of original mammograms originally classed as screen normal	Prognosis of interval cancers may be no different from those arising symptomatically in unscreened populations; large proportion of interval cancers were potentially screen detectable	Few details of this outcome reported (not primary purpose of study). Mammograms were read independently and blind, but readers knew this was a rereading exercise
Dezateux and Godward, 1995[36] UK	Screening for congenital dislocation of the hip	Literature review with brief commentary on FNs	Little difference in prevalence of surgery in unscreened populations, and in screened populations who had not been splinted as neonates: 0.8–1.3 per 1000 live births in unscreened versus 0.1–1.6 in screened populations	No conclusions specific to FN	Traditional literature review
Gillam, *et al.*, 1990[35] UK	Screening for congenital dislocation of the hip	Audit of late presenting cases in one hospital between 1980 and 1988 (n = 20)	One-fifth of children presenting late with congenital dislocation of the hip had abnormalities at birth	Not all late presentations are failures of screening, but failure to follow up identified abnormalities and failure by parents and professionals to recognise symptoms makes a contribution	Unclear if sample is representative of other late presenting cases
Lynge, *et al.*, 1993[50] Denmark	Cervical screening	Retrospective comparison of 60 cases of invasive cervical cancer, with 300 controls. Review of all previous negative smears	Preventing misclassification would result in the proportion of preventable cases of invasive cervical cancer being increased from 62–72% to 83–86%	Misclassification was common and affected disease status. However, data related to 1966–1982 and may not relate to current practice	Nested case–control study with blinded review of slides
Jones, *et al.*, 1996[25] UK	Breast screening	Blinded review of 133 mammograms normal at prevalent round of screening; cancer detected at incident screen	No difference in histological features between FNs and true incidents	Prognosis for FNs may be no worse despite delay in diagnosis	
Moskowitz, 1992[42] USA	Breast screening	Literature review with model of effects of false reassurance on survival	False reassurance could reduce survival by 1 year in worst case scenario	Missed detection leads to increased interval cancer rates or overall later stage at detection or both	Traditional literature review
Van Dijck, *et al.*, 1993[37] The Netherlands	Breast screening	Review of screening mammograms of 40 interval and 44 screen-detected cases	Screening error: 13% of previous mammograms Minimal signs present: 38% Radiographically occult: 43% Radiographically occult at diagnosis: 6% In 9% of screen-detected cases, diagnosis was delayed by 2 years	Earlier detection is possible without decreasing the specificity of the screening test	Unblinded, retrospective case–control design

* *The reviews described as simply a 'review' or a 'traditional literature review' lack one or more of the following criteria: comprehensive literature search, inclusion and exclusion criteria, assessment of or details of the included primary studies. However, they are included because they may have contributed to an assessment of the implications of FN results*

Appendix 3

Primary studies and reviews contributing information on the psychological consequences of false-negative results

Study	Screening programme/ type	Design	Results	Conclusions of author(s)	Validity
Colon, *et al.*, 1996[72] USA	HIV serostatus	A total of 374 intravenous drug users participated in testing and were interviewed 6 months later	No difference between HIV-positive and HIV-negative groups in needle-risk behaviours; HIV-positive group reported decreased sexual risk behaviours	HIV testing can affect risk behaviour	Not confined to FN results. Difficult to interpret as change in behaviour because of no baseline behaviour measures
Ennever and Lave, 1995[84] USA	Antenatal testing for neural tube defects	Cost–benefit analysis of MSAFP screening, which includes assessment of costs of lifetime care and estimates of other costs by sensitivity analysis	Balance between FP and FN results depends on parental values (including individual preferences regarding fetal loss)	Parental preferences play a central role in making an informed choice because they influence the cut-off points used to define an elevated MSAFP	Question is well defined; relevant costs and consequences are considered; sensitivity analyses performed. Unclear whether all costs and consequences are valued appropriately
Fox, *et al.*, 1987[71] USA	HIV testing	Nested case–control study within prospective study; 670 men tested for HIV status	Although risk behaviour declined in all groups, disclosure of a negative test result resulted in less decline	Negative test result may result in smaller decline in risky behaviours	Good quality retrospective study; results not confined to FN results
Hall, *et al.*, 2000[64] UK	Antenatal screening for Down's syndrome	Semi-structured interviews with parents of 179 children with Down's syndrome, with one of three screening histories: FN results; not offered screening; declined screening	FN result associated with blaming others for the outcome. This was associated with lower acceptance of the child and higher levels of parenting stress	FN result has an adverse small effect on parental adjustment	Methodologically sound study; acceptable response rates, full details of methods and outcome measures. Authors caution that selection bias may have affected results
McIntosh and Poewr, 1993[57] UK	Elderly annual screening	Survey of 133 elderly patients who had undergone screening	Half of patients objectively identified as being in the medium health risk group and 68% of those identified as being in the high-risk group were less worried after screening	Inappropriate reassurance about health in those at risk may be an adverse effect of screening in the elderly	Good quality survey; based on random sample, with clear inclusion criteria and appropriate outcomes. Long-term outcome of health beliefs not known
Otten, *et al.*, 1993[69] USA	HIV testing	Historical cohort study examining the association between testing and post-test counselling, and changes in risky behaviour in 666 patients with a negative test	A 106% increase in incidence of gonorrhoea; 103% increase in any sexually transmitted disease after HIV testing in patients with a negative test	Risky behaviour increased in those testing negative but not those testing positive. Negative results may lead to false beliefs of immunity and reinforcement of risky behaviour	No control group; results not confined to FN results

MSAFP, maternal serum alpha-fetoprotein; decreased levels of this serum marker are associated with increased risk of carrying a Down's syndrome fetus

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Study	Screening programme/ type	Design	Results	Conclusions of author(s)	Validity
Phillips, *et al.,* 1995[75] USA	HIV testing	Cross-sectional study involving survey of 1583 individuals who had been tested and found to be HIV-negative	In all, 51% had been tested three or more times; 15% were tested more than once every 6 months	Repeat testing reinforces safe sexual behaviour	No baseline data, so change of behaviour following testing cannot be assessed. Study not confined to FN results
Tymstra and Bieleman, 1987[54] The Netherlands	Screening for cardiovascular risk factors	Survey of 267 men aged 30–33 years who had participated in a screening test (210 responded)	In all, 103 were stated to be 'healthy' as a result of the test; 44% of these saw this as meaning they did not need to change their way of life. This group did not differ from other respondents in unhealthy practices. They were significantly less likely to have a healthy diet	Negative result from screening may result in a 'certificate of health' effect	Difficult to generalise this group of young men with other screening pro-grammes. There was a 62% response rate to initial screening. (Results not confined to FNs)
Wilson, *et al*., 1996[73] USA	HIV testing	Prospective cohort of 808 women followed up for 4 months after testing	Receipt of negative test results did not affect sexual practices likely to affect HIV risk	Caution should be taken in situations where negative test results may strengthen perceptions of invulnerability	Results not confined to FNs

Appendix 4

Primary studies and reviews contributing information on the economic consequences or economic perspectives of false-negative results

Study	Screening programme/ type	Design	Results	Conclusions of author(s)	Validity
Seror, *et al.,* 1993[63] France	Antenatal maternal serum screening for Down's syndrome	Cost–benefit analysis based on prospective data from study of 100,000 women. Economic assessment includes FN rate in costs	Total costs of screening = $8,302,000; net potential savings = $32,186,000, based on the lifelong costs of care	Inclusion of FN and FP rates and associated ethical values into economic assessments of screening programmes may change the results	Economic evaluation component meets major relevant validity criteria.[151] Other costs of FN are raised but not measured
Wald, *et al.*, 1992[79] UK	Antenatal screening for Down's syndrome	Demonstration project involving 12,603 women followed to outcome of pregnancy	Detection rate of 48%. Estimated costs of avoiding the birth of a baby with Down's syndrome = £38,000. Estimated discounted costs of a lifetime of care = £120,000	NHS should ensure that antenatal maternal serum screening for Down's syndrome is available nationally	Appears to have assessed all major costs. Economic evaluation component meets major relevant validity criteria[151]

Appendix 5

Systematic reviews contributing information

Authors	Screening programme	Methods*	Relevant findings/conclusions
Barlow, *et al.*, 1998[53] UK	SEM	Systematic review of published and unpublished studies (e.g. 'grey' literature) of the effectiveness of the SEM as a screening procedure	In all, 16 primary studies were identified that met the inclusion criteria; no study was identified that presented data on the FN cases
Davis, *et al.*, 1997[20] UK	Neonatal hearing screening	Systematic review of published and unpublished literature on the effectiveness of current screening programmes	Specificity of the test is about 95%; sensitivity not yet established, but possibly > 90%. Model screening programme is proposed around which universal screening could be based
Pollitt, *et al.*, 1997[21] UK	Neonatal screening for inborn errors of metabolism	Systematic review	Strong parental support for screening. Early diagnosis is of value to family, even if effective treatment is not available. The majority of economic evaluations fail to address the value of the information programmes provided to parents
Ramirez, *et al.*, 1999[68] UK	Relevant to breast cancer screening programme	Systematic review of factors predicting delayed presentation of symptomatic breast cancer; data derived from cohort and case–control studies	Evidence of contribution of FN results to delay by providers found to be insufficient
Wald, *et al.*, 1998[22] UK	Antenatal screening for Down's syndrome	Systematic review of performance of serum and ultrasound markers for Down's syndrome, and evaluation of effectiveness safety and cost-effectiveness of methods of antenatal screening and diagnosis	Screening with triple test with maternal age is more effective, safe and cost-effective than the double test. The performance of the quadruple test, including inhibin A, appears better. Substantial variation in screening services for Down's syndrome exists in the UK. There is evidence that better staff education and training is needed so that patients are adequately informed about screening and its implications

* *The systematic reviews are discussed in the text of the report. They all meet all the criteria for a methodologically sound systematic review*

Health Technology Assessment panel membership

This report was identified as a priority by the Population Screening Panel.

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We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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