Journal of Medical
Screening

Editorials

Screening newborn infants for cystic fibrosis

New data published but scientific uncertainty remains

In a systematic review of antenatal and neonatal screening for cystic fibrosis, commissioned for the UK Health Technology Assessment Programme and published in 1999, Murray *et al* recommended the introduction of antenatal screening in the UK.[1] Despite an extensive review of observational as well as trial data, they were unable to make a similar recommendation for newborn screening, but observed that "the ability of (newborn) screening to alter long term prognosis has not been conclusively proven". A similar conclusion was reached in two subsequent systematic reviews of newborn screening, one published by the Catalan Agency for Health Technology Assessment[2] and the other by the Cochrane Library.[3] Do these conclusions remain valid in the light of information published subsequently, including that from newborn screening programmes in Brittany and Wisconsin?[4 5]

Scotet *et al* reported screening test performance and reproductive outcomes following screening of 343 756 newborns over a 10 year period in Brittany.[4] Clinical outcomes were not reported for the affected children. Over a 10 year period, 112 of 118 affected children (95%) were first detected through newborn screening. This detection rate accords well with that reported by Murray *et al*.[1] Twelve of the infants identified through screening were still clinically asymptomatic at the time their parents underwent prenatal diagnostic testing for cystic fibrosis in a subsequent pregnancy. The authors suggested that neonatal screening provided the opportunity for more reliable prenatal diagnosis for affected families, but did not discuss the scope for antenatal screening, a more effective strategy for allowing high risk couples the opportunity to avoid the birth of an affected child.[6]

Of greater relevance to the goals of newborn screening is the publication earlier this year of a further analysis of the Wisconsin Cystic Fibrosis Newborn Screening Trial,[5] one of only two randomised trials of newborn screening for cystic fibrosis.[3] This trial has a unique design in that all infants were screened and then randomised to either immediate disclosure of results (screened group) or delayed disclosure of results by four years of age (control group). Mean z scores for both weight and height over the first 13 years of life were reported using data available for 56 screened and 48 control subjects who had not presented with meconium ileus.[5] Repeated measures analysis revealed a marginally significant difference in weight for age z scores, while height for age z scores were significantly higher among screened compared with control patients up to the age of 13 years, after adjustment for age, sex, genotype, and pancreatic status at diagnosis. An important criticism of earlier analyses of this trial[7] related to the potential for bias in analyses comparing measurements of weight and height obtained before 4 years of age, before all those with cystic fibrosis had been diagnosed in the control group. Thus, in this latest paper, the authors also conducted analyses restricted to measurements taken after 4 years of age, when screening results were disclosed in the control arm and there was uniform probability of diagnosis in the two arms of the trial. Similar findings were reported, although data were not presented in the paper. Pulmonary outcomes are not yet available from this trial although these, together with data on quality of life and cognitive outcome, are currently being collected (Phillip Farrell, personal communication).

The relevance of early nutrition in cystic fibrosis was highlighted more than ten years ago by Corey *et al*,[8] who identified marked differences in growth and survival between children with cystic fibrosis managed in clinics in Boston and Toronto and suggested that these might reflect differences between the two clinics in dietary management, particularly in relation to percentage of fat intake. However, in a subsequent report based on cohorts of patients born between 1970 and 1989 and who were included in the Canadian Patient Data Registry (where newborn screening is not undertaken),[9] pulmonary function was reported to be the best predictor of survival. While poor pulmonary function was associated with poorer weight in females, the interrelation of declining pulmonary function, weight maintenance, sex, and mortality remained unclear.

The association between pulmonary colonisation with *Pseudomonas aeruginosa* and poor pulmonary function in cystic fibrosis is well recognised. It has been suggested that early asymptomatic diagnosis by screening may defer acquisition, or even reduce the prevalence, of such infection. However, in a recently published analysis of the US National Cystic Fibrosis Patient Registry, the risk of acquiring *P aeruginosa* in the first 10 years of life was not found to differ significantly between children diagnosed early, late, asymptomatically, or symptomatically, which suggests that early asymptomatic diagnosis of cystic fibrosis does not influence acquisition of *P aeruginosa*.[10] This is consistent with an earlier report from the Wisconsin trial.[11]

Scientific uncertainty therefore remains as to whether newborn screening improves longer term surrogate outcomes for better survival or quality of survival from cystic fibrosis. As mortality from cystic fibrosis shows a strong cohort effect,[12] and is also influenced by social class and region of residence,[13] randomised trials of screening provide the least biased evidence of effectiveness. A combined individual patient data meta-analysis of the Wisconsin, and Wales and West Midlands newborn screening trials is in progress,[3] and will allow future outcomes for both trials to be

combined, eventually contributing unbiased information regarding pulmonary, cognitive, and quality of life outcomes.

These data are clearly some years away. In the interim, decision-makers might wish to review newborn screening policies in the context of potential antenatal screening policies, for which there is more compelling scientific evidence.[1] Antenatal screening is likely to have a marked effect on the birth prevalence of cystic fibrosis, as was reported recently from Edinburgh, the only city in the UK with an established routine antenatal screening programme for cystic fibrosis.[14] Although the goals of antenatal and newborn screening for cystic fibrosis differ, the development of screening policies for either requires an integrated approach, comparable to that taken recently when formulating antenatal and neonatal screening policies for haemoglobinopathies in the UK.[15]

In the USA, newborn screening for cystic fibrosis is not mandatory but is offered, either as an established or a pilot programme (http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.htm), in six states covering less than 7% of all US births. Antenatal screening for cystic fibrosis has been recommended by the US National Institutes of Health and national guidelines for this programme have been published recently.[16] In the UK, the recommendation to introduce antenatal screening for cystic fibrosis made by Murray *et al*[1] is under active review by a subgroup of the National Screening Committee. The conclusions of this subgroup may have important implications for the recently announced UK national newborn screening programme for cystic fibrosis (http://www.doh.gov.uk/nsc/library/lib_ind.htm).

Editor's note

Yvette Cooper, the UK Public Health Minister, announced on 30 April 2001 that a government decision had been made to introduce screening for cystic fibrosis. (http://tap.ccta.gov.uk/doh/intpress.nsf/page/2001-0208?opendocument)

Conflict of interest:

Dr Dezateux is a member of the Cochrane Newborn Cystic Fibrosis Screening Review Group. She is also a member of the Child Health Sub-Group of the National Screening Committee. This editorial is written in a personal capacity and is not intended to represent the views of either of these groups.

CAROL DEZATEUX

Centre for Paediatric Epidemiology and Biostatistics
Institute of Child Health
30 Guilford Street
London WC1N 1EH
UK
c.dezateux@ich.ucl.ac.uk

1 Murray J, Cuckle H, Taylor G, *et al*. Screening for cystic fibrosis. *Health Technol Assess* 1999;**3**:1–104.
2 Serra-Prat M. *Neonatal screening in cystic fibrosis*. Barcelona: Agència d'Avaluació de Tecnologies i Recerca Mediques; 2000. Report: BRO1/2000.
3 Merelle ME, Lees CM, Nagelkerke AF, *et al*. Newborn screening for cystic fibrosis. *Cochrane Database Syst Rev* 2000;CD001402.
4 Scotet V, De Braekeleer M, Roussey M, *et al*. Neonatal screening for cystic fibrosis in Brittany, France: assessment of 10 years' experience and impact on prenatal diagnosis. *Lancet* 2000;**356**:789–94.
5 Farrell PM, Kosorok MR, Rock MJ, *et al*. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Pediatrics* 2001;**107**:1–13.
6 Brock DJ. Cystic fibrosis. In: Wald NJ, Leck I, eds. *Antenatal and neonatal screening*. Oxford: Oxford University Press, 2000:325–49.
7 Wald NJ, Morris JK. Neonatal screening for cystic fibrosis. *BMJ* 1998;**316**:404–5.
8 Corey M, McLaughlin FJ, Williams M, *et al*. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;**41**:583–91.
9 Corey M, Farewell V. Determinants of mortality from cystic fibrosis in Canada, 1970–89. *Am J Epidemiol* 1996;**143**:1007–17.
10 Wang SS, FitzSimmons SC, O'Leary LA, *et al*. Early diagnosis of cystic fibrosis in the newborn period and risk of Pseudomonas aeruginosa acquisition in the first 10 years of life: a registry-based longitudinal study. *Pediatrics* 2001;**107**:274–9.
11 Farrell PM, Shen G, Splaingard M, *et al*. Acquisition of Pseudomonas aeruginosa in children with cystic fibrosis. *Pediatrics* 1997;**100**:e2.
12 Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.
13 Britton JR. Effects of social class, sex, and region of residence on age at death from cystic fibrosis. *BMJ* 1989;**298**:483–7.
14 Cunningham S, Marshall T. Influence of five years of antenatal screening on the paediatric cystic fibrosis population in one region. *Arch Dis Child* 1998;**78**:345–8.
15 Zeuner D, Ades AE, Karnon J, *et al*. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. *Health Technol Assess* 1999;**3**:1–186.
16 Grody WW, Desnick RJ. Cystic fibrosis population carrier screening: here at last—are we ready? *Genet Med* 2001;**3**:87–90.

The threat to the use of records and stored blood samples in medical screening research

There can be no doubt about the importance of medical records and stored blood samples in medical research in general, and specifically screening research or the audit of screening programmes. The development of antenatal screening for neural tube defects and Down's syndrome depended entirely on the use of such samples, and the samples had been collected before screening for these disorders was even contemplated. The potential value of prostate specific antigen as a screening test for prostate cancer emerged from similar data sets. The safety of diagnostic amniocentesis was studied using record linkage in this way.[1]

In these examples, consent from the individuals concerned about the later use of records or samples was not judged necessary,[2] even though in some situations, for example specific cohort studies, consent will have been sought to participate in the study. In other circumstances the records simply exist in medical institutions, sometimes with associated biological samples that have been kept.

There is now a threat to the conduct of this safe and valuable means of advancing medical knowledge. The position has become serious in Britain. Even the proper functioning of cancer registries is now in question.[3] The General Medical Council is requiring that explicit consent be obtained from every individual in relation to the use of any sample or specimen or record relating to that individual.[4] This would be impractical in many circumstances, but more importantly we believe it would be ethically wrong, causing needless anxiety to healthy individuals. Such research would be greatly limited and sometimes blocked completely. There is evidence that this is already happening.[5] The policy would deprive the community of information that could help improve medical services and do so for no good reason. The regulations seem to have emerged from a perceived need to protect individual rights without recognising the duties that go with those rights,[5] and the harm that would arise by interpreting such rights so strictly that valuable research will be halted. The new rules will harm those they are designed to help.

The guidelines issued by the General Medical Council acknowledge that "disclosure of information about patients for purposes such as epidemiology, public health safety, or the administration of health services, or for use in education or training, clinical or medical audit, is unlikely to have personal consequences for the patient." Despite this, it goes on

to recommend that "in these circumstances you should still obtain patients' express consent to the use of identifiable data or arrange for members of the health care team to anonymise records."[4] The Medical Research Council Guidelines issued last year go further,[6] advocating (in fig 1) that a researcher "consider an alternative setting for a study" if patients are not already made aware their information may be used for research and action cannot be taken to remedy this. If the research has had no detrimental effect on anyone, how can it be right to stop an activity that may improve health and medical care, when no harm can arise, which is the case if standard and well established safeguards are followed about not revealing the identity of individuals?

Paterson, in a recent article on the threat to the work of cancer registries, concluded that "we will effectively wreck legitimate epidemiological research."[3] This view is corroborated by others.[8] The Department of Health recently considered the legal status of blood samples that remain after a clinical test has been carried out, and stated[10]: "In the past, there seems to have been an assumption that such tissue has been 'abandoned' by patients and that it may freely be used for any ethically acceptable purpose without the patient's consent being sought. This assumption is increasingly being challenged, on the basis that patients should be given the opportunity to give or refuse their consent for such use." No argument is given for rejecting the notion of "abandonment" for the remnants of a blood sample that would now be discarded if it were not used for research. The Medical Research Council similarly states that "written documentation must always be obtained"[10] but other than asserting this as a self-evident principle, no reasons are given. The right of individuals to control personal details about themselves has become too much of an absolute principle, at the cost of the right of society to learn from such information for the benefit of all. A better balance is needed.

It is perceived that the public are so concerned over privacy that doctors need to be restrained in the use of medical information in this way. We believe that this perception is unjustified. The public expect doctors to use existing medical information to improve their practice. The Royal College of Physicians in 1999,[11] in a statement from their Committee on Ethical Issues in Medicine, expressed concern "that emerging legislation or regulation designed to protect the rights of patients . . . should not inhibit the conduct of some types of harmless research which have previously been conducted without difficulty and have formed the basis of important medical advances."

The editorial in this issue by Ben Traynor on Consenting Adults (reproduced with permission from the *Guardian*) sets out the problem clearly, and reveals that the public are largely unaware of the importance of this kind of record based research and how it is now under threat in spite of its freedom from harm.

Since Ben Traynor wrote his article, Parliament has passed an Act that covers the use of medical records for research. The Health and Social Care Act became law in May 2001. The Act restricts the use of medical research without consent, except in special circumstances. A new statutory body, the Patients' Information Advisory Group (PIAG), will determine these circumstances and advise the government on the implementation of the Act. The present atmosphere is fundamentally wrong and inappropriately views research using medical records with suspicion. The new legislation and the setting up of the PIAG, whatever the background, provides an opportunity to put things right if its membership includes individuals with experience of conducting such research as well as other professional and lay representatives. The aim should be to produce clear and simple guidelines so that stored samples and existing medical records can be used for research without explicit individual consent, provided this is done properly. An often overlooked report of the Royal College of Physicians published in 1994,[12] sets out guidelines that would serve us well. Its most important safeguard is that the information should be held confidentially by the custodians of the data and the research team without disclosure of the identity of any individual in the study. If an individual who has contributed data or samples were to be approached, research ethical committee approval would be required, but not otherwise. We would do well if we were to adopt this report as our code of practice. It would protect the interests of individuals and encourage the use of existing data to improve medical care without unnecessary obstruction. We believe that this approach is the right one and, if properly explained, should have the support of the public and public authorities. Medical research using existing personal records or samples in accordance with these guidelines is a worthwhile and ethical activity that should be encouraged.

NICHOLAS J WALD
MALCOLM LAW

Department of Environmental & Preventive Medicine
Wolfson Institute of Preventive Medicine
St Barts and the Royal London School of Medicine & Dentistry
Charterhouse Square
London EC1M 6BQ
n.j.wald@mds.qmw.ac.uk

1 Wald NJ, Terzian E, Vickers PA, *et al*. Congenital talipes and hip malformation in relation to amniocentesis: a case control study. *Lancet* 1983;**ii**:246–9.
2 Wald N, Law M, Meade T, *et al*. Use of personal medical records for confidential research purposes. *BMJ* 1994;**309**:1422–4.
3 Paterson ICM. Consent to cancer registration—an unnecessary burden. *BMJ* 2001;**322**:1130.
4 General Medical Council. *Confidentiality: protecting and providing information*. London: GMC, 2000.
5 Macdonald V. Cancer research halted. Channel 4 News, 21 May 2001. http://www.channel4news.co.uk/home/20010521/story03.htm
6 Doll R, Peto R. Rights involve responsibilities for patients. *BMJ* 2001;**322**:730.
7 MRC Working Group. *Personal information in medical research*. London: Medical Research Council, 2000.
8 Silman AJ, Macfarlane GJ. Effects of changes to data protection act. *Lancet* 2001;**357**:1452.
9 Department of Health. *Reference guide to consent for examination or treatment*. London: Department of Health, 2001.
10 Medical Research Council. *Human tissue and biological samples for use in research. Report of the Medical Research Council Working Group to develop Operational and Ethical Guidelines*. London: Medical Research Council, 1999.
11 Royal College of Physicians Committee on Ethical Issues in Medicine. Research based on archived information and samples. *J R Coll Physicians Lond* 1999;**33**:264–6.
12 Working Group to the Royal College of Physicians Committee on Ethical issues in medicine. Independent ethical review of studies involving personal medical records. *J R Coll Physicians Lond* 1994;**28**:439–43.

Consenting adults

Every time you step inside a hospital, the chances are that someone, somewhere is watching you—though that someone is more benevolent than your average stalker, and it is your disease and your data that he or she is interested in, not you.

Epidemiologists, or medical statisticians, watch the figures for health across the country, spotting trends. They work by trawling through information from the records of millions of people. It is epidemiologists who assess the dangers of the contraceptive pill, whether ethnic minorities

have equal access to health care, and whether electricity pylons cause leukaemia. It is they who work out which treatment is best for breast cancer—and whether your GP might be quietly murdering old ladies in their homes.

Because they work with whole populations, epidemiologists can see what is dangerous and what isn't, whether particular illnesses are becoming more or less common, what treatment works and what doesn't, and—in the case of surgeons—who is dangerous and who isn't. Epidemiology has helped save more lives than any of the other more glamorous branches of medicine.

Every time a doctor advises you about your health or decides how best to treat you, he or she is using the evidence provided by epidemiologists. Universal clean water and sewage facilities, and advising people not to smoke, were among their most famous ideas.

But all of this may have to come to an end. The General Medical Council (GMC) has decided that this kind of purely observational work is an infringement of patients' rights—even though it reveals nobody's identity and does nothing to alter or withold anyone's treatment.

The GMC has declared that each study should go ahead only with every patient's expressed and informed consent, and that doctors should not provide data about their patients to any other doctors without that consent. It's a nice idea: patient autonomy and patient confidentiality are crucial, and it would be wrong to dismiss them out of hand. But because such consent is often unworkable—for a host of practical and scientific reasons—the change might stop epidemiology and clinical audit in their tracks and severely impede further advances in medicine.

Ironically, epidemiologists and other doctors who use records purely for research and statistical purposes are the people in medicine who have taken confidentiality and data encryption most seriously. Anyone worried about the confidentiality of material relating to their health should be more concerned about the underpaid temporary staff working on the front desk of their local GP surgery than about a group of medical statisticians cooing over a meta-analysis of 50 000 cases of cancer. There are no scandals in epidemiology.

The problem is that the data being shared must, at some stage, include the identity of the patient. Looking at how our world-renowned national network of cancer registries works, you can see why. For decades, 11 cancer research centres around the country have collected morsels of data on patients afflicted with cancer in their region. From the type of cancer to how they were treated, from the details of their laboratory investigations to their death certificate, all the information is collated, stored and analysed in order to improve the care of the next generation of patients.

There is a good reason that it is not possible for this information to be filed entirely anonymously, without identification of the patients attached. The cancer registry system collates data from innumerable diverse and unrelated bodies: the registrar of deaths in the town hall, the GP, the hospital pathologist. And the patient's identity is the only thing that unifies these disparate pieces of information, allowing the registry to match up tissue diagnosis with symptoms with death certificate and trace the life of one person's cancer.

But it is not as if the information is being broadcast on the nine o'clock news. This is the confidential transfer of information between doctors, which is then held with obsessive security, with the doctors being accountable to the GMC if they treat the information irresponsibly.

It is the most comprehensive national cancer database ever constructed and is the envy of the world. Every doctor in the country is expected to file data to the cancer registries on their patients. But the GMC has given a deadline of October 2001 for the cancer registries to put mechanisms in place for seeking and recording the consent of everyone on their books. Without this consent, doctors will have to stop the flow of information to them. Because this is impractical, cancer registries may have to close.

But if the GMC wants us to, why can't we just ask people for consent? Can it really be so difficult? In some circumstances it may be, and not just for practical reasons. Insisting on consent can systematically skew the data, and give answers that are weaker, or simply wrong.

If you ask people to agree to having their data used in an observational study, some will refuse. That, of course, is the reason you are asking them in the first place. And when they refuse, particularly if certain types of people are consistently more likely to refuse, such as the demented, the psychotic, the homeless, or those embarrassed by their health problems, that skews your data.

This is what medical statisticians call "consent bias". It is important because it can turn your data on its head, render it useless and give the wrong conclusions. In medicine, that costs lives.

There are unscalable practical barriers to seeking consent from the whole population. It remains a Herculean task even if, instead of considering specific cases with patients, we assume that we only want to ask everyone in the country the rather uninformative and vacuous question: "Do you consent to your data being shared, on a confidential basis, for anything we can think of?" There are 60 million of us, after all.

How quickly can you get informed consent, and explain why you want it? Will three minutes tacked on to the first consultation with a GP be enough? A tick-box? Who will keep a central record? What about the patient with Alzheimer's who can't give consent? What if you change your mind? What if you switch GPs? What if you never go to a GP, but just pitch up in accident and emergency one day? It is a far bigger undertaking than the census, and it is hard to imagine it ever happening.

It would be far easier to legislate to protect the work of cancer registries and other organisations concerned with epidemiology and health services research, to ensure that the confidential data they need could never be used for non-medical purposes. That would protect the public and promote new medical knowledge.

As a doctor, I don't expect patients just to tolerate the kind of work that the cancer registries and epidemiologists do: I believe they would be astonished if it weren't done. Epidemiology is the foundation on which all preventive medicine is based. Without it, much would be just anecdote and small drug trials. This move to tie its legs together can only be motivated by some unthinking adherence to an abstract philosophical doctrine about privacy. The point of the principle of confidentiality was to protect the patient from untoward disclosure of information which could be used to his or her detriment. It should not be a moral absolute, at so great a cost.

Is our adherence to principles about privacy so important that we would sagely shave months or years off our life expectancies? I'd rather have another birthday, thanks.

BEN TRAYNOR