



Tay Sachs Disease carrier screening in the Ashkenazi Jewish population

A needs assessment and review of current services



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Tay Sachs Carrier Screening: a review for the National Screening Committee

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Executive Summary and Recommendations

March 2009

This report is a needs assessment and review of screening services for Tay Sachs Disease commissioned by the National Screening Committee and undertaken by a joint project team from Guy's and St Thomas' NHS Foundation Trust Clinical Genetics Service and the PHG Foundation, Cambridge.

Tay Sachs disease (TSD) is an autosomal recessive degenerative neurological disease caused by deficiency of the enzyme hexosaminidase A (HexA). It is one of a small number of conditions that is more common in Jewish populations of Ashkenazi origin (Jews originating from Central or Eastern Europe) than in the overall population. The most common form of the disease is lethal in infancy or early childhood. There is currently no cure or effective treatment. Increased incidence of the disease in Ashkenazi Jews is due to a higher carrier frequency - around 1 in 25 to 1 in 30, compared to a carrier frequency of about 1 in 250 to 1 in 300 in the general population.

Carrier testing can be undertaken either using a biochemical test, which looks for the relevant enzyme activity, or a molecular (DNA) test that aims to detect one of the mutations responsible for the condition. Carriers so detected can reduce their risk of having a child affected by Tay Sachs disease, either by avoiding marriage to another Tay Sachs disease carrier or, if both partners are carriers, opting for prenatal diagnosis and termination of affected pregnancies. In some communities (particularly the Strictly Orthodox community) carrier screening has been used as part of the procedure for arranging marriages, to avoid bringing together carrier couples. The provision of carrier screening to individuals through an NHS programme is important in ensuring that people can decide for themselves whether to be tested and what to do with the results. Carrier screening was approved in 1999 by the National Screening Committee (NSC) and funded as an NHS service. Carrier testing for Tay Sachs disease and several other conditions is also available on a private basis through the international Dor Yeshorim programme and a number of companies.

Tay Sachs disease carrier screening in the UK offers reproductive choice to the Ashkenazi Jewish population and has been welcomed by the Jewish community. Nearly a decade after the introduction of the service within the NHS however, it has been recognised that there is a need to review the service in order to assess whether it meets both the quality standards set by the NSC and the needs of the Ashkenazi Jewish community.

Main findings

The condition

Tay Sachs is a very rare condition that can include classical, late onset and other variant forms. Both classical and late onset forms are more common in Ashkenazi Jews. The typical clinical features for the classical form include a gradual neurological degeneration beginning in the first 3-6 months of life and progressing by the age of two to a vegetative state, cortical blindness and the requirement for continual nursing care, with death by the age of four years.

In Ashkenazi Jews between 94 and 98% of cases are caused by one of three Tay Sachs disease mutations in the *HEXA* gene (+TATC1278, +1IVS12 and G269S). These mutations are less

common as a cause of TSD in Jews of other ethnic origins and non-Jewish populations, which have a much wider set of disease causing mutations.

Before the advent of screening, TSD was 60-100 times more common in Ashkenazi Jews than in the overall population in the US. In the UK, without screening, the small size of the Jewish population (about 2,700 children born each year) means that we would still expect only one birth of an affected child per year. Nevertheless, this condition is of concern to the Jewish community in UK and internationally. There is some limited evidence in our report that, since the availability of carrier testing in the UK, the number of affected children has been approximately halved, with Jewish cases now being fewer than those from the non-Jewish population.

The Jewish population

Screening for Tay Sachs carrier status is focused on the Ashkenazi Jewish population, which is the ethnic origin of about 95% of British Jews. The project team used data from the 2001 census, which was analysed in a report prepared by the Institute for Jewish Policy Research, to provide a description of the population and its distribution in the UK. The size of the Jewish population in the UK is relatively small at about 270,000.

Almost 97% of UK Jews live in England, with major concentrations in certain areas of London and to a lesser extent in Manchester. Our report on distribution showed that the majority could be reached by focussing efforts on a small number of districts in the London region (including parts of Hertfordshire and Essex) and Greater Manchester. For school children, about 30% of all Jewish secondary-school children could be reached by targeting 7 mainstream Jewish secondary schools in London (4), Manchester (1) and Hertfordshire (2). 62% of Jews who are married have a spouse who is also Jewish; this relatively high level of endogamy indicates a continuing need for carrier screening.

The current carrier screening service

In this report we differentiate where possible between screening - the systematic, proactive identification and offer of a test to individuals who are at increased risk, and testing - the provision of a test in response to an individual who seeks advice.

For the screening programme overall, our review has highlighted the fact that there is no routine or readily available information about the service, its activity or its outcomes. Information collected by the project group through ad hoc analysis, surveys and a questionnaire to patients is summarised below.

Tay Sachs disease carrier testing is available through NHS laboratories in London (Guy's Hospital) and Manchester (Willink laboratory). In London, weekly walk-in clinics are run by a genetic counsellor at Guy's Hospital (provided by the Guy's and St Thomas' NHS Foundation Trust Clinical Genetics Service) and the Barnet District General Hospital. Individuals elsewhere in the country can request referral to their regional genetics centre in order to obtain carrier testing. Samples are sent either to the Guy's laboratory or to the Willink.

Outreach community screening sessions are run on a voluntary basis in Jewish schools and community organisations. All samples are sent to Guy's Laboratory for testing provided by the NHS.

In Manchester, community screening sessions are run by voluntary organisations in schools and universities, with samples sent to the Manchester Willink laboratory for testing that is paid for by the voluntary sector.

Carrier testing is also available on a private basis through two UK-based companies, the international Dor Yeshorim organisation, and other private laboratories based outside the UK.

Outreach carrier screening in the Jewish community thus currently depends heavily on the commitment and voluntary work of individuals and charitable organisations from the Jewish community. There has been no NHS support for this activity (except for the laboratory testing itself, and then only in London) and many of the people who have organised outreach community screening sessions over the last 10 years are nearing retirement. The future viability of community screening in Manchester, in particular, is seriously in doubt.

The offer of carrier screening in the antenatal service was reviewed in detail through a survey of antenatal screening coordinators. There were no clear and consistent protocols or pathways for Tay Sachs carrier screening within the antenatal setting; no agreed question for seeking information about Ashkenazi Jewish family origin; no evidence that midwives even in areas with substantial Jewish populations are routinely suggesting screening to Jewish patients; and little or no awareness of local Jewish populations and their uptake of screening. Finally there was confusion about the appropriateness of offering screening in different situations and many coordinators acknowledged that they needed further advice on this issue.

A survey of patients attending the Guy's walk-in clinic corroborated some of these findings and provided further information about the patients who were attending for testing. The ethnic background of individuals and couples attending for testing was predominantly Ashkenazi Jewish. Most individuals were aware of their ethnic origins and able to say how many of their grandparents were Ashkenazi Jewish, suggesting that it would be feasible to ask such a question as a way of identifying individuals who might benefit from carrier screening. It was of concern to find that most people had found out about screening from family, friends or the internet rather than through health care professionals such as GPs or midwives. About one third of the testing was in the antenatal period - however there was no evidence that midwives in areas with substantial Jewish populations are routinely suggesting Tay Sachs disease screening to Jewish patients at the antenatal booking-in appointment, as in the 7 month period of the survey, none of the patients surveyed described this route to testing. Interestingly, just under one fifth of patients attending for testing were aware of known carriers of Tay Sachs disease in their family, or a family history of Tay Sachs disease, indicating that there is a cascade effect occurring naturally which influences who attends for testing. Five of the 7 carriers in the surveyed sample of patients came from this group.

The laboratory testing service

Two laboratories (Guy's Hospital in London and the Manchester Willink) currently test samples for Tay Sachs disease carrier screening. Testing at the Manchester Willink has been unfunded since a one-year research project finished at the end of 1989, and since then has been running at a loss. Dr Alan Cooper has indicated that the Willink intends to stop performing carrier screening tests for Tay Sachs disease when Dr Sybil Simon (who organises the community outreach programme) retires. This would leave Guy's as the only laboratory offering carrier screening tests.

Data collection from laboratory testing needs to be improved. In particular, the Guy's database has not in the past distinguished carrier screening tests from diagnostic tests, or recorded the ethnic origins of those tested, making accurate audit of the programme impossible. There has been no standardisation between the Guy's and Manchester Willink databases. Between 1999 and 2007 the Guy's laboratory performed a total of 26,152 assays on samples from 5,330 individuals, of whom approximately 55% were female and 45% male. Overall, 6.1% of those tested, or 1 in 16, were recorded as carriers of Tay Sachs disease. This carrier frequency is significantly higher than the expected figure of 1 in 25-30 for the Ashkenazi Jewish population again suggesting that the data may contain an appreciable number of results from professional- and patient-initiated cascade testing in families (both Jewish and non-Jewish) in which there was a known carrier.

At the Willink laboratory in Manchester 36 carriers were found out of a total of 462 individuals tested, a carrier frequency of 1 in 12.8. 368 of those tested were of Ashkenazi Jewish origin, but it is not known how many of the carriers were Ashkenazi Jewish. The high carrier frequency suggests that a significant percentage of those tested probably had a family history of Tay Sachs disease.

The testing protocol for Tay Sachs disease carrier screening has not been standardised or fully evaluated. Manchester Willink uses only biochemical testing in leucocytes. Both biochemical testing and mutation testing are carried out at Guy's but the testing protocols have developed in an ad hoc way.

Overall, screening coverage by the NHS programme appears to be very low, possibly as low as 6% of the Jewish population. A major difficulty in obtaining an accurate estimate of screening coverage throughout the whole Ashkenazi population is the lack of data both from private non-UK testing services used by the Association for the Prevention of Jewish Diseases, and from Dor Yeshorim. There is some anecdotal evidence that an increasing proportion of the Jewish population, perhaps particularly in the Strictly Orthodox community, is choosing private testing in preference to the NHS service because the private services offer testing for a wider panel of up to 9 or 10 diseases.

Other models for carrier screening in recessive disorders

The review built on the experiences of genetic counsellor Sara Levene in undertaking international visits to Tay Sachs screening programmes in Israel, Canada, Australia and the United States under the Department of Health-funded Visiting Fellowships in Genetics in Health Care Programme. The Advisory Group also examined the UK Sickle Cell and Thalassaemia screening programme to see if there were valuable learning points.

Tay Sachs disease carrier screening programmes in Israel, Australia, Canada and the US have both strengths and weaknesses that may be relevant in considering options for the UK programme. The Israeli system is universal and systematic but such a system may not be feasible in countries where Jews constitute a much smaller proportion of the population. Antenatal screening programmes (Israel, New York) target the population at a time when screening is directly relevant, but have the disadvantage that additional stress and worry

may be caused at this time, and that they are not acceptable to Strictly Orthodox Jews. Preconception screening (Canada, Australia and Philadelphia) may be less traumatic but is not systematic and is dependent on high-quality education programmes to ensure that test results are understood and recalled correctly. This approach also potentially tests twice as many people as necessary because it is not couple-based.

There is a tendency in most Tay Sachs disease screening programmes to move towards offering molecular-genetic (DNA) Tay Sachs disease carrier testing rather than the biochemical test, mainly because screening can then be readily extended to include other genetic conditions. Pressure for this change is coming largely from the Jewish community itself.

The antenatal carrier screening programmes for haemoglobin disorders in the UK provide another example of carrier screening for recessive conditions. This programme is already well developed, and many aspects of its standards and operating procedures are likely to be relevant to the development of antenatal carrier screening for Tay Sachs disease. However, the target population for these screening programmes is larger and the carrier frequencies higher than for Tay Sachs disease in the Ashkenazi Jewish population. Thus it may not be feasible to achieve a comparably systematic, national carrier screening programme for Tay Sachs disease.

The Family Origin Questionnaire (FOQ) has proved to be an effective tool for systematically identifying couples at high risk of having a child affected by a haemoglobin disorder. The FOQ is the result of a process of extensive consultation and validation involving a range of clinical, community and religious groups; however, it should be possible (after due process) to add a question to ascertain ethnic Jewish origin. Educational initiatives among antenatal health professionals across the country would be essential to ensure understanding of the reason for the question and the referral pathway for women taking up the screening offer.

Evaluation of different methods of laboratory testing

Carrier testing for Tay Sachs disease can be carried out by a biochemical assay of hexosaminidase A (HexA) activity in serum, leucocytes or platelets, and/or by direct DNA testing for one or more of the known causal mutations in the *HEXA* gene. At present the laboratories provide testing by the biochemical assay method in leucocytes, and the Guy's laboratory also provides DNA testing for further characterisation of those identified as carriers and for those whose biochemical test result is inconclusive.

Members of the PHG Foundation team undertook a literature review and carried out modelling to provide an evaluation of the performance of the two testing methods.

Insufficient information is available to enable full evaluation of the biochemical and DNA tests. In particular, the true sensitivity of the DNA test and the true specificity of the biochemical test in leucocytes cannot at present be accurately estimated. DNA tests for Tay Sachs disease are not currently included in the UK Genetic Testing Network's list of tests approved for use in the NHS, and have not yet had Gene Dossiers prepared for them. (Gene Dossiers assess the available evidence regarding a DNA test's analytical validity, clinical validity and clinical utility). Preparation of a Gene Dossier for the Tay Sachs disease mutation test, which is currently being undertaken by Dr Christine Patch, is a useful step.

From the limited data available, the risk that a mutation-negative Ashkenazi Jewish person could still have an affected child lies in the range 1 in 22,000 - 234,000 if their partner is an unscreened Ashkenazi Jew, and in the range 1 in 206,000 - 2,168,000 if their partner is an unscreened non-Jew. The higher residual risk figures relate to a sensitivity of 87.3% for the DNA test in Ashkenazi Jews. However this figure, calculated from the performance of the DNA test in people identified as carriers by use of the biochemical test in screening programmes, is almost certainly an underestimate. A more reliable 'gold standard' for judging the test may be the detection of obligate Tay Sachs carriers; by this criterion, the sensitivity of the DNA test is 98.8%. Nevertheless, if a decision were made to use DNA testing rather than the biochemical test as the initial screening test, it might be prudent to advise both members of a couple to be screened if both are Ashkenazi Jews.

The extremely high sensitivity of the biochemical test (at least 99%) means that the residual risks for those tested by this method are very low. However, this sensitivity comes at the cost of reduced specificity, leading to significant numbers of (probably) false positive results if this test is used as a screening test, and creating additional costs and counselling difficulties.

We have suggested that screening should be offered to those with at least one Ashkenazi Jewish grandparent. This policy would represent a cut-off for screening at a prior risk of 1 in 80 (corresponding to a risk of having an affected child of 1 in 8,640 with an unscreened Ashkenazi Jewish partner, or 1 in 80,000 with an unscreened non-Jewish partner). If mutation testing became the screening test, and a couple was of mixed Ashkenazi Jewish/non-Jewish ancestry, it would be advisable to ensure that the partner with the higher number of Ashkenazi grandparents had been tested.

There are additional issues about the best method of screening for a small group of Jews of North African Sephardi origin. These individuals also have an increased carrier risk, but due to a different set of mutations, meaning that, if mutation testing were to replace biochemical testing, the latter would need to be retained for use in certain circumstances. Similarly whichever test is chosen as the initial screening test, biochemical testing should be used in the antenatal setting to test the partner of any known carrier (whether Jewish or non-Jewish).

Opinion in the Advisory Group was divided on the question of whether the NHS Tay Sachs disease carrier screening programme should continue to offer the biochemical test as the initial screening test, or move towards replacing the biochemical test by a DNA test. The arguments for and against the different protocols are discussed in this Report. It should be kept in mind that the reason for offering screening to the Jewish community is the higher risk that individuals from this community carry one of three specific mutations. Use of a screening test that goes beyond a test for these mutations, therefore, needs careful justification. One important factor about which we have insufficient information is the view of the Jewish population itself. There appears to be a trend, particularly in the Strictly Orthodox community, towards a preference for services that offer DNA carrier testing for a panel of 'Ashkenazi Jewish diseases', rather than Tay Sachs disease alone. It is possible that individuals may prefer to offset the (possibly) lower sensitivity of the DNA test against the perceived advantage of testing for a wider range of conditions. A survey of attitudes on this question would be useful in helping to formulate NHS screening policy.

Recommendations for developing the Tay Sachs disease screening programme

The Advisory Group was charged with the task, following review of the current service, of making recommendations to develop a more systematic screening programme with equity of access. Based on our analysis of need, our review of current services and our evaluation of evidence from the literature and from other services worldwide, we set out here a series of recommendations for the development of the Tay Sachs disease National Screening Programme.

The rarity of the condition and the relatively small size of the Ashkenazi Jewish population in the UK mean that the screening programme should be viewed, not as solving a major public health problem in disease incidence, but as putting in place a service for a community that is identified and sees itself as high risk. Benefits thus arise from the ability of carrier testing to reduce anxiety in Jewish communities for individuals and couples for whom prenatal diagnosis is acceptable and to enable carrier couples to enter into or continue relationships with the option to avoid the birth of an affected child. In some communities (such as the Strictly Orthodox community) where there is a tradition of arranged introductions leading to marriage, carrier testing has also helped to avoid bringing together carrier couples. The provision of carrier screening to single individuals through an NHS programme is important in ensuring that people can decide for themselves whether to be tested and what to do with the results.

Worldwide, communities with high Jewish populations have put carrier screening programmes in place, with high degrees of success in reducing the birth prevalence of Tay Sachs disease in Ashkenazi Jews to below the overall population rate. In 1999 the case was made for a carrier screening programme in the UK and the programme gained formal agreement from the NSC. It was not, therefore, the role of this Advisory Group to revisit whether or not Tay Sachs disease screening fulfilled all the screening criteria, but to review the implementation of the programme against a current assessment of need and evaluation of available services.

Our review has shown that the present programme has built on considerable NHS laboratory resources, professional expertise and voluntary sector experience and commitment. Nevertheless, it is currently running without formal agreements, documentation, channels of accountability, quality assurance and evidence of effectiveness. We identified several important gaps in the service, such as lack of a systematic approach to the offer of screening in antenatal services, and vulnerability of the community and laboratory elements in the Northwest. Most importantly, this means that there is risk of a child with Tay Sachs disease being born to an unscreened couple. Also important is the likelihood of suboptimal services for users and potential users, inequity, poor cost effectiveness and low responsiveness to technological, clinical or patient-desired changes. Putting these aspects of the service in order is not only vital to proper implementation of Tay Sachs disease carrier screening but would also provide a valuable basis for introduction of carrier screening for other conditions for which the Ashkenazi Jewish population is at increased risk, should the NSC wish to do so following formal evaluation of such conditions against screening criteria.

The Advisory Group has made the following recommendations, grouping them into *immediate recommendations* to ensure the continuation of the Programme, *programme recommendations*, to ensure that over time the Programme achieves necessary quality standards and *longer term recommendations*, which includes consideration of the related issue, not addressed by this Report, of including a wider panel of diseases exhibiting higher frequency in the Ashkenazi Jewish population.

Immediate recommendations

Recommendation 1: Continuation of the programme

The Advisory Group recognises the clinical need for Tay Sachs disease carrier screening and the valuable work being undertaken in clinical, laboratory and voluntary services. We recommend that the UK National Screening Programme (NSP) for Tay Sachs disease carrier screening should continue but with renewed commitment to achieving a high quality and equitable service that maximises choice for high risk individuals and couples.

Recommendation 2: Formal constitution of the programme

The Advisory Group recommends that the Tay Sachs disease programme should be formally constituted as with any other screening programme.

Recommendation 3: Linked antenatal and community programmes

The National Screening Programme for Tay Sachs should include antenatal and community carrier screening and these programmes should be linked.

The Tay Sachs screening programme is included in the antenatal section of the National Screening Programme. The principle for carrier screening for pregnancies at high genetic risk in antenatal care is well established through the UK Sickle Cell and Thalassaemia programmes. Like Tay Sachs disease, the antenatal screening programme focuses on identifying carrier couples and offering prenatal testing with the option of termination of pregnancy if the fetus is affected.

Although the antenatal service provides an important safety net for at risk couples, ideally Tay Sachs carriers, and more specifically carrier couples, would be identified before pregnancy so that couples at risk of having an affected child could carefully consider their options before conception. They could be referred to the appropriate genetic services and, when pregnant, could receive early referral (as a high risk pregnancy) to obstetric services for counselling and advice. If they wish they could then proceed to testing, decision making and possible pregnancy termination in a timely and unhurried fashion. Chapter 4 shows that the current provision of Tay Sachs disease screening in UK does indeed include a service for adults prior to conception, including couples, single adults and older school children. This service is also important for individuals who would not consider prenatal diagnosis or termination of pregnancy, but wish to reduce their risk of having an affected child by avoiding marriage to another carrier.

Recommendation 4: Developing antenatal carrier screening

The Advisory Group recommends that consolidation and development of the quality of antenatal screening should be the first priority and that this should be first focussed on Trusts serving large Jewish communities.

For antenatal screening, Chapter 5 shows that there is no effective system for screening Jewish patients. This represents a risk to the NSP of a child with Tay Sachs disease being born to a Jewish carrier couple who had received no information about screening. This is of particular concern in areas where there are large Jewish communities.

Recommendation 5: Securing carrier testing and community carrier screening in the short term

The Advisory Group recommends that lead commissioners for the Programme should urgently put in place interim contractual measures to secure current carrier testing and screening services in the short term, pending further development and integration with the antenatal screening programme. These services include current clinical 'walkin' services (e.g. the Guy's Hospital service), testing provided on request to regional genetics services, and community carrier screening services provided by voluntary organisations; all with associated laboratory elements. This is likely to require provision of some further NHS resources for these services.

For community carrier screening, Chapter 4 shows that NHS walk-in clinics and voluntary organisations such as Jewish Care and the Association for the Prevention of Jewish Diseases provide access to testing through the NHS laboratory testing service, although these services are not running as a coherent screening programme. The Advisory Group notes the potential vulnerability of all these services, and particularly that services in the Northwest are likely to come to an end in 2009 with the retirement of key personnel.

Programme recommendations

Following agreement in principle about the continuation of the Tay Sachs disease Screening Programme as set out in Recommendations 1 - 4, the NSC should set out its programme in detail. In the following sections we make recommendations about some of the key issues that the Programme will need to consider.

Recommendation 6: Target group

The NSP will need to decide who will be the target group for the Programme. The Advisory Group recommends that the Programme should be focussed primarily on the Jewish population of Ashkenazi Jewish origin, with a cut-off for an offer of screening at a prior risk for carrier status of approximately 1 in 80 (the risk of an individual who has one Ashkenazi Jewish grandparent). In practice, individuals with other Jewish origin (eg Sephardi) should not be excluded but are likely to be small in number. This decision might need to be reviewed at a later stage. In the antenatal setting screening should be offered if either partner is Jewish or part-Jewish. If only one partner is Jewish or part-Jewish that partner should be tested first.

Recommendation 7: Target population

The Advisory Group recommends that antenatal carrier screening should be developed first in those London and Manchester Trusts that serve the largest Jewish populations. Community screening should first be offered in mainstream Jewish secondary schools. Information should also be provided in Strictly Orthodox schools (if possible), in private schools that have a large number of Jewish pupils, and through Hillel houses (Jewish Halls of Residence) in universities.

The Advisory Group considered the question of equity and in particular whether it was fair

to develop carrier screening programmes to reach specific populations based in particular locations such as schools or geographical areas, rather than Jews in the population as a whole. Chapter 3 provides a detailed description of the structure of the Jewish population throughout the UK. The Advisory Group noted the relatively small total population and the particular concentration in certain boroughs in and around London and in the Northwest and, for children, in a small number of Jewish schools.

Recommendation 8: Developing an ethnic screening questionnaire for Jewish patients

Work needs to be done in the antenatal setting to develop a tool for systematically identifying Jewish couples and offering them testing. The Advisory Group recommends that work is undertaken in conjunction with the Sickle Cell and Thalassaemia Programme to add a question on Jewish ethnicity to the Family Origin Questionnaire.

Recommendation 9: Integration of antenatal screening into antenatal care

The Tay Sachs disease Programme needs to work with antenatal services to introduce carrier screening into the care pathway for maternity services to ensure a systematic offer of screening at an appropriate stage of pregnancy. The Advisory Group recommends that this should be achieved by the end of the first trimester. The Advisory Group recommends that such work should be led by the antenatal screening coordinators and will require investigation of feasibility, practicality and resource aspects as well as a substantial awareness-raising and educational programme with midwives, health visitors, primary care teams and GPs and the development of high quality information for patients. Initial work should be undertaken in areas of high Jewish populations where there will be greater motivation of health professionals and more immediate outcomes for patients.

Recommendation 10: Development of community screening

Community screening is currently undertaken by voluntary organisations such as Jewish Care and the Association for the Prevention of Jewish Diseases. The Advisory Group recommends that interim measures to secure these services should be followed by development of a contractual agreement that integrates these services with NHS services and includes protocols, standards and reporting arrangements.

Recommendation 11: Choice of initial screening test

The NSP will need to take a major decision on whether the biochemical or the DNA test should be the initial screening test. The NSP should ask laboratory providers and clinical services to look into the advantages and disadvantages of moving to DNA testing as the initial screening test, with retention of the biochemical test where clinically appropriate. In particular, a distinction should be made between the testing that is done to screen potential carriers, and testing for high-risk couples. The Advisory Group recommends that services should consider using DNA testing as the method of choice in the screening programme for:

- 1. All specimens from individuals where there is not a pregnancy.
- 2. All specimens where there is a pregnancy and one or more partners is an Ashkenazi Jew. If both partners are Ashkenazi Jewish, both should be tested.

As a preliminary, laboratories should work with services to agree an optimum panel of mutations to be tested for in the UK and provide practical and literature based evidence for its likely sensitivity in the UK Jewish population.

Biochemical testing should be retained for:

- 1. All specimens where there is a pregnancy and one or more partners is of known or suspected North African Sephardi origin.
- 2. All partners of known carriers (both Jewish and non-Jewish).

Laboratories should develop detailed protocols and standards for the agreed tests.

The debate about the choice of screening test is set out in Chapter 7. Chapter 4 also demonstrates the current lack of information about the laboratory performance of the tests currently in use, and included recommendations for development.

Recommendation 12: Developing information systems

Laboratories and clinical providers should develop a standardised database and IT infrastructure recording essential patient information and able to produce standard reports, to support audit and monitoring requirements of the programme and to link with relevant diagnostic laboratories.

Longer term recommendations

Recommendation 13: Extending carrier screening to other genetic conditions

The Advisory Group recommends that the NSC also consider whether to extend the Tay Sachs disease NSP to include other genetic diseases that are more common in the Ashkenazi Jewish population, following on from the work previously submitted to the NSC in 2006 and which is enclosed as Appendix 8.

Although consideration of this issue was outside of the scope of this report, the view has frequently been expressed within the Jewish community and was endorsed by members of the Advisory Group that screening should be extended to a wider panel of conditions with increased frequency in the Ashkenazi Jewish community.

1 Introduction and background

Introduction

- 1.1 Tay Sachs disease is an autosomal recessive degenerative neurological disease caused by deficiency of the enzyme hexosaminidase A (HexA). The most common form of the disease is lethal in infancy or early childhood. There is no cure or effective treatment.
- 1.2 The carrier frequency for Tay Sachs disease in Ashkenazi Jews (those originating from Central or Eastern Europe) is around 1 in 25 to 1 in 30, compared to a carrier frequency of about 1 in 250 to 1 in 300 in the general population. (See Chapter 3, paragraph 3.7, for further explanation of the different ethnic groups within the Jewish population.) The increased risk of Tay Sachs disease in Ashkenazi Jews is due to a higher frequency of three Tay Sachs disease mutations in this population. A biochemical test for Tay Sachs disease carrier status became available in the 1960s and DNA testing for Tay Sachs disease mutations in the late 1980s. The availability of these tests has enabled Ashkenazi Jews who test positive for carrier status to reduce their risk of having a child affected by Tay Sachs disease, either by avoiding marriage to another Tay Sachs disease carrier or opting for prenatal diagnosis and termination of affected pregnancies.
- 1.3 In the UK, carrier screening for Tay Sachs disease in Ashkenazi Jews was first suggested in 1972 but at that time it was controversial in the Jewish community and carrier testing only became available during the 1980s. In 1999 it was approved by the National Screening Committee (NSC) and funded as an NHS service. Carrier testing for Tay Sachs disease and several other conditions is also available on a private basis through the international Dor Yeshorim programme and a number of companies. Tay Sachs disease screening or testing programmes currently operate in several other countries including Israel, USA, Canada and Australia. Since the advent of carrier testing, the birth prevalence of Tay Sachs disease in Ashkenazi Jewish populations in several countries, including the USA and Israel, has fallen to below the level in the general population.
- 1.4 Tay Sachs disease carrier screening in the UK offers reproductive choice to the Ashkenazi Jewish population and has been welcomed by the Jewish community. Nearly a decade after the introduction of the service within the NHS, however, it has been recognised that there is a need to review the service, in order to assess whether it meets both the quality standards set by the NSC and the needs of the Ashkenazi Jewish community.
- 1.5 This review arose out of a national meeting examining the Tay Sachs screening programme. The meeting concluded that the programme required review to ascertain how it could be made more systematic and provide equity of access across the NHS.

Aims of the Advisory Group

1.6 The aims and objectives of the Advisory Group were as follows:

Aim

To undertake a needs assessment and review of the current service provision for Tay Sachs disease screening in the UK.

Scope

- To include only Tay Sachs disease
- To include screening and testing programmes provided within and outside of the NHS To include England, Wales, Scotland and Northern Ireland
- To include the at-risk population as persons of Ashkenazi Jewish descent

Objectives

A To undertake a needs assessment/service review covering the following main aspects:

1. To engage relevant stakeholders in a consideration of the programme.

2. To provide a basic overview of Tay Sachs disease and its epidemiology in the UK, including cases and numbers of prenatal diagnostic procedures.

3. To define the 'at risk' population and who is included in the term 'of Ashkenazi Jewish descent'.

4. To map out the demographics of the Ashkenazi Jewish population in the UK.

5. To collect data on the numbers of Ashkenazi Jewish adults (and teenagers) in the UK who have previously utilised Tay Sachs disease screening and the routes through which they have accessed this service.

6. To detail the facilities and methods available across the UK for Tay Sachs disease screening, both in the public and private sectors.

7. To describe and evaluate testing technologies.

8. To detail current gaps and deficits in the service and likely emerging gaps in the light of current service trends, and changing needs.

9. To assess different models of screening programmes (including other screening in the UK for other recessive disorders, and Tay Sachs disease screening abroad) and review their appropriateness. Pathways of care for areas of high and low prevalence will be considered, and the different cultural needs of various sections of the population will also be taken into account.

10. To engage with patient and voluntary groups to obtain their views on available services, gaps in the services and the need for service improvement.

11. To suggest a screening algorithm including the stages of screening, sensitivity and specificity of the tests.

B To report to the NSC with recommendations on future actions one year after the commencement of the project.

Method

- 1.7 The work was undertaken by a Project team comprising individuals from Guy's Hospital and the PHG Foundation. Sara Levene, from Guys Hospital, the genetic counsellor to the main Tay Sachs carrier screening service in London, provided the main clinical input and NHS clinical service review information, supported by Christine Patch, the genetic counsellor manager. The PHG Foundation provided Project Management (Corinna Alberg), and analytic support through Hilary Burton (Public Health), Alison Stewart (epidemiology and technology assessment) and Calvin Cheah (data analysis).
- 1.8 An Advisory Group was chaired by Dr Sue Halliday from the Eastern Region Public Health Observatory and included experts on clinical, laboratory and population screening aspects of Tay Sachs disease and representatives from Jewish religious and community organisations involved in Tay Sachs screening. The National Screening Committee was represented on the Advisory Group by the Strategic Director for the National Newborn Screening Programme and more general expertise on screening was provided by the Programme Director for the NHS Sickle Cell and Thalassaemia Programme and two regional antenatal screening coordinators. The full list of Advisory Group Members is given in Appendix 1.
- 1.9 The Project took place between October 2007 and November 2008, during which time the Advisory Group met four times. The meetings were used to
 - agree terms of reference
 - discuss and agree likely sources of data
 - receive expert input from professional and voluntary sectors
 - design review and undertake review of antenatal screening via the screening coordinators
 - review emerging analysis and evidence and discuss further requirements
 - consider and agree final recommendations
 - achieve ownership of the final Report amongst a wide stakeholder group

1.10 The Report is in 8 chapters:

Chapter 1 sets out the background to the project, the terms of reference and methods.

Chapter 2 covers the aetiology, clinical features and epidemiology of Tay Sachs and related diseases, including the mutations associated with Tay Sachs disease in different populations, the estimated birth frequency of the condition in the UK, and the options for screening. This chapter was prepared with the assistance of David Swienton (University of Cambridge Clinical School).

Chapter 3 outlines the demography of the Jewish population in the UK, including its size, geographic distribution, age distribution, distribution of the target populations for screening (sixth form school students, other young adults and pregnant couples), marriage patterns and family structures, and proportions of Ashkenazi Jews and those of other origins.

Chapter 4 describes current carrier testing and screening services for Tay Sachs disease in the UK, including carrier screening sessions in hospital and community settings, antenatal screening, NHS laboratory services, private testing services and the spectrum of test results. We have also analysed the available data on the numbers screened and their area of residence, and attempted to estimate screening coverage within the target population.

Chapter 5 provides detailed information on the current functioning of Tay Sachs disease screening through a survey of antenatal screening co-ordinators and through a questionnaire for patients that provides demographic details of those being currently tested as well as highlighting the experience of patients in accessing services and in particular their pathway to testing. Summary information from a survey of young Jewish people's attitudes to carrier screening is also included in this chapter.

Chapter 6 describes carrier testing and screening initiatives for Tay Sachs disease in other countries and also outlines current carrier screening programmes, in the UK, for other autosomal recessive conditions that are found more frequently among specific ethnic groups.

Chapter 7 describes current testing methods for Tay Sachs disease carrier status and compares the performance of the biochemical and DNA tests. We have also attempted to calculate the residual carrier risks for individuals tested by different methods, and compared these with the carrier risk in the general (non-Jewish) population.

Chapter 8 sets out the Advisory Group's recommendations for developing the Tay Sachs disease carrier screening programme in the UK to ensure that an equitable and effective service is provided.

An Executive Summary summarises the conclusions and recommendations of this Report.

Chapters of the Report were written by Alison Stewart and members of the Project Team and the whole Report was edited by Alison Stewart.

2 Aetiology, clinical description and epidemiology

Aetiology of Tay Sachs disease

- 2.1 Tay Sachs disease is caused by a deficiency of the lysosomal enzyme hexosaminidase A (HexA) (Gravel 1995), which degrades GM2 ganglioside. GM2 ganglioside belongs to a family of gangliosides, glycosphingolipids that contain sialic acid residues, which are components of all animal cell membranes and are particularly abundant in the plasma membranes of neurons (Sonnino 2007). This inborn error of metabolism leads to accumulation of GM2 ganglioside within the lysosomes of nerve cells, causing neuronal dysfunction and death, possibly by interfering with calcium homeostasis (Ginzburg 2004).
- 2.2 HexA is a dimer of two different subunits: an α-subunit encoded by the *HEXA* gene and a β-subunit encoded by the *HEXB* gene (Sandhoff 2001). A related enzyme, HexB, consists of two β-subunits (both encoded by *HEXB*) (Fig 2.1). The subunits are inactive on their own. A protein called GM2 activator protein extracts GM2 ganglioside from the plasma membrane and allows hydrolysis at the active site of HexA.





2.3 Tay Sachs disease is one of a group of disorders called the GM2 gangliosidoses (Table 2.1), themselves part of a larger group of lysosomal storage disorders. The GM2 gangliosidoses have related phenotypes and are all characterised by deficiencies in hexosaminidase enzymes or their activator protein (Kolodny 1993).

Disease	Protein defect	Gene defect
Classical Tay Sachs disease	Loss of HexA protein	HEXA mutations
Late-onset Tay Sachs disease	Reduced HexA activity	HEXA mutations
B1 variant Tay Sachs disease	Loss of HexA activity ¹	HEXA mutations
Sandhoff disease	Loss of HexA and HexB	HEXB mutations
AB variant Tay Sachs disease	Deficiency of GM2 activator protein	GM2A mutations

Table 2.1 The GM2 gangliosidoses

¹ Sulphated form of the substrate only

- 2.4 Tay Sachs disease is an autosomal recessive disorder: all affected individuals carry two mutant *HEXA* alleles, one inherited from each parent. If two parents are both carriers (that is, they are each heterozygous for a disease-causing mutation), there is a 1 in 4 risk of an affected child at each pregnancy. The condition is fully penetrant; that is, any individual carrying two disease-associated mutations will be affected.
- 2.5 Ashkenazi Jews have an increased carrier frequency both for the classical form of Tay Sachs disease, caused by loss of HexA protein, and the late-onset form caused by reduced HexA enzyme activity (Triggs-Raine 2001). The epidemiology of Tay Sachs disease is discussed further below.

Clinical description

2.6 Kolodny (1993) has reviewed the clinical phenotypes of the GM2 gangliosidoses.

Classical Tay Sachs disease

- 2.7 In classical Tay Sachs disease, also known as infantile hexosaminidase A deficiency, affected infants appear normal at birth. At three to six months of age mild motor weakness is noted. The child may startle easily at loud noises, appear listless and fail to follow objects in their visual field. It is usually in this period that parents become concerned about their child's development.
- 2.8 At six to ten months of age the infant fails to achieve new motor milestones and may even regress. For example, head control that may have been gained at four months is lost in this period. Visual attentiveness decreases and abnormal eye movements are seen. Examination of the retina reveals a prominent fovea centralis, the 'cherry red spot', and progressive pallor of the macula. These retinal changes are a key diagnostic sign of Tay Sachs disease.

- 2.9 After ten months progression of the disease is rapid. Voluntary movements and vocalisation cease and muscle tone and tendon reflexes increase. By eighteen months symmetrical myoclonic jerking develops and seizures start to occur and become progressively worse.
- 2.10 By the age of two the child is typically in a vegetative state, cortically blind and requires constant nursing care. Death usually occurs by age four and is most often due to aspiration bronchopneumonia.

Late onset Tay Sachs disease

2.11 The late onset form of the disease, also known as adult onset or chronic GM2 gangliosidosis, affects people in their adolescent years. Subtle motor or developmental deficits may be noticed in childhood but these may be thought of as within normal limits. Presentation is normally in adolescence, with difficulty in climbing stairs and rising from a chair. Later there is difficulty with walking and unsteadiness develops, leading to falls. Psychiatric problems can occur and range from anxiety to frank psychosis. Unlike classical Tay Sachs disease, there are no changes in the retina and vision is preserved. Patients may be able to walk, with aids, into their 40s or 50s. Life expectancy is normal for most adults with late onset Tay Sachs disease.

B1 variant

2.12 B1 variant GM2 gangliosidosis, caused by mutations in the *HEXA* gene that reduce its activity towards some substrates, usually presents at around 3-7 years of age. The rate of deterioration is variable, with some patients dying within a few years whereas some may survive for five years or more. Cherry red spots are often not found (Gravel 1995).

Sandhoff disease

2.13 Sandhoff disease is caused by mutations in the *HEXB* gene. Because this gene encodes the B-subunit of both HexA and HexB, affected individuals lack both of these enzymes. Sandhoff disease has three forms relating to age of onset: a late infantile form very similar to classical Tay Sachs disease, a juvenile form starting after one year of age, and a late onset form which follows a similar clinical course to late-onset Tay Sachs disease. Macular cherry red spots are also seen. Unlike in Tay Sachs disease, there may be non-neurogenic tissue involvement such as hepatosplenomegaly (Gravel 1995).

AB variant

2.14 The final GM2 gangliosidosis, the AB variant, is slightly different from the other disorders in that the structure of the hexosaminidase A and B enzymes is intact. People with this variant have a deficiency in the GM2 activator protein necessary for the activation of hexosaminidase A. The few reports of this disease suggest that it is clinically identical to classical Tay Sachs disease although affected individuals have a relative microcephaly in the second year.

Epidemiology

- 2.15 Estimates for the birth prevalence of Tay Sachs disease (live births) vary. Estimates of 0.45 per 100,000 and 0.41 per 100,000 have been published for the populations of Australia and The Netherlands respectively, while for Northern Portugal an estimate of 3.13 per 100,000 has been reported (Meikle 1999, Poorthuis 1999, Pinto 2004). Assuming that the overall UK population is similar to that of Australia or the Netherlands, and given that there are approximately 650,000 live births per year in England and Wales (National Statistics Online), the predicted number of affected children born each year in England and Wales is between two and three. Responses to a questionnaire sent to all biochemical genetics laboratories in the UK (i.e. including Scotland and Northern Ireland) indicate that 29 affected UK-born children were diagnosed with Tay Sachs disease in the 9 years from 1999 to 2007; that is, approximately 3 per year. As would be expected for an autosomal recessive condition, there is no gender bias. The carrier frequency for Tay Sachs disease in the general population has been estimated at approximately 1 in 250.
- 2.16 Tay Sachs disease is relatively more common in certain ethnic groups. For example, in Ashkenazi Jews, estimates of the carrier frequency range from 1 in 25 to 1 in 30 (Aronson 1962, Myerowitz 1997). These carrier frequencies correspond to a risk of 1 in 2500-3600 that a couple from this population would have an affected child.
- 2.17 More recently it has been found that the carrier frequency of Tay Sachs disease is also elevated in some other ethnic groups: French Canadians, Louisiana Cajuns, Pennsylvania Dutch and Old Order Amish (Akerman 1997, Kaback 2006). In Moroccan Jews, who are a subgroup of Sephardi Jews, a Tay Sachs disease carrier frequency of 1 in 60 has been reported (Navon 1991). In other Sephardis, the carrier frequency is not elevated above that of the non-Jewish population.
- 2.18 Before the advent of prenatal diagnosis and carrier testing, the birth prevalence of Tay Sachs disease was 60 to 100 times higher in the Ashkenazi Jewish population of the US than in the overall population (Kaback 1993, Kaback 2006). In the UK, no accurate data are available for the number of Ashkenazi Jewish children diagnosed with the condition; however, based on a carrier frequency of 1 in 27, without any intervention a birth prevalence of 34 per 100,000 (approximately 1 in 3,000) would be expected. As approximately 2,700 Jewish children are born each year (see Chapter 3), the expected number of affected births would be about 1 per year; that is, about one-third of the affected children born each year would be expected to be Jewish.
- 2.19 The first biochemical tests for Tay Sachs disease relied on assaying the activity of the HexA enzyme and were developed in the late 1960s (Okada 1969, O'Brien 1970). These tests not only enabled diagnosis of the disease but also testing to determine whether a person was a carrier (as carriers have reduced enzyme activity). Between 1970 and 1985, as a result of the reproductive choice offered by Tay Sachs disease testing and screening, the birth prevalence of Tay Sachs disease in the Jewish population in the US and Canada fell from around 55 cases per year to around 5 cases per year, a reduction of over 90% (Kaback 2001). In the US, it has been documented that the birth prevalence of the disease is now higher in the non-Jewish than the Jewish population (Kaback 2001). In the UK, only the Manchester Willink hospital has data on the number of affected

children who are Jewish: of the 15 affected children diagnosed in the Willink between 1999 and 2007, 2 were Jewish. If it is assumed that a similar proportion of the affected children diagnosed in other laboratories were also Jewish, the number of affected Jewish children diagnosed between 1999 and 2007 would be about 4, compared to the expected number of 9 (assuming that affected children are diagnosed very soon after birth). This very imprecise estimate suggests that there has been a reduction of about 55% in the birth prevalence for the condition in the Jewish population.

2.20 The reason for the higher Tay Sachs disease carrier frequency in some ethnic groups is unknown but the most likely explanation is genetic drift or a founder effect (Frisch 2004, Risch 2003). It is thought that the current population of Ashkenazi Jews is descended from a much smaller ancestral population and that this genetic 'bottleneck' has led to increased carrier rates for several deleterious recessive alleles, including those causing Gaucher disease, familial dysautonomia, cystic fibrosis, Fanconi anaemia and Canavan disease as well as Tay Sachs disease.

Mutations causing Tay Sachs disease

2.21 The development of molecular genetic technology, beginning in the late 1970s, allowed the identification of specific DNA mutations associated with Tay Sachs disease and the related GM2 gangliosidoses. It became apparent that some mutations were more common than others and that some were associated with specific ethnic groups. Table 2.2 lists the most common *HEXA* mutations identified in Ashkenazi Jewish (AJ) and non-Jewish populations.

Mutations		Heterozygotes Obligate Tay Sachs				
Mulations	Allele status	disease car	riers ¹	Screenin	g²	
detected		AJ	Non-Jewish	AJ	Non- Jewish	
+TATC1278	Null	81%	32%	80%	8%	
+1 IVS12	Null	15%	0	9 %	0	
+1 IVS9	Null	0	14% ³	0	10%	
G269S	Adult onset	2%	0	3%	5%	
R247W	Pseudodeficiency	0	0	2%	32%	
R249W	Pseudodeficiency	0	0	0	4%	
All of the above	N/A	98%	46%	94%	59%	

Table 2.2 *HEXA* mutations in Ashkenazi Jewish and non-Jewish populations (from Kaback 2006)

¹ Parents of a child with Tay Sachs disease.

² Individuals identified as heterozygotes in tests of HexA activity

³ A much higher frequency of 42% has been reported for the +11VS9 mutation in the UK non-Jewish population (Landels 1993)

- 2.22 The first *HEXA* mutations to be studied were those in Ashkenazi Jewish populations (reviewed in Triggs-Raine 2001). The most common mutation is a 4-bp (base pair) insertion in exon 11 (+TATC1278) which leads to a premature stop codon. The second most common mutation, a G to C transversion in the donor splice site of intron 12 (+1IVS12), leads to abnormal mRNA splicing. Both of these are null mutations; that is, no functional HexA protein product is formed. The final mutation is a missense mutation (805G \rightarrow A, Gly269Ser or G269S), which causes the resulting enzyme to have a reduced activity. The first two mutations cause the classical form of Tay Sachs disease whereas the third, either in the homozygous state or in compound heterozygosity with one of the null variants, causes the late-onset form of the disease.
- 2.23 Seven mutations have been found to account for about 93.5% of biochemically defined carriers of Moroccan Sephardi origin (Kaufman 1997). Of these, the three most common (accounting for about 88% of biochemically defined carriers) are a 3 bp deletion in exon 8 of the *HEXA* gene (910 del3), a G to A transition that results in substitution of Arg170 by glutamine (R170Q), and an A to G mutation in the second nucleotide of the 3' splice site of intron 5 (IVS5-2 (A \rightarrow G)). All of these mutations cause severe, early-onset disease.
- 2.24 Specific mutations associated with Tay Sachs disease in other ethnic groups, including French Canadians and Louisiana Cajuns, have also been reported (reviewed by Triggs-Raine 2001, Kaback 2006).
- 2.25 In non-Jewish populations, the most common *HEXA* mutations are the null allele, +TATC1278, and a second null allele, +1IVS9, which also causes severe early-onset disease (Kaback 2006). The latter allele appears to be absent in the Jewish population (Risch 2001). A review by Kaback (2006) reports that 14% of obligate Tay Sachs disease carriers from the non-Jewish population carry the +1IVS9 allele but a study by Landels (2003) puts the figure at 42% for non-Jewish Tay Sachs disease carriers in the UK population.
- 2.26 Since the first *HEXA* mutations were described in the late 1980s, many more mutations have been found. By 2001, 74 *HEXA* mutations had been reported (Triggs-Raine 2001) and the figure may now exceed 100 (Kaback 2006). Multiple mutations in the *HEXB* and *GM2A* genes, causing other GM2 gangliosidoses, have also been described (Triggs-Raine 2001). None of these mutations, or the associated diseases, shows an elevated frequency in the Ashkenazi Jewish population.
- 2.27 Correlating genotype with phenotype is possible with some of the more common *HEXA* mutations but becomes increasingly difficult when the mutations are rare. Many of the reported mutations are functionally null, preventing the formation of the HexA protein, and are therefore predicted to cause the classical form of Tay Sachs disease. Others are associated with sub-acute and chronic forms of the disease, which have a more variable phenotype and vary markedly in age of onset and severity.

Pseudodeficiency alleles

2.28 Two HEXA mutations (739C → T, Arg247Trp and 745C → T, Arg249Trp) have been found that have no clinical effect but cause reduced hexosaminidase A activity with

the synthetic substrate that is used in HexA biochemical testing. These mutations are known as pseudodeficiency alleles (Triggs-Raine 1992, Kaback 1993). Pseudodeficiency alleles lead to false-positive results in carrier testing by the biochemical method. In the general population, about 36% of people identified as Tay Sachs disease carriers by the biochemical assay are actually carriers of pseudodeficiency alleles (Kaback 2006). In the Ashkenazi Jewish population, however, the figure is only 2%.

Carrier testing and screening options

- 2.29 Tay Sachs disease is a serious condition that causes substantial suffering both to affected individuals and to their families. As no effective treatment is available, and the classical form of the disease is fatal in infancy or early childhood, many people feel that it is appropriate for carrier couples to have the option of avoiding the birth of an affected child, either by avoiding marriage to another carrier or by prenatal diagnosis and termination of affected pregnancies. In order to be able to exercise either of these options, individuals must be able to find out whether they are carriers.
- 2.30 Because Tay Sachs disease is very rare in the overall population, whole-population carrier screening for this condition is not appropriate. However, the carrier frequency for Tay Sachs disease in Ashkenazi Jews (approximately 1 in 25-30) is similar to the carrier frequency for cystic fibrosis in populations of North-western European origin; autosomal recessive conditions with carrier frequencies of this magnitude are considered potentially suitable candidates for population screening programmes.
- 2.31 Carrier screening may be offered to individuals at any stage of life, or to couples in the antenatal period. Screening in childhood, although possible, is not generally considered ethically acceptable because the child would not be able to provide valid consent to screening and might prefer not to know his or her carrier status. Screening is in general only justified where there is a health benefit to the child. British Society for Human Genetics guidelines (1994) state that it is 'unlikely to be justifiable to test children for carrier status for recessive disorders if the only reason is to enable reproductive choice in the future'.
- 2.32 Carrier screening in late adolescence or early adulthood, generally before the individual has embarked on a partnership (often referred to an preconception screening), enables those who find they are carriers to use this information, if they marry another carrier, to consider their options carefully either before or in early pregnancy.
- 2.33 In the Strictly Orthodox community (see Chapter 3, paragraph 3.6, for a summary of the religious denominations within Judaism), marriages traditionally arise out of arranged introductions, which are organised by the parents of the young people and a professional matchmaker. A family history of illness, particularly a genetic disease, can be a barrier to marriage. In addition, Strictly Orthodox Jews are opposed to abortion on religious grounds and therefore do not regard prenatal diagnosis as an option for avoiding the birth of an affected child. In order to avoid genetic disorders for which carrier testing is available, this population prefers to avoid arranging an introduction between two carriers of the same disorder.

- 2.34 Even though there is no disease risk associated with carrier status as long as the other partner is not a carrier, some in the Strictly Orthodox community are concerned that carrier status will be perceived as undesirable by the family of a potential spouse. As a result, an alternative service was established in the 1980s. The principle of the international programme known as Dor Yeshorim ('Righteous Birth') is that genetic test results should be confidential, including from the client themselves. Dor Yeshorim offers testing to people in their late teens, before arranged marriage introductions. A code or PIN number is assigned to each blood sample, and the test results are stored in the Dor Yeshorim database attached only to that number. The clients (or their parents) are given only the code number, not the test result. At the time of arranging introductions, the code numbers of both parties are given to Dor Yeshorim by the matchmaker or an intermediary. Dor Yeshorim will give a result of either 'compatible' or 'incompatible'. If a potential couple would be incompatible, the introduction is not pursued. In this way, carriers can be introduced to non-carriers without any associated stigma (because they are only told that they are 'compatible') and marriages between two carriers can be avoided. When Dor Yeshorim began, it only tested for Tay Sachs disease. However, in recent years other tests have been added to the service, so that now up to 10 genetic carrier tests are offered.
- 2.35 Some in the Strictly Orthodox community find this service meets their needs well. However, there are others who question the ethics of keeping test results confidential from the client. For those who wish to know their results or who disagree with the principle of Dor Yeshorim, an organisation known as the Association for the Prevention of Jewish Diseases was set up in the Strictly Orthodox population of North London, to offer Tay Sachs screening through the NHS. This organisation also uses private laboratories which, like Dor Yeshorim, offer testing for several other genetic conditions in addition to Tay Sachs disease. People who access screening through the Association for the Prevention of Jewish Diseases receive their own test result. A degree of competition, or even conflict, has arisen from time to time between Dor Yeshorim and the Association for the Prevention of Jewish Diseases.
- 2.36 Jews other than those in the Strictly Orthodox community may also opt for preconception carrier testing for Tay Sachs disease. However, the information is generally only put to use once a couple has married and embarked on a pregnancy. An alternative option is to delay testing until the antenatal period. Carrier screening at this time has the advantage that individuals receive results when the information is directly relevant to them. It also avoids the danger that results are forgotten or not remembered correctly. Testing can be either sequential or simultaneous. In sequential testing, one member of the couple is tested first and only if (s)he is a carrier is the other member tested. This approach has the advantage that it reduces the number of tests that need to be performed. However, a disadvantage is that the time taken for sequential testing can mean that couples are faced with difficult choices about termination at a relatively late stage in pregnancy.
- 2.37 The NHS Tay Sachs carrier screening programme offers both preconception and antenatal carrier screening. The current NHS service is discussed in more detail in Chapter 4. All those tested are given their results. The NHS programme at present covers only Tay Sachs disease. However, there is anecdotal evidence that some in the Jewish population would prefer to have information on their carrier status for a wider range of diseases and, for that reason, are preferring to use private testing services

that carry out DNA carrier tests for up to 9 genetic conditions for which Jews are at increased risk. This issue is discussed further in Chapter 7.

Conclusions

- 2.38 Tay Sachs disease is a serious recessive genetic disease that is currently untreatable and usually fatal in early childhood. In the UK, couples who are at risk of having a child affected by a serious genetic condition are offered the opportunity to use prenatal diagnosis and termination, if they wish, to avoid the birth of an affected child.
- 2.39 Tay Sachs disease is rare in the general UK population and therefore not considered a suitable candidate for population carrier screening. However, the carrier frequency is 10 times higher in the Ashkenazi Jewish population (approximately 1 in 25-30), because of the presence of three known founder mutations. Carrier screening is therefore feasible within this population. Both biochemical and molecular-genetic tests for carrier status are available and carrier testing or screening programmes have been in operation in several countries since the 1980s.
- 2.40 Without intervention, one-third of the Tay Sachs disease births in the UK population would be expected to be within the Ashkenazi Jewish population, with one affected child being born in this community every year. The estimated current birth prevalence of Tay Sachs disease in the UK Ashkenazi Jewish population suggests that the birth prevalence of the condition has fallen by about 50% in the UK since carrier testing became available during the 1980s. Although this figure suggests that the Ashkenazi Jewish community is taking up the option of reproductive choice for Tay Sachs disease, it may also indicate that the offer of carrier screening is not effectively reaching all of the target population.

3 Demography of the UK Jewish population

Introduction

- 3.1 The rationale for carrier screening for Tay Sachs disease in the UK is the higher carrier frequency for this condition in the Ashkenazi Jewish population. In order to ensure that the offer of carrier screening for Tay Sachs disease reaches all those who might benefit, it is important to have as accurate a picture as possible of the size of the Jewish population in the UK and its geographical distribution.
- 3.2 The main target group for preconception screening is teenagers and young adults between the ages of 16 and 25. For this group, information about the age structure of the Jewish population, and the numbers and proportions of Jewish children attending Jewish schools, is relevant.
- 3.3 The number of Jewish babies born each year gives an upper estimate of the size of the target group for antenatal carrier screening. However, some of these couples will already have taken up the option of preconception screening. This is particularly likely to be the case for couples from the Strictly Orthodox community, who are opposed to abortion and may have used either the Dor Yeshorim screening service or the NHS service as part of their procedure for arranging marriages.
- 3.4 In addition to Ashkenazi Jews, Sephardi Jews of Moroccan origin also have an elevated carrier frequency for Tay Sachs disease. In other Sephardis, the risk of Tay Sachs disease is no higher than in the general (non-Jewish) population. Ideally, therefore, estimates should also be made of the extent of non-Jewish and Sephardi Jewish (including Moroccan Sephardi) admixture in the Ashkenazi Jewish population, and of the proportions of endogamous and exogamous marriages in the Jewish community.

Definitions of Jewishness

- 3.5 There is an on-going debate in the Jewish community about who is a Jew, and different Jewish religious authorities have differing views on this. According to Jewish law, a person is a Jew if his or her mother is or was a Jew. This is the most widely accepted religious definition.
- 3.6 There are several different religious subdivisions within Judaism.
 - Strictly Orthodox Jews (also known as ultra-Orthodox or Haredim) believe that the Torah and associated Jewish laws are divine and immutable; they adhere strictly to traditional beliefs and practices including dietary laws, modes of dress, separate worship for men and women, and segregation from non-Jewish society.
 - Central (also known as Mainstream or Modern) Orthodox Jews believe that it is possible to maintain many or all of the Jewish customs, laws and ritual observances, while engaging fully with the modern secular and scientific world.
 - The Reform and Liberal movements are both branches of Progressive Judaism, which is more socially liberal than Orthodox Judaism, takes a less strict approach to dietary and other laws, and believes in full and equal participation of men and women in religious life.
 - The Conservative or Masorti Jewish movement attempts to find a middle ground between Orthodox and Liberal/Reform Judaism.

The different religious groups within Judaism are relevant to this report as they take different stances on social and ethical issues such as prenatal diagnosis and abortion and tend, as a consequence, to vary in their attitude to carrier screening for genetic diseases. Strictly Orthodox Jews oppose abortion and therefore believe in using carrier screening only as part of the choice of marriage partners. Mainstream Orthodox Jews, Masorti Jews and Progressive (Liberal or Reform) Jews may regard abortion as acceptable in order to enable a couple to avoid the birth of a severely disabled child.

- 3.7 As well as religious subgroups, there are also different ethnic subgroups of Jews. As discussed in Chapter 2, these different groups have different carrier frequencies for Tay Sachs disease and certain other genetic conditions.
 - Ashkenazi Jews are defined as Jews originating in Central and Eastern Europe, mainly from Germany, Poland and Russia.
 - Sephardi Jews are descended from Jews who were expelled from Spain and Portugal in the 15th century and settled in parts of the Ottoman empire (modern Turkey) and North Africa. Some Sephardis in modern Spain, Italy and Greece descend from Jews who converted to Christianity and later re-converted to Judaism. Historically, Sephardi Jews had separate languages from Ashkenazi Jews. They attend different synagogues and have different customs, liturgy and Hebrew pronunciation (Hebrew being the liturgical language).
 - Mizrahi Jews, who usually also practise Sephardi customs and forms of worship, originate from the countries of the Middle East and North Africa.
- 3.8 The legacy of the holocaust and the migrations of Jewish populations around the world, particularly during the last century, have dispersed the different ethnic groups of Jews from their traditional homelands. The vast majority of Ashkenazi Jews no longer live in Central or Eastern Europe but in the US, Israel, Western Europe, South Africa and Australia. Many Sephardi and Mizrahi Jews (including most Moroccan Sephardis) have migrated to Israel. Approximately 80% of Jews worldwide are of Ashkenazi origin. However, as a result of intermarriage and migration the boundaries between the different ethnic groups are becoming less distinct.
- 3.9 For the purposes of this review, an Ashkenazi Jew is a Jewish person who defines him or herself as Ashkenazi based on one or more Jewish grandparents having family origins in central or Eastern Europe.

The size of the Jewish population

- 3.10 The 2001 census results provide the only systematic information on the Jewish population of the UK. The data from the 2001 census have been analysed in a recent report prepared by the Institute for Jewish Policy Research (JPR, 2007). The data derive from the Census in the UK carried out by the Office of National Statistics for England and Wales, the General Register Office for Scotland and the Northern Ireland Statistics and Research Agency.
- 3.11 The total number of people who identified themselves as belonging to the Jewish religion was 266,740. However this figure does not include Jews who identify by ethnicity only in England and Wales. Nor does it include people in Scotland or Northern Ireland who identified themselves as Jewish by upbringing but held no current religion.

(This question was not asked in England and Wales). These broader definitions brought the figure to 270,499.

3.12 The census data rely entirely on self-identification. They provide no information on descent (that is, whether an individual's parents and/or grandparents were Jewish) and do not distinguish between Ashkenazi and Sephardi Jews. The census question on religion was voluntary and it is possible that a significant number of Jewish people may have decided not to identify themselves as being Jewish, perhaps because of fears that the information could be used in a discriminatory manner. Both the Strictly Orthodox community and the most secular Jews may be particularly under-represented in the data. The JPR report suggests that the census data underestimate the Jewish population by about 10%.

Geographical distribution

- 3.13 According to the 2001 census, 96.7% of British Jews live in England, 2.5% in Scotland and 0.8% in Wales. Only about 365 Jews live in Northern Ireland. Although Jews are dispersed throughout Britain, the population tends to be clustered in a small number of predominantly urban areas: 78% of the Jewish population lives in 41 of the 408 local authority districts (Table 3.1), and 52% in just 10 districts. Of these 10 districts, 7 are within Greater London (Barnet, Redbridge, Harrow, Camden, Hackney, Westminster and Brent), one in South Hertfordshire (Hertsmere), one in Greater Manchester (Bury) and one in Leeds. The clustering of the Jewish population is even more evident at the level of individual wards, with half of all Jews in England and Wales living in 79 out of 8,800 wards, and quarter of the Jewish population living in just 20 wards.
- 3.14 The major centres of the Jewish population are in the London region (64% of the total Jewish population); Greater Manchester (8.4%); and Leeds (3.1%).

Greater London, Hertfordshire and Essex

- 3.15 In Greater London, almost a quarter of British Jews live in the two London boroughs of Barnet and Redbridge, with Barnet accounting for 17.5% of the UK's Jewish population. Over 5% of the population is Jewish in five London boroughs: Barnet (14.8%), Harrow (6.3%), Redbridge (6.2%), Camden (5.6%) and Hackney (5.3%) These figures do not give an entirely accurate reflection of the concentration of Jewish communities, as many Jewish communities straddle local authority boundaries but perceive themselves as being part of the same community.
- 3.16 Of the 79 wards that account for half the Jewish population of England and Wales, 64 are in London (41 in Outer London, 16 in Inner London and 7 in adjacent areas). Only 4 of the 663 wards in Greater London have no Jewish residents.
- 3.17 Significant numbers of Jews also live in parts of Hertfordshire and Essex that are contiguous with centres of Jewish population in the North and Northeast of London. In particular, Hertsmere (South Hertfordshire), which borders Barnet to the north, is an area in which many Jews have settled in recent years. In Hertsmere, Jews comprise 11.3% of the population. In Southwest Essex, the Epping Forest local authority district, which neighbours Redbridge in Outer London, also has a substantial Jewish population.

Table 3.1 Clustering of the UK Jewish population in local authority districts (data from the 2001 census)

The Table lists local authority districts in which the Jewish population accounts for at least 0.5% of the total population of the district, or at least 0.8% of the total Jewish population of the UK. These cut-off percentages were chosen in order to pick up any districts in which there was either a fairly large total Jewish population (more than 1,000 people), and/or a Jewish population that accounts for an appreciable fraction of the total population. (Source: ONS Table KS07, GROS Table KS07)

Region or county	Local	Jewish	% of total	% of the
	authority	population	Jewish	district
	district	in 2001	population	population
				that is
				Jewish
Greater London	Barnet	46,685	17.5	14.8
	Redbridge	14,795	5.55	6.2
	Harrow	13,112	4.92	6.3
	Camden	11,153	4.18	5.6
	Hackney	10,730	4.02	5.3
	Westminster	7,736	2.90	4.3
	City of London	226	0.08	3.1
	Brent	6,464	2.42	2.5
	Haringey	5,724	2.15	2.6
	Enfield	5,336	2.00	2.0
	Kensington and Chelsea	3,548	1.33	2.2
	Hillingdon	1,971	0.74	0.8
	Islington	1,849	0.69	1.1
	Tower Hamlets	1,833	0.69	0.9
	Wandsworth	1,689	0.63	0.6
	Richmond	1,576	0.59	0.9
	Ealing	1,487	0.56	0.5
	Waltham Forest	1,440	0.54	0.7
	Hammersmith & Fulham	1,312	0.49	0.7
	Lambeth	1,212	0.45	0.5
	Havering	1,128	0.42	0.5
Hertfordshire	Hertsmere	10,709	4.01	11.3
	Three Rivers	1,728	0.65	2.1
	St Albans	1,187	0.45	0.9
	Watford	893	0.33	1.1

Essex	Epping Forest	3,715	1.39	3.0
	Southend on Sea	2,726	0.85	1.7
Sussex	Brighton and Hove	3,353	1.26	1.4
Greater Manchester	Bury	8,923	3.35	4.9
	Salford	5,179	1.94	2.4
	Manchester	3,079	1.15	0.8
	Trafford	2,314	0.87	1.1
	Stockport	1,654	0.62	0.6
West Yorkshire	Leeds	8,265	3.09	1.2
Merseyside	Liverpool	2,699	1.01	0.6
Tyne and Wear	Gateshead	1,562	0.59	0.8
West Midlands	Birmingham	2,343	0.88	0.24
South West	Bournemouth	1,666	0.62	1.0
Oxfordshire	Oxford	1,098	0.41	0.8
Cambridgeshire	Cambridge	846	0.32	0.8
Total for 40 districts (England)		205,883	77.18	
Scotland	East Renfrewshire	3126	1.17	3.50
Total (England and Scotland)		209,009	78.36	

The Jewish population outside London

3.18 Outside London, 21,733 Jewish people live in Greater Manchester: 8.4% of the Jewish population of England and Wales. 97% of Greater Manchester's Jewish population lives in 5 local authority districts: Bury, Salford, Manchester, Trafford and Stockport. Two thirds live in 10 contiguous wards. In Leeds there is a similar concentration of the Jewish community, with three-quarters of the Jewish population living in just 3 wards. In Scotland, over 75% of Jews live in just three districts, with almost half in East Renfrewshire near Glasgow.

Migration patterns

3.19 As is the case for the general population, the Jewish population is geographically fairly stable, with only 12% reporting a change of address in the year before the 2001 census. However, among those who did move, the census data report a general trend away from the northern cities and towards London and South Hertfordshire. A relatively high percentage of Jewish people who had moved in the previous year had come from outside the UK (12.4% compared to 0.7% for the general population). Many of these people moved into Jewish communities in inner and outer London; almost half of the Jewish population in Kensington and Chelsea was born outside the UK.

Age structure of the Jewish population

3.20 The Jewish population tends to be significantly older than the general population. For example, the median age of females is 38.1 years for the general population but 44.3 for Jewish females. Table 3.2 shows the numbers of individuals in a range of age bands, as recorded by the 2001 census.

Table 3.2 Age structure of the Jewish population

Data from Table S149, 2001 census

Age band	Number	% of total
0-4	13,858	5.33
5-7	8,405	3.23
8-9	5,686	2.19
10-14	13,943	5.36
15	2,685	1.03
16-17	5,600	2.15
18-19	5,142	1.98
20-24	14,746	5.67
25-29	15,820	6.09
30-34	16,203	6.23
35-39	16,912	6.51
40-44	16,640	6.40
45-49	16,810	6.47
50-54	20,157	7.75
55-59	16,460	6.33
60-64	13,004	5.00
65-69	12,557	4.83
70-74	12,818	4.93
75-79	12,164	4.68
80-84	9,333	3.59
85-89	7,005	2.69
90 and over	3,978	1.53
Total	259,927	100

- 3.21 There are more females than males for each of the age bands above the age of 14. The age structure of the population varies in different local authority areas. For example, the local authority district of Barnet has a greater proportion of older people than Hertsmere (South Hertfordshire), which has a higher proportion of adults aged 35-45 and young children. This trend reflects the general pattern of migration of young Jewish adults with families outwards from the 'traditional' Jewish areas of North and Northwest London, and into the neighbouring districts of South Hertfordshire. Jewish families have also migrated into the South Hertfordshire area from the regions.
- 3.22 In several regional cities the Jewish population tends to be elderly. In Leeds for example, 16% of Jews are over the age of 75 and only 12.2% under the age of 14; the corresponding proportions are 12.4% and 16.1% for the total Jewish population. Ageing Jewish populations are also evident in Bury, Liverpool, Bournemouth and Brighton.
- 3.23 In some areas, a decline in the proportion of young Jewish people has been offset by the contribution of the Strictly Orthodox population, which has high fertility rates: 22% of the Jewish population of Greater Manchester is aged 14 and younger, and in Salford which has a large Strictly Orthodox population, the figure is 35.4%. The presence of a Strictly Orthodox community has had a similar effect in the London borough of Hackney, where 34.4% of the Jewish population is under the age of 14. A growing scarcity of suitable housing in Hackney has also led to movement of some Orthodox families into Barnet. With its young age profile, the Orthodox community has considerable potential for growth in future years.

The school-age population

3.24 A 2007 report by the Community Policy Research Group (CPRG) of the Board of Deputies of British Jews estimates the Jewish school-age population by area in 2005/06, extrapolating from the figures in the 2001 census (Table 3.3).

Region	Primary (age 4-10)	Secondary (age 11-17)	Total
London region	13,801	13,186	26,987
Manchester	2,205	2,319	4,524
Leeds	434	537	971
Gateshead	294	254	548
Glasgow	219	276	495
Liverpool	156	195	351
Southend on Sea	141	162	303
Birmingham	127	150	277
Brighton & Hove	121	143	264
Rest of Britain	2,239	2,750	4,989
Great Britain	19,737	19,972	39,709

Table 3.3 Estimated Jewish school-age population by area, 2005/06

3.25 About 27,000 of these children, representing about two-thirds of the total school-age

Jewish population of Britain, are estimated to be enrolled in Jewish schools (Table 3.4). 73% of these children attend schools in the London region, including neighbouring districts of Hertfordshire and Essex. Of the remainder, around 70% attend schools in Greater Manchester.

Region	Number of schools			Number of Jewish pupils				
	Mainstream Strictly Mainstream		Mainstream Strictly					
	Ortho-	Plural-	Ortho-	Total	Ortho-	Plural-	orthodox	Total
	dox	ist	dox		dox	ist		
London	40	13	38	91	9,513	1,074	8,649	19,236
Manchester	8	1	17	26	1,961	32	3,276	5,269
Rest of Britain	11	1	5	17	1,070	12	919	2,001
Total	59	15	60	134	12,544	1,118	12,844	26,506

Table 3 1	Enrolment in	lowish schoo	le hy ar	aa (lawich	nunile	only)
		Jewish school	πουγαιί		pupits	only

- 3.26 Children from Strictly Orthodox families account for almost half of all Jewish children attending Jewish schools; this proportion is expected to increase in future years, while the number of mainstream Jewish school-age children is likely to decrease, perhaps by up to 20%. Outside London, and particularly in Liverpool and Birmingham, the number of non-Jewish pupils attending Jewish day schools exceeds the number of Jewish pupils in those schools.
- 3.27 The 134 Jewish schools in Britain include 42 schools that have some secondarylevel provision. Of these, 8 are mainstream secondary schools, of which one (Jewish Community Secondary School) is a newly-opened school in Barnet and one (Yavneh College) is projected to open in September 2010 in Hertfordshire.
- 3.28 In 2005/06 approximately 4,000 pupils were enrolled in three mainstream Jewish secondary schools in the London area, with 555 at a secondary school in Hertfordshire (see Appendix 2). In addition, approximately 2,000 pupils were enrolled in Strictly Orthodox secondary schools in London and about 4,000 in Strictly Orthodox schools that span both primary and secondary education. (The CPRG report does not say how many of the latter pupils are secondary school age.) With the exception of one mainstream school in Redbridge, all of the London Jewish secondary schools are located in the boroughs of Hackney, Barnet and Brent.
- 3.29 Manchester and Liverpool each have just one mainstream Jewish secondary school, with enrolments of 834 and 606 respectively. However, enrolment by Jewish pupils is falling and the Liverpool school contains a majority of non-Jewish students. Strictly Orthodox secondary schools in Greater Manchester have a combined enrolment of about 600, with an additional 1000 in combined primary/secondary schools.
- 3.30 In Gateshead (Newcastle), two Strictly Orthodox secondary schools have a combined enrolment of about 250. There is only one, very small Jewish school in Leeds, with an enrolment of fewer than 50 pupils.
- 3.31 The enrolment data for Jewish secondary schools account for approximately 10,000

of the estimated 20,000 Jewish children of secondary-school age. Anecdotal evidence suggests that many of the remaining 50% of secondary-age Jewish children attend academically selective private schools.

Jewish 'students'

- 3.32 The target population for preconception Tay Sachs carrier screening is adolescents over the age of 16 and young unmarried people. Many of these young people are likely to be students. Those still at school are generally living with their parents, while university students are likely to be living away from home. The census records 15,457 Jewish 'students' between the ages of 16 and 24 in England and Wales in 2001. This figure includes both university students and those in their final years of secondary school education, so there is some overlap between these numbers and the figures for secondary school pupils discussed above. 'Students' account for approximately 60% of the Jewish population in the 16-24 age group. No information is available on the locations of the remaining 40%.
- 3.33 Table 3.5 shows the major locations of Jewish students in England and Wales (that is, where they are studying rather than where they are normally resident). The Jewish populations of university towns such as Manchester, Leeds, Birmingham, Oxford and Cambridge include significant numbers of Jewish students, as reflected in the relatively high numbers in the 20-24 age band in these cities.

Location	No. of students	Percentage
Outer London	4,516*	29.2*
Inner London	2,975*	19.2*
Greater Manchester	1,598*	10.3*
Leeds	979	6.3
Manchester (LAD)	673	4.4
Birmingham	625	4.0
Gateshead	452	2.9
Oxford	324	2.1
Cambridge	303	2.0
Liverpool	257	1.7
Bristol UA	242	1.6
Brighton and Hove UA	237	1.5
Nottingham UA	211	1.4
Sheffield	111	0.7
Other	1,954	12.6
Total	15,457	100.0

Table 3.5 Study location of Jewish students aged 16-24, England and Wales

* The JPR report suggests that these figures, in particular, are likely to include substantial numbers of school students aged 16 and 17. UA = Unitary Authority; LAD = Local Authority District
Partnerships and family structure

- 3.34 There were 111,697 married Jewish individuals at the time of the 2001 census. 75.4% of married Jewish men and 77.5% of married Jewish women reported that they had a Jewish spouse.
- 3.35 Of all 69,010 married couples in England and Wales in which at least one partner identified themselves as Jewish, 42,687 (61.9%) were couples in which both partners were Jewish, while 26,323 (38.1%) were couples in which one partner did not report being Jewish (Table 3.6). An increasing number of Jewish people are in cohabiting relationships rather than married relationships, and these are more likely to be relationships with non-Jews: of the 9,726 cohabiting couples, only about 1,449 (15%) were of Jew with Jew, while 8,267 (85%) were of Jews with partners who did not report they were Jewish.
- 3.36 Combining results for both married and cohabiting couples, 44,146 (56%) of the 78,736 mixed-sex partnerships were endogamous (Jew with Jew) and 34,590 (44%) were of a Jew with a partner who did not report that they were Jewish. The JPR report notes that the figure of 34,590 apparently mixed marriages may overestimate the number of truly exogamous marriages, as it includes 11,356 couples in which one member reported either 'no religion' or did not specify a religion, and some of these people may actually be Jewish by ethnic origin.

	Married	Cohabiting	Total
Jewish x Jewish	42,687	1,459	44,146
Jewish x non-Jewish (or unknown)	26,323	8,267	34,590
Total	69,010	9,726	78,736

Table 3.6 Partnerships in which at least one member is Jewish

Couples with children

- 3.37 The census data provide information on dependent children in households in which the Household Reference Person (HRP) identified themselves as Jewish. 84.5% of dependent children in such households lived in a married-couple household, 11.2% in a lone parent household and 3.6% in a cohabiting couple household.
- 3.38 The JPR report includes partial information on the geographical distribution of couples (both married and cohabiting), and couples with children, in households with a Jewish HRP. Although the highest absolute numbers of couples are found in the districts with the highest total Jewish population (for example, Barnet, Camden and Hertsmere), there are geographical differences in the relative numbers of married and cohabiting couples. For example, relatively higher proportions of married-couple households were found in suburban areas of Southeast Hertfordshire (Hertsmere, Three Rivers and St Albans) and Essex (Epping Forest), while cohabiting-couple households, although much fewer in number, were relatively more frequent in Inner London (for example, Camden, Islington and Tower Hamlets). Consistent with the finding that cohabiting couples were less likely than married couples to have children, the proportion of couples with

children was lower in areas with relatively higher proportions of cohabiting couples (for example, Islington and Tower Hamlets).

Births

3.39 Estimates of the numbers of Jewish children born each year can be obtained from circumcision data recorded by the Orthodox Initiation Society and the Reform Initiation Society, and from the national ratio of male to female births. For the period 1993-2002 the average annual number of births was estimated to be 2,720, of which about 85% were Orthodox. This figure is thought to underestimate the actual number of births by about 10%. From the census data, assuming the number of births per year is one-fifth of the number of children in the 0-4 age group, the estimated birth rate is 2,772 per year, which tallies well with the estimate based on circumcision data.

Ethnicity

- 3.40 97% of Jews in the 2001 census identified themselves as 'white', 0.7% identified themselves as Asian, 0.3% as Black or Black British, and 0.9% as 'Other ethnic group'. 83.2% of Jews were born in the United Kingdom. Of those born abroad (approximately 44,000 people), 9,128 came from the Middle East, 1,156 from North Africa and 10,440 from Western Europe.
- 3.41 Although indirect, these data suggest that the number of Sephardi Jews in the UK is relatively small and, in particular, that there are likely to be very few Moroccan Sephardis (the other Jewish group with an increased risk of Tay Sachs disease). Some Moroccan Jews may come to the UK from the North African population in France but the number of these individuals is not known.
- 3.42 The CPRG report also sheds some light on the proportions of the different Jewish denominations in the British Jewish community, listing the numbers of Jewish marriages in synagogues of these denominations for the years 1996-2005 (Table 3.7). Orthodox, Masorti, Reform and Liberal Jews are all overwhelmingly of Ashkenazi origin, suggesting that Ashkenazi Jews represent about 95% of the UK Jewish population, with Sephardi Jews accounting for the remaining 5%. Sephardi synagogue membership totals only about 6,000 (David Graham, personal communication), again suggesting that the proportion of Sephardis in the UK population is very small.

	No. of marriages	% of total
Strictly Orthodox	2135	22.6
Central Orthodox	4969	52.6
Sephardi	426	4.5
Masorti	254	2.7
Reform	1199	12.7
Liberal	458	4.9
Total	9441	100

Table 3.7 Total Jewish marriages by denomination, 1996-2005

Conclusions

- 3.43 Because the total Jewish population of the UK is small, the expected number of affected children in the absence of screening is only about 1 per year. Although this does not represent a significant problem in overall public health terms, Tay Sachs disease does represent a significant risk within the Jewish community.
- 3.44 The clustering of the UK Jewish population revealed by the 2001 census data suggests that the majority of the target population for Tay Sachs carrier screening, whether preconception or antenatal, can be reached by concentrating efforts on a small number of districts in the London region (including parts of Hertfordshire and Essex) and Greater Manchester. Most other districts of the UK where Jews are relatively prevalent contain an ageing Jewish population for whom carrier screening is less likely to be relevant. Migration trends for the Jewish population suggest that the clustering of the Jewish population, particularly in London and South Hertfordshire, will continue. South Hertfordshire, in particular, has become a favoured location for young Jewish families.

Preconception screening

- 3.45 The target population for preconception screening is predominantly the 16-24 age group. The vast majority of school students in this age group also live in the London region and Greater Manchester but it should be noted that a significant number of university students in the upper part of this age band live in cities such as Birmingham, Leeds, Gateshead (Newcastle), Oxford and Cambridge. Measures to inform this group about the availability of carrier screening may be appropriate, as a way of reaching some individuals who might not have had the opportunity of carrier screening while in secondary school.
- 3.46 About half of all Jewish children of secondary-school age attend Jewish schools. Jewish schools with secondary school provision are confined to just 11 local authority districts, most of which are in London, Manchester or Hertfordshire. Only 8 of these schools are mainstream Jewish schools, suggesting that targeting this population with outreach screening programmes is likely to be relatively easy. Anecdotal evidence suggests that 40-50% of secondary-school age Jewish children attending non-Jewish schools are enrolled in private schools in London and Manchester. In London, this applies particularly to the children of parents in the higher-income areas of inner Northwest London. It may be possible to reach at least some of these children by identifying schools which hold a separate Jewish assembly.
- 3.47 The school-age Strictly Orthodox population is dispersed over a much larger number of schools, many of which have mixed-age provision. The marked geographical concentration of these schools in just a few local authority areas may make it feasible to include them in an outreach programme. The likely uptake of NHS-based carrier screening by this group is not clear. As arranged introductions leading to marriages are the norm within the Strictly Orthodox community, it is possible that Strictly Orthodox Jews may prefer to use the services of the privately run Dor Yeshorim programme. However, there is ongoing controversy about the Dor Yeshorim programme within the Strictly Orthodox community, with some members of this community preferring to be

screened via NHS services or other private laboratories, in order to receive their results directly.

Antenatal screening

- 3.48 The couples at greatest risk of having a child with Tay Sachs disease are those in which both partners are Ashkenazi Jewish. Most Jews still marry Jews, but there is a significant and increasing number of exogamous marriages and of cohabiting partnerships, which also tend to be between Jews and non-Jews. If this trend were to continue, it would be expected to lead to a decline in the birth prevalence of Tay Sachs disease, even in the absence of screening.
- 3.49 The exception to this changing pattern of partnerships in the Jewish population is the Strictly Orthodox community, which tends to be highly endogamous and to include families with large numbers of children. However, as abortion is unacceptable to the Strictly Orthodox community, couples are unlikely to be interested in screening in the antenatal period.
- 3.50 The geographical distribution of married couples largely matches the distribution of dependent children, suggesting that provision for antenatal screening should concentrate on hospitals and GP practices in these areas, assuming that married couples resident in these areas do predominantly use their local services. Cohabiting couples tend to be more widely dispersed geographically but are much less numerous than married couples, less likely to be Jewish x Jewish partnerships and significantly less likely to have children, suggesting that efforts to target this group specifically may not be justifiable.
- 3.51 There are a number of caveats in drawing conclusions from the 2001 census data. A major one is that the data are for individuals who identified themselves as belonging to the Jewish religion; that is, people who are self-declared Jews. The number of Ashkenazi Jews who decided not to identify themselves as Jewish is not known. Of those who did declare that they were Jewish, a significant but unknown proportion is likely to be of mixed descent (that is, with fewer than four grandparents of Ashkenazi origin), and therefore at lesser risk of being a carrier.

4 Tay Sachs disease carrier screening in the UK: current practice

Introduction

4.1 In order to review the programme for Tay Sachs disease carrier screening in the UK, we have sought information at several levels: central information from NSC on the formal arrangements for the programme itself; information on screening in the antenatal setting; and carrier screening initiatives in schools and other community settings. We compared data on service provision and numbers of individuals tested at different centres with demographic information about the distribution of the Jewish population (Chapter 3). We have also reviewed current laboratory practice for Tay Sachs disease carrier testing and analysed data on test results from carrier screening initiatives over the last 9 years.

Formal structures for the National Screening Programme

- 4.2 Information was sought from Jennie Carpenter (Department of Health Lead for Screening and Specialised Services) about the formal organisation of the service and from Frances Flinter and Shehla Mohammed, previous and current head of service at the main NHS provider service in London. Information requested included the following questions:
 - What are the formal arrangements for Tay Sachs screening?
 - In which division of the NSC does formal responsibility for Tay Sachs screening rest?
 - Who is the lead commissioner?
 - Who is responsible for provision of services? (eg Trust lead manager or clinician)
 - How is the service quality assured?
 - What formal documentation exists in NSC? (Please provide copies if possible)
 - What are the lines of accountability?
 - Have any formal reporting arrangements been in operation and if so are there any formal reports available?
- 4.3 The documentation that was forwarded in response to this request included information from a policy review meeting held in 2004. At this meeting the NSC supported the funding of carrier screening for Tay Sachs disease for members of the Ashkenazi Jewish population but agreed that further work needed to be done to make the screening more systematic and to cover the whole population more equitably. The then Programme Director (Professor Muir Gray) would take this forward. The current review arose out of this decision.
- 4.4 In general, as with all other antenatal and child health programmes, advice on Tay Sachs screening comes to the NSC from the Fetal and Maternal Child Health subgroup of the NSC. There is no formal documentation related to the functioning of the programme. Funding and contracting for the clinical and laboratory elements of the service at Guy's Hospital are included in the commissioning arrangements of the London genetics consortium but not identified separately. Few patients or samples are received from outside the consortia area and funding for this activity is recouped from the PCT of the patient's residence on a case by case basis. There were no contracting documents with

any of the Northwest services. Further there was no overall coordinator for provider elements of the service, no Steering Group and there have been no formal reports from the Programme.

Carrier testing and screening

- 4.5 In our consideration of services provided within the UK we differentiate between carrier testing, provided on request to an individual who identifies him/herself as being at risk and seeks the service, and screening, in which the offer of testing is proactively made by the service following a systematic means of identifying at risk individuals. There are three main settings for current Tay Sachs disease carrier testing/screening:
 - The antenatal setting, in which a midwife routinely enquires about ethnic origin and offers a Tay Sachs carrier test to individuals of Ashkenazi Jewish origin. [The actual testing might be provided through an NHS clinic such as the Guy's clinic or the Barnet District Hospital clinic (see below)]. We would consider this service to be screening.
 - The provision of a Tay Sachs carrier test to individuals or couples who identify themselves as being at risk, because of their ethnic origin and/or a known family history of the condition. We would consider this as testing and thus technically outside the screening programme (although some individuals may recognise their increased risk as a result of publicity or educational initiatives provided by the screening programme).
 - The proactive offer or a Tay Sachs carrier test to young people before they marry or form a relationship (e.g. older school children, students or young adults) with a view to ensuring that they are aware of and able to act on known carrier status in advance of pregnancy. We would consider this to be screening. (This is generally termed 'preconception' screening though it may precede conception by several years.) The advantage of offering this through schools is achieving greater coverage, although the disbenefits of possible anxiety or even stigma for carriers should be borne in mind.
- 4.6 In practice there seems to be very little antenatal screening (discussed below and in more detail in Chapter 5) and the patients who attend the walk-in and district general hospital clinics generally do so not in response to an offer of screening but because they have heard about carrier testing through friends or family or because they have a family history of the condition. The only real 'screening' is thus currently undertaken through the voluntary organisations through the community programmes. When looking at laboratory data, it is impossible to differentiate between the results of testing and screening services.

Availability of antenatal carrier screening

- 4.7 Carrier screening should be available through the antenatal services. Antenatal services have the option of sending blood samples to either Guy's laboratory or to the Willink or referring women to the Guy's walk-in service or to their regional genetics service.
- 4.8 No data were available on activity in antenatal carrier screening, or on the criteria applied by antenatal services in identifying those who might benefit from screening. We

therefore sent a short questionnaire to all Regional Antenatal Screening Coordinators (ANSCs) in England and, through them, cascaded to all local ANSCs. No information is available from Scotland. The results of this survey are reported in more detail in Chapter 5.

- 4.9 The questionnaire (see Appendix 4) asked whether the Trust offers antenatal carrier screening for Tay Sachs disease to Jewish patients and, if so:
 - how those who are offered screening are identified
 - whether any questions are asked about the ethnic origin of either the woman or her partner
 - how many tests are performed per year, and
 - how results are monitored.

If no screening was offered, the ANSC was asked to state the reason for this decision.

Summary data

- 4.10 Questionnaires were sent to ANSCs in 155 NHS Trusts. 114 completed questionnaires (74%) were returned.
- 4.11 77/114 Trusts reported that they offer antenatal carrier screening if requested by the patient. 13 of those Trusts claim also to offer screening proactively. 37 Trusts reported that they offer screening neither proactively nor on request. No Trust reported doing more than 10 tests per year.

Carrier testing and screening services

- 4.12 Tay Sachs disease carrier testing is available through NHS laboratories in London and Manchester. In London, weekly clinics are run at Guy's Hospital and Barnet District General Hospital. In addition, outreach screening sessions are run on a voluntary basis in Jewish schools and community organisations. All samples are sent to Guy's Laboratory. In Manchester, community screening sessions are run in schools and universities, with samples sent to the Manchester Willink laboratory.
- 4.13 Individuals elsewhere in the country can request referral to their Regional Genetics Centre in order to obtain carrier testing. Samples are sent either to Guy's laboratory or the Willink.
- 4.14 Carrier testing is also available on a private basis through two UK-based companies, the international Dor Yeshorim organisation, and other private laboratories based outside the UK.

Guy's Hospital walk-in clinic

4.15 A weekly walk-in session is held every Monday morning. Patients are seen by a Genetic Counsellor in a 15-20 minute appointment and results are sent directly to the patient by post (or given by telephone if the patient is pregnant at the time of testing). Results are also sent to the patient's GP. The turnaround time is 3-4 weeks for routine tests or 2 weeks for urgent tests (that is, if the patient is already pregnant).

Barnet District Hospital clinic

4.16 Weekly sessions are held on Thursday mornings. Either a referral or an appointment is required, and patients are seen only by a phlebotomist, who takes samples for testing at Guy's laboratory. Approximately 70 individuals are tested per year. Most referrals are from local GPs but some are from GPs in other areas who have located the service from its website or a Tay Sachs disease information pamphlet. Some patients self-refer after hearing about the service from friends or relatives. Dr Charles Andrew talks to as many patients as possible either in person or by telephone before blood is taken but not all patients receive pre-test explanation or counselling. All those with a positive test result receive counselling from the Guy's Hospital genetic counsellor.

London outreach community screening sessions

- 4.17 Jewish Care is a health and social care charity serving the Jewish community in London and the south east. Dr Philip Koch and Jess Clare, together with other volunteers from Jewish Care, organise annual screening sessions at Hasmonean Girls' and Boys' Schools, Immanuel College and JFS School. Screening is offered to 6th form students (Years 12 and 13). The service is also offered to other London schools with a significant Jewish enrolment but response from these schools has so far not been encouraging: schools either do not respond, or are not prepared to offer adequate time for the session. Jewish Care is not permitted to organise sessions at schools serving the Strictly Orthodox community.
- 4.18 At screening sessions, pupils are given a leaflet and a talk accompanied by a short video that explains Tay Sachs disease and its inheritance. Questions are taken and answered by Dr Philip Koch, and pupils may talk either to him or to Jess Clare confidentially. A letter is sent home, requesting signed consent for testing by pupils' parents/guardians. Jewish Care estimates that a total of about 470 school students attend its screening sessions each year (around 240 from JFS, 80 from Hasmonean Girls', 75 from Hasmonean Boys' and 75 from Immanuel).
- 4.19 Jewish Care also organises between 4 and 6 community screening sessions per year, by agreement with or invitation from Synagogues. Screening sessions are advertised as widely as possible through relevant websites, Jewish Community Radio, and Jewish newspapers and magazines. Posters and leaflets are sent to GPs, maternity units, youth groups and Rabbis, asking them to publicise forthcoming screening sessions. Leaflets are used to explain the purpose of carrier screening.
- 4.20 The outreach programme to schools and community groups is funded entirely by donations to Jewish Care. The estimated annual direct cost of the programme (excluding the cost of the test itself, which is NHS-funded through Guy's laboratory) is £7,706. This figure does not include the cost of production and distribution of the leaflet or management costs, nor does it put a value on the services of Jewish Care's volunteers, all of whom have professional skills in medicine, counselling or administration.
- 4.21 In the Strictly Orthodox community, community screening sessions are organised by Rabbi Rosner and the Association for the Prevention of Jewish Genetic Diseases. The Guy's laboratory database records 401 samples from individuals referred by Rabbi

Rosner over the period 1999-2007. Results are sent to the individuals by post and those who test positive are offered counselling. The numbers referred per year vary from 17 to 97; numbers have tended to be low (fewer than 30 per year) over the last few years. Increasingly, individuals are choosing to use the testing services of private laboratories, if they can afford to do so, because these services offer testing for 9 genetic diseases whereas the NHS service offers testing only for TSD. The Association for the Prevention of Jewish Diseases sends samples for DNA testing either to a private laboratory in London (presumed to be The Doctor's Laboratory) or to two laboratories abroad. Those in lower socioeconomic brackets, who cannot afford to pay for private testing, are more likely to choose the NHS service (Rabbi Rosner, personal communication).

Outreach community screening in Manchester

- 4.22 Dr Sybil Simon of Booth Hall Children's Hospital runs a community outreach screening service to mainstream Jewish schools, universities and community organisations in Manchester and (less frequently) in other large cities in the Northwest and the midlands. Community screening is funded as a charitable activity by the Jewish community.
- 4.23 School screening sessions begin with an invitation to pupils aged 16-18 to attend a talk on Tay Sachs disease and its genetic basis. Pupils are given an information pack, a questionnaire and a letter to take home requesting parental consent to testing. Those who wish to take up the offer of screening return their completed consent form and questionnaire the following week, when a blood sample is taken for testing. King David High School and Yavneh Girls' school in Manchester (which are on the same campus) are offered annual screening sessions. Sessions were also held at the Jewish Grammar School for Boys until two years ago, when a new Rabbinical head changed policy and urged families to use a different screening scheme (presumed to be Dor Yeshorim). Occasional sessions have also been held at non-Jewish schools popular with Jewish families (for example, Manchester High School for Girls, Withington Girls' School and Manchester Grammar School for Boys). Some sessions have been held at Liverpool King David High School but this school now has a minority of Jewish pupils, and many leave at 16 to attend sixth-form colleges.
- 4.24 Screening for Jewish university students is generally offered through Hillel houses (Jewish halls of residence), and for other adults through Jewish community organisations. Local GPs and community volunteers assist with these sessions. Hillel houses in Manchester, Leeds and Liverpool have had annual visits, and occasional visits have been made to houses in Birmingham, Leicester, Nottingham and Lancaster. Glasgow has had 3 biennial visits.
- 4.25 Samples are sent to the Willink laboratory, which levies a charge for testing. Results are sent by post to the individuals. Those who are carriers are invited to contact Dr Simon for further information. Wherever possible, she takes a brief family history to check if there are any young single, engaged or newly married relatives.
- 4.26 Table 4.1 shows Dr Simon's data for the uptake of screening between 2001 and 2007. A total of 551 individuals were screened, of whom the majority (68%) came from school screening sessions. Almost 90% of those screened were unmarried and 57% were female,

522 (95%) were Jewish, 475 individuals (86%) said they were of Ashkenazi origin, 13 (2%) said they were mixed Ashkenazi/Sephardi, 29 (5%) said they were Sephardi and 5 (1%) did not know their ethnic origin.

- 4.27 Funding for the Manchester community screening service is becoming increasingly difficult to secure and sessions in universities and community centres outside Manchester have recently had to be cancelled. Dr Sybil Simon estimates that the total annual cost of the programme is £20,000. (This figure is assumed to include the cost of the time contribution from medical professionals, as well as the direct costs of running screening sessions and testing samples.)
- 4.28 Some GPs in areas with a significant Jewish population have requested postal kits and have sent blood from interested patients to the Willink laboratory using a peel-off address label attached to their letter. Several antenatal clinics have requested postal kits and information leaflets for their wall display.

Centre	No. individuals	% of total
Jewish schools	310	56
Non-Jewish schools	66	12
Hospital	4	0.7
Health centre	7	1.3
Postal	111	20
University	48	8.7
(Blank)	5	0.9
Total	551	100

Table 4.1 Uptake of community screening initiatives in Manchester

Private Tay Sachs disease carrier testing services

- 4.29 The Doctor's Laboratory (http://www.tdlpathology.com), a private laboratory in London, offers DNA testing for carrier status for Tay Sachs disease and up to 8 other recessive conditions that are more common in the Ashkenazi Jewish population. Results are provided within 9 days.
- 4.30 In Leeds, Genome Screening Services is a recently established private testing service offering the 'Alef8' carrier test for Tay Sachs disease and up to 8 other recessive conditions.
- 4.31 The Dor Yeshorim organisation (based in New York) offers anonymised carrier testing for Tay Sachs disease and up to 9 other conditions. No results are given to individuals, only a PIN number that is used during the procedure for arranging marriages, to ensure that prospective marriage partners are not both carriers (see Chapter 2 for further details). Dor Yeshorim will not offer testing to those who have already been tested elsewhere and so having been tested by the NHS precludes testing by Dor Yeshorim.

Some Strictly Orthodox individuals who have been tested by Dor Yeshorim subsequently request repeat testing through the Association for the Prevention of Jewish Diseases because they wish to know their result (Rabbi Rosner, personal communication).

The NHS laboratory service

- 4.32 Responses to a questionnaire sent to all NHS genetic testing laboratories in the UK confirmed that only two laboratories (Guy's and St Thomas's in London, and the Manchester Willink) test samples in connection with population carrier screening for Tay Sachs disease; that is, in Jewish individuals who (generally) have no family history of Tay Sachs disease.
- 4.33 Guy's, Manchester Willink and an additional 5 laboratories (Birmingham, Edinburgh, Great Ormond Street (GOSH), Glasgow and Bristol) undertake diagnostic HexA assays. Of these additional 5 laboratories, two (Birmingham and GOSH), offer prenatal diagnosis for Tay Sachs disease and two (GOSH and Bristol) offer cascade testing to family members of affected individuals. None of the 5 laboratories carries out DNA testing for Tay Sachs disease mutations. (Note that prenatal diagnosis can be carried out either by mutation testing or by the biochemical assay on amniocentesis or CVS samples.)

Guy's laboratory

- 4.34 The Guy's laboratory performs the biochemical assay on both leucocytes and serum and considers the results together (see Chapter 7 for further information on testing methods for Tay Sachs disease carrier status). Leucocyte results are considered to be the most reliable and are the results reported.
- 4.35 The laboratory also tests for the three mutations found in the Ashkenazi Jewish population, for a further severe mutation common in non-Jewish carriers from the UK (+1IVS9), and for the Arg247Trp pseudodeficiency allele in all individuals with a positive or inconclusive carrier status result in the biochemical test. The assay used over the period covered by this review was a biallelic discrimination assay using fluorogenic TaqMan probes (Ward 2000). Mutation testing is carried out in the SAS (Supra-Regional Assay Service) laboratory to follow up all confirmed carriers and as an additional test for individuals who have borderline biochemical results.
- 4.36 The Guy's laboratory participates in the External Quality Control scheme organised by the US-based Tay Sachs and Allied Diseases Association. This programme evaluates laboratory performance of HexA biochemical testing in serum and leucocytes. Guy's performance is 100% detection of carriers and non-carriers.
- 4.37 For internal quality control, large batches of control samples (serum and leucocytes) from a known Tay Sachs carrier and a normal control are prepared every 24-30 months and individual aliquots stored at -80°C. These are run with each batch of test specimens to ensure run-to-run reproducibility of results. If values for these controls fall outside acceptable limits, the batch is rejected.
- 4.38 The current costs of the tests offered by the Guy's laboratory are: biochemical test only £108; DNA test (panel of 5 mutations) £84; sequencing of the HEXA gene (14 fragments) £193. (Note that sequencing was not available over the period covered by this review

but the laboratory expects to be able to make it available in the near future.) The laboratory's practice is to spread the cost of the mutation test, for those who require it (i.e. those with positive or inconclusive results in the biochemical test) across all those who are screened. This single charge is currently set at £126 per patient. These costs are those charged by the laboratory service and do not include counselling costs.

Test results

- 4.39 Records from the Guy's database have been analysed to determine the numbers of carrier tests performed, and the results of these tests, in the 9 years since the NHS carrier screening programme was approved in 1999 (Table 4.2). As far as possible, records relating to diagnostic tests were excluded from the analysis but information on the indications for testing is very incomplete.
- 4.40 Between 1999 and 2007 the Guy's laboratory performed a total of 26,152 assays on samples from 5,351 individuals, of whom approximately 55% were female and 45% male. (Note that each assay for example, total Hex in leucocytes, HexA in leucocytes, total Hex in serum, HexA in serum etc is given a separate assay number; hence the apparently large number of assays per sample. See Chapter 7 for further details about the testing methods.)
- 4.41 The database generally does not distinguish between individuals who were tested for carrier status because they were Jewish, and those tested for other reasons such as family history. Only 27 individuals are specifically identified in the database as Jewish, or of Jewish descent, but the data are incomplete. 77 individuals were identified as 'not Jewish' or 'non-Jewish'.
- 4.42 The database also does not distinguish reliably between antenatal samples (pregnant women and their partners) and samples from other individuals. 575 of the nondiagnostic records included the term 'pregnant', 'preg' or 'gestation' (excluding those that included the term 'not pregnant'). These records relate to 351 pregnancies, as in the majority of cases both members of the couple were tested. However, this number is likely to be an underestimate of the true number of pregnancies for which antenatal testing was carried out over the 9 years of data collection.
- 4.43 325 carriers of Tay Sachs disease were identified, as well as 18 carriers of Sandhoff disease and 3 carriers of the B1 variant. Some of the Sandhoff and B1 carriers may have been Jewish. However, neither the *HEXB* mutations causing Sandhoff disease, nor the B1 variant mutations, are more common in the Ashkenazi Jewish population, and the chance of two carriers marrying is extremely small. We have therefore restricted our analysis to Tay Sachs disease.

Category	Individuals	%
Normal	4988	93.6
TS Carrier	325	6.10
Inconclusive	17	0.30
Total	5330	100

Table 4.2 Tay Sachs disease carrier testing results from Guy's Hospital laboratory, 1999-2007

- 4.44 The flowchart in Box 4.1 sets out the testing protocol carried out by the Guy's laboratory and the numbers of samples passing along each pathway.
- 4.45 Overall, 6.1% of those tested, or 1 in 16, were recorded as carriers of Tay Sachs disease. This carrier frequency is significantly higher than the expected figure of 1 in 25-30 for the Ashkenazi Jewish population, suggesting that the data may contain an appreciable number of results from cascade testing in families (both Jewish and non-Jewish) in which there was a known carrier.
- 4.46 81% of individuals who tested positive for carrier status by biochemical testing (a total of 263 individuals) also received mutation analysis (Table 4.3). Of these, 10% carried the +1IVS9 mutation, which is relatively common among non-Jewish Tay Sachs disease carriers in the UK but not found in Ashkenazi Jews. These data show that Jewish mutations accounted for 77% of the samples for which mutation analysis was performed. Considering only these mutations, the relative percentages of the three mutations were:

83%
13.5%
3.5%

Box 4.1 Flow chart of the carrier testing protocol at Guy's laboratory, 1999-2007

The flow chart shows the testing pathway for samples from a total of 5,330 individuals. Note that of the 285 samples initially classed as 'inconclusive', all but 17 were eventually reported as carrier or normal, and appear in those totals (325 and 4988 respectively). Thus the three shaded boxes together account for the reported results for the 5,330 individuals.



Mutation	No. samples	% of total analysed
+TATC1278	168	64
+1IVS12	28	10.5
G269S	7	2.5
+1IVS9	26	10
Pseudodeficiency	0	0
No mutation	34	13
Total	263	100

Table 4.3 Mutation analysis

- 4.47 No mutation was found in 34 (13%) of enzyme-positive individuals. Follow-up of records for these individuals revealed that 2 were subsequently reported as non-carriers. Of the remaining 32, 10 were Jewish, 1 had distant Jewish ancestry, 1 was unsure of their ancestry, 18 were non-Jewish, and no information was available for 2.
- 4.48 Between 1999 and 2007, 285 individuals (approximately 5% of those tested) received inconclusive results from the leucocyte hexosaminidase A assay. These results were compared with the serum %HexA levels if those data were useful (that is, if the patient was not pregnant or taking medication), and DNA mutation analysis was performed.
- 4.49 Of these individuals, 17 (0.3% of the total tested) retained inconclusive status after further investigations. Repeat samples for biochemical and/or mutation testing were requested for these 17 but the majority were not received, perhaps because these individuals' partners were known to be non-carriers of Tay Sachs disease. The repeat samples that were received did not change the individuals' inconclusive status. In the past, individuals with inconclusive biochemical test results and no mutation were generally advised that carrier status could not be excluded. More recently, there has been a change of emphasis in that such individuals have been advised that it is unlikely they are carriers. The option of gene sequencing may resolve many such cases.
- 4.50 Table 4.4 shows the distribution of test results by the origin of the tested sample. 57% of samples came from individuals who accessed testing through a hospital; in most cases, this is likely to have been either the walk-in clinic at Guy's or the weekly clinic at Barnet Hospital. 11% of those tested were school pupils and 31% came from community screening sessions. Significantly, the carrier frequency in school children (3.6% or 1 in 28) is closer to the expected figure for the Jewish population.

Table 4.4 Distribution of Guy's laboratory Tay Sachs disease carrier testing results by origin of sample

Origin of sample	Individuals	% Ind.	Carriers	%Carriers	% non- carrier
Hospital	3205	56.9	199	6.2	93.8
School	666	11.8	24	3.6	96.4
C. Centre	1765	31.3	104	5.9	94.1
Total	5636 ¹				

¹ This is higher than the total number of individuals (5330) due to instances of multiple specimens of the same person from different sources. It has not been possible to resolve this discrepancy.

Manchester Willink laboratory

- 4.51 The Manchester Willink laboratory performs the biochemical HexA assay on leucocytes only. The laboratory does not have an official 'inconclusive' range as this is considered unnecessary for the leucocyte assay.
- 4.52 Carrier testing began in 1989 as a one-year research project. Initially, mutation testing was carried out as well as biochemical testing but this was discontinued in the early 1990s.
- 4.53 The Willink laboratory does not take part in the Tay Sachs and Allied Diseases Association external quality control scheme but is CPA accredited. The laboratory holds a large pooled batch of white cell aliquots for use in internal quality control. One aliquot is run three times at the start of each run to check for reproducibility before any diagnostic samples are tested.
- 4.54 The Willink charges approximately £15 per carrier test for the Manchester community screening programme, and £102 for tests referred from hospital (usually antenatal tests). Testing for the community carrier screening programme has been unfunded since 1989, and runs at a loss. The equipment used for testing was purchased in 1989 and is nearing the end of its life.

Test results

4.55 Table 4.5 shows the results of carrier tests performed at the Willink from 2004-2007. Unfortunately, no results are available before 2004 owing to computer failure.

Year	Total	AJ	Carriers	Repeats*
2004	154	122	8	1
2005	93	80	11	1
2006	92	67	4	0
2007	123	99	13	1
	462	368	36	3

Table	4.5	Carrier	testing	results	from	the	Mancheste	er Willink	laboratory

* Repeat testing was carried out if the sample was considered inadequate or had been in the post too long.

^{4.56 36} carriers were found out of a total of 462 individuals tested, a carrier frequency of 1 in 12.8. 368 of those tested were of Ashkenazi Jewish origin, but it is not known how many of the carriers were Ashkenazi Jewish. The high carrier frequency suggests that a significant percentage of those tested probably had a family history of Tay Sachs disease.

Private testing services

The Doctors Laboratory

- 4.57 A total of 548 samples have been tested by The Doctors Laboratory (TDL) since 2002, using DNA analysis for the 3 common Ashkenazi Jewish mutations. The number of individuals tested per year has varied from around 20 to just over 100 (but without any upward trend). TDL does not offer biochemical testing.
- 4.58 22 carriers have been detected: a carrier frequency of 4.0% (1 in 25). Of these carriers, 5 had the +1IVS12 mutation, 15 had the +TATC1278 mutation and 2 had the G269S mutation.
- 4.59 TDL is CPA accredited and participates in the UK NEQAS scheme for external quality assessment of its molecular genetic testing.
- 4.60 TDL charges £392.00 for carrier testing for a panel of 9 Ashkenazi Jewish diseases. The cost of the 3-mutation test for Tay Sachs disease alone is £93.05.

Dor Yeshorim

4.61 It has not been possible to obtain any information about the spectrum of test results for British Jews accessing the Dor Yeshorim testing service. Dor Yeshorim charges about £150 for carrier testing for up to 10 genetic conditions. Results are available after 2-3 weeks. Discounted rates of £100 per person are offered for group screening sessions but results take 3-4 months.

Uptake of carrier testing and screening

- 4.62 We have attempted to estimate the uptake of carrier testing and screening in the UK Ashkenazi Jewish population by comparing the available information on numbers of individuals tested with demographic information on the size and age distribution of the Jewish population (Chapter 3). This exercise is difficult because the census information is essentially a snapshot of the population at a single point in time (2001), while the data on individuals tested cover the period 1999-2007 for the Guy's database, 2004-2007 for the Manchester database and 2002-2007 for the TDL service. In addition, we have no way of knowing how many individuals from the Strictly Orthodox community have accessed private testing through the Association for the Prevention of Jewish Diseases or the Dor Yeshorim service (though most of the individuals referred for private testing by the Association for the Prevention of Jewish Diseases were probably tested by TDL).
- 4.63 A very crude estimate of testing and screening coverage by the NHS programme and TDL may be obtained by comparing the number of individuals passing through the 16-44 age cohort (the approximate target cohort for screening) since screening began with the number in this cohort who accessed testing during the same period. To make this calculation, we have assumed that all the individuals in the Guy's database were Jewish and in the target age range when they were tested, that approximately 80 Jewish people per year were tested in Manchester in 1999 and 2000, and 522 Jewish

people have been tested in Manchester between 2001 and 2007. We have also taken into account the 548 people tested by the private laboratory TDL, and assumed that all were Jewish.

- 4.64 From the 2001 census data, approximately 113,295 Jewish people passed through the 16-44 age band between the years 1999 and 2007. Of these, 5,330 were tested at Guy's hospital, 548 by TDL and an estimated 682 in Manchester. These individuals represent 5.79% of the total Jewish population in the target age band. Even halving the number in the target population (assuming that only one person in each couple needs to be screened) suggests that effective screening has been achieved for only about 12% of the population.
- 4.65 This figure is only a very crude estimate, with many sources of possible error. A major difficulty is that the Guy's data do not distinguish Jewish individuals from those of other backgrounds; this would lead to an over-estimate of testing and screening coverage. However, there are other factors that could lead to the figure being an underestimate of coverage:
 - It assumes that no-one was tested before 1999
 - It does not take into account the unknown number of people who have accessed the private Dor Yeshorim service, or the number of people referred to laboratories abroad by the Association for the Prevention of Jewish Diseases
 - Some individuals in the target cohort might already have known that they were not carriers and therefore did not require testing (for example, if both of their parents had been tested and were known to be non-carriers).
- 4.66 A rough estimate of antenatal testing and screening coverage may be obtained by comparing the estimated number of pregnant couples tested per year with the total number of Jewish births per year. The total number of Jewish births per year is an over-estimate of the target population because only couples experiencing their first pregnancy would need to be screened. Approximately 2,700 Jewish children are born each year. Unfortunately no data are available for the number of these who are firstborn children. We have no reliable data on the number of couples accessing antenatal carrier testing and screening each year. The survey of ANSCs suggests that fewer than 50 samples are sent for testing annually, while the incomplete Guy's database suggests a minimum number of 351 accessing testing over a 9 year period (that is, approximately 39 per year).
- 4.67 This estimate of testing and screening coverage may be unduly pessimistic because it assumes that no pregnant women or their partners had already been tested.
- 4.68 Although all of our estimates are, unfortunately, very imprecise because of the lack of reliable data, they do suggest that coverage of the target population for carrier screening is low. The fact that there have not been more births of Jewish babies with Tay Sachs disease can probably be explained by the small total size of the Jewish population, and some self-organised cascade testing in families containing known carriers.

Geographic coverage of testing and screening in the NHS

- 4.69 In order to assess the geographic coverage of testing and screening in the NHS, we attempted to map postcode data for individuals recorded in the Guy's database to the distribution of the Jewish population identified by the 2001 census. This mapping exercise proved difficult for several reasons. Firstly, we did not have access to a reliable means of translating postcodes into geographic identifiers and coordinates, or to mapping software that would enable the distribution of samples to be plotted on a map of the UK. Although Google Maps enables translation of postcodes into geocoordinates online, the reproduction of such a map for print is prohibited by ONS copyright. In addition, postcode information in the UK is copyrighted by Royal Mail.
- 4.70 We were able to partially overcome these problems by using a database of postcodes and geographical positioning data available on the internet (http://www.jibble.org. uk/ukpostcodes) and then superimposing this estimated positioning data onto a basic UK map outline obtained online (http://www.statistics.gov.uk/geography/maps. asp). We are not able to reproduce the resulting map in this report, due to copyright restrictions. Purchase of mapping software or of the services of an organisation (such as the Eastern Region Public Health Observatory) that would have been able to perform the mapping on our behalf was felt to be disproportionately expensive.
- 4.71 However, it is possible from the Guy's data to obtain an approximate view of testing and screening coverage by grouping samples from postcodes covering a roughly similar area; for example, N, NW or HA postcodes for North and North-west London; M, WA, BL and SK postcodes for Greater Manchester, and so on. Table 4.6 shows the approximate numbers of samples from each area, with and without the addition of the 522 Jewish samples from the Manchester community screening programme (all allocated to Manchester). The Table also shows the Jewish population of each area as a percentage of the total Jewish population.
- 4.72 The results show that 96.4% of samples originated from greater London, south east Hertfordshire, south Essex, Manchester, Gateshead, Brighton, Oxford, Leeds, Glasgow and Birmingham. Samples from North and North-west London alone accounted for over 60% of the total. The remaining samples originated from postcodes scattered across the whole of the UK, with minor clusterings (totalling fewer than 15 samples each) in cities including Cambridge, Cardiff, Liverpool, Nottingham and Leicester. Comparing these results with the demographic information in Chapter 3 suggests a fairly good match between the major centres of Jewish population and the origins of samples tested for Tay Sachs disease carrier status. However, while these population clusters account for about 78% of the total Jewish population, they provided 96% of the samples tested, suggesting some relative under-representation from the rest of the country.
- 4.73 68% of the total samples tested at Guy's and the Willink originated from greater London, slightly higher than the percentage of the Jewish population that lives in the capital. Refining the data by areas within London and the wider London region, however, suggests some bias towards North and Northwest areas, with North and Northwest London plus neighbouring Hertfordshire accounting for 67.5% of the samples but only about 34% of the population. Northeast London and south Essex appear to be relatively under-represented, with only 4% of the samples but 8% of the population. Manchester,

with 15.7% of the total samples if the Guy's and Willink data are combined, but only 8.3% of the total Jewish population, appears somewhat over-represented but it should be noted that not all of the 522 Jewish samples tested as part of the Manchester community screening programme will have come from Manchester; some of these samples originated from other cities in Northern England and from Glasgow.

Area	No. samples	% of total samples (Guy's)	Jewish population of area as % of total	% of total samples (Guy's + Willink)
N and NW London	3333	62.5	27.2	57.0
W London	121	2.27	1.58	2.01
NE London and S Essex	234	4.39	8.01	4.00
S London	129	2.42	2.63	2.20
Inner London	178	3.33	18.7	3.04
Hertfordshire	616	11.6	6.4	10.52
Manchester	399 (921*)	7.49	8.3**	15.7
Gateshead/Newcastle	27	0.51	0.90	0.46
Oxford	27	0.51	0.41	0.46
Brighton	22	0.41	1.28	0.38
Birmingham	19	0.36	0.89	0.32
Leeds	17	0.32	3.1	0.29
Glasgow	15	0.28	1.17	0.27
Total	5137 (5659*)	96.4	80.57	96.65

Table 4.6	Geographical	origins of sa	mples tested	at Guy's and	d Willink La	boratories
				- 1		

* Including 522 Jewish samples from thé Manchester community screening programme between 2001 and 2007

** Greater Manchester

Conclusions

- 4.74 For the screening programme overall, our review has highlighted the fact that there is no routine or readily available information and, in particular, no overall description of organisation, structure, activity or outcome information. Current commissioning arrangements with funding only available in London do not allow equitable availability of screening across the country.
- 4.75 Outreach carrier screening in the Jewish community currently depends heavily on the commitment and voluntary work of individuals and charitable organisations from the Jewish community. There has been no NHS support for this activity (except for the laboratory testing itself, and then only in London) and many of the people who have organised outreach community screening sessions over the last 9 years are nearing retirement. The future viability of community screening in Manchester, in particular, is seriously in doubt.

- 4.76 Very little carrier screening is occurring in the antenatal setting, even in Trusts located in areas with a substantial Jewish population. This part of the service is discussed in greater detail in Chapter 5.
- 4.77 Two laboratories (Guy's Hospital in London and the Manchester Willink) currently test samples for Tay Sachs disease carrier screening. Testing at the Manchester Willink has been unfunded since a one-year research project finished at the end of 1989, and since then has been running at a loss. Dr Alan Cooper has indicated that the Willink intends to stop performing carrier screening tests for Tay Sachs disease when Dr Sybil Simon retires. This would leave Guy's as the only laboratory offering carrier screening tests.
- 4.78 Data collection from laboratory testing needs to be improved. In particular, the Guy's database has not in the past distinguished carrier screening tests from diagnostic tests, or recorded the ethnic origins of those tested, making accurate audit of the programme impossible. There has been no standardisation between the Guy's and Manchester Willink databases.
- 4.79 The testing protocol for Tay Sachs disease carrier screening has not been standardised or fully evaluated (see Chapter 7 for further discussion of testing technology). Manchester Willink uses only biochemical testing in leucocytes. Both biochemical testing and mutation testing are carried out at Guy's but the testing protocols have developed in an ad hoc way. Marie Jackson, who was not at Guy's Laboratory during the period covered by this review, has recently produced new, detailed specifications for the protocols used by the laboratory. The current flowchart for the testing protocol is included as Appendix 3. Dr Christine Patch is currently working towards producing an evaluation (known as a Gene Dossier) for the mutation test carried out at Guy's Laboratory; this step is a prerequisite to inclusion of the test in the UK Genetic Testing Network's database of tests formally approved for use in the NHS.
- 4.80 Overall, carrier testing screening coverage by the NHS programme appears to be very low. However, there is evidence, from the high carrier frequency observed in the laboratory results, that families in which there is a known carrier may be more aware of their risk, and seeking testing proactively.
- 4.81 A major difficulty in obtaining an accurate estimate of testing and screening coverage throughout the whole Ashkenazi population is the lack of data both from private non-UK testing services used by the Association for the Prevention of Jewish Diseases, and from Dor Yeshorim. There is some evidence that an increasing proportion of the Jewish population, perhaps particularly in the Strictly Orthodox community, is choosing private testing in preference to the NHS service because the private services offer testing for a wider panel of up to 9 or 10 diseases.

5 Pathways to Tay Sachs disease carrier testing and screening in the UK: a survey of antenatal clinic co-ordinators and the patients' perspective

Introduction

- 5.1 As part of the review of carrier screening, two surveys were undertaken. The first survey was of all the antenatal screening coordinators (ANSC) in all 155 Trusts in England. This survey investigated whether antenatal clinics were offering Tay Sachs disease carrier screening, and if so to whom. If no screening was offered, ANSCs were asked the reason for this policy. Nadia Permalloo and Jane Hibbert assisted in undertaking the survey of antenatal services through the antenatal screening teams; data were collected and analysed by Sara Levene. A copy of the questionnaire is included as Appendix 4.
- 5.2 The second survey, carried out by Sara Levene, was a prospective survey of patients undergoing Tay Sachs carrier testing between 12 November 2007 and 30 June 2008. The results of this survey provided information about the current level of testing activity, and the sources of referrals. A subset of these patients was asked to complete a questionnaire that included questions about their postcode of residence; whether they or their partner were Jewish and if so whether of Ashkenazi, Sephardi or mixed Sephardi/Ashkenazi origin; whether they or their partner were pregnant; and whether there was a family history of Tay Sachs disease. Their pathway to testing and the results of the testing were also noted. A copy of the questionnaire is included as Appendix 5.
- 5.3 A third survey, independent of this review, has recently been carried out by Kate Simon of the NE Thames Regional Genetics Service, Sara Levene and K Thirlaway of the Department of Psychology, University of Wales Institute, Cardiff (Simon 2008). This survey gauged knowledge and interest in carrier testing among Ashkenazi Jewish university students. A brief summary of the results of the survey is included in this chapter as it sheds light on attitudes to carrier testing in a key target group.

Antenatal Survey

- 5.4 114 questionnaires were returned, a return rate of 74%. 77 (68%) of these Trusts reported that they offer Tay Sachs disease testing if requested by patients, 13 (11%) reported that they offer screening proactively and 37 (32%) of Trusts reported that they neither offer Tay Sachs disease screening proactively nor on request. No Trust claimed to do more than 10 tests per year. These results suggest that very few patients are accessing screening through routine antenatal services.
- 5.5 The Trusts that offered screening proactively were Stoke Mandeville, Basildon, Ipswich, Royal Surrey County Hospital, Queen Mary's Sidcup, Ealing, Hillingdon, Newcastle RVI, Queen Charlotte's, St Mary's Paddington, UCLH, Whipps Cross and the Royal Free Hospital. Only the last 6 of these are likely to have significant numbers of Jewish patients. It should also be noted that the last 5 of these do not actually take blood for screening but refer patients to Guys Hospital walk-in clinic.

5.6 The clinics that did not offer Tay Sachs disease screening were asked why screening is not offered. The most common reason given (Fig 5.1) was that there is a small or no Jewish population. The response to this question was examined in more detail in the 10 Trusts that serve areas with a substantial Jewish population (Table 5.1).



Figure 5.1 Reasons why screening is not offered

Table 5.1 Hos	pital Trusts in areas	with the highest Jewish	populations
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Hospital	Location	Testing offered on request	Screening offered proact- ively	No. samples per year	Reason given for not offering screening	Additional notes provided by ANSC
Barking, Havering and Redbridge NHS Trust	South Essex	No	No	0	Not a large Jewish population in area. No funding for screening.	Midwives do ask if patient or partner are Jewish
Barnet and Chase Farm Hospitals NHS Trust	London	Yes	No No reference to weekly Tay Sachs disease screening service offered in this Trust.	1-5	Most have had screening through their synagogue or would not do anything if TS carrier.	Midwives do ask if patient and partner are Jewish. Only screen if both partners Jewish

Homerton Hospital NHS Trust	London	Yes via referral to fetal medicine	No	0		Large Strictly Orthodox population, most of whom have been screened before marriage. Ask if woman is Jewish but not partner
Northwick Park Hospital (part of Northwest London Hospitals NHS Trust)	London	No	No	0	No funding for screening	Very few Jewish women use antenatal service although Trust serves large Jewish population.
Royal Free Hampstead NHS Trust	London	Yes	Yes	1-5		Screening suggested if both partners are AJ. Report that most couples have been screened before pregnancy
University College London Hospitals NHS Foundation Trust	London	Yes	Yes (but no clear protocol)	Do not take bloods; refer to Guy's walk-in clinic		Offer screening if only one partner Jewish. Patients referred to Guy's clinic
Whipps Cross University Hospital NHS Trust	London	Yes	Yes	Not known, local lab does not record		

Whittington Hospital NHS Trust	London	Yes	No	1-5		Report that most have been screened before pregnancy. Refer patients to Guy's clinic - 1 referral in last 2 years.
Watford General Hospital (part of West Hertfordshire Hospitals NHS Trust)	Hertford- shire	No	No	0	No funding for screening	Considered to be responsibility of GP. Patient requesting screening might be told about Guy's or Barnet clinic.
Pennine Acute Hospitals NHS Trust (includng North Manchester General, Royal Oldham, Bury General, Rochdale)	Manchester	No	No	0		Would refer to Genetics if screening requested. Report that most Jewish women have been screened before marriage
Gateshead	Gateshead	No	No	0		Claim that many women screened before marriage

- 5.7 The responses from these 10 Trusts indicate a widespread belief that there is no funding for Tay Sachs disease carrier screening. Most ANSCs in these Trusts also believed that all Jewish women would have been screened before marriage; as the analysis in Chapter 4 shows, this belief is not well founded. It appears that there is no area, however large the Jewish population, where screening is being offered systematically within the antenatal setting.
- 5.8 Coordinators were asked whether women were routinely asked about their ethnic origin. Figure 5.2 shows that most of the Trusts that answered this question claim to do so. However, it should be noted that most ethnic origin forms and the current Family Origins Questionnaire (FOQ) would not pick up Ashkenazi Jewish patients. One ANSC commented that it is difficult to be proactive because 'Jewish' is not on the list of ethnic origins. This point should be considered when examining how best to make

screening for Tay Sachs disease more systematic. It may be that in some Trusts women are being asked about their religion as part of a general care plan. However, a response of Jewish religion is not linked to consideration of whether Tay Sachs carrier screening might be appropriate.



Figure 5.2 Whether women are asked about their ethnic origin including if they are Jewish

5.9 14 (12%) of the Trusts ask whether Jewish women are of Ashkenazi or Sephardi origin. Half of these Trusts are in areas with very small Jewish populations and only 3 are in areas with large Jewish populations. This may suggest that midwives do not understand that the Ashkenazi Jewish population is at risk for Tay Sachs disease rather than all Jews, and suggests the need for education of antenatal staff. When the ANSC was asked whether testing was offered to both Ashkenazi and Sephardi women, 24 Trusts answered this question. Again the response, shown in Figure 5.3, suggests the need for education.



Figure 5.3 Do you offer testing to both Ashkenazi and Sephardi women?

5.10 Half of the Trusts answered the question about whether they seek information on the Jewish status of the partner (Figure 5.4). Just under half of these (25/57) did ask whether the partner was Jewish. 9 suggested that this information was obtained from a general ethnic origin questionnaire.

Figure 5.4 Do you ask if partner is Jewish?



5.11 Trusts were asked whether they offered Tay Sachs disease screening if the partner is not Jewish; responses were received from 45 trusts (Figure 5.5). Once again a variety of responses was evident suggesting the need for a coherent policy on who is offered screening, and education so that staff understand the policy.



Figure 5.5 Do you offer Tay Sachs disease testing if partner is not Jewish?

Prospective survey of patients' experience

5.12 A prospective survey was undertaken of patients attending for testing in those services that sent samples to the Guy's laboratory during a 7 month period from 12 November 2007 to 30 June 2008. The total number of samples received during this period was 326, with the largest numbers coming from Jewish Care school screening (44%), Guy's hospital (25%), Barnet Hospital (10%) and Jewish Care community screening (7%). Only 8 samples came directly from GP referrals. Small numbers of samples were received from a variety of hospitals across the country. Table 5.2 provides full information about the source of referrals.

Table 5.2Source of referrals Nov 07 to Jun 08

Source	No. of samples
Jewish Care school screening (four schools)	144
Guy's Hospital	82
Barnet Hospital	34
Jewish Care community screening (one session)	23
GP referrals	8* [§]
Private laboratory (HCA)	7

Source	No. of samples
Northwick Park Hospital / Kennedy Galton Centre	4
Addenbrooke's Hospital, Cambridge	3
Princess Royal Hospital, Haywards Heath	3
Royal Free Hospital, London	3*
Queen Charlotte's Hospital, London	3
Deriford Hospital, Devon	2
Great Ormond Street Hospital, London	2
Royal Sussex County Hospital, Brighton	2
Southampton/Salisbury	2
King George Hospital, Ilford, Essex	2
Princess Alexandra Hospital, Harlow, Essex	1
Newcastle-upon-Tyne Hospital	1
Eastbourne District General Hospital	1
TOTAL	326*

^{*} Royal Free sent the wrong sample for a pregnant woman. The same person then had the correct sample sent by the GP two weeks later; therefore the total has been adjusted from 327 to 326 actual patients

- [§] One of these patients had 2 samples sent in, 2 days apart, by different GPs, because the first GP sent the blood in the wrong bottles and the test was not possible
- 5.13 An attempt was made to collect more detailed information about patients accessing testing, through a questionnaire on a subset of individuals who included patients attending the Guy's walk-in clinic, the Barnet Hospital Chemical Pathology weekly clinic and a Jewish Care community session. There were two main purposes of the patient questionnaire. Firstly, due to the inadequacies of the information on the Guy's laboratory database, the review team wanted further information on the Jewish/ non-Jewish background of the patients being tested, as this information had been poorly recorded. Other details, such as whether those being tested were Ashkenazi or Sephardi, were not included on the database at all, nor was information on the ethnicity/religion of the patient's partner. The second purpose of the questionnaire was to obtain information on the patient pathway to testing. The review team felt it was important to gain the patients' perspectives on how they had accessed testing and any obstacles they had encountered in their pathways to testing. It had been hoped to hold a patient focus group but when this was offered to those who had attended testing, no patients indicated that they were able to attend.
- 5.14 The questionnaire was completed by a total of 96 individuals: 68 (83%) of the patients who had attended Guy's walk-in clinic during the survey period, 10 (29%) of those who had attended the Barnet Hospital Chemical Pathology weekly clinic, and 18 (73%) of those who had attended a Jewish Care community screening session. Not all the questionnaires completed were answered fully. The questionnaire was also circulated to genetic counsellors across the UK, with a request for the questionnaire to be

completed should any patients take up Tay Sachs testing in the specified period. No completed questionnaires were received.

5.15 The age range of patients completing the questionnaire was 16-69 years, with most in the 30-44 age band; the distribution of ages is given in Figure 5.6. 47% were male and 53% female. Of the 96 individuals, three quarters lived in North London/North west London or adjoining Hertsmere and Bushey areas of outer London. This was again representative of the areas with the larger Jewish populations (see Chapter 3).

Figure 5.6 Age distribution of individuals undergoing testing



Age Distribution

- 5.16 99% (95/96) of patients defined themselves as Jewish; the remaining 1 patient had a Jewish partner and a family history of an affected cousin. This suggests that those being tested by the main providers of testing (Guy's hospital walk-in clinic, Barnet chemical pathology service and Jewish Care) are the target population either Jews or occasionally non-Jews who may be at risk for being a carrier of Tay Sachs disease.
- 5.17 62 patients were asked how many Jewish grandparents they had. This information is useful to obtain an indication of how far the screening programme is targeting those at highest risk of being a carrier. The vast majority of patients reported having 4 Jewish grandparents (60/62 that is 97% of those completing the questionnaire). 1 patient had two Jewish grandparents and 1 had a single Jewish grandparent.
- 5.18 Patients were asked whether they were of Ashkenazi or Sephardi origin or of mixed Ashkenazi/Sephardi origin. Of the 95 people who answered this question, 85% reported that they were Ashkenazi, 13% reported mixed Ashkenazi/Sephardi lineage and 2% reported that they were Sephardi. This once again confirmed that those being tested come mostly from the 'at risk' (Ashkenazi) population, but also indicated some admixture of Sephardi ethnicity within the predominantly Ashkenazi population.

- 5.19 The partnership status of all those being tested was asked. 93% were in partnerships at the time of testing and 7% were single. One third (16 couples) attended as couples. An additional 3 couples were tested separately but within 2 weeks of each other. Of those who were in partnerships (89 individuals) 79 had Jewish partners (89%); 3 (3%) described their partner as not Jewish and 7 described their partner as mixed Jewish/ non-Jewish (defined as 1-3 Jewish grandparents).
- 5.20 74 patients whose partners were either fully or partly Jewish were asked about the Ashkenazi/Sephardi origins of their partners: 66 (89%) reported their partner to be Ashkenazi, 1 (1%) reported their partner to be Sephardi and 7 (10%) reported their partners to be of mixed Ashkenazi/Sephardi origin. This indicated that the target population (that is, couples where both partners are Ashkenazi Jewish) is predominantly the population that is being tested.
- 5.21 From the raw data it is also possible to extract the number of couples in different risk categories for being a Tay Sachs disease carrier couple. The category with highest risk is obviously where both members are fully Jewish (4 grandparents) and Ashkenazi ie. an AJ/AJ couple. 19 couples were tested together (or within a short time frame of each other) and data were collected on their status as an Ashkenazi Jewish couple or otherwise. Complete information was obtained for 18 of these couples. 58 patients who have partners were tested alone, and data on their partners' Jewish status was collected. 39 of these patients provided complete data, thereby giving complete information for another 39 couples. Complete Ashkenazi Jewish status information was thus available for 57 couples (18+39). Figure 5.7 shows that for two thirds (38/57) of the couples tested, both partners were of Ashkenazi Jewish descent with 4 Jewish grandparents. In 3 couples, 1 partner was non Jewish and in other couples there was mixed Jewish or non Jewish lineage.
- 5.22 Almost a third of patients (31%) were pregnant, or the partner of a pregnant woman, at the time of testing. The gestation age was 8-25 weeks with an average of 13 weeks. Figure 5.8 shows the distribution of testing times in pregnancy. It can be seen that half the pregnant patients/partners were attending in the second trimester of pregnancy a finding that is of concern as it allows little time for consideration and acting on positive carrier results. Of the 66 patients who were not pregnant, 63 (96%) were attending for preconception testing. The remainder were attending testing later in life to discover whether their adult children would need to be tested.



Figure 5.7 Jewish status of couples being tested

Jewish Status Key:

AJ: Ashkenazi, all 4 Grandparents Jewish

MJ: Mixed Ashkenazi/Sephardi, all 4 Grandparents Jewish

SJ: Sephardi, all 4 Grandparents Jewish

AM: Ashkenazi lineage on Jewish side of family, mixed Jewish/Non-Jewish Grandparents NJ: Non-Jewish

Figure 5.8 Distribution of testing time in pregnancy



5.23 17 patients (18%) reported having a family history of Tay Sachs disease either through having an affected relative, or a relative or partner who is a known carrier of Tay Sachs disease. Of the 17 patients, 4 had an affected relative; 2 of the patients were from the same family and 1 of the 4 patients was not Jewish. The remainder (82%) had no family history.

Pathways to testing

5.24 Patients were asked how they became aware of Tay Sachs disease testing. It can be seen (Fig 5.9) that health care providers are very rarely mentioned: only 4 (4%) of the 96 patients were informed in this way, in both cases by their GP. The most common source of information was a relative (37% of patients) or a friend (13%).



Figure 5.9 How did you first become aware of Tay Sachs disease testing?

- 5.25 Patients were also asked how they had accessed testing and to note any problems they had encountered. These questions were answered by 77 of 96 patients. 18 of the 77 patients (23%) had asked their GP about Tay Sachs disease testing. A third of GPs knew of testing and had given patients the correct information. 4 of the 18 GPs were initially unaware of Tay Sachs disease testing, but researched it and subsequently provided the patient with information about the walk-in clinic at Guys, the Barnet Hospital chemical pathology service or Jewish Care. 2 of the 18 GPs referred to a Regional Genetics Clinic who forwarded the referral to Guys. But a worrying one-third of GPs gave either no information, or incorrect information, to their patients.
- 5.26 30 patients or partners attended for testing during pregnancy. As some of these patients attended as pregnant couples, this data relates to 20 pregnancies. 10 patients reported that they proactively asked their antenatal care providers about Tay Sachs disease testing. Of these, 3 were given information about the Guy's walk-in clinic (including 1

who was given this information by a private obstetrician). However, the remaining 7 reported negative experiences.

- 4 were given no information by antenatal clinic staff but succeeded in finding information about the Guy's walk-in clinic on the internet.
- 1 was told by her midwife that testing was available but later learned that the local laboratory had discarded the sample because they did not know what to do with it. The patient continued investigating alone and found information about Guy's walk-in clinic on the internet. By this time she was 17 weeks pregnant.
- 1 patient received conflicting information from 3 different health professionals and did not finally find information about the Guy's walk-in clinic until she was 25 weeks pregnant.
- 1 patient was referred by her midwife to her GP, and by her GP (after researching the subject) to the local genetics department, who contacted the patient and told her about the Guy's clinic. By this time, she was 18 weeks pregnant.

It is noteworthy that 6 out of the 7 patients who reported these negative experiences were in 4 Trusts that are in areas with high Jewish populations. Their experiences are at odds with the claims from 3 of these Trusts that they offer testing if requested by the patient (as in these cases), and from 2 of the Trusts that they offer screening proactively.

- 5.27 Aside from the 10 patients described above, 20 other patients/partners were tested during pregnancy. A breakdown of their pathways to testing is as follows:
 - 6 were partners of the above women who came along to the walk-in clinic together once they had discovered this as the way to access testing.
 - 5 patients were told by a relative how to access testing.
 - 5 patients asked their GPs about Tay Sachs disease testing in pregnancy (the experiences of these patients are also included in the GP pathway section above, but that section does not break down the group into pregnant/non-pregnant patients). Of these 5 patients, 1 was correctly told about the Guy's clinic; 1 was told about the testing service at Barnet but was not successful in accessing testing there and eventually found out by herself about the Guy's clinic; and in 3 cases the GP did not initially know about Tay Sachs disease testing, but researched it and found information for the patients.
 - 3 were partners of the 5 women who asked their GPs.
 - 1 accessed a Jewish Care leaflet that contains contact details for various clinics. The patient was unsuccessful in accessing testing at the Barnet clinic, so chose another suggestion on the leaflet and came directly to the Guys walk-in clinic.
- 5.28 Figure 5.10 shows that the majority of patients (51/96) were able to access Tay Sachs disease testing after making an enquiry through one route. Of these, the most common sources were through the internet (18/51) and from a relative or friend (16/51). 26 of the 96 patients (27%) described having more steps in their pathway to testing. These patients had to be more persistent, as they had to consult more than one health professional or source of information before finally finding out how to get a Tay Sachs disease carrier test.





Figure 5.11 Source of screening information for 51 patients who had a single step pathway to testing



5.29 Irrespective of the number of steps in the pathway to testing, the final source of information that actually led the patient to access testing is shown in Figure 5.12. The most common final step was via the internet, a relative or friend, or Jewish Care.



Figure 5.12 Final source of information

Test results

5.30 7 out of 96 patients were found to be carriers. 5 of these patients were from families in which there was a known carrier or affected individual. In addition, 1 patient was detected as being a carrier of a B1 variant.

Knowledge and attitudes about carrier testing in young Jewish people

- 5.31 A quantitative web-based questionnaire to assess attitudes to carrier testing was emailed to members of the Union of Jewish Students (Simon 2008). The questionnaire consisted mainly of closed, multiple-choice questions that examined degree of religiousness, awareness of Tay Sachs disease, knowledge about the characteristics and genetics of Tay Sachs disease, general attitudes towards carrier testing, and interest in the Tay Sachs disease carrier test.
- 5.32 The questionnaire was returned by 107 students. 92% of the students had heard of Tay Sachs disease and 90% of these individuals were aware of the screening test. 30% had already been tested. 72% of those who had not yet been tested indicated that they definitely or probably wanted testing in the future.
- 5.33 Religious outlook was found to affect interest in carrier testing: 86% of those who considered themselves religious or somewhat religious had been tested or were interested in testing, compared to 69% of those who were more secular in outlook. Individuals with a positive general attitude towards carrier testing were significantly more likely to want the Tay Sachs disease carrier test than those with a less positive attitude.
5.34 There was no correlation between interest in the test and level of knowledge about Tay Sachs disease and its genetics. These findings differ from those of some other surveys, which have suggested that increasing knowledge has a positive effect on uptake of testing (Barlow-Stewart 2003). The researchers suggest that their sample may be a particularly knowledgeable subset of the overall target population.

Conclusions

- 5.35 The results of the two surveys carried out as part of this review provide further evidence that the NHS is not providing effective access to testing for the target population. Most people undergoing testing find out about it via family, friends or the internet rather than through health care professionals such as GPs or midwives. Although these other sources of information are important and to be encouraged, their effective use depends on patients being proactive in seeking out testing. As the analysis in Chapter 4 has shown, the result is that testing coverage is very incomplete.
- 5.36 Just under one fifth of patients are aware of known carriers of Tay Sachs disease in their family, or a family history of Tay Sachs disease, indicating that there is a cascade effect occurring naturally which influences who attends for testing. 5 of the 7 carriers in the surveyed sample of patients came from this group.
- 5.37 About one-third of carrier testing is taking place in the antenatal period, but the majority of testing is preconception. These proportions would be appropriate if it could be assumed that most people had already been tested before pregnancy. Although many Trusts in areas with large Jewish populations assume that this is the case, this assumption is unlikely to be justified, particularly in the segment of the Jewish population that is not Strictly Orthodox.
- 5.38 The independent survey of Jewish students suggests that even amongst those who are aware of and interested in Tay Sachs disease carrier testing, this does not always translate into immediate uptake of testing. If these findings are generalisable to the wider Jewish population, they suggest that preconception screening must be complemented by prompt and effective access to testing in the antenatal period, when it is immediately relevant.
- 5.39 There was no evidence that midwives in areas with substantial Jewish populations are routinely suggesting Tay Sachs disease screening to Jewish patients at the antenatal booking-in appointment, as in this 7 month period, none of the patients surveyed described this route to testing. No clear and consistent protocols or pathways seem to exist for Tay Sachs screening within antenatal screening services; for example, there is no agreed question for seeking information about Ashkenazi Jewish family origin. Hence there is confusion about the appropriateness of offering screening in different situations, and many ANSCs acknowledged that they require further advice on this issue. Several patients had experienced delays in seeking access to testing during pregnancy, even in Trusts that serve areas with high Jewish populations and that claim to offer screening proactively and/or on request. More proactive advertising of the Guy's service, together with information and training for midwives and ANSCs, might help to remedy this situation.

5.40 The ethnic background of individuals and couples attending for testing is predominantly Ashkenazi Jewish. Most individuals were aware of their ethnic origins and able to say how many of their grandparents were Ashkenazi Jewish, suggesting that it would be feasible to ask such a question as a way of identifying individuals who might benefit from carrier testing. However, it should be kept in mind that the surveyed group, many of whom had been proactive in seeking testing, may be more knowledgeable than average.

6 Other models for carrier screening for Tay Sachs disease and other recessive disorders

Introduction

- 6.1 Several other countries, as well as the international Dor Yeshorim organisation, have in place state-funded and/or private programmes or facilities for Tay Sachs disease carrier testing or screening, sometimes as part of screening for carrier status for a wider panel of diseases for which the Ashkenazi Jewish population is at increased risk. Some programmes offer only antenatal screening, while other programmes include preconception screening as an outreach activity in schools and/or community groups. Carrier testing or screening programmes for Tay Sachs disease in Israel, Canada, Australia and the United States were investigated by Sara Levene during 2005 as part of a Department of Health-funded Visiting Fellowship in Genetics in Health Care. The relevant sections in this Chapter are taken from her Fellowship report and from further, more recent information provided by Dr Gideon Bach of Hadassah University Hospital, Jerusalem.
- 6.2 In the UK, antenatal carrier screening is available as an NHS service for sickle cell disease and thalassaemia, both of which, like Tay Sachs disease, are recessive genetic conditions that are relatively more prevalent in particular ethnic groups. Experience with these programmes may be relevant to efforts to achieve a more systematic approach to Tay Sachs disease antenatal carrier screening and may offer opportunities for combining some aspects of practice or resources. Preconception carrier screening for sickle cell disease and thalassaemia are under consideration but the NSC has not so far taken a decision to extend carrier screening beyond the antenatal setting.

Tay Sachs disease carrier screening in other countries

Israel

- 6.3 In Israel, Tay Sachs screening is an official population screening programme funded by the Ministry of Health, and therefore free to the population under Israel's public health insurance scheme.
- 6.4 Approximately 45% of the Israeli population are Ashkenazi Jews, 35% are Sephardi or Mizrahi and 20% are of other origin (including Arab). The carrier frequencies for Tay Sachs disease have been estimated to be 1 in 25 for Israeli Ashkenazis, and 1 in 80 for Israeli Sephardis of North African origin. Unlike in previous generations, it is now more common for Israeli Jews from different ethnic backgrounds to marry, but 25% of marriages are still between two Ashkenazim. The Israeli Society of Medical Genetics recommends a cut-off point for screening at a carrier risk of 1 in 60.
- 6.5 Screening is targeted at the antenatal period but preconception testing is available to individuals on request. Screening is carried out at Genetics Departments and other screening centres, which may also offer screening for other conditions; however, only screening for Tay Sachs disease and cystic fibrosis is Government-funded.

- 6.6 In the antenatal screening programme, one member of a couple is tested first; only if he/she is a carrier is their partner tested. Screening policy has recently been changed. Previously, all screening was by the biochemical assay. The current policy (effective from 1 August 2008, G. Bach, personal communication) is that Ashkenazi couples (that is, where all four grandparents are Ashkenazi) are screened only by analysis for the 3 Ashkenazi founder mutations. For those of North African origin (that is, full or partial origin from Morocco, Libya, Algeria or Tunisia), the screening panel is the 3 Ashkenazi mutations plus 3 North African founder mutations. If one member of a couple is found to be a carrier and his/her partner has North African roots, biochemical testing in leucocyte samples is carried out in addition to mutation analysis.
- 6.7 At the screening centres a 5-minute educational video and leaflet about Tay Sachs disease are provided by the Ministry of Health. The video also mentions that some other genetic conditions are common in the Jewish community and that carrier testing for these is available as a private service. Each patient attending the walk-in service is seen by a nurse, who checks that the patient has a basic understanding of the test. Detailed information on family origins is recorded for every patient (place of birth of the person's four grandparents, and their partner's four grandparents) and their risk of being a carrier is calculated.
- 6.8 Two audits have been carried out by the Ministry of Health, to assess patients' knowledge and understanding of Tay Sachs disease screening. Disappointingly, these showed that most patients have very little knowledge before screening, and many still have poor understanding after viewing the video.
- 6.9 Negative results are sent to patients by letter and positive results are communicated by telephone by a genetic counsellor. Carriers are then advised that their partner should be tested. Carrier couples are offered full genetic counselling, and so presumably it is at this time that patients become better informed about the implications of carrier status.
- 6.10 Genetics centres also offer molecular-genetic carrier testing for several other genetic conditions (for example, Canavan disease, familial dysautonomia, Bloom syndrome, Fanconi anaemia C) on a private basis. These testing services are separate from the government-funded Tay Sachs disease screening programme and compete with each other. Walk-in clinics are held, often on several days each week, and are attended both by pregnant couples and occasionally those planning to conceive. In some clinics, patients receive only written information about the tests and blood is taken by a nurse. In others, a genetic counsellor sees all patients. Positive results are given by phone by a genetic counsellor, and negative results by letter.
- 6.11 Although the initial carrier testing for these conditions is only offered on a private basis, the Ministry of Health does fund carrier testing for the partners of those who test positive, and also prenatal diagnosis and termination of pregnancy (if requested) for those couples who are found to be both carriers of the same condition.
- 6.12 There is anecdotal evidence from geneticists and genetic counsellors that the Israeli public, who are now well-informed about the availability of genetic testing and screening, and are culturally disposed to utilise all available tests during pregnancy,

are preferentially choosing to use the services of genetics centres that offer the largest number of tests. It is extremely rare for patients to decline any test that is offered as part of a panel, even for conditions that might be regarded as less severe (such as Gaucher disease, or Connexin 26 mutations associated with non-syndromic deafness).

Canada (Montreal)

- 6.13 Tay Sachs disease carrier screening for Jewish secondary school students was pioneered in Montreal in 1972-76 by Clow (1977) and was initially driven by community pressure. It is publicly funded by the Canadian healthcare system and is hosted by the genetics department of the Montreal Children's Hospital. The programme is run by a dedicated Screening Coordinator, who is not a genetic counsellor, but who has developed the knowledge and skills to deliver the educational aspects of the programme and to handle results. Long-term research has demonstrated the success of the Canadian programme, and a lack of harmful effects (Zeesman 1984, Mitchell 1996).
- 6.14 Each Jewish school is visited annually and screening offered to students over the age of 16. An initial educational session is followed by a screening session within one week, when blood samples are taken from those who wish to take up the screening offer. Under Quebec law, individuals over the age of 14 are able to self-consent for genetic testing.
- 6.15 The programme was initially run jointly with Dor Yeshorim in Montreal, in that students could choose to be assigned a Dor Yeshorim PIN number and their sample would go forward for anonymous testing. However, over time problems developed with this arrangement and Dor Yeshorim now operates independently of the state-run secondary school screening programme.
- 6.16 Testing is by the biochemical method in serum samples but the Genetics Department is currently considering whether to switch to DNA testing. The decision is likely to depend on whether to move towards offering multiplex testing for a panel of Ashkenazi Jewish genetic conditions. It is thought that there would be community interest in such a service, as some Jewish patients are already accessing the panel test via private laboratories in the US. A research project has been proposed to compare serum testing with molecular testing, including testing for other diseases.
- 6.17 Soon after the establishment of the Tay Sachs disease screening programme, the Greek and Italian communities in Montreal requested a similar programme for thalassaemia screening. This programme now runs side by side with the Tay Sachs programmes, targeting Catholic and Greek Orthodox secondary schools. Interestingly, thalassaemia carrier screening is also offered to Sephardi Jewish students. In certain pockets of the French Canadian community there is also an increased risk of Tay Sachs disease. However, carrier testing in these groups is generally done by a cascade approach in families rather than by general population screening.

Australia

6.18 Secondary school screening programmes have been independently established in Sydney and Melbourne, and are based on the model of the Montreal screening programme.

The programmes, which began in Sydney in 1995 and Melbourne in 1997, are hosted by the Genetics Departments of the North Shore Hospital in Sydney and the Royal Victoria Children's Hospital in Melbourne. In Sydney the programme is overseen by a working party that includes geneticists and representatives of Jewish organisations. This programme was initially funded by Jewish philanthropy through the Wolper Jewish Hospital but has since received state funding. The Melbourne programme is funded by a charitable grant from a Jewish organisation.

- 6.19 Screening in Jewish secondary schools and a small number of private schools was found to be significantly more successful than screening in other community settings (youth groups, sports groups etc). The Sydney programme was given Rabbinical approval provided an option of anonymous screening was available. In this system (Programme A), students are given a PIN number and tested anonymously. The PIN number is used in the future for checking the compatibility of potential partners. (This programme was initially run jointly with Dor Yeshorim but, as in Canada, this arrangement has now stopped.) Under Programme B, students are given their results directly. A third option (Programme D) allows students to defer receiving their results until a later date. They are initially given a PIN number that is held, together with the individual's details, by a 'Gene Trustee' at the Wolper Jewish Hospital. When, at a later date, they wish to access their results, they can contact the laboratory or, if they have lost their PIN number, the Gene Trustee. They can elect to receive their result or to be placed in Programme A. Only a minority of students, even in Orthodox schools, choose Programme A. The Melbourne programme offers variations of schemes A and D, allowing students to receive a PIN number which they can use to obtain their result directly from the genetics centre at any time in the future, or which can be used for arranged introductions prior to marriage.
- 6.20 A significant aspect of the success of the Sydney and Melbourne programmes is their education programme. A genetic counsellor visits the school several days before the day of sample collection and gives an hour-long presentation to students in the last two years of school. The presentation includes details of Tay Sachs disease, recessive inheritance, and how the screening programme works. The programme has been formally evaluated and found to be effective. Educational alternatives using computer-based resources are also being explored.
- 6.21 Screening is by molecular genetic testing using a buccal swab sample. However, the laboratories retain the ability to offer the biochemical test where necessary. In Melbourne, the switch from blood samples to buccal samples has increased the uptake of screening from 80% to 95%. In Sydney, the granting of state funding for Tay Sachs disease carrier screening enabled the charitable funds to be used to extend screening to an additional 4 conditions [Fanconi anaemia, Canavan disease, cystic fibrosis (Ashkenazi Jewish mutations) and familial dysautonomia]. Most students in Sydney opt for all 5 tests.
- 6.22 The Sydney secondary school screening programme has been extended to target state schools where there is a large proportion of Jewish students, and also students from a variety of other ethnic backgrounds. In these schools, cystic fibrosis carrier screening is offered to students of white European background, and thalassaemia carrier screening to students of Asian origin.

USA

- 6.23 Healthcare in the US is a fully privatised system. The availability of carrier testing is very variable and may or may not be covered by an individual's medical insurance. Two examples of testing provision in the US are antenatal testing in New York and community testing in Philadelphia.
- 6.24 Tay Sachs disease testing in New York is paid for by the patient or their medical insurance policy. Testing is targeted at the antenatal period but preconception testing is also available on request. Testing is initially offered to one member of a couple (and preferably the member from the Ashkenazi Jewish population if the couple is of mixed background) up to 14 weeks of pregnancy. After that time, testing is offered to both members.
- 6.25 Testing is offered at several Clinical Genetics departments around the New York area. Patients may be referred by obstetricians or may self-refer. The carrier testing clinics are staffed by genetic counsellors who see each patient/couple, but only basic genetic counselling is considered necessary. Some obstetricians send samples directly for testing.
- 6.26 At one clinical genetics centre, group information sessions are held twice weekly. A genetic counsellor gives a presentation on Ashkenazi Jewish ancestry, autosomal recessive inheritance, prenatal diagnosis and reproductive options for carrier couples. Blood is then taken from those who would like to proceed with testing.
- 6.27 Testing is performed by either molecular-genetic testing or biochemical testing (this varies between centres). Each centre processes its own samples. Molecular testing for other Ashkenazi Jewish genetic diseases is offered at the same time and the panel of diseases tested for is increasing. Turnaround time for results is typically 2 weeks. All carriers are contacted by phone and all carrier couples are seen for genetic counselling.
- 6.28 The Strictly Orthodox population in New York is served almost exclusively by the Dor Yeshorim programme, which has few links with the mainstream genetics centres but whose activities have been influential in leading to the inclusion of more diseases in the testing panels offered by genetics centres.
- 6.29 In Philadelphia, a community screening programme based in a local Clinical Genetics department targets screening at university students, young professionals, engaged couples and newly-weds. Secondary school screening is not undertaken because US law requires parental consent for genetic testing in under 18s.
- 6.30 The programme was initially funded by a research grant but now receives additional support from Jewish philanthropists. The funding is used to employ a full-time outreach worker who is not a genetic counsellor but has been trained to provide education and information on the screening programme. The charitable funding allows screening to be offered free, as insurers do not generally cover the costs of preconception testing.

- 6.31 Community screening sessions take place annually at Penn University for Jewish students. All screening sessions are staffed by genetic counsellors. Following a screening session an outreach worker gives out negative results and a genetic counsellor gives out positive results. The project has also recruited a group of Jewish students who organise fundraising activities. The outreach worker also attends regular meetings of community groups which organise activities aimed at young Jewish adults, and gives educational talks to various groups in the community, including at Jewish secondary schools.
- 6.32 Molecular testing is used for Tay Sachs disease screening and testing for other Ashkenazi Jewish genetic diseases is offered simultaneously.

Antenatal sickle cell and thalassaemia screening in the UK

- 6.33 The haemoglobinopathies (sickle cell disease and the thalassaemias) are autosomal recessive genetic disorders of haemoglobin production. In the UK, sickle cell disease affects mainly Black Caribbean, Black African and Black British communities, with carrier frequencies ranging from about 1 in 6 (Black Caribbeans) to 1 in 4 (Black Africans) (Zeuner 1999). The highest prevalence of thalassaemia is in the population of Cypriot, Indian, Pakistani, Bangladeshi or Chinese origin, with carrier frequencies ranging from 1 in 5 (Cypriots) to about 1 in 13 (Bangladeshis). It was estimated in 1999 that about 140-175 babies with sickle cell disease were born each year, and about 10-25 with beta-thalassaemia (Hickman 1999).
- 6.34 The NHS Sickle Cell and Thalassaemia (SCT) Screening Programme includes two linked programmes:
 - Antenatal screening for sickle cell disease and thalassaemia: the aim of this programme is to allow informed reproductive choice by identifying couples at risk of an affected infant at an early stage in pregnancy.
 - Neonatal screening for sickle cell disease: early diagnosis of sickle cell disease allows interventions that reduce complications and deaths from this condition in infants.
- 6.35 Some preconception carrier testing for thalassaemia and sickle cell disease occurs in families where there is a known carrier or affected individual, but a systematic population carrier screening programme has not so far been approved and would require a Ministerial decision.
- 6.36 The form of antenatal haemoglobinopathy screening varies in different regions of the country according to the prevalence of the conditions.
 - Thalassaemia screening using routine blood indices is available to all women as part of routine antenatal care. Partners of identified carriers are also offered screening.
 - For sickle cell disease and other significant variants, trusts in high prevalence areas (fetal prevalence >1.5 babies with sickle cell disorders per 10,000 births) offer laboratory screening to all pregnant women, and to all partners of identified carriers. All other areas offer laboratory testing to women who are assessed as being at increased risk on the basis of a Family Origin Questionnaire, and to the partners of identified carriers.

- 6.37 The Family Origin Questionnaire (FOQ; see Appendix 6) seeks information about the geographical origins of the families of both the pregnant woman and her partner, going back at least two generations, or more if possible. Accompanying guidance for health professionals explains that the FOQ is used both to identify women who are at the highest risk of having a baby affected by a haemoglobin disorder, and to aid in the interpretation of carrier testing results, particularly those for the thalassaemias.
- 6.38 Standards for the programme state that carrier testing should be carried out by 10 completed weeks of pregnancy and the whole process by the end of the 12th week of pregnancy, including termination of pregnancy if the baby is affected and the couple wishes to take up this option.
- 6.39 The antenatal screening programme has formal objectives and standards covering aspects including:
 - Screening coverage
 - Timeliness of screening offer
 - Laboratory standards and quality control
 - Reporting times
 - Expert counselling for women/couples with high risk pregnancies
 - Minimising adverse effects of screening
 - Clear responsibilities for all professional groups
 - Ensuring appropriate knowledge, understanding and skills of professionals involved in the screening programme
 - Education and awareness of the screening programme in the wider community
 - Regular evaluation, reporting and feedback on the operation of the programme.
- 6.40 Implementation of the SCT Programme can provide some insight into what might be required for an antenatal Tay Sachs screening programme, although the target populations are larger, with higher carrier frequency for the conditions. The recent consolidated annual report for the programme documents six years of development time from the setting up of the programme in 2001. Full implementation of the antenatal programme to include low prevalence areas was due at the end of September 2008. Major areas for programme development included:
 - developing laboratory capacity
 - establishing working relationships with laboratories
 - developing quality assurance for the laboratories
 - major work to develop and evaluate the FOQ as a tool for identifying individuals of target ethnic background
 - developing counselling skills and capacity
 - a large education programme (Pegasus) to develop and provide education and training for a wide range of health professionals
 - work on communication
 - the development of public information.

Conclusions

6.41 Tay Sachs disease carrier testing or screening programmes in Israel, Australia, Canada and the US have both strengths and weaknesses that may be relevant in considering options for the UK programme. The Israeli system is universal and systematic but

such a system may not be feasible in countries where Jews constitute a much smaller proportion of the population. Antenatal testing or screening programmes (Israel and New York) target the population at a time when testing is directly relevant, but have the disadvantage that additional stress and worry may be caused at this time, and that they are not acceptable to Strictly Orthodox Jews. Preconception screening (Canada, Australia and Philadelphia) causes less trauma but is not systematic and is dependent on high-quality education programmes to ensure that test results are understood and recalled correctly. This approach also potentially screens twice as many people as necessary because it is not couple-based.

- 6.42 There is a tendency in most Tay Sachs disease screening programmes to move towards offering molecular-genetic Tay Sachs disease carrier testing rather than the biochemical test, mainly because screening can then be readily extended to include other genetic conditions. Pressure for this change is coming largely from the Jewish community itself.
- 6.43 Antenatal carrier screening programmes for haemoglobin disorders in the UK are already well developed, and many aspects of their standards and operating procedures are likely to be relevant to the development of antenatal carrier screening for Tay Sachs disease. However, the target population for these screening programmes is larger, and the carrier frequencies higher, than for Tay Sachs disease in the Ashkenazi Jewish population. It is probably not feasible to achieve a comparably systematic, national carrier screening programme for Tay Sachs disease.
- 6.44 The Family Origin Questionnaire has proved to be an effective tool for identifying couples at high risk of having a child affected by a haemoglobin disorder, and could be revised to include a question on Ashkenazi Jewish origin. The FOQ is the result of a process of extensive consultation and validation involving a range of clinical, community and religious groups. A similar process would be required to add a question on Jewish ethnic origin, and educational initiatives among antenatal health professionals across the country would be essential to raise awareness of how to use the questionnaire and how to refer women appropriately.

7 Tay Sachs disease carrier testing methods

Introduction

7.1 Carrier testing for Tay Sachs disease can be carried out by a biochemical assay of hexosaminidase A (HexA) activity in serum, leucocytes or platelets, and/or by direct DNA testing for one or more of the known causal mutations for Tay Sachs disease.

Biochemical testing

- 7.2 Both HexA and the HexB enzyme will cleave the synthetic substrate 4-methylumbelliferyl-B-D-N-acetylglucosamine, breaking it down to a fluorescent product, 4-methylumbelliferone, which can be used to determine the amount of enzyme present (Kaback 1977). HexA can be measured in the presence of HexB by making use of the different properties of the two enzymes: HexA is heat- and acid-labile, whereas HexB is heat- and acid-stable.
- 7.3 The assay is performed by measuring the enzyme activity twice. In the first assay, the total hexosaminidase activity is determined. In the second assay, the sample is heated to 50°C to destroy the HexA activity. By subtracting one result from the other, the amount of HexA activity can be determined and expressed as a percentage of the total activity:

%HexA activity = [(Total Hex activity - Stable HexB activity) / Total Hex activity] x 100

- 7.4 Cut-off points are chosen from standard curves for the percentages of HexA activity in carriers and non-carriers. Each laboratory must build up its own reference ranges for carriers and non-carriers.
- 7.5 Internal quality control procedures for these assays are essential. Samples from confirmed carriers and normal controls are always run with the samples under test, to confirm the reproducibility of each assay.

Choice of samples for testing

- 7.6 HexA activity may be measured in serum, leucocytes or platelets. The serum-based assay has often been used for population-based carrier screening because it is simple, inexpensive and applicable to all populations regardless of ethnic origin. As it can be carried out on specimens that have been frozen, samples can be stored before analysis if necessary, and repeat tests can be carried out without the need to return to the patient for a further blood sample.
- 7.7 However, the serum assay is not always reliable. In particular, in women who are pregnant or on oral contraceptives, or in individuals who are diabetic or taking various medications, the presence of other heat-stable isoenzymes raises the total hexosaminidase activity, and therefore the %HexA activity appears proportionately lower, giving a false-positive result. According to Bach (2001), in the Ashkenazi Jewish population about 7.7% of samples tested by the serum assay are inconclusive, while 87.5% are non-carriers and 4.8% are in the carrier range. (These data come from the

Dor Yeshorim programme and therefore do not include any pregnant women.) Fewer inconclusive results are obtained with the leucocyte assay and many laboratories do not use an 'official' inconclusive range, but there are still some samples for which the results are borderline or difficult to interpret, and for which further analysis is required.

7.8 A further source of false-positive results in the biochemical assay are pseudodeficiency alleles (see Chapter 2): benign alleles that do not cause Tay Sachs disease but are associated with reduced degradation of the synthetic substrate used to measure HexA activity. Pseudodeficiency alleles account for about a third of enzyme-diagnosed non-Jewish carriers who do not have a family history of Tay Sachs disease, but are rare in Jewish individuals.

Molecular genetic testing

- 7.9 Molecular genetic testing may be carried out on DNA extracted from blood or from cells obtained by a non-invasive method such as a buccal swab.
- 7.10 In Ashkenazi Jews, targeted mutation analysis is used to detect the three most common Tay Sachs disease mutations in this population (+TATC1278, +1IVS12 and G269S; see Chapter 2). In non-Jews, the testing panel normally includes the +TATC1278 and G269S mutations, plus the +1IVS9 mutation (which is not found in Ashkenazi Jews). If mutation testing is being used to investigate samples (from either Jews or non-Jews) that test positive for the biochemical assay, the pseudodeficiency allele Arg247Trp and sometimes the much rarer pseudodeficiency allele Arg249Trp are included in the testing panel.

Characteristics of the DNA and biochemical tests

7.11 Accurate calculation of the sensitivity and specificity of a test requires the definition of a 'gold standard' against which test performance can be measured, and a defined population in which the test is being assessed. In the case of Tay Sachs disease carrier testing, both of these parameters are difficult to define in practice.

Test characteristics in Ashkenazi Jews

- 7.12 The most comprehensive analysis of the biochemical and DNA tests in Ashkenazi Jews has been carried out by Bach et al (2001) using data from the international Dor Yeshorim programme. In Table III of their paper, Bach et al quote sensitivities of 98.82% for the DNA test, and 99.08% for the biochemical assay when the protocol involved testing in serum followed by testing of inconclusive samples in leucocytes or platelets, with any results that were still inconclusive classed as positive. They designate this test ES+EL-IAP. The respective specificities are stated as 100% and 99.01%.
- 7.13 Using these figures, and assuming a carrier frequency of 1 in 27 in Ashkenazi Jews, the positive and negative predictive values of the DNA test are 100% and 99.97% respectively, the false negative rate 1.18% and the false positive rate 0%. The left part of Table 7.1 summarises these results. The false-positive and false-negative rates for the biochemical test are roughly similar to those for the DNA test (around 1%) but,

because of the lower specificity of the biochemical test and the comparative rarity of Tay Sachs disease even within the Jewish population, the positive predictive value (PPV) of the biochemical test (73.5%) is significantly lower than that of the DNA test.

	Bach et al (2001)		Combined literature analysis	
	ES-EL-IAP protocol	DNA	Biochemical leucocyte	DNA
Sensitivity (%)	99.08	98.82	99.77	87.29
Specificity (%)	99.01	100	89.32	99.89
False-positive rate (%)	0.99	0	10.68	0.11
False-negative rate (%)	0.92	1.18	0.23	12.7
PPV (%)	73.53	100	26.41	98.47
NPV (%)	99.97	99.97	99.99	99.37

Table 7.1 Test characteristics for the	e 3-mutation	DNA test	and the	biochemical	l test
(in leucocytes) in Ashkenazi Jews					

- 7.14 In their paper, Bach et al do not clarify the source of their estimates of sensitivity and specificity for the two tests. Gideon Bach (personal communication) has informed us that they were calculated by population geneticist Neil Risch, using both data quoted in the paper and additional data from the Dor Yeshorim programme.
- 7.15 As an alternative method, we have carried out a reciprocal comparison of the DNA test and the biochemical test in leucocytes, using data from 5 papers (including Bach et al) in which data are provided for both tests (Table 7.1, columns on right). We have assumed that inconclusive results in the biochemical test are classed as positive, and that the biochemical test in leucocytes and the ES-EL-IAP test are equivalent. We have also assumed that pseudodeficiency alleles give false positive results in the biochemical test. Only 3 of these papers provide data for test results in non-carriers, and for biochemical test results in mutation-defined carriers; therefore, our calculations for the sensitivity of the leucocyte assay, and the specificity of both assays, are based on these 3 papers. The evidence for our calculations is set out in Table 7.2.

	DNA test (vs leucocyte test as gold standard	Leucocyte test (vs DNA test as gold standard)
Sensitivity	79.2% (228/288) Ref A 82% (177/216) Ref B 94.3% (115/122) Ref C 93% (402/432) Ref D 92.9% (26/28) Ref E Overall 87.29% (948/1086)	100% (228/228) Ref A 99.4% (177/178) Ref B 100% (26/26) Ref E Overall 99.77% (431/432)
Specificity	100% (747/747) Ref A 99.3% (151/152) Ref B 100% (12/12) Ref E Overall 99.89% (910/911)	91.7% (740/807) Ref A 79.5% (151/190) Ref B 85.7% (12/14) Ref E Overall 89.32% (903/1011)
False-positive rate	0.11%	10.68%
False-negative rate	12.7%	0.23%
PPV	96.82%	26.41%
NPV	99.51%	99.99%

Table 7.2 Reciprocal comparison of DNA and biochemical tests, by combined analysis of data reported in the literature

Ref A Bach 2001; Ref B Triggs-Raine 1990; Ref C Grebner 1991; Ref D Kaback 2000; Ref E Landels 2003.

- 7.16 The major differences between our analysis and that of Bach et al are the values for the sensitivity of the DNA test, and the specificity of the biochemical test, which are both significantly lower when calculated from the published data than in the paper by Bach et al: 87.29% vs 98.82% for the sensitivity of the DNA assay, and 89.32% vs 99.01% for the specificity of the biochemical test. The lower specificity of the biochemical test leads to a large drop in the PPV, from 73.5% to 26.4%, while the drop in the sensitivity of the DNA test increases the false-negative rate from just over 1% to more than 12%.
- 7.17 The sensitivity of the DNA test is much higher if it is calculated from data on obligate Ashkenazi Jewish carriers rather than by comparison with the biochemical test. There is a strong argument for saying that the performance of the test in obligate carriers should be regarded as the gold standard. Bach et al tested 151 chromosomes from affected individuals and obligate carriers who had all four grandparents of Jewish origin from central or Eastern Europe, and found that all 151 contained one of these three mutations, giving a sensitivity of 100%. Other studies have reported sensitivities of 92% (Grebner 1991), 98% (Triggs-Raine 1990), 99% (Kaback 2000) and 100% (Landels 2003). Combining the results of all of these studies gives a sensitivity of 98.82% (337/341). This is the same as the value quoted in Table III of the paper by Bach et al.
- 7.18 It seems likely, therefore, that the true sensitivity of the DNA test in Ashkenazi Jews is higher than the value (87.29%) calculated using the leucocyte test as the gold standard. Bach et al carried out further analysis of 10 samples from the Dor Yeshorim programme that tested positive or inconclusive in the leucocyte biochemical assay, but negative for the three Ashkenazi mutations. Two were found to have pseudodeficiency alleles. Full sequencing of the *HEXA* gene in the remaining 8 samples revealed no mutation.

Test characteristics in non-Jews

- 7.19 Insufficient data are available to enable evaluation of the biochemical and DNA carrier tests in non-Jews. The sensitivity of the leucocyte assay is probably similar in Jews and non-Jews, but the specificity is likely to be considerably lower in non-Jews because of the much higher proportion of pseudodeficiency alleles. This low specificity, combined with the much lower carrier frequency for Tay Sachs disease in non-Jews, would be expected to lead to a very low PPV for the test.
- 7.20 By contrast, the specificity of the 3-mutation DNA test would be predicted to be similar in Jews and non-Jews but the sensitivity of the test is much lower in non-Jews because of the broad spectrum of pathogenic mutations in the non-Jewish population. From figures quoted in Kaback's 2006 Gene Reviews article (see Table 2.2), the sensitivity of the 3-mutation DNA test in non-Jews is only 20% (after correcting for pseudodeficiency alleles) in individuals identified as heterozygotes by the biochemical test, or 32% in obligate heterozygotes and affected individuals. If the +11VS9 mutation is included, the sensitivity rises to 36% for enzyme-defined carriers and 46% for obligate heterozygotes and affected individuals.
- 7.21 It is possible that the sensitivity of the DNA test might be higher in the non-Jewish population than is indicated by Kaback's review, particularly if the +1IVS9 mutation is included in the analysis. According to Landels (1992), this mutation accounts for 42% of Tay Sachs disease chromosomes in the UK non-Jewish population. In their study, DNA testing for the +1IVS9, +TATC1278 and +1IVS12 mutations in non-Jewish affected individuals and Tay Sachs disease carriers (including 11 obligate carriers and 4 enzymedefined carriers) detected mutations in a total of 15 out of 24 chromosomes, an overall sensitivity of 62.5%. However, the study is a small one and it is not clear whether these results can reliably be extrapolated to the whole non-Jewish population. It is also noteworthy that a mutation (+1IVS12) was detected in only 1 out of the 4 enzyme-defined carriers. Branda (2004) compared the Tay Sachs disease carrier frequency in individuals of Irish ancestry with those of English, Welsh or Scottish origin. Using the biochemical assay, they found an apparently elevated carrier frequency in the Irish individuals (1 in 25). However, only 2 out of 23 Irish putative heterozygotes carried a detectable pathogenic mutation (+1IVS9 in both cases) and 9 carried pseudodeficiency alleles. If all the enzyme-positive, mutation-negative individuals are classed as positive, the sensitivity of the DNA test as calculated from this dataset is only 2/(23-9) or 14.3%.

Residual risks after carrier screening

- 7.22 The performance of the tests can also be investigated by using Bayes' Theorem to calculate the probability that an individual who tests negative in the screening test is a false negative and thus actually a carrier of Tay Sachs disease. The risk that such an individual will have a partner who is a carrier can also be calculated, depending on whether the individual's partner is a screened or unscreened Ashkenazi Jew, Moroccan Sephardi Jew or non-Jew. (For Sephardis other than Moroccan Sephardis, the results of this analysis are the same as for the non-Jewish population.)
- 7.23 We have undertaken this analysis firstly for DNA testing (see spreadsheets in Appendix 7). The results of the calculations depend on the panel of mutations tested and the values chosen for the sensitivity of the test in Ashkenazi Jews and non-Jews. From the

information available, it appears that the best mutation panel for the UK population would be the three 'Ashkenazi Jewish mutations' plus +1IVS9; this (with the addition of one of the pseudodeficiency alleles) is the panel currently used in Guy's laboratory. The sensitivity of this test in Ashkenazi Jews lies somewhere between 87.3% and 98.8%. In non-Jews in the UK the sensitivity is much more difficult to estimate but likely to be substantially lower, probably falling somewhere within the range 20-50%. The sensitivity of this 4-mutation test in Moroccan Sephardis is unknown, but for this analysis has been assumed to be the same as for non-Jews.

- 7.24 The calculations show that, for the sensitivities at the lower end of the range (87.3% in Ashkenazi Jews and 20% in non-Ashkenazis) the probability that a screen-negative Ashkenazi Jewish person is actually a carrier is 0.00486, or 1 in 205. This value is higher than the 1 in 250 carrier risk for the general non-Jewish population. It is important also to consider the couple risk, because of the likelihood that the person's partner would also be an Ashkenazi Jew who may not themselves have been screened for carrier status. The couple risk ranges from 1 in 64,237 if the partner of a screened Ashkenazi Jew. As the risk that a carrier couple will have an affected child is 1 in 4 for each pregnancy, the risk that a screen-negative Ashkenazi Jew and an unscreened Ashkenazi Jew will have an affected child is 1 in 22,220. For comparison, an unscreened non-Jewish couple has a risk of 1 in 62,500 of both being carriers, and a risk of 1 in 250,000 of having an affected child.
- 7.25 At higher values of sensitivity for DNA testing (98.8% in Ashkenazi Jews and 50% in non-Jews), the residual risk for a screen-negative Ashkenazi Jew drops to 0.00046, or 1 in 2,167. The couple risk ranges from 1 in 4,698,779 if their partner is a screened Ashkenazi Jew to 1 in 58,527 if their partner is an unscreened Ashkenazi Jew. The latter risk is comparable to that of an individual from the unscreened non-Jewish population, and the former is very much lower.
- 7.26 In summary, if both members of an Ashkenazi Jewish couple have been screened by DNA testing, the risk that they are both carriers is small: 1 in 42,323 if the sensitivity of the test is at the lower end of the range, and 1 in 4,698,778 if it is at the upper end.
- 7.27 Table 7.3 shows ranking of the risks to a couple following screening of one partner by DNA testing, depending on the ethnic origin of the screened partner, and on both the screening status and the ethnic origin of the other partner. It shows that, at the lower sensitivity for DNA testing (87.3%) the risk of having an affected child is 11 times greater for an Ashkenazi Jewish couple if only one partner is screened than for the general population. At higher levels of sensitivity (98.8%) the risk to the couple where only one member is screened is broadly similar to that of the general population.

Table 7.3 Ranked risks for couples after screening of Ashkenazi	, non Jewish and
Moroccan Sephardi Jews by a 4-mutation DNA test	

		Couple risk	Risk of child
Lowest sensitivity (87.3%)		1 in	1 in
Unscreened AJ co	uple	729	2,916
Screened MS X Un	screened AJ	2,018	8,072
Screened MS X Un	screened MS	4,485	17,940
Screened AJ X Ur	screened AJ	5,555	22,220
Screened MS X Scr	reened MS	5,588	22,352
Screened Non-J X	Unscreened AJ	8,431	33,724
Screened AJ X Uns	screened MS	12,343	49,372
Screened MS X Scr	eened AJ	15,378	61,512
Screened MS X Un	screened Non-J	18,688	74,752
Screened Non-J X	Unscreened MS	18,735	74,940
Screened MS X Scr	eened Non-J	23,341	93,364
Screened AJ X Sc	reened AJ	42,323	169,292
Screened AJ X Uns	screened Non-J	51,431	205,724
Unscreened Non-J	ewish couple	62,500	250,000
Screened AJ X Scr	eened Non-J	64,237	256,948
Enzyme-screened AJ X Unscreened AJ		76,331	305,324
Screened Non-J X Unscreened Non-J		78,063	312,252
Screened Non-J X Screened Non-J		97,500	390,000
Enzyme-screened AJ X Enzyme-screened AJ		7,992,421	31,969,684
Highest sensitivit	y (98.8%)		
Unscreened AJ co	uple	729	2,916
Screened MS X Un	screened AJ	3,213	12,852
Screened MS X Un	screened MS	7,140	28,560
Screened Non-J X	Unscreened AJ	13,473	53,892
Screened MS X Screened MS		14,161	56,644
Screened Non-J X Unscreened MS		29,750	119,000
Unscreened Non-J X Unscreened MS		29,940	119,760
Screened AJ X Unscreened AJ		58,527	234,108
Screened Non-J X Screened MS		59,381	237,524
Unscreened non-Jewish couple		62,500	250,000
Enzyme-screened AJ X Unscreened AJ		76,331	305,324
Screened Non-J X Unscreened Non-J		124,750	499,000

Screened AJ X Unscreened MS	130,060	520,240
Screened Non-J X Screened Non-J	249,001	996,004
Screened MS X Screened AJ	257,952	1,031,808
Screened AJ X Unscreened Non-J	541,917	2,167,668
Screened AJ X Screened Non-J	1,081,666	4,326,664
Screened AJ X Screened AJ	4,698,779	18,795,116
Enzyme-screened AJ X Enzyme-screened AJ	7,992,421	31,969,684

Carrier frequencies: AJ 1 in 27; MS 1 in 60; Non Jew 1 in 250

7.28 For individuals of mixed AJ/non-AJ origin, the chance of being a carrier is lower than for those of pure Ashkenazi descent but the sensitivity of the DNA test is also lower. We have suggested in Chapter 3 that the target population for carrier screening should be individuals with at least one Ashkenazi grandparent. This represents a carrier risk of 1 in 80. Individuals who are half-Ashkenazi (2 Ashkenazi Jewish grandparents) have a carrier risk of 1 in 49. In Table 7.4 we have calculated some illustrative residual risks for couples of mixed AJ/non-AJ descent, assuming that a screened individual of mixed descent marries an unscreened individual and using the higher figures for the sensitivity of the DNA test (98.8% in Ashkenazi Jews and 50% in non-Jews). In all cases the residual risk of a couple is higher than the risk of an unscreened non-Jewish couple (1 in 62,500), but even the highest residual risk that a couple might have an affected child (approximately 1 in 20,000) is still very small.

Table 7.4 Risks for mixed-descent couples after screening of one partner (hal	f-
Ashkenazi or quarter-Ashkenazi) by the 4-mutation DNA test	

	Couple risk 1 in	Risk of affected child
Screened half-AJ X Unscreened AJ	5,089	20,356
Screened half-AJ X Unscreened half-AJ	9,236	36,936
Screened half-AJ X Unscreened non-J	47,125	188,500
Screened quarter-AJ X Unscreened AJ	5,812	23,248
Screened quarter-AJ X Unscreened half-AJ	10,548	42,192
Screened quarter-AJ X Unscreened quarter AJ	17,646	70,584
Screened quarter-AJ X Unscreened non-J	53,821	215,284

7.29 For comparison with the performance of the DNA test, we have calculated the residual risk for individuals screened by the biochemical test in leucocytes. Using Bayes' Theorem we estimate that, with a test sensitivity of 99.08% in Ashkenazi Jews (as reported by Bach et al), there is a residual risk of 1 in 2,827 that a screened Ashkenazi Jew is a carrier. This means that the risk to an Ashkenazi Jewish couple if one partner is screened is 1 in 76,331 and if both are screened is 1 in 7.9 million. For comparison, these residual risks after biochemical screening are also shown in Table 7.3.

Other comparative factors

- 7.30 A range of other factors are also relevant to comparisons between the biochemical and DNA tests, including cost, speed, technical difficulty, and acceptability to the target population.
- 7.31 The biochemical test suffers from the disadvantage that the more reliable leucocyte test requires fresh samples. If samples are inadequate or degraded, repeat samples must be taken, leading to delays and additional cost. These problems make the test unsuitable for direct use in the antenatal setting; hence, currently, patients must make separate arrangements to attend the clinics at Barnet Hospital or Guy's Hospital for blood to be taken.
- 7.32 The need for a blood sample for the biochemical test may lower the acceptability of the test when compared to a DNA test, which requires only a simple, non-invasive buccal swab. This factor may be particularly relevant when the target population for screening is teenagers, as has been found in Australia.
- 7.33 The biochemical test is technically demanding and requires specific training for laboratory staff. The DNA test is more generic in nature and more readily undertaken by laboratory staff with general training in DNA testing.
- 7.34 Representatives from Jewish Care expressed the view that, if carrier screening is offered at all, there is an ethical duty to offer the most sensitive test available, which is the biochemical test. They also point out that the use of this test makes explanation easier, obviates the need to ask whether individuals are of Ashkenazi or Sephardi origin, and takes account of the possibility that some individuals may (knowingly or unknowingly) have Moroccan Sephardi ancestry.

Cost analysis

- 7.35 The costs of the biochemical (serum plus leucocyte) and DNA tests as carried out in Guy's Laboratory are similar, at approximately £108 and £84 respectively. However, the necessity for repeat testing and follow-up of samples giving positive or inconclusive results in the biochemical assay increases the overall cost of this protocol. According to the Guy's database, approximately 5% of samples tested by the leucocyte assay give inconclusive results that require additional investigation by mutation testing and/ or comparison with serum %HexA results. In addition, all positive biochemical test results should be followed up by mutation analysis, as mutation testing is preferable to the biochemical test if prenatal diagnosis is subsequently required. Samples that are positive or inconclusive in the leucocyte assay but negative for the 5-mutation test may in the future be tested by sequencing of the *HEXA* gene, at a cost of £193.
- 7.36 Using the data from Guy's laboratory (Box 4.1), crude estimates can be made for the cost of analysing 1000 samples by the biochemical test, the 4-mutation test, full gene sequencing or a combination of methods (Table 7.5). (Note that where mutation testing is used to follow biochemical testing, the 5-mutation panel, which includes the major pseudodeficiency allele, is used. We have assumed that the 4-mutation screening test would cost the same as the 5-mutation diagnostic/follow-up test that is currently in use).

Table 7.5 Estimated costs of different testing protocols, using NHS laboratory data for test results

Protocol	Cost per 1000 samples (£)
Biochemical test only for all samples, including repeats for inadequate samples	109,080*
Biochemical test (including repeats), plus 5-mutation test for all enzyme-positive and inconclusive samples**	118,228
Biochemical test (including repeats), plus 5-mutation test for positives and inconclusives, and gene sequencing for samples still unresolved***	120,258
4-mutation test only for all samples	84,000
Gene sequencing only for all samples	193,000

*Assumes that 1% of individuals need repeat samples taken, as reported by the Willink **Assumes 10.9% of biochemical test results are positive or inconclusive

- *** Assumes 12.9% of enzyme-positive samples are negative for the DNA test and 6% of enzyme inconclusive samples (0.3% of the total samples) are still unresolved after the DNA test
- 7.37 This analysis shows that the least expensive protocol is the 4-mutation test for all samples, while the most expensive is gene sequencing for all samples. For 1000 samples, initial biochemical testing followed by mutation testing for all enzyme-positive and inconclusive samples (the current protocol) costs approximately £34,000 more than the 4-mutation test alone.
- 7.38 DNA testing offers the option of extending carrier screening to include a wider panel of mutations associated with other conditions that are found in the Jewish community, such as Canavan disease, cystic fibrosis and familial dysautonomia.
- 7.39 The cost of extending DNA carrier testing in an NHS setting to cover other conditions is not known. Test kits for carrier screening in Ashkenazi Jews are available from some commercial suppliers. For example, the Ashplex1 test from Tepnel Diagnostics, which tests for a panel of mutations associated with Tay Sachs disease (3-mutation test), Fanconi anaemia, Canavan's disease and familial dysautonomia, costs £930.00 for a 50-test kit, a cost of £18.60 per sample. Although this figure does not take into account the cost of professional time to run the test and interpret the result, purchase of a kit such as this may be a feasible option for the NHS in the future, should a decision be taken to extend carrier screening to other conditions. (Note, however, that the available commercial kits do not include the non-Jewish +1IVS9 mutation that is included in the current Guy's panel.)

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Screening flow charts





7.40 We have attempted to formulate theoretical flow charts for screening 1000 patients using either the biochemical test or the 4-mutation test as the screening test, based on the available data for the characteristics of the tests. Box 7.1 shows the flow chart for the DNA test, based either on the published data of Bach (2001) or our own literature analysis (Table 7.1). Box 7.2 shows the corresponding flow charts for the biochemical test. We have also calculated, for each protocol, the numbers of true carriers missed (false negatives) and false-positives per 1,000 individuals screened.



Box 7.2 Screening flow charts for biochemical test



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7.41 Using these flow charts (rather than the Guy's laboratory data used in Table 7.5), we calculate the costs for screening 1,000 individuals by each of the protocols to be as follows:

£84,000
£84,000
£113,962
£140,772

These calculations do not include the costs of any repeat sampling or testing for inadequate or inconclusive biochemical test results, or the costs of other aspects of the screening programme such as counselling or costs to patients (for example, attendance

costs), which could vary among the different protocols. It has been assumed that all inconclusive biochemical test results are classed as positive, and go on to mutation testing. If approximately 1% of blood samples for biochemical testing are inadequate and re-testing is required, the cost of the biochemical + DNA protocols (test only, not including re-sampling costs) would increase by approximately £1,000 per 1,000 individuals screened.

7.42 The screening flow charts illustrate, once again, the essential differences between using the biochemical test or the DNA test as the initial screening test: the biochemical test will pick up virtually all carriers but will produce between 10 and 100 (probable) false-positive results for every 1000 individuals tested, while the DNA test will have essentially no false positives but will miss between 0.5 and 5 true carriers for every 1000 individuals tested. Whichever test is chosen, care must be taken to provide accurate information and counselling for those who choose to take up the offer of screening.

Conclusions

- 7.43 Insufficient information is available to enable full evaluation of the different testing technologies for Tay Sachs disease carrier status. In particular, the true sensitivity of the DNA test and the true specificity of the biochemical test in leucocytes cannot at present be calculated accurately. DNA tests for Tay Sachs disease are not currently included in the UK Genetic Testing Network's list of tests approved for use in the NHS, and have not yet had Gene Dossiers prepared for them. (Gene Dossiers assess the available evidence regarding a DNA test's analytical validity, clinical validity and clinical utility.) Preparation of a Gene Dossier for the Tay Sachs disease mutation test, which is currently being undertaken by Dr Christine Patch, is a useful step.
- 7.44 From the limited data available, the risk that a mutation-negative Ashkenazi Jewish person could still have an affected child lies in the range 1 in 22,000--234,000 if their partner is an unscreened Ashkenazi Jew, and in the range 1 in 206,000-2,168,000 if their partner is an unscreened non-Jew. The higher residual risk figures relate to a sensitivity of 87.3% for the DNA test in Ashkenazi Jews and 20% in Moroccan Sephardis and non-Jews. Athough this figure is probably lower than the true sensitivity of the test, at least in Ashkenazi Jews, it might suggest that, if a decision were made to use DNA testing rather than the biochemical test, both members of a couple should be screened if both are Ashkenazi Jews.
- 7.45 The extremely high sensitivity of the biochemical test (at least 99%) means that the residual risks for those tested by this method are very low. However, this sensitivity comes at the cost of reduced specificity, leading to significant numbers of (probably) false positive results if this test is used as a screening test, and creating additional costs and counselling difficulties.
- 7.46 We have suggested that screening should be offered to those with at least one Ashkenazi Jewish grandparent. This policy would represent a cut-off for screening at a prior risk of 1 in 80 (corresponding to a risk of having an affected child of 1 in 8,640 with an unscreened Ashkenazi Jewish partner, or 1 in 80,000 with an unscreened non-Jewish partner). If mutation testing became the screening test, and a couple was of mixed

Ashkenazi Jewish/non-Jewish ancestry, it would be advisable to ensure that the partner with the higher number of Ashkenazi grandparents had been screened.

- 7.47 At present, the mutation analysis performed by the Guy's laboratory does not include any of the 3 mutations most commonly found in Tay Sachs disease carriers of North African Sephardi origin. If mutation testing became the screening test, it would be advisable to retain biochemical testing as a back-up antenatal test for any couples where both partners were of known or suspected North African Sephardi origin. In a mixed Ashkenazi/North African Sephardi couple, it is important to ensure that at least one partner has been screened (the Ashkenazi partner by the mutation or biochemical test, or the North African Sephardi partner by the biochemical test).
- 7.48 Whichever test is chosen as the initial screening test, biochemical testing should be used in the antenatal setting to test the partner of any known carrier (whether Jewish or non-Jewish).
- 7.49 Opinion in the Advisory Group was divided on the question of whether the NHS Tay Sachs disease carrier screening programme should continue to offer the biochemical test as the initial screening test, or move towards replacing the biochemical test by a DNA test. The arguments for and against the different protocols are discussed in this Chapter. It should be kept in mind that the reason for offering screening to the Jewish community is the higher risk that individuals from this community carry one of three specific mutations. Use of a screening test that goes beyond a test for these mutations, therefore, needs careful justification. One important factor about which we have insufficient information is the view of the Jewish population itself. There appears to be a trend, particularly in the Strictly Orthodox community, towards a preference for services that offer DNA carrier testing for a panel of 'Ashkenazi Jewish diseases', rather than Tay Sachs disease alone. It is possible that individuals may prefer to offset the (possibly) lower sensitivity of the DNA test against the perceived advantage of testing for a wider range of conditions. A survey of attitudes on this question would be useful in helping to formulate NHS screening policy.

8 Recommendations for developing the Tay Sachs disease screening programme

Introduction

- 8.1 The Advisory Group was charged with the task, following review of the current service, of making recommendations to develop a more systematic screening programme with equity of access. Based on our analysis of need, our review of current services and our evaluation of evidence from the literature and from other services worldwide, we set out here a series of recommendations for the development of the Tay Sachs disease National Screening Programme.
- 8.2 Tay Sachs is a serious condition with potential for high morbidity in Ashkenazi Jewish communities. Carrier rates are about 1 in 27, meaning that, without intervention, we would predict a birth prevalence in Ashkenazi Jewish communities of about 1 in 3000. Because the Jewish population in UK is relatively small and, in particular, there are only about 2,700 births per year, the expected numbers of affected children born each year will be low even without carrier screening (we can expect on average 1 per year). The screening programme must therefore be viewed not as solving a major public health problem in disease incidence, but as putting in place a service for a community that is identified and sees itself as high risk. Benefits thus arise from the ability of carrier testing to reduce anxiety in Jewish communities for individuals and couples for whom prenatal diagnosis is acceptable and to enable carrier couples to enter into or continue relationships with the option to avoid the birth of an affected child. In some communities (such as the Strictly Orthodox community) where there is a tradition of arranged introductions leading to marriages, carrier testing has also helped to avoid bringing together carrier couples. The provision of carrier screening to single individuals through an NHS programme is important in ensuring that people can decide for themselves whether to be tested and what to do with the results.
- 8.3 Worldwide, communities with high Jewish populations have put carrier testing or screening programmes in place, with high degrees of success in reducing the birth prevalence of Tay Sachs disease in Ashkenazi Jews to below the overall population rate. In 1999 the case was made for a carrier screening programme in the UK and the programme gained formal agreement from the NSC. It was not, therefore, the role of this Advisory Group to revisit whether or not Tay Sachs disease screening fulfilled all the screening criteria, but to review the implementation of the programme against a current assessment of need and evaluation of available services.
- 8.4 Our review has shown that the present programme has built on considerable NHS laboratory resources, professional expertise and voluntary sector experience and commitment. Nevertheless, it is currently running without formal agreements, documentation, channels of accountability, quality assurance and evidence of effectiveness. We identified several important gaps in the service, such as lack of a systematic approach to the offer of testing in antenatal services, and vulnerability of the community and laboratory elements in the Northwest. Most importantly, this means that there is risk of a child with Tay Sachs disease being born to an unscreened couple. Also important is the likelihood of suboptimal services for users and potential users, inequity, poor cost effectiveness and low responsiveness to technological, clinical or

patient-desired changes. Putting these aspects of the service in order is not only vital to proper implementation of Tay Sachs disease screening but would also provide a valuable basis for introduction of Tay Sachs disease carrier screening for other Ashkenazi Jewish based disease, should the NSC wish to do so following formal evaluation of such conditions against screening criteria.

8.5 In this chapter we set out the recommendations of the Advisory Group for the National Screening Committee.

Immediate recommendations

Recommendation 1: Continuation of the programme

8.6 The Advisory Group recognises the clinical need for Tay Sachs disease carrier screening and the valuable work being undertaken in clinical, laboratory and voluntary services. We recommend that the UK National Screening Programme (NSP) for Tay Sachs disease carrier screening should continue but with renewed commitment to achieving a high quality and equitable service that maximises choice for high risk individuals and couples.

Recommendation 2: Formal constitution of the programme

8.7 The Advisory Group recommends that the Tay Sachs disease programme should be formally constituted as with any other screening programme.

Recommendation 3: Linked antenatal and community programmes

- 8.8 The National Screening Programme for Tay Sachs should include antenatal and community carrier screening and these programmes should be linked.
- 8.9 The Tay Sachs screening programme is included in the antenatal section of the National Screening Programme. The principle for carrier screening for pregnancies at high genetic risk in antenatal care is well established through the UK Sickle Cell and Thalassaemia programmes. Like Tay Sachs disease, the antenatal screening programme focuses on identifying carrier couples and offering prenatal testing with the option of termination of pregnancy if the fetus is affected.
- 8.10 Although the antenatal service provides an important safety net for at risk couples, ideally Tay Sachs carriers, and more specifically carrier couples, would be identified before pregnancy so that couples at risk of having an affected child could carefully consider their options before conception. They could be referred to the appropriate genetic services and, when pregnant, could receive early referral (as a high risk pregnancy) to obstetric services for counselling and advice. If they wish they could then proceed to testing, decision making and possible pregnancy termination in a timely and unhurried fashion. Chapter 4 shows that the current provision of Tay Sachs disease screening in UK does indeed include a service for adults prior to conception, including couples, single adults and older school children. This service is also important for individuals who would not consider prenatal diagnosis or termination of pregnancy,

but wish to reduce their risk of having an affected child by avoiding marriage to another carrier.

Recommendation 4: Developing antenatal carrier screening

- 8.11 The Advisory Group recommends that consolidation and development of the quality of antenatal screening should be the first priority and that this should be first focussed on Trusts serving large Jewish communities.
- 8.12 For antenatal screening, Chapter 5 shows that there is no effective system for screening Jewish patients. This represents a risk to the NSP of a child with Tay Sachs Disease being born to a Jewish carrier couple who had received no information about screening. This is of particular concern in areas where there are large Jewish communities.

Recommendation 5: Securing carrier testing and community carrier screening in the short term

- 8.13 The Advisory Group recommends that lead commissioners for the Programme should urgently put in place interim contractual measures to secure current carrier testing and screening services in the short term, pending further development and integration with the antenatal screening programme. These services include current clinical 'walk-in' services (e.g. the Guy's Hospital service), testing provided on request to regional genetics services, and community carrier screening services provided by voluntary organisations; all with associated laboratory elements. This is likely to require provision of some further NHS resources for these services.
- 8.14 For community carrier screening, Chapter 4 shows that NHS walk-in clinics and voluntary organisations such as Jewish Care and the Association for the Prevention of Jewish Diseases provide access to testing through the NHS laboratory testing service, although these services are not running as a coherent screening programme. The Advisory Group notes the potential vulnerability of all these services, and particularly that services in the Northwest are likely to come to an end in 2009 with the retirement of key personnel.

Programme recommendations

8.15 Following agreement in principle about the continuation of the Tay Sachs disease Screening Programme as set out in Recommendations 1-4, the NSC should set out its programme in detail. In the following sections we make recommendations about some of the key issues that the Programme will need to consider.

Recommendation 6: Target group

8.16 The NSP will need to decide who will be the target group for the Programme. The Advisory Group recommends that the Programme should be focussed primarily on the Jewish population of Ashkenazi Jewish origin, with a cut-off for an offer of screening at a prior risk for carrier status of approximately 1 in 80 (the risk of an individual who has one Ashkenazi Jewish grandparent). In practice, individuals with other Jewish origin (eg Sephardi) should not be excluded but are likely to be small in number. This decision might need to be reviewed at a later stage. In the antenatal

setting testing should be offered if either partner is Jewish or part-Jewish. If only one partner is Jewish or part-Jewish that partner should be tested first.

Recommendation 7: Target population

- 8.17 The Advisory Group recommends that antenatal carrier screening should be developed first in those London and Manchester Trusts that serve the largest Jewish populations. Community screening should first be offered in mainstream Jewish secondary schools. Information should also be provided in Strictly Orthodox schools (if possible), in private schools that have a large number of Jewish pupils, and through Hillel houses (Jewish Halls of Residence) in universities.
- 8.18 The Advisory Group considered the question of equity and in particular whether it was fair to develop carrier screening programmes to reach specific populations based in particular locations such as schools or geographical areas, rather than Jews in the population as a whole. Chapter 3 provides a detailed description of the structure of the Jewish population throughout the UK. The Advisory Group noted the relatively small total population and the particular concentration in certain boroughs in and around London and in the Northwest and, for children, in a small number of Jewish schools.

Recommendation 8: Developing an ethnic screening questionnaire for Jewish patients

8.19 Work needs to be done in the antenatal setting to develop a tool for systematically identifying Jewish couples and offering them testing. The Advisory Group recommends that work is undertaken in conjunction with the Sickle Cell and Thalassaemia Programme to add a question on Jewish ethnicity to the Family Origin Questionnaire.

Recommendation 9: Integration of antenatal screening into antenatal care

8.20 The Tay Sachs disease Programme needs to work with antenatal services to introduce carrier screening into the care pathway for maternity services to ensure a systematic offer of screening at an appropriate stage of pregnancy. The Advisory Group recommends that this should be achieved by the end of the first trimester. The Advisory Group recommends that such work should be led by the antenatal screening coordinators and will require investigation of feasibility, practicality and resource aspects as well as a substantial awareness-raising and educational programme with midwives, health visitors, primary care teams and GPs and the development of high quality information for patients. Initial work should be undertaken in areas of high Jewish populations where there will be greater motivation of health professionals and more immediate outcomes for patients.

Recommendation 10: Development of community screening

8.21 Community screening is currently undertaken by voluntary organisations such as Jewish Care and the Association for the Prevention of Jewish Diseases. The Advisory Group recommends that interim measures to secure these services should be followed by development of a contractual agreement that integrates these services with NHS services and includes protocols, standards and reporting arrangements. Recommendation 11: Choice of initial screening test

- 8.22 The NSP will need to take a major decision on whether the biochemical or the DNA test should be the initial screening test. The NSP should ask laboratory providers and clinical services to look into the advantages and disadvantages of moving to DNA testing as the initial screening test, with retention of the biochemical test where clinically appropriate. In particular, a distinction should be made between the testing that is done to screen potential carriers, and testing for high-risk couples.
- 8.23 The Advisory Group recommends that services should consider using DNA testing as the method of choice in the screening programme for:
 - 1. All specimens from individuals where there is not a pregnancy.
 - 2. All specimens where there is a pregnancy and one or more partners is an Ashkenazi Jew. If both partners are Ashkenazi Jewish, both should be tested.

As a preliminary, laboratories should work with services to agree an optimum panel of mutations to be tested for in the UK and provide practical and literature based evidence for its likely sensitivity in the UK Jewish population.

8.24 Biochemical testing should be retained for:

- 1. All specimens where there is a pregnancy and one or more partners is of known or suspected North African Sephardi origin.
- 2. All partners of known carriers (both Jewish and non-Jewish).
- 8.25 Laboratories should develop detailed protocols and standards for the agreed tests.
- 8.26 The debate about the choice of screening test is set out in Chapter 7. Chapter 4 also demonstrates the current lack of information about the laboratory performance of the tests currently in use, and included recommendations for development.

Recommendation 12: Developing information systems

8.27 Laboratories and clinical providers should develop a standardised database and IT infrastructure recording essential patient information and able to produce standard reports, to support audit and monitoring requirements of the programme and to link with relevant diagnostic laboratories.

Longer term recommendations

Recommendation 13: Extending carrier screening to other genetic conditions

8.28 The Advisory Group recommends that the NSC also consider whether to extend the Tay Sachs disease NSP to include other genetic diseases that are more common in the Ashkenazi Jewish population, following on from the work previously submitted to the NSC in 2006 and which is enclosed as Appendix 8.

8.29 Although consideration of this issue was outside of the scope of this report, the view has frequently been expressed within the Jewish community and was endorsed by members of the Advisory Group that screening should be extended to a wider panel of conditions with increased frequency in the Ashkenazi Jewish community.

Conclusion

- 8.30 The design, implementation and eventual provision of a formal screening programme that includes antenatal and community screening elements is a major task that will require leadership, commitment and close cooperation from many professionals and the voluntary sector. Commissioning organisations, particularly in areas with large Jewish populations, will need to take a lead in consultation with professional and community stakeholders. Not least there will need to be a commitment of the necessary financial and management resources and the ability to interact in an appropriate and sensitive manner with the Jewish population.
- 8.31 This Report has set out a direction of travel and an outline of the detailed work that will need to be undertaken.

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Appendices

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Dr Sue Halliday (Chairman)	Consultant in Public Health Medicine, Eastern Region Public Health Observatory, Institute of Public Health, Cambridge
Jane Hibbert	Regional Antenatal & Child Health Screening Coordinator, East of England, Cambridgeshire
Marie Jackson	Consultant Clinical Scientist and Director of Biochemical Genetics Laboratory, Guy's & St Thomas' NHS Foundation Trust
Dr Barbara Judge	Programme Centre Director, UK Newborn Screening Programme Centre, Great Ormond Street Hospital for Children NHS Trust, London
Professor David Katz	Professor of Immunopathology, UCL and Board of Deputies of British Jews
Eli Kernkraut	Orthodox Jewish Community Representative
Dr Philip Koch	Pathologist, consultant to Jewish Care
Antony Lerman	Executive Director, Institute for Jewish Policy Research
Sara Levene	Registered Genetic Counsellor, Department of Clinical Genetics, Guy's & St Thomas' NHS Foundation Trust
Dr Helen Mundy	Consultant in Paediatric Metabolic Medicine, Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust
Dr Christine Patch	Consultant Genetic Counsellor and Manager, Department of Clinical Genetics, Guy's & St Thomas' NHS Foundation Trust
Nadia Permalloo	Antenatal Screening Coordinator (London) Westminster PCT
Rabbi Joshua Rosner	Association for the Prevention of Jewish Genetic Diseases, London
Dr Sybil Simon	Tay Sachs Centre, Screening & Research Programme, Booth Hall Hospital, Manchester
Dr Alison Stewart	Principal Associate, PHG Foundation, Cambridge
Dr Allison Streetly	Programme Director, NHS Sickle Cell & Thalassaemia Screening Programme, Kings College London School of Medicine, London

Appendix 2

Enrolment in Jewish schools with secondary provision

Region	School	Туре	LEA	Enrolment 2005/06 ¹
London	Hasmonean High School	Mainstream secondary	Barnet	1,084
London	Immanuel College	Mainstream secondary	Herts	555
London	Jewish Community Secondary School ²	Mainstream secondary	Barnet	-
London	JFS School	Mainstream secondary	Brent	1,864
London	King Solomon High School	Mainstream secondary	Redbridge	981
London	Yavneh College ³	Mainstream secondary	Herts	-
Manchester	King David High School	Mainstream secondary	Manchester	834
Liverpool	King David High School	Mainstream secondary	Liverpool	6064
London	14 schools	Strictly Orthodox primary/secondary	Hackney	4,265
London	5 schools	Strictly Orthodox secondary	Barnet	825
London	2 schools	Strictly Orthodox secondary	Hackney	338
London	Menorah High School for Girls	Strictly Orthodox secondary	Brent	126
Manchester	Beis Rochel Girls' School	Strictly Orthodox primary/secondary	Manchester	201
Manchester	4 schools	Strictly Orthodox secondary	Salford	334
Manchester	4 schools	Strictly Orthodox primary/secondary	Salford	794
Manchester	Etz Chaim School	Strictly Orthodox secondary	Manchester	98
Manchester	Manchester Mesivta School	Strictly Orthodox secondary	Bury	166
Gateshead	2 schools	Strictly Orthodox secondary	Gateshead	249
Leeds	Leeds Menorah School	Strictly Orthodox primary/secondary	Leeds	48

¹ Figures for mainstream schools include non-Jewish pupils

² Opened September 2006

³ Projected to open September 2010, admitting 180 each year
⁴ Approximately three-quarters non-Jewish
Testing protocol in use at Guy's Laboratory from 2008



Survey Questionnaire for Antenatal Screening Coordinators

Service Review for Tay Sachs screening Questionnaire for Antenatal Screening Services

Screening Region: Hospital Name:

Disease if the partner is NOT Jewish?			
Do you offer the testing for Tay Sachs			
Do you ask whether the woman's partner is Jewish?			
If yes – do you offer testing to both Ashkenazi and Sephardi women?			
Do you find out whether Jewish women are of Ashkenazi or Sephardi origin? *			
Do you ask all women their ethnic origin including whether they are Jewish?			
Who is offered screening?			
Is carrier testing offered proactively or is it available only on request?			
If yes, please answer the following questions	-		
If no, please say why.			
Do you offer antenatal carrier testing for Tay Sachs Disease to Jewish patients?			

* Ashkenazi Jews are Jews whose family originated in Eastern Europe, Sephardi Jews are Jews whose family originated in Southern Europe (eg: Italy or Spain) or the Middle East.

Thank you for completing this questionnaire and please return it by 17th March to

Sara Levene, Clinical Genetics, 7th Floor Borough Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT Or email to <u>sara levene@gstt.nhs.uk</u>

Tay Sachs Carrier Screening: a review for the National Screening Committee

Appendix 5

Patient Questionnaire

Name of Genetics Laboratory (please circle): Guys/Willink Name of Referring Centre: Date sample taken:

Patient name	
Patient DOB	
Is patient or their partner pregnant? (Y/N)	
If yes - weeks gestation	
Age	
Sex (M/F)	
Post code	
Is the patient of Jewish descent? (Y/N)	
If Yes - how many grandparents are Jewish?	
If less than 4 - please specify which of maternal and	
paternal grandparents are Jewish	
Ashkenazi (A)/Sephardi (S)/Mixed (M) *?	
Is the partner of Jewish descent? (Y/N)	
If Yes - how many of the partner's grandparents are Jewish?	
If less than 4 - please specify which of maternal and paternal grandparents are Jewish	
If partner is of Jewish descent - is the partner Ashkenazi (A)/Sephardi (S)/Mixed (M) *?	
Does the person being tested have a relative/partner	
who is a carrier or affected with Tay Sachs disease?	
lf yes - relationship	
Does the partner of the person being tested have a relative who is a carrier or affected with Tay Sachs disease? (Y/N)	

How did the person find out about testing for Tay Sachs disease? (Please specify school/ community programme/ relative/ friend/ GP/ other)

Please specify other

What was the patient pathway to testing? Please note any problems the patient encountered in accessing testing.

Have any other family members not mentioned above been tested?

Would patient be interested in participating in this review? (eg. focus group/ questionnaire) Y/N

To be completed by research team:

Test result: carrier (C), non-carrier (N) or unclear result (U)	
Date reported	

*Ashkenazi Jews are Jews whose family originated in Eastern or Central Europe, Sephardi Jews are Jews whose family originated in Southern Europe (eg: Italy or Spain), North Africa or the Middle East, Mixed being Jews having both Ashkenazi and Sephardi Jewish grandparents.

The Family Origin Questionnaire



Residual risks following screening by a 4-mutation DNA test

The spreadsheets show the residual risks that a screened individual of Ashkenazi Jewish, Moroccan Sephardi Jewish or non-Jewish origin could have a child affected by Tay Sachs disease, depending on whether the screened individual's partner is a screened or unscreened individual from one of these three ethnic groups. Separate spreadsheets have been worked for the lowest and highest sensitivities of the DNA test.

The following worked example, for a screened Ashkenazi Jewish person with an unscreened Ashkenazi Jewish partner, explains how the calculations were done.

If the carrier rate in Ashkenazi Jews is 1 in 27 and the sensitivity of the DNA test is 98.8% (higher sensitivity spreadsheet), then the prior odds that an Ashkenazi Jewish person is a carrier are 1/27 (0.03704) and the prior odds that they are a non-carrier are 26/27 or 0.96296.

The conditional probability that an Ashkenazi Jewish carrier has a negative DNA test is 1-0.988 = 0.012 (this is equal to the false-negative rate). The conditional probability that an Ashkenazi non-carrier has a negative DNA test result is 1.0.

The joint probability that a given individual is both a carrier and has a negative test result is $0.03704 \times 0.012 = 0.00044$. The joint probability that the individual is not a carrier and has a negative DNA test result is $0.96296 \times 1.0 = 0.96296$.

The relative probability that a DNA-negative individual is actually a carrier is then 0.00044 / (0.00044 + 0.96296) = 0.00046, or 1 in 2167.7 (the final probability).

Looking then at the couple risks (lower section of spreadsheet), the relative probability that a screened Ashkenazi Jewish individual is a carrier is 0.00046 and the risk that an unscreened Ashkenazi Jewish individual is a carrier is 0.03704 (that is, 1 in 27). The risk that both are carriers is the product of the individual risks, that is 0.00046 x 0.03704 = 0.000017, or 1 in 58,527. The risk that both are carriers and that they have an affected child is (1/58,527) x (1/4), or 1 in 234,108.

Tay Sachs Carrier Screening: a review for the National Screening Committee

Spreadsheet 7.1

LOWER SENSIT	VITY				
	Carrier Rate	DNA Pick Up			
Ash.	27	0.87300			
Non-Jewish	250	0.20000			
Moroccan	60	0.20000			
Seph	00	0.20000			
				_	
	Jewish	CARRIER	NON-CARRIER		
Prior Odds		0.03704	0.96296		
Conditional	DNA -ve	0.12700	1.00000		
Joint Prob.		0.00470	0.96296		
Rel. Prob.		0.00486	0.99514		
Final Prob.	1/	205.72441			
	Non- Jewish	CARRIER	NON-CARRIER		
Prior Odds		0.00400	0.99600		
Conditional	DNA -ve	0.80000	1.00000		
Joint Prob.		0.00320	0.99600		
Rel. Prob.		0.00320	0.99680		
Final Prob.	1/	312.25000			
	Moroccan	Senh			
Prior Odds	moroccurre	0.01667	0.98333		
Conditional		0.80000	1 00000		
loint Prob	DIA VC	0.01333	0.98333		
Pol Prob		0.01338	0.98662		
Final Prob	1/	74 75000	0.90002		
Tillat Prop.	17	74.75000			
Dicks for cour					
KISKS IOI COUP					
		Distantia	Jewish screened i		
Partner		Risk of Deing	Risk of Deing	Couple	1 in
Unscreened Ash		0.03704	0.00486	0.000180	5,555
Unscreened No	n-J	0.00400	0.00486	0.000019	51,431
Seph		0.01667	0.00486	0.000081	12,343
Screened AJ		0.00486	0.00486	0.000024	42,323
Screened NonJ		0.00320	0.00486	0.000016	64,237
Screened Moroccan Seph		0.01338	0.00486	0.000065	15,378
			NonJewish screened individual		
Partnor		Risk of being	Risk of being	Couple	1 in
raiulei		carrier	carrier	risk	1 111
Unscreened As	h	0.03704	0.00320	0.000119	8,431
Unscreened No	n-J	0.00400	0.00320	0.000013	78,063
unscreened Mo	roccan	0.01667	0.00320	0 000053	18 735
Seph		0.01007	0.00320	0.000000	10,135

r	1		1	1
Screened AJ	0.00486	0.00320	0.000016	64,237
Screened NonJ	0.00320	0.00320	0.000010	97,500
Screened Moroccan Seph	0.01338	0.00320	0.000043	23,341
Danta an	Risk of being	Risk of being	Couple	4 :
Partner	carrier	carrier	risk	1 10
Unscreened Ash	0.03704	0.01338	0.000495	2,018
Unscreened Non-J	0.00400	0.01338	0.000054	18,688
unscreened Moroccan	0.01667	0.01338	0.000223	4,485
Seph	0.00496	0.01229	0.000045	15 279
Screened Non I	0.00460	0.01330	0.000003	13,370
Screened Noraccan Conh	0.00320	0.01330	0.00043	Z3,341
Screened Moroccan Seph	0.01338	0.01338	0.000179	5,588
FINAL TABLE OF RISK				
lowish		Coroonod individual		
Jewish	Dick of boing	Disk of boing		
	carrier	carrier	Couple risk	1 in
		0.00486	0.000180	5 555
Unscreened Non- I	0.00400	0.00486	0.000100	51 431
unscreened Moroccan	0.00400	0.00400	0.000017	42.242
Seph	0.01667	0.00486	0.000081	12,343
Screened AJ	0.00486	0.00486	0.000024	42,323
Screened NonJ	0.00320	0.00486	0.000016	64,237
Screened Moroccan Seph	0.01338	0.00486	0.000065	15,378
NonJewish		Screened individual	1	
	Risk of being	Risk of being	Couple risk	1 in
	carrier	carrier	-	0.424
Unscreened Ash	0.03704	0.00320	0.000119	8,431
Unscreened Non-J	0.00400	0.00320	0.000013	78,063
Seph	0.01667	0.00320	0.000053	18,735
Screened AJ	0.00486	0.00320	0.000016	64,237
Screened NonJ	0.00320	0.00320	0.000010	97,500
Screened Moroccan Seph	0.01338	0.00320	0.000043	23,341
Moroccan Sephardi Jewish		Screened individual		
· ·	Risk of being	Risk of being		4
	carrier	carrier	Couple risk	1 10
Unscreened Ash	0.03704	0.01338	0.000495	2,018
Unscreened Non-J	0.00400	0.01338	0.000054	18,688
unscreened Moroccan	0.01667	0.01338	0.000223	4,485
Seph	0.00496	0.01229	0.0000/5	15 279
	0.00400		0.00005	10,3/0
Screened NonJ	0.00320		0.00043	L3,341
Screened Moroccan Seph	0.01338	0.01338	0.000179	5,588
				1

National Screening Committee Criteria Evaluation of Ashkenazi Jewish Population Carrier Screening for Familial Dysautonomia, Canavan disease, and Cystic Fibrosis.

Feb 2006

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Please note that the contents of the DH visiting fellowship report to observe Tay Sachs screening programmes abroad which is referred to in appendix 8 is summarised in chapter 6 in other models for carrier screening for Tay Sachs disease.

1. The condition should be an important health problem.

Familial Dysautonomia

FD is a serious progressive genetic condition for which there is no cure. Affected individuals require on-going multi-disciplinary medical care to manage autonomic crises, and are admitted to hospital on average 2-3 times per year due to multiple complications and procedures e.g. feeding problems and failure to thrive, scoliosis, gastrostomy, bronchiectasis. In the UK all affected patients are dependent on a carer and are not capable of living independently. There is also a high risk of sudden death. 50% of affected individuals die before the age of 40y. FD can be avoided by prenatal diagnosis (PND) or pre-implantation genetic diagnosis (PGD) (Rechitsky et al 2003), although PGD for FD is not currently available in the UK. It has been shown that early intervention may promote better survival (Axelrod et al 2002).

Canavan disease

Canavan disease (CD) is a serious, progressive, neurodegenerative condition for which there is no cure. Symptoms appear by 3-5 months of age. These include macrocephaly, lack of head control and developmental delay. Developmental delay becomes more pronounced with time, especially motor skills, and the affected child will be unable to sit, stand, walk or talk. As the disease progresses hypotonia turns to spasticity. Other features include optic atrophy, sleep disturbance, seizures, and feeding difficulties which may require assisted feeding with a nasogastric tube or a permanent gastrostomy. Life expectancy is variable: some die in first year, most by age 4 and some may survive into their teens. CD can be avoided by prenatal diagnosis (PND) or pre-implantation genetic diagnosis (PGD).

Cystic Fibrosis

Cystic Fibrosis (CF) is a serious, progressive genetic condition for which there is no cure. The disease is characterised by progressive respiratory and gastro-intestinal problems. CF has been found to be

highly variable, but the majority of cases require on-going multi-disciplinary medical care, including physiotherapy, antibiotics, and enzyme supplements. Modern management methods have resulted in slower disease progression and have extended survival to at least 40 years. An HTA review in 1999 has already recommended population screening for CF (Murray et al 1999), and newborn screening is already underway.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

Familial Dysautonomia

Approximately 1 in 30-32 Ashkenazi Jews (AJ) are carriers of this autosomal recessive genetic trait (Dong et al 2002, Lehavi et al 2003). The condition is predicted to affect 1 in 3600 births to Ashkenazi Jews. (FD is almost unheard of in the non-Jewish population). Although symptoms are present from birth, some overlap with other conditions, and accordingly some cases may remain undiagnosed, especially in the early stages. Six diagnostic criteria must be met in order for the diagnosis of FD to be made (Shohat 2003):

- Decreased taste and absence of fungiform papillae of the tongue, giving it a smooth pale appearance.
- Absence of axon flare response after histamine injection.
- Decreased or absent deep tendon reflexes.
- Hypotonia in infancy.
- Absence of overflow tears with emotional crying (alacrima).
- Pupillary hypersensitivity to parasympathomimetic agents.

FD is a progressive degenerative neurodevelopmental disorder, with regular autonomic crises and secondary effects on multiple systems. Associated problems include:

Aspiration of feeds and gastroesophageal reflux leading to recurrent wheezing, bronchiectasis and pneumonia.

- Abnormalities in the central control of breathing leading to diminished responses to hypoxia and hypercarbia, and breath-holding spells. Irregular breathing can also cause sleep apnoea.
- Progressive scoliosis and kyphoscoliosis generally occurring during mid-childhood but accelerating during puberty and adolescence. This further compromises respiratory function. Osteoporosis has been reported in affected adolescents.
- Autonomic crises induced by stress. Leads to vomiting or retching, ineffective coughing, excessive drooling/salivation, hypertension (or hypotension).
- Cardiovascular irregularities including orthostatic hypotension without compensatory tachycardia and supine hypertension.
- Insensitivity to pain (except hands, soles of feet, neck and genital areas).

(Axelrod 1996; Shohat 2003; Dinwiddie and Sonnappa 2004)

The causative FD gene, IKAP, was discovered in 2001 (Slaugenhaupt et al 2001) and 99% of AJ carriers have a founder mutation - an intronic splice site mutation (the 'major mutation'). A rarer missense mutation in exon 19 has been found in 4 affected Jewish patients (the 'minor mutation'). Therefore these 2 mutations would account for >99% of AJ carriers (Dong et al 2002).

Canavan disease

CD belongs to a group of conditions known as leukodystrophies, characterized by defects in myelin, commonly known as the "white matter" in the brain. Myelin protects nerves and allows messages to be sent to and from the brain. All CD symptoms (see section 1) are explained by the progressive loss of myelin.

As with Tay-Sachs disease (TSD), children with CD have an enzyme deficiency. The enzyme, aspartoacylase (ASPA), is responsible for hydrolyzing N-acetylaspartic acid (NAA) into aspartic acid

and acetate in the brain. The abnormal alleles make no (or less active forms of) aspartoacylase. Although aspartoacylase is expressed widely throughout the body, its absence in the CNS leads to the specific build-up of NAA in the brain that leads to demyelinization and other symptoms of the disease (Matalon 2003).

Aspartoacyclase is encoded by the gene *ASPA* (chromosome locus 17pter-p13). Approximately 1 in 40 Ashkenazi Jews are carriers of CD (Matalon 2003). Three common mutations account for 99% of cases of CD in the AJ population (and 50-55% of non-Jewish cases). The three mutations are known as E285A, Y231X and A305E. The first two, together, account for 98% of cases and A305E accounts for an additional 1% of cases.

Cystic Fibrosis

The natural history of CF was set out comprehensively in the HTA review by Murray et al (1999). According to this report the UK carrier frequency of CF is 1 in 24 and over 800 different mutations have been characterised. Current genetic testing methods can identify around 30 common mutations in the UK population, detecting 85-90% of carriers. In the AJ population, the carrier frequency is thought to be 1 in 24 to 1 in 29, but just 5 mutations account for 97% of carriers (Abeliovich 1992, Eng et al 1997, Kronn et al 1998). These five mutations are: W1282X, Δ F508, G542X, N1303K, and 3849+10kbC-T. Whereas the Δ F508 mutation accounts for 75% of carriers in the Northern European white population, this mutation is found in less than one-third of AJ carriers. However, half of AJ carriers carry the W1282X mutation, which is rare in non-AJ carriers (Abeliovich 1992). Since there are a small number of common CF mutations in the AJ population, and since Tay Sachs screening is already established in this population, carrier screening for CF would be easier to set up and run in the AJ population compared to the general population of the UK.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

Carrier screening, and the subsequent offer of genetic counselling, is the only primary prevention intervention for FD, CD, and CF.

A secondary prevention intervention for CF is newborn screening, as this would warn parents of the recurrence risk before they extend their family. Newborn screening for CF is already being planned, and it is important to ensure that this programme is also successful at detecting affected individuals in different ethnic groups.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

There are no known health implications of carrier status for FD, CD or CF. Studies of the psychological impact of carrier testing for some genetic conditions (eg. CF, Tay Sachs disease, Sickle cell anaemia) show that, on average, carrier screening does not adversely affect mood or self-esteem (Henneman et al 2002; Bekker et al 1994; Marteau et al 1997; Zeesman et al 1984; Schneiderman et al 1977). Since Tay Sachs screening began in the Jewish population in the 1980s there have not been any reports of major psychological sequelae. However the psychological effects of simultaneous multiple genetic testing have not been studied, and this research should go hand in hand with the further development of the screening programme. Multiple genetic screening for several AJ disorders has already been established in the USA and Israel, and to date there have not been any reports of major psychological sequelae. The report of a DH Visiting Fellowship (to observe these screening programmes abroad) further discusses the observation that there have not been any major adverse psychological effects noted in this screening programme.

5. There should be a simple, safe, precise and validated screening test.

Familial Dysautonomia

Carrier screening in the Ashkenazi Jewish population, for the two known mutations would detect >99% of carriers (Dong et al 2002). All the FD patients who have been tested to date carry at least one copy of the major mutation. Most are homozygous for this mutation but a small number are heterozygous for the minor mutation. There is one reported non-Jewish case of FD in the USA, and the patient is heterozygous for the major mutation and another mutation which had not been previously detected (Leyne et al 2003).

Canavan disease

Carrier screening in the Ashkenazi Jewish population, for the three common mutations would detect 98-99% of carriers.

Cystic Fibrosis

Carrier screening in the Ashkenazi Jewish population, for five common mutations would detect 97% of carriers. One commercially available kit (Elucigene 2005) also includes two other CF mutations - 1717-1G>A and D1152H (making seven in total). However, the literature available at the present time seems to suggest that only the 5 mutations mentioned in section 2 are included in most AJ CF screening panels worldwide.

Several commercial kits are available which can be used for screening for all these mutations in one multiplex molecular test. Most of these kits also include other founder mutations for other genetic diseases which are common in the AJ population, e.g. Fanconi anaemia (AJ carrier frequency 1 in 80). It may be possible to use such kits or develop an in-house kit in an NHS diagnostic DNA laboratory. Another alternative might be to use the services of a laboratory in another country which already has a high-throughput, low cost, screening service set up. However the issues of sample transportation and quality control would need to be addressed.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Yes, see above. (NB. A DNA based test is not based on quantitative levels, but gives a qualitative result on the presence or absence of a mutation).

7. The test should be acceptable to the population.

Tay Sachs disease (TSD) screening has been shown to be acceptable to the Jewish population (Eng et al 1997, Kronn et al 1998, Gason et al 2003). Eng et al (1997) and Kronn et al (1998) both suggest that adding other tests to the screening programme will be acceptable to the majority of Ashkenazi Jews, after finding that the addition of Cystic Fibrosis and Gaucher Disease genetic testing was acceptable to the majority of individuals taking part in Tay Sachs screening. FD, CD and CF screening are already offered in several countries around the world (NYU 2004, Mount Sinai Hospital 2004 and Hadassah Hospital 2004) and are recommended by the American College of Medical Genetics and the American College of Obstetricians and Gynaecologists for patients of Ashkenazi Jewish ancestry (ACMG 1998 and 2001, ACOG 2004). The acceptability of the tests among the UK population of Ashkenazi Jewis should be assessed as part of the early stages of the screening programme. The report of a DH Visiting Fellowship (to observe these screening programmes abroad) further discusses the observation that similar panel screening programmes are broadly acceptable to the Jewish communities where they are offered.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

Couples who are both carriers of the same disease will be offered genetic counselling and an explanation of the reproductive options available to them. This policy has been established for Tay Sachs screening and has resulted in a significant reduction in number of cases of Tay Sachs in the Jewish population (Kaback et al 1993).

Familial Dysautonomia and Cystic Fibrosis

Since the phenotypes of FD and CF can be variable, carrier couples should be given the opportunity to meet specialist clinicians and affected families to help with decision-making. For FD this service is based at Great Ormond Street Hospital. Centralised specialist CF units are already established. If a carrier couple chooses to continue an affected pregnancy then early intervention may improve survival of affected individuals (Axelrod et al 2002; Murray et al 1999).

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

Carrier screening should include the two common FD mutations; the three common CD mutations; and the five common AJ CF mutations (as described above), based on the very high frequency of founder mutations in this population.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

1st trimester prenatal diagnosis is available, with the option of termination of pregnancy. PGD may also be available for carrier couples in the future.

Familial Dysautonomia and Cystic Fibrosis

As described above, for couples that opt to continue an affected pregnancy, early intervention may improve survival of affected individuals.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

Screening should be offered to all Ashkenazi Jews, and non-Jewish partners of carriers.

Consideration needs to be given to screening policy for individuals with mixed family origins. The report of a DH Visiting Fellowship (to observe these screening programmes abroad) further discusses the different routes for offering screening to this population, and the issue of how to approach screening of non-Jewish partners.

Familial Dysautonomia

There has only been one known case of FD in a non-Jewish patient (Leyne et al 2003) but screening could also be offered to individuals from other ethnic groups who have a family history of FD, if a case arises. (It is important to note that non-FD dysautonomia is a different condition with a different aetiology and hence is not covered by this screening programme).

Canavan Disease

The carrier frequency in the non-Jewish population is not known, although it is assumed to be lower than in the AJ population (Matalon 2003).

Cystic Fibrosis

Due to the high carrier frequency in the Northern European white population, it is not only the AJ population who are at risk of CF. If universal antenatal carrier screening is subsequently introduced for CF, it may be necessary to integrate this with the AJ screening programme so as not to duplicate CF screening.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The established network of Regional Genetics Centres will be able to offer genetic counselling to carriers.

Familial Dysautonomia and Cystic Fibrosis

The Dysautonomia Society of Great Britain (DSGB) and the CF Trust can also provide support and information. Carrier couples (and babies/children newly diagnosed with FD or CF) should be given the opportunity to meet specialist clinicians, to help with decision-making and management. For FD this service is based at Great Ormond Street Hospital. Centralised specialist CF units are already established.

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, Cystic Fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

For all the proposed carrier screening tests there will be a very small residual risk that a patient given a negative result could carry an undetectable mutation. This must be explained to all patients undergoing testing.

Patient information leaflets will be developed and distributed in areas of large Jewish populations. An education programme for both health professionals and the Jewish community will be required. Currently, public education for the Tay Sachs programme is carried out sporadically by the communal charity 'Jewish Care'. The organisation of joint education programmes for Tay Sachs, FD, CD and CF will need to be reviewed with the NHS, Jewish Care, the DSGB, and other relevant organisations.

The report of a DH Visiting Fellowship (to observe these screening programmes abroad) further discusses the education programmes that are running in other countries for similar panel screening tests in this population. There are a wide variety of patient education resources available from these programmes, which could be easily adapted for a similar screening programme in the UK.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

As discussed in section 7, and in the Visiting Fellowship report, there is evidence to suggest that the screening programme will be acceptable to the Jewish population.

In addition, the involvement of a charity as large as Jewish Care in the current screening programme demonstrates the importance of the programme to the Jewish community. They run (in conjunction with the Genetics department at Guy's Hospital) regular community screening sessions for Tay Sachs, in synagogues, community centres, and Jewish secondary schools in London. Other organisations in the Jewish community sometimes request Tay Sachs screening programmes to be arranged to coincide with other community events.

At several district general hospitals in areas of London with substantial Jewish populations, Tay Sachs screening is already offered through established services. Some other local hospitals in these areas require further input into the development of their screening services. Many GPs in these areas are also proactive in offering screening. This activity demonstrates the support of health professionals for

the current Tay Sachs screening programme.

Also, the consensus opinion of the national meeting on 3rd June 2004, was that it was important to investigate the possibility of population screening for FD and CD. The consensus at this meeting regarding the question of CF screening in the AJ population, was that this must be considered in the light of CF screening provision nationally.

In the Strictly Orthodox section of the AJ population, screening is acceptable as long as it is conducted prior to marriage, as this group seeks to avoid the use of PND and TOP and therefore chooses to avoid marriages between two carriers. Therefore, as long as screening can be available to this community in a way which accommodates their need for pre-marital screening, it will be acceptable to this section of the population.

Two different organisations in the Strictly Orthodox community in London have arisen to offer screening in a way which meets this cultural need. One organisation is called 'Dor Yeshorim' and works outside of the NHS, using laboratories in the USA, which test for up to 10 AJ genetic diseases, including TSD, FD, CD, and CF.

However, those individuals who choose to use the Dor Yeshorim system would not use the NHS screening programme as disclosure of test results is not desirable for this group. The Dor Yeshorim system does not release test results, but each individual has an identity number, and together with the identity number of a potential partner, Dor Yeshorim will advise that a potential partnership is 'compatible' or 'incompatible' (i.e. if they are both carriers of the same gene). This system has become part of the system of 'arranged introductions' (prior to marriage) in this population. Because they have a cultural and religious need for this anonymised testing service, the NHS service is not currently able to serve this population. As a result the individuals who require this service are currently paying up to £150 for their screening tests. Dor Yeshorim has recently raised the question of whether there would be any possibility of some NHS subsidy towards their screening costs.

The other genetic screening organisation in the Strictly Orthodox community in London is called the 'Association for the Prevention of Jewish Genetic Diseases', and currently this organisation runs its own public screening sessions and sends blood samples to Guy's Hospital for Tay Sachs testing, and sometimes to a private laboratory in London for other genetic tests for AJ disorders, including FD, CD, and CF. Those individuals who are screened through the 'Association for the Prevention of Jewish Genetic Diseases' do desire disclosure of results, and hence the NHS screening programme would be acceptable to this group.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

Appropriate education and counselling during and after the testing procedure should circumvent any psychological harm caused by a positive carrier test. It has been shown that higher levels of knowledge about the implications of Tay Sachs testing are predictive of lower levels of anxiety after the test result (Gason et al 2003).

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money).

Currently, Tay Sachs screening in the UK uses biochemical methods. The Genetics Centre at Guy's Hospital performs approximately 700 Tay Sachs tests annually and the laboratory costs are £120 per patient (allowing for DNA analysis for inconclusive and positive results). This represents annual laboratory costs of around £84,000. The Willink Laboratory in Manchester tests approx 120 samples per year and the laboratory costs are £87 per test (biochemical testing only, no DNA analysis performed)

representing annual laboratory costs of around £10,440.

Other costs associated with the current screening programme are as follows (as estimated according to current costs from the Clinical Genetics Service at Guy's Hospital during 2005):

£53 per 'walk-in clinic' appointment at Guy's £230 for a full Genetic Counselling appt (eg. when a carrier couple is detected) £330 CVS procedure £374 CVS analysis (£214 Biochem + £160 Cyto)

In addition, some costs of the current screening programme are borne by the charity 'Jewish Care' rather than the NHS. At the moment this specifically encompasses the production of patient information leaflets and some aspects of the organisation of community screening sessions in schools and community centres in London. In Manchester a significant proportion of the screening costs (both laboratory and organisational) are raised through charitable donations from the local Jewish population.

It is likely that the most cost effective laboratory method for offering additional genetic screening to the Jewish population will be to use multiplex kits (molecular methods), which test for several AJ mutations in one procedure. Several multiplex kits for AJ screening are already produced by various private companies. Most established kits detect the common AJ mutations for TSD, FD, CD, CF and also Fanconi anaemia. Some kits also include yet other genes that are more common in this population. It may be appropriate to develop (either within the NHS or in conjunction with a private company) a kit which only tests for those genes for which screening is deemed desirable. Alternatively, if a ready-made kit was purchased, suppliers may be prepared to remove primers for the unwanted tests from their kits. It may also be worthwhile to consider the case for offering population screening for the other diseases included in the kits, as this would not add any additional laboratory costs to the screening programme. For instance the laboratory costs of screening using a commercially available multiplex kit (which includes TSD, FD, CD, CF and Fanconi anaemia) has been estimated as around £95 (depending on which kit is used) per patient. If testing continues at a similar rate, this would imply laboratory costs of £66,500 p.a for the London population. Therefore, after accounting for the set up costs of the new testing method, the overall laboratory costs are likely to be similar to the current screening programme.

As noted above, commercially available kits include the three common Tay Sachs founder mutations. In some AJ population screening programmes internationally, there is a move away from biochemical testing for Tay Sachs to molecular testing (Bach et al 2001). Bach et al report 100% specificity for DNA analysis alone in TSD screening, and also report a high sensitivity providing AJ ancestry is assured. Therefore, a move away from biochemical screening for Tay Sachs could result in a financial saving, at the expense of a very small false negative rate. If biochemical screening for Tay Sachs was retained, and molecular methods were added for screening for FD, CD and CF, this would be an expensive method of screening, but it may give a smaller false negative rate for Tay Sachs.

The prior existence of screening services at Guy's Hospital, and at other local hospitals and Genetics centres, will mean that additional genetic tests can be added to the TSD screening programme using the current infrastructure for laboratory services, genetic counselling, administration and quality assurance. Therefore, large investment into new infrastructures in these areas will not be required.

However, there will be some additional costs, and these will be in the following areas:

- The set up of the multiplex kit, and the organisational costs of a potential transfer of Tay Sachs screening from biochemical testing to a molecular testing.
- Screening 700 samples annually will require one whole-time equivalent Clinical Scientist within an established regional DNA laboratory. If biochemical screening for Tay Sachs was replaced by mutation analysis then manpower resources can be re-allocated, which

would be cost-neutral. However it may be appropriate to run Tay Sachs biochemical and mutation analysis concurrently for the first year to compare the two methods and establish best practice.

- Additional referrals to the genetic counselling services for carrier couples identified, and PND/TOP if requested.
- The expanded screening programme will require improved education programmes for the Jewish community and training for health professionals. It may be appropriate to consider providing additional staff/facilities for education programmes for the Jewish community and for health professionals, and for the overall running and monitoring of the screening programme on a national level.
- The issue of NHS subsidisation for those patients who require screening through the Dor Yeshorim system will need to be considered.

The current Tay Sachs screening programme may not be equally accessible to Jewish patients living in different geographical locations, and a review of the service is planned. The results of this review would then impact on the structure of the whole AJ screening programme.

Therefore, there will be additional costs associated with an expansion of the current Tay Sachs screening programme to cover these other diseases. There may also be potential savings in the long-term, with regard to the use of molecular testing methods.

This must assessed in the light of the costs of not offering screening. The Dysautonomia Society have estimated that it costs just under £79,000 per year (during the 2-18 years age group, costs are less at other ages) to manage each individual affected with FD (this includes the social costs due to benefits claimed etc). There are currently 11 known cases in the UK.

In 1998 when Tay Sachs was approved as a population screening programme, it was estimated that it cost around £25,000 per year to care for an affected individual, with an average lifespan of 4 years. The costs of caring for an individual affected with CD are likely to be in this region, and individuals with this condition may live into late childhood or teens. Murray et al (1999) reports a range of costs per year for caring for a CF patient, ranging from £5,310 in the 0-5 years age group in the UK in 1996; to £37,000 per year in the pre-terminal phase of the disease in a Dutch study in 1991. These figures do not include the social costs due to benefits claimed.

As discussed in section 8, screening for Tay Sachs has resulted in a significant reduction in the number of affected individuals born with the condition.

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

CPA accredited laboratories will be used for the screening programme in order to guarantee quality assurance. If laboratory services in other countries were to be considered for handling samples, this issue would need further consideration.

In addition, an annual report will be submitted to the NSC outlining:

- The number of tests performed and number of carriers identified, and a breakdown of the geographical spread of the screening programme, relative to the Jewish population size in different areas.
- The activity of the education programme
- Any problems encountered or issues arising

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

As discussed above, the prior existence of screening services at Guy's Hospital, and at other local hospitals and Genetics centres, means that facilities for laboratory services, genetic counselling, administration and quality assurance are already in place. The possible transfer from biochemical testing for Tay Sachs to multiplex molecular testing for several AJ diseases will require a change in laboratory facilities. Tay Sachs testing and FD testing are currently set up at the Genetics Centre at Guy's Hospital. In addition, the Willink laboratory in Manchester also undertakes biochemical screening for Tay Sachs, although discussions are currently underway to look into the possibility of transferring this activity to Guy's Hospital. CD testing is currently set up at the Molecular Genetics Laboratory at Northwick Park Hospital. Currently the FD diagnostic and carrier testing at Guy's, and the CD diagnostic and carrier testing at Northwick Park, are available to affected families only. Some consolidation of laboratory facilities would need to be negotiated.

It may be appropriate to consider providing additional staff / resources for education programmes for the Jewish community and for health professionals, and for the overall running and monitoring of the screening programme on a national level.

19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

Limited symptomatic management for FD, CD, and CF is feasible, although there are no cures for these diseases. Outcomes in FD and CF may improve with earlier diagnosis and this could be aided by carrier screening. However, the only preventative measure is prenatal diagnosis (or PGD), which would be an option for carrier couples found through screening. For those individuals who choose to be screened in the Strictly Orthodox Jewish population, the primary intervention is to avoid marriages between carriers of the same condition.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

Patient information leaflets will be available to all those considering screening. The existing information leaflet about Tay Sachs testing is written, published and distributed by Jewish Care. Dor Yeshorim also produces its own leaflet. Options for creating a new leaflet covering AJ screening in the NHS will need to be discussed jointly with Jewish Care, the DSGB and the Association for the Prevention of Jewish Genetic Diseases. This should happen prior to the commencement of the screening programme.

Similarly community education about Tay Sachs is currently undertaken by Jewish Care. However a new programme will need to be developed in conjunction with these organisations prior to the commencement of screening for FD and CD and CF (and other AJ diseases).

A psychosocial research programme should also be established, alongside screening in the initial phases, to gather additional evidence about the psychosocial issues raised by simultaneous screening for multiple disorders.

The report of a DH Visiting Fellowship (to observe these screening programmes abroad) further discusses methods of providing patient information and community education. As discussed above, information resources available from screening programmes abroad could be adapted for use in the UK.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

The most likely source of public pressure on the screening programme will be to increase the number of AJ disorders screened for. Various screening programmes internationally are now offering up to 14 genetic tests to AJ patients. It is therefore inevitable that that there will be requests for tests for additional genes, from patients who are aware of these screening programmes abroad. In addition the Dor Yeshorim programme currently screens for up to 10 genes. This could lead to a perception of disparity between those in the Jewish population who choose to use different screening programmes.

The use of multiplex kits for testing means that several additional tests could theoretically be added with negligible additional laboratory costs. But the additional costs of education about other tests, and counselling the additional carriers detected will need to be considered.

Several of these other diseases have a lower carrier frequency and so the parameters of screening could be justified according to an agreed cut off point of carrier frequency. The American College of Medical Geneticists (ACMG) recommends that population genetic 99screening be considered for severe autosomal recessive conditions with a carrier frequency of 1 in 60 or more. Therefore, it may be appropriate, in the initial stages of the screening programme, to establish a parallel research programme to define the carrier frequencies in the UK Jewish population, for some of the other genetic diseases that are included in other screening programmes, for instance, Fanconi anaemia, Mucolipidosis IV etc. If these founder mutations are found to be carried by 1 in 60 of the population, or more, then it might be reasonable to consider including them in the screening programme.

The most common genetic disease in the Jewish population is Gauchers disease (carrier frequency around 1 in 15). However, this is a disease of variable phenotype, with a large proportion of homozygotes being asymptomatic, and for which treatment is available. The Gauchers Association in the UK have therefore issued a policy statement explaining their position that population screening for this disease, for the purpose of PND, would not be appropriate.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

As discussed in section 7 and in the Visiting Fellowship report, there is evidence to suggest that the screening programme would be acceptable. In addition the on-going activity and support of the DSGB in this area demonstrates the acceptability of screening for FD to affected families.

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