Appraisal of screening the UK Ashkenazi Jewish population for risk of Tay Sachs disease

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Introduction

1.This paper reviews screening for risk of Tay Sachs disease (TSD) in the UK Ashkenazi Jewish population against the UK National Screening Committee criteria for appraising effectiveness and appropriateness of a screening programme (National Screening Committee 2003).

2.There are a group of autosomal recessive diseases which, because of genetic drift, historical and social factors, have been found to occur at a higher incidence or almost exclusively in the Jewish population (Gross et al 2008). The three main Jewish groups are Ashkenazi (Eastern European origin), Middle Eastern (mostly from Israel and Iraq), and Sephardic (originating from Spain, the Balkans, Turkey, Lebanon and Syria). Individuals of Ashkenazi Jewish descent are at increased risk of having offspring with particular genetic diseases such as TSD that have significant morbidity and mortality (Klugman and Gross 2010). In the UK of the estimated 270,000 British Jews 95% are likely to be of Ashkenazi origin (Burton et al 2009).

3.In 1999 the National Screening Committee considered the TSD carrier testing services that had been set up by some charities in the Ashkenazi Jewish community and secured some limited funding to support laboratory costs that charities were no longer able to fund. Minutes from the UK National Screening Committee meeting held on June 9th 1999 state that:

'*4.4.1 Dr O'Grady reported that actions had been successful in securing NHS funding for laboratory costs associated with the hereditary neurological disorder Tay Sachs. The service provided to the Jewish community would continue uninterrupted following the withdrawal of charitable sector funding' (UK NSC Minutes June 9th 1999 page 3)*

4.In March 2009 a report commissioned by the NSC carried out a needs assessment and reviewed services providing TSD testing (Burton et al 2009). The report also made a number of recommendations about implementing a full UK NSC formal screening programme for TSD based on the assumption that generic carrier screening had been approved by the NSC in 1999. TSD carrier testing had not been fully approved by the NSC although some funding had been secured to ensure the continuity of the service funded by the charitable sector. The response by the NSC to the report was to recommend that the commissioners of specialised services should be contacted regarding the continuity of the testing service, particularly that provided in Manchester and that a full review of the evidence for screening for risk of Tay Sachs disease should be undertaken.

5.A knowledge update (Coles 2010) was carried out in October 2010 to inform the current review against the screening criteria. The update found that between 2000 and October 2010 152 references were relevant to screening for TSD (Appendix 1).

6.The latest review of UK TSD testing (Burton et al 2009) and the relevant papers identified by the Knowledge Update form the basis of this review.

7.This review considers evidence for preconception, antenatal and neonatal screening in the UK Ashkenazi Jewish population. The aims of screening in these scenarios may be quite different. For newborn screening the emphasis is on interventions to prevent or facilitate early management of disease. Screening during the preconception and antenatal period aims to identify carrier status of the parents/couple to enable reproductive decision making, the available choices being determined by the context.

The Condition

Criterion: The condition should be an important health problem.

8.Tay Sachs disease is an autosomal recessive degenerative neurological disease caused by deficiency in the enzyme hexoaminidase A. This enzyme degrades GM2 ganglioside and without hexaminidase A it accumulates within the lysosomes of nerve cells causing neuronal dysfunction (Burton et al 2009). There are nearly 100 mutations which result in the absence or reduction of hexaminidase A. However, in the Ashkenazi Jewish population 92-98% of cases are caused by one of seven mutations (Park et al 2010).

9.The carrier frequency of TSD in the Ashkenazi Jewish population is between 1:25-1:30 (leading to an incidence of around 1:3000). For comparison, in the general population the carrier rate is 1:250 (Burton et al 2009) with an incidence of around 1:250,000.

10.Classical TSD is caused by a loss of Hex A protein as a result of HEXA mutations. The condition becomes apparent from 3 to 6 months of age with the onset of mild motor weakness. As the disease progresses the infants motor skills, and visual attentiveness decrease. At 18 months often seizures start and become progressively worse. By two years the child is typically in a vegetative state leading to death between 3 to 5 years of age (Burton et al 2009, ACOG 2008).Most identified HEXA mutations are associated with the classical form of the disease (Burton et al 2009). There are three mutations of the HEX A gene which are commonly associated with classical TSD in the Ashkenazi Jewish populations. These mutations are +TATC1278, +1 IVS12, and +1 IVS9 and they account for 98% of Ashkenazi Jewish parents who have an affected child (Burton et al 2009).

11.Late onset TSD is much rarer than classical TSD and starts to affect people in adolescence when difficulties in walking and unsteadiness begin to be noticed. People may be able to walk with help into their 40s and 50s. Psychiatric problems are common. Life expectancy is normal for most adults with the disease. Burton et al (2009) reported that only 2% of parents with an affected child have the mutation for late onset TSD (G269S).

12.Other GM2 ganglioside diseases include Sandoff disease (due to mutations in HEX B gene), AB variant where there are no HEXA or HEX B mutations but there is a deficiency of a protein required to activate HEXA, and the B1 variant where HEXA mutations cause reduced activity towards some substrates (Burton et al 2009).These mutations are very rare and are not found in higher frequencies in the Ashkenazi Jewish population (Burton et al 2009).

13.TSD is clearly an important health problem for those individuals affected.

Criterion: 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.

14.Many of the autosomal recessive disorders in the Ashkenazi Jewish population are attributed to mutations thought to arise in a single individual many generations ago. Due to the way in which the Ashkenazi Jewish population has migrated and expanded these mutations have become more common. Known as the founder effect, this type of genetic drift has been proposed as the reason why TSD is more common in the Ashkenazi Jewish population

(Zhang et al 2004). There is a theory that the high frequency of these mutations is due to people carrying them having a better reproductive or survival advantage such as increased resistance to infectious pathogens (Zhang et al 2004).

15. The 2001 census is the only systematic information about the Jewish population in the UK. Burton et al (2009) reported that the figure of 270,000 Jewish people in Britain may be an underestimate (by approx 10%). Geographically Burton et al (2009) reports that 96.7% of British Jews live in England and these are clustered in a small number of mainly urban areas with 36% living in 5 London Boroughs. Other areas where populations are concentrated are Hertfordshire (5.5%), Greater Manchester (8%) and Leeds (3%).

16. The religious orthodoxy of the UK Jewish population is important when considering what type of screening will be acceptable. Jewish people adhering most strictly to traditional beliefs are least likely to take up the offer of antenatal screening. Burton et al (2009) summarised the definition of the different strands of Jewish orthodoxy:

- Strictly Orthodox Jews (also known as ultra-Orthodox or Haredim) 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.

17. From data about marriages of Jewish people in the UK based on Synagogue records Burton et al (2009) reported that between 1996 and 2005 out of 9441 marriages 22% (2135) were strictly orthodox and 4969 (52.6%) were central orthodox. Around 4.5% of marriages were between Jews not of Ashkenazi origin (mostly Sephardic).Of all the married couples in the UK where at least one person was Jewish 62% were in couples were both partners reported being Jewish and 38% were couples with only one reported Jewish partner (Burton et al 2009).

18. There were an estimated 2772 births per year between 1993 and 2002 in the UK Ashkenazi Jewish population (Levene 2005) and with an incidence of around 1 affected birth in 3000 we would expect 1 affected child born per year in this community.

19. In comparison in England and Wales in 2010 there were 723,165 births (Office of National Statistics 2011) with a carrier rate of 1:250-1:300 we would expect 2 to 3 affected children to be born each year. Burton et al (2009) reported that between 1999 and 2007 29 children in total with TSD had been diagnosed.

20. The Willink Centre in Manchester reported that between 1999 and 2007 15 children with TSD had been diagnosed of which only 2 were of Ashkenazi Jewish origin (Burton et al 2009). It is not clear how large the catchment population is for this centre but it will be serving the Ashkenazi Jewish populations in the north of England.

21. This criterion is partially met as the nature of the disease is clearly described in the literature but there is limited understanding of how many cases and carriers there are in the UK

Jewish population. From the available evidence this condition is not significant from a public health perspective in the UK.

Criterion: All the cost effective primary prevention interventions should have been implemented as far as is practicable.

Pre-conception

22. Funding of testing for TSD in the UK is via the National Specialized Commissioning Group (http://www.specialisedservices.nhs.uk/info/about-us). This group directly commissions medical genetics services from designated hospitals in the UK to undertake testing and genetic counselling for people who are carriers of rare genetic diseases such as TSD. The National Service Framework for Children, Young People and Maternity Services published by the Department of Health, (2004) outlines the services that should be offered to women pre-conceptually and during pregnancy. These include 'specialist pre-conception advice and support for prospective or existing parents with a family history of a genetic disorder and those who are concerned about familial disease and disabilities' (Department of Health 2004).The framework also states that staff working with people before conception should be competent in recognizing, advising and referring people who would benefit from more specialized services. This would include people who request a test for carrier status of TSD on the basis of familial disease or ethnicity.

23. GPs may refer people to the regional genetics service for genetic counselling and testing. Alternatively, if GPs consider that they have a significant Jewish population in their catchment they can give information to high risk patients about testing. A survey by Burton et al (2009) showed that out of 77 people who responded to questions about how they had accessed TSD testing one third reported that GPs either gave no information or incorrect information when asked. This suggests that GP awareness and subsequent referral practice of people who are possible carriers is not optimal. The Royal College of General Practitioners (2009) outlines the knowledge, skills and attitudes a GP requires when relating to patients and families with genetic conditions or who present with anxiety about family history and the likelihood of having a genetic condition. GPs should be able to access up to date information about particular conditions, make appropriate referrals to regional genetics services and understand how the make-up of the local population may affect the prevalence of genetic conditions (RCGP 2009).

24. People who are concerned that they may be at high risk of being a carrier can visit the specialist weekly walk in clinics in London at Guys Hospital and Barnet General Hospital.

25. Sessions where tests are offered in Jewish schools and community organizations in London are run by voluntary groups. In Manchester a community outreach screening service to Jewish schools universities and community groups is run by Booth Hall Children's hospital and funded by Jewish charities. Sessions from this outreach service are infrequently held in other cities in the Northwest and Midlands (Burton et al 2009).

26. The Dor Yeshorim organization offers anonymised carrier testing for TSD and nine other conditions. No results are given only a number that relates to the result. When a couple want to check their genetic compatibility Dor Yeshorim will only inform them whether they are compatible or not, based on the results of the tests for all ten conditions (Raz & Vizner 2008).

27. The 'Association for the Prevention of Jewish Genetic Diseases' in the Strictly Orthodox Jewish community in London runs public screening sessions for TSD (amongst other diseases) and sends blood samples to a private laboratory for processing. The results are disclosed to the person tested.

28. A complete picture of the level of testing via the various routes in the UK are not known although Burton et al (2009) have calculated that in 2007 at least 862 tests were carried out either in the NHS or via one of the private laboratories (The Doctors Laboratory). Burton et al (2009) estimates that 22.6% of marriages between 1996 and 2005 were of strictly orthodox couples who may well have used Dor Yeshorim prior to an arranged marriage. There is no data about the level of testing within this organisation.

Antenatal

29. It is debatable whether current antenatal testing for TSD is primary prevention however if women and their partners are identified as carriers during pregnancy it is possible to prevent a baby being born with the condition and there is the opportunity to access genetic counselling to aid future reproductive decision making.

30. The National Service Framework for Children, Young People and Maternity Services published by the Department of Health (2004), outlines the services that should be offered to women during pregnancy. The framework states that during the antenatal period staff should be competent in recognizing, advising and referring women who would benefit from more specialized services. This would include women who request a test for carrier status of TSD on the basis of familial disease or ethnicity.

31. During antenatal appointments midwives routinely ask about ethnic origin as this can be a factor for a number of inheritable conditions such as sickle cell disease. Midwives have a Family of Origin Questionnaire (FOQ) to complete and although it doesn't ask about Jewish origin it is a point at which a woman may request a test for the TSD mutations. Burton et al (2009) suggests modifying the FOQ to include Jewish origin and recommends that that any woman with a grandparent of Ashkenazi Jewish origin should be carrier tested for TSD. The knowledge update by Coles (2010) did not identify any publications which assessed the effectiveness of this approach in reducing the likelihood of affected children being born.

32. A survey by Burton et al (2009) showed that out of the 155 trusts that were asked if they carried out TSD testing 114 responded. Of those that replied 77 said they would carry out screening on the request of the patient, 13 reported that they proactively offered screening and 37 did not do any testing either proactively or on request. No trust carried out more than 10 tests per year. This suggests that some antenatal services are not aware of referral pathways for testing of TSD.

33. GPs can refer pregnant women to specialist weekly walk in clinics in London at Guy's Hospital and Barnet General Hospital.

Neonatal

34. If a child is born with Tay Sachs disease it may not be immediately obvious and will only be diagnosed when symptoms present and are investigated. The parents of an affected child may be more likely to access advice via the regional genetics service about planning further pregnancies (Green et al 2004).

35. Primary prevention to reduce the number of children born with TSD is not optimised and this criterion is not met for all three screening settings.

Criterion: 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 implication.

36. People identified as carriers of TSD mutation will not go on to develop the disease. TSD can only be passed on to the next generation if both partners of a couple carry the mutation then there is a 1 in 4 risk of having an affected child (Alberg et al 2010).

Pre-conceptual

37. Gason et al (2003) evaluated the predicted feelings and attitudes towards TSD testing in Jewish high school students (15-18yr olds). They reported that students with a higher level of knowledge were significantly ($p<0.01$) more likely to accept testing and have lower levels of predicted anxiety if found to be carriers. In a more recent study Ioannou et al (2010) compared multi-disease carrier testing with the single TSD testing in the Gason et al (2003) study. They concluded that the students offered multi-disease screening had a lower level of knowledge than those offered the single TSD test and their predicted anxiety of being identified as a carrier was higher. These predicted anxiety levels were not however the most influential factors on uptake of screening and in the Ioannou et al (2010) study 271 out of 273 (99.3%) students undertook the tests. No significant psychological effects of screening have been reported in the literature.

The Dor Yeshorim testing programme takes blood samples from people prior to marriage and tests them for a panel of genetic diseases. Individual results are not released, but when a couple is being matched for marriage Dor Yeshorim will inform them whether they are compatible or not (Raz & Vizner 2008). By anonomizing the results the programme aims at reducing stigma. However, there are debates as to whether this approach succeeds in its objective as it means people often have little understanding about the different genetic diseases in question or the psychological impact of having a 'non compatible' result. Raz and Vizner (2008) question whether the consensus by Dor Yeshorim and community leaders that 'you don't need to know' the results is ethical. There are other private testing programs for Strictly Orthodox Jews such as the 'Association for the Prevention of Jewish Genetic Diseases' in the UK which do disclose results to those tested.

Antenatal

38. A systematic review of the psychosocial aspects of genetic screening for carrier status of other autosomal recessive diseases reported that anxiety was raised in the short term in women receiving positive results. However, there have been few studies of longer term anxiety as a result of carrier testing (Green et al 2004).

Neonatal

39. Green et al (2004) carried out a systematic review of the impact of newborn screening of a range of different genetic conditions (not TSD) on parents. There were only 28 relevant publications identified. The review concluded that increased anxiety in parents from a positive result was linked to a lack of understanding about the condition and the true health status of the child. One argument for carrying out neonatal screening where there is no clear benefit to the child is that this will aid decision making about future pregnancies. Green et al (2004) found six studies which looked at possible reproductive behaviour change due to previous newborn screening tests. The studies showed varying results, ranging from one Australian study showing a 69% uptake in genetic counselling by parents following the diagnosis of cystic fibrosis in a first affected child to only 21% uptake in a study in Wisconsin. It was assumed that these differences between the studies may be a reflection of the attitude of different groups to termination of pregnancy.

40. The natural history and psychological implications for people who are either TSD carriers or cases is understood and this criterion is met.

The Test

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

41. There are typically two types of testing for TSD carrier status. A biochemical assay of hexaminidase A activity in either serum, leucocytes or platelets can be used or direct DNA testing for an agreed number of causal mutations (Schneider et al 2009). Both the biochemical assay and the DNA testing can be carried out using a blood test. In some studies DNA testing has been carried out using cheek brush samples (Gason et al 2005).

Biochemical tests

42. Burton et al (2009) reviewed the literature and reported that the leucocyte test had a sensitivity of 99.77% and specificity of 89.32% with a false positive rate of 10.68% and false negative rate of 0.23%. However, this test requires fresh samples and if they are inadequate then repeat testing is necessary.

43. Schneider et al (2009) compared biochemical assays of hexaminidase A activity in serum and platelets with genetic testing of the 7 most common TSD mutations in 1069 individuals participating in a TSD screening programme in the US.

44. The serum assay identified 29 carriers and an additional 169 (16.3%) of results were inconclusive (however, 83 were from females using oral contraceptives and should not have been offered the test as this can give a false positive result). The platelet assay identified 35 carriers (including all those identified by serum testing) and four were inconclusive (also inconclusive with serum testing). Of the 35 individuals identified by the platelet assay 31 had detectable mutations with the DNA analysis. Two individuals who had inconclusive results with both serum and platelet tests had detectable DNA mutations.

45. The advantages of the platelet assay are that it is an effective method of TSD screening associated with a high detection rate and a low inconclusive rate (Schnieder et al 2009). Serum testing generates a high proportion of inconclusive results and it cannot be used for women who are taking oral contraceptives or who are pregnant. However, it is a simpler test to process on a large scale than platelet assays.

Genetic tests

46. With genetic screening, the number of mutations to be tested must be agreed by the screening programme. Some mutations for TSD are more common than others and some are associated with particular ethnic groups other than the Ashkenazi Jewish populations (e.g. French Canadians). Two mutations (pseudo-deficiency alleles) have been found that have no clinical effect but still give a positive result with biochemical assays.

47. A panel of seven mutations and pseudo –deficiency alleles identifies 92%-98% of carriers in Ashkenazi Jewish populations (Park et al 2010). In the non-Jewish population this panel of tests would only detect approximately 50% of the carriers with the other 50% attributed to nearly 100 other mutations (Park et al 2010). With more mixed populations of Ashkenazi Jews and non-Jewish carriers there will be a higher number of mutations and the standard panel of tests would have a lower sensitivity and higher false negative rate with these groups. Schneider et al (2009) found that genetic analysis of a broad based mixed sample missed 4 out of 35 carriers indicating a false negative rate of 11.4% and sensitivity of 88.6%. Park et al (2010) compared serum testing with DNA testing and gene sequencing (determining the exact order of base pairs in the segment of DNA concerned with Hexaminidase A alleles). They found that in a sample of 33 self reported TSD carriers, none

of which claimed to be of Ashkenazi Jewish origin, the biochemical assay identified 30 out of 33 (91%) carriers, as did the gene sequencing. The DNA test however only detected 52% of carriers. A combination of biochemical assay and gene sequencing detected all carriers, whilst the combination of the assay and DNA testing identified 97% of carriers. No one modality is able to identify all carriers (Park et al 2010).

48. Burton et al (2009) reviewed the literature about all the types of tests for TSD available and concluded that although in their opinion the current tests used were valid, precise and safe, if a formal screening programme were implemented there would have to be a debate about which combination of tests should be used for the UK Jewish population. The decision would be based on cost, technical difficulty, acceptability to the target population and the consequences of a higher proportion of false negative (DNA test) or false positive (biochemical assay) results.

49. There is a suitable test for screening for TSD so this criterion is met for all three screening settings.

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

50. Cut off points for biochemical assays are agreed from standard curves of hexaminidase A activity in carriers and non-carriers. Each laboratory would build up a reference range of curves for carriers and non-carriers (Burton et al 2009).

51. There is a suitable methodology for determining test values for carriers and non-carriers therefore this criterion is met for all three screening settings.

Criterion: The test should be acceptable to the population.

52. The biochemical assay uses a blood sample whilst the DNA test can use either a blood test or a swab from the inside of the cheek (Gason et al 2005). Targeted screening programs have typically used blood samples to test for TSD and these programs have been implemented successfully in Ashkenazi Jewish communities in the US, Australia, Israel and Canada (Burton et al 2009).

Pre-conceptual

53. Gason et al (2005) found that in a sample of 450 students aged 14-17 a significantly higher proportion of students had a test when a cheek brush swab was used (96%) compared to a blood sample being taken (84%). There was significantly higher anxiety reported about the test when a blood sample was taken than when a cheek brush swab was used ($p<.001$).

54. Ioannou et al (2010) showed that where people where offered a single test (for TSD for example) knowledge gained prior to screening had the effect of reducing anxiety. However, where there was testing for a number of genetic diseases at the same time it was more difficult to relay information in a way that increased knowledge and decreased anxiety as people felt they had more risk of being positive for at least one condition.

Antenatal

55. Testing for TSD in the UK is carried out in a range of settings both prior to conception and during the antenatal period. In reviewing TSD testing in the UK Burton et al (2009)

concluded that the type of tests that will be used will be acceptable to the Ashkenazi Jewish population.

Neonatal

56. There were no studies of neonatal screening for TSD. Other newborn screening programmes in the UK routinely use a blood spot test (sickle cell disease) and have met the NSC criterion for acceptability.

57. A blood test has been used in a variety of settings for TSD carrier status and to identify cases in the Jewish population in the UK. This type of test has been found to be acceptable for screening for other autosomal recessive genetic conditions and so this criterion is met for all three screening settings.

Criterion: 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.

Pre-conceptual

58. A confirmed positive test result prior to conception would not require any further intervention although individuals should be given the option of pre-conceptual counselling to aid decision making about reproductive options (Human Genetics Commission 2011, Department of Health 2003).

Antenatal

59. A positive result for a woman who is pregnant will lead to the partner being tested if available and then aminiocentesis or chorionovillus (CVS) sampling to test whether the foetus has TSD (Royal College of Obstetricans and Gynaecologists (RCOG, 2010).

Neonatal

60. Babies who have a positive test result will be referred to the appropriate specialty for management of the condition. There are no effective curative treatments for children with TSD. However, the National Specialised Commissioning Group has a set of standards about care for people with lysosomal disorders which includes TSD (http://www.specialisedservices.nhs.uk/library/25/National_Lysosomal_Storage_Disorder_Standards.pdf. Parents of affected children should be offered genetic counselling to support them in planning further children (Human Genetics Commission 2011).

61. There are agreed policies on the further diagnostic investigation of individuals with a positive test result so this criterion is met for all three screening settings.

Criterion: 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.

62. Three of the most common mutations in the Ashkenazi Jewish population are usually targeted with DNA testing (Burton et al 2009). A formal screening programme in the UK would have to agree the mutations to be tested based on likely rates of different mutations in the UK Ashkenazi Jewish population. This criterion is met.

The Treatment

Criterion: 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.

Pre-conceptual intervention

63. The current intervention available for people who are identified as positive carriers of TSD is the offer of genetic counselling to enable them to think through their reproductive options (Henneman 2004, Department of Health 2003, Human Genetics Commission 2011).

Antenatal intervention

64. The intervention available to women who are pregnant with a baby diagnosed with TSD is genetic counselling and the option of termination of pregnancy (RCOG 2010).

Neonatal intervention

65. There are no effective curative treatments for children with TSD. However, the National Specialised Commissioning Group has a set of standards about care for people with lysosomal disorders which includes TSD (http://www.specialisedservices.nhs.uk/library/25/National_Lysosomal_Storage_Disorder_Standards.pdf.

66. Parents of affected children should be offered genetic counselling to support them in planning further children (Human Genetics Commission 2011). However, it is not clear whether parents of an affected child would take up genetic counselling. Green et al (2004) found six studies which looked at possible reproductive behaviour change due to previous newborn screening tests which had variable results (see para 34).A further two studies asked parents of children with CF, some of whom were detected through a newborn screening programme, about attitudes to terminating a future pregnancy. Of 18 Welsh parents 11 (61%) said they would terminate a future pregnancy if there was a positive CF diagnosis whereas in a Colorado study 17%of 40 parents said they would terminate a future affected pregnancy whilst 61% would not and 22% were unsure(Green et al, 2004).

67. For preconception and antenatal screening interventions are offered to people who are carriers but they are only effective if the interventions are acceptable to the UK Jewish population. This criterion is mostly met for these settings. For neonatal screening there is little evidence that the outcome of early management of people with TSD will lead to better outcomes than late treatment so this criterion is not met for this setting.

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

Pre-conceptual carrier testing

68. An individual identified as a carrier should be able to access genetic counselling (Human Genetics Commission 2011, Department of Health 2003).

Antenatal management

69. In May 2010 The Royal College of Obstetricians and Gynaecologists (RCOG) published evidence based recommendations on the 'Termination of pregnancy for foetal abnormality'.

The guidance is intended to assist doctors and other health professionals to support women when a foetal abnormality is diagnosed and help women decide whether or not to have a pregnancy terminated.

Neonatal management

70. There are no effective curative treatments for children with TSD. However, the National Specialised Commissioning Group has a set of standards about care for people with lysosomal disorders which includes TSD (http://www.specialisedservices.nhs.uk/library/25/National_Lysosomal_Storage_Disorder_Standards.pdf.

71. Parents of affected children should be offered genetic counselling to support them in planning further children (Human Genetics Commission 2011).

72. There are agreed approaches for people identified as carriers of a genetic mutation for TSD and standards for those children identified as a case therefore this criterion is met for all three settings.

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

73. From the study by Burton et al (2009) it is clear that the management of people at risk of carrying a mutation for TSD is not optimised in all health care providers. It is also unknown if the clinical management of people born with the condition receive optimal clinical management by all healthcare providers. This criterion is not met for all three settings.

The Screening Programme

Criterion: 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" (e.g. 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.

74. There have been no high quality randomized controlled trials to show that screening to determine TSD carrier status of people within the Ashkenazi Jewish population in the UK is effective in reducing mortality or morbidity. This is the case for preconception and antenatal screening programmes. No neonatal screening studies of TSD could be identified.

75. Long running programmes for TSD screening targeting the higher risk Jewish populations in other countries have reported a 90% reduction in the incidence of the disease. Kaback (2000a) reported that between 1971 and 1999 the combined TSD screening programmes (includes preconception and antenatal screening) in Jewish populations across nine countries tested 1.4m people and identified 50,986 carriers. Of those carriers 2,800 were in a relationship with another carrier and had a 1 in 4 chance of conceiving a child with TSD. 3,261 pregnancies of couples at risk of having a child with TSD (identified through screening or prior offspring with TSD) were monitored between 1969 and 1999. Of those 3,261

pregnancies 628 foetuses were identified as having TSD, 609 of which were terminated. There were 3 foetuses of those monitored who were born with infantile TSD who were incorrectly diagnosed as being unaffected (Kaback 2000a).

76. In 1970 there were estimated to be 50-60 infants newly diagnosed with TSD in the US and Canada (Kaback 2000b). Of those 40-45 were of Jewish ancestry and 10-15 non-Jewish. In 1998 Kaback (2000a) reported that the average number of new cases per year was 12 with approximately 4 per year from Jewish origin. The reduction in the incidence of TSD is attributed to the identification of carriers of TSD by either preconception or antenatal screening programmes in these countries.

77. There is significant evidence already outlined that a combination of tests will accurately measure risk (Burton et al 2009) to inform people for both preconception and antenatal screening programmes.

78. There is no evidence that a screening programme in any of the three settings in the UK would significantly reduce morbidity or mortality therefore this criterion is not met.

Criterion: 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.

Pre-conception carrier testing.

79. Burton et al (2009) recommend that preconception screening is carried out in a variety of settings focused on the UK Ashkenazi Jewish population. This includes continuing current testing in mainstream Jewish high schools supporting walk in centres and funding testing services provided by Jewish charities.

80. The Human Genetics Commission (2011) advised the national Screening Committee on the social, legal and ethical implications of preconception genetic testing. They reported that after reviewing the evidence there were no specific ethical, legal or social principles that would make pre-conception genetic testing within a framework of a population based screening programme unacceptable. However this was contingent upon the NSC UK screening criteria being met for each potential preconception screening programme proposed.

Antenatal screening.

81. Burton et al (2009) recommend that antenatal screening is implemented initially in London and Manchester where the most Ashkenazi Jews reside. The programme would use a modified ethnic origin questionnaire to identify women who have at least one Jewish grandparent (carrier rate of 1:80). It is suggested that the programme would eventually be rolled out nationwide to ensure equal access to screening for all pregnant women of Ashkenazi Jewish origin. It is not clear whether testing for the possible 38% of marriages of mixed Jewish and non-Jewish origin would be acceptable given that the risk of an affected pregnancy would be extremely low.

82. Antenatal screening for carrier status followed by amniocentesis or CVS if the test is positive is the model used for TSD screening in a number of countries. This model has been used for other genetic diseases such as sickle cell and thalassaemia in the UK (Davies et al 2000). However, this form of testing and intervention would not be acceptable to the strictly orthodox Jewish community who are opposed to the termination of pregnancy (Burton et al 2009 estimate this equates to approximately 22% of marriages in the UK Jewish population).

Neonatal

83. Neonatal screening for other autosomal recessive genetic diseases including sickle cell disease and cystic fibrosis havebeen implemented in the UK indicating that this type of testing isacceptable to health professionals and the public (Streetly et al 2010). However no studies about the acceptability of screening specifically for TSD have been identified.

84. This criterion is mostly met as although there are no direct studies about preconception, antenatal or neonatal screening for TSD carrier status or case identification in the UK Jewish population there is indirect evidence that screening for this condition in other countries is acceptable. Similar screening programmes for other genetic conditions in all three settings have been found acceptable by the UK populations.

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

Pre-conceptual

85. A carrier screening programme prenatally enables couples and individuals to make informed reproductive choices. The primary harm to an individual will be the perceived stigma of carrying the disease (Frumkin & Zlotogora 2008). Anonymous testing is an option if individuals only want to determine their compatibility with a potential partner although there is an argument that this could reinforce possible stigma and misunderstandings about the disease (Raz & Vizner 2008).

Antenatal

86. Testing for carrier status during pregnancy then testing the foetus for TSD with a view to terminating the pregnancy will cause psychological and physical distress and prenatal diagnosis carries a small risk of miscarriage to the 75% of foetuses that are not affected by TSD. However, this is unlikely to outweigh the distress of the birth of an affected infant where there is no treatment and the only option is to care for the child until they die. In strictly orthodox Jews antenatal testing would not be effective as termination of pregnancy is not an option (Raz and Vizner 2008).

Neonatal

87. There is no evidence about the benefits or harms of a neonatal screening programme for TSD.

88. This criterion is partially met for antenatal and preconception screening settings but not for neonatal programmes where there is no evidence.

Criterion: 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 (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

89. There has been no detailed cost benefit or cost effectiveness analyses carried out for antenatal, preconception or neonatal screening programmes for TSD in the UK Jewish population.

90. Burton et al (2009) reported that between 1999 and 2007, a total of 6,560 known tests (preconception and antenatal) were carried out in UK laboratories not including those who have accessed the DorYeshorim service. This averages 820 tests per year and represents 5.8% of the total Jewish population in the target age band 16-44 years. This is a very rough estimate and does not take into account the fact that some individuals may already know their carrier status prior to 1999 (so not take up testing) and those families with known carriers may be more likely to self-organize testing for a number of other family members. Even as a rough estimate the coverage for the target age group is very low. Burton et al (2009) have costed different testing protocols using information from the laboratories. The cheapest test (4 mutation test for all samples) would be £84,000 per 1000 samples and the most expensive was £193,000 for per 1000 samples (gene sequencing for all samples). This then would be the cost of testing per year if the number of tests was increased from 820 to 1000 per year. However, clinical costs of diagnosis, administration, training and quality assurance have not been estimated in the UK.

91. Burton et al (2009) estimated that one child per year is likely to be born with Tay Sachs disease out of the estimated 2772 babies born of Ashkenazi Jewish origin. Children with classical TSD live for around 4 years so in the UK you would expect there to be 4-5 children with TSD, in the Jewish population, at any one time requiring management for the condition. Currently there are no detailed costs of the medical management of the condition in the UK.

Pre-conception.

92. Kinzler et al (2002) outlines the variables that underlie cost efficacy for TSD preconception screening for carrier status in Jewish populations stating that there is an assumption that the program may have value without defining monetary worth of benefits. Screening for TSD carrier status allows for informed reproductive choice and a net increase in the health of carrier couples by preventing an affected infant and knock on clinical and psychological costs. Estimates in early literature about TSD screening of a small Ashkenazi Jewish population (24,000 population of which 1900 were screened) in the US suggest that the benefits for carrier screening for each $1.00 spent was between $3.20-$6.40 (Nelson et al 1978). Burton et al (2009) note that in 1998 when Tay Sachs was proposed as a screening programme in the UK Jewish population the cost was estimated to be £25,000 per year to care for an affected child with an average lifespan of 4 years. However, when modelling the costs, carrier frequency, test sensitivity, laboratory costs, coverage and termination acceptance rates all need to be taken into account and changes in any of the variables will change the costs/savings balance.

Antenatal

93. Caughey (2005) outlined the methodological issues around determining cost effectiveness for antenatal screening and concluded that screening for severe conditions where a diagnosed

foetus was terminated had greater economic gains than screening for less severe conditions where children were born with chronic conditions that required significant ongoing interventions to support physical and mental disabilities.

Neonatal

94. There is no evidence for the costs effectiveness of a neonatal TSD screening programme.

95. Overall there is no evidence that a screening programme in any setting for TSD would be cost effective so this criterion is not met.

96. **Criterion: 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.**

97. Burton et al 2009 has shown that the current system of testing through referral to regional genetics services either pre-conception or during antenatal care is not optimal. It may be cost effective to optimize the current referral process and access to genetic counselling compared to implementing a screening programme. The cost effectiveness of an antenatal, pre-conception or neonatal screening programme is unknown in comparison to optimizing the current referral pathway.

98. Other options for managing people at risk of being a carrier of a TSD mutation or having the disease have not been considered so this criterion is not met.

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

99. There are recommendations about how the programme should be consolidated, developed and monitored set out by Burton et al (2009). The criterion is partially met as monitoring and managing the programme has been considered but not agreed.

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

100. TSD testing exists in the UK although it is not a formalized screening programme. Burton et al (2009) suggest that a formal screening programme would build from the facilities and workforce already available. A formal programme board would plan how the new service was developed and quality assured.

101. This criterion is not met as it is currently not clear what staff and facilities would be required for all three screening settings.

Criterion: 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

102. This would be developed by the screening programme and is not yet available so this criterion not met for all three screening settings.

Criterion: 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.

103. The screening programme would agree the eligibility criteria for screening. Burton et al (2009) recommended that pre-conception screening should be offered in Jewish schools and antenatal screening should be offered to those women who had at least one grandparent of Ashkenazi Jewish origin (which equates to a 1in 80 chance of having the TSD mutation).

104. Once an individual has been tested and their carrier status is known they will not need to have the test repeated as their status will not change. Therefore there are no intervals between tests as there are for cancer screening programmes for example.

105. The screening programme would agree which tests to use in which circumstances. Burton et al (2009) have made recommendations about which tests to use for particular groups within the population.

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

Pre-conception and antenatal

106. Pre-conception and antenatal screening programmes in Israel, Canada, the US and Australia have had a high participation rate. These programmes have shown a drop in the incidence of TSD over a period of years (Kaback 2000b). This indicates that participation in the programme is acceptable and uptake is high enough to ensure the screening programme is effective in its aim to reduce TSD in the Ashkenazi Jewish community. However it is not known whether both pre-conception and antenatal screening are equally effective or if one form of screening is more effective than the other.

107. Testing for TSD during the preconception or antenatal periods is already offered on request by charities and private organisations to the UK Jewish community and is considered acceptable. This criterion is met for these two settings.

Conclusion

108. There is evidence worldwide that if the Ashkenazi Jewish population is targeted effectively with a screening programme couples can make informed reproductive choices and there is a reduction in the number of TSD affected children born (Kaback 2000a).It is not clear from the evidence whether the most effective strategy is pre-conceptual or antenatal screening.

No neonatal screening programmes have been identified. In order to assess the potential for TSD screening in the UK this review has appraised the evidence against the UK NSC criteria.

109. The evidence base informing discussion of Tay Sachs screening is limited with only 152 references identified from the literature for the period covering 2000 to October 2010. This covered three potential settings for screening, the pre-conception, antenatal and neonatal periods. This has significantly limited the assessment of key issues in this review.

110. Testing for Tay Sachs disease carrier status both prior to conception and for pregnant women has been available in areas with a high Jewish population in the UK since 1999 (Levene et al 2005).This is organised as a self selecting NHS service (eg: walk in clinics) and as a more proactive community based service within the Ashkenazi Jewish population (eg: Dor Yeshorim). The review by Burton et al (2009) outlined how testing access to, and uptake of services and data about outcomes was variable across the country.

111. Protecting the continuity of these services was a factor in the Burton et al (2009) review which recommended that they should be formalized and funded centrally by the UK National Screening Committee. The proposed NHS service would include pre-conception screening in Jewish high schools and walk in clinics and antenatal screening using an ethnic origin questionnaire to identify women with Jewish ancestry who are therefore at highest risk of being a carrier of a TSD mutation. It is suggested that an advantage of this approach would be the promotion of choice about testing and autonomy in subsequent decisions about marital partner and reproductive decision making. This would be in contrast to the purpose of testing in some communities (eg :Strictly orthodox). As such there is a social or cultural outcome to the proposal for pre-conception screening for Tay Sachs carrier status.

112. Despite the severity of Tay Sachs disease in affected babies the first UK NSC criterion that the condition should be an important health problem is difficult to maintain from a public health perspective. Indeed Burton et al (2009) suggest that a screening programme will not solve a major public health problem and they do not consider this to be the basis for putting a programme in place. Burton et al (2009) state:

'The rarity of the condition and the relatively small size of the Ashkenazi Jewish population in the UK mean that a 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.'Burton et al (2009:8)

113. A programme, targeted at the Ashkenazi Jewish population would only have the potential of reducing the number of babies born with TSD by at most one a year as only one baby born per year is expected to have TSD in the UK Ashkenazi Jewish population.

114. The UK Jewish population is relatively small compared to the total UK population. This means that although the carrier rate in this group is 10 times that of the non-Jewish population there will still always be more non-Jewish children than Jewish children identified with TSD annually in the UK. 2-3 babies are expected to be born each year from the non-Jewish population who would not have access to screening.

115. There have been no randomized controlled trials that show that putting in place a pre-conception, antenatal or neonatal TSD screening programme either for the whole population or within the Ashkenazi Jewish population in the UK will significantly reduce morbidity and mortality. As such the benefits of screening over the current service are uncertain.

116. Detailed evidence of the cost effectiveness of a potential pre-conception, antenatal or neonatal screening programme has not been carried out. Some information about costs is available but not in the detail required by the UK NSC.

117. In relation to antenatal carrier testing there were no studies that reported on the effectiveness of a family origin questionnaire in identifying women with a 1/80 risk of having a TSD mutation and who would be eligible for testing. Termination as the outcome of antenatal testing would be unacceptable to a significant proportion of couples at highest risk eg: 22% of the Ashkenazi Jewish marriages which are strictly orthodox. It is highly likely that this group will continue to use a service such as Dor Yeshorim prior to an arranged marriage in order to establish genetic compatibility. Mixed marriages with one Jewish and one non Jewish partner will tend to be extremely low risk. Burton et al (2009) reported that of all marriages where there was at least one Jewish partner, 62% reported that the second partner was also Jewish and 38% didn't report that the second partner was Jewish, indicating that the marriage may be mixed. No studies of newborn screening were found and this approach is unlikely to be an effective screening setting. In countries where screening has been implemented the focus has been on preconception and antenatal programmes. As identifying cases in newborns will not change the outcome of the condition the only benefit of screening early will be to alert the parents to the likelihood of having a further affected child and offer genetic counselling.

118. As evidence is lacking for key criteria in appraising a potential UK NSC screening programme; low public health importance, no RCTs showing a reduction in morbidity or mortality and no evidence of cost effectiveness, it is not recommended that a pre-conception, antenatal or neonatal screening programme for TSD targeted at the Ashkenazi Jewish community is implemented at the current time.

119. There is some pre-conception and antenatal testing targeted at the UK Ashkenazi Jewish population across a range of private and NHS organizations, but it is unclear how many tests are taken in total and the impact of a positive test result on subsequent reproductive decisions. More information about people with TSD in the UK (eg: a full picture of current numbers of people with the disease, ethnic origin and age), the impact of ad hoc testing currently offered by private and NHS organizations and a detailed cost benefit analysis needs to be understood. This will inform how testing can be optimised by specialised services; the part of the NHS where the funding for rare genetic diseases is held. More generally, the UK NSC is currently reviewing the case for pre-conception screening for Sickle Cell and Thalassaemia and this may identify issues of relevance to TSD.

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Appendix 1

Knowledge update on screening for Tay Sachs disease

Paula Coles, Information Scientist

October 2010

BACKGROUND: A literature search was performed to find citations on screening for Tay Sachs diseasefrom January 2000 to October 2010.

A review on Tay Sachs disease carrier screening was published by the PHG Foundation in 2009.

Full reference for the report: Burton H, Levene S, Alberg C *et al*. (2009) Tay Sachs disease carrierscreening in the Ashkenazi Jewish population. A needs assessment and review of current services.
http://www.phgfoundation.org/reports/4987/ [accessed 22 October 2010]

SOURCES SEARCHED: Medline (OvidSP), Embase, PsycINFO, Cinahl, Web of Science and theCochrane Library.

DATES OF SEARCH: January 2000 – October 2010

SEARCH STRATEGY:
Tay-Sachs Disease/ (992)
2. tay sachs.tw (1275)
3. 1 OR 2 (1661)
4. Limited to January 2000 – October 2010 (288)
All searches carried out on 8 October 2010
Results
Medline 288
Embase 496
PsycINFO 23
Cinahl 32
Web of Science 492
Cochrane Library 2
Total 1333

The above search strategies retrieved 1333 references in total. After duplicate references were removed a total of 771 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for Tay Sachs disease, focussing on all the NSC criteria:

a)The condition

b)The test

c)The treatment

d)The screening programme

152 references were deemed to be relevant and are classified in to the categories below according to the NSC criteria. There will inevitably be some overlap between categories.

Systematic reviews and meta-analyses 1

Guidelines/Recommendations 4

Non-systematic reviews 5

The condition 33

a)Prevalence (5)

b)Natural history (6)

c)Mutations (22)

The test 33

a)Enzyme analysis (4)

b)DNA analysis (18)

c)Comparison of enzyme and DNA analysis (3)

d)Misdiagnosis (6)

e)Patents (2)

The treatment 2

The screening programme 74

a)Carrier screening (42)

b)Preimplantation screening (5)

c)Antenatal screening (10)

d)Newborn (2)

e)Attitudes to and knowledge of screening (10)

f)Genetic counselling (5)

Total number of relevant references = 152