Appraisal of screening the UK Ashkenazi Jewish population for risk of Canavan disease

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Introduction

1. This paper reviews screening for Canavan disease (CD) 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, including Canavan disease, 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 with 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 2005 a report for the National Screening Committee of a meeting held to discuss genetic testing for Tay Sachs disease in the UK Ashkenazi Jewish population raised the question of whether a screening programme for other genetic conditions, primarily Canavan disease and Familial Dysautonomia (Levene 2005) should be considered. The meeting concluded that there may be case for screening for Canavan disease and that an appraisal of the disease against the NSC criteria should be undertaken.

4. 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 54 references were relevant to screening for Canavan disease (Appendix 1).

5. This review considers evidence for pre-conception, antenatal and neonatal screening for Canavan disease 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.

6. Canavan disease (CD) is an untreatable degenerative neurological disorder. People with CD have a deficit of the enzyme aspartoacyclase which breaks down N-acetylaspartic acid (NAA). The accumulated NAA causes the destruction of myelin necessary for normal brain function (Maria et al 2003). Symptoms usually occur in the first few months of life and include generalized weakness, macrocephaly, severe mental retardation, sleep disturbance and blindness. As the condition develops the child may have seizures, feeding difficulties and either stiffness/or weakness of muscles alongside developmental delays. The course of the disease is variable (even comparing those with the same genotype) and those affected may die in infancy or survive until their teens (Monaghan et al 2008). There is no treatment for the disease and symptom management is the only option for affected children.

7. Canavan disease is 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.

8. Many of the autosomal recessive disorders (including CD) 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 Canavan disease 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).

9. The 2001 census is the only systematic information available 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 96.7% of British Jews live in England, clustered in a small number of mainly urban areas with 36% living in 5 London Boroughs (Burton et al 2009). Other areas where populations are concentrated are Hertfordshire (5.5%), Greater Manchester (8%) and Leeds (3%).

10. 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.

11. 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). In the 2001 census 44,146 couples indicated that both partners were Jewish and 34,590 of couples had one confirmed Jewish partner but the other partner was of a different religion, 'no religion' or none was specified (Burton et al 2009. The Institute for Jewish Policy Research (2011) reported that although around a quarter of marriages where strictly Orthodox this resulted in 40% UK Jewish babies also being strictly Orthodox. The number of children born to the rest of the UK Jewish community is decreasing overall in comparison to the strictly Orthodox group.

12. Canavan disease is not exclusive to the Ashkenazi Jewish population although it does occur at a higher incidence than in other ethnic groups. More than 50 different mutations

associated with CD have been reported, most are rare and linked to individual families (Monaghan et al 2008). Three mutations account for over 98% of Ashkenazi Jewish CD alleles, but account for only 3% of non-Jewish mutations (Monaghan et al 2008).

13. In order to be passed on, the Canavan disease mutation must be carried by both parents – each child will have a 25% chance of having CD, a 25% of not carrying the mutation and a 50% chance of carrying the mutation, but not having the disease (Weinstein 2007). Results of studies to determine the carrier frequency of CD vary from 1:38 to 1:59 in the Ashkenazi Jewish population (Feigenbaum et al 2004). These carrier frequencies lead to an incidence of 1:5776-1:13,924 if both parents are of Ashkenazi Jewish origin. Strom et al (2004) looked at 19,790 assays from across the US from people reporting to be of Ashkenazi Jewish origin and reported a carrier frequency of 1 in 65 (incidence =1:16,900). In comparison there is very little information about the carrier frequency in the non-Jewish population although this has been estimated at approximately 1 in 500 (leading to an incidence of 1 in a million) and is usually just described as 'very rare' in publications (Gross et al 2008, Zhang et al 2004).

14. There is no specific information about the carrier rate of CD in the UK Ashkenazi Jewish population so it is difficult to predict how many affected children will be born. Between 1993 and 2002 there were an estimated 2,772 total births per year within the UK Jewish population (Burton et al 2009). Using the range of carrier frequencies between 1 in 38 and 1 in 65 from studies of populations outside the UK we would expect 1 affected child to be born once every 2 to 6 years within the Ashkenazi Jewish community in the UK.

15. For comparison, in the UK non-Jewish population using a carrier rate of 1:500 (Gross et al 2008) we might expect one baby to be born with Canavan disease every two years (based on the 723,165 births in England and Wales in 2010 reported by the Office of National Statistics, 2011).

16. This criterion is partially met as the nature of the disease is understood but there is very limited knowledge about the number of cases in either the general population or UK Jewish populations. 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

17. Funding of testing for Canavan disease 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 CD. 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 should include people who request a test for carrier status of CD on the basis of familial disease or ethnicity. Whether any carrier testing is actually carried out via this route is unlikely as clinicians may not be aware of the services that should be offered to people and couples may not be aware of their risk and so don't request them.

18. 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 accessed a Tay Sachs disease testing service (a different autosomal recessive mutation also commonly occurring in the Jewish community) one third reported that GPs gave either no information or incorrect information. This suggests that GP awareness and subsequent referral practice of people who are possible carriers is not optimal for Tay Sachs disease and is likely to be largely non-existent for Canavan disease which is a rarer and less well known condition. 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).

19. People who are concerned that they may be at high risk of being a carrier can access a testing service being piloted at Guys and St Thomas' Hospital. This service runs alongside the Tay Sachs drop in clinic and people can be tested for carrier status for 9 genetic conditions more commonly found in people of Ashkenazi Jewish origin. The cost of this service is currently £212 (http://www.guysandstthomas.nhs.uk/our-services/genetics/clinics/tay-sachs/patients.aspx#na) .

20. The Dor Yeshorim organization offers anonymised carrier testing for Canavan disease 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).

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

22. It is not known how many people have been tested for CD mutations privately within the Jewish community or if anyone has been referred by a GP to regional genetics services in the NHS. If a quarter of marriages are strictly Orthodox then couples may well use either the 'Association for the Prevention of Genetic Diseases' or Dor Yeshorim prior to an arranged marriage. It is also possible that cascade testing of relatives of an affected child may have been requested.

Antenatal

23. It is debatable whether antenatal testing for CD 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.

24. 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. As with pre-conception testing it unlikely that any testing for CD occurs through this route due to lack of awareness by clinicians that the service should be offered and couples not knowing they are at risk of carrying an affected baby.

25. A survey by Burton et al (2009) showed that out of the 155 trusts that were asked if they carried out testing for Tay Sachs disease 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. Canavan disease is similar to Tay Sachs disease in that it is an autosomal recessive condition that has a higher incidence in the Ashkenazi Jewish population than the non-Jewish population. There is less awareness of CD than TSD and so it is highly unlikely (although unknown) that any testing has been accessed through normal antenatal services.

Neonatal

26. If a child is born with Canavan 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).

27. Primary prevention to reduce the number of children born with Canavan disease is not optimised and this criterion is not met.

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.

28. People identified as carriers of Canavan disease mutation will not go on to develop the disease. Canavan disease can only be passed on to the next generation if both partners of a couple carry the mutation and then there is a 1 in 4 risk of an affected child (Weinstein 2007).

Pre-conception

29. Gason et al (2003) evaluated the predicted feelings and attitudes towards testing for another autosomal recessive disease common in the Ashkenazi Jewish community. The study looked at Tay Sachs Disease testing in Jewish high school students (15-18yr olds) and 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 (including CD) 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.

30. Dor Yeshorim receives 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

31. 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 possible longer term anxiety as a result of carrier testing (Green et al 2004).

Neonatal

32. Green et al (2004) carried out a systematic review of the impact of newborn screening of a range of different genetic conditions (not CD) 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.

33. The natural history and psychological implications for people who are either Canavan disease carriers or cases is understood and this criterion is met for all three settings.

The Test

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

34. The test to detect a Canavan disease mutation is the same regardless of whether it is carried out before conception during the antenatal period or after birth.

35. Molecular genetic testing using a blood sample can be used to determine if someone is carrying a CD mutation. If testing is performed for two of the most common mutations then 94.9% (CI 95% 88.4%-98.2%) of individuals in the Ashkenazi Jewish population carrying the CD mutation could be detected (Monaghan et al 2008). There have been no studies detailing the specificity of the test although Monaghan et al (2008) suggest that 'general laboratory experience indicates that occasional false positive results are likely to occur'.

36. There is a suitable test for screening for Canavan disease 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.

37. Molecular genetic testing determines the presence or absence of the mutation and therefore cut off points are not applied. There is a suitable methodology for determining carriers and non-carriers therefore this criterion is met for all three screening settings.

Criterion: The test should be acceptable to the population.

38. Targeted screening programs have typically used blood samples to test a range of autonomic recessive disorders such as CD and these programs have been implemented successfully in Ashkenazi Jewish communities in the US, Australia, Israel and Canada (Burton et al 2009).

Pre-conception

39. There is no direct evidence that a blood test taken to determine carrier status pre-conception for CD would be acceptable to the Ashkenazi Jewish population in the UK. Due to the success and uptake of CD screening programs in other countries and the use of Dor Yeshorim and the Association for the Prevention of Jewish Genetic Diseases, in this country, the assumption has been made that the test is acceptable to the UK Ashkenazi Jewish population.

40. 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%) for TSD screening. There was higher significantly higher anxiety reported about the test when a blood sample was taken than when a cheek brush swab was used ($p<.001$).

41. 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

42. In reviewing TSD testing in the UK and their consideration of CD screening, Burton et al (2009) concluded that blood tests will be acceptable to the UK Ashkenazi Jewish population as similar tests are acceptable to these communities in a number of other countries.

Neonatal

43. There is no evidence to indicate that neonatal screening for CD would be acceptable as no neonatal programmes could be identified. Other newborn screening programmes in the UK routinely use a blood spot test (sickle cell disease) and have met the NSC criterion for acceptability.

44. A blood test has been used for screening for a range of genetic autosomal recessive conditions to determine carrier status and to identify cases in the UK (eg: sickle cell and thalassaemia diseases and cystic fibrosis). This type of test has been found to be acceptable therefore 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-conception

45. A confirmed positive test result prior to conception would not require any further intervention but genetic counselling should be made available (Henneman 2004, Department of Health 2003).

Antenatal

46. A positive result for a woman who is pregnant will lead to the partner being tested (if they are available) and then amniocentesis or chorionovillus (CVS) sampling to test whether the foetus has CD (Royal College of Obstetricians and Gynaecologists 2010).

Neonatal

47. 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 CD however the National Specialised Commissioning Group has a set of standards about care for people with lysosomal disorders which includes CD (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).

48. 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

49. 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. Burton et al (2009) recommends that three mutations (E285A, Y231X and A305E) would account for over 98% of all affected babies in the UK Ashkenazi Jewish population. This criterion is met for all three screening settings.

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-conception

50. The current intervention available for people who are identified as positive carriers of CD 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

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

Neonatal

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

53. 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 30). A further two studies asked parents of children with cystic fibrosis (CF) some who 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 only17% of 40 parents said they would terminate a future affected pregnancy whilst 61% would not and 22% were unsure (Green et al, 2004).

54. 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 (which may not be the case for strictly Orthodox couples). This criterion is mostly met for these settings. For neonatal screening there is little evidence that the outcome of early management of people with CD 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-conception

55. An individual identified as a carrier should be able to access genetic counselling (Henneman 2004, Department of Health 2003, Human Genetics Commission 2011).

Antenatal

56. 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

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

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

59. There are agreed approaches for people identified as carriers of a genetic mutation for Canavan disease and standards for those children identified as a case therefore this criterion is met.

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

60. It is unknown whether the people who carry a mutation for Canavan disease identified either prior to conception or during the antenatal period are offered genetic counselling. It is also unknown if the clinical management of people born with the condition receive optimal clinical management by all healthcare providers. Therefore this criterion is not met in all three screening settings.

The Screening Programme

Criterion: There should be evidence from high quality Randomized 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.

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

62. There is significant evidence already outlined that a combination of tests will accurately measure risk (Burton et al 2009). Information given in high school programmes prior to offering screening has been evaluated (Gason et al 2003, Ioannou et al 2010) and shows that increased understanding of the programme reduces anxiety about the test and the outcome. The information can be conveyed in a way that can be readily understood by the individual being screened.

63. There is no evidence that a screening programme in any of the three settings in the UK would significantly reduce morbidity or mortality or evidence from high quality trials which would help to inform people about the test. This criterion is not met for all three settings.

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

64. 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.

Antenatal

65. Antenatal screening for carrier status followed by amniocentesis or CVS if the test is positive is the model used for CD screening in a number of countries. This model has been used for other genetic diseases such as sickle cell and thalassemia in the UK (Davies et al 2000). However this form of testing is generally not acceptable to the one quarter of Jewish couples who are strictly Orthodox and are opposed to the termination of pregnancy. The Jewish Genetic Disorders UK, highlights that termination of pregnancy isn't always unacceptable and that rabbinical advice could be sought on a case by case basis (JGD UK Pers comm.).

Neonatal

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

67. This criterion is partially met for all three screening settings as there is evidence that the full screening programme in preconception settings may be acceptable, whereas in antenatal settings acceptability may depend on Jewish orthodoxy of the individual. There is no direct evidence for acceptability of newborn screening, although genetic screening for other autosomal recessive conditions in the UK is acceptable.

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

Pre-conception

68. A carrier testing screening programme prior to conception 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

69. Testing for carrier status during pregnancy then testing the foetus for CD with a view to terminating the pregnancy will cause psychological and physical distress and antenatal diagnosis carries a small risk of miscarriage to the 75% of foetuses that are not affected by CD. 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

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

71. This criterion is partially met for preconception and antenatal screening settings but not for neonatal programmes where there is no evidence about the benefits or harms.

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 criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

72. There has been no detailed cost benefit or cost effectiveness analyses carried out for antenatal, pre-conception or neonatal screening programmes for CD in the UK Jewish population.

73. Using carrier frequencies in populations outside the UK, and taking the estimate of 2772 babies born of Ashkenazi Jewish origin each year, it is anticipated that one child is likely to be born with CD in the UK every 2-6 years. Children with CD have often died by their fourth birthday although some live into their teens. At a rough estimate we would expect at most 2 children in the Jewish population to have CD at any one time if there was no testing in the community. There is some ad hoc pre-conception and antenatal testing in the UK Ashkenazi Jewish population and it is possible that cascade testing has occurred in families with children who have been affected. It is unknown what impact this has had on the number of children born with the disorder. Currently there are no detailed annual costs of the medical management of the condition or the cost of a potential screening programme in the UK.

74. As this condition is rare, in order to identify couples at risk before conception or pick up affected fetuses during the antenatal period, there would need to be a very high uptake of the invitation for screening and a similarly high level of action taken if a positive test result was confirmed in order for the programme to maximize cost effectiveness. If a quarter of marriages are strictly Orthodox and those couples have 40% of the UK Jews births then their view and decision making in relation to screening and the options available to them will be key to whether a screening programme would be cost effective.

75. There is a lack of evidence about whether a screening programme in any setting would be cost effective so this criterion is not met.

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

76. 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 for Tay Sachs disease and is likely to be largely non-existent for Canavan disease. It may be cost effective to optimize the current referral route as outlined by the NSF for Children, Young People and Maternity Services (Department of Health, 2004) and access to genetic counseling 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 and cascade testing families where a family member has the condition.

77. 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.

78. Other options for managing people at risk of being a carrier of a Canavan disease mutation or having the disease have not been considered so this criterion is not met for all three screening settings.

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

79. There is no plan for managing and monitoring the screening programme and no agreed set of quality assurance standards have been developed. This criterion is not met for all three settings.

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

80. The workforce and laboratory facilities required for a potential programme has not been assessed so this criterion is not met.

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.

81. This would be developed by the screening programme.

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.

82. The screening programme would agree the eligibility criteria for screening. Burton et al (2009) recommend that preconception 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.

83. 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.

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

Preconception and antenatal screening

84. Pre-conception and antenatal screening programmes in Israel, Canada, the US and Australia have been successfully implemented indicating that a CD screening programme is acceptable to a number of different populations (Burton et al 2009).

85. Ad hoc testing of a range of genetic conditions with a higher incidence in the UK Ashkenazi Jewish population has been available in some UK communities. Tests are carried out by request by an individual so clearly in these cases the test is acceptable although whether that can be generalized to the whole UK Ashkenazi population is unknown given the significant proportion of strictly Orthodox couples who may not want to be tested.

86. It is not clear whether an antenatal or preconception screening programme would be acceptable to a quarter of UK Ashkenazi Jewish couples and so this criterion is not met.

Conclusion

87. Canavan disease is an extremely rare disease in the UK. It is devastating for the very small number of people who have a child born with the condition and worrying for potential parents concerned that they are at high risk of carrying the disorder. Children born with the disease usually die within the first few years of life. There is no treatment, although symptoms can be managed.

88. The evidence base informing discussion of Canavan disease screening is limited with only 54 relevant 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.

89. It is not possible to determine the number of people with Canavan disease in the UK although an understanding of the carrier rates mean that the number of babies likely to be born with the disease can be estimated. The carriage rate in the UK Ashkenazi Jewish population is unknown however studies in other countries have indicated rates ranging from 1:38 to 1:65 in Ashkenazi Jewish populations. This is in comparison to rates of around 1:500 in the non-Jewish population. Using these rates 1 child every 2 to 6 years would expect to be diagnosed with CD from the UK Jewish population without screening in place. It is possible that a further 1 child every 2 years would expect to be diagnosed from the non-Jewish population.

90. Despite the severity of Canavan 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. A programme targeted at the UK Ashkenazi Jewish population would therefore have a maximum potential of reducing the number of babies born with CD by at most one child every 2-6 years. This would only be achieved if a very high proportion of Ashkenazi Jewish couples took up the offer of testing (preconception or antenatal) and then acted on the results of a positive test. With a quarter of couples being strictly Orthodox who may not take up the offer of antenatal testing and may prefer testing prior to marriage via and anonymous route this is unlikely to be achieved
.

91. 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.

92. There has been no detailed analysis of the cost effectiveness of a potential pre-conception, antenatal or neonatal screening programme and given the rarity of the condition and the lack of knowledge about how many children have the disorder in the UK, this may be difficult to achieve.

93. There is very little evidence that in the UK where the condition is very rare that a formal UK NSC screening programme would be effective in reducing the number of cases further. Evidence is lacking for key criteria including; low public health importance, an RCT or similar that given the rarity of the condition a screening programme would reduce morbidity or mortality and a formal evaluation of cost effectiveness. At the current time therefore it is not recommended that a formal UK NSC screening programme in the preconception, antenatal and neonatal settings is implemented for Canavan disease.

94. There is limited pre-conception testing targeted at the UK Ashkenazi Jewish population and this is pre-dominantly private with very limited access to testing in the NHS (eg: possible cascade testing of families with an affected relative). The number of tests carried out privately and the impact of a positive test result on subsequent reproductive decisions has not been studied. More information about people with CD 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 organisations needs to be understood. This may inform how testing could be optimised by specialised services; the part of the NHS where the funding for rare genetic diseases is held. It is clear that the National Service Framework for Children, Young People and Maternity Services published by the Department of Health, (2004) is not implemented equitably (probably not at all in the case of CD) and this may be a route where testing for rare genetic diseases such as CD can be developed in the preconception and antenatal settings for the UK Ashkenazi Jewish community. For example in geographical areas where there are significant Jewish populations local NHS services should have an enhanced awareness of the consequences of the higher risk of CD in the community and be clear and informed about how individuals can access testing. Information for individuals should be readily available from primary care and health promotion strategies should include awareness raising in the community.

95. 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 CD.

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Appendix 1

Knowledge update on screening for Canavan disease
Paula Coles, Information Scientist

May 2010, Updated October 2010

BACKGROUND: A literature search was performed to find citations on screening for Canavan disease from January 2000 to 6 May 2010.
A review on Tay Sachs disease carrier screening was published by the PHG Foundation in 2009.
Appendix 8 of this report included an evaluation of Ashkenazi Jewish population carrier screening for Canavan disease.
Full reference for the report: Burton H, Levene S, Alberg C *et al.* (2009) Tay Sachs disease carrier screening in the Ashkenazi Jewish population. A needs assessment and review of current services.
http://www.phgfoundation.org/reports/4987/ [accessed 20 May 2010].

SOURCES SEARCHED: Medline, Embase, the Cochrane Library, PsycINFO, Cinahl, Web of Science and Centre for Reviews and Dissemination (CRD) databases. A simple search of the HTA database for work that is currently going on but not yet published was also performed.

DATES OF SEARCH: January 2000 to May 2010

SEARCH STRATEGY: Medline Ovid
The strategy was designed to be as broad as possible to ensure nothing related to screening for Canavan disease was missed. As a result many hits that were not relevant were also retrieved.
1. canavan disease/ (203)
2. canavan$.tw. (929)
3. Hereditary Central Nervous System Demyelinating Diseases/ (146)
4. 1 or 2 or 3 (1118)
This was then limited by year (2000 to May 2010).
The strategy was kept fairly simple due to the wide-ranging scope of the review which would focus on
assessment against the UK NSC criteria, and in particular:
• natural history
• penetrance
• incidence and prevalence (in Ashkenazi Jews and the general population)
• whether screening is acceptable
• the test
• the treatment
• services for those affected

RESULTS: The above strategy retrieved 469 citations from Medline. A similar search was conducted in Embase, the Cochrane Library, CRD databases, PsychINFO, Cinahl and Web of ScienceDatabase Number of references
Medline 469
Embase 359
Cochrane 1
CRD databases 0
PsycINFO 13
Cinahl 18
Web of Science 457

Total 1317
After duplicate references were removed a total of 741 potentially relevant references were left. The titles and abstracts of these citations were scanned for relevance to screening for Canavan disease, and **51** citations were deemed to be relevant.
October 2010 Update
The search was repeated on 8 October 2010 and 76 results were retrieved.
Results (May 2010 – October 2010)
Medline 13
Embase 9
Cinahl 0
PsycINFO 2
Cochrane Library 0
Web of Science 12
Total 36
After duplicate references were removed a total of 24 potentially relevant references were left. The titles and abstracts of these citations were scanned for relevance to screening for Canavan disease, and **3** citations were deemed to be relevant. These additional 3 references are identified by **