Appraisal of screening the UK Ashkenazi Jewish population for Risk of Familial Dysautonmia

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Introduction

1. This paper reviews screening for Familial Dysautonomia (FD) 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 Familial Dysautonomia, 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 (TSD) 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 Familial Dysautonomia 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 85 references were relevant to screening for Familial Dysautonomia (Appendix 1).

5. This review considers evidence for pre-conception, antenatal and neonatal screening for Familial Dysautonomia in 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. Familial Dysautonomia (FD) is a genetic disease which leads to the absence of a protein crucial to the development of sensory and autonomic systems resulting in episodes of vomiting, lung disease, decreased pain and temperature perception, absence of tears, cardiovascular instability, severe spinal curvature and ataxic gait (Lerner 2009). During infancy there may be onset of autonomic crises, sometimes leading to sudden death. Progressive neuronal degeneration continues throughout life and Axelrod (2006) reported that of all cases known between 1969 and 2001 19% of individuals surviving to age 25 required renal dialysis due to deterioration of kidney function. Improved management of the condition has led to people surviving longer. Axelrod et al (2002) predicted that 50% of people with FD born after 1981 should reach the age of 40 and latest figures show that 59% of current patients are over 18 with the oldest being 67 (Axelrod 2012).

7. FD is an important health problem for those people 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 FD) 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 FD 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) summarized 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. Two mutations in the gene encoding IKBKAP causes 99.5% of all cases of FD. One other mutation has been described which contribute to the remaining 0.5% of cases (Gold-von Simson & Axelrod 2006). Only one non-Jewish individual has been found with a mutation of the IKBKAP gene (Leyene et al 2003). Dong et al (2002) reports that in the Ashkenazi Jewish population just one mutation is responsible for over 99.5% of FD cases and the remaining less that 0.5% are caused by a second mutation

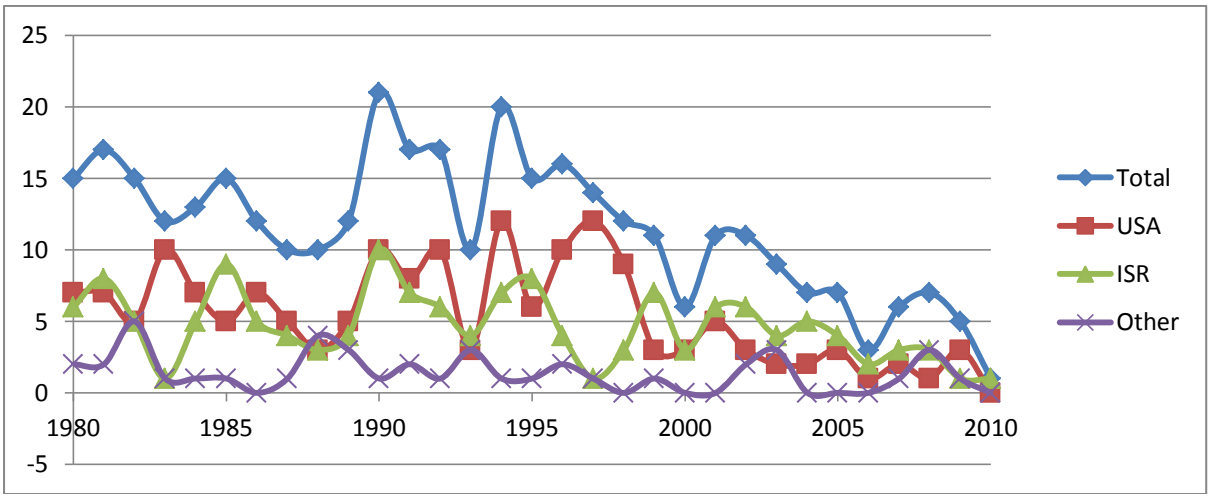
13. In order to be passed on, the FD mutation must be carried by both parents – each child will have a 25% chance of having FD, a 25% of not carrying the mutation and a 50% chance of carrying the mutation but not having the disease. Between 1 in 17, to 1 in 32 Ashkenazi Jews carry the mutation for FD which leads to disease incidence of one in 3703 if both parents are of Ashkenazi Jewish descent (Maayan et al 2010). Between 1993 and 2002 there were an estimated 2,772 total births per year in the Jewish population (Burton *et al* 2009). Given the carrier rate it would be expected that less than one child per year would be born with FD (3 within a four year period) within the Ashkenazi Jewish community in the UK.

14. Maayan et al (2010) report that between 1970 and 2010 17 patients were reported to Great Ormond Street Hospital and to the international FD NYU database. Four cases were reported between 2002 and 2009 (Axelrod pers. comm. 2011). Of the four most recent cases two were not diagnosed until aged 6 years. If the number of births per year in the UK Ashkenazi Jewish population was consistent at 2772 we would have expected approximately 30 children to be diagnosed with the condition in that 40 year period (using a disease incidence of 1:3703). It is unclear whether the reason for fewer than expected cases is because some babies were mis-diagnosed or died before a correct diagnosis was made or that pre-conception testing prior to an arranged marriage has had an impact on the incidence. It is also possible that the proportion of mixed marriages between Jews and non-Jews where the incidence will be negligible has had an impact on the number of cases in the UK (only one individual world-wide of non-Jewish descent has been diagnosed with FD). Currently FD-UK (pers comm. 2012) reported that there are 14 people in the UK known to have FD.

15. World- wide the number of cases of FD reported has reduced significantly since 2001 when screening programmes were introduced in the US and Israel (Lerner 2009). Almost 90% of the 657 cases that have been reported worldwide have been from these two countries (Axelrod 2012). Figure 1 (Axelrod, pers comm. 2011) shows the total number of cases reported by year for Israel, the USA and all other countries to the International FD NYU Database. The total number of cases per year world-wide varied between 10 to 20 prior to pre-conceptual and antenatal screening programmes implemented in Israel and the USA. Once screening was in place in the USA and Israel, a downward trend of fewer cases per year was seen. There is no downward trend for the rest of the world however the numbers are very small – less than 5 cases per year in total from all ‘other countries’ apart from US and Israel. Axelrod (2012) reported that in 2011 the number of worldwide FD births was zero.

16. This criterion is met in that there is an adequate understanding about the epidemiology of the condition. The rarity of the disease means that although the condition is significant for individual families it is not important from a public health perspective.

Figure 1: Number of cases of Familial Dysautonomia reported to the International FD NYU database per year. Source: Axelrod (2011)



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

17. Funding of testing for FD 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 counseling for people who are carriers of rare genetic diseases such as FD. 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. The organization Jewish Genetic Disorders UK (pers comm.) indicated that this isn't a route for testing that people at risk of being carriers for FD are able to access. It may be that clinicians are 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 counseling 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 TSD 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 TSD and awareness is likely to be similarly limited for FD. 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 for FD 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 FD 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 Tay Sachs Disease but on request will direct people for testing of other Jewish genetic disorders including FD. The results are disclosed to the person tested.

22. It is not known how many people have been tested for FD mutations within the Jewish community either privately or via GP referral to regional genetics services. If a quarter of marriages are strictly Orthodox then couples may well have used 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 FD 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 counseling 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. This policy should include women who request a test for carrier status of FD on the basis of familial disease or ethnicity. As with pre-conception testing it unlikely that any testing for FD 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 TSD 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. FD is similar to TSD 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 FD 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 FD 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 FD is not optimized 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 the FD mutation will not go on to develop the disease. As FD 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-conceptual

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 TSD 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 FD) 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 to reduce 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 FD) 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 behavior change due to previous newborn screening tests. The studies showed varying results with one Australian study showing a 69% uptake in genetic counseling by parents following the diagnosis of Cystic fibrosis in a first affected child to 21% 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 FD 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 an FD mutation is the same regardless of whether it is carried out before conception during the antenatal period or after birth.

35. The two most common mutations account for 99% of cases of FD which can be detected using DNA testing. Data from large scale testing suggest that the analytic sensitivity for these mutations is 98% so for 2% of carriers a false negative result will be reported.The clinical sensitivity has been estimated at 95% (Monaghan et al 2008).

36. There is a suitable test for screening for FD so this criterion is met for all 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. DNA testing determines the presence or absence of the mutation. This criterion is met for all 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 autosomal recessive disorders such as FD and these programs have been implemented successfully in Ashkenazi Jewish communities in the US, Australia, Israel and Canada (Burton et al 2009).

Pre-conceptual

39. There is no direct evidence that the blood test or cheek brush swab taken for a pre-conception screening programme for FD would be acceptable to the Ashkenazi Jewish population in the UK. Due to the success and uptake of FD 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 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%). There was significantly higher anxiety reported about the test when a blood sample was taken than when a cheek brush swab was used ($p<.001$).

41. Ioannou et al (2010) showed that where people were 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 FD 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 FD 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 and thalassemia) and have met the NSC criterion for acceptability.

44. A blood test has been used to determine carrier status in the Jewish population in the UK for other genetic conditions (TSD) and has been accepted. This type of test has been found to be acceptable for screening for other autosomal recessive genetic conditions during the antenatal period (for carrier status) and at birth (to identify affected babies) and so this criterion is met for all 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

45. A confirmed positive test result prior to conception would not require any further diagnostic investigation but genetic counseling 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 fetus has FD (Royal College of Obstetricians and Gynecologists 2010).

Neonatal

47. Babies who have a positive test result will be referred to the appropriate specialty for management of the condition.

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) showed that the two mutations (IKAP and a rarer mutation in exon 19) account for over 99% of all carriers or affected babies in the UK Ashkenazi Jewish population. This criterion is met for all screening settings.

The Treatment

50. **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

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

52. **Antenatal intervention**

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

Neonatal Intervention

54. The organization Familial Dysautonomia - UK can provide support and information to families with a child newly diagnosed with FD. It is recommended that families should be given the opportunity to meet specialist clinicians, to help with decision-making and management of the condition based at Great Ormond Street Hospital (Burton et al 2009). Axelrod et al (2002) suggests that early intervention may improve survival of affected individuals.

55. Parents of affected children should be offered genetic counseling to support them in planning further children (Human Genetics Commission 2011). However, it is not clear what proportion of couples of an affected child would take up genetic counseling. Green et al (2004) found six studies which looked at possible reproductive behavior change due to previous newborn screening tests (which had variable results see para 28).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 only 17%of 40 parents said they would terminate a future affected pregnancy whilst 61% would not and 22% were unsure (Green et al, 2004).

56. 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

evidence that the outcome of early management of people with FD will lead to better outcomes than late treatment so this criterion mostly met.

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

57. An individual identified as a carrier should be able to access genetic counseling (Henneman2004, Department of Health 2003, Human Genetics Commission 2011).

Antenatal management

58. In May 2010 The Royal College of Obstetricians and Gynecologists (RCOG) published evidence based recommendations on the 'Termination of pregnancy for fetal abnormality'. The guidance is intended to assist doctors and other health professionals to support women when a fetal abnormality is diagnosed and help women decide whether or not to have a pregnancy terminated.

Neonatal management

59. The charitable organization Famililial Dysautonomia – UK (pers comm. 2012) reported that all known FD sufferers in the UK are offered annual evaluations and treatment plans by an international FD specialist.

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

61. There are agreed approaches for people identified as carriers of a genetic mutation for FD but national standards and evidence based policies have not been identified for those children identified as a case.

62. This criterion is mostly 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

63. The charitable organization Familial Dysautonomia – UK (pers comm. 2012) reported that all known FD sufferers in the UK are offered annual evaluations and treatment plans by an international FD specialist (organized by the charity).

64. Clinical management of the condition and patient outcomes are likely to be optimized in the small number of healthcare providers that offer specialized care for known FD sufferers.

65. This criterion is met.

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.

66. There have been no high quality randomized controlled trials to show that screening to determine FD 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 FD could be identified.

67. There is 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.

68. There is no evidence that a screening programme in any of the three settings in the UK would significantly reduce morbidity or mortality or that there is 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 carrier testing

69. 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 screening

70. Antenatal screening for carrier status followed by amniocentesis or CVS if the test is positive is the model used for other genetic diseases such as sickle cell and thalassaemia 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 screening

71. 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 FD have been identified. There is no direct evidence that an FD neonatal screening programme targeting the UK Ashkenazi Jewish population would be acceptable.

72. This criterion is mostly met as although there are no direct studies about preconception, antenatal or neonatal screening for FD 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-conception

73. A carrier testing screening programme during the pre-conception period enables couples and individuals to make informed reproductive choices. The primary harm to an individual will be the perceived stigma of carrying the mutation (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

74. Testing for carrier status during pregnancy then testing the fetus for FD 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 fetuses that are not affected by FD. 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 ultra-Orthodox Jews antenatal testing would not be acceptable as termination of pregnancy is not an option (Raz and Vizner 2008).

Neonatal

75. There is no evidence about the benefits or harms specifically for a neonatal screening programme to identify cases of FD. There is some evidence that early diagnosis of FD combined with registration on the international database and access to treatment from an international specialist offered via the charity FD UK is likely to improve patient outcomes (FD-UK pers comm. 2012).

76. There is some evidence that a screening programme in each of the three settings would outweigh the physical and psychological harm so this criterion is mostly met.

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.

77. No detailed cost benefit or cost effectiveness analyses were identified from the literature for a UK NSC antenatal, pre-conception or neonatal screening programme for FD in the UK Jewish population. The charity FD-UK (pers. comm.) have undertaken some brief costings and concluded that a preconception or antenatal screening programme would be cost effective.

78. 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 FD in the UK approximately once every 16 months if no testing at all was in place. Currently some testing is in place in the UK Jewish community via the routes described in sections 19-21 and it isn't clear how that has impacted on the current number of cases in the community. Currently FD-UK (pers.comm.) report that there are 14 cases of FD in the UK.

79. Children born with FD will require significant medical interventions to manage the multi-system conditions that develop throughout their life and Axelrod et al (2002) predict that 50% of children born after 1981 will reach 40 years. Burton et al (2009) noted that in 2006 the Dysautonomia Society of Great Britain estimated that costs per affected person between the ages of 2-18 was £59,787 per year (including benefits). In 2003 DSGB estimated a life time cost of someone with FD at 1.446 million. If this is the case then the cost of the 14 cases in the UK could be approximately £20m over their lifetimes.

80. 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.

81. Overall there are indications that a preconception or antenatal screening programme may be cost effective but this is based on informal personal communications between organizations. In order for this criterion to be fully met a formal cost effectiveness analysis would need to be undertaken.

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.

82. 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 used for TSD testing and it is assumed that this is also the case for FD. 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.

83. Other options for managing people at risk of being a carrier of an FD 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.

84. There are some brief recommendations about how the programme should be consolidated, developed and monitored set out by Burton et al (2009). There is no detail about how this would work for the different screening settings so this criterion is not met however if a screening programme was implemented this would be part of the process of development.

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

85. A full assessment of the workforce and laboratory facilities required for a potential programme has not been assessed in detail so this criterion is not met 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.

86. This would be developed by the screening programme and is not yet available so this criterion is 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.

87. The screening programme would agree the eligibility criteria for carrier screening. Burton et al (2009) recommended that carrier screening should be offered to those people who had at least one grandparent of Ashkenazi Jewish origin.

88. 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

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

90. 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.

91. 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

92. Familial Dysautonomia is a life threatening condition that cannot be cured which in 50% of cases are predicted to die before their 40th birthday. In the UK 17 cases have been reported between 1970 and 2010 when given the number of Jewish births we would expect 30 affected children to be born in that 40 year period. The lower than expected number of affected births may be due to lack of awareness of the condition by clinicians combined with private testing especially in the strictly Orthodox community who use the result to inform potential arranged marriages.Information, education and testing for FD mutations in the UK Ashkenazi Jewish populations may also lead to discussions about other autosomal recessive conditions such as FD leading to requests for testing.

93. Despite the severity of FD 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 program targeted at the UK Ashkenazi Jewish population would have a maximum potential of reducing the number of babies born with FD by at most one child every 16 months. 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.

94. There have been no randomized controlled trials that show that putting in place a pre-conception, antenatal or neonatal FD screening programme within the Ashkenazi Jewish population in the UK will significantly reduce morbidity and mortality. As such the benefits of screening over the current arrangements, such as cascade testing of families with an affected child, are uncertain.

95. Detailed published evidence of the cost effectiveness of a potential pre-conception, antenatal or neonatal screening programme has not been carried out and in order to evaluate the benefits of such a programme a formal analysis would need to be commissioned.

96. 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. Currently there are no policies about the management of this condition although here is currently a service supported by FD-UK to provide annual assessments of people with FD in the UK by an international specialist.

97. There is well organized charitable support for FD sufferers in the UK and the attempts worldwide to reduce the number of cases of this rare condition to zero is impressive. There is however limited published 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 Familial dysaytonomia.

98. It is recommended that a formal evaluation of clinical and cost effectiveness is undertaken which should include a sensitivity analysis for different levels of uptake for the preconception

and antenatal settings. There should also be a view as to the kind of testing that might be acceptable to the strictly Orthodox UK Jewish community.

99. There is limited pre-conception and antenatal testing targeted at the UK Ashkenazi Jewish population and this is pre-dominantly private with access to testing in the NHS very limited (eg: cascade testing of families with an affected relative). It is unclear how many tests are taken in total and the impact of a positive test result on subsequent reproductive decision making. More information about people with FD 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 (eg: cascade testing of affected families) will inform how effective current arrangements are in the UK. This will inform how testing could be optimized by specialized 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 (and probably hardly at all in the case of FD) and this may be a route where testing for rare genetic diseases such as FD 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 FD 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. 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 FD.

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Appendix 1

Knowledge update on screening for Familial dysautonomia
Paula Coles, Information Scientist

May 2010, updated October 2010

BACKGROUND: A literature search was performed to find citations on screening for Familial dysautonomia 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 forfamilial dysautonomia.

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 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 familial
dysautonomia was missed. As a result many hits that were not relevant were also retrieved.
1. Dysautonomia, Familial/ (1053)
2. "Hereditary Sensory and Autonomic Neuropathies"/ (526)
3. familial dysautonomia.tw. (451)
4. riley-day syndrome.tw. (97)
5. 1 or 2 or 3 or 4 (1684)
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 392 citations from Medline. A similar search was conducted in
Embase, the Cochrane Library, CRD databases, PsychINFO, Cinahl and Web of Science.
Database Number of references
Medline 392
Embase 774
Cochrane 1
CRD databases 0
PsycINFO 10
Cinahl 18
Web of Science 251
Total 1446

After duplicate references were removed a total of 1880 potentially relevant references were left. The titles and abstracts of these citations were scanned for relevance to screening for familial dysautonomia, and **84** 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 11
Embase 53
Cinahl 0
PsycINFO 0
Cochrane Library 0
Web of Science 12
Total 76

After duplicate references were removed a total of 69 potentially relevant references were left. The titles and abstracts of these citations were scanned for relevance to screening for familial dysautonomia, and 4 citations were deemed to be relevant. These additional 4 references are identified by **

All 88 citations were classified into the categories below. There will inevitably be some overlap of the categories within these citations.