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Genetic Counseling: Amongst Ashkenazi Jews

Introduction:

Genetic counseling is often thought of as a communication process which deals with problems associated with the occurrence of a genetic disorder in a family. The process involves an attempt by one or more appropriately trained persons to help the individual or family to: (1) understand the medical facts, including diagnosis, probable course of the disorder, and the available management, (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action which seems appropriate for the family in view of their risk, their family goals, and their ethical and religious standards, and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder[1] (American Society of Human Genetics).

In the first half of this paper I will cover the general methods of screening and diagnosing genetic disease and in the second half I will apply those applicable to individuals of Ashkenazi Jewish heritage in regard to family planning. Amongst Ashkenazi Jews it has been estimated that one in four individuals is a carrier of one of several genetic conditions. These disease include Tay-Sachs Disease, Canavan, Niemann-Pick, Gaucher, Familial Dysautonomia, Blood Syndrome, Fanconi anemia, Cystic Fibrosis and Mucolipidosis IV. I will only cover a few of these disease in this paper as examples. The ones presented here are just some of the more common genetic diseases that affect Ashkenazi Jews. There are several other diseases that can be inherited amongst Ashkenazi Jews and are still being incorporated into recommended Genetic test.

Genetic Testing/Screening Methods:

Today, genetic screening programs for the detection of carriers of severe genetic diseases exist in many ethnic and diverse communities. These diagnostic test can include pre/post-natal, pre-gestational, and pre-marital screening[2] The genetic testing can examine chromosomes, genes or proteins.

Cytogenetic Testing- This type of testing examines the shape of the chromosomes present in a patients sample. This type of testing is useful when looking at the chromosomes as a whole, however, it does not provide any information about specific genes or proteins that may also be associated with a genetic disease[3]. For example, cytogenetic testing can be used to obtain a blood sample and look for extra chromosomes. A disease like Down Syndrome could be

picked up due to the additional extra chromosome 21 but a disease like Cystic Fibrosis will not. This is due to the test not being able to pick up a single gene change, such as in CF.

Fluorescence in situ hybridization (FISH) Testing- This is a technique that uses a specific protein, a probe, that has been designed to stick to unique DNA in a cell. The probes are fluorescent. The cells can then be examines to detect common chromosome problems caused by an extra chromosome such as Down syndrome (trisomy 21) and in prenatal diagnosis when results are needed rapidly. FISH is also able to detect subtle chromosome rearrangements such as identifying marker chromosomes (extra pieces of unidentified chromosomal material) and test for common diseases caused by duplication or deletion of large pieces of DNA[4]. The recommendations for pregnancy management decisions and diagnosis problems are to not use FISH alone but also take into account the results of the full chromosome analysis and clinical findings[5]

Biochemical Testing- This type of testing measures the level of protein or enzyme present in a patients sample to help determine if the gene that produces that protein is functioning properly[6] An example of a biochemical test is the enzyme analysis for Tay-Sachs disease. The disease is an inherited disorder that causes neurological deficits, developmental delay, and death by age 4. Its cause is due to the lack of an enzyme called hexoseaminidase A (hex A). By measuring levels of hex A in the blood, the test can determine if a person is affected by Tay-Sachs disease or is a carrier.

Indirect (linkage) Testing- Not every single gene has been located yet. For some genes, for example, we know only approximately where the gene is on a chromosome but not exactly. Indirect testing requires blood from several family members, including those that are known to be carriers or affected with a specific condition. They can then compare genetic material between family members and determine who is most likely to be a carrier or affected[7]. In families with hemophilia A, a genetic disorder resulting in excessive bleeding after injury or surgery, the gene mutation causing the disease cannot be identified with common lab test methods. The DNA contains markers ,however, that are unique to individuals and families. If they can find the markers unique to hemophilia family near the hemophilia gene, the markers from at least two affected family members can be compared to the marker in the family member in whom the diagnosis or carrier status is in question. If the unique sequence from the affected family member are presented in the person being tested. the individual is predicted to be affected or a carrier. Linkage can also be used for prenatal diagnosis[8]

Direct Testing- Direct gene testing can be performed when it is known where the exact gene is located on a chromosome and what changes in that gene cause a specific disease. Labs can then examine the disease causing gene changes in a person who is either suspected of having a genetic disease, or who may be a carrier for the disease[9]. An example of direct testing is the mutation analysis for Cystic Fibrosis. CF is an inherited disease that causes lung and digestive problems. Common mutations in the CF gene have been identified. The American College of Obstetricians and Gynecologist (ACOG) and the American College of Medical Genetics (ACMG) recommend that CF carriers screening be offered to all couples when at

least one member of the couple is Caucasian and pregnant or considering pregnancy[10]. The carrier screening can consist of direct detection for the 25 most common CF mutations. It is also further recommended by ACOG and ACMG that CF screening be made available to individuals of other racial and ethnic groups.

Array-comparative genomic hybridization- A relatively newer genetic test that allows a more detailed examination of the genome when compared to a standard chromosome analysis. CGH microarray or chromosome microarray analysis combines chromosome and fluorescence in situ hybridization analysis allowing detection of both aneuploidies and also micro-deletion and micro-duplication disorders, including telomere rearrangements. The advantages of this type of exam are that it allows for simultaneous evaluation of multiple disease specific loci and sub-telomeric regions, that results in a more efficient consideration of possible diagnosis and cost savings of ordering testing for each locus individually[11].

There are several reasons why a genetic test may be offered:

Carrier screening: This is the most common type of testing performed today. There are several disorders where either one parent or both parents must be carriers of a certain gene or mutation to have an affected child, such as in CF. In these circumstances, the carrier will have no symptoms of the disease, but may have a baby with the disease if the other parent is also a carrier. It has become standard medical practice to offer couples who are expecting a baby or planning a pregnancy screening for some of these disease. It is important to note that some types of carrier screening are not definitive; negative genetic test results mean the likelihood a person is a carrier is reduced, but do not entirely eliminate the possibility.

Diagnostic Testing: This may be offered to a person when a physician suspects that the patient has a specific genetic disease.For example, if the patient has symptoms associated with a specific genetic disease, the physician may choose to offer a genetic test to definitively diagnose or rule out that disease.

Prenatal Screening: Some test are available that can screen for certain types of birth defects in a baby before it is born. This type of testing performed during a pregnancy cannot diagnose birth defect, but only determine if a fetus is at increased risk for certain genetic disorders. Maternal serum screening is an example of prenatal screening. AFP X-tra is a maternal serum screening test that identifies pregnancies at increase risk for open neural tube defects, Down Syndrome, and trisomy 18. The blood test is a screening test and does not provide definitive diagnosis.

Prenatal Diagnostic Test: These types of test are available during a pregnancy to determine if a baby has a specific disease. The results of this type of testing are conclusive enough to diagnose or rule out a genetic condition before the baby is born. Testing is usually performed on amniotic fluid or chorionic villi samples[12]. Amniocentesis is an example of a potential prenatal diagnosis. In this exam, a small amount of amniotic fluid is withdrawn and the

chromosomes are examined. If ,for example, an extra chromosome number 21 is seen, a diagnosis of Down syndrome can be made.

Pre-implantation Diagnostic Testing: This type of testing is available for a limited number of genetic disorders on a single cell of an embryo from a procedure called in vitro fertilization. In vitro fertilization involves the fertilization of the egg outside the womb in a laboratory. Certain genetic test may be performed on a single cell removed from an embryo. After the testing, selected embryos may then be implanted in the womb.

Jews of Ashkenazi Ancestry:
Currently, for those of Jewish ancestry planning to have children, it is generally recommended to be screened for certain genetic disorders/diseases. This generally involves a prenatal testing panel that will include some common Jewish genetic diseases. Due to the vast accumulation of knowledge acquired throughout the years, most panels will include those disease that are very common amongst Ashkenazi Jews. Recently, however, there have been questions as to if the panel should include additional disorders/diseases that are less common.

Table 1. Incidence of Ashkenazi Jewish genetic disorders.

Disease	Disease incidence	Carrier frequency	Carrier detection rate in Ashkenazi
Bloom syndrome	1 in 40,000	1 in 110	95–97%
Canavan disease	1 in 6400	1 in 38	98%
Dystonia	Unknown	1 in 900	98%
Familial dysautonomia	1 in 3700	1 in 30	99%
Fanconi anemia (type C)	1 in 32,000	1 in 89	99%
Gaucher disease (type 1)	1 in 900	1 in 10	95%
Mucolipidosis IV	Unknown	1 in 100	95%
Niemann–Pick disease (type A)	1 in 32,000	1 in 70	95%
Tay–Sachs disease	1 in 3000	1 in 26–30	94–98%
Cystic fibrosis	1 in 2500	1 in 25–29	97%
DFNB1 (congenital deafness)	6 in 10,000	1 in 20	95%
Non-classical adrenal hyperplasia	1 in 27	1 in 3	95%

*List of common genetic disorders with frequency [13]

Characteristics of Ashkenazi Diseases [14]

Table 2. Characteristics of Ashkenazi Jewish genetic disorders.

Disease	Effects	Definitive therapy	Outlook
Bloom syndrome	High risk for malignancy	None	Individuals can be functional, some are retarded. Mean survival 27 years
Canavan disease	Neurodegeneration	None	Fatal, from early childhood through early teens
Dystonia	Movement disorder	None	Individuals can be functional
Familial dysautonomia	Neurodegeneration	None	50% live to 30 years of age
Fanconi anemia (type C)	High risk for malignancy	None	Onset ranges from 17 months to 22 years. Usually fatal by 30 years
Gaucher disease (type 1)	Thrombocytopenia, anemia, bone disease	Enzyme replacement therapy	Varies from mild to debilitating
Mucolipidosis IV	Neurodegeneration	None	Mild to severe progressive developmental delay. Shortened lifespan
Niemann–Pick disease (type A)	Neurodegeneration	None	Fatal by 3–5 years of age.
Tay–Sachs disease	Neurodegeneration	None	Classical infantile form fatal in early childhood
Cystic fibrosis	Pulmonary disease, malabsorption	None	On average fatal by age 30 years
DFNBI (congenital deafness)	Deafness	None	Profoundly deaf
Non-classical adrenal hyperplasia	Virilization	Hormone replacement	With early treatment symptoms are reversed

In-Depth look at 2 common Diseases amongst Ashkenazi Jews:

Gaucher Disease- This is recognized as the most common of the Mendelian Ashkenazi disorders. It is so variable that is is thought to have 3 types, although all three result from mutations at the same locus (the glucocerebrosidase gene)[15]. The most common phenotype and the one especially common in Jews is known as type 1 or the non-neuronopathic type. The pathology is related to the accumulation of the glucocerebroside in monocyte macrophages; the disease will therefore affect organs in which these cells are abundant such as the spleen, liver, bone marrow and lungs. 4 mutations account for 90% of the alleles found in Ashkenazi patients, the most common being N370S[16]. The homozygosity for this allele is often associated with a relatively mild form of the disease, an average age of diagnosis in the late twenties or early thirties. At the same time it is well recognized that Gaucher disease may be so mild that it is detected incidentally in the later years of life, during evaluations of unrelated symptoms. The only concrete generalization to be made about the N370S allele is that it is never present in patients with neuronopathic disease (types 2 and 3; no significant increase in frequency amongst Ashkenazi Jews). The treatment for Gaucher disease generally involves recombinant human gluccocerebrosidase, which very effectively reduces storage of glucocerebroside and reverses many of the clinical manifestations of the disease.

Tay-Sachs Disease- The classic presentation of this disease is usually present in the infantile age with a decline in the rate of development during the first 3-6 months of life. It is usually fatal by 5-8 years of life and will affect almost every aspect of brain functioning. There are 2 Ashkenazi mutations associated with classic infantile onset disease (1278ins4 and 1421 + 1G>C), account for 95-98% of the mutant alleles. An additional mutation, G269S, is

typically associated with a neurological disorder with later onset and slower progression (chronic GM2 gangliosidosis). Additionally, in the GM2 gangliosdosis, the psychomotor regression can be mild or even absent and psychiatric disturbances are high occurring in 40% of the patients.
Due to the stored substrate in Tay-Sachs disease found primarily in neurons, the enzyme replacement therapy is precluded by the blood-brain barrier. Recent development of inhibitors of ganglioside syntheses has raised the possibility of treating the chronic forms with these agents, in attempts to slow the progress of the disease.

Intervention in the Jewish Community:

In the Ashkenazi Jewish community to combat or reduce the incidence of genetic disorders in offspring a variety of strategies have been used. When both members of a couple are screened and found to be carriers of a disorder, a variety of reproductive options are now available. Some of these include pre-natal diagnosis by amniocentesis or chorionic villus sampling, pre-implantation genetic diagnosis, artificial insemination by donor, egg donation, and adoption. As discussed previously, prenatal diagnosis allows the couple to terminate an affected pregnancy, while the pre-implantation diagnosis allows the implantation of only the embryos that are not affected.
Some additional strategies employed amongst Orthodox Jews, sponsored by Dor Yeshorim organization, is to prevent the marriages between two carriers[17]. In this program the participants are screened for 4-5 genetic disorders, but do not receive their results, they only receive identification numbers. in order to avoid any stigma if one is found to carry any of the disorders. Then, participants can learn if they are genetically compatible by submitting their identification numbers to Dor Yeshorim. As long as the individuals are not carriers for the same genetic disorders, they are considered compatible. This type of intervention has been so successful that the rates of Tay-Sachs disease have been drastically reduced[18].

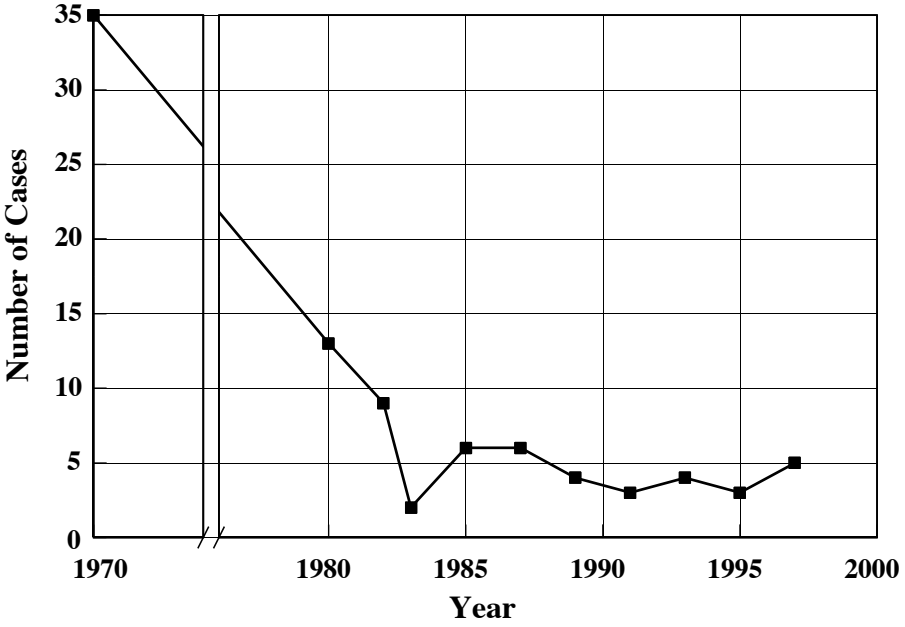

Figure 1. Number of Jewish infants born with Tay–Sachs disease in the United States and Canada, based on data from Table 153-5 in Gravel et al. [5].

Recently there have been thoughts of expanding genetic testing panels to include less common genetic disorders. On the other hand some experts such as Joel Charrow, question the idea of adding so many additional tests to the panels. According to him "I don't think we could in any meaningful way truly inform people about everything they need to know about each of these conditions before testing for them."[19] This brings up the idea that even if we have additional information, it may not always be beneficial in preventing or treating disease. Other experts such as John Mitchell says"Are you creating more anxiety than benefit?" he asks. "I think that's where sometimes the line has to be drawn."[20] The experts have yet to agree on the benefit of additional tests in the panels. The recommendations as such are as follows:

"Professional societies alike remain divided. In 2009, the American College of Obstetricians and Gynecologists recommended screening for just four of the most common diseases—Tay-Sachs, cystic fibrosis, Canavan's disease and familial dysautonomia—all of which have carrier frequencies among Ashkenazi Jews greater than one in 40 (*Obstet. Gynecol.* **114**, 950–953, 2009). In contrast, the American College of Medical Genetics (ACMG) in 2008 backed a larger panel of nine specific disorders, some with carrier rates as low as one in 100 and others that are not life threatening, with detailed criteria for adding other disorders to the list (*Genet. Med.* **10**, 57–72, 2008)."

Table 2. Prior risk and revised carrier risk for a Jewish consultant with no family history after a negative mutation analysis for common Ashkenazi Jewish mutations.

Disease	Prior risk	Detection rate	Revised risk
Tay–Sachs disease	1 in 25	0.92	1 in 301
Gaucher disease, type I	1 in 15	0.95	1 in 284
Canavan disease	1 in 40	0.98	1 in 1951
Cystic fibrosis	1 in 26	0.97	1 in 801
Familial dysautonomia	1 in 30	0.99	1 in 3223
Niemann–Pick disease, types A and B	1 in 90	0.90	1 in 891
Fanconi anemia, group C	1 in 89	0.99	1 in 9889
Bloom syndrome	1 in 107	0.97	1 in 3303
Mucolipidosis type IV	1 in 122	0.96	1 in 3307

Either way, the reduction of risk in those who choose to get screened for genetic mutations is significant as is shown in the table above[21]

Conclusion:

The use of genetic counseling to identify couples at risk for having children with genetic diseases, and identifying individuals who are genetically predisposed to specific diseases, is often possible through the use of DNA- or gene-product- based testing. These test can be deployed for population screening, especially when specific populations are known to be at increased risk for particular disorder(s). Ashkenazi Jews are at increased risk for a number of inherited disorders and inherited disease predispositions, and have embraced genetic screening for these disorders, with measurable reductions in specific diseases (e.g., Tay–Sachs disease). However, screening may not only be ineffective, but may be harmful, if the complexity of the relationship between mutation and disease are not appreciated. These include variable expressivity and penetrance, inconsistent correlation between genotype and phenotype, and modification of phenotypes by other unidentified genes. The importance of genetic counseling in family planning cannot be overstated.

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