What does it mean to be told that you (or your child) has a bad gene?

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What's a "Bad" Gene?

- An altered gene, or a gene with a mutation
- Mutations alter the instructions in the gene which direct the synthesis of a specific protein
- The mutation may result in:
  - an altered protein (typically one that doesn't function very well)
  - a decreased amount of protein ("deficiency")

Consequences of Having a “Bad” Gene

- You may have a disease
- You may have a predisposition to a disease
- You may be a carrier of a gene which could produce disease in your children
- You may feel different from others
- You may feel defective
- You may feel undesirable

What does it mean?

- If you have a bad “dominant” gene:
  - You may have a genetic disease (e.g., torsion dystonia)
  - You may have a genetic predisposition to a disease (e.g., breast cancer)
- If you have one bad copy of a “recessive” gene:
  - You are a “carrier” of a genetic disease
- If you have *two* bad copies of a “recessive” gene:
  - You have a genetic disease (e.g., Gaucher disease)

Mendel's Laws Simplified

- If you have a gene which causes a dominantly inherited disorder:
  - You will have the disorder (most often)
  - Each of your children will have a 50/50 chance of inheriting the gene (and the disorder) from you
- If you have a gene which causes a recessively inherited disorder:
  - You will not have the disorder, but….
  - *If your spouse has the same gene*, each of your children will have a 1 in 4 (25%) chance of having the disorder
  - Each of your children will have a 50/50 chance of inheriting the gene from you

Why are there bad genes?

- Genes undergo random alterations (mutations), usually for reasons we don't understand
- Mutations may
  - Be helpful
  - Be harmless
  - Contribute to our physical traits
  - Produce disease or predisposition to disease
  - Be fatal

How do we discover bad genes?

- When someone has a genetic disease
- When we test someone because they are at “high” risk for having a bad gene

- Testing is typically performed on a blood sample, but may be performed on cheek washings in some cases
- Most often the test looks for *specific* changes (mutations) in the DNA sequence of the gene of interest

Jewish Genetic Disorders

- Disorders which are more common among Jews
- These are not *uniquely* Jewish disorders, but are found more commonly among Jews

Screening for “bad” genes

- Began with screening for Tay-Sachs disease in the early 1970’s
  - Tay-Sachs disease was common among Ashkenazi Jews: 1 in 3600 live births
  - Tay-Sachs produced damage to the brain beginning early in infancy
  - All children with classical Tay-Sachs died in early childhood
  - There was no effective treatment for Tay-Sachs
  - Carriers could avail themselves of reproductive options

Carrier Screening Options

Interventions available for couples at risk:

- Don’t have children
- Take your chances (1 in 4)
- Have prenatal diagnosis and consider selective termination of pregnancy
- Adopt
- Conceive by artificial insemination by donor

More Recently Developed Options

Reproductive technology offers more choices:

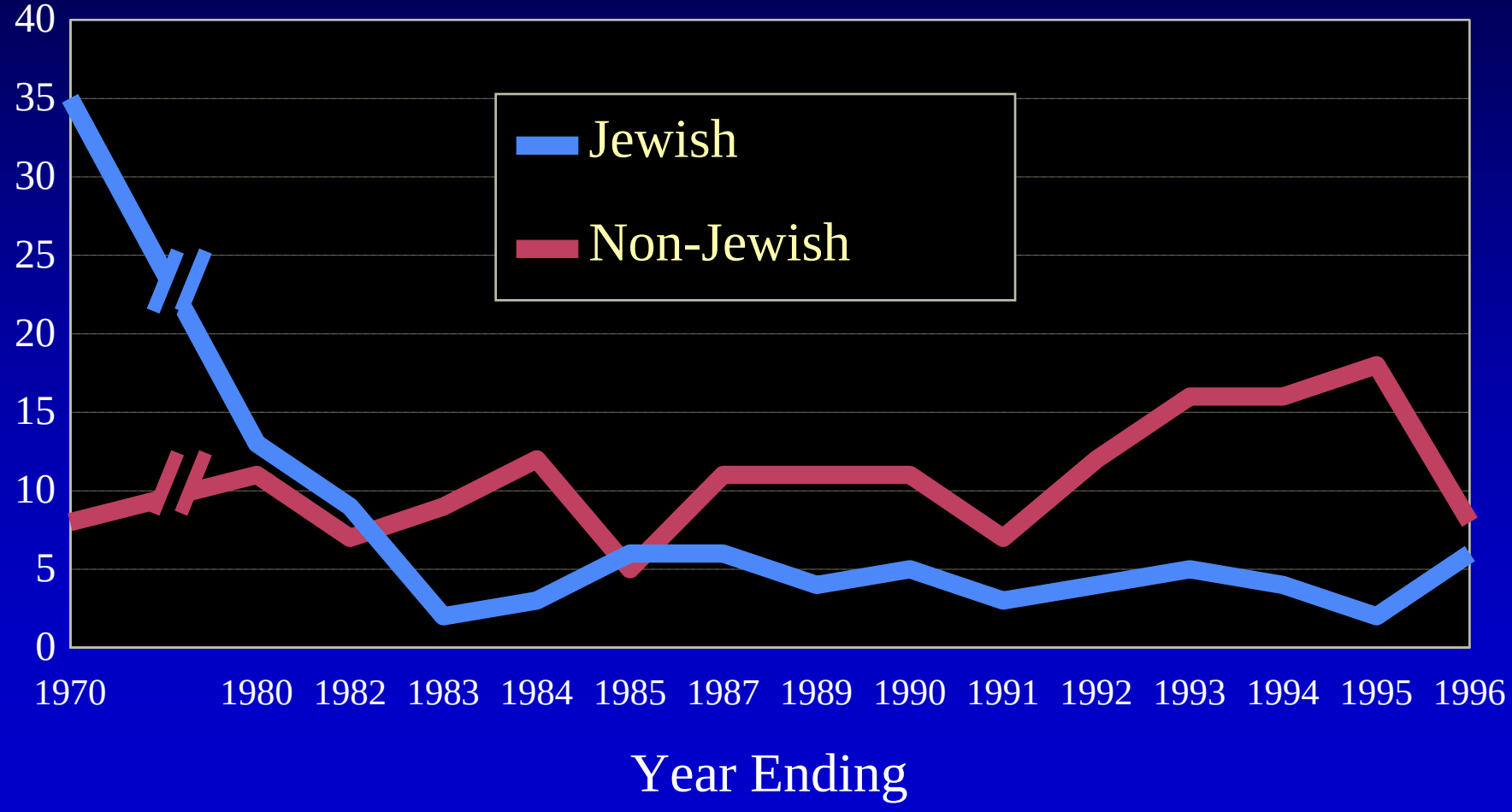
- Egg donation
- Pre-implantation diagnosis

These result in greater cost and greater potential for test-related morbidity and mortality

Screening the Orthodox

- Termination of pregnancy may not be an acceptable option
- Development of Dor Yeshorim:
  - Everyone is anonymously screened during High School or early adult years, and assigned a number
  - Individuals do not know their results
  - Before an engagement, the parties submit their identifying numbers to determine if the match is “compatible”

Incidence of Classical Tay-Sachs Disease in the U.S. and Canada



Ashkenazi Jewish Prenatal Panel

Disease	Mutations tested	Detection rate %	Carrier frequency
Bloom Syndrome	1	97	1 / 100
Canavan Disease	4	98	1 / 40
Cystic Fibrosis	87	97	1 / 26
Fanconi Anemia C	1	99	1 / 89
Familial Dysautonomia	2	99.5	1 / 30
Gaucher Disease	5	95	1 / 15
Mucolipidosis Type IV	2	96	1 / 122
Niemann-Pick Type A	3	95	1 / 90
Tay-Sachs Disease	8	94	1 / 30

What does it mean?

- A “positive” screening result means there is a mutation present
- A “negative” screening result means that a mutation was not detected (but maybe it wasn’t tested for…)
- A “negative” screening result *reduces* the risk of disease, but does not eliminate it.

Ashkenazi Jewish Prenatal Panel

Both parents screened negative

Disease	Carrier Risk		Risk of Disease	
	Before	After	Before	After
Bloom	1/100	1/3,300	1/40,000	1/43,560,000
Canavan	1/40	1/2,000	1/6,400	1/16,000,000
Cystic Fibrosis	1/26	1/834	1/2,704	1/2,782,224
Fanconi Anemia C	1/89	1/8,900	1/31,684	1/316,640,000
Familial Dysautonomia	1/30	1/6,000	1/3,600	1/144,000,000
Gaucher Disease	1/15	1/281	1/900	1/315,844
Mucolipidosis Type IV	1/122	1/3,026	1/64,516	1/36,626,704
Niemann-Pick Type A	1/90	1/1,781	1/32,400	1/12,687,844
Tay-Sachs	1/30	1/363	1/3,600	1/527,026

Thank you for participating in the Chicago Center for Jewish Genetic Disorders (CCJGD) genetic screening. Enclosed please find the results from your carrier screening. You were screened for nine disorders, including Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, mucolipidosis type IV, Niemann-Pick disease type A, and Tay-Sachs disease. All of these disorders are inherited in an autosomal recessive manner, and are either more common in Ashkenazi Jews or have relatively high carrier frequencies in that population. Both you and your wife were screened at the same time. A copy of these results has also been sent to your wife□s physician, as you requested.

Neither you nor your wife were found to carry any of the most common mutations (or changes) in the genes for eight of the nine disorders included in the screening. Since this screening cannot detect all carriers of these conditions, a negative result means that your risk of being a carrier has been *reduced* but not eliminated. The remaining risk of being a carrier after a negative screen result (for Ashkenazi Jewish ancestry) is as follows for each of you:

Bloom syndrome: 1/10,700
Canavan disease: 1/1367
Cystic fibrosis: 1/400
Familial dysautonomia: 1/3100
Fanconi anemia group C: 1/8900
Gaucher disease: 1/360
Mucolipidosis IV: 1/2540
Niemann-Pick type A: 1/3000

As we discussed with your wife by phone, she was found to be a carrier of Tay-Sachs disease (TSD). This means that she has one functional copy of the TSD gene and one non-functional copy. The functioning copy makes enough protein product so that she has no symptoms of TSD now, nor will she in the future. She does, however, have an equally likely chance (50%) of giving either the non-functional copy or the functional copy of the TSD gene to each of your children.

Your testing was negative, however there is still a residual 1 in 1550 risk that you are a carrier for TSD. Your enzyme analysis was also negative, however, which makes it even less likely that you are a carrier. Because of the residual risk, your risk as a couple to have a child with TSD is 1 in 6200 (significantly less than 1%). Prenatal testing is available for TSD should you wish to pursue testing during a pregnancy.

Since you are both of Ashkenazi Jewish descent and screened negative for eight of the above disorders, the risk of having a child with any of these disorders is significantly less than 1%. The specific risks are as follows:

Bloom syndrome: 1 in 43,586,404
Canavan Disease: 1 in 15,225,604
Cystic Fibrosis: 1 in 640,000
Familial dysautonomia: 1 in 8,421,604
Fanconi anemia group C: 1 in 309,830,404
Gaucher disease: 1 in 518,400
Mucolipidosis IV: 1 in 14,455,204
Niemann-Pick type A: 1 in 19,820,304

Please note that you have not received testing for all of the disorders that we discussed during the educational session. You may contact us to arrange for this testing or if you would like to know of testing centers near you. The other disorders discussed and the frequency of carrying a mutation in the Ashkenazi population is:

Glycogen Storage Disease type 1a	1 in 71
Maple Syrup Urine Disease	1 in 81
Torsion Dystonia	1 in 1000 - 3000

We hope this information has been helpful. If you have any questions or concerns, please do not hesitate to contact us at 773-880-4462.

What does it mean?

- Some bad genes are *really*, *really* bad
  - Result in progressive brain damage and death in early childhood (e.g., Tay-Sachs, Canavan, Niemann-Pick)
- Some bad genes are *really* bad
  - Require lifelong treatment and still result in shortened lifespan (e.g., Cystic Fibrosis, Familial Dysautonomia)
- Some bad genes are not *so* bad
  - Require lifelong treatment, but are compatible with normal intelligence and lifespan (e.g., Gaucher disease)

More Ashkenazi Jewish Prenatal Panel

Disorder	Carrier Frequency	Disease Incidence
Dihydrolipoamide dehydrogenase deficiency	1 / 96	1 / 36,864
Familial hyperinsulinism	1 / 66	1 / 17,424
Glycogen storage disease type 1a	1 / 71	1 / 20,164
Maple syrup urine disease	1 / 81	1 / 26,244
Nemaline myopathy	1 / 149	1 / 88,804
Usher syndrome Type IF	1 / 141	1 / 79,524
Usher syndrome Type III	1 / 107	1 / 45,796

What diseases are Sephardic Jews at increased risk for?

- Thalassemia
- Familial Mediterranean Fever
- Glycogen Storage Disease
- G6PD Deficiency

Cancer is NOT More Common In Ashkenazi Jews

But, *some* cancers *are* MORE common…

- Bloom syndrome
- Ataxia telangiectasia
- Endometrial carcinoma
- Polycythemia vera
- *BRCA1* and *BRCA2* related breast and ovarian cancer
- Colorectal cancer, Crohn's disease, ulcerative colitis
- Fanconi anemia
- Hairy cell leukemia

Cancer is NOT More Common In Ashkenazi Jews

And other cancers are LESS common…

- Cancer of the cervix
- Lung cancer (in men)
- Cancer of the penis
- Prostate cancer

Cancer Predispositions

Type of Cancer	Frequency
Breast and Ovarian	1 in 40
Colon Cancer	1 in 7

Hereditary Breast and Ovarian Cancer

- *BRCA1* and *BRCA2* mutations are found in 2.5% of Ashkenazi Jews, compared to 0.1 – 0.3% in non-Jews
- It is unclear if breast cancer is more common in Jews, but these mutations play a greater role in the genesis of breast cancer in Jews, accounting for 10% of breast cancer in women, and 19% of breast cancer in men
- Penetrance is very high: ~85% for breast cancer and ~40% for ovarian cancer

Inherited Predisposition to Colorectal Cancer (CRC)

- Inflammatory bowel disease is more common in Ashkenazi Jews, and predisposes to CRC, accounting for 1-3% of cases
- Although genetic mechanisms are probably responsible for the increased risk of CRC in Ashkenazi Jews, the currently recognized predisposition genes account for only a fraction of this increase.

Inherited Cancer Predispositions…

- Inheritance of predisposition is autosomal dominant
- Penetrance varies
- Specific cancers occur more frequently in relatives
- Have earlier age of onset/diagnosis
- May be multicentric

Inherited Cancer Predispositions…

- When an inherited cancer predisposition is suspected (or proven):
  - more frequent and intense cancer surveillance is indicated
  - prophylactic measures may reduce cancer risks (e.g., mastectomy, ovariectomy)
  - other family members should be screened for the predisposition
  - family members at increased risk for cancer should be evaluated more frequently and intensely

Conclusions

- Bad genes create a medical and psychological burden:
  - Disease
  - Disease predisposition
  - Reproductive burden
  - Effects on identity, self-worth, desirability
- Decisions regarding screening for bad genes are complex
- Genetic counseling should be part of all screening efforts, and is often not performed prior to screening, or before an abnormality is discovered.