Genomic Medicine 2010-2011
Lecture 3

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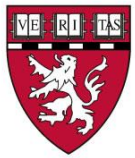


A teaching hospital of Harvard Medical School

Genetic Counseling & Genomics Outline

- What is genetic counseling?
- Case examples to explore:
  - What tests/information are currently used to assess genetic risk?
  - How might genomic testing be incorporated into genetic risk assessment?
  - What practical and ethical concerns might such testing raise?

Genetic Counseling

- Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

- We provide information and support to patients and families with or at risk of having birth defects, genetic disorders or inherited conditions.

- Genetic counselors are health professionals with masters degrees and experience in the fields of human genetics and counseling.

Adapted from NSGC.org

Risk Assessment

Genetic risk assessment is based on:

- Family history
- Personal history
- Test results
  - Biochemical, cytogenetic, molecular . . .
  - DTC personal genomic testing?, whole genome or exome sequencing?

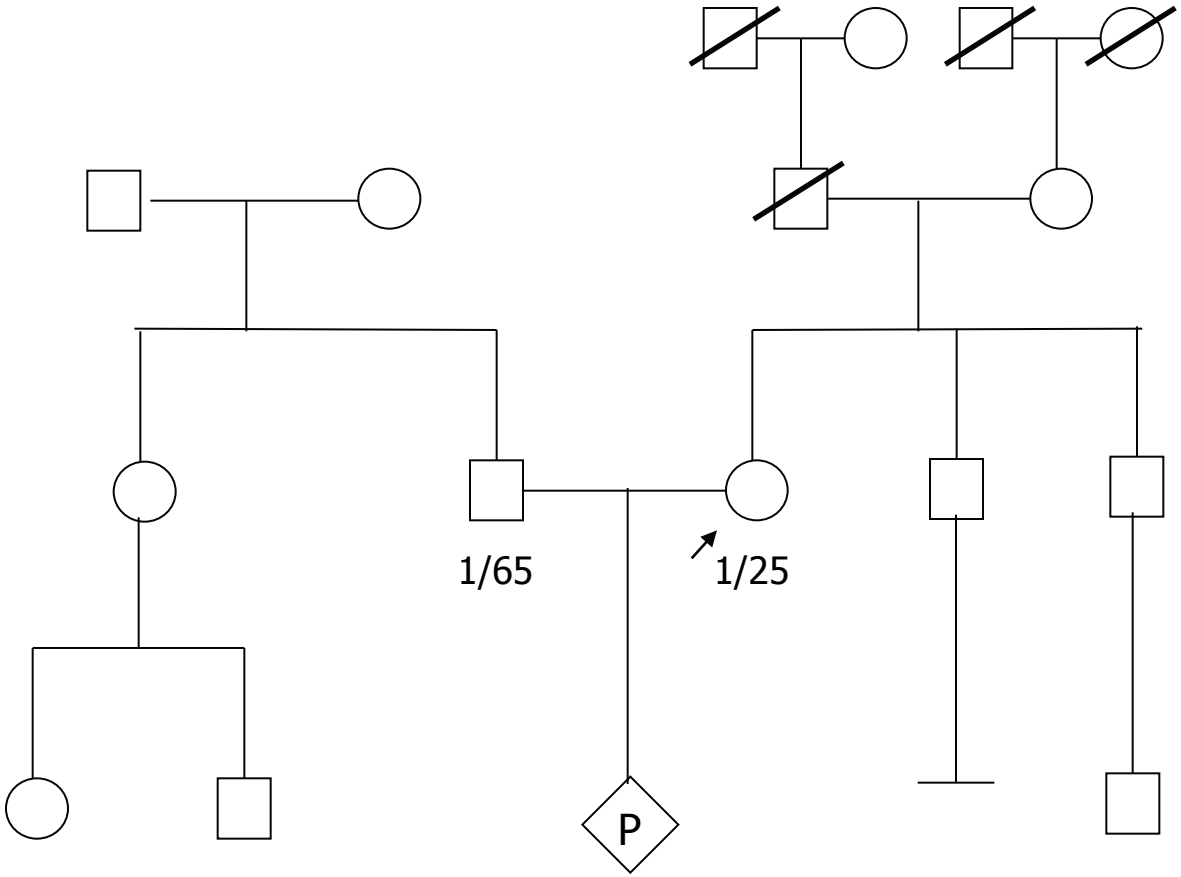
Case Examples

Case 1 - Cystic Fibrosis

Patient presents for preconception counseling. She is Italian and Irish. Partner is African American. No concerns in family history, though she has limited knowledge of partner's history. Ethnicity-based carrier screening offered for cystic fibrosis (ACOG 23-mutation panel).

African American

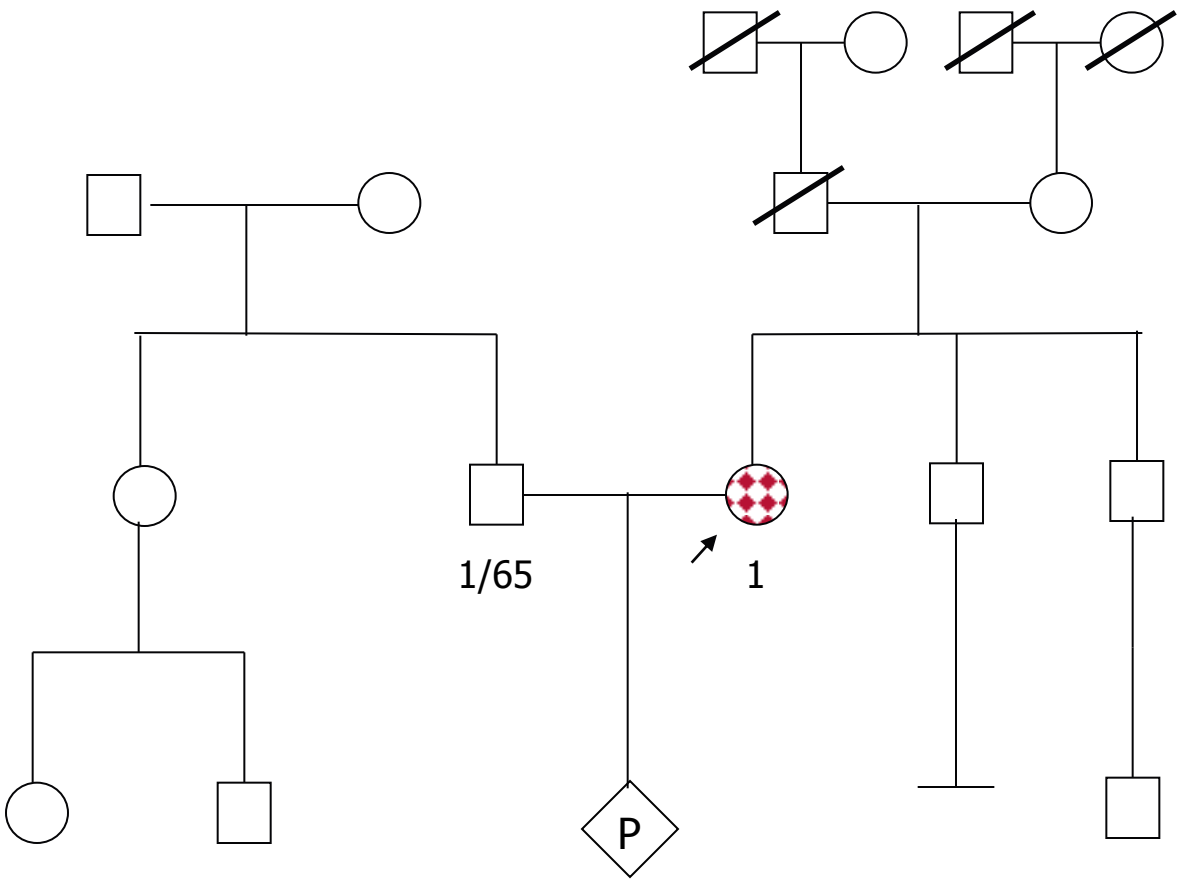
Italian & Irish



Fetus (*A priori*): 1/65 * 1/25 * ¼ → 1/6,500

African American

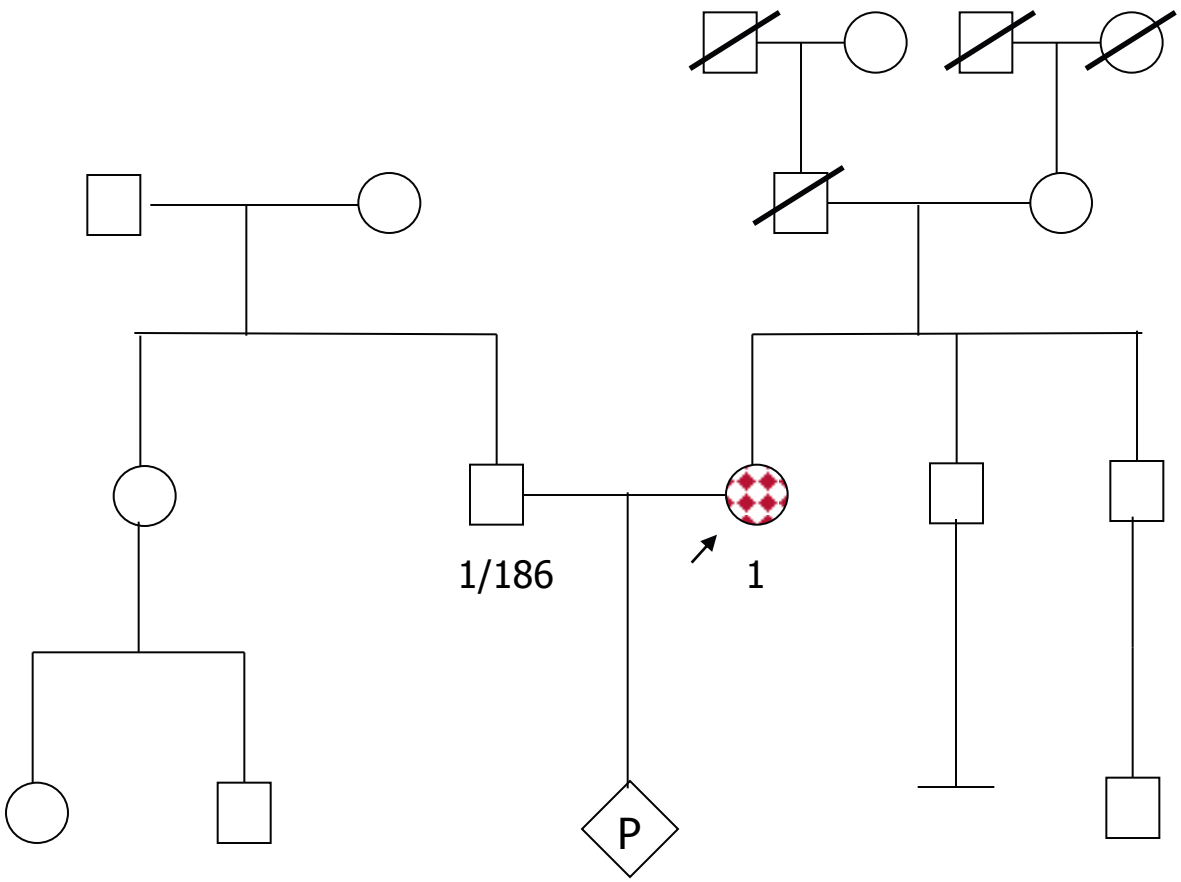
Italian & Irish



Fetus: 1/65 * 1 * ¼ → 1/260

African American

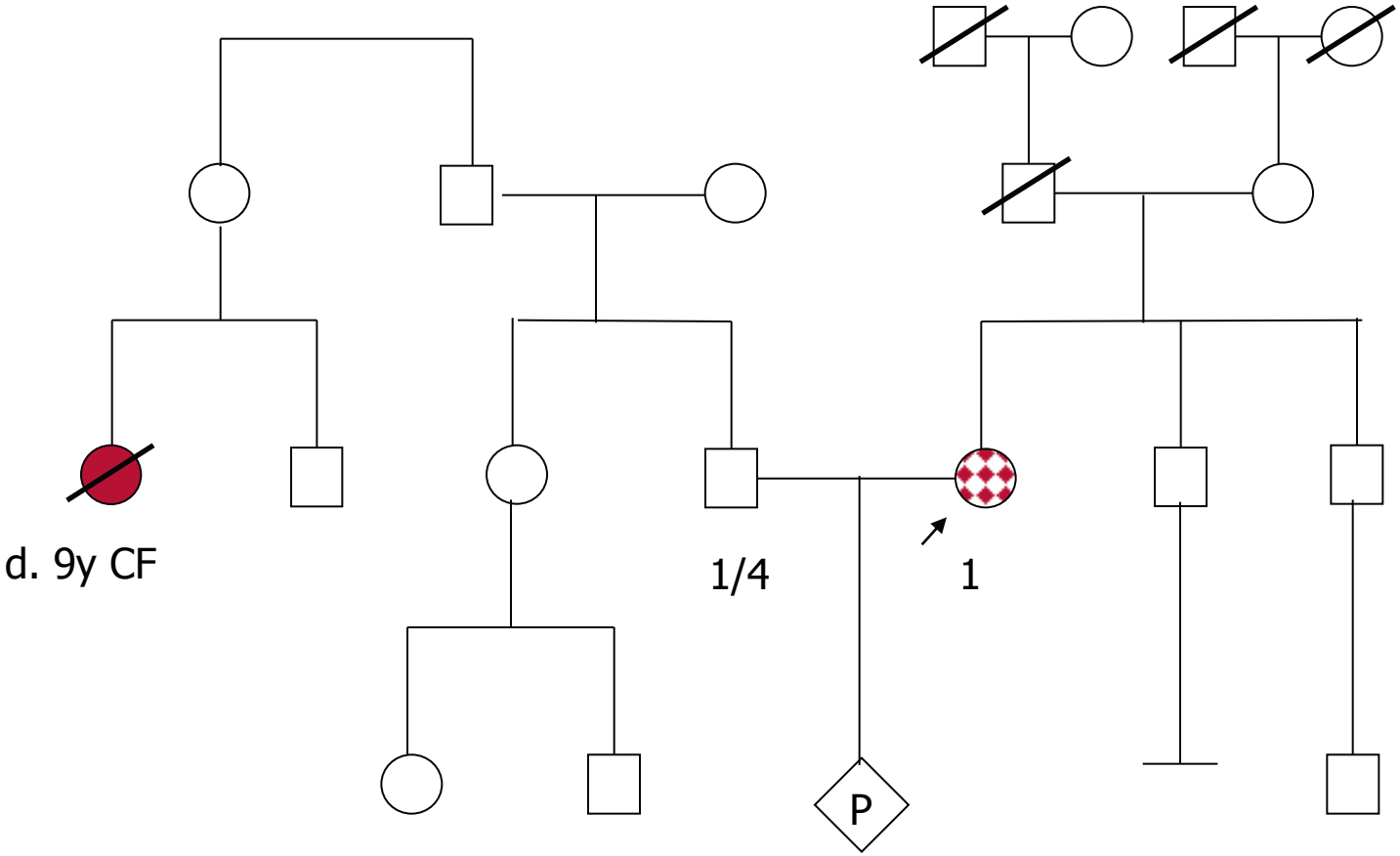
Italian & Irish



Fetus: 1/186 * 1 * ¼ → 1/744

African American

Italian & Irish



Fetus 1 * ¼ * ¼ → 1/16

Bayesian Analysis

	Carrier	Non-Carrier
Prior	1/4	3/4
Conditional	35/100	100/100
Joint	35/400	300/400
Posterior	35/335 = 1/10	300/335 = 9/10

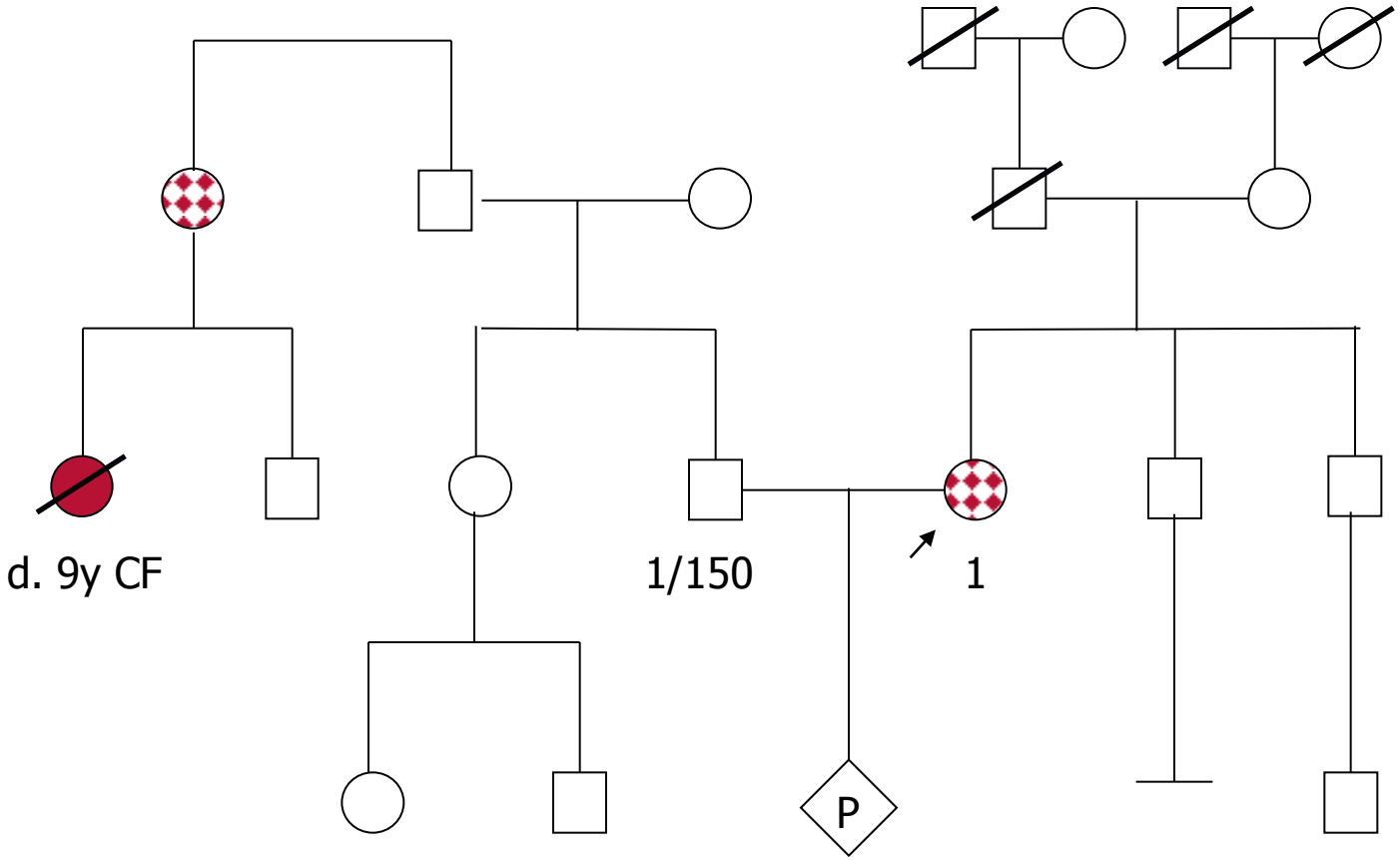
Fetus: 1/10 * 1* ¼ → 1/40

Sequencing

- 27 exons, splice site regions, clinically-relevant regions of introns
- 98% detection rate (residual risk ~ 1/150)
- Variant of uncertain significance

African American

Italian & Irish



Revised: 1 * 1/150 * ¼ → 1/600

Case 2 - Breast Cancer

Patient is a 34 year old female of partial Ashkenazi Jewish ancestry. She has no personal history of cancer but has strong family history of breast cancer, and her cousin was found to carry a *BRCA2* mutation (Ashkenazi Jewish founder mutation). The patient would like to be tested for this mutation.

Should she worry about discrimination?

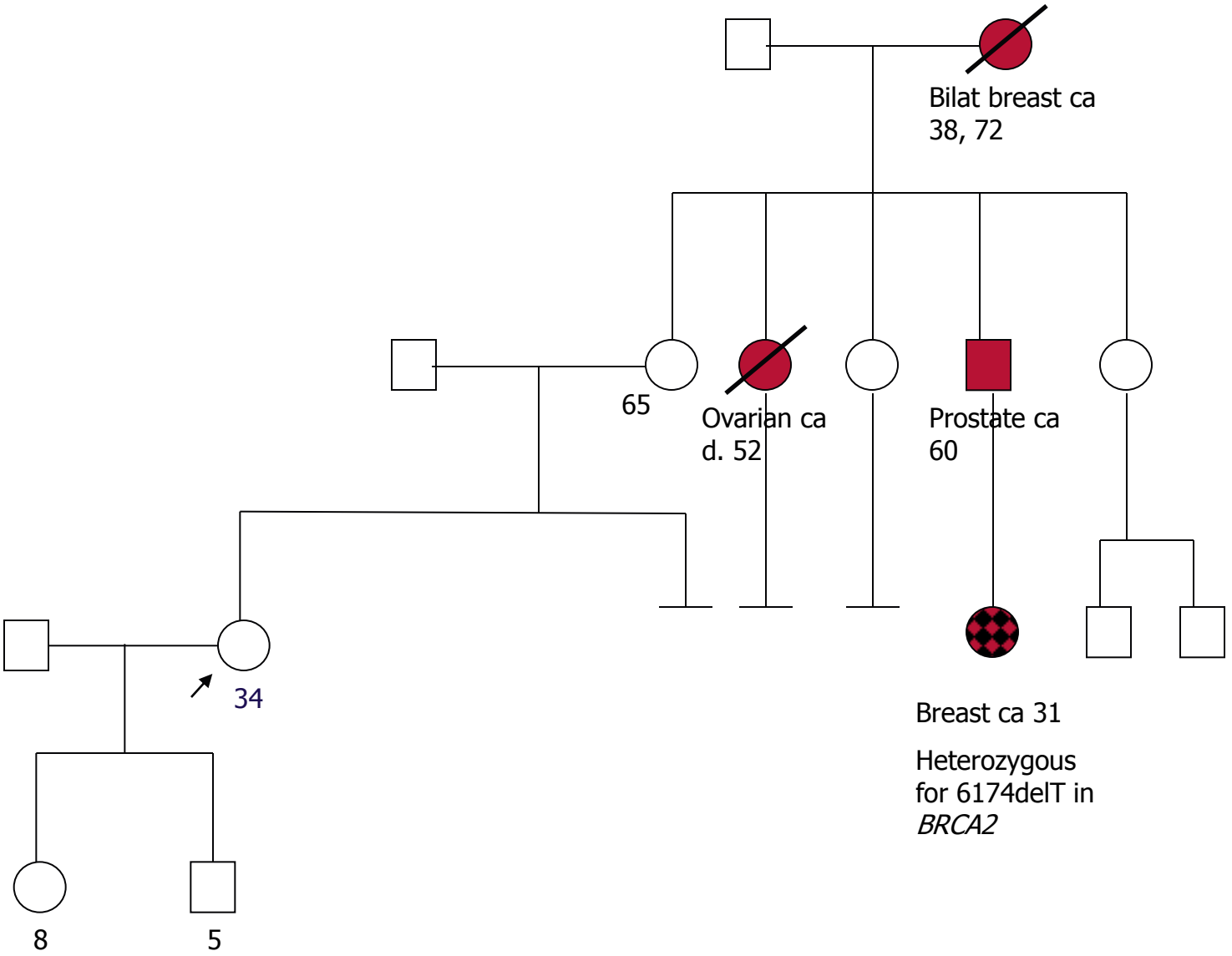
Should she worry about discrimination?

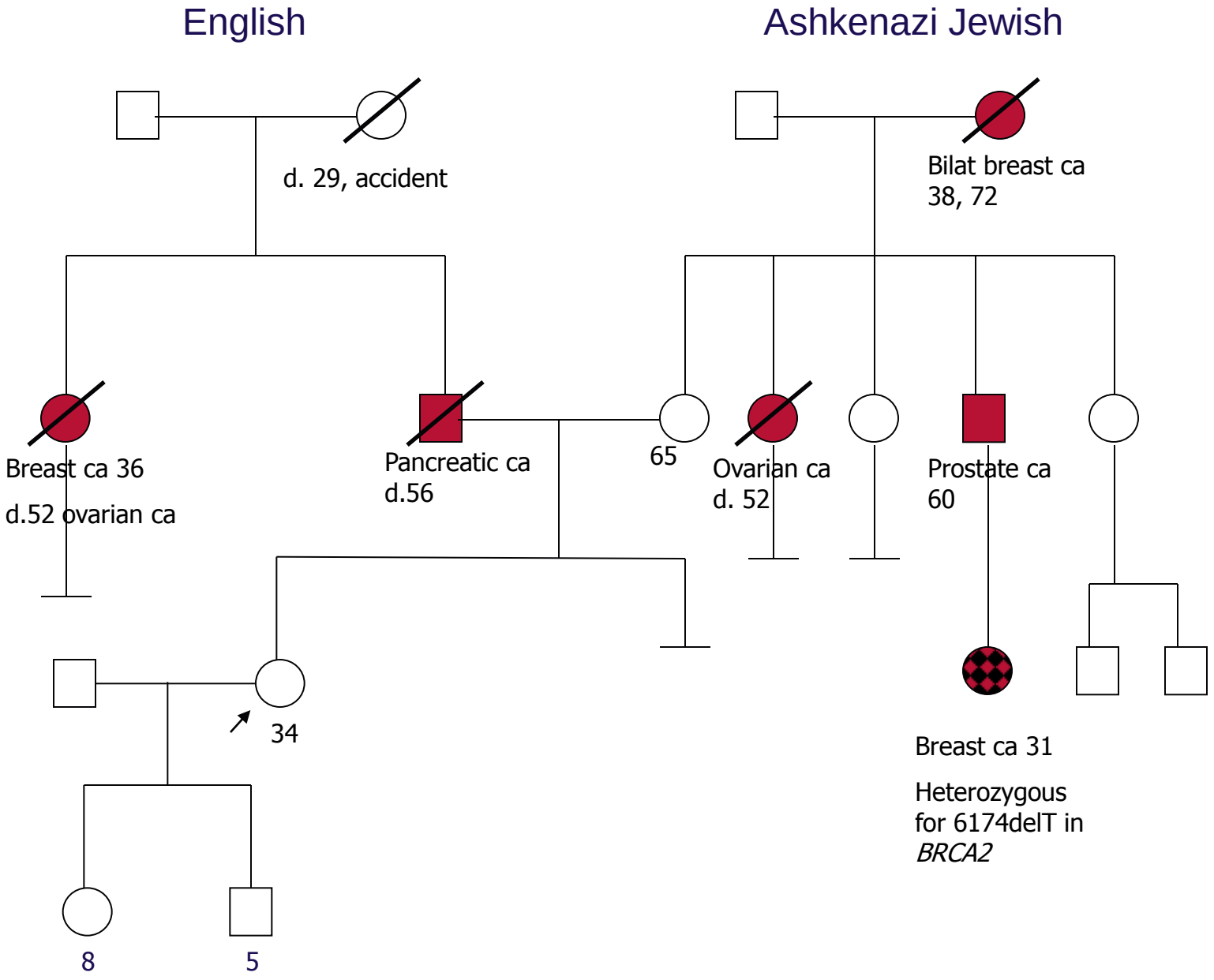
Genetic Information Nondiscrimination Act (GINA) of 2008

- Signed into federal law by George W Bush on May 21, 2008.
- Protections:
  - Group health insurance
  - Employment
- Does not apply to:
  - Life insurance, disability insurance, long-term care insurance
  - Employers with less than 15 employees

English

Ashkenazi Jewish




English
Ashkenazi Jewish
d. 29, accident
Bilat breast ca
38, 72
Breast ca 36
d.52 ovarian ca
Pancreatic ca
d.56
65
Ovarian ca
d. 52
Prostate ca
60
34
Breast ca 31
Heterozygous
for 6174delT in
BRCA2
8
5

BRCA Testing

- Sequencing of *BRCA1* and *BRCA2*
- Results:
  - *BRCA1* mutation, presumably inherited from father
  - No *BRCA2* mutation
- Bilateral oophorectomy & increase breast cancer screening
- Share results with paternal relatives?

What if the patient had instead had DTC GWAS testing for breast cancer risk?

- **Navigenics** and **deCODEme** – does not include *BRCA1* or *BRCA2*
- **23andMe** – tests only for the three Ashkenazi Jewish founder mutations in *BRCA1* and *BRCA2*

Case 3 - Type 2 diabetes

Patient and husband present for preconception genetic counseling. Both are in good health. Ethnicity based carrier screening is offered. Pedigree analysis is unremarkable with the exception of type 2 diabetes in the patient's mother. Patient wants to know chance she'll develop diabetes.

Type 2 Diabetes

- Empiric Data:
  - General population – 30% lifetime risk
  - Relative risk to individual with an affected parent – 2.0

- Assessment and recommendations:
  - Based on family history, patient has a 60% chance to develop T2DM in her lifetime
  - Share family history with GP
  - Diet and exercise

What if patient had Navigenics Testing?

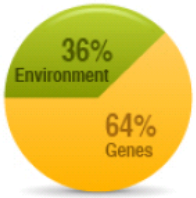
Navigenics®

navigenics.com / (866) 522-1585 / +1 (650) 585-7743

This report is for personal use only. Please consult the website if you wish to print a report for your physician.

Diabetes, type 2

Your estimated lifetime risk: **30%**
Average lifetime risk: **30%**



You have **17** of the **36** risk markers we looked for.

Gene or location [1]	Risk marker [2]	Your markers [3]	Odds ratio [4]	Source [5]
chr11.41871942	**C**	**C C**	2.61	Science, 2007
TCF7L2	**T**	A **T**	1.36	Nature, 2007
LOC441171	**A**	G G	1.0	American Journal of Human Genetics, 2007
KCNQ1	**A**	**A A**	1.54	Nature Genetics, 2008
PPARG	**C**	**C C**	1.53	Science, 2007
CDKAL1	**G**	A **G**	1.15	Nature Genetics, 2007
FTO	**A**	**A** C	1.16	Science, 2007
CDKN2A/B	**T**	**T T**	1.39	Science, 2007
SLC30A8	**C**	**C** T	1.18	Science, 2007
NOTCH2	**T**	G G	1.0	Nature Genetics, 2008
KCNJ11	**C**	**C** T	1.12	Science, 2007
JAZF1	**T**	C **T**	1.1	Nature Genetics, 2008
IGF2BP2	**T**	Pending	-	Science, 2007
HHEX	**C**	**C** T	1.06	Science, 2007
WFS1	**G**	A A	1.0	Nature Genetics, 2007
17q12-TCF2	**G**	A A	1.0	Nature Genetics, 2007
ADAMTS9	**C**	**C** T	1.09	Nature Genetics, 2008
TSPAN8	**C**	**C** T	1.09	Nature Genetics, 2008

see page 5 for an explanation of this table format

Navigenics' Interpretation

What does it mean?

Your risk for type 2 diabetes is about average — but for this condition, even the average risk is still pretty high. If you want to lessen your chances of getting diabetes, changing your diet and exercise habits can have a powerful preventive benefit.

As type 2 diabetes progresses, it damages internal organs such as your heart and kidneys. There is no cure, but you can control it with diet, exercise, weight control and, in some cases, oral medication or insulin injections.

- How do we interpret these results in light of the family history?
- Was this information helpful?
- What if her results had showed a lower risk or a higher risk?

Case 4 - Glaucoma

- A man uses Navigenics and finds that he is at high risk for glaucoma. He shares the information with his parents and suggests they have the same testing.

- His parents agree. Taken in combination, their results indicate that man's father is not his biological father.

Case 5 – ADPKD

- A woman is diagnosed with autosomal dominant polycystic kidney disease (ADPKD), an adult onset condition with no preventative treatment. Genetic testing reveals the causative mutation.

- She wants to have her 10-year-old daughter tested for the mutation. Should this be done?

- What if she wanted to have her newborn test, or a pregnancy?

Case 6 – Whole genome sequencing

A patient with Charcot Marie Tooth disease has whole genome sequencing performed to determine the molecular cause of the condition. The causative mutation is found, which allows for discussion of recurrence risk at for testing of at-risk relatives.

What if:

- The patient is also found to have a *BRCA1* mutation
- She found to have a Huntington's disease expansion mutation
- Many variants of uncertain significance are found
- Years later, a disease association is determined for some of those variants

Important Issues

- Detection rate and residual risk
- Variants of uncertain significance
- Unanticipated results
- Duty to warn at risk relatives
- Don’t ignore family history
- Genetic discrimination
- Genetic testing of minors
- Clinical utility of DTC GWAS
- Informed consent

Databases & Resources

- OMIM (Online Mendelian Inheritance in Man) - http://www.ncbi.nlm.nih.gov/omim
- GeneTests – to be replaced by GTR – www.genetests.org
- National Society of Genetic Counselors – www.nsgc.org
- American College of Medical Genetics – www.acmg.net

Recommended Reading

- Challenges in the Clinical Application of Whole-genome Sequencing. (Lancet 2010; 375: 1749-51)
- Medical Ethics for the Genome World (J Mol Diagn. 2008; 10:377-82)
- Genomewide Association Studies and Assessment of the Risk of Disease (N Engl J Med 2010; 363: 166-76)