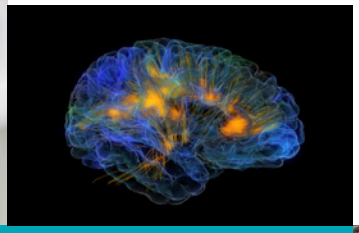

Genetic Results Interpretation

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UCSF Weill Institute for Neurosciences

Memory and Aging Center

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My patient pursued prior dementia genetic testing. What do his/her genetic results mean?

The interpretation of results from genetic testing varies. This handout is intended to be an overview of genetic result interpretation. This should not be used as a substitute for clinical judgment regarding your patient's genetic test results. For individualized interpretation of your patient's information, please consult with or refer your patient to a genetics professional with expertise in dementia.

Genetic test results are context-specific. Dementia genetic testing may be pursued for different reasons:

- For diagnostic purposes
- For predictive purposes

Genetic testing could also include dementia susceptibility testing. *APOE* genotyping is the only susceptibility test that is clinically available to determine Alzheimer's disease risk. *APOE* genotyping is not recommended [See "When Should I Order Genetic Testing?"].

Diagnostic testing

Diagnostic or symptomatic testing is pursued to confirm or exclude an underlying single gene cause of a person's dementia diagnosis. In this scenario, the family mutation is not already known prior to testing. The patient or family usually seeks genetic information in order to confirm a diagnosis and to quantify dementia risk for relatives. In most cases, identification of a single gene cause of dementia does not alter treatment or prognosis.

Predictive testing

Predictive or asymptomatic testing is pursued by people with no symptoms who wish to confirm or rule out the **known** single gene cause of dementia in the family. In this scenario, the family mutation must already be known. With few exceptions, if a familial mutation has not already been identified, the most appropriate person in whom to begin testing is a relative who has dementia, not your unaffected patient. Your patient's relative with dementia most suggestive of a single gene etiology should first pursue diagnostic genetic testing. If an unaffected person proceeds with genetic testing in the absence of first identifying the family mutation in an affected relative, uninformative or ambiguous results may arise. In this scenario, the person undergoing genetic testing should be counseled accordingly about the implications before the test is performed.

Susceptibility testing

Susceptibility testing could be pursued by healthy people or people with a dementia diagnosis. Susceptibility testing determines risk for dementia without single gene etiology. In this scenario, no prior knowledge of genetic information in the family is required. APOE genotyping is the only test that is clinically available to determine risk for Alzheimer's disease with complex or multifactorial inheritance. Dementia susceptibility testing is not recommended [See "When Should I Order Genetic Testing?"]. Interpretation of genetic test results is summarized here:

Type of genetic test	Purpose of genetic test	Interpretation of a positive result	Prior knowledge of a family member's genetic information	Recommended?
Diagnostic	To confirm or exclude a diagnosis in a person with dementia	Person has a genetic form of dementia	Not necessary	Depends on a person's clinical and family history [See "Family Health History"]
Predictive	To determine future risk of monogenic dementia in a healthy person	Person has very high risk to near certainty of developing dementia	Required	This is a personal choice. Among adults, the test is neither recommended for nor against. Not recommended for healthy minors.
Susceptibility	To determine future risk of multifactoral dementia	Results are not called positive (or negative). Typically, a risk genotype is either present or absent. If present, a healthy person has an increased risk to develop dementia, but it is not certain. This test should not be viewed as a supportive adjunct to clinical diagnosis in a person with dementia [See "When Should I Order Genetic Testing?"].	Not necessary	No

What are the possible outcomes of *diagnostic* genetic testing?

Genetic testing for diagnostic purposes occurs when a patient with dementia undergoes genetic testing to confirm or exclude a single gene cause of illness. No prior knowledge of a pathogenic mutation in the family is known. There are three possible results:

- Positive
- Negative
- Variant of uncertain significance

Positive result (person tested has dementia)

A positive result means that a pathogenic variant(s) was detected. This confirms that the patient's diagnosis has a single gene etiology. The use of this result to predict precise progression and/or duration of dementia is limited. The determination of risk for relatives to carry the same pathogenic variant(s) depends on the associated inheritance pattern.

Negative result (person tested has dementia)

A negative result means that a pathogenic variant(s) was not detected. The patient's diagnosis is not due to a disease-causing mutation in the gene(s) that were analyzed. The patient's diagnosis could still have a single gene etiology, depending on his/her clinical and family history [See "Family Health History"]. Typically, in the absence of a significant family history of a similar or related condition, the residual risk of a single gene etiology is greatly reduced. Residual risk depends on which genetic test platform was used (i.e. single-gene analysis, multi-gene panel, exome sequencing, etc.). It also depends on the sensitivity and specificity of the test and the degree of genetic heterogeneity of the inherited dementia. If the genetic test is comprehensive and highly accurate, a negative result virtually rules out an inherited dementia.

Variant of uncertain significance (person tested has dementia)

A variant of uncertain significance is an uninterpretable result. The test detected a genetic change, but it is unclear if the change represents a neutral variant that has nothing to do with dementia or if it is pathogenic. Information may or may not be available to facilitate interpretation. This result should not be used to guide medical management.

What are the possible outcomes of *predictive* genetic testing?

Genetic testing for predictive purposes occurs when a patient, who has no signs or symptoms of dementia, undergoes genetic testing to confirm or exclude the presence of a known pathogenic variant in an affected relative. Prior knowledge of the family's pathogenic mutation is required. The Huntington's disease protocol sets the minimum clinical standard for the provision of predictive genetic testing. If your patient had a known pathogenic mutation in the family, your patient's predictive genetic testing would yield one of two possible results:

- Positive
- Negative or true negative

If your asymptomatic patient pursued predictive genetic testing in the absence of a known pathogenic variant in the family there would be three possible results:

- Positive
- Uninformative negative
- Variant of uncertain significance

Positive result (person tested has no dementia)

A positive result means that the family's known pathogenic variant was detected. The patient has a very high risk to near certainty of developing the dementia in the family. This result seldom alters medical management, but rather may influence a person's future care, financial, and/or family planning. The ability of this result to predict precise age of onset, first symptom, progression, and/or duration of dementia is limited. The risk for relatives to carry the same pathogenic variant(s) depends on the inheritance pattern of the dementia.

Negative result (person tested has no dementia)

A negative result means that the family's known pathogenic variant was not detected. This is sometimes called a true negative result. This is different from a negative result arising from diagnostic testing (person tested has dementia). This is also different from an uninformative negative result (see below). With a true negative result, the patient's risk to develop the dementia in the family is no greater than it is for those in the general population. Offspring of the person with this result are not at increased risk to develop the dementia in the family. Genetic testing for offspring of the person with this result is unnecessary.

Uninformative negative (person tested has no dementia)

An uninformative negative result means a pathogenic variant was not detected among the gene(s) analyzed. In the absence of a known pathogenic mutation in an affected family member, this result cannot discriminate someone who has a true negative result from either (1) someone who has a pathogenic variant in a gene that was not included in the ordered test (wrong test was ordered) or (2) someone whose dementia-causing gene variant is not yet known due to limitations of disease knowledge and/or technology.

Variant of uncertain significance (person tested has no dementia)

A variant of uncertain significance is an uninterpretable result. Information may or may not be available to facilitate interpretation. This result cannot be used to determine if a person is at increased risk for dementia.

If *diagnostic* testing is appropriate for my patient, what principles of genetic counseling should be discussed?

Capacity to consent is an essential element of dementia genetic testing. The genetics of inherited dementia and implications for family members are complex and demand significant cognitive ability to understand. A family member or legally authorized representative should be present during the discussion of genetic testing prior to blood draw, the acquisition of signed informed consent, and the result disclosure. The decision to pursue genetic testing should be the patient's or representative's choice. Genetic testing outcomes rarely alter a patient's medical management. People usually choose genetic testing to identify other at-risk family members and to obtain information to guide future care, financial, and/or family planning. When the patient is cognitively impaired and the representative is making medical decisions on the patient's behalf, discussion about the family's reasons for testing should occur before any blood draw. In genetic forms of dementia, a representative who is the patient's blood relative and therefore at risk to inherit the pathogenic variant may have their own agenda for encouraging or discouraging genetic testing.

Topics to discuss prior to diagnostic genetic testing:

- Suspected genetic diagnosis and why it is being considered
- Review of family history
- Previous experience with the disease in the family
- Review of patient's current mood, mood disorder history, psychiatric hospitalizations, suicidal ideation and/or attempt(s)
- Review of patient's emotional and social support, including family, friends, community-based, or professional help
- Inheritance pattern of disease and risk to first-degree relatives [See "Family Health History"]
- Reduced penetrance and variable expressivity, if applicable [See "Family Health History"]
- Possible test results
- Whether results will be communicated to family members and how
- Possibility of predictive testing for family members
- Resources for additional information and disease support

If *predictive* testing is appropriate for my patient, are there recommended procedures by which to pursue testing?

Once a pathogenic variant is identified in your patient's affected family member, predictive genetic testing becomes available to your patient. Predictive testing should not be ordered on demand. Your patient should instead be encouraged to think carefully about the decision to test. Predictive testing requires considerable time, self-reflection, and self-care. Predictive testing is a multi-step process, and it should be provided in accordance with the Huntington's disease or HD protocol.

The HD protocol

The Huntington's disease or HD protocol is the gold standard of procedures surrounding genetic testing for adult-onset neurodegenerative conditions. The protocol aims to protect at-risk individuals by helping them make an informed decision about predictive genetic testing, while minimizing the risk of adverse outcome. The protocol is also meant to provide clinicians with a reference point about ethical and clinical dilemmas that arise from genetic testing for incurable dementia among people with no symptoms.

The protocol begins with genetic counseling. It recommends baseline neurologic and cognitive assessment as well as psychological evaluation, prior to blood draw. It recommends in-person result disclosure with a support person and genetic counseling after disclosure The protocol also states that predictive genetic testing should not be offered to asymptomatic minors. Additional guidelines about genetic testing of minors for adult-onset conditions also support the recommendation that asymptomatic minors should defer predictive testing until adulthood or an age at which they could provide appropriate informed consent.

The HD protocol is reviewed every 2 years to ensure that clinical recommendations reflect current practice and knowledge.

As at-risk individuals proceed through the HD protocol, they should consider all the benefits, harms, and limitations of predictive genetic testing. A positive predictive test result will not alter a person's medical care until the person becomes symptomatic. Knowledge of having a pathogenic mutation provides no insight about exact onset age or first symptom of dementia in an individual. No proven health and/or lifestyle behaviors are known to reduce risk of dementia. A minimum recommendation of a heart-healthy diet and regular cardiovascular exercise, as per American Heart Association guidelines is recommended.

Benefits of predictive testing:

- Alleviates anxiety, reduces uncertainty
- Informs future care, career, and financial planning
- Informs family planning
- Informs general health and lifestyle behaviors

Drawbacks of predictive testing:

- If mutation-positive
  - Introduces or exacerbates sadness, anxiety, hopelessness
  - Creates potential for "symptom-seeking" behavior
  - Creates potential for genetic discrimination
- If mutation-negative
  - Creates potential for "survivor's guilt"
  - Does not eliminate the illness experience if other at-risk relatives develop dementia

Limitations of predictive testing:

- Cannot predict onset age or first symptom of disease
- Does not change doctors' recommendations about diet, exercise or lifestyle habits

In which instances is predictive genetic testing not appropriate for my patient?

If your patient has no dementia diagnosis but seeks to confirm or exclude risk for the single gene form of dementia in the family, they must already know or be able to obtain information about the family's pathogenic gene variant.

If the family's pathogenic variant has not been previously identified, your patient should have an affected relative first pursue diagnostic genetic testing if warranted by the relative's clinical and family history of dementia [See "Family Health History"]. This should occur before your patient considers predictive genetic testing. Reasons not to begin predictive testing in your patient in the absence of a known pathogenic family mutation are several-fold:

- Symptoms overlap considerably across all dementia diagnoses. The identification of an affected relative's pathogenic variant would confirm the diagnosis and would clearly indicate which genetic test is appropriate for your patient. In the absence of confirmation, the relative's diagnosis could be inaccurate and your patient's pursuit of a genetic test could be misinformed.Your patient might unintentionally pursue dementia gene testing that is irrelevant to the family illness. This could lead to costly, unnecessary testing that is falsely reassuring. Your patient could still be at increased risk for the family's single gene form of dementia. Dementia due to a single gene cause is rare. However, familial clustering of dementia, particularly Alzheimer's disease, can occur frequently. Familial clustering of dementia occurs when multiple people in a family have dementia in a pattern not consistent with autosomal dominant inheritance. Only one or two relatives may be affected. Familial clustering of dementia is not due to a single gene cause.

  Familial clustering of dementia is due to complex or multifactorial inheritance. [See "Family Health History"]. People from families facing dementia due to multifactorial inheritance have a moderate risk for dementia. Genetic testing is not recommended. Genetic testing is usually only recommended people from families facing high risk for inherited dementia.

- Detection of gene variants of uncertain significance may complicate risk assessment. If genetic testing were to begin with your patient in the absence of a known pathogenic variant in the family, the testing strategy should be broad. Comprehensive testing would include analysis of numerous dementia-causing genes. Testing could identify variants of uncertain significance, the likelihood of which could exceed the likelihood of detecting a pathogenic variant. The interpretation of a gene variant of uncertain significance may be complicated by the variant's low frequency in the population, scant evidence of its clear association with dementia, and the absence of discernable signs of dementia in your patient.

What are the possible outcomes of APOE genotyping, and what is the interpretation of each?

There are six possible APOE genotype results [See Table 1]. About 60% of people with European ancestry have the ε3/ε3 genotype. About 2–3% of people of European ancestry have the ε4/ε4 genotype. Genotype frequencies vary among individuals of different ethnic backgrounds [See Table 2].

Data show that the likelihood of developing Alzheimer's disease increases with each copy of the ε4 allele [See ""When Should I Order Genetic Testing?] Between 18–35% of people with European ancestry with one ε4 allele will develop Alzheimer's disease by age 85 years. Between 51–60% of people of European ancestry with two ε4 alleles will be affected [See Table 3].

Although APOE gene testing is clinically available, it is not recommended [See "When Should I Order Genetic Testing?"].

Table 1

Genotype	Interpretation (Impact on Alzheimer's disease risk)
ε2/ ε2	Neutral to possibly protective*
ε2/ ε3	Neutral to possibly protective*
ε3/ ε3	Neutral
ε2/ ε4	Risk-conferring
ε3/ ε4	Risk-conferring
ε4/ ε4	Risk-conferring

* The effects of the genotype will vary, depending on a person's ethnic background.

Table 2

	Frequency (%)			
APOE genotype	European ancestry (Framingham, MA, USA)	Mexican-American ancestry	African-American ancestry	Japanese ancestry
ε2/ ε2	0.6	0.2	1.6	0.3
ε2/ ε3	13.1	6.7	17.7	6.1
ε3/ ε3	62.8	73.8	44.4	71.9
ε2/ ε4	1.7	0.7	5.3	0.7
ε3/ ε4	18.8	17.3	27.2	19.3
ε4/ ε4	3.0	1.1	3.8	1.7

[Eichner 2002]

Table 3

	Alzheimer's risk by age 85 years (%)	
	Men	Women
Without regard to genotype	10-11	14-17
ε2/ ε2 or ε2/ ε3	4-5	6-8
ε3/ ε3	7-8	10-12
ε2/ ε4	18-20	27-31
ε3/ ε4	22-23	30-35
ε4/ ε4	51-52	60-68

[Genin 2011]

What is genetic discrimination, and how best could I address my patient's concerns about it?

Genetic discrimination is the prejudicial treatment of a person because they have a genetic mutation that causes or increases risk of disease.

The Genetic Information Nondiscrimination Act (GINA) of 2008 is designed to protect people against genetic discrimination in health insurance and employment. Some states have laws augmenting GINA protections.

GINA and health insurance

GINA makes it illegal for health insurers to:

- Request, require, or use genetic information to make decisions about eligibility, premiums, and coverage terms
- Consider a test a pre-existing condition

GINA and employment

GINA makes it illegal for employers to:

- Request, require, or use genetic information to make decisions about hiring, firing, and promotion
- Limit, segregate, or otherwise mistreat an employee

What is not covered by GINA?

- Life, long-term care, and long-term disability insurance
- People with symptoms due to a genetic cause
- People in the US military or veterans receiving health care through the Veterans Health Administration.

You should discuss GINA and similar state laws with your patient before predictive genetic testing is ordered. For more information, please see links below or consult a genetics professional.

- Gina Help: GINAhelp.org
- National Human Genome Research Institute: genome.gov
- Genome Statute and Legislation Database: genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm