The Genetics of Alzheimer Disease

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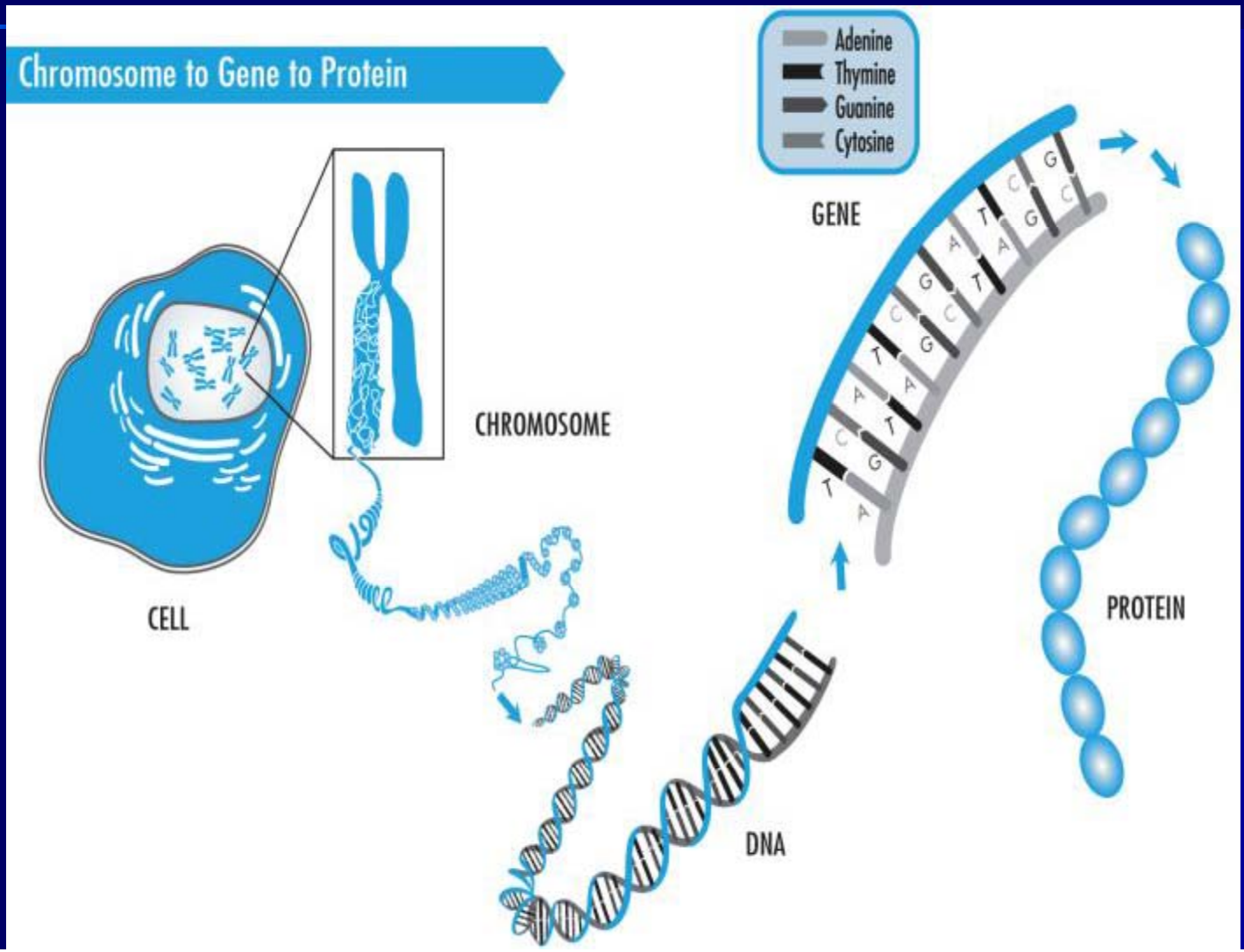
Overview

- Risk factors for Alzheimer disease (AD)
- Basic genetics
- Types of AD
- Genes involved in AD
- Genetic testing protocols

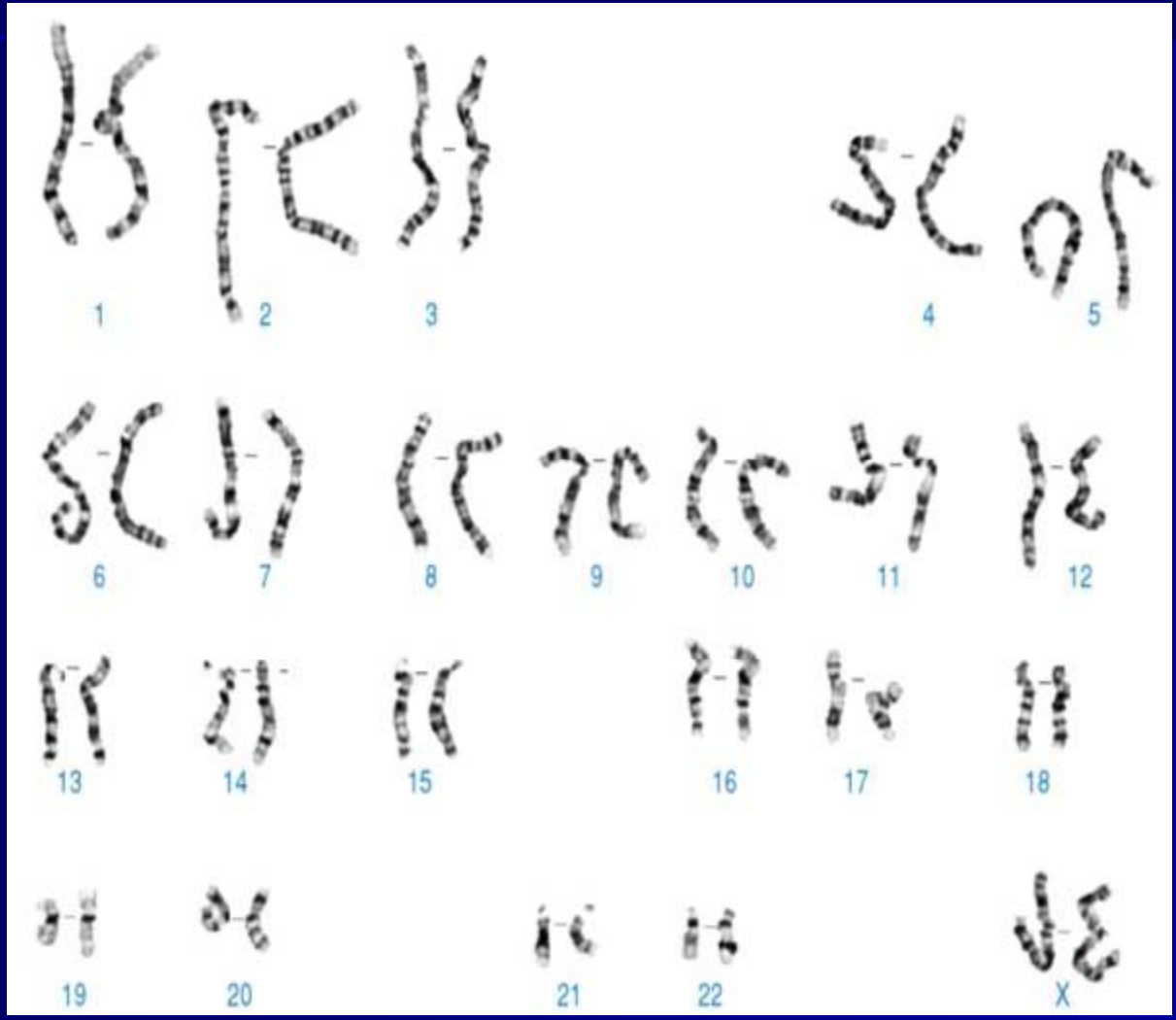
Known Risk Factors

- Age
- Head injury
- Family history

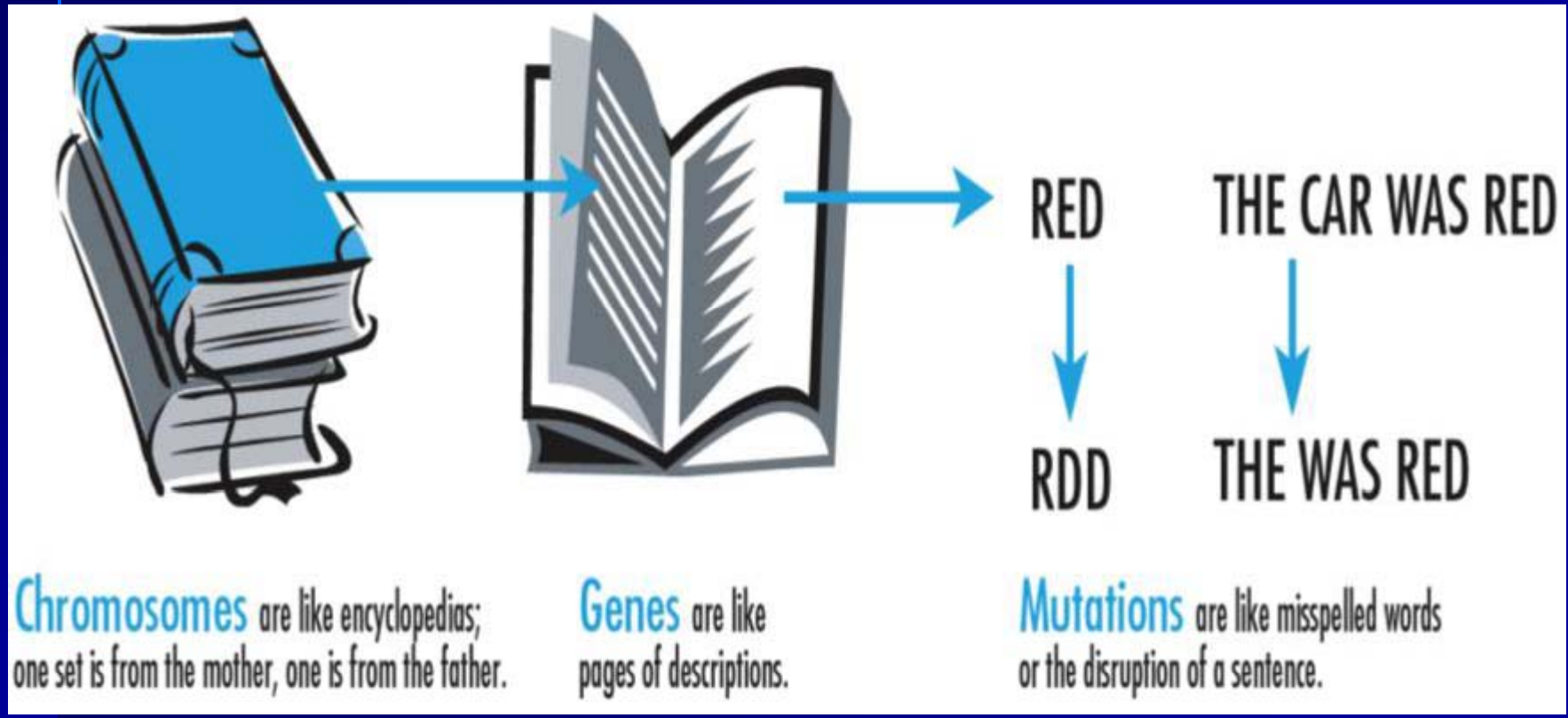
Basic Genetics



Basic Genetics



Basic Genetics



Types of AD

- Heritability
  - Sporadic versus familial AD
    - Number of affected individuals within a family
- Age of onset
  - Early onset versus late onset
    - 60-65 years is boundary

Types of AD

	Early onset AD (EOAD)	**Late onset AD (LOAD)**
Familial	Early onset familial AD	Late onset familial AD
Sporadic	Early onset sporadic AD	Late onset sporadic AD

Types of AD

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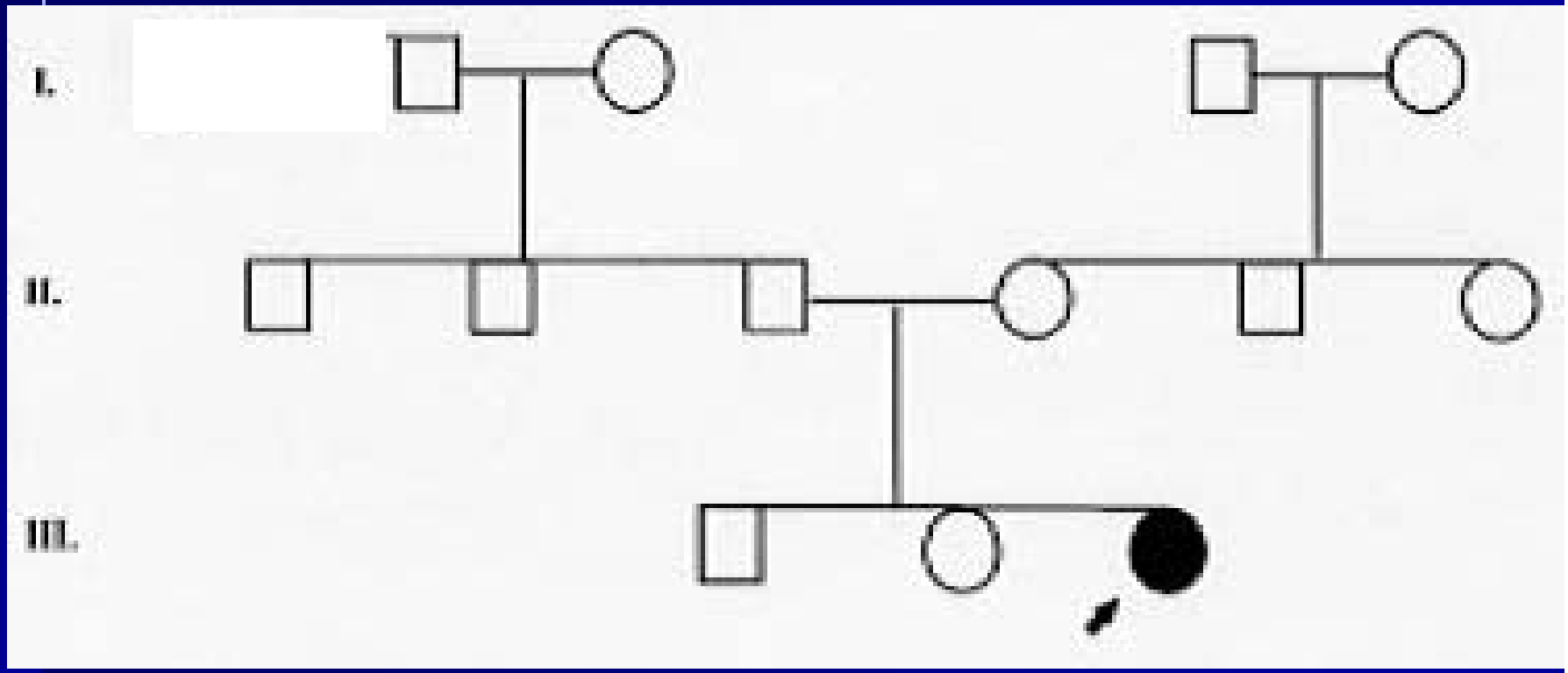
Sporadic	*Early onset sporadic AD*	*Late onset sporadic AD*

Sporadic AD



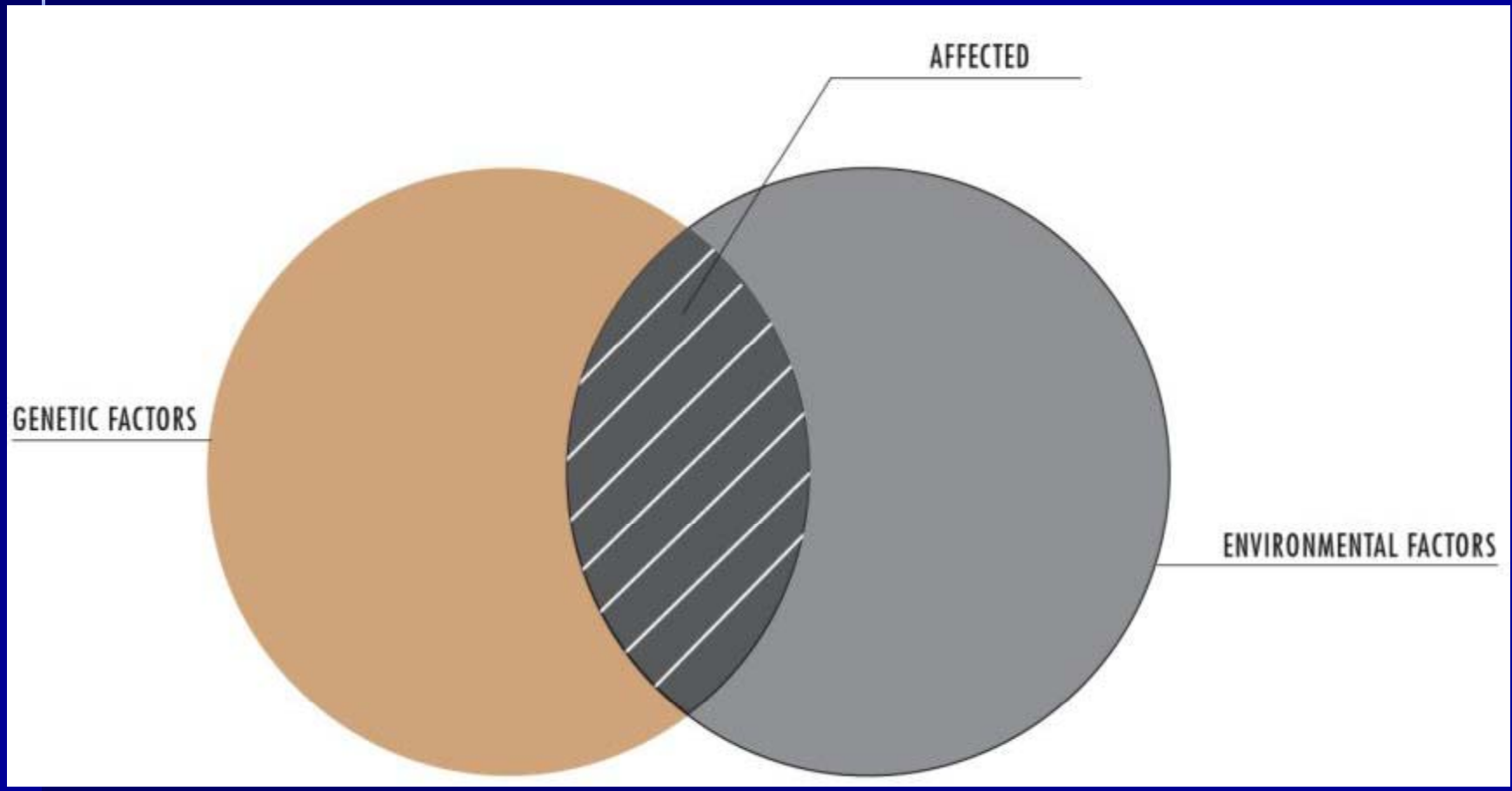
No AD

AD

Sporadic AD

- 75% of AD
- “Unpredictable”
- Typically late onset (60+ years)
- Cause is usually unknown:
  - Aging
  - Environmental factors
  - Susceptibility genes

Sporadic AD



Sporadic AD

- Is the risk of developing AD increased for family members?

Sporadic AD

- Is the risk of developing AD increased for family members?
- YES! Research shows there is a higher chance of family members developing AD
  - Probably up to 25% risk for 1st degree relatives

Sporadic AD

- Is the risk of developing AD increased for family members?
- Risk to 1st degree relative (parent, child, sibling) is probably up to 25%
- Lifetime risk to general population is about 10%

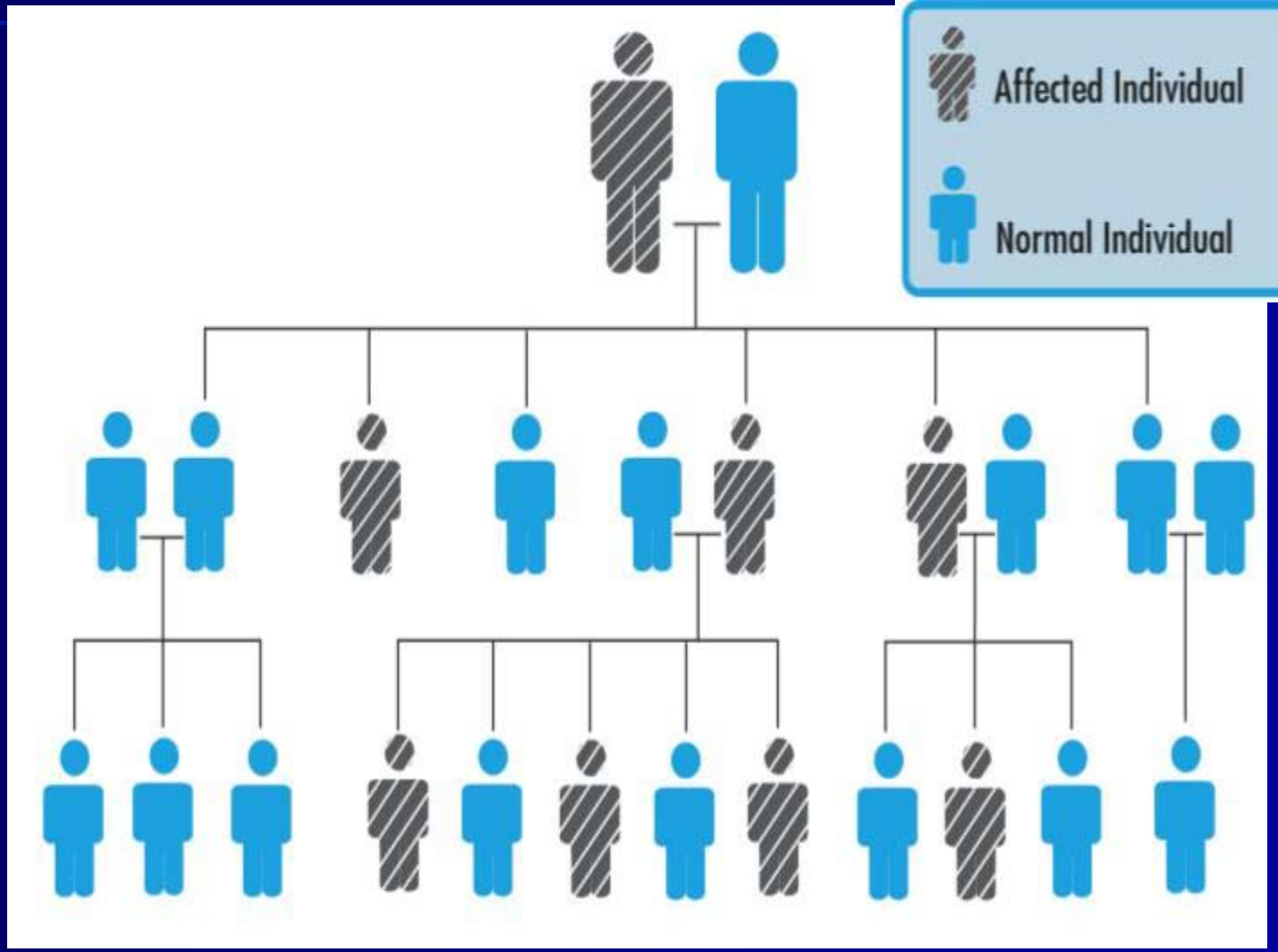
Types of AD

	Early onset AD (EOAD)	**Late onset AD (LOAD)**
Familial	*Early onset familial AD*	*Late onset familial AD*
Sporadic	Early onset sporadic AD	Late onset sporadic AD

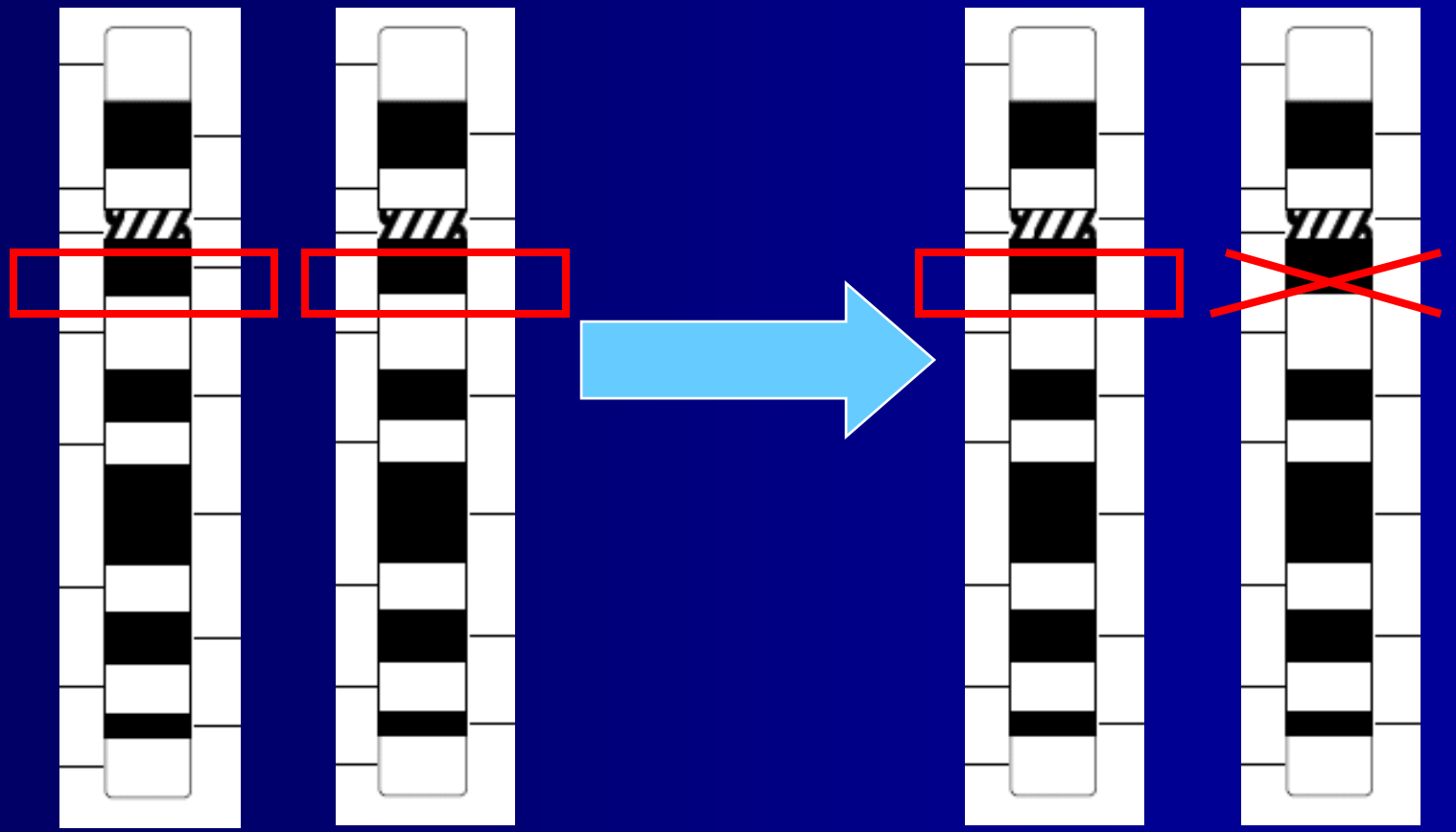
Familial AD

- 25% of AD
  - 2+ individuals with AD in a family
  - 95% of familial cases are late onset
- Risk may be increased above 25% for individuals with 2+ closely related family members

Familial AD



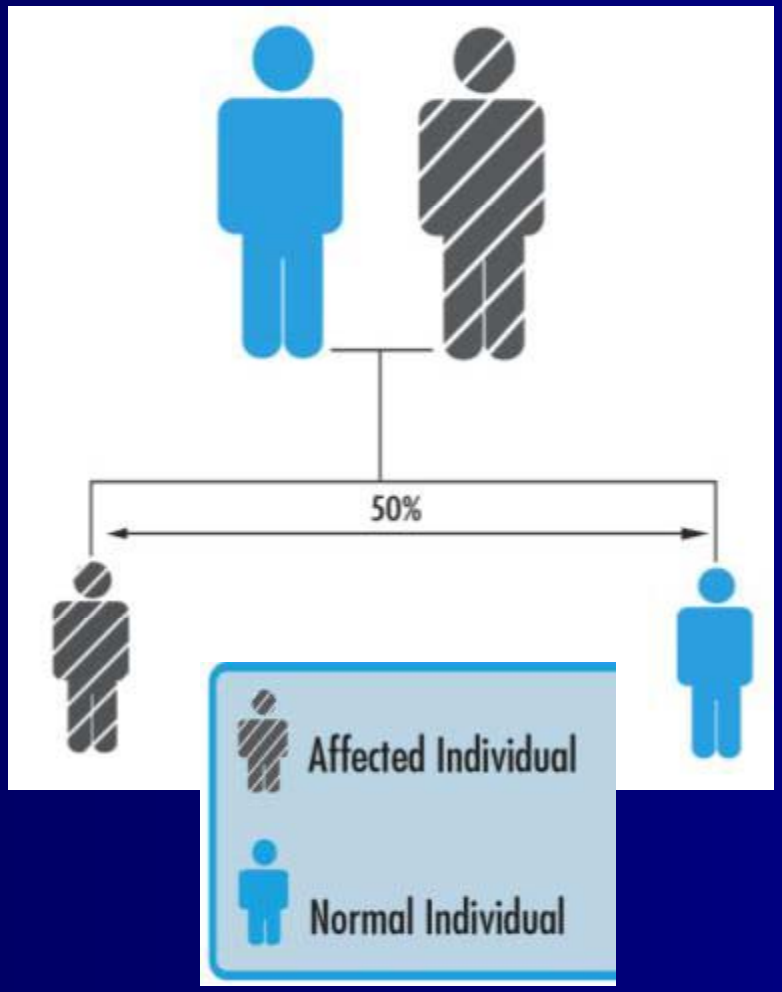
Autosomal Dominant Inheritance



Autosomal Dominant Inheritance

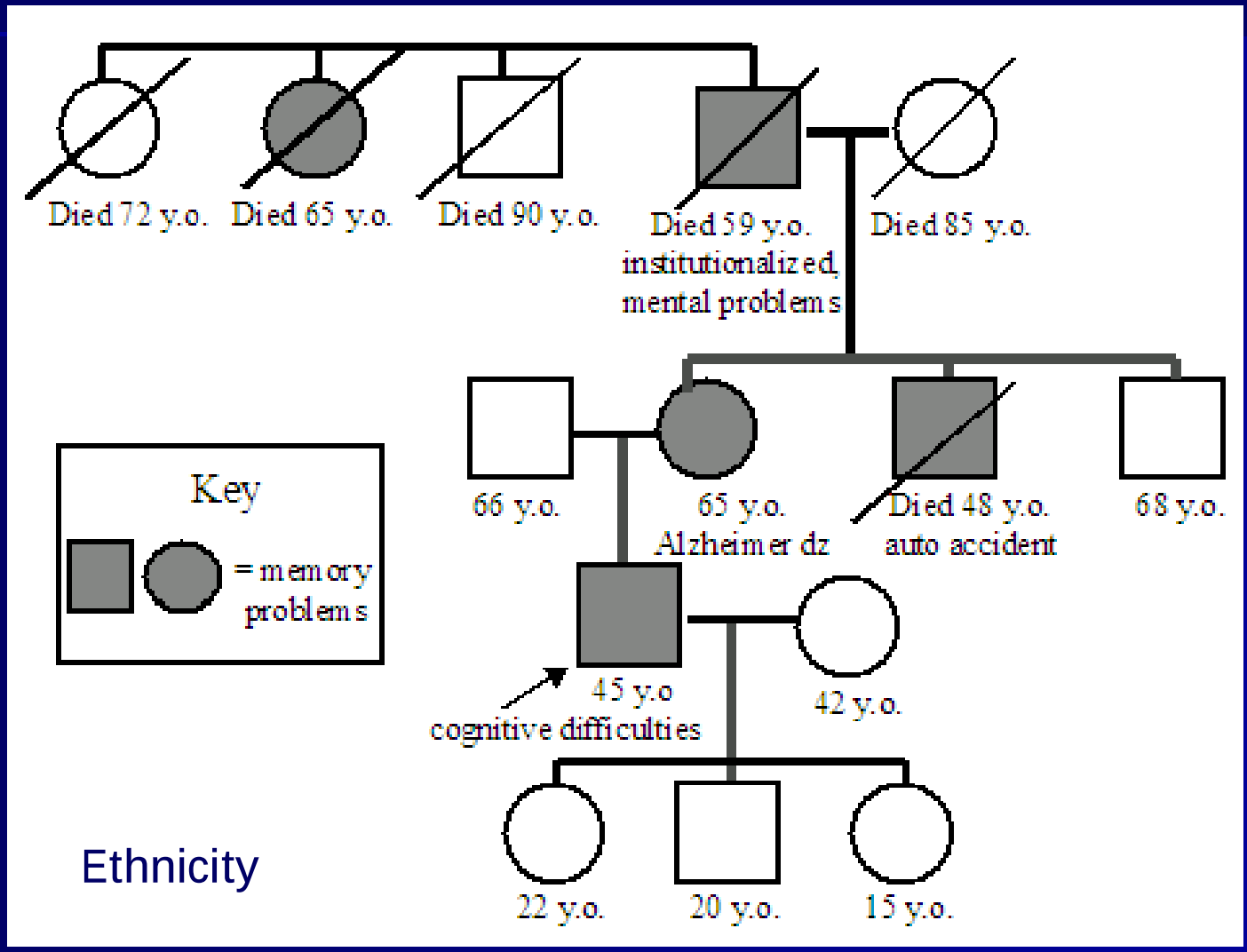
- Multiple individuals affected in EACH generation
- Males and females equally likely to be affected
- Male to male transmission

Autosomal Dominant Inheritance



- Chance of inheriting mutation: 50% (1 in 2) for EACH child
- AD WILL likely develop

Family History



Ethnicity

Autosomal Dominant Inheritance

- Family history may appear negative:
  - Undiagnosed in other family members
  - Early death of affected relatives
  - Small family
  - Late onset of symptoms
  - Gene change was NOT inherited from a parent
    - New change that occurred (very rare)

Types of AD

	Early onset AD (EOAD)	**Late onset AD (LOAD)**
Familial	*Early onset familial AD*	Late onset familial AD
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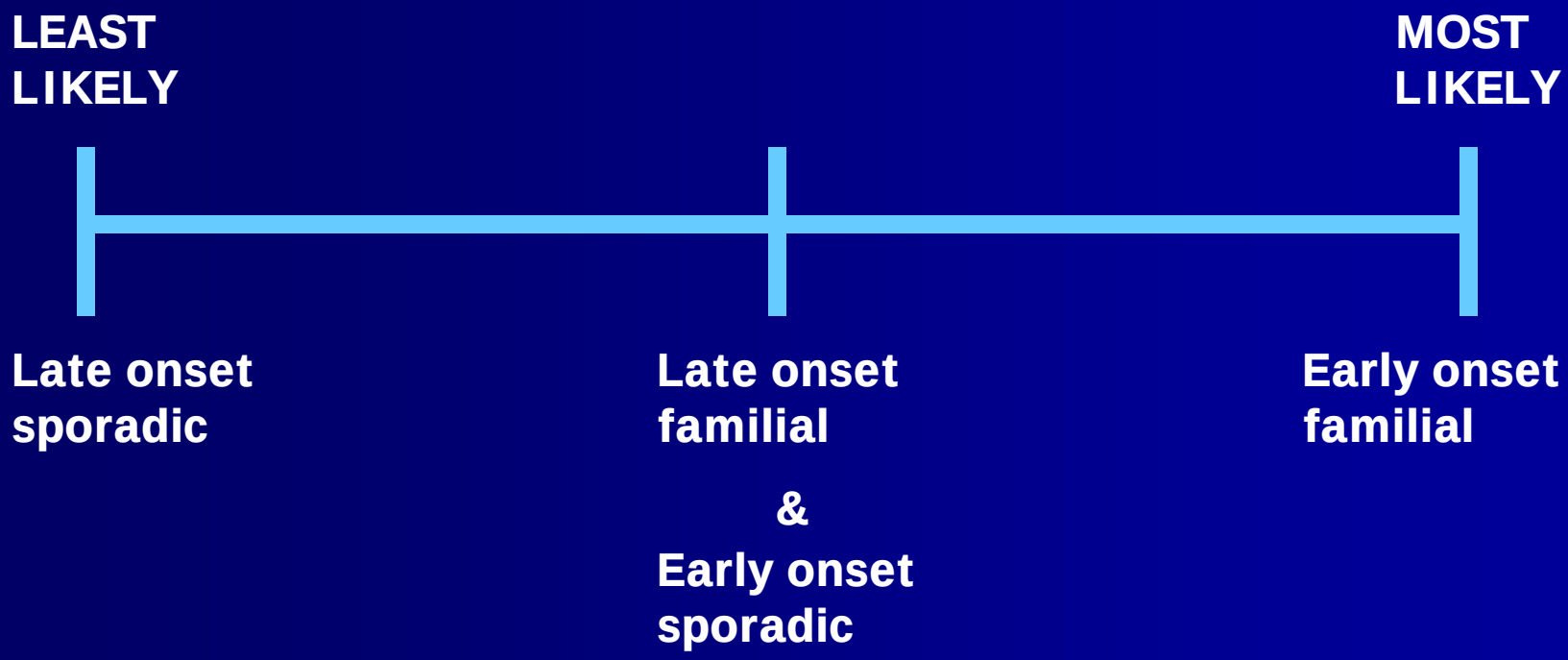
Early Onset AD

- Onset before 60 years of age
- More likely to have a genetic basis
- 5% of all AD
- 40% of these individuals do not have affected relatives
  - Up to 5% may have genetic cause that can be identified

Early Onset Familial AD

- Likelihood of identifying a gene mutation: 30-80%
- Clinical signs: similar to sporadic AD

Likelihood of Identifying a Specific Genetic Cause



Early onset, familial AD (EOFAD) cases are most likely to have a genetic cause that can be identified!

Genes Involved in AD

- 1 susceptibility gene
  - Apolipoprotein E (APOE)
- 3 causal genes:
  - Presenilin 1 (PSEN1)
  - Presenilin 2 (PSEN2)
  - Amyloid precursor protein (APP)

APOE

- Chromosome 19
- Susceptibility gene for late onset AD
- 3 variations of gene (labeled APOE 2, APOE 3, APOE 4)
- APOE2 may provide some protection
  - AD can still develop
- APOE4 may increase susceptibility
  - Not everyone will develop AD

APOE4

- 40% of affected individuals do NOT have APOE4
  - Its absence does not rule out diagnosis of AD
- Two copies of APOE4 found in:
  - 1% healthy individuals
  - 19% affected individuals

APOE

- Usefulness of testing is unclear at this time
- Testing may not be particularly helpful for individuals with AD
- Testing is NOT recommended for individuals without AD
  - Results cannot determine whether AD will develop

PSEN1

- Chromosome 14
- 30-70% of EOFAD
- Onset: <65 years (average: 40-50)
- Other features: seizures, myoclonus, language problems
- 150 different gene mutations
- If mutation is present, AD will develop

PSEN2

- Chromosome 1
- 5% of EOFAD
- Onset: 40-75
- Few individuals reported with familial mutation and no signs of AD
- 10 mutations
- Ethnicity: Volga German, Italian, Spanish

APP

- Chromosome 21
- 10-15% of EOFAD
- Onset: 40-60 years
- 25 gene mutations identified

Physicians: When to Consider Testing

- Patient with:
  - Early onset AD
  - Multiple family members with AD consistent with autosomal dominant inheritance

Physicians: When to Consider Testing

- Sporadic, late onset AD
  - APOE available, but not often used
- Sporadic, early onset AD or familial, late onset AD
  - PSEN1, PSEN2, APP
- Familial, early onset AD
  - Ideal for testing
  - PSEN1, PSEN2, APP

Patients and Families: When to Consider Testing

- The best way to determine if gene testing is an option is to speak with a genetic counselor or your physician

Testing Availability

- Athena Diagnostics
  - APOE: $500
  - PSEN1: $1700
  - PSEN2: $1500
  - APP: $1000
  - Early onset, familial AD panel: $3700
    - PSEN1, PSEN2, APP
- Cost is typically lower, depending on insurance plan

Limitations of Testing

- It is likely there are unknown genes that cause AD
- Gene testing cannot determine age of onset or severity

Who Seeks Genetic Counseling/Testing?

- Individuals diagnosed with AD (or family members of individual)
  - Diagnostic testing
- Individuals without symptoms of AD, who have a family history of AD
  - Predictive or pre-symptomatic testing

Diagnostic Genetic Testing

- Genetic counseling may be beneficial prior to testing and is recommended

Test Results for Diagnostic Testing

- Negative
- Positive
- Inconclusive

Negative Test Result

- Does NOT rule out a hereditary form of dementia in the family
  - Possibility of other unknown genes
- No testing recommended for unaffected relatives
- Consider family studies

Positive Test Result

- Cause of AD is identified
- Testing is available to unaffected relatives at reduced rate
  - Predictive testing protocol

Inconclusive Test Result

- A “change” was identified within the gene, but it cannot be interpreted
  - Disease-causing
  - Benign
- Research and family studies may be beneficial

Predictive Testing

- Reasons for predictive testing (at-risk family members):
  - Family planning
  - Reproductive decisions
  - Life and financial planning
  - Eliminate uncertainty

Caution

- Affected relative MUST be tested first, before predictive testing is an option for unaffected relatives
- Genetic testing for AD is not generally appropriate for unaffected children (individuals <18 years of age)

Predictive Testing Protocol

- Neurological exam
  - Are symptoms present?
- Pre-test genetic counseling
- Additional counseling with psychiatrist, therapist, etc.
- Blood draw
- Genetic counseling follow up to discuss test results

Discussion

- Why test now?
- What will you do with this information?
- Change in relationships, family dynamics
- Psychological impact
- Testing limitations
- Genetic discrimination

Test Results for Predictive Testing

- Negative: gene mutation identified in family is not present
  - Risk reduced to that of general population
- Positive: same gene mutation identified
  - AD will develop

Pros

- May find cause
- Clarify risk for family members
  - Eliminate some concern about risk to family
- Planning: financial, family, life

Cons

- Results do not change outcome or treatment: no cure
- Costly
- Concerns about insurance, employment, relationships
- Cannot determine age of onset, severity
- “Inconclusive” result

Other Points

- DNA banking of affected individual
  - Useful for future genetic testing
- Prenatal diagnosis and reproductive options are available

Conclusion

- Gene testing is available for some families with AD
  - Early onset, familial AD is ideal for testing
- Genetic counseling is available to:
  - Help determine if genetic testing is right for patient and the family
  - Clarify the risk of AD for family
- It is likely there are other genes that cause AD for which testing may be available in the future

Contact Information

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