Genetic Testing for Patients with Autism Spectrum Disorders

2024 SFASA-Stanford Bay Area Adult Autism/DD Conference

Jon Bernstein MD, PhD
Stanford School of Medicine

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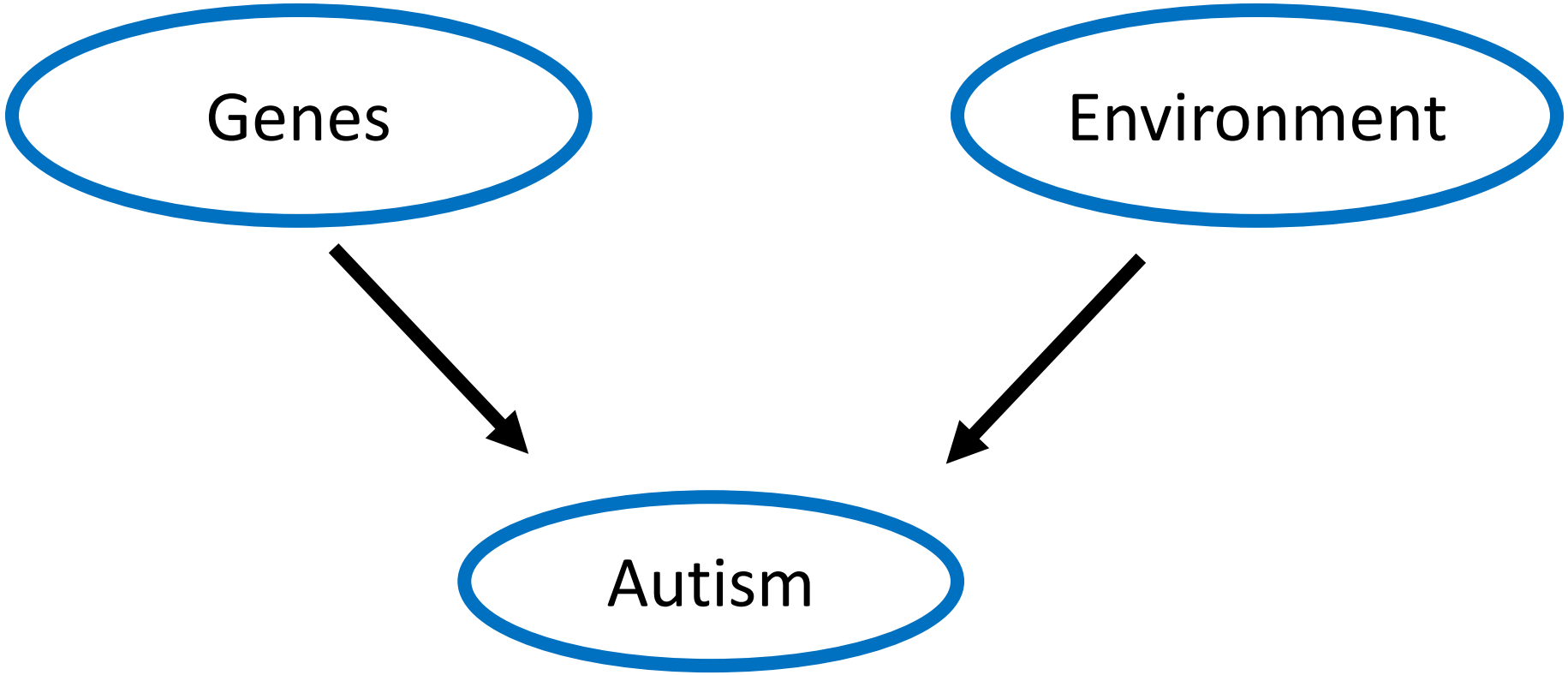
Autism and Genetics

Autism is defined by observable aspects of learning and behavior



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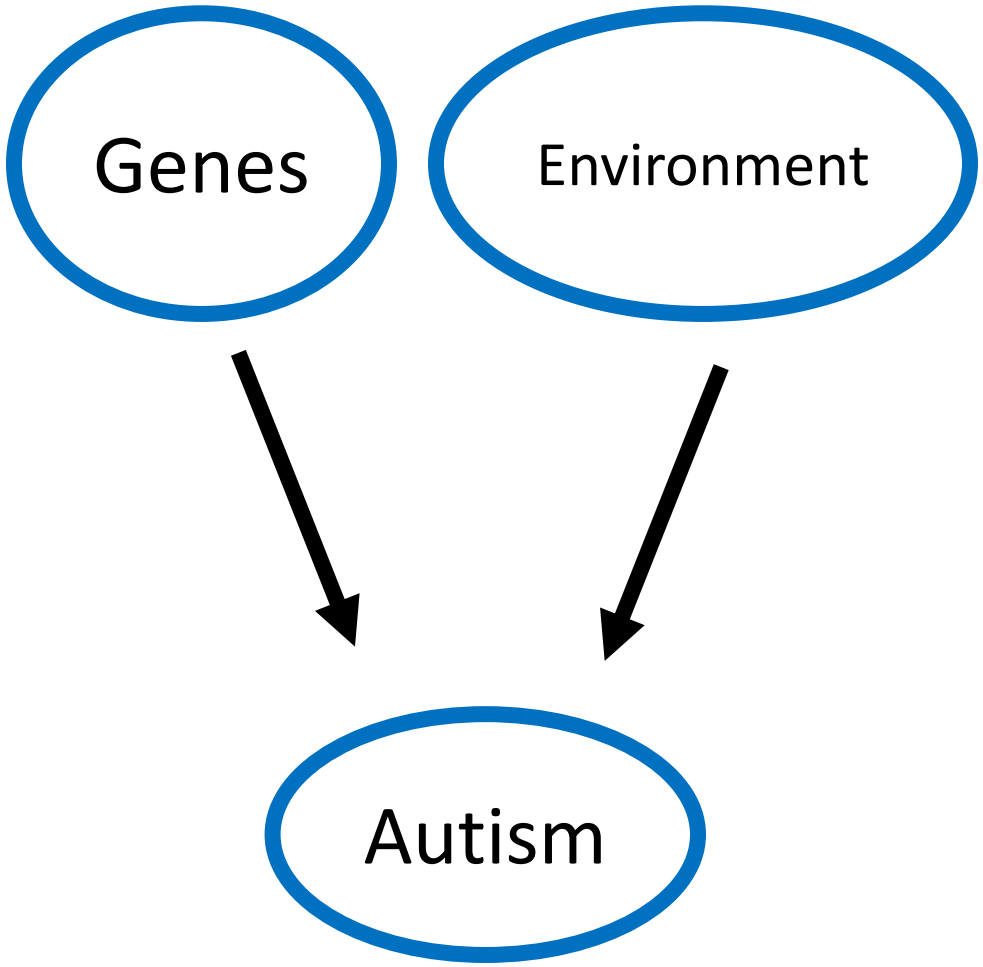
Genetic Testing for Autism Spectrum Disorders

- Autism results from a combination of genetic and environmental factors
  - The relative contributions can vary substantially between individuals
  - Genetic causes or contributors to autism risk can be of varying strength
    - One large genetic factor can largely explain some cases of autism
    - Weaker genetic factors when combined with each other explain many cases of autism
- At present genetic testing is most effective in identifying large/strong genetic factors related to autism



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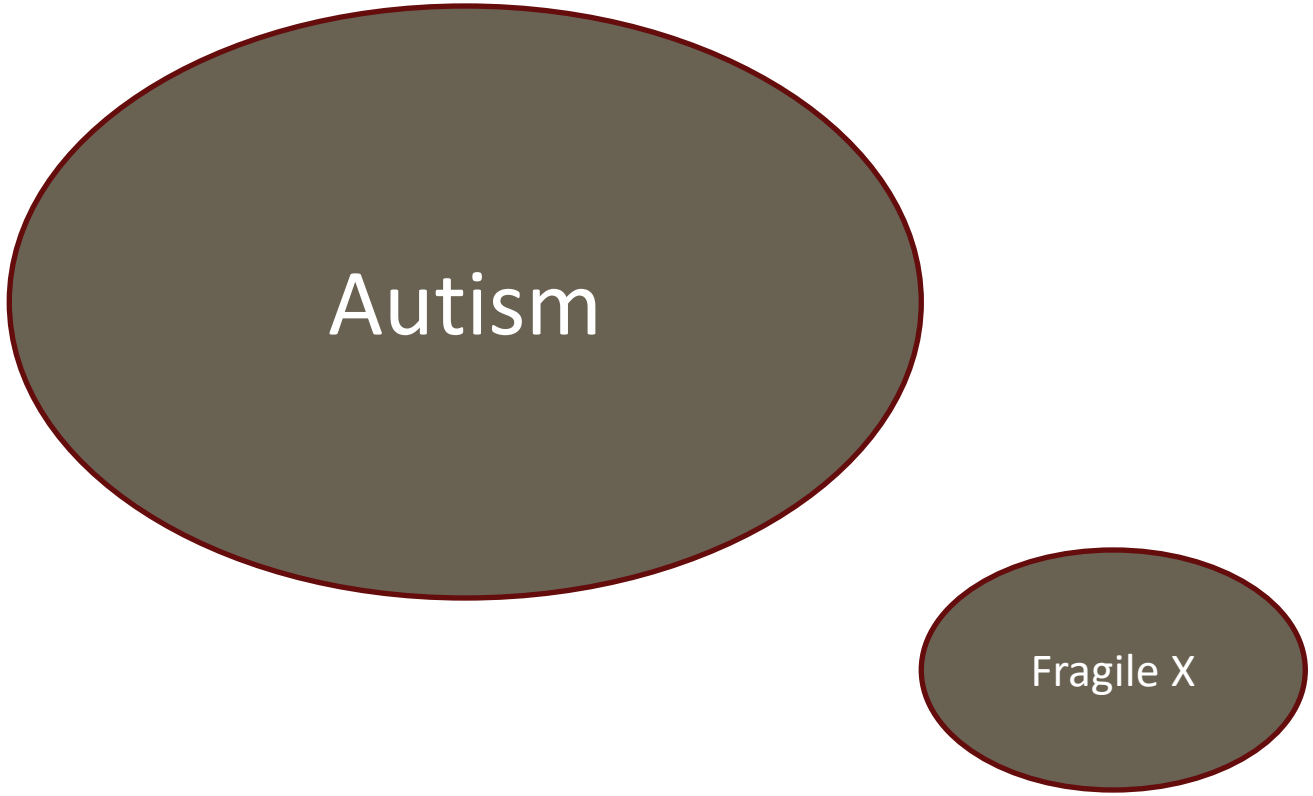
The Autism Spectrum



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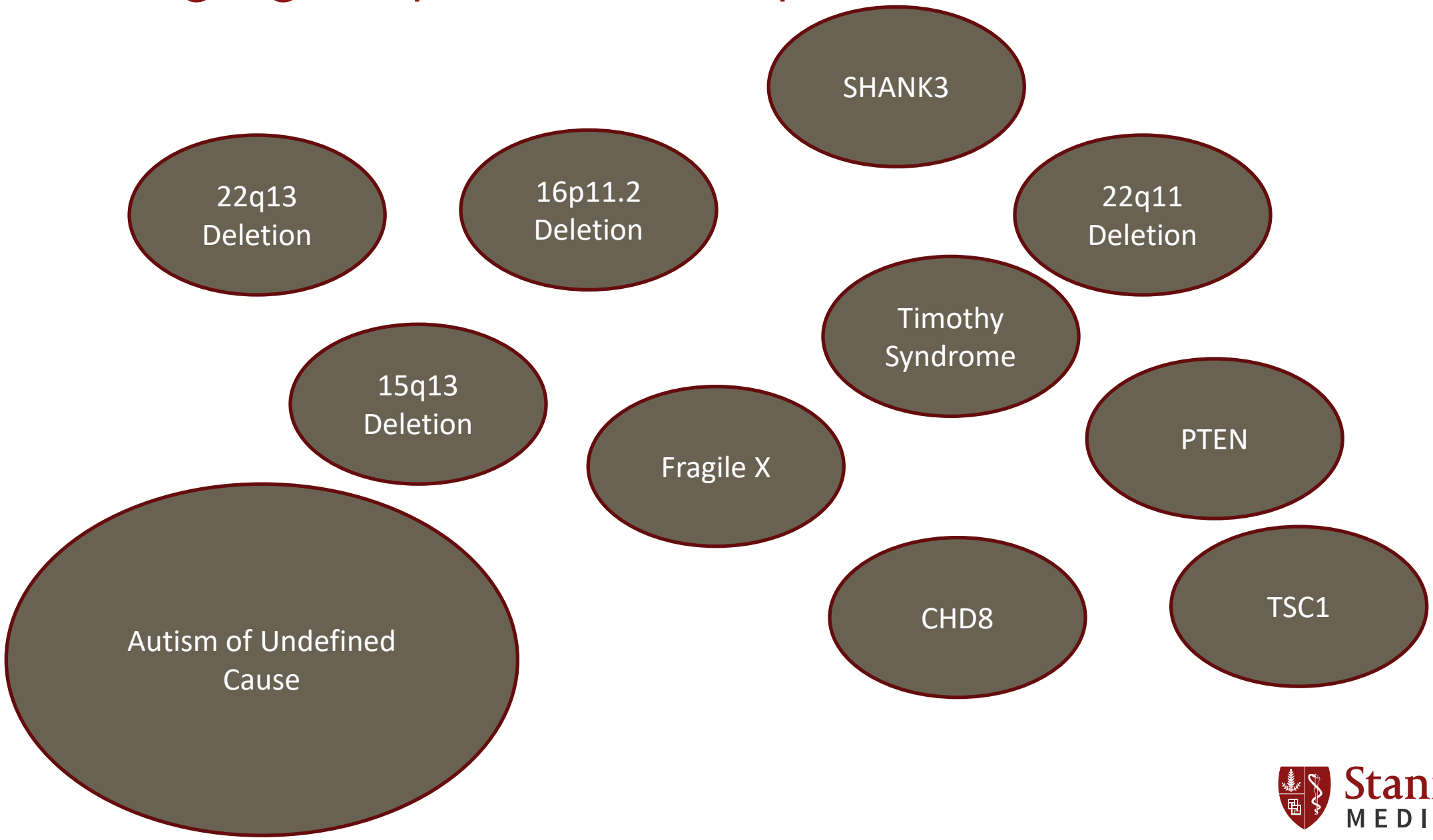
An emerging map of autism spectrum disorders



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Autism care without a genetic diagnosis

- **Management** may include
  - Behavioral therapy
  - Psychiatric care
  - Educational planning
  - Financial and legal planning
  - Vocational training
  - Identification of residential living options
  - Accessing resources

- **Prognosis**
  - Dependent on severity and response to treatment

- **Genetic** counseling
  - Familial recurrence risk
    - The risk to the male sibling of an affected male is commonly estimated as 7-14% for classic autism. The risk of an autism spectrum disorder is higher.
    - If there are two affected siblings in a family the risk to the next child may be approximately 35%.
  - Option to participate in patient and family support groups

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Autism care with a genetic diagnosis

- **Management** may include
  - Behavioral therapy
  - Psychiatric care
  - Educational planning
  - Financial and legal planning
  - Vocational training
  - Identification of residential living options
  - Accessing resources

  - Monitoring for specific symptoms
  - Screening for medical and developmental issues

  - Eligibility for clinical trials

- **Prognosis**
  - Dependent on the specific genetic cause as well as other factors

- **Genetic** counseling
  - Familial recurrence risk
    - Can be estimated precisely, sometimes <1%, less commonly 25% or up to 50%
  - Option to participate in patient and family support groups

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Motivations for Genetic Testing

- Guide management
- Inform prognosis
- Inform recurrence risk counseling

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Yield of testing for autism with intellectual disability

- DNA Microarray testing for DNA deletions or duplications
  - Up to approximately 10%
- Whole genome sequencing
  - With current methods, up to approximately 30% in the presence of intellectual disability
    - Fragile X syndrome, specialized testing method, approximately 1%

- Yield in high functioning autism is significantly lower

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Findings suggestive of an identifiable genetic cause of autism

- Family history suggesting X-linked or other monogenic inheritance pattern
- Intellectual disability
- Microcephaly
- Macrocephaly
- Overgrowth
- Atypical physical features
- Marked developmental regression
- Vascular or pigmented birthmarks
- Multi-system disease

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Utility of Genetic Testing

- Guiding care
  - Increasing confidence in current care
- Predicting the future
  - Often less informative in older children and adults
- Family planning

- Reducing uncertainty
- Relief from feelings of responsibility

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The process of genetic testing

1. Pre-test counseling and consent for testing
2. Insurance benefits verification
3. Sample collection
   - Blood or saliva samples most commonly used
4. Testing
5. Post-test counseling and disclosure of results
   - Screening recommendations
   - Changes in management
   - Updated recurrence risk counseling

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Insurance coverage for genetic testing

- Varies between plans and payors
  - May not cover any testing
  - May only cover certain types of tests
  - May only cover if ordered in a specific sequence or by a particular type of specialist

- Options if not covered or incompletely covered
  - Testing companies that limit out of pocket expenses
  - Can consider research testing

- Recent trends are towards lower costs overall and increased coverage of testing by health plans

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Pre-test counseling

- Genetic testing may identify
  - A positive result explaining a patient's symptoms
  - A negative result
  - A result of unclear significance that potentially may be clarified by testing additional family members
  - A positive result related to a disease unrelated to the indication for testing
  - Some types of genetic testing can reveal that a family's structure is different than currently believed

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Secondary or incidental findings

- Some types of testing can identify genetic changes that are not associated with the reason testing was performed
  - Risk for a specific disease
    - Cancer, cardiomyopathy, arrhythmia

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Methods of Genetic Testing

- Cytogenetic testing
  - Chromosome analysis
  - DNA Microarray

- Molecular genetic testing
  - Assessing for trinucleotide repeat expansions (Fragile X)
  - *DNA sequencing*
    - Gene Panels
    - Whole exome/genome sequencing

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How long does testing take

- Usually, 2-4 weeks for routine testing such as fragile X or DNA microarray studies
- Sequencing based tests can be expedited, but are routinely completed in 2-8 weeks

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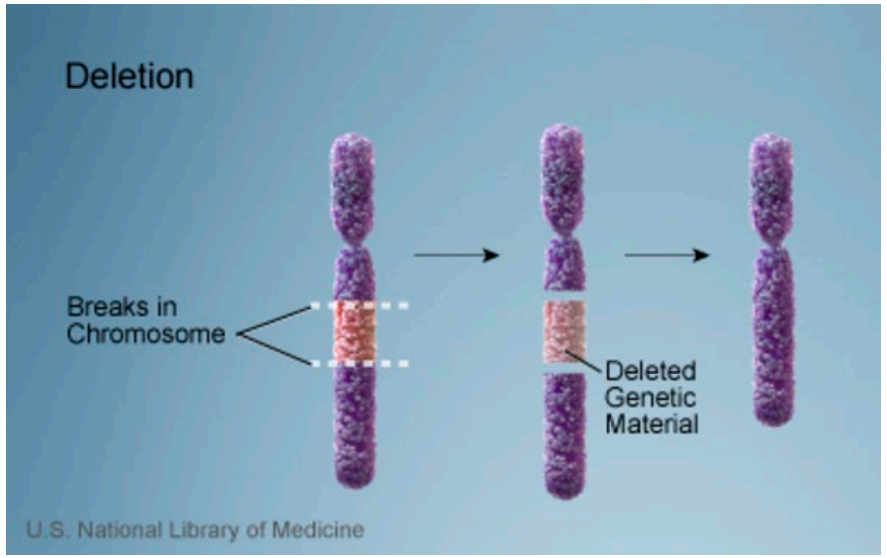
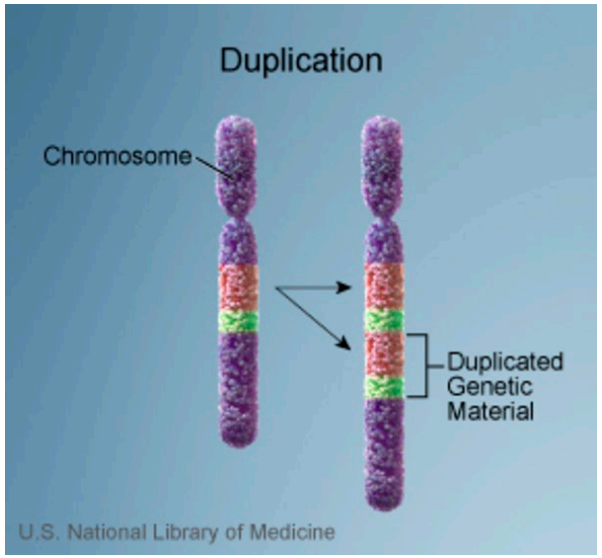
Example 2

- A 19-year-old female with a history of high functioning autism has developed unexplained agitation, distress and is no longer able to perform several tasks she was previously able to. DNA microarray testing is performed.





Source: MedlinePlus, National Library of Medicine.

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Example 2

- The results of testing identify the absence of 1 copy of the *SHANK3* gene on chromosome 22. This finding is consistent with a diagnosis of Phelan-McDermid syndrome.
  - Management
    - Screening evidence of seizures
    - Ultrasound of kidneys (less likely in this patient)
    - Cardiovascular evaluation
    - Screening for lymphedema (less likely in this patient)
    - Consultation with expert clinicians regarding psychiatric symptoms in Phelan-McDermid syndrome
    - Eligibility for clinical trials
  - Prognosis
    - Increased risk of seizures, lymphedema and psychiatric conditions
  - Genetic counseling
    - Option to test parents for the gene deletion.
    - Recurrence risk often low for siblings of an affected individual, but possibly as high as 50%
    - Option to be involved with patient and family groups

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Example 3

- 28-year-old female with a history of autism, intellectual disability and a large head circumference has previously had fragile X testing and a DNA microarray. Additional genetic testing is performed by sequencing.

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Example 3

- Genetic testing identified a disease-causing change in the *PTEN* gene.
  - Management
    - Cancer screening
    - Eligibility for clinical trials
  - Prognosis
    - Increased risk of cancer in patient and potentially in other family members if the genetic change were inherited
  - Genetic counseling
    - Option to test parents for the gene mutation.
    - Option to be involved with patient and family groups.
    - Option to pursue clinical trials

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Example 4

- 2-year-old typically developing girl with a family history of high functioning autism in her older brother. DNA microarray identifies a deletion on the long arm of chromosome 15 at 15q13.3.

- The deletion is also present in her brother, her mother and her maternal grandfather

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Example 4

- Genetic testing identified a deletion on chromosome 15 at 15q13.3
- Management
  - Consider echocardiogram
  - Consider renal ultrasound
  - Eye exam

  - Eligibility for clinical trials

  - Prognosis
    - Increased risk for neurodevelopmental symptoms

  - Genetic counseling
    - Individuals with the deletion have a 50% risk of passing it on to each of any offspring, however, the associated risk of symptoms is less than this

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Summary

- For patients with autism and intellectual disability there is an appreciable likelihood that a single genetic change may explain the diagnosis
  - Commonly utilized testing includes Whole exome sequencing, DNA microarray and fragile X testing
- Genetic diagnoses can have implications for management, prognosis and counseling and in some cases for the health of other family members
- The utility of genetic testing may vary from patient to patient and family to family
- The utility cannot be fully defined until testing results are available

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