Genetic Testing in the US: The GeneTests Perspective

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GENETests

- What GeneTests is
- What GeneTests is not
- International component
- Future directions

www.genetests.org

Information resource for healthcare providers to help integrate genetic services into patient care

Located at
University of Washington
Seattle, WA

Funded by
National Institutes of Health

- ***GeneReviews*: "User manual" for genetic testing for specific diseases**
  - >400 *GeneReviews*
  - One new Review added each week
- **Laboratory Directory: "Yellow Pages" of genetics labs**
  - ~615 Clinical and research laboratories
  - ~1430 Inherited diseases
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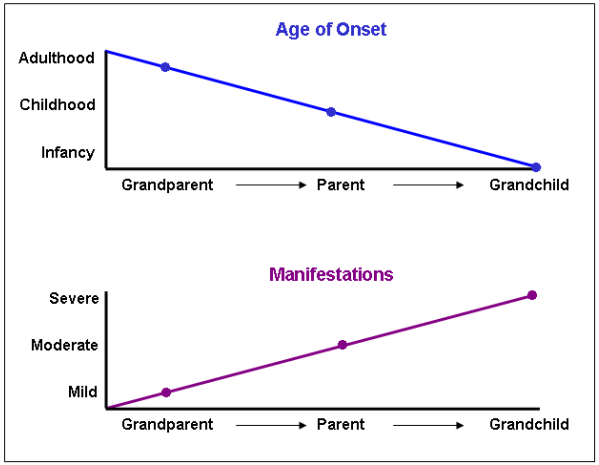
anticipation: The tendency in certain genetic disorders for individuals in successive generations to present at an earlier age and/or with more severe manifestations; often observed in disorders resulting from the expression of a **trinucleotide repeat mutation** that tends to increase in size and have a more significant effect when passed from one generation to the next

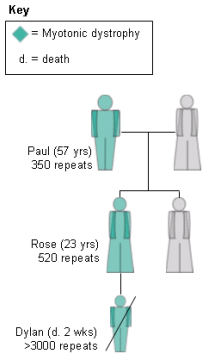
Case Example (anticipation): Myotonic dystrophy

Paul is a 57-year-old man with myotonic dystrophy, a neuromuscular disorder caused by a trinucleotide repeat mutation inherited in an autosomal dominant manner. Paul noticed muscle weakness in his late 20s and now has difficulty opening jars and climbing stairs. His 23-year-old daughter, Rose, experienced onset of muscle cramping and weakness as a teenager. Her son, Dylan, born after a pregnancy complicated by polyhydramnios and poor fetal movement, was extremely hypotonic and expired at two weeks of age of respiratory failure. Trinucleotide repeat analysis of the *DMPK* gene reveals that Paul has 350 CTG repeats, Rose has 520 repeats and Dylan over 3000 repeats, consistent with the observed increase in severity of the disorder in subsequent generations.

Learn More



Case Example



	DMPK gene CTG Repeats	Onset	Clinical Findings
Paul	350	3rd decade	Myotonia, weak facial muscles, general muscle weakness
Rose	520	2nd decade	Myotonia, weak facial muscles, general muscle weakness
Dylan	>3000	Prenatal	Severe weakness, respiratory failure

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Testing for Inherited Disorders From the Clinician's Perspective

- Molecular genetic testing
- Biochemical genetic testing
- Specialized cytogenetic testing (e.g., FISH, chromosomal breakage studies)

GeneTests Clinical Laboratories

- US: Must be certified by CLIA (US federal laboratory regulations)
- Non-US: Self-declared

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- Helps clinicians with diagnosis, management and genetic counseling of patients and their families
- Allows non-expert clinicians to manage the first encounter with a patient with a given diagnosis
- Correlates information on uses of testing with test availability per GeneTests Laboratory Directory

GeneTests Laboratory Listings

- Usually not recruited
- Occasionally recruited when a *GeneReview* author states that clinical testing is available, but no clinical laboratory is currently listed in GeneTests

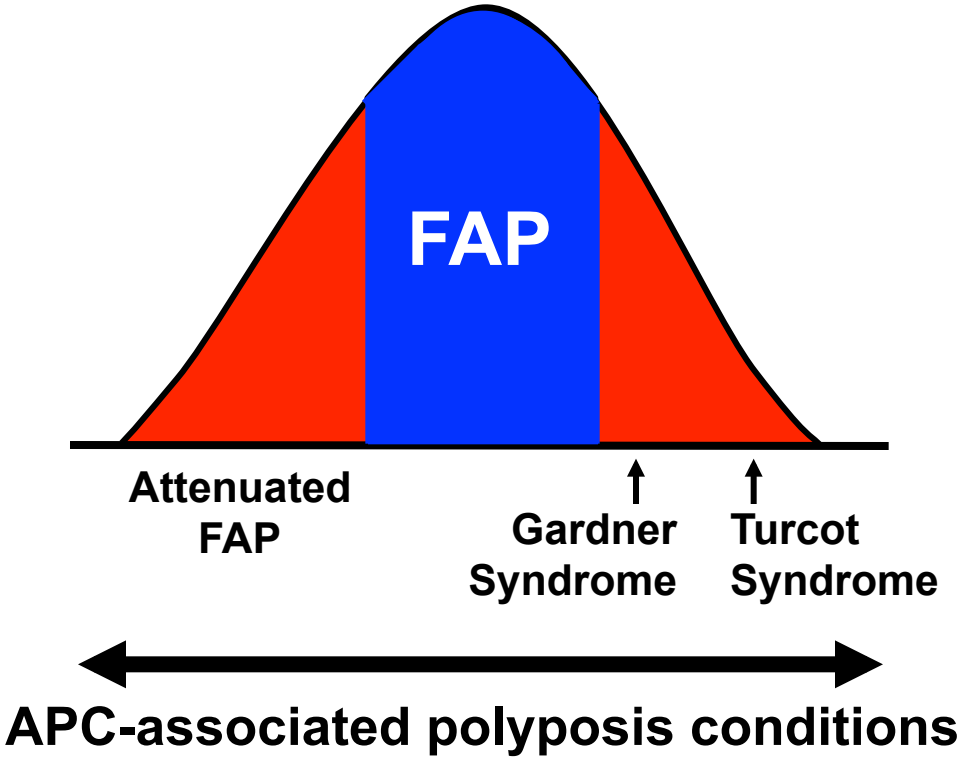
GENETests Disease Naming System

- **Laboratory:** Testing detects alterations in a gene, not a phenotype
- **Clinician:** Patients present with altered phenotypes
- **Disease name**: Relate to genes for laboratories; relate to phenotypes for clinicians

Disease Naming

1. Pre-gene discovery: Phenotype is narrowly defined - Essential to gene discovery

2. Post-gene discovery: Phenotypic spectrum expands as patients are tested - Essential to patient care



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Naming Hierarchy

Altered gene

***APC*-Associated Polyposis Conditions** Testing

Phenotypes

- Attenuated FAP
- Familial Adenomatous Polyposis
- Gardner Syndrome
- Turcot Syndrome

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Naming Hierarchy

Altered gene ***FMR1*-related disorders** Testing

Phenotypes

- Fragile X syndrome
- FMR1-related premature ovarian failure
- Fragile X-associated tremor/ataxia syndrome

Naming Hierarchy

Phenotype

Hereditary Hemorrhagic Telangiectasia

Altered gene

- **ACVRL1-Related HHT** Testing
- **ENG-Related HHT** Testing

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GENETests does NOT:

- Regulate
- Accredit
- Assess proficiency/quality

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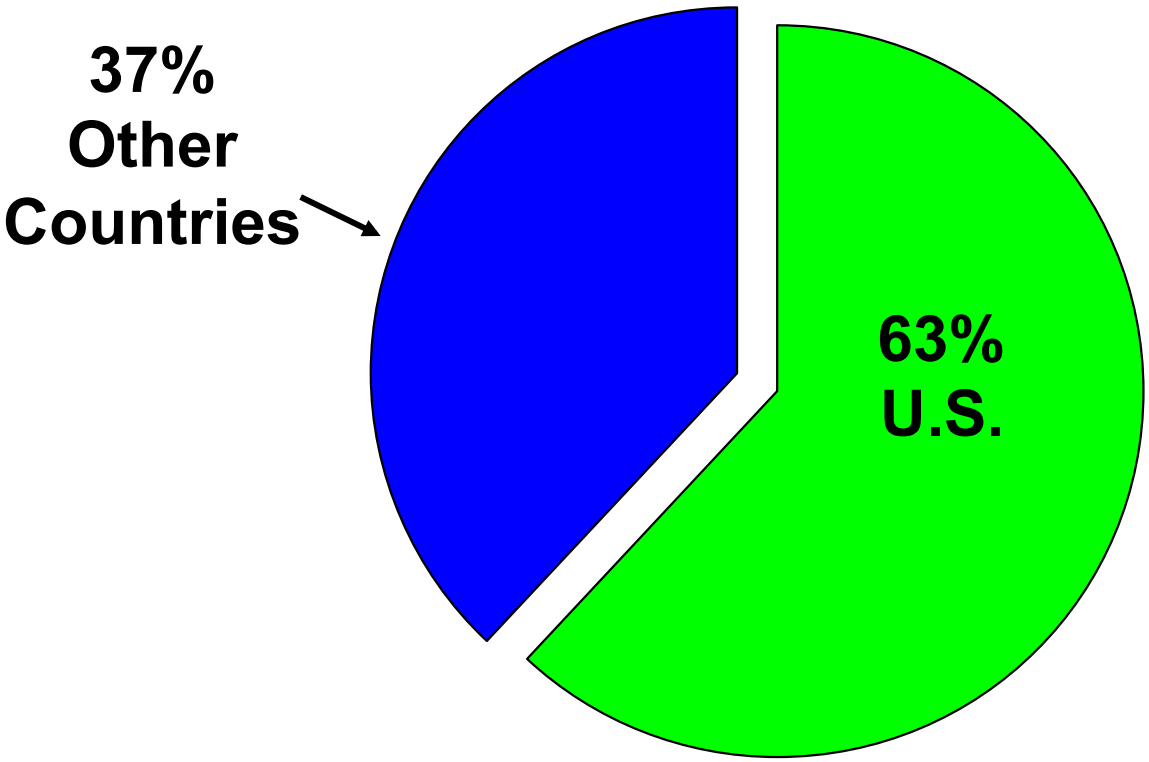
913 International Expert Authors



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Authors

- **No financial compensation**
- **Must**
  - Adhere to *GeneReviews* format, style
  - Reflect clinical test availability as per GeneTests Laboratory Directory
  - Respond to internal and external peer review
- **Term of authorship**
  - Revise when test availability/methods change
  - Update every two to three years

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Reviewers

- **No financial compensation**
- **Review for:**
  - Accuracy
  - Currency
  - Suitability for healthcare providers

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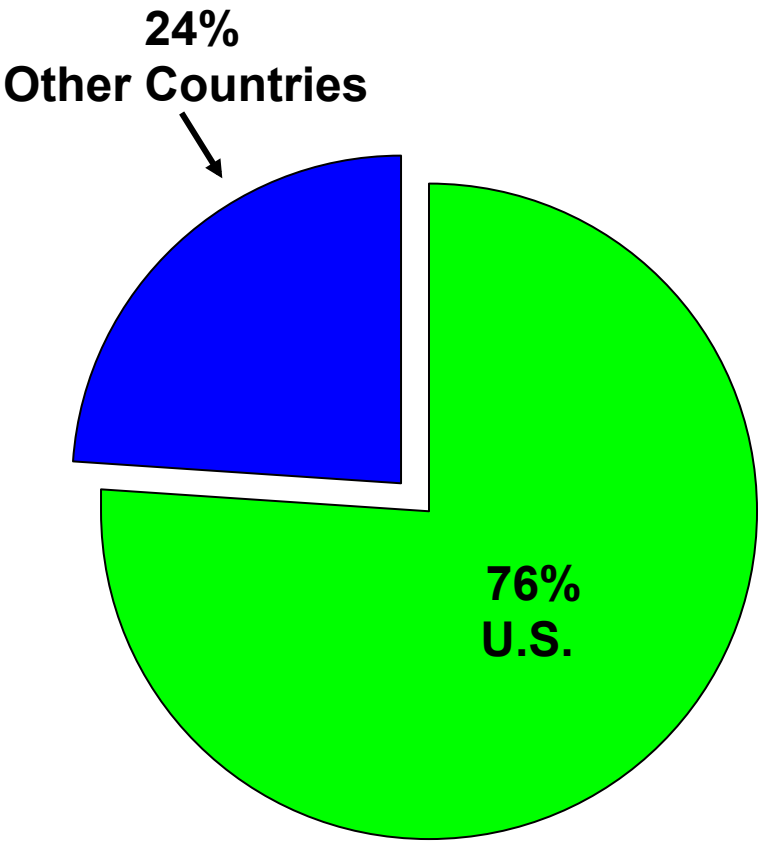
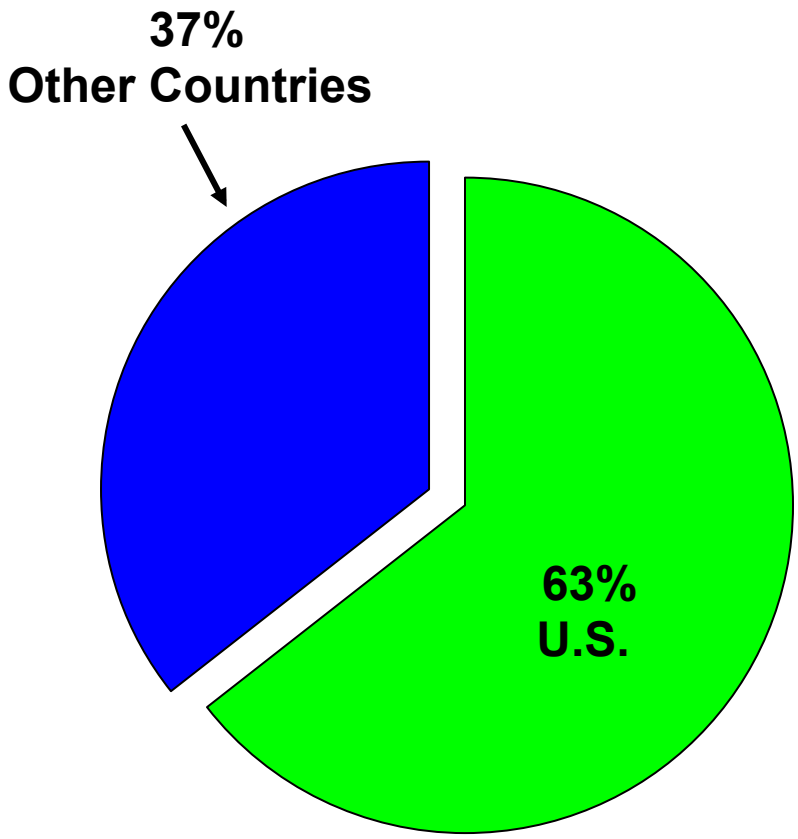
Laboratories

2001 (N = 498)



2007 (N = 616)



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GENETests Future Directions

- Use of standard mutation nomenclature with reference sequence to enable data sharing with mutation databases
- Collaboration with EuroGentest

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Standard Mutation Nomenclature[1]

[Gene Symbol] Allelic Variants Discussed in this *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Aliases [2])	Protein Amino Acid Change	Reference Sequence [3]
Normal			
Pathologic			

[1]per Human Genome Variation Society (www.hgvs.org).
[2]Variant designations that do not conform to current naming conventions
[3]Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

GENETests Future Directions

- Use of standard mutation nomenclature with reference sequences to enable data sharing with mutation databases
- Collaboration with EuroGentest

Collaboration

- **GeneTests:** Display information about testing for inherited diseases provided by clinical laboratories listed in EuroGentest
- **EuroGentest:** Display information about testing for inherited diseases provided by clinical laboratories in the US and Canada listed in GeneTests

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EuroGentest

Collaboration Benefits to GT/EGT Users and Labs

- Users: Improved access to worldwide information on clinical testing for rare inherited diseases
- Labs: Broader market for rare disease testing

Collaboration Benefits

Improved care for people with inherited diseases and their families

www.eurogentest.org

www.genetests.org