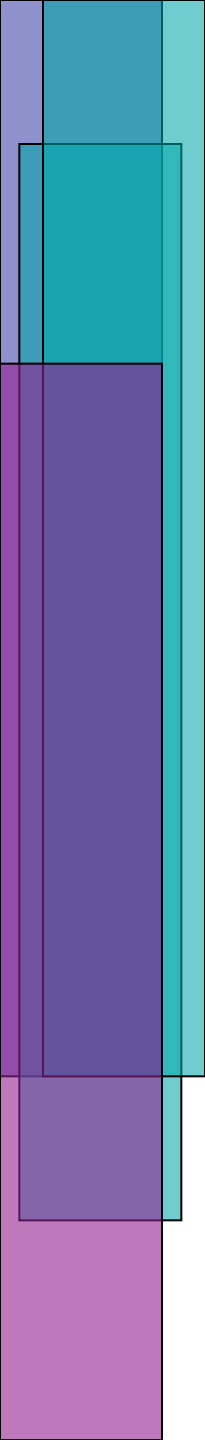



Finding a Genetics Laboratory: The U.S. Experience

First International Conference on
Rare Diseases and Orphan Drugs
Stockholm, Sweden 2005

Roberta A Pagon, MD
University of Washington, Seattle

- 
- Introduction to  **GENE**Tests
 - Availability of Genetic Testing
 - Future Directions



www.genetests.org

PRINCIPAL INVESTIGATOR: Roberta A Pagon, MD

FUNDED BY

National Institutes of Health
Contract No. N01-LM-3503

SPONSORING INSTITUTION

University of Washington
Seattle, WA

DNA Testing in Early 1990' s

- Human Genome Project: Accelerating gene discovery
- Molecular genetic testing: High complexity, rare diseases, often one laboratory only
- Finding a laboratory: Required “memory, colleagues, literature, and luck”
- 1993 Helix (now GeneTests Laboratory Directory = "Yellow Pages")
- 1997 GeneClinics (now *GeneReviews* = "User's Manual")
 - Free: Government-funded, university-based
 - Audience: Healthcare professionals

Funded by the
National Institutes of Health



02/08/05

282 *GeneReviews*

1,078 Clinics

577 Laboratories testing for

1,105 Diseases

785 Clinical

320 Research only

[More usage statistics](#)

Welcome to the **GeneTests** Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the [terms of use](#).

Direct questions to genetests@genetests.org.

At This Site

- ▶ ***GeneReviews***
Online publication of expert-authored disease reviews
- ▶ **Laboratory Directory**
International directory of genetic testing laboratories
- ▶ **Clinic Directory**
International directory of genetics and prenatal diagnosis clinics
- ▶ **Educational Materials**
 - ◆ [Illustrated glossary](#)
 - ◆ [About genetic services](#)
 - ◆ [PowerPoint® slide presentations](#)

Administrative Use

(For Laboratory/Clinic Contacts,
User Groups)

What's New

New Features

- ▶ **Online Registration for Laboratories and Clinics**
- ▶ **Updated PowerPoint® Presentation**

New in *GeneReviews*

New Lab Listings

- ▶ **14 new listings**

GeneReviews

- Genetic disease descriptions
 - 285 Reviews (Feb 2005)
 - One new Review added each week
- Expert-authored, peer-reviewed
- Current information on genetic test use in diagnosis, management, genetic counseling
- Links to genomic databases, patient resources, PubMed citations, policy statements/guidelines

International Laboratory Directory

~600 Clinical and research laboratories

~1050 Inherited diseases

- ~700 clinical tests
- ~350 research only

Genetics and Prenatal Diagnosis Clinics

- **United States:** ~ 1000 Clinics
- **International:** ~ 100 Clinics

Educational Materials

- Genetic counseling and testing concepts
- PowerPoint™ presentations on genetic testing issues
- Illustrated Glossary of >220 terms

Funded by the
National Institutes of Health



02/08/05

282 *GeneReviews*

1,078 Clinics

577 Laboratories testing for

1,105 Diseases

785 Clinical

320 Research only

[More usage statistics](#)

Administrative Use

(For Laboratory/Clinic Contacts,
User Groups)

Welcome to the **GeneTests** Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the [terms of use](#).

Direct questions to genetests@genetests.org.

At This Site

- ▶ **GeneReviews**
Online publication of expert-authored disease reviews
- ▶ **Laboratory Directory**
International directory of genetic testing laboratories
- ▶ **Clinic Directory**
International directory of genetics and prenatal diagnosis clinics
- ▶ **Educational Materials**
 - ◆ [Illustrated glossary](#)
 - ◆ [About genetic services](#)
 - ◆ [PowerPoint® slide presentations](#)

What's New

New Features

- ▶ **Online Registration for Laboratories and Clinics**
- ▶ **Updated PowerPoint® Presentation**

New in *GeneReviews*

New Lab Listings

- ▶ **14 new listings**

Funded by NIH



About Search Options

GeneReviews & Laboratory Directory

[Disease](#)[Gene](#)[Locus](#)[Protein](#)[Feature](#)[OMIM #](#)

GeneReviews

[Author](#)[Titles](#)[Text](#)

GeneReviews • Laboratory Directory

Search by Disease

Enter a disease name (or at least one character)

OR select [Advanced Search by Disease](#).

[Home Page](#)

[About GeneTests](#)

 [Reviews](#)

[Laboratory Directory](#)

[Clinic Directory](#)

[Educational Materials](#)

FAP [Familial Adenomatous Polyposis]

Attenuated FAP

Gardner Syndrome

Turcot Syndrome

[Testing](#)

[Research](#)

[Reviews](#)

[Resources](#)

[\[Printable Copy\]](#)

Familial Adenomatous Polyposis

[Summary](#)
[Diagnosis](#)
[Clinical Description](#)
[Differential Diagnosis](#)
[Management](#)
[Genetic Counseling](#)
[Molecular Genetics](#)
[Resources](#)
[References](#)
[Author Information](#)
[Top of Page](#)

[Enable Glossary](#)

(Returns to top)

[Title Index](#)

Familial Adenomatous Polyposis

[Adenomatous Polyposis Coli (APC), FAP. Includes: Gardner Syndrome; Turcot Syndrome; Attenuated FAP (Attenuated Polyposis Coli, AAPC)]

Authors: Cindy Solomon, MS
Randall W Burt, MD

[About the Authors](#)

Initial Posting:
18 December 1998

Last Update:
15 March 2004

Summary

Disease characteristics. Familial adenomatous polyposis (FAP) is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop, beginning at a mean age of 16 years (range 7-36 years). By age 35 years, 95% of individuals with FAP have polyps. Without colectomy, colon cancer is inevitable. The mean age of colon cancer in untreated individuals is 39 years (range 34-43 years). Extracolonic manifestations are variably present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retina pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, and associated cancers.

Diagnosis/testing. Familial adenomatous polyposis is caused by mutations in the *APC* gene. The diagnosis of FAP relies primarily upon clinical findings. Molecular genetic testing of *APC* detects disease-causing mutations in up to 95% of probands. Such testing is clinically available. Molecular genetic testing is most often used in the early diagnosis of at-risk family members and in the confirmation of the diagnosis of FAP in patients with equivocal findings (e.g., fewer than 100 adenomatous polyps.)

Genetic counseling. FAP is inherited in an autosomal dominant manner. Approximately 75-80% of individuals with FAP have an affected parent. Offspring of an affected individual have a 50% risk of inheriting the altered *APC* gene. Prenatal testing is possible if a disease-causing mutation is identified in an affected family member; however, prenatal testing for typically adult-onset disorders is uncommon and requires careful genetic counseling.



Summary

Diagnosis

Clinical Description

Differential Diagnosis

Management

Genetic Counseling

Molecular Genetics

Resources

References

Familial Adenomatous Polyposis

Molecular Genetic Testing



Test Method	Mutation Detection Rate	Test Availability
Sequence analysis	~95%	Clinical Testing
Mutation scanning and protein truncation testing (PTT)	~80-90%	
Protein truncation Testing (PTT)	~80%	

Funded by NIH



About Search Options

Laboratory Directory & GeneReviews

Disease

Gene

Locus

Protein

Feature

OMIM #

Laboratory Directory

Services

Director

Location

Laboratory

Laboratory Directory • GeneReviews

Search by Disease

Enter a disease name (or at least one character)

FAP

Search

Optional Parameters (use CONTROL key for more than one state/country; leave blank to retrieve all labs)

Select a US state

- All US Labs
- AL
- AZ
- CA
- CO
- CT
- DC
- DE
- FL
- GA
- HI

Select a country

- All International Labs
- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Canada
- Chile
- Cyprus
- Czech Republic
- Denmark

OR select [Advanced Search by Disease](#).

FAP [Familial Adenomatous Polyposis]

Attenuated FAP

Gardner Syndrome

Turcot Syndrome

[Testing](#)

[Research](#)

[Reviews](#)

[Resources](#)

Familial Adenomatous Polyposis

Includes: Attenuated FAP | Gardner

Sequencing of entire coding region **Multigene sequencing** **Clinical confirmation of mutations identified in a research lab**

Laboratories offering clinical testing:

Academic Medical Center
[DNA Diagnostics Laboratory](#)
Amsterdam, The Netherlands
Marcel M.A.M. Mannens, PhD

Auckland Hospital
[Molecular Genetics Laboratory](#)
Grafton, New Zealand
Karen Snow-Bailey, PhD, FACMG, FHGSA

Baylor College of Medicine
[Diagnostic Sequencing Laboratory](#)
Houston, TX
Benjamin B Roa, PhD

Boston University School of Medicine
[Center for Human Genetics](#)
Boston, MA
Aubrey Milunsky, MD, DSc

Chapman Institute of Medical Genetics
[DNA Laboratory](#)
Tulsa, OK
Nancy J Carpenter, PhD, FACMG; Frederick V Schaefer, PhD, FACMG

Mayo Clinic
[Molecular Genetics Laboratory](#)
Rochester, MN
Stephen N Thibodeau, PhD; D Brian Dawson, PhD ; W Edward Highsmith, PhD; Kevin Halling, MD, PhD

	Sequencing of entire coding region	Multigene sequencing	Sequencing of select exons										
Academic Medical Center DNA Diagnostics Laboratory Amsterdam, The Netherlands Marcel M.A.M. Mannens, PhD													
Auckland Hospital Molecular Genetics Laboratory Grafton, New Zealand Karen Snow-Bailey, PhD, FACMG, FHGSA													
Baylor College of Medicine Diagnostic Sequencing Laboratory Houston, TX Benjamin B Roa, PhD													
Boston University School of Medicine Center for Human Genetics Boston, MA Aubrey Milunsky, MD, DSc													
Chapman Institute of Medical Genetics DNA Laboratory Tulsa, OK Nancy J Carpenter, PhD, FACMG; Frederick V Schaefer, PhD, FACMG													
Mayo Clinic Molecular Genetics Laboratory Rochester, MN Stephen N Thibodeau, PhD; D Brian Dawson, PhD ; W Edward Highsmith, PhD; Kevin Halling, MD, PhD													

Clinical Laboratory

GENE**Tests****Mayo Clinic****[Molecular Genetics Laboratory](#)** 

Rochester, MN

Director: Stephen N Thibodeau, PhD

US Genetic Board Certification: American Board of Medical Genetics (Clinical Molecular Genetics, PhD Medical Genetics)

Director: D Brian Dawson, PhD**Director: W Edward Highsmith, PhD**

US Genetic Board Certification: American Board of Medical Genetics (Clinical Molecular Genetics)

Director: Kevin Halling, MD, PhD

US Genetic Board Certification: American Board of Medical Genetics (Clinical Molecular Genetics), American Board of Pathology

Genetic Counselor: Kara A Mensink, MSemail: gcmolgen@mayo.edu phone: (800) 533-1710**Genetic Counselor: Kelle Steenblock, MS, CGC**

US Genetic Board Certification: American Board of Genetic Counseling

email: gcmolgen@mayo.edu phone: (800) 533-1710 fax: (507) 284-0670**Contact: Kelle Steenblock, MS, CGC**email: gcmolgen@mayo.edu phone: (800) 533-1710 fax: (507) 284-0670**No direct patient consultation provided.****Methods:** [Linkage analysis](#), [Mutation scanning](#), [Protein truncation testing](#), [Sequencing of select exons](#)**Comments:** Reason for referral is required for correct interpretation of results. Linkage analysis requires specimens from several family members.**CLIA#:** 24D0404292 expires: 02/2005**GeneTests Laboratory Directory listing status:** Current**Last updated:** 10-FEB-04 **LID#:** 14[List of diseases tested for by this laboratory.](#)

Funded by NIH



About Search Options

Laboratory Directory & GeneReviews

- Disease
- Gene**
- Locus
- Protein**
- Feature**
- OMIM #
- Laboratory Directory
- Services
- Director
- Location
- Laboratory

Laboratory Directory • GeneReviews

Search by **Disease**

Enter a disease name (or at least one character)

Optional Parameters (use CONTROL key for more than one state/country; leave blank to retrieve all labs)

Select a US state

- All US Labs
- AL
- AZ
- CA
- CO
- CT
- DC
- DE
- FL
- GA
- HI

Select a country

- All International Labs
- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Canada
- Chile
- Cyprus
- Czech Republic
- Denmark

OR select [Advanced Search by Disease](#).

Genetics in Specialty Care

Tests : Feature Search*

Behavior Disorder (15)	Endocrine (91)	Liver (62)
Blood (97)	Eye (259)	Premature Aging (5)
Skeletal Bone (216)	Gastrointestinal (90)	Pulmonary (49)
Cancer (82)	Genitourinary (99)	Mitochondrial (16)
Connective Tissue (34)	Growth (119)	Metabolic (225)
Craniofacial (184)	Heart (162)	Neurologic (All) (907)
Deafness (122)	Immune (36)	Skin (210)
Dental (32)	Renal (86)	Vascular (40)
Ear (11)	Limb Malformation (76)	

*Clinical laboratories

Genetics in Specialty Care

Tests : Feature Search*

Neurologic (907)

Ataxia (75)

Dementia (33)

Lethargy/Coma (28)

Mental Illness (26)

Mental Retardation (212)

Motor Neuron (11)

Movement Disorder (68)

Myopathy (91)

Neuropathy (49)

Seizures (127)

Spasticity (143)

Autonomic Dysfunction (5)

Brain Tumor (9)

Headache (9)

Hyptonia (75)

Stroke (7)

Structural Brain Malformation (39)

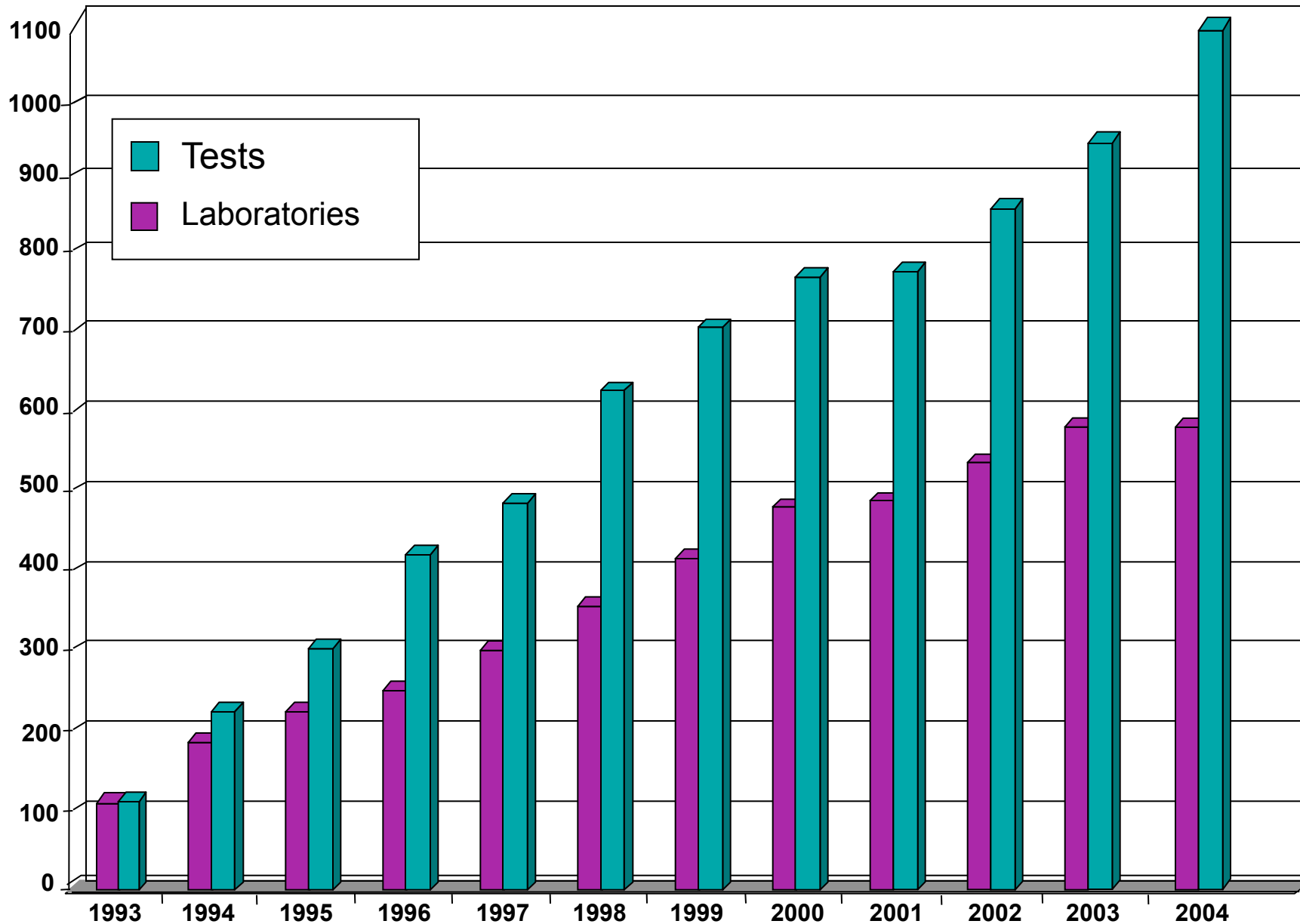


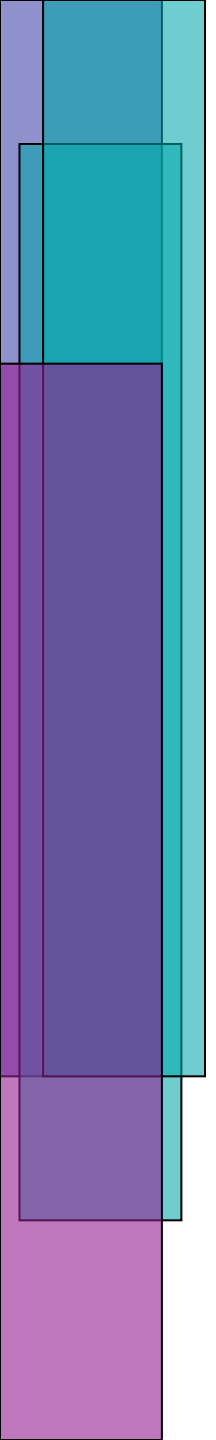
- Introduction to **GENETests**

- **Availability of Genetic Testing**

- Future Directions

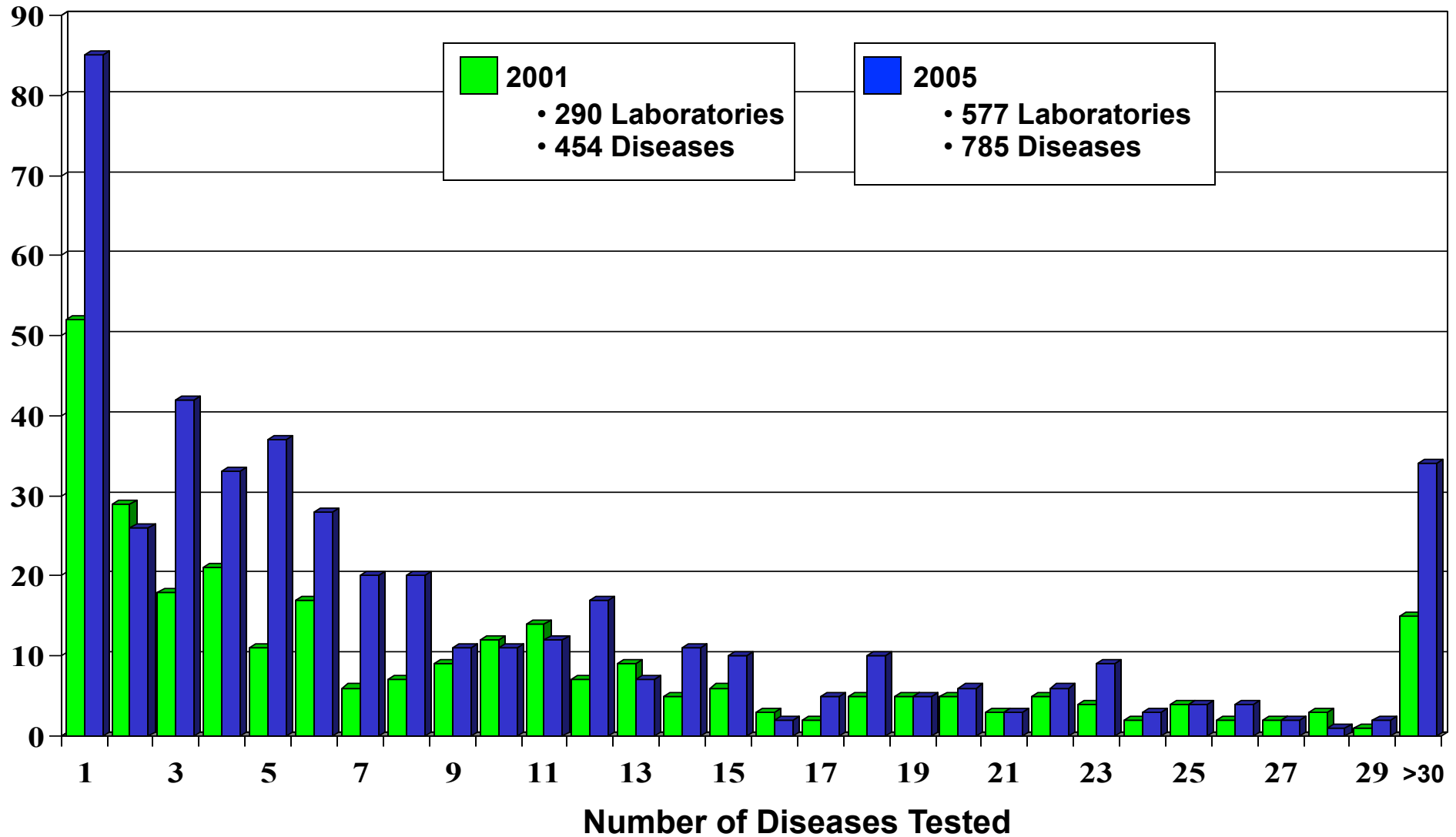
GENETests : Number of Tests and Laboratories



- 
- Most laboratories only test for a few diseases.
 - For many diseases only one laboratory provides testing.

Number of Clinical Laboratories by Number of Diseases

Number of
Clinical Laboratories



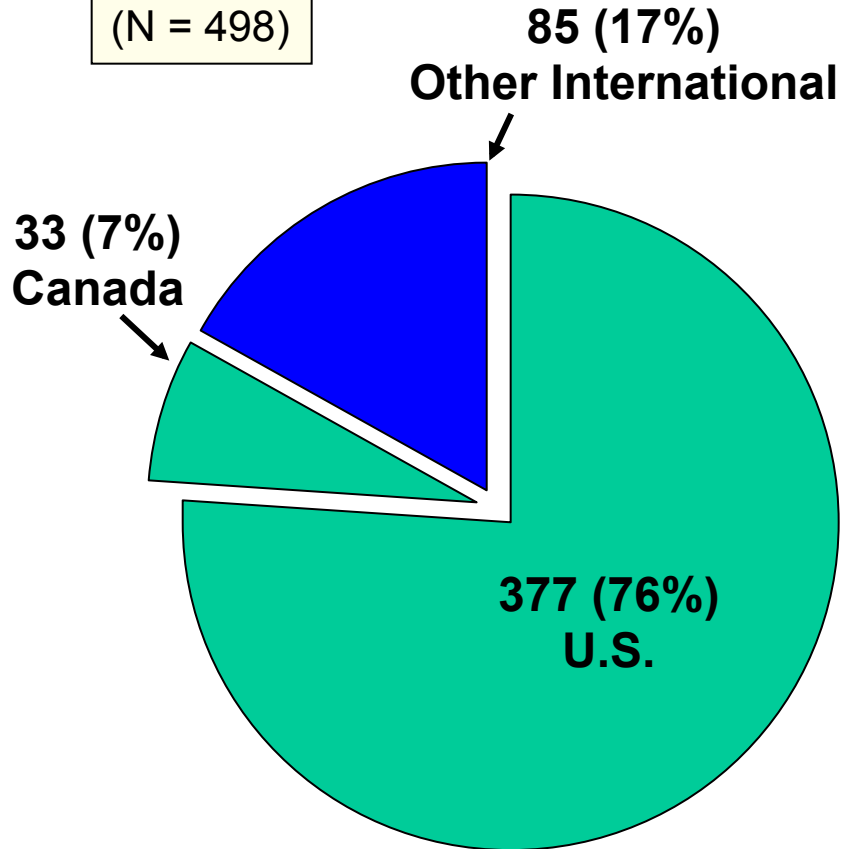


GENE Tests : Research Testing Only

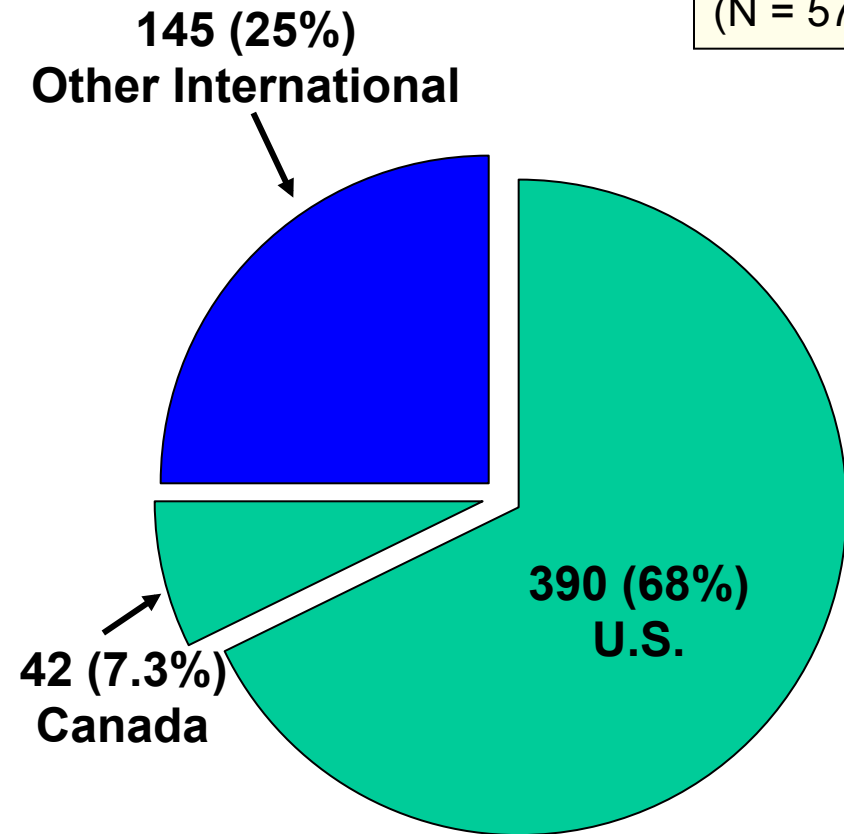
# of Diseases	# of Laboratories
233	1
68	2
19	≥ 3

GENE Tests: Clinical and Research Laboratories

2001
(N = 498)



2005
(N = 577)

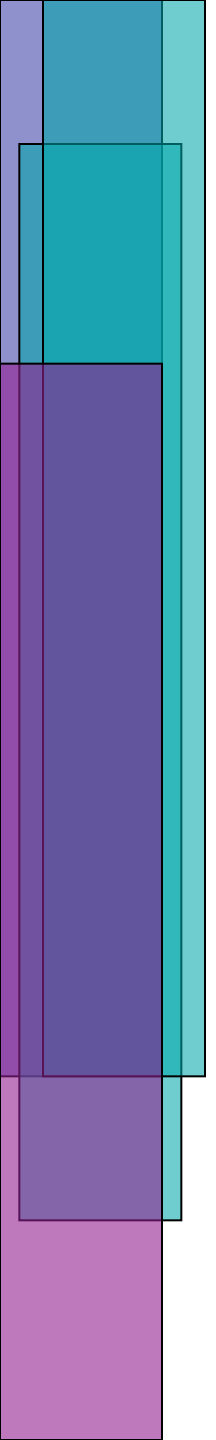


-  U.S. and Canada: Emphasis on inclusiveness
-  Other International: Emphasis on rare diseases



GENE Tests : International Laboratories (N=145)*

- 22** Germany
- 19** United Kingdom
- 11** Netherlands
- 9** Italy
- 7** France, Spain
- 6** Belgium, Japan, Switzerland
- 5** Israel, Australia
- 4** Argentina, Czech Republic, New Zealand
- 3** Turkey
- 2** Chile, Cyprus, Denmark, Finland, Norway, Portugal, Sweden
- 1** Austria, Brazil, Greece, India, Korea, Malta, Poland, Russia, Saudi Arabia, Scotland, Singapore, South Africa, Taiwan ROC

- 
- Introduction to **GENETests**
 - Availability of Genetic Testing
 - **Future Directions**



GENE Tests: Future Directions

Seamless network of international databases

- Shared disease naming system
- Shared terminology for genetic testing methods
- Shared data model



Tests: Disease Naming System

- Parent-child hierarchy
 - Parent can be the name related to an altered gene or a phenotype
 - Children can be the name related to an altered gene or a phenotype, but all must be the same
- Clinical testing links to a name related to an altered gene

GENE Tests: Disease Naming System

Altered gene:

Familial Adenomatous Polyposis

Testing

Phenotypes

Attenuated FAP

Gardner Syndrome

Turcot Syndrome

Phenotype:

Jervell and Lange-Nielsen Syndrome

Altered gene:

LQT1 **Testing**

Altered gene:

LQT5 **Testing**

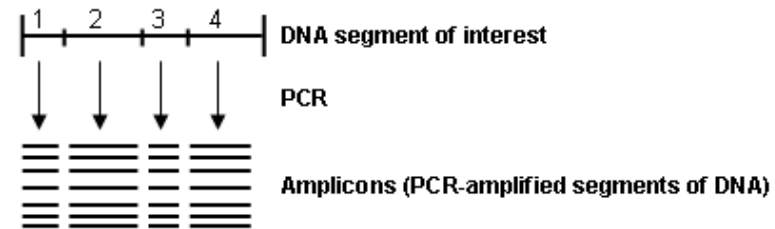
Shared terminology for genetic testing methods

mutation scanning

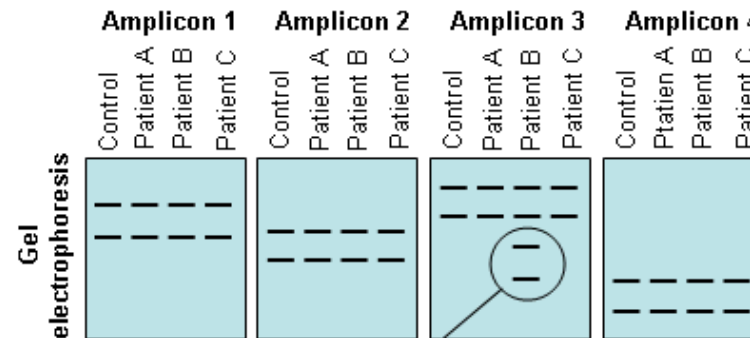
mutation scanning: (synonym: mutation screening) A two step process by which a segment of DNA is screened via one of a variety of scanning methods to identify variant gene region(s); variant regions are further analyzed (by sequence analysis or mutation analysis) to identify the sequence alteration

Step 1: Scanning.

A. PCR amplification of the DNA segment(s) of interest to create enough DNA for analysis



B. **Visualization and comparison.** Patient and control amplicons are compared using one of several different scanning methods (e.g., SSCP, CSGE, DGGE, DHPLC). In the SSCP example below, gel electrophoresis separates amplicons by size.



Interpretation: The additional bands and an abnormal migration pattern indicate a DNA sequence alteration is present in amplicon 3 of Patient B.

Step 2: Characterization of sequence alteration. The sequence alteration in amplicon 3 of Patient B is identified with additional testing (usually sequence analysis) in order to determine if it is likely to be a benign polymorphism or a pathogenic mutation.



GENE Tests : Shared data model

Next steps?

Principal Investigator Roberta A Pagon, MD

GeneReviews

Editor-in-Chief Roberta A Pagon, MD

Executive Managing Editor Patricia K Baskin, MS

**Associate Editors Thomas D Bird, MD
Cynthia Dolan, MS
Gerald Feldman, MD, PhD
Richard JH Smith, MD, PhD**

Suzanne Cassidy, MD

Assistant Editor Kathi Marymee, MS

Resources Liaison Cynthia Abair, MA

Monica Smersh

**Graphics Editor Carla Gifford
Malissa Robertson**

Update Coordinator

Directories

**Genetic Counselors Cynthia R Dolan, MS
Shannon DeVange, MS**

Directory Support Gina McCullough Grohs

Informatics

Programmer Sergey Mikhaylov, MS

Brad Willson

Systems Administration

Miriam Espeseth, MA

**Web Information
Specialist**