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

GENETests

- Introduction to GeneTests
- 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

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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

GeneTests

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**

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

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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)

FAP Search

OR select Advanced Search by Disease.

FAP [Familial Adenomatous Polyposis]
Attenuated FAP
Gardner Syndrome
Turcot Syndrome

[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

GeneReviews
www.genetests.org

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.

GeneTests

GeneReviews

Familial Adenomatous Polyposis

GeneReviews

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

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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**.

GeneTests

FAP [Familial Adenomatous Polyposis] Testing | Research | Reviews | Resources

Attenuated FAP

Gardner Syndrome

Turcot Syndrome

Familial Adenomatous Polypo

Includes: Attenuated FAP | Gardne

Sequenc entire codir

Mu sca

Clinical confirmation of mutations identified in a research lab

Laboratories offering clinical testing:	Seq ng of entire g region	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

GeneTests

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, MS
email: 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.

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About Search Options

Laboratory Directory & *GeneReviews*

Disease

Gene

Locus

Protein

Feature

OMIM #

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Location

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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**.

Genetics in Specialty Care

GeneTests : Feature Search*

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

*Clinical laboratories

Genetics in Specialty Care

GeneTests : 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)

*Clinical laboratories

- Introduction to GENETests
- **Availability of Genetic Testing**
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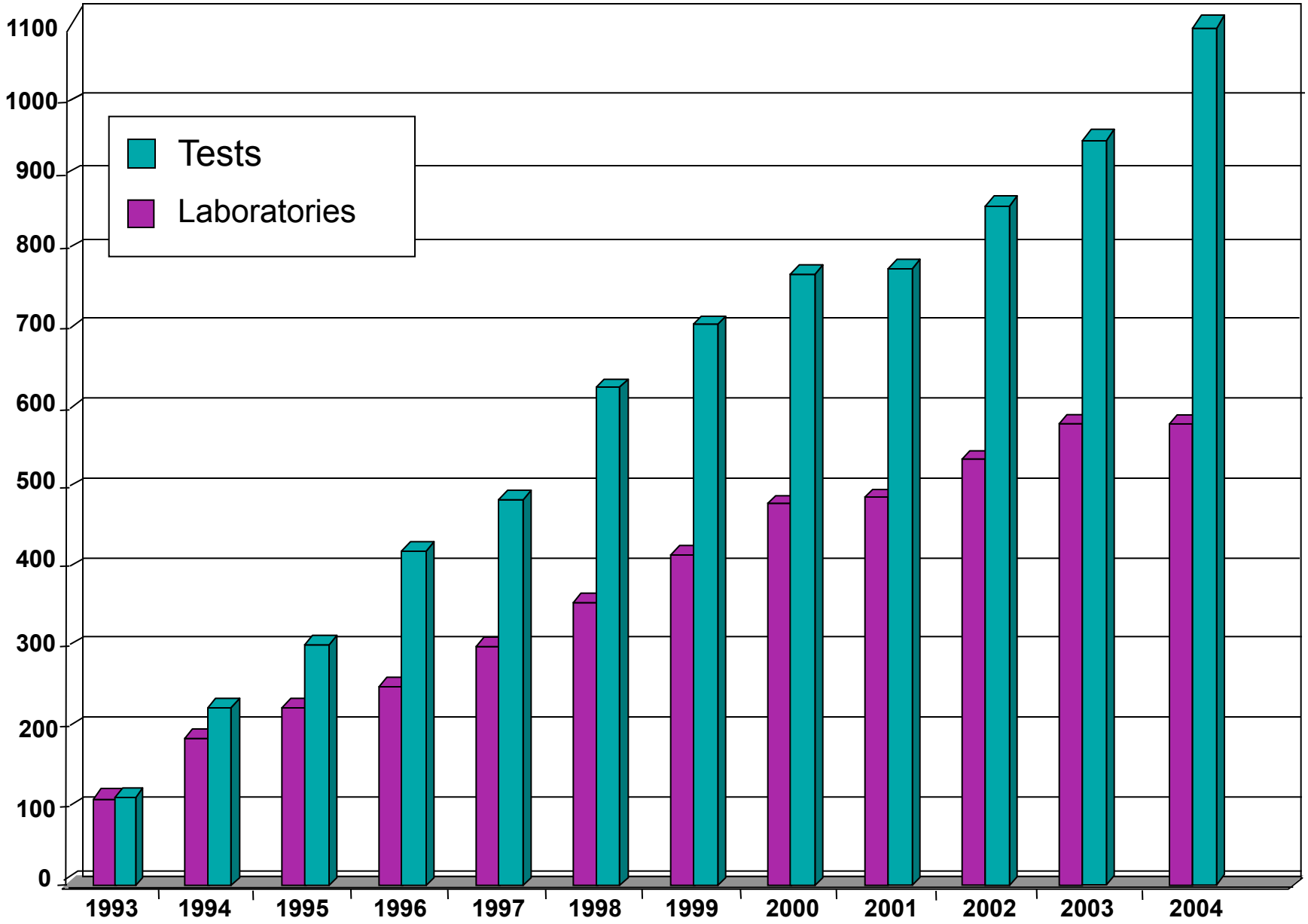
GeneTests : Number of Tests and Laboratories

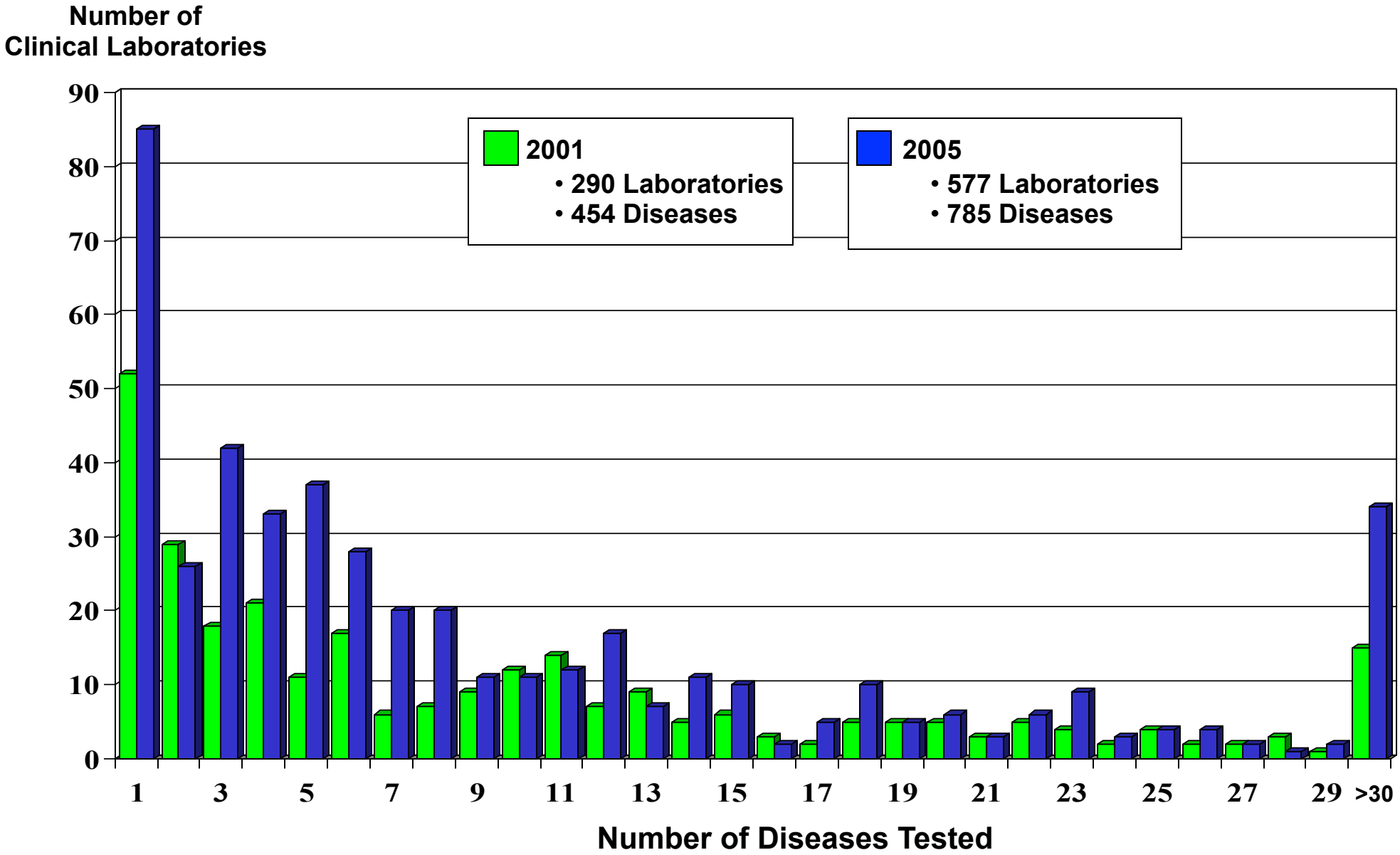


Data source: GeneTests database (2004) / www.genetests.org

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

GENETests

Number of Clinical Laboratories by Number of Diseases

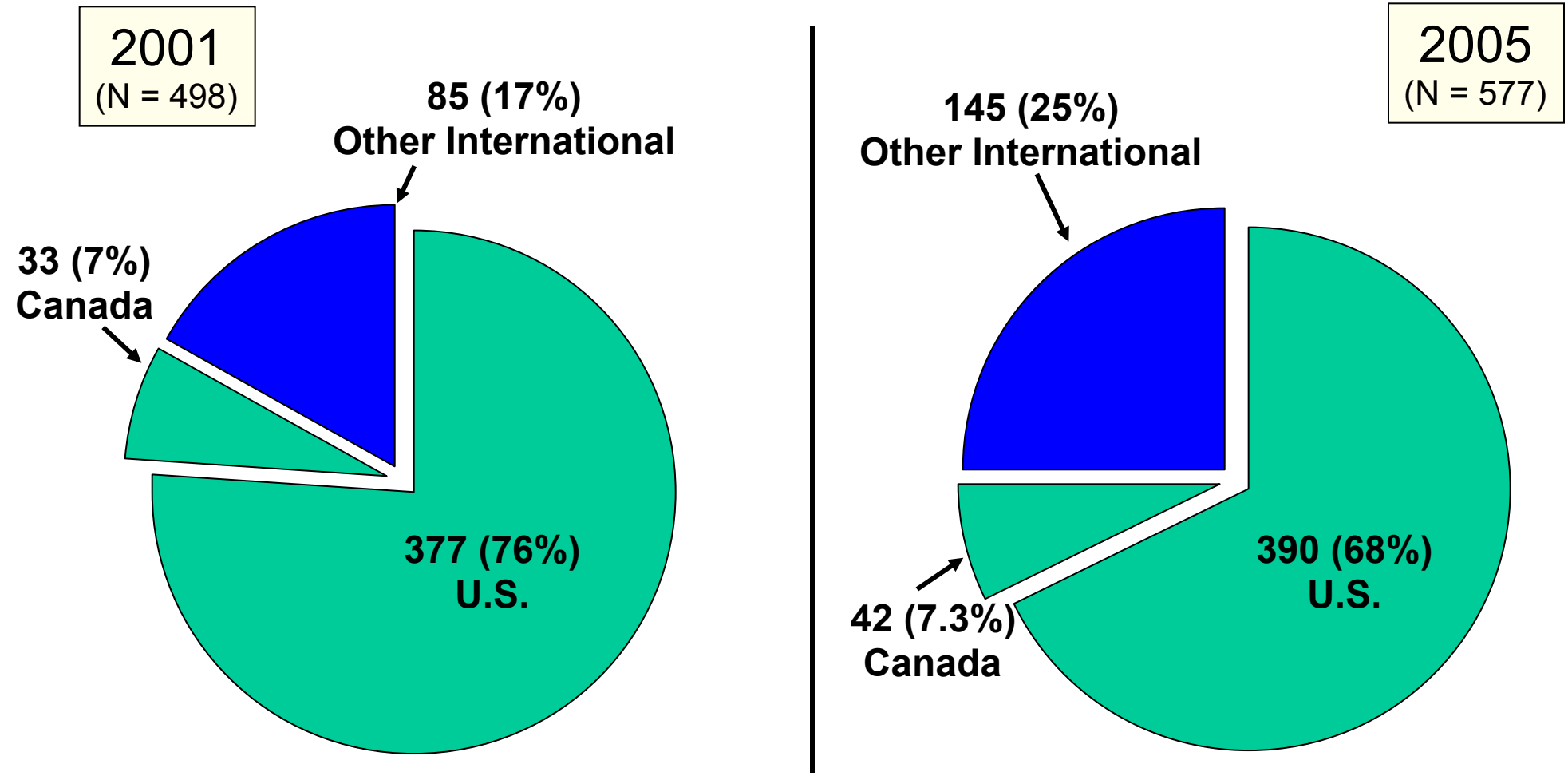


GeneTests : Research Testing Only

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

2005

GeneTests: Clinical and Research Laboratories



U.S. and Canada: Emphasis on inclusiveness

Other International: Emphasis on rare diseases

GeneTests : 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, Portgual, Sweden
1	Austria, Brazil, Greece, India, Korea, Malta, Poland, Russia, Saudi Arabia, Scotland, Singapore, South Africa, Taiwan ROC

*Excludes Canada

2005

- Introduction to GENETests
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GENETests: Future Directions

Seamless network of international databases

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

GENETests: 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

GeneTests: 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

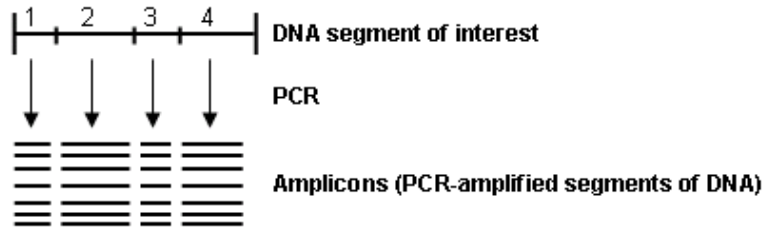
Altered gene: LQT5 Testing

Shared terminology for genetic testing methods

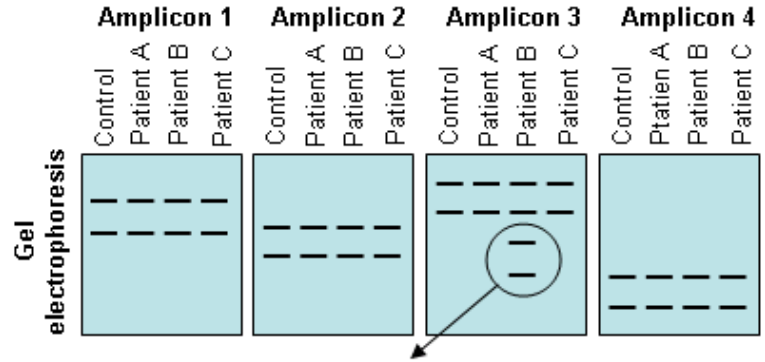
mutation scanning

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.

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GENETests : Shared data model

Next steps?

GeneTests Staff

Principal Investigator Roberta A Pagon, MD

GeneReviews

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