GeneTests: Integrating Genetic Services into Patient Care*

Roberta A. Pagon

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I thank the society and its Education Committee for the ASHG 2006 Award for Excellence in Genetics Education. I greatly appreciate this honor.

This award focuses around my work on the GeneTests project (http://www.genetests.org/), an information resource for health care providers to help integrate genetic services into patient care. GeneTests is located at the University of Washington, Seattle, and is funded by a contract from the National Institutes of Health. We are particularly grateful to the National Library of Medicine (NLM), National Human Genome Research Institute (NHGRI), and the National Cancer Institute (NCI) for their continuous support of GeneTests since its inception in 1992.

GeneTests comprises four sections:

1. GeneReviews, which serve as the user's manual for genetic testing for specific diseases. Currently, over 360 GeneReviews are posted on the Web site. One new GeneReview is added each week.
2. The Laboratory Directory, which serves as the "Yellow Pages" of genetics laboratories. Currently, over 600 clinical and research laboratories list information on tests for about 1,225 inherited diseases. Of these, approximately 930 are clinical tests, and approximately 295 are research-only tests.
3. The Clinic Directory, which serves as the "Yellow Pages" of genetics clinics. Currently, over 1,100 clinics are listed, providing services in pediatric and adult genetics, biochemical genetics, cancer genetic counseling and risk assessment, prenatal diagnosis, and preimplantation genetic diagnosis.
4. Educational Materials, which include an illustrated glossary of genetic counseling and testing terms. Over 200 illustrations provide graphics and case vignettes, to familiarize nongeneticist health care providers with these terms that are integral to our work as genetics professionals.

GeneTests has focused on molecular genetic testing for inherited disorders, because

1. The test menu is ever changing, as new genes are discovered and new test methods are introduced to improve mutation detection rates,
2. There are many laboratories, each testing for a few diseases, and
3. Molecular genetic tests can be used, not only in a traditional paradigm for diagnosis and predictive testing when treatment is available, but also in an untraditional paradigm of personal decision making (i.e., predictive testing when no treatment is available, carrier testing for autosomal recessive or X-linked disorders, prenatal diagnosis, and preimplantation genetic diagnosis).

In its goal to integrate genetic services into patient care, GeneTests has relied on the expertise and good will of collaborators and users around the globe. Over 800 international expert-authors have written over 360 GeneReviews. Sixty-two percent of authors are from the United States and 38% from other countries. Authors receive no financial compensation and must adhere to GeneReviews format and style and respond to internal and external peer review. Authors agree to serve for a 2-year term of authorship, during which they revise their entries when test availability or methods change, and they update the entry every 2 years in a formal, comprehensive process. Those who serve as reviewers for each GeneReview also receive no financial compensation. They are asked to review each entry for accuracy, currency, and suitability for health care providers.

The GeneTests Laboratory Directory has grown continuously. In 2001, about 500 laboratories were listed, of which 76% were from the U.S. and 24% were from other

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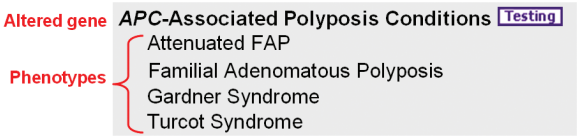

Figure 1. Naming hierarchy for *APC*-associated polyposis conditions

countries. Currently, in 2006, 642 laboratories are listed, 64% from the U.S. and 36% from other countries.

The educational issues that GeneTests' staff, authors, and reviewers have identified are many. One example is familiarizing others with the unique vocabulary of medical genetics. We know that geneticists "talk funny," but we also have to ask ourselves if we are being as clear as possible when trying to communicate information about genetic diseases and genetic tests. For example, what are we really saying when we use the terms "sporadic" and "simplex"? These are quite different terms and have different recurrence-risk implications. "Sporadic" refers to a chance event. "Simplex" refers to a single occurrence of a condition in a family. We geneticists know that simplex cases can result from autosomal recessive inheritance, X-linked inheritance, and autosomal dominant inheritance, caused by either a de novo mutation or reduced penetrance. Furthermore, nongenetic causes of a simplex case can include alternate paternity or adoption. Thus, we in the genetics community need to be very clear when we use the term "sporadic" that it is a chance event with little risk of recurrence and that when we use the term "simplex," risk of occurrence in relatives remains a possibility.

Another educational issue is disease naming. Because of new gene discoveries, gene-based lumping and splitting of phenotypes is a daily occurrence. We may find ourselves in the dilemma of trying to figure out "What disease is this?" From the laboratory perspective, testing detects alterations in a gene, not a phenotype. From the clinician's perspective, patients present with altered phenotypes. A disease name must relate to genes for laboratories and to phenotypes for clinicians. Furthermore, disease naming has become more of a process than a static phenomenon. Often, in naming a disease (phenotype) before the causative gene(s) is known, the phenotype is defined narrowly, in order to reduce heterogeneity and facilitate gene discovery. However, after the causative gene is discovered, the phenotypic spectrum typically expands as patients are tested. Understanding of the broadest aspects of the phenotypic range is essential to patient care and genetic counseling of at-risk relatives. Using familial adenomatous polyposis (FAP) as an example, the following can be said about naming. Before the causative gene was known, the phenotype was narrowly defined; however, once the *APC* gene was discovered, it became apparent that the spectrum of *APC*-associated polyposis conditions included attenuated FAP at the mild end of the spectrum and Gardner syndrome and Turcot syndrome at the more severe end of the spectrum.

To relate information about the altered gene and its associated phenotypes, the GeneTests staff developed a naming-hierarchy convention in which the spectrum of disorders caused by mutation in a given gene is designated "gene-related condition" (e.g., *APC*-associated polyposis conditions). Its "children" then become the associated phenotypes (fig. 1). In this way, information about testing can be linked to the name "*APC*-associated polyposis conditions," and the phenotypes (children) are listed under it, so that clinicians who have searched on one of those terms will see that term in correct relationship to information on the altered gene and other associated phenotypes.

Another example of this naming hierarchy is fragile X syndrome (fig. 2). Initially, the GeneTests database had stand-alone information on fragile X syndrome. However, over the past several years, continuing clinical investigations resulted in broader understanding of the phenotypes associated with mutations in *FMR1,* leading to creation of the hierarchy "*FMR1*-related disorders," with fragile X syndrome, *FMR1*-related premature ovarian failure, and fragile X-associated tremor/ataxia syndrome as its phenotypic children.

Finally, the GeneTests staff would like your help in improving GeneTests. We would like you to contact us so that we can correct errors, hear your ideas on how to improve the site, and explore potential collaborations. We would like you to refer new laboratories and clinics to be listed in GeneTests and new users to the information contained on the Web site. We are hoping that disease experts will consider volunteering to write a GeneReview. We would welcome working with you if you would like to assign a student to conduct a project that in some way touches on GeneTests.

Thank you from the Directories staff: Gina McCullough Grohs, Laboratory Directory Coordinator; Clinic Directory staff; Roberto Spiro, M.S., Genetic Counselor; and Kathi Marymee, M.S., Genetic Counselor and Resources Liaison; GeneReviews Editorial staff: Cynthia R. Dolan, M.S., Genetic Counselor, Associate Editor; Thomas D. Bird, M.D., Associate Editor; Gerald L. Feldman, M.D., Ph.D., Associate Editor; Karen Stephens, Ph.D., Associate Editor; Suzanne B. Cassidy, M.D., Assistant Editor; and Mary Beth P. Dinolus, M.D., Assistant Editor; GeneReviews Production team: Monica Smersh, Managing Editor; Miriam Espeseth, M.A., Online Production Editor; Cynthia Abair, M.A., Graphics Editor; and Carla Gifford, Editorial Assistant; and Information Technology staff: Sergey Mikhaylov, M.S., Database Administrator; and Brad Willson, Systems Administrator.

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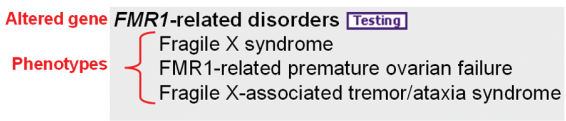

Figure 2. Naming hierarchy for *FMR1*-related disorders