The Practical Guide to the Genetic Family History

Robin L. Bennett

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To Scott, Mom, and Mr. Tougaw:
thanks for believing in me

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Foreword

Robin Bennett's book is a superb introduction to clinical approaches in medical genetics. Centered on the most traditional diagnostic tool in clinical genetics—the family history—she presents a well-balanced discussion of all of its aspects including the many applications for diagnosis of genetic disease. The book is based on extensive personal experience and provides much practical and useful information. But there is much more! The book's contents reflect the most recent genetic developments in all medical specialties, not just pediatric and obstetric aspects. Thus the rapidly expanding knowledge in cancer genetics is covered, as are various genetic considerations about assisted reproduction for women as well as for men (intracytoplasmic sperm injection). There are many helpful tables for a variety of potential genetic problems including hearing loss, mental retardation, dementia, seizures, and many others. A useful general chapter covers classical Mendelian patterns of inheritance as well as the relatively recently discovered mechanisms of genetic transmission such as imprinting and dynamic mutations.

Unlike in many books on medical genetics there is emphasis on the personal and human side of dealing with patients and families at all times. Useful lists cite reference books with critical discussions of their content. Historical and personal vignettes enliven the text.

This volume will be an essential resource for every genetics clinic and will aid medical geneticists and genetic counselors, whether experienced or in training. In addition, this text will be very helpful for both primary care and specialist physicians and allied health professionals, as well as for students of medicine, nursing, midwifery, and genetic counseling who need an up to date reference that emphasizes both the science and art of modern clinical genetics.

I have worked with Robin Bennett side by side in our genetics clinic at the University of Washington Medical Center for 15 years. She is superb in helping patients, families, and her colleagues with a multitude of practical, logistical, psycho-

logical, and diagnostic problems. This book demonstrates that she is even better informed with excellent judgment in more areas then I had realized. We can be grateful that her wise counsel and up to date knowledge can now be shared with a wide community of professionals whose patients will greatly benefit from these insights.

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Preface

When I consider the changes that have occurred over the past 15 years of my career as a genetic counselor, I feel the excitement that Anthony van Leeuwenhoek must have experienced in the early 1700s when he discovered a whole new world by using lenses to study microscopic objects. The simple rules of Gregor Mendel are no longer sufficient to explain complex patterns of inheritance reflecting such fascinating phenomena as imprinting and mitochondrial inheritance (see Chapter 2). The distinction blurs between environmental and genetic factors in the expression of disease. Genes do not operate in a vacuum; they interact with each other and with the environmental milieu. We are at the cusp of the chasm in understanding these complex gene–environment interactions. Every specialist in health care needs a basic foundation in human genetics to be able to recognize inherited disorders and familial disease susceptibility in patients, and to provide them with appropriate medical care.

The gateway to recognizing inherited disorders in a patient is a thorough medical–family history recorded in the form of a pedigree. A pedigree can assist the clinician in medical diagnosis, deciding on testing strategies, identifying patterns of inheritance, calculating risks, determining reproductive options, distinguishing genetic from other risk factors, making decisions on medical management and surveillance, developing patient rapport, and patient education (see Chapter 1). A pedigree is an important component of the medical record.

Although most clinicians have a cursory knowledge of the symbols that are used in constructing a pedigree, many are unaware that a standard set of symbols was developed through a peer review process, by the Pedigree Standardization Task Force of the National Society of Genetic Counselors, and adopted by the medical genetics community as a system of nomenclature. Pedigrees are of little value if each clinician uses a unique system of nomenclature. Using the appropriate pedigree symbolization is important for correct interpretation of a pedigree.

My intent in writing this book is to provide clinicians not only with the "hows" of taking a medical–family history and recording a pedigree, but also the "whys." Pedigree nomenclature and the approach to recording a medical–family history are

reviewed in Chapter 3. Chapter 4 may remind you of the "Cliff's Notes" you read in college to understand a classic tome of English literature. It is meant to provide a basic overview of the directed questions to ask when recording a medical-family history for a specific medical indication (e.g., renal disease, hearing loss, mental illness). I have not reviewed every medical system. My choice of disease categories is based on my experience of operating a toll-free genetic resource line for health care professionals; these are the categories of disease that I receive the most questions about. Because of the ever-growing importance of genetic susceptibility factors in cancer, Chapter 5 is devoted solely to this topic. Sample cases for practicing drawing pedigrees are provided in Appendix A.6.

Throughout the book I use clinical examples to illustrate certain themes. The case scenarios and pedigrees are based on hypothetical families. The names, family relationships, and psychosocial issues are fictitious, although the clinical information is often based on facts drawn from several families I have seen in my practice. The pedigrees of the Darwin–Wedgwood family (Figure 3.11) and of actress Elizabeth Taylor's immediate family (Figure 3.6) were drawn from information available in the public domain.

Pedigree analysis requires that the health facts recorded on individuals be accurate. This requires obtaining medical records on family members. Although this is often time consuming, it is necessary. Chapter 6 details how to assist a patient in obtaining medical records, including death certificates. There is also information about how patients can research their medical–family history and learn to record their own medical pedigree. It is helpful to the clinician if a patient has done the footwork in obtaining medical-family history information in advance of an appointment.

Adoption and assisted reproductive technologies using gamete donation provide challenges in taking a medical–family history (see Chapters 7 and 8, respectively). A model medical-family history form to be used for adoption is detailed in Appendix A.4. This form was developed by the Education Committee of the Council of Regional Genetics Networks (CORN). This form can easily be adapted for use by programs providing assisted reproductive technology services.

Genetic information carries unique personal, family, and social consequences. If a potential genetic disorder is identified through pedigree analysis, it is important that the patient and family members be referred to a board-certified genetic counselor or medical geneticist with the appropriate expertise. Information on how to find a genetic specialist in your geographic area, and what to expect from a genetic consultation, is given in Chapter 9.

Some of the numerous ethical issues to consider in recording a pedigree are detailed in Chapter 10. Researchers and individuals who are considering publishing a pedigree will find valuable information regarding issues to consider when involved in a family study or in publishing a case report.

This volume is meant to be a handy reference—a "Cliff's Notes" for making a genetic risk assessment, with a pedigree being the primary tool. To find more information about a specific condition, you will need to turn to one of the many excellent references on genetic disorders outlined in The Genetics Library (Appendix A.5). Any health care provider including physicians, nurses, medical social workers, and physician assistants will benefit from learning this approach to pedigree analysis.

Many people assisted me with the development of the ideas for this book as well as reviewing drafts of the manuscript. I am indebted to Robert Resta, Leslie Ciarleglio, and Amy Jarzebowicz for their perceptive reviews and suggestions. Patrick Clark provided graphic design. Skylar Sherwood, Debbie Olson, Leigh Elston, and Laura Burdell assisted with research, manuscript review, and moral support. The members of the NSGC Pedigree Standardization Task Force, particularly Kathryn Steinhaus, Stefanie Uhrich, Corrine O'Sullivan, and Debra Lochner-Doyle, helped seed the ideas for this book. I am grateful to the following individuals who took time from their busy schedules to review portions of the manuscript and provide valuable insights: Shari Baldinger, Dr. Thomas Bird, Dr. Peter Byers, Dr. Julie Gralow, Dr. Hanlee Ji, Dr. Gail Jarvik, Dr. Marshall Horwitz, Dr. Louanne Hudgins, Dr. Robert Kalina, Dr. Arno Motulsky, Dr. Roberta Pagon, Janine Polifka, Dr. Michael Raff, Dr. Al La Spada, Dr. C. Ronald Scott, Dr. Virginia Sybert, Ellen Nemens, Hillary Lipe, Marilyn Ray, Kathleen Delp, Joan Burns, Kerry Silvey and Linda Clapham. I appreciate the opportunity to work as a genetic counselor in the stimulating environment of the University of Washington, surrounded by a primordial soup of researchers in human genetics. My editors, Ann Boyle and Kristin Cooke, and the professionals at John Wiley and Sons have been generous in their patience and support. I thank my grandmother, Marjorie Warvelle Harbaugh, for teaching me respect and awe for my ancestors. Bill Tougaw, my high school biology teacher, deserves a special thank-you for opening my eyes and mind to the worlds of science and genetic counseling. I express my love and gratitude to my incredibly supportive family, especially Marjorie Bennett and J. J. Olsen, my husband Scott MacDonald, and my children, Colin, Evan, and Maren, for tolerating an "absent" Mom while I completed my dream.

Finally, I want to thank the families I have worked with through the years—you impress me with the strength you have in dealing with the cards life has dealt. Without question genes are important, but they are not our destiny. As Thomas Murry writes, "Why not regard our genes as a list of the obstacles we are likely to encounter and perhaps as a somewhat better prediction of how long we will have to do what matters to us, to be with the people we love, and to accomplish the tasks we have set for ourselves? Our genes no more dictate what is significant about our lives than the covers and pages of a blank diary dictate the content of what is written within. Our genes might be regarded metaphorically as the physical but blank, volume in which we will create our diary. Some volumes have fewer pages in which to write, some more. Certain pages, often toward the back of the volume may be more difficult to write on. And some leaves may require great skill and effort to open at all. But the physical volume is not the content of the diary. The content we must write ourselves."*

Robin L. Bennett
Seattle, Washington

*From TH Murry (1997). Genetic exceptionalism and "future diaries": Is genetic information different from other medical information? In: MA Rothstein (ed) *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. New Haven, London: Yale University Press.

1

The Language of the Pedigree

Pedigrees are a challenge. With their intricate patterns of geometric symbols, pedigrees are like biological crossword puzzles which dare the clever and creative geneticist to solve them for clues about inheritance, family dynamics, or the localization of a gene.
—Robert G. Resta (1995)

WHY TAKE THE TIME TO RECORD A GENETIC FAMILY HISTORY?

The field of human genetics is revolutionizing the practice of medicine. The cyberspace bible of human genetics—Victor McKusick's *Online Mendelian Inheritance in Man* (better known as OMIM*)—lists more than 10,000 hereditary conditions! Identification of genetic mutations through the International Human Genome Project makes genetic testing for most of these conditions a reality. Genetic susceptibility mutations are now being identified as part of the causal nexus for common complex medical conditions such as cancer, diabetes, heart disease, Alzheimer disease, and mental illness. Human genetics is no longer just a topic for obscure medical journals. Headlines heralding genetic advances are splashed across the fronts of newspapers and popular magazines. The gripping stories of people making heart-wrenching decisions about genetic testing and diagnosis increase the Nielsen ratings of Oprah Winfrey-style talk shows. Patients now come to *you* wanting to know if they need to worry about a genetic disease in their pregnancies, in their children, or in relation to their own health care.

How can you as a clinician identify individuals at risk for genetic disorders? The first step is to take a genetic family history, recorded in the shorthand form of a pedigree. A pedigree, commonly referred to as a family tree, is a graphic represen-

*http://www.ncbi.nlm.nih.gov/omim/

tation of a medical-family history using symbols. A concise pedigree provides both critical medical data and biological relationship information at a glance. In many circumstances, the pedigree is just as important for providing medical services to the patient as any laboratory test. The pedigree is truly the symbolic language of clinical genetic services and of human genetic research.

Genetic diseases affect all organ systems. Therefore health professionals from all specialties need to learn how to "think genetic." You do not need to be a "clever and creative geneticist" to take a genetic family history. The purpose of this book is to provide you with practical screening tools to make assessments as to which of your clients might benefit from more extensive genetic evaluation and/or testing. The goal is to teach you not just the questions to ask in making this assessment, but the logic behind these questions. Health professionals working with clients in family practice, internal medicine, pediatrics, and obstetrics will find these screening tools particularly useful. A special focus of this book is genetic screening questions for clinical specialists by disease system (see Chapter 4), with a particular emphasis on identifying individuals with an inherited susceptibility to cancer (see Chapter 5, and the cancer family history screening questionnaire in Appendix A.3). Researchers in human genetics will find useful information on how to obtain family history information, as well as ethical issues to consider in family studies and the publication of pedigrees (see Chapter 10). For the benefit of professionals involved in adoption, Chapter 7 discusses the unique issues surrounding a genetic family history and adoption. A medical-family history questionnaire for a child being placed for adoption is included in Appendix A.4.

WHAT DO CRANES HAVE TO DO WITH ANYTHING?

The word "pedigree" comes from the French term *pie de grue* or "crane's foot." The term first appeared in the English language in the 15th century. It described the curved lines, resembling a bird's claw, that were used to connect an individual with his or her offspring (Resta, 1993). Such vestiges of a bird's talons are obvious in the example of a *sippschaftstafel* drawn by Ernst Rüdin shown in Figure 1.1. The sippschaftstafel was a form of depicting family ancestry used by German eugenicists in the early 20th century (Mazumdar, 1992; Resta, 1993).

A pedigree is of limited value if the symbols and abbreviations cannot be easily interpreted. Historically, many different pedigree styles have been used in the published medical literature and in patient medical records (Bennett et al., 1993; Resta, 1993; Steinhaus et al., 1995). In fact, genetics professionals probably use as many "pedigree dialects" as there are dialects in the human language! As Francis Galton (an early geneticist and cousin to Charles Darwin) observed, "There are many methods of drawing pedigrees and describing kinship, but for my own purposes I still prefer those that I designed myself"(Galton, 1889). By using uniform symbols, it is possible to reduce the chances for incorrect interpretation of patient, family, medical, and genetic information. Through a peer-reviewed process, the Pedigree Standardization Task Force (PSTF) of the National Society of Genetic

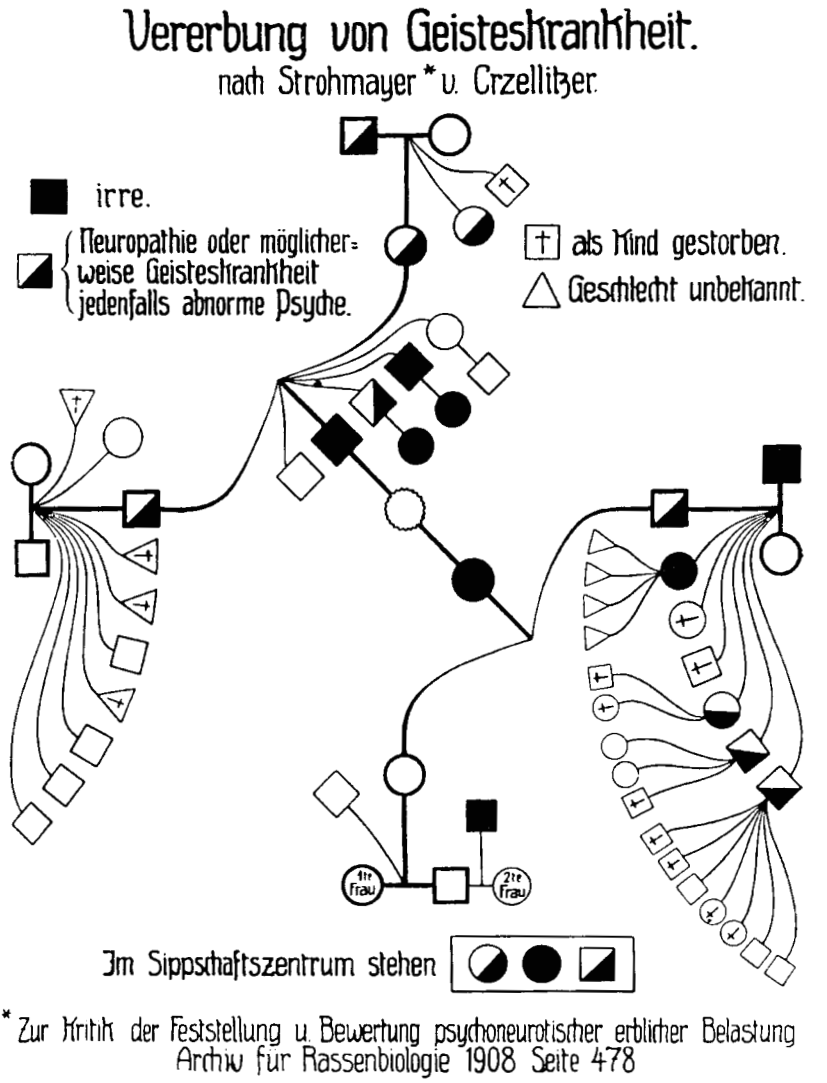

Figure 1.1 *A sippschaftstafel drawn by German eugenicist Ernst Rüdin in 1910. Note the proband (circle with irregular edge) is placed in the center of the pedigree and the maternal and paternal lineages radiate from curved lines drawn to the proband. Here the proband is shown being crushed by the weight of her dysgenic ancestry (from Mazumdar, 1992; and Resta, 1993). Reprinted with permission.*

Counselors (NSGC) developed standardized nomenclature for symbolizing pedigrees (Bennett et al., 1995). All pedigree symbols in this book conform to these standards.

THE PEDIGREE IS A COST-EFFECTIVE TOOL FOR GENETIC DIAGNOSIS AND RISK ASSESSMENT

"But who has time to take a family pedigree?" is a common lament from the busy practitioner. Most clinicians record some information about a patient's family illnesses in textual form. This can be just as time consuming as recording a pedigree, and the text may be much less concise, and much less specific, than a pedigree. For example, take a look at this excerpt from a medical record:

> Linda's grandmother and two aunts died of breast cancer.

Did the cancer occur in Linda's maternal or paternal grandmother? Are the aunts the sisters of Linda's mother or Linda's father? The exact relationship of these affected relatives to Linda, their ages at death, and if the breast cancer was unilateral or bilateral can make a critical difference in your clinical assessment of Linda's risk for developing breast cancer. Instead, using the associative icons of a pedigree, the relevant family and medical information can be recorded quickly and precisely, in an easily interpretable format. A family pedigree is a tool for:

- Making a medical diagnosis
- Deciding on testing strategies
- Establishing the pattern of inheritance
- Identifying at-risk family members
- Calculating risks
- Determining reproductive options
- Distinguishing genetic from other risk factors
- Making decisions on medical management and surveillance
- Developing patient rapport
- Educating the patient
- Exploring the patient's understanding

Notation of a genetic family history is likely to become an essential component of a patient's medical record. The ability to elicit a comprehensive medical-family history, including drawing a family pedigree, is stated as a fundamental skill in providing familial cancer risk assessment by the American Society of Clinical Oncologists (ASCO, 1997). The American College of Obstetrics and Gynecology issued a similar statement on the importance of the genetic family history in obstetrical eval-

uations (ACOG, 1987). Dr. Peter Schwartz, Vice Chair of Obstetrics and Gynecology at Yale University School of Medicine, states that for early screening and detection of gynecologic malignancies, "Family history is crucial, and it's not a superficial history. You have to go into depth" (ACOG, 1998). Taking a directed genetic history is a primary step in the evaluation of most disorders. Dr. Barton Childs of Johns Hopkins University (1982) predicts that "to fail to take a good family history is bad medicine and someday will be criminal negligence."

Using a pedigree to symbolize a patient's medical and genetic history is no more time consuming than dictating a detailed summary for the medical chart. A pedigree is a way to compress pages and pages of medical information onto an 8½″ × 11″ piece of paper. I always keep the patient's pedigree in the front of his or her medical file. This saves me time at subsequent visits because most of the critical information I need is readily accessible and succinctly summarized on one page. The pedigree gives me an immediate image of the family's health and sociological structure without wading through stacks of medical records. Once a pedigree is obtained, the patient's family history can be easily updated on return visits.

The Pedigree as a Diagnostic Tool

Reviewing a family pedigree can aid the clinician in diagnosis. For example, in making a diagnosis of a familial cancer syndrome it is imperative to know the cluster of types of cancers; the ages of the individuals diagnosed with cancer; and how closely the individuals with cancer are related to each other (i.e., first- as compared to second-degree relatives). The family history will even influence the kind of genetic diagnostic tests that are ordered.

Take, for example, the family history of Susan, a 30-year-old computer technologist, and a mother of three. She is interested in information about how she can be screened for renal cell cancer because her father, Sam, was recently diagnosed with clear-cell renal carcinoma. If Susan has any family members with brain or spinal tumors (hemangioblastomas), renal cysts or cancer, adrenal tumors (pheochromocytomas), or retinal angiomas, a diagnosis of von Hippel–Lindau syndrome should be considered.

Von Hippel–Lindau syndrome (VHL) is an autosomal dominant condition with 80–90% penetrance and variable expressivity. Direct molecular genetic testing is available for VHL. With current molecular technology, about 80% of the mutations are identified (Huson and Rosser, 1997). Therefore, a negative molecular study does not rule out the diagnosis of VHL. A diagnosis of VHL in Sam will have very different implications for screening Susan, her children, and extended family, than does a diagnosis of an isolated clear-cell renal carcinoma. Isolated clear-cell renal carcinoma is not known to "run in families"—if Susan does not have additional family members with renal cell or other cancers, screening for any type of cancer in Susan will likely be the same as for any other woman her age (Linehan and Klausner, 1998). Susan's pedigree is depicted in Figure 1.2.

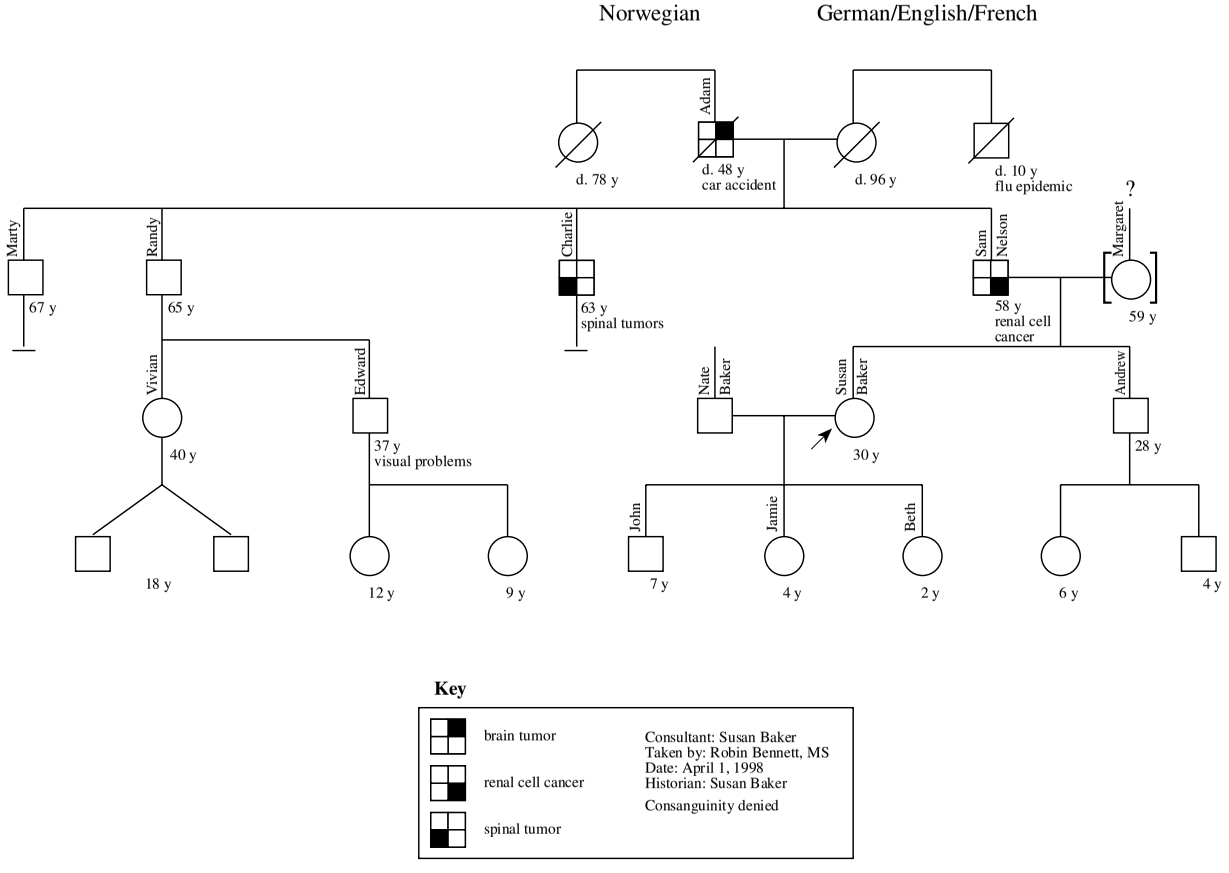

Figure 1.2 *A hypothetical pedigree representative of a family with von Hippel–Lindau syndrome.*

Using the Pedigree to Decide on Testing Strategies and for Evaluating At-risk Family Members

Susan's pedigree is suggestive of VHL. The most cost-effective approach to genetic testing is to obtain a blood sample from Sam to look for mutations in the VHL gene. Because VHL is inherited in an autosomal dominant pattern, an affected individual has a 50:50 chance to pass the mutation on to each son or daughter (see Chapter 2 for a review of patterns of inheritance). If a mutation is identified in Sam, then accurate mutation analysis is available for Susan, her siblings, and other family members. The pedigree helps you determine who else in the family should be tested.

Using the Pedigree to Establish the Pattern of Inheritance and to Calculate Risks

John was born with a profound hearing impairment. He and his fiancée are planning a family, and they want to know if they have a high probability of having children who will also have severe congenital hearing impairment. This question is impossible to answer without obtaining a family history. Congenital deafness can have an autosomal recessive, autosomal dominant, X-linked, or mitochondrial inheritance pattern, or have a maternal teratogenic etiology (see Chapter 4, Section 4.3). How to use a pedigree to identify patterns of inheritance is detailed in Chapter 2. Once an inheritance pattern is identified or suspected, John and his fiancée can be given appropriate genetic counseling.

A Pedigree Can Help Distinguish Genetic from Other Risk Factors

A pedigree can be just as useful in determining that a condition is *not* genetic as in establishing that a condition is inherited in a family. This is particularly true for common complex health conditions such as mental illness, heart disease, and cancer. For example, Jean is a 42-year-old premenopausal woman with unilateral breast cancer. Her mother is healthy at age 65 years, but Jean's maternal grandmother, Pamela, died of breast cancer at age 63. This limited family history may raise your initial suspicion for a familial breast cancer. Yet when you take an extended family history, you find that Jean's mother has three healthy sisters between the ages of 68 and 72 years. You also find that Pamela had two sisters who were cancer free in their mid-70s when they died of heart disease. This "negative" family history is just as important as the "positive" family history of cancer in risk assessment and determining cancer screening protocols.

A Pedigree Can Help Identify Medical Screening Needs for Healthy Individuals

A brief family history can identify genetic and medical screening needs for an otherwise healthy person. For example, carrier testing for Tay–Sachs disease can be offered to a healthy couple of Jewish ancestry who are interested in planning a preg-

nancy. (Tay-Sachs disease is an autosomal recessive neurodegenerative disease leading to death usually by the age of 5 years. Approximately 1 in 30 Ashkenazi Jews carries this mutation as compared to 1 in 300 individuals of non-Ashkenazi heritage.) Serum cholesterol screening can be considered for someone with a strong family history of coronary artery disease. For a person with a significant family history of colon cancer, colonoscopy should be offered at a younger age than usual (Burke et al., 1997b). A young woman with a strong family history of breast cancer should have screening mammography (or possibly breast ultrasounds) at an earlier age than is usually recommended (Burke et al., 1997a).

TAKING A FAMILY HISTORY IS A WAY TO ESTABLISH CLIENT RAPPORT AND FACILITATE PATIENT DECISION-MAKING

Your patients are more likely to comply with your medical advice if they trust you and have a relationship with you. The process of taking a medical-family history provides an excellent opportunity to establish rapport with a client. A clear picture of family dynamics and the patient's life experiences usually unfolds while taking a patient's medical-family history. These family relationships and life experiences will have an impact on a patient's decisions about medical care and genetic testing. Compare Amanda, a healthy 37-year-old pregnant woman who has experienced 10 years of infertility, with Beth, who is also 37 years old but has two healthy children. Both women have the same age-related risk to have a child with a chromosome anomaly, yet each woman may make different choices about genetic testing during her pregnancy. Or consider two 45-year-old women who each has a mother who died of breast cancer at age 38 years. Their genetic risk assessments (drawn from factual empiric risk tables) are the same, but the emotional feelings each woman has about medical screening and genetic testing are likely to differ based on each woman's individual experience with her mother's illness.

The symbols of a pedigree represent more than the geometric pieces of a biological crossword puzzle, as described by Robert Resta (1993) in the introductory quote to this chapter. I view a pedigree like a quilt, stitching together the intimate and colorful scraps of medical and family information from a person's life (Fig. 1.3). Familiar pedigree patterns are the clinician's matrix for providing pedigree risk assessment, as well as clinical and diagnostic recommendations. Yet just as the quilter takes artistic liberty with tried-and-true patterns to make each quilt a unique work of art, each pedigree has a unique human story behind it. It is from the interwoven fabric of a patient's family, cultural, and life experiences that the patient pieces together his or her decision-making framework.

A PEDIGREE CAN BE USED FOR PATIENT MEDICAL EDUCATION

"A picture is worth a thousand words," or so the popular saying goes. Reviewing the pedigree with a patient is a vital visual tool in patient education (Table 1.1). Let us