UNDERSTANDING GENETICS

A Primer for Couples and Families

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Myths about Inheritance and Birth Defects

Myth: Blue eye color is recessive to brown eye color. Blue-eyed parents cannot have a brown-eyed child.

Fact: Eye color is not controlled by just one gene. Inheritance of eye color is as complex as inheritance of skin color or height.

Myth: Birth defects are caused by things that the mother sees or hears.

Fact: There are many superstitions about what causes birth defects. Increasingly, the true cause can be identified. Birth defects are neither caused nor prevented by supernatural, astrologic phenomenon or by maternal experiences.

Myth: The fetus is protected by the placenta from anything that happens to the mother.

Fact: The placenta is not a strong barrier. The fetus is exposed to all the same things to which the mother is exposed. Maternal alcohol intake causes mental retardation. Maternal smoking causes growth retardation. Some fetal problems can be treated by giving medication to the mother.

Myth: If the problem is not present at birth, it isn't genetic.

Fact: Genetic diseases can be diagnosed at any age.

Myth: All genetic disease happens in childhood.

Fact: While genetic diseases and birth defects are most significant in childhood, genetic problems can manifest at any age.

Myth: All problems present at birth are genetic.

Fact: Infections, chemicals, and other things can cause problems that are present at birth.

Myth: It is only genetic if someone else in the family has it, too.

Fact: Conditions can be hidden, or very mild, or cause problems that are not talked about, and they are all equally genetic.

Myth: All persons with genetic disease or birth defect are mentally retarded or disabled.

Fact: There is a wide spectrum. Some conditions can be managed with diet, medications, or surgery. Some conditions cause no real problem at all.

Myth: Using infertility treatments lowers my risk of having a child with a birth defect.

Fact: A child conceived with infertility treatments is at the same general risk as a child conceived naturally. Some assisted reproductive techniques may contribute to passing on genetic disease.

Myth: Now that the human genome is sequenced, we know everything.

Fact: Sequencing the genome is the end of the beginning, rather than the beginning of the end.

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For Alan

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Introduction

How do we experience genetics in our everyday lives? There are announcements about new discoveries in the paper or on the radio. We get into debates about genetically modified food and human cloning. Or someone in our family is diagnosed with a birth defect or genetic disease.

Most books or classes about genetics start with the basics and move forward from there. Such a strategy is useful in school, but school and life are different things. This book aims to cover the same information but in a way that reflects how most people have their first brush with genetics: when a disease is diagnosed in your family.

Outside of school, you are more likely to encounter genetics in a doctor's office than in a laboratory. But what does that mean? The first part of this book describes the different professionals you are likely to meet in a genetics clinic, explains the information they gather, and gives an overview of some tricky concepts. It also includes a chapter on the basics of DNA and chromosomes. The second part focuses on pregnancy and prenatal diagnosis. Parts three, four, and five discuss genetic problems and birth defects as they affect children, teens, and adults, respectively.

The last chapter of each section I have devoted to some other considerations. These matters are tangential to genetics but are very much a part of patients' lives. Some of these are ethical issues, such as when to involve a teenager in medical decision making. Others are strictly legal definitions or food for thought. I do not presume to be an expert in psychology or law, and readers who would like more information in these

areas are encouraged to seek out advice from their own physician, lawyer, or other counselor.

In my own discussions with patients, I try to uphold two principles: (1) information itself is valueless—neither good nor bad; and (2) the only bad decision is the uninformed decision. May this book help you toward making good decisions.

PART I

Basic Things to Know

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1 What Is a Genetics Doctor?

So, you've been referred to a clinical geneticist. What sort of doctor will you see? The geneticists you read about in the paper or see on television are usually laboratory scientists rather than clinical doctors. Your primary care physician has explained that a geneticist can assist you, but exactly who is this person?

GENETICS PHYSICIANS

Doctors who practice genetics have been around for a long time. Historically, they are doctors who have had an interest in inherited diseases or birth defects, so they informally focused their practice in these areas. Remember that it has only been within the last one hundred years that medical specialties as we know them came into being. Before then, a physician's "specialty" was dictated by a particular interest or local need rather than by the area of formal schooling. The most obvious specialties formed first: surgery and obstetrics became separate from general medicine, for example.

In the second half of the 1900s, as our understanding of genetics increased, genetic training became more formal. At that point, doctors who had completed training in a wider field pursued and received more training specifically in genetics. This early instruction tended to be a type of apprenticeship. These doctors would then practice genetics as a subspecialty within the context of their primary specialty.

In 1981 the American Board of Medical Genetics was formed. This

board monitors and regulates genetics training and administers certification tests. In 1991 genetics was given the status of a full medical specialty on par with others such as internal medicine, pediatrics, surgery, and ophthalmology. Because genetics deals with the "not normal," the residency training is combined with a primary care specialty—pediatrics, obstetrics and gynecology, or internal medicine. Over the course of four or five years, a doctor receives training in both specialties. That doctor must then pass tests and maintain skills in both specialties.[1]

Clinical geneticists are physicians with an MD or DO degree. They are different from genetic counselors, who have a specialized master's degree (MGC). Some clinical geneticists are trained in more than one aspect of genetics and may direct a diagnostic laboratory, or they may even run a research laboratory. The majority of genetics physicians are pediatricians, but some are obstetricians, internists, or pathologists.

Genetics is now becoming so involved that genetics doctors are subspecializing—seeing a particular set of patients within the larger context of genetics. A pediatric geneticist will concentrate on birth defects and genetic diseases that show up in children. Obstetric geneticists probably do detailed prenatal testing and counseling when a problem is found. They may also do preimplantation diagnosis testing or help women who themselves have genetic diseases. Genetic internists may work with genetic diseases that come on in adulthood or with common diseases with a genetic component, such as high cholesterol or diabetes. Some genetic internists deal with cancer. Others care for people who have survived childhood with a birth defect or genetic disease and have now outgrown their pediatricians.

Patients are referred to a genetics physician or counselor because their problem is thought to have a significant genetic component or to be the result of a problem in fetal development. Table 1.1 shows some reasons for referral. Most commonly, patients are referred to a clinical geneticist by another physician. Children may be referred by their school or foster care program. And certainly, as with all other doctors, patients may come to a geneticist of their own accord because of a specific concern.

The majority of geneticists work at medical schools, but a growing number are in private practice either individually or as part of a multispecialty group. As of 2002 there were 1,075 medical doctors certified in clinical genetics in the United States. Additionally, there were 151 persons with a PhD who were certified to see and counsel patients and 1,410 genetic counselors. Some of these people also hold certification in other areas of genetics, indicating that they received training and passed tests in at least one additional genetics field.

Table 1.1 Possible Reasons for a Genetics Consultation

Obstetric:	Woman with recurrent miscarriages or stillbirths
	Woman or man as part of an infertility evaluation
	Pregnant woman after an abnormal test of the fetus
	Couple if either member has a genetic or heritable condition
Pediatric:	Family history of a genetic or heritable condition
	Pregnant woman with an abnormality in the fetus
	Fetus miscarried/stillborn with a birth defect
	Infant with a birth defect
	Infant with a metabolic problem
	Family history of early infant deaths
Adult:	Diagnosis of a late-onset genetic condition
	Counseling and testing of a late-onset condition
	Family history of a "common" disease
	Extremely high cholesterol
	Early-onset dementia
	Cancer, particularly if early, multifocal, or otherwise unusual

THE GENETICS CLINIC VISIT

In practice, a visit to a geneticist is no different from any other doctor visit. You may be called and asked for some information ahead of time or be asked to bring family photos and to research your family history. The biggest difference you will see is likely to be the level of detail. The genetic interview includes an in-depth family history. You are probably used to telling what caused your parents' or grandparents' deaths. A clinical geneticist will want much more. This is discussed in Chapter 2. If the problem in question is a birth defect or mental retardation in your child, there will be questions about the pregnancy and the time around conception.

The genetics physical exam is not unusual except for the measurements taken. In addition to height, weight, and head circumference, common measurements include hand and foot length, arm span, ear length, distance apart of the eyes, and chest circumference. Other measurements may be done depending upon the problem under consideration. Clinical geneticists examining a child may ask who else in the family has particular features. They may also want to examine one or both parents or a sibling. Many clinical geneticists, particularly those dealing with birth defects and syndromes, will take photographs because, in this

business, a picture really is worth a thousand words. If photographs are to be taken, you will be asked to sign a permission form.

Tests done by a clinical geneticist are most frequently blood tests. Occasionally, a test is done on a small piece of skin or other tissue. If any tests are needed, the details will be explained to you during the clinic visit. The clinical geneticist may suggest tests that are familiar, such as X rays and ultrasounds, or may want unusual tests done on common samples. For example, a blood sample, a familiar thing, may be tested for DNA methylation patterns (a way to see whether genes are turned on or off), an unusual test.

Tests for genetic disease are developed first in research labs and then moved to clinical or "diagnostic" labs. Diagnostic labs must maintain quality control procedures not required of research labs and will only offer tests that have recognized usefulness and documented sensitivity and specificity. Diagnostic labs obtain and hold accreditation established by the Clinical Laboratory Improvement Amendments (CLIA), which certify that the labs meet specific professional and functional standards. This allows the labs to release test results to patients.

After the history and physical exam, and after any test results are back, you will receive as much information as is available. This is best done at a second in-person visit. Increasingly, clinical geneticists can give a specific diagnosis. There may be treatment options available, although not always. You will also receive counseling about what can be expected with the condition, what might be helpful at a child's school or in planning for the future, and what the chance is that this same condition will occur again in the family. The more common, or more classic, genetic risk predictions are dealt with in the following chapters.

There are some things that clinical geneticists cannot do. They cannot examine a child and say that the child is guaranteed to be genetically normal. They cannot predict future development, behavior, or illness any better than a child's pediatrician (or grandmother). A clinical geneticist may offer possibilities based on knowledge of a particular condition, but those will be generalizations about the condition more than specific information about you or your child. And a clinical geneticist will not tell you whether or not you should have children or make other specific life decisions: he or she will give you all the information you may need to balance risk and choices, but the final decision about your family structure and life choices is up to you.

As of this writing, all major insurance companies, including Medicaid, cover genetic services—doctor visits and testing. As with any medical situation, it is always a good idea to check with your insurance

company about their coverage and your particular plan. Because of discrimination concerns, some patients prefer to pay for the clinic visit and testing themselves. A clinic visit to a genetics doctor may cost a few hundred dollars. Costs for testing varies but can range from $50 to $2,000 depending upon the test. If your insurance plan covers genetic clinic visits and testing, your out-of-pocket costs will be the same as for any other medical specialist.

DISEASE INFORMATION ON THE INTERNET

Seventy percent of medical information on the Internet is wrong or outdated. It is common now for patients to research problems themselves, and the Internet is both useful and fraught with problems. There are two facts to be remembered.

First, stick to the big, well-established sites: the March of Dimes, the National Organization for Rare Disorders, the specific disease support group website. These pages are most likely to have updated, correct information that is free from bias. It must be remembered that these sites have to be useful to anyone who may use them. This means that there are long lists of symptoms and problems for each condition. These lists usually contain anything that has ever happened to anyone with the diagnosis. I caution patients and parents not to read such lists and assume that all these things are relevant to their family. Pick and choose what applies.

Second, list servers and chat groups can be very helpful. However, the anecdotes and comments that are shared lean toward the negative. People complain about their situation, their doctor, their insurance company, and so on. There are a few reason for this. One is that patients and families with more complicated cases are more likely to use the chat rooms. They have more things going on, so they have more things to think and talk about. Another is that the chat groups and list servers can serve a sort of "group therapy" function. They tend to be useful for people to vent their frustrations. People who are doing well are less likely to spend their time typing on their computers. Thus, the discussions are skewed and are not representative of the "average" experience.

GENETIC RESEARCH STUDIES

During your genetics clinic visit, you may be approached about participating in a research study, of which there are thousands. Some people

are not comfortable participating in studies, whether they are simple, like answering a few questions, or more complex, like helping test a new drug. That is fine. You will never be "punished" for not participating in a study; you will receive the same care that is otherwise available.

If you choose to participate, you will be helping others even if you get no direct benefit. Remember that information and treatment are available to you because others gave a blood sample or kept a diet diary or took a test. Many studies can be carried out using information in your medical chart or blood samples that you have given for other reasons, so there is no extra burden to you. You do not have to pay to participate in a study, but there may be some small expenses, such as parking. Insurance companies are not informed of a person's participation in a study, although, under some circumstances, they may be petitioned to pay for a medication or cover some other expense.

Some tests that are new or that are for rare diseases may remain in the research lab for a long time. They may not be available to you unless you are part of a study. Historically, research labs would share test results with their study subjects. In the 1990s this practice was made illegal because of quality control concerns, although it still took place under the table. Since 2000 there has been increased emphasis on patient privacy and segregating research from patient care. This has effectively ended the informal practice of releasing research study results to individual patients.

If you agree to participate in a research study, it is important to understand that you will probably not learn the test results. If the research lab has obtained CLIA certification, as mentioned above, you may have legal access to your results, although the burden may be upon you to contact one of the researchers and inquire. It is important to understand that obtaining and maintaining CLIA certification is a bureaucratic and financial burden to labs, so that most research labs will not have CLIA certification. Also, research labs that straddle this line—do research but have CLIA certification—may charge a fee for some or all of the sample processing.

Whatever the study, it is your right to know the risks and benefits. Giving "informed consent" does not just mean signing a piece of paper. It means understanding to the best of your ability what is happening. Table 1.2 lists some questions you can ask if you are approached about participating in a study. The person explaining the study should be able to answer all these questions—and any others you may have—to your satisfaction. If they are not, and you are interested in the study, ask to speak to another researcher before consenting to participate.

Table 1.2 Questions to Ask When Considering a Genetic Research Study

Financial disclosure
Who is doing the study?
Who is paying for the study?
Will there be any charge to my insurance company?
Goals of the study
What does the study test?
Is this a long-term or a short-term project?
Can I have a copy of any papers already written?
How will the results of the study be reported?
Will I get to know my own results?
Logistics
What do I have to do?
How many times do I have to do it?
Will I have to come back or do something over time?
Will I be admitted to the hospital for testing?
Will I be reimbursed for parking and other expenses?
Will the study arrange with my work/school for me to be absent?
Study subject rights
How will the study differ from routine care/treatment?
What are the risks of the study?
What are the potential benefits of the study to me? To others?
What happens if I get sick during the study?
What if a problem occurs during the study?
Can I drop out at any time?
If I've given a sample, how can I get it back if I drop out?
Will my sample be used for studies other than this one?
If so, will I be contacted beforehand?

Some groups of people are concerned about medical research in general, and genetic research in particular, because of historic study subject abuse. Because of that history, research involving human subjects is overseen by review boards and committees that require all research protocols to protect their participants. Even with these protections, some minority groups are understandably distrustful when approached about studies and choose not to participate. The unfortunate result is that diagnostic tests and treatments most helpful to these groups will be delayed. If you have concerns about genetic research because of your race, ethnicity, age, sex, socioeconomic status, or something else, please discuss

this with the researcher. The people most assisted by your participation are people just like you.

THE BIG PICTURE

Unlike other branches of medicine, genetics has developed a mystique. Some of this is understandable: genetics addresses health and illness at a level not previously available. On the other hand, genetics is not magic. It is just a tool. Genetics does not change the general aspects of medicine, it just expands them. For example, it was possible one hundred years ago to estimate someone's life span based upon the longevity of the parents or to predict the health and normality of a baby based upon the family and its environment. The idea of making predictions is not different. All genetics has done has improved, or at least formalized, our ability to predict.

So, you've been referred to a clinical geneticist. It is disturbing enough to have to see a specialist when a problem suddenly is found or suspected, but the mystique surrounding genetics makes this referral doubly uncomfortable. There is, however, nothing mysterious about genetics. In some ways it is more scientific than other branches of medicine. In other ways it is more about the "art" part of medicine. Whatever the reason for the visit, it will be about telling and receiving information, learning what decisions may need to be made, and realizing that you are not as alone in your situation as you may think.