Licensure of Genetic Counselors is critical to protect the public and ensure that Coloradans receive the advantages that personalized healthcare and genomic medicine have to offer.

Organizations Supporting HB15-1147:

The Arc of Colorado
Bright Pink
Children's Hospital Colorado
Colorado Academy of Family Physicians
Colorado Hospital Association
Colorado Medical Society
Colorado Ovarian Cancer Alliance
FACES of Colorado and Wyoming (chapter of Parent Project Muscular Dystrophy)
FORCE (Facing Our Risk of Cancer Empowered)
Huntington's Disease Society of America, Rocky Mountain Chapter
Invitae
Little People of America, Front Range Chapter
22Q Colorado
Miracles for Mito
Rocky Mountain Down Syndrome Association
University of Colorado Health

Licensure of Genetic Counselors is critical to protect the public and ensure that Coloradans receive the advantages that personalized healthcare and genomic medicine have to offer.

Individual Supporters of HB15-1147:

Denver Metro Area

Administrators

Susan Ash-Lee, MSW, LCSW, OSW- Director, Genetic Counseling Department, Rocky Mountain Cancer Centers
Stephen R. Daniels, MD – Chair, Department of Pediatrics, Children's Hospital Colorado
Susan Hicks, President and CEO, Sky Ridge Medical Center
David A. Schwartz, MD - Director, Center for Genes, Envt. and Health, National Jewish Health; Chair, Dept. Medicine, CU-SOM
Reginald L. Washington, MD – Chief Medical Officer, Rocky Mountain Hospital for Children

Clinical and Laboratory Genetics

Gary Bellus, MD, PhD
Peter Baker II, MD
Ellen R. Elias, MD
David K. Manchester, MD
Naomi Meeks, MD
Laura Pickler, MD, MPH
Margarita Sifuentes Saenz, MD
Elaine B. Spector, PhD
Matthew Taylor, MD, PhD
Janet M. Thomas, MD

Obstetrical Genetics

Lizbeth McCarthy, MD
Marsha Wheeler, MD

Maternal Fetal Medicine

Nick Behrendt, MD
Darleen Cioffi-Ragan, MD
Meghan Donnelly, MD
Henry Galan, MD
Teresa C Harper, MD
Jennifer Hodges, MD
Shane Reeves, MD
Julie Scott, MD
Joyce Sung, MD
Michael Zaretsky, MD

Surgery

Kenneth Blake, MD
Jane Kercher, MD
Joyce Moore, MD

Oncology (all subspecialties)

Virginia Borges, MD
Sami Diab, MD
Anthony Elias, MD
Christine Fisher, MD
Saketh Guntupalli, MD
Peter Kabos, MD
Lillian Klancar, MD
Nicole Kounalakis, MD
Catherine Klein, MD
Wells Messersmith, MD
Colleen Murphy, MD
Rachel Rabinovitch, MD
James Young, MD
Anne Zobec, NP

Radiology

Lora D. Barke, DO
Christine Bliven, MD
Kristin Freestone, MD
Kevin Lampert, MD, RIA/ISJ
Michael Lin, MD
Kay Denise Spong Lozano, MD
Michael Otte, MD
Peter Ricci, MD
Alison Sandberg, MD
Tara Tredennick, MD
Shane Wheeler, MD
Dulcy Wolverton, MD

Pathology

Dara Aisner, MD, PhD
Mark Lovell, MD
R. Weslie Tyson, MD

Neurology/Neuromuscular

Tim Benke, MD, PhD
Tim Bernard, MD
Amy Brooks-Kayal, MD
Kevin Chapman, MD
Abbie Collins, MD
Kristen Park , MD
Anne Stratton, MD

Physical/Rehabilitation Medicine

Mike Dichiaro, MD
Dennis J. Matthews, MD

Other Specialists

Dennis Ahnen, MD – Gastroenterology
Jennifer Barker, MD – Endocrinology
Nancy Miller, MD – Orthopedic Surgery
Frederic Deleyiannis, MD – Plastic Surgery
Jan Kief, MD – Internal Medicine, Former President, Colorado Medical Society
Luisa Mestroni, MD - Cardiology
Eric Silverstein, MD – Reproductive Endocrinology
Olrik Streubel, MD – Otolaryngology
Nicole Tartaglia, MD – Developmental Pediatrics
Duncan Wilcox, MD - Urology

Individual Supporters - Outside of Denver Metro Area

Mountains and Western Slope

Amy Gagnon, MD – Maternal Fetal Medicine
Mark Hancock, MD – Oncology
Paula Marchionda, MD – Oncology
Gayle Miller, MD – Radiation Oncology
Diana Morneault, RN - Oncology
Albert Schaefer, MD – Maternal Fetal Medicine

Southern Colorado

Sharon Halla, RN – Oncology
Laura Klein, MD – Maternal Fetal Medicine

Background Information on Genetic Conditions for Testimony of Patients & Parents regarding HB15-1147

Mindy – Parent of a child with 22q11.2 deletion syndrome

22q11.2 deletion syndrome (also known as DiGeorge syndrome, Velocardiofacial syndrome and several other terms) is a condition caused by the deletion of a small piece of chromosome 22 at location q11.2. This results in the loss of 30-40 genes from one copy of the 22nd chromosome, while the other copy of chromosome 22 is intact.

22q11.2 deletion syndrome has dozens of signs and symptoms that can affect almost any part of the body which can vary widely, even among affected members of the same family. Common signs and symptoms include congenital heart defects, cleft palate, disorders of the immune system due to abnormal development of the thymus, low levels of calcium in the blood due to parathyroid dysfunction which can result in seizures, growth delays and many other medical concerns. Many children with 22q11.2 deletion syndrome have developmental delays, including delayed growth and speech development, and learning disabilities. Later in life, they are at an increased risk of developing mental illnesses such as schizophrenia, depression, anxiety, and bipolar disorder. Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder are also more common.

22q11.2 deletion syndrome affects an estimated 1 in 4,000 people. However, the condition may actually be more common than this estimate due to under diagnosis.

Over 90% of cases of 22q11.2 deletion syndrome result from a random event (new genetic change). There is usually no family history of the condition. However, a person who has 22q11.2 deletion syndrome can pass the condition to their children with a 50% probability in any pregnancy. The condition may be more or less severe in a child who inherits the deletion. In some cases, a person may not realize they have the condition until their child is born with a much more severe form of the syndrome.

Adapted from Genetics Home Reference: http://ghr.nlm.nih.gov/condition/22q112-deletion-syndrome

Sarah – Individual with Spondyloepiphyseal Dysplasia

Spondyloepiphyseal dysplasia (SED) is an inherited disorder of bone growth that results in short stature (dwarfism), skeletal abnormalities, and problems with vision and hearing. This condition affects the bones of the spine (spondylo-) and the ends (epiphyses) of long bones in the arms and legs, and is present from birth. Diagnosis is based on the recognition of characteristic clinical features, X-ray findings and genetic testing.

People with SED have short stature from birth, with shortening of the spine and limbs. Adult height typically ranges from 3 feet to just over 4 feet though some individuals approach 5 feet. Progressive curvature of the spine can cause problems with breathing, and instability of the spine in the neck may increase the risk of spinal cord damage. Hip and foot problems can also occur. Arthritis and decreased joint mobility often develop early in life and are progressive. Vision problems and hearing loss occur more frequently in people with this condition.

SED is considered a rare genetic condition -- its exact incidence is not known. It results from changes in the *COL2A1* gene which provides instructions for making a protein that forms type II collagen. The *COL2A1* gene is essential for the normal development of bones and other tissues that form the body's supportive framework (connective tissues). Mutations in the *COL2A1* gene prevent bones and other connective tissues from developing properly.

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases of this condition result from new changes in the gene, with no prior family history of the condition. A person with SED has a 50% chance with each pregnancy to pass the altered gene down to a child, who will also have SED assuming that the other parent passes down a normally functioning copy of the *COL2A* gene. In some instances, if the other parent also has a form of dwarfism, there is the possibility that a child could have a more severe or even lethal form of dwarfism. Women with SED or other forms of dwarfism should be followed closely during any pregnancy as they may be at higher risk for obstetrical complications.

Adapted from Genetics Home Reference: http://ghr.nlm.nih.gov/condition/spondyloepiphyseal-dysplasia-congenita

Noelle – Individual with Li-Fraumeni syndrome

Li-Fraumeni syndrome (LFS) is a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults.
The cancers most often associated with Li-Fraumeni syndrome include breast cancer, a form of bone cancer called osteosarcoma, and cancers of soft tissues (such as muscle) called soft tissue sarcomas. Other cancers commonly seen in this syndrome include brain tumors, cancers of blood-forming tissues (leukemias), and a cancer called adrenocortical carcinoma that affects the outer layer of the adrenal glands (small hormone-producing glands on top of each kidney). Several other types of cancer also occur more frequently in people with Li-Fraumeni syndrome.

Li-Fraumeni syndrome results from mutation in a gene called *TP53* which normally functions as a tumor suppressor in cells. Typically, a person is born with a germline mutation in one copy of the *TP53* gene. If the remaining normal copy of TP53 gets "knocked out" and no longer functions in various cells during the individual's lifetime, cancers are more likely to develop in those organs.

Li-Fraumeni syndrome is inherited as an autosomal dominant condition. Usually, it is passed down through a family from affected individuals to their children, though it can sometimes occur "by chance" in a person who has no family history of the condition. Each child of a person with Li-Fraumeni syndrome has a 50% chance of also developing the condition.

Early identification of individuals at risk for Li-Fraumeni syndrome is very important because it allows for careful surveillance and early detection of cancers that may rise in any person carrying the genetic change. Currently, it is recommended that:

(1) children and adults undergo comprehensive annual physical examination
(2) women undergo breast cancer monitoring, with annual breast MRI and twice annual clinical breast examination beginning at age 20 years. The use of mammograms in this age group has been controversial because of radiation exposure and limited sensitivity.
(3) beginning at age 30 years, annual mammograms alternating with breast MRI, with one modality every six months
(4) consider routine screening for colorectal cancer with colonoscopy every 2-5 years beginning no later than age 25 years
(5) individuals consider organ-targeted surveillance based on the pattern of cancer observed in their family. Intensified surveillance with whole-body MRI protocols for adults and children who carry a germline *TP53* mutation are being evaluated in investigational settings.

People with germline *TP53* mutations should: (1) avoid known carcinogens including sun exposure, tobacco use, occupational exposures, and excessive alcohol use; and (2) minimize exposure to diagnostic and therapeutic radiation.

Adapted from Gene Reviews www.ncbi.nlm.nih.gov

Children's Hospital Colorado

www.childrenscolorado.org

February 17, 2014

Colorado General Assembly
House Health, Insurance, and Environment Committee
200 East Colfax Avenue
Denver, CO 80206

RE: Please support House Bill 15-1147

Dear Members:

On behalf of Children's Hospital Colorado, we respectfully submit this letter of support for House Bill 15-1147, concerning the regulation of genetic counselors. Licensure of genetic counselors will support the families and children that we care for. Additionally, this legislation will help us ensure that as a large employer, we are able to hire professional staff with appropriate credentials and training, and licensure of the profession will lead to more appropriate and efficient utilization of health care resources.

As you know, the field of medical genetics has experienced tremendous growth in recent years. Genetic counselors are master's trained health care professionals who provide support to patients with information, education and advocacy related to medical conditions that are either entirely or partially determined by genetic factors. This legislation would permit licensure and title protection for this expanding profession, and Colorado would join 19 other states that currently provide licensure for genetic counselors. The legislation will not prohibit other licensed health care providers such as physicians or nurses from providing genetic counseling services under their existing scope of practice.

There are several types of specialties within the profession, including pediatrics, that focus on caring for children and adolescents. Currently, 29 percent of genetic counselors in Colorado serve in a pediatric-specific capacity. Children's Hospital Colorado currently contracts with or employs 19 genetic counselors through the Anschutz Medical Campus to support families and children prior to the diagnosis of a genetic disease and as needed for subsequent outpatient visits. They are a critical member of the health care team at Children's Hospital Colorado, providing care for children diagnosed with conditions such as birth defects, chromosomal abnormalities, autism spectrum disorder and Fragile X Syndrome.

We ask for your support of House Bill 15-1147. Please do not hesitate to contact us if you have any additional questions. Thank you for your consideration.

Sincerely,

Stephen Daniels, MD, PhD
Pediatrician-in-Chief

Suzy Jaeger
Senior Vice President,
Ambulatory & Network of Care

Heidi Baskfield
Executive Director of Advocacy

Marcie Schulz
1564 Lane 1 N.
Alamosa, CO 81101

January 23, 2015

Members of General Assembly,

In December of 2014 I was diagnosed with early stage III triple negative breast cancer. At 44 years of age and no family history of the disease it was a devastating diagnosis. I chose to go to the University of Colorado Cancer Center. The first appointment I had was with a Genetic Counselor by the name of Lisa Ku. With no knowledge of what the purpose of the genetic counseling was I can honestly say that by the end of my appointment I had more knowledge about the cancer I had, how it develops, why treatments work based on the rapid rate of the cancer cell division, what genes panels they are able to test for and what the results of the genetic testing can mean to me.

As a young breast cancer patient the information from the genetic testing gave me additional information that I didn't know at the time I needed to know. It has the ability to tell me if I have markers for other cancers and what my odds are a developing a second cancer in the other breast. It also has the ability to tell me if I had the mutated gene BRACI or BRACII that is based off of a mix of Spaniard Ancestors and Jew Ancestors that migrated to our country. They intermixed and a mutated gene was formed that made those with the gene more susceptible to getting cancers. Ironically my ancestors are from Spain and no one knew if there was a mixture in our family. Also the biggest concentration of these cases have been found in the San Luis Valley. I have lived in the San Luis Valley my whole life and had never heard of this gene.

These markers became crucial to me and my wellbeing because I could make better decisions about my treatment plan. Knowing the percentage chance of getting a second cancer in the other breast will definitely aid me in my decision of whether to have a lumpectomy, mastectomy or bi-lateral mastectomy. The information I gained made me not want to be threatened by my diagnosis but as aggressive and pro-active as I could with all the additional information I had gained. I was very fortunate and all of my markers came back negative but had they not I would have definitely been looking at my options to prevent the other cancers.

For everyone to have the same opportunity as I did and receive the genetic testing would be a blessing during the treatment process. It gives you the ability to make better, more informed decisions and be pro-active about your health. At a time when my life felt

overwhelming and out of control it gave me a peace to know that I could find out more than just my current diagnosis and have some plan in place to give myself better odds.

Regards,

Marcie Schulz

Children's Hospital Colorado

www.childrenscolorado.org

January 20, 2015

Colorado General Assembly
State Capitol
200 E. Colfax Ave.
Denver, CO 80203

RE: Licensure of Genetic Counselors in Colorado

Dear Members of the Colorado General Assembly:

We are writing to urge you to vote in favor of the bill for licensure of genetic counselors currently before the 2015 Colorado General Assembly. We are all American Board of Medical Genetics (ABMG) certified clinical, metabolic and/or molecular geneticists on the faculty of the University of Colorado School of Medicine. We are writing as individual physicians and are not presenting an official position of the University of Colorado. We provide medical care and laboratory diagnostic services to children and their families at Children's Hospital Colorado in Aurora, its Network of Care sites in Denver and Colorado Springs, and at five outreach genetics clinic sites in Colorado (Alamosa, Durango, Grand Junction, Greeley and Pueblo). Genetic counselors play a critical role in the provision of quality genetic services to the citizens of Colorado.

New advances in medical genetics are announced every week. Genetic testing is being used routinely in most medical specialties. Public demand for genetic services has surged dramatically over the past decade. Critical healthcare decisions regarding medical and surgical treatments are increasingly being based upon recognition of genetic risk factors and the results of an expanding menu of genetic tests. These tests are often quite complex, and must be selected appropriately and interpreted carefully in the context of each patient's specific history. Correct use of genetic tests is critical to ensure that the results will be directly applicable to the patient's medical issue, and that healthcare dollars will not be wasted. In some instances, screening of the general population for genetic predispositions to development of chronic diseases is done so that early prevention strategies can be implemented with the goals of reducing morbidity and mortality, and saving healthcare dollars.

Currently, the number of physicians in the United States with specific training and certification in medical genetics specialties is small. We increasingly depend upon genetic counselors to help us provide quality genetic services to patients. Additionally, the growing utilization of genetic information in oncology, cardiology and other medical fields means that a large proportion of genetic testing is now being performed outside of traditional clinical genetics departments in academic medical centers. Community hospitals and private medical practices often rely upon genetic counselors to provide appropriate genetic risk assessment, genetic test selection, and pre- and post-test informed consent and education to patients. Most genetic counselors in Colorado now work in specialty settings such as oncology clinics where they are expected to be the "genetics expert" for their center, without involvement of a medical geneticist. Employing institutions may not be familiar with the standards critical for identifying and hiring appropriately trained professionals for these positions. Licensure provides assurance to hospitals that they can identify qualified genetic counselors for their staffs, thus promoting public safety and access to quality services for patients.

Currently, there is no legal standard in Colorado that defines who can represent themselves as genetic counselor or establishes minimal standards for education, certification or continuing education. Although the American Board of Genetic Counseling (ABGC) certifies genetic counselors, genetic counselors in Colorado are currently not required to be board certified/ eligible, to maintain certification, or to engage in continuing professional education, despite the ongoing rapid advances in the field. Licensure would provide a mechanism by which claims of incompetent, unethical, and/or unlawful behavior of a genetic counselor could be investigated and for sanctions to be placed against a genetic counselor for proven offenses of these claims. Revocation of ABGC certification has limited, if any, consequences; it does not prevent a genetic counselor from continuing to practice in Colorado. Therefore, regulation via title protection and/or certification alone does not adequately protect the public.

Some examples of how improper practice by genetic counselors can lead to public harm include:

- Inaccurate risk assessment of medical and family history
- Incorrect selection of genetic testing
- Misinterpretation of genetic test results
- Provision of information that leads to inadequate surveillance for or the under/overtreatment of a genetically-based disease
- Failure to refer a patient to a medical doctor for further evaluation/treatment if a genetic disease is identified or suspected during the course of genetic counseling

In many situations, errors by a genetic counseling can also adversely affect the patient's family members, who may also be at risk for the genetic condition present in the patient.

To date, 19 states have passed statutes licensing genetic counselors, including several in our region: Utah, New Mexico, Nebraska, South Dakota and North Dakota. Several additional states are considering licensure bills during the current legislative session. ***We believe that Colorado should likewise be <u>proactive</u> in this effort rather than waiting for patient harm to occur.***

For all of the above reasons, we believe that it is essential that statutory regulation of the genetic counseling profession through licensure is approved in Colorado. Please do not hesitate to contact Dr. Gary Bellus, Interim Section Head of Genetics, on our behalf if we may address any additional questions or concerns.

Sincerely yours,

Gary Bellus, MD., PhD
Associate Professor, Pediatrics
Interim Section Head & Clinical Medical Director
Section of Genetics, Department of Pediatrics
University of Colorado, Anschutz Medical Campus
Phone: 303 724-2330
Gary.bellus@childrenscolorado.org

Also affirmed by:

Peter Baker II, MD
Assistant Professor, Pediatrics
Clinical Genetics and Metabolism

Ellen R. Elias, MD
Professor, Pediatrics and Genetics
Director, Special Care Clinic

Naomi Meeks, MD
Instructor, Pediatrics
Clinical Genetics and Metabolism
Assistant Director, DNA Diagnostic Laboratory

David K. Manchester, MD
Professor, Pediatrics
Director, Regional Genetics Program
Clinical Genetics and Metabolism

Laura Pickler, MD, MPH
Assistant Professor, Pediatrics and Family Medicine
Special Care Clinic

Margarita Sifuentes Saenz, MD
Assistant Professor
Clinical Genetics and Metabolism

Elaine B. Spector, Ph.D.
Professor, Pediatrics
Director, Denver Genetics Laboratories at CHCO - DNA Diagnostic Laboratory

Janet Thomas, MD
Associate Professor, Pediatrics
Director, Inherited Metabolic Diseases Program

Huntington's Disease Society of America

Rocky Mountain CHAPTER

February 4, 2015

Colorado General Assembly, State Capitol
200 E. Colfax Ave. Denver, CO 80203

RE: Licensure of Genetic Counselors in Colorado

Dear Members of the Colorado General Assembly:

The Huntington's Disease Society of America's Rocky Mountain Chapter Board of Directors and Licensed Clinical Social Worker are writing to urge you to vote in favor of the bill for licensure of genetic counselors currently before the 2015 Colorado General Assembly.

Currently there is no legal standard in Colorado that defines who can represent themselves or use the title of 'genetic counselor'. This lack of regulation puts the Huntington's disease (HD) community at risk. Huntington's disease is an inherited, degenerative, and terminal neurological illness. If a person has the gene that carries HD, his or her children are at 50% risk of inheriting the gene that causes HD. If a person has the gene that causes HD, he or she will develop the disease in their lifetime, usually between the ages of thirty and fifty. The process of genetic testing for HD requires professional competency due to the very sensitive nature of finding out the results of a test that will have a profound effect on a person's life as well as their family members and offspring.

Not only is there currently no title protection for genetic counselors, but there is no legal requirement in Colorado for genetic counselors to be board certified or board eligible in order to practice. Also, there is no current requirement for continuing education of genetic counselors. A new Board of Genetic Counselors would provide a mechanism for investigations of improper, illegal, unethical, or incompetent actions of genetic counselors.

Lack of regulation of genetic counselors can lead to public harm. We have heard many stories of people receiving their HD genetic testing results improperly. Some have heard that they have the gene that causes HD through a voicemail message. Some have been told, "I *think* you are gene negative". This is a highly sensitive time for people hearing their results; in fact the most dangerous time for suicide completion for the HD community is the first 6 weeks after a positive HD gene test result.

The HDSA Rocky Mountain Chapter strongly supports State licensing for genetic counselors in Colorado. Please do not hesitate to contact us if you would like more information. Our Licensed Clinical Social Worker can be reached at (303) 321-5503.

Sincerely,

Marcella DeVargas
Marcella DeVargas
Vice President, Board of Directors
HDSA Rocky Mountain Chapter

Sharon R. Cascone
Sharon R. Cascone, MSW, LCSW
Chapter Social Worker
HDSA, Rocky Mountain Chapter

6545 W 44th Avenue #1, Wheat Ridge CO 80033 | T. 303.237.9937 F 303.837.8083 | www.hdsa.org/co

Children's Hospital Colorado

www.childrenscolorado.org

February 10, 2015

Colorado General Assembly
State Capitol
200 E. Colfax Ave.
Denver, CO 80203

RE: Licensure of Genetics Counselors in Colorado

Dear Members of the Colorado General Assembly:

I am writing to urge you to vote in favor of the bill for licensure of genetic counselors currently before the 2015 Colorado General Assembly.

By way of introduction, I am the Chair of the Department of Pathology and Laboratory Medicine at Children's Hospital Colorado and have been directly involved with the clinical application of molecular genetics throughout most of my 30-year career. I am a licensed physician in the State of Colorado and am board certified by the American Board of Pathology in anatomic and clinical pathology, pediatric pathology and molecular genetic pathology. I am also board certified by the American Board of Medical Genetics as a clinical molecular geneticist. I helped found the Association for Molecular Pathology, serving as its President in 2005, and am currently a member of the committee that certifies new molecular genetic pathologists. Most of my professional career has centered on applying our new knowledge of molecular genetics to clinical testing for infectious disease, inherited disorders, leukemia and cancer, especially in children. Through my work I have come to value the essential contribution of genetic counselors in providing direct patient care.

Our society has benefited from a virtual explosion in our knowledge of the human genome over the past few decades with over 5000 specific genetic diseases now recognized with specific tests to diagnose them in patients and at-risk family members. In addition, our understanding of cancer and its effective treatment is increasingly dependent on specific molecular markers which allow targeted lifesaving therapy.

Most physicians do not have the time or expertise to keep pace with the flood of information that is currently available related to this revolution in personalized medicine.

Genetic counselors are uniquely qualified to help fill this gap and assist the medical community in applying this new knowledge appropriately for the benefit of patients and their families.

I have benefited directly from working with genetic counselors in a variety of settings. Genetic counselors possess the knowledge and skills to analyze the clinical presentation, family history, and medical record, and then suggest the most appropriate and cost effective testing.

Genetic counselors impact not only an individual patient, but generations of a family. Some disorders, such as Fragile X syndrome, not only impact the intellectually impaired boy, but his mother who suffers from premature ovarian failure, and his grandfather who develops a movement disorder later in life. Genetic counselors also help families understand what their risks are for having more children affected with the condition so that they can make informed reproductive decisions.

Many cancers run in families. Identifying individuals who carry these mutations so they can be tested and monitored before the cancer develops, not only spares them from suffering or even dying of cancer, but saves health care dollars as well.

As the laboratory medical director at Children's Hospital Colorado, I have relied on a genetic counselor to help save the expense of unnecessary testing ordered by well meaning, but uninformed clinicians, who don't understand how to appropriately and cost effectively apply the powerful genetic testing we now have available.

I have directly observed the value of genetic counselors in a variety of settings. Their knowledge combined with their skills in calculating risk and taking the time to appropriately counsel a family in making difficult decisions carries a real potential for harm either through commission or omission. Perhaps what I admire most about the clinical practice of genetic counselors is that they do not insert their personal opinions or beliefs into their work. They are dedicated to providing the most complete, objective information possible, ensuring that the family understands this information and their options, so that the family can decide what course of action is best for them to follow.

Licensure is a means of ensuring patient safety by establishing minimum standards for education, certification, and continuing education in this rapidly changing and challenging field. It is in the best interests of the citizens of Colorado that we follow the lead of 19 other states, including Utah, New Mexico, Nebraska, and North and South Dakota, to protect their well-being by licensing genetic counselors.

If I can provide additional information regarding any questions or concerns you have about this important public health and safety issue, please contact me and thank you for your consideration.

Sincerely,

Mark A. Lovell, MD
Professor of Pathology and Vice Chair for Pediatric Pathology
Department of Pathology, School of Medicine
University of Colorado Denver, Anschutz Medical Campus
Chair and Laboratory Medical Director
Children's Hospital Colorado

St. Mary's
Advanced Medicine
Pavilion

Regional Cancer Center

Colorado General Assembly
State Capitol
200 E. Colfax Ave.
Denver, CO 80203

RE: Licensure of Genetic Counselors in Colorado

Dear Members of the General Assembly:

This letter is written in support of licensure for genetic counselors in Colorado. St. Mary's Cancer Center supports the importance of genetic counselors as an essential member of the health care team. St. Mary's Hospital and Regional Medical Center is the only health care organization between Denver and Salt Lake City to employ a full time genetic counselor.

St. Mary's Hospital and Regional Medical Center relies on our health care providers to provide appropriate and accurate information to our patients. Licensure serves as a mechanism of assuring that quality health care is provided by appropriate by trained genetic professionals. The increasing complexities of medical genetics and the increasing number of tests available for clinical application necessitates the move to regulation and monitoring of those providing this information to patients.

St. Mary's Hospital and Regional Medical Center values continuing education for our associates. Continuing education provides opportunities for our health care providers to stay current in their respective medical specialties. Licensure for genetic counselors that includes continuing education requirements would assure that practicing genetic counselors remain current in their knowledge of genetic testing and changes in a rapidly advancing field.

Genetic counseling is a time intensive process. St. Mary's Hospital and Regional Medical Center recognizes that as mid-level providers, genetic counselors can take the appropriate time necessary to meet a patient's needs. Formal recognition of genetic counselor through licensure may enhance the frequency with which patients are referred to genetic counselors and may improve access to genetic counselors in the more remote areas of the state.

Thank you for your consideration,

Diana Morneault

Diana Morneault, RN, MS, OCN
Director of Oncology Services
St. Mary's Regional Cancer Center
Grand Junction, CO 81502
970-298-2435

PLEASE SUPPORT HB 15-1147:

LICENSURE OF GENETIC COUNSELORS

(Sponsored by Rep. Joann Ginal; Sen. Nancy Todd)

Background Information:

Genetic Counselors are Master's trained health care professionals who provide consumers with assessment, information, education, resources and emotional support for medical conditions that are either entirely or partially determined by genetic factors.

New genetic discoveries are impacting all areas of medicine. The provision of quality genetic counseling services is critical, as consumers increasingly make healthcare decisions based upon genetic risk factors. Results of genetic tests guide care for pediatric and adult patients with cancer, neurological disorders, heart conditions and hundreds of other health problems. Thousands of new genetic tests have been developed and technologies are changing rapidly. Many of these tests are complex and the results may be difficult for patients or healthcare professionals to clearly understand.

Colorado should be proactive in affording this protection to the public, as 19 other states, including several in our immediate referral region (Utah, New Mexico, Nebraska, South Dakota, North Dakota) have already done.

HB 1147 and Licensure of Genetic Counselors will:

- Define who can represent themselves as a Genetic Counselor, has met the state's minimum education, board certification and continuing professional competency standards and is qualified to perform genetic risk assessment, order genetic testing, explain the results, and assist other health care providers in identifying appropriate management approaches for the patient.
- Provide a mechanism by which claims of incompetent or "out of scope" behavior of a Genetic Counselor could be reported, investigated and addressed.
- Allow Coloradans to easily identify practitioners specifically trained to work with them to ensure that the right genetic tests are selected, informed consent is properly provided, and test results are accurately understood for use in medical and family decision-making.
- Expand access to genetic counseling services in hospitals, clinics and other healthcare settings as demand for genetic services continues to increase.
- Assist hospitals and other employers with recognizing, hiring and, as appropriate, credentialing qualified Genetic Counselors.
- Promote a quality, integrated healthcare approach by requiring that Genetic Counselors refer patients with a genetic condition needing medical evaluation or treatment to a physician for further assessment.
- Save healthcare costs to employers, health insurers and taxpayer funded programs like Medicare and Colorado Medicaid.
- *Not* prohibit other licensed healthcare providers (e.g. physicians and nurses) from providing genetic counseling services as per their scope of practice.

For additional information on HB15-1147 please call

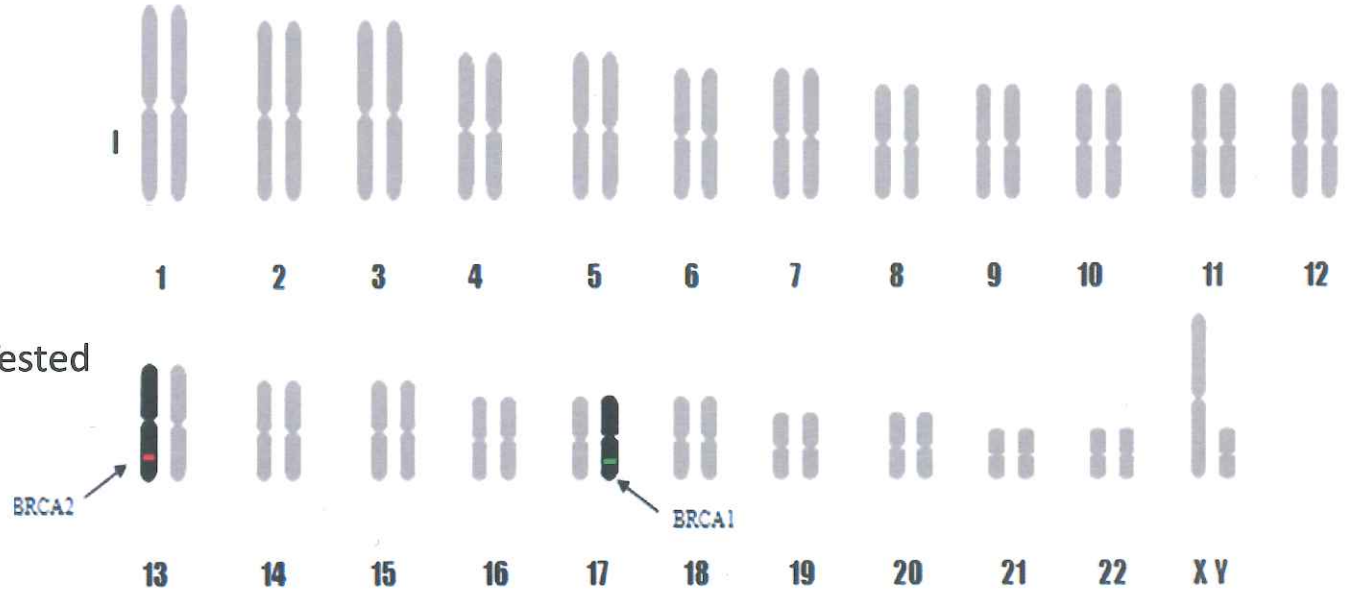
Betsy Murray 303-478-1207 **Ellen Caruso 720-530-3034**

Advances in Genetic Testing for Hereditary Cancer Predisposition

1995

BRCA1 and BRCA2

Only Breast Cancer Genes Tested



2015

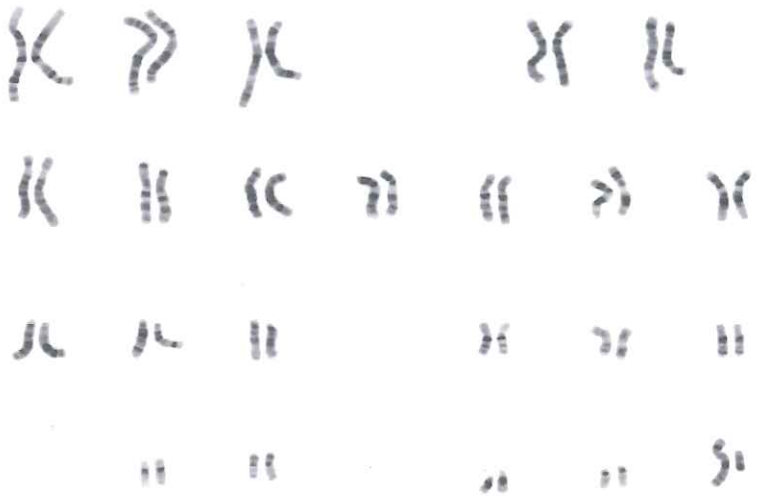
Multi-Gene Panels

Several Cancer Genes Tested

	Breast	Ovarian	Colon	Endometrial	Melanoma	Pancreas	Gastric	Prostate	Other Cancer / Clinical Features
BRCA1	BR	OV				PA		PR	
BRCA2	BR	OV			ME	PA		PR	
MLH1		OV	CO	EN		PA	GA		OC
MSH2		OV	CO	EN		PA	GA		OC
MSH6		OV	CO	EN		PA	GA		OC
PMS2		OV	CO	EN		PA	GA		OC
EPCAM		OV	CO	EN		PA	GA		OC
APC			CO			PA	GA		OC
MUTYH			CO						OC
CDKN2A					ME	PA			
PALB2	BR					PA			
STK11	BR	OV	CO			PA	GA		OC
PTEN	BR		CO	EN					OC
TP53	BR		CO			PA			OC
CDH1	BR		CO				GA		
BMPR1A			CO				GA		OC
SMAD4			CO				GA		OC
ATM	BR					PA			OC
BARD1	BR	OV							OC
BRIP1	BR	OV							
CDK4					ME				
CHEK2	BR		CO					PR	
NBN	BR								
RAD51C	BR	OV							
RAD51D		OV							

From Karyotype to Microarray

A major advance in the detection of sub-microscopic chromosome abnormalities, significantly increasing the likelihood of identifying a specific genetic diagnosis in the patient.



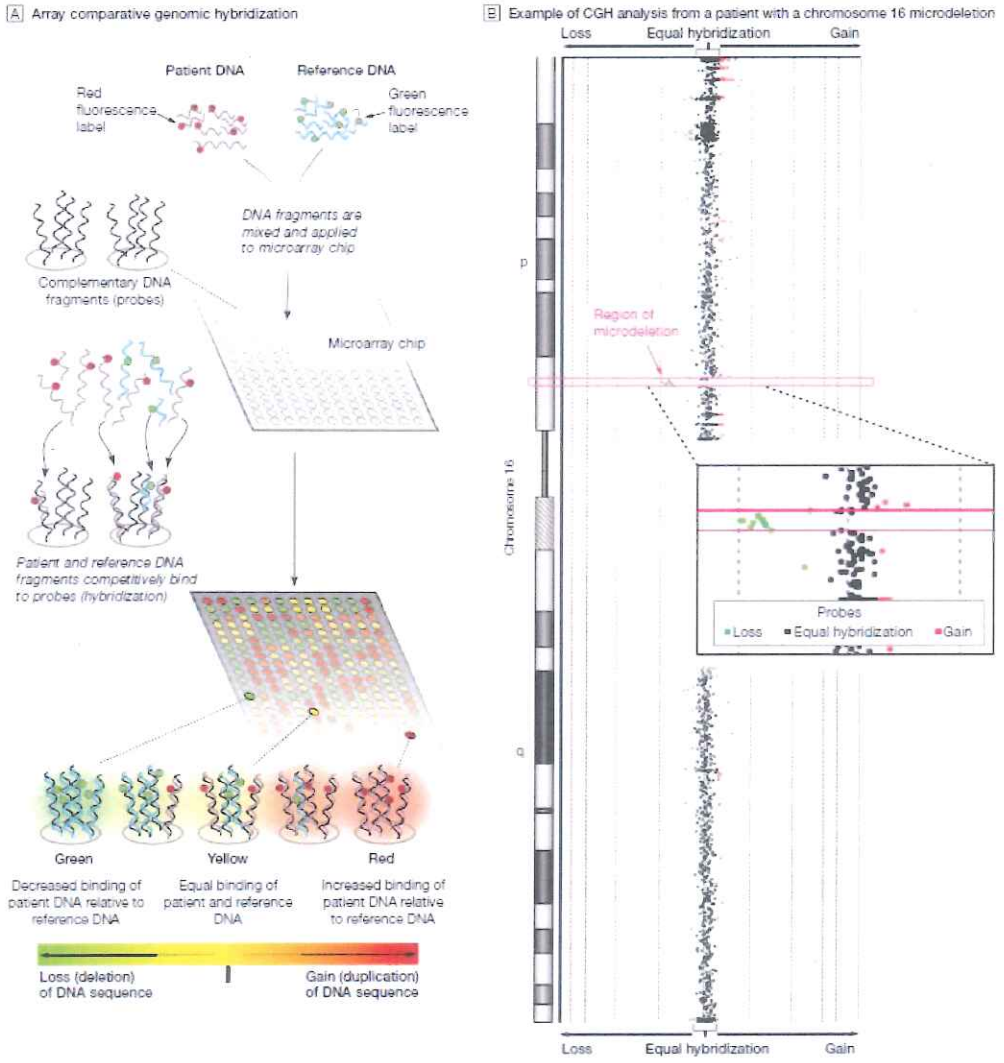
Humans typically have a total of 46 chromosomes arranged into 23 pairs. One copy of each chromosome pair is inherited from each parent. Each chromosome is a tightly condensed strand of DNA containing the genetic code of hundreds to thousands of different genes. Approximately 20,000 different genes are arranged along the chromosomes in a human cell.

The diagram above is called a "Karyotype" or picture of the chromosomal content of one cell as seen using a high-powered microscope. Until recently, detection of chromosome imbalances relied primarily on this visual recognition of missing or extra pieces of chromosomes.

In 2015, the first-line test for detection of chromosome imbalance is called a "Microarray" as shown to the right. It detects much smaller imbalances in the DNA using molecular laboratory techniques coupled with computer analysis. This tells the clinician precisely which genes are deleted or duplicated in the patient.

Microarray has greatly improved the ability to confirm diagnoses in patients with congenital anomalies, disorders of growth, intellectual disability, autism and other genetic conditions. However, informed consent, results interpretation and genetic counseling can be quite complex due to microarray's increased sensitivity and resulting ability to detect small DNA changes of unclear clinical significance.

Figure 2. Detection of Chromosome Deletion or Duplication by Array Comparative Genomic Hybridization



A, Array comparative genomic hybridization (CGH) consists of mixing fragmented DNA from the patient and a reference sample labeled with different fluorescent dyes (red and green, in this case). These fragments are allowed to bind (hybridize) by base pairing to complementary genomic DNA fragments (probes) that have been immobilized on a glass chip. If there is equal binding of patient and reference DNA, yellow fluorescence results. Deletion of a DNA segment in the patient sample results in decreased binding of patient DNA relative to reference DNA and green fluorescence (loss). Duplication of a DNA segment in the patient sample results in increased binding of patient DNA relative to reference DNA and red fluorescence (gain). B, Example of array CGH analysis from a patient with a chromosome 16 microdeletion. Data markers represent probes on the array and are plotted next to the corresponding position on the chromosome ideogram (left). Black data markers are probes within an established range representing equal binding. Probes that fall outside this range are indicated as loss or gain.

Molecular Genetics & Genomic Medicine

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INVITED COMMENTARY

From genetic counseling to "genomic counseling"

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Genetic counseling is "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease." Traditionally, this process includes collecting and interpreting the family and medical history, risk assessment, a comprehensive educational process for potential genetic testing, informed consent, and psychosocial assessment and support (National Society of Genetic Counselors' Definition Task Force et al. 2006). While genetic counseling falls within the scope of many health care professionals, clinical geneticists (physicians) and masters level genetic counselors have been working in the United States for more than 40 years, providing genetic counseling primarily for single-gene conditions. Debate about what "genomic counseling" will include and who will practice it has been fueled by the transition from single-gene focused genetic counseling and testing to a full genomic medicine approach. The routine incorporation of genomic medicine will likely induce differences in the *scope*, *approach* and *process* of genetic counseling (Table 1). In this commentary, I will discuss the several areas where practice will likely change as we move toward "genomic" counseling, with a focus on the unique skills and roles that genetic counselors and clinical geneticists provide.

The Family History and Risk Assessment

A cornerstone of a genetic assessment is obtaining and interpreting the family history, whether by phone, through a paper or web-based interface, or as part of a clinic visit. Traditionally, the personal and family medical histories have been used to develop a differential diagnosis, to identify and quantify risk for family members, and to select the appropriate test and proband (Pyeritz 2012). Taking an oral family history orally has also been useful in learning about the health beliefs and risk perceptions of family members and assessing communication patterns related to disclosure of genetic information (Bennet 2004). This is especially important when there is a family history of inherited disease, and individuals have experiential knowledge, and often come in with knowledge of the lived experience, and often strong feelings about the condition, their own potential risks and whether they wish to obtain predictive knowledge about genetic risk. As discussed later, this leads to self-selection in those who ultimately undergo predictive testing and when they choose to be tested.

Further emphasizing the importance of the family history, whole exome sequencing (WES) and whole genome sequencing (WGS) may not provide full coverage of critical genes, and the family history allows the genetic team to generate a differential diagnosis and order more sensitive genetic testing if necessary. As WES/WGS increases in sensitivity, however, family history will be critical for prioritizing variant analysis and adding perspective (pretest probability) to the interpretation of susceptibility genes and findings "incidental" to the clinical indication for testing. (e.g., Ashley et al. 2010; Dewey et al. 2011). Additionally, family history will provide a roadmap for evaluating how variants of unknown significance segregate with affected family members. Genetic counselors and clinical geneticists are well positioned for obtaining tailored family histories, using it to provide anticipatory guidance regarding what a genomic study may identify, identifying the relevant individual and family health beliefs, and supporting family communication about genetic risks, especially until a time when genome sequencing becomes the ubiquitous part of medical care.

Education and Informed Consent

The traditional approach to genetic counseling for single-gene disorders is highly education focused, and genetic counseling sessions can last 30–90 min or more. A recent practice analysis suggests typical genetic counseling

Table 1. Changes that will impact the transition to "genomic counseling."

Scope	Approach	Process
Increased number of conditions included in testing	A move from testing based on a specific clinical indication to broader testing approaches	Importance of bioinformatics and EMR to facilitate clinical incorporation of genomic results effectively
Increased number of "positive" and uncertain results, and overall increased number of disclosed results	Balancing increased uncertainty around variable (and changing) clinical validity and utility of genomic results	"Who, what and when" aspects of genomic testing and counseling still under debate
Increased time spent with clinicians	A move from a diagnosis focused approach toward a preventative approach where genomics influences both medical and personal aspects of healthcare	A likely but controversial shift from the historical focus on patient autonomy and nondirectiveness toward a more preventative health approach emphasizing behavior change

EMR, electronic medical record.

sessions can include (but are not limited to): a review of general genetic principles, modes of inheritance, family/individual specific risk assessment, an in depth discussion of the diagnosis and natural history, potential testing options, and case management for the condition occurring within the family or for which they are at risk (Hampel et al. 2009). Ideally, in a genetic counseling session, a psychoeducational and person-centered approach allows the information to be tailored to the person's understanding level, culture, and personal context. As genomic medicine progresses, genetic counselors and geneticists remain well positioned as experts in the benefits and limitations of the technology and the clinical implications of Mendelian and non-Mendelian genetic conditions. Additionally, genetic counselors have expertise in risk communication, genetic and health literacy, and numeracy. It remains to be seen if the genomic revolution will require genetics practitioners to subspecialize in order to master the increasing amount of genetic information, or to become clinical generalists in order to address the full range of information a genome will provide. I suspect we will need both to navigate the future genomic revolution.

Given the issues in "scope" mentioned in Table 1, pretest informed consent for genomic testing can no longer maintain the traditional "comprehensive" educational approach for single gene disorders described above, as patients neither have the ability nor desire to comprehend that volume of information. We are seeing this already in clinical practice; as "panel tests" become more commonly used for specific clinical indications, many genetic counselors have already transitioned their pretest informed consent discussions to broadly explain the indications for testing, the focus of the test, the range of findings that may result, and the potential benefits and limitations of testing. However, result sessions remain focused on the disorder and its potential management when a pathogenic variant is identified, emphasizing testing limitations, additional testing options, and residual risks when a variant of uncertain significance (VUS) or no variant is identified. Educationally, this benefits the patients, who may be overwhelmed by the sheer volume of pretest information and find many of the clinical conditions personally irrelevant until a result is demonstrated in their family. As genetic counselors develop variations on the concept of "generic consent" (Elias and Annas 1994), research should be performed to examine not only what patients hypothetically believe they want to know in order to consent to genome testing, but also retrospectively, to examine what approaches are most effective and useful for patients in deciding whether to undergo genetic testing, and which variables most influence the desired pretest information.

A new challenge in genetic counseling will be discussing which incidental findings, if any, will be assessed and returned to patients, creating a plan for such return of results, and documenting the patients' decline of such information if applicable. As part of these discussions, it will be important to remember that patients may have low familiarity and few formed opinions about the "lived experience" for this wide range of conditions, which could make it more challenging to make informed decisions in this area.

Finally, genetic counseling has developed models of service delivery that go beyond the traditional "face to face" approach – these include phone or telemedicine counseling, and both static and interactive e-learning approaches, sometimes to augment "live" genetic counseling and sometimes as a stand-alone education approach,. In recent years, direct-to-consumer (DTC) approaches have evolved from these educational approaches. Genetic counselors and geneticists are trained in patient education and will continue to find roles in developing interactive educational content across many of these venues. I encourage research on the effectiveness of these approaches, and clinicians may need to have multiple educational approaches available to address the varied learning styles of patients.

Ordering and Interpreting Genetic Tests

Genetic counselors and clinical geneticists have traditionally served as the "genetic experts," in medicine, often in a consulting role despite being a primary medical specialty. In the past decade, genetic counselor roles have expanded significantly from the original prenatal and pediatric genetic counselor roles. A significant minority have taken on "laboratory genetic counselor" roles (National Society of Genetic Counselors 2012), serving a critical role in assuring that the proper genetic testing is ordered on the correct person, and that the ordering physicians understand the result and its implications (Scacheri et al. 2008). Clinical genetic counselors in specialty areas (e.g., oncology, cardiology, neurology) often serve as the primary experts with regards to genetic testing while working in conjunction with the nongeneticist specialist physician. These role expansions are likely to continue as genomic medicine matures. Across all specialties, but particularly in cancer and cardiology genetics where VUS results are frequent outcomes to panel-based genetic testing, genetic counselors have had to understand variant interpretation and, in many cases, perform manual annotation of variants reported by a laboratory. Genetic counselors and geneticists already sit on interpretation panels for determining what warrants disclosure, and will remain experts in this area. This role will become increasingly relevant for all genetic counselors, whether they work directly with patients or not, and our training and continuing education processes will need to ensure that all genetic counselors are proficient in variant interpretation and understand the laboratory and bioinformatics processes.

Psychosocial Support and Adjustment

One thing that separates genetic counselors from other health professionals with expertise in genetics is their stated focus on the psychosocial adaption to genetic conditions or genetic risk (Biesecker and Peters 2001). It will remain critical that genetics counselors help patients personalize their choices about whether and when to undergo genomic testing, and the implications of learning genomic variation, along with all its concomitant medical and social implications as individuals and within their family structure. I will discuss below two areas where I believe the genetic counselor's approach to psychosocial counseling may change as we move toward genomic medicine, based both on the more generalized testing approach and the hopes for preventative genomic medicine.

We have moderately good data about the psychosocial impact of learning carrier status (Lewis et al. 2011) or predictive risk for a highly penetrant genetic condition (e.g., Evers-Kiebooms et al. 1997; Bleiker et al. 2013). Data are also emerging on testing children for adult onset conditions ranging from familial adenomatous polyposis (FAP) (e.g., Michie et al. 2001; Codori et al. 2003) to breast cancer (Bradbury et al. 2008) to carrier status for autosomal recessive diseases. However, the vast majority of this data come from a population of individuals who were aware of their family history and opted for predictive genetic testing on the basis of pretesting psychological features, social support, and expectations of how the results may impact them. Self-selection also varies by disease characteristics; testing uptake for certain highly penetrant cancers where surveillance is available hoovers near 50% of the at-risk population, whereas for Huntington disease it can be below 20%. (Evers-Kiebooms et al. 1997). Limited data regarding the receipt of low penetrance genotyping risk data suggest that for most individuals, neither anxiety nor depression is clinically increased in the short or long term (e.g., Bloss et al. 2011). But data regarding the psychosocial responses of individuals who receive unexpected but highly penetrant genetic risk information (e.g., BRCA test results unexpectedly) from genome testing are limited (Francke et al. 2013, F. A. Dewey, M. Grove, C. Pan, B. A. Goldstein, J. Bernstein, H. Chaib, R. Goldfeder, C. Caleshu, K. Kingham, K. E. Ormond, T. E. Klein, M. Whirl-Carillo, K. Sakamoto, M. T. Wheeler, A. Butte, J. Merker, J. Ford, L. Boxer, J. Ioannidis, A. C. Yeung, A. Altman, T. L. Assimes, M. Snyder, E. A. Ashley, T. Quertermous, pers. comm.), and is biased by the fact that healthy individuals undergoing DTC genotyping and/or WGS are early adopters who may have specific psychosocial characteristics limiting the generalizability of this data. While these cases are likely to be rare, and a rigorous pretest family history may identify some high-risk individuals, more research is needed on the short- and long-term psychosocial implications of receiving such information.

Given the psychosocial implications of learning that one carries a highly penetrant condition that may have limited medical actionability, and given the worldwide history of eugenics and stigma associated with genetic conditions, there has been a strong focus on individual autonomy and non-directiveness around genetic testing decisions and future medical management (Weil et al. 2006). For those with a family history of a single-gene condition, a values-based decision-making approach toward genetic testing will remain its relevance in years to come. However, in the past decade, specialist genetic counselors have started to change toward more "directive" health promotional counseling, particularly in highly penetrant but medically actionable conditions such as cancer and sudden death cardiac conditions (e.g., Albada et al. 2013). This may strike some as a radical departure from nondirective genetic counseling until one reframes the approach in terms of providing patient-centered

counseling that identifies relevant values, beliefs and barriers toward health behavior change, and then supports such change while respecting and supporting the patient's values. As such, health education and promotion becomes an important part of the genetic counselor's job, and in fact meets the definition of genetic counseling that we started with: "helping people understand and adapt to the ... genetic contributions to disease" (National Society of Genetic Counselors' Definition Task Force et al. 2006). Data from early genome wide association (GWA) studies suggest a limited behavior change after genetic risk prediction for common complex disease (e.g., Bloss et al. 2011), but these studies were primarily conducted in a DTC setting with limited health provider intervention. The "promise of genomic medicine" has always been preventative health care; if we can find patient-centered ways to galvanize preventative health behaviors, we can empower a generation of patients toward better health. Genetic counselors are already well positioned to play a pivotal role in this area, but to do so, will need to become more familiar with health promotion models, apply them in practice and perform longitudinal outcomes studies to determine their utility and effectiveness.

The profession of genetic counseling has undergone many transitions since its inception over 40 years ago; it has expanded from a primarily pediatric and obstetric focus at a time when genetic testing did not even exist, into multiple medical specialties that have access to rapidly changing genetic tests. The unique skills and roles of clinical geneticists and genetic counselors will become even more paramount, and genomic counseling will evolve in ways that preserve the central tenets of values-based decision making for patients while also promoting patient health outcomes.

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Conflict of Interest

None declared.

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New Approaches to Molecular Diagnosis

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Advances in understanding the molecular basis of rare and common disorders, as well as in the technology of DNA analysis, are rapidly changing the landscape of molecular genetic and genomic testing. High-resolution molecular cytogenetic analysis can now detect deletions or duplications of DNA of a few hundred thousand nucleotides, well below the resolution of the light microscope. Diagnostic testing for "single-gene" disorders can be done by targeted analysis for specific mutations, by sequencing a specific gene to scan for mutations, or by analyzing multiple genes in which mutation may lead to a similar phenotype. The advent of massively parallel next-generation sequencing facilitates the analysis of multiple genes and now is being used to sequence the coding regions of the genome (the exome) for clinical testing. Exome sequencing requires bioinformatic analysis of the thousands of variants that are identified to find one that is contributing to the pathology; there is also a possibility of incidental identification of other medically significant variants, which may complicate genetic counseling. DNA testing can also be used to identify variants that influence drug metabolism or interaction of a drug with its cellular target, allowing customization of choice of drug and dosage. Exome and genome sequencing are being applied to identify specific gene changes in cancer cells to guide therapy, to identify inherited cancer risk, and to estimate prognosis. Genomic testing may be used to identify risk factors for common disorders, although the clinical utility of such testing is unclear. Genetic and genomic tests may raise new ethical, legal, and social issues, some of which may be addressed by existing genetic nondiscrimination legislation, but which also must be addressed in the course of genetic counseling. The purpose of this article is to assist physicians in recognizing where new approaches to genetic and genomic testing may be applied clinically and in being aware of the principles of interpretation of test results.

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KNOWLEDGE OF THE HUMAN GENOME sequence and the plummeting cost of genomic analysis are driving substantial advances in genetic and genomic testing. As a result, a greater variety of rare genetic and chromosomal disorders can be diagnosed, risk of common disorders can be estimated, and drug treatment can be tailored to individual needs. In this article, we will review new approaches to genetic and genomic diagnosis of both rare and common disorders. We will do this in light of 4 questions that should be asked about any genetic/genomic test.[1] Is the test result correct (analytic validity)? Does the result correctly diagnose disease or its absence (clinical validity)? Does the result guide medical management (clinical utility)? Does the result place the patient at risk of discrimination, stigmatization, guilt, etc (ethical, legal, and social issues)? Understanding the concepts presented in this article requires basic knowledge of the principles of genetics (BOX); refer to recent reviews for further background.[2,3] Although DNA and genomic testing has also been applied to infectious disease and microbiological testing, this article will focus only on testing of the germline or of somatic variants associated with cancer. A summary of the indications for genetic and genomic testing is provided in TABLE 1.

See also p 1533.

CME available online at www.jamanetworkcme.com and questions on p 1536.

Diagnosis of Genetic Disorders

A genetic disorder can be defined as a condition due to an alteration of DNA present in the germline, either inherited or acquired as a new mutation in the sperm or egg cell. Pathological genetic changes can involve large blocks

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Box. Glossary

Cytogenomics: Technologies that assess the presence of copy number variants at locations throughout the genome, one example of which is comparative genomic hybridization.

Exome: The portion of the genome consisting of protein coding sequences (as opposed to introns or noncoding DNA between genes).

Next-generation/high-throughput sequencing: DNA sequencing technology that permits rapid sequencing of large portions of the genome; so called because it vastly increases the throughput over classic Sanger sequencing.

Pharmacogenetic polymorphism: Genetic variants that alter the way an individual metabolizes or responds to a specific medication.

For a complete list of genomic terms, see the Appendix in this issue.

of genetic material spanning multiple genes or can occur at the level of an individual gene. The former are referred to as genomic changes and can range from trisomy or monosomy of an entire chromosome to deletion or duplication of thousands of bases. Diagnosis of such genomic copy number variations (CNVs) has been revolutionized by the advent of cytogenomic testing, and advances in genome sequencing technologies have vastly improved the diagnosis of single gene disorders.

Cytogenomics. *A 6-year-old boy is diagnosed with autism spectrum disorder. At 4 years of age, he had normal chromosomal analysis and fragile X testing. Now a cytogenomic array test has revealed deletion of 550 000 bases of DNA from chromosome 16* (FIGURE 1 and FIGURE 2). *Neither of his parents is found to have the deletion, and this deletion has been seen in others with autism spectrum disorder. His parents are informed that this deletion likely explains the cause of his autism spectrum disorder diagnosis, which indicates that the condition is unlikely to recur if they have other children but does not point toward a specific treatment.*

Cytogenomic approaches have transformed chromosomal analysis, permitting detection of gains or losses of genomic segments far too small to be seen with the microscope.[4] A variety of techniques can be used to survey the entire genome for copy number changes. Array comparative genomic hybridization compares intensity of hybridization between a reference genome and a patient's genome to hundreds of thousands of genomic segments on a microarray. Another approach quantifies hybridization of patient DNA to microarrays of single-nucleotide polymorphisms (SNPs), which can also identify stretches of homozygosity to infer consanguinity or uniparental disomy.[5]

Cytogenomic analysis is now a first-line genetic test for multiple congenital anomalies, delayed intellectual development, and autism spectrum disorder.[4,6] Following a recent clinical trial, it has now been validated for use in prenatal detection of copy number changes in pregnancies at risk for a chromosomal abnormality (for example, based on abnormal ultrasound findings).[7] Cytogenomic testing does not detect balanced rearrangements, such as balanced translocations or inversions. Cytogenomic testing is therefore not the first-line test for a couple with multiple miscarriages that may be due to a balanced translocation, for example. The clinical utility of cytogenomic testing is in making a diagnosis, often ending a frustrating and expensive "diagnostic odyssey" and providing a basis for recurrence risk counseling and prenatal testing.

Although the analytical validity of cytogenomic testing is very high, interpretation of clinical validity can be challenging. On average, cytogenomic microarrays identify approximately 1 to 2 CNVs per person that are greater than 1000 bases in size.[8] Databases containing population data on CNVs have grown over the years, making it easier to rule out certain variants as disease-causing,[9] but many CNVs are rare with limited population data. Testing parental samples can determine if the variant occurred de novo. Laboratories usually assume a pathogenic role for a CNV larger than 400 000 bases (400 kb) that occurs de novo and a benign role if inherited from a healthy parent.[4] The latter assumption may be incorrect if a CNV is recessive and inherited from both parents or if the affected child has a combination of a CNV inherited from one parent along with a second sequence variant inherited from the other parent or occurring de novo.[10] Examination of a genome for CNVs can also lead to the identification of secondary findings unrelated to the indication for testing (eg, finding a deletion of a region that includes a tumor suppressor gene, conveying a risk of cancer).[11] Thus, thorough pretesting education and consent is critical.

Disease-Targeted Testing. *A healthy newborn female showed signs of hearing impairment from her hearing screen. After a diagnostic auditory brainstem response test confirms bilateral profound sensorineural hearing loss, she is referred to an otolaryngologist and geneticist to determine the cause. A large hearing loss test panel with more than 70 genes analyzed by next-generation sequencing is ordered. She is found to have 2 recessive pathogenic mutations in the* MYO7A *gene, a well-known cause of Usher syndrome (retinitis pigmentosum and deafness). The family chooses to pursue cochlear implantation to manage the deafness and enroll her in a gene therapy clinical trial for treatment of the anticipated onset of retinitis pigmentosum associated with Usher syndrome.*

Genetic tests can be divided into 3 categories based on the extent of genetic heterogeneity associated with a phenotype (FIGURE 3). The first are tests that identify one or a few well-defined mutations. An example is detection of the sickle cell mutation in the beta globin gene, which is the same in all carriers or affected individuals. Analytical validity of such testing is very high. The second are tests for disorders attributed to a

Table 1. Indications for Genetic and Genomic Tests, Analytical Validity, Clinical Validity, Clinical Utility, and Examples of Relevant Ethical, Legal, and Social Issues

Type of Test	Indications	Analytical Validity	Clinical Validity	Clinical Utility	Ethical, Legal, Social Issues
Diagnosis of Genetic Disorders					
Cytogenomics	Diagnosis of individual with multiple congenital anomalies, intellectual disability, signs of chromosomal abnormality	Current standards are to only report copy number changes >400 kb pairs in size	Requires validation of pathogenicity, as some CNVs are benign variants	Diagnosis, counseling	May detect CNV in parents of affected child
Disease-targeted testing	Suspected genetic disorder based on signs and symptoms, risk of inheriting genetic disorder based on family history, risk of being carrier for autosomal-recessive trait based on ancestry	Clinical laboratories must assess analytical validity for assays used for clinical reporting	May be unable to detect all possible pathogenic mutations, variants of unknown significance may be difficult to interpret	Diagnosis, counseling; may provide guidance toward surveillance for complications and/or specific therapy	Potential for stigmatization, anxiety, guilt for those found to carry mutation
Exome/genome sequencing	Suspected genetic disorder based on signs and symptoms but no known single gene condition fits phenotype	Mutations suspected as being pathogenic should be validated by Sanger sequencing	May reveal a previously annotated pathogenic mutation or a mutation that can be shown to be pathogenic; requires bioinformatic analysis to filter large number of variants, with high chance of finding variants of unknown significance	Diagnosis, counseling, end to "diagnostic odyssey"; in some cases may provide guidance toward surveillance for complications and/or specific therapy	Potential identification of incidental findings that are medically significant
Molecular Testing for Noninherited Disorders					
Pharmacogenetic testing	Dosage adjustment of medication known to be subject to variable metabolism or efficacy based on pharmacogenetic polymorphisms, choice of medication best suited to treat specific condition defined by genetic variant	High for standard pharmacogenetic polymorphisms and known disease stratification variants	Evidence of clinical validity needs to be evaluated for specific pharmacogenetic tests on case-by-case basis	Can be valuable for optimal choice of drug or drug dosage	Cost-benefit analysis required to incorporate testing into routine use
Tumor genetic testing	Guide choice of cancer therapy based on presence of specific mutation or genetic rearrangement that predicts response to specific drug	Depends on specific genetic variant and degree of purity of tumor sample (ie, minimal presence of nontumor cells in biopsy)	High in some instances (eg, detecton of Philadelphia chromosome) but differs for different variants and tumor types	Can identify optimal drug for treatment of specific tumor type	May identify incidental germline mutations that are unrelated to cancer
Genomic testing for risk assessment	Assess odds of development of common disorders (eg, type 2 diabetes) in advance of symptoms	Generally high, but some examples of variants that cannot be determined or may be in error are expected when very large numbers are genotyped in a specific sample	Odds of disease are calculated differently by different testing laboratories and may be based on studies in populations that are different from ancestry of individual being tested; therefore, clinical validity often not well documented	Clinical utility largely not supported by evidence	Potential lack of health professional involvement, marketing direct-to-consumer

Abbreviations: CNV, copy number variation; kb, kilobase.

single gene in which different mutations may occur in each affected individual. These tests are usually done by DNA sequencing. An example is neurofibromatosis type 1.[12] Analytic validity is high if a mutation is found, but most tests do not detect all possible mutations, so a negative result may be harder to interpret. The third group is tests for conditions, such as congenital deafness or cardiomyopathy, that result from mutation in any one of multiple different genes. In the past, it was necessary to test these genes one at a time, usually only testing the most commonly affected genes to reduce costs. Now it is possible to use the technology of massively parallel sequencing (ie, next-generation sequencing) to simultaneously sequence the coding regions (exons) of large numbers of genes for little more than the cost of testing any one gene.[13-15] A positive result is confirmed by conventional sequencing, so analytical validity is high, but a negative result does not entirely rule out mutation, especially one that changes the gene structure (eg, an intragenic inversion or gene deletion) or that occurs deep within an intron (a noncoding sequence that separates the segments that encode protein).

Genetic testing can establish a diagnosis in a symptomatic individual or in a person or fetus at risk based on family history. Genetic testing for a germline condition (ie, not an acquired condition such as cancer) can be done using any source of tissue, usually blood, obviating the need for biopsy of affected tissue. Genetic testing can also be performed long before onset of symptoms, allowing surveillance, risk reduction strategies, and family planning. Testing for mutations in the *BRCA1* and *BRCA2* genes in individuals with a family history of breast and ovarian cancer, for example, can identify those at very high risk of cancer, leading to surveillance as well as surgical or medical strategies to reduce risk.[16] A positive result (ie, presence of a known pathogenic mutation) can guide management in an individual; a negative result does not necessarily indicate that the person is not at increased risk of cancer, unless it occurs in a setting where those in the family with cancer are known to have tested positive for a specific mutation. In addition to providing diagnostic information, in some cases genetic testing can be a prelude to treatment. Children with congenital deafness due to connexin 26 gene mutations, for example, tend to respond better to cochlear implants than those with deafness due to other causes.[17] Genetic testing can also reveal carrier status for recessive disorders such as cystic fibrosis, indicating risk of disease if both parents are carriers. This usually is done by testing for well-annotated mutations; a next-generation sequencing approach has been tested, but the problem is that many variants detected are of unknown pathogenic significance.[18]

There are currently hundreds of clinically available tests. The GeneTests database[19] has provided a list of laboratories that provide genetic testing on a clinical or research basis. GeneTests is now being phased out, replaced by the National Institutes of Health Genetic Testing Registry.[20,21]

Clinical validity of well-described variants, such as the sickle cell mutation, is well established, but significant challenges can arise in other settings. Finding a mutation may not invariably predict phenotype if there is incomplete penetrance (ie, a person with a mutation may not develop the

Figure 1. Deletions and Duplication of Multiple Genes Within a Chromosomal Segment

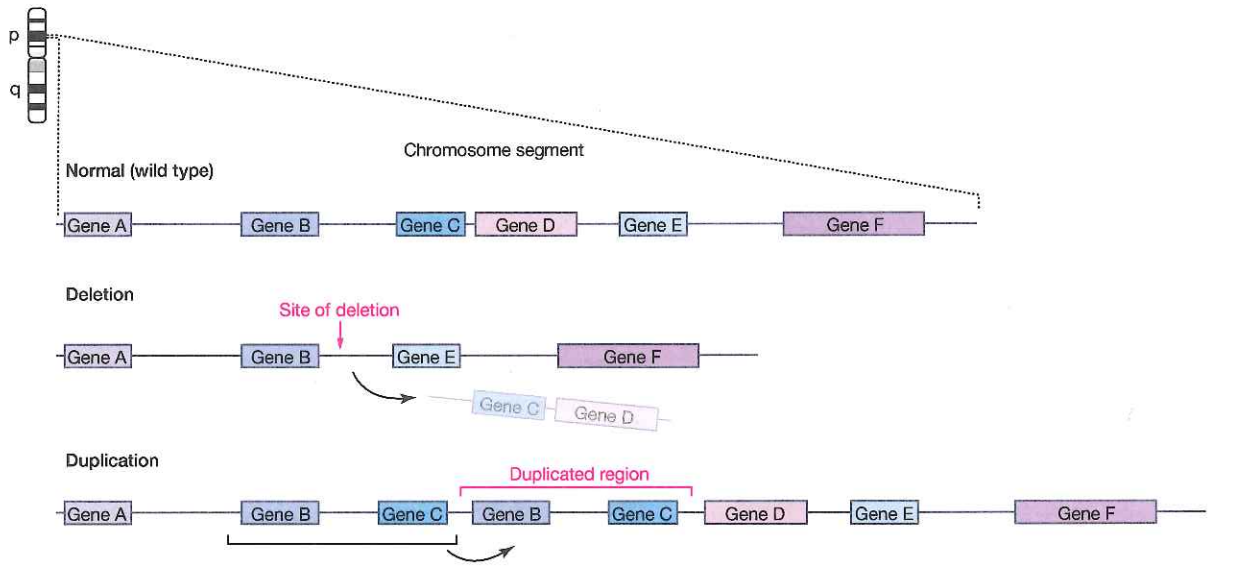
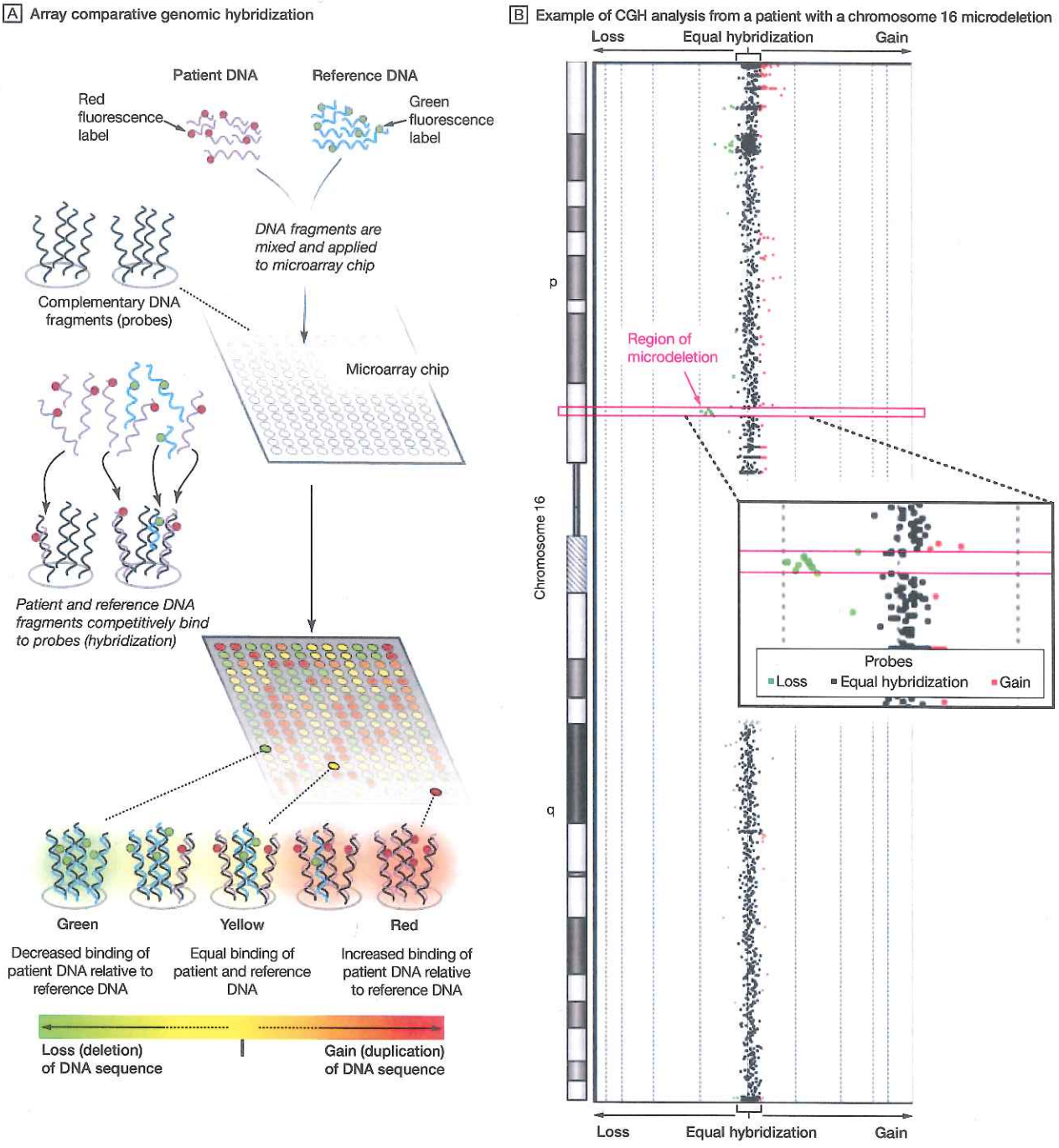


Figure 2. Detection of Chromosome Deletion or Duplication by Array Comparative Genomic Hybridization



A, Array comparative genomic hybridization (CGH) consists of mixing fragmented DNA from the patient and a reference sample labeled with different fluorescent dyes (red and green, in this case). These fragments are allowed to bind (hybridize) by base pairing to complementary genomic DNA fragments (probes) that have been immobilized on a glass chip. If there is equal binding of patient and reference DNA, yellow fluorescence results. Deletion of a DNA segment in the patient sample results in decreased binding of patient DNA relative to reference DNA and green fluorescence (loss). Duplication of a DNA segment in the patient sample results in increased binding of patient DNA relative to reference DNA and red fluorescence (gain). B, Example of array CGH analysis from a patient with a chromosome 16 microdeletion. Data markers represent probes on the array and are plotted next to the corresponding position on the chromosome ideogram (left). Black data markers are probes within an established range representing equal binding. Probes that fall outside this range are indicated as loss or gain.

phenotype). This is the case, for example, in homozygotes for mutations in the *HFE* gene involved in hemochromatosis[22] or in *BRCA1* or *BRCA2* mutation carriers.[23] In addition, techniques that rely on scanning an entire gene or group of genes may detect variants of unknown significance, where there may be insufficient evidence to determine whether they are pathogenic changes or rare benign variants. Evidence for pathogenicity might include demonstrating that the change is not seen in unaffected individuals, demonstrating interspecies conservation for the sequence found in the general population, computer modeling to detect the effect on protein function, testing for segregation of the mutation with disease in the family (or de novo origin for a new mutation), and using animal models.[24]

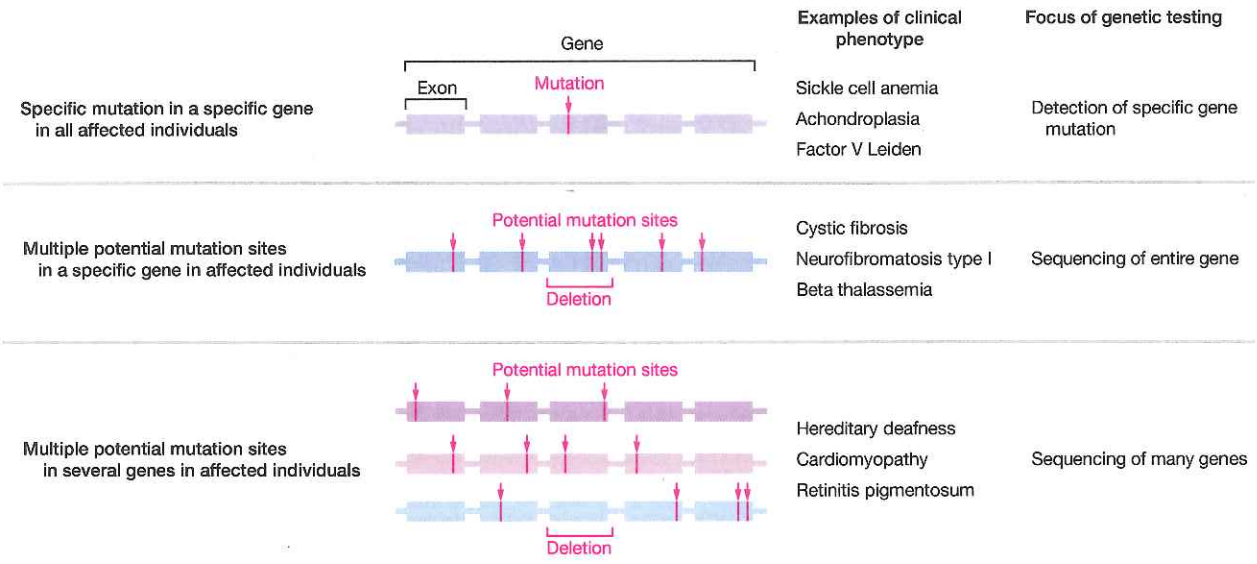
Exome and Genome Sequencing. *A 6-year-old boy has severe intellectual disability and seizures. Numerous medical evaluations and cytogenomic microarray testing failed to reveal an etiology. Exome sequencing is performed on him and both of his parents. A stop mutation in the* SCN2A *gene is found in the child but is not found in either parent. This gene encodes a subunit of a sodium channel that is expressed in the brain and has been found to be mutated in others with a similar phenotype.*

Exome and genome sequencing are both available as clinical diagnostic tests and are performed using next-generation sequencing.[25-27] The exome is limited to approximately 1% to 2% of the genome, consisting of the protein encoding regions of genes (FIGURE 4).[28] Exome sequencing can be done at far lower cost than genome sequencing and identifies most currently interpretable pathogenic mutations. As sequencing costs continue to decrease, genome sequencing, which detects mutations in non–protein coding regions of the genome, is likely to become more cost-effective. It is important to note that complete analysis of even the coding regions of genes is not achieved with either approach. On average, 90% to 95% of these regions are covered, and for certain genes, coverage may be extremely low or absent.[29] Moreover, certain types of mutations may not be detected. It is therefore important to understand what the coverage may be for any genes that are critical candidates for a patient's phenotype. In some cases, it may be necessary to first use targeted testing to examine some of these genes and use exome or genome sequencing if no mutation is found in these candidate genes.

Exome or genome sequencing is helpful in the detection of mutations that might not be anticipated based on clinical phenotype. For many genetic conditions, the phenotypes are either nonspecific (eg, intellectual disability without congenital anomalies), very obscure (due to the rarity of the condition), or variable from patient to patient, making it difficult to choose a particular gene to test. The clinical utility is the ability to establish a diagnosis, often bringing peace of mind to the family, avoiding further expensive and fruitless testing, providing a basis for genetic counseling, informing surveillance for complications, and even suggesting possible avenues of therapy.[30] The costs of testing are rapidly decreasing; currently commercial and academic laboratories offer exome testing and interpretation for less than $10 000, with many third-party payers accepting this cost as preferable to a long series of expensive, unproductive tests.

Exome or genome sequencing is often performed on a trio consisting of an affected child and both parents (or

Figure 3. Variations in Types of Mutations Accounting for a Specific Phenotype and Associated Category of Genetic Testing



an affected individual and other affected or nonaffected siblings). This offers a chance to filter the total variants to a smaller number. Examining parental samples allows detection of new dominant mutations observed in the proband that are not present in either parent. If other family members are also affected, the mutation should segregate with the disorder in the family. In a recessive condition, variants should be found in both gene copies, one inherited from each parent. Thousands to millions of variants will be found in any individual genome/exome, so data are filtered to remove previously described benign variants, and computer modeling can help prioritize variants that are more likely than others to affect function of the gene product.

A sometimes unintended consequence of exome sequencing is the identification of secondary findings, ie, mutations in genes that are potentially clinically significant yet unrelated to the patient's phenotype.[31] An example would be finding a mutation in the *BRCA1* gene that can lead to hereditary breast and ovarian cancer syndrome, which may not be apparent in the family history. It is important for the clinician and the patient as well as parents to be aware of this possibility and to be aware of the policy of the laboratory regarding return of secondary findings.

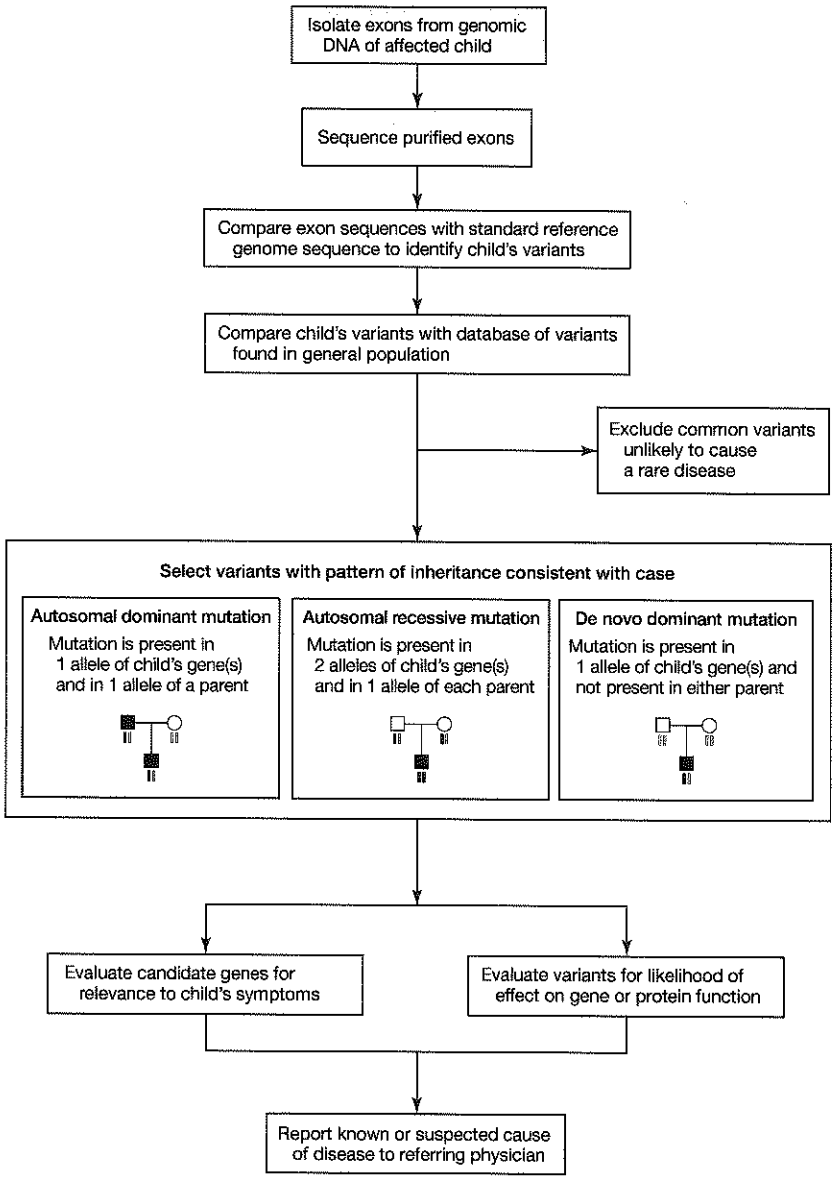
Molecular Testing for Noninherited Disorders

DNA and genomic tests can now be used to tailor drug dosage and choice of medication to individual needs, to achieve more precise diagnosis of cancer, and in some cases to predict risk of common disorders.

Pharmacogenetic Testing. *A 40-year-old woman who does not smoke is diagnosed as having lung cancer. DNA from a biopsy of her tumor is sequenced for genes implicated in lung cancer, including the* EGFR *and* KRAS *genes. Testing reveals an activating* EGFR *variant, leading the oncologist to recommend therapy with a tyrosine kinase inhibitor. Her tumor responds well to the treatment.*

As the molecular bases of diseases are understood, pharmacologic therapies can be developed to target the specific underlying defect. In addition, the absorption, metabolism, and excretion of many drugs are influenced by variants

Figure 4. Example of Exome Sequencing to Identify Genetic Basis of an Undiagnosed Disorder in an Affected Child



Exome sequencing is performed on exons—the protein encoding regions of genes—that are isolated by a process of DNA fragmentation and hybridization. Using next-generation sequencing, purified exons are sequenced and compared with a standard reference human genome sequence to identify variants. To determine inheritance of a possible genetic disorder, exome sequencing can be performed on an affected child and both parents. Analysis is limited to those variants that are not known to be benign and that have potential for a damaging effect on protein function. If inheritance is recessive (biallelic), each parent carries 1 of the damaging variants as a heterozygous carrier. If inheritance is dominant (monoallelic), either parent carries the variant and would be phenotypically affected unless the mutation is nonpenetrant. Alternatively, a dominant mutation may have arisen de novo in the child, in which case neither parent carries the variant.

in genes that encode enzymes that catalyze reactions involved in these processes.[32] Variants in genes that encode proteins that are the targets of specific drugs may also influence response to the drug. The effect of a pharmacogenetic polymorphism on drug concentration depends on the nature of the chemical reaction. Reduced activity of an enzyme involved in activating a drug can result in inadequate tissue levels, whereas reduced activity of an enzyme involved in conversion of the drug to an inactive form can result in excessive tissue concentrations. Other pharmacogenetic polymorphisms can lead either to excessive sensitivity of a target and consequent adverse effects or to resistance and consequent lack of efficacy. TABLE 2 provides a list of some important pharmacogenetic tests to exemplify the various ways that testing can be used to guide therapy.

The analytic validity of pharmacogenetic tests is very high, as testing focuses on well-characterized SNPs or copy number changes. Clinical validity differs with different polymorphisms (Table 2). In some cases, such as testing for variants in *CYP2C9* and *VKORC1* involved in warfarin metabolism, the results can guide adjustment of dosage to avoid over- or undertreatment.[37] In others, such as *CYP2C19* testing for clopidogrel sensitivity, the testing predicts nonresponse, in which case an alternative antiplatelet drug should be used.[38] The US Food and Drug Administration mandates labeling of both warfarin and clopidogrel with a notice to consider pharmacogenetic testing when prescribing these drugs.

The clinical utility of pharmacogenetic testing is a matter of debate. Questions arise as to whether testing can be done quickly enough for results to be available when the drug is needed and whether pharmacogenetic testing is cost-effective; that is, are the savings from avoiding adverse effects and achieving therapeutic benefit sufficient to justify wide-scale testing whenever the drug is prescribed? Clinical trials are now under way to assess these issues for some of the more common pharmacogenetic polymorphisms.[39] In addition, physicians may not know how to adjust drug dosage based on pharmacogenetic test results unless the information is provided by the manufacturer or available in an electronic prescribing system.

Application of genetic testing to determine the optimum choice of drug is most advanced in oncology. Testing a tumor for an *EGFR* mutation in non–small cell lung cancer, as described in the case example, can predict responsiveness to tyrosine kinase inhibitors.[40] Similarly, melanomas with an acquired V600E mutation in the *BRAF* oncogene show more favorable response to the kinase inhibitor vemurafenib than tumors with the wild-type sequence.[41] Next-generation sequencing approaches are now being used to characterize the complement of genetic changes in malignant cells in the hope of identifying new drug targets and eventually customizing the choice of treatment to the specific genetic constitution of the tumor in an individual.[42] Clinicians need to be aware when pharmacologic testing is indicated. A good resource for indications is Giacomini et al.[43] In addition, numerous electronic medical records are now embedding indications for such testing in the systems.

Genomic Testing for Risk Assessment. *A 42-year-old man in good health recently heard about the possibility of personal genomic testing arranged over the internet. The testing involves analysis of around 1 million SNPs. He creates an online account with a company and receives a tube, which he fills with saliva and then mails back. A few weeks later, he is directed to a website with information about his genomic data. Among other things, he learns that he is a carrier for a cystic fibrosis mutation, that he has greater than average sensitivity to warfarin, and that his risk of type 2 diabetes is about 15% increased over the population risk.*

It has long been known that there is a genetic contribution to risk of many types of common disorders, but until recently the genetic contributions were not known. In the past few years, genome-wide association studies have revealed association of particular genetic variants with an increased odds of developing common diseases. The most common variants tested for association are SNPs, each of which consists of a single base at a specific site that may vary between individuals. These SNPs are not usually thought to be causative for disease but are believed to be closely linked to other unidentified genetic variants that influence risk of disease. Most tests examining risk for common diseases use arrays containing more than a million SNPs distributed throughout the genome.

Several companies have been offering such testing, some using a direct-to-consumer model with little or no involvement from health professionals. The approach has generated controversy based on a number of issues.[44] First, different companies use different approaches to calculate risk, taking into account different combinations of genetic markers and other nongenetic factors, and may reach different conclusions from the same data.[45] Although the analytical validity of testing is high, the clinical validity may be uncertain. Second, study populations used to estimate risk may have different characteristics from an individual being tested. Third, there are usually few options to mitigate risk. Fourth, the lack of direct professional involvement creates concern that information might be misinterpreted. It remains unknown whether genomic data will motivate individuals to follow advice (such as advice to lose weight) or whether those found to have decreased odds of disease will ignore such advice to their detriment.[46]

On the other side, risk assessment has not been demonstrated to increase utilization of health services (thereby increasing health care costs) or to cause serious psychological harm to consumers.[47] Some argue that an individual has a right to access personal genomic information. There may not be sufficient access to professionals who are experienced in interpreting genomic

information, so innovative models of patient and health professional education may provide a better long-term solution to making genomic information widely accessible. Some of the companies that initially began to offer such testing have left this business, and the long-term viability of this approach remains to be seen.

Ethical and Legal Issues

A 60-year-old woman is diagnosed with breast cancer. She has a family history of breast cancer in her mother and a sister, which prompts her to seek genetic counseling about the possibility of testing. Her major motivation is that she has 2 daughters, ages 28 and 30 years, who would be at risk if she were found to carry a mutation. She wonders whether her daughters getting tested would place them at risk of losing their health insurance.

Genetic testing can identify individuals at risk of disease long before onset of signs or symptoms, raising concern about stigmatization and discrimination. The former should be addressed in pretest counseling. The latter can be mitigated through legislation. Many US states and other countries have enacted laws to protect individuals from discrimination based on genetic information. The Genetic Information Nondiscrimination Act of 2008 (GINA) addresses these concerns on a federal level in the United States.[48] The GINA prohibits employers and health insurers from using genetic information (including family history and genetic testing) in making decisions about employment, promotion, and health insurance coverage and premiums. However, it does not prohibit the use of genetic information in making decisions related to disability or life insurance.

Concerns have also been raised about testing children for risk of adult-onset disorders. Guidelines issued by professional societies recommend that children only be tested when they will im-

Table 2. Examples of Pharmacogenetic Associations and Their Rationale for Testing

Drug	Indication	Genetic Association	Sample	PharmGKB Evidence[a]	FDA Label[b]	Rationale[c]
Abacavir	HIV	*HLA-B* 5701	Germline	1A	Yes	Avoid adverse drug reaction (immunological hypersensitivity) in 5%-8%
Carbamazepine	Seizures, bipolar disorder	*HLA-B* 1502	Germline	1A	Yes	Avoid adverse drug reaction (skin detachment) in 5% of Asian individuals
Azathioprine	Rheumatoid arthritis	*TPMT*	Germline	1A	Yes	Avoid adverse drug reaction (potentially fatal myelotoxicity) by avoiding drug or lowering dose
Thioguanine	Acute myeloid leukemia	*TPMT*	Germline	1A	Yes	Avoid adverse drug reaction (potentially fatal myelotoxicity) by avoiding drug or lowering dose
Clopidogrel	Atherothrombosis	*CYP2C19*	Germline	1A	Yes	Switch to other therapy if poor metabolizer (26%)
Voriconazole (VFEND)	Fungal infection	*CYP2C19*	Germline	NA	Yes	Lower drug dose if poor metabolizer (26%)
Warfarin	Anticoagulation management	*VKORC1/ CYP2C9*	Germline	1A	Yes	Use genotype to assist in drug dosing
Oral contraceptives[d]	Familial thrombophilia	Factor V	Germline	NA	No	Switch oral contraceptive to avoid VTEs in women homozygous for factor V allele
Simvastatin	Cholesterol-lowering treatment	*SLCO1B1*	Germline	1A	No	Avoid adverse drug reaction (potentially fatal muscle toxicity) in 2% of patients
Erlotinib	Non–small cell lung cancer	*EGFR*	Tumor	1B	Yes	Identify mutation-positive patients (10%-20%) for targeted therapy
Imatinib for CML	CML	*BCR-ABL* translocation	Tumor	NA	Yes	Identify *BCR-ABL* translocation–positive patients for targeted therapy
Lapatinib	Breast cancer	*HER2* expression	Tumor	NA	Yes	Identify *HER2*-positive breast cancer patients for targeted therapy
Tamoxifen (ER/PR)	Breast cancer	ER/PR expression	Tumor	NA	Yes	Identify ER/PR-positive breast cancers with high recurrence risk for tamoxifen treatment
Imatinib for GIST	GIST	*cKIT*	Tumor	NA	Yes	Identify *cKIT*-positive GIST patients for targeted therapy
Lenalidomide	Myelodysplastic syndrome	5q deletion	Tumor	NA	Yes	Identify patients with 5q deletion for targeted therapy
Peginterferon A and ribavirin	Hepatitis C	HCV virus genotype	Infectious	1A	No	Extend duration of therapy from 24 to 48 wk in 20% with HCV type 1 or 4
Maraviroc	HIV	CCR5 viral tropism	Infectious	NA	Yes	Predict resistance to CCR5 inhibitors and avoid drug use

Abbreviations: CML, chronic myeloid leukemia; ER/PR, estrogen receptor/progesterone receptor; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable; VTEs, venous thromboembolisms.

[a] The Pharmacogenomics Knowledgebase (PharmGKB) provides an assessment of the level of evidence for the clinical validity of variant-drug associations.[33] Levels of evidence range from 1A through 3 and criteria can be found at the website.[34] (Note that levels do not represent an assessment of the clinical utility of implementing testing for the variant.)

[b] Indicates whether the FDA recommends inclusion of pharmacogenetic testing in drug labeling.

[c] Percentages indicate portion of population thought to have the at-risk variant.

[d] The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Workgroup is an effort supported by the US Centers for Disease Control and Prevention to evaluate both the clinical validity and clinical utility of genomic applications in medicine.[35,36] For oral contraceptives, testing is not recommended according to the EGAPP guideline.

mediately benefit from the results of testing (eg, achieve a diagnosis that explains existing signs or symptoms of a genetic disorder, whether or not it is treatable[49]). The advent of exome and genome sequencing, as discussed earlier in this article, may make this guideline difficult to follow if testing reveals secondary findings that may eventually be important for the health of the child or are important for adult relatives.

Another legal issue concerns restriction of access to tests due to patents and proprietary databases. About 20% of the genome is currently subject to patents, and in some cases exclusive licensing limits which laboratories are able to offer testing.[50] The legality of gene patenting is currently the subject of challenge in the courts. It will also be important to enable broad sharing of genomic data sets and accompanying phenotypic data and to crowdsource the labor-intensive interpretation of DNA variants among groups of experts.[51] This will require support of widespread data sharing and the development of community standards for how to structure, store, and analyze data and annotations, as well as how to document the evidence and relevance of genomic variants in human disease.

Conclusions

For individuals with rare genetic disorders, the possibility of a definitive diagnosis has never been greater; the precision of diagnostic testing is likely to continue to increase and the cost to decrease. Molecular genetic and genomic testing to guide treatment of common conditions will increasingly be incorporated into day-to-day medical practice. Pharmacogenetic tests are likely to be incorporated into electronic prescribing systems, with testing and dosing recommendations built in. Health professionals will need to become familiar with the indications for and interpretation of molecular genetic and genomic tests, with backup and support from medical geneticists and pathologists to assist with complex cases. Some have predicted that the day will come when everyone has his or her genome sequenced, perhaps prenatally, perhaps at birth, or perhaps later in life. The clinical utility of such testing for most individuals is a long way from being established, but technical feasibility and even cost are unlikely to be major obstacles.

Author Contributions: Dr Korf had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Drafting of the manuscript: Rehm, Korf.
Critical revision of the manuscript for important intellectual content: Rehm, Korf.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Korf reported serving on the board for the Neurofibromatosis Therapeutic Acceleration Project, receiving grants from the National Institutes of Health and US Department of Defense, receiving payment for lectures to academic groups, receiving royalties from John Wiley and Elsevier, and receiving funds for travel for multiple academic meetings. Dr Rehm reported being employed by a fee-for-service nonprofit molecular diagnostic laboratory; having served on advisory boards for Knome, Complete Genomics, GenomeQuest, and Omicia; having consulted for Generation Health; having received honoraria for lectures to academic groups; having owned stock or stock options for Generation Health; and having received travel support for multiple academic meetings; she also reported that her institution has received support for GeneInsight software development from Illumina.

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Beyond *BRCA1* and *BRCA2*

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Introduction

Hereditary breast and ovarian cancer (HBOC) syndrome associated with mutations in the *BRCA1* or 2 genes comprises the largest single portion of known hereditary breast cancer syndromes. However, there are several other, less common hereditary cancer syndromes that also include a substantially increased risk for breast cancer. When evaluating a family for possible genetic testing, it is important to ensure that all appropriate syndromes are considered. Identifying the correct hereditary breast cancer syndrome can have significant effect on quality and length of life for the patient and their relatives. Using a case-based approach, we review lesser understood hereditary breast cancer syndromes that should be included in the differential diagnosis of a patient presenting with a possible risk for a hereditary breast cancer syndrome.

Case 1

The patient presented for genetic counseling in 2010 after a recent diagnosis of a second primary breast cancer at 42 years of age. Her original breast cancer diagnosis (stage 2 invasive ductal carcinoma) occurred 8 years earlier at 34 years of age. At the time of her original diagnosis, the patient was treated with a lumpectomy followed by chemotherapy and radiation. She had been doing well after her treatment and underwent a mammogram every 6 months. The findings of her most recent mammogram were abnormal. The findings of the breast biopsy revealed a second primary cancer (stage 2 invasive ductal carcinoma) in the contralateral breast. Both breast cancers were estrogen and progesterone receptor positive. Genetic testing was not offered at the time of her first breast cancer diagnosis in 2002. The patient presented to genetics following the contralateral breast cancer diagnosis for evaluation for genetic testing. The patient reported a negative family history for cancer, but had no information about her paternal relatives.

Genetic testing

BRCA1 and *BRCA2* genetic testing was performed and no mutation was identified. The patient elected to have a bilateral mastectomy, and tamoxifen was started to reduce the risk of

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recurrence. She was encouraged to contact the genetics department with any changes in her family history, such as additional cancer diagnoses in her relatives.

The patient recontacted the genetics department in 2012 shortly after her maternal half-brother was diagnosed with an adrenocortical carcinoma (ACC) at 42 years of age. He underwent genetic testing at a nearby academic institution and was found to carry a deleterious mutation in the *TP53* gene, which causes Li-Fraumeni syndrome (LFS). It is noteworthy that this brother had been diagnosed with a sarcoma at 35 years of age shortly after the patient's second primary breast cancer. This information was not reported by the patient to her oncologist. The patient's brother died shortly after his diagnosis of ACC (Fig 1).

The patient underwent single-site testing and was positive for the known *TP53* mutation identified in brother. Based on this information, the patient elected to have a prophylactic bilateral salphingo-oophorectomy. She also initiated colon cancer screening and was seen at the National Institutes of Health Li-Fraumeni clinic for evaluation and development of a treatment

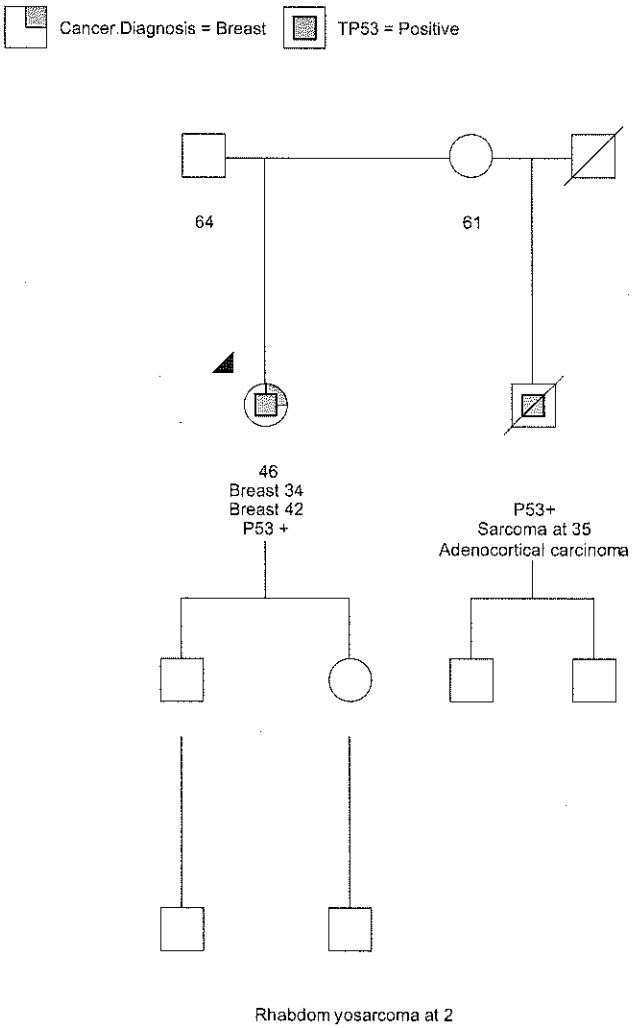

Fig. 1. Family pedigree of case 1. (Color version of figure is available online.)

plan. Testing was recommended for her 2 children in their 20s. The patient's daughter also tested positive for the familial *TP53* mutation. Shortly thereafter, the patient's grandson, related through her daughter, was diagnosed with a rhabdomyosarcoma at 2 years of age (Fig 1). He has received successful treatment for this condition. The grandson has not yet had genetic testing, but his rhabdomyosarcoma diagnosis is likely a result of LFS.

It is noteworthy that the patient's mother is most likely an obligate carrier of the *TP53* gene mutation identified in her children, as they are related through different fathers. Though an obligate carrier, she has not had any symptoms of LFS. Although LFS is a highly penetrant hereditary cancer syndrome, gene mutation carriers do not have a 100% risk to develop cancer in their lifetime. Another possible explanation for the mother's cancer-free status at 61 years of age is gonadal mosaicism, though this is a rare phenomenon. This patient's mother should undergo single-site analysis to confirm her carrier status so that she can be offered the appropriate screening and risk-reducing surgical options.

Li-Fraumeni syndrome

LFS is characterized by the presence of early-onset breast cancer, soft tissue sarcomas, osteosarcomas, ACC, brain cancers, and leukemia.[1-3] Additionally, increased risks for cancers of the ovaries, colon, and lung have been reported.[2-4] A germ-line mutation in the *TP53* gene is found in approximately 70% of families with features of classic LFS.[3] Classic LFS is characterized as follows: (1) a proband with a sarcoma diagnosed before 45 years of age, (2) a first-degree relative with any cancer before 45 years of age, (3) a first- or second-degree relative with any cancer before 45 years of age or a sarcoma at any age.[5] Approximately 20% of individuals meeting the revised Chompret criteria (Table 1) will have a detectable germ-line *TP53* mutation.[6] It has also been found that approximately 4%-8% of *BRCA1*- and *BRCA2*-negative women diagnosed with breast cancer before 30 years of age will carry a *TP53* mutation.[2,7]

Although somatic mutations in the *TP53* gene are seen in approximately 50% of all malignancies,[8] LFS is the only hereditary cancer syndrome associated with a germ-line *TP53* mutation. Individuals with LFS are estimated to have up to a 50% risk to develop an associated cancer by 30 years of age, and a 90% risk by 60 years of age.[9] The average age of onset of breast cancer in women with LFS is 33 years.[10] Women with a *TP53* germ-line mutation are advised of the option of a bilateral mastectomy as part of their treatment plan based on the high risk for a second primary cancer, which may in part result from previous radiotherapy.

Effect on medical management

Owing to the wide variety of cancers within LFS families, comprehensive cancer screening uses physical examination and imaging. Table 2 illustrates management recommendations according to National Comprehensive Cancer Network (NCCN) guidelines.[11]

Research studies continue to be performed to investigate the most effective screening modalities for LFS. Affected family members should be offered participation in a research study. Additional surveillance may be recommended based on the family history, and education should be provided about signs and symptoms of cancer.

Table 1
Chompret criteria for LFS.[6]

Proband with a tumor belonging to the LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, and lung bronchoalveolar cancer) before 46 y of age AND at least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before 56 y of age or with multiple tumors; OR
Proband with multiple tumors (except multiple breast tumors), 2 of which belong to the LFS tumor spectrum and the first of which occurred before 46 y of age; OR
Proband with adrenocortical carcinoma or choroid plexus tumor, regardless of family history

Table 2
NCCN Guidelines for management of patients with LFS.[11]

Recommendation	Timing
Annual breast MRI	Starting at 20-29 y of age or individualized based on earliest diagnosis of breast cancer in the family
Annual mammogram and breast MRI	Ages 30-75 y
Discuss risk-reducing mastectomy	Based on patient preference
Annual physical examination with high index of suspicion for rare cancers and second malignancies	Starting in childhood in identified mutation carriers
Colonoscopy every 2-5 y	Starting by 25 y of age

Familial implications

LFS is an autosomal dominant genetic disorder. Each first-degree relative of an individual testing positive for a *TP53* mutation will have a 50% chance to also carry the identified mutation. However, this will not be true in all cases as the rate of de novo mutations in the *TP53* gene has been estimated between 7% and 20%.[12] If the family history is otherwise negative for LFS cancers, parental testing of the proband should be pursued to identify who in the family is at risk. All at-risk family members should be offered genetic counseling and testing for the known familial mutation.

Most hereditary cancer syndromes increase risk for adult onset cancers. When an individual is at risk for these conditions, genetic testing is typically deferred until the 18 years of age. LFS is an exception to this recommendation. The array of cancers associated with LFS includes childhood-onset diseases such as choroid plexus carcinoma—a rare childhood brain cancer, and ACC.[2,13,14] Because of the association with very early ages of onset of cancer, genetic testing should be offered for children at risk to carry a *TP53* gene mutation. Recommended cancer screening should be initiated at the time a *TP53* mutation is identified.

Identification of a *TP53* gene mutation can place a psychological toll on individuals and families owing to the wide array of associated cancers, extremely early ages of onset, and lack of proven effective screening modalities for some. Patients with LFS may experience significant anxiety based on their increased risk for a variety of cancers, many of which are associated with a poor prognosis.[15] There can also be extreme stress and guilt felt by affected parents who have passed the gene mutation on to their young child. Patients may benefit from psychological counseling services if quality-of-life concerns arise. Peer support may also be beneficial for some families. The LFS Association is available to provide peer and professional support to families dealing with this difficult diagnosis.[16]

Keys points

- Genetic risk assessment is an ongoing process for patients with cancer. Family history concerns can change based on new diagnoses of cancer in the patient or his or her relatives. A follow-up appointment with the medical oncologist may be the ideal time to inquire about changes in family or personal history that could influence the patient's probability to have a hereditary cancer syndrome.
- Genetic testing guidelines also change with time. The current NCCN guidelines recommend genetic testing for LFS for any woman with a breast cancer diagnosed at 35 years of age or younger.[11] These guidelines were not in place in 2010. Newer genetic testing options include targeted gene panels that allow the practitioner to order testing concurrently for *BRCA1* and 2, as well as *TP53* and other highly penetrant breast cancer genes. This option facilitates genetic testing for the NCCN recommended syndromes in a cost-effective manner for the patient. However, comprehensive pretest counseling would be encouraged to prepare the patient for a possible diagnosis of a lesser known, or understood, hereditary breast cancer syndrome.
- The presence of a rare cancer within the family is often the first sign of a hereditary cancer syndrome. For example, the diagnosis of ACC, even in the absence of family history, should

lead to an evaluation for LFS. In a study, 5.8% of individuals diagnosed with an ACC after 18 years of age carried a germ-line TP53 gene mutation.[17] By identifying a *TP53* gene mutation in the index patient, additional at-risk relatives can be tested and if their results are positive, they are offered aggressive screening and management options with the hope of preventing cancer morbidity or mortality. Relatives who have negative test results are considered at general population risk for cancer.

Case 2

A 47-year-old woman was referred to the genetics clinic by her gastroenterologist. She had recently established care owing to fears generated after the death of her sister. The patient reported that her sister died a few years ago from stomach cancer diagnosed in her mid-30s. The sister was treated at an academic institution in a nearby state and died shortly after the diagnosis. The patient also reported that her mother died of stomach cancer, which was diagnosed in her 40s when the patient was a young child. Additionally the patient's maternal grandmother died of ovarian cancer and her father died of early-onset colon cancer (Fig 2).

Genetic testing

The patient was offered genetic testing for hereditary diffuse gastric cancer syndrome (HDGC) based on her family history of multiple relatives with early-onset stomach cancer and

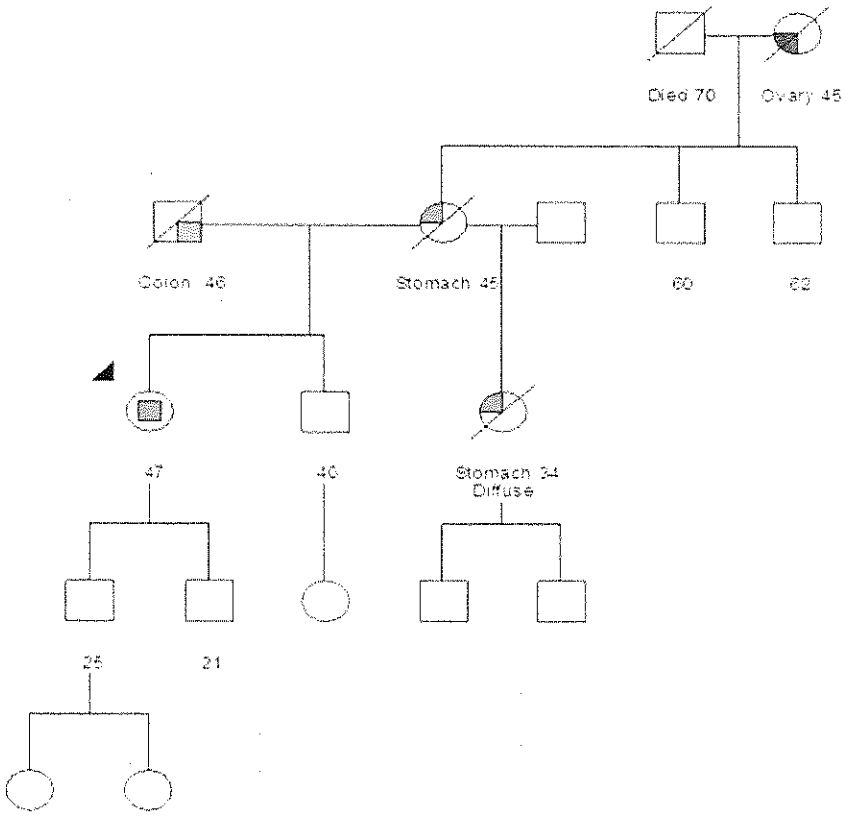

Fig. 2. Family pedigree of case 2. (Color version of figure is available online.)

pathological confirmation of the diffuse subtype in the sister. According to the NCCN guidelines,[18] genetic testing for HDGC should be offered in the presence of a family history of diffuse gastric cancer (DGC) when there is at least one diagnosis in a person younger than 50 years. The patient was also offered genetic testing for HBOC owing the history of early ovarian cancer in her maternal grandmother, and frequent colonoscopies owing to her father's history early-onset colon cancer.

The patient was found to carry a mutation in the *CDH1* gene, leading to a diagnosis of HDGC. Based on this gene mutation, the patient was referred to a surgical oncologist to discuss the option of the prophylactic gastrectomy. The patient also met with a counselor and nutritionist before deciding to undergo prophylactic surgery. After recovery from her surgery, the patient established care with a breast specialist even though there was no history of breast cancer in the family.

Hereditary diffuse gastric cancer syndrome

HDGC is a rare hereditary cancer syndrome caused by mutations in the *CDH1* gene. The condition is known to cause a risk for diffuse DGC by 80 years of age of up to 67% in men and 83% in women, in comparison with the general population risk of less than 1%.[19] The average age of diagnosis is the mid-30s, but ranges from 14-69 years.[20] In addition, women with a *CDH1* gene mutation have up to a 40% lifetime risk for lobular breast cancer, with a mean age of onset at 53 years.[19]

HDGC should be considered for patients meeting the following criteria: (1) 2 gastric cancer (GC) cases in a family, in which one individual who was younger than 50 years developed confirmed DGC; (2) 3 confirmed individuals with DGC in first- or second-degree relatives independent of age; (3) a simplex case (ie, a single occurrence in a family) of DGC occurring before 40 years of age; or (4) a personal or family history of DGC and lobular breast cancer, one diagnosed before 50 years of age.[21]

Medical management

Screening endoscopy is not recommended for patients with HDGC because of the diffuse nature of the GC. Studies have shown that current screening options for stomach cancer are not effective for patients with a known *CDH1* mutation.[21] Patients are advised to consider a prophylactic gastrectomy between 20 and 40 years of age.[21,22] This can be a very difficult decision for many patients as the thought of living a significant portion of life after a gastrectomy can be overwhelming. Patients are encouraged to consult with a number of medical specialists such as an upper gastrointestinal cancer surgeon, gastroenterologist, genetics specialist, nutritionist, and counselor when planning for prophylactic surgery.

Women with a *CDH1* gene mutation have a lifetime risk for breast cancer that warrants aggressive breast cancer screening. This screening should include yearly mammogram and breast magnetic resonance imaging (MRI) beginning at 35 years of age.[18,21] Patients may also wish to discuss the option of risk-reducing mastectomy with their physicians.

Familial implications

HDGC is an autosomal dominant genetic condition leading to a 50% risk of transmission from parent to child with each pregnancy. This is a highly penetrant condition and most family histories are striking for early-onset GC and death owing to poor screening and treatment options. Parents can feel tremendous guilt when they realize they have passed a gene mutation on to their child that could dramatically affect their length or quality of life. Patients respond best when this feeling is normalized and discussed openly to allow for emotional support from clinicians and relatives.

In this case, the patient shared her genetic testing result with her siblings, children, and niece and nephews. None of her at-risk relatives have chosen to undergo genetic testing to our knowledge. The patient was provided with documentation to share with her relatives including screening and management options for *CDH1* gene mutation carriers. These guidelines included recommendation for endoscopy starting at 20 years of age and consideration for gastrectomy, as well as breast screening starting, at 35 years of age.

Key points

- The pathology of cancer diagnosed in the patient or their relative can aid in genetic risk assessment. HDGC is strongly associated with lobular breast cancer, but not other breast cancer pathologies. HDGC is specifically associated with DGC, but not associated with more common GC types. By verifying the pathology of affected relatives, a more accurate risk assessment can be provided.
- The *CDH1* gene has been added to genetic testing panels designed to assess the risk for hereditary breast cancer. Numerous unexpected findings related to the *CDH1* gene have been reported based on recent testing experiences. A handful of test results have identified a *CDH1* mutation in a patient with breast cancer without a family history of GC. Clinicians are struggling with management recommendations under these circumstances, as there is limited understanding of the risk for GC in such families. The consequences could be drastic for a patient struggling to make treatment decisions. If there is not a significant risk for GC as suggested by lack of penetrance in additional relatives, the patient could be advised to undergo gastrectomy unnecessarily. However, if the risk for GC is underestimated, the patient could later be diagnosed with a DGC associated with a very poor prognosis. Additional studies are needed to address these critical management decisions for patients.

Case 3

A 50-year-old woman presented for an endoscopy to evaluate her gastric reflux disease. She was noted to have 2 Peutz-Jeghers–type hamartomatous polyps of the small intestine. The findings led to a referral to the genetics department for risk assessment. The patient noted that she had no family history of cancer, but had limited access to information about her relatives as both her parents died at young ages of noncancerous causes (Fig 3). On physical examination, the patient was noted to have dark pigmentation on the inside of her mouth. She reported that the pigmentation has gotten lighter with age.

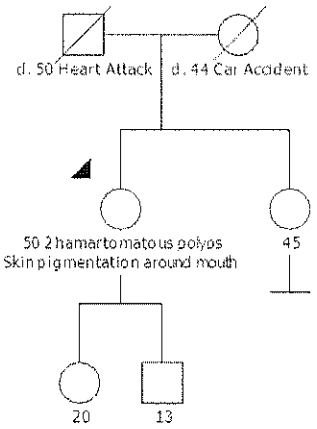

Fig. 3. Family pedigree of case 3. d., Age at death.

Genetic testing

Based on her presentation, the patient underwent genetic testing for Peutz-Jeghers syndrome (PJS) and was found to carry a mutation in the *STK11* gene. She was referred to a specialty clinic experienced in the management of patients with PJS, and her sister was encouraged to consider the option of single-site genetic testing.

Peutz-Jeghers syndrome

PJS is a rare hamartomatous syndrome associated with an increased risk for numerous cancers often of early onset (Table 3), as well as mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers.[23,24] The risk for breast cancer in women with PJS is similar to that of *BRCA1* and *BRCA2* mutation carriers, with a mean age of diagnosis of 44 years.[25,26] Clinical diagnostic criteria for PJS include the following: (1) 2 or more histologically confirmed PJS-type hamartomatous polyps, (2) any number of PJS-type polyps detected in one individual who has a family history of PJS in a close relative(s), (3) characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative(s), or (4) any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation.[23] Most families with a clinical diagnosis of PJS will have a mutation in the *STK11* gene.[24] Although 45% of affected individuals have will not have a family history, the exact de novo mutation rate is unknown.

Medical management

Because of the various cancers risk associated with a PJS diagnosis, patients are offered comprehensive cancer screening, which requires integration of numerous medical specialties, including gastroenterology, oncology, dermatology, and genetics. The screening plan summarized in Table 3 is based on the NCCN recommendations for individuals affected with PJS.[27]

Familial implications

PJS is an autosomal dominant hereditary cancer syndrome. Individuals with a *STK11* gene mutation have a 50% risk to pass the gene on to each of their children. Genetic testing of children is recommended by 10 years of age, as some of the screening is recommended to be initiated in

Table 3
PJS-associated cancer risk and screening recommendations.[23-27]

Associated cancers	Lifetime risks	Screening recommendations
Breast	45%-50%	Mammogram and breast MRI annually starting at 25 y of age.
Colon	39%	Colonoscopy every 2-3 y starting in the late teens.
Gastric	29%	Gastric screening using CT or MRI enterography with baseline at 8-10 y of age and then every 2-3 y by 18 y of age.
Small intestine	13%	Upper endocscopy every 2-3 y starting in the late teens.
Pancreas	11%-36%	Magnetic resonance cholangiopancreatography or endoscopic ultrasound every 1-2 y starting by 30-35 y of age.
Ovary, cervix, or uterus	18%-21%, 10%, and 9%, respectively	Consider transvaginal ultrasound along with yearly pelvic examination and Papanicolaou test.
Testes	Increased, but risks unclear	Annual examination starting at 10 y of age.
Lung	15%-17%	Smoking cessation.

CT, computed tomography.

childhood.[28] Dermatology features such as mucocutaneous hyperpigmentations are known to become less prominent later in life. A lack of dermatology features in an adult at-risk for a *STK11* gene mutation should not be used as exclusion criteria when assessing an individual's genetic risk for PJS.

Key points

- Medical specialists outside oncology may be the first to encounter a patient at risk for a hereditary cancer syndrome. A working knowledge of the most common hereditary cancer syndromes is suggested for all clinicians regardless of their area of specialty.
- Although not all individuals with a PJS-type polyp will go on to have a *STK11* gene mutation or a clinical diagnosis of PJS, referral for genetic counseling and testing is appropriate.
- Given the increased risks for numerous types of cancer with PJS, management requires the coordination of various medical specialties or referral to a high-risk center.
- Abnormal pigmentations, skin findings, or dysmorphology is a possible indication of a hereditary cancer syndrome.
- Intussusception related to polyp burden is a very common complication associated with PJS. It is estimated that 50% of individuals with the diagnosis of PJS will experience event of intussusception in their lifetime. Routine endoscopic evaluation with polypectomy starting in childhood will reduce this occurrence.[28]
- Although not studied specifically in the PJS population, prophylactic bilateral mastectomy and bilateral salphingo-oophorectomy and hysterectomy may be appropriate options considering the high risk of breast and gynecologic cancers compared with the general population.
- Individuals with PJS can develop many types of polyps including adenomas of the colon, which might lead to its confusion with familial adenomatous polyposis (FAP). Polyps have also been reported in the renal pelvis, urinary bladder, ureters, lungs, nares, and gall bladder.[11] The use of a gene panel test including numerous hereditary colon cancer syndromes could be a helpful tool for patients with overlapping clinical features.
- Patients with PJS are at risk for pancreatic and lung cancers.[25] Clinical trials evaluating screening for these malignancies should be considered.

Case 4

A 49-year-old woman who was diagnosed on screening mammography with a left breast invasive ductal carcinoma. The cancer is estrogen and progesterone receptor positive, HER-2/neu negative with no evidence of nodal involvement. She has lived in fear of developing breast cancer, ever since her mother was diagnosed 22 years ago. She sought genetic testing to help support her desire to obtain contralateral prophylactic mastectomy. She was also very concerned about her daughter's breast cancer risk. The patient reported that her mother was diagnosed with breast cancer at 58 years of age and cervical or uterine cancer in her maternal grandmother at 62 years of age. No other history of cancer is reported (Fig 4).

Genetic testing

Although the likelihood of finding a mutation is low based on the ages of diagnosis for the 2 breast cancer cases in the family, this patient meets NCCN criteria for *BRCA1* and *BRCA2* genetic testing.[11] *BRCA* testing is ordered and as expected, the analysis did not identify a mutation in either gene. Thus, there is no genetic evidence to support contralateral prophylactic mastectomy, and the patient's decision regarding this must be based on other factors. In addition, there is no reason to offer genetic testing to her daughter. Her daughter's lifetime breast cancer risk can be estimated from empiric data from the Claus model.[28] For a woman with a mother diagnosed with breast cancer in her 40s and a maternal aunt (an approximation for a mother-grandmother pair) diagnosed in her 60s, the Claus model estimates approximately a 24% lifetime risk for breast cancer.

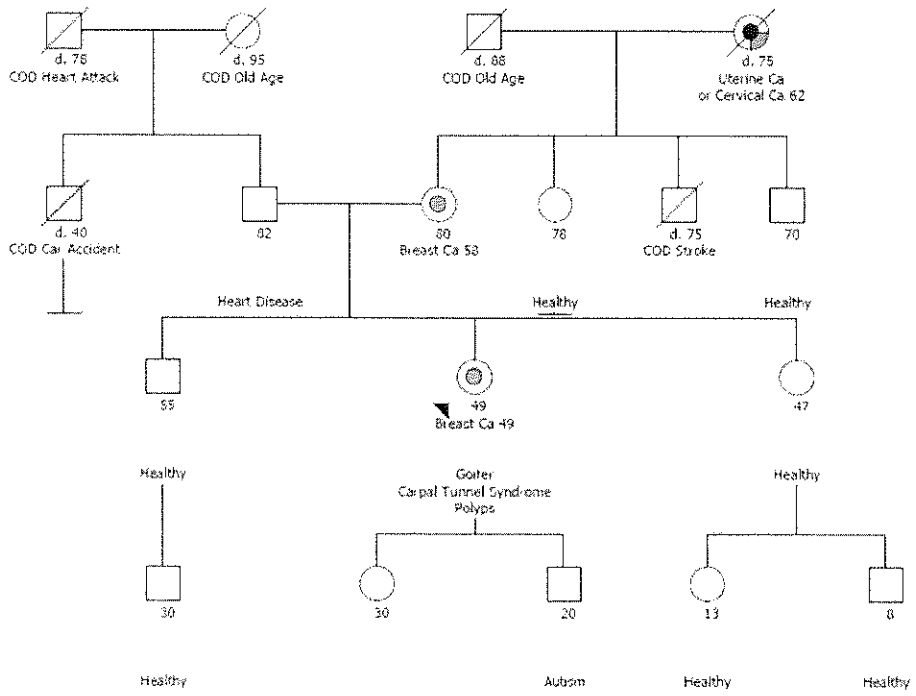

Fig. 4. Family pedigree of case 4. Ca, cancer, d., age at death. (Color version of figure is available online.)

At this risk level, the American Cancer Society recommends screening by annual breast MRI as well as annual mammograms.[29] As there is no proven genetic risk, the general approach is to start screening close relatives 5-10 years before the youngest age of breast cancer diagnosis in the family. Thus, her daughter's screening should start around 39 or 40 years of age, the same age for baseline screening in the general population.

Unsatisfied with her negative test results, the patient asks about the possibility of additional genetic testing. A review of her medical history reveals multinodular thyroid goiter, carpal tunnel syndrome, and head circumference measuring 58.5 cm (> 97th percentile). A baseline colonoscopy done this year revealed 4 hyperplastic polyps. There are no other significant findings noted unrelated to her breast cancer. The patient also mentions that she cares for her 20-year-old son with autism.

Her personal history also meets NCCN testing criteria for *PTEN* genetic testing.[11] *PTEN* mutations are associated with a spectrum of clinical syndromes collectively called the *PTEN* hamartoma tumor syndrome (PHTS). These include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), and autism spectrum disorders associated with macrocephaly. The testing criteria established by the NCCN[11] are presented in Table 3. *PTEN* testing is then ordered and a deleterious mutation is identified, confirming a diagnosis of PHTS.

PTEN Hamartoma tumor syndrome

PTEN mutations have historically been associated with estimated cancer risks of 25%-50% for breast cancer, 3%-10% for thyroid cancer, and 5%-10% for endometrial cancer, whereas more recent studies have suggested increased risks for colon and renal cell cancers as well.[30] Several groups have recently projected lifetime cancer risks much higher than these figures, up to 77%-85% for breast cancer, 21%-38% for thyroid cancer, 20%-28% for endometrial cancer, 15%-34% for renal cell carcinoma, and 9%-16% for colon cancer.[31-34] However, the patients in these cohorts

were tested based upon the presence of multiple PHTS clinical features, including cancers. The selection bias inherent in this approach suggests that these may be overestimates.[31]

PTEN mutations are also associated with a range of nonmalignant clinical features as noted in Table 4. The most common of these are macrocephaly and gastrointestinal polyps (hamartomas or ganglioneuromas), found in more than 80% of patients.[35] Skin lesions are reportedly found in almost 100% of patients, but this may be an overestimate based on selection bias. Multiple trichilemommas are highly suggestive of the diagnosis, although it is not clear if they are pathognomonic. Thyroid structural lesions including multinodular goiter, nodules, and adenomas are also frequently seen.

Effect on medical management

All individuals with *PTEN* mutations require the same careful clinical screening, regardless of their specific clinical diagnosis (Cowden syndrome, BRRS, or autism spectrum disorders). NCCN[11] management recommendations for women with *PTEN* mutations include the following:

- Clinical breast examinations every 6-12 months starting at 25 years of age.
- Annual mammography and breast MRI beginning at 30-35 years of age.
- Discussion of options of prophylactic mastectomy and hysterectomy.
- Consideration of annual random endometrial biopsies from 30-35 years of age.
- Annual comprehensive physical examination.
- Annual thyroid ultrasound from 18 years of age.
- Colonoscopy starting at 35 years of age, every 5 years if no polyps found.
- Consider renal ultrasound every 1-2 years, starting at 40 years of age.

Thus at minimum, breast MRI screening is indicated for this patient, but consideration of prophylactic contralateral mastectomy and hysterectomy is also appropriate. Increased colon and thyroid cancer screening are also indicated.

Table 4
Cowden syndrome and PHTS testing criteria. (Adapted with permission from NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian.[11])

Testing criteria	
PTEN mutation already identified in family	OR:
Clinical diagnosis of CS or BRRS	Macrocephaly plus one other major criterion*
Adult diagnosis of Lhermitte-Duclos diseases (dysplastic cerebellar gangliocytoma)	Three major criteria without macrocephaly
Autism spectrum disorder with macrocephaly	One major and three minor criteria**
Two or more biopsy-proven trichilemmomas	Four major criteria
*Major criteria**	*Minor criteria***
Breast cancer	Autism spectrum disorder
Endometrial cancer	Colon cancer
Follicular thyroid cancer	Esophageal glycogenic acanthosis
Multiple GI hamartomas or ganglioneuromas	Lipomas
Macrocephaly (head circumference ≥ 97th percentile)	Intellectual disability
Mucocutaneous lesions:	Thyroid cancer—papillary or follicular variant
One biopsy-proven trichilemmoma	Thyroid structural lesions including multinodular goiter, nodules, and adenomas
Multiple palmoplantar keratoses	Renal cell carcinoma
Oral mucosal papillomatosis	Single gastrointestinal hamartoma or ganglioneuroma
Multiple cutaneous facial papules	Testicular lipomatosis
	Vascular anomalies

* major criteria.
** minor criteria.

Familial implications

PHTS is an autosomal dominant condition, implying each of this patient's first-degree relatives has a 50% chance of having inherited this *PTEN* mutation and should be offered genetic counseling and single-site testing. Although de novo mutations do occur in PHTS, more often the mutation has been present in previous generations, but the diagnosis was missed because the clinical features were subtle or they were ignored because they are common in the general population. The son with autism most likely has the mutation, but this should be confirmed through testing. The most dramatic changes in management will occur for the daughter for whom screening will increase significantly if she has the mutation. If the results of screening are negative, she would follow screening recommendations for an average risk woman.

This case highlights the importance of considering testing for genes beyond *BRCA1* and *BRCA2* in breast cancer families. This is one of a small number of hereditary cancer syndromes where benign clinical features can be important indicators of the syndrome. PHTS clinical features should be kept in mind when evaluating any patient with a history of breast cancer. For patients who meet NCCN testing criteria, *PTEN* testing might be indicated before *BRCA* testing, or together through panel testing.

It is noteworthy that it is also entirely possible that the *PTEN* mutation in this family could have been identified by a pediatrician. Children with signs of BRRS (most commonly macrocephaly, developmental delay or autism, lipomas, and penile freckling in boys) should undergo testing for *PTEN* mutations. If a mutation is identified, both the parents should then be tested to determine which side of the family is at risk.

Case 5

A 35-year-old woman with a recently diagnosed invasive ductal carcinoma presented for a second opinion. Interestingly, she also carries a clinical diagnosis of FAP based on the identification of multiple polyps on colonoscopy performed the previous year owing to rectal bleeding. There is no family history of colon cancer or polyps, but she does have a sister with thyroid cancer.

FAP is a hereditary condition affecting an estimated 1 in 8000 individuals, who generally present with hundreds to thousands of adenomatous polyps found throughout the colon and is discussed in detail elsewhere in this monograph.[36] Because the risk for breast cancer is not increased in FAP, and it is unlikely, but not impossible that this patient has 2 separate hereditary cancer syndromes, her colonoscopy and pathology reports were requested and reviewed. The pathology results indicated that she primarily had ganglioneuromatous and hamartomatous or hyperplastic polyps, but few adenomas that would be consistent with FAP. It is unfortunately not uncommon that a patient is mislabeled as having FAP based solely on the number of polyps, regardless of whether they are adenomatous.

The findings of the examination of the patient revealed small papillomas of the gums and a head circumference of 59 cm (over the 97th percentile). No other significant features are noted. *PTEN* testing is ordered for this patient, but no mutation is identified. However, the combination of colonic ganglioneuromatosis, macrocephaly, breast cancer, and oral papillomatosis meet the NCCN diagnostic criteria for a clinical diagnosis of PHTS.[11] Thus, she should be managed following the NCCN PHTS guidelines despite the absence of a detectable *PTEN* mutation. However, genetic testing cannot be offered to her close relatives to determine whether they are also genetically at risk, and there is no consensus on how to screen close relatives if they do not have signs of PHTS.

Key points

- PHTS is one of the few hereditary cancer syndromes that can present with benign clinical signs in addition to the cancer history. PHTS signs should be kept in mind when assessing hereditary risk for patients with breast cancer.

- *PTEN* testing should be considered for any patients with breast cancer with signs of PHTS meeting the NCCN testing criteria.
- Depending on the patient-family presentation, *PTEN* testing might be ordered as a stand-alone test or as part of a panel including *BRCA1* and *BRCA2* and other genes.
- Cancer risks, and cancer screening and management recommendations differ significantly between patients with *PTEN* and *BRCA* mutations. Thus, identifying the correct hereditary syndrome has significant medical implications.
- Current data suggest that a significant proportion of individuals meeting the current clinical diagnostic criteria for PHTS do not have an identified PTEN mutation. Under these circumstances, management recommendations for at-risk relatives remain uncertain.

Summary

A hereditary breast cancer syndrome can present in a variety of ways ranging from an index case of early-onset breast cancer to an incidental finding during an endoscopy or a dermatological examination. A comprehensive review of the patient's personal and family history is essential to accurately assess the risk for a hereditary cancer syndrome. Clinicians should be aware of the wide variety of hereditary breast cancer syndromes beyond *BRCA1* and *BRCA2*-associated HBOC. Failure to identify a rare hereditary breast cancer syndrome can lead to additional cancer diagnoses in the patient or relatives that might have been prevented with appropriately aggressive management and screening. Effective identification and management of patients with a hereditary breast cancer syndrome requires a team approach.

The use of cancer gene panels, although they can be beneficial in many cases, may also reveal incidental information, unexpected diagnoses, and inconclusive findings. Patients should be offered comprehensive counseling about the potential impact of this type of genetic testing before deciding to pursue a gene panel test. This counseling should include information about the numerous genetic syndromes analyzed. When performed in the context of thorough pretest and posttest counseling, genetic testing is a powerful tool that can aid the patient, his or her family members, and their physicians in making appropriate medical management decisions.

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