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6 things
physicians
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about
GENETICS



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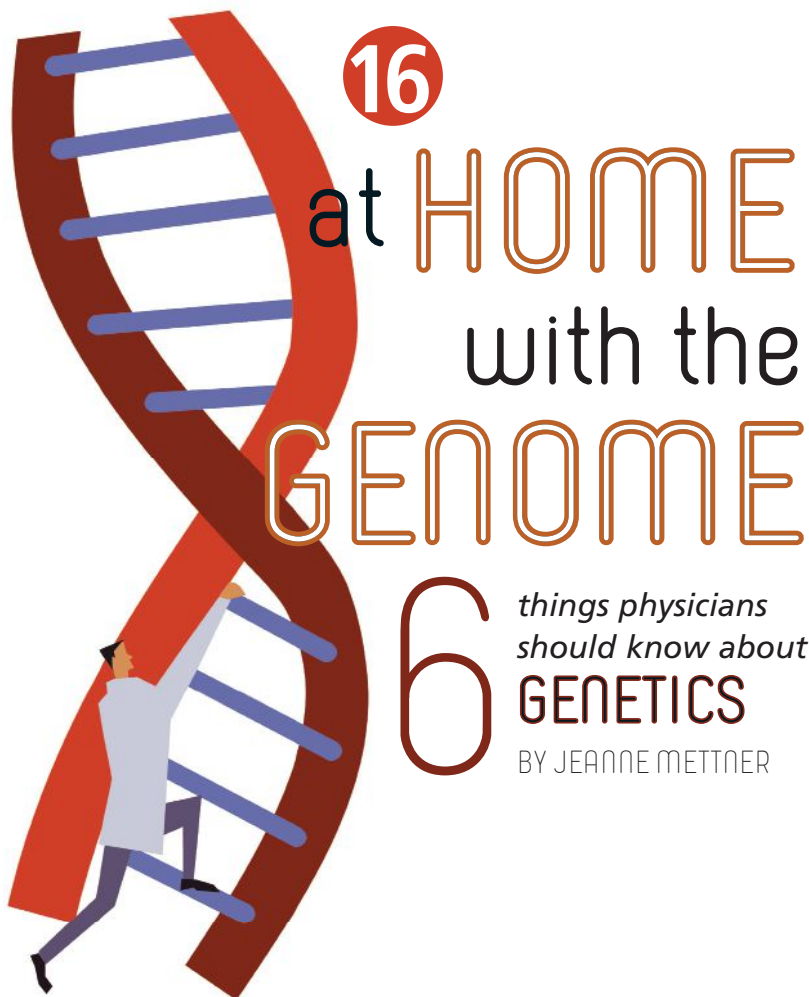
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The most specialized generalists
- When to refer for
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- Diagnostic challenges in **cystic fibrosis**



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OCTOBER 2012

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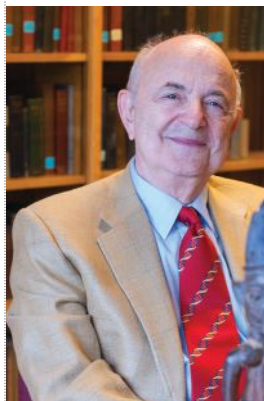
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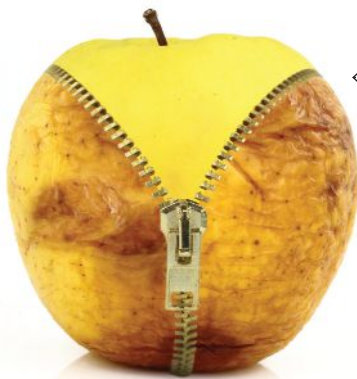
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Contact Us

Minnesota Medicine, 1300 Godward Street, Ste 2500,
Minneapolis, MN 55413.
Phone: 612/378-1875 or 800/DIAL MMA
Email: mm@mmed.org
Web: minnesotamedicine.com

Owner and Publisher

Minnesota Medical Association

Editor in Chief

Charles R. Meyer, M.D.

Editors

Carmen Peota
Kim Kiser

MMA Communications Director

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Annual subscription - \$45 (U.S.), \$80 (all international)

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Photo by Scott Walker

Most practicing physicians have only casual knowledge of the connection between genes and disease.

Becoming Sherlock

My wife and I have almost finished the second season of the BBC series, “Sherlock,” a remake of Sir Arthur Conan Doyle’s classic in which a 21st century Sherlock Holmes texts and employs a modern-day pathology laboratory to solve crimes. A bit haughtier and ruder than Conan Doyle’s hero, especially as he was portrayed by Basil Rathbone in the 1930s films, this Sherlock is still the crack diagnostician, gleaning clues from stains on pants, watches set one hour ahead and scratches on cellphones. Yet the series stops short of showing Sherlock using one of the emerging sciences, genetics, which promises to support future diagnosticians, medical and forensic, and perhaps make us all into veritable Sherlocks.

That promise felt almost palpable when Francis Collins announced the successful sequencing of the human genome in 2000. For years, the DNA code seemed like a hieroglyph, whose cracking would unlock the mysteries of life, disease and, possibly, death. Once we knew the instruction sequence for human life, surely the identification of the genetic basis for disordered life would follow quickly. Yet 12 years have passed since Collins’ announcement and most practicing physicians have only casual knowledge of the connection between genes and disease, and their daily practice is free of chromosomal complications except for the rare family that wants testing.

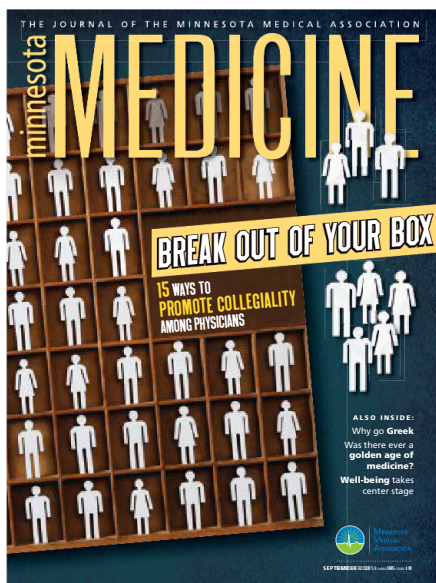
Except for the oncologist. For decades, medical science has known that chromosomal abnormalities lie at the root of the genesis of cancer. The Philadelphia chromosome of chronic myelogenous leukemia (CML) was identified in 1960. Since then, many genetically based diagnostic procedures and therapies have benefited

oncologists and their patients. Genetically determined subtypes of cancers now predict tumor behavior and can help oncologists preselect chemotherapy protocols. Chemotherapeutic agents such as Gleevec were custom-designed with the knowledge of the chromosomal abnormalities in CML. Oncologists seem to have all the genetic fun.

Yet genetics is creeping onto the radar of the general practitioner. We get faxes asking us if we want to test our patients on warfarin for a genetic variation that affects the way they metabolize the anticoagulant. DNA sequencers have gone from the slow, room-filling goliathans of the Human Genome Project to near-desktop models that can crank out a person’s genome in days, faster if they look only for active DNA segments called exons. With that progress have come the inevitable entrepreneurial shysters who, like carnival palm readers, offer Internet surfers a complete map of their medical future based on a buccal smear. For legitimate medical applications, it seems like that promise of 2000 will be delayed but is still forthcoming, and maybe one day the DNA sequencer will sit right next to the CBC machine in doctors’ offices.

Despite “Sherlock’s” popularity in Britain, a third season has yet to be announced. If the producers do decide to bring back the misanthropic, icy detective, perhaps they’ll have him bending over an exon sequencer unraveling the incriminating DNA of his prime suspect. I can’t wait.

.....
Charles Meyer can be reached at
meyer073@umn.edu.



Osteopaths overlooked

I read with great interest Dr. Peter Kernahan's article "Was There Ever a 'Golden Age' of Medicine?" (September, p. 41). I found his short history to be thought-provoking. Yet although the article is quite encompassing, it never mentions osteopathic medicine.

Since osteopathic medicine's founding in 1874 by Andrew Taylor Still, D.O., M.D., in Kirksville, Missouri, the profession has grown to the extent that there are currently 26 osteopathic medicine schools in the United States that graduate approximately 3,600 new osteopathic physicians (DOs) annually. The number of graduates is projected to increase to 4,700 by 2013.

At this time, there are more than 82,000 DOs in the United States. This number is on the rise, as more than 20,000 students are currently enrolled in osteopathic medical schools nationwide. (One in five medical students in the United States is enrolled in a college of osteopathic medicine.)

Osteopathic medicine has also had a rich history within our state. Red Wing was the first city outside of Kirksville to

have a permanent office for the practice of osteopathic medicine. This was the office of Doctors Harry and Charlie Still, the sons of Dr. Andrew Still, D.O., M.D.

In 1896, Minneapolis was the site of the third osteopathic medical school ever established. The Northern College of Osteopathy graduated about 230 students before it merged with the osteopathic medical college in Des Moines, Iowa, in 1902.

The predecessor of today's Minnesota Osteopathic Medical Society was organized in 1899. The first Minnesota osteopathic practice law was passed in 1903, giving D.O.s every right they desired, and. Today, nearly 600 osteopathic physicians are practicing in Minnesota. Many, like me, are members of the Minnesota Medical Association.

Leonid Skorin, Jr., D.O., O.D., M.S.
President, Minnesota Osteopathic
Medical Society

Author's response

I thank Dr. Skorin for his very informative letter. He rightly directs our attention to the history of osteopathic medicine, particularly in Minnesota, and to the prominent role of D.O.s in today's health care system. I will only add that the article was not intended to be a comprehensive history of medicine but was written to address some of the questions raised by posing a "golden age" of medicine. For readers interested in learning more about the history of osteopathic medicine, I would recommend Norman Gevitz' *The D.O.s: Osteopathic Medicine in America* (Johns Hopkins University Press, 2004), E. C. Goblirsch's *The History of Osteopathy in Minnesota* (Minnesota Osteopathic Medical Society, 1982) and Thomas A. Quinn's *The Feminine Touch: The History of Women in Osteopathic Medicine* (Truman State University Press, 2011).

Peter J. Kernahan, M.D.



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■ Genetics research

Minnesotans make discoveries

Almost daily, researchers are identifying genes that are implicated in disease. Here are two recent findings by Minnesota investigators:

Discovery of a genomic variant that increases a person's risk for developing certain types of brain tumors by six fold by Mayo Clinic researchers working with a team from the University of California, San Francisco (UCSF).

This work builds on previous studies in which they observed that a portion of chromosome 8 contained single nucleotide polymorphisms (SNPs) associated with brain tumors and identified seven low-frequency SNPs on that site that are strongly associated with oligodendroglial glioma risk. The one with the strongest association is rs55705857.

In their most recent study, the findings of which were published online in *Nature Genetics* in August, the Mayo/UCSF team found that having the “G” guanine version of this SNP was more strongly associated with slower-growing gliomas than having the more common “A” adenine version.

Robert Jenkins, M.D., Ph.D., a Mayo Clinic Cancer Center pathologist and senior author of the study, says that the findings could lead to blood tests that may be able to tell what kind of tumor a patient has.

New insights into the genetics of colon cancer by researchers from the University of Minnesota in partnership with geneticists from Genentech.

The team analyzed more than 70 pairs of human colon tumors and found that when two types of R-spondins—proteins that activate cell proliferation during embryonic development—are reactivated in adults through certain genetic mutations, they can signal cells to restart the proliferation process. The R-spondins involved are RSPO2 and RSPO3.

The findings, which were published in the August 15, 2012, online issue of *Nature*, could be a key to developing personalized therapies based on a tumor's genetics.

■ Genomic basics

Talking genomic

One of the difficulties with trying to follow developments in genetics and genomics is keeping up with the language. Unless you work in the field, you're likely behind. Here are three terms you need to know to begin to have a sense of what's going on.

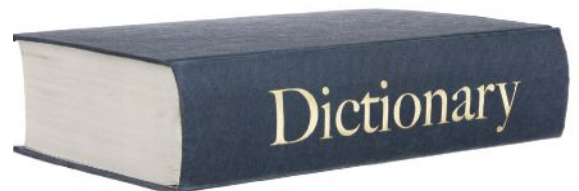
Next-generation sequencing: refers to various technologies that allow for rapid sequencing of large numbers of DNA segments. Also referred to as “massively parallel” sequencing.

Whole-genome sequencing: refers to the process of determining the sequence of *most* of the DNA content comprising an individual's entire genome.

Whole-exome sequencing: refers to the process of sequencing the part of the gene that codes for amino acids or protein. The exome is the portion most likely to include mutations that result in clinical phenotypes.

For a brief history on the machinery of genomic sequencing, check out “High Throughput, High Content Technologies,” a presentation by David I. Smith, Ph.D., from the division of experimental pathology and laboratory medicine at Mayo Clinic. Smith starts by describing the equipment used for the initial sequencing of the human genome, which processed 96 DNA strands at a time, and goes on to discuss the exponential increases in speed and capacity of subsequent sequencers. The presentation is online at www.mayomedicallaboratories.com/articles/hottopics/transcripts/2009/2009-5b-high-throughput/5b-36.html.

Sources: American College of Medical Genetics and Genomics, Mayo Clinic, National Human Genome Research Institute



■ Disclosing research results

A question of consent

| BY CARMEN PEOTA

As a genetic epidemiologist focused on pancreatic cancer, Mayo Clinic's Gloria M. Petersen, Ph.D., studies DNA in hundreds of tumor samples that were taken from people sometimes years earlier. Each of the individuals who donated a sample signed a Mayo consent form indicating, among other things, whether he or she wanted to be informed about research results that might be personally significant. But that consent doesn't apply to their family members.

Petersen first realized this might be a problem about six years ago, when she and her colleagues discovered that mutations in genes in certain people with pancreatic cancer were also linked to breast cancer and melanoma. She realized she had genetic information for 73 individuals that might benefit their family members. Complicating things was the fact that most of the people who had donated samples had already died. "I don't know what my obligation is to the family members because they were not consented into the study. I consented the person who's now deceased," Petersen says.



She discussed her dilemma with Mayo bioethicist Barbara Koenig, Ph.D., who suggested they approach University of Minnesota law professor Susan Wolfe, J.D., who was working on similar concerns. Together, the three applied for and got a federal grant to study the issue of returning results to family members. Thus far, they have convened a working group and begun interviewing other researchers. They plan to develop recommendations based on those interviews.

For now, Petersen is not returning results to family members. But she won't be surprised if that changes. "This is a new area because it's genetic information that has implications for kin. Who controls that information? That's never been worked out in a way that could lead to some kind of recommendation for how

biobanks should manage the information, if it is discovered," she says. Then there's the question, What is the best way to disclose research findings? "It will affect biobank practice," Peterson says their study. "There's no question about that."

check this out

The National Human Genome Research Institute has released a free app "Talking Glossary of Genetic Terms." The app includes written definitions of terms as well as recorded explanations. The app also contains more than 150 illustrations and more than 30 animations that show genetic concepts at the cellular level.

The app is available for the iPhone, iPad and iPod Touch.

Returning results to subjects

Minnesota researchers have taken the lead in crafting recommendations for investigators who uncover genetic/genomic information that might affect the health of individual study subjects. The April 2012 issue of *Genetics in Medicine* includes an article by University of Minnesota legal scholar Susan M. Wolf, J.D., and 25 colleagues including Mayo Clinic's Gloria M. Petersen, Ph.D., that provides the first set of consensus recommendations on what to do with findings about research participants that have implications for their health. The authors state that if a biobank is able to identify individual specimen and data contributors and that if the findings are "analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable," they generally should be offered to consenting contributors.



Irving I. Gottesman now works with many of the researchers he trained.

■ Irving I. Gottesman, Ph.D.

Pioneer in behavioral genetics

Irving I. Gottesman was one of the first to show the genetic underpinnings of mental illness. | BY SUZY FRISCH

When Irving I. Gottesman worked on his doctorate in psychology at the University of Minnesota in the late 1950s, the predominant thinking was that poor parenting—especially by one’s mother—caused people to develop schizophrenia. Gottesman wasn’t so sure, and he set out to see if there was a biological basis for the mental illness.

He did just that and over the course of a career spanning more than 50 years has become one of the world’s most

influential voices on the causes of schizophrenia. His abundant work, which includes nearly 250 articles and 20 books and monographs, has been cited in other publications more than 20,400 times. He wrote several of those just in the past decade, including a 2011 chapter in *Psychology and the Real World* called “Predisposed to Understand the Complex Origins of Behavioral Variation” and a 2010 article in *Archives of General Psychiatry*, “Severe Mental Disorders in Offspring of Dual

Matings with Two Psychiatrically Ill Parents.”

Gottesman, who at 81 years of age exudes the energy of someone much younger, could have retired long ago, assured of a stellar reputation in both psychology and psychiatry. But he hasn’t slowed down, continuing to go to his Elliot Hall office on the University of Minnesota campus several times a week to write and shape thinking about the complicated causes of mental illnesses. Although still involved in research, he admits his role has changed.

“I’ve shifted from being a fighter pilot to being a navigator or a bomber,” says Gottesman, who is a senior fellow in the university’s department of psychology and the Bernstein professor in adult psychiatry (retired) at the medical school. In making that shift, he continues to engage with many of the 36 Ph.D.s and seven post-docs he has produced who are currently investigating how genes interact with environmental factors to influence IQ, personality, propensity for criminal behavior, predisposition to alcoholism and more.

“Irv has been retired more than 10 years, and he’s been just about as productive being retired and maybe more so,” says Matt McGue, Ph.D., a psychology professor at the University of Minnesota who took graduate classes with Gottesman 35 years ago. “He’s done some of his best work in the past 10 years.”

One notable article, “The Endophenotype Concept in Psychiatry,” published in the *American Journal of Psychiatry* in 2003, has been cited nearly 2,500 times—an astounding number of citations in the field of psychology, where articles typically are cited only once or twice. Gottesman’s thinking about how biological phenomena such as brain-wave patterns interact with genes to cause mental illness has caught fire in human genetics circles as well as in psychology. “He’s considered one of the world’s experts on genetic schizophrenia, and to this day the books he’s written on that are considered standards,” McGue adds.

Photo by Kathryn Forss

Minnesota ties

Gottesman's Minnesota roots run deep, starting when he was in graduate school at the University of Minnesota, where he earned his doctorate in psychology in 1960. In 2001, he and his wife moved back to Minnesota from Virginia, where he served on the University of Virginia faculty, to be closer to family, including two children and three grandchildren. Although that was the main draw, Gottesman also felt a debt of gratitude to the university that launched his career. "I was prepared at this university to think properly, and it has paid off in dividends," he notes.

Born in Cleveland, Ohio, to parents who immigrated from Hungary, Gottesman joined the U.S. Navy after high school and in 1949 headed to the Illinois Institute of Technology in Chicago through NROTC. He intended to major in physics because his favorite high school teacher encouraged him to enter that field. But a class in abnormal psychology

piqued his interest, and Gottesman ultimately switched to psychology.

During the Korean War, he served as a communications specialist on several ships, earning enough combat credits for four years of graduate school on the GI Bill. Gottesman was attracted to the University of Minnesota, whose researchers had developed the Minnesota Multiphasic Personality Inventory (MMPI) not many years earlier and were focusing on the biological and genetic roots of personality and psychological conditions—a stark contrast to the prevailing Freudian and nurture theories of the time.

For his doctoral dissertation, Gottesman used the MMPI to study the personality traits of identical and fraternal twins. He determined that certain characteristics such as social introversion and aggressive tendencies were under strong genetic control. Gottesman's work inspired numerous other important twin studies, including Minnesota researcher Thomas Bouchard's work on identical twins separated since birth. After graduating, Gottesman spent

three years at Harvard University as a lecturer in psychology before winning a fellowship in 1963 from the National Institute of Mental Health and the U.S. Public Health Service to study psychiatric genetics at the University of London and the Institute of Psychiatry, where more groundbreaking work ensued.

There, Gottesman, working with James Shields at Maudsley-Bethlem Hospital, proved the genetic underpinnings of schizophrenia. They compiled 57 case studies of same-sex twins (one or both had schizophrenia) and discovered that if one twin had schizophrenia, the other would as well in about half of the cases, while fraternal twins did so only 10 percent of the time. They also found that multiple genes, combined with environmental factors, were responsible for the disease. Gottesman and Shields published their findings in *Schizophrenia and Genetics: A Twin Study Vantage Point*, which has become a bible in the field and has been translated into Japanese and German. ↪

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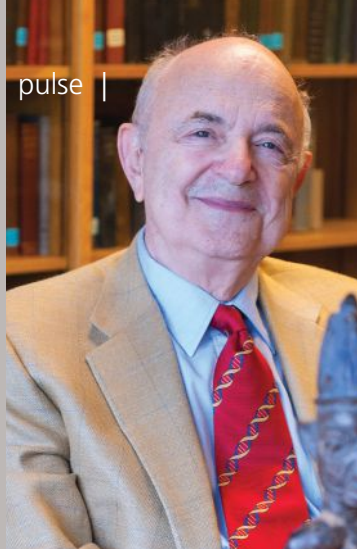
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Highly decorated

Irving I. Gottesman, Ph.D., has won numerous awards. Among them:

He became an Honorary Fellow of the Royal College of Psychiatrists in 1988, a rare honor for a psychologist.

He was the first psychologist to win the Lifetime Achievement Award from the International Society for Psychiatric Genetics in 1997.

In 2001, he earned the Distinguished Scientific Contributions Award from the American Psychiatric Association—one of the highest honors a psychologist can receive, given previously to the likes of Jean Piaget and B.F. Skinner.

This month, he travels to London to receive an Honorary Fellowship from King's College.

"It's probably the best twin study to this day that's ever been undertaken," McGue says. "That study, along with some other research at the time, really led to the current model of schizophrenia and most mental illnesses—that they are neurological disorders that are in part inherited. It's really changed the way people do research on mental disorders."

Gottesman talks fondly of the work he did in London: "I think it moved the field in the direction of biological psychiatry and psychology, which then turns to all of the contemporary techniques like brain imaging in connection with genetic research."

Mind shift

Returning from London to Minnesota in 1966 to launch the university's Behavioral Genetics Center, Gottesman continued his thought-changing work, including finding a genetic link for alcoholism in men and women. In 1972, he took a Guggenheim Fellowship—funded sabbatical to do research at Denmark's Psykologisk Institut, Kommunehospitalet, and serve as a visiting professor at the University of Copenhagen. There, Gottesman again studied sets of twins in which one had schizophrenia, this time focusing on their children. They found the children of the identical twin without schizophrenia were just as likely to develop schizophrenia as the children of the twin with schizophrenia. "We wrote a paper to explain our theory called unexpressed genotypes—that just because you have a gene doesn't mean that it's turned on," he explains. They also found factors including divorce, and drug use also played a significant role in determining whether an individual developed the disease.

After leaving Minnesota in 1980, Gottesman spent time at Washington University in St. Louis and Stanford University, where he was a fellow at the Center for Advanced Study in the Behavioral Sciences. He headed to the University of Virginia in 1985 to establish a research-based clinical psychology training program and stayed there until he retired in 2001.

Gottesman doesn't travel much these days, preferring instead to connect with former colleagues and fellow researchers online and in Minnesota. His work has been especially influential in Japan and China; he helped Chinese post-docs who did work at the University of Minnesota set up a twin registry in Beijing and guided them in their research. Gottesman's eyes light up when he talks about his work in Denmark, which has been going on

for 40 years. Today, he is examining whether the grown children in families where both parents are mentally ill are more likely to develop mental illnesses than children of just one parent with a psychiatric illness. So far, he has found that they are, "but not as likely as you would fear," he says. "I'm using an extremely rare sample and strategy, and I love rare strategies because I won't be imitated right away. I can only carry it out because I have connections to people in the Danish system."

Gottesman is clearly still motivated by the same goal that drew him to study schizophrenia in the first place: finding the cause of the disease so it can be cured. "The thing that keeps me going is that we don't yet have an answer, but we're always on the verge of an answer," he says.

The impact of his work becomes most real when he meets parents of children with schizophrenia, who inevitably ask how their son or daughter became ill and how the latest thinking might help their child. "I have to tell them that I regret I can't answer either question, but we're working on it," he says.

A multifaceted legacy

Gottesman has influenced the way psychologists, psychiatrists and others think about the causes of mental illness. For that, he has received numerous awards. Modest about these accolades, he says he was fortunate to work with talented colleagues and cites the famous phrases "It takes a village" and the Beatles' "With a little help from my friends."

Those who've worked closely with him talk about the personal impact he has had. Bill Iacono, Ph.D., a Regents professor of psychology at the University of Minnesota, says Gottesman has an ability to connect people who have common research interests. "He has a catalytic effect on how people think about things," Iacono says. "He's skillful at bringing people together with different points of view in ways that produce a few sparks that get people closer to common ground."

Because he has trained and mentored many other researchers, Gottesman's influence will be felt for generations. Of that he seems especially proud. "It's sort of like throwing a rock in the pond and watching all of these ripples. They keep going and going," he says. "There is a tremendous bibliography, if you look at mine and each of my Ph.D.s, and then each of their Ph.Ds. If I'm the rock in the water, I'm happy to have these ripples." **MM**



Photo courtesy of CentraCare Health System

CentraCare's David Tilstra, M.D., says being a medical geneticist can be like being a detective in that you sometimes are trying to uncover the unknown.

■ Medical genetics

The “most specialized generalists”

Medical geneticists find themselves in demand as research makes its way into practice. | BY TROUT LOWEN

Human genetics research is rapidly changing the practice of medicine, and few specialties are or will be more affected than medical genetics. Often mistaken for their Ph.D. brethren who generally do research, medical geneticists are shedding their reputation as the custodians of rare and orphan diseases and increasingly taking on new roles at the center of patient care.

Over the past decade, research has shown that common diseases including diabetes, high blood pressure, obesity and coronary artery disease have strong genetic components. And the development of better, cheaper, faster genetic tests may soon enable physicians to parse out who is at risk for these diseases and design individualized therapies. As clinicians, medical geneticists are positioned to translate the new research into practice.

“We are at the cutting edge of medicine,” says Salman Kirmani, M.D., assistant professor of medical genetics and pediatrics at Mayo Clinic. “It’s very exciting. Things are changing rapidly.”

That wasn’t always the case. Medical genetics emerged as a specialty after World War II, and for most of the next 40 years, the medical geneticist’s primary role was to diagnose, manage and treat a few well-known disorders such as cystic fibrosis as well as rare ones such as Batten disease, which affects just a few hundred people in the world. But things began to change significantly—and rapidly—with the mapping of the human genome more than a decade ago.

Now, testing technologies such as microarrays and comparative genomic hybridization have vastly increased physicians’ ability to diagnose these and other conditions, says David Tilstra,

M.D., a clinical geneticist and president of CentraCare Clinic in St. Cloud. “Just the complexity of the information that you get out of that kind of diagnostic test has really changed what we do and how much we can do,” he says. “You can diagnose many many more disorders than we ever could in the past and come to a much more precise diagnosis than what was available 15 to 20 years ago.”

Part physician, part sleuth

As a field, genetics offers physicians essentially two career paths: research and clinical work. Clinical or medical geneticists work with patients of all ages, diagnosing and coordinating long-term care for those with complex conditions. The American Board of Medical Genetics (ABMG) certifies M.D., D.O. and Ph.D. medical geneticists. Certification requires completion of a medical genetics residency or a combined program with pediatrics or internal medicine, for example. Clinical geneticists can specialize in medical biochemical genetics with an additional year of training or pursue a fellowship in clinical molecular genetics, clinical cytogenetics or clinical biochemical genetics.

“We see patients just like a primary care provider,” Kirmani explains. That’s something he often finds he needs to clarify. Many people, and even other physicians, think he spends all day in the research lab. Clinical geneticists are the “most specialized generalists,” Kirmani says, borrowing a phrase from the president of the American College of Medical Genetics. As specialists, they are expected to be knowledgeable about all genetic disorders and treatments; but they interact with patients much like primary care physicians do. For example, managing a patient with Marfan syndrome, a connective tissue disorder that can affect the skeletal and cardiovascular systems, eyes and skin, may involve a cardiologist, an orthopedic surgeon and an ophthalmologist as well as a medical geneticist, he says. But it’s up to the geneticist to make sure that each physician has a view of the whole picture.

Often that picture isn’t entirely clear, and medical geneticists have to play something of a detective role. “With patients who come in with the unknown disease, you never quite know where the path is going to lead you,” Tilstra says. “You’ll end up with a disorder that you may never have seen before in your life, and you have to figure out what the treatment plan is.”

From volumes to missing pages

Playing detective has become easier, however. When Tilstra began practicing in St. Cloud back in the mid-1990s, medical genetics focused on biochemical analysis and the relationships between genes, proteins and metabolism. There were a few chromosome tests, the test for Fragile X syndrome, for example, but not much else. Now, there are massively parallel sequencing technologies that can look at all of the genes known to be related to a particular defect. For example, you can examine more than 70 genes known to cause hearing loss simultaneously. Microarrays enable scans of the genome at a much higher reso-



Clinicians needed

The state of the medical genetics workforce in the United States is of significant concern to the American Board of Medical Genetics (ABMG), which published a three-page article on the topic in its newsletter in 2010. Here are a few highlights from that article:

- Of the 2,511 individuals in the United States holding one or more certificates from the ABMG, about 1,326 are certified in clinical genetics. Of those, only about 1,200 are thought to be actively practicing.
- According to a survey conducted in 2007, the average clinical geneticist spends only about 45 percent of his or her time on direct patient care.
- There are approximately 1.76 full-time clinical geneticist per million people.
- A 2004 study by the Royal College of Physicians concluded there should be one full-time clinical geneticist per 250,000 people. With the current U.S. workforce, we are meeting 44 percent of that goal.

Although demand for medical geneticists is expected to rise, few young physicians are selecting medical genetics as a career. Yet, if each U.S. medical school produced just one graduate in medical genetics per year, it would triple the number of residents in the pipeline.

lution than standard chromosomal studies and provide precise information about the parts of the chromosome and the genes involved in a disorder.

The difference, Tilstra tells patients, is like the difference between seeing a stack of books and looking inside those books. “If you think of the chromosome as a book, what we’re looking at now is, Are there any missing pages in those books? Whereas, the old technology was pretty much saying, We can count those books and we can see if there’s anything obviously wrong with them.”

This newfound knowledge is changing the way physicians treat some diseases. For example, medical geneticists are now using gene profiling to better target warfarin therapy for individuals at high risk for stroke. Warfarin has a narrow therapeutic window: Too much can cause bleeding, too little can cause clotting. “Based on their genetic profile, people metabolize the drug differently,” Kirmani says. “In those patients, knowing that genetic information can guide your therapy.”

In the not-too-distant future, Kirmani says, physicians will be able to develop more effective therapies for cancers and other diseases based on a patient’s genetic profile. To reflect that expanded role, the American College of Medical Genetics Foundation announced in April that it was changing its name to the ACMG Foundation for Genetic and Genomic Medicine signaling its place at the “forefront of the integration of genetics and genomics into broader medical practice.”

For now, Tilstra says, just being able to offer a diagnosis provides real relief for some patients and families because they no longer have to search for answers and can instead focus on managing the disease.

Changing role

As medical geneticists play a bigger part in caring for patients with diseases such as breast cancer and coronary disease, they’ll find their role overlapping with that of other specialists. And that is a good thing, Kirmani says. There aren’t enough medical geneticists to meet future demand, and genetics isn’t attracting as many students as will be needed (see *Clinicians needed*). In part, that’s because salaries are lower for geneticists than for other more procedure-focused specialists, and the subject matter can seem intimidating.

As research unlocks more information, clinical geneticists will likely need to become more specialized, focusing on particular diseases and treatments, and other physicians will need to know more about the role genetics plays in the treatment of diseases, says Kirmani, who is teaching a class at Mayo in which he stresses that.

“We now realize that genetics will pervade all medical fields, and it has—that even primary care physicians and specialists will have to know genetics,” he says. “That is the way of the future as I see it.” MM

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many unknowns
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at HOME with the GENOME

6

*things
physicians
should know
about*

GENETICS

By Jeanne Mettner



On April 14, 2003, the International Human Genome Sequencing Consortium, led in the United States by the National Human Genome Research Institute and the U.S. Department of Energy, announced an achievement that at one time could have only been the stuff of a Ray Bradbury

novel: The 20,000 or so genes in the human body and the sequences of the 3 billion DNA base pairs that make up that collection of genes had been identified. At the time scientists completed the endeavor, known as the Human Genome Project, many researchers speculated that the accomplishment would have profound implications for medicine. Nearly 10 years later, we're seeing some of those. The sequencing of the human genome has, in fact, done a lot of what researchers initially predicted: It's enabled us to offer new approaches for bringing individualized, targeted treatments to patients; it's helping make pharmacotherapy safer; and it's

afforded new opportunities to confirm diagnoses and even prevent disease. These changes have prompted some experts to warn that we need to be careful about how we further integrate our new capabilities and knowledge with medical practice. What follows is a short list of developments related to genomics that physicians should be aware of—and discussion about what they could mean for clinical practice.

1 Next-generation sequencing

The Human Genome Project took \$3 billion and 10 years to complete—as the process required to home in on and analyze all of the different components of human genes was painstaking and laborious. By the late 2000s, the process investigators used to sequence the genome was practically antiquated. Today, scientists can sequence a whole human genome in a couple of weeks at a cost of \$2,500 to \$5,000 using what's called “next-generation sequencing.”

With next-generation (or massively parallel) sequencing, the coding of millions of DNA segments can be accomplished simultaneously, allowing sequencing to occur exponentially faster than during the original sequencing of the human genome. Researchers can sequence either the entire genome or just the protein-coding regions—called exons—which comprise just 3 percent of the human genome and are where most of the known disease-causing mutations occur. Costs for this drilled-down “exomic

sequencing” or “whole-exome capture” can be as little as a thousand dollars.

“With exomic sequencing, in particular, it becomes incredibly cost-effective for us to look at massive amounts of genetic information, and that's had meaningful implications for medicine,” explains Matt Bower, a genetic counselor with the University of Minnesota. “We can look at all the genes, not just a few, that may be involved in a condition. It's changing the paradigm of how we diagnose and even treat disease.” Bower notes that the technology can be used for detecting genetic abnormalities in families whose members are exhibiting similar types of illnesses or symptoms. It also can help identify the genetic causes of conditions with unknown etiology—for instance, learning delays or neurological problems.

But use of this technology is in its infancy. “We are in an investigation phase—in terms of research, not practice—of new diagnostic ascertainment of disorders through exomic sequencing,” notes Susan Berry, M.D., division director for genetics and metabolism in the University of Minnesota's department of pediatrics. “Down the road, it will emerge into daily practice rather routinely and will be a part of our armamentarium for diagnosis.”

2 Targeted cancer treatment

Arguably, no medical specialty has been more affected by

these advances than oncology. In the 1980s, researchers were already regarding cancer as a genetic disease having demonstrated how specific mutations in DNA (oncogenes and tumor-suppressor genes) could cause abnormal growth patterns in cells. By the late 1990s, families with a strong history of breast or colon cancer were undergoing screening for mutations in the genes known to cause these familial cancers.

During the next decade, oncologists and cancer researchers developed therapies that targeted some of the genetic mutations that caused certain cancers to be so deadly. Then came human genome sequencing. “As one of my colleagues so aptly explains, what the Human Genome Project has essentially done is give us the equivalent of the parts list to an aircraft carrier,” notes Tom Amatruda, M.D., an oncologist and director of the Cancer Genetics Program at Minnesota Oncology. “Now we just have to figure out how they fit together and how to fix things when they don't work.”

Learning how those parts interact is the goal of The Cancer Genome Atlas (TCGA). Using samples from 500 different tumors, TCGA investigators are performing whole-genome sequencing, gene-expression profiling and pathology testing to chart genetic changes in 20 types of cancer. Since they began working on the project in September of 2009, the investigators have finished banking samples of cancerous tumors of the breast, colon, rectum, ovary, uterus and kidney. Sample collection continues for tumors

located in other sites including the brain and lung.

The project is slated for completion in 2014, but important findings have already emerged. For example, investigators have identified subtypes of glioblastoma, a highly invasive brain cancer. This knowledge could lead to diagnostic tests and, ultimately, to therapies better directed to a patient's tumor subtype. In addition, the TCGA team learned that the genomic patterns of colon and rectal cancers are very similar, and they identified novel genetic mutations in both that can be targeted with chemotherapy agents.

“In the future, I see sequence analysis occurring for all cancers,” says Amatruda. “From those results will come individually targeted therapies and integration of different treatments in order to outwit the cancer.”

If this sounds like science fiction, consider the story of Lukas Wartman, M.D., a genetics researcher and medical oncologist at Washington University. In the summer of 2012, he experienced a relapse of adult acute lymphoblastic leukemia, a cancer that he himself had been studying. (He was first diagnosed with the leukemia in 2003.) Wartman had undergone numerous rounds of chemotherapy and a bone marrow transplant. Knowing Wartman had no remaining options, his colleagues decided to perform whole-genome sequencing of Wartman's cancer cells as well as his healthy cells. By comparing the two, they found that an overactive *FLT3* gene was fueling the cancer's aggressive growth and located

an unlikely drug that could shut it off—sunitinib (Sutent), which was used for advanced kidney cancer and was known to target *FLT3*. Within just two weeks of being treated with sunitinib, Wartman's cancer went into remission. Wartman's colleagues want to look for the same mutation in others who have the cancer and eventually conduct a clinical trial to test whether the drug can help others with the leukemia.

3 New prevention tools

Next-generation sequencing also has prompted researchers to look for new ways to screen for diseases. At Mayo Clinic, for example, gastroenterologist David Ahlquist, M.D., and his team have developed a stool-based DNA (sDNA) screening test for colon cancer. "The whole idea really stemmed from our looking at colon cancer screening in a fresh way and asking ourselves: 'If you had to start all over again and define the ideal test, what characteristics would it have?'" recalls Ahlquist. The team came up with a list: It would be highly sensitive for precancerous changes as well as early stage cancer, noninvasive, lifestyle-friendly (requiring no bowel preparation or dietary restrictions) and convenient—so convenient that specimen collection could be done at home and mailed to the lab.

Before the human genome was sequenced, only a few DNA alterations were known to be related to colorectal

cancer. Thus, genetic screening couldn't detect all cancers. Ahlquist explains that massively parallel genome and methylome sequencing has made it possible to detect 100 percent of colorectal cancers and precancers. At the same time, the technology used to assay targeted stool markers was becoming more sensitive. "We learned early on that trace amounts of DNA were continually shed from tumors, polyps and healthy cells in the colon," he says. "But it was only in the last five years that practical analytical tools reached the level of sensitivity required to reliably detect these low amounts of DNA."

The resulting sDNA screening test has met all of the team's requirements. Patients can collect a stool sample at home and send it to the lab for analysis. No preparation is needed, and no medication or dietary changes are needed. In a recent case-control study, optimized sDNA testing detected 98 percent of colon cancers and between 64 percent and 73 percent of precancers—a detection rate that is "higher than what a Pap smear is for cervical cancer and precancer," notes Ahlquist.

Mayo has licensed the technology to a Madison, Wisconsin, company for commercial production; currently, the researchers are working to secure Food and Drug Administration (FDA) approval so the sDNA test kit can be widely used.

4 Noninvasive prenatal screening

Many pregnant women concerned about fetal abnormalities have had to make a difficult choice: Rely on the nondefinitive information provided by the "quad-screen" or "triple-screen" tests, which measure hormone levels and are commonly done during a woman's second trimester, or undergo amniocentesis or chorionic villus sampling (CVS), which provide definitive information about chromosomal abnormalities but also carry a risk of miscarriage.

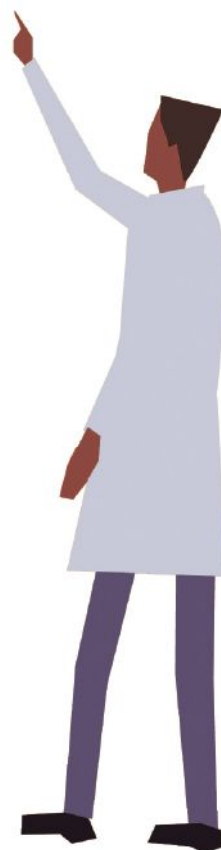
Now, however, cell-free fetal DNA testing allows for measuring fetal DNA in maternal blood. The test, which can be done as early as the 10th week of pregnancy, was found to be nearly 100 percent, 97 percent and 78 percent accurate for detecting Down syndrome, trisomy 18 and trisomy 13, respectively, by Tufts University researchers, who published their results in *Obstetrics and Gynecology* earlier this year.

"Occasionally, we field questions from patients who are asking about noninvasive prenatal screening; but typically, we are the ones initiating the conversations about it," says Heidi Thorson, M.D., a maternal-fetal medicine and clinical genetics specialist with Minnesota Perinatal Physicians. She says they have used it in patients with a family history of Down syndrome, advanced maternal age, and those who have ultrasound markers for aneuploidy or who are not candidates for invasive testing. Results are typically available within two weeks.

She says they still recommend amniocentesis or CVS for many patients because those tests provide more information than the noninvasive tests, are diagnostic rather than screening tests and yield results in approximately 24 hours.

5 Gene-drug interactions

Pharmacogenomics—using genomic information to predict how a patient might respond to a drug and then tailoring treatment to that patient—is already part of clinical practice. In recent years, the FDA has required drug labels to include information



on 1) specific variations in certain genes that may cause a patient to react differently to a medication, 2) recommended genetic testing to determine whether a patient has those genetic biomarkers and 3) specific actions that can be taken on the basis of the testing conducted. An example is the antiplatelet drug clopidogrel (Plavix), which requires activation in the body by the cytochrome P450 2C19 (CYP2C19) gene. If a patient has a variation in that gene, taking clopidogrel could result in a number of adverse events, most of which cause the drug to be less effect. To determine whether a patient has a gene variation that would affect the drug's efficacy, clinicians can order a relatively inexpensive test; if the test is positive, they can prescribe a different drug.

Many health systems have begun incorporating pharmacogenomic information into their electronic medical record systems. At Mayo Clinic, for example, a team is working on incorporating information about three potential gene-drug interactions: HLA-B*1502 and the antiseizure medications carbamazepine, oxcarbazepine, and perhaps phenytoin, fosphenytoin and lamotrigine; HLA-B* 5701 and abacavir, an HIV medication; and *IL-28B* and interferon plus ribavirin, a treatment for hepatitis C.

When a physician orders one of these medications, he or she will be prompted to consider testing for genetic variations that may affect the outcome in that patient, ex-

plains John Black, M.D., co-director of Mayo's Nucleotide Polymorphism Laboratory, which does much of Mayo's pharmacogenomics testing. It then lists the genetic test the physician can order—and what recommendations to follow if the test is positive for a gene variant. The team hopes to implement the prompts by the end of the year. “You can imagine, for example, that if you can avoid a single case of Stevens-Johnson syndrome, which often results in intensive care treatment, you would be able to cover the costs for perhaps thousands of these pharmacogenomic tests,” Black says.

Meanwhile, University of Minnesota researchers are collaborating with investigators at HealthPartners and Mayo Clinic to create a database that can be queried for both research and treatment purposes. “As part of this effort, patients consent to undergo a broader screening that involves various genetic panels, and that information then becomes part of their medical record,” explains Brian Van Ness, Ph.D., head of the department of genetics, cell biology and development. “Five years later, if that patient ends up needing to take clopidogrel, we can query the database to determine if they could have an adverse reaction to that drug.”

6 Commercial testing

Given that many now want to demystify their own genetic makeup, it's not surprising that commercial ventures have formed to help people do just that. Through one company, 23andMe, a person can mail in a saliva sample and for a few hundred dollars receive a smaller-scale analysis (*not* genome sequencing) of the genes related to more than 100 traits and diseases. 23andMe is currently piloting Exome 80x, which does whole-exome sequencing for \$999.

Although the University of Minnesota's Bower finds these offerings fascinating, he cautions people about them. “I tell patients that if you use this service, you have to be careful about how you interpret the results.” He says that even if the company provides a summary of what the results mean, patients should talk to a geneticist or genetics counselor about them. “You need the context and background of someone who has worked in genetics who knows what the pattern in a family could mean,” he explains.

“What patients often fail to understand is that if they were to have someone sequence their whole genome, they still are not going to get all the answers,” says Nancy Mendelsohn, M.D., a geneticist with Children's Hospitals and Clinics of Minnesota. “The reason is that we don't know what all of these genes do, we don't know how they are all regulated and there may be other processes, like methylation, that can modify genes.”

Finding its place

Our ability to accumulate information about our genes will likely outpace our ability to apply that information for some time. And clinicians not yet well-versed in genetics and genomics will struggle to know what information is important. Says Berry: “Even for us geneticists, it's intimidating. It's like drinking from a fire hose. These are complicated new technologies that are forging ahead full force, almost faster than we can make use of them.” And if it's hard for geneticists to make medically appropriate decisions around the information these technologies yield, it is certainly going to be difficult for primary care physicians to do so.

What it comes down to, Van Ness says, is the difference between scientific validity and clinical utility. “Ultimately, physicians need to select genetic tests that demonstrate clinical utility,” he says, meaning they are a better option than other currently available diagnostic tests. Mendelsohn says interpreting results involves the art of medicine: marrying patients' symptoms and the right test at the right time in order to provide an accurate diagnosis and treatment regimen. “Yes, it's really cool that we sequenced the human genome,” she says. “But it's not the end, it's the beginning.” **MM**

Jeanne Mettner is a Minneapolis writer and frequent contributor to *Minnesota Medicine*.

Age-appropriate

The harsh realities of getting older

By Marshall I. Hertz, M.D.

I have a new doctor. Well, he's actually the first primary doctor I have had since I left my pediatrician more than 40 years ago. Before Dr. X, I basically had do-it-yourself health care. I know, I know, the doctor who treats himself has a fool for a patient. But it took too much time and was too much of a bother to actually make an appointment, go to the office and fill out all the forms.

With the help of my professional colleagues, I correctly diagnosed and treated my hyperlipidemia and GERD. I was also worked up by a cardiologist friend for palpitations that turned out to be PACs.

My wife, a real estate agent, also pitched in. A month before my 50th birthday, she asked if I had made an appointment for a colonoscopy. "You're supposed to get one when you turn 50," she said.

I told her that they didn't mean on your actual birthday, just within a year or two. Yet I went ahead and made an appointment for the next month. While there, I asked the gastroenterologist to do an upper endoscopy, "You know, to see if I have Barrett's after 20 years of almost-daily GERD. I mean as long as you're doing a test that has a less than 1 percent chance of finding colon cancer, why don't you also do an upper to find the esophageal tumor that I actually have?"

"Everyone your age has GERD, and not all of them need endoscopy," he told me.

Finally, he gave in and did the tests. (To my relief, both were normal.)

When my wife told me she had read in a news magazine that every American over age 55 should see their primary physician once a year, I tried to ignore her—but she was relentless. When I told her which doctor I was going to see, she exclaimed, "He's your age! By the time you have problems, he'll either be retired or dead." She had a point—so I made an appoint-

ment with Dr. X, a recent graduate of one of our local internal medicine training programs.

On my first visit with Dr. X, I had a bad cold and a cough. When he listened to my lungs, he heard "a few rales" and ordered a chest X-ray "just to make sure." "What else?" he asked.

"Well, I feel like my quads are fatiguing more easily than they used to while rollerblading or climbing stairs. I wonder if it's my statin."

"Could be, but most likely you're just getting old," he told me. Then he asked how I felt about having my PSA checked.

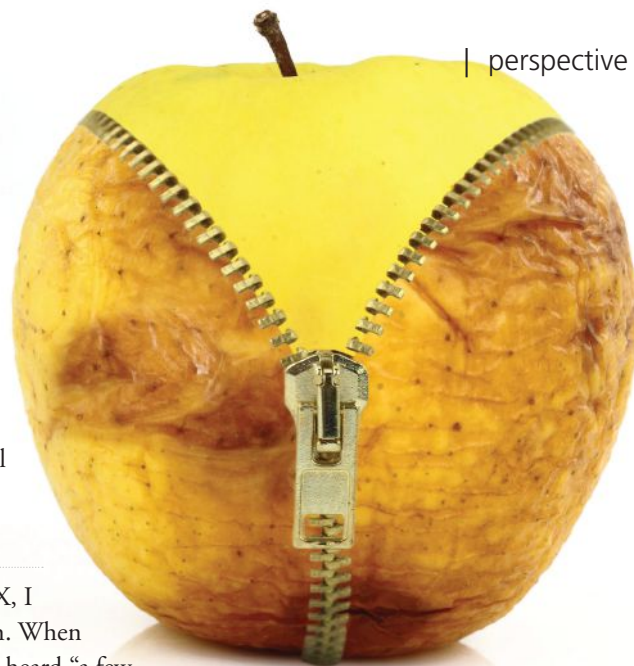
"Well, I guess so, but don't you think I'm a little young?" During the exam, he judged my gland to be "age-appropriate."

Age-appropriate? What person older than 50 wants to be age-appropriate? Not me—I wanted my old maximal heart rate back and my old pulmonary function test results and my old bladder pressure. I think the endocrinologists are the only ones to get it right: Who wants a Z-score? What I really care about is my T-score.

Dr. X called me the day after my appointment to let me know that my chest X-ray was normal. Since I am a pulmonologist, I asked if he would send me a CD so I could see for myself. It came a few days later, and I took it to clinic to view between patients. The PA image looked fine, but when I saw the lateral, my heart sank. There, plain as day, was a mass, not a pleural effusion or cardiomegaly but an osteophyte. I called Dr. X: "I have a spinal osteophyte, and your radiologist missed it."

"Well," he replied, "she probably doesn't mention things that are age-appropriate."

I told him I wasn't very happy. At yoga the next day, the instructor said, "Anyone



who has a spine problem shouldn't try the next pose." I didn't.

As a physician, I frequently see patients whose complaints boil down to not being able to do what they used to. When I was younger, I had no problem telling them this was a normal part of aging. But lately, I have been taking a little more time to talk things over with them. "I know you want to be able to do everything you once did, but this happens to everyone. Look at Michael Jordan. Look at Brett Favre. Look at Madonna. Everyone." I don't think it helps much, but I say it anyway.

And now I have a new strategy when I see my own doctor. When Dr. X asks how my vision is, I say, "age-appropriate." Hearing? "Age-appropriate." Memory? "Age-appropriate." Urination? "Age-appropriate."

When he asks why I give the same answer to every question, I tell him, "Just so I don't have to hear you tell me." Actually, the reason is that this way, I can decide what gets worked up and what doesn't.

"And by the way," I tell him, "the next time you order an X-ray, don't send it to the same radiologist. I've known her for years, and she's a blind old quack." **MM**

Marshall Hertz is medical director of lung transplantation and director of the Center for Lung Science and Health at the University of Minnesota Medical Center, Fairview and Judith H. and John M. Murphy Professor of Pulmonary and Critical Care medicine at the University of Minnesota Medical School.



Reading letters in the dark

A story about caring

By Ari Holloway-Nahum

I was on a train traveling north to Paris. It was the summer between my freshman and sophomore years of college, and several high school friends and I were making our way through Spain and France. We had started the trip in Barcelona, crept along the coast, then traveled over the mountains, past Marseilles, and rounded the corner at Nice. My friends were spending an extra week in Lyon. I was on my way to Paris to catch a flight home.

A gentleman in his 60s sat across from me. He wore an old green jacket and gazed out the window. He smelled faintly of pipe tobacco. I guessed him to be a physics professor. Now and then, his face would light up as if he were seeing an old friend for the first time in years.

About a third of the way into our journey, he broke the silence: “Do you enjoy the classics?” he asked. He spoke in a low voice, without a French accent.

I was reading Dostoevsky’s *Crime and Punishment*. “I enjoy the stories, but sometimes I get bogged down in the language,” I replied honestly.

From there, we went on to discuss the basic framework of our lives as strangers momentarily linked on a journey often do. He was an American who had come to Paris 40 years earlier to work as an engineer for a construction company. The job was

supposed to last three years, but he had fallen in love, gotten married and accepted a full-time position with the company. He had recently retired and was teaching engineering part-time at a Parisian college. He was on his way back from Lyon, where he had been attending a conference about a new type of “green” sewage system.

“How did you meet your wife?” I inquired.

“Ah, I met her shortly after I arrived. We shared friends. I think it was at a pub in Paris. To tell you the truth, I don’t remember.” He gestured carelessly upward with his right hand. “We dated casually for a few months before I was sent to Lyon to start work on the construction site.”

“How long were you there?” I asked.

“18 months.”

“Wow,” I said, widening my eyes for effect. “So you’ve made this trip many times before.”

“Actually, this is only my second time.”

“Really?”

He chuckled, “I know, you think I would have been able to get away for a weekend or something. But things were busy, and to be honest, I wasn’t that interested in her until we were apart. Before that, it was just casual—nothing serious.” He smiled.



The look on my face must have shown I was intrigued because he continued. “Well, we began sending letters to each other.” He leaned closer for a moment. “I’m pretty sure she sent the first one.” He pulled away smiling. “It started casually. Things like ‘How’s the weather?’ and ‘Any good restaurants in Lyon?’ But eventually it became more serious.” He paused. “You know, there’s something very intimate about a letter. You feel like someone has shared a secret with you that know no one else knows. Especially when you read them in the dark.”

I furrowed my brow at his puzzling statement.

“I kept her letters on my nightstand. Just before bed, I read them in the light of my bedside lamp, surrounded by total darkness. Sometimes I used a candle. Her words lingered in the darkness. I felt like I knew all of her secrets. It was as intimate as any physical contact I’ve ever experienced.”

“Jeez, that’s amazing.”

“Yeah, it was. I didn’t see her that whole time, but I became infatuated with her.” He gazed out the window. “I remember the last time I took this train was 38 years ago—on my way to back to Paris. The countryside hasn’t changed much.” He shook his head and smiled, then looked toward the floor and chuckled. After a brief moment, he returned his gaze out the window and continued admiring the countryside.

In many ways, we experience life through stories, and most ways, medicine is a reflection of life. Through the stories our patients tell us, we come to understand disease and its effect on human life. Sometimes, by creating our own narrative, we can discover and reveal things that otherwise remain concealed. This story came to me one night after I had spent the day in a dark room reading chest X-rays with a radiologist as I was nearing the end

of my three-week radiology rotation. In writing it, I tried to capture a fundamental lesson I learned from the experience.

Many would argue that because technology has become so instrumental in how we practice medicine, we have sacrificed the human element, which may prevent us from forming emotional connections with our patients. Now if you go to the hospital, instead of finding doctors with their patients, they are sitting in front of computers—writing notes, reviewing results or reading scans. It is arguable that in no other specialty is the influence of technology more pronounced than in radiology.

Halfway through my radiology rotation, as I went over scan after scan without ever laying eyes on a patient, I found myself feeling detached from the individuals we were caring for. But as I sat half awake in a classroom one morning, one of the attending radiologists said something that changed my thinking. “You have to care,” the radiologist said. It was 7 a.m., and she was beginning her lecture on the radiological findings of musculoskeletal tumors. Yes, it is an exhilarating subject. But the profound nature of her words resonated with me, and I promptly began ignoring all sensory input. As she went on to talk about a sarcoma or something, all I could think of were her opening words.

Radiologists rarely meet their patients; but it is vital that they feel an emotional connection to them—that they care for them. The next time I found myself sitting in a dark room lit only by the glow of a computer screen, I watched as the radiologist read his scans, his eyes moving methodically through the images, his brain translating them into a story that was unfolding in front of him. It came to me then that to be a radiologist, one must appreciate the intimacy of reading letters in the dark. **MM**

Ari Holloway-Nahum is a fourth-year medical student at the University of Minnesota.



THE PHYSICIAN ADVOCATE

The MMA's monthly report on policy, people and politics

House of Delegates votes to reduce number of trustees

The MMA's House of Delegates (HOD) voted at the Annual Meeting to restructure the Board of Trustees, reducing it from 33 members to between 12 and 14 members.

The shrinking of the board was one of several governance changes debated at the meeting held in Minneapolis last month.

Other proposals discussed were:

- changing the membership of the board from being solely geography-based to being competency-based with a sensitivity to geographic differences (passed)
- replacing the HOD with multiple Policy Council Forums to increase opportunities for member input (did not pass)
- gaining a better understanding of member concerns through multiple listening sessions held throughout the state (passed)
- giving all MMA members the opportunity to vote in elections (did not pass).

During testimony, a number of physicians argued that more study of the proposal was needed before voting to eliminate the HOD. A reference committee agreed, and the issue will be taken up at a later date.

However, many physicians favored holding listening sessions and policy forums. The MMA will now move forward to flesh out both ideas.

With the change to the board, it will now have between nine and 11 trustees representing different competencies and Trustee Districts.

Some of the competencies identified include expertise in state and federal health policy, strategic and financial planning, membership growth and engagement, public relations and com-

munications, governance and revenue generation through new products.

One trustee will come from each Trustee District; and no more than 50 percent of the trustees will come from any one Trustee District.

The president, president-elect, immediate past president, speaker of the House and vice speaker of the House will be additional voting board members. The chair of the AMA delegation and the MMA CEO will serve as ex-officio members without voting rights unless the AMA delegate chair has been also elected as a trustee.

Although the HOD did not adopt all of the Governance Task Force's recommendations, it directed the MMA to continue its work on needed governance changes and bring the issue back to the next HOD meeting.

The House of Delegates weighs in on proposed governance changes at the 2012 MMA Annual Meeting.





Daniel Maddox, M.D.

MMA selects 2012-2013 officers

PRESIDENT: **Daniel Maddox, M.D.**, an allergist at the Mayo Clinic, Rochester

PRESIDENT-ELECT: **Cindy Firkins Smith, M.D.**, a dermatologist at Affiliated Community Medical Centers, Willmar

SECRETARY/TREASURER: **Paul Sanford, M.D.**, an internist at St. Luke's Internal Medicine Associates, Duluth

IMMEDIATE PAST PRESIDENT: **Lyle Swenson, M.D.**, an interventional cardiologist at East Metro Cardiology, St. Paul

SPEAKER OF HOUSE OF DELEGATES: **Robert Moravec, M.D.**, a family and emergency medicine physician at St. Joseph's Hospital, St. Paul

VICE SPEAKER OF THE HOUSE: **Mark Liebow, M.D.**, an internist at Mayo Clinic, Rochester

AMA DELEGATES: **Ken Crabb, M.D.**, an OB/GYN physician at Advanced Specialty Care for Women, St. Paul, and **Benjamin Whitten, M.D.**, an internal medicine physician at Abbott Northwestern General Medicine Associates, Edina

AMA ALTERNATE DELEGATES: **Will Nicholson, M.D.**, a family physician at St. John's Hospital, Maplewood, and **David Luehr, M.D.**, a family physician at Raiter Clinic, Cloquet

MMA BOARD OF TRUSTEES: The following physicians were elected to the MMA Board of Trustees: **Juan Bowen, M.D.**, (Southeast District) and **Randy Rice, M.D.**, (Northeast District). Re-elected to the Board were **Benjamin Chaska, M.D.**, (Twin Cities District), **V. Stuart Cox III, M.D.**, (Twin Cities District), **Roger Kathol, M.D.**, (Twin Cities District), **David Thorson, M.D.**, (Twin Cities District) and **Keith Stelter, M.D.**, (Southwest District).

MMA honors top physicians

During the annual meeting, the MMA and its members acknowledged special individuals for their dedication to the profession and the great work they perform on behalf of the organization. This year, the following physicians were honored with the distinguished service, president's and community service awards.

Distinguished Service Award

The MMA's highest honor goes to a physician who has made outstanding contributions to medicine and to the MMA during his or her career. This year's recipient was **John Van Etta, M.D.**, who works in internal medicine at St. Luke's Hospital in Duluth.

Van Etta has been active in the MMA for 30 years, sitting on a variety of committees and task forces as well as serving as its president in 1999.

Along with his MMA work, Van Etta has been involved with his component medical society and with the AMA, serving as a delegate since 2002 and being a member of its Council for Legislation for 10 years, including one year as chair. During that time, he served as an advisor to the AMA Board and testified about Medicare issues on behalf of the AMA in Washington, D.C. He has also served on the Quality, Safety and Health Information Task Force, the Medical Liability Reform Task Force and three other national committees.

President's Award

The MMA President's Award for leadership went to St. Cloud's **George Schoephoerster, M.D.**, who currently practices with Geriatric Services of Minnesota.

Schoephoerster has been active in the MMA for the past 30 years and currently serves on its marketing and communications committee. He also is a member of the Stearns Benton Medical Society and has been involved with the MMA House of Delegates

since 1993.

In addition, he served as North Central trustee from 2000 to 2003 and has worked with the MMA Committee on Membership and Finance, the End-of-Life Task Force, the Nursing Home Work Group and the Health Care Reform Task Force. He is a member of the AMA, the American Geriatrics Society and the American Academy of Family Physicians. Schoephoerster also is a member of MEDPAC and has served on MMIC's Board of Directors.



2012 President Lyle Swenson, M.D., (left) presents George Schoephoerster, M.D., with the President's Award.

Community Service Award

This year's recipient of the MMA Community Service Award is St. Paul's **Kent Wilson, M.D.**

Wilson has led a community-wide program called Honoring Choices Minnesota that is designed to help individuals and families engage in conversations about end-of-life care in order to ensure they receive care that reflects their wishes.

As medical director of the program, he has raised significant funds to support the work, and recruited community partners to advance it.

Wilson has been active in the MMA for many years. He first joined in 1974 and served as its president in 1997.

Annual Meeting unites physicians from



More than 100 physicians gathered September 14 and 15 in Minneapolis for the MMA's 159th Annual Meeting. The group discussed governance changes as well as dozens of other resolutions,

attended CME sessions, elected new officers and honored three physicians for going above and beyond their duties.

Photos by Steve Wewerka



1



2

1 Medical students listen intently during a CME session.

2 Keynote speaker Joseph Bujak, M.D., (left) talks with AMA guest Andrew Gurman, M.D., and Erick Reeber, M.D.

3 Joseph Bujak, M.D., leads a discussion on bringing physicians together.

3

4 Thomas Siefferman, M.D., testifies during the governance discussion.

5 Nearly two dozen vendors displayed during the Annual Meeting exhibition.



4



5



across Minnesota



10 The annual meeting attracted physicians young and old.

11 Noel Peterson, M.D., (left), student Evan James, Ken Kephart, M.D., CMD, and Daron Gersch, M.D., hear testimony during a reference committee.

12 Roger Kathol, M.D., takes in testimony during the House of Delegates session.

6 Physicians collaborate during a policy forum on the future of health care in Minnesota.

7 HC/MC, a band featuring several physicians, provided Friday evening's entertainment.

8 Carolyn McClain, M.D., leads part of the House of Delegates discussion.

9 John Van Etta, M.D., accepts the Distinguished Service Award.

House of Delegates passes slate of resolutions

The House of Delegates approved 21 of the 27 resolutions submitted for discussion at the 2012 MMA Annual Meeting. Following are some of the actions the MMA will take in 2013 and beyond:

- By January 1, 2013, the MMA should write a letter of support for the statewide systems currently being developed by the Minnesota Department of Health for acute stroke, acute myocardial infarction and sudden cardiac arrest. (R200)
- The Minnesota delegation to the American Medical Association (AMA) should encourage the AMA to advocate for U.S. Farm Bill budget allocations to be directed through a newly created advisory board that includes, among other stakeholders, physicians and public health officials. (R201)
- The MMA should work closely with the Minnesota Department of Health's E-Health Advisory Committee and its members to develop a policy that provides for careful monitoring of prescription refills so that duplication errors can be caught at the pharmacy level to avoid overprescribing of medications. If the issue cannot be resolved with the Minnesota E-Health Advisory Committee, then the MMA should explore legislation to require pharmacies to monitor prescriptions for duplicates. (R202)
- The MMA should write a letter of support for the work of the Twin Cities Obesity Prevention Coalition, a project of the Twin Cities Medical Society, whose mission is to provide leadership in mobilizing community-based coalitions of organizations, physicians and individuals who are committed to improving public health by advocating for healthy-eating active-living strategies in Twin Cities metro area communities. The MMA should also write a letter to the Minnesota League of Cities and the Minnesota Local Public Health Association encouraging Minnesota communities to develop and implement healthy eating and active-living resolutions. (R203)
- The MMA should request that the state determine and publish the costs to clinics of mandatory Statewide Quality Reporting and Measurement System (SQRMS) requirements. The MMA should also lobby for full reimbursement to clinics from the state for time, equipment and other costs associated with gathering and submitting clinical quality data unique to the mandatory SQRMS. (R204)
- The MMA should support efforts to encourage Minnesota physicians to use "5-2-1-0" as a guide to discuss healthy weight at every well-child visit. The numbers stand for five fruits and vegetables per day; two hours or fewer of computer or television time (no screen time for children under age 2); one hour of physical activity per day; and zero sugary beverages (replace with water or milk/breast milk). (R205)
- The MMA should support the idea that comparative effectiveness research (CER) should recognize that both clinical care and health behaviors are valid determinants that improve health care quality and control costs. The MMA should also add a phrase to current MMA CER principles to read: "CER should seek to impact health care quality, patient experience and the costs of health care. New delivery system designs are simultaneously encouraging improvements to the health of the population, enhancing the patient experience, and reducing or controlling the per-capita cost of health care. CER should as well. While the likelihood is minimal that CER can simultaneously impact all three components of the Triple Aim, priority should be given to research on conditions with important public health consequences, on improving patient adherence to clinical and behavioral treatment plans, on improving health care quality and access to care, and on addressing overuse and inappropriate use in health care. CER, first and foremost, must be based on improving outcomes for patients rather than on minimizing health care costs." (R207)
- The MMA, together with the Minnesota Chapter of the American Academy of Pediatrics, should encourage the Minnesota Department of Health to update in a timely fashion Minnesota school and day care requirements for vaccination so that they are consistent with current and future recommendations by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. (R208)
- The MMA, the Minnesota Chapter of the American Academy of Pediatrics and the Minnesota Academy of Family Physicians should jointly contact the Centers for Disease Control and Prevention and the Minnesota Department of Health, and respectfully request that the Minnesota Vaccines for Children Program permit private practices to provide and receive payment for Vaccines for Children vaccines given to underinsured children and adolescents. (R209)
- The MMA should endorse the following:
 - 1) Maintaining the Minnesota Newborn Screening Program, as administered by the Minnesota Department of Health, as an "opt out" public health program to save newborn lives; 2) increasing the length of newborn bloodspot retention from 71 days (for negative test results) and two years (for positive test results) to 18 years for all newborn bloodspots collected; and 3) supporting the efforts of the Minnesota Department of Health to implement parental consent for use of stored bloodspots for future public health test development. (R210)
- The MMA should work to explore alternative mechanisms to ensure access to care for Medicaid enrollees in lieu of Rule 101. (R300)
- The MMA should clarify and disclose to members its criteria and processes for reviewing and recommending physicians to serve on the Board of Medical Practice. (R302)
- The MMA should implement policies to encourage physician practices to discuss the utility and importance of advance directives in end-of-life decisions with every adult patient on an ongoing basis. The MMA should also provide resources to practices to use with patients to assist in completion of an advance directive. The MMA should promote a nonbinding goal for physician groups to document a discussion about advance directive completion with at least 80 percent of adult patients. (R303)
- The MMA should support policy that specifically exempts from the legal definition of abortion procedures to treat ectopic pregnancies. (R304)
- The MMA should explore strategies for how to best improve access to and increase the availability of high-quality geriatric care. (R305)
- The MMA should support legislation that would add the National Committee for Quality Assurance's Patient-Centered Medical Home designation as an alternative for meeting the requirements of certification as a Health Care Home in Minnesota. (R306)
- The MMA should support public and private health insurance coverage for treatment of gender-identity disorder as recommended by a patient's physician. (R307)

LEGISLATIVE REVIEW



ABOVE: Assistant Minority Leader Rep. Erin Murphy (left) talks with Lisa Erickson, M.D., and Janette Strathy, M.D.
BELOW: Rick Morris, M.D., (left) interacts with House Speaker Kurt Zellers.

MEDPAC hosts breakfast meeting with state leaders

In August, MEDPAC, the MMA's political action committee, hosted separate breakfast meetings with state Republican and Democratic leaders to discuss a variety of health care issues in preparation for the 2013 legislative session.

Fifteen physicians attended the Republican event and 21 met with the Demo-

crats. All of the physicians had a chance to speak one on one with lawmakers.

Topics of discussion included the future of the Affordable Care Act and how it will be implemented in Minnesota; the access problems caused by underfunded public programs and the fact that their payments do not cover physicians' overhead costs; the concerns about the potential physician workforce shortage; the added health care costs caused by defensive medicine; and the added administrative burden on small clinics as more reporting and paperwork requirements are expected of practices.

Republican legislators in attendance included House Speaker Kurt Zellers (Maple Grove), House Majority Leader Matt Dean (Stillwater), Rep. Jim Abeler (Anoka) and Rep. Steve Gottwalt (St. Cloud). Abeler is chair of the Health and Human Services Finance Committee, and Gottwalt is chair of the Health and Human Services Reform Committee.

Democrats included House Minority Leader Rep. Paul Thissen (Minneapolis), Assistant Minority Leader Rep. Erin Murphy (St. Paul) and Health and Human Services Finance Committee Ranking Member Rep. Tom Huntley (Duluth).

MEDPAC conducts candidate interviews

Over the summer, Dave Renner, MMA director of state and federal legislation, and Eric Dick, MMA manager of legislative affairs, met with candidates for state office and discussed a number of issues the MMA has identified as important including reimbursement rates, the potential physician workforce shortage, tobacco policy and public health initiatives.

Thus far, Renner and Dick have met with nearly 30 candidates for open legislative seats; more meetings are scheduled before the November elections. Renner and Dick will report on the candidates' positions to the MEDPAC board, a group of physicians from around the state representing a variety of specialties and political affiliations, who will decide which candidates MEDPAC will support with endorsements and contributions.

For more information on MEDPAC visit www.mnmed.org/Advocacy/MEDPAC.aspx.

New health care laws take effect

Several laws that were adopted by the 2012 Minnesota Legislature went into effect August 1. Those that may be of interest to physicians include the following:

- Chapter 278 creates new civil penalties for those other than licensees who are required but fail to report a violation of the Medical Practice Act to the Board of Medical Practice.
- Chapter 246 clarifies the narcotics laws to allow controlled substances to be prescribed electronically.
- Chapter 175 makes it a felony to intentionally deprive a vulnerable adult of food, clothing, shelter, health care or supervision when the caregiver or operator is reasonably able to make the necessary provisions. This new law applies to any patient who is in a hospital or nursing home, as well as those cared for at home.
- Chapter 166 authorizes the use of automated drug distribution systems in specified nonpharmacy health facilities and authorizes physicians to dispense drugs in pharmacies located in a designated health professional shortage area where a pharmacy is not readily available.
- Chapter 216 expands the safe place for newborns program, increasing the timeframe newborns can be left from 72 hours after birth to seven days after birth. Newborns can be left at hospitals, urgent care facilities or with an ambulance dispatched for this purpose.
- Chapter 216 also changes the classification of Department of Human Services investigations of possible overpayments of public funds to a service provider so that the public can now view them.

EDITOR'S NOTE: Keep track of legislative events through MMA News Now, delivered to your email box free each Thursday. To subscribe, go to www.mnmed.org and look for "MMA News Now" under the "Publications" tab.

VITAL SIGNS

MMA NEWS IN REVIEW

ACO-type models on the rise

Accountable care organizations (ACOs) in Minnesota continue to gain momentum.

In mid-September, Blue Cross and Blue Shield of Minnesota and Allina Health System announced a new insurance offering for large employers called Blue Choice featuring the Allina Health Network. Although the two companies are not referring to it as an ACO, it appears to be as such.

The Blue Cross/Allina partnership follows in the wake of the Park Nicollet Health Services and HealthPartners merger announced in late August. Although that deal still requires federal approval, it sets the stage for the creation of a substantial integrated delivery system that encompasses both the eastern and western halves of the Twin Cities metro area.

The merger news comes on the heels of Medica's string of recent partnerships with four metro-area health systems to form ACOs that test new payment and delivery models.

In April, Medica and Fairview Health Services began offering Fairview Health Advantage. In July, Medica teamed up with Ridgeview Medical Center to introduce the Ridgeview Connect ACO. That same month, Medica and Park Nicollet introduced Park Nicollet First. Then in August, Medica and HealthEast Care System announced Inspiration Health by HealthEast.

These new ACOs join one of the state's first ACOs—the Northwest Metro Alliance, which is a collaboration between Allina Health and HealthPartners. In August, the Alliance reported that for the second straight year it had improved health, lowered the cost of health care and improved the patient experience for patients in northwestern suburbs of the Twin Cities.

Since the Alliance was formed in 2010, medical costs are nearly \$8 million lower than what they would have been based on projected trends. Medical cost increases were 3 percent in 2010, and less than 1 percent last year. The Alliance, which serves 27,000 people who live in Anoka County and southern Sherburne County, is considered a learning lab, modeling many of the rules that are being promoted by the U.S. Department of Health and Human Services.

The role of small independent physician practices in ACOs has yet to be determined.

That issue was the focus of a meeting held earlier this year between MMA representatives, a group of physicians from independent practices and Sen. Al Franken's staff. Dave Renner, MMA director of state and federal legislation, considered the meeting a good start. "While we support new models designed to align incentives for quality patient care, ACOs need further testing before we rule out other options," he said.

MMA leaders make magazine's Top 100 list

It may not quite be the Who's Who of Minnesota health care but it's close.

A number of MMA officers, members and staff were named among "100 Influential Health Care Leaders" in a recent issue of *Minnesota Physician* magazine. In fact, those affiliated with the MMA make up nearly half the list.

Among those included were: MMA Immediate Past President **Lyle Swenson**, M.D., Board Chair **David Thorson**, M.D., 2011 President **Patricia Lindholm**, M.D., Vice Speaker **Robert Moravec**, M.D., MMA CEO **Robert Meiches**, M.D., and **Dave Renner**, MMA director of state and federal legislation. Twin Cities Medical Society CEO **Sue Schettle** also made the list.

In all, 39 MMA member physicians made the list, which also included Senators Amy Klobuchar and Al Franken, Congressman Erik Paulson and state Rep. Jim Abeler (Anoka). The publication compiles the list once every four years based on submissions from its readers.



Lyle Swenson, M.D.



David Thorson, M.D.

Another Minnesota city joins fight for healthier eating

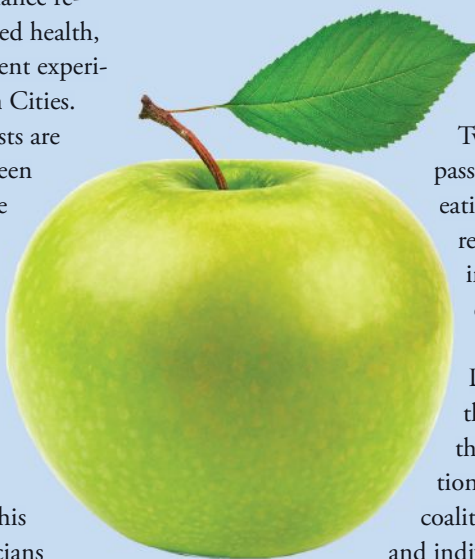
Two Minnesota cities have now passed resolutions promoting healthy eating and active living among their residents. Eagan was the first; then in late August, Eden Prairie became the second.

The Healthy Eating Active Living resolution was brought to the Eden Prairie City Council by the Twin Cities Obesity Prevention Coalition, a community-based coalition of organizations, physicians and individuals committed to improving public health. The coalition is a project of the

Twin Cities Medical Society and is funded by Blue Cross and Blue Shield of Minnesota.

Strategies called for in the resolution include:

- Developing community gardens, farmers' markets and "edible" playgrounds, where children are taught how food is produced



- Considering or including green spaces adjacent to all new housing developments

- Developing and implementing a healthy vending machine and concessions policy for all city-owned and operated concessions in facilities, parks and programs.

According to Blue Cross, more than 63 percent of Minnesota adults are overweight or obese and at risk for serious illnesses such as high blood pressure, type 2 diabetes, heart disease and some cancers.



TCMS-public TV partnership results in Emmy

Sometimes stories are best told through visuals. That's the thinking behind a video storytelling effort by Honoring Choices Minnesota that received a local Emmy Award from the National Academy of Television Arts and Sciences, Upper Midwest Chapter, in September.

In 2011, the Twin Cities Medical Society (TCMS) partnered with Twin Cities Public Television to produce a series of documentaries on end-of-life decisions for Honoring Choices.

The award is in the "Making a Difference" category, which honors pieces that change the life of an individual or the lives of members of the larger community.

Honoring Choices uses the training, principles and methodology of

Respecting Choices, a nationally recognized model created by Gundersen Lutheran Health System in La Crosse, Wisconsin. What makes Honoring Choices different is its Minnesota-specific governance, customized forms, patient education materials and family stories.

"This is great recognition of the overall initiative and mission of Honoring Choices Minnesota," says Sue Schettle, TCMS CEO. "The program's goal is to make advance care planning the standard of care for adults and to ensure every person's health care choices are clearly defined and honored."

Members making a difference

Ben Pederson, a University of Minnesota medical student and MMA member, is one of five students named as a 2012 Pisacano Scholar.



Ben Pederson

The scholarships, valued up to \$28,000 each, are awarded to students attending U.S. medical schools who demonstrate a strong commitment to the specialty of family medicine. In addition, each applicant must show demonstrable leadership skills, superior academic achievement, strong communication skills, identifiable character and integrity, and a noteworthy level of community service.

The Pisacano Leadership Foundation, Inc. was created in 1990 by the American Board of Family Medicine in tribute to the founder and first executive director of the ABFM, the late Nicholas J. Pisacano, M.D. Pisacano is acknowledged as a leader in the effort to recognize family medicine as a specialty.

MMA member **David Rothenberger**, M.D., has been awarded the 2012 Harold S. Diehl Award for his outstanding professional contributions to the University of Minnesota Medical School, the university and the community.

The MMA's Quality Committee selected member **Therese Zink**, M.D., to receive the 2012 Contribution to Quality Healthcare in Minnesota Award from the Minnesota Medical Association Foundation. The Minnesota Academy of Family Physicians (MAFP) nominated Zink based on her leadership in family medicine research and quality improvement. The MAFP especially called out her work on developing chronic kidney disease guidelines for primary care practices.

MMA member **John Noseworthy**, M.D., president and CEO of Mayo Clinic, was named to *Modern Healthcare's* "100 Most Influential People in Healthcare," a list that also includes President Barack Obama, Republican presidential nominee Gov. Mitt Romney and Republican vice presidential nominee Rep. Paul Ryan. Noseworthy ranked 17th.

EDITOR'S NOTE: Keep track of news through MMA News Now, which is delivered to your email box free each Thursday. To subscribe, go to www.mnmed.org and look for "MMA News Now" under the "Publications" tab. We are also on Facebook, Twitter, LinkedIn and YouTube.





T. Michael Tedford, M.D., has been actively involved in MEDPAC for the past decade.

MEET A MEMBER

T. Michael Tedford, M.D.

For someone who spends much of his free time discussing political strategy, T. Michael Tedford, M.D., invested very little time watching the recent Republican and Democratic national conventions. When asked why, he responds, “One of my great disappointments in our political system is the wedge that is driving deeper and deeper between the parties. These conventions just feel like preaching to the choir. It’s the true believers talking to the other true believers rather than opening up the dialogue so that everybody can come to a greater understanding so we can make progress together.”

Instead of all of the “preaching,” he’d prefer to see party leaders “start saying out loud that the perspective of the opposition is valid for a lot of reasons. Until you agree that the opposition’s positions actually have some basis in reality, there’s no common

ground to start to talk about a better way.”

Tedford has been working on creating political common ground for the past decade as a member of MEDPAC, the MMA’s political action committee. He has chaired the group for the last four years.

An ear, nose and throat physician, he became politically active after a few persuasive MMA members convinced him how difficult it was to work with lawmakers when they don’t share your ideology. It’s more efficient, he was told, to help those who already agree with your views get elected.

Getting involved in politics doesn’t have to be complicated, Tedford points out. The easiest way, of course, is to write a check to either a candidate or a political action committee such as MEDPAC. Another way is to find a candidate you support, work on his or her campaign and “exercise leadership from your position as a physician, the expert in health care, helping the candidate, the campaign and the voters understand the real issues that we are trying to grapple with.”

For physicians who want to do even more, he suggests attending a precinct caucus. “That’s sometimes hard to do, though,” he admits. “That gets into the heart of party politics, which so many physicians have a distaste for.”

Tedford points out that one way physicians can play a role without getting involved in a campaign or attending a caucus is by meeting with state legislators at the MMA’s annual Day at the Capitol (scheduled for February 7, 2013). The MMA also organizes Capitol Rounds, which offers members the opportunity to tour the Capitol and meet with their lawmakers, as well as District Dialogues, in which the MMA brings your state senators and representatives to you and your clinic staff. These casual hour-long meetings can be held in a home, at a coffee shop, at a clinic or at any other venue that’s convenient.

Tedford acknowledges that becoming politically active is not for everyone. However, he insists that those who want to see a “more patient-friendly, clinician-supported environment” need to accept that government plays a huge role and then do something about it. “If we are not active in influencing who is in government, we are missing an opportunity to impact our ability to deliver care better,” he says.

EDITOR’S NOTE: Election Day is fast approaching. This year, significant change is possible because all 201 legislative seats are up for grabs due to redistricting. Plus, nearly 25 percent of last session’s legislators either retired or are running for a different post. Exercise your right and vote!

AT A GLANCE

MEDICAL SCHOOL

University of Cincinnati

RESIDENCY

University of Minnesota

CURRENT PRACTICE

The Ear, Nose and Throat Clinic and Hearing Center in Edina

MMA INVOLVEMENT

Member of the Independent Practice Task Force; chair of MEDPAC

HOBBIES

Rowing (he’s a member of the Minneapolis Rowing Club); photography; and reading (Lately, he’s been recommending Parker Palmer’s *Healing the Heart of Democracy: The Courage to Create a Politics Worthy of the Human Spirit.*)



Cancer Genetic Counseling

When to Refer for Cancer Risk Assessment and Genetic Testing

By Barbara Kunz, M.S., CGC, Denise Marty, M.S., CGC, and Katherine Baker-Lange, M.S., CGC

■ Identifying hereditary cancer risk saves lives through individualized surveillance and prevention efforts. Advances in testing technologies and genetic knowledge are providing us with new tools for identifying individuals and families who are at highest risk for cancer. This article reviews our current genetic testing abilities, describes the role of genetic counselors, and offers guidance and resources for physicians as they determine who ought to be referred for genetic cancer risk assessment and testing.

We are in a period of rapid change with regard to both our ability to do genetic testing and the resulting knowledge it produces. The number of genes that can now be tested and the sensitivity of mutation detection are increasing, while the cost of doing many of these tests is decreasing.¹ This is the result of technological advances that grew out of the Human Genome Project. Until recently, testing targeted only one or a couple of genes linked with a specific condition; now, through massively parallel sequencing (also known as next-generation sequencing), we can look at dozens to hundreds of genes linked with many syndromes at the same time. In addition, some labs now offer partial or full exome sequencing, which targets portions of thousands of genes at a time.^{2,3}

The number and scope of new tests is expected to rapidly increase in the next few years. As a result, we will learn more about the consequences of carrying mutations in specific genes or in multiple genes, and these discoveries will help us better understand how genetic factors contribute to diseases. Until then, many of these tests may provide information that is complex and difficult to use clinically.

In oncology, these advances already have led to new clinical tests. Just this year, for example, several commercial labs introduced tests for multiple genes linked with colon, breast and ovarian cancer. Since the introduction of *BRCA1* and *BRCA2* testing more than 15 years ago, the clinical use of genetic tests that identify patients with hereditary cancer risk has enabled more appropriate cancer surveillance and prevention; this has saved the lives of many individuals found to be at risk.^{4,6} If a mutation is found, genetic testing also benefits the relatives of these individuals, as they can be offered single-mutation testing to determine their risks as well. In the future, improved genetic testing will benefit even more families who may be at risk.

The task of identifying candidates for cancer risk assessment or testing is complex, requiring busy clinicians to assess

patients' personal and family histories. Finding clear, effective ways to identify those who would most benefit from genetic services would not only help patients and their families but also physicians, who may be legally responsible when patients with hereditary risk are not identified.⁷ This article provides information as well as resources to assist physicians in better identifying individuals who are candidates for cancer genetic services.

Hereditary Cancer Clinics

Minnesota now has more than 20 hereditary cancer clinics, which see patients who have been referred by other clinicians or who have sought genetic counseling on their own (Figure). These clinics are staffed by genetic counselors with expertise in providing cancer risk assessment and genetic counseling.

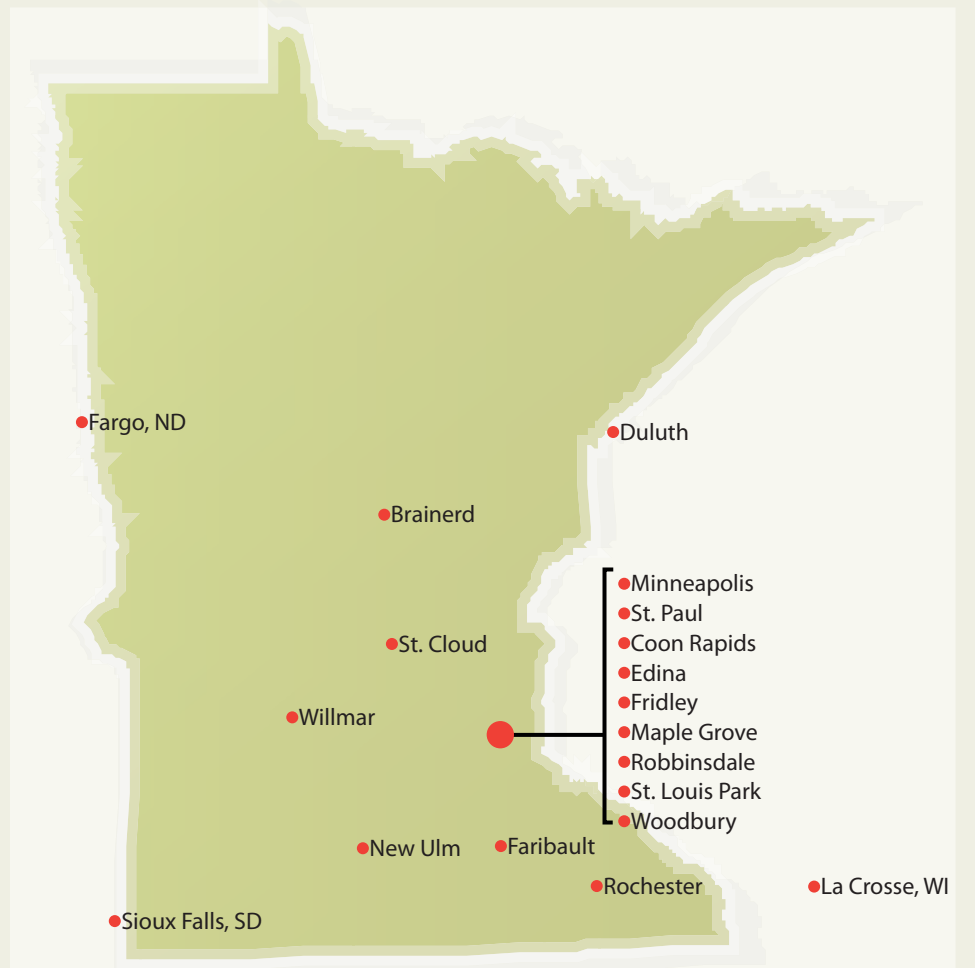
Genetic counselors hold master's degrees from accredited training programs and are certified through the American Board of Genetic Counseling. They are trained in human genetics, other areas of science, inherited diseases and the diagnostic process including testing. They also learn communication and counseling skills.⁸ Many genetic counselors specialize in particular areas including pediatrics, perinatal medicine and cancer; and they work in a variety of settings including hospitals, clinics and laboratories.

Hereditary cancer risk assessment typically begins with analysis of the patient's personal and family history to determine the likelihood that a cancer syndrome is present. The genetic counselor looks specifically at patterns and types of cancers and the ages at which an individual was diagnosed and then calculates the likelihood that a mutation is present.⁹ For example, if the counselor sees a pattern of colon cancers and a uterine cancer, then testing for Lynch syndrome would be considered. If the history suggests a hereditary syndrome, then the counselor discusses genetic testing options, the implications and limitations of test results, and personal concerns and family dynamics that may have an impact on decisions. The

counseling process alone can be valuable because it includes a review of screening guidelines that may be appropriate for a patient who has a given family history.

When a patient chooses to undergo testing, counselors coordinate it and provide post-test counseling, which includes interpretation of positive, negative and ambiguous results in the context of a family history. Generally, genetic counselors send summary information back to the patient's physician. Most often, a counselor will meet with the patient independently; but in some cases, the patient will meet with both a counselor and a physician such as an oncologist. Although genetic counselors discuss with the patient options for medical management including screening, chemoprevention and surgery, they do not make recommendations. Patients then meet with physicians who make recommendations and provide their care. Counselors also work with families to optimize the disclosure of information to other at-risk relatives.

FIGURE
Where to Find Genetic Counseling Services in and Around Minnesota



For specifics about the services in these communities, go to the Minnesota Genetic Counselors Association website at www.mygenepool.org. For telephone-based services, go to Informed Medical Decisions at www.InformedDNA.com.

Referral Guidelines and Resources

A number of resources, including cancer risk assessment referral guidelines and syndrome-specific testing criteria, can aid physicians in making referral decisions.¹⁰ Referral guidelines are broader than testing criteria, but both are useful tools that are evolving as our knowledge increases. Among the resources on the National Comprehensive Cancer Network (NCCN) website are guidelines on testing and management of specific cancer syndromes such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, Cowden syndrome and Li-Fraumeni syndrome.^{11,12} These are updated frequently, so reading the information on the NCCN website from time to time is the best way for physicians to keep current.

Clinicians should first triage their patients based on personal history alone, as certain indications signal the need for automatic referral (Table 1). Individuals who have a first-degree relative who meets the criteria are also candidates for referral. For example,

a woman diagnosed with breast cancer at age 40 and her daughter, are both candidates for referral. When possible, it is better to test the mother first, since she is more likely to carry a mutation. Genetics referral is also indicated for someone with certain family histories as well. Collectively, the indications listed in Tables 1 and 2 signal the possibility of many hereditary cancer syndromes.

Common Cancer Syndromes

The following is a brief overview of the most common syndromes identified in cancer genetics clinics. These and additional syndromes are listed in Table 3.

■ Hereditary Breast and Ovarian Cancer Syndrome

It is estimated that 5% to 10% of breast cancers and 10% to 15% of ovarian cancers occurring in the United States are associated with a hereditary predisposition, the most common of which are mutations in the *BRCA1* and *BRCA2* genes.^{13,14} Because of the presence of founder mutations, the incidence rate of *BRCA*-mutation carriers can vary by ethnic background. The highest incidence rate is in the Ashkenazi (Eastern European) Jewish population, where one in 40 individuals

carries one of three founder mutations.¹⁵ This is significantly higher than the incidence rate in the general population in the United States, which is estimated to be between one in 300 and one in 800.

TABLE 1

Genetics Referral Based on Personal History

Genetics referral is medically indicated for anyone with a personal history of or a first-degree relative with a personal history of any of the following:

- Breast cancer diagnosed at age 50 or younger
- Breast cancer with triple-negative histology diagnosed at age 60 or younger
- Ovarian, fallopian tube or peritoneal cancer diagnosed at any age
- Breast or ovarian cancer diagnosed at any age for anyone with Ashkenazi Jewish ancestry
- Colon cancer diagnosed at age 50 or younger
- Uterine (endometrial) cancer diagnosed at age 50 or younger
- Gastric cancer, diffuse type, diagnosed at age 45 or younger
- Polyps
 - 10 or more adenomatous colorectal polyps, synchronous or metachronous
 - 3 to 5 juvenile polyps in the colon and rectum, or multiple juvenile polyps throughout the GI tract
 - 2 or more Peutz Jeghers-type polyps of the small intestine
 - Specific skin lesions (trichilemmomas, fibrofolliculomas, multiple facial angiofibromas or multiple neurofibromas)

Any of the following rare tumors:

- Adrenal cortical carcinoma
- Choroid plexus tumor (not cysts)
- Hemangioblastoma
- Male breast cancer
- Medullary thyroid cancer
- Paraganglioma /carotid body tumor
- Pheochromocytoma
- Retinoblastoma
- Wilms tumor

Sources: National Comprehensive Cancer Network (NCCN), www.nccn.org; Hampel H, et al. Journal of Medical Genetics 2004; Gonzalez KD, et al. Journal of Clinical Oncology; 2009

Studies have shown that deleterious mutations in the *BRCA1* or *BRCA2* genes increase the risk for developing breast cancer in both men and women. Risk estimates vary significantly among studies, from a 50% to 82% lifetime risk for female breast cancer and an 18% to 54% risk for ovarian cancer.^{16,17} Prostate, pancreatic, male breast and melanoma cancer risk is also elevated in these individuals, particularly in *BRCA2* gene mutation carriers.¹⁸ Multiple primary cancers are common in *BRCA* mutation carriers. For example, a *BRCA2* mutation carrier who develops breast cancer at age 60 has a 17% chance of developing a contralateral breast cancer in the next 25 years. A *BRCA1* mutation carrier who develops breast cancer before age 40 has a 63% chance of developing a contralateral breast cancer in the next 25 years.¹⁹ Pathologic features can also signal an increased chance of a *BRCA* mutation. For example, the NCCN recently recommended *BRCA* testing for all women diagnosed with a triple-negative breast cancer before age 60 because of the increased chance that they carry a *BRCA1* mutation.²⁰ ↪

TABLE 2

Genetics Referral Based on Family History

Genetics referral is indicated for someone with a family history of any of the following:

- A first-degree relative whose personal history fits a criterion in Table 1
- A known gene mutation in a hereditary cancer predisposition syndrome
- An inherited cancer predisposition syndrome in a relative
- A pattern of three or more similar cancers* in one lineage, regardless of age of diagnosis
- A relative with an early-onset cancer diagnosis
- Pattern of cancers* in one lineage that are suggestive of a specific syndrome:
 - Breast and ovarian cancer
 - Colon and uterine cancer
 - Breast, thyroid and uterine cancer
 - Lobular breast cancer and diffuse gastric cancer
- A relative with multiple primary cancers including bilateral cancers in paired organs
- Anyone who is concerned about their family history of cancer; wants to clarify their risk for cancer; is making medical decisions based on their family history of cancer; or wants to make an informed decision about genetic testing

*Include first-, second- or third-degree relatives

TABLE 3

Common Hereditary Cancer Syndromes, Features and Associated Genes

BREAST CANCER SYNDROMES	CANCERS/FEATURES	GENE(S)
Hereditary Breast and Ovarian Cancer	Breast, ovarian, male breast, prostate, melanoma, pancreatic	<i>BRCA1, BRCA2</i>
Cowden Syndrome	Breast, thyroid, uterine, colon, renal	<i>PTEN</i>
Li-Fraumeni Syndrome	Breast, sarcoma, brain, adrenal cortical	<i>Tp53</i>
Diffuse Gastric Cancer	Lobular breast, diffuse gastric	<i>CDH1</i>
COLON CANCER SYNDROMES	CANCERS/FEATURES	GENE(S)
Lynch Syndrome	Colon, uterine, ovarian, gastric, ureter, kidney, hepatobiliary, duodenal	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>
Familial Adenomatous Polyposis	Colon, >100 polyps, thyroid	<i>APC</i>
Attenuated Familial Adenomatous Polyposis	Colon, 10-100 polyps	<i>APC</i>
MYH-Associated Polyposis	Colon, up to 500 polyps	<i>MUTYH</i>
Juvenile Polyposis	Colon, hamartomatous polyps	<i>SMAD4, BMPR1A</i>
Juvenile Polyposis/Hereditary Hemorrhagic Telangiectasia	Colon, hamartomatous polyps, HHT symptoms	<i>SMAD4</i>
Peutz-Jeghers Syndrome	Colon, testicular, breast, uterine	<i>STK11</i>

Adapted from: Lindor N. Concise Handbook of Familial Cancer Susceptibility Syndromes; Journal of the National Cancer Institute Monographs, No. 38, 2008.

■ **Li-Fraumeni Syndrome**

Li-Fraumeni syndrome is caused by inherited mutations in the *Tp53* gene and associated with a high risk for a variety of cancers including breast cancer, sarcoma, brain tumors and adrenal cortical carcinoma. It is estimated that at least 7% of women diagnosed with breast cancer before age 30 who do not have a family history of cancer will carry a new mutation in the *Tp53* gene.^{21,22}

■ **Cowden Syndrome**

Cowden syndrome, also known as *PTEN* Hamartoma tumor syndrome (it involves mutations in the *PTEN* gene), is associated with an increased risk for benign and malignant tumors of the breast, thyroid and endometrium. Macrocephaly and benign skin lesions (trichilemmomas, papillomatous papules) are often present.²³

■ **Lynch Syndrome**

It is estimated that 3% to 5% of all colon cancers and 2% to 3% of all endometrial cancers are associated with Lynch syndrome, which is caused by mutations in a number of genes involved in DNA mismatch repair.^{24,25} Early studies of families with identifiable Lynch syndrome gene mutations showed an approximately 80% risk for colon cancer, a 60% risk for endometrial cancer, a 13% risk for gastric cancer and a 12% risk for ovarian cancer.²⁶ Work to refine cancer risk estimates continues, with recent re-

search showing lower cancer risks particularly associated with mutations in the *MSH6* and *PMS2* genes.²⁷ Lynch syndrome is also associated with other cancers including those in the upper urinary, upper GI and hepatobiliary tracts. There is evidence that the colon cancers associated with Lynch syndrome develop

Insurance Coverage for Genetic Testing

Most insurers now provide coverage for genetic counseling services and appropriate testing, and many allow genetic counselors to directly bill for their services. Some require that pre- and post-test counseling be provided by trained genetic providers. When considering testing for some of the more common syndromes such as hereditary breast and ovarian cancer syndrome and Lynch Syndrome, keep in mind that many payers including Medicare have clearly defined criteria for determining whether testing is covered. The cost of genetic testing varies depending on the lab, the gene being tested and the test ordered. Single-gene sequencing and rearrangement testing can cost up to \$2,000. Single-mutation testing, which is done when a mutation has been found in a family, costs \$200 to \$500. Many of the new multi-gene panels cost between \$2,500 and \$5,500.

more quickly than typical adenomas; therefore, screening needs to be performed every one to two years beginning at a young age (20 to 25 years). Appropriate screening has been shown to decrease colorectal cancer risk by 62%²⁸ and decrease mortality from colorectal cancer by 70%.⁴

Family history fails to identify nearly half of the families with Lynch syndrome.²⁹ In 2009, the Centers for Disease Control and Prevention's Evaluation of Genomic Applications in Practice and Prevention working group recommended screening all individuals diagnosed with colon cancer for Lynch syndrome. This is done by looking for features (microsatellite instability or absence of staining of specific proteins) in a colorectal tumor. This process was found to be cost-effective, as it alters care both for the individual with cancer and for their at-risk relatives.³⁰

■ Hereditary Polyposis Syndromes

Familial adenomatous polyposis (FAP) classically presents with hundreds to thousands of adenomatous polyps beginning in childhood. Individuals with FAP have a nearly 100% lifetime risk of developing cancer. Features of FAP include a risk for developing polyps and cancers in the GI tract, thyroid cancer, desmoid tumors, dental anomalies, soft-tissue tumors, congenital hypertrophy of the retinal pigmented epithelium and hepatoblastoma. FAP, which is related to mutations in the *APC* gene, has considerable clinical overlap with a newly defined syndrome, *MYH*-associated polyposis (MAP), which is caused by inherited mutations in both copies of the *MYH* gene. FAP and MAP also can present in an attenuated form, with a smaller number of polyps that develop over a lifetime, making it important to document the total number of polyps seen over time. Other polyposis syndromes (such as juvenile polyposis and Peutz-Jeghers syndrome) are associated with specific pathologic features.

Conclusion

Patients can benefit from cancer genetic services. Because they often turn to their primary care physicians first with concerns about cancer risk, these physicians need to be aware of genetic syndromes that put people at increased risk for various cancers. Although physicians need to be knowledgeable, they do not have to become experts in genetics, as a number of genetic counseling specialty clinics around the state now offer such expertise as well as counseling services that can benefit patients. **MM**

Barbara Kunz is a genetic counselor with North Memorial's Humphrey Cancer Center; Denise Marty is with the Virginia Piper Cancer Institute of Unity Hospital; and Katherine Baker-Lange is with Park Nicollet's Fraumenschuh Cancer Center. All are members of the Minnesota Genetic Counselors Association's board of directors.

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Molecular Targeted Therapy in Lung Cancer

By Naomi Fujioka, M.D., and Peter B. Bitterman, M.D.

■ Genetic sequencing has allowed better understanding of non-small-cell lung cancer, leading to improvements in the ability to diagnose and treat the disease through targeted therapy. This article describes some of the past and ongoing studies of targeted therapies for lung cancers, the genetic mutations in lung cancers that develop in people who never smoked, and the role of Minnesota researchers in understanding the pathogenesis of lung cancer.

Dramatic developments related to non-small-cell lung cancer (NSCLC) provide a striking example of how genetic tools have been integrated into lung cancer diagnosis and treatment. Lung cancer is deadly, claiming an estimated 160,000 lives a year in the United States alone¹ and more than 1.4 million worldwide.² The fact that what was once among the rarest of cancers³ has become the most common cause of cancer death in this country—more than prostate, breast and colorectal cancer combined¹—is largely attributable to cigarette smoking.

It is well-established that more than 85% of lung cancers are directly related to tobacco use. The incidence has stabilized in women and is decreasing in men,¹ reflecting changes in tobacco use in the United States. Traditionally, lung cancers have been categorized as non-small-cell, which comprises approximately 80% of lung cancers, or small-cell. Until the last decade, treatment was based solely on these categorizations, with little to no differentiation among the histological subtypes of NSCLC. The vast majority of NSCLCs are diagnosed at an advanced stage, and the efficacy of traditional chemotherapeutic agents for treating them plateaued long ago, with first-line treatment producing response rates of 20% to 35% and the median overall survival being nine to 12 months.⁴

Genetic Heterogeneity of Lung Cancer and Targeted Therapies

Efforts to elucidate the molecular mechanisms of NSCLC have led to the discovery that NSCLCs, even those of the same histological subclass (adenocarcinoma being the most common), are genetically heterogeneous. Many harbor a known “oncogenic driver.” Typically, these are signaling

proteins that belong to pathways controlling proliferation, survival and invasiveness. The apparent reliance of tumor cells on such a single oncogenic driver has been termed “oncogene addiction.”⁵ The discovery of these drivers has fostered the development of targeted molecular therapies designed to neutralize the effect of the driver. It has been nearly 10 years since a study published in *JAMA* reported the results of a randomized, Phase II trial of gefitinib, a tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR) in symptomatic, advanced NSCLC that had progressed during standard chemotherapy.⁶ The objective response rate was low (12%) in the unselected population, although nearly half of patients reported a rapid improvement in symptoms. A second international study confirmed these results.⁷

Although gefitinib and another EGFR TKI, erlotinib, were initially developed to target overexpression of EGFR in NSCLC, a remarkable observation from these studies was that the patients who responded tended to be those who are considered “never smokers” (generally defined as having smoked fewer than 100 cigarettes in their life), females and patients with tumors of adenocarcinoma histology. Furthermore, Japanese women had higher response rates to gefitinib compared with their counterparts in the United States and Europe. In 2004, three landmark studies presented the first insight into genetic differences between tumors from patients who responded to gefitinib and tumors from those who did not.⁸⁻¹⁰ Sequencing of the exons in the EGFR gene from the tumors of the responders revealed heterogeneous somatic point mutations in the tyrosine kinase domain of EGFR, specifically in exons 19 and 21. Notably, none of these mutations were found in adjacent histologically normal lung tissue or in any

of the tumors from patients who did not respond to gefitinib. A number of subsequent studies confirmed these findings, with in-frame deletions in exon 19 and a point L858R mutation in exon 21 comprising nearly 90% of EGFR mutations in human NSCLC.¹¹ Individuals harboring those mutations showed exquisite sensitivity to gefitinib or erlotinib. Currently, approximately 10% to 15% of all patients with NSCLCs have EGFR driver mutations; such mutations are more prevalent in women, Asians (~30% compared with 15% in Western Europeans) and people who have never smoked (~50% prevalence).¹¹⁻¹³

In prospective trials, response rates to EGFR-targeted therapies in patients with advanced NSCLC whose tumors harbored EGFR mutations were approximately 75%,¹⁴ much better than the response rates to any traditional chemotherapeutics. Two prospective, randomized studies done in China and Japan, and one conducted in Europe in which patients with EGFR mutations were randomized to treatment with an EGFR TKI or chemotherapy showed a three-fold increase in progression-free survival in the EGFR TKI arms from 4.6 to 13.1 months (HR 0.16, 95% CI 0.1-0.26, $P<.001$),¹⁵ 6.3 to 9.2 months in another (HR 0.49, 95% CI 0.34-0.71, $P<.001$),¹⁶ and 5.2 to 9.7 months in the third (HR 0.37, 95% CI 0.25-0.54, $P<.0001$).¹⁷ Of note, at least two studies showed that patients whose tumors did not harbor EGFR mutations actually did worse when initially treated with an EGFR TKI.^{17,18} Therefore, treatment guidelines from the American Society of Clinical Oncology recommend testing upfront if an EGFR TKI is being considered as a first-line treatment for NSCLC.¹⁹ Such testing has become feasible in a community setting and is covered by insurance, as is the treatment.

Another striking example of how genetic analysis has translated into the identification of a molecular target and led to the development of an effective therapy for NSCLC stems from the discovery of echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) translocations in NSCLC.²⁰ In 2011, less than four years after EML4-ALK translocations in NSCLC were described (contrast this with the 26 years from the initial discovery of the *egfr* gene to treatment), an ALK-targeted therapy, crizotinib, was approved by the FDA for ALK-positive lung cancer based on ongoing Phase I and II data. Found in approximately 5% of NSCLCs, ALK translocations typically are not found concurrently with EGFR or other driver mutations; tend to occur in younger patients; and, like EGFR mutations, occur more frequently in people who have never smoked or who were light smokers.²¹ Although a seemingly low percentage, this translates into tens of thousands of patients per year because of the high overall incidence of lung cancer. In the Phase I trial of crizotinib, response rates on the order of 61% were seen, and side effects were manageable.²² These results are holding true in the Phase 2 trial thus far;²³ Phase III trials are ongoing. Unfortunately, although a number of patients have a durable and prolonged response, neither crizotinib nor EGFR TKIs are curative. However, genetic and molecular analyses are being

used to investigate mechanisms of acquired or intrinsic resistance with very promising results.

The Role of Next-Generation Sequencing

The ability to detect driver mutations in NSCLC tumors illustrates a revolution that is occurring in cancer classification, prognosis and treatment. The age of using chemotherapy aimed at treating cancer based on its organ of origin with nonspecific genotoxic therapies is ending; and an era of selecting patients for therapeutic studies based on the genetic or molecular makeup of the tumor is being ushered in. Much of this work has been enabled by rapid advances in large-scale DNA sequencing, including next-generation or massively parallel sequencing.²⁴ Investigations using this technology to understand cancer genetics are ongoing. For example, the Cancer Genome Atlas project (<http://cancergenome.nih.gov>), an initiative launched by the National Cancer Institute and National Human Genome Research Institute, began in 2006 with the goal of genetically characterizing more than 20 tumor types. The recently established National Cancer Institute Lung Cancer Mutation Consortium (www.golcnc.com), is composed of 14 institutes nationwide; the goal is to prospectively enroll at least 1,000 patients to test their tumors for 10 well-characterized genetic changes and match those patients to optimal therapy based on those changes.

Sequencing has identified an increasing number of biomarkers and potentially targetable alterations in addition to EGFR and EML4-ALK for NSCLC. Such information is being used to guide treatment. In one study, 51% of patients with newly diagnosed NSCLC were found to have an identifiable driver mutation, and 22% of those patients began a driver-mutation-specific therapy with an average turnaround time of less than three weeks.²⁵ In another study, 90% of patients with NSCLC possessed a mutation in just four targets—*EGFR*, *v-Ki-ras2* Kirsten rat sarcoma viral oncogene homolog (*KRAS*), *ALK* or human epidermal growth factor 2 (*HER2*).²⁶ Drugs either have been FDA-approved or are in clinical testing for three of these four targets (*EGFR*, *ALK*, *HER2*); *KRAS* mutations in smokers are predictive of resistance to EGFR TKI.²⁷ The first trial in which randomization to treatment was done based on prospective determination of molecular and genetic biomarkers in NSCLC was completed in 2011. This Phase 2 Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial demonstrated the feasibility of performing real-time biomarker assessment on patients refractory to standard chemotherapy who underwent biopsies for the purpose of treatment assignment.²⁸ This trial and others are indicative of the rapid shift in clinical trial design for nearly all cancer types.

Lung Cancer in Nonsmokers

Although most NSCLC cases are still caused by smoking, approximately 15% in the United States and Europe occur among people who have never smoked. In East and Southeast Asia, lung cancer in people who have never smoked accounts for up

to 40% of cases and up to 50% of lung cancers in women.^{29,30} The raw numbers are sobering: Lung cancer accounts for up to 24,000 cancer deaths among people in the United States who have never smoked.³¹ Nearly all lung cancers in people who have never smoked are adenocarcinomas. Several known etiologic risk factors include exposure to second-hand smoke (also called environmental tobacco smoke or ETS), radon, asbestos or polycyclic aromatic hydrocarbons related to indoor cooking and pulmonary infections. Second-hand smoke has been shown to increase risk by about 25% and is responsible for approximately 3,000 to 5,000 deaths from lung cancer per year.^{25,26} Furthermore, the incidence of EGFR mutations appears to be correlated with environmental tobacco smoke exposure in a dose-dependent fashion.³² Radon exposure is associated with the development of lung cancer in a dose-dependent fashion in those exposed to indoor radon as well as those who worked as uranium miners.³¹ However, in the majority of cases, there is no identifiable risk factor leading to the disease, and little is known about its pathogenesis. Lung cancers in people who have never smoked appear to be genetically distinct from the lung cancers that arise in smokers. For example, in smokers *K-ras* mutations can be found in approximately 25% of adenocarcinomas, typically characterized by G→T or G→C transitions; but they are less common in lung cancers occurring in people who never smoked (~15%) and are typically G→A transitions.³³

Minnesota Contributions

In the last several years, advances in next-generation DNA sequencing and bioinformatics have provided us with critical insights into the pathogenesis of lung cancer. Several Minnesota research teams have been involved in this work. Ping Yang, M.D., Ph.D., leader of the Epidemiology and Genetics of Lung Cancer Research Program at Mayo Clinic in Rochester, led the first genomewide association study of people who have never smoked, in which genotyping of nearly 60,000 single-nucleotide polymorphisms (SNPs) were analyzed in 377 matched case-control pairs. The top candidate SNPs (n=44) were validated in two separate cohorts that were each composed of nearly 1,000 people who had never smoked. The top SNP, rs2352028, at chromosome 13q31.3 was analyzed in a fourth cohort and found to be associated with development of lung cancer (combined OR 1.46 (95% CI 1.26-1.70, $P=5.94 \times 10^{-6}$) via downregulation of *GPC5* expression.³⁴ The *GPC5* protein plays a role in a number of cellular functions.³⁵ In addition, Yang and Christine Wendt of the University of Minnesota are leading an ongoing collaborative study funded by the NIH to determine whether COPD is on the causal pathway to lung cancer. Their goal is to define the entire gene-expression landscape—from gene to RNA to protein—looking for molecular footprints that are harbingers of cancer in the lungs of people with COPD.

Summary

In the vast majority of adult cases, cancer arises from genetic changes in somatic cells. Although the examples described demonstrate that some lung cancers originate under the control of a single driver, it is also clear that the cancer circuitry is flexible, adaptable and complex. Since complete sequencing of the human genome was first reported in April 2003 and sequencing of the first cancer genome (acute myeloid leukemia) was reported in 2008, use of omics technologies (DNA, RNA, protein and metabolites analyzed genome-wide) has resulted in an explosion of data, rapidly changing the landscape of cancer research and translating from discovery to therapeutic options that affect patients' lives. In that light, it is now standard to perform molecular testing on NSCLC tumors from all patients with characteristics predictive of the presence of an actionable target—particularly in those who have never smoked, who have adenocarcinoma histology, and who are younger, female and/or of East Asian descent. The work of elucidating the molecular biology of NSCLC has brought attention to the issue of lung cancer in people who have never smoked and hopefully will result in less stigma associated with a diagnosis of lung cancer, more funding to address this issue and more public awareness that lung cancer is not a disease that only occurs in smokers or former smokers.

With the development of powerful tools to study, analyze and aggregate data on cancer genomes, transcriptomes, proteomes and metabolomes in conjunction with the general trend toward personalization in all aspects of medical care, it is certainly within reason to expect that risk stratification, diagnosis and treatment of cancer will largely be based on such information in the near future. **MM**

Naomi Fujioka and Peter Bitterman are with the department of medicine and the Masonic Cancer Center at the University of Minnesota.

This work was supported by NCI award CA077598 and by the Order of the Eastern Star.

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CF versus CRMS

Diagnostic Challenges in Cystic Fibrosis

By Renee Temme, M.S., CGC, Jennifer Roggenbuck, M.S., CGC, and John McNamara, M.D.

■ In Minnesota and other states, all newborns are screened for cystic fibrosis (CF). CF is a common genetic condition that affects the sinopulmonary, hepatobiliary and male urogenital systems. Cystic fibrosis is caused by mutations in both copies of the CF transmembrane conductance regulator (*CFTR*) gene. In Minnesota, infants who have elevated immunoreactive trypsinogen (IRT) at birth are tested for a panel of 39 mutations. Newborn screening detects most infants with two *CFTR* mutations as well as some who are CF carriers. This method of newborn screening leads to the identification of some individuals with milder forms of *CFTR* dysfunction whose clinical diagnosis is unclear. The Cystic Fibrosis Foundation has designated diagnostic and management guidelines for *CFTR*-related metabolic syndrome (CRMS) for infants who have evidence of *CFTR* dysfunction but who do not meet the diagnostic criteria for CF. This article discusses the clinical impact of CRMS in Minnesota.

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population, with an incidence rate of approximately one in 3,500 individuals in the United States.¹⁻⁴ It is a progressive disorder that affects the sinopulmonary system, exocrine pancreas, hepatobiliary system, male urogenital system and exocrine sweat glands. The basic underlying defect involves varying degrees of dysfunction of the chloride channel cystic fibrosis transmembrane-conductance regulator (*CFTR*) protein in the membrane of epithelial cells. The *CFTR* protein regulates salt and fluid balance in secretory organs; dysfunction results in dehydration of extracellular fluid and impaired airway clearance.

Pulmonary disease is the leading cause of morbidity and mortality in persons with CF. Affected persons develop chronic airway inflammation and infection, leading to end-stage lung disease and death at a median age of 37 years.⁵ The majority of individuals with CF have pancreatic insufficiency with maldigestion. More than 95% of males with CF are infertile due to congenital bilateral absence of the vas deferens. Treatment advances and early diagnosis have resulted in a steady increase in median survival. Currently, more than 45% of the CF population is older than 18 years of age.⁵

Cystic fibrosis is caused by mutations in both copies of the CF transmembrane conductance regulator (*CFTR*) gene. Each parent of an affected child typically carries one mutation, and there is a 25% chance of recurrence of CF in a pregnancy. Carrier frequency varies by population, ranging from one in 24 in the Ashkenazi Jewish population, to one in 25 in the non-Hispanic white population, to one in 94 in the Asian-American population.^{6,7} Molecular genetic testing of the *CFTR* gene is used for carrier detection in population screening programs, as well as in many newborn screening programs, including Minnesota's. Testing is complicated by the extreme diversity of the *CFTR* mutations. More than 1,700 different

mutations have been identified, and the disease-causing potential of many is not well-understood.⁸

Historically, CF was diagnosed in symptomatic individuals who presented with one or more characteristic manifestations and additional laboratory evidence of abnormal *CFTR* function (most commonly, two abnormal sweat chloride values).^{1,9} With the advent of universal newborn screening for CF, the diagnosis is now more frequently made in an infant at birth or shortly thereafter. This change in diagnostic patterns has led to a reassessment of the natural history of CF, the spectrum of CF-related symptoms and treatment practices.

Newborn Screening for CF

Most infants are diagnosed with CF after newborn screening (NBS) during the first weeks of life, allowing for prompt treatment and genetic counseling for at-risk couples. Affected children identified through NBS have shown improved clinical outcomes, particularly with respect to their nutritional and pulmonary status.¹⁰⁻¹³ All 50 states and the District of Columbia are now screening newborns for CF.¹⁴ Minnesota began screening newborns for CF on March 1, 2006.

Multiple NBS protocols for CF exist. In all NBS programs, the first stage involves measuring immunoreactive trypsinogen (IRT), which is elevated in the blood of most infants with CF.^{14,15} Some programs perform a second IRT analysis to look for persistent elevation. Most states, including Minnesota, measure IRT then conduct genetic testing. In Minnesota, infants who have IRT levels in the top 4% or who have IRT levels >170 ng/mL are tested for a panel of 39 *CFTR* mutations. Infants who have one or two mutations, or who have no mutations and persistently elevated IRT (>170 ng/mL) are reported as having a positive screen. In such cases, a sweat chloride test is recommended. Sweat chloride testing has traditionally been considered the gold standard for CF diagnosis. Sweat chloride values <30 mmol/L are considered negative for infants younger than 6 months of age; sweat chloride values

TABLE **Diagnostic and Clinical Characteristics of Cystic Fibrosis vs. CFTR-Related Metabolic Syndrome**

	AT DIAGNOSIS*		SYMPTOMS		
	SWEAT CHLORIDE [†]	CFTR MUTATIONS	RESPIRATORY	GASTROINTESTINAL	UROGENITAL
CYSTIC FIBROSIS	≥60 mmol/L	Two disease-causing mutations	<ul style="list-style-type: none"> • Persistent colonization with typical CF pathogens • Chronic cough and sputum production • Chest radiograph abnormalities • Airway obstruction • Nasal polyps • Digital clubbing 	<ul style="list-style-type: none"> • Intestinal obstruction • Pancreatic insufficiency (85%) or pancreatitis • Hepatic disease • Failure to thrive/protein calorie malnutrition 	<ul style="list-style-type: none"> • Obstructive azoospermia (congenital bilateral absence of the vas deferens) in >95% of males
CRMS	Intermediate (30 to 59 mmol/L) [‡]	Fewer than two clearly disease-causing mutations	<ul style="list-style-type: none"> • Asymptomatic • At risk for respiratory symptoms, and/or sinusitis, which could be later-onset 	<ul style="list-style-type: none"> • Asymptomatic • At risk for pancreatitis 	<ul style="list-style-type: none"> • Asymptomatic • Obstructive azoospermia (congenital bilateral absence of the vas deferens) in some males
	Normal (<30 mmol/L)	Two CFTR mutations, no more than one that is clearly disease-causing			

*Infants diagnosed with CRMS may eventually be diagnosed with CF as symptoms present and/or laboratory evidence becomes diagnostic for CF.

[†]Sweat chloride values for infants <6 months of age.

[‡]On two separate occasions.

Sources: Farrell PM, Rosentstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: cystic fibrosis foundation consensus report. *J Pediatr.* 2008;153(suppl):S4-S14; Borowitz D, Parad RB, Sharp JK, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr.* 2009;155:S106-16.

>60 mmol/L are considered diagnostic for CF. Sweat chloride values in the intermediate range (30 to 59 mmol/L) indicate the need for further evaluation and testing.¹

The vast majority (>90%) of infants who screen positive have negative sweat chloride tests and are unaffected carriers. In Minnesota, genetic counseling is typically provided at the time of the sweat chloride test to educate families about the implications of their child's carrier status.

CFTR-Related Metabolic Syndrome (CRMS)

The classic symptoms of CF typically appear in childhood and are well-known to physicians and other health care providers. Milder forms of CF, which have been termed "variant," "atypical," "nonclassic" or "CFTR-related disease" may present later in life. Patients with these milder forms of the disease may present with manifestations of CF in only one or two organ systems (such as bilateral absence of the vas deferens or pancreatitis) and sweat chloride concentrations may not be clearly diagnostic.

Newborn screening has led to earlier identification of patients with potential CFTR dysfunction. These infants may have sweat chloride concentrations in the intermediate (30 to 59 mmol/L) range and are typically healthy. Alternatively, infants may be identified as having two CFTR mutations and a normal sweat chloride test. Some CFTR mutations may allow partial CFTR protein function, which may result in mild CF-like symptoms in some individuals. However, for many CFTR mutations, information about the potential for causing disease is very limited or unknown.

The Cystic Fibrosis Foundation has designated CFTR-related metabolic syndrome (CRMS) to describe infants who have laboratory or genetic evidence of possible CFTR dysfunction but who do not meet the diagnostic criteria for CF. CFTR-related metabolic syndrome is diagnosed in asymptomatic infants who either have 1) sweat chloride concentrations in the intermediate range at two separate times and fewer than two mutations that are clear disease-causing mutations; or 2) sweat chloride concentrations in the normal range and two CFTR mutations, no more than one of which is a clear disease-causing mutation.¹⁶ The table contrasts the characteristics of CF and CRMS.

Some children with CRMS will develop symptoms of CF over time such as later-onset lung disease, sinusitis or pancreatitis. However, most patients with CRMS remain relatively healthy. Because it is not possible to know who may develop symptoms, careful monitoring of patients with CRMS has been recommended. The CF Foundation Practice Guidelines for managing patients with CRMS include the following:¹⁶

- Clinical assessment with a CF specialist should take place within the first two months of life. Care may be provided by a CF specialist alone with members of the CF team (social worker, genetic counselor, dietician, respiratory therapist) as needed.
- Assessment should be conducted in a clinic that adheres to the CF Foundation guidelines for patients with CF.
- The initial assessment should include a history and physical exam, accurate weight and height measurements, pancreatic function testing (eg, fecal elastase) and a throat culture. If respiratory symptoms are present, a chest X-ray or chest CT

is recommended. Because patients may become pancreatic insufficient over time, a repeat fecal elastase test and abdominal imaging should be considered in the presence of poor weight gain, excessive flatus, loose stools or abdominal pain.

- *Pseudomonas aeruginosa* (a recognized CF pathogen rare in the normal pediatric population) should be treated according to the CF protocol if present in a throat culture.
- Assessment of asymptomatic CRMS patients should be done by a CF specialist at least twice during the first year of life and yearly thereafter.
- Routine airway clearance therapy should not be prescribed in the absence of clinical or radiological lung disease.
- Patients with CRMS should not be exposed to cigarette smoke.
- Patients with CRMS should receive an annual influenza vaccine.
- Families of a child with CRMS should be educated about signs and symptoms of CF.

Clinical Impact of CRMS

The natural history of CRMS is not yet understood. Ren et al. reported outcomes of 12 patients with CRMS diagnosed between 2002 and 2010; most remained healthy and asymptomatic during the study period.¹⁷ However, 25% of the patients with CRMS had a throat culture positive for *Pseudomonas aeruginosa*, and one patient was diagnosed with CF after a repeat sweat chloride test at 1 year of age was positive (73 mmol/L). In summary, CRMS patients may develop symptoms of CF, which are typically milder. Therefore, close initial monitoring of patients with CRMS is warranted.

The incidence of CRMS has not been well-studied. However, emerging data suggest that CRMS is not rare. Several authors have shown the ratio of CF to CRMS cases detected by NBS to be approximately 2:1.^{17,18} In 2011, NBS identified five patients with CF and seven with CRMS who are being followed at Children's Hospitals and Clinics of Minnesota. As more infants are screened, more infants with CRMS will be identified.

Conclusion

Clearly, there is much evidence that NBS for CF is beneficial. Infants can be diagnosed and treatment initiated within the first few weeks of life. And because of early diagnosis and advancements in therapy, the health of patients with CF is improving.

However, NBS has also raised new questions about the clinical spectrum of CF and appropriate follow-up of infants with intermediate or unclear results. Communication of intermediate results to families presents a challenge for genetic counselors, as families often experience confusion and uncertainty surrounding a CRMS diagnosis. More data regarding long-term clinical outcomes of patients with CRMS are needed in order to provide accurate counseling and anticipatory guidance. Further characterization of *CFTR* mutations will likely aid in diagnosis and clinical care in the future. Current information on the disease-causing potential of specific *CFTR* mutations is available at www.cftr2.org/. Recommendations for the management of

CRMS will likely change with further study of the natural history and genetics of this condition.

Primary care providers are not only the first to communicate positive results from NBS to the family but also are often the first to encounter the onset of CF-related symptoms in patients. Although most patients with CRMS will remain asymptomatic, some will develop CF symptoms; close follow up is necessary in those cases. Therefore, it is important that both primary and specialty care providers give ongoing support to families and help them cope with the uncertainty surrounding a CRMS diagnosis. **MM**

Renee Temme and Jennifer Roggenbuck are genetic counselors at Children's Hospitals and Clinics of Minnesota. John McNamara is medical director of the CF affiliate center, home care services, chronic ventilator unit, transitional technology supported programs, and hospice at Children's Hospitals and Clinics of Minnesota.

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The Quality of Metabolic Newborn Screening Specialty Care Services

Results of a Survey of Primary Care Providers

By Carolyn Stady Anderson, M.S.P.H., R.N., Ph.N., PNP, Kristi Bentler, M.S., R.N., Ph.N., CPNP, Nancy Vanderburg, R.N., Ph.N., and Susan A. Berry, M.D.

■ Since 2001, approximately 500 children with inborn errors of metabolism (IBEM) have been identified through the Minnesota newborn screening program. The vast majority of them receive specialty care at the Pediatric Metabolism Clinic or the Phenylketonuria (PKU) Clinic at the University of Minnesota. In order to determine provider satisfaction with the quality of services at those clinics, we surveyed primary care physicians, certified nurse practitioners and a certified physician assistant, collectively referred to in this article as primary care providers, who referred patients with IBEM to one of the clinics. Our objective was to evaluate the quality of metabolic team specialty services for children with IBEM; identify strategies to ensure coordinated and comprehensive care for children with IBEM; improve metabolic specialty care and connection to services for children with IBEM and their families; and gather data to inform newborn screening programming through the Minnesota Department of Health. Responses revealed a high level of overall satisfaction with the referral processes, 2) the quality of verbal communications and written reports, 3) feedback to the primary care team and 4) the management plans for addressing the needs of children with IBEM within the primary care setting. Improvement in communication about emergency planning for children with IBEM is needed, as is more information about specific metabolic conditions. This article also discusses changes that have taken place at the two clinics as a result of the survey findings.

Implementation of tandem mass spectrometry by newborn screening programs has increased the number of rare genetic metabolic conditions that can be detected. The unique health needs of children found to have such conditions warrant effective communication and collaboration between their primary care teams and clinicians who specialize in metabolic conditions in order to optimize health outcomes.^{1,2} Currently, there is no standard method by which primary care provider (PCP) satisfaction with metabolic specialty care is assessed or used by specialty practices for quality improvement.³⁻⁵

Since 2001, approximately 500 children with inborn errors of metabolism (IBEM) have been identified through the Minnesota newborn screening program. More than 96% of those infants receive specialty care in the Pediatric Metabolism Clinic or the Phenylketonuria (PKU) Clinic at the University of Minnesota, where they may be seen by geneticists, pediatric nurse practitioners, metabolic dietitians, genetic counselors and a pediatric neuropsychologist. We sought to evaluate PCP satisfaction with regard to the quality of metabolic specialty services children with IBEM receive at these two clinics, identify strategies to better coordinate and provide more comprehensive care for children with IBEM, improve metabolic specialty care and connection to services for children with

IBEM and their families, and gather data to inform newborn screening follow-up programming through the Minnesota Department of Health. To our knowledge, no published studies have documented PCP satisfaction with multidisciplinary metabolic specialty care services for children with IBEM identified through newborn screening. One previous Minnesota study explored satisfaction with genetic counseling services for infants and children with abnormal metabolic newborn screening results.⁶ Another study evaluated referral patterns in a clinical genetics setting.⁷

Methods

We mailed surveys to pediatricians, family physicians, certified nurse practitioners and a certified physician assistant who cared for children with IBEM born between June 1, 2001, and June 1, 2008, who were identified through Minnesota's newborn screening program and who were seen at one or more of the University of Minnesota's multidisciplinary specialty clinics between July 1, 2007, and July 1, 2008. One hundred-seventy children met the selection criteria. Those PCPs who had multiple patients with IBEM who met the selection criteria were asked to complete a maximum of one survey for each specialty clinic, if applicable. Survey recipients

TABLE **Primary Care Provider Survey: Satisfaction with the Quality of Pediatric Metabolic Services**

SURVEY QUESTIONS	PERCENT (%) RESPONSES											
	METABOLISM CLINIC						PHENYLKETONURIA CLINIC					
	SA	A	D	SD	NA	NR	SA	A	D	SD	NA	NR
1. I found it easy to make a referral to the Metabolic or PKU Clinic.	59	30			11		62	24			14	
2. I feel comfortable calling the health care providers at the metabolic clinics.	54	40			6		62	33			5	
3. I get satisfactory responses/answers from the health care providers at the clinic when I call.	59	25			16		57	19			24	
4. I receive feedback on the diagnosis and/or treatment from the providers at the metabolic clinic in a timely manner.	54	34		2	5	5	81	19				
5. I receive a useful treatment plan to manage this child’s medical condition in the primary care setting.	52	39	3	3	3		76	14	5		5	
6. I am satisfied with the content and quality of the written reports I receive from the clinic providers.	55	35	2	2	5	1	76	24				
7. I have received a copy of this child’s emergency medical alert letter.	43	22	10	3	16	6	NA	NA	NA	NA	NA	NA
8. The health care providers at the clinic communicate well with me.	49	43	2	3	3		62	24			14	
9. The health care providers at the clinic make appropriate recommendations for referrals to other specialists, early intervention, child care, school or vocational services.	39	32	2		27		52	24			24	
10. The health care providers at the clinic communicate with me about recommendations for referrals to other specialists, early intervention, childcare, school or vocational rehabilitation services.	32	33	8	3	22	2	43	33			24	
11. I feel these health care providers work collaboratively with me.	43	49	3	2	2	1	66	19	5		5	5
12. I am satisfied with the services provided to the children and families at this clinic.	54	43		1	2		71	29				
13. I am interested in getting more information on specific metabolic conditions.	25	35	5		19	16	24	19	19	5	14	19

were asked not to record any protected health information about their patient on the survey form; they were also asked to avoid identifying themselves, unless they wished to do so.

The study methods were reviewed and approved by the University of Minnesota Institutional Review Board and supported and approved as a quality-improvement activity by the Minnesota Department of Health.

The “Primary Care Provider Survey: Satisfaction with the Quality of Pediatric Metabolic Services” (Table) is a one-page questionnaire, the development of which was guided by a pe-

diatric geneticist, a public health nurse, specialists from the newborn screening program, a pediatric nurse practitioner and a literature review.

Key issues asked about included 1) whether there was an established referral process for specialty care, 2) whether the provider received timely feedback after their patient saw the specialist, 3) whether they received information from the specialist about the diagnosis and treatment plan, and 4) whether there was cooperative ongoing care management between PCPs and specialists.^{3,8,9} A pilot survey was conducted with six primary care

pediatricians who were familiar with the newborn screening program and who worked with diverse urban patient populations.

Based on feedback from the pilot study, a revised 13-question survey was created. The survey questions were presented as Likert scale items, with participants being able to choose from the following responses: *strongly agree*, *agree*, *disagree*, *strongly disagree* and *does not apply*. Questions were organized into categories relating to 1) the effectiveness of the referral process, 2) communication about the child's condition including emergency care planning, 3) collaboration between the primary care provider and metabolic specialty providers, 4) overall satisfaction with services and 5) interest in IBEM condition-specific education. An open-ended comment section elicited suggestions for improving the delivery of metabolic services. Surveys were coded to differentiate responses regarding the Pediatric Metabolism Clinic (M) and the Pediatric PKU Clinic (P). Surveys also were coded with the respondent's ZIP code to detect satisfaction or dissatisfaction trends by geographic distribution.

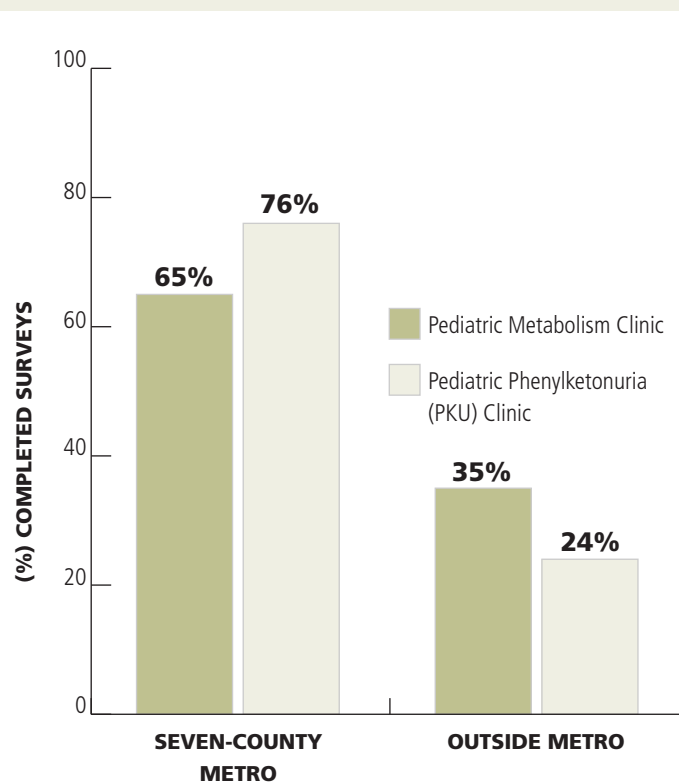
Surveys (118 M, 36 P) were mailed in December of 2008 to 152 physicians, certified nurse practitioners and a certified physician assistant. They were accompanied by a cover letter explaining the purpose of the study. A follow-up survey was sent approximately four weeks later. The cover letter of the second survey instructed recipients to discard that survey if they had already completed and returned the first one. Surveys were mailed from and returned to the Department of Health's newborn screening program in an effort to decrease the perception of bias related to direct mailings from and to the University of Minnesota clinics.

Results

Survey responses were aggregated by newborn screening program staff, then analyzed in collaboration with co-investigators from the department of pediatric genetics and metabolism at the University of Minnesota.

Sixty-three responses about the Pediatric Metabolism Clinic (M) (53% response rate) and 21 about the Pediatric PKU Clinic (P) (58% response rate) were returned for a total of 84 completed surveys. Returned surveys were divided into two groups according to ZIP code. One consisted of responses from the seven-county metropolitan area and the other was made up of those from other Minnesota cities and rural areas (Figure). No

FIGURE **Geographic Distribution Completed PCP Surveys**



significant differences in satisfaction were reported by geographic distribution.

The referral process (Questions 1 and 2) was found to be highly effective for both clinics: 91% (M) and 90% (P) of respondents indicated they found it easy to make a referral to the clinics and that they felt comfortable calling providers at those clinics (Table). Participants commented on the ease of referral, the value of the specialty center's newborn screening coordinator in facilitating communication and the effectiveness of speaking directly with metabolic specialists to obtain an initial action plan.

Eighty-seven percent (M) and 88% (P) of respondents indicated they were satisfied with the quality of verbal responses and the content of the written reports they received from the metabolic multidisciplinary teams (Questions 3 and 6). Respondents offered positive comments regarding the availability and responsiveness of specialists. One suggestion was for the clinics to offer more patient-specific dietary information, which is important to managing a child with a chronic metabolic condition.

Eighty-eight percent (M) and 100% (P) of respondents said they received timely feedback about a patient's diagnosis and treatment from metabolic specialists (Question 4). Ninety-one percent (M) and 90% (P) said they received a useful plan for

managing the patient's condition within the primary care setting (Question 5). Sixty-five percent said they received an emergency letter from the Pediatric Metabolic Clinic for those children whose IBEM requires specific emergency management (Question 7); 13% did not receive a copy of the letter.

Questions 9 and 10 speak to the role of co-management by multidisciplinary and primary care teams in addressing an array of health and developmental matters—specifically, the need for metabolic specialists to initiate referrals to health, educational and community resources and to communicate information about those referrals to the primary care team. Of the respondents, 68% (M) and 76% (P) said they felt appropriate referrals were made and that they received adequate communication about those referrals.

Ninety-four percent (M) and 90% (P) indicated overall satisfaction with communication, collaboration and services provided (Questions 8, 11 and 12). Comments indicated that specialists from the multidisciplinary team were “very responsive and helpful.” Respondents also appreciated the ongoing interaction with specialty providers and patients and their families during and between specialty visits.

Sixty percent (M) and 43% (P) of respondents indicated a desire for more information about specific metabolic conditions (Question 13).

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Discussion

Survey respondents expressed a high level of overall satisfaction with the quality of metabolic specialty services their patients received. Results indicated effective specialty referral processes. The most common reason cited by the respondents for specialty referrals is to obtain information about diagnosis or treatment.¹⁰ Respondents reported that receiving calls and written information from the specialty team early in the referral process may help to convey the complexities of IBEM diagnoses and the intricacies of management plans. Communication at the time of or prior to the specialty visit can improve care coordination and result in a visit that better meets the needs of the family.¹¹ Primary care providers want to have a collaborative relationship with the specialists who care for the patients they refer.^{3,12} Cooperative management, an indicator derived from the Center for Medical Home Improvement's original Medical Home Index, emphasizes the importance of clarifying co-management roles among families, primary care providers and specialists, and determining how feedback should be shared.¹³

Kinchen et al. proposed that when primary care physicians are familiar with physicians at a specialty clinic it may increase communication;¹⁴ this potential bias is a limitation of our study. Studies that are limited to a single multidisciplinary metabolic center may produce results that cannot be generalized to other centers that manage children with IBEM.

Emergency care planning for children with rare metabolic disorders and other chronic conditions is important to improving patient outcomes.¹² Responses to Question 7 (“I have re-

ceived a copy of this child's emergency medical alert letter”) are of particular interest because of the importance of appropriate co-management of potential metabolic crises related to acute illness, injury or other emergency situations. Having an emergency information form that is shared with the patient and his or her family, their specialty providers and their primary care provider is one way to communicate recommendations regarding emergency assessment and intervention. Use of such a form has been supported by the American Academy of Pediatrics, the American College of Emergency Physicians, and the Maternal and Child Health Bureau. Responses to our survey indicated the need for improvement in communication about emergency planning for children with IBEM. This feedback prompted revision of written emergency protocols to better define signs and symptoms of concern, condition-specific complications, and immediate assessment and treatment needs. In response to the need for improved emergency communications, the Pediatric Metabolic Clinic continues to support patients' use of a web-based emergency information form that is easily accessible by families, primary care teams and specialty providers.¹⁵

One practice change at the specialty clinics prompted by our survey was the reformatting of written reports that are typically sent to both primary care providers and families after each outpatient clinic visit. Reports now include the metabolic management plan (dietary modifications, medication changes, laboratory and/or imaging recommendations, genetic counseling and other suggested referrals, and follow-up plans) at the beginning, where it can be quickly noted, rather than at the end. The follow-up specialist at the Minnesota Department of Health newborn screen program also provides primary care providers with information about specific resources shared with their patients and/or the metabolic specialty clinics, thus further promoting comprehensive and collaborative co-management.

Our surveyed respondents wanted to see copies of the condition-specific educational information provided to families of children with IBEM during specialty team visits. They also indicated a desire for more in-depth information about these rare metabolic conditions. In response, the Department of Health now sends the primary care providers a STAR-G summary describing in greater detail the child's particular IBEM.¹⁶ Primary care providers also receive a one-page fact sheet on the specific condition along with the ACT sheet at the time a positive newborn screening result is reported.¹⁷

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Conclusion

Responses to our survey prompted changes at specialty clinics aimed at improving the quality and coordination of care for children with rare metabolic conditions. They also provided the Minnesota newborn screening program with information regarding the quality of communication and level of collaboration between metabolic providers and primary care providers and prompted development of new provider education activities. Future research focused on the families of children with IBEM

would inform health care providers and newborn screening programs about whether the degree of collaboration between multidisciplinary metabolic specialty clinics and their primary care providers is meeting their needs. **MM**

Carolyn Stady Anderson and Nancy Vanderburg are with the Minnesota Department of Health. Kristi Bentler and Susan Berry are with the department of pediatrics, division of genetics and metabolism, University of Minnesota Amplatz Children's Hospital.

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Contrasts

By Kathie Culhane-Pera, M.D., M.A.

A dark-skinned rough-faced massive man,
Whom, if we met on the street, I would not want to ignore,
For I would not want to feel my prejudices, or be perceived as prejudiced,
But whose eyes I would avoid nonetheless,
Conditioned as I am to avoid potentially dangerous men before I know their danger.

A dark-skinned street-wise disheveled man
Who is bent over, crying in his pillow.

A dark-skinned wrinkled-faced agonized man
Whom I crouch on the floor with so we can be face-to-face,
Whom I listen to,
Whose suffering I feel.

I cry with him—my tears filling my eyes and his tears glistening on his face.
I reach out, to connect with his agony.
I touch his arm, to relieve the weight of his suffering.

Who am I to be present for him?
A light-skinned fair-haired thin doctor, a few years older than he
Who has not faced her own mortality,
Who has not given up hope of a loving God.
But a fellow human being who is present.

For that, he thanks me.
And I thank him.

Kathie Culhane-Pera is a family physician at West Side Community Health Services. She is currently conducting research and teaching in Thailand on a Fulbright Scholarship.