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BIOMEDICAL INFORMATICS: A NUMBERS GAME TO IMPROVE HEALTH
Welcome to the World of Biomedical Informatics

In this issue of UNMC Discover, we introduce you to the world of biomedical informatics, which translates information into knowledge.

Biomedical informatics has become critical to the conduct of science and improved clinical care. It has redefined how we can look at small gene differences and predict how a person might respond to a specific medication. It allows us to identify new relationships between proteins or genes that we never knew existed before. It allows us to better predict how many people have diabetes now and may have diabetes in the near future. It helps us find new ways to deliver health care and what areas of the country might benefit the most. As a result, the vocabulary that goes with biomedical informatics and general approaches have become important to many health professions as well as research education programs. And there is a critical need to rapidly expand the number of faculty and trainees proficient in biomedical informatics focused on many different areas.

You will learn about people working in biomedical informatics, which is often divided into three areas:

- **Bioinformatics** — the study of scientific and laboratory data, like genes or proteins;
- **Clinical or health informatics** — the study and use of health information for patients or patient care, and;
- **Public health informatics** — the study and use of population or community health data to understand and make population or health system level decisions.

With this background, UNMC has to rapidly increase the number of investigators and collaborators with the skills needed to work on all types of research and with all types of researchers, as well as health practitioners and public health experts.

In this issue, we also will introduce you to comparative effectiveness research that uses biomedical informatics to help us make better choices among available health care options.

Because of its importance, UNMC will continue to recruit and train scientists with skills in biomedical informatics, as well as build organizational structures that enhance intercampus interactions, as much of our research already does. With this expertise, we will be able to evaluate ever more complex scientific health questions for the benefit of all.

Jennifer Larsen, M.D.
UNMC Vice Chancellor for Research
FALL 2013

ON THE COVER:
Biomedical informatics uses patient’s medical data to improve health care.

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Most of us know BMI as body mass index. But, for medical researchers, it represents the evolving world of “biomedical informatics,” which is transforming science before our eyes.

The American Medical Informatics Association, the premier organization focused on biomedical informatics, defines it as the use of biomedical data, information and knowledge to understand science, solve problems and make decisions, to improve human health.

Simply put, it’s using computers to make sense of the mountains of data generated by a myriad of medical tests and research.

It connects computer science, medicine, biology and health care, and creates a synergy that goes beyond anything that researchers in any single domain can provide.

The domain encompasses three major sub-fields: clinical, biology and public health. It can move basic research findings from bench to bedside, evaluate interventions across communities and assess the impact of health innovations on health policy. In short, it translates numbers into solutions.

To understand how overwhelming this data can be, it’s important to first understand the complexity of the human DNA.

Human DNA, the code of life, is made up of four chemicals, A, G, C and T, and consists of about three billion bases — more than 99 percent of those bases are the same in all people and link to make 23 pairs of chromosomes.

The Human Genome Project estimates that humans have between 20,000 and 25,000 genes. Every person has two copies of each gene, one inherited from each parent.

The first time a genome was sequenced, it took hundreds of scientists 13 years and $3 billion to complete. Now, the same thing can be achieved in two days for about $5,000 using UNMC’s Illumina 2500 sequencer, the most robust sequencer in the world. A team of people and an extremely powerful computer would now require two days to analyze the data.

Consider this — in the course of your lifetime, you will generate massive amounts of medical data from medical records, genetic tests, X-rays images, CAT scans, MRIs and tissue samples — all of which is being digitized and takes an enormous amount of computer space.

A slide that contains a single slice of tissue equals 1 terabyte of data — that’s 1,000 billion pieces of data.

Now, magnify that by the tens of thousands of patients seen each year in one hospital, the hundreds of thousands of operations performed and the 350 million people in the United States who seek medical care.

For comparison, Wal-Mart, a retail giant, handles more than one million customer transactions every hour, feeding databases estimated at more than 2.5 petabytes — the equivalent of 167 times the books in the United States Library of Congress (1,000 terabytes equals 1 petabyte).

Twenty years from now all patient medical records will be in digital form to allow researchers and physicians to cross reference disease risks and preventative treatments and expand their ability to use the patient’s DNA to customize treatment.

Along the way, we must find ways to manage the mountains of data. Enter a new breed of computer scientists who understand computer science and program analysis, can translate a researcher’s hypothesis into algorithms and knows how much a geopbyte (a one followed by 30 zeroes) is.

With the help of genetics, math and data computation, researchers can look for patterns in diseases and treatments that help physicians tailor treatments to individual patients and also safeguard populations.

Researchers can compare DNA profiles of thousands of people to find candidate genes and then use prediction algorithms of known protein interactions to identify new interactions between proteins previously thought unknown to each other.

The science of biomedical informatics is about investigators who can make those connections from all that data in the electronic health records, the human genome or across several genomes, between proteins and public health documents.

These stories will begin to demonstrate how informatics has become integral to medical research and ultimately, clinical care.
All over campus, UNMC scientists are using comparative effectiveness research. It’s a science that looks at large data sets, or uses meta-analysis, to evaluate health outcomes. It compares different interventions and strategies to prevent, diagnose, treat and monitor health conditions.

For example:

- In rheumatology and immunology, James O’Dell, M.D., also in his role as chief of the Veterans Administration Nebraska-Western Iowa Health Care System’s Omaha medical center, and his colleagues, authored a study comparing the effectiveness of drug therapies for rheumatoid arthritis.

- In the School of Allied Health Professions, Katherine Jones, Ph.D., and her team study a theory-driven, longitudinal evaluation of the impact of team training on safety culture in hospitals.

- At the College of Public Health, Preethy Nayar, Ph.D., has two projects comparing outcomes and costs of care with different treatment modalities for elderly pancreatic cancer patients. Drs. Chandra Are, Fang Yu, Ph.D. and James Schwarz, M.D. are co-investigators.

- Fausto Loberiza Jr., M.D., is part of a multicenter study testing whether programs improve depression and health-care adherence in hematopoietic stem cell transplant survivors.

And there are more.

“In a typical randomized clinical trial (RCT) a comparison is made between people taking an active drug and those taking an inactive placebo. The question we want to answer is, ‘can the drug work? Is it better than placebo?’” said Gary Cochran, Pharm.D., assistant professor of pharmacy practice.

“But we’re trying to answer a broader question. If there are several treatments, which is best and for which group of people?”

Oftentimes this requires a different type of study design. “Typical” RCTs are meant to determine whether a drug is efficacious and are required for drug approval. Comparative effectiveness research (CER), in contrast, is used in real-life conversations between patients and their health care providers. Based on what we know, which treatment is likely best for you? How can narrowing down all of this knowledge be used in my individual treatment plan?

“Dr. O’Dell continues to address the most important questions pertaining to rheumatoid arthritis, the questions that matter most to patients. What therapy is best?” said David Wofsy, M.D., past president of the American College of Rheumatology. “In a field that has largely avoided comparative effectiveness trials since the advent of biologic therapies, the triumph of O’Dell’s team has been to replace hype with data that compel us to challenge conventional wisdom and keep an open mind. That is clinical science at its best.”

To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations.

Investigators can look at several variables — age, gender, genomics, ethnic group. They can pool data from previous trials, even tap into hospital and insurance data sets.

Thus, they can get an idea of what will work not just for the people carefully selected for a study group — but all kinds of people.

You’re probably not going to get as precise an answer as you would with a single clinical trial. But then, that isn’t the goal.

“If you’re a physician treating a patient with high blood pressure,” Dr. Cochran said, “you can’t just throw up your hands and say ‘I don’t know.’ CER compares all of the relevant treatment options and provides patients and clinicians with evidence-based information to help select the best treatment option for the individual.

“So, when the doctor and the patient have that conversation, where do we start? What’s the evidence out there? We pool all of our data, we look at people like you … and identify the treatments most likely to work.”
Julie Oestreich, Pharm.D., Ph.D., knows prescription drugs don’t work the same for everyone.

But, she wants to better understand how genes influence individual drug responses so doctors can prescribe the drug and dosage that works best for the patient being treated.

“I want to know how medicines work and how they change the body to create good — and to sometimes cause harm. Throw genetics into the picture and it’s an interesting and important area of study.”

Although the field of pharmacogenomics is relatively new, it has the potential to one day eliminate the “one size fits all” medicinal approach and lead to more effective, safe medications and doses tailored to a person’s genetic makeup.

The use of genetic information to guide treatments is growing as physicians better predict who will benefit from a drug, who will not respond at all or who will experience a negative side effect.

An assistant professor of pharmacy practice in the College of Pharmacy, Dr. Oestreich (pronounced ace-try) researches personalized anti-platelet therapy (which medicines, and how much, work best) and genetic tests for risk factors for cardiovascular events among the area’s American Indian population.

She drives to Martin, S.D., and its surrounding area to find and interact with her research participants. Together, the UNMC team collaborates with Lyle Best, M.D. and Turtle Mountain Community College at Belcourt, N.D. Both entities also work with Missouri Breaks Industries Research Inc., which is American Indian-owned and has offices on both the Pine Ridge and Cheyenne River Sioux Reservations in South Dakota.

The project goes through not just UNMC’s Institutional Review Board (IRB) but one with the tribe itself, and one with the Aberdeen Area Indian Health Service.

Dr. Oestreich previously had been interested in the variability of platelet function and response to antiplatelet agents with regard to protecting people from adverse cardiovascular events. She was intrigued by the idea that ethnicity might be one factor in this variability.

After studies with a small group of American Indians, the team now plans to expand its research to a larger population and further test whether genetic variants impact drug response. Finding answers, she knows, will benefit patients far into the future.

“We don’t want to leave a population behind,” she said.
Imagine asking a question and getting 30,000 answers coming at you like water from a fire hose.

How would you sort through all that information and find the one answer you’re looking for?

Babu Guda, Ph.D., an associate professor in the department of genetics, cell biology and anatomy at UNMC, knows how.

Enlist the help of a computational biologist who runs a data coordination center and can categorize, sift through and bring some sense of order to all that information. As director of the Bioinformatics and Systems Biology Core Facility and as the principal investigator of a National Institutes of Health-funded computational biology lab, Dr. Guda is well versed in how to help researchers find what they are looking for when it comes to data.

“Data output from biology experiments has exploded in the past 10 years,” Dr. Guda said. “Before, people worked with one gene and generated a small amount of data, but now with advances in technology they are getting results they can’t possibly analyze manually.”

With a background in molecular biology combined with formal training in computer science, Dr. Guda is uniquely positioned to help researchers weed through the plethora of data generated.

“We are not looking for a needle in a haystack; rather we are looking for pieces of a needle in a haystack that we hope to use to assemble the needle,” Dr. Guda said. “Finding all the pieces of the needle is our biggest challenge.”

Dr. Guda has collaborated on several projects at UNMC, including the Nebraska BioBank led by Jennifer Larsen, M.D., vice chancellor for research; the National Neuro Aids Tissue Consortium — Data Coordination Center led by Howard Fox, M.D., Ph.D., senior associate dean for research in the UNMC College of Medicine; and the Agenda pilot project on breast cancer genomics led by Ken Cowan, M.D., Ph.D., director of the Fred & Pamela Buffett Cancer Center and the Eppley Institute.

In addition, his group collaborates on scores of research projects led by individual researchers from different clinical and basic science departments.

“We give investigators an understanding of their data by helping them formulate the right questions that draw out what they are looking for in their research,” Dr. Guda said.

Dr. Guda came to UNMC in 2010 from SUNY at Albany in New York to start the core facility. Since then, he has collaborated with numerous investigators on a variety of projects from neuroscience to cancer research to analyzing the rapid autopsy pancreatic cancer data with Tony Hollingsworth, Ph.D., professor and director of pancreatic cancer research in the Eppley Institute.

He works with Dr. Hollingsworth to identify patterns in the cancer genomes that are unique to pre-metastatic conditions compared to metastatic conditions in pancreatic cancer patients.

“We look at the complete exome of one patient, mapping the affected genes in pre-metastatic and metastatic samples and see exactly which genes are differently altered in each stage and the effect these alterations have on the cell in relationship to the progression of the cancer,” Dr. Guda said.

One of the goals of this type of research is providing the researcher computational tools that helps them identify the specific subtypes of a cancer (applicable to most of the cancers), which will help lead to individualized medicine, and directed drug therapy, he said.

“If we could meet these goals, it’s personalized medicine at its finest.”
leukemia was his research niche until five years ago when breast cancer hit too close to home for San Ming Wang, M.D.

A relative’s wife had just been diagnosed with the disease; her mother and two aunts also had the disease.

Dr. Wang, associate professor of genetics, cell biology and anatomy, decided to switch his research to familial breast cancer after joining UNMC in 2010.

Now his research challenges the status quo approach to identifying breast cancer in families with a genetic link.

He received support from the Eppley Institute for Research in Cancer and Henry Lynch, M.D., who provided access to his vast DNA bank, which is one of the nation’s best collections of DNA from familial cancer patients.

Globally, breast cancer is the most frequently diagnosed cancer in women, with an estimated 1.38 million new cases per year. Worldwide, there are 458,000 deaths per year from breast cancer, making it the most common cause of female cancer death in both the developed and developing world.

Nearly 20 years ago, mutations in two genes, BRCA1 and BRCA2, leading to breast and ovarian cancer, were identified. In BRCA 1 families, up to 80 percent of the family members who inherited BRCA1 mutations will develop breast cancer by age 70. Since then, genetic causes for 30 percent to 40 percent of women with familial breast cancer have been discovered — with BRCA 1 and BRCA 2 being the most common ones. One troubling finding, Dr. Wang said, is that with each passing generation, the age of cancer occurrence can come earlier and the numbers of genetic mutations can increase.

“Most studies focus on finding mutations shared among different disease families. But this approach has not made significant progress after almost 20 years of practice.”

In a study that was published in October’s issue of The Breast Journal, Dr. Wang and his research team used exome sequencing — which targets 20,000 or so protein-coding genes in a human genome — and discovered that KAT6B, a gene playing important roles in epigenetic modification, was mutated in two generations of a family. But, five members affected by breast cancer carried normal BRCA1 and BRCA2 genes. The gene is known to be associated with many types of genetic diseases, but never with breast cancer.

“Our data shows it’s very likely that many families have different mutations related with the disease, which supports our concept that ‘same disease, different causes’ may be a better model to study the genetic cause for familial breast cancer,” Dr. Wang said.

Based on the strength of his initial results, Dr. Wang received a two-year, $400,000 grant from the National Institutes of Health. He will continue to study the families to look for genetic predispositions — and identify resistant mutations.

“What’s puzzling is that about 20 percent of the family members who also carry the mutation won’t get the disease,” he said. “We call this phenomenon breast cancer resistance. The presence of a genetic basis for resistance could lead to a new direction in breast cancer study. If we can identify resistance genes, we will be able to understand better the mechanisms of breast cancer and use the knowledge to block the early development of breast cancer.”

To become part of a cancer study, call:

Liz Fleissner
Clinical Study Nurse Coordinator
Breast Cancer Collaborative Registry
Fred & Pamela Buffett Cancer Center
Eppley Institute for Research in Cancer
Phone: (402) 559-8160 (Wed)
(402) 596-3129 (Th-Fri)
22-YEAR-OLD SEES PROMISE IN BREAST CANCER RESEARCH

by Vicky Cerino

It’s not often that those affected by breast cancer come face to face with researchers trying to find a cure for the disease.

It was an emotional experience for Brandi Preston, 22, and breast cancer researcher, San Ming Wang, M.D., associate professor of genetics, cell biology and anatomy, when they met after he spoke to Bright Pink, a support group for those affected by familial breast cancer.

“I use DNA material from patients to study, but that was the first time I had direct contact with patients,” Dr. Wang said. “I learned from them all how psychologically stressful it is to have a breast cancer gene — like carrying a time bomb. It was a good experience.

“What we’re doing is trying to save peoples’ lives in the long run. It’s not so simple anymore to think of my research work as just science. I hope our observation can be applied to benefit patients as soon as possible,” Dr. Wang said.

Preston said meeting Dr. Wang gave her hope for the future.

Preston’s genes means she has decided to get a double mastectomy.

The women in Preston’s family have a history with the BRCA 1 gene, which was carried by her mother, grandmother, great-grandmother and great-great-grandmother. Breast and ovarian cancer struck the two oldest generations and skipped the grandmother.

But, Preston’s mother was diagnosed with breast cancer and died at the age of 40. Two years earlier, the family found out there was a test to see if the cancer was hereditary. Before she died, Preston’s mother asked Brandi to get tested when she turned 19. She did, and was found positive for BRCA I.

Physicians and preventive care are now part of Preston’s life. Every six months she gets a breast exam, then an annual breast MRI, ovarian screening and a pap smear.

“If my mom had known she had this gene, she could have done so many things,” Preston said.

Preston wants others to know about Bright Pink, the only national non-profit organization focusing on the prevention and early detection of breast and ovarian cancer in young women.

“There’s an 87 percent chance. “After each breast exam I say ‘whew, no cancer, I’m good for another 6 months.’ But why wait until I develop it? That’s why I’m having the double mastectomy. It’s better to be proactive with my health rather than reactive.

“I look forward to watching Peyton participate in school activities, graduate high school, go to college, get married and start a family. All things my siblings and I didn’t get to experience with our mother.”

On the day of her operation, Preston’s entire family will be on campus for support and to participate in a comprehensive genomic study that crosses multiple generations. “This is a rare opportunity to study the genetic basis of familial breast cancer in one family,” Dr. Wang said.

Preston wants others to know about Bright Pink, the only national non-profit organization focusing on the prevention and early detection of breast and ovarian cancer in young women.

“No one really knows what it is like to have this gene,” Preston said. “Bright Pink empowers us to reach out and help others. Before, we just waited to hear about new research studies.”
As information technology becomes more integral to health care, the need grows for specialists who can turn biomedical data into knowledge that will improve people’s health and wellbeing.

That’s why earlier this year UNMC and the University of Nebraska at Omaha (UNO) integrated three programs to offer master’s and doctorate degrees in biomedical informatics. The multidisciplinary, interprofessional biomedical informatics program is unique as it joins the bioinformatics program from the UNO College of Information Science and Technology and the UNMC Health Informatics Program and the UNMC Bioinformatics program and uses faculty from both universities.

“We pulled all the informatics programs together under one umbrella, leveraged expertise and opened the door to training and research grants,” said Jim McClay, M.D., biomedical informatics program director and associate professor of emergency medicine at UNMC.

Individualized programs of study accommodate students’ existing knowledge and career goals around the four areas of biomedical informatics:

- Clinical informatics: Dr. McClay leads work on advanced design of clinical information systems and mining electronic health records;
- Bioinformatics: Babu Guda, Ph.D., associate professor in the department of genetics, cell biology & anatomy, leads the UNMC Bioinformatics and Systems Biology Core studies intracellular processes;
- Public health informatics: Ashish Joshi, M.D., Ph.D., assistant professor, Health Services Research & Administration, designs systems to promote and protect the health of communities, improve public health systems and deploy information technology internationally; and
- Translational research informatics: integrate biological and clinical discoveries to improve health care.

“Without collecting and processing data, medical practice is like looking for a needle in a haystack,” McClay said. “We can’t continue to advance medicine and population health without collecting and processing data.”

Jim McClay, M.D., (left), said that Scott Campbell is an example of the perfect biomedical informatics student. Dr. Campbell received his Ph.D. at the end of 2012 and today is assistant professor of pathology/microbiology and director of the Public Health Informatics & Path Lab Informatics.
analyzing the large amount of data generated during biomedical research and health care. Biomedical informatics seeks to organize, analyze and interpret this data generated to improve human health,” Dr. McClay said.

The program is multidisciplinary, he said, and attracts applicants with training in biology, research and clinical medicine, computer science, statistics, engineering and related disciplines.

The perfect student, he said, is “passionate about using information management to advance biomedical science to create insight for health care providers on a global scale in a collaborative environment.”

The program has been a dream ever since Dr. McClay arrived at UNMC in 2001. With a background in physics and engineering and a Harvard University fellowship in bioinformatics, he immediately developed a health informatics program and pushed for an integrated biomedical informatics program. The new biomedical informatics program, with eight students in its inaugural class, will continue to grow.

Scott Campbell, Ph.D. sees the benefits. He was 44 when he started work on his Ph.D. in biomedical informatics at UNMC. That was in 2009 when the program was under the Medical Sciences Interdepartmental Area.

Dr. Campbell completed his Ph.D. at the end of 2012 and today is assistant professor of pathology/microbiology and director of the Public Health Informatics & Path Lab Informatics. “As a non-traditional student (in the program), I had the great benefit of life experiences and could readily apply what I learned.”

Dr. Campbell works with digital microscopes (whole slide imaging) to capture, step-by-step, the information that a pathologist looks for — patterns, architecture of cells, tissue morphology — and give it a name that a computer could understand as a means to record physicians microscopic findings at the time of discovery. This information can be used to complete the diagnostic report and satisfy the additional administrative uses for the data.

Computers can detect subtle cell differences unseen by the human eye. By digitally capturing tissue features associated with pathology diagnoses, computers can be used to expand the range of diagnostic analytics to allow pathologists to catch diseases earlier and suggest individual treatment changes.

“This is all geeky stuff, but practical too,” Dr. Campbell said. “It’s applied science and the research continues to justify itself by producing practical outcomes.”

Now, he wants to develop ways to make pathologist microscopic findings understandable to a computer by using SNOMED-CT (Systematized Nomenclature of Medicine - Clinical Terms).

“This will help develop clinical decision support systems for pathologists and improve the efficiency of completing burdensome administrative functions associated with pathology report writing.”

“We pulled all the informatics programs together under one umbrella, leveraged expertise and opened the door to training and research grants.”

Jim McClay, M.D.
There is the old joke about not being able to walk and chew gum at the same time. But there’s something to it, scientifically, said Dawn Venema, Ph.D., assistant professor of physical therapy education. As a clinician, she saw it all the time. Now she studies it.

When she was a physical therapist in the field, she worked with geriatric clientele, and with some, she noticed, “People literally couldn’t walk and talk at the same time.” Those who were frail, or had dementia, “Their cognitive resources had to be focused on walking,” Dr. Venema said. Or they might fall. They could not afford any distraction from that basic task.

When Dr. Venema joined the faculty at UNMC it seemed like a natural line of research. She collaborated with Joseph Siu, Ph.D., who was then at the College of Public Health and now her next-door neighbor in PT. He’s also studied dual-task costs — how it affects us when we do two things at once. Like texting and driving?

“It’s the same thing,” Dr. Venema said. “As much as we like to think we can multitask, the quality of the task suffers as we try to do more than one thing at a time.”

But even more so among older adults who have dementia: “Their dual-task cost is really great because they don’t have as many cognitive resources to draw on,” Dr. Venema said. And that’s part of why those with dementia move so slowly, and are more prone to falls.

Drs. Venema and Siu did a study, published in the Journal of Geriatric Physical Therapy. They found that older adults doing a walking test were slowed when asked to simultaneously complete a cognitive (counting/math) task. The results were more dramatic among patients who started off with lower cognitive scores.

But, interestingly, no one completely shut down, mentally or physically.

“Perhaps we can challenge people with dementia more than we think,” Dr. Venema said. And that led to a second pilot study of physical therapy/cognitive training among a small group with dementia: those given “easy” cognitive tasks improved on about half of their outcomes; but those in the “hard” cognitive-task group improved on all outcomes and by greater margins.
So maybe there’s hope.
They aim to expand to a full study, but they need more enrollees with dementia, whose families would need to give permission. Those spots are understandably tougher to fill.

For information about the study, call 402-559-6594 and for further information on clinical trials please call the Research Subject Advocate Office at 402-559-6941.
They say knowledge is power.

But, what do you do with that knowledge?

Julia Houfek, Ph.D., professor of community-based health in the College of Nursing, is interested in how people understand and think about their health care conditions, what they have to do to stay well or get better.

So with the emergence of an easy and relatively inexpensive genetic test for a gene that has been linked with nicotine dependence, cigarette smoking and lung cancer — the nicotinic acetylcholine receptor gene known as CHRNA3 — Dr. Houfek couldn’t help but wonder: How are people going to understand and use this information?

“This has real clinical value in the long run,” she said, “because more and more people are going to be in a situation where some type of genetic information is being used to make decisions about their health care.”

So Dr. Houfek, a specialist in psychiatric mental health nursing, embarked on an effort to find the answer. The study was not a smoking cessation project — the primary purpose was to determine the impact of providing smokers with an understandable educational session about genetic contributions to smoking and personal genetic information related to smoking.

With a genetic test for a specific area of the CHRNA3 gene now being offered commercially through websites such as “23 and Me” or “Decode Me,” Dr. Houfek arranged with the Munroe-Meyer Institute for Genetics and Rehabilitation lab to do this test on her research participants — an experimental group of 12 with another control group of 12.

Participants were tested for the specific CHRNA3 area, which can be found in three forms:

- CC allele, not related to an increased risk for nicotine dependence;
- CT allele, which puts people at a slightly higher risk; and
- TT allele, which has been linked to early adoption of smoking and higher incidences of nicotine dependence.

They then met with Gwendolyn Reiser, MMI genetic counselor, for genetic counseling.

“Interestingly, almost everyone in both the control group and the experimental group believed testing would show they had the TT allele that made them genetically predisposed to smoking,” Dr. Houfek said.

“We wanted to see how people would respond, first, to having the test offered. But our big research questions were ‘How did they understand the information’ … and then ‘How did they use the information in terms of cigarette smoking, especially quitting?’”

Dr. Houfek also hoped that in the long run, the results of the study would be used to develop patient-education materials and help health care professionals learn how to discuss genetic test results with their patients.

The study results showed that people are not afraid to learn more about their genes. Of the 12 participants in the experimental group, 10 came back for their results. And after the study was concluded, the 12 members of the control group were offered their results as well; nine of them came back for the information.

The people in the study — Dr. Houfek called them the “early adopter group” — were interested in the genetics of smoking.

“They were interested in getting their results, and they were invested enough in the study that most completed the follow-up data collection,” she said.

Dr. Houfek was pleased with the results.

“People understood the information, and we got excellent feedback about what they understood and what they didn’t understand.

“We looked for any psychological distress related to receiving personal genetic testing. Of course, genetic testing and the possible implications of the test can cause anxiety, especially if there is a history of a genetic disorder in a family. But the people in this study felt the test was a good thing and that it was useful for making decisions about their health care.”

Dr. Houfek expects that this study will have wide-reaching implications for the future of genetic testing, especially for smoking cessation.

“Eventually, genetic testing will become a part of normal care,” she said. “People will get genetic tests to help guide their health care decisions. As genetic testing becomes more common, we need to be prepared to help people understand what the information means and how to use it.”
information, especially results that put a person at higher risk." But no matter what form of allele presented, subjects put a positive spin on knowing the results.

“They were glad they had the information, and they expressed their intent to use the information to stop smoking,” Dr. Houfek said. The people who were not at higher risk for nicotine dependence genetically reported that they would use the information to go forward with a smoking cessation program. And even the people who got the higher risk allele said they would make use of the knowledge by looking for a more structured or professionally run smoking cessation program.

Another finding: Nearly everyone who returned the post-study questionnaire reported that they had talked with their health care provider about smoking cessation; some had smoking cessation medications.

“The people in the project made an effort to use the information to further their smoking cessation, which is a process,” Dr. Houfek said. Now, Dr. Houfek is considering her next steps.

“Some of the published literature says that giving smokers genetic risk information doesn’t necessarily help them quit, so this shows the complexity of using genetic risk information to change health behavior,” she said.

“For smoking cessation, we need to explore if incorporating personal genetic risk information into active counseling by health care providers is helpful to increase quitting behaviors and also long-term cessation.”

Dr. Houfek noted that many genes are involved in nicotine addiction and smoking-related diseases.

“As more genetic tests become available, we will explore how people understand and use information about the multiple genes involved in determining health risks,” she said. “It is likely that the risk will be presented in some type of score—but it will be important that people understand the genetic information behind the score.”

She’s excited to help people learn to understand and use these increasingly available avenues of information.

“That is why this work is so important,” she said. “We are learning how to present information and answer questions, and in so doing we will help people learn how to use this information to improve their own health.”

At MMI, Warren Sanger, Ph.D., director of cytogenetics, facilitated the project while Janet Williamson and Erin Kaspar worked on genotyping. Stephen Rennard, M.D., professor of pulmonology; Tricia LeVan, Ph.D., associate professor of epidemiology; Gwendolyn Reiser, MMI genetic counselor; and Victoria Graeve-Cunningham from the College of Nursing, helped design the study. It was funded by LB 506, the Nebraska Cancer and Smoking Disease Research grant.

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In the marathon to obtain both M.D. and Ph.D. degrees, there are moments when one wonders if he or she should keep going. “When everyone graduates from medical school and you’re sitting in a lab and your experiment failed,” said Allison Cushman-Vokoun, M.D., Ph.D., assistant professor and medical director of molecular diagnostics in the department of pathology and microbiology. “It’s not such a fun day.”

But as you can see by her title, she persevered. Those who take on the M.D./Ph.D. track tend to have that kind of drive. UNMC’s M.D./Ph.D. Scholars Program turns out graduates who have not only the desire to help patients clinically, but also the drive and curiosity to tackle deeper questions. It’s the perfect track for becoming a physician-scientist.

UNMC is invested in turning out more physician-scientists. “These particular scientists are key translators,” said Jennifer Larsen, M.D., vice chancellor for research. “Not only between branches of science investigation but between groups of investigators — clinical and basic science. Without investigators trained in both, our laboratory research takes a lot longer to move toward clinical application.”

The demand for these physician-scientists has prompted UNMC to expand its program from 18 students in 2007 to 32 students today. Students have their medical school paid for by the College of Medicine and UNMC, and graduate school costs are picked up by respective departments and faculty extramural funding. The program is working toward becoming a National Institutes of Health Medical Scientist Training Program to obtain additional support. The goal is to alleviate medical school debt so graduates can have time in their careers to devote to research.

The program is a tough grind — typically two years of medical school, then, three or four years of the Ph.D. program, followed by the last two years of M.D. Then residency. Maybe a fellowship. Twelve years minimum.

But it’s been worth it, program graduates on faculty said, to have the backgrounds they have, to be able to do the kind of work they wanted to do. “The combination of the two does give you a unique perspective,” said Dan Anderson, M.D., Ph.D., assistant professor of cardiology. “I’ll find myself at clinical conferences, asking, ‘What could we do to understand the molecular biology of this?’ Or, we’ll be looking
at the molecular biology and I’ll think, ‘Oh, that makes sense clinically.’ ”

That’s the kind of translation Dr. Larsen encourages.

And the students in the program already are thinking in terms of translation: “My hope is that I will be able to use my engineering training to solve problems I encounter in the delivery of health care while treating patients,” said Jake Riggle, who is in his sixth year of the program. “This could range from the creation of a surgical tool to the development of a training program for residents to the analysis of current medical interventions.”

“Graduates from the program have spread across the country,” said Shelley Smith, Ph.D., program director, “carrying the name of UNMC.”

To qualify for the M.D./Ph.D. program

So, how does one get into UNMC’s M.D./Ph.D. Scholars Program?

The qualifications of scholars currently in the program are comprised of a mean MCAT score of 32 and undergraduate grade-point average of 3.71.

Hopefuls must first apply to med school, filling out a primary application from the American Medical College Application Service (AMCAS). There’s a spot to indicate you also are applying to an M.D./Ph.D. program. From there, applicants will receive a secondary application from UNMC.

Those who make it past that round will come to campus for a Wednesday-through-Friday process, which alternates between more informal get-togethers with current scholars and mentors, and formal interviews. In 2011, UNMC had 47 applications, and interviewed 21 candidates. The number of openings each year can vary, but there are currently 32 scholars in the program.

And yes, midway through med school, a promising student can decide to change course, and apply to the M.D./Ph.D. track. For those accepted, all schooling is paid for. But program alumna Allison Cushman-Vokoun, M.D., Ph.D., said “Do it because you have the drive and initiative to attack problems from both the clinical and scientific perspectives, not for the money.”

After all, if you started earning a salary instead, for the number of years it takes to earn a second degree, “in the long run,” she said, “it probably all evens out.”

“These particular scientists are key translators. Not only between branches of science investigation but between groups of investigators — clinical and basic science.”

Jennifer Larsen, M.D.
Physicians had lost hope for 65-year-old Randy Whisnant of Morganton, N.C., advising him and his wife, Quteen, that it was time for hospice.

Quteen, however, refused to accept that nothing else could be done to stop the aggressive stage IV mantle cell lymphoma from spreading in her husband. Diagnosed in 2010, Randy had extensive chemotherapy and radiation, which only partially eliminated the cancer.

Then, one day a friend told her to take Randy to Nebraska.

“I immediately searched the Internet, found Dr. (Julie) Vose and left a message. I didn’t even know where Nebraska was.”

The next day, Randy’s disease took a serious turn. In the emergency room, three quarts of fluid (caused by tumors) were removed from his stomach. The physician recommended hospice.

Quteen held her ground. “We’re going to wait for the call from Omaha.”

When the call came, family and friends worried about logistics. There were tickets to buy and arrangements to make for motel and transportation. Quteen answered with dogged determination: “There’s always a way.”

Still, Nebraska felt like the end of the world for a couple who had never flown or ventured far from their home state. “Here we are in our 60s and now we’re traveling,” Quteen said.

When they arrived in Omaha, Randy couldn’t breathe well. His stomach was so swollen he couldn’t walk and he was confined to a wheelchair. Sleeping and lying down were problematic.

They met with Julie Vose, M.D., chief of the division of hematology and oncology and Neumann M. and Mildred E. Harris Professor. After an evaluation and tests, Randy qualified for an experimental drug study with Ibruitinib.

To participate, he needed medication, monitoring and tests every three weeks — up to 40 times over the course of treatment — in Omaha.

“This drug is so promising that the Federal Drug Administration gave it fast track designation, which rarely happens,” Dr. Vose said. “Patients who’ve been on the treatment have had remarkable results with limited side effects.”
Before its approval in November, the FDA had designated ibrutinib as a breakthrough therapy. The designation is intended to expedite the development and review of drugs for serious or life-threatening conditions that demonstrate the drug may have substantial improvement over available therapy. UNMC was one of 18 sites in the U.S. testing the drug.

When Randy began taking the drug in February, he was wheelchair-bound. By his next visit to Omaha he was able to walk. “Without this drug he wouldn’t be alive,” Quteen said. “The people are amazed that he’s doing so well and able to do things now. No one we saw in North Carolina knew about the experimental drug study for mantle cell.”

Meanwhile, all the tumors in Randy’s neck are gone and the ones in his stomach have shrunked.

Quteen, 62, is Randy’s rock. But, now her trips to Omaha are even more personal. In September, breast cancer was discovered. “How will we do both cancers now?” she thought.

The surgeon in Asheville, N.C., wanted to do surgery, putting her out of commission for weeks. “This was not what I wanted. I don’t mind being sick a few days, but weeks would not do.”

So, Quteen got on the Internet and read all she could about breast cancer. Along the way, she discovered UNMC oncologist Beth Reed, M.D., and a second opinion. “The doctors in Nebraska have a better outlook on this cancer. I trust them - they have my best interest at heart.”

Quteen finished chemotherapy at the end of November.

“My wife is going to keep me around,” Randy said. “She doesn’t want to break another one in.”

“I’m thankful there’s somebody out there trying to find different things to help people cause if I hadn’t have gotten the drug, I’d have been dead now. So far it seems to be working. It gives me hope and I’m thankful for that.”

It’s a difficult time for the Whisnants and a challenge to travel, stay in motels and be away from home, family and friends. Yet, they persevere.

“God has his hands on us and we will make it,” Quteen said.

About 5 percent of lymphoma cases are classified as mantle cell. The disease is called mantle cell lymphoma because tumor cells originally come from the mantle zone of the lymph node. It’s usually diagnosed as a late-stage disease that has typically spread to the gastrointestinal tract and bone marrow.

Mantle cell lymphoma most often affects men over the age of 60. The average survival rate is three to five years.

“It gives me hope and I’m thankful for that.” — Randy Whisnant
New accreditation a ‘gold standard’ for UNMC

UNMC is the first academic institution to receive Human Research Protection Program (HRPP) accreditation by Alion Science and Technology HRPP Accreditation Services. The HRPP includes all human subject research conducted at UNMC, The Nebraska Medical Center, the University of Nebraska at Omaha, Children’s Hospital & Medical Center and the Bellevue Medical Center.

The accreditation means that UNMC is recognized as running effective and compliant human research protection programs involving more than 2,000 active protocols, said Ernest Prentice, Ph.D., associate vice chancellor for academic affairs.

“Under the visionary leadership and profound influence of our chancellor, we have a culture of compliance and conscience here at UNMC,” Dr. Prentice said. “Consequently, this is a good place to do research, where investigators are conscientious and good people.”

The accreditation is important, he said, just like JCAHO is important to demonstrate a hospital’s compliance with national standards.

Following the three-day site visit and accreditation, Alion asked permission to refer other institutions seeking HRPP accreditation to UNMC to learn about the process.

“They’re holding us up as a model,” Dr. Prentice said.

Dr. Jeffrey Gold named UNMC’s new chancellor

Jeffrey Gold, M.D., chancellor and executive vice president of biosciences and health affairs and executive dean of the College of Medicine at the University of Toledo in Ohio, is the new chancellor of UNMC.

In late November, the University of Nebraska Board of Regents made the appointment effective Feb. 1.

Dr. Gold will serve as UNMC’s chief executive officer, with responsibility for all aspects of campus administration. UNMC has an annual operating budget of about $600 million, a staff of more than 5,000, and about 3,700 students.

Dr. Gold will be expected to:

■ Lead the development of a vision and plan for UNMC’s future.
■ Continue the important work of creating an integrated clinical enterprise.
■ Enhance UNMC’s research and academic profile and capacity.
■ Continue to strengthen the work of UNMC and its partners in offering the highest-quality health care.
■ Cultivate a highly collaborative, supportive and diverse workplace; represent and advocate for the campus within the University of Nebraska and more broadly.
■ Represent UNMC in the private sector; and attract and develop the financial resources necessary to achieve the campus’ ambitions, among other duties.

Dr. Gold will chair the board of the recently announced integrated clinical enterprise. He also will hold a health professions appointment in the department of surgery.

UNMC receives renewal of two COBRE grants

UNMC has received more than $16.1 million from the National Institutes of Health for the renewal of two Institutional Development Award Center of Biomedical Research Excellence (COBRE) grants.

More than $11.2 million from the National Institute of General Medical Sciences will continue and expand cutting-edge, interdisciplinary research into nanotechnology.

UNMC researcher Tatiana Bronich, Ph.D., principal investigator on the grant, is the Parke-Davis Professor in Pharmaceutics, and codirector of the Center for Drug Delivery and Nanomedicine.

In addition, the grant will support the bioimaging and the nanomaterials core facilities.

The second COBRE renewal went to Keith Johnson, Ph.D., director of the department of oral biology’s Nebraska Center for Cellular Signaling (NCCS), who was awarded $4.9 million.

This is the third phase of funding for NCCS. The late Margaret Wheelock, Ph.D., obtained the awards for Phases I and II. The program started in 2003, and with this award funding will now run through 2018. The three awards total $25 million.

The award, administered by the National Institute of General Medical Sciences, will:

■ Provide support to sustain collaborative research and mentoring of new investigators in the realm of cellular signaling.
■ Strengthen research capabilities, innovation and funding support for investigators affiliated with the NCCS.
■ Move NCCS from IDeA funding to a self-sustaining center of research excellence in cellular signaling.
Howard Gendelman, M.D., took top honors, receiving the Innovator of the Year award, and Keshore Bidasee, Ph.D., claimed the Most Promising New Invention to close out the seventh annual Innovation Week at UNMC.

Drs. Gendelman and Bidasee received their awards in October during the UNMC Research Innovation Awards Ceremony, sponsored by UNeMed Corporation, the technology transfer office at UNMC. The Innovation Awards also honored all the UNMC technologies that were invented, patented or licensed during the previous year.

Dr. Gendelman, chairman of pharmacology/experimental neuroscience, was honored for his work against degenerative and infectious brain diseases. In early 2013 he built a partnership with a major pharmaceutical company for an improved treatment and the possible eradication of HIV. Later the same year, Dr. Gendelman’s new therapy for Parkinson’s disease entered a human proof-of-concept study.

Both may revolutionize how those diseases are treated, and both are based off an initial discovery he made soon after completing graduate school in 1979.

Jonas Salk, M.D., famed inventor of the Polio vaccine, was among those who reviewed Dr. Gendelman’s discovery all those years ago and was not impressed by the young researcher’s work.

He advised Dr. Gendelman to choose a new path of study. Dr. Gendelman chose to prove him wrong.

“There’s going to be many hurdles,” Dr. Gendelman said. “It takes determination to get over those hurdles.”

Dr. Bidasee, associate professor of pharmacology, was honored with the Most Promising New Invention for his work in diabetes. Dr. Bidasee, who joined UNMC in 2002, developed a potentially groundbreaking treatment for complications associated with diabetes.

Dr. Bidasee and his team think a small molecule called methylglyoxal, a naturally occurring byproduct of high blood-sugar, can cause a cell to “misbehave.” The misbehaving cells can then set off a chain reaction that destroys the endothelium, the single layer of cells that line the inner walls of blood vessels that control blood flow and pressure.

The team created a harmless virus that “injects” methylglyoxal-producing cells with an enzyme called Glyoxalase-1. The enzyme eliminates the “troublemaker” where it causes problems, while leaving it free to perform its beneficial functions.

Early testing shows the treatment not only stops damage in the kidneys, eyes and heart, but also shows promise in halting cognitive decline—a major concern in elderly diabetics.

The gene transfer strategy even significantly reduces blood sugar levels.

“That was completely unexpected,” Dr. Bidasee said.
Ibuprofen vs. emphysema? UNMC leads national study

UNMC will lead a clinical research study that will evaluate if a common, over-the-counter drug has potential to reverse the devastating effects of emphysema.

The phase II, three-year study funded for $4.4 million by the National Institutes of Health (NIH) National Heart, Lung and Blood Institute, will look at whether ibuprofen can reduce inflammation in the lungs. Ibuprofen is a non-steroidal, anti-inflammatory drug commonly used to treat pain and swelling.

“Emphysema has been regarded as an irreversible type of chronic obstructive pulmonary disease (COPD) involving damage to the air sacs in the lungs. But, in fact, it may be reversible,” said Stephen Rennard, M.D., Larson Professor of Medicine in the Pulmonary and Critical Care Medicine Section of the Department of Internal Medicine.

Dr. Rennard, principal investigator of the study and a recognized expert in COPD, said current treatments — medication, rehabilitation, and sometimes surgery — can help with symptoms and can reduce exacerbations, but nothing yet can reverse the course of the disease.

“Recent studies support the concept that the ability of the lung to repair damage is suppressed. If you can remove the suppression, then maybe lungs can be repaired. This would be important and entirely new,” Dr. Rennard said.

UNMC will coordinate the study and analyze the data. Four other medical centers also are involved in the study. They will recruit 140 patients with emphysema who participated in a previous large NIH emphysema study. The medical centers are National Jewish Health in Denver, Brigham and Women’s Hospital in Boston, Temple University in Philadelphia and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

UNMC’s lung cancer research program making strides

A decade ago there were clinical trials for lung cancer patients at UNMC, but the research enterprise was not what it could have been.

“Today,” said Apar Ganti, M.D., associate professor of internal medicine, oncology and hematology, “although not where we would like to be yet, we have a number of researchers across the campus who are engaged in lung cancer research that encompasses the spectrum, including basic science, translational research, clinical research and patient-based research.”

Some areas of emphasis include:

- Clinical research which has included extensive publication on outcomes from lung cancer in older patients and those who cannot tolerate standard therapy, led by Dr. Ganti and Anne Kessinger, M.D., professor of oncology and hematology.

- A grant from the Affordable Care Act-devised Patient-Centered Outcomes Research Institute that focuses on patient satisfaction from chemotherapy in stage four lung cancers. Research will help patients and medical practitioners make better decisions on treatment options. Monirul Islam, M.D., Ph.D., assistant professor of epidemiology in the College of Public Health, serves as principal investigator.

- Research on MUC4 and other mucins and their roles in early-stage lung cancer by Dr. Ganti and Surinder Batra, M.D., professor and chairman, department of biochemistry and molecular biology. Some promising preliminary research was published in the April 2013 Journal of Thoracic Oncology. A Career Development Grant to Dr. Ganti from the Department of Veterans Affairs supports this work.

- Karin Trujillo, M.D., assistant professor of cardiovascular and thoracic surgery, leads the effort to develop a lung cancer registry, tumor bank and tumor registry.

- Similarly, there is a movement toward developing a lung cancer screening program at UNMC. Rudy Lackner, M.D., professor of cardiovascular and thoracic surgery, spearheads this effort.

- The Batra and Ganti labs are currently developing new spontaneous animal models for lung cancer.
Recording molecules at the nanoscale

Before Yuri Lyubchenko, Ph.D., professor of pharmaceutical science in the College of Pharmacy, explains his research, he has a question: “Are you familiar with the concept of a record player?”

When the answer is “Yes,” Dr. Lyubchenko is relieved. So many students these days know only iPods, MP3s and streaming. They’ve never put a needle on vinyl.

But that — a record-player needle — is the principle behind the atomic force microscope (AFM).

In much the way a phonograph needle can decipher music in a record’s grooves, the atomically sharp AFM is capable of visualizing molecules and, under the right circumstances, even atoms. It has the capability to watch the interaction of molecules by performing time-lapse observations in water.

Among its nine various AFM instruments, UNMC houses a unique atomic force microscope, high-speed AFM. This instrument is capable of the time-lapse nanoscale imaging of molecules with video rate. It is one of the foremost tools for imaging, measuring and manipulating matter at the nanoscale.

Until the University of California, Berkley recently acquired a similar instrument, UNMC’s was the only one of its kind in the U.S.

Yet it’s kept without fanfare at the College of Pharmacy, behind an ordinary (locked) door, housed in a closet-sized room. Chances are you haven’t even heard it’s on campus.

But it allows Dr. Lyubchenko’s lab and others to do the kind of work that moves the needle — so to speak.

How so? Scientists know the DNA-binding enzyme APOBEC3G is a natural anti-HIV defense. But with the AFM, Dr. Lyubchenko and his team study the nanoscale structure and dynamics of APOBEC3G complexes with their DNA targets — the first step toward developing AIDS treatments based on nature.

AFM is also able to uniquely manipulate single molecules and measure their interaction.

This is especially important when looking into neurodegenerative disorders like Alzheimer’s, Huntington’s and Parkinson’s diseases.

Those diseases are caused when proteins, called amyloids, fold abnormally and aggregate. Knowledge of these “misfolded” molecular structures, and understanding how they assemble, is key to developing treatments, preventions and diagnostics of these devastating diseases.

UNMC scientists have pioneered an AFM force spectroscopy approach to probe misfolded states of amyloids, and to characterize their properties when they are first starting to come together as dimers (two-molecule complex). This is when these diseases first take root, and where treatments should be focused.

AFM, Dr. Lyubchenko said, is perfectly set up for testing drug-treatment candidates for this, and selecting the most efficient ones.
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