



Christa Lese Martin,
PhD, FACMG

Dear friends,

I'd like to introduce myself as the new Chief Scientific Officer (CSO) at Geisinger responsible for overseeing clinical research across our system, including MyCode. I've been at Geisinger for 8 years — I was initially

recruited as the Founding Director of our Autism & Developmental Medicine Institute — and I'm excited to serve a broader role as CSO with a goal of learning from every patient to maximize better health for all.

I want to thank the more than 280,000 Geisinger patients who already participate in MyCode — which is now one of the largest cohorts in the world that contains participant health information paired with DNA sequence!

It took a creative mind and bold vision to develop MyCode, and I want to recognize Dr. David Ledbetter, previous Executive Vice President and Chief Scientific Officer, for pushing Geisinger to the forefront of precision health. His innovation and leadership have been internationally recognized and many other groups are now developing similar programs.

The pandemic largely halted our ability to invite patients to participate in MyCode, but we've geared back up and added more electronic and telehealth capabilities to make consenting easier. Our teams have also been busy working on exciting studies that use our MyCode data, and I hope you enjoy learning about some of them in this newsletter.

As always, thank you for being a part of MyCode.

– Christa Lese Martin, PhD, FACMG

MyCode participants are aware of the importance of DNA and what it can tell us about health. But how DNA works might still be a mystery. Here's a simplified explanation.

DNA 101

What is DNA?

DNA is our genetic code. It's what we inherit from our parents and pass on to our children. DNA is the reason for our unique traits like height, eye color and the shape of our nose. It also sets our body's programming to grow and function. Think of it as the "instruction manual" for our bodies.

While the actual building blocks of our DNA are complex, researchers and medical providers refer to the basic units of DNA as letters: A, T, G, C. If you read your own genetic code, you'll be reading a book made of only these 4 letters. The body interprets long combinations and sequences of these As, Ts, Gs, and Cs in small specific sections called "genes."

What is a gene?

A gene is a section of DNA that provides the body with instructions to do a specific task. We refer to genes as the individual sentences in the body's instruction manual.

What is a gene variant?

Most of our different traits can be explained by changes or "variants" in the spelling of our DNA. We're all born with genetic variation. Some DNA changes or variants are common and

don't cause any health problems. But a DNA change's impact on the body depends on many factors.

In which gene (sentence) is this DNA change located?

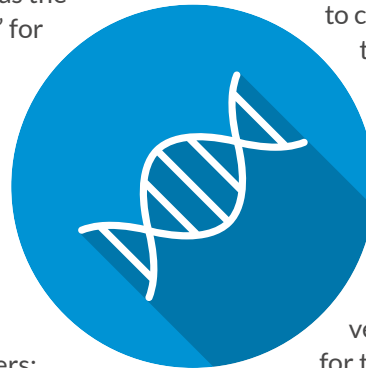
A DNA change in a gene linked to how the body processes caffeine compared to cholesterol will matter when thinking about the overall impact on your health.

What type of DNA change do we see in that gene?

Some DNA changes are simply alternate spellings of the same gene (think "gray" versus "grey") and may be easy for the body to read. Other DNA changes are major misspellings or typos that the body can no longer read and understand. In these cases, we can see certain diseases, or higher chances for developing a certain disease, because the body can't read those genetic instructions to complete that specific task.

We use genetic testing as DNA's spell-checker. Genetic testing can tell us "on page 15, sentence 2, the third letter 'A' has been replaced with a letter 'G' which refers to the exact "mutation" or genetic change that was found in a specific gene.

The body has at least 20,000 genes. With your help, we continue to uncover more about our genetic code every day.



MyCode data can be used to measure genetic risk of disease

One of the challenges of studying genes associated with rare diseases is that scientists tend to study those genes only in people who are already sick. This can produce misleading conclusions about how many people have certain genetic changes and how often these changes cause the disease in question.

MyCode provides a way to answer these questions by looking for these kinds of genetic changes more broadly, and not just in people who are already sick; such information is critical in deciding how to use genetic data to predict disease risk.

DICER1 syndrome, named for the specific gene *DICER1*, is a condition that produces rare lung tumors, called pleural pulmonary blastoma, or PPB. Geisinger investigators, in collaboration with experts at the National Cancer Institute, searched MyCode data for the kinds of changes in the *DICER1* gene that have been associated with PPB. Since PPB is such a rare disease, the investigators weren't even sure if any *DICER1* variants would be found. But in the first 91,000 MyCode participants to be analyzed, 24 had one of these variants. While that's a small number (1 in 3,800), it was the first time such an estimate had been determined, and it was higher than what had been guessed previously.

Surprisingly, none of these people had PPB or other lung tumors. If *DICER1* variants cause PPB in some people, why not in all people? The reason is that an additional factor, probably a second genetic variant, is needed to produce PPB.

Were there other diseases that people with these *DICER1* genetic variants were at risk of developing? The investigators used MyCode data to show that people with these variants are more likely to develop thyroid disease, including thyroid cancer. Other rare

cancers were also seen.

MyCode data showed that *DICER1* gene variants that cause PPB are rare but more common than previously thought, the chance of getting PPB if you have one of these variants is less than expected and these variants can increase risk of other diseases in some people. This pattern has also been observed in MyCode data for other genes and diseases.

The success of this research led to the formation of a long-term collaboration between Geisinger and the National Cancer Institute to study other genes that are thought to increase cancer risk.



MyCode identifies a new treatment for chronic liver disease

Geisinger scientists are using MyCode data to conduct research that has significant benefits for health and disease treatment.

A particularly exciting example is the use of MyCode data to develop a drug to treat non-alcoholic steatohepatitis (NASH). NASH is a liver disease that starts as a buildup of fat in the liver. While not a serious health issue on its own, in some people the fat causes an influx of immune cells into the liver (called inflammation). This can lead to an accumulation of fibrous connective tissue (called fibrosis) that's similar to the tough tissue that forms around scars. Over time, this connective tissue can displace normal liver cells, so the liver no longer works properly. There are no approved drugs that are effective in treating NASH. If NASH progresses to advanced liver failure, the only treatment is liver transplant.

Using MyCode data, Geisinger investigators, with the collaboration of scientists at Regeneron Pharmaceuticals, found a gene that was linked to blood markers of liver disease. This gene – *HSD17B13* – had not been known to affect liver disease. Of particular interest was a specific defect in *HSD17B13*. Although the defective gene had no effect on fat accumulation in the liver, the people who inherited the defective gene were much less likely to progress to inflammation and fibrosis.

If a naturally occurring defect in *HSD17B13* prevents liver disease, it was logical to assume that a drug that interfered with the function of the gene would also prevent liver disease. Such a drug that targets *HSD17B13* is now being developed as a treatment for NASH, with clinical trials to begin within the next few months. If successful, the drug will provide a new way to treat a life-threatening disease for which there is no effective treatment.

MyCode gave her family members peace of mind.

A little more than 20 years ago, tragedy struck Teresa Kapusniak and her family. Her seemingly healthy and athletic 26-year-old nephew passed away from cardiac arrest — a loss that would live with her every day, in more ways than one.

“After my nephew’s death, my cardiologist was very proactive,” explained Ms. Kapusniak. “A thorough checkup showed that I was at high-risk for sudden death syndrome (SDS) and I received an implantable cardioverter-defibrillator (ICD), like several of my family members.”

SDS is a loosely defined umbrella term for a series of cardiac syndromes that can cause sudden cardiac arrest and death (SCA/SCD). An ICD is a battery-powered device placed under the skin to keep track of heart rhythm and shock the heart if an abnormal rhythm occurs. This helps to prevent these SCA/SCD from happening.

Because these events can be defined by several syndromes and root causes can be unclear, Ms. Kapusniak wanted more answers.

“Although we didn’t have a pinpoint diagnosis, I was reassured knowing I was taking precautions,” said Ms. Kapusniak. “But it does make you a little uneasy, especially because I have children and didn’t know if it would affect them.”

Then one day, while sitting in the waiting room before an appointment, Ms. Kapusniak was approached about [Geisinger’s MyCode Community Health Initiative](#). She signed up on the spot.

“It was simple,” she recalled. “I just had to get additional samples of blood taken during my routine blood work.”

The genomic screening provided as part of MyCode revealed Ms. Kapusniak has a disease-associated variant in the *SCN5A* gene, which is associated with Brugada syndrome — a rare genetic disorder that can cause a dangerous irregular heartbeat and may lead to sudden death.

“I was relieved to know my results,” she said. “It meant the precautions I had been taking all these years were necessary. Truthfully, it gave me the confirmation I needed.”



Megan Betts

Soon after, Megan Betts, a cardiovascular genetic counselor at Geisinger, met with Ms. Kapusniak to help her navigate her cardiac care — including coordinating referrals to specialists — and assist in genetic testing for relatives.

“Being a genetic counselor goes beyond providing education,” said Ms. Betts.

“We get to know what’s important to our patients, listen to their experiences and help them navigate family dynamics so we can best advocate for them.”

Fortunately, tests revealed that neither of Ms. Kapusniak’s children carried the genetic variant responsible for Brugada syndrome.

“I’m grateful for the work MyCode is doing to help families like mine learn more about their health,” said Ms. Kapusniak. “Knowledge is important. Being active about my health and practicing preventive measures will always be better than worrying about the ‘what ifs.’”

The feeling is mutual for Ms. Betts.

“It’s rewarding to see your patient understand complex genetics concepts and close a decade-long diagnostic journey,” she said. “And we’re helping patients and their family members slowly heal from the grief of losing a loved one by ensuring preventive medical management for the family members who are still living.”

Physician perspective

Greg Burke, MD Internal Medicine Specialist



Greg Burke, MD

Since its beginning, MyCode has given people the opportunity to participate in research that has strong potential for improving the quality of life for patients everywhere. Allowing routine blood samples to be shared so possible new medical treatments and technologies can be developed to reduce suffering and save lives is a “win-win” for everyone.

My family and I all consented to have our blood samples used and were pleased that it did not require any extra steps, needle sticks or complex paperwork. It’s hard to imagine an easier way to participate in research — and knowing our genetic findings were to be kept private was very reassuring.

Several years ago, I took part in a discussion with Geisinger’s ethics committee to determine the best approach to take when genetic findings that might affect a person’s health were discovered. Previous guidelines strongly prohibited sharing research data with participants. But was it ethical to withhold such important information knowing a patient could benefit from its disclosure?

After interviewing patients and other stakeholders, we decided that this type of information should prompt an alert to the patient and their physician. It just seemed like the right thing to do.

Since then, genetic findings that require medical investigation have been routinely shared and through MyCode, Geisinger has become a leader in a new level of research transparency that keeps the well-being of the participant at the center of everything we do.

As a physician, it’s been heartening to see so many of my patients participate in the project. And even so, only 15 of



them have had genetic findings that needed further investigation. This included cardiac rhythm problems, cancer risk and even emotional difficulties.

In an amazing stroke of good fortune, one of my patients was found to have a rare genetic form of cancer before any symptoms had developed. I’m convinced that the elective surgery she had to remove her tumor was lifesaving. However, the story didn’t end there. Her son was then found to have the same genetic disorder and underwent similar surgery given the high risk of developing the same cancer.

I couldn’t have imagined all these advances when I consented to adding my own blood draw to MyCode over 10 years ago. It is with great pride that I’ve promoted Geisinger’s innovative research program as it expanded to protect the health of those who consented to become participants.

I anticipate many more good things to come from MyCode and more stories to be shared in the future!

FAQ:



If I donate a sample to MyCode, will it affect my insurance?

The Genetic Information Nondiscrimination Act (GINA) is a federal law that makes it illegal for some companies to use genetic information against you. These companies include:

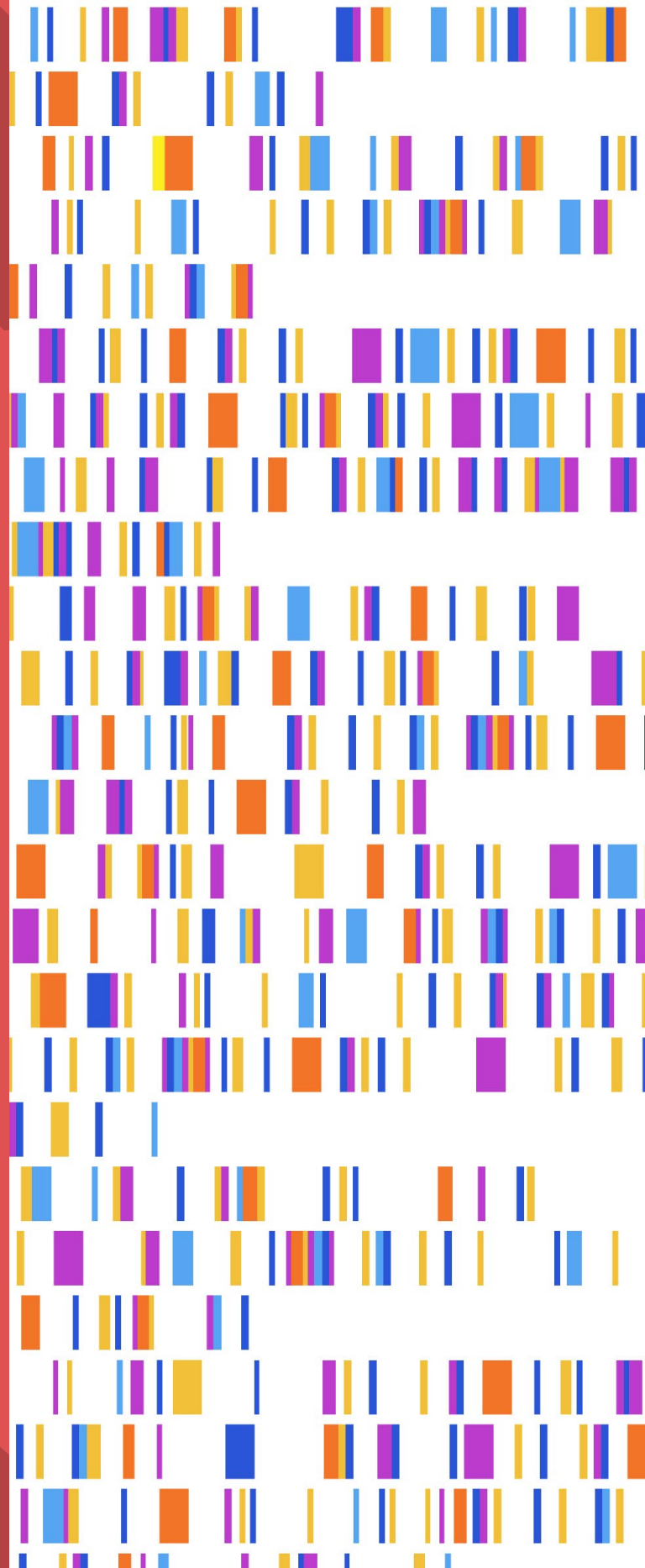
- Health insurance companies
- Group health plans
- Most employers

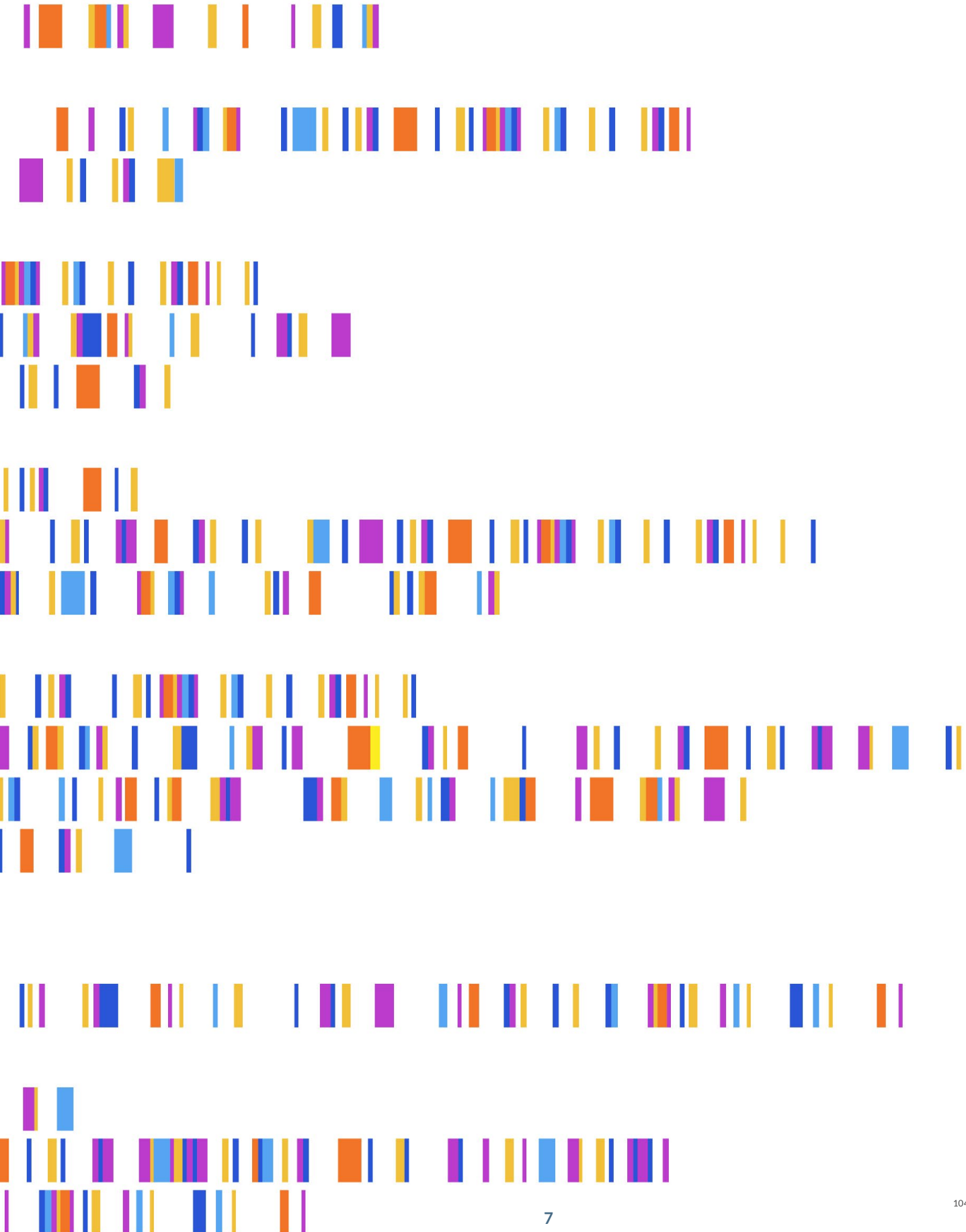
The Genetic Information Nondiscrimination Act does not protect against discrimination by companies that sell life, disability or long-term care insurance. At this time, the chances are very small that we would be required to share your genetic information with companies like this.

What does it mean if I don't hear anything after donating my sample to MyCode?

If you don't hear from anyone on the MyCode team, it means:

- Your sample may not have been studied yet.
- You may not have any of the gene changes we're studying.





Geisinger

Geisinger Medical Center
100 N. Academy Ave.
Danville, PA 17822