The analogy might seem a little dated, but if you’ve ever had a video tape break, you know how recorded information can be lost. Similarly, when a gene called ARID1A mutates, a protein called chromatin, which keeps DNA compacted in cells, loses its structure, and the genetic code goes haywire, allowing some kinds of cancer to grow.

“You need to maintain proper chromatin structure to have your DNA properly read,” Ronald Chandler said.

His research has shown that ARID1A is “a bona fide tumor-suppressor.” Normally, it is “the guardian of chromatin structures,” he said. If the ARID1A gene mutates, the chromatin loses its structure, and “you end up with a cancer cell.”

ARID1A appears to play an important role in several kinds of cancer—including bladder, stomach, kidney and lung—but it is particularly significant in ovarian and endometrial cancers, the two types on which Chandler’s research is focused. Because the female reproductive tract undergoes frequent changes for pregnancy to occur, it likely increases the risk that ARID1A will mutate, he believes.

Endometriosis, a benign, although often painful, condition in which cells that normally line the uterus grow in other areas of the abdomen, increases a woman’s risk of endometrial and ovarian cancer.

Currently there is no test to identify when ARID1A has mutated. “That is our goal,” Chandler said. “Then we might be able to work in reverse to understand the genes and pathways that are involved in going from endometriosis to cancer.”

That could allow researchers to develop new treatments to counteract the ARID1A mutation and prevent cancer.

“I’m driven by the path to discovery. At the end of the day, the reward for that drive is we think we’re doing something good for the patient.”
Preeclampsia, a disorder that occurs only during pregnancy and the post-partum period, can cause organ failure and even death of the mother and her unborn baby. Yet despite its severity and frequency, occurring in 5–8 percent of pregnancies, it is little understood, and the only cure is delivery of the baby.

That is a knowledge gap Sascha Drewlo hopes to fill. His research is aimed at understanding the molecular causes of preeclampsia, characterized by dangerously high blood pressure, and developing a method of identifying women most at risk of the disease. With a grant from the National Institutes of Health, he is studying a drug normally used for treating diabetes that, in laboratory tests, shows promise of interrupting the biological process that causes preeclampsia.

“What we think happens is the placenta as it grows releases something”—such as a protein—“that causes hypertension,” Drewlo said. The drug, Rosiglitazone, appears to block that process. In his lab, Drewlo is studying exactly how the drug works on placental tissue.

Although preeclampsia symptoms usually don’t appear until after the twentieth week of pregnancy, “we believe the disease starts very early in pregnancy,” he said.

He and a colleague, Randall David Armant, a Wayne State University professor, developed a method for collecting cells from the mother’s cervical canal that could identify those at risk of developing preeclampsia. Drewlo and Armant have applied for NIH funding to study the method, which also could test for genetic disorders of the baby.

“It really changes the paradigm,” Drewlo said. “It’s nice to know we can do something so meaningful.”
As director of Women’s Health Research at the College of Human Medicine, Asgi Fazleabas focuses on infertility and endometriosis, a chronic and painful disorder in which tissue that normally lines the uterus grows in other areas of the abdomen. It affects six to ten percent of reproductive-age women and more than 176 million worldwide.

Women with endometriosis endure an average of eight to ten years from initial onset of the disease to diagnosis and see an average of seven physicians before they are accurately diagnosed.

Research in Fazleabas’s laboratory has focused on understanding how endometriosis affects the uterine environment, making it less conducive for a successful pregnancy. The uteri of women with endometriosis typically become resistant to progesterone, which is the hormone of pregnancy. As a result, the uterus does not develop appropriately each cycle to make it hospitable to a developing embryo.

Fazleabas has been honored as a fellow of the American Association for the Advancement of Science and has received both the Research and Distinguished Service awards from the Society for the Study of Reproduction. His research has been continuously funded by the National Institutes of Health for 30 years. He currently has two grants to study the biology underlying the mechanisms that contribute to the development of endometriosis and the associated infertility.

“Everything we do is focused on helping the woman suffering from endometriosis to lead a healthier and more productive life...”

“Everything we do is focused on helping the woman suffering from endometriosis to lead a healthier and more productive life,” he said, “and ensuring that our research in the long run helps her to have both a better quality as well as a healthier reproductive lifespan.”
Jae-Wook Jeong’s research into endometrial cancer could hold profound significance for thousands of women. The National Cancer Institute estimates 61,380 new cases of endometrial cancer, the fourth most common form among women, will be diagnosed in 2017 in the United States, and 10,920 women will die of the disease.

Most cases of endometrial cancer are found in women aged 50 and over, but in recent years the age of diagnosis has been decreasing, even below age 40, possibly due to unhealthy diet, environmental factors and obesity. As a result, the most common treatment – hysterectomy – is not a desirable option for women of child-bearing age.

“Prevention, I think, is more important,” Jeong said.

Endometrial cancer can occur when the hormones estrogen and progesterone are out of balance, particularly when estrogen levels are elevated, he said.

Jeong has identified a gene, called Mig-6, a progesterone mediator that could be a target to treat and prevent endometrial cancer. Knowing that Mig-6 is involved in progesterone function also could suggest other genetic pathways as possible targets for treatment.

“That’s my goal—to understand what’s going on—and that tells me how to treat it. That’s what we call personalized medicine.”
NIRAJ JOSHI, PhD
Research Assistant Professor
Department of Obstetrics, Gynecology and Reproductive Biology

The Endometriosis Foundation of America recently awarded Niraj Joshi a grant to study the molecular and genetic processes that cause many women to suffer with endometriosis.

He believes the key to finding better treatments for endometriosis, which causes pelvic pain for one in ten women worldwide, lies along what is called “the hippo signaling pathway,” which plays a key role in regulating organ size and growth in the female reproductive tract. Research has shown that the hippo signaling pathway is necessary for the normal growth and death of cells in the body.

But when something goes wrong along that pathway, endometriosis occurs. It is a painful disease in which cells that normally line the uterus grow in other areas of the abdomen. It is a common cause of infertility and is a risk factor for endometrial and ovarian cancer. Researchers estimate that endometriosis costs the U.S. economy $85 billion a year in medical expenses, lost productivity and other costs.

“You need to understand this is a disease of the reproductive years,” Joshi said. Many of the 7.5 million women in the U.S. who suffer it are “in a lot of pain, are unable to focus on their careers, can lose the opportunity for promotions and lose future earnings potential.”

Endometriosis also can adversely affect the women who suffer it emotionally and socially, he said.

Joshi hypothesizes that when hippo signaling is turned off, a protein called YAP downstream in the signaling pathway is highly expressed, promoting the uncontrolled growth of endometrial cells outside the uterus. His study could suggest new targets for treatment that could turn hippo signaling on or suppress the expression of the YAP protein.

“My thinking is that understanding this hippo signaling and YAP, this will give us some basic understanding of this tissue growth outside the uterus,” Joshi said. “If we can suppress the YAP expression, then perhaps we can prevent the observed aberrant cell proliferation in endometriosis lesions.”
Tae Hoon Kim knows that a gene called MIG-6 is important in protecting women against endometriosis and uterine cancer, as well as other forms of cancer. Now he wants to know exactly how it works.

“We know the physiological function” of MIG-6, he said, “but we don’t know the exact mechanism.”

That’s because cancer and endometriosis – a painful disorder that occurs when tissue that normally lines the uterus grows in other parts of the body – result not from a single genetic variation but from a complex chain reaction of genetic and molecular changes. In his lab, Kim has shown that when MIG-6 is “knocked down,” or turned off, it sets off a series of changes, activating some molecular signaling pathways and deactivating others. As a result, endometrial hyperplasia, a precursor to uterine cancer, results.

When activated, MIG-6 suppresses tumor growth, Kim said. In uterine cancer cases (also known as endometrial cancer), that gene is switched off, he said. The hormone progesterone, a common treatment for uterine cancer, is less effective when MIG-6 is turned off, his research has shown.

Among infertile women, the expression of MIG-6 often is very low.

Kim said he is driven to unravel the mystery of MIG-6, because the answer could lead to new treatments for infertility, endometriosis and uterine cancer. After completing his post-doctoral training at the Baylor College of Medicine in Houston, Kim joined the College of Human Medicine, where he works closely with Jae-Wook Jeong, Ph.D., one of the country’s top endometrial cancer researchers.

In the Department of Obstetrics, Gynecology and Reproductive Biology, “everybody knows each other, and we collaborate,” Kim said. “I think that’s our strength.”
Under Richard Leach’s guidance, the College of Human Medicine’s Department of Obstetrics, Gynecology and Reproductive Biology has become a leader in the clinical translation of research into women’s health. The department’s faculty members have achieved international recognition for ensuring that their work is focused on meeting the health care needs of women across their lifespans and throughout diverse communities.

Since Leach joined the department in 2007, it has recruited researchers, including physicians, clinical translational scientists, nurses and epidemiologists, all focused not only on the medical aspects, but on the social disparities that threaten women’s health. The department is continuing to attract accomplished researchers through the support of the University’s Global Impact Initiative, said Leach, whose own work centers on implantation early in pregnancy.

Collaborating with each other, as well as with health care partners worldwide, the researchers are:

- Unraveling the causes and pursuing better treatments for infertility;
- Seeking better therapies for endometriosis, a painful condition that affects one in ten women of reproductive age;
- Identifying the causes of fibroid tumors in the uterus, which affects one in five women, causing pelvic pain and often leading to hysterectomies;
- Identifying the causes of uterine and ovarian cancers;
- Researching the causes and early diagnosis of premature births and preeclampsia and developing ways to prevent them;
- Examining the health implications of assisted reproductive technology, including whether it is associated with birth defects and later health problems in children and their mothers;
- Collaborating with health care agencies and community groups to give Medicaid recipients the best prenatal care in the most cost-effective way and helping assure that they and their babies will be healthy;
- Working with families and in cooperation with state agencies and community partners to eliminate health disparities and raise awareness among African-American and Latino women about the importance of health screenings.

“We are focused on ensuring that our research is translated to the health care needs of women across their life spans and in the diverse communities we serve.”

“All of our research rests on three pillars,” Leach said. Those include supporting the best health services for women in Michigan, nationally and around the globe; educating exemplary physicians and scholars; and discovering the disseminating innovative medical knowledge.
Jeff MacKeigan describes his cancer research much as a detective might explain how he cracks a case.

“I find targets in human disease,” MacKeigan said, “and then I go after them.”

Targets are clues that lead scientists to new therapies. In many ways, the fight against cancer and complex diseases is a never-ending investigation into the precise genetic causes and the most effective therapies.

Much of MacKeigan’s research seeks to understand how cancer cells use autophagy (a process whereby cells consume their own damaged cellular components) to resist death and withstand chemotherapy. During treatment, cancer cells use autophagy to increase their energy and avoid death.

Before joining the College of Human Medicine, MacKeigan’s lab at the Van Andel Research Institute analyzed thousands of FDA-approved drugs and their biological targets. That knowledge has allowed his research to impact diseases beyond cancer. The lab’s 2017 article in the journal *Nature Communications* offers a detailed genetic roadmap of tuberous sclerosis, a disorder that causes benign tumors to form in many different organs, including the brain, heart, kidneys, eyes, skin and lungs.

MacKeigan’s comprehensive study on the FDA compounds revealed that the drug fasudil, used for treating blood vessel spasms in the brain, also might be an effective treatment for Parkinson’s disease. He approached Caryl Sortwell, a College of Human Medicine professor who has spent her career unraveling the mystery of Parkinson’s, to collaborate on a project evaluating the drug’s potential.

“We find targets in human disease,” MacKeigan said. “And then I go after them.”

Targets are clues that lead scientists to new therapies. In many ways, the fight against cancer and complex diseases is a never-ending investigation into the precise genetic causes and the most effective therapies.

Much of MacKeigan’s research seeks to understand how cancer cells use autophagy (a process whereby cells consume their own damaged cellular components) to resist death and withstand chemotherapy. During treatment, cancer cells use autophagy to increase their energy and avoid death.

Before joining the College of Human Medicine, MacKeigan’s lab at the Van Andel Research Institute analyzed thousands of FDA-approved drugs and their biological targets. That knowledge has allowed his research to impact diseases beyond cancer. The lab’s 2017 article in the journal *Nature Communications* offers a detailed genetic roadmap of tuberous sclerosis, a disorder that causes benign tumors to form in many different organs, including the brain, heart, kidneys, eyes, skin and lungs.

MacKeigan’s comprehensive study on the FDA compounds revealed that the drug fasudil, used for treating blood vessel spasms in the brain, also might be an effective treatment for Parkinson’s disease. He approached Caryl Sortwell, a College of Human Medicine professor who has spent her career unraveling the mystery of Parkinson’s, to collaborate on a project evaluating the drug’s potential.

““To be associated with a large medical school and with patients motivates us and makes our work more clinically relevant.”

The opportunity for more interdisciplinary collaboration is one reason MacKeigan decided to join the College of Human Medicine, he said.

“It’s an exciting time to be associated with Michigan State,” he said. “To be associated with a large medical school and with patients motivates us and makes our work more clinically relevant.”
Stacey Missmer was drawn to MSU after more than 20 years at the Harvard Medical School and the Harvard T.H. Chan School of Public Health because of MSU’s commitment to community health and its interdisciplinary approach to research.

“It’s a great opportunity. I love the spirit of community health that this medical school has,” said Missmer, who joined the College of Human Medicine in September 2016. The Department of Obstetrics, Gynecology and Reproductive Biology “has an incredibly strong multi-disciplinary approach to mission-based research,” she added.

Missmer, author of more than 200 peer-reviewed publications, reviews and book chapters, has focused her research on identifying risk factors for infertility and endometriosis. Her team was the first to recognize that endometriosis—a painful condition in which tissue that normally lines the uterus grows in other areas of the abdomen—is more common among lean women.

Endometriosis is surgically identified in at least 10 percent of reproductive aged women, although Missmer suspects it is much more common.

“Girls don’t talk about pelvic pain,” she said, and physicians and others often discount it as a normal part of the menstrual cycle. Yet endometriosis can negatively affect a woman’s social life, career and earning potential, and it can increase her risk for other illnesses, including ovarian cancer and cardiovascular disease, Missmer said.

With data from the Boston Center for Endometriosis, which she co-founded in 2012 and where she is still scientific director, Missmer is conducting a long-term study of some 1,300 adolescent girls and young women to identify risk factors for the disease.

“We’re also hoping at MSU to capitalize on the diversity of the population in Michigan and strong community partnerships to establish another cohort to look at gynecological health,” she said.
Karen Racicot wants to know how a viral infection in a pregnant woman affects her pregnancy and her child, not only before birth but also for a lifetime.

“The placenta is the barrier, and viruses typically can’t get through it,” she said.

Yet researchers believe that viral infections during pregnancy—including those with severe symptoms, such as influenza, and subclinical viruses that often have no symptoms in the mother—can indirectly cause a lifetime of health problems for her child.

“Viral infections seem to be especially detrimental for the developing brain, and this is an active area of research in our group,” Racicot said.

Sexually transmitted viral infections also can affect mom and baby by increasing the risk for preterm labor.

“It is becoming increasingly clear that these relatively common infections can affect a pregnant woman’s ability to maintain her pregnancy to term,” Racicot said. This is significant, because children born preterm, or before 37 weeks, are much more likely to suffer from a host of medical issues throughout their lifetime.

Racicot also studies non-infectious factors that might affect development in utero.

“Chronic stress during pregnancy is actually associated with increased risk for the development of allergic asthma in children,” she said.

Racicot has developed models to study chronic stress in the lab and also studies the link between maternal stress and childhood asthma.

“We cannot ask women to not feel stress,” she said, “but if we understand how stress affects fetal development, we might be able to intervene and reduce its impact.”
John Risinger leads a team of researchers studying the underlying molecular and genetic characteristics that cause ovarian and endometrial cancers and make some forms more resistant to treatment.

“We’re trying to understand what makes these cancers behave the way they do,” Risinger said, specifically the genetic variations and differences in gene expression.

With a mass of data from The Cancer Genome Atlas, Risinger and his team study gene mutations and expressions in specific cases to identify which ones appear to play a role in endometrial and ovarian cancers. Understanding those differences could lay the foundation for improved cancer prevention, detection and treatment.

While with the National Cancer Institute, before joining the MSU College of Human Medicine, Risinger identified a protein as a potential therapeutic target to treat advanced endometrial cancer. A vaccine targeting that protein is in clinical trials.

At the National Institute of Environmental Health Sciences, he made a discovery that identified a certain type of DNA repair defect in some endometrial cancers. Ultimately, that led to a test to identify whether these tumors were due to a hereditary genetic defect called Lynch syndrome, which causes a predisposition to colorectal, endometrial and several other kinds of cancer.

Risinger also is studying less-common forms of ovarian cancer that are more resistant to chemotherapy, hoping to understand what makes them resistant and identify other avenues for treatment.

Working with clinicians at Spectrum Health in Grand Rapids, he collects tumor samples for analysis and research. That, he said, is when “we realize it’s somebody’s challenge, somebody’s life, and we have the opportunity to do something about it. We can make a meaningful impact on human lives. That’s incredibly satisfying.”

“(That’s when) we realize it’s somebody’s challenge, somebody’s life, and we have the opportunity to do something about it.”
Lee Anne Roman, PhD
Professor
Department of Obstetrics, Gynecology and Reproductive Biology

Lee Anne Roman likes to say that a healthy baby becomes a healthy child, and a healthy child tends to become a healthy and productive adult. That’s why, partnering with organizations throughout the state, she has spent many years researching how to improve health care for women and their children.

She works with a team of researchers and providers — including health economists, bio-statisticians, nurses, physicians and epidemiologists — who conduct research and generate new knowledge about issues and programs relevant to the health of women and children.

“We take our research skills and partner with local agencies to build capacity for discovery, analysis, and innovation in community settings,” Roman said.

She has overseen studies aimed at reducing socio-economic and ethnic health disparities, particularly among African-American women and their babies, who have twice the rate of adverse birth outcomes, including infant mortality. She and her collaborative team are conducting a five-year study to develop a system of care for Medicaid-insured women, including increasing participation in Michigan’s Maternal and Infant Health Program.

In partnership with Strong Beginnings, a federal Healthy Start program aimed at improving health and early childhood development outcomes for high-risk mothers and their babies, Roman’s team provides research to determine the program’s impact. She calls her work “engaged scholarship” that is partnering with communities to discover new knowledge that can be practically applied and disseminated to improve the health of people in Michigan and nationally.

“It’s important to determine how communities and providers can adopt evidence-based practices to apply it...”
Even before a baby is born, the amount of chronic stress a mother experiences – including that caused by domestic violence, poverty, drug use by others and legal problems – can adversely affect the health of her child.

As a perinatal epidemiologist, Kelly Strutz studies such factors around the time of pregnancy that can affect the health of a mother and her baby. Chronic stress for a mother, for example, is associated with low birth weight for her baby, which can lead to many health problems throughout a child's life.

With a background in biological science, Strutz earned a master's degree in public health and a doctoral degree in maternal and child health.

“As soon as I discovered public health, I switched over to the social science side,” she said. “I wanted to do something that was broader and more directly applicable to human health. We are starting to see more and more that what happens in utero can affect that person's life.”

Working with colleagues Cristian Meghea and Lee Anne Roman, Strutz studies Medicaid-funded initiatives, such as the state's Maternal and Infant Health Program and the Strong Beginnings Program, and offers data on which services are working well and which ones need improvement.

“It's so easy to see the human faces behind the data,” she said, adding that through research, it becomes “much more clear that we can do things to improve people's health.”

Much of her research is aimed at reducing health disparities for minority and low-income women and their children.

“I'm really interested in closing those gaps so that all infants start off from a position of equity,” Strutz said. “Ultimately, I want to make sure that pregnant and post-partum women stay healthy and their children stay healthy.”

“We are starting to see more and more that what happens in utero can affect that person's life.”
Uterine fibroid tumors affect 25 to 75 percent of women, often producing extreme discomfort and infertility, and they are the leading cause of hysterectomies.

“It’s a huge healthcare burden that doesn’t get a lot of attention,” Jose Teixeira said. “For the women involved, however, it’s very important.”

His laboratory is concentrating its efforts on the genetics of how fibroids form and grow. Teixeira, a developmental biologist, has spent years studying reproductive tract development to better understand these benign tumors, as well as two other areas of research directly related to women’s gynecological health: endometrial and ovarian cancer.

His interest in ovarian cancer – the most deadly gynecological cancer because it is usually detected in later stages—stems from his early training. Chemotherapy can send the cancer into remission, but “invariably, the cancer comes back, is resistant to chemotherapy, and is almost always deadly,” Teixeira said. “We need better, more patient—and tumor-specific therapies.”

His laboratory is trying to determine alternative targets for therapy by studying the gene pathways that are disrupted during progression of the disease.

Teixeira was an associate professor at the Harvard Medical School before joining the College of Human Medicine.

“It helps to be at a place like Michigan State,” he said. “We have a fantastic group of scientists studying women’s health issues. It’s great working with them.”