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On the Cover
Main photo: In the Reproductive Sciences Lab, graduate student Emma Dolan works on the functional role of a protein called MAL that Duke researchers have identified as being markedly elevated in tumors from women with more aggressive ovarian cancer. Her overall objective is to determine if there is a way to target this protein and/or the pathways in which it is involved as a new therapeutic strategy for ovarian cancer.
Photo credit: Ken Huth, Huth Photography

Insets: Left and far right — Graduate student Rose Schrott and researcher Zahra Mohseni use a pyrosequencer to measure DNA methylation; assistant professor Zhiqing Huang and medical student Cassie Hobbs examine ovarian cancer cells that are engineered to produce green fluorescent protein. Center: a new addition to the Duke community, born at Duke Hospital.

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MESSAGE FROM THE CHAIR
Research. Education. Patient Care — Locally, Nationally & Globally

When Duke Ob/Gyn published its inaugural edition of this publication last spring, the Department’s Mission, Vision and Values (outlined on the back cover) also were communicated. One year later, our commitment to innovation in research, education and patient care has never been more evident.

Locally, nationally and globally, our dedication to delivering better health and hope to all women and their families comes to life on the pages of this issue. Here are a few of the topics highlighted:

• Initiatives to improve patient care through telemedicine — which holds great promise to help high-risk populations that face challenges accessing care. Through technology and education, we strive to bridge the gap in communities where much-needed services are not readily accessible. Anthony E. Swartz, B.S., RT(R), RDMS, explains how, through state-of-the-art video visits and radiology, the future is encouraging.

• Research by Division Chief of Reproductive Sciences Susan K. Murphy, PhD, and colleagues on how exposure to cannabis alters the epigenetic profile of sperm has garnered notable recognition and attention. (Please reference the Spotlight, and article on page 4).

• Julia Woodward, PhD, has presented to a broad spectrum of Reproductive Endocrinology and Infertility specialists and lay audiences alike on a the topic, “How Old Is Too Old?” about the rise of parenting at advanced reproductive age. Long-term medical and psychosocial risks to the children born to older parents are identified.

• Last year, the Duke Global Health Institute launched the Center for Global Reproductive Health, led by Megan Huchko, MD, MPH. Through this Center, and in partnership with Duke University’s Pratt School of Engineering, great strides are being made to enhance women’s health — and that of their babies. The Pratt Pouch is one vehicle through which this is possible. Both of these impactful initiatives are featured.

• In response to the United States’ relatively high maternal mortality and morbidity rates, as well as its socioeconomic and racial disparities, the Society for Maternal-Fetal Medicine has developed an initiative designed to focus on maternal healthcare in recent years. An informative Q/A on this subject offers insight by Brenna Hughes, MD, MSc, Maternal-Fetal Medicine specialist and chair of Duke Ob/Gyn’s new Quality, Safety and Peer Review Committee.

I hope you not only enjoy this issue, but are encouraged to keep in touch with the Duke Ob/Gyn throughout the year by visiting obgyn.duke.edu, and by following us on Twitter @dukeobgyn.

Sincerely,

Matthew D. Barber, MD, MHS
E.C. Hamblen Professor and Chair, Duke Ob/Gyn

SPOTLIGHT:
Duke Ob/Gyn Research: Exposure to Cannabis Alters Epigenetic Profile of Sperm

• According to Altmetric, which tracks and demonstrates the reach and influence of research to key stakeholders, the study achieved a metric of 552, which is the highest output from articles in Epigenetics.

• The study ranks in the top 5% of all research outputs scored by Altmetric, and in the 99th percentile compared to outputs of the same age.

• The research achieved mentions by 49 news outlets, 6 blogs, 177 Tweeters, 6 Facebook pages, 2 Google+ users and 3 Redditors, among others.

• Publications that picked up the story include Men’s Health, Forbes, Popular Mechanics and Business Insider.

For citation, see page 5.

SOURCE: ALTMETRIC
As legal access to marijuana continues expanding across the U.S., more scientists are studying the effects of its active ingredient, tetrahydrocannabinol (THC), in teens, adults and pregnant women.

New research from Duke Health suggests men in their child-bearing years should also consider how cannabis use could impact their sperm and possibly the children they conceive during periods when they’ve been using the drug.

Much like previous research that has shown tobacco smoke, pesticides, flame retardants and even obesity can alter sperm, the Duke research shows cannabis also affects epigenetics, triggering structural and regulatory changes in the DNA of users’ sperm.

Experiments in rats (using THC) and a study with 24 men found that exposure appears to target genes in two major cellular pathways and alters DNA methylation, a process essential to normal development.

The researchers do not yet know whether DNA changes triggered by cannabis are passed to users’ children and what effects that could have. Their findings were published online Dec. 19, 2018 in the journal *Epigenetics*.

“‘What we have found is that the effects of cannabis use on males and their reproductive health are not completely null, in that there’s something about cannabis use that affects the genetic profile in sperm,’” said Scott Kollins, PhD, professor in psychiatry and behavioral sciences at Duke and senior author of the study.

“We don’t yet know what that means, but the fact that more and more young males of child-bearing age have legal access to cannabis is something we should be thinking about,” Kollins said.

National research has shown a steady decline in the perceived risk of regular marijuana use. This, combined with the demand and wide availability of marijuana bred specifically to yield higher THC content, make this research especially timely, Kollins said.

The study defined regular users as those who smoked marijuana at least weekly for the previous six months. Their sperm were compared to those who had not used marijuana in the past six months and not more than 10 times in their lifetimes.

The higher the concentration of THC in the men’s urine, the more pronounced the epigenetic changes to their sperm were, the authors found.

THC appeared to impact hundreds of different genes in rats and humans, but many of the genes did have something in common — they were associated with two of the same major cellular pathways, said lead author Susan K. Murphy, PhD, chief of the Division of Reproductive Sciences in obstetrics and gynecology at Duke. One of the pathways is involved in helping bodily organs reach their full size; the other involves a large number of genes that regulate growth.

**EXPOSURE TO CANNABIS ALTERS THE EPIGENETIC PROFILE OF SPERM**

**WHETHER CHANGES CAN BE REVERSED OR ARE PASSED ON TO CHILDREN IS STILL UNKNOWN**

*We know that there are effects of cannabis use on the regulatory mechanisms in sperm DNA, but we don’t know whether they can be transmitted to the next generation.*

— Susan K. Murphy, PhD, Division Chief, Reproductive Sciences, Duke Obstetrics and Gynecology
The Duke team plans to continue its research with larger groups. They intend to study whether changes in sperm are reversed when men stop using marijuana. They also hope to test the umbilical cord blood of babies born to fathers with cannabis-altered sperm to determine what, if any epigenetic changes, are carried forward to the child.

“We know that there are effects of cannabis use on the regulatory mechanisms in sperm DNA, but we don’t know whether they can be transmitted to the next generation,” Murphy said. “We don’t know whether they are going to be permanent. I would say, as a precaution, stop using cannabis well before trying to conceive.”

In addition to Kollins and Murphy, study authors include Nilda Itchon-Ramos; Zachary Visco; Zhiqing Huang, MD, PhD; Carole Grenier; Rose Schrott; Kelly Acharya, MD; Marie-Helene Boudreau; Thomas M. Price, MD; Douglas J. Raburn, PhD; David L. Corcoran; Joseph E. Lucas; John T. Mitchell; F. Joseph McClernon; Marty Cauley; Brandon J. Hall; and Edward D. Levin.

The research was supported by a grant from the John Templeton Foundation.

**Editor’s Note:** Based on the pilot study, the Templeton Foundation has authorized funding for a larger scale three-year, $3 million investigation into how THC exposure influences the alteration of epigenetic information in sperm across the full genome, how such changes influence offspring behavior, and to what extent such altered methylation can be transferred across generations.

For more information on the Duke team’s continued research, visit [sites.duke.edu/ciphers](http://sites.duke.edu/ciphers), or follow CIPHERS on Twitter: @Duke_CIPHERS


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**How does use of marijuana affect sperm?**

Cannabis affects genes in two major cellular pathways and alters DNA methylation, a process essential to normal development. The effects of cannabis use on males and their reproductive health affects the epigenetic profile in sperm. Exactly what and how are still being determined, but appears to affect hundreds of different genes. Many of them were associated with two of the same major cellular pathways. One of the pathways plays a role in organs reaching their full size, while the other is involved in regulating growth during development.

**Is sperm affected by cannabis healthy enough to fertilize an egg and continue its development into an embryo?**

This has not yet been determined. Research is continuing. Precautions should be taken by those who plan to conceive, since we don’t know whether effects are permanent. Cannabis use should be ceased for as long as possible before trying to conceive.

**In addition to this recently published study, what will researchers focus on in the future?**

Researchers plan to study larger groups of men to find out which, if any, epigenetic changes in cannabis-altered sperm are passed on to children and if those epigenetic changes in sperm are reversed if a man stops using marijuana.
Ovarian cancer has historically had few effective treatment options, particularly for patients with advanced or platinum-resistant disease. Anti-angiogenics and poly(ADP-ribose)polymerase (PARP) inhibitors have demonstrated promising anti-tumor activity and prolonged survival for select patients. Immunotherapies, which have been game changers for cancers with a high mutational load like melanoma and lung cancer, have shown modest effects in ovarian cancer. New treatment options and drug combinations continue to emerge and many are being tested in clinical trials.

“It’s an exciting time for ovarian cancer research,” says Duke gynecologic oncologist Rebecca Previs, MD, MS, who serves as Duke’s liaison for Phase 1 Gynecologic Clinical Trials. “PARP inhibitors are approved now in a variety of clinical scenarios. We are using them in patients with recurrent disease, measurable disease, and for women with BRCA mutations, in the frontline setting as maintenance after chemotherapy.”

Angeles Alvarez Secord, MD, MHSc, gynecologic oncologist and director of Gynecologic Oncology Clinical Trials at Duke agrees, adding: “We are moving toward combining these exciting agents (anti-angiogenics, PARP inhibitors and immunotherapies) together or with chemotherapy in a rational manner. Hopefully the many ongoing studies will lead to personalized precision medicine approaches and help us treat our patients with the right drug(s) at the right time.”

Duke was involved in several recent clinical trials that were presented at the European Society of Medical Oncology meeting in October 2018.

**Recent Clinical Trials**

**QUADRA:** A single-arm, multicenter phase 2 trial evaluating safety and efficacy of niraparib as fourth or later line of therapy. Enrolling 463 patients with platinum-resistant or refractory ovarian cancer—more than 30 of whom were from Duke—the trial had a high response rate in women with BRCA mutations (31 percent overall), including patients with platinum-sensitive (39 percent), resistant (33 percent) and refractory (19 percent) disease. The findings were particularly exciting, says Secord, who coordinated the study at Duke, because the response to chemotherapy beyond fourth line is less than 10 percent, so this study suggests these patients may have a better option.

**SOLO-1:** A randomized, placebo-controlled, phase 3 trial evaluating olaparib monotherapy in patients with BRCA-mutated advanced ovarian cancer following first-line platinum-based chemotherapy (451 participants). Olaparib reduced the risk of disease progression or death by 70 percent in patients with newly diagnosed advanced BRCA-mutated ovarian cancer. Of patients administered the PARP inhibitor, 60 percent remained progression-free at three years, compared with 27 percent of those taking placebo. Of note, Secord says, olaparib is the only PARP inhibitor to demonstrate an improvement in progression-free survival as a first-line maintenance treatment for advanced ovarian cancer.

**CORAIL:** An international, randomized, phase 3 study of lurbinectedin versus standard of care drugs in patients with platinum-resistant ovarian cancer (442 participants). The drug failed to meet the trial’s primary endpoint of improved progression-free survival, according to results presented by Duke adjunct professor Stephanie Gaillard, MD. Still, Gaillard and her co-authors noted, the drug showed activity and had a favorable safety profile, suggesting that lurbinectedin may have a place in treating patients with platinum-resistant disease, for whom there are not many options.

**Upcoming trials**

Duke has many more trials in progress, Previs says, including a large number of phase 1 trials she coordinates for a variety of different patient populations. Secord leads a number of ongoing phase 2 and 3 clinical trials for ovarian cancer, including four immunotherapy trials for frontline therapy.

Secord is also involved in a study of pembrolizumab combined with paclitaxel chemotherapy for patients with platinum-resistant ovarian cancer. She and the other investigators hope that the addition of chemotherapy to the immunotherapy regimen will enhance its modest antitumor activity.

“When drugs reach phase 3 development, we know the dose to use and that
MIMICKING THE HUMAN PLACENTAL BARRIER

BY MARA CATHERINE SHURGOT, DUKE MED ALUMNI NEWS

The United States has one of the highest rates of preterm birth — up to 10 percent of all pregnancies — in the world. And many pregnancy complications, such as pre-eclampsia, which contributes to preterm birth, are associated with abnormal placenta development.

“One of the reasons we don’t understand pregnancy well is that we don’t understand the human placenta, which is extremely complex,” says Liping Feng, assistant professor of obstetrics and gynecology, who studies pregnancy complications and improving pregnancy outcomes.

“The placenta is one of the most understudied organs because we lack a model for research.”

Researchers have been stymied by the absence of an effective placental research model. Attempts to develop an in vitro model of the placenta that mimics its unique cellular properties have been unsuccessful, and ethical considerations prevent researchers from using the placenta in vivo. As the placenta collects after birth can’t be used to model placental dynamics.

To address this challenge, Feng aimed to create a novel placenta model that would enable researchers to better understand the organ, the cellular interface and the transport of nutrients and foreign components from the mother to the fetus.

Nutrients, oxygen, immunoglobulins and waste all pass through the placenta.

A placenta model would serve multiple purposes. Researchers could study both normal function and disease states; better understand the mechanism of viral transmission, such as Zika, cytomegalovirus (CMV) and HIV; study immune regulation and nutrient transfer; and environmental toxicology. “A system such as this ‘microfluidic placenta on a chip’ is critical for researchers to understand how to optimally protect and nurture a developing fetus, and the design of strategies to avoid some of the perils of pregnancy, including congenital infections, adverse exposures, and preterm birth,” says Permar.

Permar’s team researches maternal and infant immune systems and strategies to prevent the transmission of viral and environmental pathogens between mother and child.

Feng approached George Truskey, MD, PhD, the R. Eugene and Susie E. Goodson Professor of Biomedical Engineering, because of his expertise in microfluidics — the manipulation of small amounts of fluid — and his pioneering research in engineering model tissues and blood vessels.

Truskey’s lab has developed a polycarbonate membrane that is seeded with placental cells drawn from patients who have had a C-section and given consent for a research donation of the placenta. A channel above and below the membrane allows the researchers to draw fluid across at a very low rate, mimicking blood flow through an active placenta. Ultimately, they wish to dissect the route that molecules and virus particles take as they travel between mother and fetus.

A placenta model would serve multiple purposes. Researchers could study both normal function and disease states; better understand the mechanism of viral transmission, such as Zika, cytomegalovirus (CMV) and HIV; study immune regulation and nutrient transfer; and environmental toxicology. “A system such as this ‘microfluidic placenta on a chip’ is critical for researchers to understand how to optimally protect and nurture a developing fetus, and the design of strategies to avoid some of the perils of pregnancy, including congenital infections, adverse exposures, and preterm birth,” says Permar.
The transmission of HIV from mother to child during the birthing process can be largely prevented by antiretroviral drugs such as Nevirapine (NVP) or Zidovudine (AZT). However, in order to be effective, the child must receive the medication within 72 hours of birth; preferably within 24 hours. In Sub-Saharan Africa, many clinics have the drug, but a large percentage of mothers deliver at home. This leaves millions of children at risk of becoming HIV+ during the birthing process or during breastfeeding. In the past, it has not been possible to provide NVP to mothers months before delivery because the drug quickly loses potency once placed in a syringe, the most common delivery method.

Duke’s Pratt School of Engineering has developed a packaging method that extends the life of the NVP and AZT (or any other liquid formulation antiretroviral) by up to twelve months. The Pratt Pouch is a foilized, polyethylene pouch that resembles a fast-food ketchup pouch in appearance. Local pharmacist fill the pouch with the appropriate pediatric dosage under sanitary conditions and label them according to national guidelines. The filled pouches are distributed during antenatal care visits at district hospitals, clinics and on outreach trips to more rural communities by nurses and healthcare workers.

This novel medicine packaging method has received wide acclaim, including recognition from WHO and USAID.

A few months before earning his degree in biomedical engineering, Michael Spohn BS ’09, Duke University Pratt School of Engineering, sat side-by-side with his advisor, Bob Malkin, at a table in Malkin’s office, staring at a graph on a laptop. The figure gave Spohn and Malkin an answer they’d been chasing for a year and a half — and launched one of the most heralded global health innovations to come out of Duke: The Pratt Pouch. This is a proven innovation for fighting mother-to-child HIV transmission in low-resource settings.

Spohn had been conducting dozens of experiments to figure out why antiretroviral medications for babies were degrading over time, a problem that was making it harder to prevent transmission of HIV to newborns in many parts of the world. The World Health Organization recommends that infants receive antiretrovirals immediately after birth, or at least within the first 72 hours, to prevent HIV-positive mothers from passing the virus through birth and breastfeeding.

In low-resource settings, where as many as half of all births take place at home, medications are usually given to pregnant women during prenatal visits, with instructions to begin giving the medication to their babies after birth. Typically, the medications are stored in plastic bottles and given to babies with a spoon, miniature cup or syringe. Not only has this made it challenging for mothers to accurately administer single doses, but the medications degrade when stored for months before the baby arrives.

Spohn had been testing the effect of putting the medication into a heat-sealed pouch, an approach no one had tried before. “It was immediately clear that we’d found the solution,” says Malkin, a professor of biomedical engineering and global health.

With that discovery, the Pratt Pouch was born. The pouch — a small, almost weightless, foilized packet similar to a ketchup packet — preserves a single dose of antiretroviral medicine for up to a year. A mother can squeeze its contents into her baby’s mouth in the critical hours, days and weeks after their birth. It’s currently in use in Ecuador and Uganda, and studies in four countries have demonstrated the pouch’s remarkable promise as an effective, easy-to-use and — at a production cost of four cents — inexpensive method of preventing mother-to-child transmission of HIV.

A decade-long effort

But the pouch, named after Duke’s Pratt School of Engineering, is far more complicated than it appears on the surface. And so too is the decade-long effort that has taken the pouch and the team, including an impressive number of
That journey began in 2008, when Malkin first heard about the problem of antiretrovirals degrading in storage while往往
mediating as a colleague at a conference. He came back to his lab and determined to figure out why this deterioration was happening. He tasked Spohn with testing the two prevailing theories, which had to do with moisture loss from the medication and leaching of the parabens in the medication into the plastic containers. He discovered the problem was that when transferred to a smaller container, such as a spoon or syringe, the liquid medication was turning solid.

Spohn and Malkin started working on a pouch that would hold a single dose of the medication. It took another five years to perfect the design, whose humble appearance conceals some complex engineering.

“It’s actually a sophisticated sequence of five thin layers,” Malkin says. “You need to control the exposure to light and air, the surface-to-volume ratio and the volume-to-volume ratio and determine the optimal thickness of each layer.” The first three layers, which took about three years to formulate, are the critical components that preserve the medication.

When the team began testing the pouch with mothers in the field, the initial reactions surprised them. While foilized pouches are commonplace in Western countries, they were unfamiliar to the women in the study, and many had difficulty opening the packets without a knife or scissors.

After several years of field testing, however, the Pratt Pouch has won women over. Its potential to significantly increase access to antiretroviral medication for babies is critical. Without intervention, the risk of mother-to-child transmission of HIV can be as high as 45 percent, but antiretroviral therapy at delivery potentially reduces the risk to less than five percent. And prevention gives the child the best chance at survival, as more than half of HIV-infected children die before age two.

In addition, women have deemed the Pratt Pouch easier to use and far more helpful in ensuring proper medication dosage for their babies than the conventional spoon, cup and syringe delivery methods. The pouch also gives women control over their babies’ fate, says Humberto Mata, co-founder of Fundación VIDHA, a non-profit organization that’s facilitating the distribution of the Pratt Pouch across Ecuador. “The women who have used the pouch are empowered,” he says. “It has helped them see themselves not as a victim but as powerful and capable of saving their child from this disease.” And the pouch offers yet another benefit: its tiny size allows mothers to maintain discretion about their HIV status.

In 2016, Malkin selected Maternova as the exclusive distributor of the Pratt Pouch. Maternova sells proven obstetric and newborn technologies to private hospitals, governments, Ministries of Health, NGOs (Non-governmental Organizations) and healthcare professionals around the world. In Uganda, for example, where two-thirds of HIV-exposed infants don’t receive antiretrovirals, the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) facilitates distribution with the Pratt Pouch team. The team recently built a high-tech facility at Hospice Uganda in Kampala with semi-custom equipment that fills and seals a pouch in four seconds — one quarter the time it takes to fill pouches manually.

The women who have used the pouch are empowered... It has helped them see themselves not as a victim but as powerful and capable of saving their child from this disease.

Once the pouches are filled at the facility, distribution to hospitals, clinics and, ultimately, expectant mothers with HIV, is coordinated.

“Our goal is to make Pratt Pouch part of the health systems responses to mother-to-child transmission, rather than a standalone initiative,” says Joanne Moore, a former vice president at Chemonics, who established Pratt Pouch Consulting in 2016 to promote the use of the pouch and support governments, NGOs and the private sector in their efforts to expand access to antiretroviral medication for babies born to women with HIV.

Duke Ob/Gyn sees great potential for the Pratt Pouch.

“This is a great example of ways to harness technology to address multifaceted challenges in global health. In the areas where the Center for Global Reproductive Health works in Uganda and Kenya, there is an increasing focus on how to effectively provide community-based care, as their are a host of issues related to logistics, workforce and stigma that may keep patients out of health facilities,” says Megan Huchko, MD, MPH, and director of the Center. “In some of these settings, almost half of women still deliver at home, and, in fact, some women will avoid facility delivery as they fear their HIV status may be disclosed. The Pratt Pouch would meet these women’s needs while still helping them reduce the risk of transmission to their infant, which can be empowering,” notes Huchko.

The pouch — a small, almost weightless, foilized packet similar to a ketchup packet — preserves a single dose of antiretroviral medicine for up to a year. A mother can squeeze its contents into her baby’s mouth in the critical hours, days and weeks after their birth.

PHOTOS BY MARC-GRÉGOR PHOTOGRAPHY
NEW DGHI CENTER ADDRESSES GLOBAL REPRODUCTIVE HEALTH

Over the last decade, much has been learned about the human microbiome. Research on the gastrointestinal microbiome has shown that the carpet of bacteria that live in the gut can impact health in many ways. Studies now show that aside from direct effects on digestion, bacteria in the GI tract have wide-ranging effects on many things, from mental to cardiovascular health.

Despite the information we have gained about the gut microbiome, very little is known about the bacteria that occupy the urinary tract. Recently, researchers conclusively demonstrated that a urinary microbiome exists. We know that this urinary microbiome appears different in women of different ages, and in those with certain bladder conditions like overactive bladder. Nazema Siddiqui, MD, MHSc, associate professor in the Division of Urogynecology and Pelvic Reconstructive Surgery, is conducting pioneering research to study how the urinary microbiome changes with aging and in association with different treatments for recurrent urinary tract infections (UTIs). Siddiqui and her team are combining their knowledge of clinical research with state-of-the-art bioinformatics and analytics to sift through complex urinary microbiome data with the hopes of finding innovative solutions for age-old urologic problems.

**UMICRO**

- Post-menopausal women with recurrent UTIs end up taking a lot of antibiotics over time. Approximately 90 women have enrolled to help us understand how the urinary microbiome changes when using long-term antibiotics.
- Monique Vaughan, MD, third year Urogynecology fellow, is working toward completion of the first set of analyses.
- This work is done in collaboration with Lisa Karstens, PhD, from Oregon Health & Science University, and is funded by the National Institute on Aging (NIA) and the Duke University Pepper Older Americans Independence Center (OAIC).

**ACCEPT**

- What happens when you place probiotics directly into the bladder through an instillation therapy? Could this be helpful to shift bladder bacteria to a more healthful state? Duke University School of Medicine student Emily Romanoff has been working with a team of scientists including collaborators from afar (Tanya Sysoeva, PhD, prior Duke KURe Scholar who is now at University of Alabama-Huntsville) and within the Department (Liping Feng, MD and Zhiqing Huang, PhD) to validate an instillation agent, which will soon be submitted to the FDA for approval.
- In the future, the ACCEPT study will investigate what happens to the urinary microbiome when a probiotic is directly instilled, and also how long these changes may last.

**Innovative Microbiome Analyses**

- Jialing Mao, PhD candidate, received a Duke FORGE grant to work on new and improved modeling techniques for urinary microbiome data. The purpose of Duke FORGE is to bring clinical and analytic communities together to advance “big data” science. His work is mentored by Li Ma, PhD, from the Duke Department of Statistical Science, and Siddiqui.
- Ma is bringing updated statistical modeling and machine learning approaches to microbiome analyses. He is developing new analytic tools that he plans to make publicly available.

— Nazema Siddiqui, MD, MHSc
One of the first things Anthony E. Swartz, B.S., RT(R), RDMS, learned as health education leader for GE in North America, and in the U.S. Navy, was versatility.

“Versatility is key to launching new solutions to complex problems,” says Swartz, Director of Telehealth Development for Duke Ob/Gyn. Previously, he served as a radiographer and sonographer at the Naval Hospital in Beaufort, SC, among other locations, and as a Hospital Corpsman in the U.S. Navy — which he calls the “backbone of healthcare” in Naval medicine. This role in enabled him to function in many “theaters,” varying from nursing, to operating room, to radiology and combat medicine.

Telemedicine, Swartz believes, is a vital element of healthcare’s shift from individual care to population health. “In a global healthcare community, telemedicine is an important part of extending our hand into the communities that are not geographically close to the academic centers where extraordinary expertise is located. With telemedicine, we can deliver our expert care in a less disruptive way to the people who need us the most.”

A primary benefit for patients, Swartz notes, is reduced anxiety. As telemedicine provides exemplary care without an overwhelming drive to an intimidating environment, patients experience less disruption. Also, after initial care, patients hindered by distance are more likely to forgo follow-up care, but telemedicine helps to minimize that gap. New technologies will improve this.

While “video visits” are a large part of telemedicine, one of the field’s greatest advancements is teleradiology, which allows images to be transmitted from remote locations to physicians for interpretation. Maternal-Fetal Medicine benefits from these advancements.

“With steady improvements in technology, we now have the ability to put a ‘virtual MFM physician’ in a prenatal diagnosis/ultrasound room with the ability to see a real-time high-resolution video feed, alongside the still images and ‘cine clips’ that are part of the examination,” Swartz explains. “During or at the end of the exam, the MFM physician may provide guidance to the performing clinician, discuss findings and develop a plan with the patient virtually. Our unique program will use the latest technologies and our advanced clinical expertise to deliver this outcome.”

Telemedicine will not only aid patients, but also community healthcare providers.

“One of our priorities in our program is to extend the clinical capabilities of the sonographers who are providing care in Ob/Gyn practices throughout our state,” Swartz states. “These sonographers, as well as Ob/Gyn clinicians, perform and interpret basic fetal anatomy sonograms in offices around the state. However, when patients need comprehensive, advanced-level sonograms, they would traditionally be referred to academic centers.”

“Telehealth will improve access to excellent care, which is a pressing issue for many patients, particularly those who are disenfranchized,” adds Women’s Community Population Health’s Dmitry Fridman, MD, PhD. He notes that through telemedicine, community health professionals could learn to perform sonograms locally, while remote practitioners provided the interpretations.

“Duke has always been at the leading edge of medicine,” Swartz states. “It takes courage and leadership to step out into telemedicine and to investigate a way to be disruptive in the way we deliver care. The willingness to take risks is a requirement. Others ‘talk’ about telemedicine, we are actually going to do it in a way that has never been done, by connecting providers, equipment, education and patients all on a single cloud-based platform.”
In response to the United States’ relatively high maternal mortality and morbidity rates as well as its socioeconomic and racial disparities, the Society for Maternal-Fetal Medicine has developed an initiative designed to focus on maternal healthcare in recent years. Here, Brenna Hughes, MD, MSc, Maternal-Fetal Medicine specialist and chair of Duke Ob/Gyn’s new Quality, Safety and Peer Review Committee, discusses her work to develop and study quality improvement efforts to address mortality and morbidity rates.

Tell us about your research on interventions for improving maternal outcomes.

The American College of Obstetricians and Gynecologists (ACOG) has a committee opinion with treatment algorithms and recommendations (see sidebar) for caring for patients with severe hypertension in pregnancy—one of the most significant causes of maternal mortality. In response, one of my fellows when I was at Brown pulled together a multidisciplinary task force to review the committee opinion, revise institutional policies for gestational hypertension and preeclampsia, and update electronic order sets. She also made badge buddies and reminders for the physician work rooms and similar locations to make it easy for people to do the right thing.

We then assessed outcomes, with a primary outcome of reaching goal blood pressure (systolic 150 mm Hg and diastolic 100 mm Hg or less) within one hour of the initial intervention—ACOG’s recommended target. Although this goal was not met, we did see decreased time to achieve goal blood pressure after the intervention. That’s significant because, for any individual woman, that decreased time could be the difference between having a stroke or not. So, while we were disappointed that the intervention wasn't as effective as we had hoped, we were encouraged that it did lead to improved care.

Now that you are at Duke, how are you building on your research to address the high incidence of maternal mortality and morbidity?

One of the goals of the Quality, Safety and Peer Review Committee is to ensure we’re optimizing this ACOG committee opinion. Duke has already implemented a similar approach at Duke to the study I did at Brown, including an electronic order set for the management of severe hypertension.

Our plan is to start auditing its use and seeing how well we’re using the order set and controlling hypertension. And even though we have not measured outcomes yet, our acuity at Duke is quite high, and our nurses are very comfortable working with patients with high-risk pregnancies.

So, I anticipate that our highly trained unit will quickly be able to demonstrate improved care.

What are important components of an effective quality improvement effort?

It’s critical to keep in mind that quality improvement is a continuous process. First, you start an initiative, and second, you continuously monitor your quality as quality measures get implemented. You need to be constantly thinking about how to optimize the initiative and what the potential barriers are. Then you need to make iterative changes to make sure you continue to move quality forward.

Our acuity at Duke is quite high, and our nurses are very comfortable working with high-risk pregnancies.
Physicians specializing in women's health are treating increasing numbers of women pursuing parenthood for the first time in their forties, fifties and beyond. Between 1996 and 2016, the CDC reported a 171% increase in the number of women having a child between age 45 and 49 and a 446% increase in the number of women delivering between ages 50 and 54 (CDC National Vital Statistics System, 2016). The rise in later-life parenting can be linked to factors ranging from the advent of assisted reproductive technologies (ART) and donor oocytes to elective egg freezing, delayed marriage, greater professional opportunities for women and the highly publicized pregnancies of older celebrities like Janet Jackson and Brigitte Nielsen. The American Society for Reproductive Medicine hosted a postgraduate course in October 2018 to explore the implications of this trend and assist clinicians in managing these high-risk patients.

The medical implications of conceiving at a significantly older age have been well characterized. Physicians can expect that many older patients will not experience complications, but that a substantial minority will face Cesarean delivery, gestational diabetes, preeclampsia and preterm labor and that a few will cope with fetal demise, myocardial infarction, acute renal failure, pulmonary embolism, or maternal death. From a psychological perspective, women delivering a child over the age of 35 face an increased risk of depression during pregnancy and in the postpartum period.

Delivering a baby only places an individual at the starting line of parenting, a journey that continues in varying intensities for the rest of one's life. Patients who became first-time parents through ART in their 40s report benefits of later parenting including feeling more mature, emotionally ready for parenthood and financially secure, as well as disadvantages such as facing the stress and expense of infertility treatment, having a smaller family size than originally desired, lack of physical energy and awareness of having fewer years of life to spend with their child. Two-thirds of these later-life mothers and fathers concluded that the optimal age for becoming a parent is in one's early to mid-30s and 90% recommended that people should try to conceive before age 40.

Increasingly, researchers are beginning to examine the long-term medical and psychosocial risks to the children born to older parents. Children of older mothers, but not older fathers, may have higher IQ scores, better language development and fewer behavioral problems, but also higher rates of Asperger’s syndrome and Pervasive Developmental Disorders. Children of fathers over age 45 face significantly higher rates of Schizophrenia, Autism, ADHD and Bipolar Disorder, likely due to de novo mutations that accrue over a lifetime of spermatogenesis.

From an actuarial perspective, the later in life a person becomes a parent, the sooner their child will face caregiving responsibility and parental death. Author Tom Scocca (2018) framed it this way: "...The inverse of the question of when you feel old enough to have a baby: When will your children be old enough to have dying parents?" A woman who becomes a mother at the age of 50 has a 15% chance of death by the child's 20th birthday and is likely to be deceased by the time her child reaches the age of 32. A man who becomes a father at age 50 has a 22% chance of death by the child's 20th birthday and is likely to be deceased by the time his child reaches the age of 29. Children who experience the loss of a parent at an earlier developmental stage are at risk for lower academic achievement, social withdrawal, psychiatric disorders and health problems into adulthood.

Clinical Implications: A review of these data suggest that becoming a parent over the age of 40 is likely to be associated with both unique joys and significant challenges. Physicians providing care to women across the reproductive life cycle can have a significant impact on patient and family outcomes.

Reproductive Endocrinologists providing ART to older patients must follow guidelines established by the American Society for Reproductive Medicine (ASRM, 2016), which state: Treatment of women over age 55 should be discouraged.

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Duke Ob/Gyn’s Minimally Invasive Gynecologic Surgery Division recently performed a procedure on a unique patient — Ruby the chimpanzee — at the North Carolina Zoo. The request was made to MIGS after veterinary medicine specialists at the zoo determined that, due to health concerns and complications with oral birth control, the procedure was necessary. Former resident Laura Newcomb, MD (and current MIGS fellow at the University of Pittsburgh) and Craig Sobolewski, MD, MIGS Division Chief, share their experience operating on a lovable primate.

**Why was working with the N.C. Zoo such a unique and beneficial opportunity as a teaching tool for Duke Ob/Gyn trainees?**

LN: Operating on Ruby was truly an incredible experience for me. My name was given to a veterinarian surgeon, Meghan Kruse, DVM, DACVS-SA, at Veterinary Specialty Hospital of the Carolinas, who was looking for an Ob/Gyn consultant to help perform a bilateral tubal ligation on a chimp from the N.C. Zoo. While I’ve operated with a variety of surgeons from different specialties, I never considered or appreciated the challenges of working with animals. Thankfully, the amazing Dr. Sobolewski agreed to join and help out.

The experience was a great exercise in taking me out of my comfort zone and forcing me to think on my feet, which is invaluable as a physician.

CS: The appreciation with the similarities between primate and human anatomy was remarkable and the opportunity to share our vast experience in laparoscopy with our veterinarian colleagues to provide best-of-care treatment for such a precious life was a truly memorable and rewarding experience. The realization of ways that we can collaborate and innovate across disciplines was profound.

**Why was a MIGS procedure recommended, rather than a traditional open procedure?**

LN: In most all situations, a minimally invasive approach to these types of procedures is recommended for all animals — humans, dogs, apes, etc. — due to the decreased risk of complications and faster recovery. In the case of a chimpanzee, this is especially true as the idea of “taking it easy” is somewhat lost on an animal as soon as their soreness has resolved.

CS: Chimpanzees are fastidious groomers. They cannot be easily distracted from large wound closures associated with traditional open surgery. As with humans, a minimally invasive approach will allow Ruby to get back to her normal activities more rapidly, with less concern for wound related complications.

**What accommodations did you have to make in order to accomplish success while working in this setting?**

CS: We really left most of that up to the excellent veterinary staff from the N.C. Zoo and Veterinary Specialty Hospital of the Carolinas. Once they had anesthetized our patient, the approach to the surgery itself was very collaborative. There were a few times that we had to improvise solutions due to a lack of chimpanzee-specific instruments, but for the most part, the similar anatomy and outstanding facilities made for a case that, in many ways, closely simulated a similar procedure if it were being performed on a human.

**What was your main takeaway?**

LN: I never would have imagined that I would be operating on a chimp, but I am thankful for the opportunity to grow as a surgeon. I enjoyed the experience of working on a multi-disciplinary team, and learning new and exciting things; I would do it again in a heartbeat!

CS: The compassion to give the best of care to all of our patients transcends disciplines.
**Division of Women’s Community & Population Health Established**

The Division of Women’s Community and Population Health, led by interim Director Beverly Gray, MD, was established in 2018. It is structured around a common mission: to improve the health of women in our communities, particularly the underinsured and underserved in NC. Faculty provide essential women’s health programs like the Family Planning Clinic and Cervix Clinic. The Division also encompasses Global Reproductive Health (through the Duke Global Health Institute).

**Duke Ob/Gyn, Duke Children’s Collaborate on Initiatives for Mothers and Babies**

**Stop CMV!**
Maternal-Fetal Medicine specialist Brenna Hughes, MD, MPH, and Sallie Permar, MD, PhD, pediatric infectious disease specialist, presented at the National Institute of Allergy and Infectious Diseases (NIAID) Conference on Congenital Cytomegalovirus infection. The NIH conference discussed advancing strategies for prevention and treatment of CMV to decrease the burden of congenital CMV — the most common viral infection passed to the fetus during pregnancy.

Hughes also received a $200,208 grant to further study CMV from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); Permar is co-investigator.

**Human Development (NICHHD) and NIAID**
The conference brought together scientists to discuss research needed to advance development of a vaccine and treatment strategies to decrease the burden of congenital CMV — the most common viral infection passed to the fetus during pregnancy.

**Project Hope1000**
Project Hope 1000, a Children’s Health & Discovery Initiative (CHDI) research study, launched in November. The cohort study is led by Permar and Geeta Swamy, MD, Vice Dean and Associate Vice Provost for Scientific Integrity for the Duke University School of Medicine, and Vice Chair for Research and Faculty Development for Duke Ob/Gyn. Project Hope 1000 is comprised of 1000 mother-infant pairs and focuses on biological measures during the first 1000 days of life to understand the links between pregnancy factors and mother/infant health outcomes.

New participants will be eligible to enroll in the study during the next three years. Further information is available at childrensdiscovery@dm.duke.edu.

**How Old is Too Old continued from page 13**

Oocyte and embryo donation should be strongly discouraged or denied if patients age 45-54 have underlying medical problems that will further increase their obstetrical or neonatal risks.

It is ethically permissible to decline treatment to women >45 years “based on concerns over health and well-being of patient and offspring.”

When treating patients of advanced reproductive age, ASRM Recommends:

- Medical evaluation of women > 45 by a high-risk OB
- Counseling about the medical risks associated with use of autologous sperm over age 45
- Consideration of the use of a gestational carrier if pregnancy is medically contraindicated
- Strong recommendation for single embryo transfer
- Psychosocial evaluation to determine if adequate supports exist to raise a child to adulthood
- Psychological counseling about the implications of delayed parenthood

Undoubtedly, this is an area where an ounce of prevention is worth a pound of cure. Discussing optimal timing of parenting and the risks of waiting too long is much more helpful when a woman is in her 20s and has time to consider her options. Given the emphasis in early health education on preventing unwanted pregnancy, the majority of young men and women have poor fertility awareness. Gynecologists treating women in their 20s and 30s should discuss the natural reproductive life cycle, risks of delayed parenting and dispel myths about egg freezing. Obstetricians caring for women delivering over age 35 should screen for perinatal mood (both the PHQ-9 and Edinburgh Postnatal Depression Scale are endorsed by ACOG) and educate partners about warning signs of poor coping in the perinatal period. Obstetricians and gynecologists are uniquely positioned to provide young people with accurate data and thus empower them to make informed choices about the optimal timing of family-building.

References available by contacting julia.woodward@duke.edu
MISSION
Deliver better health and hope to all women and their families through compassionate care, innovation, education and discovery

VISION
Set the global standard of excellence and lead the future of women’s healthcare

CORE VALUES
Excellence
Integrity
Innovation
Diversity and Inclusion
Teamwork
Continuous Improvement
Community
Advocacy

More than 250 Attend Inaugural Donald T. Moore, MD Endowed Lecture at the Durham Armory

Duke Ob/Gyn’s Inaugural Donald T. Moore, MD Endowed Lecture was held October 24, 2018 at the Durham Armory and was attended by more than 250 community leaders, Duke executives, members of the Durham community and several generations of the Moore family. Distinguished speakers Henry Foster, MD (far left) and Louis Sullivan, MD (far right) gave powerful talks on achieving health equity in the U.S., and racial and ethnic diversity in medical schools, respectively. Pictured with the speakers are Sarahn Wheeler, MD; Matthew Barber, MD, MHS; and A. Eugene Washington, MD, MPH, MSc, Chancellor for Health Affairs at Duke University, President and CEO of DUHS. The event was co-sponsored by Duke Health’s Office of the Chancellor, the Duke University School of Medicine and the Office of Diversity & Inclusion. The next lecture will take place in 2020. Details will be publicized on the Department’s website and Twitter.