Cleveland Clinic

Glickman Urological & Kidney Institute

2016 Year in Review

Contents

Glickman Urological & Kidney Institute

AT A GLANCE

The Glickman Urological & Kidney Institute's activities encompass a unique combination of high-volume and challenging clinical cases, extensive basic and translational scientific efforts, and innovative laboratory research conducted in an environment that nurtures the future leaders of its specialties.

INSTITUTE VITAL STATISTICS (2015)	
55	Urologists
28	Nephrologists
26	Advanced Practice Providers
30	Urology Residents
15	Urology Fellows
9	Nephrology Fellows
290	Employees

U.S. News & World Report's "Best Hospitals" survey has ranked the institute's urology program as one of the top two programs in the United States every year since 2000. In 2016, the survey ranked the institute's urology and nephrology programs No. 2 in the nation.

U.S. NEWS & WORLD REPORT RANKINGS		
YEAR	NEPHROLOGY	UROLOGY
2012	1	1
2013	2	2
2014	2	1
2015	2	2
2016	2	2

BY THE NUMBERS

(2015)

96,353
OUTPATIENT VISITS

9,658
CASES

18,329
DIALYSIS TREATMENTS

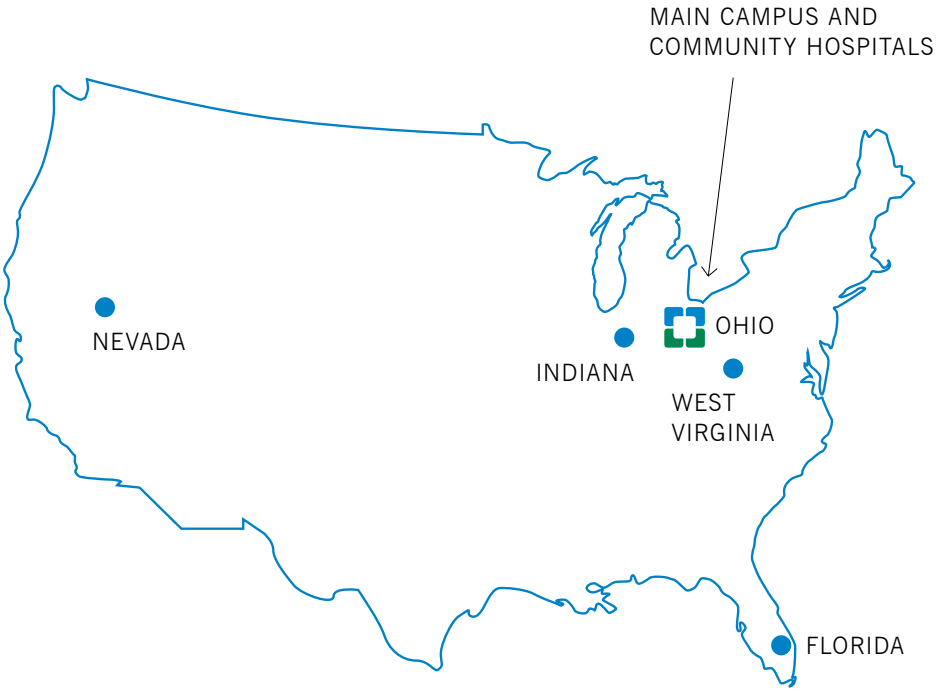
2,736
ADMISSIONS

12,668
PATIENT DAYS

4.63
MEAN LENGTH OF STAY (DAYS)

NUMBER OF SURGICAL CASES (2015)	
482	Benign Prostatic Hypertrophy
903	Endourology and Stone Disease
783	Female Urology
207	Male Fertility
286	Pediatric Urology
656	Genitourinary Reconstruction
243	Renal and Pancreas Transplant
2,863	Urologic Oncology

LOCATIONS



CENTERS

NEPHROLOGY

- Blood Pressure Disorders
- Chronic Kidney Disease
- Dialysis
- Renal and Pancreas Transplant
- Renal Diseases

UROLOGY

- Endourology and Stone Disease
- Female Urology
- Genitourinary Reconstruction
- Kidney and Pancreas Transplant
- Male Fertility
- Men's Health
- Minority Men's Health
- Pediatric Urology
- Robotic and Image-Guided Surgery
- Urologic Oncology

PATIENT ORIGINS (2015)

- All 88 Ohio counties
- All 50 U.S. States
- 70 countries

PUBLICATIONS (2015)	
47	Books
474	Chapters
200	Articles

ERIC A. KLEIN, MD
CHAIRMAN, CLEVELAND CLINIC GLICKMAN UROLOGICAL & KIDNEY INSTITUTE

MESSAGE FROM THE CHAIRMAN

Dear Colleagues,

At Cleveland Clinic, we are relentless quantifiers and consumers of healthcare data. This analytical trait is in our institutional DNA. As one of our founders, genitourinary surgeon William E. Lower, MD, explained more than a century ago in a 1914 annual report of the group practice that spawned Cleveland Clinic, "the careful computing of our clinical results … is a guide as to the value of any method of treatment. It is only by summing up the year's work that we can get a keen appreciation of what we have accomplished."

So what did the Glickman Urological & Kidney Institute accomplish in 2016? As the following pages reveal, we leveraged data and technology (in amounts and ways that likely would have astounded Dr. Lower) to improve our patients' outcomes and lives. We strived to continue the tradition of innovation that has consistently placed our urology and nephrology programs among the nation's best in *U.S. News & World Report*'s annual rankings.

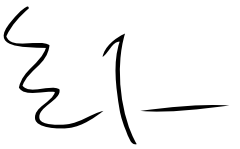
Innovation is an attitude, an instinct — a drive to know more and do better and push boundaries. It can be a difficult thing to quantify. But the results are undeniable, as I think you will recognize in these accounts, such as our work to re-create a vaginal canal from a bowel segment; to preserve renal function by cooling the kidney with ice slush during robotic partial nephrectomy; and to develop new prostate cancer diagnostic tools.

In 2016 we also prepared to expand and improve services for dialysis patients with the construction of the Cleveland Clinic East dialysis facility, opening in 2017. And we contributed to medical education with the publication of "Andrological Evaluation of Male Infertility," a comprehensive laboratory guide for reproductive professionals, along with more than 400 published peer-reviewed manuscripts.

Finally, speaking of Dr. Lower, in 1921 he organized the inaugural meeting of the Clinical Society of Genito-Urinary Surgery in Cleveland, a gathering of the nation's most prominent urologists to review medical issues and observe surgical demonstrations. In October 2016 the Urological & Kidney Institute was honored to host the 94th annual meeting of the organization, since renamed the Clinical Society of Genitourinary Surgeons. It was an outstanding opportunity to share ideas and discuss our specialty's challenges and opportunities, as well as to show off the best of Cleveland.

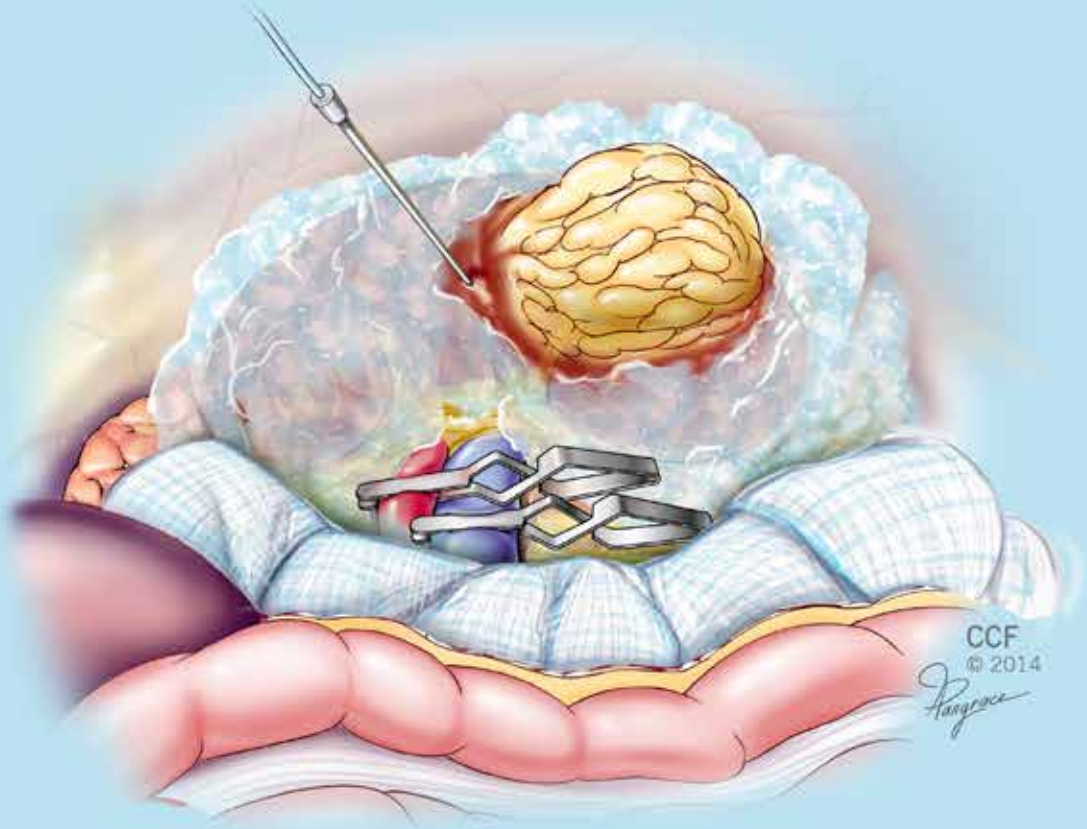
I welcome your feedback on what you read in *Year in Review* and invite you to collaborate with us on patient care and research in the year ahead.

Sincerely,



Eric A. Klein, MD

Chairman, Glickman Urological & Kidney Institute
Professor, Cleveland Clinic Lerner College of Medicine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2016 HIGHLIGHT

Icing During Robotic Partial Nephrectomy for Complex Tumors Mirrors the Open Technique

Urologic surgeons are using robot-assisted systems in increasingly complex cases due to the equipment's pinpoint control, high magnification and minimal invasiveness.

One such application is partial nephrectomy (PN), where the robot's precision aids removal of large, deeply infiltrating renal tumors while enabling surgeons to spare valuable nephrons.

To ensure proper visualization of the surgical field during PN, the renal hilum must be temporarily clamped. "Cooling the kidney to temperatures of 10°-20°C allows for more prolonged clamp times which can be very helpful for complicated excisions. Our experience with over 5,000 partial nephrectomies suggests that hypothermia provides the strongest and most consistent protection against irreversible ischemic injury," says urologist Steven Campbell, MD, PhD.

Maintaining adequate renal hypothermia while protecting adjacent bowel can be difficult in minimally invasive settings. In 2003, Cleveland Clinic surgeons were the first to perform laparoscopic PN using ice slush.

In 2014, they introduced a novel, easily reproducible robotic PN intracorporeal renal hypothermia technique employing ice slush. In 2016, the surgeons continued to refine this technique and gained experience, having performed about 40 procedures to date.

"We developed a cost-effective, minimally invasive approach with minimal additional morbidity to the patient," says Jihad H. Kaouk, MD, the Urological & Kidney Institute's Vice Chair for Surgical Innovations and Director of the Center for Robotic and Image-Guided Surgery.

A Way to Buy Time

The sterile ice slush used in the robotic PN procedure is preloaded into modified 20 mL syringes and injected into the abdomen and packed around the kidney via a lateral 12 mm accessary port. Approximately half a liter of slush can be introduced within five minutes and achieves consistent renal cooling in the range of 15°C. A laparoscopic sponge is placed around the kidney as a thermal barrier to protect nearby intestine. Renal and core body temperatures are monitored during the procedure. After tumor excision and renorrhaphy, the remaining slush is suctioned or placed along with the specimen in an entrapment sac.

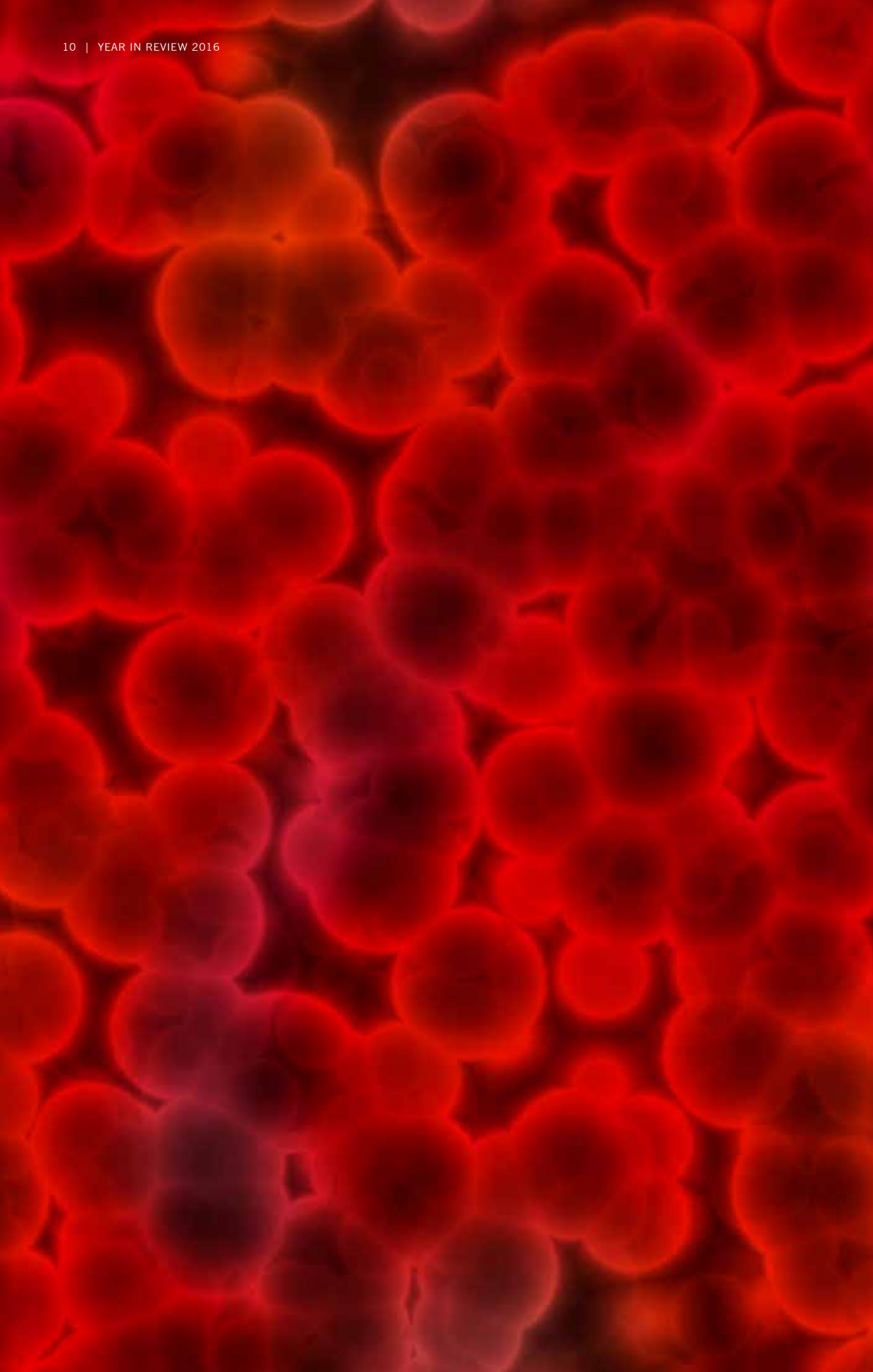
"Intracorporeal ice cooling of the kidney allows the surgeon more time to cut out complex kidney tumors and reconstruct the kidney," Dr. Kaouk says. "This technique is not for every case, but is beneficial whenever ischemia time is anticipated to be longer than 25 minutes."

Short- and Long-Term Impacts

The team analyzed the postoperative renal function of patients with similar preoperative estimated glomerular filtration rates (eGFR), tumor size and complexity who underwent robotic PN using either cold or warm ischemia.

The comparison showed that ice slush robotic PN was associated with a 12.9 percent greater preservation of eGFR in the short-term (one- to three-week) postoperative period. There was no difference in eGFR between the cold and warm ischemia cohorts after six months. Additional research will better define icing's short- and long-term impacts, Dr. Kaouk says.

LEFT — A 10 x 45 cm laparoscopic sponge around the kidney protects the bowel from ice slush.



2016 HIGHLIGHT

The Shape of Things to Come in Prostate Cancer Testing

Although the prostate-specific antigen (PSA) assay revolutionized the early detection of prostate cancer, over time its shortcomings have made its use as a mass screening test controversial.

Benign conditions such as inflammation and infection can elevate PSA serum levels, driving the test's false-positive rates as high as 75 percent. And in cases where an abnormal PSA result indicates cancer, the test can't distinguish indolent from aggressive disease. The result can be patient anxiety, overtreatment and unnecessary expense.

Is there a better way? Cleveland Clinic researchers believe they've found one with the IsoPSA™ test, a new approach to prostate cancer diagnosis developed in collaboration with Cleveland Diagnostics Inc. In 2016, the researchers reported promising preliminary results from a multicenter clinical trial validating IsoPSA.

"We took an out-of-the-box approach that has shown success in detecting prostate cancer and indicating its aggressiveness," says Glickman Urological & Kidney Institute urologist Mark Stovsky, MD, who is Cleveland Diagnostics' Chief Medical Officer and has an investment interest in the company.

Protein Concentration Versus Structure

PSA and similar tests measure expression of a biomarker as determined by its concentration in either blood or urine. While a tumor may trigger PSA overexpression, so can benign prostatic hyperplasia and other nonmalignant conditions. Conversely, some prostate tumors don't elevate PSA levels.

Rather than relying on altered expression levels, IsoPSA detects specific structural modifications, or isoforms, of the PSA protein that are characteristic of cancer, directly related to structural changes likely stemming from oncogenic mutation.

The test uses a customized biphasic aqueous-based solvent system to separate PSA isoforms based on their structure and interaction with other proteins. Each of the two solvent phases contains different amounts of the various PSA isoforms. A standard enzyme-linked immunosorbent assay measures the aggregate PSA isoform concentration in each solvent phase. A unique ratio, K, expresses the relative concentrations of PSA isoforms in the two phases and represents a composite structural index, which is subsequently calibrated using blood samples from patients with known clinical status.

In preliminary results from an ongoing clinical trial reported in 2016, IsoPSA was substantially more accurate than PSA in distinguishing patients with and without biopsy-confirmed prostate cancer. IsoPSA also was reliably able to differentiate patients with high-grade (Gleason score ≥ 7) cancer from those with low-grade (Gleason $= 6$) disease and benign findings.

An update, reflecting the analysis of 217 patient samples, shows that for high-risk cancers, defined by the test composite index KP > 64 percent, IsoPSA's specificity is 95.2 percent, positive predictive value (PPV) is 79 percent and negative predictive value (NPV) is 75 percent. For low-risk cancers, defined by KP < 15 percent, the test's sensitivity is 95.8 percent, NPV is 96 percent and PPV is 47 percent. Prospective use of IsoPSA would have reduced unnecessary biopsies in the low-risk cohort by 52 percent.

"These findings show that using structural changes in the PSA protein to detect cancer is effective and can help prevent unneeded biopsies in low-risk patients," says Urological & Kidney Institute Chairman Eric Klein, MD, a co-author with Dr. Stovsky of the preliminary IsoPSA evaluation.

The trial will expand to additional sites in 2017.

LEFT — Red blood cells.

2016 HIGHLIGHT

Surgical Innovation: Fashioning a Vagina from Intestinal Segment

Re-creating a missing or malformed body part is one of surgery's biggest challenges. Cleveland Clinic pediatric urologic surgeon Audrey Rhee, MD, faced that prospect when a 17-year-old patient born without a vagina contacted her in March 2016.

At birth the patient was diagnosed with complete androgen insensitivity syndrome. Although the patient possessed a Y chromosome, unresponsiveness to androgenic hormones prevented masculinization during fetal development, and she was phenotypically female. Her genitalia were somewhat ambiguous but mostly female. Gonads were in the expected position of the ovaries and were surgically removed when the patient was 8 months old. At age 11 she began supplemental estrogen for secondary sexual development and bone mineralization.

As the patient prepared for college, she decided that she wanted a functional vagina. "She wanted the ability to have a sexual relationship, which most of us take for granted," Dr. Rhee says. "She wanted to be like her peers. I spoke to her extensively to make sure she was ready for the surgery. I give credit to her family, who completely supported her decision."

An Uncommon Procedure

Surgeons have devised numerous vaginal reconstruction techniques, including grafting autologous skin or mucosal tissue, tissue-dilation balloon vaginoplasty, transplantation of acellular porcine intestinal submucosa, and autologous bowel (either ileum or sigmoid colon) vaginoplasty. The latter technique, which the patient opted for, was introduced in 1904 but is relatively uncommon. Dr. Rhee had performed the procedure twice prior to joining the institute faculty in 2012.

Dr. Rhee elected to use a vascularized sigmoid segment, which is more robust and trauma-resistant than the ileum, produces less mucus and can be easily repositioned due to its proximity to the perineum.

Operative Teamwork

The complex 12-hour laparoscopic procedure involved two pediatric urologic surgeons and two pediatric general surgeons. The neovagina was created from a 12 cm sigmoid segment that was fashioned into a pouch, rotated with its blood supply into the plane between the bladder and rectum, and secured by suturing the proximal, open end of the pouch to the dissected neo-introitis in the perineum and suturing the distal end to the sacral promontory. Dr. Rhee performed a labiaplasty using bilateral V flaps to construct the labia majora and redundant tissue around the clitoris to form the labia minora, and created a clitoral hood. The surgeons also performed laparoscopic excision of the prostatic utricle to correct urinary incontinence.

Recovery was uneventful. The patient must dilate her neovagina daily to avoid stenosis. Clitoral sensation and mucus secretion are normal.

"This procedure has given her the ability to be intimate with a partner and to be as honest and open as she wants," Dr. Rhee says.

An advantage of having the surgery at Cleveland Clinic, Dr. Rhee says, is the extensive institutional experience in minimally invasive urologic surgery and the teamwork among pediatric and adult caregivers, making the transition of patients with congenital conditions to adult care seamless.

RIGHT — Audrey Rhee, MD.

2016 HIGHLIGHT

Early Salvage Radiotherapy at Low PSA After Prostatectomy Improves Outcomes

Biochemical recurrence of localized prostate cancer after radical prostatectomy (RP), defined as a detectable or increasing serum prostate-specific antigen (PSA) level ≥ 0.2 ng/mL, is common in men with adverse risk factors. It is associated with increased risk of metastasis and death.

Since postoperative radiotherapy is potentially curative but exposes patients (perhaps needlessly) to toxicities and risk, the question of when to initiate treatment — adjuvantly, before evidence of recurrence or as salvage therapy only after PSA levels rise — is important.

Recent research has shown that adjuvant radiotherapy in RP patients with adverse pathology reduces the risk of biochemical and local recurrence and clinical progression compared with observation.

The timing and potential benefits of salvage radiotherapy (SRT) in RP patients had not been as well-addressed. But in 2016 Cleveland Clinic researchers and their colleagues provided significant insights with the results of two retrospective studies — the largest of their kind — using a cohort of more than 2,450 men with detectable post-RP PSA (≥ 0.01 ng/mL) treated with SRT with or without concurrent androgen deprivation therapy and followed for a median of five years.

The first study, published in the *Journal of Clinical Oncology*, found that patients treated with early SRT at the lowest detectable PSA level were more likely to remain free from biochemical failure and less likely to develop distant metastases compared with patients who underwent SRT at higher PSA levels.

The second study, presented at ASTRO 2016, determined that early SRT initiated at PSA levels ≤ 0.2 ng/mL was associated with reduced rates of both prostate cancer-specific mortality and all-cause mortality, compared with SRT at higher PSA amounts.

"Mortality outcomes from salvage radiotherapy after prostatectomy have been largely unexplored, so this study provides important information," says Rahul D. Tendulkar, MD, Clinical Director of the Department of Radiation Oncology at Cleveland Clinic Cancer Center and a co-author of both studies.

"The PSA at time of salvage radiotherapy seems to be an independent predictor of mortality outcomes," Dr. Tendulkar says. "Historically, most predictors of mortality have been tumor-related. But in our study, PSA was a significant predictor of mortality, while some tumor-related factors were not." The findings are supportive of ASTRO and American Urological Association guidelines, which recommend SRT at the first sign of a PSA rise after RP.

Optimal postoperative management of men with prostate cancer is an area of ongoing research. The present SRT studies do not support basing treatment decisions solely on detectable PSA; instead, a combination of factors should be considered, Dr. Tendulkar says.

According to Andrew Stephenson, MD, Glickman Urological & Kidney Institute's Director of the Center of Urologic Oncology, "While it is intuitive to think that adjuvant radiotherapy (when the PSA is undetectable) leads to better outcomes, the data supporting adjuvant versus salvage radiotherapy is conflicting. Clinicians should administer salvage radiotherapy when convinced that the pattern of PSA rise is indicative of recurrent cancer and not necessarily wait for a prespecified PSA threshold like 0.2 ng/mL. This study suggests better outcomes when salvage radiotherapy is administered at levels less than 0.2 ng/mL."

LEFT — Rahul D. Tendulkar, MD.

2016 HIGHLIGHT

Advanced Dialysis Center Means a New Day (and Night) for Care

The water that flows from a household faucet is heavily filtered, but impurities remain — microbes; trace elements such as lead, zinc and copper from piping; and treatment additives like chlorine, fluoride and aluminum.

In miniscule amounts, these contaminants shouldn't pose problems for a healthy adult.

But a kidney disease patient undergoing hemodialysis is exposed to as many as 32 gallons of water in each treatment session, three times a week. That large volume concentrates exposure to waterborne contaminants and amplifies their potential harm, making extra filtration critical to the dialysis process.

Fortunately, among the many highlights of Cleveland Clinic's new dialysis facility, Cleveland Clinic East, is one of the nation's most advanced water filtration systems for hemodialysis.

The AquaB*plus* filtration system consists of two pairs of dual-pass reverse osmosis membranes to supply ultra-purified water to the facility's 56 hemodialysis stations.

"This is completely new technology for the United States," says Medical Director Robert Heyka, MD, Chairman of Glickman Urological & Kidney Institute's Department of Nephrology and Hypertension.

The system uses heat disinfection rather than chemicals, increasing efficiency and patients' and employees' safety. Equipment automation and programmability create the scheduling flexibility to allow nocturnal hemodialysis at the new center, a first for patients on Cleveland's East Side. Overnight dialysis, conducted in seven- to eight-hour sessions rather than the usual four, increases the amount of waste removal from larger patients, making them feel better. For all patients, it frees up daytime hours for work or other activities.

The two-level, 32,575-square-foot facility, a joint venture of Cleveland Clinic, Fresenius Kidney Care and the MetroHealth Medical System operating as Ohio Renal Care Group, is purpose-built for dialysis care.

Hemodialysis stations are on the first level, making access easy for patients with mobility issues. Expansive windows, a waiting area with a fireplace and outdoor picnic tables maximize patients' and caregivers' well-being.

Dialysis chairs are heated, reclining and massaging and are equipped with TVs and internet access. "Sitting in a dialysis chair for four hours is like taking a cross-country flight three times a week," Dr. Heyka says. "We're going from coach to first class in terms of improving our patients' comfort."

The facility's upper level houses services for home-dialysis patients, including training areas for peritoneal dialysis and hemodialysis, and exam rooms for appointments with physicians, nurse practitioners, dietitians and social workers.

"Cleveland Clinic East will be the premier dialysis facility in Northeast Ohio," Dr. Heyka says. "It will expand the number of patients we're able to treat, and will improve their care and comfort."

LEFT — The highly automated components in Cleveland Clinic East's filtration system remove contaminants in water before dialysis.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2016 HIGHLIGHT

New Guide Aims to Elevate Quality in Andrology Labs Worldwide

The incidence of male infertility is a global concern due to increasing rates of obesity and diabetes. High rates of smoking, especially in the Middle East and parts of Asia and Eastern Europe, also are a serious risk factor for deterioration in semen quality.

At the same time, sperm testing is becoming increasingly important for couples trying to conceive, but the reliability of results remains highly inconsistent.

"We see in the literature that the quality of andrology testing varies considerably between labs and can be highly inaccurate and unreliable," says Ashok Agarwal, PhD, Director of the Andrology Center at Cleveland Clinic's Glickman Urological & Kidney Institute. "Patients spend huge amounts of money and time but are not getting meaningful results. Clinicians and patients are not being well-served."

To address these concerns, Dr. Agarwal and his colleagues Sajal Gupta, MD, the Andrology Center's supervisor, and Rakesh Sharma, PhD, its coordinator, have co-authored *Andrological Evaluation of Male Infertility: A Laboratory Guide*. The 215-page book, published in 2016, is a comprehensive one-of-a-kind volume intended for reproductive professionals, specialists, clinicians and lab technologists involved in infertility testing, diagnosis, counseling and treatment.

The editors have more than 50 years of combined experience in andrology testing. Dr. Agarwal has edited more than 30 medical textbooks, and his research group has published hundreds of peer-reviewed journal articles in the past 24 years. A recent study in the journal *Andrology* determined that Dr. Agarwal's research group has produced the largest number of peer-reviewed, high-impact male infertility research articles in the world.

Many of the tests described in the new book were researched, developed and standardized in the Andrology Research Lab directed by Dr. Agarwal.

Practical and Simple

"Our guide informs readers about best practices and standard operating procedures for each test for male infertility," Dr. Agarwal says. "It provides streamlined protocols and A to Z information. It describes everything from equipment and supplies needed to set up a lab to licensing and accreditation to step-by-step instructions and illustrations for each clinical protocol. It is useful for everyone in the field, but especially for reproductive professionals working in in vitro fertilization and andrology laboratories around the world," he adds. "In fact, for each test we provide a one-page visual summary that can be removed from the book and displayed right at the bench.

"Our team worked nonstop for almost three years to produce the laboratory manual," Dr. Agarwal says. "It was a labor of love."

The editors hope that, by following the time-tested, evidence-based best practices and protocols presented so clearly in their book, labs worldwide will be able to better assist millions of couples trying to conceive.

LEFT — Ashok Agarwal, PhD (left), and Sajal Gupta, MD.

2016 HIGHLIGHT

Personalized Medicine for Prostate Cancer

The main question men should ask when diagnosed with prostate cancer is not, "What is the best treatment for my cancer?" but rather, "Does my cancer need to be treated at all?"

Prostate cancer is the most common cancer in men. It accounts for almost as many new diagnoses as the second and third leading cancers (lung and colorectal) combined. Unlike lung and colorectal cancers, however, prostate cancers tend to grow slowly and often cause no problems.

There is overwhelming clinical data to favor surveillance over treatment in up to 40 percent of patients. However, Glickman Urological & Kidney Institute Chairman Eric Klein, MD, says fewer than 12 percent of men with prostate cancer elect surveillance, instead opting for unnecessarily aggressive treatment. "This overtreatment has become such an epidemic in oncology that the U.S. Preventive Services Task Force now discourages routine prostate-specific antigen (PSA) screening," Dr. Klein says.

A multitude of molecular tests and algorithms has been developed to improve diagnoses, enhance patient risk stratification and identify aggressive versus indolent disease. "Cleveland Clinic is leading the charge in both developing and validating these technologies to deliver the right treatment at the right time — or no treatment at all," he notes.

Major Recent Milestones

- Medicare approval of Oncotype DX® — Available through Genomic Health Inc., this test relies on a genomic prostate score (GPS) developed at Cleveland Clinic. The test evaluates expression of 17 genes in biopsied tumors and surrounding tissue to help identify men who are good candidates for surveillance.
- Validation of IsoPSA — Developed by Cleveland Clinic in collaboration with Cleveland Diagnostics Inc., this noninvasive blood test interrogates the entire PSA isoform distribution and identifies structural changes in the PSA protein that correlate with the presence or absence of cancer and with a cancer's aggressiveness.
- Validation of Decipher® for adjuvant radiation — In collaboration with GenomeDX Biosciences Inc., and other institutions, the Institute undertook validation of the Decipher Prostate Cancer Classifier to identify tumors most likely to benefit from adjuvant radiation. Preliminary results show that evaluating expression of 22 different genes in tumors can help physicians decide whether adjuvant radiation therapy may be of benefit after radical prostatectomy.
- Decipher GRID studies — Our researchers have partnered with GenomeDx to create one of the world's largest clinically annotated genomic expression databases for urologic cancers, which they will use to develop an assay that can guide individual treatment plans for each patient, based on the molecular characteristics of individual tumors.

LEFT — Dr. Klein discusses personalized medicine with Cleveland Clinic colleagues.

2016 Achievements

Blood Pressure Disorders

Current clinical practice, endorsed by hypertension guidelines, is to lower systolic blood pressure (SBP) to less than 140 mm Hg in most patients. The recent Systolic Blood Pressure Intervention Trial (SPRINT), a multicenter, randomized controlled trial, demonstrated that more aggressive BP control (aiming for an SBP of less than 120 mm Hg) in older patients with cardiovascular risk (but without a history of diabetes and stroke) results in a significantly lower risk of cardiovascular disease and death compared with standard practice.

The benefits and risks of intensive BP control have to be weighed carefully, rather than using a blanket approach to intensify treatment in all older adults. Based on the study results, it would be reasonable to target lower SBP goals in patients who fit the SPRINT trial criteria *and* are able to tolerate intensive BP lowering, provided they can be closely monitored for potential adverse events (including hypotension, electrolyte abnormalities and change in renal function).

As more medications will likely be needed for intensive SBP control, it is important to keep in mind both the side effects and tolerability of medications with polypharmacy, as well as potential nonadherence with increasing complexity of medication regimens. Greater emphasis should be placed on educating healthcare providers and patients about proper BP measurement technique. Out-of-office BP measurements (home BP monitoring or ambulatory BP monitoring) should also be strongly considered. Lifestyle modifications need to be emphasized and reinforced, with a greater use of combination antihypertensive therapy. A team approach using pharmacists and nurse practitioners, along with optimal use of best practice algorithms and remote monitoring technology, must be implemented for efficient and effective care.

Participating clinicians: George Thomas, MD, FASN, Michael Lioudis, MD, FASN

Chronic Kidney Disease

The presence of chronic obstructive pulmonary disease (COPD) in patients with chronic kidney disease (CKD) greatly increases the risk of death, particularly due to pulmonary-related causes, a first-of-its-kind Cleveland Clinic study by has demonstrated.

In a retrospective review of one of the nation's largest registries of CKD patients, the researchers found that COPD was associated with a 41 percent increased risk for all-cause mortality and a fourfold increased risk for respiratory-related deaths.

While additional research is needed to determine the biological mechanisms that link the two conditions, the findings should further sensitize CKD caregivers to the need to closely monitor patients with respiratory comorbidities. The research identifies a very high-risk subset of CKD patients whose chances of pulmonary-related death are much greater than the chances of death due to cancer, heart disease or other causes.

Participating clinicians: Stacey Jolly, MD, Sankar Navaneethan, MD and Joseph Nally, MD

41%

INCREASED RISK FOR ALL-CAUSE MORTALITY IN CKD PATIENTS WITH COPD

Dialysis

Infections are the No. 2 cause of death in dialysis patients, after heart disease. While the dialysis community has made improvements in reducing mortality from heart disease, that is not the case with infection-related morbidity and mortality. Stopping these infections requires a transformation in the way nephrologists detect and manage infection.

As a result, the Nephrologists Transforming Dialysis Safety (NTDS) initiative, funded by the U.S. Centers for Disease Control and Prevention (CDC), aims to reduce the infection rate in dialysis clinics to zero over the next three years. Cleveland Clinic is participating in the project along with 17 nephrology community experts and four CDC representatives.

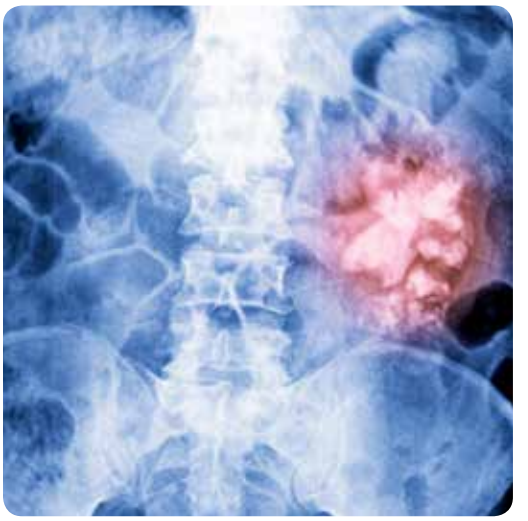
The project will focus on four areas: (1) current and emerging threats; (2) quality, assessment, improvement and education; (3) training programs; and (4) state and federal healthcare-associated infections programs. Leslie Wong, MD, Director of End-Stage Renal Disease at Cleveland Clinic, will serve on the executive committee of the NTDS on behalf of the American Society of Nephrology.

Participating clinician: Leslie Wong, MD

Endourology and Stone Disease

A simplified 12-hour nighttime urine collection may represent a new paradigm in stone prevention. The traditional 24-hour urine collection is burdensome to patients, resulting in poor compliance and incomplete collections. Typically patients collect urine on weekends as weekday collections can be challenging in that it requires taking a large jug to work. As such, the results may not be reflective of the patient's stone risk through the majority of the week; diet, fluid and activity likely vary between workdays and weekends. Prior studies have demonstrated that supersaturation of urine is highest at night.

With this in mind, we asked patients to divide their 24-hour urine collections into a daytime and nighttime collection. Night 12-hour and the 24-hour urine collections correlated closely for citrate ($R2 = 0.96$), oxalate ($R2 = 0.91$), calcium ($R2 = 0.89$) and uric acid ($R2 = 0.88$). Nighttime collections were more likely to identify patients with urine supersaturated for CAOX and CAPH compared with 24-hour collections. Diagnosis of underlying metabolic abnormalities was concordant in 92 percent of patients.



In conclusion, the results of the 12-hour nighttime collection correlated strongly with those from the 24-hour collection. As such, simplifying the metabolic evaluation to a 12-hour overnight collection may be feasible and would likely improve compliance and decrease patient burden. In addition, it would decrease the dependency on weekend collections, which may not reflect the risk during the workweek.

Participating clinicians: Bryan D Hinck, MD; Vishnuvardhan Ganesan, BS; Sarah Tarplin, MD; John Asplin, MD; Ignacio Granja, BS; Juan Calle, MD; Sriharan Sivalingam, MD; Manoj Monga, MD

Female Urology

Cleveland Clinic was one of the lead institutions in a study that assessed whether injection of onabotulinumtoxinA (Botox A) is superior to sacral neuromodulation (use of an implanted electrode for bladder control) in controlling episodes of refractory urgency urinary incontinence in women.

For this study, conducted at nine U.S. medical centers, the researchers randomly assigned women with refractory urgency urinary incontinence to an injection of onabotulinumtoxinA (N = 192) or sacral neuromodulation (N = 189). Of the 364 women (average age, 63 years) in the intention-to-treat population, 190 in the onabotulinumtoxinA group had a statistically significant greater reduction in the six-month average number of episodes of urgency incontinence per day than did the 174 in the sacral neuromodulation group (-3.9 versus -3.3 episodes per day). Participants treated with onabotulinumtoxinA showed greater improvement on an overactive bladder questionnaire for symptom bother, treatment satisfaction and treatment endorsement than patients treated with sacral neuromodulation.

However, there was no significant difference for quality of life or for measures of treatment preference, convenience or adverse effects. OnabotulinumtoxinA did increase the risk of urinary tract infections and need for self-catheterizations. Overall, the findings make it uncertain whether onabotulinumtoxinA provides a clinically important net benefit compared with sacral neuromodulation.

Participating clinician: Sandip Vasavada, MD

Genitourinary Reconstruction

Previously, many patients with congenital conditions, such as spina bifida, had limited life spans and care was provided predominantly by their pediatric care providers. As pediatric urologic care has improved, many of these patients now survive well into adulthood and with a high quality of life. The pediatric urological community is under-resourced to provide full-spectrum urological care for this unique and growing population of patients. As a result, many patients have lost access to specialty and preventive care, and endured a lower quality of health than they experienced in childhood.

The American Urological Association and several subspecialty societies have acknowledged this service gap by supporting the Genitourinary Congenitalism Working Group, chaired by Cleveland Clinic urologist Hadley Wood, MD. The working group's objective is to bring together urological providers who care for individuals with congenital anomalies across their life spans. In 2016, this workgroup focused particularly on adults with spina bifida and on controversies in care among the pediatric and adult urological communities.

Participating clinician: Hadley Wood, MD

Male Fertility

Researchers in the Center for Male Fertility continue to critically assess and develop new approaches to the diagnosis and treatment of male infertility. Conventional semen analysis testing offers limited predictive value for future fertility. Our team introduced a novel method for assessment of oxidative stress in semen samples.

Oxidative stress is recognized as one of the most important mechanisms of male factor infertility. However, clinician access to such a test remains difficult. Currently, independent direct (reactive oxygen species) and indirect methods (antioxidants, lipid peroxidation, modified proteins) are used to measure oxidative stress in semen. These methods are not readily accessible, require large sample volumes and are time-sensitive, limiting their clinical practicality.

More recently, we validated a novel measure of oxidative stress called oxidation-reduction potential (ORP). ORP, which is measured on the MiOXSYS™ System (Aytu BioScience Inc., Englewood, Colorado), yields a complete picture of oxidative stress in a given semen sample, providing a functional component not contained in the semen analysis. A recent *Fertility and Sterility* article regarding the MiOXSYS System establishes that ORP overcomes the specific limitations of current methods for assessing seminal oxidative stress. The study not only highlights the convenience and robustness of ORP, but also provides the first indication of how specific oxidative stress cutoffs, as measured by MiOXSYS, might be used to help characterize an abnormality first identified using semen analysis. This is significant as it is well-understood that abnormal levels of oxidative stress can lead to poor sperm function and severe male factor infertility if not treated through lifestyle or therapeutic management.

Participating clinicians: Ashok Agarwal, PhD and Edmund Sabanegh, MD

Men's Health

Orchialgia, or chronic testicular pain, is a common and poorly studied condition. In our Men's Health Clinic we are trying to advance knowledge and improve care for these often-neglected patients. Assessing symptom severity for the condition has been difficult without a validated symptom assessment tool. We recently developed the Chronic Orchialgia Symptom Index to address this problem, and we are leading a multicenter study to prove its validity and usefulness in clinical care. We are one of the few centers in the United States to offer microscopic spermatic cord denervation (MSCD) surgery for the treatment of chronic orchialgia. This outpatient surgery has a 75 percent success rate in curing orchialgia if a nerve block of the spermatic cord first demonstrates that the nerves in the cord are driving the pain. Finally we are exploring novel therapies. Low-intensity shock wave lithotripsy is approved in Europe and Canada for treating pelvic pain and erectile dysfunction. We are the first center to study its use in chronic orchialgia.

Participating clinician: Daniel Shoskes, MD

75%

SUCCESS RATE IN CURING ORCHIALGIA WITH MSCD SURGERY, WHEN PROVEN CORD NERVES ARE DRIVING PAIN

Minority Men's Health

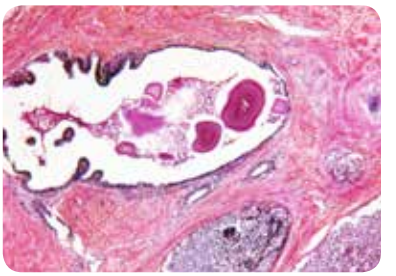
Cleveland Clinic Minority Men's Health Center (MMHC) and annual Minority Men's Health Fair, both established in 2003, are innovative population health and preventive health screening/community outreach programs dedicated to reducing health disparities disproportionately afflicting minority and underserved males. The MMHC's mission is to facilitate health access and to identify and treat previously unrecognized and/or pre-existing medical conditions. By providing health education, MMHC aims to empower these men to take advantage of preventive health screenings. This may allow for early detection of disease and ultimately reduce morbidity and mortality often associated with men in this patient population, who typically present with medical conditions in advanced stages.

The MMHC's successes result from an innovative "patients first" methodology, including community engagement, trust building, creation of community wellness partnerships, culturally competent dedicated outpatient clinics, facilitated patient access navigation, strategically directed media/marketing initiatives, health literacy education, health disparities research and health provider education/team building. These components are all necessary to engage, facilitate, empower and mobilize minority and underserved males to adopt healthier lifestyles and seek preventive healthcare.

The 14th Annual 2016 Minority Men's Health Fair engaged over 2,000 minority and underserved men, providing health examinations and health information. This included a menu of more than 35 free preventive health screenings for the early detection of disease to improve their health outcomes and lessen the economic burden associated with the morbidity/mortality of diseases diagnosed in their advanced stages.

In 2016, the MMHC continued to successfully recruit African-American (AA) males to enroll in its AA Male Biobank, which now contains nearly 500 blood/urine samples available for scientific investigation into the pathogenesis of a variety of health disparities afflicting AA males.

Participating clinician: Charles Modlin, MD



Prostate Cancer Nutrition Clinic

Increasing data in the literature implicate dietary trends as contributing to rises in prostate cancer incidence and aggressiveness. Elevated dairy and meat intake has been associated with increased incidence and aggressiveness of prostate cancer compared with diets higher in plant-based proteins and fats. Similar findings have been reported for high glycemic-load diets, which are positively associated with an increased incidence of prostate cancer (odds ratio 1.26, highest versus lowest quartile).

While additional factors clearly impact disease behavior, these dietary factors are statistically significant and warrant further investigation. The data indicate that manipulation of dietary and lifestyle factors may impact prostate cell metabolism and prostate cell behavior characteristics. Data also indicate that curcumin has multiple sites of action in prostate biochemical pathways and behavior. Cleveland Clinic is involved in dietary intervention efforts in an attempt to affect patients' prostate cancer risk and progression.

Participating clinician: David Levy, MD

Renal and Pancreas Transplant

Percutaneous pancreas allograft biopsy has been perceived as a high-risk procedure, which has limited its widespread use. The few available studies in the literature mainly focused on ultrasound (US)-guided biopsies of bladder-drained pancreases.

Cleveland Clinic nephrologists reviewed our experience with computed tomography (CT)- and US-guided biopsies of enteric-drained pancreas allografts over the past 15 years. Between 2001 and 2016, 298 enteric-drained pancreas allografts were performed at Cleveland Clinic, along with 118 percutaneous biopsies of pancreas allografts with few complications (3.3 percent). Interestingly, all the complications were managed conservatively. None required surgical intervention, and none resulted in pancreas allograft loss. Furthermore, all the complications occurred in the US-guided group.

Initial learnings are that percutaneous pancreas allograft biopsies have a low incidence of complications in the most recent era of enteric-drained pancreas transplant, and they appear to be as safe as renal allograft biopsy. The more recent use of CT-guided biopsy, rather than US-guided biopsy, appears promising in decreasing the incidence of biopsy-related complications, but more data are needed to corroborate this hypothesis. Given the recent evidence of low risk associated with the procedure, percutaneous transplant biopsies of enteric-drained pancreases should systematically be performed as part of the accurate diagnosis and management of allograft rejection. By sharing these data, we hope to reduce empiric treatment of presumed pancreas allograft rejection and to enable clinicians to generalize the use of percutaneous pancreas biopsies in an attempt to improve allograft outcomes.

Participating clinicians: Yvonne El Kassis, MD, Emilio D. Poggio, MD, Ziad S. Zaky, MD

Renal Diseases

Cleveland Clinic is participating in the ATHENA trial, the first-ever large-scale prospective study examining patients with Alport syndrome, a rare genetic disease that causes kidney failure and hearing loss. This international, multicenter, observational trial is sponsored by Regulus Therapeutics.

ATHENA's goal is to better understand how genetics and biomarkers interact to predict or identify renal failure in patients with Alport syndrome. James Simon, MD, is the site principal investigator. To date, he has screened over 40 patients for the trial and enrolled 19 participants. The study continues to actively enroll patients. The hope is that data from this study will help in the design of therapeutic agents to delay the onset of kidney failure in these patients.

Participating clinician: James Simon, MD

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PARTICIPANTS ENROLLED BY CLEVELAND CLINIC TO DATE IN THE ALPORT SYNDROME TRIAL

Robotic and Image-Guided Surgery

Robotics made a huge impact on radical prostatectomy, minimizing morbidity and improving outcomes significantly. With the introduction of robotics, a big shift occurred in moving certain surgeries from open to minimally invasive.

Open perineal prostatectomy is an old minimally invasive approach that was mostly abandoned due to poor exposure and difficulty teaching the procedure. Applying robotics to perineal prostatectomy may revive this approach and further minimize minimally invasive surgery. Two years ago, a proof of concept was performed in cadavers using the da Vinci robot for perineal prostatectomy. Surgeons made a two-inch incision in the perineum, positioned a gel port and created a carbon dioxide bubble around the prostate. The robotic instruments were positioned through the bubble to perform the surgery.

Subsequently, a clinical study was performed in which Cleveland Clinic surgeons successfully completed five robotic perineal prostatectomy cases. Patients had less pain, shorter hospitalization and minimal blood loss, and most had immediate continence since the bladder was not mobilized. Although this procedure is promising, the robotic system available was not designed to work in a single incision. Future improvements in the robotic platform, purposely built for single ports, may change the way we do radical prostatectomy.

Participating clinician: Jihad Kaouk, MD, Matthew Maurice, MD and Kenneth Angermeier, MD

Urologic Oncology

New baseline glomerular filtration rate after partial nephrectomy (PN) can impact overall survival, particularly for patients with pre-existing chronic kidney disease. Most studies suggest that the amount of nephron mass preserved with PN is the key determinant of functional recovery, with ischemia playing a secondary role as long as prolonged warm ischemia has been avoided.

Our database now contains the records of more than 400 PN patients whose parenchymal mass and function were rigorously measured, preserved specifically within the ipsilateral kidney exposed to ischemia, allowing for more refined perspectives about functional recovery. Loss of nephron mass with PN is confirmed as the major determinant of decline in function after PN, and can be due to excised parenchymal mass (EPM) that is removed along with the tumor, or devascularized parenchymal mass (DPM) related to the reconstructive phase of the procedure.

Our recent studies suggest that EPM is relatively limited in this era of “minimal margin” PN and does not correlate with functional outcomes. In contrast, DPM correlates strongly with functional recovery after PN, suggesting that the reconstructive phase of PN is of primary importance for functional outcomes.

Participating clinician: Steven Campbell, MD, PhD, Wen Dong, MD, Jitah Wu, MD and Chalairat Suk-ouichai, MD

APPLYING ROBOTICS TO PERINEAL PROSTATECTOMY MAY REVIVE THIS APPROACH AND FURTHER MINIMIZE MINIMALLY INVASIVE SURGERY.

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