Federal Health & Medicine

The Publication for Definitive Health & Medical Research Programs • 2018-2019

Listening and Working Together for Healthier and Longer Lives

By Vice Admiral Jerome M. Adams MD, MPH, Surgeon General of the United States

Observing National Public Health Week, Surgeon General Adams called for forging new partnerships to improve the nation's health and change our future together.

Every American deserves to live a long, healthy life, but we are falling short of that goal. Life expectancy in the U.S. has declined for the second year in a row. This decline marks the first time in half a century that American longevity has declined. This is a disturbing problem that faces us as we observe National Public Health Week.

Each year, the National Public Health Week, organized by the American Public Health Association, is a time to recognize the contributions of public health and highlight issues that are important to improving our nation's health. This week is an opportunity to raise awareness about public health and prevention.

My motto of "Better Health through Better Partnerships" is particularly well aligned with the theme for this year's National Public Health Week — "Changing Our Future Together." When we are addressing issues that are important to improving our nation's health, we cannot operate in silos. Whether we are looking to improve our nation's health outcomes, improve our national security, or enhance a community's resilience, we need partnerships and collaboration. We can only change our future together.

As public health professionals, we have a unique opportunity to leverage our influence and leadership to forge stronger partnerships that can more effectively promote public health and prevention. I am committed to strengthening the connections among public health communities and forging new partnerships with non-traditional partners, including but not limited to the traditional business, law-enforcement, education and faith-based communities. We cannot achieve our goals unless we are at the table together, sharing lessons learned and challenging each other to do more, to do better, and to do it together.

The power of working together was evident to me back in 2015, when I was the Indiana state health commissioner, and there was an HIV and Hepatitis C outbreak in Scott County. When we found that more than 90 percent of the people diagnosed with HIV also tested positive for Hepatitis C, we initiated a multifaceted response: expanding free HIV and HCV testing, improving Medicaid registration, monitoring HIV care through the local

Vice Admiral Jerome M. Adams MD, MPH, Surgeon General of the United States

health department, and starting Indiana's first syringe exchange program. We were only able to respond in this way and bring this outbreak under control by going out in the communities, really listening to invididuals and local leaders, and building parternships. Because of them, we were able to put in place the right prevention, healthcare, and social services.

HIV, Hepatitis C, the opioids epidemic, and antibiotic-resistant bacteria are all national problems that pose threats to the health of our nation. Thankfully, there are things that everyone can do. If we continue to work together, listen to each other, and ensure that decisions are made with people's health in mind, we can create a healthier nation. In observance of National Public Health Week, let us recommit to partnering to create a healthier nation.

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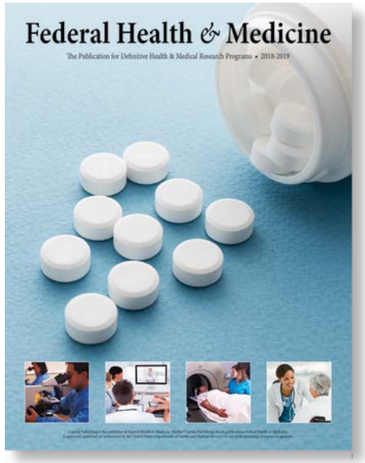

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Capital Publishing Celebrates 20 Years of Serving Medical Professionals

By Tom Adams, Publisher

This year marks the 20th anniversary of publishing, and to commemorate this special occasion we have launched two new website for both of our publications that include articles from current printed editions, plus additional editorials continuously being added throughout the year. There you will find new information from a variety of extremely reputable sources of leadership connected to the markets they serve.

www.federalhealthmedicine.com

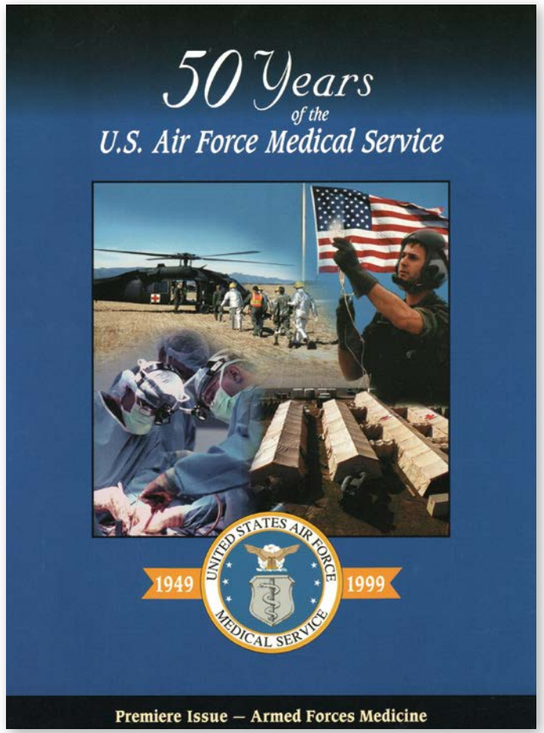
This publication, "Federal Health & Medicine", which focuses on matters related to US Public Health County, State University, and Indian Health Service facilities throughout the nation, has been released as a print publication each fall since our first edition in 2001.

www.armedforcesmedicine.com

Our other publication, "Armed Forces Medicine", focuses on the Department of Defense Health Affairs readers within the US Air Force, US Army, US Navy, and Department of Veterans Affairs. This originated from our very first release in 1999 entitled, "50 Years of the US Air Force Medical Service", which was developed to compliment the celebrations held in Wilford Hall Medical Facility at Lackland Air Force Base. We worked with the individuals in charge of commemorating the occasion that hosted speakers including the US Air Force Surgeon General and senior leaders from all US Military branches, to capture the momentous event with a special souvenir type publication containing historical perspectives of it's origins and achievements throughout both wartime and peacetime efforts over the past five decades.

Success of this very first edition of "Armed Forces Medicine" continued with its next edition, now recognizing achievements of our combined joint services of Military and VA healthcare and also promoted their latest key initiatives to our readers each and every year since.

Because each publication has it's own website, our content is twice as likely to appear in the results of online searches with similar keywords from engines like Google and Yahoo. This is uniquely valuable for us because both of our publications contain similar healthcare related articles, which are of interest to medical professionals beyond the facilities already receiving our printed magazines. After 20 years of consistency, our impact is now at its highest level and will only continue to expand each time new printed editions are released and new content is added to our websites.



We also recognize that our core audience over the past 20 years has enjoyed the personal experience of holding high quality color print magazines in their hands, just as they have become familiar with in their lifetime.

We also know that a well made publication is less likely to be thrown out, and often kept around to be discovered by other individuals who will also enjoy the look and feel of a quality production containing information related to their interests, further growing our core audience year by year.

It has truly been our privilege to work with so many respected individuals in the healthcare market over the past 20 years, and we hope to continue serving our print and now online readers for many more years to come. Thank you for your patronage and above all, thank you for your service to our nation!

Celebrating America's Health Centers: The Key to Healthier Communities

By George Sigounas MS, PhD, Administrator, Health Resources and Services Administration

In recognition of National Health Center Week, we would like to highlight the accomplishments these facilities provide to the American people.

Henry, a veteran from Baltimore, experienced post-traumatic stress disorder with terrifying nightmares, mental health issues, and drug addiction. Then he found Chase Brexton, a health center near his home. Chase Brexton not only helped Henry better manage his health, it made him feel like he's in a family. "I've been an addict for well over 20 years," he said. "If you're sick and tired of being sick and tired, come to Chase Brexton."

For Henry and millions more across the country, health centers like Chase Brexton provide affordable, high-quality and patient-centered primary health care that would otherwise be out of their reach. Health centers use a holistic approach to patient care, treating the entire person by integrating behavioral health, oral health and primary care services. Nearly 1,400 health centers operating more than 10,400 sites in communities across America are funded by the Health Resources and Services Administration (HRSA). They provided care to nearly 26 million people in 2016.

In fact, one in 12 people across every U.S. state and territory rely on health centers to be their source of health care. They see one or more of the health centers' 200,000+ staff, who help them stay healthy through preventive care like immunizations, cancer screenings, and tobacco cessation, as well as educational services on nutrition and physical activity.

These hardworking and dedicated health care providers improve the nation's and their community's health by focusing on access, quality and cost. Health centers exceed national averages for:

- Patients with good control of their diabetes,
- Hypertensive patients with well controlled blood pressures,
- Pediatric patients who receive weight assessment and counseling for healthy weight, and
- Patients screened for depression.

As a result of this comprehensive, quality care, health centers also reduce costs to health systems by decreasing the use of costlier providers of care, such as emergency departments and hospitals. A recent study demonstrated that health center

George Sigounas, MS, PhD

Medicaid patients had lower overall use and spending than non-health center patients across all services.

This National Health Center Week, we recognize health centers across our country and their important work to protect and promote the health of America. To the thousands of providers and staff who dedicate their lives to helping patients like Henry access quality health care, we thank you for making a difference in your communities.

Patients like Henry are just one of your many success stories and the care he received was the key to making him feel like a new man. As Henry said, "Percentage-wise, when I came here, I was like a 40. Now sitting here, I'm 100 percent."

hhs.gov

The Power of Rural: Celebrating National Rural Health Day

By George Sigounas MS, PhD, Administrator, Health Resources and Services Administration

Through innovative systems and unique partnerships, rural communities across the United States have made critical advancements toward improving their health outcomes.

The Health Resources and Services Administration's (HRSA) Office of Rural Health Policy and the National Organization of State Offices of Rural Health recognize National Rural Health Day on Thursday, November 16, by spotlighting the pioneering work of our rural communities.

This year's National Rural Health Day focuses on the Power of Rural, how collaborations in rural communities and throughout HRSA support the delivery of quality healthcare in rural America.

National Rural Health Day is a time to recognize the countless strides rural communities have made. More than 800,000 rural Americans receive health services thanks to rural community-based grants. HRSA's rural grantees have successfully leveraged funds to provide access to services across the healthcare spectrum.

They have increased access to primary care, established early intervention services for patients with behavioral health needs, and expanded access to healthcare via telehealth. HRSA's rural grantees have played a critical role in enhancing the quality and availability of healthcare services.

Along with acknowledging the accomplishments made by rural communities, it is also important to acknowledge the disproportionate obstacles that rural Americans must overcome. In the context of HHS priorities, rural Americans have poorer outcomes when it comes to substance abuse (particularly the opioid abuse epidemic), childhood obesity, and mental health.

While we have seen a rise in opioid abuse deaths on a national level, rural residents face an even greater disparity as rural states are more likely to have higher rates of overdose deaths, specifically from prescription opioid overdoses. Rural children face their own disparity when considering childhood obesity. Rural children aged 10-17 years have higher rates of obesity than their urban counterparts.

Additionally, while the prevalence of mental illness is comparable among urban and rural communities, the barriers lie within the availability and accessibility of mental health services.

But these challenges also present opportunities. This past September, HRSA awarded $200 million to health centers to address mental health and the opioid crisis. HRSA also awarded $3 million in grants to address the unique obstacles rural communities face in addressing the opioid crisis. This included three grants focusing on the use of telehealth to provide comprehensive substance abuse services.

Access to quality and comprehensive healthcare services is an essential focal point when thinking about the well-being of rural Americans. HRSA is working to foster access to quality healthcare through collaborative work and programs that include supporting rural health facilities, investing in Community Health Centers, and building a strong health workforce. HRSA supports nearly 1,400 health centers operating more than 10,400 service sites across the United States, with more than 40 percent of those health centers serving rural communities.

HRSA is also working to increase access to healthcare providers through our health professional training programs. Through the Area Health Education Centers (AHEC) Program, a program to enhance education and training networks in order to improve healthcare delivery to rural or underserved areas, 41 percent of students and residents came from a rural setting. Additionally, 144 Rural Health Clinics partnered with AHECs to provide training experiences to students and residents.

Also, in fiscal year 2017, roughly a third of National Health Service Corps and Nurse Corps members worked in rural communities, providing services in primary care, oral health, and mental health.

As part of National Rural Health Day, let us celebrate the successes of our rural communities and also take this time to reflect on how our partnerships, whether at the community, state, or federal level, can continue to transform and improve rural health outcomes. While rural communities face unique challenges, they also have unique ideas and solutions that bring the community together and engaged in ways to improve the lives of rural Americans.

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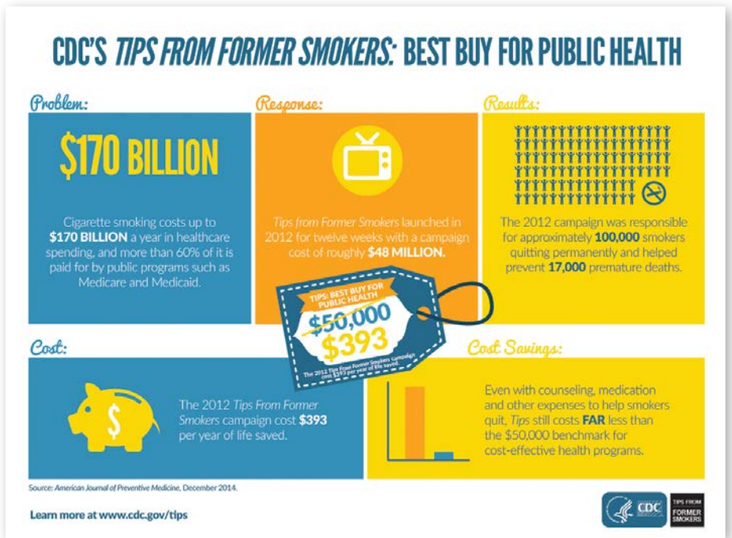
CDC's Tips From Former Smokers: Anti-smoking Campaign Launches Seventh Year

CDC's Tips From Former Smokers campaign resumes for 25 weeks on April 23, 2018. The 15- and 30-second ads will air nationally on television, online, and in print advertisements. Markets that have higher rates of cigarette smoking will have additional airings and advertisements for increased awareness.

Tips From Former Smokers will release new ads featuring:

- Brian, 63, an Air Force veteran, had his first heart attack at age 35, while on assignment overseas. He quit smoking in 2009 and received a heart transplant in July 2012. In January 2017, Brian was diagnosed with lung cancer and had part of his lung removed.
- Christine, 55, began smoking at age 16. At age 44, she was diagnosed with oral cancer, which eventually required doctors to remove half of her jaw.
- Sharon, 58, began smoking at age 13. In 1997, at age 37, she was diagnosed with stage IV throat cancer.
- Tiffany, 40, started smoking at 19, even though her mother, a smoker, died of lung cancer. Tiffany quit smoking in 2011 — wanting to be around for her own teenage daughter.



- In each campaign, there was an immediate, sustained and dramatic spike in calls to 1-800-QUIT-NOW"", and in visits to the campaign website.
- Since 2012, CDC estimates that millions of Americans have tried to quit smoking cigarettes because of the campaign, and at least half a million have quit for good.
- In addition, in the first year of the campaign alone, an estimated 6 million nonsmokers talked with friends and family about the dangers of smoking.
- Tips is cost-effective. Economic analysis of the Tips campaign has shown that for every $2,000 we spend on the ads, we prevent a death.

CDC.gov

Smoking is Down, But Almost 38 million American Adults Still Smoke

Cigarette smoking remains high among certain groups

Overall, cigarette smoking among U.S. adults (aged ≥18 years) declined from 20.9 percent in 2005 to 15.5 percent in 2016. Yet, nearly 38 million American adults smoked cigarettes ("every day" or "some days") in 2016, according to data released today by the Centers for Disease Control and Prevention (CDC).

The new data, from the National Health Interview Survey (NHIS), show that among adults who have ever used cigarettes, the percentage who have quit increased from 50.8 percent in 2005 to 59.0 percent in 2016. During 2005-2016, the largest increase in quitting was among adults ages 25-44 years.

"The good news is that these data are consistent with the declines in adult cigarette smoking that we've seen for several decades," said Corinne Graffunder, DrPH, director of the CDC's Office on Smoking and Health. "These findings also show that more people are quitting, and those who continue to smoke are smoking less."

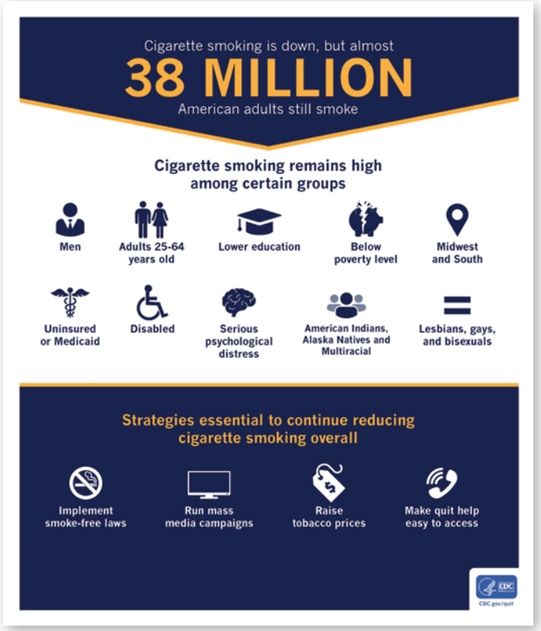
Since 1965, the NHIS has tracked cigarette smoking, the most common form of tobacco product use among U.S. adults. The U.S. Surgeon General has concluded that the burden of death and disease from tobacco use in the United States is overwhelmingly caused by cigarettes and other combusted tobacco products.

Among daily smokers, the average number of cigarettes smoked per day declined from about 17 cigarettes in 2005 to 14 cigarettes in 2016. The proportion of daily smokers who smoked 20 to 29 cigarettes per day dropped from 34.9 percent in 2005 to 28.4 percent in 2016, while the proportion who smoked fewer than 10 cigarettes per day rose from 16.4 percent in 2005 to 25 percent in 2016.

Persistent disparities in cigarette smoking

Despite this progress, disparities in smoking persist across population groups. Cigarette smoking was especially high among males, those aged 25-64 years, people who had less education, American Indians/Alaska Natives, Americans of multiple races, those who had serious psychological distress, those who were uninsured or insured through Medicaid, those living below the poverty level, those who had a disability, those who were lesbian, gay, or bisexual, and those who lived in the Midwest or South.

"The bad news is that cigarette smoking is not declining at the same rate among all population groups," said Brian King PhD, deputy director for research translation in CDC's Office on Smoking and Health. "Addressing these disparities with evidence-based interventions is critical to continue the progress we've made in reducing the overall smoking rate."



Reducing smoking-related disease: What more can be done?

Proven population-based interventions — including tobacco price increases, comprehensive smoke-free laws, anti-tobacco mass media campaigns, and barrier-free access to tobacco cessation counseling and medications — are critical to reduce cigarette smoking and smoking-related disease and death among U.S. adults, particularly among populations with the highest rates of use.

Cigarette smoking among U.S. adults has been reduced by more than half since 1964, yet remains the leading preventable cause of disease and death in the United States. It kills more than 480,000 Americans each year. For every person who dies this year from smoking, there are over 30 Americans who continue to live with a smoking-related disease. For more information or for free help quitting, call 1-800-QUIT-NOW or go to www.smokefree.gov

cdc.gov

CPG

HHS Announces the Availability of $260 million to Fund the Title X Family Planning Program

The U.S. Department of Health and Human Services (HHS) announced the availability of $260 million in a new funding opportunity for the Title X family planning program to help improve and expand quality care. The funding opportunity will assist in the establishment and/or operation of voluntary family planning projects that will offer a broad range of family planning methods and services, including information, education and counseling related to family planning, preconception care, contraception, natural family planning and infertility services.

Recognizing the announcement has been delayed, HHS is committed to ensuring that services continue unabated. Current grantees received notification today inviting them to submit a request for grant extension, so there is no gap in services.

"We encourage all qualified organizations to apply, especially those proposing innovative strategies that would increase the number of clients served and the quality of services provided," said Assistant Secretary for Health Brett P. Giroir, MD. "We are committed to ensuring that we provide access to quality family planning services to the women and men who depend on this vital public health program."

In particular, this year's funding opportunity is seeking applicants that offer a broad range of family planning and related health services tailored to the individual needs of the client and that promote optimal health outcomes. As emphasized in the statutory language governing the program, "none of the funds appropriated under this title shall be used in programs where abortion is a method of family planning."

The funding opportunity further requires that all Title X grantees develop monitoring and reporting policies, consistent with state law, in order to expand assurances that those who enter a Title X service site and who may be victims of child abuse, child molestation, sexual abuse, rape, incest, intimate partner violence or human trafficking, are afforded the help and legal protection to which they are entitled. For the first time, the funding opportunity requires that all staff are annually trained to respond to such needs.

Further, building on several years of HHS work to streamline the process of applying for Title X grants and ease burdens on applicants, interested organizations can now submit one application

Assistant Secretary for Health Brett P. Giroir, MD

that covers multiple geographic service areas, rather than having to submit multiple applications for different service areas. This year will involve just one annual funding competition, rather than multiple competitions.

This funding announcement covers all 50 states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands and the six Pacific jurisdictions. The awards are expected to be issued in September of this year.

The HHS Office of Population Affairs oversees the Title X family planning program, which currently funds 84 grantees that support nearly 4,000 family planning sites nationwide and provides services to more than 4 million women and men each year. Title X service sites serve a population of mostly female, low-income and young clients. Title X grants are awarded through a competitive process to public and private nonprofit entities. Services funded with Title X grants are provided by state and local public health departments and/or community health, family planning and other private nonprofit agencies.

Applications for the Title X family planning services grants are due at 6:00 PM Eastern Time on Thursday, May 24, 2018. Technical assistance will be provided to those who are interested in applying for grants.

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Readout of Deputy Secretary Hargan's Patient Advocacy Group Meeting

Health and Human Services Deputy Secretary Eric Hargan held a meeting with attendees from patient advocacy groups where attendees expressed their individual opinions and exchanged information pertaining to the Department's priorities.

The meeting included representatives and patients from the American Cancer Society, the American Heart Association, JDRF, the Leukemia and Lymphoma Society, the National Alliance on Mental Illness, and the National Health Council. Deputy Secretary Hargan was joined by two senior advisors Dan Best, HHS's Senior Advisor to the Secretary for Drug Pricing Reform, and Dr. Brett Giroir, HHS's Assistant Secretary for Health and Senior Advisor to the Secretary for Mental Health and Opioid Policy.

The gathering was part of Secretary Alex Azar's efforts to ensure patients and their representatives have their voices heard as HHS implements President Trump's important reforms to improve healthcare for all Americans.

Participants shared their perspectives on achieving HHS's priorities: lowering the high price of prescription drugs, making health insurance and more accessible and affordable, creating a value-based healthcare system, and combating the opioid crisis.

Deputy Secretary Hargan thanked the participants for their insights and emphasized President Trump's personal commitment to taking bold action to make health insurance and prescription drugs more affordable. He emphasized that HHS will maintain engagement with patient groups as the Department works to create a better healthcare system for every American.

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HHS Deputy Secretary Eric Hargan (center), and HRSA Administrator Dr. George Sigounas (right), pictured during a recent event recognizing Health Centers for Quality.

Service to America Medals Awarded to Three HHS Employees

One is a CDC doctor who has spent his career expanding and improving access to medicine to millions of people worldwide living with HIV/AIDS. Two are FDA employees who helped speed regulatory approval for a break-through medical device that helps people with type 1 diabetes manage their disease.

These three Health and Human Services employees were among 11 federal workers last week who were awarded the Partnership for Public Service's Samuel J. Heyman Service to America Medals exit disclaimer icon. The awards, also known as the SAMMIES, are named for the Partnership for Public Service's late founder who was inspired by President Kennedy's call to serve in 1963. The Partnership is a nonprofit, nonpartisan organization whose goal is to help make the federal government more effective.

The three HHS honorees are:

Dr. Tedd V. Ellerbrock exit disclaimer icon, Chief of the HIV Care and Treatment Branch at the Centers for Disease Control and Prevention, received the SAMMIES' Career Achievement award;

Courtney Lias, Director of the Food and Drug Administration's Division of Chemistry and Toxicology Devices, and Stayce Beck, Chief of the Diabetes Diagnostic Devices Branch, and the FDA Artificial Pancreas Team exit disclaimer icon received the Management Excellence award.

According to the Partnership, Ellerbrock was "one of the key players" behind the President's Emergency Plan for AIDS Relief (PEPFAR), an initiative launched in 2003 by the administration of President George W. Bush. Ellerbrock was credited with scaling up the system to deliver medicine to developing countries, build international partnerships, and oversee evaluations in more than two dozen countries to identify problems and recommend solutions.

In a video for the Partnership, Ellerbrock spoke of how while he was with the Peace Corps in the Philippines, he had an epiphany about what he wanted for a career—he wanted to provide modern medicine to developing countries.

"You become a doctor to try to make a difference in peoples' lives, to save lives. This effort, thanks to the generosity of the U.S. government and its people … we are saving millions of lives," Ellerbrock said.

Dr. Shannon Hader, Director of the CDC's Division of Global HIV and Tuberculosis, said in a statement for the Partnership, "He did something that had never been done before. He figured out how to roll out safe and effective treatment programs in developing countries."

The Partnership said the FDA's Lias and Beck were honored for their work for individuals living with diabetes, by transforming "a slow and cumbersome process to review and approve breakthrough medical devices like the artificial pancreas," three years earlier than expected.

For the 1.2 million Americans living with type 1 diabetes who must constantly monitor their blood sugar level and determine the correct amount of insulin to take, this device could be life-changing, according to medical experts and patient advocates.

"This is an incredible milestone. To have a system automatically dose insulin is massive. And it opens the door to tons of possibilities," Aaron Kowalski, chief mission officer for JDRF, an advocacy group for people with type 1 diabetes, said in a statement to the Partnership.

Lias and Beck treated industry, doctors and hospitals and patient advocacy groups as partners, making sure everyone had a voice and that manufacturers had a clear understanding of what documentation would be needed, how the clinical trials should be designed and how patient testing of the device could be made safer.

"Prior to their intervention," the Partnership said, "clinical investigators had to go through multiple rounds of reviews before they could start a clinical trial on systems like the one [the artificial pancreas] that Medtronic developed. Lias created a special team and timeline to expedite the clinical trials. The FDA team also worked with Medtronic to speed up the process by reviewing the device component by component, rather than wait until the entire system was complete."

The Partnership notes that federal employees like Ellerbrock, Lias and Beck are responsible for many special accomplishments that are seldom recognized, let alone celebrated. Deserving of their honors, Ellerbrock, Lias and Beck also represent the excellence of their colleagues at HHS.

hhs.gov

Keeping Faith: Bringing Hope and Healing in the Midst of the Opioid Crisis

By Vice Adm. Jerome M. Adams MD, MPH, Surgeon General of the United States

71,568 is the number of Americans the Centers for Disease Control and Prevention estimates we lost to opioids and other drug overdoses in 2017.

As your Surgeon General, I am tasked with helping to educate, equip and engage Americans in every community, along with our local, state and federal governments and our private-sector partners to promote better health and to respond to our nation's public health challenges. One of the biggest public health challenges of our time is the opioid addiction crisis ravaging our communities.

Everywhere I go, I affirm my deeply held conviction that we are stronger together, that we can — and must — achieve "Better health through better partnerships."

The opioid crisis is an all-hands-on-deck emergency, so we need to harness the powerful resources of everyone who has a stake in health, including governments, healthcare providers, law enforcement, businesses, community organizations and philanthropies.

Here, I'll talk about the special talents and calling of the faith community.

Faith organizations, service providers and communities are motivated by a calling to serve their neighbors. The participation of faith communities in the nationwide fight against drug abuse is critical to preventing and treating opioid misuse — and to supporting individuals in long-term recovery. Faith partners have demonstrated a culture of compassion for individuals struggling with addiction and have helped countless Americans overcome their drug dependence.

In support of the service of faith and community partners, HHS is working to remove barriers to care. Just last month, the HHS Center for Faith and Opportunity Initiatives (The Partnership Center) reached out to key stakeholders around the nation to affirm that states may use State Opioid Response (SOR) grant funds to support substance use disorder services by faith organizations.

Additionally, the Substance Abuse and Mental Health Services Administration (SAMHSA) has supported this outreach with a Frequently Asked Questions addendum that makes it clear that states are allowed to use a portion of their funds through indirect funding or voucher programs to support the work of the faith community in addressing substance use disorders.

This guidance can enhance client choice and increase program participation by a variety of groups, including faith partners. Likewise, these same social service providers can choose to enhance their substance abuse services through the state's portion of the new SOR grants. This freedom to select the service provider that's best for the client is a win-win-win — for the state, for faith providers, and for patients and their families.

The Trump administration values the service of faith and social service providers. The restorative work being performed in communities across the nation is key to the treatment, recovery and prevention processes, as they:

- Provide and encourage access to treatment, including medication-assisted treatment (MAT).
- Offer recovery services, such as recovery housing, employment readiness, recovery coaching, and workforce development.
- Promote peer certification programs.
- Employ critical strategies, such as administering naloxone and promoting prevention of substance use by adults and youth.

In order for us to tackle this crisis, we need partnerships and collaborations. By working together, including with faith-based organizations, we can overcome this opioid crisis and create a brighter future.

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U.S. Surgeon General Jerome Adams, MD visited the Opioid Memorial Display on the National Ellipse in April 2018.

HHS Awards Over $1 Billion to Combat the Opioid Crisis

The U.S. Department of Health and Human Services awarded over $1 billion in opioid-specific grants to help combat the crisis ravaging our country. The awards support HHS's Five-Point Opioid Strategy, which was launched last year and enhanced this week. New data unveiled recently by HHS suggests that efforts are now yielding progress at the national level.

"Addressing the opioid crisis with all the resources possible and the best science we have is a top priority for President Trump and for everyone at HHS," said Secretary Alex Azar. "The more than $1 billion in additional funding that we provided this week will build on progress we have seen in tackling this epidemic through empowering communities and families on the frontlines."

"HHS updated its strategic framework for tackling the opioid crisis, which uses science as a foundation for our comprehensive strategy," said Admiral Brett Giroir, Assistant Secretary for Health and Senior Advisor for Opioid Policy. "With these new funds, states, tribes, and communities across America will be able to advance our strategy and continue making progress against this crisis."

The 2017 National Survey on Drug Use and Health, conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), found that the number of Americans initiating heroin use dropped by around half from 2016 to 2017.

The number of Americans misusing opioids also dropped for the second year in a row, and the number receiving specialty treatment for heroin use increased.

From January 2017 through August 2018, the amount of opioids prescribed in America has dropped by 21 percent. In the same time, the number of prescriptions filled for naloxone has increased 264 percent, while the number of prescriptions for buprenorphine, one form of medication-assisted treatment, has risen 16 percent (data from IQVIA's Total Patient Tracker).

The Trump Administration will continue working to make progress against the opioid crisis, which in 2017 claimed more than 130 lives per day.

Notification of Patient Overdose Deaths Reduces Clinician Opioid Prescriptions

NIH-funded study shows clinicians reduced prescriptions following behavioral "nudge"

Clinicians were more likely to reduce the number and dose of opioid drugs they prescribed after learning that one of their patients had died from an overdose from a controlled substance than those not notified, according to a recent study appearing in the August 10 issue of Science.

The study was funded in part by the National Institute on Aging, part of the National Institutes of Health.

Jason Doctor, PhD, of the Schaeffer Center for Health Policy & Economics at the University of Southern California, Los Angeles, and colleagues found that physicians who received a letter from the chief deputy medical examiner informing them of the overdose death of one of their patients reduced the number of opioids prescribed by 9.7 percent in the three months following the intervention.

"This finding could be very useful in the effort to reduce inappropriate prescribing of opioids without severely restricting availability of legally prescribed opioids for patients who should be getting them," said NIA Director Richard J. Hodes, MD. "It shows that physicians respond to information about adverse outcomes. "Behavioral 'nudges' like these letters could be a tool to help curb the opioid epidemic."

The research team identified 861 clinicians in San Diego County in California. Between July 1, 2015 and June 30, 2016, the county reported 222 deaths for which Schedule II, III or IV drugs were the primary or contributing cause.

Of these, 170 deaths were listed in the Controlled Substance Utilization Review and Evaluation System (CURES) database. The prescribing clinicians were divided into an intervention (388) and a control (438) group.

The intervention group received a letter from the Chief Deputy Medical Examiner of San Diego County; the control group did not receive a letter. The letter identified the patient by name, address and age, and outlined the annual number and types of prescription drug deaths seen by the medical examiner.

It also discussed how to access the state's prescription drug monitoring program and reviewed five safe prescribing strategies.

The research team noted that, while the results of this study may not be applicable to a larger population, the intervention is scalable at the county level. Prescription opioid deaths are reported to the National Center for Health Statistics.

Photo courtesy of the National Institutes of Health

Along with the state's vital records death file and the drug monitoring program that tracks prescriptions to decedent, counties and states can encourage safe prescribing by clinicians.

"The NIA has supported a number of studies on changing clinicians' behaviors through this type of intervention," said John Haaga, PhD, director of NIA's Division of Behavioral and Social Research. "This study illustrates one small and relatively inexpensive method of reducing the number of opioid prescriptions written, thus reducing the number of drugs available for misuse."

nih.gov

Methadone and Buprenorphine Reduce Risk of Death after Opioid Overdose

NIH research confirms effective treatments for opioid use disorder are underutilized

A National Institutes of Health-funded study found that treatment of opioid use disorder with either methadone or buprenorphine following a nonfatal opioid overdose is associated with significant reductions in opioid related mortality. The research, published in the *Annals of Internal Medicine*, was co-funded by the National Institute on Drug Abuse (NIDA) and the National Center for Advancing Translational Sciences, both parts of NIH.

Study authors analyzed data from 17,568 adults in Massachusetts who survived an opioid overdose between 2012 and 2014. Compared to those not receiving medication assisted treatment, opioid overdose deaths decreased by 59 percent for those receiving methadone and 38 percent for those receiving buprenorphine over the 12 month follow-up period.

The authors were unable to draw conclusions about the impact of naltrexone due to small sample size, noting that further work is needed with larger samples. Buprenorphine, methadone, and naltrexone are three FDA-approved medications used to treat opioid use disorder (OUD).

The study, the first to look at the association between using medication to treat OUD and mortality among patients experiencing a nonfatal opioid overdose, confirms previous research on the role methadone and buprenorphine can play to effectively treat OUD and prevent future deaths from overdose.

Despite compelling evidence that medication assisted treatment can help many people recover from opioid addiction, these proven medications remain greatly underutilized. The study also found that in the first year following an overdose, less than one third of patients were provided any medication for OUD, including methadone (11 percent); buprenorphine (17 percent); and naltrexone (6 percent), with 5 percent receiving more than one medication.

Photo courtesy of New York State Senate office of Terrence Murphy

In an editorial commenting on the study, Dr. Nora Volkow, director of NIDA, said, "A great part of the tragedy of this opioid crisis is that, unlike in previous such crises America has seen, we now possess effective treatment strategies that could address it and save many lives, yet tens of thousands of people die each year because they have not received these treatments. Ending the crisis will require changing policies to make these medications more accessible and educating primary care and emergency providers, among others, that opioid addiction is a medical illness that must be treated aggressively with the effective tools that are available." The editorial was co-authored by NIDA scientist Dr. Eric Wargo.

Another alarming study finding was that despite having had an opioid overdose, 34 percent of people who experienced an overdose were subsequently prescribed one or more prescriptions for opioid painkillers over the next 12 months, and 26 percent were prescribed benzodiazepines.

"Nonfatal opioid overdose is a missed opportunity to engage individuals at high risk of death," said Marc Larochelle, MD, the study's lead investigator at Boston Medical Center's Grayken Center for Addiction and Boston University School of Medicine. "We need to better understand barriers to treatment access and implement policy and practice reforms to improve both engagement and retention in effective treatment."

The authors conclude that a nonfatal opioid overdose treated in the emergency department is a critical time to identify people with OUD, and an opportunity to offer patients access to treatment inventions, providing linkage to care following their discharge, and making improvements in treatment retention.

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WARNING: IMPLANT MIGRATION, PROTRUSION, EXPULSION and NERVE DAMAGE ASSOCIATED WITH INSERTION AND REMOVAL

- **Insertion and removal of PROBUPHINE® are associated with the risk of implant migration, protrusion, expulsion, and nerve damage related to the procedure**
- **PROBUPHINE® is only available through a restricted program called the PROBUPHINE® REMS Program**

See Brief Summary of Prescribing Information for Complete Boxed Warning

INDICATION AND USAGE

- PROBUPHINE® is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).

- PROBUPHINE® should be used as part of a complete treatment program to include counseling and psychosocial support.

- PROBUPHINE® is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet equivalent or generic equivalent.

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PROBUPHINE® (buprenorphine) is a subdermal implant utilizing Titan Pharmaceuticals, Inc.'s proprietary ProNeura™ drug delivery platform[1]

For your stable patients who need on-going treatment for opioid dependence who have been maintained on transmucosal buprenorphine (<= 8 mg/day) for at least three months[1]

Contraindication
PROBUPHINE® is contraindicated in patients with a history of hypersensitivity to buprenorphine or any other ingredients in PROBUPHINE® (e.g., EVA).

Warnings and Precautions
Serious Complications from Insertion and Removal: Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion, and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion. All Healthcare Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE® REMS program, prior to performing insertions or prescribing PROBUPHINE® implants.
Addiction, Abuse, and Misuse: Buprenorphine can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.
Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with PROBPHINE®.
Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy.
Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.
Unintentional Pediatric Exposure: In the event an implant protrudes or comes out, keep the implant away from children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children.
Risk of Opioid Withdrawal with Abrupt Discontinuation: If treatment with PROBUPHINE® is discontinued, monitor patients for withdrawal and treat appropriately
Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events.
Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine and not dependent on full agonists before inserting PROBUPHINE®.
Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

Adverse Reactions
Adverse events commonly associated with PROBUPHINE® administration (>10% of subjects) were implant-site pain, pruritus, and erythema, as well as non-implant-site related events (2:5%) of headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain

Please see Brief Summary of Prescribing Information, including the Boxed Warning, on the following pages.

Reference:
1. Probuphine® (package insert). South San Francisco, CA: Titan Pharmaceuticals, Inc.; 2018

TITAN PHARMACEUTICALS

Probuphine®
(buprenorphine) implant
74.2 mg buprenorphine per implant
(equivalent to 80 mg buprenorphine HCl)

PROBUPHINE® (buprenorphine) implants
BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use Probuphine® safely and effectively. See package insert for Full Prescribing Information and Boxed Warning

IMPORTANT SAFETY INFORMATION

Contraindication

PROBUPHINE® is contraindicated in patients with a history of hypersensitivity to buprenorphine or any other ingredients in PROBUPHINE (e.g., EVA).

WARNING: IMPLANT MIGRATION, PROTRUSION, EXPULSION, AND NERVE DAMAGE ASSOCIATED WITH INSERTION AND REMOVAL

Risk Associated with Insertion and Removal

Insertion and removal of PROBUPHINE® are associated with the risk of implant migration, protrusion, and expulsion resulting from the procedure. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion. Because of the risks associated with insertion and removal, PROBUPHINE® is available only through a restricted program called the PROBUPHINE® REMS Program. All Healthcare Providers must successfully complete a live training program on the insertion and removal procedures and become certified, prior to performing insertions orprescribing PROBUPHINE® implants. Patients must be monitored to ensure that PROBUPHINE® is removed by a healthcare provider certified to perform insertions.

Warnings and Precautions

Serious Complications from Insertion and Removal: Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion, and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion. All Healthcare Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE® REMS program, prior to performing insertions or prescribing PROBUPHINE® implants.

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Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with PROBUPHINE®.

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Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

Continued on next page

IMPORTANT SAFETY INFORMATION

Drug Abuse

As a controlled drug, like morphine and other opioids, PROBUPHINE® has the potential for being abused and is subject to criminal diversion. Each PROBUPHINE® implant contains 74.2 mg of buprenorphine and can come out or protrude, resulting in the potential for accidental exposure or intentional misuse, abuse, and diversion. Healthcare Providers should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect misuse, abuse, and diversion of buprenorphine.

Abuse of buprenorphine poses a risk of overdose and death. Proper assessment of the patient, periodic re-evaluation of therapy, and proper handling and storage of PROBUPHINE® are appropriate measures that help to limit misuse, abuse, and diversion of opioid drugs.

Over Dosage

Clinical Presentation: The manifestations of acute buprenorphine overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

Treatment of Overdose: In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.
Please refer to https://probuphine.com/prescribing-information/ for detailed information

Adverse Reactions

- Serious Complications from Insertion and Removal of PROBUPHINE
- Addiction, Abuse, and Misuse
- Respiratory and CNS Depression
- Neonatal Opioid Withdrawal Syndrome
- Adrenal Insufficiency
- Opioid Withdrawal
- Hepatitis, Hepatic Events
- Hypersensitivity Reactions
- Orthostatic Hypotension
- Elevation of Cerebrospinal Fluid Pressure
- Elevation of Intracholedochal Pressure
- Infection

To report SUSPECTED ADVERSE REACTIONS, contact Titan Pharmaceuticals, Inc. at 1-844- 859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Patient Counseling Information

Advise the patient to read the FDA-approved patient labelling (Medication Guide).
Instruct patients to read the Medication Guide each time PROBUPHINE® is implanted because new information may be available.

Reference:
1. Probuphine® (package insert). South San Francisco, CA: Titan Pharmaceuticals, Inc.; 2018

Please See Full Prescribing Information Including Boxed Warning And Medication Guide
https://probuphine.com/prescribing-information/
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TITAN™ PHARMACEUTICALS

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ECG Abnormalities Warn of Heart-Related Risks in Older Women

By Vicki Contie

Even minor irregularities on a standard electrocardiogram (ECG) test can be a sign of increased risk for cardiovascular events or death in seemingly healthy older women. Previous studies have shown the predictive value of ECG in men. The new findings come from the first large-scale analysis of ECG forecasting in postmenopausal women with no history of heart disease.

To assess EGC's predictive abilities in women, Dr. Pablo Denes of Northwestern University and his colleagues drew on the extensive clinical data collected as part of the Women's Health Initiative, a series of clinical studies launched in 1991 and funded by NIH's National Heart, Lung and Blood Institute (NHLBI).

The researchers identified 14,749 postmenopausal women who had participated in the initiative's hormone replacement trial and who had no previous cardiovascular problems. At the start of the study, 66% of the women had normal ECG recordings, whereas 28% had minor and 6% had major abnormalities. Follow-up evaluations continued for an average of about five and a half years.

In the March 7, 2007, issue of the Journal of the American Medical Association, the researchers reported that, by the end of the study, women who had minor ECG abnormalities at the start were twice as likely as women with normal ECGs to have had a significant coronary heart disease (CHD) event such as a heart attack or heart-related death. Women who had normal ECGs at the start had an annual rate of CHD events of 21 per 10,000 women. In contrast, women with minor ECG abnormalities had CHD rates of 40 in 10,000, and those with major abnormalities had rates of 75 in 10,000.

The researchers also noted that, of the women who had normal ECGs at the start, 5% had developed new ECG abnormalities within three years; the annual rate of CHD events for these women was 85 per 10,000 women.

Denes and his colleagues analyzed the data to see whether hormonal treatment affected the predictive value of ECGs. About half of the study participants had been receiving hormone replacement as part of the trial, which was originally designed to examine whether estrogen plus progestin therapy might reduce cardiovascular events. The trial enrolled participants from 1993 to 1998 but was halted early, in July 2002, when scientists found that CHD, stroke, breast cancer and blood clot rates rose significantly in women taking hormone therapy. Denes and his colleagues found that hormonal treatment did not affect the predictive value of ECG readings.

Because ECG tests are low-cost and easily administered, the researchers say they may help to assess risk in seemingly healthy older women. Abnormal readings might readily identify patients most likely to benefit from further evaluation, intensive therapies or lifestyle changes to reduce risk.

nig.gov

Smartphone-based ECG Arrhythmia Detection

By Ryan D White, MS and Greg Flaker, MD

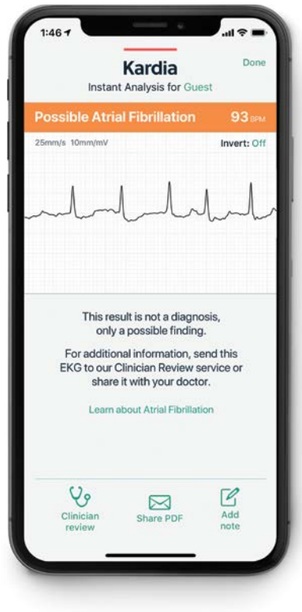
The detection of atrial fibrillation (AF) is important for stroke prevention in patients with AF. Multiple studies have shown the AliveCor smartphone ECG, called KardiaMobile, to be a reliable and accurate means of detecting atrial fibrillation. This device shows promise in arrhythmia assessment, managing patients with AF, and diagnosing AF early in high risk patients.

Atrial fibrillation (AF) is a common arrhythmia, affecting more than 2.7 million Americans[2]. This arrhythmia is associated with significant morbidity, carrying a 4- to 5-fold increased risk for ischemic stroke[3]. AF is often silent, with patients occasionally presenting with stroke as the first manifestation of the arrhythmia[4]. Other patients have troubling symptoms such as palpitations or dizziness. Smartphone monitoring of AF could also prove useful in patients with known AF. Symptomatic episodes could be documented which might alter the patient's regimen of rhythm control or rate control medications. Furthermore, the costs for treating AF are extremely high, accounting for greater than 6.5 billion dollars annually[5].

The US FDA 510(k)-cleared KardiaMobile is smaller than a credit card and consists of two metal electrodes. A bipolar ECG lead I is created when the two metal electrodes are touched by the patient's right and left hands. The ECG electrical signals are then converted into high frequency sound waves and transmitted to a smartphone on which the AliveCor Kardia App has been installed. The ECG can be reviewed on the smartphone, electronically stored or emailed, or electronically sent for professional review.

AliveCor has developed three FDA-cleared algorithms for use in the device[7]. An ECG is labeled as "Normal" when a patient's heart rate is between 50-100 beats per minute, there are no or very few abnormal beats, and the rhythm is considered normal sinus. The ECG is labeled as "Unreadable" when the detector indicates there was too much interference for an adequate recording, whether from too much movement, or poor contact between the electrodes and the patient's skin. The rhythm is labeled as "Possible Atrial Fibrillation" when the device detects the presence of atrial fibrillation. AliveCor notes that this device provides possible findings and is not capable of making a diagnosis of atrial fibrillation. The recorded ECG can then be sent to a physician or medical professional for further review.

Smartphone accessory-based arrhythmia devices currently offer a validated means of monitoring atrial fibrillation. AliveCor device has received FDA clearance and has undergone over 60 studies demonstrating its accuracy. This device is available over the counter and is marketed directly to the general public in the United States. Multiple studies have shown the device to be a reliable and accurate means of detecting atrial fibrillation. However, it is important to note that the device is not intended for use in patients with implantable cardiac devices, such as pacemakers or ICDs or pediatric patients. The detection of AF by the AliveCor device is not diagnostic, and positive findings of new AF should warrant a confirmatory ECG.



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ncbi.nlm.nih.gov

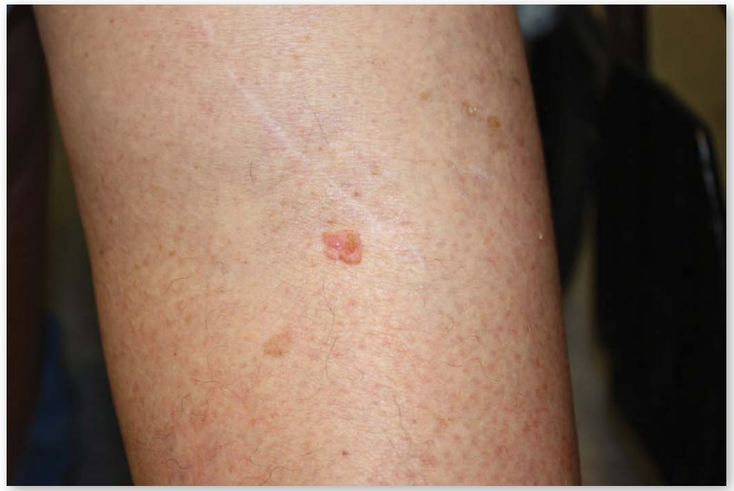
The First 30 years of the American Academy of Dermatology Skin Cancer Screening Program

By Okhovat JP, Beaulieu D, Tsao H, Halpern AC, Michaud DS, Shaykevich S, Geller AC. NIH Library of Medicine

The incidence of melanoma is rising faster than that of any other preventable cancer in the United States. The American Academy of Dermatology has sponsored free skin cancer education and screenings conducted by volunteer dermatologists in the United States since 1985.

From 1986 to 2014, records were available for 2,046,531 screenings, 1,963,141 (96%) of which were subjected to detailed analysis. Men comprised 38% of all participants. The number of annual screenings reached approximately 100,000 in 1990 and remained relatively stable thereafter.

From 1991 to 2014 (data for 1995, 1996 and 2000 were unavailable), clinical diagnoses were rendered for 20,628 melanomas, 156,087 dysplastic nevi, 32,893 squamous cell carcinomas, and 129,848 basal cell carcinomas. Only 21% of screenees had a regular dermatologist. Those with a clinical diagnosis of skin cancer were more likely than the general screening population to be uninsured.



Photograph of a pink, raised lesion (squamous cell carcinoma) on the skin of the leg.
Photo Credit: Kelly Nelson, MD, National Cancer Institute

Study findings suggest that the SPOTme program has detected thousands of skin cancers that may have gone undetected or experienced a delay in detection.

The SPOTme® Skin Cancer Screening Program is the American Academy of Dermatology's longest-standing public health program. Since its inception in 1985, dermatologists have conducted more than 2.7 million free skin cancer screenings with more than 271,000 suspicious lesions detected, and more than 30,000 suspected melanomas.

Millions of people have been educated about the importance of sun protection and early cancer detection through the skin cancer screening program. As a result, countless lives have been saved by identifying melanomas in their earliest, most treatable stage.

Their Skin Cancer Heroes" campaign features patients and survivors, the friends and loved ones who have helped and supported them, and the board-certified dermatologists who have detected and treated their skin cancer. The AAD encourages everyone to be their own "Skin Cancer Hero" by taking steps to prevent skin cancer and detect it early, when it's most treatable. This is especially important for men over 50 as they have an increased risk of developing melanoma compared to the general population.

cancer.gov

Millions of people have been educated about the importance of sun protection and early cancer detection through the skin cancer screening program.

As a result, countless lives have been saved by identifying melanomas in their earliest, most treatable stage.

Free Skin Cancer Screenings a Tremendous Success in Citrus County Florida

By Tom Adams

The Skin Cancer Foundation has reported that 1 in 5 Americans will get skin cancer by the time they turn 70, and more than 3 million Americans will be treated for it this year alone. Melanoma is the most dangerous type of skin cancer, and though it only accounts for approximately 3% of skin cancers it is responsible for the majority of skin cancer related deaths. It is also estimated that 9,320 Americans will die from Melanoma, and 4,140 Americans will die because of other non-melanoma skin cancers in 2018.

Statistics show the majority of people that participate in skin cancer screenings are senior citizens, primarily over 70 years old. According to a 2012 report from the American Medical Association, 27% of Floridians between the ages of 70 to 79 were screened that year, while only 18.5% between the ages of 60 and 69 got screened, and the number dropped to less than 7% for those between the ages of 30 and 39. This evidence proves much more needs to be done towards raising awareness for younger people to get screened, and not wait until there's an obvious problem. You are never too young to get checked, especially in areas like Florida where we have the highest exposure to the sun and, not surprisingly, the highest rates of skin cancer of anywhere else in the nation.

The five-year survival rate for people whose melanoma is detected and treated before it spreads to the lymph nodes is 99 percent, according to the American Cancer Society, but once it has spread to the lymph nodes the survival rate drops to 63 percent, and once it's spread to other parts of the body, survival drops to only 20 percent.

In part, one reason for older people being the majority of those getting screened is because skin abnormalities become more noticeable as we age, but the major factor has been discovered more younger people do not have insurance and are less likely to get screened as a result.

To combat this problem in Citrus County Florida where its population has one of the highest rates of uninsured in the state, a coalition of partners working with local public health providers has established a very successful program known as "CHIP". This came about from the Florida Department of Health, which requires all 67 County health departments to prepare and update a Health Assessment that includes a Health Improvement Plan and a Strategic Plan. From this Assessment, the Community Health Improvement Plan (CHIP) was developed. For Citrus County, the Partnership designated the name "Citrus Health Improvement Partnership" (AKA CHIP) which was formerly known as the "Citrus County Community Health Advisory Partnership (C-CHAP).

CHIP is supported by many different agencies throughout the County like 21st Century Oncology, Nature Coast Emergency Medical Services, the Centers, and the Florida Department of Health in Citrus County.

The State of Florida is responsible for monitoring the progress of this program, beginning with their strategic plan, and CHIP reports their goals and accomplishments to the State on a quarterly basis. The goal of putting together a free skin cancer screening was one of their first efforts in which everyone understood and agreed was truly needed in their community. The local health department offered to supply their facilities for the venue, and other partners offered their support for supplies and promotions to get the word out. Several medical providers offered their time

and expertise free of charge to conduct the screenings including Dr. Charles Dewberry, a Dermatologist from Florida Dermatology and Skin Cancer Center.

Turnout for the event was tremendous, and because there were almost twice as many people present as they were able to screen that day, a second day was setup to accommodate those who could not be seen. Experts from Suncoast Dermatology in Lecanto Florida volunteered their time for this second day of screening, including Dr. Ralph Massullo, a Florida State Representative that is also a Dermatologist, who brought several members from his team to help.

The generosity of these providers is noteworthy as there were so many people that showed up to get screened, they could not all be seen on these days, the providers invited them to call their offices and make appointments for free screenings at their locations to ensure everyone who wanted to get checked was able to do so. Patients with abnormalities were referred to the provider that performed the screening for follow through and treated accordingly.

One of the key organizers and promoters for the event was Helen Greene, the Physician Liaison for 21st Century Oncology. She has been extremely proactive in helping to expand this program to other communities that could also benefit, and said, "There's such a big need because of the high amount of uninsured and underinsured in our community, which was evident by the large turnout we experienced".

Helen originally got involved when the local health department held a meeting based on a community health assessment they conducted and the needs it revealed. CHIP was born from this and the community came together to organize a plan to fulfill these needs, with both short term and long terms goals. She has

been a part of this program for about two years now and says she has learned so much by being involved and encourages other public health departments throughout the country to duplicate programs like this.

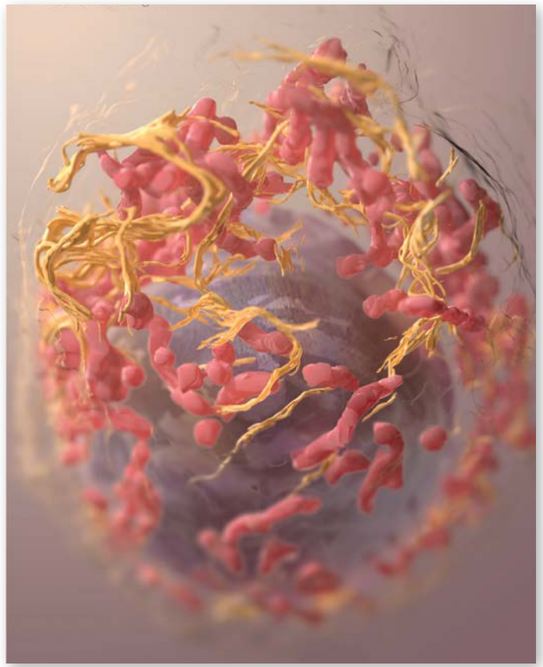
Because skin cancer screening mostly requires only visual examination, it was easily performed and accomplished. This is something Helen wants to point out in hopes that other public health departments throughout the nation can duplicate similar programs for their communities, and work with local media outlets such as newspaper, radio and television, where public service announcements can stimulate participation as it did for Citrus County.

CHIP is now setting goals for other health screenings, including prostate cancer, which they hope to begin soon. Helen welcomes public health providers to contact her directly for more information about starting a program in their community, and can be contacted at Helen.Greene@21co.com

NIH-led Research Team Develops Predictor for Immunotherapy Response in Melanoma

In a new study, researchers developed a gene expression predictor that can indicate whether melanoma in a specific patient is likely to respond to treatment with immune checkpoint inhibitors, a novel type of immunotherapy. The predictor was developed by Noam Auslander, PhD, with other researchers in the Center for Cancer Research (CCR) at the National Cancer Institute (NCI), part of the National Institutes of Health, and colleagues at Harvard University, Cambridge, Massachusetts; the University of Pennsylvania, Philadelphia; and the University of Maryland, College Park. The study was published Aug. 20, 2018 in Nature Medicine.

"There is a critical need to be able to predict how cancer patients will respond to this type of immunotherapy," said Eytan Ruppin, MD, PhD, of NCI's newly established Cancer Data Science Laboratory, who led the study. "Being able to predict who is highly likely to respond and who isn't will enable us to more accurately and precisely guide patients' treatment."



Internal organization of a melanoma cell acquired with focused ion beam scanning electron microscopy. Image credit: Donald Bliss, National Library of Medicine

Treatment with checkpoint inhibitors is effective for some patients with late-stage melanoma and certain other types of cancer. However, not all patients with melanoma respond to this treatment, and it can have considerable side effects.. But developing a predictor of response has been challenging, partly because of the limited number of patients who have received this relatively new form of treatment.

n this study, the investigators developed a predictor by first looking for clues in cases where the immune system appears to mount an unprompted, successful immune response to cancer, causing spontaneous tumor regression. They analyzed neuroblastoma, a type of cancer that frequently undergoes spontaneous regression in young children, and were able to define gene expression features that separated patients with non-regressing disease from those with regressing disease.

These features enabled the researchers to compute what they called an IMmuno-PREdictive Score (IMPRES) for each patient sample. The higher the IMPRES score for a sample, the more likely it was to undergo spontaneous regression. To see if IMPRES could be used to predict melanoma patients' responses to checkpoint inhibitors, the authors analyzed 297 samples from several studies. They found that the predictor could identify nearly all patients who responded to the inhibitors and more than half of those who did not, making it significantly superior to all other existing published predictors. Importantly, unlike other existing predictors, IMPRES was accurate across many different melanoma patient data sets.

"We now know that immunotherapy works, but we do not understand well why a particular therapy will work for some patients but not others," said Tom Misteli, PhD, director of CCR at NCI. "This study is a step forward in developing tools to address this challenge, which is of practical importance to patients."

Dr. Ruppin said that while the results obtained are encouraging, they will need to be carefully evaluated in additional patient datasets. The authors also wrote that further study of this kind of predictor is now warranted in other cancer types for which checkpoint inhibitors have been approved.

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NHLBI Studies Explore Links Between Psoriasis and Heart Disease

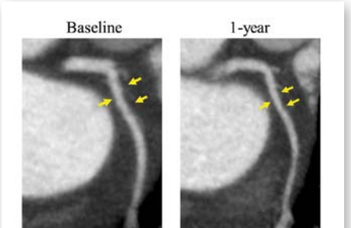
For years, researchers have been studying the surprising link between psoriasis — an inflammatory skin disease — and an increased risk for heart disease. Now, a pair of recent studies funded by the National Heart, Lung, and Blood Institute (NHLBI) offer new insights into this connection and provide exciting evidence that aggressive treatment of psoriasis may keep heart disease at bay.

Psoriasis, which is characterized by itchy patches of thick, scaly skin mostly on the elbows and knees, affects an estimated 7 million Americans, and another 3 million yet to be diagnosed. The medical community increasingly is recognizing the condition as a serious, chronic illness and acknowledges that in severe cases, it is difficult to treat.

Yet researchers are making progress. In recent years, a growing body of evidence has shown psoriasis to be a risk factor for atherosclerosis, or hardening of the arteries, which is the major cause of heart attacks. For reasons still poorly understood, people with psoriasis experience heart attacks at a younger age than those without the condition. Other studies have shown a link between psoriasis and inflammation in the large blood vessels of the body.

The new NHLBI-funded studies build on both these findings. They show that treatment of the skin disease improves both vascular (blood vessel) inflammation and coronary artery disease.

"Psoriasis is more than skin deep — the data linking it to heart disease is strong," said Nehal N. Mehta, MD, a preventive cardiologist and chief of the Section of Inflammation and Cardiometabolic Diseases at NHLBI. "The good news," added Mehta, the lead author of both journal studies, "is that there's growing evidence that treating the skin condition may also help lower cardiovascular risk factors and early vascular diseases in these patients."



High-resolution imaging reveals reduction in plaque in the left coronary artery of heart after treatment of psoriasis for 1 year. Credit: Marcus Chen, MD and Nehal N. Mehta MD, NHLBI

To find out whether treating psoriasis could lead to reduced vascular inflammation, Mehta and his colleagues conducted a study, later published in JAMA Cardiology, that used a combination of anti-inflammatory approaches, including medications and light therapy, on a group of 115 patients.

After one year of treatment, most of the patients experienced a 33 percent reduction in skin inflammation severity and a six percent reduction in inflammation of their coronary arteries. Some patients even achieved a 75 percent reduction in skin inflammation and an 11 percent reduction in artery inflammation.

"All types of treatments for psoriasis were included, which suggests that treating the disease itself may impart benefit beyond the skin," Mehta said.

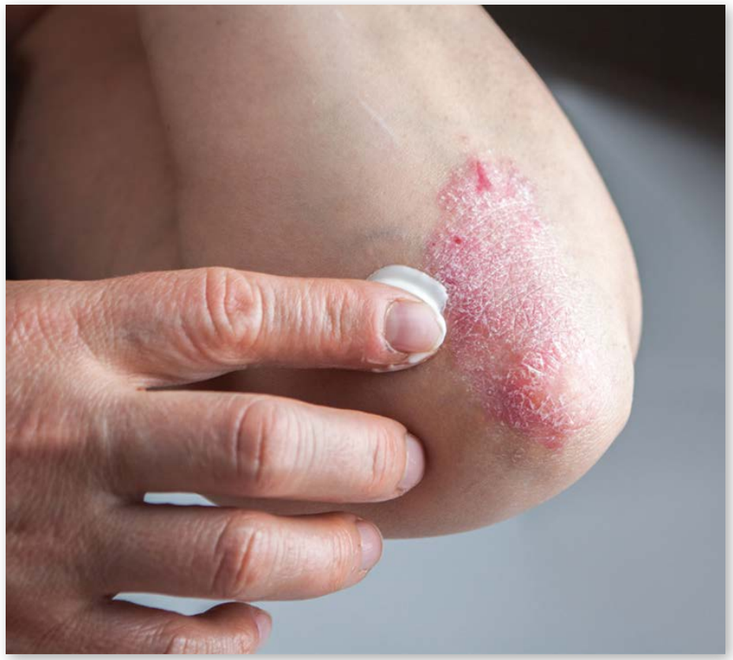
In the second journal study, published in Circulation, Mehta and his team examined whether psoriasis directly affected the coronary arteries. The scientists found evidence that psoriasis patients have higher levels of a dangerous type of coronary-artery plaque associated with heart attacks when compared to a group of patients without psoriasis of a similar age and gender.

These higher plaque levels showed up in the psoriasis patients, regardless of the severity of their condition, the researchers said.

Psoriasis, which is characterized by itchy patches of thick, scaly skin mostly on the elbows and knees, affects an estimated 7 million Americans, and another 3 million yet to be diagnosed.

Strikingly, when compared to non-psoriasis patients who were 10 years older and had high blood cholesterol, the patients with psoriasis still showed higher levels of this plaque, which can rupture and increase the likelihood of a heart attack.

As in the other study, Mehta found that patients who experienced a reduction in the severity of their psoriasis, also experienced a reduction in coronary plaque.



"These findings suggest that treating the skin of psoriasis patients may improve the health of the underlying blood vessels and thereby reduce the risk of heart disease," Mehta said. "Importantly, patients with psoriasis should be aggressively screened for cardiovascular risk factors and should be educated about their elevated cardiovascular risk."

Mehta emphasized that clinical trials are needed to confirm these early observational findings. He pointed out that association does not prove causation: The underlying biological mechanisms linking a reduction in skin inflammation to a reduction in coronary artery plaque are unclear, he noted. Future studies should attempt to characterize these mechanisms in the ongoing effort to reduce the burden of cardiovascular disease, he said.

nhlbi.nih.gov

Psoriasis is a chronic disease with a worldwide prevalence of approximately 2-3%, representing close to 5% of all cutaneous diseases. Most studies did not observe differences between genders, so almost 50% of patients are women, many of childbearing age, since the average age of diagnosis is 28 years and nearly 75% of cases occur before the age of 40.

The estimate is that 65 to 107 thousand deliveries occur annually in women with psoriasis, of which 9 to 15,000 have moderate to severe disease. Pregnancy may influence the severity of psoriasis.

Approximately 55% of patients improve during pregnancy, 21% remain stable and 23% evolve with worsening of clinical manifestations. Moreover, a worsening of symptoms in the postpartum period is observed in about 40-90% of patients.

Psoriatic arthritis occurs in 10-30% of patients with psoriasis. Pregnancy may act as a triggering factor for the articular disease and 30-40% of women relate the onset of psoriatic arthritis to the postpartum period.

Risks to the fetus are dependent on the maternal disease activity and the medications used to treat it.

The uncontrolled inflammation and excess of cytokines inherent to the process of psoriasis can influence the course of pregnancy, however, little is reported about this topic. Psoriasis autoimmune inflammation resultsfrom dysfunctional T-helper cells with concomitant amplification of proinflammatory cytokines, mainly TNF-α, IL-1 and IL-6. Cytokine excess causes endothelial dysfunction, resulting in systemic and placental vasculopathies through platelet aggregation, intermittent vasospasm and activation of the coagulation system. Placental vasculopathy has been linked to intrauterine growth retardation and low birth weight.

The stress associated with chronic and recurrent diseases tends to impact mental health, increasing the risk of alcohol abuse, depression, weight gain and smoking. Psoriasis is also associated with high rates of comorbidities, such as diabetes mellitus, cardiovascular diseases, obesity and metabolic syndromethat may also lead to complications during pregnancy and increase the risk of malformations.

Studies show that pregnant women with psoriasis frequently present overweight/obesity, depression and smoking habits in the first trimester and are also less compliant with the intake of vitamins and prenatal supplements.

THE CHALLENGES OF TREATING PLAQUE PSORIASIS **IN WOMEN OF CHILDBEARING POTENTIAL**

Insights From the CIMZIA® (certolizumab pegol) Clinical Studies

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Psoriasis imposes a substantial burden in the United States, with an overall prevalence of 3.2% among adults over the age of 20 years, as determined by a cross-sectional study using the National Health and Nutrition Examination Survey.[1] Given that surveys have also shown that psoriasis can adversely impact multiple aspects of a patient's life, including their psychosocial well-being and activities of daily living,[2] it is important that management of moderate to severe plaque psoriasis involve attainment and maintenance of skin clearance. However, women of childbearing potential (18 to 45 years) are a patient population with distinct needs and considerations. Many of the distinct needs of women involve family planning and the motherhood journey, as 82% of women in the general population will experience a pregnancy at some point in their lifetime, and, in a separate study assessing unintended pregnancy rates in the United States, 45% of pregnancies were found to be unplanned or unintended.[3,4]

There can be fluctuations in psoriasis disease activity before, during, and after pregnancy. In a prospective survey of women with psoriasis (N=47), 55% reported improvement of their psoriasis during pregnancy, 21% reported no change, and 23% reported worsening.[5] When these women were queried postpartum (N=46), 9% reported improvement of their psoriasis, 26% reported no change, and 65% reported worsening.[5] Objective assessment of these women's affected body surface area during pregnancy and postpartum revealed a similar trend; 55% experienced no change and 15% experienced worsening during pregnancy, and 52% experienced no change and 41% experienced worsening postpartum.[5] These findings were obtained in a noninterventional study with a limited sample size, and may not be generalizable to the broader population of women.

Many biologic agents approved for the treatment of moderate to severe plaque psoriasis are fully formed monoclonal antibodies (mAbs) that have a fragment-crystallizable (Fc) region of an IgG-based antibody.[6] It is well known that the Fc region of an IgG-based mAb is critical for facilitating active transport of the mAb across the placenta for materno-fetal transfer of humoral immunity.[7] Most Fc-dependent mAb transport occurs antenatally across the placental syncytiotrophoblast, which is bathed in maternal blood and internalizes blood serum containing maternal antibodies.[7] A specialized receptor, called the neonatal Fc receptor (FcRn), is present on the internal vesicles of the syncytiotrophoblast, and the FcRn binds to the Fc regions of maternal mAbs.[7] The FcRn then transcytoses these mAbs into the fetal circulation, where they are released at physiological pH.[7] However, other mechanisms of antibody transfer, including passive diffusion,[8] are not well understood in the context of placental transfer, and no conclusions about the clinical safety of a biologic agent can be drawn on the basis of its pharmacokinetics across the placenta.

When considered collectively, several experimental findings suggest that CIMZIA® (certolizumab pegol) may be an appropriate treatment option for women of childbearing age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[9-11] The clinical efficacy and safety of CIMZIA in the treatment of moderate to severe chronic plaque psoriasis were demonstrated in three multicenter, double-blind, placebo-controlled phase-3 trials (CIMPASI-1, CIMPASI-2, and CIMPACT), where patients were evaluated at either a 400 mg Q2W dose or a 200 mg Q2W dose (following a loading dose of 400 mg at Weeks 0, 2, and 4) versus placebo, as shown in Table 1.[9-11] In CIMPASI-1 and CIMPASI-2, among subjects who were PASI 75 responders at Week 16 and received CIMZIA 400 mg Q2W, the PASI 75 response rates at Week 48 were 94% and 81%, respectively.[11] In subjects who were PASI 75 responders at Week 16 and received CIMZIA 200 mg Q2W, the PASI 75 response rates at Week 48 were 81% and 74%, respectively.[11] In the placebo-controlled period of CIMPASI-1, CIMPASI-2, and CIMPACT in the 400 mg Q2W group, adverse events, such as upper respiratory tract infections and headache, occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group.[11] The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group.[11]

Although they did not specifically evaluate patients with plaque psoriasis or patients receiving the 400 mg Q2W dose of CIMZIA, multiple pharmacokinetic studies have provided additional insights that may be applicable to women of childbearing potential; these studies did not assess the efficacy or safety of CIMZIA in pregnant women. Certolizumab pegol plasma concentrations obtained from 2 studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth.[11] Note that limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes,[11] and conclusions regarding the safety of TNF inhibitors in pregnant women, risks of major birth defects, or other pregnancy outcomes cannot be drawn from these data. (MotherToBaby Pregnancy Studies were conducted by the Organization of Teratology Information Specialists [OTIS]. Contact the OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/.) The long-term effect of in utero exposure to biologic therapies is unknown, and the theoretical risks of administration of live or live-attenuated vaccines to the infants exposed in utero to CIMZIA should be weighed against the benefits of vaccinations.[11] In addition to the placental transfer studies, in a multicenter clinical study of 17 lactating women treated with CIMZIA 200 mg Q2W or 400 mg Q4W minimal certolizumab pegol concentrations were observed in breast milk.[11] In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at 4 weeks postpartum.[11] The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition. These studies were designed solely to assess the transfer of drug from mother to infant; conclusions regarding the safety and efficacy should not be made based on these data.

In summary, as development of biologic agents for the treatment of moderate to severe plaque psoriasis continues to evolve, adults with moderate to severe plaque psoriasis, including women of childbearing potential, may have additional therapeutic options become available to them. Physicians and patients alike can benefit from information regarding the clinical features of a treatment option when developing a plan for the management of moderate to severe plaque psoriasis during the family planning journey. As such, the clinical studies such as those described in this article may provide useful insights for clinical planning.

Table 1. Primary/key secondary endpoints at Week 16 across all 3 pivotal trials.[11a]

	CIMPASI-1[b]			CIMPASI-2[b]			CIMPACT[c]		
	Placebo (N=51)	CIMZIA 200 mg Q2W[d] (N=95)	CIMZIA 400 mg Q2W (N=88)	Placebo (N=49)	CIMZIA 200 mg Q2W[d] (N=91)	CIMZIA 400 mg Q2W (N=87)	Placebo (N=57)	CIMZIA 200 mg Q2W[d] (N=165)	CIMZIA 400 mg Q2W (N=167)
PGA of 0 or 1[e]	4%	45%	55%	3%	61%	65%	4%	52%	62%
PASI 75	7%	65%	75%	13%	81%	82%	4%	69%	75%
PASI 90	0%	36%	44%	5%	50%	52%	0%	40%	49%

Based on a post hoc subgroup analysis in subjects with moderate to severe PSO, stratified by ≤90 kg or >90 kg, subjects with both lower body weight and lower disease severity may achieve an acceptable response with CIMZIA 200 mg.

[a]Missing data were imputed using multiple imputation based on the MCMC method.
[b]The co-primary efficacy endpoints at Week 16 in CIMPASI-1 and CIMPASI-2 were PASI 75 and PGA 0 or 1.
[c]PGA score of 0 (clear) or 1 (almost clear) based on a 5 pt scale (0-4).
[d]Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.
[e]The primary endpoint in CIMPACT was PASI 75 at Week 12.
MCMC, Markov Chain Monte Carlo; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment.

References 1. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516. **2.** Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol.* 2001;137(3):280-284. **3.** Pew Research Center. Childlessness up among all women; down among women with advanced degrees. June 25, 2010. http://www.pewsocialtrends.org/2010/06/25/childlessness-up-among-all-women-down-among-women-with-advanced-degrees. Accessed January 3, 2018. **4.** Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med.* 2016;374(9):843-852. **5.** Murase JE, Chan KK, Garite TJ, et al. Hormonal effect on psoriasis in pregnancy and post partum. *Arch Dermatol.* 2005;141(5):601-606. **6.** Morrow T, Felcone LH. Defining the difference: what makes biologics unique. *Biotechnol Healthc.* 2004;1(4):24-29. **7.** Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol.* 2007;7(9):715-725. **8.** Verkman AS. Solute and macromolecule diffusion in cellular aqueous compartments. *Trends Biochem Sci.* 2002;27(1):27-33. **9.** Gottlieb AB, Blauvelt A, Thaçi D, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks from two phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol.* 2018;79(2):302-314.e6. **10.** Lebwohl M, Blauvelt A, Paul C, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blinded, etanercept- and placebo-controlled study (CIMPACT). *J Am Acad Dermatol.* 2018;79(2):266-276.e5. **11.** CIMZIA [prescribing information]. Smyrna, GA: UCB, Inc.; 2018.

To learn more about CIMZIA and how it may be incorporated into dermatologic practice for the treatment of moderate to severe plaque psoriasis, visit www.CIMZIAHCP.com

Please see Brief Summary of full Prescribing Information, with Boxed Warning regarding serious infections, including tuberculosis, and malignancies on following pages.

Indication

- **CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy**

Important Safety Information

CONTRAINDICATIONS

- CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylactoid reaction, serum sickness, and urticaria.

SERIOUS INFECTIONS

Patients treated with CIMZIA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue CIMZIA if a patient develops a serious infection or sepsis.
Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before CIMZIA use and during therapy. Initiate treatment for latent TB prior to CIMZIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with CIMZIA prior to initiating therapy in the following patients: with chronic or recurrent infection; who have been exposed to TB; with a history of opportunistic infection; who resided in or traveled in regions where mycoses are endemic; with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start CIMZIA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.

- Consider the risks and benefits of CIMZIA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among CIMZIA-treated patients compared to control patients.
- In CIMZIA clinical trials, there was an approximately 2-fold higher rate of lymphoma than expected in the general U.S. population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk of lymphoma than the general population.
- Malignancies, some fatal, have been reported among children, adolescents, and young adults being treated with TNF blockers. Approximately half of the cases were lymphoma, while the rest were other types of malignancies, including rare types associated with immunosuppression and malignancies not usually seen in this patient population.
- Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including CIMZIA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis, and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. Carefully assess the risks and benefits of treating with CIMZIA in these patient types.
- Cases of acute and chronic leukemia were reported with TNF blocker use.

HEART FAILURE

- Worsening and new onset congestive heart failure (CHF) have been reported with TNF blockers. Exercise caution and monitor carefully.

HYPERSENSITIVITY

- Angioedema, anaphylactoid reaction, dyspnea, hypotension, rash, serum sickness, and urticaria have been reported following CIMZIA administration. If a serious allergic reaction occurs, stop CIMZIA and institute appropriate therapy. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a plastic derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Test patients for HBV infection before initiating treatment with CIMZIA.
- Exercise caution in patients who are carriers of HBV and monitor them before and during CIMZIA treatment.
- Discontinue CIMZIA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming CIMZIA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including CIMZIA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, seizure disorder, optic neuritis, peripheral neuropathy, and Guillain-Barré syndrome.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with CIMZIA.
- Consider stopping CIMZIA if significant hematologic abnormalities occur.

DRUG INTERACTIONS

- Do not use CIMZIA in combination with other biological DMARDS.

AUTOIMMUNITY

- Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on CIMZIA should not receive live or live-attenuated vaccines.

ADVERSE REACTIONS

- The most common adverse reactions in CIMZIA clinical trials (≥8%) were upper respiratory infections (18%), rash (9%), and urinary tract infections (8%).

Please see Brief Summary of full Prescribing Information, with Boxed Warning regarding serious infections, including tuberculosis, and malignancies on following pages.

cimzia® (certolizumab pegol)

PROFESSIONAL BRIEF SUMMARY—CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

CIMZIA® (certolizumab pegol)

WARNINGS:

SERIOUS INFECTIONS

Patients treated with CIMZIA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens including Legionella and Listeria.**

The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member *[see Warnings and Precautions]*. CIMZIA is not indicated for use in pediatric patients.

INDICATIONS AND USAGE

CIMZIA is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA). CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA). CIMZIA is indicated for the treatment of adults with active ankylosing spondylitis (AS). CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylactoid reaction, serum sickness, and urticaria *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Risk of Serious Infections *(see also Boxed Warning)*

Patients treated with CIMZIA are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
- with underlying conditions that may predispose them to infection

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously or concomitantly received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating CIMZIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating CIMZIA, assess if treatment for latent tuberculosis is needed; and consider an induration of 5 mm or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite previous or concomitant treatment for latent tuberculosis, cases of active tuberculosis have occurred in patients treated with CIMZIA. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with CIMZIA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with CIMZIA.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection.

When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and risks of antifungal therapy.

Malignancies

In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. During CIMZIA studies of psoriasis, malignancies (excluding non-melanoma skin cancer) were observed corresponding to an incidence rate of 0.5 (0.2, 1.0) per 100 subject-years among a total of 995 subjects who received CIMZIA. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. CIMZIA is not indicated for use in pediatric patients.

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin's lymphoma among 1,319 placebo-treated patients.

In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma. In the CIMZIA PsO clinical trials (placebo-controlled and open label) there was one case of Hodgkin's lymphoma.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy *[see Adverse Reactions]*. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-antagonists, including CIMZIA. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully *[see Adverse Reactions]*.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, anaphylactoid reaction, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed *[see Adverse Reactions]*.

Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Test patients for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

Neurologic Reactions

Use of TNF blockers, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA *[see Adverse Reactions]*.

Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA *[see Adverse Reactions]*. The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

Use with Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to etanercept alone. A higher risk of serious infections was also observed in combination use of TNF blockers with abatacept and rituximab. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the use of CIMZIA in this combination. Therefore, the use of CIMZIA in combination with other biological DMARDs is not recommended *[see Drug Interactions]*.

Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

Patients treated with CIMZIA may receive vaccinations, except for live or live attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response to vaccine between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients developed protective levels of anti-vaccine antibodies between CIMZIA and placebo treatment groups; however patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with patients receiving CIMZIA alone. The clinical significance of this is unknown.

Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood *[see Warnings and Precautions and Adverse Reactions]*. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*
- Heart Failure *[see Warnings and Precautions)]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

In premarketing controlled trials of all patient populations combined the most common adverse reactions (≥ 8%) were upper respiratory infections (18%), rash (9%) and urinary tract infections (8%).

Adverse Reactions Most Commonly Leading to Discontinuation of Treatment in Premarketing Controlled Trials

The proportion of patients with Crohn's disease who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo. The most common adverse reactions leading to the discontinuation of CIMZIA (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% CIMZIA, 0.2% placebo), diarrhea (0.4% CIMZIA, 0% placebo), and intestinal obstruction (0.4% CIMZIA, 0% placebo).

The proportion of patients with rheumatoid arthritis who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA and 2.5% for placebo. The most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%); and pyrexia, urticaria, pneumonia, and rash (0.3%).

Controlled Studies with Crohn's Disease

The data described below reflect exposure to CIMZIA at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 patients with Crohn's disease received CIMZIA at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of CIMZIA at Weeks 0, 2, 4). In controlled and uncontrolled studies, 1,564 patients received CIMZIA at some dose level, of whom 1,350 patients received 400 mg CIMZIA. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for CIMZIA and 9% for placebo. The most common adverse reactions (occurring in ≥ 5% of CIMZIA-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with CIMZIA were upper respiratory infections (e.g. nasopharyngitis, laryngitis, viral infection) in 20% of CIMZIA-treated patients and 13% of placebo-treated patients, urinary tract infections (e.g. bladder infection, bacteriuria, cystitis) in 7% of CIMZIA-treated patients and in 6% of placebo-treated patients, and arthralgia (6% CIMZIA, 4% placebo).

Other Adverse Reactions

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, stroke and transient ischemic attack.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Thrombophlebitis, vasculitis.

Controlled Studies with Rheumatoid Arthritis

CIMZIA was studied primarily in placebo-controlled trials and in long-term follow-up studies. The data described below reflect the exposure to CIMZIA in 2,367 RA patients, including 2,030 exposed for at least 6 months, 1,663 exposed for at least one year and 282 for at least 2 years; and 1,774 in adequate and well-controlled studies. In placebo-controlled studies, the population had a median age of 53 years at entry; approximately 80% were females, 93% were Caucasian and all patients were suffering from active rheumatoid arthritis, with a median disease duration of 6.2 years. Most patients received the recommended dose of CIMZIA or higher.

Table 1 summarizes the reactions reported at a rate of at least 3% in patients treated with CIMZIA 200 mg every other week compared to placebo (saline formulation), given concomitantly with methotrexate.

Table 1: Adverse Reactions Reported by ≥3% of Patients Treated with CIMZIA Dosed Every Other Week during Placebo-Controlled Period of Rheumatoid Arthritis Studies, with Concomitant Methotrexate.

Adverse Reaction (Preferred Term)	Placebo+ MTX# (%) N =324	CIMZIA 200 mg EOW + MTX(%) N =640
Upper respiratory tract infection	2	6
Headache	4	5
Hypertension	2	5
Nasopharyngitis	1	5
Back pain	1	4
Pyrexia	2	3
Pharyngitis	1	3
Rash	1	3
Acute bronchitis	1	3
Fatigue	2	3

#EOW = Every other Week, MTX = Methotrexate.

Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs.

Patients receiving CIMZIA 400 mg as monotherapy every 4 weeks in rheumatoid arthritis controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200 mg every other week.

Other Adverse Reactions

Other infrequent adverse reactions (occurring in less than 3% of RA patients) were similar to those seen in Crohn's disease patients.

Psoriatic Arthritis Clinical Study

CIMZIA has been studied in 409 patients with psoriatic arthritis (PsA) in a placebo-controlled trial. The safety profile for patients with PsA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Ankylosing Spondylitis Clinical Study

CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a placebo-controlled study (AS-1). The safety profile treated with CIMZIA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

In clinical studies, a total of 1112 subjects with plaque psoriasis were treated with CIMZIA. Of these, 779 subjects were exposed for at least 12 months, 551 for 18 months, and 66 for 24 months.

Data from three placebo-controlled studies (Studies PS-1, PS-2, and PS-3) in 1020 subjects (mean age 46 years, 66% males, 94% white) were pooled to evaluate the safety of CIMZIA.

Placebo-Controlled Period (Week 0-16)

In the placebo-controlled period of Studies PS-1, PS-2 and PS-3 in the 400 mg group, adverse events occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group. The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the CIMZIA group than in the placebo group.

Table 2: Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Studies PS-1, PS-2, and PS-3.

Adverse Reactions	Cimzia 400 mg every other week n (%) N=342	Cimzia 200 mg[5] every other week n (%) N=350	Placebo n (%) N=157
Upper respiratory tract infections[1]	75 (21.9)	68 (19.4)	33 (21.0)
Headache[2]	13 (3.8)	10 (2.9)	4 (2.5)
Injection site reactions[3]	11 (3.2)	6 (1.7)	1 (0.6)
Cough	11 (3.2)	4 (1.1)	3 (1.9)
Herpes infections[4]	5 (1.5)	5 (1.4)	2 (1.3)

1. Upper respiratory tract infection cluster includes upper respiratory tract infection, pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral upper respiratory tract infection, viral pharyngitis, viral sinusitis, and nasopharyngitis.
2. Headache includes headache and tension headache.
3. Injection site reactions cluster includes injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site swelling.
4. Herpes infections cluster includes oral herpes, herpes dermatitis, herpes zoster, and herpes simplex.
5. Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.

Elevated Liver Enzymes

Elevated liver enzymes were reported more frequently in the CIMZIA-treated subjects (4.3% in the 200 mg group and 2.3% in the 400 mg group) than in the placebo-treated subjects (2.5%). Of CIMZIA-treated subjects who had elevation of liver enzymes, two subjects were discontinued from the trial. In controlled Phase 3 studies of CIMZIA in adults with PsO with a controlled period duration ranging from 0 to 16 weeks, AST and/or ALT elevations ≥5 x ULN occurred in 0.9% of CIMZIA 200 mg or CIMZIA 400 mg arms and none in placebo arm.

Psoriasis-Related Adverse Events

In controlled clinical studies in psoriasis, change of plaque psoriasis into a different psoriasis sub-types (including erythrodermic, pustular and guttate), was observed in <1% of Cimzia treated subjects.

Adverse Reactions of Special Interest Across Indications

Infections

The incidence of infections in controlled studies in Crohn's disease was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infections (20% for CIMZIA, 13% for placebo). The incidence of serious infections during the controlled clinical studies was 3% per patient-year for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

The incidence of new cases of infections in controlled clinical studies in rheumatoid arthritis was 0.91 per patient-year for all CIMZIA-treated patients and 0.72 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, herpes infections, urinary tract infections, and lower respiratory tract infections. In the controlled rheumatoid arthritis studies, there were more new cases of serious infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per patient-year and in the 400 mg every 4 weeks dose group were 0.04 per patient-year. Serious infections included tuberculosis, pneumonia, cellulitis, and pyelonephritis. In the placebo group, no serious infection occurred in more than one subject. There is no evidence of increased risk of infections with continued exposure over time *[see Warnings and Precautions]*.

In controlled clinical studies in psoriasis, the incidence rates of infections were similar in the CIMZIA and placebo groups. The infections consisted primarily of upper respiratory tract infections and viral infections (including herpes infections). Serious adverse events of infection occurred in CIMZIA-treated patients during the placebo-controlled periods of the pivotal studies (pneumonia, abdominal abscess, and hematoma infection) and Phase 2 study (urinary tract infection, gastroenteritis, and disseminated tuberculosis).

Tuberculosis and Opportunistic Infections

In completed and ongoing global clinical studies in all indications including 5,118 CIMZIA-treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years across all indications.

The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of disseminated (miliary, lymphatic, and peritoneal) as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, there were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials. In Phase 2 and Phase 3 studies with CIMZIA in plaque psoriasis, there were 2 cases of TB among 1112 exposed patients *[see Warnings and Precautions]*.

Malignancies

In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients *[see Warnings and Precautions]*.

Heart Failure

In placebo-controlled and open-label studies, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure *[see Warnings and Precautions]*.

Autoantibodies

In clinical studies in Crohn's disease, 4% of patients treated with CIMZIA and 2% of patients treated with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with CIMZIA developed symptoms of a lupus-like syndrome.

In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA. Four patients out of 2,367 patients treated with CIMZIA in RA clinical studies developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown *[see Warnings and Precautions]*.

Immunogenicity

Patients with Crohn's disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 6% were neutralizing in vitro. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively). The following adverse events were reported in Crohn's disease patients who were antibody-positive (N=100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma concentration, which represents 17% (152/903) of the study population. The data from these two studies do not suggest an association between the development of antibodies and adverse events.

The overall percentage of patients with antibodies to certolizumab pegol detectable on at least one occasion was 7% (105 of 1,509) in the rheumatoid arthritis placebo-controlled trials. Approximately one third (3%, 39 of 1,509) of these patients had antibodies with neutralizing activity in vitro. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Patients treated with concomitant immunosuppressant therapy (MTX) in RA-I, RA-II, RA-III had a lower rate of neutralizing antibody formation overall than patients treated with CIMZIA monotherapy in RA-IV (2% vs. 8%). Both the loading dose of 400 mg every other week at Weeks 0, 2 and 4 and concomitant use of MTX were associated with reduced immunogenicity.

Antibody formation was associated with lowered drug plasma concentration and reduced efficacy. In patients receiving the recommended CIMZIA dosage of 200 mg every other week with concomitant MTX, the ACR20 response was lower among antibody positive patients than among antibody-negative patients (Study RA-I, 48% versus 60%; Study RA-II 35% versus 59%, respectively). In Study RA-III, too few patients developed antibodies to allow for meaningful analysis of ACR20 response by antibody status. In Study RA-IV (monotherapy), the ACR20 response was 33% versus 56%, antibody-positive versus antibody-negative status, respectively *[see Clinical Pharmacology]*. No association was seen between antibody development and the development of adverse events.

Approximately 8 % (22/265) and 19% (54/281) of subjects with psoriasis who received CIMZIA 400 mg every 2 weeks and CIMZIA 200 mg every 2 weeks for 48 weeks, respectively, developed antibodies to certolizumab pegol. Of the subjects who developed antibodies to certolizumab pegol, 45% (27/60) had antibodies that were classified as neutralizing. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy.

The data reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. The assay used to measure antibodies to certolizumab pegol is subject to interference by serum certolizumab pegol, possibly resulting in an underestimation of the incidence of antibody formation. For these reasons, comparison of the incidence of antibody positivity to certolizumab pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dermatitis allergic, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope *[see Warnings and Precautions]*.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CIMZIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Vascular disorder: systemic vasculitis has been identified during post-approval use of TNF blockers.

Skin: case of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and new or worsening psoriasis (all sub-types including pustular and palmoplantar) have been identified during post-approval use of TNF blockers.

Immune System Disorders: sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of the skin) *[see Warnings and Precautions]*.

DRUG INTERACTIONS

Use with Anakinra, Abatacept, Rituximab, and Natalizumab

An increased risk of serious infections has been seen in clinical studies of other TNF-blocking agents used in combination with anakinra or abatacept, with no added benefit. Formal drug interaction studies have not been performed with rituximab or natalizumab. Because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA in these combinations. There is not enough information to assess the safety and efficacy of such combination therapy. Therefore, the use of CIMZIA in combination with anakinra, abatacept, rituximab, or natalizumab is not recommended *[see Warnings and Precautions]*.

Live Vaccines

Avoid use of live (including attenuated) vaccines concurrently with CIMZIA *[see Warnings and Precautions]*.

Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) test and Standard Target Activated Partial Thromboplastin time (STA-PTT) Automate tests from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on in vivo coagulation.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:

MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/

Risk Summary

Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth (see Data). There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed in utero to CIMZIA should be weighed against the benefits of vaccinations (see Clinical Considerations). No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFa pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four weeks.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFa, CIMZIA administered during pregnancy could affect immune responses in the in utero-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for in utero-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults (see Data). The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=54), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during the third trimester of pregnancy for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1 to 27 days). Certolizumab pegol plasma concentrations were measured in samples from mothers and infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 to 49.4 mcg/mL) were consistent with non-pregnant women's plasma concentrations in Study RA-I *[see Clinical Studies]*. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.0422 mcg/mL at birth (infant/mother plasma ratio of 0.09%). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485 mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse reaction was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn's disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range 5 to 42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in infant blood; and ranged from 1.87 to 59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

Animal Data

Because certolizumab pegol does not cross-react with mouse or rat TNFa, reproduction studies were performed in rats using a rodent anti-murine TNFa pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF.

Lactation

Risk Summary

In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol concentrations were observed in breast milk. No serious adverse reactions were noted in the 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at 4 weeks post-partum *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition.

Data

A multicenter clinical study designed to evaluate breast milk was conducted in 17 lactating women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks for rheumatological disease or Crohn's disease. The effects of certolizumab pegol on milk production were not studied. The concentration of certolizumab pegol in breast milk was not measurable in 77 (56 %) of the 137 samples taken over the dosing periods using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. The median of the estimated average daily infant doses was 0.0035 mg/kg/day (range: 0 to 0.01 mg/kg/day). The percentage of the maternal dose (200 mg CIMZIA dosed once every 2 weeks), that reaches an infant ranged from 0.56% to 4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 breastfed infants in the study.

In a separate study, plasma certolizumab pegol concentrations were collected 4 weeks after birth in 9 breastfed infants whose mothers had been currently taking CIMZIA (regardless of being exclusively breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFa, CIMZIA administered during pregnancy could affect immune responses in the in utero-exposed newborn and infant *[see Use in Specific Populations)]*.

Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Population pharmacokinetic analyses of patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly with CIMZIA *[see Warnings and Precautions]*.

OVERDOSAGE

The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without evidence of dose-limiting toxicities. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient Counseling

Advise patients of the potential risks and benefits of CIMZIA therapy. Be sure that patients receive the Medication Guide and allow them time to read it prior to starting CIMZIA therapy and to review it periodically. Any questions resulting from the patient's reading of the Medication Guide should be discussed. Because caution should be exercised in prescribing CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health.

Immunosuppression

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA.

Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. The prefilled syringe components are not made with natural rubber latex.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report promptly any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy, patients can call 1-877-311-8972 *[see Use in Specific Populations]*.

Instruction on Prefilled Syringe Self-Injection Technique

After proper training by a qualified healthcare professional in subcutaneous injection technique, a patient may self-inject with CIMZIA using the Prefilled Syringe if a healthcare provider determines that it is appropriate. A patient's ability to administer CIMZIA subcutaneous injections should be checked to ensure correct administration. Suitable sites for injection include the thigh or abdomen. CIMZIA should be injected when the liquid is at room temperature.

Full injection instructions are provided in the Instructions for Use booklet for the Prefilled Syringe, packaged in each CIMZIA Prefilled Syringe kit.

To avoid needle-stick injury, patients and healthcare providers should not attempt to place the needle cover back on the syringe or otherwise recap the needle. Be sure to properly dispose of needles and syringes in a puncture-proof container, and instruct patients and caregivers in proper syringe and needle disposal technique. Actively discourage any reuse of the injection materials.

Product manufactured by:
UCB, Inc.,1950 Lake Park Drive, Smyrna, GA 30080
US License No. 1736
For more information, go to www.CIMZIA.com or call 1-866-424-6942.

More Patients Survive Sudden Cardiac Arrest with New EMS Technique

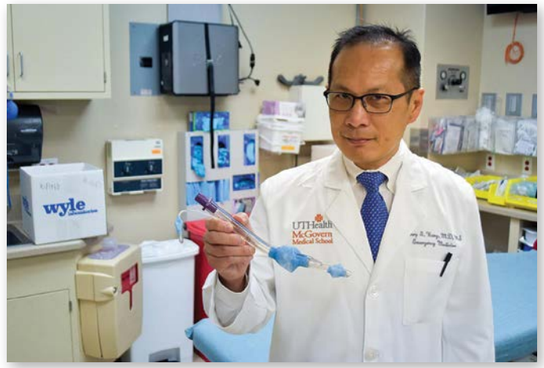
Study funded by NIH showed a change in use of breathing tube can save more lives.

A new study showed that a change in the type of breathing tube paramedics use to resuscitate patients with sudden cardiac arrest can significantly improve the odds of survival and save thousands of lives. More than 90 percent of Americans who experience sudden cardiac arrest die before, or soon after, reaching a hospital.

"During resuscitation, opening the airway and having proper access to it is a key factor for the survival of someone who goes into cardiac arrest outside of a hospital," said George Sopko, MD, MPH, program director in the NHLBI's Division of Cardiovascular Sciences and coauthor of the study. "But one of the burning questions in prehospital emergency care has been, 'Which is the best airway device?'"

Funded by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, this study is the largest of its kind to test oxygen delivery methods used by firefighters, emergency medical service (EMS) providers and paramedics. It is the first to show that a particular airway intervention can positively affect patient survival rates. The findings were published online in the Journal of the American Medical Association.

"This study demonstrated that just by managing the airway well in the early stage of resuscitation, we could save more than 10,000 lives every year," said Sopko.



UTHealth's Henry Wang, MD, displays a newer type of emergency breathing tube that could save thousands of lives.
Photo Credit: Rob Cahill, UTHealth

EMS providers treat the majority of the 400,000 out-of-hospital cardiac arrests each year. For more than three decades, their standard-of-care technique for resuscitation has been endotracheal intubation — the insertion of a plastic tube into the trachea to maintain an open airway. They use this technique in hopes that mirroring the care given by in-hospital physicians will produce better patient outcomes.

"While identical to techniques used by doctors in the hospital, intubation in these severe and stressful prehospital settings is very difficult and fraught with errors," said Henry E. Wang, MD, professor and vice chair for research in the Department of Emergency Medicine at McGovern Medical School at The University of Texas Health Science Center at Houston. Wang was the study's lead author.

Today, however, new devices such as laryngeal tubes, offer simpler alternatives to opening and accessing an airway. These tubes are easier to use, and the trial showed that cardiac arrest patients treated with this alternative had a higher survival rate.

Usually caused by a heart attack, sudden cardiac arrest occurs when the heart suddenly or unexpectedly stops beating, cutting off blood flow to the brain and other vital organs. The vast majority of out-of-hospital cardiac arrests occur at home, and only about 10 percent of people survive, according to the American Heart Association.

The Pragmatic Airway Resuscitation Trial was a multicenter research study conducted by the Resuscitation Outcomes Consortium It compared survival rates among 3,000 adults with cardiac arrest who were treated by paramedic crews from 27 EMS agencies, in Birmingham, Alabama; Dallas-Fort Worth; Milwaukee; Pittsburgh; and Portland, Oregon. Approximately half of the patients received the newer laryngeal tube treatment, while the other half received traditional endotracheal intubation.

Overall, patients in the laryngeal tube group had significantly better outcomes. For instance, 18.3 percent of patients survived three days in the hospital and 10.8 percent survived to reach hospital discharge. For the group with traditional endotracheal intubation, the survival numbers were 15.4 and 8.1 percent, respectively. Also, the proportion of patients surviving with good brain function was higher in the laryngeal tube group.

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Health and Human Services (HHS) Responds to the Needs of Americans following Hurricane Michael

"We are working closely with state health authorities and private sector partners from hospitals and other healthcare facilities to save lives and protect public health after Hurricane Michael," Secretary Azar said. "This declaration will help ensure that our fellow Americans who rely on Medicare and Medicaid have continuous access to the care they need."

HHS moved 400 medical and public health personnel along with their caches of medical equipment into impacted areas, ready to respond to medical and public health needs in Florida and Georgia. An additional 300 personnel are now on alert from the National Disaster Medical System and the U.S. Public Health Service Commissioned Corps.

Some of these medical personnel are working with Florida Urban Search and Rescue teams to triage people rescued. Other HHS medical personnel are working alongside local hospital staffs in providing medical care in hospital emergency departments in Florida.

HHS teams also can provide basic medical care for evacuees at shelters, help the health department with disease surveillance, offer behavioral health support for residents and responders, and more. HHS incident managers are working with state officials to determine whether federal medical and public health support is needed in Georgia.

HHS staff from the Office of the Assistant Secretary for Preparedness and Response (ASPR) also coordinated with the Federal Emergency Management Agency to activate a national contract that makes additional ambulances available to evacuate hospitals and nursing homes if needed. ASPR regional emergency coordinators are staffing operations centers in impacted states to stay abreast of potential public health and medical needs post-storm.

To assist state and local officials in lifesaving efforts for medically vulnerable people, HHS also provided state health officials with information on Medicare beneficiaries who rely on dialysis or use special medical equipment at home, such as oxygen concentrators, in the potentially impacted areas. For these people power outages can be life threatening within hours. CMS also activated the Kidney Community Emergency Response Program to monitor dialysis access and needs of these facilities after the hurricane.

To assist residents in the impacted area in coping with the stress of the disasters, the Substance Abuse and Mental Health Services Administration activated the Disaster Distress Helpline. The Disaster Distress Helpline provides immediate 24/7, 365-days-a-year crisis counseling and support to people experiencing emotional distress related to natural or human-caused disasters. This toll-free, multilingual, and confidential crisis support service is available to all residents

HHS Secretary Azar Declares Public Health Emergencies

in the United States and its territories. Stress, anxiety, and other depression-like symptoms are common reactions after a disaster. Call 1-800-985-5990 or text TalkWithUs to 66746 (for Spanish, press 2 or text Hablanos to 66746) to connect with a trained crisis counselor.

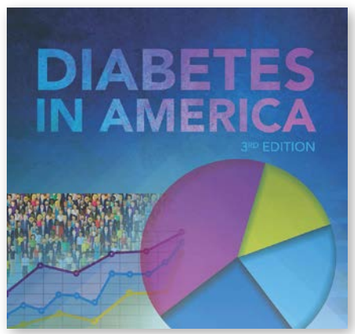
hhs.gov

New NIH Reference Book is One-stop Resource for Diabetes Medical Information

"Diabetes in America" sheds light on national burden of diabetes.

Diabetes affects a body from head to toe. Now there's a resource that illustrates its effect on both — and all the parts in between.

Thanks to research, what we know about diabetes and how to treat it has grown vastly over time. Now, researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health — along with leading diabetes experts from around the country and world — have developed the third edition of a reference designed to be a one-stop source for crucial scientific information on diabetes and its complications: "Diabetes in America."



The resource is designed to be useful to a variety of audiences. Through "Diabetes in America," patients can better understand their condition, and practitioners can determine the likelihood that their patients will develop diabetes or associated complications. Health policy makers can use the resource to help guide decision-making, while scientists can use the resource to identify areas of needed research to advance care for people with or at risk for diabetes.

"Diabetes in America" was written to serve as the go-to book for anything you ever wanted to know about diabetes," said Catherine Cowie, PhD, editor of "Diabetes in America" and senior advisor for the NIDDK Diabetes Epidemiology Program. "It's a resource for everyone, because diabetes affects just about everyone, from the more than 110 million Americans with or at risk for the disease to the many more people who care for them."

Covering the spectrum of diabetes, the book describes data and trends in the United States, complications of diabetes and related conditions, and prevention and medical care, including outlining major diabetes research findings. The effects of age, race, ethnicity, and other factors are also examined, helping practitioners develop individualized treatment plans and patients understand their unique risks and protections.

The book reports on well-known complications of diabetes, such as heart, eye, kidney and nerve diseases, and also shows the connection between diabetes and other serious conditions, including cancer, dementia, bone fractures, and urinary incontinence.

"Diabetes doubles the risk of many devastating conditions in the body, from hearing loss to heart disease to non-alcoholic fatty liver disease. With this third edition of 'Diabetes in America,' we hope to shine a light on the many consequences of this costly and chronic disease, and how research continues to improve the outlook for people with or at risk for diabetes or its complications," said NIDDK Director Griffin P. Rodgers, MD. "Written by leading experts, this guide provides everyone with crucial information about the toll of diabetes on Americans and gives scientists a resource to identify necessary research to improve health for all people with diabetes."

"Diabetes in America" also presents points of hope found through research:

Type 2 diabetes can be prevented or delayed. The NIDDK-funded Diabetes Prevention Program (DPP) found that people who are at high risk for type 2 diabetes can prevent or delay the disease by losing a modest amount of weight. A DPP-based intervention has since been disseminated nationwide.

People with type 1 diabetes are living longer, healthier lives. Findings from landmark NIDDK-funded research has made early and intensive blood glucose control the standard treatment worldwide for type 1 diabetes, contributing to longer life expectancies.

Rates of some complications are declining. Improvements in management of diabetes have led to a decline in the frequency of some complications of diabetes. For example, the number of adults with diabetes requiring lower extremity amputations has decreased.

"Diabetes in America" shows that though much progress has been made in understanding and managing diabetes, and in preventing type 2 diabetes, we are still on a long journey to good health for all," Cowie said. "We hope this edition, the first in more than 20 years, will help educate people so we can lessen this burden for everyone."

nih.gov

Native Americans Turning the Tide Against Diabetes

By Judy Sarasohn, HHS Public Affairs

The tribal elder at Fort Berthold Reservation in western North Dakota had struggled with his diabetes for years. His blood glucose level was about twice what's considered normal, his blood pressure was dangerously high, and he was overweight.

His health care provider talked to him about the need to address his diabetes and he was included in the tribal clinic's diabetes registry, so they wouldn't lose track of him. But he just didn't take the steps necessary to manage his condition. Until one day, it apparently clicked.

Jared Eagle, Director of the Indian Health Service's Special Diabetes Program for Indians (SPDI) at the reservation in New Town, said the man finally started taking advantage of the resources and care provided through the clinic. He started walking more; lost 20 to 30 pounds; and reduced his blood glucose and blood pressure levels.

"You can see him walking every day. He's walking his dog every day, even in the winter," Eagle said.

The story of this elder of the Mandan, Hidatsa and Arikara Nation (also known as the Three Affiliated Tribes) reflects the significant progress being made in Indian Country where Native Americans have a greater chance of having diabetes and kidney failure resulting from diabetes than any other U.S. racial or ethnic group, according to the Centers for Disease Control and Prevention. Nonetheless, the CDC also reported recently that kidney failure among Native Americans dropped by 54 percent between 1996 and 2013, the fastest rate for any racial or ethnic group in the U.S.

This hard-fought improvement is particularly important to American Indian and Alaska Native communities. Kidney failure from diabetes is a difficult and costly condition that requires dialysis or a kidney transplant for survival.

The progress in reducing kidney failure

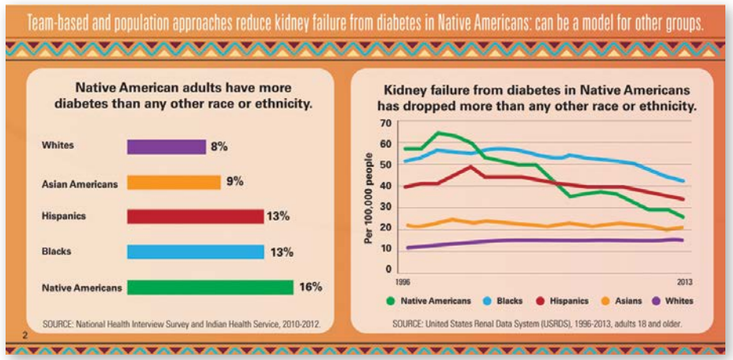
Photo Credit: Seminole Nation of Oklahoma Indian Health

has happened since the IHS began using population health and team-based approaches to diabetes and kidney care, according to the CDC and IHS.

SDPI helps fund IHS, tribal and Urban Indian programs in 35 states to implement diabetes treatment and preventive services. At Fort Berthold and other Native American communities, SDPI funds programs in prevention, physical activity and nutrition. Eagle said at Fort Berthold, they sponsor Zumba and Yoga classes, sports leagues and fitness centers, grocery store tours and lessons on how to can food.

Eagle, a member of the Three Affiliated Tribes, said that at the rural Fort Berthold Reservation, which covers 250 square miles, diabetes initiatives have involved deploying a team to the reservation's four field clinics to check on nutrition and diet; dental care; flu shots and other immunizations; blood glucose; blood pressure; and lab work. The reservation's health center keeps a diabetes registry of about 670 tribal members so that a nurse and two medical support assistants can make sure patients get — and show up for — regular appointments and that necessary lab work is ordered and reviewed.

Photo Credit: Hualapai Tribe Indian Health Department



A kidney specialist also visits patients at the field clinics once a month to assess the condition of individuals who are showing signs of progressive kidney disease. Patients can also be referred to the specialist's home office in Bismarck, but that could be a trip of 150 miles or more for some of them.

The reservation screens all school-age children to determine if they are overweight or obese. Those with a high body mass index (BMI) are then screened for diabetes, and if they show signs of being prediabetic, they are referred to the Healthy Futures clinic where they and their parents are provided follow-up services.

The Healthy Futures clinic is administered by Shasta Mandan, the RN-Certified Diabetes Educator.

Eagle says it's important to focus on younger people so they can develop healthy habits before it becomes more difficult to change unhealthy ones. As his elder patient said, "I can't believe it took me this long to figure it out."

Diabetes Prevention Youth Camp at East Central University

hhs.gov

High Blood Pressure and High Cholesterol Associated with Noisy Jobs

1 in 4 adults report having been exposed to loud noise at work

High blood pressure and high cholesterol are more common among workers exposed to loud noise at work according to a CDC study published this month in the American Journal of Industrial Medicine.

Researchers at CDC's National Institute for Occupational Safety and Health (NIOSH) also found that a quarter of U.S. workers — an estimated 41 million people — reported a history of noise exposure at work.

"Reducing workplace noise levels is critical not just for hearing loss prevention — it may also impact blood pressure and cholesterol," said NIOSH Director John Howard, MD. "Worksite health and wellness programs that include screenings for high blood pressure and cholesterol should also target noise-exposed workers."

Loud Noise Linked to Heart Disease

High blood pressure and high LDL cholesterol are key risk factors for heart disease, the leading cause of death for both men and women. Loud noise is one of the most common workplace hazards in the United States affecting about 22 million workers each year.

NIOSH researchers analyzed data from the 2014 National Health Interview Survey to estimate the prevalence of occupational noise exposure, hearing difficulty and heart conditions within U.S. industries and occupations. They also looked at the association between workplace noise exposure and heart disease. The analysis showed:

- Twenty-five percent of current workers had a history of work-related noise exposure; 14 percent were exposed in the last year.
- Twelve percent of current workers had hearing difficulty, 24 percent had high blood pressure and 28 percent had high cholesterol. Of these cases 58 percent, 14 percent, and 9 percent, respectively, can be attributed to occupational noise exposure.
- Industries with the highest prevalence of occupational noise exposure were mining (61%), construction (51%), and manufacturing (47%).
- Occupations with the highest prevalence of occupational noise exposure were production (55%); construction and extraction (54%); and installation, maintenance, and repair (54%).

"A significant percentage of the workers we studied have hearing difficulty, high blood pressure, and high cholesterol that could be attributed to noise at work," said study co-author Liz Masterson, PhD.

"If noise could be reduced to safer levels in the workplace, more than 5 million cases of hearing difficulty among noise-exposed workers could potentially be prevented. This study provides further evidence of an association of occupational noise exposure with high blood pressure and high cholesterol, and the potential to prevent these conditions if noise is reduced.

It is important that workers be screened regularly for these conditions in the workplace or through a healthcare provider, so interventions can occur. As these conditions are more common among noise-exposed workers, they could especially benefit from these screenings."

For more information on occupational hearing loss surveillance, including industry sector-specific statistics on hearing loss, tinnitus, noise exposure, and other information, please visit the Occupational Hearing Loss Surveillance webpage.

Visit the NIOSH website for guidelines and recommendations for employers and workers to help reduce noise exposure at the workplace.

cdc.gov

Surveillance for Foodborne Disease Outbreaks

By Daniel Dewey-Mattia, National Center for Emerging and Zoonotic Infectious Diseases

Public Health Action: The causes of foodborne illness should continue to be tracked and analyzed to inform disease prevention policies and initiatives. Strengthening the capacity of state and local health departments to investigate and report outbreaks will assist with these efforts through identification of the foods, etiologies, and settings linked to these outbreaks.

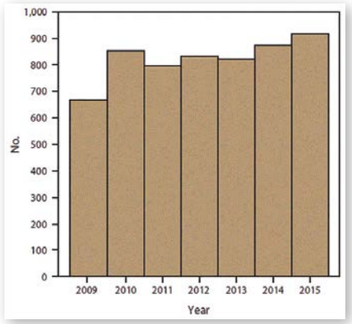
Known foodborne disease agents are estimated to cause approximately 9.4 million illnesses each year in the United States. Although only a small subset of illnesses are associated with recognized outbreaks, data from outbreak investigations provide insight into the foods and pathogens that cause illnesses and the settings and conditions in which they occur.

The Foodborne Disease Outbreak Surveillance System (FDOSS) collects data on foodborne disease outbreaks, which are defined as the occurrence of two or more cases of a similar illness resulting from the ingestion of a common food. Since the early 1960s, foodborne outbreaks have been reported voluntarily to CDC by state, local, and territorial health departments using a standard form. Beginning in 2009, FDOSS reporting was made through the National Outbreak Reporting System, a web-based platform launched that year.

During 2009–2015, FDOSS received reports of 5,760 outbreaks that resulted in 100,939 illnesses, 5,699 hospitalizations, and 145 deaths. All 50 states, the District of Columbia, Puerto Rico, and CDC reported outbreaks. Among 2,953 outbreaks with a single confirmed etiology, norovirus was the most common cause of outbreaks (1,130 outbreaks [38%]) and outbreak-associated illnesses (27,623 illnesses [41%]), followed by Salmonella with 896 outbreaks (30%) and 23,662 illnesses (35%). Outbreaks caused by Listeria, Salmonella, and Shiga toxin-producing Escherichia coli (STEC) were responsible for 82% of all hospitalizations and 82% of deaths reported. Among 1,281 outbreaks in which the food reported could be classified into a single food category, fish were the most commonly implicated category (222 outbreaks [17%]), followed by dairy (136 [11%]) and chicken (123 [10%]). The food categories responsible for the most outbreak-associated illnesses were chicken (3,114 illnesses [12%]), pork (2,670 [10%]), and seeded vegetables (2,572 [10%]). Multistate outbreaks comprised only 3% of all outbreaks reported but accounted for 11% of illnesses, 34% of hospitalizations, and 54% of deaths.

Foodborne disease outbreaks provide information about the pathogens and foods responsible for illness. Norovirus remains the leading cause of foodborne disease outbreaks, highlighting the continued need for food safety improvements targeting worker health and hygiene in food service settings. Outbreaks caused by Listeria, Salmonella, and STEC are important targets for public health intervention efforts, and improving the safety of chicken, pork, and seeded vegetables should be a priority.

Approximately 800 foodborne disease outbreaks are reported in the United States each year, accounting for approximately 15,000 illnesses, 800 hospitalizations, and 20 deaths (1). Outbreak-associated foodborne illnesses are only a small subset of the estimated 9.4 million foodborne illnesses from known pathogens that occur annually in the United States (2). However, the food sources and exposure settings for illnesses that are not part of outbreaks can be determined only rarely. Outbreak investigations, on the other hand, often link etiologies with specific foods, allowing public health officials, regulatory agencies, and the food industry to investigate how foods become contaminated. Foodborne outbreak data also can be used to identify emerging food safety issues and to assess whether programs to prevent illnesses from particular foods are effective.



Number of foodborne disease outbreaks, by year — Foodborne Disease Outbreak Surveillance System, United States and Puerto Rico, 2009–2015

This report summarizes foodborne disease outbreaks reported in the United States in which the first illness occurred between January 1, 2009, and December 31, 2015. The report highlights a few large outbreaks as well as novel foods and food-pathogen pairs responsible for outbreaks during the reporting period.

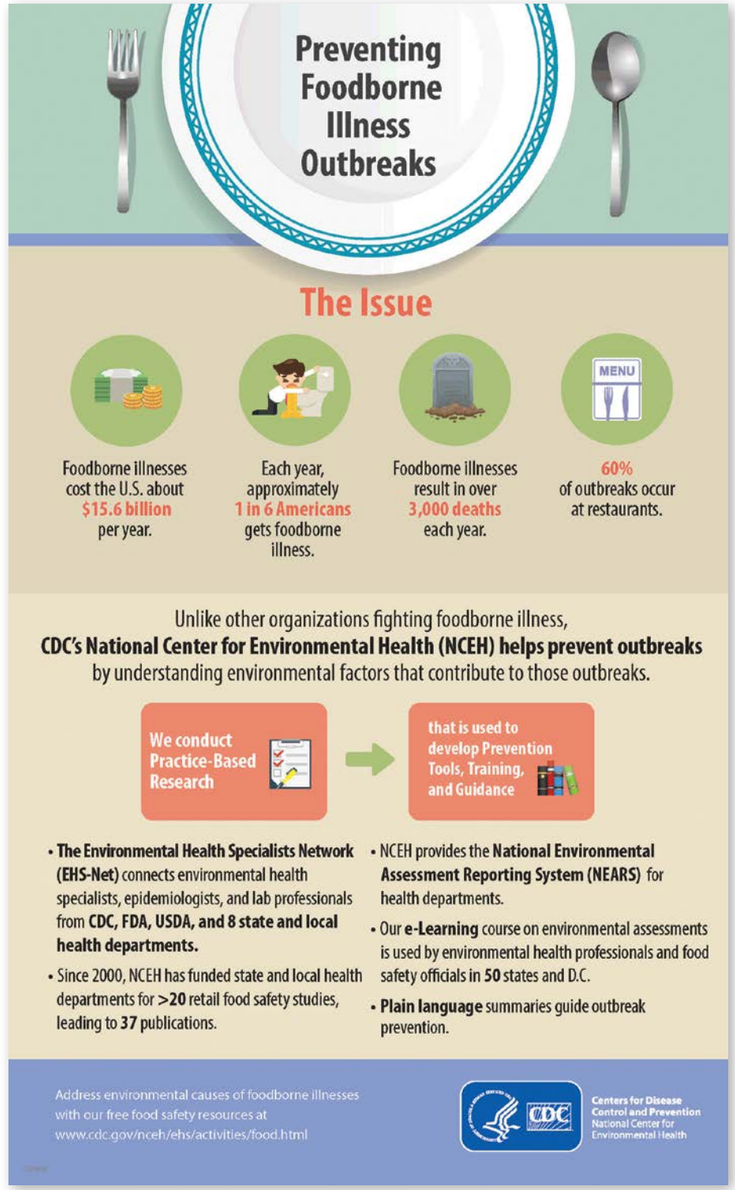
A foodborne disease outbreak is defined as two or more cases of a similar illness resulting from ingestion of a common food (3). When exposure to a contaminated food occurs in a single state, the outbreak is classified as a single-state outbreak; when exposure occurs in two or more states, the outbreak is classified as a multistate outbreak. Local, state, and territorial health departments voluntarily report foodborne outbreaks to CDC through the Foodborne Disease Outbreak Surveillance System (FDOSS) (https://www.cdc.gov/fdoss/).

CDC staff also report multistate foodborne disease outbreaks to FDOSS; these outbreaks are identified by PulseNet, the national molecular subtyping network (4). Initially a paper-based surveillance system, FDOSS reporting became electronic in 1998. In 2009, FDOSS was incorporated into the newly created National Outbreak Reporting System, a web-based platform that also includes reports of outbreaks attributable to waterborne, person-to-person, animal contact, environmental, and indeterminate or unknown modes of transmission.

Etiologies reported to FDOSS include bacterial, parasitic, and viral pathogens as well as chemicals and toxins. Outbreak etiologies are classified as unknown, suspected, or confirmed. Specific criteria (i.e., laboratory testing and clinical syndrome) are used to classify etiologies of outbreaks as suspected or confirmed (5). An outbreak is categorized as a multiple etiology outbreak if more than one agent is reported.

Foods and ingredients are identified as outbreak sources (i.e., implicated) using one or more of the following types of evidence: epidemiologic, laboratory, traceback, environmental assessment, or other data. Some outbreak investigations do not identify a source and in these instances the food is reported as unknown. CDC categorizes foods implicated in outbreak investigations on the basis of a hierarchical scheme (6). One of 24 food categories (e.g., mollusks) is assigned if a single contaminated ingredient (e.g., raw oysters) is reported as the source or if all implicated ingredients belong to the same category (e.g., raw oysters and raw clams). When a food or contaminated ingredient cannot be assigned to a single category, the outbreak is classified as not attributed to a single food category (7). The place where the implicated food was prepared is reported as one of 23 locations (e.g., a camp, farm, grocery store, or private home).

Population-based reporting rates were calculated for each state by use of U.S. Census Bureau estimates of the mid-year state populations for 2009–2015 (8). This report includes all foodborne outbreaks

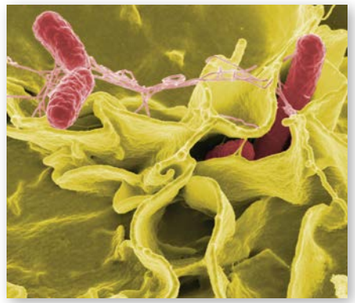


with a date of first illness onset from January, 1, 2009, through December, 31, 2015, but reported to FDOSS and finalized as of April 10, 2017.

During 2009–2015, FDOSS received reports of 5,760 outbreaks, resulting in 100,939 illnesses, 5,699 hospitalizations, and 145 deaths. Outbreaks were reported by all 50 states, the District of Columbia, Puerto Rico, and CDC. The single-state outbreak reporting rate was 2.6 outbreaks per 1 million population. The overall national reporting rate (which includes multistate outbreaks) during 2009–2015 was also 2.6 outbreaks per 1 million population. Single-state outbreaks accounted for 5,583 (97%) of all outbreaks with 89,907 cases (median: 8 cases per outbreak; range: 2–800 cases). Four percent of these ill persons (3,733) were reported as being hospitalized. Multistate outbreaks accounted for 177 (3%) of all outbreaks with 11,032 cases (median: 20 cases per outbreak; range: 2–1,939 cases). Eighteen percent of these ill persons (1,966) were hospitalized.

A single confirmed etiology was reported for 2,953 (51%) outbreaks, resulting in 67,130 illnesses, 5,114 hospitalizations, and 140 deaths (Table 1). Among 2,953 outbreaks with a single confirmed etiology, norovirus was the most common cause of outbreaks (1,130 outbreaks [38%]) and outbreak-associated illnesses (27,623 illnesses [41%]). Salmonella was the second most common single confirmed etiology reported, with 896 outbreaks (30%) and 23,662 illnesses (35%), followed by Shiga toxin-producing Escherichia coli (STEC) (191 outbreaks [6%]), Campylobacter (155 [5%]), Clostridium perfringens (108 [4%]), scombroid toxin (95 [3%]), ciguatoxin (80 [3%]), Staphylococcus aureus (35 [1%]), Vibrio parahaemolyticus (35 [1%]), and Listeria monocytogenes (35 [1%]). Listeria, Salmonella, and STEC were the most common causes of hospitalizations (82%) and deaths (82%) reported among persons in outbreaks with a single confirmed etiology.

A location of preparation was provided for 5,022 outbreak reports (87%), with



Salmonella bacteria

4,696 (94%) indicating a single location (Table 2). Among outbreaks reporting a single location of preparation, restaurants were the most common location (2,880 outbreaks [61%]), followed by catering or banquet facilities (636 [14%]) and private homes (561 [12%]). Sit-down dining style restaurants (2,239 [48%]) were the most commonly reported type of restaurant. The locations of food preparation with the most outbreak-associated illnesses were restaurants (33,465 illnesses [43%]), catering or banquet facilities (18,141 [24%]), and institutions, such as schools (9,806 [13%]). The preparation location with the largest average number of illnesses per outbreak was institutions (46.5), whereas restaurants had the smallest (11.6).

Outbreak investigators identified a food in 2,442 outbreaks (42%). These outbreaks resulted in 51,341 illnesses (51%). The food reported belonged to a single food category in 1,281 outbreaks (22%). The food category most commonly implicated was fish (222 outbreaks [17%]), followed by dairy (136 [11%]) and chicken (123 [10%]). The food categories responsible for the most outbreak-associated illnesses were chicken (3,114 illnesses [12%]), pork (2,670 [10%]), and seeded vegetables (2,572 [10%]). Scombroid toxin in fish was the single confirmed etiology and food category pair responsible for the most outbreaks (85), followed by ciguatoxin in fish (72) and Campylobacter in dairy (60). The pathogen-food category pairs that caused the most outbreak-associated illnesses were Salmonella in eggs (2,422 illnesses), Salmonella in seeded vegetables (2,203), and Salmonella in chicken (1,941). In comparison, scombroid toxin and ciguatoxin outbreaks from fish resulted in 519 outbreak-associated illnesses, an average of three illnesses per outbreak. Outbreaks of Salmonella infections from seeded vegetables resulted in an average of 88 illnesses per outbreak, and outbreaks of Salmonella infections from eggs resulted in an average of 78 illnesses per outbreak.

Several novel food vehicles caused outbreaks during the study period. In 2011, an outbreak of Salmonella serotype Enteritidis infections linked to pine nuts imported from Turkey resulted in 53 illnesses and two hospitalizations. In 2014, an outbreak of Salmonella serotypes Gaminara, Hartford, and Oranienburg in chia seed powder imported from Canada caused 45 illnesses and seven hospitalizations. An outbreak of STEC serogroups O26 and O121 infections that began in 2015 was linked to raw wheat flour produced in the United States; it resulted in 56 illnesses and 16 hospitalizations in 24 states. An outbreak of Salmonella serotype Virchow infections attributable to moringa leaf powder imported from South Africa began in 2015 and caused 35 illnesses and six hospitalizations in 24 states. It was an ingredient of an organic powdered shake mix branded to be used as a meal replacement.

Multistate outbreaks comprised only 3% of outbreaks but were responsible for 11% of illnesses, 34% of hospitalizations, and 54% of deaths. Multistate outbreaks involved a median of seven states with a range of two to 45 states in which exposure occurred. The largest of the 177 multistate outbreaks was caused by Salmonella serotype Enteritidis and due to contaminated shell eggs. An estimated 1,939 persons were infected in 10 states beginning in 2010. An outbreak of Salmonella serotype Poona infections attributed to cucumbers in 2015 had the second highest number of illnesses (907 illnesses in 40 states). This outbreak also had the most outbreak-associated hospitalizations (204 [22% of cases]). An outbreak of Salmonella serotype Heidelberg infections attributed to chicken during 2013–2014 had the second most hospitalizations (200 [32% of cases]) and involved persons from 29 states and Puerto Rico. An outbreak of Listeria monocytogenes infections attributed to cantaloupes in 28 states in 2011 had the most deaths (33 [22% of cases]), followed in 2014 by an outbreak in 12 states of Listeria monocytogenes infections attributed to caramel apples, another novel food vehicle (9), in which seven persons (20% of cases) died.

Despite considerable advances in food safety in the United States during recent decades, foodborne disease outbreaks remain a serious public health problem. The majority of the outbreaks reported had relatively small case counts, and affected persons often were exposed in a single state.

However, outbreaks with the largest case counts and most severe outcomes (e.g. highest proportion of ill persons hospitalized and most deaths) typically involved exposures in multiple states, reflecting factors such as the geographical distribution of the implicated food and the characteristics of the pathogens involved. Foods produced in other countries sometimes were implicated, highlighting the interconnectedness of the U.S. food supply with that of other nations, and the continued need to ensure that all foods are safe to eat (10).

As reported in previous summaries (11), norovirus remains the leading cause of foodborne disease outbreaks and outbreak-associated illnesses in the United States. Most foodborne norovirus outbreaks are associated with ready-to-eat foods contaminated during preparation by infected food workers in restaurants and other food service settings (12). As such, continued efforts are needed to strengthen and ensure compliance with requirements in the FDA Model Food Code (13), specifically those that exclude symptomatic and post-symptomatic workers, prohibit bare-hand contact with ready-to-eat foods, and ensure appropriate hand washing. Contaminated raw food products, specifically leafy vegetables, fruits, and mollusks, also have been implicated in norovirus outbreaks (12); thus, upstream contamination during production also should be considered in foodborne norovirus outbreak investigations.

Fish was the most frequently implicated food, but the number of illnesses associated with these outbreaks tended to be small compared with other food vehicles, largely because of the pathogens involved. Differences in outbreak size are in part attributable to how pathogens contaminate foods: toxins are produced in individual fish, whereas Salmonella and other bacterial pathogens, such as STEC, can contaminate large amounts of product across vast distribution chains (14). This helps explain why bacterial pathogens are the most common causes of multistate outbreaks and why many persons can become ill during a single bacterial disease outbreak.

Identification of novel food sources provides insight into evolving food preferences in the United States and the types of foods that pathogens can contaminate. It also raises important scientific questions regarding how these pathogens remain viable in these foods long enough to cause infection. During the study period, a few novel food vehicles were identified as the sources of multistate outbreaks of Listeria, Salmonella, and STEC infections. Some of these (chia seed powder, raw wheat flour, and moringa leaf powder) are dried, shelf-stable foods not usually considered as possible sources of illness. These outbreak reports provide additional evidence that Salmonella and STEC can survive extensive processing steps as well as months in a desiccated state. This ability of pathogens to remain viable combined with the long shelf life of these products emphasizes the need for clear, well-publicized product recall notices.

Salmonella and STEC were two of the most common causes of large outbreaks. Regulatory-focused public health interventions, such as the 2009 Egg Safety Rule, the 2011 Food Safety Modernization Act, and the 2013 Salmonella Action Plan, were designed and implemented in part to help ensure the safety of foods that can be contaminated by these pathogens (15–17). Some members of the food industry also are promoting a culture of food safety by requiring growers, producers, and distributors to adhere to strict safety guidelines designed to prevent contamination. Additional efforts will likely be needed by both government and industry to help control these pathogens.

The findings of this report are subject to at least four limitations. First, because CDC's foodborne outbreak surveillance is dynamic and agencies can submit, update, or delete reports at any time, the results of this analysis might differ slightly from previous or future reports. Second, not all outbreaks are identified and the majority of foodborne illnesses occur outside the context of a recognized outbreak. The degree to which the food vehicles, etiologies, and locations implicated in outbreaks represent the vehicles, etiologies, and locations of sporadic foodborne illness is unknown. Third, some outbreaks have an unknown food vehicle, an unknown etiology, or both, and analyses and conclusions drawn from outbreaks with an identified food vehicle and confirmed etiology might not be representative of all outbreaks. Finally, pathogens that are not known to cause illness sometimes are reported as a confirmed or suspected etiology.

Foodborne disease outbreaks remain an important public health issue. Data collected during outbreak investigations provide insight into the foods and pathogens that cause illnesses and the settings and conditions in which they occur. Continued efforts must be made to track and to analyze the causes of foodborne illness to inform targeted prevention efforts. In particular, strengthening the capacity of state and local health departments to investigate and to report outbreaks will improve foodborne disease outbreak surveillance and could help decrease the burden of foodborne illness through identification of foods, etiologies, outbreak settings, and specific points of contamination, which can inform intervention efforts.

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Illnesses from Mosquito, Tick, and Flea Bites Increasing in the US

Cases triple; better tools needed to fight mosquitoes, ticks, and fleas

Illnesses from mosquito, tick, and flea bites have tripled in the U.S., with more than 640,000 cases reported during the 13 years from 2004 through 2016. Nine new germs spread by mosquitoes and ticks were discovered or introduced into the United States during this time.

This is CDC's first summary collectively examining data trends for all nationally notifiable diseases caused by the bite of an infected mosquito, tick, or flea. It provides detailed information on the growing burden of mosquito-borne and tickborne illnesses in the U.S.

"Zika, West Nile, Lyme, and chikungunya — a growing list of diseases caused by the bite of an infected mosquito, tick, or flea — have confronted the U.S. in recent years, making a lot of people sick. And we don't know what will threaten Americans next," said CDC Director Robert R. Redfield, MD. "Our Nation's first lines of defense are state and local health departments and vector control organizations, and we must continue to enhance our investment in their ability to fight against these diseases."

Widespread and difficult to control, diseases from mosquito, tick, and flea bites are major causes of sickness and death worldwide. The growing number and spread of these diseases pose an increasing risk in the U.S. The report found that the nation needs to be better prepared to face this public health threat.
CDC scientists analyzed data reported to the National Notifiable Diseases Surveillance System for 16 notifiable vector-borne diseases from 2004 through 2016 to identify trends. Many infections are not reported or recognized, so it is difficult to truly estimate the overall cost and burden of these diseases. In 2016, the most common tickborne diseases in the U.S. were Lyme disease and ehrlichiosis/anaplasmosis. The most common mosquito-borne viruses were West Nile, dengue, and Zika. Though rare, plague was the most common disease resulting from the bite of an infected flea.

The increase in diseases caused by the bite of an infected mosquito, tick, or flea in the U.S. is likely due to many factors. Mosquitoes and ticks and the germs they spread are increasing in number and moving into new areas. As a result, more people are at risk for infection. Overseas travel and commerce are more common than ever before. A traveler can be infected with a mosquito-borne disease, like Zika, in one country, and then unknowingly transport it home. Finally, new germs spread by mosquito and tick bites have been discovered and the list of nationally notifiable diseases has grown.

"The data show that we're seeing a steady increase and spread of tickborne diseases, and an accelerating trend of mosquito-borne diseases introduced from other parts of the world," said Lyle Petersen, MD, MPH, director of the Division of Vector-Borne Diseases in the CDC's National Center for Emerging and Zoonotic Infectious Diseases. "We need to support state and local health agencies responsible for detecting and responding to these diseases and controlling the mosquitoes, ticks, and fleas that spread them."

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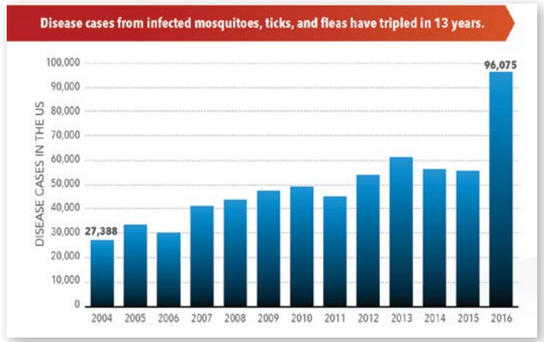

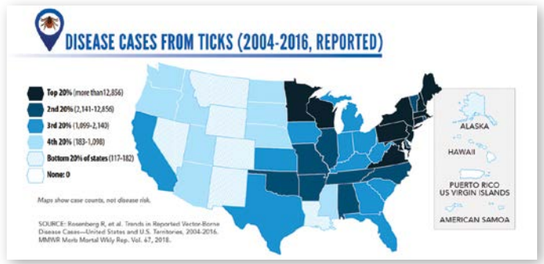

State and local public health agencies can:

- Build and sustain public health programs that test and track germs and the mosquitoes and ticks that spread them.
- Train vector control staff on 5 core competencies for conducting prevention and control activities.
- Educate the public about how to prevent bites and control germs spread by mosquitoes, ticks, and fleas in their communities

Diseases from mosquito and tick bites occur in every state and territory.

Recent outbreaks of Zika, chikungunya, and West Nile viruses and the steady increase in Lyme disease cases point to the need for state and local agencies to have comprehensive vector-borne disease prevention and control programs. The US needs better tools and more staff with greater expertise at local and state levels to reduce the growing threat of these diseases in the US

What is the federal government doing to address this problem?

- Funding states, territories, industry, university, and international groups to detect and respond to infections from mosquitoes, ticks, and fleas and report cases to CDC.
- Convening a Tick-Borne Disease Working Group established by the 21st Century Cures Act to improve federal coordination of tickborne disease efforts.
- Supporting 5 regional centers of excellence to address emerging diseases from mosquitoes and ticks.
- Conducting and developing diagnostic tests, vaccines, and treatments for these diseases.
- Educating the public about protecting themselves from diseases resulting from an infective mosquito, tick, or flea bite.

What can State and local government agencies do?

- Build and sustain public health programs that test and track germs and the mosquitoes and ticks that spread them.
- Train vector control staff on 5 core competencies for conducting prevention and control activities.
- Educate the public about how to prevent bites and control germs spread by mosquitoes, ticks, and fleas in their communities.

What can Universities and companies do?

- Study mosquitoes and ticks to better understand how to control them.
- Develop new or better methods and products to kill mosquitoes and ticks at each stage of life.
- Discover or improve tests for diagnosing new and known diseases from infective mosquito and tick bites.
- Create and sustain information-sharing networks.
- Train the next generation of entomologists and vector control professionals.

What can the general public do?

- Use an Environmental Protection Agency-registered insect repellent.
- Wear long-sleeved shirts and long pants.
- Treat items, such as boots, pants, socks, and tents, with permethrin or buy permethrin-treated clothing and gear.
- Take steps to control ticks and fleas on pets.
- Find and remove ticks daily from family and pets.
- Take steps to control mosquitoes, ticks, and fleas inside and outside your home.

cdc.gov

Tickborne Diseases Are Likely to Increase, Say NIAID Officials

By Catharine I. Paules, MD, Hilary D. Marston, MD, MPH, Marshall E. Bloom, MD, and Anthony S. Fauci, MD,

Referenced from the article Tickborne Diseases — Confronting a Growing Threat in the New England Journal of Medicine July 25, 2018

The incidence of tickborne infections in the United States has risen significantly within the past decade. It is imperative, therefore, that public health officials and scientists build a robust understanding of pathogenesis, design improved diagnostics, and develop preventive vaccines, according to a new commentary in the New England Journal of Medicine from leading scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).

Bacteria cause most tickborne diseases in the United States, with Lyme disease representing the majority (82 percent) of reported cases. The spirochete Borrelia burgdorferi is the primary cause of Lyme disease in North America; it is carried by hard-bodied ticks that then feed on smaller mammals, such as white-footed mice, and larger animals, such as white-tailed deer. Although there are likely many factors contributing to increased Lyme disease incidence in the U.S., greater tick densities and their expanding geographical range have played a key role, the authors write.

For example, the Ixodes scapularis tick, which is the primary source of Lyme disease in the northeastern U.S., had been detected in nearly 50 percent more counties by 2015 than was previously reported in 1996. Although most cases of Lyme disease are successfully treated with antibiotics, 10 to 20 percent of patients report lingering symptoms after effective antimicrobial therapy. Scientists need to better understand this lingering morbidity, note the authors.

Tickborne virus infections are also increasing and could cause serious illness and death. For example, Powassan virus (POWV), recognized in 1958, causes a febrile illness that can be followed by progressive and severe neurologic conditions, resulting in death in 10 to 15 percent of cases and long-term symptoms in as many as 70 percent of survivors. Only 20 U.S. cases of POWV infection were reported before 2006; 99 cases were reported between 2006 and 2016.

The public health burden of tickborne disease is considerably underreported, according to the authors. For example, the U.S. Centers for Disease Control and Prevention (CDC) reports approximately 30,000 cases of Lyme disease annually in the U.S. but estimates that the true incidence is 10 times that number. According to the authors, this is due in part to the limitations of current tickborne disease surveillance, as well as current diagnostics, which may be imprecise in some cases and are unable to recognize new tickborne pathogens as they emerge. These limitations have led researchers to explore new, innovative diagnostics with different platforms that may provide clinical benefit in the future.

This is an engorged femaile deer tick, or Ixodes scapularis, a species of tick that can transmit Lyme disease.
Photo credit: Graham J. Hickling, The University of Tennessee

It is also critical that scientists develop vaccines to prevent disease, the authors write. A vaccine to protect against Lyme disease was previously developed, but was pulled from the market and is no longer available. Future protective measures could include vaccines specifically designed to create an immune response to a pathogen, or to target pathogens inside the ticks that carry them.

By focusing research on the epidemiology of tickborne diseases, improving diagnostics, finding new treatments and developing preventive vaccines, public health officials and researchers may be able to stem the growing threat these diseases pose. In the meantime, the authors suggest, healthcare providers should advise their patients to use basic prevention techniques: wear insect repellant, wear long pants when walking in the woods or working outdoors, and check for ticks.

niaid.nih.gov

IMMEDIATE RABIES PROTECTION

Designed Using Advanced Manufacturing Technology

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

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Stability[1]:

- The only HRIG that can be stored at room temperature not exceeding 25°C (77°F) for up to one month. Use within one month; do not return to refrigeration

Purity[4]:

- Plasma is processed and purified using a series of chromatographic steps resulting in:
  - Reduced aggregates and coagulation factors
  - Highly pure IgG (≥95%)

Safety[1]:

- Three validated and effective viral inactivation/removal steps are employed in the manufacture of KEDRAB
- The manufacturing process reduces the level of thrombogenic activity
  - Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after administration

Available in 2-mL and 10-mL vials (NDC 76125-150-02/NDC 76125-150-10)[1]

Preservative free, latex free, and pyrogen free[1]

SELECTED IMPORTANT SAFETY INFORMATION

- Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis should only receive a booster rabies vaccine without KEDRAB, because KEDRAB may interfere with the anamnestic response to the vaccine (ACIP).
- KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. KEDRAB should be discontinued immediately if there is an allergic or anaphylactic type reaction. In case of shock, standard medical treatment should be implemented. Epinephrine should be available.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages and visit KEDRAB.com.

KEDRION BIOPHARMA

INDICATIONS AND USAGE

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IMPORTANT SAFETY INFORMATION

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- Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.
- Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.
- Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, appropriate laboratory testing should be performed and medical therapy administered as indicated.
- KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. After KEDRAB administration, immunization with measles vaccine should be avoided within 4 months; other live attenuated virus vaccines avoided within 3 months.
- A transient rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results of serologic tests after KEDRAB administration. Passive transmission of antibodies to erythrocyte antigens may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).
- KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in KEDRAB.
- In clinical trials, the most common adverse reactions in subjects treated with KEDRAB were injection site pain (33%), headache (15%), muscle pain (9%), and upper respiratory tract infection (9%).

Please see Brief Summary of Full Prescribing Information on following page.

References: 1. KEDRAB [package insert]. Fort Lee, NJ: Kedrion Biopharma Inc.; 2017. **2.** Centers for Disease Control and Prevention. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2010;59(2):1-9. **3.** Centers for Disease Control and Prevention. Human Rabies Prevention—United States, 2008 Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2008;57(RR-3):1-28. **4.** Data on file. Kamada Ltd.

KEDRAB™
Rabies Immune Globulin (Human)

KEDRION BIOPHARMA

KEDRAB Rabies Immune Globulin (Human)

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

KEDRAB is a human rabies immunoglobulin (HRIG) indicated for passive, transient postexposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine. Do not administer additional (repeat) doses of KEDRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine. Do not administer KEDRAB to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

WARNINGS AND PRECAUTIONS

Previous Rabies Vaccination: Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis should only receive a booster rabies vaccine without KEDRAB, because KEDRAB may interfere with the anamnestic response to the vaccine (ACIP). **Anaphylactic Shock:** KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. Discontinue KEDRAB injection immediately if there is an allergic or anaphylactic type reaction. In case of shock, implement standard medical treatment. Epinephrine should be available for treatment of acute anaphylactic symptoms. **Hypersensitivity:** Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB. **Thrombosis:** Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration. Patients at increased risk of thrombosis include patients with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and hyperviscosity syndromes (including cryoglobulinemias, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies). Consider measurement of baseline blood viscosity in patients at risk for hyperviscosity. **Hemolysis:** Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Patients at increased risk include those with non-O blood group types, those with underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, perform appropriate laboratory testing and administer medical therapy as indicated. **Live Attenuated Virus Vaccines:** KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. Avoid immunization with measles vaccine within 4 months after KEDRAB administration. Avoid immunization with other live attenuated virus vaccines within 3 months after KEDRAB administration. **Interference with Serologic Testing:** A transient rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results of serologic tests after KEDRAB administration. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, and D, may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test). **Transmissible Infectious Agents:** KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting an infectious agent has been minimized by: Screening plasma donors for prior exposure to certain viruses; Testing for certain viral infections; Inactivating and removing certain viruses during the manufacturing process [see *Description* in the Full Prescribing Information]. Despite these measures, KEDRAB administration can still potentially transmit infectious diseases. There is also the possibility that unknown infectious agents may be present in KEDRAB. Any infection considered to have possibly been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion Biopharma Inc. Customer Service (1-855-353-7466) or FDA at 1-800-FDA-1088.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates of adverse reactions in clinical trials of another drug and may not reflect the rates observed in clinical practice. KEDRAB was evaluated in three single-center, controlled clinical trials. Subjects in the clinical studies of KEDRAB were healthy adults, primarily white and ranged in age from 18 to 72 years. A total of 160 subjects were treated in these three studies, including 91 subjects who received single intramuscular doses of KEDRAB (20 IU/kg) with or without rabies vaccine. Table 1 summarizes adverse events (assessed by the investigator as related or unrelated to study treatment) occurring in >3% of subjects in the clinical trials of KEDRAB. The most frequent adverse events in the KEDRAB group (>6%) were injection site pain, headache, muscle pain, and upper respiratory tract infection (Table 1). **Table 1: Adverse Events Occurring in >3% of Subjects in All Studies Combined** (91 subjects receiving KEDRAB vs. 84 subjects receiving Comparator HRIG vs. 8 subjects receiving Saline Placebo + Vaccine). Data are presented as number of subjects (% of subjects). Injection site pain, 30 (33), 26 (31), 2 (25); Headache, 14 (15), 11 (13), 3 (38); Muscle pain, 8 (9), 6 (7), 0; Upper respiratory tract infection, 8 (9), 8 (10), 0; Joint pain, 5 (6), 0, 1 (13); Dizziness, 5 (6), 3 (4), 0; Fatigue, 5 (6), 2 (2), 0; Abdominal pain, 4 (4), 1 (1), 0; Blood in urine, 4 (4), 2 (2), 0; Nausea, 4 (4), 3 (4), 0; Feeling faint, 4 (4), 1 (1), 0; Bruising, 3 (3), 1 (1), 0; Sunburn, 3 (3), 0, 0; White blood cells in urine, 3 (3), 4 (5), 0. Less common adverse events were joint pain, dizziness, fatigue, abdominal pain, blood in urine, nausea, feeling faint, bruising, sunburn, and white blood cells in urine.

DRUG INTERACTIONS

Do not administer additional (repeat) doses of KEDRAB once vaccination has been initiated, since additional doses of KEDRAB may interfere with the immune response to the vaccine. Do not administer KEDRAB into the same anatomical site(s) as rabies vaccine. KEDRAB contains other antibodies that may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Avoid immunization with live virus vaccines within 3 months after KEDRAB administration, or in the case of measles vaccine, within 4 months after KEDRAB administration [see *Warnings and Precautions / Live Attenuated Virus Vaccines*].

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary.* KEDRAB has not been studied in pregnant women. Therefore, the risk of major birth defects and miscarriage in pregnant women who are exposed to KEDRAB is unknown. Animal developmental or reproduction toxicity studies have not been conducted with KEDRAB. It is not known whether KEDRAB can cause harm to the fetus when administered to a pregnant woman or whether KEDRAB can affect reproductive capacity. In the U.S. general population, the estimated background of major birth defects occurs in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies. **Lactation:** *Risk Summary.* There is no information regarding the presence of KEDRAB in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KEDRAB and any potential adverse effects on the breastfed infant from KEDRAB or from the underlying maternal condition. **Pediatric Use:** The safety and effectiveness of KEDRAB in the pediatric population have not been established. **Geriatric Use:** Clinical studies of KEDRAB did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Clinical experience with HRIG products has not identified differences in effectiveness between elderly and younger patients (ACIP).

NONCLINICAL TOXICOLOGY

Animal Toxicology and/or Pharmacology: Intramuscular administration of a single dose of KEDRAB to rats at 60 and 120 IU/kg (3-fold and 6-fold higher than the recommended human dose of 20 IU/kg), did not result in any signs of toxicity.

For a copy of the Full Prescribing Information for KEDRAB, please visit www.KEDRAB.com.

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Can Natural Disasters Elevate Rabies Infections?

CDC Morbidity and Mortality Report, Human Rabies — Puerto Rico, 2015

On December 1, 2015, the Puerto Rico Department of Health (PRDH) was notified by a local hospital of a suspected human rabies case. The previous evening, a Puerto Rican man aged 54 years arrived at the emergency department with fever, difficulty swallowing, hand paresthesia, cough, and chest tightness. The next morning the patient left against medical advice but returned to the emergency department in the afternoon with worsening symptoms. The patient's wife reported that he had been bitten by a mongoose during the first week of October, but had not sought care for the bite. While being transferred to the intensive care unit, the patient went into cardiac arrest and died. On December 3, rabies was confirmed from specimens collected during autopsy. PRDH conducted an initial rapid risk assessment, and five family members were started on rabies postexposure prophylaxis (PEP).

Given potential additional exposures, PRDH and CDC undertook contact investigations among additional community and family members (N = 32) and hospital personnel (N = 39) to identify persons who required PEP. After the contact investigations, two additional family members and two hospital staff members received PEP. PRDH recommends that persons with a history of a mongoose bite should seek medical care and receive PEP. Health care providers should maintain a high index of clinical suspicion for rabies, including taking a history of animal exposure and adhering to recommended infection control practices when examining and treating anyone with suspected rabies or with acute, progressive encephalitis. Despite a high prevalence of rabies among mongoose populations in Puerto Rico, this is the first rabies-associated death directly related to a mongoose bite in Puerto Rico. In 2003, a case of human rabies occurred in a person infected with a mongoose variant of the virus after a dog bite[1]. This case represents only the third documented rabies death in Puerto Rico during the past century. In Puerto Rico, public health outreach activities should continue to educate members of the community on mongoose-associated rabies and PEP.

Case Report

The patient, a man aged 54 years, was a resident of southeastern Puerto Rico. On the evening of November 30, he came to a local emergency department with fever, difficulty swallowing, hand paresthesia, cough, and chest tightness. He had refused most food and drink for the preceding 5 days and had difficulty managing his oral secretions. No history of animal exposure was elicited. He was given a preliminary diagnosis of lower respiratory tract infection and started empirically on antibiotics and antiemetics. A subsequent chest radiograph and computed tomography scan of his head were performed, which were both normal. The next morning, the patient left the hospital against medical advice.

The patient returned to the emergency department in the afternoon with worsening symptoms. The patient's wife, who accompanied him on this visit, reported that during the first week of October he had been bitten by a mongoose while tending to a chicken coop located on their property; he had not sought care after the encounter. Clinical suspicion of rabies triggered notification to PRDH. Shortly thereafter, the patient experienced cardiac arrest while being transferred to the intensive care unit and could not be resuscitated.

Mongooses were originally brought to Puerto Rico and the Hawaiian islands from Asia to protect sugar cane fields from rats and snakes. This small swift predator preys on birds, reptiles, and amphibians. Without a natural predator of its own, the mongoose quickly became a burden, hurting wildlife as well as poultry farmers and hunters. So far, this invasive species is responsible for the extinction of several reptile and amphibian species on the islands where it became widespread.

An autopsy was performed on December 2 at the Puerto Rico Institute for Forensic Sciences, and specimens were submitted to the PRDH Public Health Laboratory for rabies testing. On December 3, results of direct fluorescent antibody testing were positive for rabies infection. Additional specimens sent to CDC for confirmatory testing were positive by direct fluorescent antibody and reverse transcription–polymerase chain reaction, and antigenic typing and sequence analysis were consistent with Caribbean mongoose rabies virus variant.

Public Health Investigation

Upon notification of the suspected case on December 1, PRDH collaborated with CDC's Poxvirus and Rabies Branch. An initial rapid risk assessment conducted by PRDH identified five family members who had potential exposures through close contact with the deceased patient, and all five family members were started on PEP. These persons included the patient's immediate family and household members.

Beginning on December 9, PRDH and CDC initiated contact investigations among additional family and community members as well as hospital personnel to determine other persons with potential exposure who required PEP. Based on the Advisory Committee on Immunization Practices guidelines for rabies virus exposures, PEP is recommended for persons with contact with the patient's saliva, tears, or cerebrospinal fluid to open wounds or mucous membranes during the infectious period (2 weeks before symptom onset)[2]. A total of 76 contacts were evaluated for their risk for exposure, including two additional family members who required PEP because of exposure to the patient while he was hospitalized (Table). Among the 37 family and community contacts, median age was 33 (range = 1–78), and 20 (54%) were female. Municipality of residence was the same as that of the deceased patient for the 34 community members who reported place of residence. In total, seven (19%) of the 37 family and community members received PEP.

Thirty-nine hospital personnel were reported to have had contact with the patient. These staff members worked in various positions, including intensive care, respiratory therapy, and patient transport. Median age was 35 years (range = 23–65), and 18 (46%) were female. Through the contact investigation, two (5%) of the hospital staff members who had contact with the patient received PEP because they had exposures to the patient's saliva onto open wounds or mucous membranes. These exposures resulted from not wearing gloves or masks in the situations indicated in standard precautions[3], namely intubation and management of oral secretions.

After the contact investigations, education and outreach were conducted to inform community members and hospital personnel about rabies. PRDH designed and distributed educational materials to address the most frequently asked questions and held an informational session with the community to promote open discussion. In addition, hospital personnel participated in a debriefing that highlighted the need for appropriate use of standard precautions with all patients, regardless of suspected diagnosis.

Discussion

This is the first reported case of human rabies associated with a mongoose bite in North America. Mongooses were introduced from India to the Caribbean, including Puerto Rico, during the 19th century to control rat populations in sugarcane fields[4] and have become the principal reservoir of rabies in Puerto Rico, accounting for nearly 75% of all animal rabies cases[5,6]. In Puerto Rico, mongoose-associated rabies virus is phylogenetically linked to the North Central skunk and cosmopolitan dog variants[7]. Seroprevalence of rabies virus-neutralizing antibodies in the mongoose population is estimated at 40%[8]. Seventy-five mongoose bites were reported in 2014 (1.9 bites per 100,000 persons); during 2005–2008, 97% of 151 submitted animal specimens after mongoose bites were positive for rabies virus.* PRDH recommends rabies PEP after all mongoose bites if the animal is not available for testing, and an estimated 95% of persons reporting mongoose bites receive PEP.

This case highlights the need for increased public awareness for the potential for mongoose-related rabies in Puerto Rico. The standardized risk assessment tool used in the contact investigations ensured that contacts with exposures promptly received PEP, thus mitigating costs from indiscriminate use of PEP. This tool could be adapted for use in other rabies exposure risk assessments in Puerto Rico or elsewhere. Health care providers should routinely assess for animal exposures in the medical history and maintain a high index of suspicion for rabies when animal exposure has occurred or is suspected. More generally, universal use and monitoring of standard precautions are necessary to minimize risk for exposures to infectious diseases in health care settings. Occupational exposures to rabies in health care settings frequently occur as a breach of standard precautions[9]. Among hospital personnel interviewed for this investigation, only two (5%) had an exposure, and both received PEP.

Public health measures to reduce the risk for human rabies should include increased resources for primary prevention, including routine pet vaccination (canine rabies in Puerto Rico results from transmission from mongooses) and preexposure prophylaxis for persons at highest risk. Community education should highlight measures to avoid bites from pets and wildlife. Effective oral rabies vaccine baits targeting mongooses might also be considered as they become commercially available[10]. Interventions should focus on areas with known human-mongoose contacts, as determined by overlaying bite surveillance

data and population density. Secondary prevention measures should be aimed at increasing awareness of the need for medical evaluation and PEP after any mongoose bite.

Acknowledgments

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CPG

Breaking Down Barriers, Strengthening Rabies Diagnostic Capacity Internationally

By Lauren Greenberg, MS, microbiologist with Poxvirus and Rabies Branch, DHCPP, NCEZID, CDC

Rabies is a deadly but vaccine-preventable disease that kills an estimated 59,000 people globally each year. In many countries, the greatest risk stems from dog populations that roam free with little to no care. Poor access to quality healthcare, vaccine shortages (both human and canine), lack of knowledge about appropriate bite wound care, and limited disease surveillance can further complicate the efforts to control rabies in countries that are most affected.

Over the past two years, I have worked in Ethiopia as a subject matter expert to coordinate rabies lab preparations and provide technical assistance to local public health microbiologists on rabies laboratory diagnostics. CDC and the Ethiopian Public Health Institute, along with other government institutions, are collaborating to build the country's capacity for diagnosing rabies in order to gain a more accurate assessment of the rabies burden in Ethiopia. With a clearer understanding of the disease burden, local officials will be better equipped to design targeted prevention and control programs based on community-specific recommendations.

People Are the Key

The key to building rabies diagnostic laboratory capacity resides in effective human resource development. People's discomfort working with both dogs and the rabies virus can present a significant challenge. Even though microbiologists and laboratory technologists hired for training in rabies diagnostic work receive the rabies pre-exposure prophylaxis vaccine series, they can still be unsure about how to safely work with the virus, which presents a barrier to passing along important technical knowledge.

Emphasizing how to work safely in the laboratory is the first critical step of training. Basic safety skills, including proper use of personal protective equipment (PPE) and appropriate biosafety measures, are at the forefront of the training. This helps establish that laboratory personnel safety is the number one priority, allowing local staff to feel much more comfortable and confident in their abilities to conduct rabies testing in their new labs.

Overcoming Logistical Challenges

To build fully functional rabies diagnostic laboratories equipped with sample testing and reporting capabilities, we first needed to assess availability of laboratory spaces, supplies, and equipment. Three laboratories in Ethiopia — one in the capital of Addis Ababa and two regional labs — were selected to become the country's diagnostic hubs for laboratory-based rabies surveillance.

During the process of equipping these laboratories, complications involving infrastructure conditions, field sample collection and transfer, and partner communication have been inevitable. We are working diligently with in-country counterparts and other stakeholders to overcome these challenges and prepare the labs to accurately and safely test suspect rabies samples.

Raising a New Generation of Rabies Lab Experts

Transferring supplies and providing training is not enough to help developing countries build their own rabies diagnostic laboratories. Such initiatives must be linked to national and local efforts to build trust and provide services for individual communities through long-term collaborations and hands-on activities.

Empowering regional and national laboratory workers to become the frontline experts in this manner encourages them to share these best practices with colleagues for years to come.

By working side-by-side with our in-country partners, we can help create a healthier and more engaged community.

In celebration of World Rabies Day on September 28, I am reminded of what a truly amazing opportunity it has been to work with so many bright and motivated microbiologists willing to play such a critical role in the fight against canine rabies.

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NIH Researchers Discover Highly Infectious Vehicle for Transmission of Viruses among Humans

Membrane-bound virus clusters provide promising target for the treatment of gastroenteritis, other diseases.

Researchers have found that a group of viruses that cause severe stomach illness — including the one famous for widespread outbreaks on cruise ships — get transmitted to humans through membrane-cloaked "virus clusters" that exacerbate the spread and severity of disease. Previously, it was believed that these viruses only spread through individual virus particles. The discovery of these clusters, the scientists say, marks a turning point in the understanding of how these viruses spread and why they are so infectious. This preliminary work could lead to the development of more effective antiviral agents than existing treatments that mainly target individual particles.

The researchers studied norovirus (link is external) and rotavirus (link is external)–hard-to-treat viruses that are the most common cause of stomach illness, or gastroenteritis, and that afflicts millions of people each year. The viruses cause symptoms ranging from diarrhea to abdominal pain and can sometimes result in death, particularly among young children and the elderly. Their highly contagious nature has led to serious outbreaks in crowded spaces throughout many communities; most notably in cruise ships, daycare centers, classrooms, and nursing homes. Fortunately, vaccines against rotavirus are now available and are routinely given to babies in the United States.

"This is a really exciting finding in the field of virology because it reveals a mode of virus spread that has not been observed among humans and animals," said study leader Nihal Altan-Bonnet, PhD, senior investigator and head of the Laboratory of Host-Pathogen Dynamics at the National Heart, Lung, and Blood Institute (NHLBI). "We hope that it will provide new clues to fighting a wide range of diseases involving many types of viruses, including those that cause gastrointestinal illnesses, heart inflammation, certain respiratory illnesses, and even the common cold."

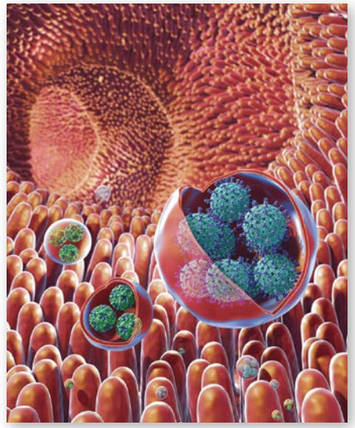

Illustration of membrane-bound vesicles containing clusters of viruses, including rotavirus and norovirus, within the gut. Rotaviruses are shown in the large vesicles, while noroviruses are shown in the smaller vesicles. NIH Medical Arts

The study was supported in part by the Intramural Research programs of the NHLBI and the National Institute of Allergy and Infectious Diseases (NIAID), both part of the National Institutes of Health.

Until a few years ago, most scientists believed that viruses, particularly those responsible for stomach illnesses, could only behave as independent infectious agents. However, in 2015 Altan-Bonnet and her colleagues showed that polioviruses could transmit themselves in packets, or membrane-bound vesicles containing multiple virus particles. The scientists compared this new model of viral transmission to a Trojan horse: A group of membrane-bound viruses arrives at a host cell and deposits viruses in the cell while dodging detection by the immune system. The scientists did not know whether this system applied to animals and humans, or how effective these packets were in infecting host cells.

To find out, they focused on rotaviruses and noroviruses, which mainly get spread by accidentally ingesting tiny particles of an infected person's stool — through, for example, contaminated food or liquids. The researchers obtained fecal samples of humans and animals (pigs and mice) and found that the viruses are shed in the stool as virus clusters inside membrane-bound packets. In addition, they found that these virus-containing vesicles were significantly more infectious than the free, unbound viruses within the samples.

The researchers determined that the high level of infectiousness was likely due to the vesicles delivering many viruses at once to the target tissues; protecting their viral cargo from being destroyed by prolonged exposure to enzymes; and possibly by making their viral cargo invisible to the antibodies that are in the stool or gut of the host. More studies are needed, but the extreme potency of the virus packets, they said, has a clear consequence: it not only enhances the virus' ability to spread more aggressively; it also increases the severity of the disease it causes. Handwashing (link is external) with soap and water helps prevent the spread of viruses.

"Our findings indicate that vesicle-cloaked viruses are highly virulent units of fecal-oral transmission, and highlight a need for antivirals targeting vesicles and virus clustering," Altan-Bonnet noted.

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How a Genetic Variant May Affect the Gut Barrier and Contribute to Inflammatory Bowel Disease

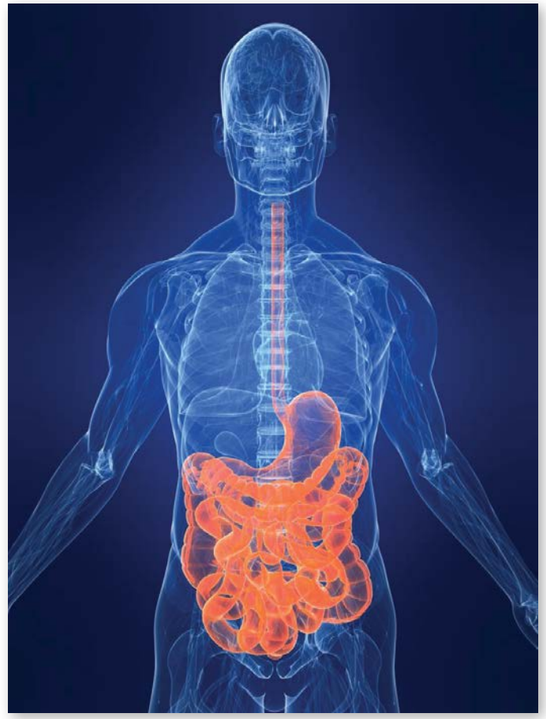
Researchers have found that a genetic variant may impart risk for inflammatory bowel disease (IBD) by disrupting the cellular "glue" that keeps the gut's lining intact. People with IBD suffer from chronic inflammation in the gut, resulting in symptoms such as diarrhea, cramping, and weight loss.

Scientists have been sorting through the complicated mix of factors that contribute to IBD, including numerous possible genetic components that are important for maintaining effective physical and immunological barriers to the multitude of bacteria that inhabit the gut. The International IBD Genetics Consortium, of which the NIDDK-supported IBD Genetics Consortium is a member, has identified over 200 regions of the human genome that are associated with IBD. Scientists are now combing through these regions to identify genes — and variants of those genes — that are involved in the disease.

One of the genetic variations that consortium scientists had identified as a risk factor for IBD was in a gene called C1orf106; however, until recently it wasn't clear exactly how variants of this gene might lead to disease. Researchers attempting to uncover the function of "normal" C1orf106 found that laboratory-grown gut cells produced high amounts of the C1orf106-encoded protein when they were in close contact with each other. This suggested that C1orf106 may contribute to cellular junctions—the "glue" that cobbles gut cells together to create a continuous sheet-like barrier.

Another hint was uncovered when the researchers found that the C1orf106 protein interacts with cytohesin-1, a protein that disrupts cellular junctions by activating a molecular switch called ARF6. Functional C1orf106 in cells caused degradation of cytohesin-1 and lower ARF6 activity, stabilizing cellular junctions. These signs pointed to a role for C1orf106 in maintaining the intestinal barrier by keeping cytohesin-1 levels in intestinal cells relatively low.

Likewise, male and female mice engineered to lack C1orf106 had higher levels of cytohesin-1 than mice whose genes were unaltered. These mice also showed greater intestinal damage after they were infected by a bacterial pathogen, supporting the idea that C1orf106 is important for maintaining a barricade against gut pathogens. However, some variants of the C1orf106 gene may not be as effective as others. In fact, when the scientists replaced C1orf106 in cells with the specific variant of the gene that is associated with human IBD, the cells were unable to make enough of the C1orf106 protein to form proper junctions. These studies strongly imply that defects in C1orf106 contribute to IBD by failing to maintain an adequate intestinal barrier. This information could help to guide the development of improved therapy for people with this genetic variant, although more work is needed to determine if the observations from the mouse model hold true in humans.



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niddk.nih.gov

Healthcare Providers: A Strong Vaccination Recommendation can be a Game-Changer this Flu Season

By Vice Admiral Jerome M. Adams MD, MPH, Surgeon General of the United States

Vice Admiral Jerome M. Adams MD, MPH, Surgeon General of the United States

It's officially flu season. Every year millions of Americans needlessly suffer from the flu, and thousands will be hospitalized or even die as a result of becoming infected with the virus. It's heartbreaking that thousands of deaths from influenza still occur in our country every year. As a health care provider, your strong recommendation to your patients to get a flu vaccine this season can be a game-changer in reducing this disease burden.

Here are five tips for communicating the importance of getting a flu vaccination this season:

1. **Tailor reasons to the individual.** Explain why someone — based on age, health status, lifestyle, occupation, or another risk factor — should get a flu shot. For example, the flu vaccine is especially important for patients age 65 or older because they are more likely to develop serious flu-related complications, such as pneumonia.
2. **Discuss how vaccination prevents illness.** From averting the flu entirely to reducing its severity if one does get sick, it's important to remind patients of the many positive benefits of flu vaccination. The Centers for Disease Control and Prevention (CDC) outlines a number of these benefits of the flu vaccine on their website.
3. **Outline the consequences of getting sick.** The flu can result in serious health complications and time lost from work or family obligations. Prevention is better than treatment when it comes to any illness, and the flu is no exception.

> ***"I get my flu vaccine every year and hope you will too. Let your patients know you've gotten your flu shot and support vaccination for yourself, your family, and your community."***
>
> **Surgeon General**
> **Jerome M. Adams MD, MPH**

4. **Explain how vaccines protect loved ones.** Influenza, like a number of other vaccine-preventable diseases, is contagious and can be serious. Vaccines do not just protect you; they also protect the people around you by limiting the spread of disease. Understanding how the flu vaccine protects their loved ones can be an important motivator for some patients to get vaccinated.
5. **Answer and solicit questions with compassion.** It's normal to have questions about vaccines. Use easy-to-understand language to talk about patient concerns including side effects, safety, and vaccine effectiveness. CDC offers great resources to help you address common questions and educate patients. Vaccines.gov is a comprehensive website you can recommend to patients to help them learn about immunization.

You're a trusted voice in the community. Patients trust you to give them the best advice on how to protect their health. Your counsel helps patients make informed decisions.

As a standard of practice, all health care providers have the responsibility to routinely assess the vaccination status of their patients.

Flu season provides yet another opportunity to make sure your patients are fully vaccinated.

hhs.gov

National Initiative to Prevent C diff Infection

As more Americans are living longer today, clinicians are treating more age related illnesses than ever before. In particular, the susceptibility of Clostridium difficile infection (C diff) in older Americans.

A recent CDC study reveals infections among patients in hospitals and nursing homes indicates in every setting that the risks of infection and death increase with age. C diff caused nearly half a million infections among US patients in a single year and almost 29,000 died within 30 days of diagnosis.

The study also revealed two thirds of every HAI C diff infection occur in patients 65 and older, and 80% of those result in death. Of those deaths, one out of nine occur within 30 days of initial diagnosis.

Inadequate disinfection practice has contributed to the rise in C diff infection, not only within the healthcare facility but also during transportation of infected patients from facility to facility. Clostridium difficile bacteria can live for long periods of time on devices and equipment surfaces like gurneys, tables, and toilets.

These and other surfaces where patients may come in contact with the bacteria should be thoroughly cleaned on a daily basis while treating a patient with C diff and then upon discharge or transfer of the patient.

C. difficile infections are at an all-time high.

- C. difficile infections are linked to 14,000 deaths in the US each year.
- Deaths related to C. difficile increased 400% between 2000 and 2007, due in part to a stronger germ strain.
- Most C. difficile infections are connected with receiving medical care.
- Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older.
- Infection risk generally increases with age; children are at lower risk.
- About 25% of C. difficile infections first show symptoms in hospital patients; 75% first show in nursing home patients or in people recently cared for in doctors' offices and clinics.

C. difficile germs move with patients from one health care facility to another, infecting other patients.

- Half of all hospital patients with C. difficile infections have the infection when admitted and may spread it within the facility.
- The most dangerous source of spread to others is patients with diarrhea.
- Unnecessary antibiotic use in patients at one facility may increase the spread of C. difficile in another facility when patients transfer.
- When a patient transfers, health care providers are not always told that the patient has or recently had a C. difficile infection, so they may not take the right actions to prevent spread.

C. difficile infections can be prevented.

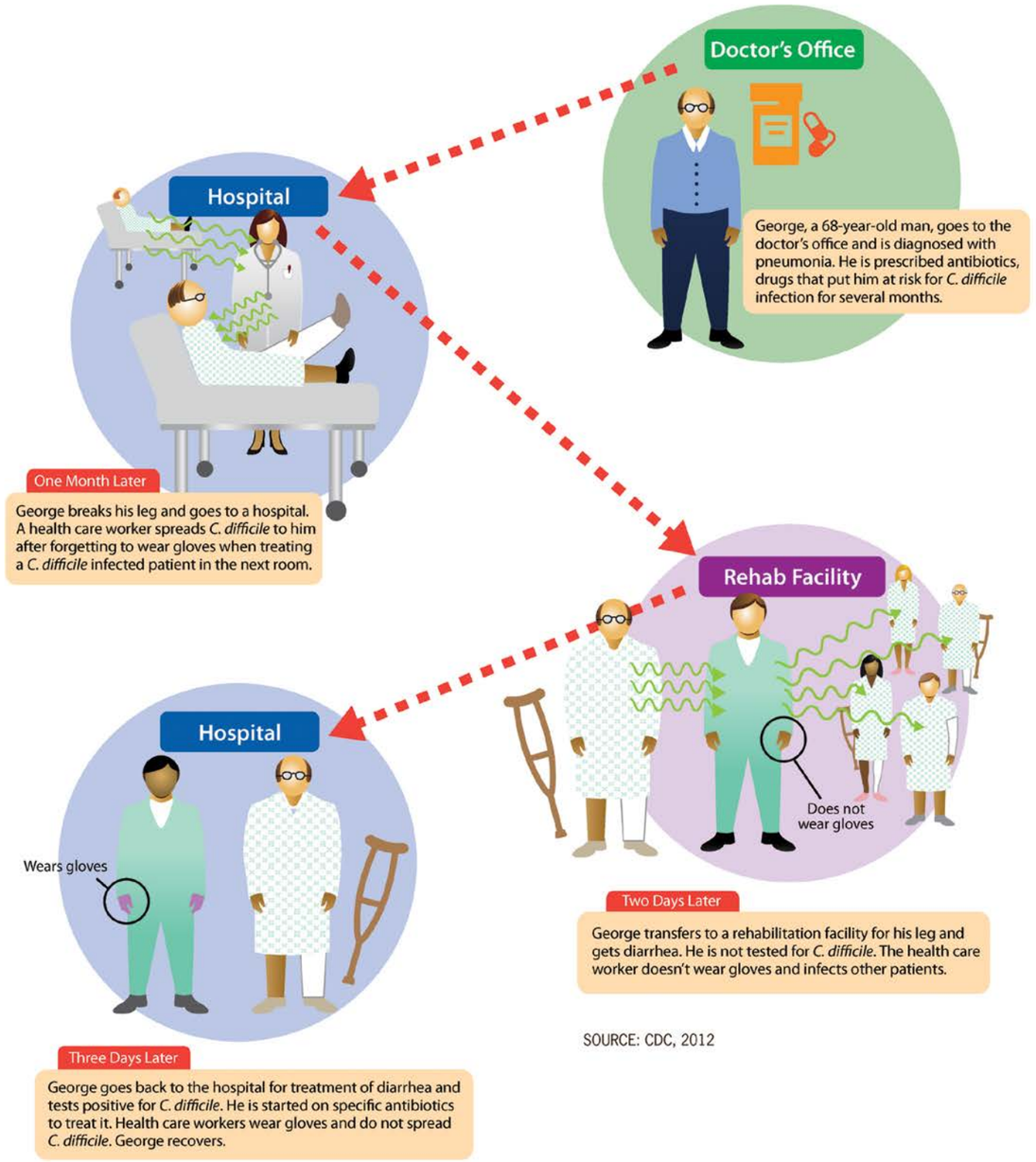
Early results from hospital prevention projects show 20% fewer C. difficile infections in less than 2 years with infection prevention and control measures.
England decreased C. difficile infection rates in hospitals by more than half in 3 years by using infection control recommendations and more careful antibiotic use.

For Clinicians: 6 Steps to Prevention

1. Prescribe and use antibiotics carefully. About 50% of all antibiotics given are not needed, unnecessarily raising the risk of C. difficile infections.
2. Test for C. difficile when patients have diarrhea while on antibiotics or within several months of taking them.
3. Isolate patients with C. difficile immediately.
4. Wear gloves and gowns when treating patients with C. difficile, even during short visits. Hand sanitizer does not kill C. difficile, and hand washing may not be sufficient.
5. Clean room surfaces with bleach or another EPA-approved, spore-killing disinfectant after a patient with C. difficile has been treated there.
6. When a patient transfers, notify the new facility if the patient has a C. difficile infection.

cdc.gov

How *C. difficile* Spreads.



SOURCE: CDC, 2012

The Critical Issue of Hand Hygiene

By John Phillips

The goal of preventing transmission of Healthcare Acquired Infections (HAIs) begins with its most important element in the process, proper hand hygiene.

For a variety of reasons, the lack of hand hygiene compliance has been identified as the greatest contributor to the problem. For years, governing organizations like the CDC and NIH have made this issue one of their top national campaigns, however, current direct observation methodology has not produced the desired outcomes, even with continued education.

And while new standards and guidelines have cleared the way for developing a complete national hand hygiene plan, no singular method has been established. As a result, leaders have created their own individual procedures, making compliance more difficult to measure and achieve.

Attention to this matter from strong Public Health awareness has revealed a challenge to create an absolute way of monitoring every healthcare worker's individual compliance. Technological advances allow for automated solutions from start to finish providing compliance above 98%, so we will soon see a positive shift in the challenge of hand hygiene compliance, which resolves the problem once and for all.

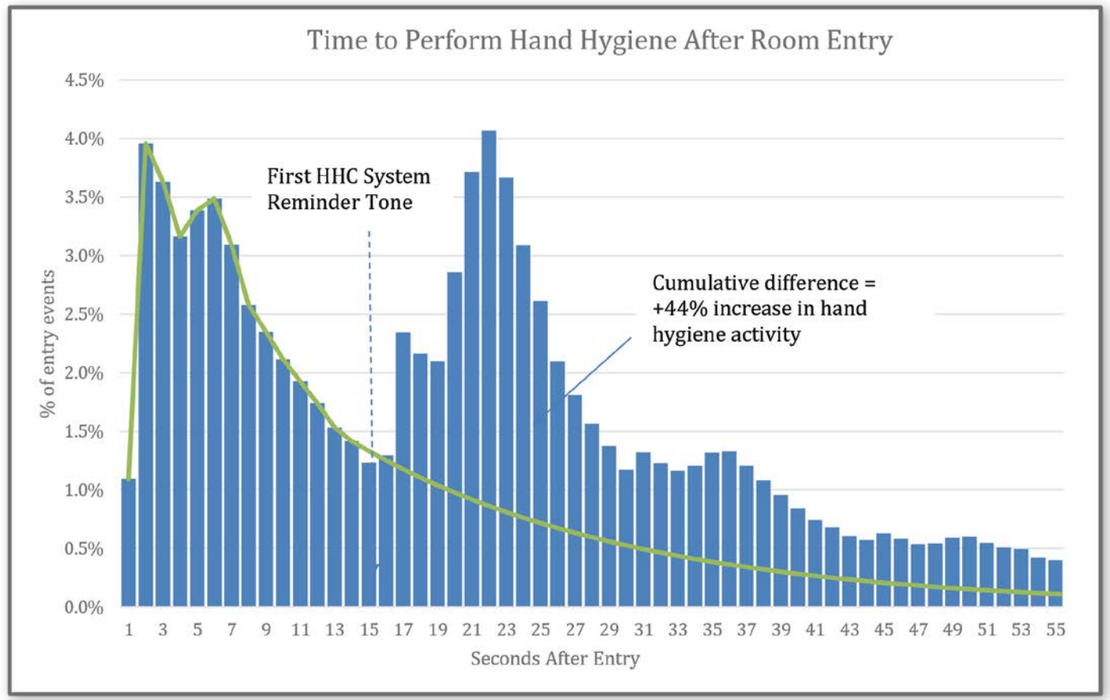
An industry leader is offering a new approach with fundamental technology, bridging gaps, and solving the breakdowns that top healthcare leaders have been striving for. By closely examining the structure of their technology, we can identify the proper methodology for compliance at each stage of the interaction between provider and patient and utilize technology to address and ensure compliance at each stage before the provider can move on to the next step of care.

Nurse wearing BioVigil badge

Development of this technology is formulated by identifying the weaknesses in the process and considering a simple and cost-effective way to achieve a straight forward monitoring solutions that any healthcare facility in the world can use regardless of size or method of hand hygiene.

Speaking with Sanjay Gupta, CEO of BioVigil, he discussed their origins that began with a world-renowned cardiovascular surgeon at the University of Michigan, Dr. Steven F. Bolling, who's brilliantly simple idea would have an impact on changing the way we look at hand hygiene completely.

"Dr. Bolling felt it didn't make sense that so much effort and expense are put into high-end technology to make sure providers can give the highest level of clinical care to their patients, yet a fundamental issue like hand hygiene is not addressed, is how the idea of BioVigil came about" said Gupta.



BioVigil saw a 44% increase in hand hygiene activity after the first reminder

"From Doctors to Nurses to EVS workers, everyone is affected by this solution which equates to positive culture change around hand hygiene. We really want to make sure our system works well with caregiver workflows for maximum effectiveness and adoption," he said.

For the last two years, Biovigil has provided a simple to use, highly accurate, and cost-effective technology to the most respected healthcare facilities with over 40 global installations, positively affecting over 150 million hand hygiene opportunities and producing meaningful outcomes. "There is clearly a link between hand hygiene and hospital acquired infections.

There were close to two million HAIs in the United States last year, with roughly 100,000 deaths related to those infections every year, and the cost to the healthcare community is between $30 to $50 Billion annually," said Gupta. "This problem has existed for over 150 years, and that's why we wanted to provide a simple technology that reminds healthcare workers to clean their hands before and after patient interaction."

BioVigil creates a technology network that facilitates reminders to healthcare workers, if they forget. What makes BioVigil's technology unique is the small, alcohol sensing badge that healthcare workers wear to confirm hand hygiene compliance, and data processing capabilites to automatically report compliance.

The badge also collects data for soap and water, which accounts for approximately 2% of hand hygiene sanitization methods as opposed of 98% from alcohol-based sanitizers. The healthcare worker is reminded to perform hand hygiene (if they forget), and once performed, the badge validates and records compliance. "Due to our reminders, we recorded and verified a 44% increase in hand hygiene compliance across our customer base, " says Gupta.

"Another unique factor about our technology is that our badge has a colored LED light in the shape of a hand, right in the middle of the badge. The hand changes color to show the stages of compliance. Green is fully compliant, Yellow is a reminder and Red is out of compliance. Most importantly, the colored light is visible to patients and families and provides assurance that their caregiver is maintaining compliance for their safety, which increases the trust between care

Hospital-acquired infections, January 2014-September 2017

Extracted from AJIC article "An Automated Hand Hygiene Compliance System is Associated With Decreased Rates of Health Care-Associated Infections" (S. McCalla et al.)

Infection*	Preintervention†	Intervention†	Incidence rate ratio (95% confidence interval)
Catheter-associated urinary tract infection	2.20	1.21	0.55 (0.35-0.87)
Central line-associated bloodstream infection	1.43	0.64	0.45 (0.23-0.89)

* Infections per 1,000 catheter days for catheter-associated urinary tract infections and infections per 1,000 central line days for central line-associated bloodstream infections.

† Units were included in the preintervention or intervention periods based on their implementation of the hand hygiene compliance system.

provider and patient. This goes back to the standard of providing the patient the best level of care possible.

Realtime feedback provides the best advantage to preventing the spread of infection from one patient to another. In the case of non-compliance (red light), anyone can prevent a non-compliant worker from continuing to another patient. Preventing cross contamination has always been a priority and having technology to ensure facilities the ability to stay in control over it is a differentiator.

"Our system is not based on a certain dispenser type or brand of product for hand cleaning, but rather that hand hygiene has been completed", says Gupta, "Which means it can work in any healthcare setting.

Even the most basic clinics in poorer nations around the world can verify and ensure hand hygiene compliance with our system because it has automated reminders and verifies hand cleaning to the worker. In addition, reports can be delivered to each individual and their supervisors/hospital executives."

Patient satisfaction experience is notably higher where BioVigil's technology has been implemented, with one hospital noting an increase from 37% to 97% satisfaction. BioVigil is currently conducting studies of other patient experiences to measure its effects and how to improve even further, as this is one of their development goals. They have noted up to 80% reduction in hospital acquired infections at the locations using their technology and even noted a reduction in healthcare workers absenteeism due to illness by as much as 18%.

"We are very proud of the recent statistically significant peer reviewed article published in the American Journal of Infection Control (https://www.biovigil.com/wp-content/uploads/2018/09/AJIC_An-Electronic_HHC_System_Decreased-HAIs.pdf). This hospital did a year over year study and saw a 45% reduction in CLABSI and a 55% reduction in CAUTI," said Gupta.

In terms of Public Health, having the entire community unite together for a simple and effective system-wide technology solution can truly eradicate this unmet need around hand hygiene compliance. BioVigil is committed to solving the hand hygiene problem to improve patient and staff safety, and in turn, increasing the trust between patient and provider says Gupta, "So there is definitely a need for public policy to end this problem once and for all".

BioVigil is an outcomes driven company and some of their Customer Outcomes are listed below:

+ 45%+reduction in CLABSI and CAUTI
+ 55% reduction in C diff
+ 18% reduction in employee absenteeism
+ Patient satisfaction increased from 37th to 95th percentile
+ 10% increase in bed capacity with reduced length of stay

NIH Statement on World Tuberculosis Day, 2018

Statement of Christine F. Sizemore, PhD, Richard Hafner, MD, and Anthony S. Fauci, MD, National Institute of Allergy and Infectious Diseases National Institutes of Health

In the 130 years since the discovery of Mycobacterium tuberculosis (Mtb) — the bacterium that causes tuberculosis (TB) — at least 1 billion people have died from TB. That death toll is greater than the combined number of deaths from malaria, smallpox, HIV/AIDS, cholera, plague and influenza.

Today, in commemoration of World TB Day, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), renews and reinvigorates its commitment to the research needed to end this ancient scourge.

Mtb is transmitted through the air and primarily affects the lungs. TB is the leading killer among infectious diseases and among the top 10 causes of death worldwide. The World Health Organization (WHO) estimates that in 2016, TB claimed the lives of 1.7 million people, including 250,000 children, and 10.4 million people were newly infected with Mtb. TB is the primary cause of death for individuals co-infected with HIV.

According to the WHO, more than 2 billion people globally are "latently" infected with TB, meaning they carry the bacteria but are currently without symptoms, which would include cough, fever, weight loss and night sweats. People with latent TB infection cannot actively transmit TB bacteria to another person.

Up to 13 million people in the United States are estimated to have latent TB infection, according to the U.S. Centers for Disease Control and Prevention. Overall, people with latent TB infection have a 5 to 15 percent lifetime risk of developing active TB disease.

This risk increases for people with compromised immune systems, such as those living with HIV, people receiving immunosuppressive therapy (such as individuals being treated for cancer), as well as diabetics, smokers and the malnourished.

WHO's End TB Strategy envisions an end to TB by 2035. To accomplish this, incremental improvements in understanding the disease and in the tools used to identify, treat, and prevent it will not be sufficient. Rather, accelerated efforts and transformative advances are needed. Recent engagement includes NIAID participation in the first "WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era: A Multisectoral Response" in Moscow.

At this November 2017 meeting, the urgent need for a more intensive biomedical research approach to controlling and ultimately eliminating TB was clearly articulated.

Specifically, we need a more intensive interdisciplinary systems biology approach (using cutting-edge methods, large data sets, and modeling to understand complex biological systems) to improve our understanding of how Mtb infection causes disease.

Additionally, we must work toward improved diagnostics that can detect Mtb in a variety of clinical specimens in addition to sputum. Also, rapid, accurate, and inexpensive "point-of-care" tests to distinguish between drug-sensitive and drug-resistant Mtb must be developed.

NIAID investments in research contributed substantially to the WHO-endorsed GeneXpert MTB/rifampicin resistance diagnostic currently in use and the institute continues to support the development of next-generation TB diagnostics.

Tuberculosis is the leading killer among infectious diseases and among the top 10 causes of death worldwide.

Today's treatment regimens for TB require too many drugs, often with toxic side effects, that must be taken for six months or longer. With the increasing incidence of multidrug resistant TB (MDR-TB), these regimens often become very lengthy (up to 20 months), more complex, costly, and more prone to failure. Extensively drug-resistant TB (XDR-TB) is even more difficult to treat, and for some patients, no effective treatment regimens exist.

Despite the urgent need for new and improved TB treatments, there is a paucity of new drugs in the clinical development pipeline. To address this deficit, NIAID-supported investigators have engaged in cross-disciplinary, international collaborations designed to spur basic science and early-stage TB drug discovery.

Additionally, NIAID has used its HIV/AIDS clinical trials networks to enhance TB clinical research by conducting key studies of potential TB treatment strategies.

For example, a NIAID-led study found that a one-month antibiotic regimen to prevent active TB disease in people with latent TB infection was as safe and effective as the standard 9-month course in people living with HIV.

Additionally, the NIAID-funded HIV/AIDS clinical trials networks have conducted studies of improved regimens for MDR-TB therapeutics geared to treat both HIV-infected and uninfected adults and children.

A broadly effective preventive TB vaccine could avert millions of new Mtb infections; however, critical knowledge gaps have made developing such a vaccine a difficult challenge.

The current Bacille Calmette-Guerin (BCG) vaccine, developed in 1921, offers protection against disseminated TB disease and death in children, but this protection does not reliably extend into adulthood.

A recent study suggests that revaccination with the vaccine could potentially prevent Mtb infections in high-risk adolescents. To reliably protect against the transmissible pulmonary form of the disease in adults, a new, more effective intervention strategy is needed. NIAID supports basic, preclinical and clinical research to find and develop new, innovative vaccines to prevent TB infection and disease.

The WHO estimates that 53 million lives were saved between 2000 and 2016 through improved TB diagnosis and treatment.

Through an intensified research agenda, a sustained commitment to supporting and conducting TB research, and a renewed effort to work with other agencies and organizations, NIAID is dedicated to helping eliminate this disease and improving and saving the lives of people with TB.

In September 2018, the United Nations General Assembly will conduct a high-level meeting on TB — representing an important step forward by governments and other partners from around the world in the fight against TB.

On this World TB Day, we stand with global leaders in response to the bold call of action to make history and end TB.

niaid.nih.gov

NIH Experts Call for Transformative Research Approach to End Tuberculosis

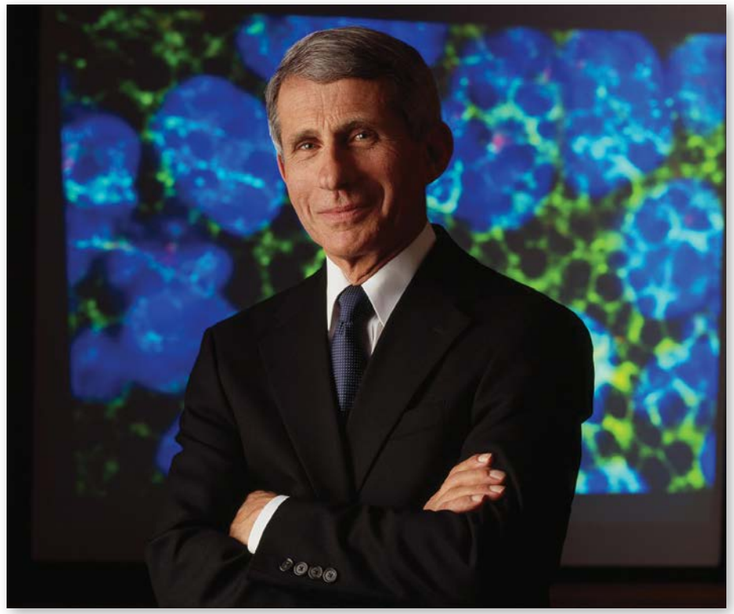
A more intensive biomedical research approach is necessary to control and ultimately eliminate tuberculosis (TB), according to a perspective published in the March 2018 issue of *The American Journal of Tropical Medicine and Hygiene*. In the article, authors Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and Robert W. Eisinger, PhD, special assistant for scientific projects at NIAID, discuss the need to modernize TB research by applying new diagnostic, therapeutic, and vaccine approaches.

The perspective is based on a lecture delivered by Dr. Fauci on Nov. 17, 2017 in Moscow at the first World Health Organization Global Ministerial Conference, "Ending TB in the Sustainable Development Era: A Multisectoral Response."

TB, a bacterial infection that typically infects the lungs, is one of the oldest known human diseases and the leading infectious cause of death worldwide. The authors recall the significant HIV/AIDS research advances made in the nearly 37 years since AIDS was first recognized, and encourage the scientific community to strive for comparable TB milestones.

Specifically, the authors call for systems biology approaches (using large data sets and modeling to understand complex biological systems) to fill critical knowledge gaps in understanding how Mycobacterium tuberculosis (Mtb) infection causes disease.

Such research could help explain why some people infected with Mtb have latent infections and show no signs of disease while others, especially those co-infected with HIV, become sick. The perspective also underscores the need for improved diagnostic tests, including those that can detect Mtb in various specimens as well as rapid, inexpensive tests that can detect drug-resistant TB.



NIAID Director Anthony S. Fauci, MD

Lengthy and complex treatment regimens and an increasing number of multi-drug-resistant TB infections make the disease increasingly difficult to cure. The authors note that the ultimate treatment goal should be drug combinations administered for shorter time periods that can cure people infected with any strain of Mtb.

Another research goal is a safe and more broadly effective vaccine, which remains one of the most difficult challenges, according to Drs. Fauci and Eisinger.

However, they explain, a vaccine and other significant advances are possible with an innovative and aggressive biomedical research program and rapid translation of results into global control strategies.

Article: AS Fauci and RW Eisinger. Reimaging the research approach to tuberculosis. *The American Journal of Tropical Medicine and Hygiene* DOI: 10.4269/ajtmh.17-0999 (2018).

nih.gov

NIAID-Funded Researchers Probe Potential TB Weaknesses

Tuberculosis (TB) kills more people annually than any other infectious disease. According to the World Health Organization (WHO), 490,000 people developed multidrug-resistant TB in 2016 alone — and infection rates are rising. Developing ways to extend the lifespan of existing antibiotics, as well as new treatments that will work alongside existing TB therapies, will be critical in the years to come.

However, traditional drug discovery can be a long and difficult process. In a newly published study, a group of NIAID-funded researchers describe an unusually detailed and fruitful exploration of a single protein pathway in Mycobacterium tuberculosis (Mtb), the bacterium that causes TB; the researchers hope to exploit this pathway's weaknesses to find a new weapon against TB.

The study, described in the April 25th edition of Science Translational Medicine, focuses on one key step in the process by which Mtb constructs its cellular membrane. A protein called biotin protein ligase (BPL) binds a biotin molecule to another construction protein. This activates the construction protein allowing it to create the lipids which later make up the bulk of the Mtb cell membrane. By introducing a BPL inhibitor, called Bio-AMS, the researchers suspected that they could significantly weaken the bacterium's ability to renovate its own cell membrane. This, in turn, might make the bacteria more vulnerable to existing antibiotics, or even halt its growth entirely.

To probe the role of BPL in Mtb survival, the researchers developed a set of experiments to test this pathway under a variety of conditions. They first applied Bio-AMS to Mtb in vitro — and confirmed that Bio-AMS was lethal to the bacteria. To see whether Mtb might eventually become resistant to Bio-AMS, the researchers also sequenced the genome of the few Bio-AMS-resistant bacteria they found, pinpointing a mutation in the rv3405c gene that grants immunity to Bio-AMS.

Colorized scanning electron micrograph of Mycobacterium tuberculosis.
Source: Clifton E. Barry III, PhD, NIAID, NIH

The researchers then wanted to prove that inhibiting the action of BPL impacts Mtb growth in the mice. Since small animals, such as mice, have a fast metabolism and quickly eliminate drugs, they could not measure the effects of Bio-AMS on BPL directly in the animals. To overcome this limitation, the researchers first went back to the test tube and used a hollow-fiber system to test the effect of precisely-measured, fluctuating concentrations of Bio-AMS on Mtb, mimicking what might occur in mice.

After observing that Bio-AMS was still effective under those conditions, the researchers then used a second strategy to study what happens when Mtb can no longer produce enough BPL to remodel its cell membrane. They infected mice with an engineered strain of Mtb in which the production of BPL could be turned down on command. When treated with human first-line TB drugs, once Mtb was deprived of the ability to make BPL, and thus unable to make a fully functional outer cell envelope, it became much more vulnerable to rifampin and ethambutol, but seemed to be better able to avoid killing by isoniazid – highlighting the role of the outer surface of Mtb in modulating drug efficacy.

In all, as the researchers concluded, BPL appears to be a promising target for future research. This approach is fairly new: Through the combined use of laboratory tests that mimic fluctuating concentrations of drugs, as they are encountered in animals, and Mtb mutants in which the production of key proteins can be regulated in animals, the researchers were quickly able to assess whether interfering with a particular protein in Mtb could have negative consequences for the pathogen. Bio-AMS may not be suitable as a viable new drug candidate, but with these studies in hand, the researchers have developed an unusually-nuanced view of how BPL helps Mtb survive, which may provide insight into how to proceed to come up with new drug molecules that have the same activity as Bio-AMS.

niaid.nih.gov

Integrating Infectious Disease Prevention and Treatment into the Opioid Response

By Corinna Dan, RN, MPH, Viral Hepatitis Policy Advisor, Office of HIV/AIDS and Infectious Disease Policy, U.S. Department of Health and Human Services and Adm. Brett P. Giroir, MD, Assistant Secretary for Health

The opioid crisis in the United States is devastating the lives of millions of Americans. Perhaps overshadowed by the alarming rise in overdoses and deaths is the accompanying numbers of injection-related infectious diseases. Opioid overdose deaths increased fivefold from 1999 to 2016, and new hepatitis C infections more than tripled from 2010 to 2016.

Some communities that have been hardest hit by the opioid crisis have also seen associated increases in hepatitis B and C and other infections, such as endocarditis, septic arthritis and abscesses, driven by increases in the numbers of people who inject opioids.

Earlier this year, the HHS Office of the Assistant Secretary for Health's Office of HIV/AIDS and Infectious Disease Policy and the Office on Women's Health sponsored a workshop at the National Academies of Sciences, Engineering and Medicine to explore the infectious disease consequences of the opioid crisis and consider opportunities to better integrate effective responses. A detailed summary of the proceedings is newly available.

One of HHS's top priorities is the implementation of a comprehensive national opioid strategy. The HHS five-point opioid strategy emphasizes the need to empower local communities to assess and respond to local needs, including both drivers and consequences of the opioid crisis.

The National Academies' workshop highlighted the importance of addressing infectious diseases as part of an improved, comprehensive opioid response.

The opioid crisis is part of a set of interconnected health problems, often called syndemics, because they have common root causes and interact synergistically, with one problem making the others worse. Because syndemics are interconnected, coordinated efforts are required across multiple programs and partners to successfully overcome the set of problems and their consequences.

The federal government can't fight this battle alone. We recognize that some of the best and most effective solutions will come from healthcare providers, community leaders and law enforcement who are dealing with the opioids and infectious diseases crisis on the ground.

ADM Brett P. Giroir, MD

Indeed, workshop participants who joined from across the country included experts in infectious diseases, addiction medicine, correctional health, harm reduction and law enforcement. They discussed patient-centered strategies that may be effective in reducing the infectious disease consequences of injection drug use, strategies that could be implemented using existing resources as well as those that require additional funding, and strategies that can work within and across the public health, healthcare and criminal justice systems. Many of the workshop strategies described could also help achieve the goals of the National HIV/AIDS Strategy and the National Viral Hepatitis Action Plan, which are also overseen by OASH.

Secretary Azar greets Adm. Giroir at the inaugural meeting of the Pain Management Best Practices Inter-Agency Task Force.

The workshop proceedings and proposed strategies can provide a springboard for intensified and informed discussions about effective approaches to support the integration of infectious disease prevention and treatment into our comprehensive opioid strategy at the federal, state and local levels.

We look forward to reviewing the published proceedings and identifying action steps we may consider as we continue our efforts together to combat the opioid crisis and the rise in related infectious diseases.

hhs.gov

CDC Has Updated Recommendations for Latent TB Infection and HIV

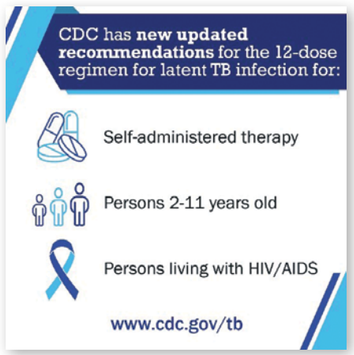
By Philip LoBue, MD, FACP, FCCP, Director, Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, MD, FACP, FCCP, Director, Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, and Jonathan Mermin, MD, MPH, RADM and Assistant Surgeon General, USPHS, Director, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) released updated recommendations for use of once-weekly isoniazid-rifapentine for 12 weeks (3HP) for treatment of latent tuberculosis (TB) infection.

The updated recommendations, published in CDC's *Morbidity and Mortality Weekly Report (MMWR)*, support expanded use of an effective, shorter treatment regimen to reach even more people with latent TB infection, including people with HIV/AIDS.

The updated recommendations include the use of 3HP:

- By directly observed therapy or self-administered therapy in persons over 2 years of age,
- In persons who are living with HIV/AIDS and taking antiretroviral medications with acceptable drug interactions with rifapentine, and
- In children and adolescents, 2-11 years old.



These updated recommendations are very good news for those with HIV and latent TB infection. Because HIV infection weakens the immune system, people with latent TB infection and HIV infection are at very high risk of developing TB disease, if not treated.

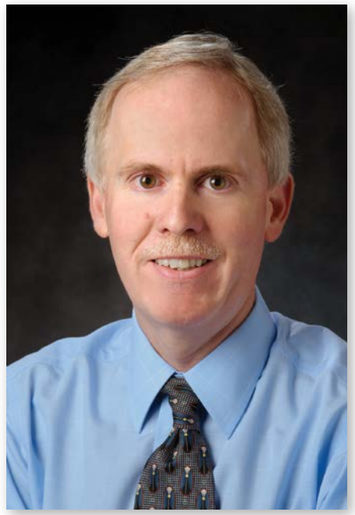
Previously, CDC only recommended the 3HP regimen for treatment of latent TB infection in people with HIV who were otherwise healthy and not taking antiretroviral medication.

At that time, we did not know enough about the interactions between rifapentine and certain antiviral medications. New data now show an absence of clinically significant drug interactions between once-weekly rifapentine and the antiviral medications efavirenz and raltegravir.

Healthcare providers treating patients with HIV infection and latent TB infection can find information about interactions between rifamycins (including rifapentine) and antiretrovirals in the Department of Health and Human Services' Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, as well as useful tables with information on other drug interactions.

For those patients on antiretroviral agents, healthcare providers should consult with experts in TB and HIV management to determine the best overall treatment regimen.

The 3HP regimen is the shortest of several regimens available to treat latent TB infection today and can remove barriers to initiate and complete treatment.



Philip LoBue, MD, FACP, FCCP

A shorter treatment timeframe, the option for self-administration, and reduced costs all contribute to increasing the number of people who complete treatment for latent TB infection, helping to prevent future cases of TB disease.

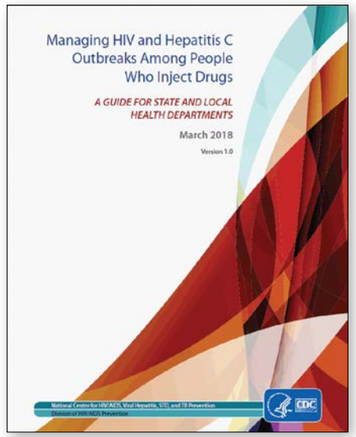
We all play an important role in TB prevention. We encourage clinicians and public health professionals to review and implement the updated recommendations, which include guidance on patient education and monitoring, and to visit the LTBI resource page for additional resources on latent TB infection.

hiv.gov

New CDC Resources: HIV & HCV Outbreak Detection and Response

By Corinna Dan, RN, MPH, Viral Hepatitis Policy Advisor, Office of HIV/AIDS and Infectious Disease Policy, U.S. Department of Health and Human Services

CDC has released Managing HIV and Hepatitis C Outbreaks Among People Who Inject Drugs: A Guide for State and Local Health Departments.



This guide is designed to help state and local health departments plan for an outbreak of HIV or hepatitis C among people who inject drugs. The guide outlines strategies to detect and investigate a possible outbreak and includes considerations for developing an outbreak response plan to minimize the impact of the outbreak on the community and stop further transmission.

The current opioid epidemic has increased the number of people who are injecting drugs in the U.S., and that has substantially increased the risk of transmission of blood-borne viruses, including HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) among this population because of increases in shared injecting equipment. Increases in injection drug use are being seen in communities not previously considered at high risk of injection-related infections. The potential for rapid spread of HIV and HCV among this new population of people at risk was realized during a 2015 outbreak in rural Scott County, Indiana. The new CDC guide draws on lessons from the response to that outbreak.

Advanced planning can facilitate an effective coordinated response for communities faced with the possibility of future outbreaks of HIV or hepatitis C among networks of PWID.

As a companion to the guide, CDC also released Tennessee Human Immunodeficiency Virus (HIV) & Hepatitis C Virus (HCV) Outbreak Response Plan [PDF, 3.0MB] a sample plan developed by the Tennessee Department of Health.

Responding to the Opioid Epidemic and Eliminating Hepatitis C Require Collaborative Efforts

Our comprehensive response to the opioid epidemic must include the prevention, detection, and treatment of the medical consequences of viral hepatitis, including overdoses and viral hepatitis and HIV infections. Many people do not realize that as the opioid epidemic continues to evolve and affect more communities, new hepatitis C infections nearly tripled between 2010 and 2015. Those infections are increasing most rapidly among young people, with the highest overall number of new infections among 20- to 29-year-olds, primarily as a result of increasing injection drug use. This is among the hidden casualties of the opioid epidemic.

Agencies and organizations in communities across the nation are already working to eliminate hepatitis B and hepatitis C in the United States, using the National Viral Hepatitis Action Plan (Action Plan) as our strategic framework. The Action Plan acknowledges the inescapable interconnections between the opioid epidemic, viral hepatitis, and other diseases that are spread by injecting drugs. To address these, the Action Plan calls for expanded access to comprehensive, integrated infectious disease services for people who inject drugs. There are opportunities to engage and mobilize partners at the federal, state, and community levels to better integrate our responses to both the opioid epidemic and viral hepatitis. A more coordinated and comprehensive response will be key to ending both the opioid and hepatitis C epidemics.

If your community is among the thousands affected by the opioid epidemic, consider joining us in implementing the Action Plan by sharing these new resources with your local health department and thinking about how you can support public health and other partners in the event of an HIV or hepatitis C outbreak among people who inject drugs.

We have seen how the opioid epidemic is changing and as with all battles, preparation is key to winning. By being prepared to respond to an HIV or hepatitis C outbreak among people who inject drugs in partnership with others in your community, you can better ensure that an outbreak will be detected quickly and that the people affected will be able to get the services they need.

hiv.gov

HHS Awards $2.34 Billion in Grants to Help Americans Access HIV/AIDS Care and Medication

The U.S. Department of Health and Human Services announced that approximately $2.34 billion in Ryan White HIV/AIDS Program grants were awarded to cities, counties, states, and local community-based organizations in fiscal year (FY) 2018. This funding through the Health Resources and Services Administration (HRSA) supports a comprehensive system of HIV primary medical care, medication, and essential support services to more than half a million people living with HIV in the United States.

"New medical advances and broader access to treatment have helped transform HIV/AIDS from a likely death sentence into a manageable chronic disease," said HHS Secretary Alex Azar. "The Ryan White HIV/AIDS Program is an important way to ensure that these life-saving treatments reach the Americans who need them, and the Trump Administration is committed to continuing to improve the care by Americans living with HIV/AIDS receive."

"The Ryan White HIV/AIDS Program plays a vital role in the United States' public health response to ending the HIV epidemic," said HRSA Administrator George Sigounas, MS, PhD. "These grants will help ensure that the most vulnerable Americans living with HIV/AIDS have access to life-saving care and treatment needed to improve their health quality and medical outcomes."

HRSA oversees the Ryan White HIV/AIDS Program, which is a patient-centered system that provides care and treatment services to low income people living with HIV to improve health outcomes and reduce HIV transmission among hard to reach populations. The program serves approximately 50 percent of people living with diagnosed HIV infection in the United States. In 2016, approximately 85 percent of Ryan White HIV/AIDS Program clients who received HIV medical care were virally suppressed, up from 69 percent in 2010.

"The Ryan White HIV/AIDS Program is critical to improving clinical and public health outcomes by reducing HIV transmission and serves as an important source of ongoing access to HIV treatment and antiretroviral medication," said Laura Cheever, MD, ScM, Associate

Ryan White HIV/AIDS Program providers often assist patients in required paperwork to ensure receipt of- and coverage for- services. This assists in breaking down barriers that may keep many women accessing care.

Administrator, HIV/AIDS Bureau. "Today people living with HIV who take HIV medication daily as prescribed and who achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner."

Under Part A of the Ryan White HIV/AIDS Program, approximately $624.3 million was awarded to 52 metropolitan areas to provide core medical and support services for people living with HIV. These grants were awarded to 24 eligible metropolitan areas and 28 transitional grant areas with the highest number of people living with HIV and AIDS and experiencing increases in HIV and AIDS cases and emerging care needs. For a list of the FY 2018 Ryan White HIV/AIDS Program Part A award recipients, visit hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-a-final-awards

Under Part B of the Ryan White HIV/AIDS Program, approximately $1.4 billion was awarded to 59 states and territories to improve the quality, availability and organization of HIV health care and support services and for the AIDS Drug Assistance Program (ADAP). Additionally, 16 states received Emerging Community grants based on the number of AIDS cases over the most recent five-year period. Thirty-three states and territories were also awarded approximately $10.5 million in Part B Minority AIDS Initiative grants. For a list of the FY 2018 Ryan White HIV/AIDS Program Part B award recipients, visit hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-b-grant-awards

Under Part C Early Intervention Services (EIS) of the Ryan White HIV/AIDS Program, approximately $181.9 million was awarded across the country to 351 local, community-based organizations to provide core medical and support services to people living with HIV. Additionally, 52 organizations were awarded approximately $6.9 million in Part C Capacity Development grants. For a list of the FY 2018 Ryan White HIV/AIDS Program Part C EIS award recipients, visit hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-c-early-intervention-services-eis-awards. For a list of the FY 2018 Ryan White HIV/AIDS Program Part C Capacity Development award recipients, visit hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-c-capacity-development-awards

Ryan White HIV/AIDS Program providers often assist patients in required paperwork to ensure receipt of- and coverage for- services. This assists in breaking down barriers that may keep many women accessing care.

Under Part D of the Ryan White HIV/AIDS Program, approximately $70.3 million was awarded to 115 local community-based organizations across the country to provide family-centered comprehensive HIV care and treatment for women, infants, children, and youth. For a list of the FY 2018 Ryan White HIV/AIDS Program Part D award recipients, visit https://hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-d-grant-awards

Under Part F of the Ryan White HIV/AIDS Program, approximately $68.6 million was awarded to support clinical training, oral health services, quality improvement, and the development of innovative models of care through several different programs. Approximately $8.9 million was awarded to 51 recipients through the HIV/AIDS Dental Reimbursement Program, and approximately $3.5 million was awarded to 12 recipients through the HIV/AIDS Community-Based Dental Partnership Program.

For a list of the FY 2018 Ryan White HIV/AIDS Program Part F HIV/AIDS Dental Reimbursement Program award recipients and HIV/AIDS Community-Based Dental Partnership Program award recipients, visit https://hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-part-f-grant-awards

Also under Part F, the AIDS Education and Training Centers Program (AETC) awarded approximately $31.2 million through 14 grants, cooperative agreements and contracts to support education and training of health care professionals, which includes a network of eight regional and two national centers. For a list of the FY 2018 Ryan White HIV/AIDS Program AETC award recipients, visit https://hab.hrsa.gov/awards/fy-2018-ryan-white-hivaids-program-aids-education-and-training-center-awards

In addition, $25 million was awarded through the Ryan White HIV/AIDS Program Special Projects of National Significance (SPNS) Program under Part F, which supports the development of innovative models of care, informing evidence-based interventions with populations living with HIV who are significantly difficult to engage, retain in care, and achieve viral suppression.

Grant awards in FY 2018 also support states, cities, counties, and communities to achieve the goals of the National HIV/AIDS Strategy for the United States: Updated to 2020. These include efforts to reduce new HIV infections, increase access to HIV care and improve health outcomes for people living with HIV infection, and reduce HIV-related disparities and health inequities.

hhs.gov

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Help them fight back with TROGARZO™ (ibalizumab-uiyk) — A breakthrough antiretroviral in a class of its own.

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Trogarzo™
(ibalizumab-uiyk)
Injection
200 mg/1.33 mL (150 mg/mL)

INDICATION

TROGARZO™, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in one patient treated with TROGARZO™ in combination with other antiretrovirals. During the initial phase of combination antiretroviral therapies, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

Adverse Reactions

- The most common adverse reactions (reported in ≥5.0% of patients) were diarrhea (8%), dizziness (8%), nausea (5%) and rash (5%).
- Most (90%) of the adverse reactions reported were mild or moderate in severity. Two subjects experienced severe adverse reactions: one subject had a severe rash and one subject developed IRIS manifested as an exacerbation of progressive multifocal leukoencephalopathy.

Use in Specific Populations

- **Pregnancy:** No adequate human data are available to establish whether or not TROGARZO™ poses a risk to pregnancy outcomes. Monoclonal antibodies, such as ibalizumab-uiyk, are transported across the placenta as pregnancy progresses; therefore, ibalizumab-uiyk has the potential to be transmitted from the mother to the developing fetus.
- **Lactation:** No data are available regarding the presence of TROGARZO™ in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for HIV-1 transmission, instruct mothers not to breastfeed if they are receiving TROGARZO™.

To report suspected adverse reactions, contact THERA patient support™ (1-833-238-4372) or the FDA (1-800-FDA-1088 or fda.gov/medwatch).

Please see brief summary of Prescribing Information on following page, and the full Prescribing Information at TROGARZO.com

THERA patient support™

435-01-09/18

Q&A: HIV and the Gut Microbiome

The gut microbiome — the community of bacteria and other microbes naturally present in the gastrointestinal (GI) tract — plays a critical role in human health. NIAID Now spoke with Jason Brenchley, PhD, about the link between the gut microbiome and HIV infection, and his lab's recent research findings. Dr. Brenchley is senior investigator of the Barrier Immunity Section in NIAID's Laboratory of Viral Diseases.

What is gut dysbiosis? Is it common in people living with HIV?

"Dysbiosis" refers to an alteration to the types of bacteria that normally inhabit the GI tract. Studies in humans have shown that the gut microbiome is dysbiotic in people living with HIV. This dysbiosis is associated with decreases in a type of bacteria that provides nutrients important for maintaining the health of the structural barrier of the GI tract, which prevents the microbiome from coming into direct contact with the GI tissues. When these bacteria are depleted in the case of HIV, the tight structural barrier of the GI tract weakens. The consequence of that is that microbial products cross the barrier into the tissues, where they can enter the bloodstream and cause systemic, or whole-body, inflammation. We refer to this as "microbial translocation."

Recent research suggests that a large degree of the gut dysbiosis observed in people living with HIV is not caused by the virus itself. Rather, gut dysbiosis may result from behaviors or risk factors associated with susceptibility to HIV infection.

How can animal models help us better understand the link between gut dysbiosis and HIV?

Animal models have certain advantages over human studies in that we can control for different variables that influence the composition of the gut microbiome — for example, diet. Using a non-human primate (NHP) model, we can follow the composition of the gut microbiome over time before and after infection with simian immunodeficiency virus (SIV), a virus similar to HIV.

Your lab published a study today in Nature Medicine describing experimental induction of intestinal dysbiosis in monkeys infected with SIV. What was the focus of that study?

The question we asked was: How does HIV-like gut dysbiosis change the nature of progressive SIV infection in our NHP model? We gave the animals an antibiotic that kills off many barrier-protecting gut bacteria, resulting in a dysbiotic microbiome very similar to that observed in people living with HIV. We infected the animals with SIV and followed disease progression over time. We also followed a control group of SIV-infected animals that did not receive the antibiotic.

What were your main findings, and what do they tell us about the situation in people living with HIV?

The dysbiotic microbiome that we induced had very little influence on how the disease progressed in the absence of antiretroviral therapy (ART). We measured multiple aspects of disease progression in the antibiotic-treated and control animals. We measured how well SIV replicated. We measured how quickly CD4+ T cells — the main cell type that SIV and HIV infect and destroy — were lost. We measured the degree of systemic inflammation and microbial translocation. None of those were altered by the dysbiotic microbiome.

Assuming these effects are similar in people, our findings suggest that very little of the systemic inflammation seen in people living with HIV who are not on ART is attributable to gut dysbiosis. In the absence of treatment, immune responses to the replicating virus and translocated microbial products are likely the main cause of systemic inflammation.

Is systemic inflammation also an issue for people living with HIV who are taking life-saving ART?

Yes. Compared to the general population, people living with HIV who have been taking ART for decades are more likely to die from conditions associated with inflammation, such as cardiovascular disease and different kinds of cancers. Research suggests that much of the systemic inflammation seen in people whose HIV is suppressed by long-term ART stems from the phenomenon of microbial translocation, which may be linked to gut dysbiosis.

What are the potential clinical applications of your research?

There are two areas in which we think targeting a dysbiotic microbiome might be important for HIV.

One is for reducing the risk of HIV acquisition. We are investigating whether gut dysbiosis changes susceptibility to HIV infection. In other words, if you have a dysbiotic microbiome, does that make it easier for you to acquire HIV? Some of our preliminary data suggests this may be the case. If you could increase the amount of good bacteria that are lacking in people at risk for HIV, it might make it harder for the person to acquire HIV.

The other potential application is for people on ART who have residual inflammation. Developing strategies to alter their gut microbiomes to a less dysbiotic state might lead to them having lower levels of systemic inflammation and reduced susceptibility to cardiovascular disease and cancers.

niaid.nih.gov

Germs with Unusual Antibiotic Resistance Widespread in U.S.

Ramped-up CDC strategy helps providers stop spread of new germs, prevents large outbreaks

Health departments working with CDC's Antibiotic Resistance (AR) Lab Network found more than 220 instances of germs with "unusual" antibiotic resistance genes in the United States last year, according to a CDC Vital Signs report released today.

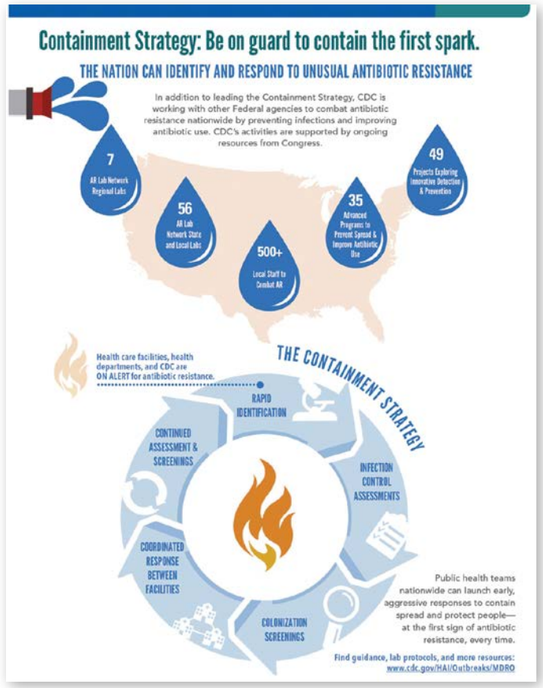
Germs with unusual resistance include those that cannot be killed by all or most antibiotics, are uncommon in a geographic area or the U.S., or have specific genes that allow them to spread their resistance to other germs. Rapid identification of the new or rare threats is the critical first step in CDC's containment strategy to stop the spread of antibiotic resistance (AR). When a germ with unusual resistance is detected, facilities can quickly isolate patients and begin aggressive infection control and screening actions to discover, reduce, and stop transmission to others.

"CDC's study found several dangerous pathogens, hiding in plain sight, that can cause infections that are difficult or impossible to treat," said CDC Principal Deputy Director Anne Schuchat, MD. "It's reassuring to see that state and local experts, using our containment strategy, identified and stopped these resistant bacteria before they had the opportunity to spread."

New strategy stops resistant bugs before they spread

The CDC containment strategy calls for rapid identification of resistance, infection control assessments, testing patients without symptoms who may carry and spread the germ, and continued infection control assessments until spread is stopped. The strategy requires a coordinated response among health care facilities, labs, health departments and CDC through the AR Lab Network. Health departments using the approach have conducted infection control assessments and colonization screenings within 48 hours of finding unusual resistance and have reported no further transmission during follow-up over several weeks.

The strategy complements foundational CDC efforts, including improving antibiotic use and preventing new infections, and builds on existing detection and response infrastructure. New data suggest that the containment strategy can prevent thousands of difficult-to-treat or potentially untreatable infections, including high-priority threats such as Candida auris and carbapenem-resistant Enterobacteriaceae (CRE). Germs will continuously find ways to resist new and existing antibiotics; stopping new resistance from developing is not currently possible. Recent, nationwide infrastructure investments in laboratories, infection control, and response are enabling tailored, rapid,



and aggressive investigations to keep resistance from spreading in health care settings.

Other study findings showed:

- One in four germ samples sent to the AR Lab Network for testing had a special genes that allow them to spread their resistance to other germs.
- Further investigation in facilities with unusual resistance revealed that about one in 10 screening tests, from patients without symptoms, identified a hard-to-treat germ that spreads easily. This means the germ could have spread undetected in that health care facility.
- For CRE alone, estimates show that the containment strategy would prevent as many as 1,600 new infections in three years in a single state—a 76 percent reduction.

cdc.gov

CPG

HHS Sponsors its Largest Exercise for Moving Patients with Highly Infectious Diseases

The largest patient movement exercise in U.S. Department of Health and Human Services' history began today to test the nationwide ability to move patients with highly infectious diseases safely and securely to regional treatment centers.

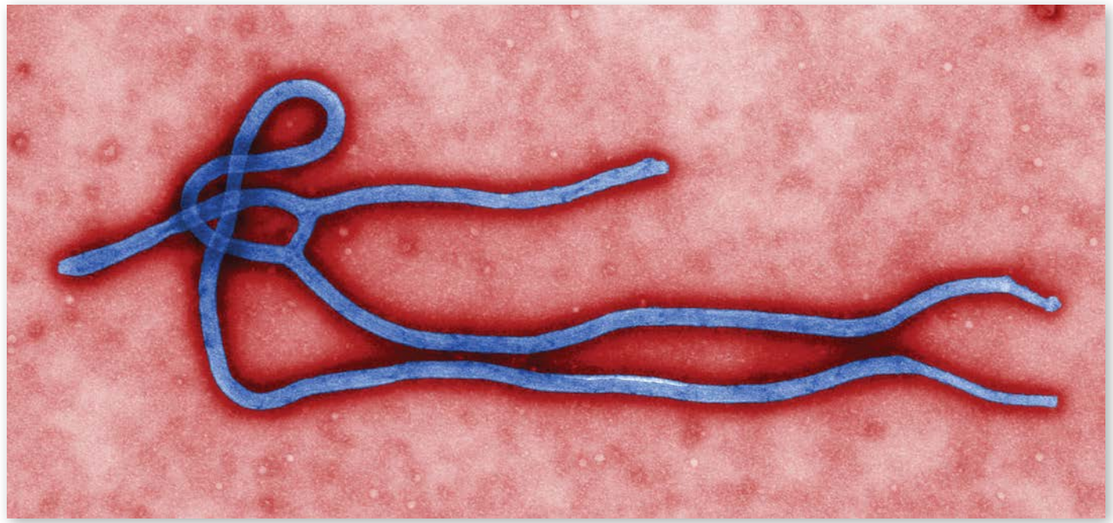
"Saving lives during crises requires preparation and training," explained HHS Assistant Secretary for Preparedness and Response Robert Kadlec, MD. "A tremendous amount of coordination, synchronization, and skill is needed to move patients with highly infectious diseases safely. We have to protect the patients and the healthcare workers caring for those patients. This type of exercise helps ensure that everyone involved is ready for that level of complexity."

Coordinated by the HHS Office of the Assistant Secretary for Preparedness and Response, more than 50 organizations will participate, including the Department of State, Department of Transportation, the Regional Ebola Treatment Centers, local and state health and emergency management agencies, hospitals, airport authorities, and non-government organizations.

Throughout the exercise, participants react as if the incident is real. They must take the necessary actions and employ the appropriate resources to manage and protect the patients, the workforce and the environment and safely transport the patients.

The exercise focuses on moving seven people acting as patients with Ebola symptoms in different regions of the country. The patients, including one pediatric patient, first present themselves at one of the following healthcare facilities: CHI St. Luke's

Robert Kadlec, MD, Assistant Secretary for Preparedness and Response (ASPR)



This colorized transmission electron micrograph shows some of the morphology displayed by the Ebola virus. The exact origin, locations and natural reservoir of Ebola virus remain unknown. Centers for Disease Control and Prevention photo by Cynthia Goldsmith

Health-The Woodlands Hospital in The Woodlands, Texas; Medical University of South Carolina in Charleston, South Carolina; Norman Regional Hospital in Norman, Oklahoma; St. Alphonsus Regional Medical Center in Boise, Idaho, and St. Luke's Regional Medical Center in Boise, Idaho.

At each facility, healthcare workers will collect and ship samples for diagnostic tests to state laboratories, which in turn will practice running the necessary laboratory tests to diagnose the patients with Ebola. As part of the exercise, each patient will receive a positive diagnosis. Using appropriate isolation techniques and personal protective equipment, health care workers then must take steps to have six of the patients transported by air to designated Regional Ebola Treatment Centers. These patients will be placed into mobile biocontainment units for these flights. The pediatric patient will be placed into protective equipment and transported by ground ambulance.

CDC collaborates with partners that conduct IPC training at the National Ebola Training Academy in Freetown, Sierra Leone. Above, the International Organization of Migration (IOM) staff are shown training frontline responders through simulation exercises. Patients for simulation exercises are Ebola survivors.

The treatment centers that will receive the patients are Cedars-Sinai Medical Center in Los Angeles, California; Emory University Hospital in Atlanta, Georgia; Providence Sacred Heart Medical Center in Spokane, Washington; and University of Texas Medical Branch in Galveston, Texas. The pediatric patient will be transported to Texas Children's Hospital West Campus in Houston, Texas. The participating airports are Boise Airport in Boise, Idaho; Charleston International Airport in Charleston, South Carolina; DeKalb-Peachtree Airport in Atlanta, Georgia; Ellington Field Airport in Houston, Texas; Los Angeles International Airport in Los Angeles, California; Spokane International Airport in Spokane, Washington; and Will Rogers World Airport in Oklahoma City, Oklahoma. Upon arrival, local emergency responders will transfer the patients to ground ambulances for transportation from the airports to the treatment centers.

HHS and the Department of State previously collaborated on exercises to move Americans acting as Ebola patients from West African countries to Ebola treatment centers in the United States. In public health emergencies or disasters, the U.S. government orchestrates the return of Americans to the United States, including Americans who are sick or injured.

hhs.gov

HHS Advances Point-of-Care Diagnostic Test for Anthrax

A point-of-care diagnostic test that may be able to determine within 15 minutes whether a patient has been infected with the bacterium that causes anthrax is moving forward in research and development with the support of the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR).

A three-year, $8.1 million contract with the Biomedical Advanced Research and Development Authority (BARDA), part of ASPR, and InBios International, Inc. of Seattle, Washington, will allow for studies needed to apply for licensure from the U.S. Food and Drug Administration (FDA).

The contract also requires the company to perform studies necessary to support its submission for pre-Emergency Use Authorization from the FDA.

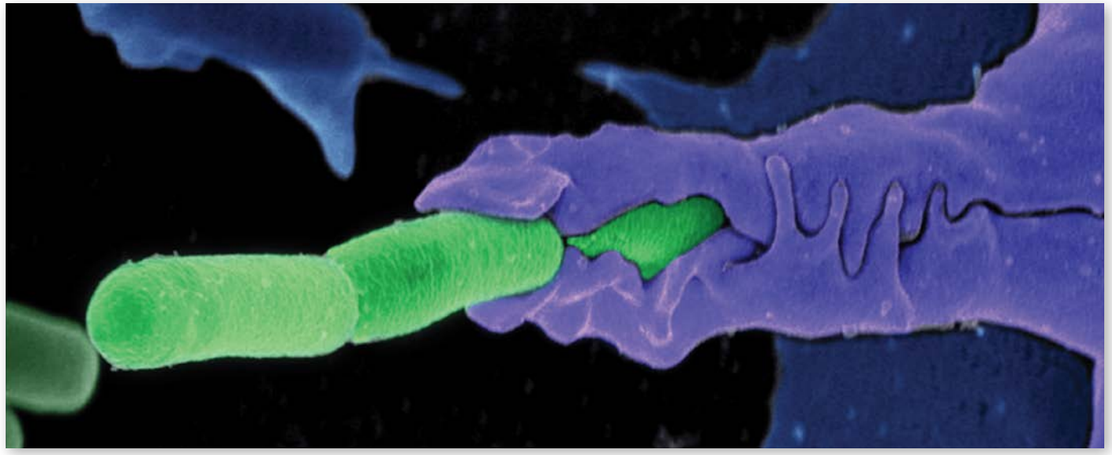
"Inhalational anthrax is a deadly disease and a significant biological threat to our nation," said BARDA Director Rick Bright, Ph.D. "To save lives during an anthrax emergency, health care providers must be able to screen patients rapidly to provide treatment as quickly as possible. That's our goal in supporting development of point-of-care tests like this."

InBios' test, a lateral flow immunoassay, determines whether a patient has been infected with anthrax-causing Bacillus anthracis bacteria by identifying specific proteins from the bacteria in a few drops of a person's blood. In studies to date, the test has identified the bacterial proteins within about 15 minutes.

The test has the potential for use in hospital emergency rooms, local health clinics, and at a patient's bedside. It also could be used by first responders.

Protecting health after anthrax exposure requires not only detecting but also preventing and treating anthrax infections. To meet this national health security need, BARDA's portfolio includes supporting three anthrax antitoxin drugs approved by the FDA. BARDA also supports advanced development of vaccines to prevent illness after exposure to anthrax and improvements to the only anthrax vaccine licensed for use post-exposure so that fewer doses are needed to protect human health.

hhs.gov



Multiple anthrax bacteria (green) being enveloped by an immune system cell (purple). Anthrax bacteria live in soil and form dormant spores that can survive for decades. When animals eat or inhale these spores, the bacteria activate and rapidly increase in number. Today, a highly effective and widely used vaccine has made the disease uncommon in domesticated animals and rare in humans.

From the image bank of NIH, National Institute of General Medical Sciences. Credit: Camenzind G. Robinson, Sarah Guilman and Arthur Friedlander, United States Army Medical Research Institute of Infectious Diseases

HHS, Regeneron Partner on Portfolio of Treatments for Pandemic Influenza, Emerging Infectious Diseases

The U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) and Regeneron Pharmaceuticals, Inc. of Tarrytown, New York, will forge a public-private partnership to drive development of an entire portfolio of products to treat influenza and other emerging infectious diseases.

The Biomedical Advanced Research and Development Authority (BARDA), a component of ASPR, and Regeneron will share the oversight and cost of developing new therapeutics to treat influenza and emerging pathogens that pose a significant risk to public health. BARDA initially will contribute $18.7 million.

"Influenza and other emerging infectious diseases present serious threats to our nation's health security," explained BARDA Director Rick Bright, PhD. "This partnership will support much-needed treatment options for those who are severely ill with influenza and the rapid drug development that is critical to save lives when a new disease emerges."

The products developed through this partnership will leverage Regeneron's monoclonal antibody discovery platform which the company used in developing treatments for MERS coronavirus and Ebola. The technology directly links antibody discovery to clinical manufacturing. This technology shortened the development timeline during those emergency responses to months instead of years.

Monoclonal antibodies are produced by a single clone of cells or a cell line with identical antibody molecules. These antibodies bind to certain proteins of a virus to disable it and also stimulate the patient's immune system to attack the virus-infected cells.

Rick A. Bright, PhD, Deputy Assistant Secretary for Preparedness and Response; Director of the Biomedical Advances Research and Development Authority, U.S. Department of Health and Human Services

Initially the partners will use the technology platform to develop a next-generation monoclonal antibody treatment for patients hospitalized with severe influenza. In addition, the flexibility of the partnership allows development of therapeutics to treat infections caused by pathogens that emerge in the future. The partners also could use the technology in rapidly developing products during a public health emergency.

Rather than a standard agreement, ASPR and Regeneron will collaborate using an Other Transaction Agreement (OTA) under authority granted to HHS under the Pandemic and All Hazards Preparedness Act of 2006. The OTA provides a funding and collaboration vehicle to promote innovation in technology for advanced research and development of medical products needed in a public health emergency.

This portfolio partnership is the sixth that BARDA has formed using Other Transaction Authority. One of the previous partnerships focused on influenza therapeutics and vaccines, and the other four focused on developing new products to address chemical, biological, radiological and nuclear (CBRN) threats and antimicrobial drug resistance.

As a division of ASPR, BARDA takes a comprehensive integrated portfolio approach to advanced research and development, innovation, acquisition, and manufacturing of vaccines, drugs, diagnostic tools, and non-pharmaceutical products for CBRN and naturally occurring public health medical emergencies.

BARDA partners with other federal agencies, in particular the National Institutes of Health, as well as private industry to develop medical products needed to mitigate the health effects of disasters and other public health emergencies. Potential products may transition from basic research and early clinical trials at NIH to BARDA for support of the advanced development necessary to support approval or licensure by the U.S. Food and Drug Administration.

HHS is the principal federal agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves. ASPR leads HHS in preparing the nation to respond to and recover from adverse health effects of emergencies, supporting communities' ability to withstand adversity, strengthening health and response systems, and enhancing national health security.

phe.gov

Highly Pathogenic H7 Avian Influenza Confirmed by USDA in a Commercial Flock in Lincoln County, Tennessee

The United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) has confirmed the presence of highly pathogenic H7 avian influenza (HPAI) of North American wild bird lineage in a commercial chicken breeder flock in Lincoln County, Tennessee. This is the first confirmed case of HPAI in commercial poultry in the United States this year. The flock of 73,500 is located within the Mississippi flyway. Samples from the affected flock, which experienced increased mortality, were tested at Tennessee's Kord Animal Health Diagnostic Laboratory and confirmed at the APHIS National Veterinary Services Laboratories (NVSL) in Ames, Iowa. Virus isolation is ongoing, and NVSL expects to characterize the neuraminidase protein, or "N-type", of the virus within 48 hours.

APHIS is working closely with the Tennessee Department of Agriculture on a joint incident response. State officials quarantined the affected premises and birds on the property will be depopulated to prevent the spread of the disease. Birds from the flock will not enter the food system.

The Tennessee Department of Agriculture is working directly with poultry workers at the affected facility to ensure that they are taking the proper precautions to prevent illness and contain disease spread. As a reminder, the proper handling and cooking of poultry and eggs to an internal temperature of 165 ˚F kills bacteria and viruses.

As part of existing avian influenza response plans, Federal and State partners are working jointly on additional surveillance and testing in the nearby area. The United States has the strongest AI surveillance program in the world, and USDA is working with its partners to actively look for the disease in commercial poultry operations, live bird markets and in migratory wild bird populations.

USDA will be informing the World Organization for Animal Health (OIE) as well as international trading partners of this finding. USDA also continues to communicate with trading partners to encourage adherence to OIE standards and minimize trade impacts. OIE trade guidelines call on countries to base trade restrictions on sound science and, whenever possible, limit restrictions to those

animals and animal products within a defined region that pose a risk of spreading disease of concern.

These virus strains can travel in wild birds without them appearing sick. People should avoid contact with sick/dead poultry or wildlife. If contact occurs, wash your hands with soap and water and change clothing before having any contact with healthy domestic poultry and birds. All bird owners, whether commercial producers or backyard enthusiasts, should continue to practice good biosecurity, prevent contact between their birds and wild birds, and report sick birds or unusual bird deaths to State/Federal officials, either through their state veterinarian or through USDA's toll-free number at 1-866-536-7593. Additional information on biosecurity for can be found at www.aphis.usda.gov/animalhealth/defendtheflock

Additional background

Avian influenza (AI) is caused by an influenza type A virus which can infect poultry (such as chickens, turkeys, pheasants, quail, domestic ducks, geese and guinea fowl) and is carried by free flying waterfowl such as ducks, geese and shorebirds. AI viruses are classified by a combination of two groups of proteins: hemagglutinin or "H" proteins, of which there are 16 (H1–H16), and neuraminidase or "N" proteins, of which there are 9 (N1–N9). Many different combinations of "H" and "N" proteins are possible. Each combination is considered a different subtype, and can be further broken down into different strains. AI viruses are further classified by their pathogenicity (low or high)— the ability of a particular virus strain to produce disease in domestic chickens.

usda.gov

Transmission of Avian Influenza A Viruses Between Animals and People

Influenza A viruses have infected many different animals, including ducks, chickens, pigs, whales, horses, and seals. However, certain subtypes of influenza A virus are specific to certain species, except for birds, which are hosts to all known subtypes of influenza A viruses. Currently circulating Influenza A subtypes in humans are H3N2 and H1N1 viruses. Examples of different influenza A virus subtypes that have infected animals to cause outbreaks include H1N1 and H3N2 virus infections of pigs, and H7N7 and H3N8 virus infections of horses.

Influenza A viruses that typically infect and transmit among one animal species sometimes can cross over and cause illness in another species. For example, until 1998, only H1N1 viruses circulated widely in the U.S. pig population. However, in 1998, H3N2 viruses from humans were introduced into the pig population and caused widespread disease among pigs. More recently, H3N8 viruses from horses have crossed over and caused outbreaks in dogs.

Avian influenza A viruses may be transmitted from animals to humans in two main ways:

- Directly from birds or from avian influenza A virus-contaminated environments to people.
- Through an intermediate host, such as a pig.

Influenza A viruses have eight separate gene segments. The segmented genome allows influenza A viruses from different species to mix and create a new virus if influenza A viruses from two different species infect the same person or animal. For example, if a pig were infected with a human influenza A virus and an avian influenza A virus at the same time, the new replicating viruses could mix existing genetic information (reassortment) and produce a new influenza A virus that had most of the genes from the human virus, but a hemagglutinin gene and/or neuraminidase gene and other genes from the avian virus. The resulting new virus might then be able to infect humans and spread easily from person to person, but it would have surface proteins (hemagglutinin and/or neuraminidase) different than those currently found in influenza viruses that infect humans.

This type of major change in the influenza A viruses is known as "antigenic shift." Antigenic shift results when a new influenza A virus subtype to which most people have little or no immune protection infects humans. If this new influenza A virus causes illness in people and is transmitted easily from person to person in a sustained manner, an influenza pandemic can occur.

It is possible that the process of genetic reassortment could occur in a person who is co-infected with an avian influenza A virus and a human influenza A virus. The genetic information in these viruses could reassort to create a new influenza A virus with a hemagglutinin gene from the avian virus and other genes from the human virus. Influenza A viruses with a hemagglutinin against which humans have little or no immunity that have reassorted with a human influenza virus are more likely to result in sustained human-to-human transmission and pose a major public health threat of pandemic influenza. Therefore, careful evaluation of influenza A viruses recovered from humans who are infected with avian influenza A viruses is very important to identify reassortment if it occurs.

Although it is unusual for people to get influenza virus infections directly from animals, sporadic human infections and outbreaks caused by certain avian influenza A viruses and swine influenza A viruses have been reported.

cdc.gov

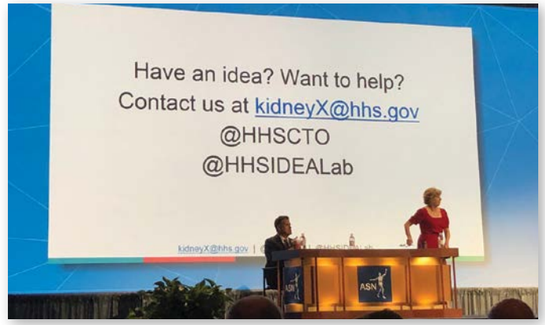
The U.S. Department of Health and Human Services and the American Society of Nephrology to Launch "KidneyX" Innovation Accelerator

The U.S. Department of Health and Human Services (HHS) is pleased to announce a partnership with the American Society of Nephrology to launch the Kidney Innovation Accelerator (KidneyX), KidneyX will engage a community of researchers, innovators, and investors to enable and accelerate the commercialization of therapies to benefit people with and at risk for kidney diseases through a series of prize competitions and coordination among federal agencies and the private sector.

More than 40 million Americans live with kidney diseases and 703,243 experience kidney failure. With an aging population and rising prevalence of diabetes and hypertension, more Americans need dialysis than ever before. Patients with chronic kidney disease continue to have limited treatment options and are particularly vulnerable in natural disasters when local dialysis centers are damaged or closed for more than a few days.

HHS Chief Technology Officer, Bruce D. Greenstein shakes hands with Mark D. Okusa, MD, FASN, President of the American Society of Nephrology

"Over the last decade, patients with cancer and heart disease have benefitted from innovative improvements in therapies, drugs, devices and digital health tools. Patients suffering from kidney disease deserve the same opportunity. With KidneyX, HHS sends an important message to innovators and investors regarding the desire and demand to help patients suffering from chronic kidney disease," said HHS Chief Technology Officer, Bruce D. Greenstein.



To prevent kidney diseases as well as improve the lives of the 850,000,000 people worldwide currently affected, KidneyX will accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases. KidneyX will address the barriers innovators commonly identify as they look to bring new drugs and technologies in kidney care to market by:

- Providing funding through prizes to promising innovators selected through a prize competition;
- Encouraging better coordination across the HHS agencies including the National Institutes of Health, the Food and Drug Administration, and the Centers for Medicare & Medicaid Services in order to help clarify the path toward commercialization;
- Creating a sense of urgency to develop new therapies to treat chronic kidney disease

"By launching KidneyX, ASN and HHS have sent a clear signal that the kidney space is ripe for accelerating innovation in the fight against kidney diseases. KidneyX will serve as that catalyst while encouraging the venture capital community that has previously been reluctant to invest in kidney therapeutics to revisit it as a target for potential investments," said ASN President, Mark D. Okusa, MD, FASN.

KidneyX will accept applications for its first round of prize funding in late summer 2018. Individuals who are interested in learning more about KidneyX are encouraged to visit www.kidneyx.org and join the mailing list.

hhs.gov

Creating a Foundation for Potential New Kidney Cancer Therapies

By Courtney Coombes, PhD, NHLBI AAAS Science and Technology Policy Fellow

NHLBI researcher Richard Childs, MD, has developed a method to genetically modify a patient's T-cells to specifically recognize and kill kidney cancer cells.

In addition to fighting off infections, the human immune system also has the capacity to detect and destroy cancer cells lurking in the body. Cancer immunotherapy involves boosting or refining this response to more effectively treat cancer. There have been many advances in this field, but identifying the patients who would most benefit and understanding how to keep the immune system from over-responding are still areas of active research.

Each year, about 60,000 Americans will be diagnosed with kidney cancer, and 92 percent of them will have clear-cell kidney cancer, in which cancer forms in the small tubules of the kidney. Kidney cancer can often be treated successfully with surgery or radiation in its early stages, and the five-year survival rate for all kidney cancers is 71.2 percent. If the cancer spreads to other parts of the body, the prognosis worsens, and there may be a need for more aggressive treatments, such as immunotherapy. However, it's estimated that less than 20 percent of patients with clear-cell cancer respond to currently available immunotherapies.

Researchers at the National Institutes of Health have developed a novel immunotherapy approach to treat clear-cell kidney cancer by targeting a protein found only in the cancer cells, and are now testing the approach in a clinical trial.

The approach leading to this new clinical trial is built on decades of discovery science led by Rear Adm. Richard Childs, MD, clinical director at the NIH's National Heart, Lung, and Blood Institute, chief of the Transplantation Immunology Hematology Branch, and an officer in the U.S. Public Health Service Commissioned Corps.

Childs' early work as an NIH fellow spun off the concept of using a bone marrow transplant to treat leukemia and other blood cancers, where immune cells, called T cells, in the donor's bone marrow are used to destroy leukemia cells in the patient's body. He hypothesized that this so-called graft-versus-cancer effect could also be effective for treating patients with kidney cancer that had become metastatic — spreading to other parts of the body.

In a pilot clinical trial, Childs' group found that half of patients who had not responded to other immunotherapies exhibited a graft-versus-cancer response from an immune cell transplant. However, it was not clear which donor T cells were actually killing the cancer, and the transplant also sometimes led to graft-versus-host disease in which the donor cells attack vital organs.

Attendees at the Commissioned Corps all-hands meeting at Stone House included (front, from l) RADM (ret.) Richard Wyatt, RADM Joan Hunter, RADM Richard Childs, RADM Susan Orsega, RADM Helena Mishoe and RADM Peter Kilmarx.

So, Childs and fellow researchers isolated and grew T cells from the blood of a patient whose cancer had regressed after the transplant. From those T cells, Childs' team then isolated a novel protein on kidney tumors that the T cells were recognizing. That protein was discovered to be made from a piece of viral DNA that lodged itself into the human genome millions of years ago: called a human endogenous retrovirus (HERV-E). While all people have the HERV-E gene, this gene is only turned on in kidney cancer cells.

The team has now developed a method to genetically modify a patient's own T cells, thus avoiding the risk of graft-versus-host disease, to specifically recognize the HERV-E antigen to enhance the T cells' ability to target and kill kidney tumor cells.

A trial is now underway to determine if this strategy is safe. The trial is recruiting 24 adult patients who have clear-cell kidney cancer and who have not responded to other types of immunotherapy or to drugs known as kinase inhibitors that are designed to interrupt tumor growth.

hhs.gov

25 Years Since Discovery of First Gene Linked to Kidney Cancer

Twenty-five years ago, scientists from the National Cancer Institute uncovered the VHL gene, a gene whose mutation can lead to the development of kidney tumors. The discovery, the result of a decade-long partnership between CCR scientists and families affected by the disease, paved the way for new targeted therapies that have improved the prognosis for patients with advanced kidney cancers.

"We're seeing increased progression-free survival for kidney cancer patients," says W. Marston Linehan, MD, Chief of CCR's Urologic Oncology Branch, who co-discovered VHL with his NCI colleagues in 1993. "We're thrilled about the progress that has been made."

When Linehan began his career as a surgeon in the 1970s, patients with advanced kidney cancers were treated with a standard regimen of surgery and chemotherapy, but the drugs did little to stop the cancer's spread. Today, kidney cancer is recognized as not a single disease but made up of a number of diseases, each driven by distinct genetic features that shape its clinical course and response to therapy, and targeted therapies are available for the most common form, renal clear cell carcinoma.

This more nuanced view builds on decades of research, much of which can be traced to a bold decision by Linehan and his NCI colleague Berton Zbar, MD, to begin searching for a kidney cancer gene in the early 1980s. At the time, few genes had been linked to cancer of any type. Genetic analyses were far more laborious and costly than they are today, and Linehan says many researchers were skeptical that their efforts would turn up anything useful.

Linehan and Zbar turned to patients who were at risk to develop tumors in several organs, including the kidneys, associated with an inherited syndrome called von Hippel-Lindau (VHL). Although most kidney cancers do not run in families, the team hoped that patients with VHL might share a genetic abnormality that would help explain how kidney cancers arise — and ultimately, how to treat and/or prevent them.

The hereditary renal cancer program that Linehan and Zbar established at NCI brought hundreds of patients and their families to the NIH Clinical Center in Bethesda, Maryland. With the support of colleagues from across the NIH, the patients received expert clinical care for their complex disease, while they and their family members became part of a massive search for clues that might point the way to an effective treatment.

Working with another NCI colleague, Michael Lerman, MD, PhD, and an international team including Eamonn Maher, Linehan and Zbar began comparing their patients' DNA with their unaffected family members' DNA. Answers did not come quickly, but the scientists persisted. "We saw these patients every week and I told them, 'We are going to continue going to work on this. We're not working on anything else,'" Linehan recalls.

As more and more families affected by VHL volunteered for the study, the researchers were able to close in on their target. In 1993, after analyzing the DNA of a large number of individuals, the team found what it had been looking for: a gene that was altered in patients with VHL but intact in family members without the disorder.

The researchers soon found that mutations in the VHL gene are not only responsible for the inherited syndrome, they are also found in the tumors of most patients who have developed clear cell kidney cancers without a family history of the disease. In contrast, the gene was rarely mutated in the tumors of patients with other types of kidney cancer.

This seminal discovery paved the way for studies that tied VHL to a key oxygen-sensing pathway and revealed how a failure in the pathway promotes tumor growth. Researchers around the world used that knowledge to explore ways to block tumor growth.

As a result, the U.S. Food and Drug Administration has approved nine drugs that target the VHL pathway for the treatment of patients with advanced kidney cancer. Linehan and his colleagues and others have also gone on to link sixteen more genes to various forms of kidney cancer, offering insight into those diseases and hope for targeted treatments.

Twenty-five years after the VHL gene's discovery, Linehan is pleased to see drugs that target the VHL pathway having a real impact. He's quick to note, however, that his work is far from finished.

"We have a long way to go," he says. "There are remarkable responses, but we need to do a whole lot better to be able to cure the majority of patients with this disease." Linehan continues to see patients weekly, while he and his team investigate kidney cancer's causes and test new treatment strategies in clinical trials. "When I see patients in the clinic who have these cancers that have spread, I think, I don't care what it takes. We owe it to these people."

cancer.gov

4 Things Women Need to Know About Stroke

By Dr. Cheryl Bushnell, MD, MHS, Professor of Neurology, Vice Chair of Research, and Stroke Division Chief, Wake Forest Baptist Medical Center

Stroke happens to 1 in 5 women. In the United States, someone has a stroke every 40 seconds. This is unfortunate because most strokes are preventable.

The brain is complex, so not all strokes look alike, but symptoms can come on suddenly. Stroke is a serious health concern for women and can happen to anyone, at any age.

Here are four things every woman should know about stroke.

1 Women have unique risk factors for stroke:

Major risk factors for stroke, such as having high blood pressure, high cholesterol, and diabetes, can happen to anyone. But women have unique risk factors for stroke, including:

- Having problems during pregnancy, such as preeclampsia or high blood pressure. These complications can increase the risk of stroke for many years, even beyond childbearing years.
- Smoking cigarettes while taking combination birth control (birth control that has both estrogen and progesterone). Women 35 and older who smoke and use this type of birth control are at especially high risk
- Taking hormone replacement therapy that contains estrogen plus progesterone. Ask your doctor if you can safely take these medicines to ease menopause symptoms, such as hot flashes.
- Having migraines with aura, or migraines that start with visual symptoms before the headache.
- Having atrial fibrillation (Afib), a type of irregular heart beat that can cause blood clots to form in the heart. This is more common in women, especially in women older than 75. It is important to know if you have Afib so your doctor can give you medicine to prevent blood clots.

2 You can learn the common symptoms of stroke with the F.A.S.T. test:

- **F**ace: Is one side of the person's face drooping?
- **A**rm weakness: Is one arm weak or numb? Try lifting the person's arms to see if one drifts down or cannot be lifted.
- **S**peech: Is she having trouble speaking, such as slurring words, or is she not able to get the right words out?
- **T**ime: Call 911 right away if someone is experiencing any of these symptoms! Every minute counts when it comes to your brain.

Other common symptoms include numbness and tingling on one side of the body; vision loss or trouble seeing; severe dizziness, vertigo, or loss of balance; or sudden severe headache. Women are also more likely to have unique symptoms that can slow down or delay a stroke diagnosis, such as difficulty thinking straight or being excessively sleepy. When these symptoms happen, even when common stroke symptoms are also present, doctors and emergency providers might should consider the potential of stroke right away.

3 Acting quickly during a stroke improves chances of survival and making a full recovery.

F.A.S.T. is not just an acronym; it's also an important action: Act F.A.S.T. when a stroke happens because treatments need to happen right away. Inform your patients to call 911 if they think they are or someone near them is having a stroke. Advise them not go to sleep or wait to see if the symptoms improve, but to go to the hospital or call their doctor's office immediately. All of these actions can delay needed stroke treatment.

4 The best way to treat stroke is to prevent it from happening in the first place. Here's what can be done to lead a healthy life and prevent stroke:

- Maintain a healthy weight.
- Exercise for 30 minutes a day.
- Make healthy food choices most of the time. Learn more about healthy eating.
- Know your numbers, including blood pressure, blood sugar levels, and cholesterol levels. These numbers are clues about your risk of stroke. Talk to your doctor about your numbers and what they should be.
- Don't smoke. Your doctor can help you come up with a plan to quit.

womenshealth.gov

CPG

Brain-scan Guided Emergency Stroke Treatment Can Save More Lives

By Barbara I. McMakin

Advances in brain imaging can identify a greater number of stroke patients who can receive therapy later than previously believed, according to a new study. The results of the Endovascular Therapy Following Imaging Evaluation for the Ischemic Stroke (DEFUSE 3) trial, presented at the International Stroke Conference 2018 in Los Angeles and published on Jan. 24 in the New England Journal of Medicine, demonstrated that physically removing brain clots up to 16 hours after symptom onset in selected patients led to improved outcomes compared to standard medical therapy. The study was funded by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

"These striking results will have an immediate impact and save people from life-long disability or death," said Walter Koroshetz, MD, director NINDS. "I really cannot overstate the size of this effect. The study shows that one out of three stroke patients who present with at-risk brain tissue on their scans improve and some may walk out of the hospital saved from what would otherwise have been a devastating brain injury."

DEFUSE 3 was a large, multi-site study supported by NINDS' StrokeNet, which is a network of hospitals providing research infrastructure for multi-site clinical trials. This study was conducted at 38 centers across the United States and was led by Gregory W. Albers, MD, professor of neurology and neurological sciences at Stanford University School of Medicine, in California, and director of the Stanford Stroke Center. The study was ended early by the NIH on recommendation of the independent Data and Safety and Monitoring Board because of

Advances in brain imaging technology may help identify more patients who are eligible for stroke treatment. Image courtesy of Greg Albers, MD, Stanford University Medical Center

overwhelming evidence of benefit from the clot removal procedure.

Ischemic stroke occurs when a cerebral blood vessel becomes blocked, cutting off the delivery of oxygen and nutrients to brain tissue. Brain tissue in the immediate area of the blockage, known as the core, cannot typically be saved from dying, and it can enlarge over time. However, it has long been thought that the area surrounding the core (known as the ischemic penumbra) has the potential to be saved based on how quickly the blood flow can be restored. Over the past two decades, scientists have been working to develop brain scanning methods, called perfusion imaging, that could identify patients with brain tissue that can still be salvaged by removing the blockage. In perfusion imaging, a standard dye is injected and scanned for a few minutes as it passes through the brain.

Using an automated software known as RAPID to analyze perfusion MRI or CT scans, the DEFUSE 3 researchers identified patients thought to have salvageable tissue up to 16 hours after stroke onset. The participants were randomized to either receive endovascular thrombectomy plus standard medical therapy or medical therapy alone.

Endovascular thrombectomy, or the physical removal of the blockage, is currently approved for use up to six hours following onset of stroke symptoms. Dr. Albers and the DEFUSE 3 researchers discovered that this intervention can be effective up to 16 hours after symptoms begin in this select group of patients. The findings showed that patients in the thrombectomy group had substantially better outcomes 90 days after treatment compared to those in the control group. For example, 45 percent of the patients treated with the clot removal procedure achieved functional independence compared to 17 percent in the control group. In addition, thrombectomy was associated with improved survival. According to the results 14 percent of the treated group had died within 90 days of the study, compared to 26 percent in the control group.

"Although stroke is a medical emergency that should be treated as soon as possible, DEFUSE 3 opens the door to treatment even for some patients who wake up with a stroke or arrive at the hospital many hours after their initial symptoms," said Dr. Albers.

DEFUSE 3 builds on results from the two earlier DEFUSE studies as well as the industry-sponsored DAWN trial, which used perfusion imaging technology to identify patients most likely to benefit from interventions such as thrombectomy. Those studies suggested that the advanced brain imaging could identify which patients could benefit from restoring blood flow in an extended treatment window.

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CPG

Epilepsy Study Links Mossy Brain Cells to Seizures and Memory Loss

NIH-funded study in mice suggests loss of mossy cells plays a critical role in both

A small group of cells in the brain can have a big effect on seizures and memory in a mouse model of epilepsy. According to a new study in Science, loss of mossy cells may contribute to convulsive seizures in temporal lobe epilepsy (TLE) as well as memory problems often experienced by people with the disease. The study was funded by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

"The role of mossy cells in epilepsy has been debated for decades. This study reveals how critical these cells are in the disease, and the findings suggest that preventing loss of mossy cells or finding ways to activate them may be potential therapeutic targets," said Vicky Whittemore, PhD program director at NINDS.

Mossy cells, named for the dense moss-like protrusions that cover their surface, are located in the hippocampus, a brain area that is known to play key roles in memory. Loss of mossy cells is associated with TLE, but it is unknown what role that plays in the disease. Using state-of-the-art tools, Ivan Soltesz, PhD, professor of neurosurgery and neurosciences at Stanford University, Palo Alto, California, and his team were able to turn mossy cells on and off to track their effects in a mouse model of epilepsy.

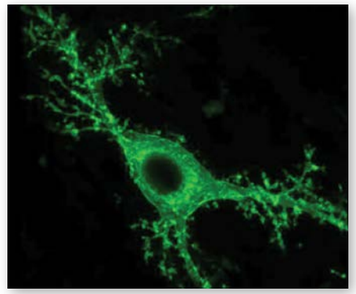
"This study would not have been possible without the rapid advancement of technology, thanks in part to the BRAIN Initiative, which has encouraged scientists to develop innovative instruments and new ways to look at the brain," said Dr. Soltesz. "It's remarkable that we can manipulate specific brain cells in the hippocampus of a mouse. Using 21st century tools brings us closer than ever to unlocking the mysteries behind this debilitating disease."

In TLE, many seizures, known as focal seizures, originate in one part of the brain and are evident on electroencephalography (EEG) scans that show the brain's electrical activity. These seizures can result in symptoms such as twitching or a strange taste or smell, and many people with TLE might not be aware that these symptoms are seizures. Sometimes, focal seizures can spread throughout the entire brain becoming generalized, resulting in involuntary muscle spasms, or convulsions, that affect the limbs and other parts of the body as well as loss of consciousness.

When Dr. Soltesz' group detected focal seizures on the mice's EEG scans, they turned mossy cells on or off to see whether they had any effect on the seizures. The researchers found that turning on the cells prevented the focal seizures from transitioning into convulsive ones. When the mossy cells were turned off, however, convulsive seizures were more likely to occur. Mossy cells had only a minor effect on the occurrence of focal seizures.

"This was the first time we were able to show specifically that mossy cell activity can control convulsive seizures," said Anh Bui, an MD, PhD student at the University of California-Irvine, and first author of the paper. "These mice were missing most of their mossy cells, yet we were able to see effects just by manipulating the small number of surviving cells."

People with TLE often experience temporary changes in thinking and long-term problems with memory. Dr. Soltesz and his colleagues looked at the role of mossy



Mystery of missing mossy cells may be solved. New findings in a study of mice suggest that a loss of mossy cells may contribute to seizures and memory problems in a form of epilepsy. Image courtesy of Ivan Soltesz, Ph.D., Stanford University.

cells in two specific types of memory: object recognition and spatial memory, which refers to identifying where objects are located and navigating around the environment. In these experiments, the mice were placed in a chamber with two identical items. The following day, one of the items was replaced with a different one (to test for object recognition) or moved to a different location (to test for spatial memory).

The epileptic mice had trouble with spatial memory tasks but their ability to recognize objects was unaffected. In addition, turning off mossy cells in healthy mice also led to problems with spatial memory in those animals. These findings suggest that a decrease in mossy cells may lead to convulsive seizures as well as memory deficits.

More research is needed to further understand the role of mossy cells in seizure progression as well as their effects early in the disease.

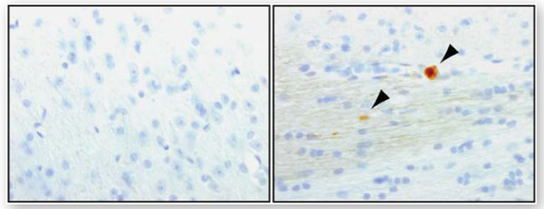
ninds.nih.gov

Scientists Find a Role for Parkinson's Gene in the Brain

By Carl P. Wonders, PhD

A new study published in the journal Neuron sheds light on the normal function of LRRK2, the most common genetic cause for late-onset Parkinson's disease. The study was supported by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

For more than 10 years, scientists have known that mutations in the LRRK2 gene can lead to Parkinson's disease, yet both its role in the disease and its normal function in the brain remain unclear. In a study in mice, researchers have now found that LRRK is necessary for the survival of dopamine-containing neurons in the brain, the cells most affected by Parkinson's. Importantly, this finding could alter the design of treatments against the disease.



Cell death in the absence of LRRK. In the region of the brain affected by Parkinson's disease, mice lacking LRRK (right) have an increase in cell death (brown; arrowheads) compared to normal mice (left).
Image courtesy of Shen lab

"Since its discovery, researchers have been trying to define LRRK2 function and how mutations may lead to Parkinson's disease," said Beth-Anne Sieber, Ph.D., program director at NINDS. "The findings in this paper emphasize the importance of understanding the normal role for genes associated with neurodegenerative disorders."

LRRK2 is found along with a closely related protein, LRRK1, in the brain. A mutation in LRRK2 alone can eventually produce Parkinson's disease symptoms and brain pathology in humans as they age. In mice, however, LRRK2 loss or mutation does not lead to the death of dopamine-producing neurons, possibly because LRRK1 plays a complementary or compensatory role during the relatively short, two-year mouse lifespan.

"Parkinson's-linked mutations such as LRRK2 have subtle effects that do not produce symptoms until late in life. Understanding the normal function of these types of genes will help us figure out what has gone wrong to cause disease," said Jie Shen, Ph.D., director of the NINDS Morris K. Udall Center of Excellence for Parkinson's Disease at Brigham and Women's Hospital and senior author of this study.

To better understand the roles of these related proteins in brain function using animal models, Shen and her colleagues created mice lacking both LRRK1 and LRRK2. They observed a loss of dopamine-containing neurons in areas of the brain consistent with PD beginning around 15 months of age. When the researchers looked at the affected brain cells more closely, they saw the buildup of a protein called α-synuclein, a hallmark of Parkinson's, and defects in pathways that clear cellular "garbage." At the same time, more dopamine-containing neurons also began to show signs of apoptosis, the cells' "self-destruct" mechanism.

"Our findings show that LRRK is critical for the survival of the populations of neurons affected by Parkinson's disease," said Dr. Shen.

While the deletion of both LRRK1 and LRRK2 did not affect overall brain size or cells in such areas of the brain as the cerebral cortex and cerebellum, the mice showed other significant effects such as a decrease in body weight and a lifespan of only 15 to 16 months. Thus, the scientists were unable to study other Parkinson's-related effects such as changes in behavior and movement nor were they able to conduct a long-term analysis of how LRRK's absence affects the brain.

Interestingly, the most common disease-linked mutation in LRRK2 is thought to make the protein more active. As a result, most efforts to develop a treatment against that mutation have focused on inhibiting LRRK2 activity.

"The fact that the absence of LRRK leads to the death of dopamine-containing neurons suggests that the use of inhibitory drugs as a treatment for Parkinson's disease might not be the best approach," said Dr. Shen.

Dr. Shen and her colleagues are now developing mice that have LRRK1 and 2 removed only in the dopamine-containing neurons of the brain. This specific deletion will allow the researchers to study longer-term and behavioral changes while avoiding the other consequences that lead to a shortened lifespan.

ninds.nih.gov

"Don't Ask, Don't Treat" Insomnia Treatment

By Gautam Ganguly, MD, FAASM

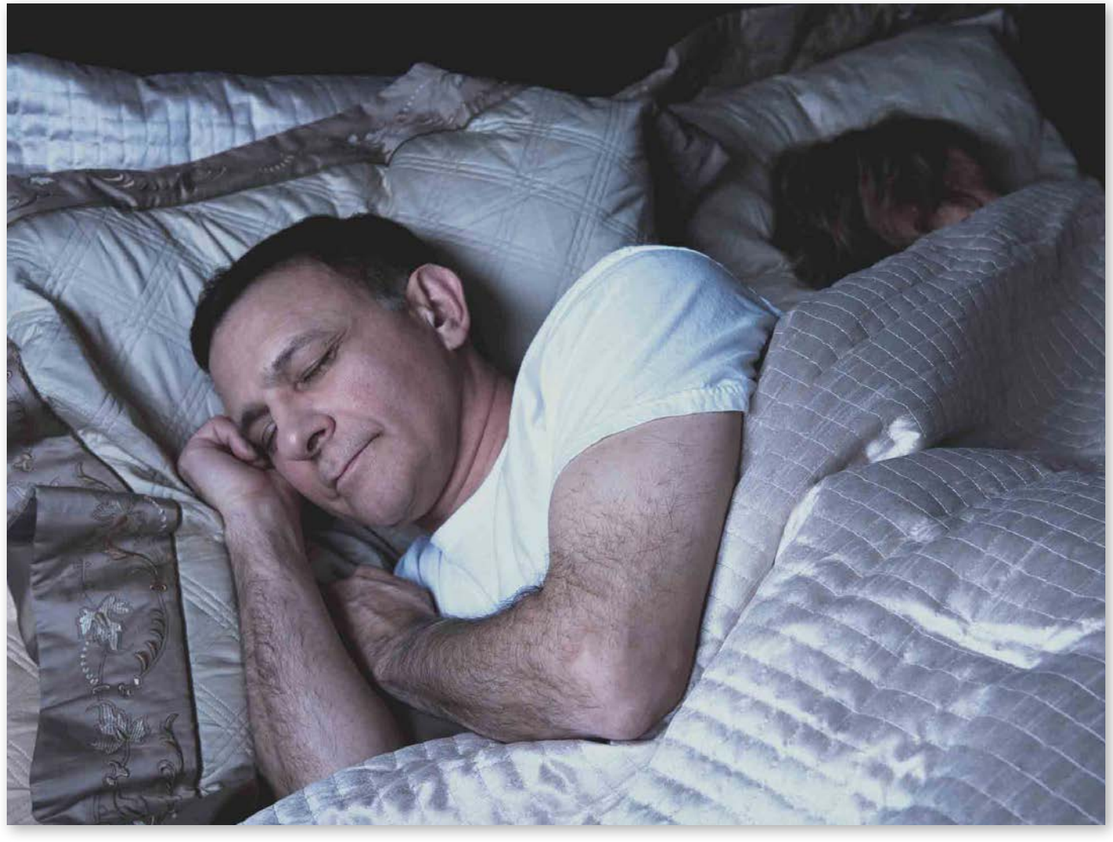
I read with great interest the article by Ulmer et al. along with the commentary by Grander and Chakravorty.[1,2] Surprisingly we observe a similar trend in treating insomnia among the community primary care physicians (PCPs). So, it raises a question of whether we as sleep physicians are doing enough to change the misperceptions of insomnia treatments among the PCPs.

The study highlights the tendency of Veterans Affairs PCPs to inadequately document insomnia. Can this be a reflection of their own perception about sleep?

Many physicians often are used to chronic sleep deprivation by virtue of their profession. So, are the PCP responses partly from their own belief of sleep being a "not so important issue"?

It was also obvious from PCP responses that they lack confidence in cognitive behavioral therapy for insomnia (CBT-I). Eligible patients were not referred for CBT-I despite 86% of the respondents being aware of CBT-I.

Was this only because of unavailability of CBT-I or an "out of sight, out of mind" phenomenon?



Army veteran Manuel "Al" Alcantara, right, and Vietnam veteran Jim Alderman share stories beside a duck pond after a day's therapy at the inpatient post-traumatic stress disorder clinic at Bay Pines Veterans Affairs Medical Center in Bay Pines, Fla., Oct. 29, 2015. DoD photo by EJ Hersom

Currently, PCPs are under severe time constraints for patient visits. They are being evaluated according to the value-based care they provide in controlling diabetes, hypertension, vaccinations, or cancer screening in their patient population.

Sleep disorders, including insomnia and sleep apnea, are underdiagnosed because it is not part of their value-based care. There is no incentive for a PCP to discuss sleep issues with their patients, especially when they believe they have limited treatment options. It only adds more time for each patient visit.

So, the sleep community needs to provide these PCPs with tools they can use in the electronic medical record to help with their workflow. One possibility is a pop-up reminder to use CBT-I when encounter forms show insomnia or pharmacotherapy for insomnia is being prescribed. This may increase the use of CBT-I by default. Also, major payors such as Medicare need to endorse CBT-I as the primary treatment for insomnia among its members and their PCPs.

Availability and affordability are the basic requirements for any treatment to be acceptable. Unfortunately, in addition to significant shortage for CBT-I therapists, there is confusion about CBT-I among payors, too. A patient often has to pay up-front for the treatment before getting reimbursed by Medicare.

These hassles make CBT-I less acceptable as a primary therapy for insomnia by the PCPs and their patients, forcing them to choose the next-best standard of care with medications or sleep hygiene. Until we provide our primary care colleagues with the tools to tackle some of these problems, we should not hope to see any difference in insomnia evaluation and treatment, and it will remain in the "don't ask, don't treat" category.

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IMPORTANT SAFETY INFORMATION

WARNING: HYPONATREMIA

See full prescribing information for complete boxed warning.

- **NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.**
- **NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia. See Important Safety Information below for full contraindications.**
- **Ensure serum sodium is normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor patients ≥65 years of age and those at increased risk of hyponatremia.**
- **If hyponatremia occurs, NOCTIVA may need to be discontinued.**

INDICATIONS AND USAGE

NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation of Use: Not studied in patients younger than 50 years of age.

CONTRAINDICATIONS

NOCTIVA is contraindicated in patients with the following conditions: hyponatremia or a history of hyponatremia, polydipsia, primary nocturnal enuresis, concomitant use with loop diuretics or systemic or inhaled glucocorticoids, estimated glomerular filtration rate <50 mL/min/1.73 m^2, syndrome of inappropriate antidiuretic hormone secretion (SIADH), during illnesses that can cause fluid or electrolyte imbalance, congestive heart failure (New York Heart Association Class II-IV), and uncontrolled hypertension.

WARNINGS AND PRECAUTIONS

- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

ADVERSE REACTIONS

Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension, back pain, epistaxis, bronchitis, and dizziness.

DRUG INTERACTIONS

Monitor serum sodium more frequently when NOCTIVA is concomitantly used with drugs that may cause water retention and increase the risk for hyponatremia.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use of NOCTIVA is not recommended.
- Pediatric: Do not use NOCTIVA for primary nocturnal enuresis in children.

To report SUSPECTED ADVERSE REACTIONS, contact Avadel at 1-877-638-4579 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

Please see full Brief Summary on the following pages.

References: 1. NOCTIVA [package insert]. Chesterfield, MO: Avadel Specialty Pharmaceuticals, LLC; 2017. **2.** US Food and Drug Administration. Orange Book Noctiva. https://www.acessdata.fda.gov/scripts/cder/ob/search_product.cfm. Accessed August 13, 2018. **3.** Data on file. Avadel Specialty Pharmaceuticals, LLC.

Avadel™

Avadel Specialty Pharmaceuticals, LLC

Noctiva™ (desmopressin acetate) Nasal Spray

NOCTIVA™ (desmopressin acetate) Nasal Spray
The following is a brief summary. Please consult Full Prescribing Information for complete details.

WARNING: HYPONATREMIA

- **NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.**
- **NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.**
- **Ensure serum sodium concentrations are normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia.**
- **If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued.**

INDICATIONS AND USAGE

NOCTIVA is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Nocturnal polyuria was defined in the NOCTIVA clinical trials as nighttime urine production exceeding one-third of the 24-hour urine production.

Before starting NOCTIVA:

- Evaluate the patient for possible causes for the nocturia, including excessive fluid intake prior to bedtime, and optimize the treatment of underlying conditions that may be contributing to the nocturia.
- Confirm the diagnosis of nocturnal polyuria with a 24-hour urine collection, if one has not been obtained previously.

Limitation of Use: NOCTIVA has not been studied in patients less than 50 years of age.

CONTRAINDICATIONS

NOCTIVA is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:

- Hyponatremia or a history of hyponatremia *[see Warnings and Precautions]*
- Polydipsia
- Primary nocturnal enuresis *[see Use in Specific Populations]*
- Concomitant use with loop diuretics *[see Warnings and Precautions]*
- Concomitant use with systemic or inhaled glucocorticoids *[see Warnings and Precautions, Drug Interactions]*
- Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 *[see Use in Specific Populations]*
- Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection

NOCTIVA is contraindicated in patients with the following conditions because fluid retention increases the risk of worsening the underlying condition:

- Congestive heart failure (New York Heart Association Class II to IV) *[see Warnings and Precautions]*
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

Risk of Hyponatremia: NOCTIVA can cause hyponatremia *[see Boxed Warning and Adverse Reactions]*. Severe hyponatremia can be life-threatening if it is not promptly diagnosed and treated, leading to seizures, coma, respiratory arrest, or death.

NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as those with excessive fluid intake, those who have illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids *[see Boxed Warning, Contraindications, and Drug Interactions]*.

Before starting or resuming NOCTIVA, ensure that the serum sodium concentration is normal. Consider the 0.83 mcg dose as the starting dose for patients who may be at risk for hyponatremia.

When NOCTIVA is administered, fluid intake in the evening and nighttime hours should be moderated to decrease the risk of hyponatremia. Monitor the serum sodium concentration within 7 days and approximately 1 month of initiating NOCTIVA or increasing the dose, and periodically thereafter. The frequency of serum sodium monitoring should be based on the patient's risk for hyponatremia. For example, more frequent monitoring is recommended for patients 65 years of age or older or those on concomitant medications that can increase the risk of hyponatremia, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine, and thiazide diuretics *[see Drug Interactions]*.

If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia.

Fluid Retention: NOCTIVA can cause fluid retention, which can worsen underlying conditions that are susceptible to volume status. Therefore, NOCTIVA is contraindicated in patients with New York Heart Association Class II to IV congestive heart failure or uncontrolled hypertension *[see Contraindications]*. In addition, NOCTIVA is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with New York Heart Association Class I congestive heart failure.

Concurrent Nasal Conditions: Discontinue NOCTIVA in patients with concurrent nasal conditions that may increase systemic absorption of NOCTIVA (e.g., atrophy of nasal mucosa, and acute or chronic rhinitis), because the increased absorption may increase the risk of hyponatremia. NOCTIVA can be resumed when these conditions resolve.

ADVERSE REACTIONS

The following adverse reaction is described elsewhere in the labeling:

- Hyponatremia *[see Boxed Warning and Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized, double-blind, placebo-controlled, multicenter trials conducted in adults 50 years of age and older evaluated the efficacy and safety of NOCTIVA nasal spray compared to placebo. At baseline, 1045 patients treated with NOCTIVA 0.83 mcg or 1.66 mcg, or placebo, had nocturia due to nocturnal polyuria, wakening at least 2 times per night to urinate. Nocturnal polyuria was defined as nighttime urine production exceeding one-third of the 24-hour urine production. The mean age of the patients studied with nocturia due to nocturnal polyuria was 67 years with 42% between 50 and 64 years of age, and 58% aged 65 years and older. Fifty-seven percent were men and 43% were women. Caucasians comprised 79%, Blacks 12%, Hispanics 6%, and Asians 2% of the trial population.

During these trials, serious adverse reactions were reported in 2%, 2%, and 3% of patients with nocturia due to nocturnal polyuria treated with NOCTIVA 0.83 mcg, NOCTIVA 1.66 mcg, and placebo, respectively. There was one case of hyponatremia in the 1.66 mcg group and one case in the placebo group classified as serious adverse reactions.

Adverse Reactions Leading to Discontinuation: Among patients with nocturia due to nocturnal polyuria, the discontinuation rate due to adverse reactions was 4.0% with NOCTIVA 0.83 mcg, 4.4% with NOCTIVA 1.66 mcg, and 2.3% with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in patients with nocturia due to nocturnal polyuria.

Table 1: Most Common Adverse Reactions (≥2 Incidences) Leading to Discontinuation in Patients With Nocturia Due to Nocturnal Polyuria in 2 Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	NOCTIVA 1.66 mcg (n=341)	NOCTIVA 0.83 mcg (n=354)	Placebo (n=349)
Hyponatremia/Blood Sodium Decreased	4 (1.2%)	3 (0.9%)	1 (0.3%)
Nasal Discomfort	2 (0.6%)	0	3 (0.9%)
Nasal Congestion	2 (0.6%)	0	0
Atrial Fibrillation	2 (0.6%)	0	0
Dizziness	0	2 (0.6%)	1 (0.3%)
Dysuria	1 (0.3%)	2 (0.6%)	0

Most Common Adverse Reactions: Table 2 summarizes the most common adverse reactions reported by patients with nocturia due to nocturnal polyuria. This table shows adverse reactions reported in at least 2% of patients treated with NOCTIVA and at a higher incidence with the 1.66 mcg dose than with placebo.

Table 2: Common Adverse Reactions (Reported by ≥2% of NOCTIVA-Treated Patients and at a Higher Incidence With the 1.66 mcg Dose Than With Placebo) in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Adverse Reactions	NOCTIVA 1.66 mcg (n=341)	NOCTIVA 0.83 mcg (n=354)	Placebo (n=349)
Nasal Discomfort	20 (5.9%)	12 (3.4%)	17 (4.9%)
Nasopharyngitis	13 (3.8%)	8 (2.3%)	10 (2.9%)
Nasal Congestion	10 (2.9%)	5 (1.4%)	5 (1.4%)
Sneezing	9 (2.6%)	8 (2.3%)	5 (1.4%)
Hypertension/Blood Pressure Increased	9 (2.6%)	6 (1.7%)	4 (1.1%)
Back Pain	8 (2.3%)	4 (1.1%)	3 (0.9%)
Epistaxis	7 (2.1%)	7 (2.0%)	4 (1.1%)
Bronchitis	7 (2.1%)	3 (0.8%)	3 (0.9%)
Dizziness	6 (1.8%)	7 (2.0%)	5 (1.4%)

No overall changes were observed in the safety profile during the open-label, uncontrolled extension trial with up to 126 weeks of follow-up.

Hyponatremia: Table 3 shows the incidence of serum sodium concentrations below the normal range reported in the 2 placebo-controlled trials.

Table 3: Hyponatremia in 2, Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Serum Sodium Concentrations (mmol/L)	NOCTIVA 1.66 mcg (n=341)	NOCTIVA 0.83 mcg (n=354)	Placebo (n=349)
130-134	42 (12.3%)	33 (9.3%)	18 (5.2%)
126-129	7 (2.1%)	8 (2.3%)	0
≤125	5 (1.5%)	0	1 (0.3%)

Of the 5 patients on NOCTIVA 1.66 mcg with serum sodium ≤125 mmol/L, all were 65 years of age or older. Four were men. The onset of the hyponatremia ranged from 6 days to 12 weeks after the start of dosing. Four of these patients were taking a concomitant systemic or inhaled glucocorticoid and 3 were taking an NSAID.

Sex: The incidence of hyponatremia with NOCTIVA was similar in men and women.

Age: Patients 65 years of age and older treated with NOCTIVA had a higher incidence of hyponatremia compared to those younger than 65 years of age (see Table 4).

Table 4: Hyponatremia, Based on Age, in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Serum Sodium Concentrations (mmol/L)	NOCTIVA 1.66 mcg <65 years (n=146)	NOCTIVA 1.66 mcg ≥65 years (n=195)	NOCTIVA 0.83 mcg <65 years (n=148)	NOCTIVA 0.83 mcg ≥65 years (n=206)	Placebo <65 years (n=144)	Placebo ≥65 years (n=205)
130-134	14 (9.6%)	28 (14.4%)	8 (5.4%)	25 (12.1%)	7 (4.9%)	11 (5.4%)
126-129	0	7 (3.6%)	2 (1.4%)	6 (2.9%)	0	0
≤125	0	5 (2.6%)	0	0	0	1 (0.5%)

DRUG INTERACTIONS

No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions between NOCTIVA and other medications.

Drugs That May Cause Severe Hyponatremia: Concomitant use of NOCTIVA and loop diuretics or systemic or inhaled glucocorticoids is contraindicated because of the risk of severe hyponatremia *[see Boxed Warning, Contraindications, and Warnings and Precautions]*. NOCTIVA can be started or resumed 3 days or 5 half-lives after the glucocorticoid is discontinued, whichever is longer.

Drugs That May Cause Water Retention: Monitor serum sodium more frequently in patients taking NOCTIVA concomitantly with medications that may cause water retention and increase the risk for hyponatremia (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, opioid analgesics, NSAIDs, lamotrigine, and carbamazepine) *[see Warnings and Precautions]*.

Drugs Administered Intranasally: The drug interaction potential between NOCTIVA and other intranasally administered drugs has not been studied. NOCTIVA is not recommended for use in patients who require treatment with other drugs via the nasal route.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: There are no data with NOCTIVA use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of desmopressin during organogenesis to pregnant rats and rabbits at doses approximately <1 and 31 times, respectively, the maximum recommended human dose based on nasal surface area (see Data).

NOCTIVA is not recommended for the treatment of nocturia in pregnant women. Nocturia is usually related to normal physiologic changes during pregnancy that do not require treatment with NOCTIVA.

In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Desmopressin acetate did not cause fetal harm in teratology studies in rats and rabbits at doses from 0.05 to 10 mcg/kg/day, which is approximately <1 times (rat) and 31 times (rabbit) the maximum recommended human dose based on nasal surface area.

Lactation: Desmopressin is present in small amounts in human milk and is poorly absorbed orally by an infant. There is no information on the effects of desmopressin on the breastfed infant or on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for NOCTIVA and any potential adverse effects on the breastfed infant from NOCTIVA or from the underlying maternal condition.

Pediatric Use: NOCTIVA is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal formulations of desmopressin. Studies of NOCTIVA have not been conducted in pediatric patients *[see Contraindications]*.

Geriatric Use: Patients 65 years and older treated with NOCTIVA had a higher incidence of hyponatremia compared to patients less than 65 years old treated with NOCTIVA *[see Warnings and Precautions, and Adverse Reactions]*.

Renal Impairment: Desmopressin is mainly excreted in the urine. The area under the concentration-time curve (AUC) and terminal half-life of desmopressin in renally impaired patients with an eGFR below 50 mL/min/1.73 m^2 is 3- to 4-fold greater than in patients with an eGFR above 50 mL/min/1.73 m^2. Therefore, NOCTIVA is contraindicated in patients who have renal impairment with an eGFR below 50 mL/min/1.73 m^2 *[see Contraindications]*.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of desmopressin has not been studied.

OVERDOSAGE

Signs of overdose may include effects from hyponatremia such as seizure, altered mental status, cardiac arrhythmias, and worsening edema. Other signs of overdose may include oliguria and rapid weight gain due to fluid retention *[see Warnings and Precautions]*. In case of overdosage, NOCTIVA should be discontinued immediately, serum sodium should be assessed, and appropriate medical treatment initiated.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hyponatremia: Inform patients that NOCTIVA can cause hyponatremia, which may be life-threatening. Inform patients to moderate fluid intake in the evening and nighttime hours, to monitor for symptoms of hyponatremia (such as headache, nausea or vomiting, restlessness, fatigue, drowsiness, dizziness, muscle cramping, or altered mental status), to undergo recommended serum sodium measurements, to inform their health care provider about new medications, and to stop NOCTIVA during illnesses that can cause fluid or electrolyte imbalance *[see Boxed Warning, Dosage and Administration, Contraindications, and Warnings and Precautions]*.

Nasal Conditions: Inform patients to discontinue NOCTIVA if nasal conditions occur that may increase systemic absorption of NOCTIVA (e.g., atrophy of nasal mucosa, and acute or chronic rhinitis). NOCTIVA can be resumed when these conditions resolve *[see Warnings and Precautions]*.

Priming and Dosing: Instruct patients to prime NOCTIVA before using it for the first time by pumping 5 sprays into the air away from the face and to re-prime it by pumping 2 sprays into the air if the bottle has not been used in more than 3 days. Instruct patients not to administer 2 sprays of the 0.83 mcg dose.

Manufactured for:
Avadel Specialty Pharmaceuticals, LLC
Chesterfield, MO 63005

Rev 03/2018 [Ref 12/2017]

PM-US-NTV-0164-0.4

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Nursing at the IHS Hospital Where She was Born

By Candace Lee, Assistant Chief Nursing Officer, Ambulatory Care, Phoenix Indian Medical Center

The Phoenix Indian Medical Center is where I was always meant to be. I was born in this hospital, and I've always felt a connection to it. My grandmother was a Pima native, and my grandfather was African-American. I'm enrolled in the Gila River Indian Community Tribe.

I'm proud of my heritage and I know I can celebrate it here.

When I was little, I wanted to be a doctor. But I saw how patients really relate to their nurses, so I went for nursing instead. I always felt I would work here. When I graduated, they couldn't take me right away. I took a job somewhere else, but it felt empty, without mission or purpose. Finally I got the call to re-apply and I've been here ever since. I've been here a little over 12 years. It feels like home. You're part of a community here.

I'm married with a little girl, and I love family time. In my job, work-life balance is strongly supported. We practice relationship-based care, which means we take care of ourselves, our colleagues and our patients. I've gotten to know many patients and their families. We are here for them their whole lives. You don't know them just by their health record number, you really actually get to know them.

And it's also about recognizing the importance of family in the Native American culture, so it's not just about taking care of that patient, it's about taking care of their family, too. We're all interconnected because our patients are sometimes our families, so it's really about taking care of the whole community.

At this hospital, every unit has an action plan, and we strive to reach our goals and to fix any problems. In primary nursing, we take ownership of each patient and their progress. I was part of a multi-disciplinary team that won a 2015 HHS Innovates award for our POSH initiative — Peri-Operative Surgical Home program — to ensure that care is patient-centered and tailored to the needs of individual surgical patients.

My early home life was turbulent, which was one of the things that made me want to become a nurse and care for others. I love that feeling of having the power to help.

I've had many opportunities at the Phoenix Indian Medical Center to expand my nursing and leadership capabilities. I'm now working on my master's in nursing, which I hope to complete next year.

Working for the Indian Health Service is not about a pay check. I do this because it's my calling. It's not just a job, it's a way of being.

I'm Candace Lee and I'm a nurse for the Indian Health Service. And I am HHS.

Candace is one of more than 79,000 people who make HHS run every day.

hhs.gov

NIH Study Finds Probiotic Bacillus Eliminates Staphylococcus Bacteria

Additional studies of common supplement planned

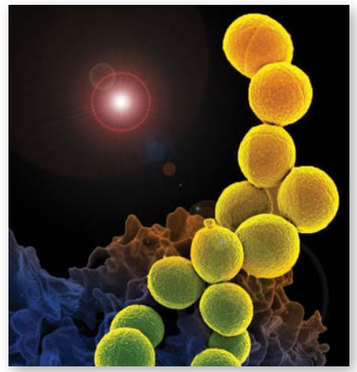
A new study from National Institutes of Health scientists and their Thai colleagues shows that a "good" bacterium commonly found in probiotic digestive supplements helps eliminate Staphylococcus aureus, a type of bacteria that can cause serious antibiotic-resistant infections. The researchers, led by scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID), unexpectedly found that Bacillus bacteria prevented S. aureus bacteria from growing in the gut and nose of healthy individuals. Then, using a mouse study model, they identified exactly how that happens. Researchers from Mahidol University and Rajamangala University of Technology in Thailand collaborated on the project.

"Probiotics frequently are recommended as dietary supplements to improve digestive health," said NIAID Director Anthony S. Fauci, MD. "This is one of the first studies to describe precisely how they may work to provide health benefits. The possibility that oral Bacillus might be an effective alternative to antibiotic treatment for some conditions is scientifically intriguing and definitely worthy of further exploration."

Staphylococcus infections cause tens of thousands of deaths worldwide each year. Methicillin-resistant Staphylococcus aureus, or MRSA, is familiar to many people as a cause of serious disease. Less well known is that S. aureus often can live in the nose or gut without causing any harm. However, if the skin barrier is broken, or the immune system compromised, these colonizing bacteria can cause serious infections.

One strategy to prevent Staph infections is to eliminate S. aureus colonization. However, some decolonization strategies are controversial because they require considerable amounts of topical antibiotics and have limited success, partly because they target only the nose and bacteria quickly recolonized from the gut.

The scientists recruited 200 volunteers in rural Thailand for the study. This population, they speculated, would not be as affected by food sterilization or antibiotics as people in highly developed urban areas. The scientists first analyzed fecal samples from each of the study participants for bacteria correlated with the absence of S. aureus. They found 101 samples positive for Bacillus, primarily B. subtilis — the type found mixed with other bacteria in many probiotic products. Bacillus bacteria form spores that can survive harsh environments and commonly are ingested naturally with vegetables, allowing them to temporarily grow in the intestine. The scientists then sampled the same 200 people for S. aureus in the gut (25 positive) and nose (26 positive). Strikingly, they found no S. aureus in any of the samples where Bacillus were present.



Colorized scanning electron micrograph of a white blood cell eating an antibiotic resistant strain of Staphylococcus aureus bacteria, commonly known as MRSA. Photo Credit: NIH

In mouse studies, the scientists discovered an S. aureus sensing system that must function for the bacteria to grow in the gut. Intriguingly, all of the more than 100 Bacillus isolates they had recovered from the human feces efficiently inhibited that system.

Using chromatography and mass spectrometry techniques, the scientists identified fengycins, a specific class of lipopeptides — molecules that are part peptide and part lipid—as the specific Bacillus substance that inhibited the S. aureus sensing system. Additional tests showed that fengycins had the same effect on several different strains of S. aureus — including high-risk USA300 MRSA which causes most community-associated MRSA infections in the United States and is an increasingly common cause of healthcare-associated MRSA infections.

To further validate their findings, the scientists colonized the gut of mice with S. aureus and fed them B. subtilis spores to mimic probiotic intake. Probiotic Bacillus given every two days eliminated S. aureus in the guts of the mice. The same test using Bacillus where fengycin production had been removed had no effect, and S. aureus grew as expected.

The NIAID and Thai scientists next plan to test whether a probiotic product that contains only B. subtilis can eliminate S. aureus in people. They plan to enroll more Thai volunteers for the project. Michael Otto, PhD, the NIAID lead investigator, says, "Ultimately, we hope to determine if a simple probiotic regimen can be used to reduce MRSA infection rates in hospitals."

nih.gov

Spotlight on Women's Health: An Interview About Thyroid Cancer

One woman shares her story about finding out she had papillary thyroid cancer, the most common of type, when she was only 19. This is her story from diagnosis to treatment, to being cancer-free.

Were you experiencing any symptoms?

No, I had not experienced any symptoms prior to my diagnosis.

How was it discovered?

The lump (tumor) on my thyroid was discovered by my very thorough nurse practitioner. Similar to the way a gynecologist typically checks your breasts for lumps, this nurse practitioner also routinely checked for lumps throughout my neck area. I am so glad she did! The lump was not large, but she still referred me to another doctor to have it checked out — just in case.

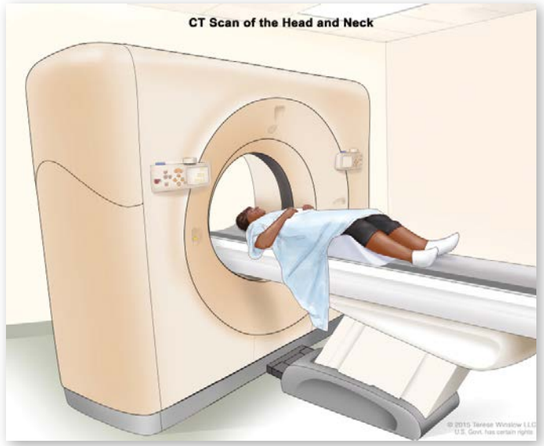
Physician examination of patient

Do you remember how you felt when you got your diagnosis?

I was confused and shocked! Even though I had gone through several tests before the diagnosis, there was still a part of me that thought it wouldn't be cancer. It didn't make sense to me. I was young and healthy, and I had no symptoms. But sometimes that's how thyroid cancer works.

What was your treatment like?

Treatment for the cancer involved a complete removal of my thyroid, along with the removal of several of my parathyroid glands and lymph nodes where the cancer had spread. After the surgery, I spent many months preparing for radioactive iodine treatment by eating a specialized diet that limited my iodine



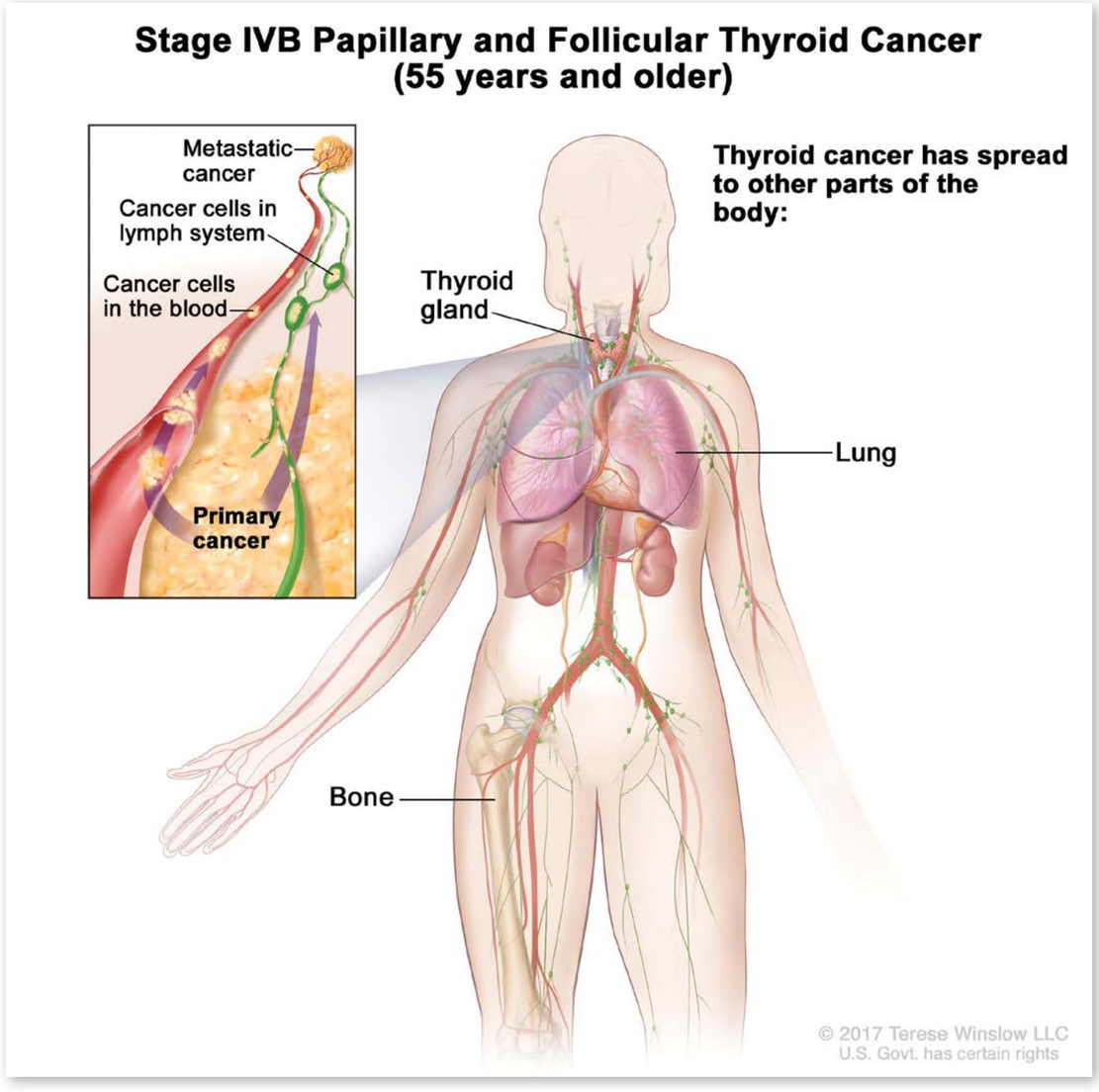
Computed tomography (CT) scan of the head and neck. The patient lies on a table that slides through the CT scanner, which takes x-ray pictures of the inside of the head and neck

intake. (It's in a lot of processed foods.) I had to do this so that my radioactive iodine treatment would be as effective as possible. I was fortunate to have excellent doctors that supported my wish to stay in school during this time, so I was able to work out a treatment plan with them that allowed me to continue my studies at my university and return home on a regular basis for checkups.

During my summer break, I checked into the hospital for several days for radioactive iodine treatment (radiation). This involved taking pills with radioactive iodine and then staying isolated in a hospital room until I had removed most of the radiation from my system. Any remaining thyroid cancer cells would have immediately taken up the radioactive iodine, effectively destroying those cells. I had to drink lots of water and take showers every couple of hours to move the remaining radioactive iodine out of my system as quickly as possible.

Do you need routine care now or special medications?

Since I no longer have a thyroid, I have to take thyroid medication daily in order to provide my body with the hormones it needs to survive. I also see an endocrinologist at least once a



year to check my thyroid hormone levels and make adjustments to my medication as needed.

How many years have you been cancer-free, and how does it feel?

I have been officially cancer-free for five years now, and it feels great!

How has this experience, especially at such a young age, altered your life?

Having been diagnosed with thyroid cancer at a young age has made me extremely grateful for the excellent medical care I have access to. I'm also more diligent about seeing doctors.

What would you say to other women who may have recently learned they have thyroid cancer?

Find a highly rated medical team that you trust, do your own research so that you understand your diagnosis and treatment options, and surround yourself with supportive friends and family.

womenshealth.gov

Don't Die of Embarrassment. Get Screened for Colon Cancer

By Judy Sarasohn, HHS Public Affairs

For National Colorectal Cancer Awareness Month, the author gets over her embarrassment to talk about her colonoscopy and the importance of screening.

I'm a relatively modest person. I don't go in for cleavage, but I also don't mind having a male doctor, and if you ask me a personal question, I'll answer it. That's why I was surprised recently for feeling embarrassed at telling my colleagues that I was taking the day off to get a colonoscopy.

A colonoscopy is one of the best lines of defense against colorectal cancer — cancer of the colon or rectum, and the second leading cause of death from cancers that affect both men and women (lung cancer is number one). The tragedy is that more than 50,000 Americans die every year from a disease that's highly preventable with screening. There are other screening options, and you should discuss the most appropriate course with your doctor.

Through a colonoscopy, doctors can search for and remove any precancerous polyps. The screening can also find cancerous growths early, when treatment can be very effective.

Yet too many people forgo screening because the parts of our body involved in a colonoscopy are generally taboo in polite conversation. And, they hear, the prep for cleaning out the colon for the screening is terrible.

After her husband, Jay Monahan, died of colon cancer, TV journalist Katie Couric underwent a colonoscopy on live television. She said no one should die of embarrassment.

I'm not going to do a full Katie Couric, but in observance of National Colorectal Cancer Awareness Month in March, I will work through my embarrassment to talk about my experience in the hopes that I can convince others to get screened.

I should have had my first colonoscopy long ago. My mother was diagnosed 20 years ago with colon cancer after a routine screening — like many people, she had no symptoms. Because the cancer was caught early, she fortunately never had another problem with it. She urged me to get screened. My primary doctors over the years urged me. Friends urged me.

But I couldn't do it. Too distasteful a thought. And in earlier years, the mixture you had to drink to clean out your system in preparation for the screening was too foul.

Recently, however, my colleague Gloria wouldn't let go of the subject, and, as it turned out, my husband's new primary doctor was married to a specialist at a local hospital. I gave in and met with him to go over my medical history and the logistics — and see if I was comfortable with him. I was sent home with easy-to-understand instructions to prepare.

Different doctors recommend different preps, but this is what mine recommended: I had to eat a bland, colorless diet for the week before the screening. Red Jell-O may seem bland, but the color causes problems for the doctor to clearly see the insides of the colon. The day before the procedure, I had to go on a clear liquid diet the entire day.

The prep also called for 64 ounces of Gatorade that I had to mix with a bottle of MiraLax, a powdered laxative, and drink the day and hours before the procedure. It wasn't difficult to drink, although because of the schedule for drinking and the early screening appointment, I had to get up at 4 a.m. to finish the last 32 ounces.

With the drink and the laxative pills that I had to take, I wanted to be near my bathroom for my frequent visits, but the experience wasn't bad.

What I greatly appreciated was that the doctors, nurses and technicians were all matter-of-fact and professionally pleasant. I was treated with respect and appropriate modesty.

I did not stay awake like Katie while my insides were scoped. There was no pain or discomfort during or after the procedure, although I did feel a bit unsteady after waking up. My husband, who had been waiting for me (the hospital won't allow you to leave on your own), took me out for sushi afterward.

About a week later, I received a letter from my doctor saying that he had removed some polyps during the procedure and that they were benign, confirming what he said he thought was the case when I woke up. He recommended a repeat colonoscopy in three years.

The Centers for Disease Control and Prevention recommends that if you're aged 50 to 75, get screened regularly. If you're older, consult with your doctor about whether you should get screened.

According to the CDC, some symptoms may include blood in or on the stool; stomach pains that don't go away; and losing weight for an unknown reason.

CDC notes that precancerous polyps and early stage colorectal cancers don't always cause symptoms, so don't wait to feel sick before making that appointment. Also, most colorectal cancers are not related to family history, so you're not home free because the cancer hasn't shown up in relatives.

You can get more information from the CDC's Screen for Life campaign, which partners with state and tribal health departments across the U.S. to raise awareness about the benefits of screening.

I was fortunate, and I understand that some people don't have as easy an experience. But it's important that no one let embarrassment get in the way of going for a potentially lifesaving examination.

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Incidence and Mortality

Estimated new cases and deaths from colon cancer in the United States in 2018:

- New cases: 97,220 (colon cancer only).
- Deaths: 50,630 (colon and rectal cancers combined).

Risk Factors

Increasing age is the most important risk factor for most cancers. Other risk factors for colorectal cancer include the following:

- Family history of colorectal cancer in a first-degree relative.
- Personal history of colorectal adenomas, colorectal cancer, or ovarian cancer.
- Hereditary conditions, including familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).
- Personal history of long-standing chronic ulcerative colitis or Crohn colitis.
- Excessive alcohol use.
- Cigarette smoking.
- Race/ethnicity: African American.
- Obesity.

Screening

Because of the frequency of the disease, ability to identify high-risk groups, slow growth of primary lesions, better survival of patients with early-stage lesions, and relative simplicity and accuracy of screening tests, screening for colon cancer should be a part of routine care for all adults aged 50 years and older, especially for those with first-degree relatives with colorectal cancer.

Prognostic Factors

The prognosis of patients with colon cancer is clearly related to the following:

- The degree of penetration of the tumor through the bowel wall.
- The presence or absence of nodal involvement.
- The presence or absence of distant metastases.

These three characteristics form the basis for all staging systems developed for this disease.

Other prognostic factors include the following:

- Bowel obstruction and bowel perforation are indicators of poor prognosis.[13]
- Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance.

Follow-up and Survivorship

Limited data and no level 1 evidence are available to guide patients and physicians about surveillance and management of patients after surgical resection and adjuvant therapy. The American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend specific surveillance and follow-up strategies.

Following treatment of colon cancer, periodic evaluations may lead to the earlier identification and management of recurrent disease.[33-36] The impact of such monitoring on overall mortality of patients with recurrent colon cancer, however, is limited by the relatively small proportion of patients in whom localized, potentially curable metastases are found. To date, no large-scale randomized trials have documented an OS benefit for standard, postoperative monitoring programs.

CEA is a serum glycoprotein frequently used in the management of patients with colon cancer. A review of the use of this tumor marker suggests the following:

- A CEA level is not a valuable screening test for colorectal cancer because of the large numbers of false-positive and false-negative reports.
- Postoperative CEA testing should be restricted to patients who would be candidates for resection of liver or lung metastases.
- Routine use of CEA levels alone for monitoring response to treatment should not be recommended.

The optimal regimen and frequency of follow-up examinations are not well defined because the impact on patient survival is not clear and the quality of data is poor.

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Improving Cancer Control in Rural Communities

By Robert T. Croyle, PhD, Director of the National Cancer Institute's Division of Cancer Control and Population Sciences

The decrease in cancer death rates in the United States has been uplifting news for the nation. A point of frustration, however, has been the continued ethnic/racial and socioeconomic disparities in cancer outcomes.

Two new studies are putting a spotlight on disparities that have received less attention: those in rural communities across the country. The studies — one by NCI researchers (on which I'm a co-author) and one led by researchers from the Centers for Disease Control and Prevention — found that cancer death rates are higher in rural areas than in urban areas.

The CDC study also showed that, although cancer deaths rates are decreasing in rural areas, they are doing so more slowly than they are in urban areas.

Rural health disparities are not a new issue for NCI. In an interview for Cancer Currents last year, in fact, I discussed cancer disparities in rural communities across the country, and some of our early efforts toward revisiting this long-standing public health challenge.

What I did not and could not predict at the time, however, was the impact the recent presidential election would have on the visibility of rural America in the national debate about our economy, the future of the middle class, and the role of poverty and geography in access to quality health care.

Cancer in Rural America: An Ongoing Dialogue

The cancer community has long been part of the dialogue about cancer in rural America.

NCI-funded researchers in Kentucky, Ohio, and West Virginia, for example, have conducted seminal research on cancer control in Appalachia, with signature efforts in cancer surveillance, colorectal cancer screening, and more recently, HPV vaccination.

The increased attention toward rural health has been driven not only by politics but also by important advances in population health research, including the availability of more granular data that has allowed scientists to describe disease patterns in regions of the United States at a more localized level, and the publication and dissemination of compelling work in health geography (e.g., the University of Wisconsin's County Health Rankings and Roadmaps exit disclaimer icon and CDC's MMWR Rural Health Series).

In particular, this research has effectively used data visualizations, such as maps, to powerfully highlight the stark differences in disease trends between urban and rural areas, further highlighting the need for additional studies that can identify the factors that contribute to these trends.

Reaching Out to the Community

To inform NCI's efforts to better address cancer disparities in rural communities, the institute has been busy consulting a wide variety of experts and analyzing the research evidence on rural cancer control.

These efforts will dovetail with work on rural health already underway by other federal agencies, including the Health Resources and Services Administration's Federal Office of Rural Health Policy, the Centers for Medicare and Medicaid Services' Rural Health Council, and the CDC's recently launched rural health initiative.

At the recent 5th Annual Public–Private Collaborations in Rural Health Meeting exit disclaimer icon, participants discussed challenges in many areas — including health reform (especially Medicaid), rural hospital closures, and the hollowing out of local public health infrastructure — and shared lessons learned from a wide variety of research projects and programs.

An important conclusion that emerged from this meeting is that NCI can respond to the needs of government agencies and nonprofit partners working on rural health by supporting implementation science that informs the allocation of precious resources at the local level.

For instance, during this meeting, telehealth was often cited as a tool that can help to solve some of these disparities. Unfortunately, the evidence base on how best to scale-up and implement telehealth solutions is incomplete.

Clearly, we and our colleagues in the cancer community need to make better use of the wealth of experience and knowledge within these organizations, and we plan to do just that.

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Study Shows Experimental Screening Test Can Detect Endometrial and Ovarian Cancers

By NCI Staff

Researchers have shown that an experimental screening test can detect some endometrial and ovarian cancers at their early, more treatable stages. The test, called PapSEEK, is a type of liquid biopsy that identifies cancer-related alterations in DNA obtained from fluids collected during a routine Pap test.

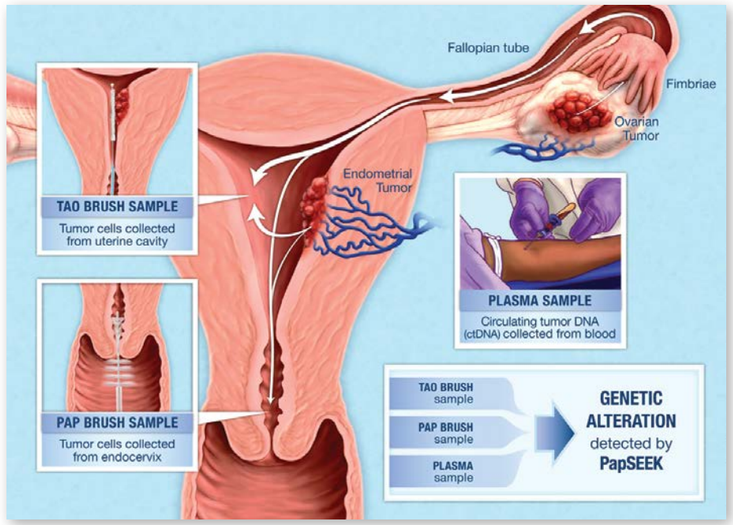
In the NCI-funded study, which used Pap test samples from women already diagnosed with cancer, PapSEEK correctly identified most women with endometrial cancer and one-third of women with ovarian cancer. The test's ability to accurately identify cancer (its sensitivity) improved when the researchers also tested DNA collected from blood and other tissues.

Sudhir Srivastava, PhD, MPH, of NCI's Division of Cancer Prevention, called the findings "a good start" for developing an effective screening test for early-stage endometrial and ovarian cancer. "This lays the foundation for future studies," added Dr. Srivastava, who was not involved in the study.

The retrospective study was published March 21 in Science Translational Medicine. Additional prospective studies are needed to determine whether PapSEEK can correctly identify women with cancer who have not yet been diagnosed, the investigators noted.

Screening for Ovarian and Endometrial Cancers

For many years, researchers have strived to develop a feasible and reliable way to detect early-stage endometrial and ovarian cancers in women who do not have any symptoms. To date, there is



PapSEEK detects genetic alterations in DNA that ovarian and endometrial tumors have shed into the uterus, cervix, and blood plasma. Photo Credit: Sidney Kimmel Comprehensive Cancer Center, John Hopkins University

no clinically validated biomarker for either cancer type that can be detected noninvasively.

But in an earlier study, Nickolas Papadopoulos, PhD, of Johns Hopkins University School of Medicine, and his colleagues found that they could detect trace amounts of DNA from endometrial and ovarian cancers in Pap test samples. For a Pap test, an instrument called a Pap brush is used to scrape the surface of the cervix to collect a sample of cells and DNA. While most of this DNA comes from cervical cells, endometrial and ovarian tumors also shed DNA that can reach the cervix.

Building on these findings, the research team developed PapSEEK, a test that analyzes Pap test samples for certain DNA mutations that are commonly found in endometrial and ovarian cancers. The test also detects aneuploidy, a genetic alteration associated with cancer in which cells have an abnormal number of chromosomes.

When the investigators used PapSEEK to analyze Pap test samples from women with cancer, the test identified cancer-related alterations in 81% of women with endometrial cancer and 33% of women with ovarian cancer. Alterations were detected in more women with late-stage than early-stage endometrial cancer and about the same fraction of women with early- and late-stage ovarian cancer.

PapSEEK is a type of liquid biopsy that identifies cancer-related alterations in DNA obtained from fluids collected during a routine Pap test.

In addition, PapSEEK gave only 1.4% of women without cancer a false-positive test result, showing that "the specificity of PapSEEK was high," the researchers wrote.

Enhancing PapSEEK's Sensitivity

To increase the test's sensitivity, the investigators decided to test samples taken from a location that is closer to the site of endometrial and ovarian cancers. They analyzed fluid samples collected from the lining of the uterus using an instrument called a Tao brush, which is approved by the Food and Drug Administration as a tool to diagnose endometrial cancer.

The test found cancer-related alterations in 93% of Tao samples from women with endometrial cancer, including 98% of women with late-stage endometrial cancer. It also identified cancer-related alterations in 45% of Tao samples from women with ovarian cancer.

No cancer-related alterations were detected in any of the Tao samples collected from women without cancer — an "ideal" characteristic for a screening test, Dr. Srivastava noted.

Testing Tao samples may have provided greater sensitivity for detecting ovarian and endometrial cancer than testing Pap samples because these tumors are located closer to the uterus than the cervix, Dr. Papadopoulos noted. Indeed, the researchers found that Tao samples contained more endometrial and ovarian tumor DNA than Pap samples, he explained.

Tumors can also shed DNA and tumor cells into the bloodstream. When the researchers tested blood samples from women with ovarian cancer, the sensitivity of PapSEEK was 43%. Combining PapSEEK results from blood and Pap samples from the same woman, however, increased the test's sensitivity to 63%.

There are likely several reasons why the sensitivity of PapSEEK was lower, across the board, for ovarian cancer than for endometrial cancer, Dr. Papadopoulos said.

One limitation, Dr. Srivastava said, is that the genetic mutations included in the PapSEEK panel appear to be "more common in endometrial cancer than ovarian cancer." Indeed, the test identified mutations in 97% of endometrial tumor samples but only 80% of ovarian tumor samples, the researchers found.

Another potential issue is that not every tumor sheds DNA into certain body fluids. When the investigators measured the amount of tumor DNA in Pap and Tao samples, they found comparatively more DNA from endometrial tumors than from ovarian tumors, Dr. Papadopoulos explained. This could be due to the location (ovarian cancers are further away from the site where Pap and Tao brush sampling are performed) or the biology of ovarian tumors, he added.

Overall, Dr. Papadopoulos said, "I think a shift in thinking needs to happen. A screening test with less than 100% sensitivity does not make the test useless. The important thing is to try to catch cancer early to reduce the number of people who may unknowingly have cancer and are doing nothing about it until it is too late."

While Dr. Srivastava agreed that a screening test for ovarian cancer is much needed, a test with low sensitivity "means you miss out on catching cancer," he noted. And false-positive results "can bring undue burden — physical, psychological, and financial burdens from the additional testing that is triggered. That's something that needs to be taken into consideration," he added, though PapSEEK produced very few false-positive results.

Not Reinventing the Wheel

While more studies of the PapSEEK test are needed before it can be considered for patient care, it does have several theoretical advantages for potential clinical use, Dr. Papadopoulos explained. For example, it is inexpensive, noninvasive, and easily administered.

"Women already go for Pap smears. We're using the same material, so we're not introducing a new type of exam," he added. "We didn't want to invent a new device or approach for [sample] collection."

The PapSEEK test is potentially "very doable and amenable to clinical use," Dr. Srivastava noted. "It could be performed at the same time women undergo a Pap test for cervical cancer."

The investigators are continuing to explore whether combining PapSEEK results from different body fluids increases the test's sensitivity for ovarian cancer.

Dr. Papadopoulos and his colleagues have also developed another liquid biopsy test, called CancerSEEK, that scans blood samples for a combination of genetic mutations and proteins that occur in eight different types of cancer.

In a similar retrospective study, CancerSEEK had 98% sensitivity for ovarian cancer, with a false-positive rate of less than 1%. As with PapSEEK, additional prospective studies are needed to determine whether CancerSEEK can identify cancer in asymptomatic people.

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A Physician Faces Her Own Ovarian Cancer

By Dr. Tracie Miller, National Cancer Institute, Center for Cancer Research

Drs. Tracie Miller and Steve Lipshultz have spent their careers caring for pediatric patients and conducting research at well-known medical institutions across the country. Tracie's research focuses on the intersection of HIV and nutrition for children, Steve's on pediatric cardiology. In some ways, those years of providing patient care and conducting medical research prepared the couple for Tracie's ovarian cancer diagnosis, and in other ways, it didn't.

Four years ago, Tracie was diagnosed with ovarian cancer when a mass was discovered during a routine medical exam. Initially, Tracie responded well to standard therapies and was in remission for 16 months before the cancer relapsed. Despite undergoing surgery and additional treatment, her cancer persisted.
Ovarian cancer forms in the tissues of the ovary, one of a pair of female reproductive glands in which the ova, or eggs, are formed. Because it may not cause early signs or symptoms and there is no effective screening test, ovarian cancer is often found at advanced stages. It has the highest mortality rate of all gynecological cancers.

As active members of the scientific community, Tracie and Steve sprang into action and consulted with their friends and colleagues at various cancer centers to gain a better sense of the treatment options available to Tracie once conventional treatments had failed her. When Steve reached out to long-time colleagues at the National Institutes of Health (NIH) in the spring of 2016, they helped connect the couple to Jung-Min Lee, MD, NIH Lasker Scholar Investigator in the Women's Malignancies Branch in the Center for Cancer Research (CCR). At the time, Dr. Lee was heading multiple clinical trial protocols for ovarian cancer at the National Cancer Institute on the NIH campus in Bethesda, MD.

Tracie Miller and Steve Lipshultz Photo credit: Marleen Van den Neste

It took about a week after their introduction before Tracie became eligible to participate on a clinical trial, as she was experiencing complications from a recent surgery. During that week, Tracie and Steve recalled how compassionate and responsive Dr. Lee was despite the fact Tracie wasn't yet enrolled on a clinical trial. "Dr. Lee is amazing," said Tracie. "Even though I wasn't her patient, she was extremely responsive. I felt like she would give her right arm to make things work for me." "We were reaching out everywhere, and Dr. Lee's program was one of only a few we reached out to that showed great compassion and sincerity," recounted Steve.

The treatment involves administering a single-agent drug, prexasertib, every two weeks. Although the U.S. Food and Drug Administration has not approved prexasertib for use in treating ovarian cancer or any other disease, interim findings from the clinical trial suggest it may be effective for women with a similar genotypic profile to Tracie; that is, women who have platinum-resistant recurrent ovarian cancer and no BRCA mutation — a known prognostic factor for ovarian cancer.

"With the type of ovarian cancer I have, there's a specific biomarker that becomes elevated," explained Tracie. "It plummeted after the first month of therapy, so fortunately I fit into the bucket of people that may have a response to the drug." Tracie has had to modify her work schedule since enrolling on the clinical trial, which has been a difficult adjustment. "In terms of providing patient care, it's just not been possible for me at this point," she said. "Some days I'll wake up and have this complication over the course of the day or that evolves into a week-long issue. Caring for patients really isn't an option because I might not be able to go in."

Despite the professional setbacks, Tracie maintains a positive outlook and recognizes the importance of taking care of herself — she is, after all, a patient. She also keeps up with her research. "I try to stay positive and just take things as they come," said Tracie. "I'm hoping one day I'll be able to see patients again, but the research keeps me going for now."

Tracie and Steve are in the unique position of having experienced both sides of the patient-provider relationship. "You see the world in another way when you're the patient or the family – that's what we try to teach in academics," said Steve.

Coming from the perspective of a physician, Tracie understands the significance of patients advocating for themselves. "For someone that's just getting a diagnosis, you can't just sit back," said Tracie. "You have to take ownership. Your doctor is a really busy person and has a lot of priorities. Nobody has your best interests in mind as much as you do. If you want to go out and find something, you better go out and make it a priority for yourself."

"Our mission is to improve the lives of cancer patients by solving important and challenging problems in cancer research and patient care," said Dr. Lee. "I fully understand that it must have been hard for Tracie to be in the 'patient' position after being on the physician side. However, I think Tracie has made a significant contribution to our mission, and I thank all my patients and their caregivers for their contributions to cancer research and drug development."

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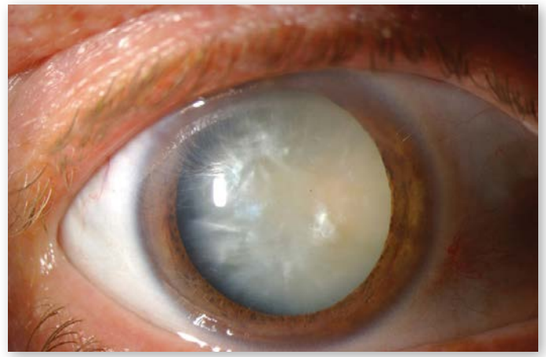
Ovarian Cancer Statistics

Each year, about 20,000 women in the United States get ovarian cancer. Ovarian cancer causes more deaths than any other cancer of the female reproductive system, but it accounts for only about 3% of all cancers in women. When ovarian cancer is found in its early stages, treatment works best.

In 2018, there will be approximately 22,240 new cases of ovarian cancer diagnosed and 14,070 ovarian cancer deaths in the United States. Herein, the American Cancer Society provides an overview of ovarian cancer occurrence based on incidence data from nationwide population-based cancer registries and mortality data from the National Center for Health Statistics. The status of early detection strategies is also reviewed. In the United States, the overall ovarian cancer incidence rate declined from 1985 (16.6 per 100,000) to 2014 (11.8 per 100,000) by 29% and the mortality rate declined between 1976 (10.0 per 100,000) and 2015 (6.7 per 100,000) by 33%. Ovarian cancer encompasses a heterogenous group of malignancies that vary in etiology, molecular biology, and numerous other characteristics. Ninety percent of ovarian cancers are epithelial, the most common being serous carcinoma, for which incidence is highest in non-Hispanic whites (NHWs) (5.2 per 100,000) and lowest in non-Hispanic blacks (NHBs) and Asians/Pacific Islanders (APIs) (3.4 per 100,000). Notably, however, APIs have the highest incidence of endometrioid and clear cell carcinomas, which occur at younger ages and help explain comparable epithelial cancer incidence for APIs and NHWs younger than 55 years. Most serous carcinomas are diagnosed at stage III (51%) or IV (29%), for which the 5-year cause-specific survival for patients diagnosed during 2007 through 2013 was 42% and 26%, respectively. For all stages of epithelial cancer combined, 5-year survival is highest in APIs (57%) and lowest in NHBs (35%), who have the lowest survival for almost every stage of diagnosis across cancer subtypes. Moreover, survival has plateaued in NHBs for decades despite increasing in NHWs, from 40% for cases diagnosed during 1992 through 1994 to 47% during 2007 through 2013. Progress in reducing ovarian cancer incidence and mortality can be accelerated by reducing racial disparities and furthering knowledge of etiology and tumorigenesis to facilitate strategies for prevention and early detection. CA Cancer J Clin 2018;68:284-296.

New Research Sheds Light on How UV Rays May Contribute to Cataract

A new study offers an explanation for how years of chronic sunlight exposure can increase the risk of cataract, a clouding of the eye lens that typically occurs with aging. The study firms up a link between the sun's damaging rays and a process called oxidative stress. It was funded in part by the National Eye Institute (NEI).



Photograph of a patient's right eye with a dense mature cataract.
Courtesy of James Gilmore, Photography Department at the Moran Eye Center.

It's well known that exposure to ultraviolet (UV) light from the sun can cause skin damage. But many studies show that UV light can also increase the risk of cataract and other eye conditions.

Oxidative stress refers to harmful chemical reactions that can occur when our cells consume oxygen and other fuels to produce energy. It's an unfortunate consequence of living, but it's also considered a major contributor to normal aging and age-related diseases-including cataract formation in the lens.

The cells within the lens contain mostly water and proteins, and lack the organelles (literally "tiny organs") typically found in other cells. This unusual make-up of lens cells renders the lens transparent, uniquely capable of transmitting light and focusing it on the retina at the back of the eye. When a cataract forms, the proteins inside lens cells show signs of oxidative damage, and they ultimately become clumped together, scattering light rather than transmitting it. So, the theory goes, oxidative stress (or something like it) is responsible for destroying the neatly ordered proteins inside the lens and producing a cataract.

The theory might sound simple, but there is a puzzling fact that doesn't fit: The oldest cells in the lens are not only devoid of the organelles that keep most other cells alive and functioning, they also get little to no oxygen. So how can they suffer from oxidative stress?

The new study, led by researchers at Case Western Reserve University in Cleveland, Ohio, suggests that UV light may provide an answer. The study shows that UV light can damage lens proteins in a distinct way (called glycation) that is typically seen in cataract and in cells damaged by oxidative stress. In other words, UV light can substitute for oxygen to trigger harmful oxidative reactions in the lens.

Prior studies have supported this theory. But the Case Western team has unveiled a detailed play-by-play of the chemical changes induced in the lens by UV light.

Many clinical studies, including an NEI-funded study of fishermen in the Chesapeake Bay, have pointed to UV light exposure as a risk factor for age-related cataract. UV light rays are invisible and have shorter wavelengths than visible light. In the earth's atmosphere, UV light comes in two varieties: UVA and UVB. Their relative contributions to cataract remain unclear, but UVA penetrates more deeply into the body and may be more likely to reach the lens. NEI's National Eye Health Education Partnership (NEHEP) recommends wearing sunglasses with both UVA and UVB protection to shield your eyes from the sun. A hat can help, too.

"UV light has long been suspected to have a role in cataract formation, but the mechanism has not been clear," said Ram Nagaraj, PhD, the study's senior author and a professor of ophthalmology and visual sciences at Case Western.

Dr. Nagaraj and his colleagues tested the effects of UVA light on proteins and chemicals found in lens cells. They found that in the absence of oxygen, UVA light can trigger a chain reaction that begins with amino acid derivatives called kynurenines, and ends with protein glycation in the lens. In earlier work, they also showed that mice genetically engineered to over-produce kynurenines develop cataract by 3 months of age. In the current study, when lenses from these mice were exposed to 2 hours of intense UVA light, they accumulated damaged (glycated) proteins.

Photo credit: Betsy Lehman Center for Patient Safety

It's well known that exposure to ultraviolet (UV) light from the sun can cause skin damage. But many studies show that UV light can also increase the risk of cataract and other eye conditions.

"Our study shows how UV light could promote cataract development, and reiterates the importance of wearing sunglasses to protect your eyes the sun's harmful rays," Dr. Nagaraj said.

Unfortunately, the researchers found that a natural antioxidant in the eye and other tissues, called glutathione, offered little protection against the damaging effects of UV light.

Several clinical studies have tested the potential for antioxidant supplements to prevent or slow age-related cataract, with mixed results.

Overall, there is a need to better understand the extent to which natural antioxidants or other mechanisms within the lens might offer some protection against the sun, said Houmam Araj, PhD, who oversees programs on lens, cataract and oculomotor systems at NEI.

One such mechanism includes proteins called chaperones, which can help prevent damaged proteins from clumping together.

"When do these mechanisms work in the lens and when do they fail? Answering those questions might lead to drug treatments for preventing cataract, and perhaps even skin cancer," Dr. Araj said. "The eye and lens provide a useful, accessible system to study general countermeasures the body might have for defending itself against UV radiation."

The current study was done in collaboration with the Iladevi Cataract and IOL Research Center in Ahmedabad, India. It was funded by NEI (grants EY022061, EY023286, EY011373 and EY007099), Research to Prevent Blindness and the Ohio Lions Eye Research Foundation.

Reference:

Linetsky M, Raghavan CT et al. "UVA light-excited kynurenines oxidize ascorbate and modify lens proteins through the formation of advanced glycation end products: implications for human lens aging and cataract formation." Journal of Biological Chemistry, May 2014. DOI: 10.1074/jbc.M114.554410.

nei.nih.gov

Percutaneous Peripheral Nerve Stimulation in the Non-opioid Management of Acute and Chronic Pain

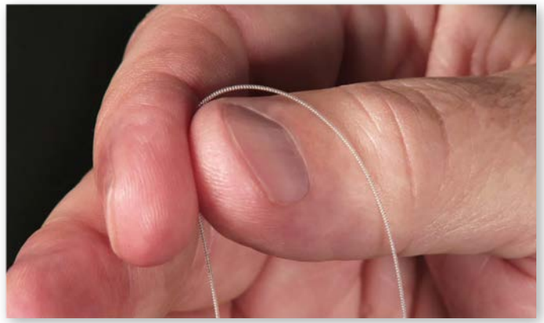
Given their interests in effectively managing chronic and acute pain without opiates, the Department of Defense, the National Institutes of Health and the Veterans Administration have all recently provided grants to support research regarding the use of percutaneous Peripheral Nerve Stimulation (PNS). The most recent research funding has been directed toward the management of chronic and acute post-amputation pain, chronic low back pain and acute pain following total knee arthroplasty using PNS. An update on the outcomes of the research was recently provided at the Military Health System Research Symposium (MHSRS), a venue for presenting new scientific knowledge resulting from military-unique research and development.

To date, these federally-funded grants and contracts, totaling $30M, have been awarded to research technology developed by SPR Therapeutics, Inc of Cleveland, OH and their SPRINT® PNS System, the only percutaneous PNS system FDA-cleared for the treatment of acute as well as chronic pain.

Although PNS was initially described as a treatment for pain in the late 1960's, until recently it had required the neurosurgical implantation of a lead connected to an implanted battery-operated pulse generator under the belief that stimulation would be required indefinitely to provide pain relief. Due to invasiveness and cost, conventional PNS has been relegated to a treatment of last resort for chronic pain and not remotely considered as a treatment for acute pain.

The Sprint PNS system includes a wearable 1-ounce pulse generator connected to an implanted lead and controlled by a small hand-held Bluetooth® remote. The lead is constructed of a 100-micron helically wound wire that is placed under ultrasound guidance via a 20-gauge introducer approximately one centimeter remote to the targeted nerve. The lead is intended to remain implanted for up to 60 days after which it is withdrawn.

Chronic postoperative pain occurs in a substantial proportion of patients following many surgeries and can be as high as 80% in individuals following limb amputation. Research using the Sprint PNS System has demonstrated that peripheral nerve stimulation may be used effectively in the management of acute as well as chronic pain, and that stimulation for up to 60 days can provide significant and sustained relief.



MicroLead™ PNS Lead

SPRINT® Pulse Generator and Hand-held Bluetooth® Remote

The SPRINT® PNS System
Images provided courtesy of SPR Therapeutics, Inc.

PNS of the Femoral and Sciatic Nerves for Post-Amputation (Neuropathic) Pain

Percutaneous PNS for the treatment of chronic neuropathic post-amputation pain were presented at the MHSRS in August 2018. The findings in regard to residual and phantom limb pain at baseline and at lead withdrawal (EOT) are presented below. Seventy-five percent of subjects experienced highly clinically significant reductions (≥ 50%) overall in average post-amputation pain at EOT and 81% had highly clinically significant reductions (≥ 50%) overall in average post-amputation pain interference at EOT.

One cohort of 12 subjects with post-amputation pain was followed for up to 12 months, and average pain was evaluated monthly. At EOT in the per protocol treatment group, 8 of 10 patients reported at least 50% reductions in pain. Four of the 5 responders who have reached the 12 month endpoint have reported >50% pain relief. Prospective follow-up is ongoing.

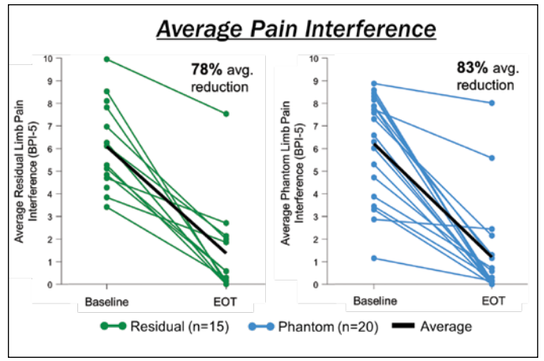
Preliminary findings from the first patient in a VA-funded trial evaluating PNS in the management of post-amputation pain were presented at the American Society of Regional Anesthesiologists in April 2018. According to clinicaltrials.gov, the Hunter Holmes McGuire Veteran Affairs Medical Center is evaluating percutaneous PNS in 16 patients with new nontraumatic transfemoral or transtibial amputation.

Patients are being randomized to either a treatment group, in which they undergo placement of PNS leads within 7 days of amputation surgery, or to a standard of care group. Patients in both groups are treated with standard pain therapies and evaluated weekly for 8 weeks, then at 3, 6, and 12 months post-amputation. The principal investigator of this trial is Denise Lester, MD.

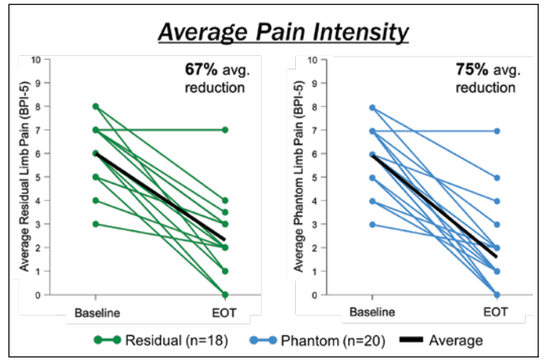
PNS of the Femoral and Sciatic Nerves for Post-TKA Pain

At 1-month post-TKA 15 of 18 subjects (83%) implanted with PNS leads pre-operatively had mild and well-controlled pain (<4/10). At 3 months, 94% of subjects (17/18) had pain ≤ 2/10 and all subjects had pain <4/10. This compares very favorably versus historical controls in which persistent pain is typically reported in ~20% or more of patients ≥3 months after TKA.

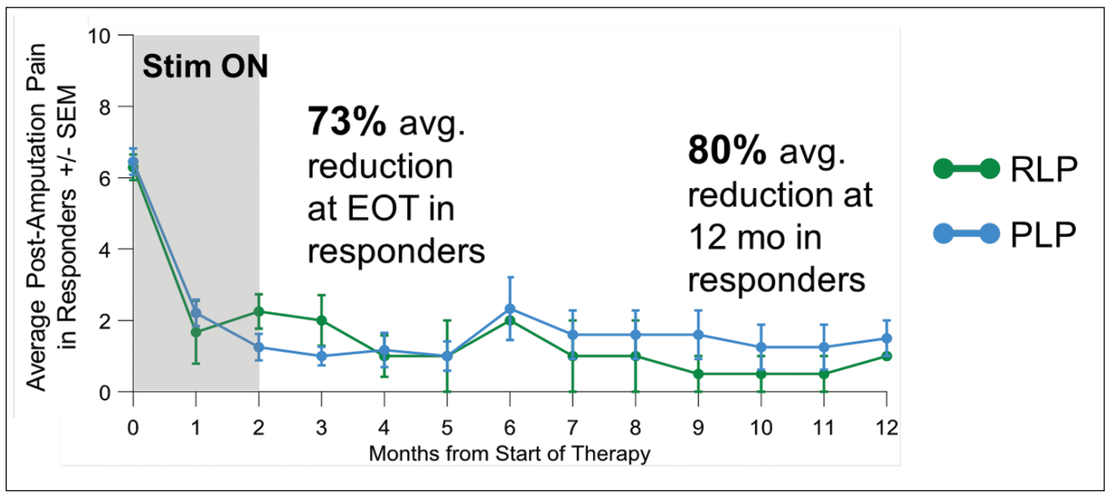
Pain Interference Related to Percutaneous PNS Therapy



Baseline and End of Treatment Pain Relief



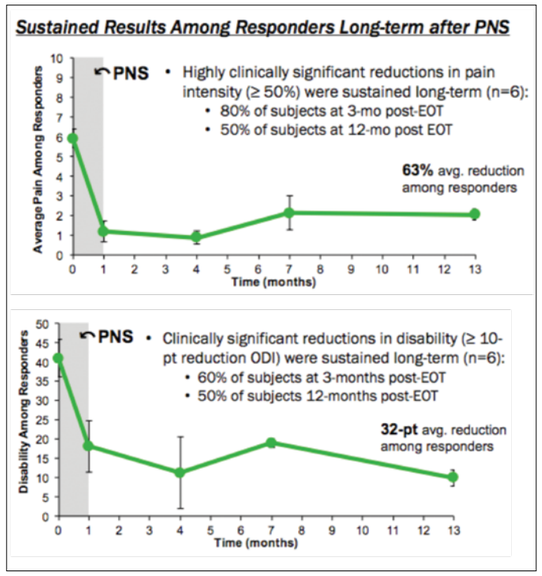
Sustained Pain Relief Related to SPRINT PNS use in Patients with Post-amputation Pain



In regard to opioid cessation, 14/18 subjects (77%) ceased opioid use by 62 days following surgery and 16/18 (89%) had ceased opioid use by 3 months. This also compares favorably versus historical controls in which 25-40% of patients are still using opioids at 90 days (3 months) after TKA (Namba et al 2018; Goesling et al 2016; Hah et al 2014).

PNS of the Medial Branch for Low Back Pain

Finally, significant results were also reported at the MHSRS in the use of PNS for the management of low back pain. In this application, PNS was delivered for up to 30 days resulting in 50% or greater pain relief in 6 of 9 patients. This relief endured in 80% of responders at 3 months post treatment and in 50% of responders at 12 months post-treatment.



Similar durable reductions in disability among responders were also reported in which the average improvement in the Oswestry Disability Index (ODI) was 32 points among responders at 12 months. To provide context relative to the thirty-two point reduction, the minimal clinically important difference (MCID) for the ODI is ten points. MCID are patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient.

Safety

No lead infections, falls, motor block, or other serious device-related adverse events (AE's) have been reported in clinical studies. The most common adverse events have been skin irritation and erythema. More information may be found at the manufacturer's website: https://www.sprtherapeutics.com/physicians/safety-information/

CPG

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A New Non-Opioid Approach Being Used to Treating Pain within the VA

By John Phillips

Denise Lester, MD, a board-certified anesthesiologist and pain management physician at the Hunter-Holmes-McGuire VA Medical Center in Richmond, Virginia recently spoke with us about research they are conducting regarding their efforts to treat pain without opioids.

"The Hunter-Holmes-McGuire VA Medical Center is taking a comprehensive approach to pain management. "We're looking at what we can do to reduce or hopefully eliminate the use of opioids".

Our VIP (Veterans Integrative Pain) center offers several complementary pain management therapies such as Acupuncture, Biofeedback, Music Therapy, Mindfulness Meditation and Anti-Inflammatory Diet. We also offer a variety of injections as well as a state-of-the-art systems to implant peripheral nerve electrical stimulating catheters (peripheral nerve stimulators).

Using this system peripheral nerves are stimulated using low levels of electricity delivered through a very small (300 micron) implanted wire, or "lead" for pain control.

Neuromodulation pain management therapies have been used for decades to stimulate structures in the deep brain and the spinal cord. Earlier peripheral nerve stimulation (PNS) systems were first evaluated in the 1960's but until recently they required a very invasive neurosurgical procedure. We now have access to significantly less invasive devices that can be implanted through the skin (percutaneously) using a small needle making use of PNS much more reasonable early in the treatment continuum.

Our facility has evaluated and championed many different types of pain management therapies as we endeavor to combat the opioid crisis. Our goal for our patients is to minimize the need for them to return to the hospital for their pain care.

For example, we would like to see their effects of our injections lasting at least three months while providing at least a fifty percent reduction in pain. Our peripheral nerve stimulation patients are implanted with a lead that is connected to wearable device before being withdrawn up to sixty days later. Most patients have pain relief that is sustained long after the lead has been withdrawn, in many cases up to a year or longer.

Some neurostimulation systems are permanently implanted and are designed to stay in the body for the life of the patient. In most cases, the patient doesn't have to return to the pain clinic to receive further care.

The VA recently spearheaded an initiative to foster physician involvement in research in which they made fifty-thousand dollar research grants available to six physicians whose applications were accepted as having high-potential. I was awarded this grant last year..

I had been primarily in clinical care for the twenty-one years I've been with the VA. Additionally I had always held an interest in research to assist our veterans in pain. The project we submitted in the application for the pilot grant involved a pilot study to evaluate the effect of stimulating the femoral and sciatic nerves of the legs for up to 60 days in patients who have recently undergone an amputation. In this project we wanted to assess whether percutaneous peripheral nerve stimulation (PNS) could reduce acute post-amputation pain and opioid use while also assessing whether it could prevent chronic pain including phantom pain and stump pain. These pain states are both very difficult to treat once they present themselves. We've been enrolling patients since October of 2017 and are very satisfied with the results thus far. We're very hopeful that this will lead us in the direction of helping many other Veterans.

It was clear from prior studies that percutaneous PNS helped patients with chronic pain, but our study is evaluating how providing the therapy perioperatively may prevent pain from becoming chronic or disabling.

This study is the first-of-its kind to assess the potential to prevent chronic pain in amputations patients with peripheral nerve stimulation at time of amputation.. In our study, PNS is initiated at five to seven days post-operatively and after their continuous peripheral nerve block catheter has been removed.

We have also recently been invited to participate in another very large study using the same system for the management of low back pain. If it's also successful it will have a tremendous impact on our veterans given that low back pain is one of the main reasons patients see a doctor. We look forward to being involved and are honored to have been invited."

Capital Publishing Inc.

About 3,500 Babies in the U.S. are Lost to Sleep-Related Deaths Each Year

Need for more caregivers to follow safe-sleep practices

There are about 3,500 sleep-related deaths among U.S. babies each year, including sudden infant death syndrome (SIDS), accidental suffocation, and deaths from unknown causes.

In the 1990s, there were sharp declines in sleep-related deaths following the national "Back to Sleep" safe sleep campaign. However, the declines have slowed since the late 1990s — and data from a new Vital Signs report from the U.S. Centers for Disease Control and Prevention shows the risk for babies persists.

The CDC urges every family follow the American Academy of Pediatrics (AAP) recommendations — babies should sleep on their backs, without any toys or soft bedding, and in their own crib. Parents are encouraged to share a room with the baby, but not the same bed. These strategies will help reduce the risk and protect our babies from harm.

Unsafe Sleep

For the Vital Signs report, CDC analyzed Pregnancy Risk Assessment Monitoring System (PRAMS) data to describe sleep practices for babies. PRAMS, a state-based surveillance system, has monitored self-reported behaviors and experiences before, during, and after pregnancy among women with a recent U.S. live birth since the late 1980s.

CDC examined 2015 data reported by mothers about unsafe sleep positioning, bed sharing, and use of soft bedding from states with available data. Unsafe sleep positioning means placing the baby on his or her side or stomach to sleep. Soft bedding includes pillows, blankets, bumper pads, stuffed toys, and sleep positioners.

In 2015, within states included in the analysis:

- About 1 in 5 mothers (21.6 percent) reported placing their baby to sleep on their side or stomach, more than half of mothers (61.4 percent) reported any bed sharing with their baby, and 2 in 5 mothers (38.5 percent) reported using any soft bedding in the baby's sleep area
- The percentage of mothers who reported placing their baby on his or her side or stomach to sleep varied by state, ranging from 12.2 percent in Wisconsin to 33.8 percent in Louisiana.
- Placing babies on their side or stomach to sleep was more common among mothers who were non-Hispanic black, younger than 25, or had 12 or fewer years of education.

Safe sleep practices recommended by the AAP include:

- Placing the baby on his or her back at all sleep times — including naps and at night.
- Using a firm sleep surface, such as a safety-approved mattress and crib.
- Keeping soft objects and loose bedding out of the baby's sleep area.
- Sharing a room with baby, but not the same bed.

"This report shows that we need to do better at promoting and following safe sleep recommendations," said Jennifer Bombard, MSPH, scientist in CDC's Division of Reproductive Health and lead author of the analysis. "This is particularly important for populations where data show infants may be at a higher risk of sleep-related deaths."

In recent years, state public health agencies have worked with partners to promote safe sleep. These efforts include communication campaigns, messages shared during visits through WIC and through home-visiting programs, safe sleep policies, and quality-improvement initiatives in hospitals and childcare centers.

Healthcare providers can increase the likelihood that parents follow AAP recommendations by giving them accurate advice about safe sleep for babies.

A previous study shows that only 55 percent of mothers report receiving correct advice about safe sleep during pregnancy and baby care visits, while 20 percent say they get no advice and 25 percent report getting incorrect advice.

At CDC, we have a number of efforts underway to address safe sleep. We will continue to monitor sleep practices for babies through PRAMS. CDC also supports the monitoring of sleep-related deaths in 16 states and two jurisdictions through its Sudden Unexpected Infant Death (SUID) Case Registry, which is built upon the HRSA-supported National Center for Fatality Review and Prevention.

This tracking effort, which captures 30 percent of all SUID cases in the US, focuses on improving data quality and completeness of SUID investigations to inform strategies to reduce sleep-related deaths.

cdc.gov

Asthma Attacks Declining among U.S. Children

More work needed to continue progress

Children with asthma in the U.S. are having fewer asthma attacks, missed school days, and visits to the hospital, according to a new Vital Signs report from the U.S. Centers for Disease Control and Prevention.

Today's report shows that the percentage of children with asthma who experienced one or more asthma attacks in the preceding 12 months declined from 2001 (61.7%) to 2016 (53.7%). Even so, approximately half of children with asthma had one or more asthma attacks in 2016.

"We are making progress — but healthcare providers, parents, caregivers, and schools can do more to help children avoid asthma attacks," said CDC Acting Director Anne Schuchat, M.D. "Asthma attacks can be terrifying for children and their families. Over the past decade, we've identified asthma management actions that work — not alone but in combination. Now we need to scale up these efforts nationwide."

Asthma is the most common chronic lung disease of childhood, affecting approximately 6 million children in the United States. Although asthma cannot be cured, asthma symptoms can usually be controlled by avoiding or reducing exposure to asthma triggers (allergens and irritants) and by following recommendations for appropriate medical care.

Asthma in U.S. children: Key findings

Today's report shows that some children are more likely to have asthma than others, including boys, children ages 5-17 years, non-Hispanic black children, children of Puerto Rican descent, and children from low-income families. In 2016, asthma attacks were most common among the youngest children, 4 years old and under.

Other study findings:

- Asthma hospitalizations for children with asthma declined from 9.6 percent in 2003 to only 4.7 percent in 2013.
- The percentage of children who reported asthma-related missed school days also was lower in 2013 than it was in 2003.
- More children with asthma are getting asthma action plans and being taught how to recognize the signs and symptoms of an asthma attack and how to respond quickly.
- Despite this progress, 1 in 6 children with asthma still ends up in the emergency department and about 1 in 20 is hospitalized each year.

Asthma attacks in children: How can doctors, nurses, and other healthcare providers help?

No single strategy is the magic bullet that prevents asthma attacks. But recent evidence from small CDC-funded projects show that a combination of actions can be highly effective:

- Work with children and parents to determine the severity of each child's asthma, to develop an action plan for each child, and to share the plan with families, schools, and others.
- Teach children and parents how to manage asthma by using control and rescue medicine properly and avoiding asthma triggers such as tobacco smoke, mold, pet dander, and outdoor air pollution.
- Work with community health workers, pharmacists, and other community providers to help ensure that children with asthma receive the services they need.

CDC's efforts to control asthma

CDC launched the National Asthma Control Program in 1999. Its mission: helping people with asthma breathe easier. The program currently funds partners in 24 states and 1 territory to use data, science, communication, and evaluation to reach this goal.

In addition, CDC promotes proven medical management of asthma, based on CDC's 6/18 initiative. Such management includes proven actions such as trigger reduction, guidelines-based medical management, and self-management education. The initiative also promotes flu and pneumonia vaccination for all children, improvements in indoor air quality through smoke-free air laws and policies, and partnering with healthcare providers and others to lower asthma costs through improved control.

cdc.gov

Genetics and Pollution Drive Severity of Asthma Symptoms

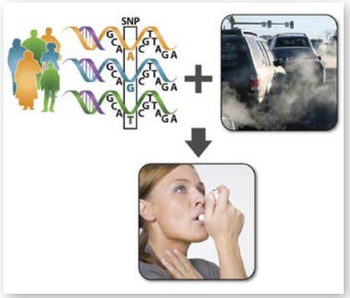
Asthma patients, with a specific genetic profile, exhibit more intense symptoms following exposure to traffic pollution, according to researchers at the National Institutes of Health and collaborators. The study appeared online in Scientific Reports.

The research team, made up of scientists from the National Institute of Environmental Health Sciences (NIEHS), part of NIH, and Rice University, Houston, also found that asthma patients that lack this genetic profile do not have the same sensitivity to traffic pollution and do not experience worse asthma symptoms. The work brings scientists closer to being able to use precision medicine, an emerging field that intends to prevent and treat disease based on factors specific to an individual.

Co-lead author Shepherd Schurman, MD, associate medical director of the NIEHS Clinical Research Unit, stated the results are based on genetic variation, the subtle differences in DNA that make each person unique. He further added that to understand the concept, one should think of human genes, which are made up of DNA base pairs A, C, G, and T, as written instructions for making proteins.

"All humans have the same genes, in other words the same basic instructions, but in some people one DNA base pair has been changed," Schurman said. "This common type of genetic variation is called a single nucleotide polymorphism or SNP, and it can alter the way proteins are made and make individuals more or less prone to illness."

Schurman is also head of the Environmental Polymorphisms Registry (EPR), the DNA bank in North Carolina that provided volunteers for the study. The EPR studies how SNPs impact disease risk in combination with environmental exposures.



The research suggests when individuals with specific variations in certain genes are exposed to traffic pollution, they display more intense asthma symptoms than people that lack those same gene variations. Photo courtesy of National Institute of Environmental Health Sciences.

Together with NIEHS colleague and lung disease expert Stavros Garantziotis, MD, medical director of the NIEHS Clinical Research Unit, the two scientists examined four SNPs that are involved in a biochemical pathway that leads to inflammatory responses in the body. They explained that SNPs are usually studied one at a time, but they wanted to learn if different combinations of these SNPs, along with pollution exposure, could worsen symptoms in a person with an inflammatory disease like asthma.

Schurman and Garantziotis gathered information about the SNPs, severity of asthma symptoms, and residential addresses of 2,704 EPR participants with asthma. Using the SNPs data, they divided the participants into three groups: hyper-responders, or those very sensitive to air pollution and likely to develop inflammation; hypo-responders, or those insensitive to air pollution and less likely to develop inflammation; and those in between. With the help of collaborators at Rice University, the team used the participants' addresses to calculate their distance from a major road. Participants were categorized depending on whether they lived more or less than 275 yards from a major roadway. Data suggest that air pollution levels are elevated closer to major roads.

The researchers found that asthma sufferers who were hyper-responders and lived closer to heavily travelled roads had the worst asthma symptoms, such as difficulty breathing, chest pain, cough, and wheezing, compared to the other groups. In contrast, asthma patients who were hypo-responders and lived further away from busy roads had milder symptoms. Garantziotis concluded the work could greatly enhance the quality of life for people with asthma.

"Based on this research, we could propose that hyper-responders, who are exposed to traffic pollution, receive air purification intervention, such as HEPA filters, for their home," Garantziotis said.

NIEHS Clinical Director Janet Hall, MD, said the results emphasize the importance of gene-environment interactions in the progression of disease.

"This research is a great example of how we can approach disease prevention on a personal level, and tailor our treatments to suit individual patients," she said. "That way we can be more efficient with our treatments and preventative measures, while at the same time cutting health care costs."

nih.gov

Updated Estimates Suggest a Higher Number of U.S. Adults with Arthritis

By Carol Torgan, PhD

About 91 million U.S. adults may have some form of arthritis, according to a new statistical analysis of data from a self-reported national survey from 2015. This estimate is 68 percent higher than the previously reported estimate for arthritis — a term that includes multiple conditions that affect the joints, tissues around the joints, and other connective tissues. Further research based on other surveys, along with data based on direct observation and clinical diagnosis by medical professionals, will help refine these estimates and monitor arthritis prevalence in the future.

Background

Arthritis is a leading cause of disability. Knowing how many people have arthritis and other chronic disorders is important for anticipating health care system needs and addressing the impact on those affected and their families.

About 54 million U.S. adults were previously estimated to have arthritis based on an answer of "yes" to the question, "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" in the 2015 National Health Interview Survey (NHIS).

Adults who didn't see a physician for joint pain or who didn't have access to health care may have answered the survey question as "no" despite having arthritis. Thus, many cases of arthritis may have potentially gone unreported.

Re-examining the number of people with arthritis

The NHIS is a self-reported questionnaire

Researchers estimated that the number of U.S. adults who have arthritis may be much higher than previously determined.
Photo Credit Ken Tannenbaum/Shutterstock.com

administered by the U.S. Census Bureau that includes other questions related to arthritis. Drs. David T. Felson and S. Reza Jafarzadeh of Boston University School of Medicine developed a statistical model to estimate arthritis prevalence that incorporated answers to two additional survey questions.

Their model started with responses to the original question of a person having been told by a health professional that they had some form of arthritis. They also included responses to a question about whether the person had any symptoms of pain, aching or stiffness in or around a joint (but not the back or neck) during the past 30 days. If this answer was "yes," the researchers incorporated responses to a third question that asked whether the joint symptoms first began more than three months ago. Their new statistical model considered various combinations of "yes" or "no" answers to these three questions. The research was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and reported in Arthritis & Rheumatology.

Based on the broader classification of data from 33,672 participants in the survey, the researchers estimated that arthritis affected 91 million U.S. adults (37 percent of the U.S. population of 248 million). This estimate, which includes 61 million people between the ages of 18 and 64, is 68 percent higher than the previously reported estimate.

The model revealed that many young-to-middle aged adults with arthritis symptoms may have been misclassified as healthy based on the doctor-diagnosed criterion alone, and were counted by including questions on joint pain, aching or stiffness and symptom duration. The prevalence of arthritis was found to be 30 percent in men and 31 percent in women aged 18 to 64 years, and 56 percent in men and 69 percent in women aged 65 years and older.

"Our findings are important because of underestimated, yet enormous, economic and public health impacts of arthritis including healthcare costs and costs from loss of productivity and disability, including in adults younger than 65 years of age," Dr. Jafarzadeh said.

niams.nih.gov

Lupus Diagnosis and Treatment Progress

By Mariana Kaplan, MD, Chief of the Systemic Autoimmunity Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Significant progress in the diagnosis and treatment of lupus has been made over the last several decades. Discoveries have been recently accelerated due to exciting advances in molecular biology, new technologies, etc. There has been a significant improvement in understanding potential mechanisms that lead to lupus and its associated complications and, for the first time in decades, a drug was specifically approved by the FDA for the treatment of lupus.

We also understand better how chronic complications of lupus develop and we are becoming more aware of the variables that need to be monitored in patients to diagnose and prevent these complications more effectively. There are still many challenges and many questions that remain to be answered and that is why it is so important to continue to support research efforts that are focusing on answering these problems.

Although this is not entirely clear, there is recent evidence indicating that the incidence of lupus (diagnosis of new cases) has remained stable over the last decade. On the other hand, data obtained through epidemiologic studies funded by the CDC suggest that the ratio of prevalent (existing cases) to incident cases (new cases) seems to be higher than before, which may suggest that survival has increased in lupus, thereby increasing overall number of cases in the population. There may be significant variation by region of the world, ethnicity, etc.

Lupus patients have significant increases in the risk of developing vascular complications such as myocardial infarction, angina, stroke, etc. It appears that having lupus poses by itself a significant risk for these complications. Many patients with lupus also have other risk factors for vascular disease such as smoking, hypertension, diabetes, etc.

As such, management of these patients needs to include measures for improving vascular health and proper control of disease activity. We need to identify what the best cardiovascular preventive strategies are for these patients and we need to establish clear preventive guidelines.

As many patients develop lupus when they are young, these strategies should ideally be implemented early on during the course of the disease to have the chance of higher impact to prevent devastating consequences due to vascular disease.

As chief of the Systemic Autoimmunity Branch at NIAMS, Dr. Mariana Kaplan heads a research program focusing on adult rheumatic diseases.
Photo Courtesy of Richard W. Clark NIAMS

Currently, our research focuses on studying how the immune system contributes to the development of chronic complications of lupus, with emphasis on cardiovascular complications. In addition, we are trying to understand how the innate immune system (the part of the immune system that functions as first line of defense) may contribute to the development of lupus, flares, and associated organ damage.

We are hoping to identify novel treatments that target these complications.

niams.nih.gov

Early Detection of Patient Deterioration Using Novel Monitoring System

By Dr. Kevin White, Chief of the Spinal Cord Injury Center
and Nurse Educator, Ann Wilson at the James Haley VA Hospital in Tampa, Florida

Patient safety for chronically ill Spinal Cord Injury patients in the hospital is an ongoing challenge. The SCI Center incorporated a novel technology system to detect early patient condition changes and reduce adverse events.

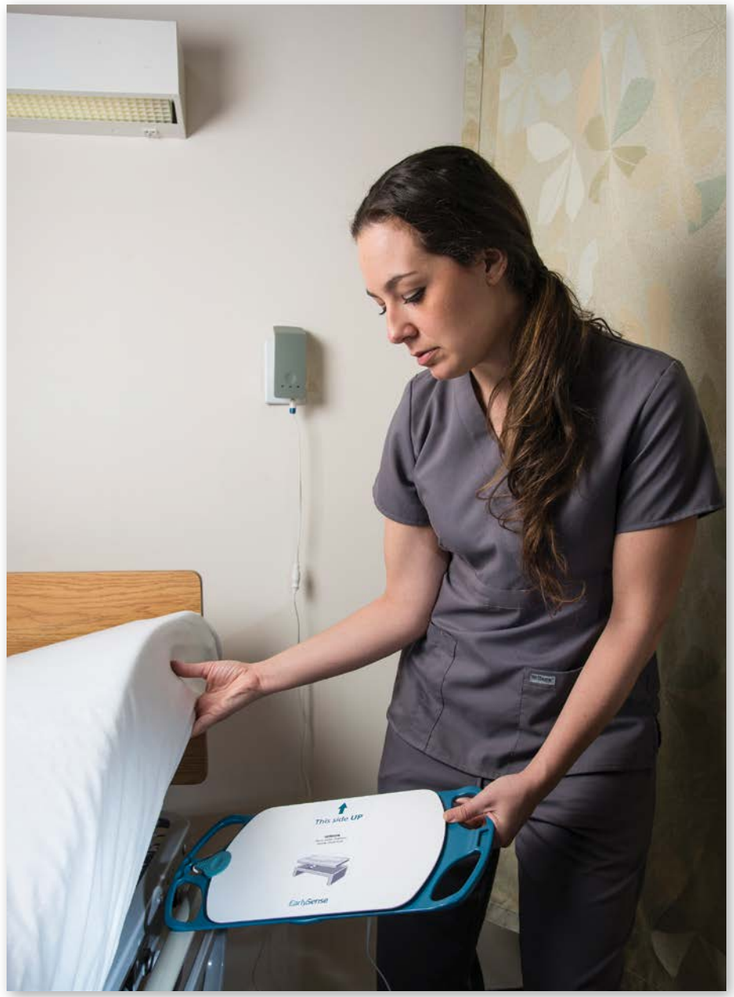
Here in our facility we are using the monitoring system called EarlySense, which is connected underneath the patient's mattress so nothing touches them. Within about a minute, it picks up their heart rate and their respiratory rate through measurement of vibrations. This provides continuous monitoring for the patient the entire time they are in bed.

When considering what type of monitoring is best for patients, the most important feature we look for are trends that show changes in their bio signs. Most of the time this is not a sudden change, but rather a gradual one, so this type of monitoring allows us to recognize changes much earlier and allows us to respond quicker.

A chief advantage to the patient using contact free monitoring is that since nothing touches the patient, they can go about their day or night without any inconvenience to them from wires and leads attached to their body.

Patients are not hindered with movement as a result, which provides a much more comfortable experience for them overall. And because the device senses if the person is moving, it can alert staff if the patient is trying to get out of bed so they can help with fall prevention.

Another important advantage is that if a sudden change occurs in the patient's vital signs, including a medical emergency, the staff is aware of it right away and can respond far more quickly. We have noticed significant improvements in emergency response outcomes as a result since we have implemented this system.



Another advantage contact free monitoring has over traditional monitoring systems with leads is that, leads connected to the patient with tape tend to fall off or disconnect, which gives incorrect readings or even false alarms to the staff. This is never an issue with contact free monitoring.

We began using this system as a pilot program four years ago, and because of the significant improvements and advantages we've seen, contact free monitoring is now our standard practice. We have seen a fifty percent reduction in our MRT/code blue activation rates, and whenever there is an emergency situation the mortality rate has gone down eighty three percent. We've also found that mortality within two days of an MRT/code blue, mortality has gone down eighty three percent.

We've found enough benefit overall that we have moved all of our patients to the EarlySense monitoring system.

EarlySense
Proactive Patient Care

Early Detection of Patient Deterioration Using Novel Monitoring System

Outcomes

Results reported at large VAMC

-67%
Reduced Medical Response Team (MRT) Activations

-50%
Reduced Code Blue Activations

-40%
Reduced ICU Transfers

-83%
Reduced Mortality following MRT/Code Blue Activations

Results have remained consistent for over four years

NIH Research Program to Explore the Transition from Acute to Chronic Pain

The National Institutes of Health has launched the Acute to Chronic Pain Signatures (A2CPS) program to investigate the biological characteristics underlying the transition from acute to chronic pain. The effort will also seek to determine the mechanisms that make some people susceptible and others resilient to the development of chronic pain.

A2CPS is part of the NIH-wide HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. The high prevalence of chronic pain in the United States, and the reliance on opioids for its management, has created an urgent need for safer, more effective pain control. Though A2CPS is part of the HEAL Initiative, its anticipated $40.4 million four-year budget is supplied by the NIH Common Fund, and is an additional investment to enhance research on pain and opioid addiction beyond funds already allocated to HEAL.

A major challenge in pain care is to prevent chronic pain from developing after an initial painful event. For most people, pain goes away as an injury heals. For many others, the pain persists beyond healing of the initial event, and can last for years or even a lifetime. Changes that occur in the body and brain during the development of chronic pain are poorly understood.

NIH Director Francis S. Collins, MD, PhD and U. S. Surgeon General Dr. Jerome Adams at the 13th Annual NIH Pain Consortium Symposium.
Photo Credit: Andrew Propp

The high prevalence of chronic pain in the United States, and the reliance on opioids for its management, has created an urgent need for safer, more effective pain control.

"Our lack of understanding of how acute pain becomes chronic pain has limited our ability to target effective preventive and treatment strategies to patients," said NIH Director Francis S. Collins, MD, PhD. "The ability to identify those at risk will increase our understanding of pain, accelerate therapy development, and ultimately may guide chronic pain prevention strategies tailored for those at risk for chronic pain."

The A2CPS program will collect data from patients with acute pain associated with a surgical procedure, and patients with acute pain from a musculoskeletal trauma such as a broken bone.

Neuroimaging, high-throughput biomedical measurements, sensory testing, and psychosocial assessments collected periodically after the acute pain event will form a comprehensive data set to help predict which patients will develop chronic pain.

The goal of these studies is to identify individual patient features that together will provide clinically meaningful, predictive "signatures" of transition or resilience to chronic pain. If these large-scale longitudinal studies successfully identify predictive signatures, then additional studies that include patients with other acute pain events will be considered. The data gathered from this NIH Common Fund project and any later studies will enable the research community to explore additional signatures predictive of transition or resilience to chronic pain.

Using biological signatures to predict who might be at risk for developing chronic pain would be valuable in guiding precision medicine approaches to prevent chronic pain, and by doing so, reduce reliance on opioids.

Funding Opportunity Announcements for researchers to apply to participate in the A2CPS program are now available. NIH is seeking applications for multisite clinical centers for the surgical and musculoskeletal pain studies, a clinical coordination center, omics data generation centers, and a data integration and resource center.

Applications are due October 24, 2018. Once the program's researchers are selected, they will enter a planning year to prepare for study launch and patient recruitment. Recruitment for approximately 1,800 participants per study could begin as soon as 2019.

The A2CPS program is supported by the NIH Common Fund and is managed by a trans-NIH working group representing multiple NIH Institutes and Centers, led by the Office of the Director, the National Institute on Drug Abuse, and the National Institute of Neurological Disorders and Stroke.

nih.gov

Can Treatment during Surgery Reduce Postoperative Opioid Use?

With the current concerns related to opioid addiction and overdose, researchers from the National Institute on Drug Abuse (NIDA) are exploring ways to reduce the use of opioids for pain relief, while still effectively managing pain.

In a randomized clinical trial, 422 patients undergoing a variety of operations were given the medicine gabapentin during and after surgery, while other patients were given placebos. Gabapentin is an anti-epileptic medication (an anticonvulsant) and is also used in adults to treat certain kinds of nerve pain.

After surgery, researchers then noted the patient's use of opioids. They measured not only their need for opioids to manage postsurgical pain, but also how quickly these patients were ready to stop using opioids.

The study showed that 72 hours of perioperative gabapentin did not eliminate postsurgical pain more quickly, but it did significantly reduce the duration of opioid use.
These findings suggest that gabapentin may be a valuable adjuvant to prevent the development of postoperative chronic opioid use.

The study was sponsored by the National Institute on Drug Abuse and the Stanford Department of Anesthesiology.

drugabuse.gov

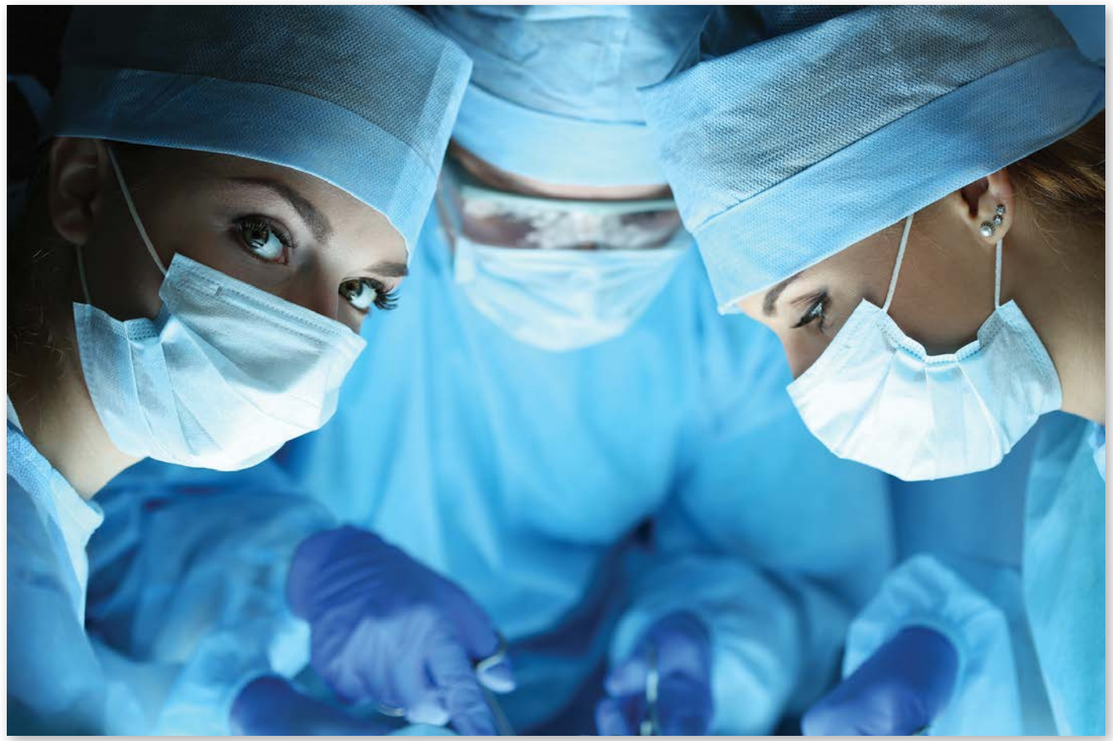


Photo Courtesy of NIH

Prostate Cancer Journey Leads to Immunotherapy

People who say doctors make the worst patients haven't met Tom, a retired surgeon who has brought extraordinary insight and empathy to his 14-year battle with prostate cancer.

An abnormal prostate exam in 2004 raised the first alarm. A subsequent blood test showed that Tom had rising levels of prostate-specific antigen (PSA), a protein produced by the prostate, a walnut-sized gland that sits just below the bladder in males. Rising PSA can be the first indicator of prostate cancer, so Tom's doctor ordered a biopsy, which was indeed positive for cancer. "At that time, it was what I'd consider garden-variety prostate cancer," Tom recalls, "the type most guys get. I'm a surgeon, so there was no question what I was going to do — have an operation. Get that bad boy out of there, be done with it and just go on with my life." However, surgery to remove Tom's prostate was just the first leg in a long, difficult journey.

Six weeks after surgery, further tests showed that Tom's was a very aggressive tumor. "The radiation oncologists wanted to irradiate the area, but I was concerned that my cancer was so aggressive, it may have already spread to other parts of my body." So, Tom and his doctor opted for a standard post-surgery regimen of chemotherapy and androgen-deprivation therapy (ADT). Androgens (male hormones) stimulate prostate cancer cells to grow. The goal of lowering androgens, particularly testosterone, is to make prostate tumors shrink or grow more slowly.

Tom went through six cycles of chemo followed by two years of ADT. At the end of those two years his hair had come back but shortly after so did his testosterone, and his PSA just kept rising. Scans showed no cancer beyond the area where his prostate had been, so in late summer 2008 Tom underwent radiation therapy. Finally, his PSA dropped to undetectable levels and stayed that way for the next four years. "I started to think that maybe I'd beaten this thing, but just before the five-year mark, my PSA was back and rising rapidly," Tom says. "In fact, my PSA level increased by 100 percent in less than three months, so my prognosis wasn't good."

Tom turned next to immunotherapy, enrolling in a clinical trial at NIH. Unfortunately, his PSA continued to rise and after trying a second form of immunotherapy that only lowered his PSA for two months, another study at NIH was just starting to enroll patients.

The study Tom enrolled on in late summer 2016 is for men with metastatic castration-resistant prostate cancer. This means that the cancer has spread from its original point of origin and is no longer responding to drugs that suppress male hormones. "That's the kind of cancer I had by this time," Tom explains. "The cancer had spread to my bones and into my bladder and ureters. I had to have stents placed in both ureters to prevent urine blockage."

The study is led by James Gulley, MD, PhD, Chief of the Genitourinary Malignancies Branch in the Center for Cancer Research at the National Cancer Institute. The trial combines two different types of immunotherapy drugs. PROSTVAC is a vaccine designed to make the immune system recognize and attack cancer cells that express PSA. Nivolumab is an immune checkpoint inhibitor. As Tom explains, "Cancer sends up signals that tell the immune system, 'I'm not something you need to worry about. Just ignore me.' But nivolumab shuts down cancer's ability to do that, so the immune system can get in there and attack the cancer and kill it." Two weeks after receiving the study drugs, Tom started feeling more energetic. "I thought, 'Wow! Something is going on here!'" But that wasn't the only surprise. After three weeks, his PSA level had dropped by 80 percent, and three weeks after that it had dropped a further 80 percent.

In autumn 2017 a series of new scans showed a significant decrease in the size of Tom's original tumor where his prostate had been and less active bone metastases. His PSA had also dropped to nearly undetectable levels, and there was no evidence of cancer in his bladder and ureters.

Tom is philosophical about his prognosis. Referencing his treatment, he says, "But even if they stop working someday, at least they've given me many months of energy and joyful living. This is beyond anything I could have hoped for." These days he sees advising other prostate cancer patients about their options and what to expect from treatment as a form of service. "That's my joy now. It's what I went into medicine for."

As for his experience at the Clinical Center, Tom describes Dr. Gulley and his team as "brilliant and compassionate." For patients considering a clinical trial, his advice is to examine the risks and benefits. "There's a lot of benefit to being in a trial at the NIH because the doctors here are totally focused on your medical care," he says. "And as a patient, you're helping to advance their knowledge."

cancer.gov

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International Awareness to Improve Management

Scholar Advocates for Kosovars with Ostomies

As head of the Kosovo Ostomy Association, Arta Uka works to help Kosovars who have ostomies — artificial openings in an organ of the body created during a surgical operation. She is currently working on a project to inform citizens about the condition with leaflets and brochures in Albanian and Serbian. She also plans to organize doctor lectures on how to best live with an ostomy.

Uka's participation in a USAID leadership program helped get her where she is today.

In 2015, Uka finished a semester's worth of credits at the University of California Berkley, earning a professional certificate in Management and Leadership under USAID's Transformational Leadership Program — Scholarships and Partnerships. The program is implemented by World Learning and co-funded by the Government of Kosovo.

"My experience at Berkley was absolutely incredible," says Uka. "Both academically and socially. The way of life there is very inspirational. If it hadn't been for my experience with the Transformational Leadership Program and my time at Berkley, I wouldn't have been able to apply for Advancing Leaders Fellows."

In 2016, Uka became one of World Learning's seven Advancing Leaders Fellows worldwide. The fellowship, which is open to all alumni of World Learning programs, provides training in social innovation and project management and leadership as well as providing grants and mentor networks to selected high-achieving fellows who have social innovation projects in their home countries.

Arta Uka, far left, and other recipients of the Advancing Leaders Fellowship Award
Photo Credit: WorldLearning

In the initial stage, Uka was one of around 50 people who were selected for the two-month online portion of the fellowship with online lectures and webinars on project management and leadership.

"Every week we had to submit homework, and this was all done to prepare us for writing a social innovation project proposal to help our community," says Uka. "Because we would peer-review each other's homework assignments, I learned a great deal from my competition and classmates. My classmates' projects focused on providing shelter, nutrition and help with abuse."

At the end of those two months, the "survivors" who completed all assignments were qualified to apply for the Washington, D.C. portion of the Advancing Leaders Fellowship.

Uka was accepted into the fellowship and her project proposal was to further her work to help Kosovars with ostomies.

"The initial idea started from my mother," she explains. "My mother had colon cancer and we had to go through a lot of researching to help us manage."

Following her mother's diagnosis, Uka started learning about the illness and founded the association. Her subsequent participation in the scholarship and fellowship programs has strengthened her ability to advocate for the association's cause.

"The goal is to have all Advancing Leaders Fellows complete their projects by April. My personal target is to have a website, conduct two focus groups, and start producing the information brochures by that time," says Uka. "I've already met with the minister of health and he has been very supportive." One hundred beneficiaries are expected to benefit from Uka's project by April.

Uka has already received help and donations from London (which donated bags in the past), Luxemburg and the United States for her association. All her work has been purely voluntary.

USAID's five-year Transformational Leadership Program — Scholarships and Partnerships began in 2014 and strives to develop a cadre of leaders that will drive change in priority economic, political and social areas in Kosovo.

usaid.gov

Six WOC Nurses that Inspire the Ostomy Community

By Ed Pfueller, United Ostomy Associations of America, Inc.

There is no doubt the world would be a better place with more wound, ostomy and continence (WOC) nurses. For many, WOC nurses are the first sign of hope after a life-changing surgery. The right nurse can provide confidence when there is doubt, and comfort when there is pain or fear.

April 15-21, 2018 marks WOC Nurse Appreciation Week and this year is also the 50th Anniversary of the Wound, Ostomy and Continence Nurses Society™ (WOCN®). For those of us at UOAA these nurses are so much more than medical professionals. They are our affiliated support group leaders, advocacy champions, cheerleaders, advisors, friends, national leaders, speakers, stoma clinic volunteers, event organizers, fundraisers and so much more.

It is one of our great joys (but also one of our biggest challenges) to select just one recipient of our WOC Nurse of the Year Award. Unsung and unrecognized nurses can be found in every corner of our national network of support.

Prepare to be inspired by these testimonials from our Affiliated Support Groups who nominated this year's amazing group of nurses. Feel free to share with us in the comments a special nurse who has helped you on your journey and learn a bit about the people behind the credentials.

2017 Recipient of the UOAA WOC Nurse of the Year Award Frances Wilson with President Susan Burns

Anne Marie Knudsen

ANNE MARIE KNUDSEN – SOUTH BAY OSTOMY SUPPORT GROUP IN CALIFORNIA

Anne has served as the group's program coordinator 330 months (or 30 years and 11 months the nominators say.) She encourages doctors to utilize ostomy visitors to make a difference from day one. She provides free home visits to members and encourages all to attend meetings.

"She is always available, a mentor, has a compassionate heart, loves all ostomates and is an inspiration. She gives free time to the group and uses her own money to present gifts of appreciation to speakers. She will visit all who are desperate for care at no charge. I have the greatest respect for Ms. Knudsen she is an angel for sure!!"

GINA DAY – OSTOMY SUPPORT GROUP OF THE POCONOS IN PENNSYLVANIA

Gina founded the group last year bringing much-needed ostomy support to the region. Gina provides educational programs for the group and heavily promotes the group in her area by hosting a Run for Resilience Walk Ostomy 5k walk, appearing in local media stories and last year even got the mayor to declare Ostomy Awareness Day.

"Her dedication, persistence and passion brought an awareness to our community that it so greatly deserves. Her positive

Gina Day

personality and motivational disposition is an inspiration for our members. Gina Day connects with group members in an indescribably sincere manner. The support group slogan is "You will never be alone" and Gina sees to it that people are not. Gina fills the void and disconnect that some patients feel after they leave the hospital through her support and forums to share stories. Her outstanding expertise has benefited those living with an ostomy in our area greatly."

CHARLOTTE POPOVICH – OSTOMY ASSOCIATION OF METRO DENVER

Charlotte is a tireless volunteer with a deep connection to the doctors and ostomates in her community judging by the pages of praise that accompany her nomination. They say she has an instinct for knowing when patients need that extra push of confidence to take matters into their own hands.

Charlotte Popovich, center with UOAA President Susan Burns to her left and WOCN President Kelly Jaszarowski to her right

"Her strongest attribute is her total commitment to the ostomy community's needs. It is amazing her attention to our new members' medical and emotional needs as well as being available to them 24/7 at a moment's notice. Her rate of referrals from surgeons is unmatched. After working all day, she voluntarily attends all evening support group meetings and does question and answer sessions to address patient concerns."

And in a Letter from Dr. Sandosh Nandi

"The dedication to her craft is unparalleled. She is diligent, caring, knowledgeable and thorough. She has helped so many patients and the praises they sing go on and on. She not only teaches patients about their ostomy but helps them with social and mental hurdles as well. She takes calls on vacation and stops by someone's house for an emergency change in the middle of the night. She is nothing short of amazing. Big heart and a very caring tough love approach."

LARA LEININGER – TRIANGLE AREA OSTOMY ASSOCIATION IN NORTH CAROLINA

Lara is known as her group's cheerleader in her role as a WOCN support nurse. She supports guest speakers and is available to participants for one on one questions after formal meetings. She also makes her contact information available should questions arise from participants between monthly meetings. She supports the health and wellness of her group through her commitment to living a healthy lifestyle through exercise and helps others to believe that an ostomy does and should not limit a person's life in any way.

Lara Leininger, (right)

"Lara, in her many years of working as a WOCN for the University of North Carolina Hospital, has shown love, compassion, care and kindness to her many ostomy patients and has shown ongoing support for her WOCN colleagues in her community.

Lara has been so devoted to the ostomy community that in 2014 she co-founded the Wanna War One Ostomy Awareness 5K in Durham, NC. This empowering event now known as the Run For Resilience Ostomy 5K, supports the educational and advocacy programs of the UOAA.

The event will be celebrating its fifth anniversary on October 2018 and will represent nine locations across the country. Lara has also been a dynamic volunteer and speaker at two UOAA national conferences and has shared the story of caring for her mother, an ostomate, through the Phoenix Magazine, Spring issue 2017. As stated in this article from her colleagues "Lara is a person and nurse of great care. She fills with emotion when talking about her love for her patients. When her mom became ill and it was evident that she was facing ostomy surgery, Lara dove deep into the journey with her mom. This is what Lara does and who she is".

ANGELA LADNER – GULFPORT MISSISSIPPI OSTOMY SUPPORT GROUP

As part of the first UOAA support group in Mississippi Angela secured the location at Memorial Hospital for groups and arranges for local home health, pharmacies and manufacturer participation with the group.

"She encourages patients to participate in the group's activities mentally and emotionally with body image issues. She is a liaison with physicians to encourage participation and outreach. She is caring and supportive of her population. Willing to assist in the needs of the patient and the family. She helps the indigent population with resources for supplies.

She also coordinated an effort to assist flood victims in Houston with ostomy supplies. She is respected by patients, colleagues, and families."

Angela Ladner, (right) with her husband Kyle

KATHRYN BAXTER – UNITED OSTOMY SUPPORT GROUP OF ORANGE COUNTY NY

Kathy has been a devoted liaison, exceptional WOC/ET Nurse for the group for over 25 years. The group counts on her expertise and knowledgeable background as a PA in the busy NYC Hospital Mt. Sinai.

"Kathy" as we all know her has always from the very first time she came to a meeting has been interested in the complete rehabilitation of every ostomate. She finds ways often to resolve the most difficult ostomy problems for those who think they will never have a resolution.

Kathryn finds the time to help in programming and acquisition of products for the Chapter. If it weren't for her support over the years this Chapter would cease to exist. We are grateful for all the time and talent she has brought to us clinical evaluations, information support on newest equipment and surgeries, caring and advising meeting participants on what is available medically as well as psychologically.

Ostomy surgery is a life-saving procedure that allows bodily waste to pass through a surgically created stoma on the abdomen into a prosthetic known as a 'pouch' or 'ostomy bag' on the outside of the body or an internal surgically created pouch for continent diversion surgeries. An ostomy may be necessary due to birth defects, cancer, inflammatory bowel disease, diverticulitis, incontinence and many other medical conditions. They are also necessary in cases of severe abdominal or pelvic trauma resulting from accidents or from injuries sustained during military service.

Between 725,000 and 1 million Americans are living with an ostomy, and approximately 100,000 new life-saving ostomy surgeries are performed annually in the United States.

If you have a patient who will have an upcoming ostomy or continent diversion surgery and could benefit from an ostomy support group, please visit the group finder page at the United Ostomy Associations of America, Inc. (UOAA) website: www.ostomy.org/support-group=finder

Currently there are approximately 300 affiliated ostomy support groups throughout the United States which provide local support to their communities. UOAA also welcomes medical professionals to start a support group of their own and can provide assistance to help.

WOC nurses are the first sign of hope after a life-changing surgery. The right nurse can provide confidence when there is doubt, and comfort when there is pain or fear.

When President Ronald Reagan signed Proclamation 5231 on August 28, 1984 to designate National Ostomy Awareness Month, it was referred to as "the secret surgery" because ostomates did not want others to know about their condition.

Today, largely through the efforts of the United Ostomy Association, Americans needing this treatment are becoming more aware of the opportunities for education, mutual aid, and support that are of such great benefit to them and to their families. Increased public understanding of ostomy will eventually help dispel the fear of those about to undergo this surgery as well as the fear that confronts their families. Both the Federal government and the private sector are deeply committed to the proper care and advancement of knowledge about gastrointestinal diseases and public education about ostomy.

CPG

History of the Office of the Surgeon General

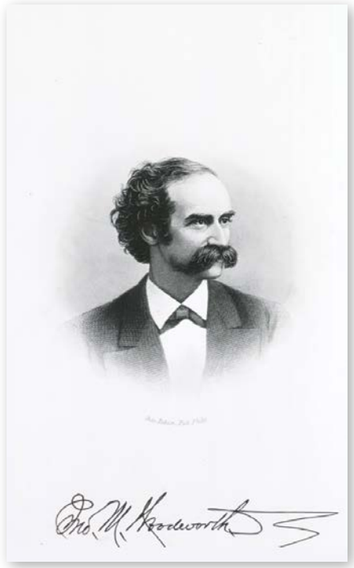
In 1798, Congress established the U. S. Marine Hospital Service — predecessor of today's U.S. Public Health Service — to provide health care to sick and injured merchant seamen. In 1870, the Marine Hospital Service was reorganized as a national hospital system with centralized administration under a medical officer, the Supervising Surgeon, who was later given the title of Surgeon General.

Dr. John Woodworth, was appointed as the first Supervising Surgeon in 1871, and established a cadre of medical personnel to administer the Marine Hospital System. On January 4, 1889, the Congress recognized this new personnel system by formally authorizing the Commissioned Corps. The Corps was established along military lines to be a mobile force of professionals subject to reassignment to meet the needs of the Service. Originally, the Corps was composed only of physicians.

However, over the years, as the functional responsibilities of the Public Health Service (PHS) and the Corps have broadened, a commensurate broad range of health professionals has been included.

Prior to 1968, the Surgeon General was the head of the PHS, and all program, administrative, and financial management authorities flowed through the Surgeon General, who reported directly to the Secretary of Health, Education, and Welfare. In 1968, pursuant to a reorganization plan issued by President Lyndon B. Johnson, the Secretary delegated line responsibility for the PHS to the Assistant Secretary for Health.

The Office of the Surgeon General was



Dr. John Maynard Woodworth

abolished and the position of Surgeon General became that of a principal deputy to the Assistant Secretary for Health with responsibility for advising and assisting on professional medical matters.

In addition, a primary role developed in which the Surgeon General became the PHS spokesperson on certain health issues. (Note: In 1972, the Surgeon General again became an advisor to the Secretary rather than the ASH. In 1977, the positions of ASH and Surgeon General were combined; in 1981, they were separated again.)

In 1987, the Office of the Surgeon General (OSG) was reestablished as a staff office within the Office of the Assistant Secretary for Health. Concomitant with this action, the Surgeon General again became responsible for management of the Commissioned Corps personnel system. (Note: The Surgeon General does not directly supervise all Commissioned Officers; most work in PHS or other agencies and report to line managers of those agencies who may or may not be in the Corps.)

In carrying out all responsibilities, the Surgeon General reports to the Assistant Secretary for Health, who is the principal advisor to the Secretary on public health and scientific issues.

In April 1987, Surgeon General C. Everett Koop launched a major effort to revitalize the Corps. Actions were taken to enhance all aspects of Corps management, including recruitment, especially of women and minorities, assignment, career development, and communication. Special efforts were made to make sure that agencies utilizing officers are actively involved in the formulation and review of policies and procedures related to administration of the Corps.

There currently are more than 6,700 officers on active duty. Officers are assigned to all of the PHS Agencies and to a number of agencies outside of PHS, including the Bureau of Prisons, U. S. Coast Guard, Environmental Protection Agency, Health Care Financing Administration, and the Commission on Mental Health of the District of Columbia.

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