



Pulmonary specialists at HUP discuss various aspects of chronic obstructive pulmonary disease, pulmonary fibrosis, and asthma.

Feature Article:

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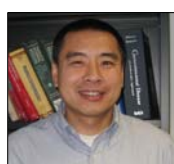
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Q&A: A Discussion of Various Lung Disorders

In this feature Q&A article, we are considering various pulmonary conditions that are occasionally mentioned in the news but may often fly beneath the radar despite notable prevalence rates. Unless an individual knows someone with pulmonary fibrosis, awareness of this often fatal condition, if it enters a person's consciousness at all, likely registers upon hearing that a celebrity has been felled by it. Indeed, in the last few years pulmonary fibrosis was the cause of or contributing factor to the deaths of singer/actor Robert Goulet; daredevil Evel Knievel; authors Peter Benchley and Peter

Stone; actors Marlon Brando, James Doohan, and Gordon Jump, and most recently, comic book writer and creator of "Howard the Duck," Steve Gerber. Samuel Johnson, British literary figure of the 1700s, is also said to have died of pulmonary fibrosis and the steroid treatment for pulmonary fibrosis was cited for comedian Jerry Lewis's dramatic weight gain just a few years ago.

Chronic obstructive pulmonary disease (COPD) and asthma are much more prevalent and more often acknowledged or discussed in mainstream media, but may be eclipsed in health-related news by stories on higher profile conditions. According to the

National Heart Lung and Blood Institute, approximately 13.5 million Americans (or roughly 1 in 20) have COPD. Considerably fewer people are afflicted with pulmonary fibrosis in the US, with an estimated 200,000 patients, according to the Pulmonary Fibrosis Foundation. However, the mortality rate from this disease is nearly 40,000 annually, which is the same as the number of individuals that die from breast cancer, suggests the Pulmonary Fibrosis Foundation. Asthma is believed to affect 20 million Americans

(approximately 1 in 15), and across all demographic

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Faculty Profile:



Justine Shults, PhD, Assistant Professor of Biostatistics, Senior Scholar, CCEB

Justine Shults, PhD, collaborates on research in the Longitudinal Analysis for Diverse Populations (LADP) program

Justine Shults was born near Sydney, Australia, moved to London at age one, and then to the US at age five. Her father was a refugee from Estonia who moved to Australia, where he eventually attended medical school, met and married Justine's mother, and then continued his medical training in London, eventually settling with his family in the US. Justine ran track in high school and participated on the debate team. When considering potential colleges, the service academies were appealing to her because they offered a well rounded education that focused on military training and physical education, in addition to offering strong academic programs. The fact that they were totally free was also very attractive. She applied to West Point, the Air Force Academy and the United States Naval Academy (USNA) and was accepted to the three schools, but decided to attend USNA because it seemed to be the strongest academically. She stayed at USNA for plebe summer, her freshman (plebe year), and then half of her sophomore year, but then decided to resign. There was (and perhaps continues to be) resistance to women in USNA. In addition, Justine had not identified a career in the Navy that was worth staying for, unlike her classmates who for example, knew that they wanted to become pilots, or submariners, or go into surface warfare.

After resigning from USNA she worked as a door-to-door fundraiser for the Citizens Action Coalition of Indiana for six months, where she learned a lot about raising money and communicating with different types of people. She then transferred to the University of Notre Dame, where she graduated with a BS in mathematics in 1985. After graduation she married fellow Notre Dame classmate Eugene Charles (Chuck) Shults, who was in Navy ROTC at Notre Dame with the goal of becoming a Navy pilot. After moving to Pensacola, FL for flight school, Justine and Chuck were stationed in Hampton Roads, Virginia.

Justine then completed a secondary school teaching certificate in mathematics at Virginia Wesleyan College in 1988 and took a job as a high school math teacher in a public school in Virginia Beach. While working as a teacher, Justine passed some preliminary actuarial exams and also enrolled in evening courses in statistics at Old Dominion University. She was planning to complete a master's degree at night while teaching during the day, but Dr. Ram Dahiya (the graduate program director at the time) called her and encouraged her to give up her teaching job and enroll in their PhD program in Applied Mathematics (Statistics Option) as a full-time student.

Justine was initially planning to do her dissertation research in mathematical statistics, but her career plans changed when Dr. Ardythe Morrow, Dr. Larry Pickering and colleagues, moved to Norfolk, VA from Houston, TX to found the Center for Pediatric Research (CPR) at Eastern Virginia Medical School. Justine was given the opportunity to do her work for her research assistantship (RA) at the CPR. She was funded by an NIH program project in human milk that had been continuously funded for 25 years. The main hypothesis of this study was that human milk protects against infectious disease. A unique feature of the project was that the main study site was in Mexico City, Mexico; most NIH-funded program projects are conducted in the US. Consequently, Justine traveled to Mexico several times, where she was able to meet the study investigators in Mexico and collaborate on manuscripts related to the project.

While working at the CPR, Justine learned the importance of combining theory with applications. After earning her MS in applied and computational mathematics (statistics option) in 1993, she began work on her dissertation research in mathematical statistics with Dr. N. Rao Chaganty, who had done his dissertation research in large deviations. For her RA work, her mentor at the CPR, Dr. Morrow, asked her to learn about a relatively "new method," generalized estimating equations (GEE), that Ardythe had heard about through her previous RA, who had left Houston to attend graduate school in biostatistics at Harvard. GEE is widely used in biostatistics because it allows for extension of generalized linear models for

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Faculty Profile:

Yu-Xiao Yang, MD, MSCE, studies the various health effects of acid-suppressive drugs, especially proton pump inhibitors

Yu-Xiao Yang was born and raised in Shanghai, China. The political turmoil in China during the Cultural Revolution prompted Yu-Xiao's parents to accept an opportunity to pursue their doctoral educations in the United States in the early 1980s. After finishing his first year of college in Shanghai, Yu-Xiao finally reunited with his parents in New York City in June of 1988. Knowing little English at the time, he enrolled in an English as a Second Language course that summer and resumed his college education in the fall at the City College of New York. Although he chose electrical engineering as his major because of his limited English skills, his real aspiration was to become a physician like his father and grandfather, and it was not until the end of his sophomore year, when his English had improved enough, that he ventured into pre-med courses.

In 1992, Yu-Xiao graduated *summa cum laude* with a bachelor's degree in electrical engineering and began his medical training at New York University School of Medicine. In 1996, he completed his MD and really had his heart set on one of the internal medicine residency programs in New York City. However, after a visit to HUP, he became convinced that the ideal place for his residency training really was at Penn.

In 1999, Dr. Yang completed his internship and residency

in medicine at HUP. Although his original plan had been to return to New York City, Philadelphia had grown on him. More importantly, he was not going to pass on the opportunity to pursue his GI fellowship training at the nationally renowned GI Division at Penn and at the same time receive formal training in clinical epidemiology in the MSCE program in the Penn CCEB.



Dr. Yang became an Instructor in Medicine and a faculty/fellow in the CCEB in 2002 and earned his MSCE degree in 2003. In 2005, Dr. Yang was appointed Assistant Professor of Medicine and Epidemiology, University of Pennsylvania SOM, and a Senior Scholar, Epidemiology, CCEB. In addition to his academic positions in the Penn SOM and CCEB, Dr. Yang is an attending physician at HUP, Presbyterian Medical Center, and the VA Medical Center. He is also a member of the American Gastroenterological Association, American College of Epidemiology, and the International Society for Pharmacoepidemiology. He is board certified in internal medicine and in gastroenterology.

As a gastroenterologist, his

clinical areas of focus are in gastrointestinal cancer, acid peptic disease, and GI motility disorders. From the standpoint of epidemiology, his main research interest is in GI cancer epidemiology and pharmacoepidemiology. His research program reflects these interests.

Dr. Yang credits his mentors, Drs. Jim Lewis and Brian Strom, with introducing him to pharmacoepidemiology research. Within the field of pharmacoepidemiology, he has been particularly interested in phase IV post-marketing surveillance. He believes that many common drugs can have clinically important harmful or beneficial effects that are not apparent in the pre-marketing stage. These effects will only emerge from large-scale post-marketing observational studies that are based on well-conceived hypotheses. The advent of large computerized medical records systems over the past two decades has provided an ideal data source for such studies. In the process of such work, Dr. Yang has become very fond of the General Practice Research Database (GPRD).

One major focus of Dr. Yang's pharmacoepidemiology research program relates to the safety of the widely used acid-suppressive drugs, particularly the proton pump inhibitors (PPIs). For example, he recently led a landmark study pub-

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From the Director:



Brian L. Strom, MD, MPH

Thank you for your continued interest in the CCEB Newsletter, which serves as a forum for us to keep you informed of activities within the CCEB. In each issue, we highlight one of the services provided by the CCEB for faculty, residents, and fellows within UPHS and those external to Penn; present feature articles on a few members of our faculty; identify newsworthy events likely to be of broad interest; and provide feature articles on topics of interest.

In this issue, we include an article about the Outcomes Measurement Methods Core (OMMC), a new service funded by the Clinical and Translational Science Award. The OMMC is designed to assist investigators and others in the selection and use of measurement tools needed for the development, conduct, and analysis of translational and clinical research projects. Multiple levels of collaboration and assistance are available. Please see the article for more information about the services provided by the

OMMC and our website (<http://www.cceb.upenn.edu/services/>) for the full range of services we provide.

We also include in this issue a feature article about chronic obstructive pulmonary disease, pulmonary fibrosis, and asthma. Andrea Apter, MD, MSc, Professor of Medicine, Chief of the Allergy and Immunology Section of the Division of Pulmonary, Allergy, and Critical Care Division, and Associate Scholar in the CCEB, and Jeffrey Munson, MD, a Fellow in the Division of Pulmonary, Allergy, and Critical Care Division and MSCE student, respond to a series of questions about these respiratory diseases.

Two members of our faculty also are featured in this issue: Yu-Xiao Yang, MD, MSCE is Assistant Professor of Medicine, Gastroenterology Division, and Senior Scholar in the CCEB. His research interests include gastrointestinal cancer and pharmacoepidemiology. Justine Shults, PhD is Associate Professor of Biostatistics at HUP (effective July 1, 2008) and Senior Scholar in the CCEB. Justine's methodologic research interests focus on clustered data, longitudinal methods, and repeated

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In Memoriam:

The CCEB mourns the loss of Dr. Joel David Portnoy, who passed away in early March. He is survived by his wife, Dr. Eron Y Friedlaender, who is an attending in Pediatric Emergency Medicine at CHOP, their children Alexander and Emma, and Joel's parents, Jaclyn and Lawrence F. Portnoy. Joel was a fellow (1998-2001), and subsequently an attending (2001-2004) in Critical Care Medicine at CHOP. He received training in clinical epidemiology from the CCEB from 1999 to 2001 and received a K award from AHRQ evaluating the importance of medical errors in the care of critically ill children. He practiced in the Pediatric Intensive Care Units at CHOP,

Lehigh Valley Hospital, and Temple Children's. He subsequently received an MBA at Wharton and was working at McKinsey & Co. where he consulted in the areas of health care.

Donations can be made in Joel's memory to the Joel Portnoy Memorial Fund at autismspeaks.org.



Dr. Joel Portnoy

The CCEB Newsletter is published by the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, for the dissemination of information and as a reference for its constituents. The CCEB Newsletter is published periodically free of charge, and distributed to the Medical Center community. If you are interested in receiving hyperlinks to the newsletter, please contact us at the address below.

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categories, the prevalence of asthma has increased since the early 1980s, according to the National Center for Environmental Health.

In this issue, Jeff Munson, MD, Fellow, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, and the CCEB, and Andrea Apter, MD, MA, MSc, Professor of Medicine, Pulmonary, Allergy, and Critical Care Division, Hospital of the University of Pennsylvania, Associate Scholar, Epidemiology, CCEB, discuss aspects of these diseases with an eye toward promoting awareness of these troubling conditions.

Q: *What are the symptoms and risk factors for COPD? Is this one of the more avoidable pulmonary diseases? What is the standard treatment protocol?*

JM: Many patients are diagnosed with COPD after developing slowly progressive shortness of breath and impaired activity tolerance related to the loss of functional lung tissue. Some patients have a chronic productive cough related to injury of the airways that in turn impairs normal clearance of respiratory secretions. Additionally, a subset of patients have a disease phenotype characterized by acute exacerbations during which they develop wheezing and severe shortness of breath. These symptoms are generally reversible with short courses of more intensive therapy but often require hospitalization for adequate management.

The most common risk factor by far for the development of COPD is cigarette smoking. Although there are rare enzymatic deficiencies and other uncommon risk factors that can cause early COPD, the overwhelming majority of cases are related to the use of cigarettes. The obvious implication of this is that

most cases of COPD are likely preventable.

Treatment of COPD typically involves the use of inhaled bronchodilators for symptomatic relief, formal pulmonary rehabilitation to reverse deconditioning and improve exercise tolerance, and the provision of supplemental oxygen when a patient's lung function deteriorates to the point that his or her blood oxygen level falls with exertion. Also, inhaled corticosteroids may reduce the rate of acute exacerbations in appropriate patients. Of these therapies, only the use of supplemental oxygen when indicated has been shown to prolong a patient's life. Annual influenza vaccination is critical in these patients as infection with respiratory viruses can be severe or even fatal. In certain cases of advanced disease, lung volume reduction surgery or the experimental use of airway valves may be considered. Finally, in the most severe cases, lung transplantation remains an option.

Q: *The Pulmonary Fibrosis Foundation states that pulmonary fibrosis is often misdiagnosed, suggesting that the number of patients with this disease is higher than the estimated 200,000 in the US. How much of an impact might misdiagnosis play in the course of treating this disease?*

JM: It is important to understand that pulmonary fibrosis is not in fact a single disease entity. It is a pathologic description of the end result of several different diseases, some of which we understand (somewhat), many of which we don't. The most common of these diseases is idiopathic pulmonary fibrosis (IPF).

There are two forms of misdiagnosis that may have important implications for patients with

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Faculty News and Notes

Several CCEB faculty have appeared in the news recently. A brief summary dating from late Dec. follows in alphabetical order.

John Farrar, MD, PhD, Assistant Professor of Epidemiology, University of Pennsylvania School of Medicine, Senior Scholar, Epidemiology, CCEB, is cited in a [Reuters](#) wire service article on the 11th of March about the new drug Bridion (known generically as sugammadex), which is designed to help patients more rapidly emerge from anesthesia. An FDA expert panel chaired by Dr. Farrar voted unanimously, 10-0, that the medication appears to be safe and effective, though it may not always be a better option than already existing therapies.

§

Joel Gelfand, MD, MSCE, Assistant Professor of Dermatology, University of Pennsylvania School of Medicine, and Associate Scholar, Epidemiology, CCEB, was the lead author of a [study](#) published in the *Archives of Dermatology* that linked severe psoriasis to a higher death risk. This study, co-authored by several CCEB faculty, was initially reported on by HealthDay News on the 17th of December, with reports disseminated to news organizations such as [The Washington Post](#), *U.S. News and World Report*, *Reuters* and *Agence France-Presse*.

§

Sean Hennessy, PharmD, PhD, Assistant Professor of Epidemiology and of Pharmacology, University of Pennsylvania SOM, Senior Scholar, Epidemiology, CCEB, and Director of the Ambulatory Drug Use & Effects Program, was quoted on the 27th of December in a *BusinessWeek* [analysis](#) of recalls of over-the-counter children's cough and cold remedies and FDA discussion about the medications' safety. Dr. Hennessy is a member of the FDA's Nonprescription Drugs Advisory Committee, which concluded in October that children under the age of six should not be given these medicines. In addition to concerns about overdose, he contended that there is no proof that such drugs are effective.

§

Ebbing Lautenbach, MD, MPH, MSCE, Assistant Professor of Medicine and Epidemiology, University of Pennsylvania SOM, Senior Scholar, Epidemiology,

CCEB, was quoted in the March 18th edition of the [Chicago Tribune](#) in an article about the prospect of screening all hospital patients for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. This story was prompted by the recent publication in the *Annals of Internal Medicine* of a study conducted by researchers at Evanston Northwestern Healthcare, in Illinois, who found, contrary to a previous study published in *JAMA*, that conducting such screening could significantly reduce the number of nosocomial infections. Dr. Lautenbach was interviewed to discuss the content of his [editorial](#) that accompanied the report by the Evanston team.

§

Timothy Rebbeck, PhD, Professor of Epidemiology, University of Pennsylvania SOM, Senior Scholar, Epidemiology, CCEB, was featured in a radio story on [WHYY FM](#) regarding his recent study published in the *Journal of Clinical Oncology* demonstrating that breast and ovarian cancer risk reduction after ovary removal is associated with different risk reduction rates for women with BRCA1 and BRCA2 mutations.

§

Nicolas Stettler, MD, MSCE, Assistant Professor of Pediatrics and Epidemiology, University of Pennsylvania SOM, CHOP, Senior Scholar, Epidemiology, CCEB, was interviewed by *Science Daily* for an [article](#) on the 7th of February that reviewed lead author Dr. Stettler's paper published in the January edition of *Obesity* that revealed bone mineral content increases in obese teenagers who lost weight in the year-long study. **Justine Shults, PhD**, Assistant Professor of Biostatistics, HUP, University of Pennsylvania SOM, Senior Scholar, CCEB, and **Mary Beth Leonard, MD, MSCE**, Associate Professor of Pediatrics and Epidemiology, University of Pennsylvania SOM, CHOP, Senior Scholar, Epidemiology, CCEB, were co-authors on the study.

§

Brian Strom, MD, MPH, Director, Center for Clinical Epidemiology and Biostatistics, was interviewed

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regarding the unusually long lag time between the completion of a study on Vytarin, in a comparison with Zocor, and the release of study data. The brief interview was posted on the 15th of January in the Health Blog column of *The Wall Street Journal*. Dr. Strom also appeared on ABC's *World News Tonight* on the 17th of January to discuss this issue.

Notes

ENAR Distinguished Student Paper Awards for 2008

The Department of Biostatistics & Epidemiology is pleased to announce that one of its students, **Hanjoo Kim**, was among the International Biometric Society Eastern North American Region (ENAR) Distinguished Student Paper Award winners for 2008. These highly competitive awards are presented annually to a select group of the best biostatistics students and recent graduates in eastern North America. Mr. Kim received his award and presented his paper "A unified approach for constructing a closed multiple testing procedure for a fixed sequence of families with multiple null hypotheses," at the ENAR Spring Meeting in Alexandria, VA in March 2008.

Award winners receive a certificate, reimbursement for travel up to \$500, free tuition for a short course at the meeting, complimentary issues of the *Journal of Agricultural, Biological, and Environmental Statistics (JABES)* published during the previous year, and an invitation to the Presidential Reception at the spring meeting. The winner of the John Van Ryzin Award, and an additional \$500, for best student manuscript is selected from the 20 Distinguished Stu-

dent Paper honorees.

Mr. Kim earned a BS in statistics from the George Washington University in 2005 and an MS in biostatistics from the University of Pennsylvania in 2007. His research interests include multiple comparisons and longitudinal modeling. Justine Shults, PhD, Assistant Professor of Biostatistics at HUP, Senior Scholar, Biostatistics, was a co-author on Mr. Kim's paper.

§

Shiriki Kumanyika, PhD, MPH, Associate Dean for Health Promotion and Disease Prevention, Professor of Epidemiology, University of Pennsylvania SOM, Senior Scholar, Epidemiology, CCEB, has been appointed Vice-Chair of the [US Department of Health and Human Services](#) advisory committee that will formulate recommendations for achieving national health promotion and disease prevention objectives for Healthy People 2020.

§

Hongzhe Li, PhD, Professor of Biostatistics, University of Pennsylvania, SOM, Senior Scholar, Biostatistics, CCEB, and head of the statistical genetics group in the CCEB, was recently elected to membership in the International Statistical Institute (ISI). Members are elected based on their distinguished contributions to the development or application of statistical methods, the administration of statistical services, or the development and improvement of statistical education. Candidates for elected membership must be nominated by three existing honorary or elected ISI members.

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measures. Justine's collaborative work includes applications of these methods to studies of renal diseases, depression, and obesity.

I also would like to remind those interested in training of our clinical research methods and biostatistics courses that we offer as part of our Clinical Research Certificate program. This summer, we are offering two sessions of intensive short courses. The first session runs from July 7th through July 18th. The second session runs from July 21st through August 1st. For the schedule of classes offered during these sessions, please see:

<http://www.cceb.upenn.edu/education/non-degree/coursescrtp.php>. For descriptions of these and other courses, please see: <http://www.cceb.upenn.edu/education/non-degree/courses.php#credit>. Registration for the summer sessions begins April 14th via the following registration portal: http://www.med.upenn.edu/apps/my/epi_course.

Finally, I would like to remind you to check our website (<http://www.cceb.upenn.edu/>) regularly for announcements and other newsworthy events and to find potential faculty (<http://www.cceb.med.upenn.edu/faculty/>) collaborators.

I hope you enjoy our newsletter.

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lished in *JAMA* that elucidated a novel association between chronic PPI therapy and the risk of hip fractures in the GPRD. As a core component of his NIH K08, he conducted a study investigating the association between chronic PPI therapy and the risk of colorectal cancer in the GPRD. The rationale for this study is based on the trophic effect of PPI-induced hypergastrinemia on colonic tissue. Furthermore, he has completed several studies on the associations between PPI therapy and clinical outcomes such as the risk of community-acquired pneumonia, flare of inflammatory bowel disease, and risk of spontaneous bacterial peritonitis. He is currently engaged in studies investigating the effect of PPI therapy on the risk of kidney stone and the safety of PPI therapy during pregnancy.

Dr. Yang has also developed studies on the effects of humoral/hormonal factors on GI cancer. He is currently leading a study that evaluates the role of androgens on the risk of Barrett's esophagus and adenocarcinoma of the esophagus. Funded by an NIH center Pilot Grant from the Center for Molecular Studies of Digestive and Liver Diseases at the University of Pennsylvania, he developed and completed two studies in GPRD as the core component of his master's thesis on the epidemiology of colorectal cancer among type 2 diabetes mellitus (DM) patients. This line of research is based on the hypothesis that hyperinsulinemia may induce cancer development. The first study elucidated a previously debated association between type 2 DM and the risk of colorectal cancer. The second study was based on the hypothesis that exogenous insulin therapy may expose DM patients to levels of systemic insulin much higher than endogenous hyperinsulinemia. This study identified new and compelling epidemiological evidence that chronic insulin therapy among type 2 DM patients leads to a markedly increased risk of colorectal cancer. Dr. Yang is also currently conducting a study to investigate the effect of exogenous insulin on colorectal adenoma development among type 2 DM patients. As a part of his NIH K08 he has completed a study examining the effect of statins on the risk of colorectal cancer. Along the same line of research, he is the senior author on a

study that revealed a chemopreventive effect of angiotensin-converting enzyme inhibitors on colorectal cancer, with specific attention focused on the potential effect modification of this association by the presence or absence of DM. Merging his interests in GI motility and pharmacoepidemiology, he recently completed an interventional study to determine whether a physician-targeted feedback system would lead to improved metoclopramide prescribing practices in the University of Pennsylvania Health System.

In 2005, Dr. Yang became an associate editor for *Pharmacoepidemiology and Drug Safety* and a section editor for *Drug Therapy, Disease Mechanism, GI Section*. In 2006, he began working as an associate editor for the *Annals of Internal Medicine*. He is also a reviewer for journals including: *JAMA*, *Archives of Internal Medicine*, the *American Journal of Gastroenterology*, *American Journal of Medicine*, *Epidemiology, Alimentary Pharmacology and Therapeutics* and *Gastroenterology*. Dr. Yang has several articles in press, as primary author, in publications including the *American Journal of Gastroenterology*, *Digestive Disease and Science*, *Journal of Clinical Gastroenterology*, and *Pharmacoepidemiology and Drug Safety*. He has also been the first author of papers published in *Clinical Gastroenterology and Hepatology*, *Pharmacoepidemiology and Drug Safety*, *Gastroenterology*, and *JAMA* (as cited above), and contributing author of articles appearing in the *American Journal of Gastroenterology*, *American Journal of Roentgenology*, *Annals of Internal Medicine*, *Journal of Clinical Epidemiology*, and *Journal of Clinical Gastroenterology*.

Dr. Yang enjoys time spent with his family, which includes his wife Cindy, a 7-year-old daughter named Lauren and two-year-old twin boys, Andrew and Marcus, who are fun and can cause a lot of damage. Dr. Yang's passion is soccer. He plays in local soccer leagues and despite sore knees, he is still able to keep up with the college boys. He also enjoys cooking. Dr. Yang still makes frequent trips to New York City to visit his parents and to eat Chinese food, which he claims is better in New York than anywhere else in the US.

CCEB's Clinical Research Services:

The Outcomes Measurement Methods Core (OMMC)

The CCEB serves as an interdisciplinary resource for clinical research throughout the School of Medicine and offers a range of services, primarily to faculty, residents, fellows, and research staff within the University of Pennsylvania Health System, but also to clinicians and scientists throughout the Delaware Valley with interests in such services. These services are identified and described as a regular feature of this newsletter.

The new Outcomes Measurement Methods Core (OMMC) has recently become operational as a service center funded through the institution's **Clinical and Translational Science Award (CTSA)**. The CTSA at Penn was created to transform the research process to more rapidly move science from bench to bedside to community. Please see the [CTSA website](#) for a full description of this program.

The OMMC is housed within the Center for Clinical Epidemiology and Biostatistics (CCEB), and is directed by a CCEB faculty member with assistance provided by two PhD-level staff members. All have expertise in measurement methodologies. In addition, 10 Penn faculty members from schools such as Education, Nursing, the School of Arts and Sciences, the School of Social Policy and Practice, and Wharton, and departments in the School of Medicine including General Medicine, Psychiatry, Family Medicine, and Geriatrics, are available, as needed, to provide assistance in their specific areas of expertise.

The mission of the OMMC is to assist investigators, key personnel, and trainees in the selection, modification, and/or creation of measurement tools needed for the development, conduct, and analysis of translational and clinical research projects. Services include collaboration, education, and consultation to assist in defining appropriate outcomes, locating or designing appropriate outcome measures or questionnaires, and guiding validity and reliability studies, including analyses of preliminary data for grant proposals.

Depending on the user's needs, different levels of collaboration are possible, ranging from minor assistance to faculty-level collaboration on major grants. The primary goal of the OMMC is to complete the design of a questionnaire or other measurement tool appropriate for the research question of interest to the investigator. Broadly speaking, the OMMC consultation may include help with:

1. Defining appropriate data collection variables for clinical research;
2. Locating or adapting appropriate measurement tools for psychological, medical and socio-behavioral factors;
3. Designing questionnaires or other measurement tools for the above areas where appropriate;
4. Interpreting measures and scores;
5. Writing text appropriate for grants defining the measurement tool's purpose, characteristics (including discussion of reliability and validity), and justification;
6. Choosing among various paper and electronic formats for collecting data (e.g., paper with double entry, computer readable, voice recognition, web-based, hand-held devices);
7. Developing innovative measurement tool designs (e.g., Item Response Theory techniques);
8. Advising on qualitative methods used to help create measures such as focus groups, cognitive interviewing, and feedback sessions;
9. Performing small validity and reliability studies, including analyses related to preliminary data for grant applications; and
10. Providing guidance on simple to potentially substantial and complex validation analyses.

To date, the OMMC has conducted several successful consults. As examples, in one case, the OMMC staff helped to create a survey to measure attitudes toward health resources. After meeting to assess the project goals, the OMMC identified standardized tools that were combined with a new instrument to meet the specific study needs. In other cases, assistance locating existing tools for pain measurement was provided. The OMMC has also reviewed the measures

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and constructs included in an investigator’s grant on testosterone therapy; created assessment tools to determine radiologists’ knowledge of ionizing radiation dose risks; developed a questionnaire to determine usefulness of an internet-based tool to aid in the transition of pediatric cardiology patients to adult congenital care; prepared a questionnaire and reviewed a tool to determine what puts women at risk for an unplanned pregnancy while in a clinical trial; reviewed a population-based survey of physicians and nurses regarding their attitudes toward regionalization, as well as the potential barriers to designing and adopting a tiered, regionalized system of care; and helped on the section of a grant to include the development and validation of a survey tool to assess barriers to effective

emergency cardiovascular care program implementation using a representative cohort of Ministry of Health administrators, hospital leadership personnel, healthcare providers and laypersons in Botswana.

Access to the OMMC is available via a web-based request. Request forms can be completed [here](#) by clicking “Let CCEB Help.” The inquiry will be directed to the Assistant Manager of the BAC leading to the OMMC. Requests are made both as part of an overall statistical plan or directly to the OMMC with specific need only for measurement methods help. You can also call or e-mail Dr. Abigail Cohen at 215-898-9411 or abigailc@mail.med.upenn.edu to determine if the OMMC can provide the services you need. You will be asked to register after a phone or e-mail consultation.

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pulmonary fibrosis. The first is that a patient’s non-specific symptoms of progressive shortness of breath and chronic cough may not be recognized as the manifestation of a rare disease but may be attributed to a more common disease such as COPD or even gastroesophageal reflux and deconditioning. The correct diagnosis may only be made after other manifestations of pulmonary fibrosis such as X-ray or physical exam findings become more readily apparent. While this delay may not have a significant impact on those forms of pulmonary fibrosis for which there is no definitive therapy, namely IPF, it can be important for other less common forms in which a reversible etiology can be identified. In these uncommon cases, a delayed diagnosis can result in more advanced scarring of the lung. This scarring may not be reversible even after the inciting exposure is removed.



Jeff Munson, MD, Fellow, Division of Pulmonary and Critical Care Medicine, HUP, CCEB

of the patient’s home or work environment. While these forms of pulmonary fibrosis are uncommon, it is important to distinguish them from IPF in order to appropriately tailor treatment recommendations.

Unfortunately, making this distinction is often very difficult even with a definitive diagnostic procedure such as a lung biopsy. As a result, some patients who do not have IPF are misclassified and not offered treatment, while others who in fact do have IPF are given therapies that have no significant potential for benefit but are associated with several potential toxicities.

Q: *Are certain demographic groups more susceptible to developing pulmonary fibrosis?*

JM: IPF is seen more often in men than in women and generally occurs between the ages of 40–70 years. The average age at the time of diagnosis is between 60–65 years. There appears to be no racial, ethnic, or geographic predominance. Cigarette smoking may be

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correlated data; for example, with GEE you can apply logistic regression to repeated measures data. Justine spent a considerable amount of time trying to learn about and program this procedure (which at that time was not available in standard statistical packages and was not as familiar to mathematical statisticians as it may have been to biostatisticians), much to the dismay of her dissertation advisor, who was understandably concerned that this focus on GEE was a distraction from her dissertation research. However, he eventually became interested as well and they worked on several papers that described the development of quasi-least squares (QLS), an alternative computational approach for estimation of the correlation parameter in the framework of GEE.

While working on her dissertation, Justine recognized an advantage of QLS, namely that it can be used to more easily implement complex correlation structures that have not yet been applied in the framework of GEE. For example, she proposed implementation of the Markov correlation structure that extends the AR(1) structure to data that are unequally spaced in time. The ability of QLS to allow for consideration of more complex patterns of association in the data can yield estimates of the regression parameter that are more efficient and can be useful when the correlations themselves are of scientific interest. Justine completed her PhD in applied and computational mathematics – statistics option, in 1996. In 1997, Dr. Shults became an Assistant Professor in the CPR and stayed there until she accepted the position of Assistant Professor of Biostatistics in the University of Pennsylvania SOM, Senior Scholar, Biostatistics, in the CCEB in 1999. Of note, her mentor at the CPR, Dr. Morrow, is now director of The Center for Epidemiology and Biostatistics (CEB) that was established in 2001 in Cincinnati Children's Hospital. Dr. Pickering (former director of the CPR) is now senior advisor to the director of the National Center for Immunization and Respiratory Diseases of the Centers for Disease Control and Prevention and was awarded the 2007 Pediatric Infectious Diseases Society's Distinguished Physician Award.

Dr. Shults's methodological research has continued to focus on developing theoretically and operationally novel correlation methods for the GEE

approach, via her work on QLS. Her research has primarily been motivated by collaborative studies with complex patterns of association best described with correlation structures not currently available in the major software packages that implement GEE. For example, Dr. Shults worked with Carissa Mazurick and Dr. Richard Landis to implement a banded Toeplitz correlation structure for analysis of women with interstitial cystitis. She also worked with Dr. Melicia Whitt and Dr. Shiriki Kumanyika to implement a Kronecker product correlation structure for analysis of multiple physical activity outcomes measured on African-American women. Dr. Shults is currently working with Dr. Kumanyika and Biostatistics graduate student Xiaoying Wu to implement a familial correlation structure in analysis of the NIH-funded SHARE study that is headed by Dr. Kumanyika. Their analysis goal is to determine whether high versus low social support is beneficial in a weight loss study in African-Americans in which subjects can enroll with relatives or friends. Implementation of the familial structure will allow for the comparison of weight loss between the high versus low social support conditions, with simultaneous assessment of the correlation in weight loss between primary subjects and their co-participants. Dr. Shults's methods should allow for improved understanding of the impact of social support on weight loss. In addition, as an extension of her work on the familial correlation structure, Dr. Shults is working with graduate student Jichun Xie on implementing an extended familial correlation structure for a study in ophthalmology, requested by Penn ophthalmologists Dr. Jon Peet and Dr. Dwight Stamboli, in which measurements including refractive error were collected on subjects from the Old Order Amish (OOA) community in Lancaster, PA. Graduate student Seunghee Beck is also currently working on an additional analysis with Drs. Shults, Peet, and Stamboli, for which implementation of the familial structure should also be informative.

Dr. Shults is also working with Dr. Scarlet Bellamy and graduate student Carin Kim on a tutorial on QLS that considers an NIMH-funded multi-site, randomized, controlled trial investigating the effectiveness of a sexual risk reduction intervention for African-American, sero-discordant couples living with HIV one year after completing the assigned intervention.

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Dr. Shults currently serves as the chief statistician for Dr. Jay Amsterdam's Depression Research Unit in the Penn Department of Psychiatry. She has worked on several successful NIH grant applications with Dr. Amsterdam that consider medications such as fluoxetine (Prozac) for the treatment of depression and, more recently, alternative therapies such as black cohosh and chamomile. In addition, Dr. Shults serves as lead statistician on Dr. Mary Leonard's research team to study bone disease in children with renal disease. Dr. Shults is also working on papers with two senior faculty members from the Nursing School (Drs. Terry Richmond and Barbara-Medoff Cooper).

Much of Dr. Shults's clinical research fits under the umbrella of the NIH-funded R01 Longitudinal Analysis for Diverse Populations (LADP), of which she is the principal investigator. Her co-investigators on this grant include Drs. Kumanyika, Tom Ten Have, Sarah Ratcliffe, and Bellamy. Graduate students who have worked on the grant include Wenguang Sun, Jichun Xie, Xiaoying Wu, and Hanjoo Kim. For example, Wenguang Sun has an interesting paper (under review) that compares QLS with other estimating equation-based approaches. Dr. Shults is also working with clinicians to identify new ways to apply her QLS research. For instance, she is the lead statistician on Dr. Nicolas Stettler's trial of obesity prevention in children that should benefit from these approaches to data with two sources of correlation because this study employs group randomization at the practice level for comparison of two standardized 12-month intervention strategies over time. Dr. Shults is also interested in implementing QLS for spatial correlation structures in Dr. Josh Metlay's study to examine risk factors and outcomes for community-acquired pneumonia due to drug resistant *S. pneumonia*. In addition, with Dr. Kumanyika, she is interested in extending QLS for analysis of neighborhood-level risk factors (e.g., proximity to fresh fruits and vegetables) for obesity.

Another important goal of the LADP project is software development. Dr. Shults, with colleagues Drs. Ratcliffe and Leonard, developed the xtqls procedure for implementation of quasi-least squares in Stata; this procedure (and reference to the Stata journal article that describes the procedure) is now available to all Stata users, via the "Help" and "Search

All" commands provided in the toolbar for Stata. Drs. Ratcliffe and Shults then translated the xtqls programs into Matlab for a paper that is under review at the *Journal of Statistical Software*. Graduate student Jichun Xie and Dr. Shults then translated the programs into the qlspack package for R statistical software, for another paper that is under review at the *Journal of Statistical Software*. Graduate student Hanjoo Kim has also begun work on developing programs for implementation of QLS in SAS statistical software.

Teaching is also extremely important to Dr. Shults. She is currently teaching Linear Models for the graduate program in Biostatistics and the first course in Biostatistics for the Masters of Science Program in Clinical Epidemiology. She is serving as the Biostatistics advisor for several of Dr. Leonard's students who are working on their Masters of Science Degree in Clinical Epidemiology. She is also actively involved with Drs. Landis, Leonard, and Peter Reese, in the Renal and Urology Training program in Biostatistics; students supported by this program include graduate students Arwin Thomasson, Ziyue Liu, and Angelo Elmi. In addition, she is working with graduate students Yimei Li, Xiaoying Wu, Seunghee Beck, and Jichun Xie on their dissertations for their masters' degrees in Biostatistics as well as serving as dissertation advisor for Hanjoo Kim, who recently won a travel award to attend the ENAR 2008 Statistical Conference.

Dr. Shults's father is a retired neurologist who lives with her mother in Vermont (in the winter) and in Florida (in the summer). She has a sister (Sarah Vakkur) who is an architect in Arlington, VA; a brother (Nicholas Vakkur) who is a doctoral fellow at RAND Corporation in Santa Monica, CA; and a brother (Mark Vakkur) who is a psychiatrist and novelist in Atlanta, GA. She has a son (Eugene [Chuck] Charles Shults III) who is in his third year at Drexel University and a daughter (Erika Marie Shults) who is a freshman at Notre Dame and is a member of the crew team. Her husband Chuck flies C-12s in the Navy Reserves and is stationed at Willow Grove Naval Air Station. Like most researchers at Penn, Dr. Shults's main hobbies include working on papers and grant proposals, in addition to spending time with family and friends.

a risk factor for the development of IPF; however, the association is not nearly as strong as for other tobacco-related lung diseases. Fewer than one in 50 patients will have a first-degree relative with pulmonary fibrosis suggesting a rare but real familial form of this disease.

Less common forms of pulmonary fibrosis can be associated with systemic diseases such as rheumatoid arthritis, scleroderma, and sarcoidosis. It can also be seen rarely following exposure to certain medications such as methotrexate. Finally, pulmonary fibrosis can also result from chronic exposure to an organic substance such as mold.

Q: *Although pulmonary fibrosis has a comparatively high mortality rate, it is known to be idiopathic, and the condition can be chronic for several years. What are the available treatment options for chronic and acute cases? What characteristics disqualify a patient from being eligible for lung transplantation in this scenario?*

JM: All forms of pulmonary fibrosis are associated with some scar tissue formation that is thought to be the result of an inflammatory process. The actual fibrosis, or scar tissue formation, is not reversible. In some cases, the inflammation responsible for that scar tissue formation can be blunted with the long-term use of anti-inflammatory medications such as prednisone or azathioprine, which may in turn limit or even stop the progression of disease. Unfortunately, in the most common form of pulmonary fibrosis, IPF, anti-inflammatory medications have never been shown conclusively to modify either disease progression or mortality. One trial suggested a potential benefit to the combination of anti-inflammatory medications and the

antioxidant N-acetyl cysteine. That study had significant methodological limitations, though. In acute cases of rapidly progressive pulmonary fibrosis, very high doses of corticosteroids are typically administered; however, the response to such treatment is generally poor.

The only therapy that has been shown to lower the risk of mortality in IPF is lung transplantation. With the recent implementation of new organ allocation policies that take into account the poor prognosis associated with pulmonary fibrosis, patients with this condition are given priority over patients with other diseases. Unfortunately, most transplant centers limit transplantation to patients under the age of 65, which disqualifies many patients with pulmonary fibrosis. Also, some patients are disqualified because of obesity. Finally, the often rapid deterioration of patients with IPF at the end of their lives means that they may have a very short window of opportunity in which to receive a donor organ.

Finally, to follow-up on your question regarding delayed diagnosis, since there are no effective treatments for IPF, the only potential advantage to early diagnosis is in facilitating access to experimental therapies that may be available in the setting of clinical trials. It used to matter when lung transplantation allocation decisions were based on time accrued on the wait list; however, now that we have moved to a severity of disease allocation rule, the time at which IPF is diagnosed should have no bearing on eligibility for transplant except in extreme cases when the diagnosis is delayed until the very end of life, at which point the patient may be too sick to undergo a transplantation procedure.

Q: *How do you account for the increasing prevalence*

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of asthma in the US in the last 25 years?

AA: It is quite possible that our environment has changed or that exposure to pollutants has increased. However, there are few data to support or disprove this hypothesis. Another possibility is that allergen exposure has been altered by the global climate crisis and other possibly related changes. Again, there are few data. There have also been studies of genetic risk factors that may predispose families to asthma, but the notion of differences in such factors leading to increased morbidity requires more study.¹

Q: How would you characterize the range and efficacy of the current treatment options for asthma?

AA: Asthma medications have improved measurably over time. At the same time, prevalence and morbidity has increased, suggesting that differences in access to medications and care, clinical systems, and individual practices may account for some of these observations. There is sufficient evidence of this that is so concerning that the Institute of Medicine wrote a report on this entitled *Unequal Treatment*. In that report, the authors hypothesized that adherence to medications may reflect satisfaction with and trust in medical recommendations. We have found that the less faith patients have in medical care, the more likely it is that patients would not take asthma medications. Finding better ways to communicate with patients and to take account of and appreciate the uniqueness and priorities of each patient is my research focus.

Q: Are there any new therapies for asthma on the horizon?

AA: I am somewhat biased in this regard. Omalizumab is a new, extremely expensive medication that has not demonstrated itself to be better than already available medications. This drug is interesting in that it potentially represents another mechanism for addressing asthma, that potentially would spare the use of steroids with their side effects, but research has not convincingly demonstrated its benefits and indeed its cost-effectiveness has been challenged. Currently available asthma medications safely and efficaciously treat all but the most severe asthma – the asthma that is not reversible. In that sense, very severe irreversible asthma, which is like pulmonary fibrosis (different morphology, but both are irreversible, and do not necessarily respond to medications like steroids), may not be the same disease as milder asthma. We’re not sure at this time.



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