

**S**INCE ITS FOUNDING, UNC's school of public health has encouraged innovators who developed new ways of collecting and analyzing information and solving problems. At the heart of that effort has been a synergistic collaboration of the School's basic measurement science departments—biostatistics, epidemiology, and environmental sciences and engineering—along with other departments that have strong methods and measurement science foci. These include the School's departments of health policy and management, health behavior, maternal and child health, and nutrition, as well as others outside the School.

# DATA *DRIVEN BY* CARING *AND* CHANGE





IF YOU ALWAYS DO WHAT

YOU'VE ALWAYS DONE, YOU'LL ALWAYS

GET WHAT YOU'VE ALWAYS GOT.

—HENRY FORD



[Above, left to right]: Drs. Jim Grizzle, Bernard Greenberg, Dale Williams and Michel Ibrahim discuss plans for renewal of their research grant on lipids; Drs. Gary Koch and Dennis Gillings conducted clinical trials work from a trailer on School grounds; Dr. Gillings, as a faculty member in 1971.

## DEVELOPMENT

## OF BIOSTATISTICS

## METHODS

In 1940, UNC system president Frank Porter Graham took a chance in hiring Gertrude Cox, MS, as the first woman professor and department head at N.C. State University. Cox, professor of statistics and head of the Department of Experimental Statistics, likely met Graham's highest expectations; her hiring certainly set in motion a series of events that resulted in one of the finest biostatistics departments in the world.

As the UNC system's graduate program in statistics was housed at N.C. State, it was incumbent upon Cox to develop any additional statistics programs on other campuses. In 1946, she recruited Harold Hotelling, PhD, formerly on the faculties of Stanford and Columbia, to head the new

mathematical statistics department at UNC-Chapel Hill. In 1949, less than a decade after the School began, she helped establish the Department of Biostatistics in the UNC-Chapel Hill School of Public Health, selecting her former student, Bernard Greenberg, PhD, to lead it.

Greenberg, who later became the department's first Kenan Distinguished Professor, was awarded a National Institute of General Medical Sciences grant, "Multivariate Analysis for the Health Sciences," with co-principal investigator S.N. Roy, MSc. With support from Hotelling and others in the UNC-Chapel Hill statistics department, Greenberg also competed successfully for one of the first National Institutes of Health (NIH) grants to train biostatisticians and pioneered efforts to establish the practice of cooperative multicenter trials.

This groundbreaking, transformational research changed the course of practice for the evaluation of new

drugs. Under Greenberg's leadership, the department developed a roadmap for evaluating new drugs for efficacy. Without the clinical trials methodology and infrastructure developed by UNC's biostatisticians, many advances that benefit individuals might never have been made. Members of the biostatistics faculty continue to make innovations in clinical trials.

In 1967, NIH's National Heart Institute commissioned Greenberg to develop procedures for conducting large, multicenter clinical trials. His Greenberg Report ([see \*tinyurl.com/Greenberg-report\*](http://tinyurl.com/Greenberg-report)) is still a respected document, having established methods to evaluate new drugs and cancer treatments that have been used for nearly 50 years.

The tradition of statistical innovation for the betterment of humankind continues in a program led today by Michael Kosorok, PhD, W.R. Kenan Jr. Distinguished Professor and chair of biostatistics, who

collaborates with colleagues at UNC, Duke and N.C. State universities, and SAS (*SAS.com*), a business analytics software and services company. The National Cancer Institute (NCI)-funded program, “Statistical Methods for Cancer Clinical Trials,” is pioneering new methods that will help researchers more effectively discover and evaluate cancer treatments, as well as treatments for other diseases, and to more quickly deliver effective new therapies to patients.

The biostatistics department was successful from the start in attracting financial support through contracts and grants, says Jim Grizzle, PhD, who chaired the department from 1972 to 1987.

In 1955, the NCI awarded the department a contract to become the statistical coordinating center for the Southeastern Cooperative Cancer Chemotherapy Study Group (SCCC), believed to be the first large-scale clinical trials group in the U.S. (The first such study was published in England in 1949.) Faculty members from 10 medical schools and the coordinating center collaborated to investigate the effectiveness of chemotherapy agents.

The department developed some of the new mathematics necessary to analyze data from these large-scale, multicenter trials. In 1957, Greenberg hired Grizzle as a graduate research assistant.

Grizzle led the Lipid Research Clinics Coordinating Center, established in 1971, which was among the first groups to perform distributive data entry. The unit was renamed the Collaborative Studies Coordinating Center (CSCC) in 1986, and is now the oldest,

continuously funded NIH coordinating center in the U.S., having coordinated studies with hundreds of clinical centers in the U.S. and abroad. The late H.A. Tyroler, MD, Alumni Distinguished Professor of epidemiology, was a vital contributor to the study group and provided much insight into the tools and methods used by the CSCC. Grizzle, Clarence (Ed) Davis, PhD, retired former chair of biostatistics and director of the CSCC, and Dale O. Williams, PhD, took the lead in the first study, which found that lowering cholesterol reduces the risk of heart disease.



Dr. Gary Koch, in the 1980s, stands outside his office in ‘Trailer 39.’

“With that,” Grizzle says, “biostatisticians changed the world.”

Williams, who succeeded Grizzle as principal investigator for the study, says that trial “set the stage for the drug development that led to statins and lipid-lowering compounds.”

Grizzle’s methodology for crossover trials is still referred to today, some 50 years later. Another paper by Grizzle, on analyzing categorical data and whose co-authors included Frank Starmer, PhD, now with the Duke University-National University of Singapore Graduate Medical School, and biostatistics professor Gary Koch, PhD, is among the most-cited biostatistics papers in the world.

In 1958, Greenberg undertook another landmark epidemiological study—the first large study of cardiovascular disease that included African-Americans. All other large trials in the U.S. at the time had only white participants. The Evans County, Ga., study continued through the 1990s. (See [tinyurl.com/evans-county](http://tinyurl.com/evans-county).)

“All of these studies had a real impact on the health of society,” says Ed Davis. The studies led to insights and treatment options for widespread health problems, such as high cholesterol and congestive heart failure.

The impact continues with research in progress now, including the Hispanic

Community Health Study/Study of Latinos, the largest, long-range study to date on this population. An original \$22 million grant from the National Heart, Lung and Blood Institute supported the multi-center study of more than 16,000 Hispanic adults to examine the role of acculturation in the prevalence of disease. A six-year, \$21.7 million federal contract was also awarded to conduct a second examination of study participants, beginning in October 2014.

The study was initiated by Lloyd Chambless, PhD, now retired, and Lisa LaVange, PhD, now at the U.S. Food

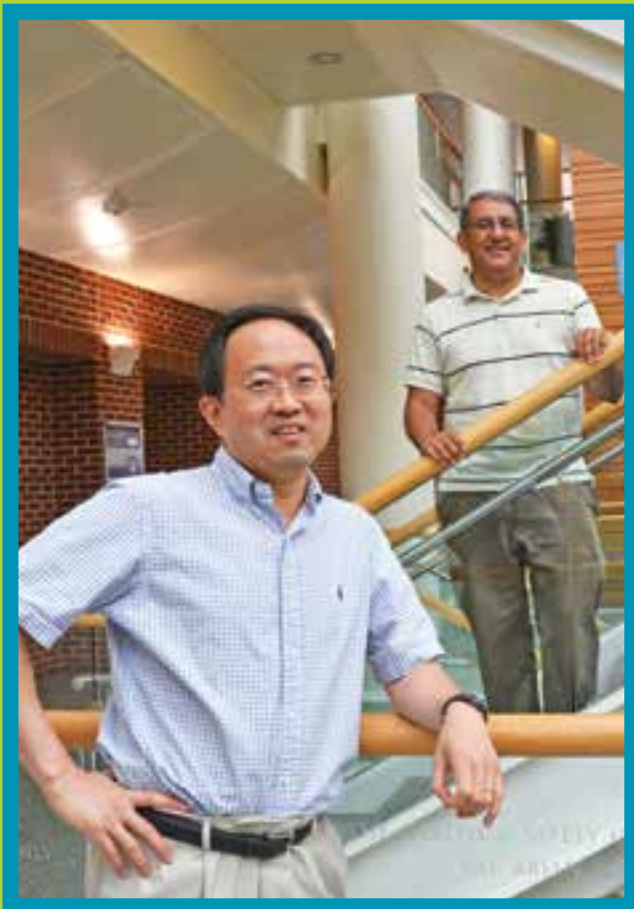
and Drug Administration, both former biostatistics professors and CSCC directors, and is currently overseen by Jianwen Cai, PhD, professor and vice chair of biostatistics. Twelve faculty members, 24 staff members and four students from UNC are involved in the study.

Grant funding reflected the biostatistics department's success. Grizzle recalled that his department's budget hovered close to \$6 million annually, but the state contributed only \$90,000. The rest came from grants and contracts. Dale Williams, who succeeded Grizzle as director of

the CSCC in 1991, had cumulative oversight of \$35 million in grants.

UNC's School of Public Health extended its international reach, particularly in the 1960s after Pranab K. Sen, PhD, DSc, Cary C. Boshamer Distinguished Professor, joined the faculty and strengthened ties to universities in India. Sen has contributed significantly to methodological studies related to diabetes, environmental health and bioinformatics, as well as clinical trials.

The lipids study also fostered a stream of global interactions, including ones with eastern European countries,



Drs. Danyu Lin (foreground) and Joseph Ibrahim

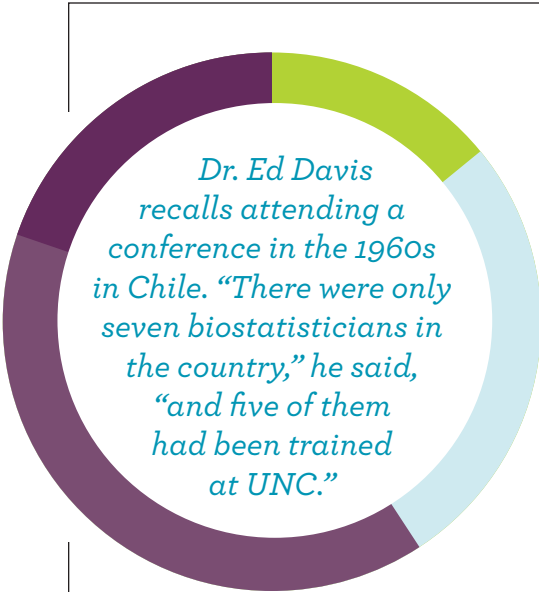
## *SPEEDING UP* DRUG DEVELOPMENT, *IMPROVING* CLINICAL TRIALS

Data pile up fast in large-scale, long-term, multisite clinical trials. As data collection methods evolve, so too must the means by which data are analyzed.

Early on, the Gillings School's biostatistics department developed a reputation for its program in Bayesian statistics, an analysis paradigm that involves determining probability of something based on particular pieces of evidence. The program is led by Alumni Distinguished Professor Joseph G. Ibrahim, PhD, who also directs the UNC Center for Innovative Clinical Trials (CICT) and the department's graduate studies program.

Ibrahim and colleagues in the CICT have conducted leading-edge research on innovative Bayesian clinical trials design, including development of new statistical methods to determine the odds that a large future clinical trial will be successful.





*Dr. Ed Davis recalls attending a conference in the 1960s in Chile. “There were only seven biostatisticians in the country,” he said, “and five of them had been trained at UNC.”*

China, Brazil, Israel, Poland and India. Excellent networks of UNC-trained statisticians in Brazil and Chile have opened the door to collaborations in teaching and training for UNC’s biostatisticians. Visiting professors and scholars from developing countries have added greatly to the development of biostatistics methodology, including clinical trials. Professor Kant Bangdiwala, PhD, whom Sen calls “our ambassador to Latin and South America,” has taught biostatistics classes around the world, including as visiting professor at Chile’s University of Valparaiso and University of Chile at Santiago.

In 2014–2015, he will be a Fulbright Scholar in Chile.

Some faculty members have established global corporations to expand the reach of their work.

In the 1970s, Gary Koch partnered with another faculty biostatistician, Dennis Gillings, PhD, CBE, to develop Quintiles, a contract research organization (CRO) that now employs some 30,000 people worldwide. Gillings led the organization; Koch remained in academia, directing UNC’s Biometric Consulting Lab, mentoring students and publishing. Quintiles provides

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“Bayesian methods are a powerful paradigm for complex clinical trials design and analysis since they can produce very efficient designs that potentially yield large reductions in the number of patients needed for a trial, and hence yield major savings in resources,” Ibrahim says.

Ibrahim and his team also have developed new statistical methods for data analysis, especially for cancer research. One such method assesses efficacy of a patient’s treatment when that course of treatment changes, as when the patient crosses over to an experimental treatment.

Missing data are a big problem in research, especially in longitudinal studies, where patients drop out before study completion. Ibrahim devises statistical models to understand why data go missing, so as to efficiently incorporate all the cases with missing values. CICT personnel also aim to develop user-friendly statistical software for the design and analysis methods they construct.

Ibrahim has received funding from several pharmaceutical companies to carry out this joint research with the CICT, and several National Institute of Health grants support his research.

Danyu Lin, PhD, the Dennis Gillings Distinguished Professor of Biostatistics, has led cutting-edge research

in many areas, particularly survival analysis and statistical genomics.

In a word, Lin says, “We do statistical research to create new tools for clinical trials.”

Survival analysis is indispensable to clinical trials. Many patients remain alive at the end of a trial, so their total survival times are unknown. Lin has developed survival analysis methods that are widely used in clinical trials. Many of them have been incorporated into standard software packages, such as SAS.

Lin received the prestigious Merit Award from the National Institutes of Health from 2005 to 2015, and the Royal Statistical Society selected one of his papers to be read and discussed at its meeting in 2007.

In recent years, he has devoted considerable energy to the development of statistical and computational tools for analyzing genomic data.

“Eventually, we want to use this information to guide the selection of treatments for personalized medicine,” Lin says. “It’s not clear how successful we’ll be, but whatever happens, statistics will be an important part of it.”

—Nancy Oates



Dr. Michael Kosorok (far left) posed recently with former CSCC directors (l-r) Drs. Lisa LaVange, Lloyd Chambless, Ed Davis, Dale Williams and Jim Grizzle.

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training opportunities for students and real-world experiences for faculty members. CSCC director Sonia Davis, DrPH, Julie MacMillan, MPH, managing director of the School's Research and Innovation Solutions, and clinical professor and former Public Health Leadership Program director William Sollecito, DrPH, are among those who held leadership positions at Quintiles.

In 1984, biostatistics professor Ron Helms, PhD, founded Rho, a CRO focused on clinical data management that now employs more than 300 people in the Triangle. In 2001, Jean Orelie, DrPH, who received his

doctoral degree from the Gillings School, launched SciMetrika, a leading population health research company based in Durham, N.C.

"Our biostatistics faculty members carry out absolutely groundbreaking theoretical work," says Dean Barbara K. Rimer, "but another great strength is their commitment to finding solutions to important health problems. They show that outstanding faculty members can excel at both theoretical and applied research."

Amy Herring, ScD, professor and associate chair of biostatistics, lauds her department's highly rigorous training in the foundations of statistics

that makes students nimble and able to adapt to ever-changing technologies and new problems in public health.

"Students benefit from the mentored hands-on experiences they get working with top-notch investigators on high-impact research across multiple domains of public health and medicine," she says.

Herring, with Rebecca Fry, PhD, associate professor of environmental sciences and engineering, and Marilie Gammon, PhD, epidemiology professor, leads a National Institute of Environmental Health Sciences (NIEHS) grant to train postdoctoral scholars in biostatistics, epidemiology and environmental sciences. The training award, renewable every five years, has been held by UNC's public health school continuously since it was awarded first to Dr. Bernard Greenberg in 1971.

Larry Kupper, PhD, retired former Alumni Distinguished Professor of

biostatistics, was instrumental in obtaining that original NIEHS grant and led it from 1972 through 2006. Kupper studied the development and application of innovative statistical methods for design and data analysis of public health studies, with particular emphasis on environmental, occupational and women's health issues. His work led to improved statistical methods for quantifying human health risks due to harmful substances in the workplace and external environment.

Today, the biostatistics department is the statistical home for many studies in the UNC schools of medicine and nursing and provides statistical support for UNC Lineberger Comprehensive Cancer Center and the N.C. Translational and Clinical Sciences Institute (NC TraCS). Educational preparation for the next generation is assured through a biostatistics leadership course, the first of its kind in the U.S., which has received national attention for its timely and meaningful content. (See [tinyurl.com/BIOS-leadership-course](http://tinyurl.com/BIOS-leadership-course).)

Kosorok says the development of data tools and methodologies begun in his department seven decades ago is still thriving.

"A number of leaders in the department are doing excellent work," he says. "I'd mention Drs. Jianwen Cai, Jason Fine, Amy Herring, Joseph Ibrahim, Danyu Lin, Hongtu Zhu, Haibo Zhou, Fei Zou, Donglin Zeng, Michael Hudgens, Wei Sun, Yun Li and others, whose methodology is being widely used. Dr. Yun Li has been

recognized by Thomson Reuters as one of the most cited researchers in the world." (See [sph.unc.edu/most-cited](http://sph.unc.edu/most-cited)).

An excellent history of the UNC biostatistics department, compiled by Drs. Jane Monaco, Jianwen Cai, Lisa LaVange and Michael Kosorok is at [tinyurl.com/unc-bios-history](http://tinyurl.com/unc-bios-history).

## EPIDEMIOLOGICAL

## AND

## OTHER TOOLS

The Gillings School's expertise in clinical methodologies extends beyond biostatistics.

Barbara Hulka, MD, MPH, joined the epidemiology department in 1967. In a discipline that traditionally analyzed medical records and surveys for disease prevalence and causes, Hulka was among the first to integrate molecular biology into the field, a transformation that shifted the emphasis of discoveries.

Kenan Distinguished Professor Gerardo Heiss, MD, PhD, who joined the epidemiology faculty in 1974 and is one of the most cited researchers in his field, is a CSCC investigator who has made a huge impact in multicultural collaborations. (See page 25.)

Today, epidemiologists often augment self-reported participant data with biological data (e.g., from blood or cheek swabs) and combine genetic analyses with other data to get a

richer understanding of issues such as genetic susceptibility to diseases. The epidemiology department now has labs for molecular biology, genotyping and immunohistochemistry.

In the health policy and management department, associate professor Bryce Reeve, PhD, concentrates on patients' experiences of risks, diseases and illness. Reeve designs Web-based questionnaires that integrate patient-reported data into electronic medical records systems to give clinicians real-time feedback from patients to improve the efficiency and value of the clinical encounter. Patients' data also may be a better way of understanding issues such as adverse events experienced by patients in clinical trials and how different medication regimens affect patients' quality of life.

"It's the wave of the future," Reeve says. "We're not replacing what doctors already do, but rather facilitating their discussions with patients. We're trying to identify what's going on in the patient's life, what's most important to him or her, so clinicians can respond quickly and thus improve the quality of care."

In preparing the next generation of researchers, Reeve deliberately allows large classes to include diverse expertise, backgrounds and interests. Medical students, residents, fellows and students from the schools of pharmacy, nursing and public health approach the same patient from different perspectives.

—Nancy Oates