

Yu Shyr, Ph.D.
Supporting statement

A. Academic Leadership

Dr. Shyr has been an academic leader both within and outside of Vanderbilt University. In 1994, when Dr. Shyr joined Vanderbilt-Ingram Cancer Center (VICC), he was not only chief biostatistician, but also the *only* biostatistician in the cancer center; in 2007, Dr. Shyr became the founding director of the Cancer Biostatistics Center within VICC; and in 2010, 15 years after his arrival at Vanderbilt, Dr. Shyr's group had grown from one to 44 members (faculty, affiliated faculty, staff biostatisticians and bioinformaticians, computer systems analysts, and administrative staff). Moreover, in 2003, with his appointment as Ingram Professor of Cancer Research, Dr. Shyr became the first biostatistician in the history of Vanderbilt University to hold an endowed professorship; and, in 2006, he was named chief of the Division of Cancer Biostatistics within the Department of Biostatistics, Vanderbilt University School of Medicine.

Dr. Shyr's group currently works on 72 grants totaling approximately \$285 million in total project direct costs, including five specialized center grants (P50), two center core grants (P30), and multiple program project grants (P01). Dr. Shyr serves as the biostatistics core director on a number of these grants, including the Vanderbilt University Breast Cancer SPORE, GI Cancer SPORE, and Lung Cancer SPORE, as well as one additional specialized center grant (P50), one program project grant (P01), and two cooperative agreement grants (U01).

In 2009, Dr. Shyr's responsibilities within Vanderbilt-Ingram Cancer Center expanded when he was appointed associate director for quantitative sciences integration. In this position, Dr. Shyr sponsored the 2009 Shanghai Center for Bioinformation Technology (SCBIT)-Vanderbilt-Ingram Cancer Center (VICC) Biostatistics and Bioinformatics Symposium; co-organized the 2009 Cancer Epidemiology, Biostatistics, and Bioinformatics retreat; and has initiated a Quantitative Sciences Seminar Series, featuring national and international speakers in the fields of biostatistics, bioinformatics, computational biology, biomedical engineering, and mathematics.

Outside of Vanderbilt, Dr. Shyr holds additional leadership positions. He is the only biostatistician to serve on the American Society of Clinical Oncology (ASCO) Cancer Research Committee; in this capacity, he represented ASCO during a 2009 ASCO/AACR Capitol Hill Day, organized to encourage members of Congress to support funding for cancer research and other important cancer-related initiatives, including the Kennedy-Hutchison bill. A bipartisan effort, this bill was the first in 50 years to focus specifically on cancer research and treatment, and included a provision to establish a nationwide bio-repository of tumor tissue specimens, to allow for more cooperative and coordinated research efforts.

Dr. Shyr also has taken numerous leadership roles in the American Statistical Association. In the mid-Tennessee chapter of ASA, he served as both council representative (1998-1999) and president (1999). He also has served as the vice-chair for the Council of Chapter Governing Board (2002-2004) and a member of the Council of Chapters Nominating Committee (2004-2005). In 2010, he was nominated as chair-elect of the Council of Chapters.

Finally, Dr. Shyr has served on multiple advisory boards and committee, including an FDA advisory committee (voting member), the External Advisory Board for Northwestern University's Robert H. Lurie Comprehensive Cancer Center, the Advisory Board for Middle Tennessee State

University's Master of Science in Professional Science (MS-PS) program, the External Advisory Board for University of Alabama at Birmingham's Comprehensive Cancer Center (ad-hoc member), and the State of Tennessee Department of Health's Cancer Registry Advisory Committee.

B. Collaborative Statistical Work

Within the Vanderbilt University community, Dr. Shyr has played a key role in elevating the status of biostatisticians to that of true scientific collaborator on projects ranging from basic science research to translational research, from high-dimensional data analysis to clinical trials. Moreover, he has set the standard for biostatistics cores, both within and outside of Vanderbilt; his GI SPORE biostatistics core was described as the "model for future projects" (*The Cancer Letter* 2002:28(16); 6-7). Similarly, all of Dr. Shyr's biostatistics cores, including those for the GI SPORE, Breast SPORE, and Lung SPORE, as well as several cooperative agreements (U01s) and program project grants (P01s), have been rated outstanding in peer review.

Dr. Shyr's contribution to research projects has resulted in more than 230 papers published in peer-reviewed journals, including high-impact clinical and basic science journals such as *Gastroenterology*, *PNAS*, *Journal of Clinical Investigation*, *New England Journal of Medicine*, *PLoS Medicine*, and *Nature Medicine*. For example, a 2009 paper published in *Journal of Clinical Investigation* ("Abrogation of TGF- β signaling enhances chemokine production and correlates with prognosis in human breast cancer") queried TGF- β -associated gene expression signatures in four human breast cancer datasets containing a total of 1,319 gene expression profiles and associated clinical outcome data. Survival analysis was performed, and the signature representing complete abrogation of TGF- β signaling was shown to correlate with reduced relapse-free survival in all patients, with the strongest association observed in patients with estrogen receptor-positive (ER-positive) tumors.

In addition to clinical trials and basic science, Dr. Shyr's collaborative work in the field of proteomics and genomics has been published in journals such as *Clinical Cancer Research* (2003), *Lancet* (2003), *Breast Cancer Research* (2003), *Lung Cancer* (2003), *Genomics* (2005), *Genesis* (2005), *Human Pathology* (2005), *Human molecular genetics* (2005), *Journal of Proteome Research* (2005), *Cancer Research* (2005), *Journal of the American Society of Nephrology* (2005), *PLoS Medicine* (2006), *Mutation Research* (2006), *Clinical Cancer Research* (2006), *Journal of Clinical Oncology* (2007), *International Journal of Oncology* (2007), *Journal of Thoracic Oncology* (2007), *Molecular Cancer Research* (2008), *American Journal of Respiratory Critical Care Medicine* (2008), *Journal of Thoracic Oncology* (2009), *Annals of Oncology* (2009), *PNAS* (2009), *Journal of Clinical Investigation* (2009), and *Molecular and Cellular Proteomics* (2009).

C. Teaching

Dr. Shyr has taught clinical trial course to students in the Masters of Public Health (MPH) and Master of Science in Clinical Investigation (MSCI) programs at Vanderbilt since 1996, garnering several excellence-in-teaching awards. The MPH and MSCI programs are designed for clinical fellows seeking an academic career in population-based medical research; the goal of the programs is to provide students with an introduction to biostatistical and epidemiological methods, as well as an opportunity to conduct a mentored research study in their area of clinical interest. In this program, Dr. Shyr teaches an intensive course on clinical trial design and analysis. The

design portion of the course covers topics such as specification of a primary objective, adherence to accepted ethical guidelines, the role of randomization and the means of its implementation, the type and assessment of blinding, the choice of design strategy and design-strengthening features, and the considerations involved in sample size determination and patient recruitment. The analysis portion of the course covers methods of analysis appropriate to various designs, such as up-and-down design, titration design, randomized controlled studies, crossover designs, nested designs, factorial designs, group allocation designs, hybrid designs, adaptive designs, Bayesian designs, meta-analysis of multiple studies, and designs with repeated measures. Methods of data collection, monitoring response variables, and data quality control also are discussed.

Also at Vanderbilt, Dr. Shyr has lectured to medical students in many preventive medicine courses, teaching classes on clinical trials as well as statistics and epidemiology, statistics in medical literature, and other topics.

Outside of Vanderbilt, Dr. Shyr has presented as an invited faculty member in the AACR annual meeting: Educational Section on Clinical Trials Design Workshop, ASCO annual meeting: Educational Section on Advanced Concepts in Clinical Trial Design and Methodology and, since 2004, has been a member of the invited faculty at the AACR/ASCO Methods in Clinical Cancer Research Workshop. He also has taught a workshop on clinical trial design and analysis for the FDA's Quantitative Safety and Pharmacoepidemiology Office of Biostatistics in the Center for Drug Evaluation and Research (CDER), as well as dozens of invited workshops and seminars at universities and other research institutions throughout the United States.

Finally, Dr. Shyr has taught in many international venues, including two-week intensive courses on both clinical trial design and analysis and high-dimensional trial design and analysis at Tokai University (Tokyo, Japan), a one-week intensive course on clinical trials at Shanghai Jiao Tong University (Shanghai, China), and multiple workshops and seminars in Taiwan, Korea and other countries.

Across courses and venues, Dr. Shyr receives consistently outstanding ratings and comments from students. Since 1996, approximately 280 Vanderbilt MPH/MSCI students have evaluated Dr. Shyr's teaching; the median rating is 9 out of 9, and the 5th percentile is 8 out of 9. Representative comments from 2009 workshops and lectures include:

- *Dr. Shyr is one of the best instructors I have had while at Vanderbilt (7+ years). He is enthusiastic about the subject matter and able to clearly present the material. He is always available for questions. Great course!*
- *This is truly one of the best courses I have ever taken. The lectures were very well organized. The lecture notes were very helpful. Dr. Yu Shyr was extremely knowledgeable and always available to answer questions by phone, email, or office visit. It would be nice to have Dr. Shyr for other courses.*
- *Dr. Shyr is an outstanding teacher and biostatistician. I thoroughly enjoyed the course and believe it has enabled me to design an RCT that I intend to write an R01 application for in the next 2-3 months. I hope he will consider serving as a consultant for the project.*
- *Best explanation of Bayesian stats that I've ever heard.*
- *Very clear and every entertaining slides; very clear and well laid out.*
- *Dr. Shyr was a dynamic speaker. I particularly enjoyed the way he structured the analysis types and designs.*

D. Statistical methodology research

In his doctoral research and early work, Dr. Shyr focused on traditional multivariate analysis, with several published papers in this field. In a 1997 publication, Dr. Shyr proposed an adaptive method of canonical correlation for more than two vector variables, to assign optimum scores to the categories of a multi-dimensional contingency table; this adaptive method eliminates categories that do not contribute significantly to the correlation. Another 1997 publication describes a canonical reduction of Anderson's classification statistic in the case of two multivariate populations with different means and the same variance matrix. As another example of Dr. Shyr's work from this period, he published a 1999 paper on statistical strategies for modeling the quasi-sinusoidality of time-qualified data.

As genomic and proteomic techniques became more and more prevalent in the field of cancer and other biomedical research, Dr. Shyr turned his attention to applying his foundational knowledge of multivariate analysis to the analysis of high-dimensional data. His group has since become a leader in the field of applied statistics for analysis of high-throughput assays, publishing several papers, for example, on wavelet-based techniques for proteomic mass spectrometry data preprocessing (*Journal of Concrete and Applicable Mathematics* 2006; *Computational Statistics and Data Analysis* 2007; *Bioinformatics* 2009). These techniques overcome several conventional difficulties seen with other preprocessing methods, thereby enhancing reproducibility of results. Additional examples of contributions to the high-dimensional data analysis field include the weighted flexible compound covariate method (WFCCM) for classifying microarray data, a 2008 paper describing a nonparametric smoothing method for assessing the adequacy of generalized estimating equation (GEE)-fitted models of longitudinal binary data (*Statistics in Medicine* 2008), as well as papers published in *Journal of Bioinformatics and Computational Biology* (2007), *Biomarkers Insights* (2007), and *BMC Bioinformatics* (2009, 2010).

In addition to his contributions to applied statistics for high-dimensional data analysis, Dr. Shyr continues to contribute to the evolution of clinical trial design. For example, a 2007 paper describes a balanced two-stage design for phase II clinical studies (*Clinical Trials* 2007). Oncology phase II trials are often designed using Simon's two-stage designs; however, these designs do not balance the sample sizes of the two stages, which can lead to highly unequal sample sizes. The balanced design, by contrast, provides a choice for two-stage phase II trials when the investigators wish to monitor the trial near the study's halfway point. An additional *Clinical Trials* publication (2006) describes study designs and methods for evaluating cancer biomarkers.

It should be noted that Dr. Shyr's career path moved him very early on from the position of junior faculty to that of mentor and project leader. Thus, many of the contributions to applied statistics described above have been the product of mentored studies, with Dr. Shyr establishing the goals and objectives for each project and serving as the senior/corresponding author on resultant publications. Dr. Shyr's mentoring role has led him to participate in projects well outside the field of biomedical research; for example, a 2009 publication in the *Journal of Economic and Social Measurement* described alternatives and extensions to Blinder-Oaxaca decomposition for discrimination studies (e.g., identifying the sources of wage differentials between two different groups of employees).

Finally, Dr. Shyr has published seven book chapters and has co-edited a book of *Quantitative Medical Data Analysis Using Math Tools and Statistical Techniques* (World Scientific Publication 2007, ISBN: 978-981-270-461-0).