

## Ethan M. Lange, Ph.D.

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### Member

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### Education

- Ph.D., University of Michigan, Ann Arbor, Biostatistics 1996-2001  
*Advisor:* Michael Boehnke, PhD
- M.S., University of Michigan, Ann Arbor, Biostatistics 1994-1997
- M.A., University of California, Los Angeles, Mathematics 1991-1994
- B.S., University of California, Los Angeles, Applied Mathematics 1986-1990

### Professional Experience

- Associate Professor, University of North Carolina at Chapel Hill 2010-2012  
Departments of Genetics and Biostatistics
- Assistant Professor, University of North Carolina at Chapel Hill 2004-2010  
Departments of Genetics and Biostatistics
- Assistant Professor, Wake Forest University, 2002-2004  
Department of Public Health Sciences, Section on Biostatistics
- Instructor, Wake Forest University, 2000-2001  
Department of Public Health Sciences, Section on Biostatistics

### Bibliography

### Book Chapters

Lange EM (2010) Identification of genetic risk factors for prostate cancer: Analytic approaches using hereditary prostate cancer families. In: Male Reproductive Cancers: Epidemiology, Pathology and Genetics (WD Foulkes and KA Cooney, Eds) Springer New York. 203-228.

Lange E, Gatti RA, Sobel E, Concannon P, Lange K (1993) How many ataxia-telangiectasia genes? In: *Ataxia-telangiectasia*. (R.A. Gatti and R.B. Painter, Eds) NATO ASI Series Vol. H 77. Springer-Verlag Berlin Heidelberg. 37-54.

#### Selected Refereed Papers/Articles Appearing in Journals (From > 100 in Total)

Ewing CM\*, Ray AM\*, Lange EM\*, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, ..., Carpten JD, Isaacs WB, Cooney KA. (2012) Germline mutations in *HOXB13* are associated with prostate cancer risk. *New England Journal of Medicine* (in press).

Croteau-Chonka DC, Wu Y, Li Y, Fogarty MP, Lange LA, Kuzawa CW, McDade TW, ..., Adair LS, Lange EM, Mohlke KL. (2012) Population-specific coding variant underlies genome-wide association with adiponectin level. *Human Molecular Genetics* 21: 463-471.

Lange EM, Salinas CA, Zuhlke KA, Ray AM, Wang Y, Lu Y, Ho LA, Luo J, Cooney KA (2012) Early onset prostate cancer has a significant genetic component. *The Prostate*. 72: 147-156.

Wang Y, Ray AM, Johnson EK, Zuhlke KA, Cooney KA, Lange EM (2011) Evidence for an association between prostate cancer and chromosome 8q24 and 10q11 genetic variants in African American men: The Flint Men's Health Study. *The Prostate* 71: 2225-231.

Ho LA, Lange EM (2010) Using public control genotyping data to increase power and decrease cost of case-control genetic association studies. *Human Genetics* 128:597-608.

Wu Y, Li Y, Lange EM, Croteau-Chonka DC, Kuzawa CW, McDade TW, Qin L, ..., Lange LA, Adair LS, Mohlke KL (2010) Genome-wide association study for adiponectin levels in Filipino women identifies *CDH13* and a novel uncommon haplotype at *KNG1-ADIPOQ*. *Human Molecular Genetics* 19: 4955-4964.

Joubert BR, North KE, Wang Y, Mwapasa V, Franceschini N, Meshnick SR, Lange EM (2010) Comparison of genome-wide variation between Malawians and African ancestry HapMap populations. *Journal of Human Genetics* 55:366-374.

Lange LA, Croteau-Chonka DC, Marvelle AF, Qin L, Gaulton KJ, Kuzawa CW, McDade TW, ..., Lange EM, Adair LS, Mohlke KL (2010) Genome-wide association study of homocysteine levels in Filipinos provides evidence for *CPS1* in women

and a stronger MTHFR effect in young adults. *Human Molecular Genetics* 19:2050-2058.

Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, Muir K,..., Lange EM, Farnham J, Khan H, Slavov C, Mitkova A, Cao G, The UK Genetic Prostate Cancer Study Collaborators/British Association of Urological Surgeons' Section of Oncology, The UK ProtecT Study Collaborators, The PRACTICAL Consortium, Easton DF. (2009) Identification of seven novel prostate cancer susceptibility loci through a genome-wide association study. *Nature Genetics* 41:1116-1121.

Bartlett JR, Friedman, KJ, Ling SC, Pace RG, Bell SC, Bourke B, Castaldo G,..., Lange EM, Durie PR, Knowles MR, for the Gene Modifier Study Group (2009) Genetic modifiers of liver disease in cystic fibrosis. *The Journal of the American Medical Association* 302:1076-1083.

Lange EM, Sun J, Lange LA, Zheng SL, Duggan D, Carpten JD, Gronberg H, Isaacs WB, Xu J, Chang BL (2008) Family-based samples can play an important role in genetic association studies. *Cancer Epidemiology, Biomarkers and Prevention* 17:2208-2214.

Sun J \*, Lange EM \*, Isaacs SD, Liu W, Wiley KE, Lange L, Gronberg H,..., Chang B-L, Isaacs WB, Zheng SL (2008) Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. *The Prostate* 68:489-497.

Lange EM, Robbins CM, Gillanders EM, Zheng SL, Xu J, Wang Y, White KA,..., Carpten JD, Isaacs WB, Cooney KA (2007) Fine-mapping the putative chromosome 17q21-22 prostate cancer susceptibility gene to a 10cM region based on linkage analysis. *Human Genetics* 121:49-55.

Lange EM, Boehnke M (2004) The haplotype runs test: The parent-parent-affected-offspring trio design. *Genetic Epidemiology* 27:118-130.

Ambrosius WT, Lange EM, Langefeld CD (2004) Power for genetic association studies with random allele frequencies and genotype distributions. *American Journal of Human Genetics* 74: 683-693

Lange EM, Lange K (2004) Powerful allele-sharing statistics for nonparametric linkage analysis. *Human Heredity* 57:49-58.

Lange EM\*, Gillanders EM\*, Davis CC, Brown WM, Campbell JK, Jones M, Gildea D,..., Montie JE, Trent JM, Cooney KA (2003) Genome-wide linkage scan for prostate cancer susceptibility genes using families from the University of Michigan Prostate Cancer Genetics Project finds evidence for linkage on chromosome 17 near BRCA1. *The Prostate* 57:326-334.

Cerosaletti KM, Lange E, Stringham HM, Weemaes CMR, Smeets D, Solder B, Belohradsky BH,..., Gatti RA, Boehnke M, Concannon P (1998) Fine localization of the Nijmegen breakage syndrome gene to 8q21: Evidence for a common founder haplotype. *American Journal of Human Genetics* 63: 125-134.

Uhrhammer N, Lange E, Porras O, Naiem A, Chen X, Sheikhavandi S, Chiplunkar S,..., Concannon P, Lange K, Gatti RA (1995) Sublocalization of an ataxia-telangiectasia gene distal to D11S384 by ancestral haplotyping in Costa Rican families. *American Journal of Human Genetics* 57: 103-111.

Lange E, Borresen A-L, Chen X, Chessa L, Chiplunkar S, Concannon P, Dandekar S,..., Yang L, Ziv Y, Gatti RA (1995) Localization of an ataxia-telangiectasia gene to an ~500 kb interval on chromosome 11q23.1: Linkage analysis of 176 families by an international consortium. *American Journal of Human Genetics* 57: 112-119.

### Research Statement

My research interests focus on the development and application of statistical methods for mapping complex trait and disease susceptibility genes. My primary areas of application have been prostate cancer and cardiovascular disease.

I started working with my closest collaborator Dr. Kathleen Cooney, an oncologist, on the then newly formed University of Michigan Prostate Cancer Genetics Project (UM-PCGP) in 1995 when I was a graduate student at the University of Michigan. At the time I had several years of experience with linkage analyses and linkage disequilibrium mapping that localized the gene responsible for ataxia-telangiectasia. In 2003, Dr. Cooney and I used linkage analysis to map a prostate cancer susceptibility gene to a region on chromosome 17q21-22. In collaboration with investigators at John Hopkins and Wake Forest Universities we subsequently fine-mapped the linkage interval in 2007 and just recently sequenced 94 unrelated subjects in our strongest families across all gene-coding regions inside the linkage candidate region. Through this effort, we identified a recurrent mutation in the gene HOXB13 – a strong candidate based on HOXB13's biological role in prostate development. We subsequently genotyped the identified mutation in ~5,000 additional unrelated prostate cancer cases enriched for positive family history and early-onset disease and 1400 screened controls. We found strong evidence for an association between this mutation and prostate cancer and found a significantly increased frequency of the mutation in prostate cancer cases with positive family history and early-onset disease compared to men absent family history diagnosed with prostate cancer later in life. This finding was recently published in the *New England Journal of Medicine* and represents the first uncommon high-penetrant mutation identified for prostate cancer. HOXB13 mutation screening should become a valuable tool for future prostate cancer screening studies. We have a number of ongoing studies including work to further characterize the role of HOXB13 mutations in prostate

cancer and expanding our search for uncommon coding variants associated with the disease. We are additionally in the process of finalizing the first stage of a two-stage genome-wide association study for common genetic variants that are associated with early-set forms of the disease.

In addition to my work with prostate cancer, I have collaborated on many genetic studies for a wide-range of quantitative traits and diseases including obesity, cardiovascular disease, type 2 diabetes, cystic fibrosis, HIV and asthma. Many of these studies have involved analyses of common genetic variants through genome-wide association studies. Recent technological advances in “next-generation” high-throughput sequencing have created exciting new opportunities to identify uncommon high-penetrant mutations like those that we found for prostate cancer. I am an investigator on several NIH funded studies, including the NHLBI funded Exome Sequencing Project and a large whole-genome sequencing project to identify uncommon genetic variants that are associated with cannabis and stimulant dependence. This latter project is headed by UNC Department of Genetics colleague Kirk Wilhelmsen. With respect to sequence data, I have a particularly strong interest in studying under-represented minority populations and subjects with “extreme” phenotypes – i.e. subjects with highly unusual quantitative measures such as extreme high and low LDL measures or case-control studies based on subjects with early-onset disease and/or strong positive family history.

In addition to my work on collaborative gene-mapping studies, I enjoy developing and applying new methods to genetic data. My methodological research has included developing novel approaches for accurately estimating statistical power in genetic association studies, designing haplotype-based association analyses using extended haplotype sharing, creating powerful nonparametric linkage statistics and using prior hypotheses and applying the false discovery rate to subsets of data to increase power of gene-trait association discoveries. I have a particularly strong interest in optimizing study designs by including existing publically available data along with investigator-collected data. Our two-stage genome-wide association study for early-onset prostate cancer is based on a method my former student, Lindsey Ho, and I devised based on using freely available genotype data on thousands of unscreened controls in Stage 1 and genotyping our own screened study controls in Stage 2. We calculate the optimal proportions of our early-onset prostate cancer cases to be divided into the two stages and use a replication-based design where the results in Stage 1 reduce the multiple test burden in Stage 2. Lindsey and I showed in our recently published manuscript in *Human Genetics*, that this kind of strategy maintains valid hypothesis tests, and results in increased statistical power and significantly decreased total costs compared to studies that do not include free public control genotype data.

Doctoral Student Primary Thesis Advisor (Graduated)

Lindsey A. Ho, Dr.P.H. 2010  
Biostatistics

Doctoral Student Committee Member (Graduated)

Kimon Divaris, Ph.D. 2010  
Epidemiology

Joel Parker, Ph.D. 2010  
Curriculum in Bioinformatics and Computational Biology

Sarah Cohen, Ph.D. 2010  
Epidemiology, UNC

Kyle Gaulton, Ph.D. 2010  
Curriculum in Genetics and Molecular Biology

Yuer Yan, Ph.D. 2009  
Epidemiology

Bonnie Joubert, Ph.D. 2009  
Epidemiology

Christy Avery, Ph.D. 2008  
Epidemiology

Moonsu Kang, Ph.D. 2007  
Biostatistics