My research interests have always been clinically oriented, in particular toward pregnancy and its complications. It is clear that many obstetric complications (failure to progress in labor, preeclampsia, spontaneous preterm birth (SPTB), hyperemesis, etc) are more common in some families than in others. Because GWAS studies have been uninformative in the great obstetric syndromes, there is now an evolving interest in enriched family pedigrees as possible keys to our enhanced understanding of pregnancy complications. The Utah Population Data Base (UPDB) provides a unique opportunity to investigate these possibilities. I have had a long-standing interest in the intergenerational pre-disposition to obstetric complications, with my first UPDB publication in this area dating back almost two decades (Obstet Gynecol 1996;87:905-11). We have documented intergenerational pre-dispositions to operative delivery, spontaneous and indicated preterm birth, and preeclampsia and more recently have begun using this resource to investigate the long-term implications of pregnancy complications on women’s future health (for example, we have shown that women whose pregnancies were complicated by preeclampsia are less likely to develop cancer across their lifespan – Am J Obstet Gynecol 2006;195:691-9).

With the additional resources made available to me via the Benning Endowment I am pursuing a number of other avenues related both to familial clustering of obstetric complications and their association with subsequent women’s health. I should note that I have involved subspecialty fellows and junior faculty colleagues in most of these projects but would respectfully submit that the ideas for almost all of the following projects are primarily, if not exclusively, mine:

1. Familial Clustering of Obstetric Complications:
   a. **SPTB** – My Benning funds were used to identify family clusters of early SPTB (<34 weeks) in the UPDB. Within the UPDB there are over 70 separate extended pedigrees with 10 or more women with at least one early SPTB. Following appropriate approvals, we funded the RGE to contact these families and have recruited 172 women from 40 separate pedigrees, including 8 pedigrees with 5 or more women who have provided us with DNA samples and access to their phi. These pedigrees form the basis for Erin Clark’s (one of my previous K23 mentees) current Utah Genome Project award. While I can’t post the initial findings at this time (June 2015) I can say that we have some spectacular preliminary results that we will be presenting at a national meeting within the next year (Stay Tuned!).
   b. **Preeclampsia** – We are now identifying familial clusters of women who have had pregnancies complicated by pre-eclampsia, with hopes of replicating our preterm labor success (vide supra). While there is almost no paternal intergenerational contribution to SPTB, we have shown that there is clearly a paternal intergenerational contribution to preeclampsia (N Engl J Med 2001;344:867-72). We will be pursuing family trios for these efforts and will also pursue long-term follow-up of men themselves delivered of preeclamptic pregnancies, with the hypothesis that they are at increased risk for early cardiovascular disease.
   c. **Abruptio** – I have used Benning funds to identify familial clusters of placental abruption. This has served as a basis for collaboration on a R01 application with Cande Ananth PhD from Columbia University (currently under review).

2. Pregnancy as a Window to Women’s Future Health:
   a. **Preeclampsia and Macular Degeneration** – The retinal findings of pregnant women with severe preeclampsia closely resemble those of macular degeneration. Most ophthalmologists believe that macular degeneration is substantially more common in women, even controlling for the fact that women outlive men. I am using a portion of my Benning funding to work with Greg Hageman PhD and ME Hartness MD (Department of Ophthalmology) to link our 1947-1957 UPDB preeclampsia cohort with JMEC macular degeneration records.
   b. **Possible Association between Preeclampsia and Alzheimer’s Disease** – I am currently collaborating with Dr. Karen Schliep from NIC HD on a UPDB-based study to try to determine whether women who have pregnancies complicated by preeclampsia are at increased risk of subsequent Alzheimer’s Disease. Both conditions are characterized by excess inflammation and many of the associated gene
polymorphisms are similar. The real impetus for this inquiry comes from several patients and personal acquaintances who have told us about anecdotal associations. We’ll see what happens!

3. Perinatal Pharmacogenomics:
   a. 17-OH Progesterone Caproate and (17-OHPC) Prevention of Recurrent SPTB – 17-OHPC has been shown to reduce the risk of recurrent SPTB by about 30%, but it has not been clear why this works in some women and not in others. Working with Tracy Manuck MD (another of my K23 mentees) and Lynn Jorde (another Benning Scholar), we have been able to identify – using a portion of my Benning funds – several specific genetic predispositions that identify women who are more or less likely to respond to the medications we use to prevent or treat pregnancy complications (Am J Obstet Gynecol 2014/210:321.e1-321.e21). This research resulted in a National March of Dimes award for the Best Research in Prematurity at the 2014 Society for Maternal-Fetal Medicine meeting.
   b. Perinatal Responsiveness to Corticosteroids Administered for Acceleration of Functional Fetal Maturity in Late Preterm Birth (LPTB) – Betamethasone has been used for decades for acceleration of functional fetal maturity in pregnancies at risk of preterm birth <34 weeks. The recent increase in preterm birth is almost exclusively in the 34-36+ week window and, since some of these newborns still have significant prematurity-related complications, it is tempting to expand the indication for corticosteroids to this window. The NICHD Maternal-Fetal Medicine Units Network (of which I have been the Utah site PI for 20 years) is finishing a RCT of corticosteroids in LPTB that includes a nested collection of maternal and fetal DNA. We will be using Benning funds to extract DNA through the CCTS TTR and then study corticosteroid receptor polymorphisms to identify infants who do, and more importantly, do not, respond to prenatal corticosteroids.

4. Clinical Research Projects:
   a. Personalized Prenatal Care – The clinical standard for prenatal care is to have all women be seen at least 12 times across pregnancy. This paradigm was developed in the 1920’s as a way to identify pregnancies complicated by preeclampsia and is clearly an unnecessary utilization of resources in women at low risk for preeclampsia (healthy women with previous term vaginal deliveries and no preeclampsia). Dr. Clark and I developed a clinical trial comparing standard prenatal care against an abbreviated telemedicine format. This was initially funded by the Program in Personalized Health Care but is now being funded by my Benning account (PPHC funding ended in FY14). We have now finished enrollment and are waiting for the women to deliver.
   b. Obstetric Family History – I am covering a portion of a research assistant’s salary to enroll women with their first pregnancy in a questionnaire study that collects an obstetric family history (obstetric outcomes of their sisters, mothers, aunts, and grandmothers. While we know from our previous studies that obstetric complications occur more commonly in certain families, it is not yet clear that such associations can be identified at the point of care with sufficient accuracy to be of any clinical value in identifying pregnant women who either will, or will not, develop complications. We are also asking their permission to link their family pedigrees in the UPDB (if available) to determine the accuracy of their knowledge of their obstetric family history.
   c. Departmental Biorepository – I am covering a portion of a research assistant’s salary to collect maternal and cord DNA samples from women experiencing pregnancy complications for subsequent pregnancy-related research.

Mentorship: I have always enjoyed facilitating career development for my younger colleagues. Besides actively integrating our fellows and faculty into the aforementioned research projects, I have developed what I believe are effective and efficient mechanisms for mentoring promising clinician scientists. In conjunction with Carrie Byington MD (another Benning Scholar and the Health Sciences Vice-President for Faculty and Academic Affairs), we are being awarded two institutional faculty research training awards (Women’s Reproductive Health Research [WRHR] and Building Interdisciplinary Research Careers in Women’s Health [BIRCWH]). These institutional NIH K-12 awards will provide four slots for promising junior faculty’s salary, research support, and – most importantly – mentoring to ensure that Utah has a cadre of well-trained women’s health researchers for the next few decades. I anticipate helping to support these research efforts with part of my Benning endowment.