**SPECIFIC AIMS:**

There are an estimated 14,000 annual deaths due to renal cell carcinoma (RCC), making this disease the urologic malignancy with the highest mortality. The incidence of RCC has risen at an alarming rate in African Americans and now is 30% greater than Caucasians. African Americans also have a worse kidney cancer outcome than any other race for unclear reasons. While various studies have found that African Americans less frequently receive standard kidney cancer systemic and surgical treatment, even when controlling for treatment, survival disparities still exist. Beyond access to care barriers, similar to other urologic malignancies such as prostate cancer, biologic differences in disease characteristics may account for racial disparity in kidney cancer.  Recent studies have shown that African Americans present at a significantly younger age than Caucasians. Early disease onset is something in kidney cancer considered a possible indictor of a hereditary predisposition. Another biologic disparity between races is that the histologic distribution is drastically different in African Americans. While clear cell RCC (ccRCC) is the most common histologic type, papillary RCC (pRCC) is three-fold more common in African Americans, accounting for 35-40% of cases. Unfortunately pRCC has been understudied and there are no current forms of effective systemic therapy for this disease.

With significant racial disparities present in kidney cancer, we set out to identify possible genomic alterations explaining these cancer disparities.  To do so we will analyze available genomic data contained in the Cancer Genome Atlas (TCGA) kidney cancer cohorts. Since there was a scarcity of African American subjects with ccRCC included in the TCGA, additional whole genomic sequencing on Yale African American subjects will be needed to make appropriate comparisons between race and histologic subtype. Coding and non-coding alterations in the germline and tumor that are associated with RCC will be identified and compared between race and subtype to help identify the genomic basis of kidney cancer racial disparity.

**Hypothesis:**

We hypothesize that 1) recurrent coding and non-coding germline and somatic alterations are associated with kidney cancer [[isn't this obvious?]] and 2) specific germline and somatic alterations are more common in African Americans with kidney cancer. We will test our central hypothesis with the following aims:

**Aim 1: To perform whole genome sequencing (WGS) of African Americans with ccRCC to complete a missing aspect of the Cancer Genome Atlas (TCGA).** WGS will be performed on a consecutive series of African Americans with ccRCC to provide a cohort useful to compare genomic alterations between race (Caucasian vs. African American) and histologic subtype (ccRCC vs pRCC).

**Aim 2: To assemble a catalog of germline and somatic mutations in coding and non-coding regions associated with kidney cancer.** We will analyze our African Americans with ccRCC and existing TCGA RCC cohorts to identify key regions in the genome associated with kidney cancer. A novel pipeline will be employed to evaluate and prioritize known coding and noncoding regions.

**Aim 3: To compare genomic alterations that differs between African and Caucasians with kidney cancer.** Our genomic datasets will assess racial and histologic differences in germline mutations, rare-high impact germline variants, and somatic mutations that may contribute to racial disparity in RCC.[[LS to rewrite ]]

**Aim 4: To validate somatic and germline coding and non-coding alterations [[Regions??]]suspected of contributing to kidney cancer racial disparity.** We will utilize an independent cohort of African American and Caucasian patients with ccRCC and pRCC (96/cohort, n=384). Tumor and normal DNA genomic regions of interest assessed using a PCR-Mass spectroscopy based system that allows multiplexing of defined genomic regions.

**Summary:** Significant racial disparities exist in kidney cancer with African Americans having increased cancer incidence, earlier age of onset, a different subtype distribution, and worse survival. While multiple studies have characterized these epidemiologic differences, to date, there has been no comprehensive investigation into a possible biologic or genetic cause of this cancer health disparity. *Our proposed research plan will improve our understanding of the genomic cause of racial differences and may have far reaching implications beyond the scope of this project. We anticipate the findings will provide insight into inherited cancer predisposition and acquired driver alterations in African Americans with RCC.*