The Clinical and Molecular Characteristics and Burden of Kidney Cancer among Hispanics and Native Americans: Steps toward Precision Medicine

Running Head: Kidney Cancer Disparities and Precision Medicine

Ken Batai PhD[1], Andrew Bergersen MD[1], Elinora Price, MPH[1], Kieran Hynes[1], Nathan A. Ellis PhD[1], Benjamin R Lee MD1

[1] Division of Urology, Department of Surgery, University of Arizona
1501 N. Campbell Ave.
P.O. Box 245077
Tucson, Arizona 85724-5077
U.S.A.

[2] Department of Cellular and Molecular Medicine
1501 N. Campbell Avenue
P.O. Box 245044
Tucson, Arizona 85724
U.S.A.

Corresponding Author
Ken Batai, PhD
Division of Urology, Department of Surgery
The University of Arizona College of Medicine
University of Arizona Cancer Center
1515 N. Campbell Ave.
P.O. Box 245024
Tucson, AZ 85724
Email: kbatai@email.arizona.edu
Phone: (520) 626-8024
Fax: (520) 626-4933

Abstract

Cancer disparities in Native Americans (NAs), Hispanic Americans (HAs) vary significantly in terms of cancer incidence and mortality rates across geographic regions. This review reports kidney and renal pelvis cancers are unevenly affecting HAs and NAs compared to European Americans (EAs) of non-Hispanic origin, and that currently there is significant need for improved data and reporting to be able to advance towards genomic-based precision medicine for the assessment of such cancers in these medically underserved populations. More specifically, in states along the U.S.-Mexico Border, HAs and NAs have higher kidney cancer incidence rates as well as a higher prevalence of kidney cancer risk factors, including obesity and chronic kidney disease. They are also more likely to receive suboptimal care compared to EAs. Furthermore, they are underrepresented in epidemiologic, clinical, and molecular genomics studies of kidney cancer. Therefore, we maintain that progress in precision medicine for kidney cancer care requires an understanding of various factors among HAs and NAs, including the real kidney cancer burden, variations in clinical care, issues related to access to care, as well as specific clinical and molecular characteristics.

(182 / 250 Words)

Keywords

Renal Cell Carcinoma, Cancer Health Disparities, Latinos, American Indians

Abbreviations

AA	African American
AN	Alaskan Natives
CHSDA	Contract Health Service Delivery Area
EA	European American
GWAS	Genome Wide Association Study
HA	Hispanic American
IHS	Indian Health Service
IRR	Incident Rate Ratio
NA	Native Americans
NAACCR	North American Association of Central Cancer Registries
RCC	Renal Cell Carcinoma
SNP	Single Nucleotide Polymorphism
TCGA	The Cancer Genome Atlas

Introduction

Kidney and renal pelvis cancer is the 6th most common cancer in men and the 10th most common cancer in women, resulting in an estimated 63,990 new cases and 14,400 deaths in 2017 [1]. Additionally, it can unevenly affect racial/ethnic minority groups. Despite the large number of Hispanic (or Latino) Americans (HAs) in the United States (U.S.), however, there is not enough research illuminating their actual kidney cancer burden or related clinical and molecular characteristics. Similarly, there are very few, and limited number of studies understanding the cause of higher differential incidence and mortality rates in Native Americans (NAs) [2].

HAs are the fastest growing and largest racial/ethnic minority group in the U.S. According to the 2012 U.S. Census, they account for approximately 17% of the total population. They are also a heterogeneous group. Many are Mexican, Cuban, or Puerto Rican, and the number of migrants from other Latin American countries is increasing. Likewise, Spanish cultural and European genomic contributions vary greatly across and within Latin American nations [3-5]. Importantly, HA subgroups have differing levels of healthcare access in the U.S., and Mexican Americans and HAs of Central and South American origin are less likely to utilize healthcare services [6]. As U.S. citizens, Puerto Ricans are eligible for Medicare and Medicaid. Cuban immigrants receive medical care benefits as refugees. Legal documentation is required for Mexican immigrants to receive health insurance. Thus, without legal status, undocumented immigrants face great barriers to health care [7]. Cancer incidence rates also vary depending on country of origin and nativity status [8, 9].

NAs and Alaskan Natives (ANs) are a smaller racial/ethnic group that account for only about 1-2% of the U.S. population. A large proportion of NAs reside in California, Arizona and the Southwest. With over 500 federally recognized tribes, NAs are also a culturally and socially heterogeneous group. Those living on reservations or in urban areas face varying degrees of structural, cultural, physical (or geographic), and economic barriers to health care [10, 11]. There is also regional variation in cancer incidence and mortality rates among NAs [12].

In this paper, we review the epidemiologic, clinical, and molecular genomic data available for NAs and HAs, two socially/culturally and biologically heterogeneous racial/ethnic

groups that are often underrepresented in biomedical studies. Furthermore, we evaluated whether there is a sufficient information in the literature currently as a foundation for kidney cancer care precision medicine, particularly in regard to selecting a renal cell carcinoma (RCC) treatment regimen based on molecular genomic information. We reviewed kidney cancer incidence rates at the national and regional level, focusing on four U.S.-Mexico Border States (Arizona, California, New Mexico, and Texas). Due to their social, cultural, and genetic heterogeneity, it is important to understand the kidney cancer burden in HAs and NAs at both the national and regional level. In the border states, there is a large number of NAs; and, a very high proportion of HAs are Mexican Americans. We show that HAs and NAs have a higher incidence of kidney and renal pelvis cancer than European Americans (EAs) of non-Hispanic origin (or non-Hispanic Whites). Kidney cancer may also have a greater impact on the lives of HAs and NAs than is generally appreciated. However, our literature review reveals that HAs and NAs are underrepresented in clinical and molecular genomics studies on kidney cancer. Thus, we maintain that as we move toward genomic-based precision medicine for kidney cancer care, it is imperative that we first understand the real kidney cancer burden and variations in the clinical care, issues related to access to care, as well as clinical and molecular characteristics in these medically underserved populations.

Epidemiology of Kidney Cancers in Hispanic Americans and Native Americans

Among the malignances of the urinary system, kidney cancer is the third most common after prostate and bladder cancer [1]. RCC is the most common type of adult kidney cancer and accounts for more than 90% of kidney cancer cases. Globally and nationally, the incidence of kidney cancer has increased since the 1980s. This rise can be attributed not only to an increase in the prevalence of obesity, a risk factor for kidney cancer, but more so with the increased use of cross sectional imaging, leading to a greater number of incidental findings of kidney tumors [13, 14]. During this period, there was a significant increase in the incidence of localized tumors, but a decrease or relatively slower rate of increase in the incidence of advanced stage kidney cancer [15, 16]. However, the rate of increase was greater in younger age groups (20-39) than older age groups (≥40) and for grade II and III tumors than grade I tumors [16].

Between 2008-2012, the kidney cancer incidence rate was **37% higher** in NA and AN men and **56% higher** in NA and AN women than in EAs [1]. It also increased at a much faster rate in NAs than in EAs between 2001 and 2009 [17]. Among NAs living in Indian Health Service (IHS) designated Contract Health Service Delivery Area (CHSDA) counties, the Northern Plains IHS region has the highest incidence rate with an age-adjusted incidence rate of 26.8 per 100,000 and a NA/EA incidence rate ratio (IRR) of 2.10, while the East IHS region has the lowest incidence rate (15.0 per 100,000) [17]. Based on data from the North American Association of Central Cancer Registries (NAACCR), age-adjusted kidney cancer incidence rates for NAs in the U.S.-Mexico Border States between 2009 and 2013 also vary. NA rates were significantly higher than EA rates in Arizona and New Mexico, but lower in California (**Table 1**). When stratified by age (i.e., the older Medicare eligible age group and the younger age group), NAs had consistently higher kidney cancer incidence rates than EAs, and the two age groups had similar IRRs. The IRR between NAs and EAs was 1.91 (95% C.I.: 1.66-2.21) and 2.03 (95% C.I.: 1.64-2.52) for the younger age group (<65) in Arizona and New Mexico, respectively (**Table 2**). In Arizona, the difference in the incidence rate between NAs and EAs was smaller in the older age group (≥65), but NAs had a significantly higher kidney cancer incidence rate than EAs (IRR of 1.45, 95% C.I. 1.19-1.76). The two age groups had very similar IRRs between NAs and EAs in New Mexico.

Nationally, HAs and EAs have similar kidney cancer incidence rates (20.7 and 21.9 per 100,000 in HA men and EA men, respectively; and, 11.9 and 11.3 per 100,0000 in HA women and EA women, respectively) [1]. In Florida, Cubans, Puerto Ricans, and Mexican American women have similar kidney cancer incidence rates as EAs, while Mexican American men have a slightly lower incidence rate than EA men (not statistically significant) [8]. In general, within the U.S, NAACCR data show that EAs have a higher kidney cancer incidence rate than HAs, but in the U.S.-Mexico Border States, HAs have a significantly higher rate than EAs. The younger age group in New Mexico has the highest IRR (IRR=1.43, 95% C.I.: 1.23-1.66). Texas has the highest kidney cancer incidence rate for HAs and EAs among the four border states. In the older age group, HAs have a rate of 85.8 per 100,000, while EAs have a rate of 72.8 per 100,000. Incidence ratios between HAs and EAs and between NAs and EAs are similar in older and younger age groups.

For EAs in the U.S., the kidney cancer mortality rate declined from 1990 to 2009 [17]. However, it did not change for NAs, who had a significantly higher rate than EAs. The likelihood of death from kidney cancer was almost twice as high in NAs as EAs. NA men from the Southern Plains (Texas, Oklahoma, and Kansas) had the highest mortality rate (13.7 per 100,000). The gap in the mortality rate between NAs and EAs was the greatest in the Southwest in adults ages 20-49 (mortality rate ratio of 3.1). Nationally, HAs had similar or slightly better kidney cancer mortality rate and 5-year cancer-specific survival than EAs, and adjusted relative risk of cancer death from kidney cancer was not statistically different between them [1, 18]. Still, given the substantial variability in mortality rates for other cancers among Hispanic subgroups [19, 20], kidney cancer mortality rates are also likely to vary among them. However, this has not been investigated or reported in the literature.

Variation in Clinical Characteristics and Disparities in Kidney Cancer Care

Established risk factors for kidney cancer include obesity, hypertension, tobacco smoking, and family history [13]. Other potential risk factors include diabetes, hypertension, chronic kidney disease, end-stage renal disease, kidney transplant, lack of physical activity, and occupational and environmental exposures. Hypertension is not as prevalent in HAs and NAs as African Americans (AAs), and HAs and NAs have a slightly lower hypertension prevalence than EAs [21]. However, obesity is more prevalent among HAs and NAs than EAs [22-24]. Obesity is now recognized as one of the major risk factors of cancer [25] and it is linked to higher kidney cancer mortality [26, 27]. The 2014 National Health Interview Survey results also show that HAs and NAs have a higher prevalence of diabetes than EAs [28]. Notably, a higher proportion of NAs reported having kidney disease (including chronic kidney disease and kidney failure) compared to other racial/ethnic groups. More HAs also reported having kidney disease than did EAs.

Among HA subgroups, the prevalence of diabetes is slightly higher in Mexican Americans, especially Mexican American men [29]. While 18.3% of Mexican Americans had diabetes, only 13.4% of Cuban Americans had it. A retrospective study showed that HA RCC patients from San Antonio, Texas, were more likely to have diabetes than EA RCC patients or Mexican Americans in the general population [30]. It showed that 29.8% of the San Antonio HA

RCC patients had diabetes, in contrast to the reported prevalence of diabetes among HAs or Mexican Americans ranging between 13.2 to 18.3%. Another study found strong and heterogeneous associations between chronic kidney disease and RCC among HAs, EAs, and AAs [31]. The association was strongest in AAs who had more than a 10-fold increased risk, followed by Asian Americans (more than 5-fold increased risk), and HAs (more than 2-fold increased risk), but chronic kidney disease was not associated with RCC in EAs.

Frequencies of RCC histologic subtypes vary between AAs and EAs. In EAs, clear cell RCC is the predominant subtype, accounting for more than 70%. In AAs, clear cell RCC is less frequent (30-40%) and papillary RCC is more common than what is seen in EAs (20-35% in AAs and 9-14% in EAs) [32, 33]. It is also likely that HAs and NAs have different frequencies of histologic subtypes from AAs or EAs. A small retrospective study conducted in Texas showed that clear cell RCC was more common among HAs than EAs (96% and 80%, respectively) [30]. Differences in histologic subtype distribution across racial/ethnic groups may reflect a difference in the prevalence of behavioral risk factors or underlying biological differences. For example, obesity was associated with increased odds of diagnosis with clear cell RCC [34, 35], and there is racial/ethnic variation in abdominal adiposity [36]. Prognosis also varies depending on the histologic subtype. One study found that patients with chromophobe RCC had better survival than patients with clear cell or papillary RCC after adjusting for tumor stage and Furman grade [37]. Another study found that patients with clear cell RCC had a worse prognosis than patients with other RCC histologic subtypes [38].

Compared to EAs, racial/ethnic minority patients often receive suboptimal cancer care [39, 40]. Because HAs and NAs have multiple barriers to health care and often underutilize it [7, 41], they are likely to receive less optimal kidney cancer care. A renal mass biopsy is a useful procedure to attempt to determine the histologic subtype and, thereby, evaluate the available treatment options. However, it is not without limitations, including cost, morbidity, and up to 15-20% indeterminate or inaccurate pathology findings [42, 43]. HAs were more likely to have renal mass biopsy than EAs in the Surveillance, Epidemiology, and End results-Medicare linked dataset between 1992 and 2007, but the reason for this is unknown [44]. Additionally, nephron-sparing surgery (partial nephrectomy and local tumor ablation) is less common in HAs for stage I RCC [45, 46]. Similarly, HA patients with metastatic RCC are less likely to undergo cytoreductive

nephrectomy [47, 48]. While there is data on how factors such as insurance type, educational attainment, and cultural beliefs affect the selection of kidney cancer treatment options, reasons for racial/ethnic differences remains relatively unexplored. Moreover, despite a high kidney cancer incidence and mortality rate, there is no study specifically addressing kidney cancer clinical care in NAs [2].

Lack of Inclusion in Molecular Genomic Studies

Germline mutations of several genes are well-known causes of hereditary kidney cancer, e.g., von Hippel-Lindau (*VHL*) tumor suppressor, *MET* proto-oncogene, *FLCN* (Birt-Hogg-Dube, BHD), and fumarate hydratase (*FH*) [49]. Recent Genome Wide Association Studies (GWAS) identified additional susceptibility loci, including 2p21, 2q22.3, 8q24.21, 11q13.3, 12p11.23, and 12q24.31 for sporadic RCC [50-54]. The Single Nucleotide Polymorphism (SNP) on 2p21 is located on *EPAS1* (endothelial PAS domain protein 1). The *EPAS1* encodes HIF2A (hypoxia-inducible-factor-2 alpha), a transcription factor that plays a key role in the VHL-HIF pathway. The SNP on 8q24.21 is located down stream of *MYC* proto-oncogene. Other SNPs on the 8q24 region have been associated with end-stage renal disease in NAs with type 2 diabetes from the Gila River Indian Community in Arizona, [55] as well as prostate cancer [56, 57] and bladder cancer [58] in other populations. GWAS showed an association with SNP rs718314 on the inositol 1,4,5-trisphosphate receptor type 2 (*ITPR2*) gene (12p11.23). This SNP was also associated with waist-hip ratio in another GWAS in European descent populations [59]. Another study found evidence for interaction of the same *ITPR2* SNP with the American/Western diet, and the SNP modified the effect of the American/Western diet on RCC risk [60]. The effect of the American/Western diet on RCC risk was stronger among individuals with the AG/GG genotypes than individuals with the AA genotype ($OR_{\text{Tertile 1 vs Tertile 3}} = 2.4$ compared to 1.7). In the 1000 Genomes Project data, the G allele is more frequent in populations from East Asia and the Americas. Although, the GWAS identified biologically important genes possibly linking diabetes and abdominal adiposity to RCC, how this knowledge can be used to predict kidney cancer aggressiveness and to improve kidney cancer therapy has not been fully investigated.

Nonetheless, RCC molecular genomics studies using tumor samples have characterized the molecular profiles of RCC in order to understand the relationship between molecular profiles and RCC prognosis. Exome sequencing of RCC tumors identified several commonly mutated genes. The *VHL* gene is the most frequently altered gene in clear cell RCC. Somatic mutations in the *VHL* are found in over 50% of clear cell RCC, and *VHL* is mutated or methylated in about 80% of all sporadic RCC [61, 62]. The second most commonly mutated gene is polybromo 1 (*PBRM1*) and it is mutated in about 32% of clear cell RCC. Other commonly mutated genes in clear cell RCC are *SETD2* (~13%), *BAP1* (~10%), *KDM5C* (~6%), and *MTOR* (~6%). In papillary RCC, mutations in *VHL* and *PBRM1* were not observed, and *SETD2*, *CUBN*, *MET*, and *PLEC* were mutated in low frequencies (9%, 9%, 8%, and 6%, respectively) [61]. Recently, molecular genomic analysis integrating The Cancer Genome Atlas (TCGA) DNA somatic alteration, methylation, mRNA expression, miRNA expression, and protein expression data identified nine molecular subtypes corresponding to major histological subtypes [63]. *VHL* and *PBRM1* mutations are enriched in clear cell RCC molecular subtype CC-e.1 and CC-e.2, which correspond to ccA subtypes based on microarray gene expression data [64], while *BAP1* (BRCA1 associated protein 1) was slightly more enriched in molecular subtype CC-e.3 (previously ccB subtype).

A molecular genomics study also demonstrated that there are differences in somatic DNA alterations and gene expression between tumors from AAs and EAs [65]. In the TCGA dataset, AAs and EAs with clear cell RCC have different frequencies of somatic mutations, and AA RCC patients had a higher frequency of CC-e.3 clear cell RCC molecular subtype than did EA patients. The *VHL* and *PBRM1* mutations that are associated with CC-e.1 and CC-e.2 subtypes were less frequently mutated in AA clear cell RCC (17% of tumors for each gene) [65]. *BAP1* mutations that are common in CC-e.3 subtypes were more frequent in tumors from AAs than EAs (17% in AAs and 9% in EAs). Based on the differences between AA and EA tumor molecular characteristics, we should not assume that RCC tumors from HA and NA patients have similar molecular profiles as those from EA patients. However, HAs and NAs are underrepresented in the TCGA. Out of 531 clear cell RCC samples, only 26 (4.9%) were from HA patients. Only 12 out of 291 (4.1%) papillary RCC and 8 out of 113 (7.1%) chromophobe RCC samples were from HA patients. There are only 2 NA or AN papillary RCC patients (0.7%) included in the TCGA. EAs (81.6%) are the predominant group in the TCGA RCC

datasets (clear cell, papillary, and chromophobe combined). The second largest group is AAs (13.7%).

Comprehensive molecular analysis of the TCGA RCC data demonstrates that molecular profiling can be more informative for reliable RCC prognosis than histological subtype. Clear cell RCC patients in the TCGA with molecular subtype CC-e.3 (ccB) had worse survival than patients with other clear cell RCC molecular subtypes [63], validating the findings from a previous study that demonstrated that ccB subtypes had worse survival than ccA subtypes (CC-e.1 and CC-e.2) [64]. Median survival time was 2.0 years among patients with CC-e.3 subtype, while patients with CC-e.1 or CC-e.2 subtype had a median survival time of 8.6 years. Among patients with papillary RCC, patients with subtype P-e.2 had shorter survival than patients with P-e.1 subtype, and patients with P.CIMP-e subtype had the worst overall survival [63]. In both clear cell and papillary RCC, patients enriched with *SETD2* and *BAP1* mutations had worse overall survival than those without. Another study showed that among clear cell RCC patients with *PBRM1* and *BAP1* mutations, patients with *BAP1* mutation had a shorter survival time than patients with *PBRM1* mutations (median overall survival of 2.5 vs. 5.4 years), and patients who had mutations on both genes had the worst overall survival (median overall survival of 0.2 years) [66]. Moreover, clear cell RCC molecular subtypes were associated with tumor size, grade, and stage [67]. Patients with ccB subtypes had a larger tumor size, higher Furman grade, and higher stage and presence of necrosis.

Alternatively, gene expression signatures can predict RCC aggressiveness and progression. Previous microarray studies identified genes, including inflammatory related genes (e.g., Interleukin 8, neutrophil cytosolic factor 2, and chemokine C-X-C ligands), that are associated with clear cell RCC aggressiveness and progression [68-71]. Immune related genes are involved in RCC development and progression [72], and neurophil-lymphocyte ratio in blood has been shown as a potential prognostic biomarker [73]. However, the research design varies greatly among these studies, and there are only a few verified set of molecular biomarkers that can be used in clinical settings to predict a patient's progression and therapeutic outcomes. There are two major limitations in some of these previous studies. First, sample size was small in the discovery phase (<30 patient samples). Second, matching non-cancerous kidney tissue samples were used for only a subset of tumor samples.

Currently, the limited evidence strongly suggests that understanding molecular subtypes within the histologic subtype or molecular signatures that are indicative of molecular subtypes will provide clinically valuable information to predict disease prognosis. Traditional protocol uses staging to guide RCC surveillance after nephrectomy. Patients with aggressive RCC and molecular signatures that predict poor prognosis may benefit from radical rather than partial nephrectomy as well as more frequent or extended follow-ups after nephrectomy, but without a verified set of prognostic biomarkers, individually tailored clinical management strategies cannot be developed. Furthermore, molecular genomic studies have been performed mainly in European descent populations. Currently, there are only a few RCC studies focused on racial/ethnic minorities, and HAs and NAs are particularly underrepresented. The molecular biomarkers found in European descent populations need to be validated in non-European populations.

Future Directions

As kidney cancer care progresses toward precision medicine, three issues need to be addressed in order to understand how biological and cultural diversity may contribute to the heterogeneity of kidney cancer presentation and progression across different racial/ethnic groups. First, we need to understand the burden of kidney cancer in NAs and HAs, and account for variation in kidney cancer incidence and mortality rate among HA subgroups, as well as regional variation in NAs. Variation in kidney cancer incidence and mortality rate has been previously illustrated, but causes for this variation are still not understood [17]. Some variation in kidney cancer incidence rates among HAs in the U.S. could be attributable to differences between Mexican Americans (who may have high Native American Ancestry) and other major HA subgroups, such as Cuban Americans and Puerto Ricans, who have different genomic ancestral backgrounds, history, and cultural traditions.

Second, differences in comorbidity, such as a high prevalence of diabetes and chronic kidney disease in NAs and HAs, as well as behavioral and cultural factors may be contributing factors in the disparity in kidney cancer incidence rates. Obesity is recognized as one of the major risk factors of cancer, including kidney cancer [27]; there is racial/ethnic variation in body

composition, abdominal adiposity [36], and obesity-related disease conditions. It is possible that obesity affects RCC in HAs and NAs through biologic mechanisms that are functionally different from other racial/ethnic groups. However, we do not fully understand the causes of high kidney cancer incidence and mortality rates among HAs or NAs, or the role of potential risk factors. The following factors may significantly contribute to a higher rate of diagnosis with advanced stage disease, delayed diagnosis and treatment, treatment choice, and, ultimately, survival among HAs and NA: access to health care (e.g., health insurance coverage, treatment costs, transportation, and geographic distance between a patient's residence and health care facilities), cultural and linguistic barriers, and cultural values . However, such factors may not be the only ones involved in the advanced stage of presentation among these groups.

The third issue that needs to be addressed is the underrepresentation of NAs and HAs in molecular genomics studies--NAs have often been excluded in these precision medicine initiatives [74, 75]. HAs and NAs are also underrepresented in the TCGA [76]. Of all of the RCC samples, only 4.9% were HAs and 0.2% was NAs, even though they make up 17% and 1-2% of the U.S. population, respectively; and, they experience similar or higher incidence rates of RCC compared to EAs. Due to a small sample size, frequencies of tumor molecular subtypes are unknown among HAs and NAs, and even common somatic mutation cannot be detected. One study on clear cell RCC, besides the TCGA, indicated having HAs (12%) and NAs (<1%) in their samples, but the authors did not explore the molecular differences in HAs and NAs compared to other racial/ethnic groups [66]. Therefore, the variations in molecular profiles in RCC among HAs and NAs are not well characterized. Moreover, precision medicine using genomic technology relies on our understandings of genomic variations or molecular profiles in tumors from patients, as well as the relationships between genomic variations and clinical outcomes. Precision medicine cannot be made available to NA and HA patients without understanding genomic variations that predispose them to kidney cancer, or without molecular profiles in tumors from such patients that allow us to predict kidney cancer prognosis and treatment response.

Furthermore, genomic-based precision medicine is only one way to improve RCC outcomes. We should not overlook the value of providing better healthcare access to underserved populations, as well as improving cancer care through better patient-physician

communication and shared decision making for cancer treatment. Overemphasis of genomic medicine takes attention away from more easily modifiable factors or policy changes to reduce health disparities [77, 78]. Precision medicine should not focus solely on the application of molecular genomics technology in the clinical setting, but should also include development of culturally or individually tailored programs to reduce risk factors for kidney cancer and improve kidney cancer care for racial/ethnic minorities.

We need to significantly advance our knowledge of the clinical and molecular characteristics of HA and NA kidney cancer patients. This will allow for effective clinical translation of molecular genomics and precision medicine to provide better advice about treatment plans. As the HA population grows and has better access to health care, there will be more HA patients diagnosed with kidney cancer. Nonetheless, despite the impact of kidney cancer on HA populations and the heavy burden of kidney cancer among NAs, vitally important risk factors and clinical characteristics of these two groups are not well understood. Racial/ethnic minority groups remain underrepresented in molecular genomics studies, and kidney tumors from NAs and HAs need further molecular characterization for clinical benefit.

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Conflict of interest

The authors do not have any conflict of interest to report.

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Table 1 Difference in Kidney Cancer Incidence Rates (2009-2013) between Native Americans (NAs) and non-Hispanic European Americans (EAs) between Hispanic Americans (HAs) and EAs in Four U.S.-Mexico Border States

	NA Rate (95% C.I.)	HA Rate (95% C.I.)	EA Rate (95% C.I.)	NA/EA Ratio (95% C.I.)	HA/EA Ratio (95% C.I.)
Arizona	24.9 (22.1-28.0)	19.1 (18.0-20.4)	14.9 (14.4-15.3)	1.67 (1.49-1.87)*	1.28 (1.20-1.37)*
California	11.7 (9.6-14.2)	15.7 (15.3-16.1)	14.8 (14.6-15.1)	0.79 (0.66-0.94)*	1.06 (1.03-1.09)*
New Mexico	23.1 (19.8-26.9)	15.6 (14.4-16.9)	11.6 (10.7-12.5)	1.99 (1.70-2.34)*	1.34 (1.21-1.50)*
Texas		20.3 (19.8-20.8)	17.8 (17.4-18.1)		1.14 (1.11-1.18)*
U.S.	23.3 (22.1-24.5)	15.9 (15.7-16.1)	16.3 (16.2-16.3)	1.43 (1.36-1.50)*	0.98 (0.96-0.99)*

Age-adjusted incidence rates (per 100,000) using 2000 U.S. standard population was obtained from the North American Association of Central Cancer Registries (NAACCR). * indicates statistically significant difference in incidence rate between NA and EA or between HA and EA

Table 2 Difference in Kidney Cancer Incidence Rates (2009-2013) between Native Americans (NAs) and non-Hispanic European Americans (EAs) between Hispanic Americans (HAs) and EAs in Four U.S.-Mexico Border States Stratified by Age Groups

	Age <65					Age ≥65				
	NA	HA	EA	NA/EA Ratio	HA/EA Ratio	NA	HA	EA	NA/EA Ratio	HA/EA Ratio
Arizona	15.7 (13.7-18.0)	10.6 (9.8-11.4)	8.2 (7.8-8.6)	1.91 (1.66-2.21)*	1.29 (1.18-1.41)*	88.0 (71.7-107.28)	78.4 (70.8-86.6)	60.8 (58.3-63.4)	1.45 (1.19-1.76)*	1.29 (1.16-1.43)*
California	6.2 (4.9-7.7)	8.0 (7.8-8.3)	7.8 (7.6-8.0)	0.79 (0.64-0.99)*	1.03 (0.99-1.07)	49.6 (36.1-66.8)	68.2 (65.7-70.9)	63.8 (62.5-65.2)	0.78 (0.58-1.04)	1.07 (1.02-1.12)*
New Mexico	12.8 (10.5-15.5)	9.0 (8.1-10.0)	6.3 (5.6-7.1)	2.03 (1.64-2.52)*	1.43 (1.23-1.66)*	93.9 (73.7-118.5)	61.2 (54.1-69.0)	48.2 (43.6-53.2)	1.95 (1.53-2.49)*	1.27 (1.09-1.48)*
Texas		10.8 (10.5-11.2)	9.8 (9.5-10.0)		1.10 (1.06-1.15)*		85.8 (82.4-89.4)	72.8 (71.0-74.6)		1.18 (1.13-1.23)*
U.S.	13.8 (13.0-14.7)	8.4 (8.3-8.6)	9.1 (9.0-9.2)	1.52 (1.43-1.61)*	0.92 (0.91-0.94)*	88.8 (81.3-96.8)	67.1 (65.8-68.5)	65.8 (65.4-66.2)	1.35 (1.24-1.47)*	1.02 (1.00-1.04)[#]

Age-adjusted incidence rates (per 100,000) using 2000 U.S. standard population was obtained from the North American Association of Central Cancer Registries (NAACCR). Values in parentheses are 95% C.I. for incidence rate and IRR. * indicates statistically significant difference in incidence rate between NA and EA or between HA and EA, and [#] indicates statistically significant difference in IRR between the younger and older age group.