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Diversifying pre-clinical research tools: expanding patient-derived models to address cancer health disparities

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Abstract

Cancer health disparities (CHDs) define a critical healthcare issue for US racial/ethnic minorities. Multiple factors contribute to CHDs, but genetic ancestry has gained a recent spotlight with more accurate estimation methods. Key findings have led to cancer treatment improvements tailored to minority patients, but such successes have been rare. Two issues continue to limit genetic ancestry-associated cancer risk research: inaccurate ancestry reporting and severe underrepresentation of racial/ethnic minority patients in sequencing cohorts and model biobanks. The emergence of patient-derived xenograft and organoid models may resolve current standstills. With particular focus on high-risk minorities, these pre-clinical models provide the genetic diversity to both genomic data and model libraries necessary to drive discoveries towards precision medicine for US racial/ethnic minority cancer patients.

Despite advances in prevention, early-detection and molecularly guided treatments, cancer remains a leading cause of death. Critically, cancer incidence and mortality rates remain high for US racial/ethnic minorities, defining significant cancer health disparities (CHDs) for these populations[1,2]. Current NCI SEER data shows that Latinos and American Indians/Alaska Natives (AI/AN) are twice as likely to be diagnosed with and die from both gastric cancer (GC) and liver cancer (LC) compared to Non-Latino Whites (NLWs). Likewise, compared to NLWs, African American (AA) men and women are twice as likely to die from prostate cancer (PrC) and breast cancer (BC), respectively. Overall, AAs have the highest cancer mortality rate among all US racial/ethnic groups while AI/ANs experience the lowest 5-year survival rates across all major cancer types[1,2]. For Latinos, cancer has surpassed heart disease to become the leading cause of mortality.

The source of CHDs is multifactorial. Social, cultural, economic, geographical, environmental and genetic factors all contribute to increased cancer burden in minority populations. Healthcare access, specifically private health insurance, has the single strongest protective effect against an advanced cancer diagnosis, while low socioeconomic status and

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comorbid diseases are all associated with increased cancer risk and late stage diagnosis[1–3]. Importantly, many of these risk factors are observed at higher frequencies in minority patients[4]. Higher rates of *H. Pylori* infection, a GC risk factor, has been documented in Latinos while AI/ANs and AAs share the highest overall comorbidity rates in the US[2].

The role of genetic ancestry as a cancer risk factor has gained greater focus in recent years with improved genomic analyses[2,4]. Acknowledging that race and racial identity are social constructs used to categorize individuals, many of these categories can be associated with specific continental ancestry that we refer to herein as genetic ancestry. Published associations of ancestry-associated genetic variation with cancer development have confirmed its role as a risk factor[1,2,4–7]. For instance, increased inflammatory signaling in PrC and BC has been associated with African ancestry and hypothesized to contribute to more aggressive tumors diagnosed among AAs[2,4,6]. Clinical translation of these discoveries has informed treatment options for AAs, such as use of immunotherapy and cancer vaccines to treat metastatic castration-resistant PrC, which showed greater efficacy in AA versus NLW men in the PROCEED registry trial[2,8]. The continuation of these discoveries and their clinical application is a critical element in advancing precision medicine for minority patients.

Heterogenous categories, inaccurate genetic ancestry reporting and underrepresentation of minority patients limit CHD research progress.

While our understanding of ancestral cancer risk factors continues to grow, there remain a number of significant hurdles hindering further progress. On such hurdle stems from the use of racial/ethnic identity as a proxy for genetic ancestry. Latinos, for example, represent a highly diverse group in terms of genetic ancestry, which can cause conflicting reports of cancer risk associations[2,4]. The Latino ethnic category includes individuals with Mexican, Cuban, Puerto Rican, Central and South American ancestry, for which overall PrC and colorectal cancer (CRC) burdens are low. However, PrC is a leading cause of cancer-related deaths among Puerto Rican men[2] and CRC incidence is significantly higher among Cubans compared to Mexicans[7]. Similarly, while BC is highly prevalent among Latinas, possessing a greater proportion of AI ancestry is associated with lower incidence. GWAS have discovered a BC protective variant of AI origin, predicted to interact with the *ESR1* gene, among Latinas [7].

In addition to geographical ambiguity, most studies reporting race/ethnicity have relied on self-reporting, which can often reflect the social and cultural environment of the individual more so than genetic ancestry[4]. In a country as genetically diverse as the US, in which the number of individuals who self-identify as multi-racial has dramatically increased within the last decade, both the social conceptualization and heterogenous nature of race/ethnicity have confounded efforts to identify mechanisms of genetic ancestry that drive cancer risk. Recently improved genetic ancestry methods have led to more accurate ancestry estimation at the individual level. While this has demonstrated marked improvements in associations with clinical outcomes and tumor biology, a study assessing race reporting in

tumor sequencing studies found that of 231 cohorts evaluated, only 85 (37%) reported race and just 7 (3%) used admixture analysis for ancestry assignments[9].

Arguably the greatest hurdle for CHD research is the extreme lack of representation of racial/ethnic minorities among sequencing cohorts and pre-clinical models (Figure 1). The vast majority of established cancer cell lines, which have provided the foundation of cancer functional variant modeling knowledge, are derived from NLW patients. Admixture analysis for 1,018 COSMIC cancer cell lines found that 697 (68.4%), including 95% of the NCI-60 cancer cell lines, were from NLW patients[10]. Large-scale sequencing efforts of cancer patient cohorts suffer from the same issue of underrepresentation. The Cancer Genome Atlas (TCGA), for example, is dominated by samples of NLW ancestry. Ancestry analysis reported only 9.8% from African and 0.4% from Native/Latin American, combining Latinos and AI/ANs, ancestry in the ~11,000 TCGA tumors[11]. This inequality becomes even more striking when considering the increased burden of certain cancers in minorities, such as GC, for which virtually no sequencing information or cell lines exist that represent Latinos and AI/ANs, the two populations with the highest GC burden (Figure 1). Most crucial, two pan-cancer studies aimed at identifying ancestry-specific genetic variations in TCGA[5,11] were unable to analyze data for Latino/a or AI/AN ancestries due to sample size limitations. While outside the scope of this review, it is critical to note that the pattern of racial/ethnic minority underrepresentation is mirrored in clinical trial participation[2].

Pre-clinical xenograft and organoid minority-patient models can resolve issues hampering genetic ancestry-associated cancer risk research.

Fortunately, development of two cancer modeling techniques, patient-derived xenografts (PDXs) and patient-derived organoids (PDOs), in association with greater focus on cancer research resource diversification have begun to change this *status quo*. PDXs are generated via implantation of biopsied tumor tissue into immunosuppressed mice[12]. Once established, PDXs can be maintained through successive mouse implantations. PDOs can be derived from both normal and cancerous tissues and grown within a 3D matrix, allowing their structures to recapitulate the organ-of-origin's architecture. Normal gastrointestinal biopsy-derived organoids, for example, form epithelial crypts[13]. Extensive characterization of PDXs and PDOs have demonstrated that these models sustain the molecular landscape of the original patient tumor, even over multiple passages[12–14]. More importantly, both models have reliably recapitulated therapeutic responses of patient donors, bolstering their utilization in pre-clinical drug screening and biomarker discovery to inform clinical trial design[12,13]. PDOs also have the added benefits of being a highly efficient strategy for tumor subtypes with low PDX implantation rates and allow for rapid expansion of even relatively small tumor biopsies. PDOs are accessible to genomic editing applications, such as the CRISPR/Cas9 system, for functional variant studies[13] and environmental interaction studies, such as *H. pylori* infection[15]. The organoids themselves can also be implanted as xenografts following manipulation, enabling use of an *in vivo* system.

Our lab and others have begun to apply PDX and PDO models within the context of CHDs. A national effort supported by the NCI to generate a robust biorepository of deeply

characterized PDX models, the PDX Development and Trial Centers (PDTCs) Research Network or PDXnet, is currently underway[14]. Importantly, two PDTCs are exclusively focused on generating PDX models from racial/ethnic minorities, including ours at the University of California, Davis. Similar initiatives are underway for PDOs[13]. Together, the data collected from these genetically diverse models will help to further our understanding of genetic ancestry as an aspect of cancer precision medicine by addressing both issues of underrepresentation and inaccurate ancestry reporting. Genomic data from model characterization will allow for accurate admixture analyses to illuminate ancestry-specific differences in tumor subtype and identify clinically actionable genetic alterations that drive cancer progression, resolving critical gaps in previous studies. Moreover, centralized storage of models and data will provide a library of pre-clinical models with appropriate genetic backgrounds to elucidate ancestry-specific mechanisms of treatment response and resistance (Figure 2). Ultimately, this information will help to improve minority cancer patient care by identifying more effective therapeutic regimens for these high-risk populations.

Conclusions and future outlook.

The issue of CHDs among US racial/ethnic minorities has gained significant focus as a major healthcare issue. While recent efforts have helped to illuminate the numerous factors that contribute to these disparities, a number of remaining hurdles must be overcome to eliminate CHDs. Among these, severe underrepresentation of racial/ethnic minorities, particularly Latinos and AI/ANs, in sequencing datasets and pre-clinical model biobanks as well as inaccurate reporting of genetic ancestry have significantly impeded efforts towards understanding the role of genetic ancestry in cancer risk and treatment response. The application and diversification of pre-clinical cancer models, such as PDXs and PDOs, will help to advance our understanding of the role genetic ancestry has in cancer risk and progression. This, of course, is just one of multiple factors driving CHDs in the US. A coordinated effort from researchers, clinicians, social workers and the federal government will be required to fully eliminate CHDs and achieve the ultimate goal of cancer health equity.

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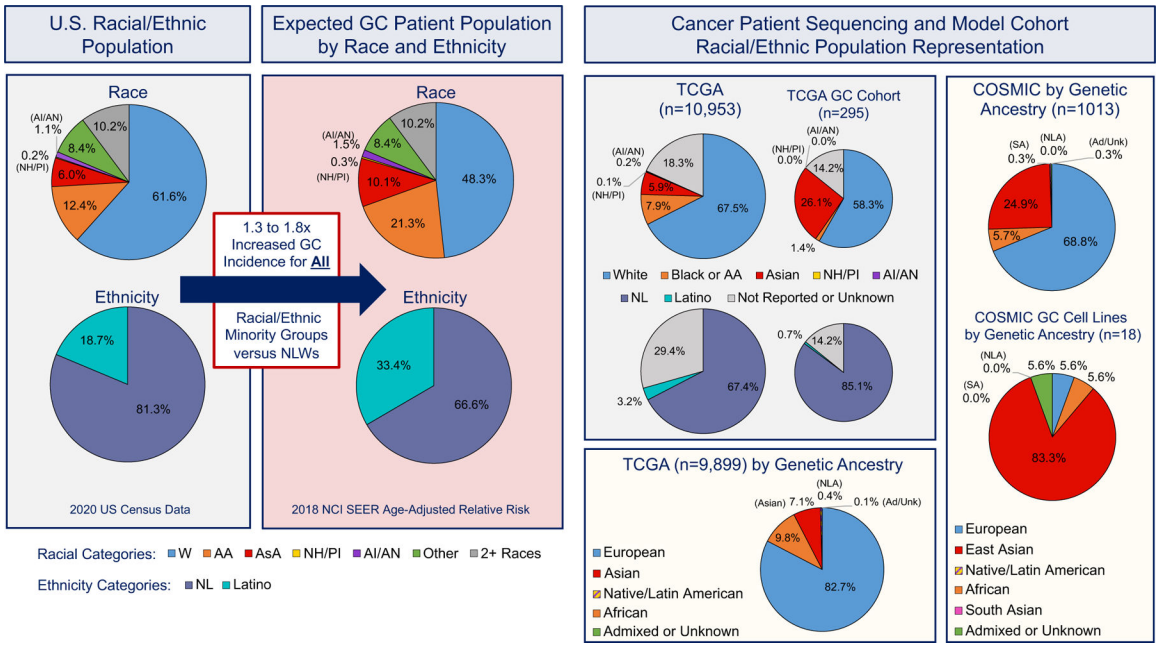

Figure 1: Lack of ethnic/racial representation in cancer genome databases and in preclinical model cohorts.

An example for the disparity-associated gastric cancer *(Left)* U.S. self-reported racial/ethnic population proportions from the 2020 census. Racial groups are represented in the top pie chart, ethnic groups are represented in the bottom pie chart. ***(Middle)*** Expected proportion of gastric cancer (GC) patients by race and ethnicity. Relative risk compared to NLWs was calculated for each racial/ethnic minority group from 2018 NCI SEER age-adjusted incidence and expected proportions for each racial/ethnic group among GC patients calculated based on increased incidence over NLWs. Racial groups are represented in the top pie chart, ethnic groups are represented in the bottom pie chart. ***(Right)*** Racial/ethnic group representation in TCGA and COSMIC pan cancer cohorts and gastric cancer subset cohort. TCGA self-reported race/ethnicity (patient samples collected globally dictate differences in racial categories compared to US census) and genetic ancestry from admixture analysis[11]. COSMIC genetic ancestry from admixture analysis[10]. ***Racial group abbreviations:*** *W = White, B = Black, AA = African American, As = Asian, AsA = Asian American; NH/PI = Native Hawaiian/Pacific Islander, AI/AN = American Indian/Alaskan Native. All racial groups can include individuals who identify as Latino.* ***Ethnic group abbreviations:*** *NL = Not Latino.* ***Genetic ancestry abbreviations:*** *SA = South Asian, NLA = Native/Latin American, Ad/Unk = Admixed or Unknown.*

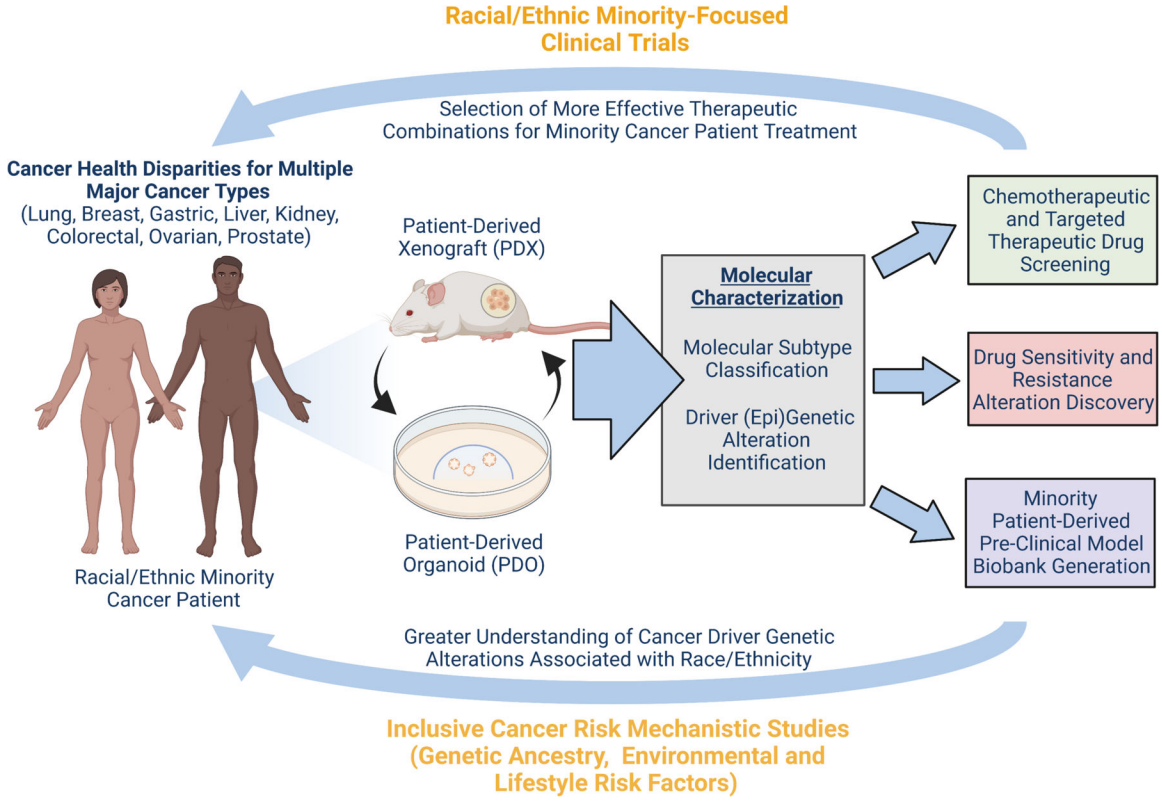

Figure 2: Cancer patient-derived mouse xenograft (PDX) and organoid (PDO) pre-clinical model generation and application to address genetic ancestry-associated cancer risk.

PDX and PDOs are derived from racial/ethnic minority tumor and normal biopsies and can be maintained and banked for further use. PDX/PDOs provide regenerative pre-clinical models for genomic analysis and molecular characterization, including subtype classification and driver alteration identification. Characterized models can be further used for therapeutic screening and drug sensitivity and resistance genetic alteration discovery, creating a biobank of deeply characterized minority patient-derived pre-clinical models for future cancer research. Altogether, model biobanks and genomic data generated from racial/ethnic minority cancer patients provide the missing data for inclusion in genetic ancestry-associated risk studies and inform minority patient-focused clinical trials to contribute to minority cancer patient precision medicine and address cancer health disparities.