Translational Efforts in Precision Medicine to Address Disparities

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Overview of Translational Research

Translational research, defined as the application of scientific knowledge into a novel or modified medical practice, is hinged upon the concept of evidence-based medicine [1]. Translational research is the foundational avenue to strategically focus efforts toward improving the health and well-being in the USA and beyond. Within the context of minority health and racial cancer health disparities, translational research could elevate fundamental discovery science that defines biological mechanisms that contribute to differences in disease risk and outcomes and translates these discoveries into strategies for disease prevention and treatment in clinical settings. To be meaningful and effective at addressing cancer health disparities, additional investments in outreach and dissemination of translational research are needed to enhance uptake and application of findings from fundamental science at the bedside and the ultimate translation of these discoveries into general adoption and implementation of strategies through healthcare policies and professional guidelines [2]. Translational research is one of the cornerstones of clinical interventions and healthcare delivery, but not all populations have benefited from these research efforts. The current guidelines for genetic counseling and testing for BRCA1 and BRCA2 mutations are key examples of the translation of research findings from discovery/basic science into a clinical intervention. Following the initial discovery of cancer susceptibility genes through preclinical and clinical association studies [3–5], large genome-wide association studies helped to determine the relative risks associated with specific deleterious alternations [6–9]. Ultimately, these

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associations were translated into specific genetic testing tools, which provide patients with genetic risk information for clinical interventions and genetic counseling [10, 11]. It is now standard practice for high-risk patients to be referred to genetic testing, typically reserved for those who have a family history of cancer and, interestingly, who have an *ancestry* associated with BRCA1/2 gene mutations [12, 13]. High-risk patients subsequently have access to preventive strategies, as indicated based on their BRCA1/2 genetic test result. However, women of color are less likely than white women to be referred to genetic counseling [14–16] largely due to lack of evidence that it would be of equal benefit [17, 18], as well as emerging evidence that genetic risk alleles are not the same in all ancestral backgrounds [16] but also due to bias and accessibility [16]. Further, non-white patients are more likely to harbor mutations in BRCA1/2 genes that are "variants of unknown significance" (VUS) [19–21]. The inability to determine the significance of these mutations is a consequence of the underrepresentation of non-white women (and men) in the GWAS and genetic risk studies that serve as the empirical data underlying these genetic tests [22, 23]. An additional consequence of homogenous GWAS populations is manifested in the recent application of combinatorial GWAS risk alleles, a calculation of polygenic risk scores (PRS). Although PRS has been proven to be a better translation of GWAS findings [24], similar to VUS in panel testing, PRS calculations do not perform well in non-white populations [25]. As a result of the lack of diversity in GWAS cohorts, genetic modifiers, which are harbored in genetic ancestry, are still widely unknown.

The Arc of Health Justice: Overcoming a History of Medical Abuse and Neglect

The first step of changing the trajectory of poor clinical outcomes in racial disparities through translational research is to understand the history of disparities and the problems that need to be addressed. Over 30 years ago, the Heckler Report, generated by a Task Force on Black and Minority Health, produced a nine-volume document [26] giving a bleak account of the perpetual disparities of minority health that has existed since the beginning of recorded US history. Racial inequality has had a pervasive impact on the general well-being and survival of Black/African American (B/AA) communities [27, 28], a persistent state of minority since the abolishment of slavery [29]. Adding to health disparities driven by limited access to care are the grave injustices of mistreatment of minority groups for the supposed cause of medical advancements. The combined neglect, marginalization, and unethical actions of the medical community have undermined the trust Black/African American communities have in both the health system and the healthcare providers, reified by ongoing racism and bias in health care [30–32]. The shift from racial discrimination to financial discriminations continues to limit health access across social strata associated with race; however, even with full access to all that is available in clinical

settings to treat cancers, treatment options may still not be equitable and suitable for the specific clinicopathology of cancer in minoritized populations.

Recent evidence in breast and prostate cancers indicate that racial disparities persist even in affluent communities where quality and access to care should not contribute to or influence survival [33, 34]. This suggests that treatment is not equally effective across race groups. Indisputable evidence indicates that certain drivers, or root causes, of disparities of incidence and survival are consequences of social determinants of health (SDOH); however, biological factors, which might interact with social intermediaries, also impact disease risks and outcomes [35]. These factors, and the effect of each, must be characterized across the diverse population of cancer patients. Studies that compare the biological determinants and tumor phenotypes across race groups have uncovered several tumorigenic mechanisms that are significantly different among self-reported race groups [36–39]. With these discoveries comes a growing acceptance that inclusion of diverse populations in clinical research is pivotal to ensure broad applications and translation of findings into treatments and strategies for health promotion and disease control [40]. Without inclusion of diverse populations in clinical research, there is a lack of scientific rigor that lessens the significance of scientific discovery, leading to clinical inefficiencies. The deprioritization of minority groups has allowed this negligence to pervade scientific research in numerous ways, including lack of funding and dampened enthusiasm of publication, therefore limiting impact through gatekeeping and policies that permit exclusion of these populations in population-based studies.

The Transformative Power of Precision Medicine on Disparities with Diversity in Translational Research

Precision medicine is one of the newest iterations of translational research that is hinged upon forward-thinking and technologically advanced research findings to tailor treatment regimens based on patient-derived data. Precision medicine refers to a personalized approach to curative treatments, tailored to fit the specific cause and drivers of disease progression. The promise of personalized medicine as first defined in NIH's "Healthy People 2000" was that, by this decade, there would be an individualized approach to disease diagnosis and treatment, hinged upon a precise understanding of pathogenic genetic drivers and a deeper characterization of individual health and genetic background. This was a laudable goal that required leaps of advancement in technology and broad applications of these technologies in clinic. Further, it was anticipated that doctors would become prophetic and could implement preventative measures to circumvent the outcome of disease diagnosis altogether as a result of personalized or precision medicine prognostic tools. Precision medicine has certainly advanced, and our understanding of genetic drivers, genetic risk, and the intermediaries of that risk have improved exponentially. However, we continue to fall short of the ultimate goal [40].

The utilization of precision medicine technologies in disparities research aims to strategically utilize population diversity to develop targeted therapeutics, prognostics, or diagnostics that leverage distinctions in disease drivers that vary among individuals, rather than perpetuating the one-size-fits-all paradigm [37, 40, 41]. When we consider the constellation of causes that align when patients acquire a malignancy, it is not a far stretch to consider every cancer case as a unique disease. Because every individual is unique in genetic makeup, in lived experiences, and in a lifetime of environmental exposures, it is therefore feasible to consider that the tumors' microenvironment, the patient's system, is unique for each case as well. Current investigations that compare the tumor microenvironments of patients in multiethnic cohorts have begun to uncover a vast array of differences that could be exploited for therapies and diagnostics, particularly related to immune phenotypes, in several types of cancers [42–48].

In the wake of personalized medicine, genomic tools have revealed biological variation across patient populations in nearly all diseases that investigate multiethnic cohorts [49–56]. For instance, nearly a decade ago, prostate cancer risk studies identified a region of chromosome 8 (8q24) as a high-risk locus with copy number variation that occurs more frequently in men of African descent [57–61]. A single variant at the same genomic locus has also been reported as an African-specific variant, attributing nearly 32% of familial prostate cancer risk in African Americans [57]. This study was the culmination of more than four different consortia that included over 17K men of African descent. Studies of with cohorts of such magnitude, comprised solely of minorities, were not considered a feasible or even necessary endeavor a decade ago. Ultimately, in order to translate into clinical applications that impact disparities, results such as these must align with the evolving concepts of diverse genomic platforms for precision medicine.

Bridging the Clinical Gap of Cancer Survival Disparities with Translational Research

Despite advancements in basic science, the impact and value of precision medicine has been slow to reach underserved communities, potentially because of the way in which early race and racial group membership were conceptualized and measured in early translational studies. The cure for cancer is not a single drug but combinations of treatment strategies that address specific details of each patient. And for some patients, these personalized approaches can be curative. For other patients, however, precision tools have proven to be much less effective, and the exclusion of racial/ethnic minorities in precision medicine research actually worsens the disparities gap. By incorporating diversity in the patient cohorts that are used in precision medicine research, there would be greater opportunity for translational research to overcome racial disparities in cancer survival.

Traditionally, research on racial disparities has been viewed mainly through a lens of socioeconomic consequences that drive inequality in marginalized race groups. Because race is embedded in the history of political social constructs, race-based research and race-modified medical applications can still be met with substantial resistance [2]. Concerns have been raised about linking race with immutable biological and genetic features; early manifestations of "race-based medicine" were met with considerable skepticism among communities, healthcare providers, and researchers [62–64]. These early iterations of race-based medicine resulted in what would be considered irresponsible conjecture and racist science by creating treatment paradigms, or clinical decision-tree branches based only on self-reported race.

To uncover the potential of population-level genetics to power precision medicine tools, large longitudinal cohort studies are needed to improve our understanding of variation in biological mechanisms of risk and disease progression across diverse patient populations. The precision medicine movement, however, has created opportunities to examine the direct and indirect contribution of biological factors to cancer health disparities. A potentially appeasing option that has been developed through precision medicine initiatives is to utilize genetic ancestry to characterize patient groups and remove self-reported/self-identified race groups from translational research altogether [39, 65–69].

At the same time, however, race captures the social and cultural exposures of individuals, and these factors do have biological implications [70]. Imperative to our plight of overcoming disparities is utilizing all of the information available and include both genetic ancestry and social race constructs as part of translational studies. If we are to overcome the multifaceted causes, we have to quantify them. There are concerted efforts to target recruitment and enrollment of diverse ethnic groups to address our gaps of knowledge where race/ethnicity specific health risks are concerned. The PolyEthnic-1000 [71] project is a prime example of an initiative providing public access to genomic data from targeted diverse populations. In addition, cancer site specific consortia, such as the International Center for the Study of Breast Cancer Subtypes (ICSBCS) [72] and the Prostate Cancer Transatlantic Consortium (CaPTC) [73] are synergizing collaborative efforts, in partnership with minoritized communities and international networks of investigators to provide unprecedented insights in biological determinants related to genetic ancestry. These efforts also recognize that generational differences in social experiences may also be modified over time and are connected to the physical or geographical residence of individuals. The neighborhood effect of social constructs is also an imperative factor to consider in translational research in cancer health disparities. Harnessing the convergence of social and biological determinants will empower our ability to truly be precise with patient needs and predictive algorithms to intervene and reduce disease risk. Effectively, this is the primary goal of translational research: to improve outcomes by applying new knowledge from scientific research. While the field has fallen short of this vision thus far, incredible capacity has been developed to interrogate the human genome, transcriptome, proteome, etc. at increasingly accessible clinical interfaces. Along the way, we have also established that there is a tremendous amount of genetic variation across the human species, which should not always

be interpreted as deleterious in nature, but rather a modified or evolved/adapted version of a canonical mechanism. Translating these revelations requires a reframing of clinical genomics, which is still in process that involves resetting the standard of a "healthy genome," or even a "reference genome." The delay of translating genomic findings is largely due to a severe lack of genetic data in diverse populations. As indicated previously, most of the initial disparity studies were underpowered due to lack of ethnic minority representation in public data [22] and lack of programmatic funding to support new initiatives to increase minority representation. However, now led by the very minority communities that are stakeholders for better outcomes, there is renewed interest in disparities research, particularly those employing ancestry measurements as opposed to race-group proxies. Importantly, this new surge of interest can empower better clinical tools to improve disparate outcomes.

As it relates to cancer, many of the most promising precision medicine endeavors involve understanding the dynamics of tumor biology to uncover drivers of tumor progression. The paucity of data from non-white populations is an example of how studies with limited racial/ethnic diversity perpetuate gaps in our knowledge about cancer biology in these groups. Of the largest consortiums of cancer databases (e.g., the CRUK, AACR-GENIE [74], TCGA [74], and Metabric), there is growing representation of non-white ethnicity in the newer iterations of these initiatives [75]. However, the non-white populations in these cohorts remain disproportionately lower, compared to their actual percentage in the general population [76, 77]. Despite a dearth of diversity in data, the contrasting differences among race groups in recent consortia are robust enough to be detected, replicated, and validated.

When genomic studies include quantified genetic ancestry as a variable in statistical models, the analyses can uncover novel findings appropriate for the broader population. Most recent GWAS are reframing study designs to include substantial numbers of non-European participants, such as the RESPOND study [78] and the AMBER consortium [79]. The resulting investigations include discoveries of population-specific risk alleles [80], shared structural variants that are conserved in patients of African descent [81], and validation of these findings in populations across the African diaspora [82–84]. Indeed, the differential prevalence of specific genetic changes among race groups began a new conversation about heritable genetic drivers in race groups that may reflect shared genetic ancestry. This postulation then made genome sequencing across admixed populations, with better representation of the world population, an imperative next step. However, not all genetic mechanisms derive from ancestral heritage, but rather the impact of the environment. Unraveling the intrinsic from extrinsic would require a convergence of data elements that were typically only investigated in siloes. The indisputable influence of social determinants was soon linked to the translation of these factors into genetic alterations [65, 85–92]. To truly find causation and inflection points of these observed differences, statistical power has to be improved, through increase in numbers of diverse ethnic/race groups.

The genomics era brought our initial mountainous puzzle of how to handle "Big Data," and it is equally challenging to integrate these terabytes of genomic information per patient with a lifetime of dynamic clinical information and medical history

that is captured in the medical record [93–99]. As these processes are vetted and benchmarked for suitability and accuracy, once feasibly deployed in clinic, data science could be transformational in disparities research. Having equal access to all patient data could eliminate the continuous issue of patient population accessibility in medical research. This has already been seen during the COVID-19 pandemic, where health systems were able to report the specific factors that were shared among patients who suffered severe or fatal outcomes [100, 101]. Research conducted to understand risk factors for adverse outcomes among COVID-19 patients can serve as a model for other disease disparities to identify both clinical and social determinants of population-level disparities. The next step will be translating these data models into actionable clinical goals.

Race-Conscious Data Science and Artificial Intelligence

Considered to be part of precision medicine, computational approaches such as machine learning, neural network simulation, and spatial statistics have opened many doors and generated new opportunities to improve clinical diagnostics and simulate the effects of therapeutics [102–104]. This adds another aspect of precision medicine, the use of artificial intelligence, and the increasingly common utility of data science [105–107]. In the current environment where data is plentiful and accessible through innovative approaches, we are poised to make exceptional progress in cancer health disparities, if the technologies are deployed and applied broadly [107, 108]. Algorithms for data science research have the capacity to integrate multimodal data sources, such as digital footprints, electronic medical records, and social media to build automated databases and chart review dashboards with language processing methods. Further, real-world data (RWD) predictive models have emerged and can identify at-risk patients within a health system. One benefit to RWD research is that it is inherently cross-sectional. While some research designs/studies require significant effort on the part of the subjects, data science does not require anything, outside of consent, as the data acquired is self-accruing through automated systems. The actual data are the real-world events, test results, and clinical and demographic variables that are already captured through the course of health care. With the mandate of all medical serving institutions to convert to electronic medical records came a tsunami of information, in the form of personal health information (PHI) data. This data could be mined to power clinical studies and translating scientific findings into applicable knowledge to treat patients.

In addition to PHI, reframing clinical pathology into computational tools also presents new opportunities to learn phenotypic distinctions across the diverse patient population. Artificial intelligence (AI) has been proffered as a method of transcending subjective bias in human observations or preconceived notions of clinical relevance. Data-driven predictions can trigger novel hypotheses that would not have otherwise been derived. Similar to GWAS and genomic research, AI is built upon deep learning algorithms by training on large subsets of patient data, and the

source of these data have been homogenous populations. This results in algorithms that are not transferrable or generalizable to the broader diverse population. Therefore, inappropriate application/interpretation of AI can be detrimental rather than beneficial, by contriving distinctions among diverse ethnic groups that are actually biases in the algorithm's performance rather than biology. Therefore, we must consider modifications to AI training sets and adjustments to account for racial bias. This all hinges on the equitable resources of minority-serving healthcare institutions to ensure comprehensive RWD is captured and harmonized in a standardized way. So, we are again at a precipice of improving disparities within the context of structural barriers that lead to reduced access to telehealth and other electronic healthcare resources (e.g., patient portals) [41].

Emerging Opportunities and Priorities for the Future Translational Research

In 2015, a pivotal and historical announcement was made by then Vice President Joseph Biden, to accelerate the momentum of cancer research and achieve a decade's worth of advances in a 5-year span – the "Cancer Moonshot Initiative." A Blue Ribbon Panel was assembled and produced several assessments [109–111] to outline the current state of cancer knowledge and identify research opportunities that could propel technology and achieve the Moonshot goals. In their assessment, the panel conveyed cancer disparities as a thematic aspect of needed research, to be threaded through all levels of the cancer continuum research agenda, from prevention, diagnostics, and therapeutics to survivorship [109, 110, 112]. The panel boldly suggested that rather than specific studies focused on disparities, that all proposed research would include some aspect of disparities investigation included in either the study design or in recruitment of the minority populations. The moonshot investigators who were awarded these coveted grants are currently reporting findings related to new aspects of cancer, such as tumor atlases and evolution maps that track mutational accumulation over time. A few of these are starting to report findings that support long-standing theories on biological determinants of disparities, which had previously not received adequate funding to address in larger populations [113–121]. While several small cohort and pilot studies first introduced the concepts of biological mechanisms driving higher prevalence of aggressive tumor phenotypes in racially disparate mortality [120, 122, 123], current research trends seek to utilize genetic ancestry, which consistently went unacknowledged, untested, and underpresented in the breadth of previous primary literature. Prior to the advent of ancestry studies, population ancestry was under-appreciated for its capacity to harbor genetic risk and genomic anomalies that are important for risk management [124] diagnostic and therapeutic research platforms [23, 125]. Among these include genomic structural changes in the 8q24 genomic region related to African Ancestry in prostate cancer risk [61, 126, 127], cancer risk alleles associated with Asian ancestry in lung cancer [124, 128, 129], and several distinctions in ancestry-associated tumor expression signatures regulated by signaling pathways that are typical

therapeutic targets [43, 130–132]. The Cancer Moonshot Initiative is another example of the future directions and strategies that are needed for translational research to advance cancer health equity. However, several critical issues still need to be addressed as part of the Cancer Moonshot and similar types of programs. That is to say, the inclusion of disparity populations in discovery science has to be increased, and the adequate representation of these groups should be considered as a criterion of scientific rigor. Relatedly, precision medicine approaches should be applied to clinical research studies to determine causes and identify potential intervention targets. Lastly, these strategies have to be available and accessible in community-serving clinics to have the greatest reach and impact on cancer health disparities. If all of the planned enrollment and integrated analyses occur across the evolving landscape of disparities research in translational medicine, we will certainly see the mitigation of several aspects of bias in cancer outcomes. As we have increased awareness and modified research policies to require inclusion of minority populations, and we utilize novel approaches to harness diversity in genomic background and social factors in translational research, the field of disparities research is poised to transform the culture of race-based research. Translational research can finally become transformative, and health justice can be achieved – in our lifetime (Figs. 1, 2, 3, 4, and 5).

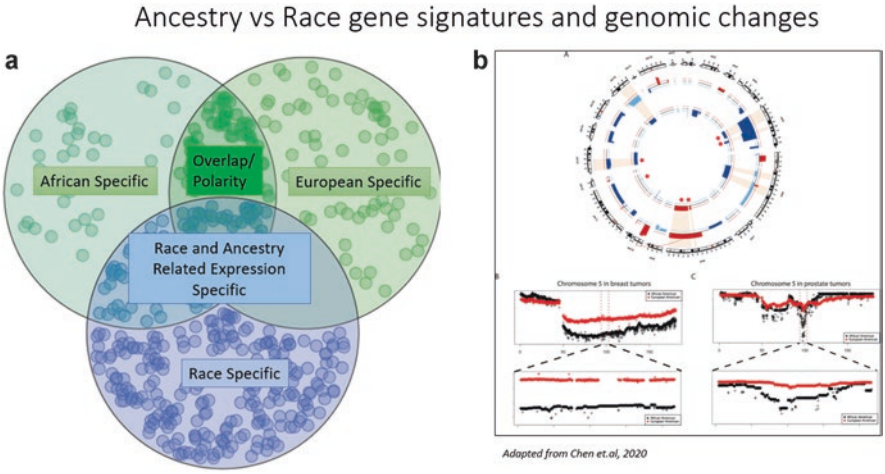

Fig. 1 The role of race versus ancestry in gene expression of tumors. (**a**) In breast cancer RNAseq analyses of triple-negative breast cancer (TNBC), gene expression has been associated with genetic ancestry of African and European origin. In addition, gene expression is also associated exclusively with self-reported race. This indicates there are factors in both genetic/inherited traits and social factors correlated with racial constructs. Therefore, utilizing the combination of ancestry and race can be impactful to define biological determinants that drive cancer phenotypes and treatment outcomes. (**b**) In analyzing genomic sequencing data, there are structural alterations in both prostate and breast cancer tumors that are conserved in self-reported race groups, without regard to ancestry, which indicated significant genetic correlations that are relevant to cancer biology. (Adapted from [81])

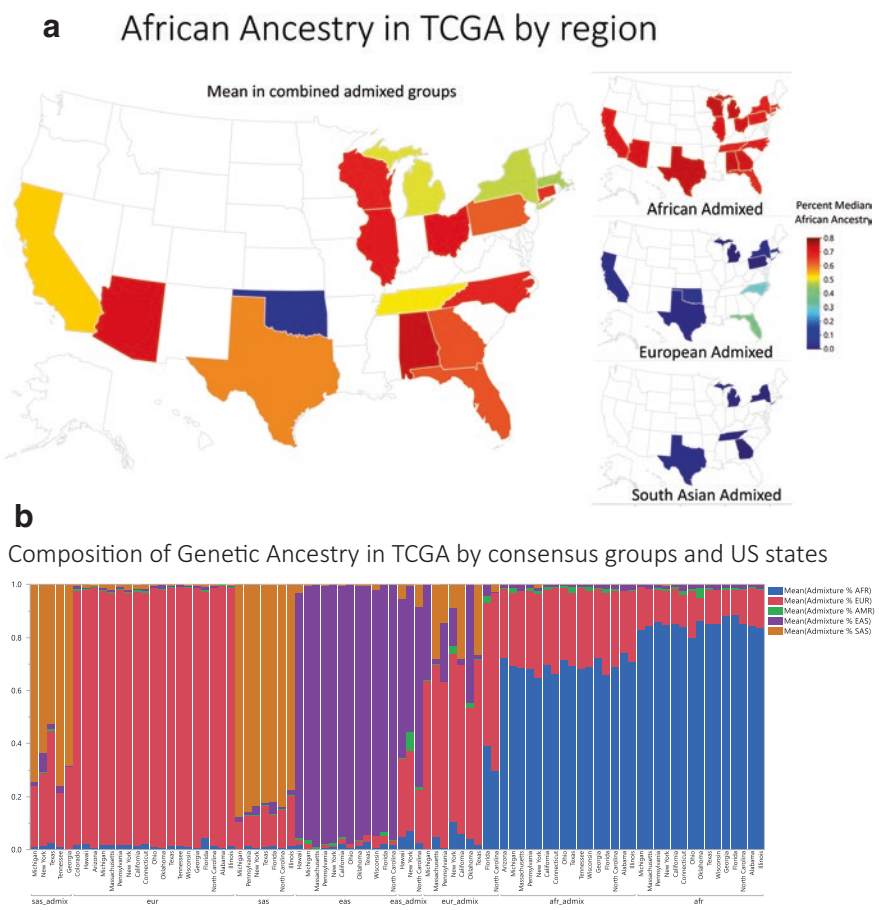

Fig. 2 The genetic composition of US patients in TCGA databases. (**a**) Regional representation of genetic ancestry of African origin indicates several states have contributed a significant proportion of samples with African ancestry. Color coding indicates the median African ancestry of all the samples donated from within the indicated states*. The highest African ancestry samples are in states in the southeast. Insets: consensus "admixed" patients as determined by Carrot-Zhang et al. African admixed patients have varying African ancestry, with the patients having highest proportions in the southeast and Texas. Some European admixed patients have nearly 40% ancestry in Florida cases. Very little African ancestry is found in South Asian admixed patients, regardless of region or state. (**b**) Average admixture composition of 1000 Genomes ancestry is shown for each state*, stratified by the consensus ancestry call groups. Of note, the highest African ancestry in the African and African-admixed groups is found in Georgia and Alabama. The largest proportion of Native American ancestry is found in the East Asian admixed population of New York. **State annotations with less than 20 samples were not included for privacy protection of patients*

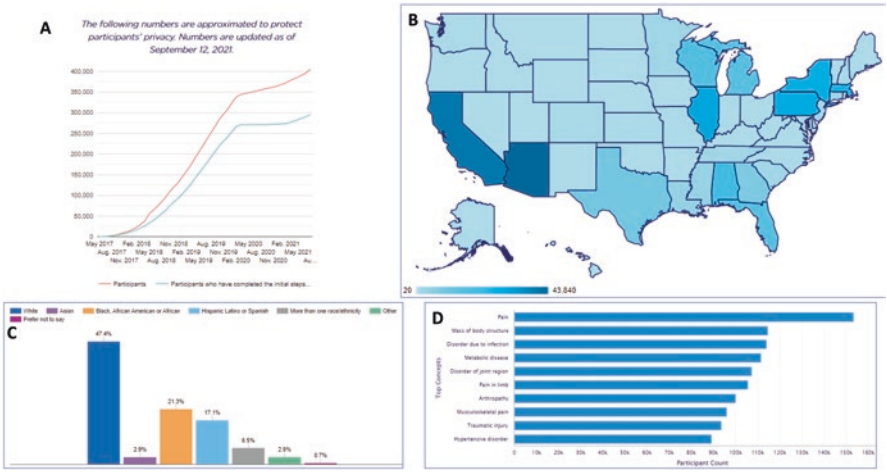

Fig. 3 Diversity in *all* of the USA. (**a**) The cumulative numbers of enrollees are upward of 400K as of September 2021. (**b**) The regional distribution of these enrollment numbers is shown as a state-centered heatmap. The most enrollments are in the west coast, with the next populous states in east and mid-west having significant enrollment. (**c**) The racial diversity of these enrollments is shown as self-reported categories, with nearly 50% representing non-European populations. (**d**) Of the top presenting medical afflictions in the cohorts, cancer/neoplasms are the second-highest reported disease

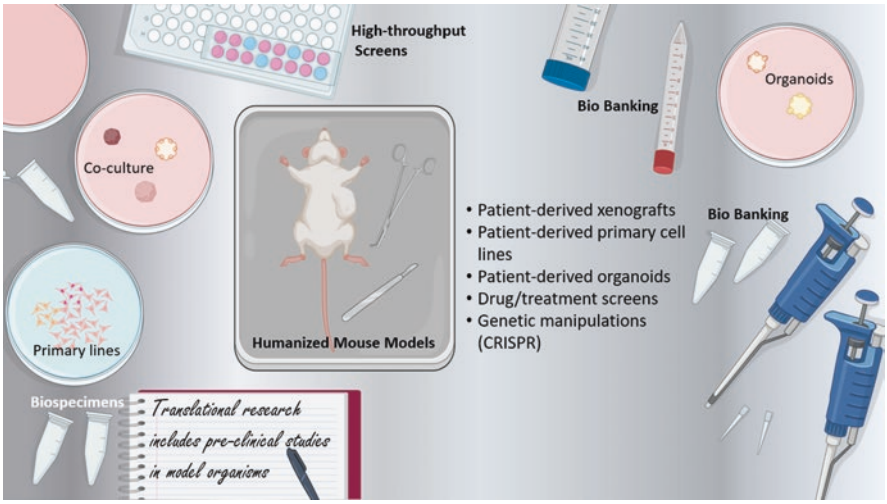

Fig. 4 Clinical and preclinical studies in disparities. Using the tools of preclinical precision medicine studies, we can leverage ex vivo and in vivo models to interrogate the findings from clinical cohorts that identify the mechanisms of varying tumor biology. Bio-banking is also a key aspect of population studies that requires the engagement and recruitment of patients from minoritized race groups. Establishing replenishable resources, such as primary 2D or 3D organoid lines, will be an instrumental step in conducting high-throughput mechanistic screens and drug screens. Preclinical studies are the bridge to translational medicine

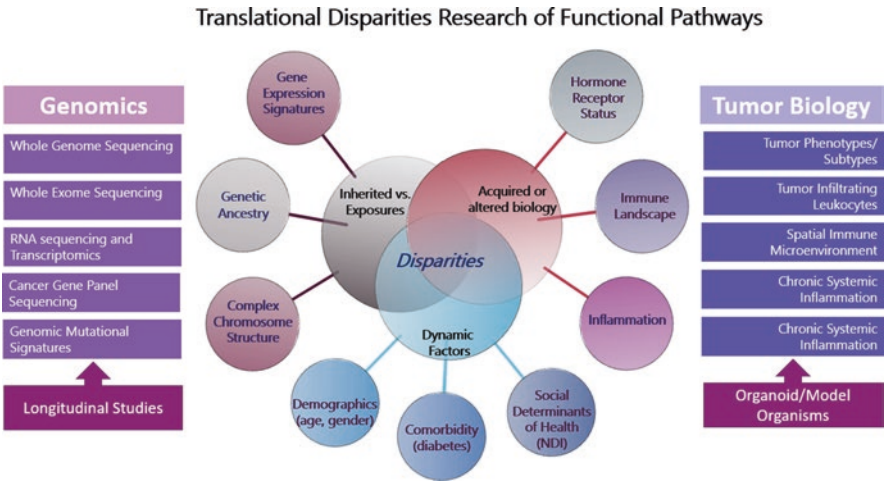

Fig. 5 The alternate lenses of research focus to employ precision medicine tools in translational cancer disparities research. The integration of multiple disciplines is required to address the multifaceted issues that can play a role in disparate outcomes. Any given patient may have a constellation of factors that track with poor outcomes, which correlate with race. To truly identify the actionable causes for individualized treatment, translational research is required to disaggregate the mechanisms that could all link together in driving tumor biology and treatment response differences

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