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COVID-19 and Social Determinants of Health in Gastroenterology and Hepatology

See "Outcomes of SARS-CoV-2 infection in patients with chronic liver disease and cirrhosis: a National COVID Cohort Collaborative Study" by Ge J, Pletcher MJ, Lai JC, N3C Consortium, on page 1487.

The coronavirus disease 2019 (COVID-19) pandemic laid bare the structural inequities in health care, with Black, Latino (LatinX/Hispanic) and American Indian/Alaska Native (AI/AN) populations in the United States experiencing disproportionately higher rates of infection, hospitalization, and death than White populations. The National Academy of Science, Engineering, and Medicine report on health equity identified social determinants of health (SDOH) as fundamental causes of racial inequities in health.[1] Although underlying comorbidities like cardiovascular diseases, diabetes, obesity, and cancer are risk factors for COVID-19 outcomes, the role of SDOH in disparities by race and ethnicity is undeniable.[2] In a cohort study of 44,000 Medicare beneficiaries hospitalized with COVID-19 across 1188 US hospitals, racial disparities in mortality and discharge to hospice were explained by differences in the hospitals to which Black and White patients were admitted after adjusting for age, sex, ZIP code–level income, and underlying comorbidity.[3] The negative impact of neighborhood deprivation for those residing in low socioeconomic conditions on the disparate COVID-19 outcomes in minoritized populations,[4] and the disproportionately higher rates of COVID-19 hospitalizations and mortality reported in ZIP codes with predominantly Black and Latino populations irrespective of socioeconomic status,[5] are the backdrop and context within which the findings by Ge et al[6] should be interpreted.

Although the primary aim of Ge et al[6] was to describe COVID-19 outcomes for individuals with chronic liver disease (CLD), the results of their secondary analyses by race and ethnicity are also noteworthy. The authors identified an association between Latino ethnicity and increased mortality among patients with COVID-19 and CLD. For the subgroup of Latino patients with cirrhosis, there was no statistical relationship between COVID-19 and mortality. The findings are consistent with studies that demonstrate an association between CLD and poor COVID-19 outcomes.[7–9] However, the results are in contrast to a recent multi-institutional study that found an association between Latino ethnicity and severe COVID-19 disease among patients with decompensated cirrhosis, but no association between Latino ethnicity and COVID-19–related mortality.[7]

There are several possible explanations for an association between Latino ethnicity and mortality in COVID-19. Given the higher prevalence of CLD, cirrhosis, and poorer CLD outcomes among Latino populations in the United States compared to other racial and ethnic groups,[10,11] the presence of CLD can confound or amplify the relationship between COVID-19 and mortality. In addition, Latino patients might have higher mortality in the setting of COVID-19 and comorbid CLD due to overall higher incidence of COVID-19,[2] high prevalence of chronic conditions, and/or poor access to health care, all of which are consequences of adverse SDOH. The profound ethnic disparities in incidence of CLD, other chronic illnesses, and COVID-19 reflect the pervasiveness of adverse SDOH in Latino communities and their harmful impact on broader health outcomes.

Of note, despite high incidence and mortality from COVID-19 among Black and AI/AN people in the United States, the authors' findings did not extend to these groups. Although unadjusted analysis found a statistically significant association between COVID-19 and mortality for Black patients, there was no significant association in controlled models. Findings for AI/AN patients were not reported. The reasons for a lack of association in these subgroups is unclear. Improved CLD outcomes in Black compared with

Latino populations, differences in comorbidities by race and ethnicity, and lack of data on AI/AN race likely play a role. More research that includes larger groups of these populations may help clarify these associations.

Existing disparities in digestive diseases are likely to worsen due to ongoing interruptions in chronic disease management and health care coverage, economic disruptions, and post-acute sequelae or long-lasting health consequences of COVID-19. The sentiment that health care providers who care for patients with digestive diseases should assume a sense of urgency in mitigating the SDOH that adversely impact populations that are marginalized due to racism or other "-isms," neighborhood segregation, and unequal access to quality housing and health care resources is a fairly new concept for those unfamiliar with health equity work. Thankfully, it is a sentiment many are now embracing. The context of this realization in which these new thoughts emanate—racial, ethnic, and socioeconomic disparities in COVID-19 morbidity and mortality; police violence disproportionately victimizing Black people; historic decline in life expectancy in Black and Latino populations over the past 18 months[12]— is beyond calamitous. But as the medical community recognizes the tragedies resulting from health inequities, such context presents an opportunity to create a shift in priorities.

Knowing that Black people have the highest rates and morbidity from many gastrointestinal cancers,[13] that nonalcoholic fatty liver disease most commonly afflicts Latino populations, and that end-stage liver disease and wait times for liver transplant are highest for Black patients,[14] the medical community cannot begin to narrow such disparities without addressing their root causes. A one-size-fits-all approach is ineffective. Rather, advocacy efforts, physician education, and community engagement initiatives that specifically focus on vulnerabilities across the care continuum must address racial and ethnic injustices in health.

Separately, increasing workforce diversity by actively enabling underrepresented minorities in medicine (URMs) to pursue careers in gastroenterology and hepatology is an important approach with the potential to advance health equity. Introducing students from URM backgrounds to science, technology, engineering, and math as early as primary school, creating and supporting programs in secondary school geared toward fostering a career in medicine and/or science, early and longitudinal mentorship programs, and engaging gatekeepers and institutional leadership about strategies to combat biases and structural racism that impact education, retention, and recruitment of talented URMs at every educational milestone are a few ways in which the medical community can advance diversity among the gastroenterology workforce. Data demonstrating that physician–patient concordance improves patient experience and health outcomes,[15,16] as well as data showing URMs are more likely to conduct health disparities research,[17,18] tell a critical story—patients benefit from a provider–patient relationship in which cultural sensitivity, experiences, and/or background are shared; and further, when disparities in outcomes exist that are rooted in SDOH, URMs may see the research needed to improve outcomes in marginalized groups as a necessary endeavor that has not historically been recognized as a priority by much of the medical community.

The field of gastroenterology and hepatology has made significant strides in these areas. Although not the primary focus of the study by Ge et al,[6] the race and ethnicity–related findings presented as ancillary analyses are not only worthy of their own attention, but also provide an opportunity to highlight the following newer initiatives in our field that work to advance workforce diversity, equity, and inclusion and health equity:

- The Association of Black Gastroenterologists and Hepatologists,[19,20] a newly founded nonprofit organization created to promote health equity in Black communities, enrich the pipeline, and develop careers of Black gastroenterologists, hepatologists, and scientists.
- The American College of Gastroenterology and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition's #DiversityinGI social media campaign[21] and programming and initiatives emanating from it, as well as the American College of Gastroenterology Institute for Clinical Research and Education's Health Equity Research Award.
- The American Gastroenterological Association's Equity Project and FORWARD (Fostering Opportunities Resulting in Workforce and Research Diversity) program and Pilot Research Award in Digestive Health Disparities[22]
- The American Association of Liver Diseases' 2021 call to action to prioritize diversity, equity, and inclusion.[23]
- The American Society of Gastrointestinal Endoscopy's Diversity Award and Gastroenterology Women's Coalition.[24]
- The Gastroenterology Intersociety Group on Diversity, created in 2020 in response to health inequities amplified by COVID-19 and police violence against Black people, is an organization with leadership representation from the 5 major gastrointestinal societies (American Association of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association; American Society of Gastrointestinal Endoscopy; and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition). It aims to work collaboratively to eradicate health disparities and increase diversity among society members and the pipeline of trainees.

These efforts are bigger than just a moment. They undoubtedly represent a movement, and a much needed one, in the right direction.

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SIRT5's GOT1 up on PDAC

See "Metabolic rewiring by loss of Sirt5 promotes Kras-induced pancreatic cancer progression," by Hu T, Shukla SK, Vernucci E, et al, on page 1584.

Pancreatic cancer represents the seventh leading cause of cancer-related mortality worldwide, and the third most common cause of cancer-related death in the United States.[1] In 2021, 48,220 individuals will die of pancreas cancer in this country.[2] The most common pancreatic neoplasm is ductal adenocarcinoma (PDAC), accounting for >90% of pancreatic malignancies.[3] PDAC is highly aggressive, with a 5-year survival rate of approximately 10%.[1] Surgery, radiation, and chemotherapy are the only treatment modalities generally available for PDAC, and there are no approved targeted or immune-based therapies. Unfortunately, only 10%–20% of PDAC patients present with surgically resectable disease.[4] These dire statistics highlight the urgent unmet need to develop new therapeutic approaches for PDAC.

Famously, the PDAC microenvironment is characterized by striking desmoplasia, a dense fibrous extracellular matrix resulting in high intratumoral pressure.[5] This pressure promotes vascular collapse, inducing hypoxia and nutrient deprivation. To cope with their hostile neighborhood, PDAC cells rely on noncanonical metabolic pathways for growth and survival. Understanding these metabolic adaptations may allow development of novel effective therapeutic interventions for this devastating disease.

In this issue of *Gastroenterology*, Hu et al[6] demonstrate that the SIRT5 protein suppresses PDAC progression by hindering noncanonical glutamine metabolism, via deacetylation and inactivation of cytosolic aspartate aminotransferase (GOT1). SIRT5 is a member of sirtuin family of NAD^+-dependent protein deacylases.[7] The seven mammalian sirtuins, SIRT1-7, exhibit diverse subcellular localization patterns, enzymatic activities, and substrate specificities. SIRT5 primarily localizes to the mitochondrial matrix; however, a fraction of active extramitochondrial SIRT5 also exists in cells.[7] SIRT5 exhibits only very weak deacetylase activity, but instead preferentially removes negatively charged lysine modifications, namely, succinyl, malonyl, and glutaryl groups. Metabolic enzymes represent a major class of SIRT5 targets. Despite SIRT5's unique catalytic activity profile, no major phenotypes or marked metabolic abnormalities are observed in SIRT5-deficient mice under basal conditions.[7] However, like other sirtuins, SIRT5 has been implicated in neoplasia, as both an oncogene and a tumor suppressor, in a context-specific manner.[7] As an oncogene, SIRT5 promotes folate metabolism via activation of mitochondrial serine hydroxymethyltransferase, facilitating cancer cell growth in vitro and in vivo.[8] Folate metabolism is a target of several approved chemotherapy drugs. Likewise, SIRT5 inhibits pyruvate kinase muscle isozyme 2, resulting in accumulation of glycolytic intermediates, driving xenograft growth.[9]

In colorectal cancer, SIRT5 promotes entry of glutamine into the TCA cycle by activating glutamate dehydrogenase 1.[10] Additionally, SIRT5 desuccinylates citrate synthase, the rate-limiting enzyme in the TCA cycle, promoting its activity.[11] Citrate synthase hypersuccinylation inhibits its function and suppresses colorectal cancer cell proliferation and migration.[11] In breast cancer, SIRT5 regulates glutamine metabolism by desuccinylating glutaminase, protecting it from ubiquitin-mediated degradation.[12] In melanoma, SIRT5 is required to maintain histone acetylation and methylation to promote expression of key genes, including *MITF*, a lineage-specific oncogene, and *c-MYC*.[13] Likewise, recent studies have documented oncogenic roles for SIRT5 in breast cancer and in acute myelogenous leukemia.[14,15]

Conversely, as a tumor suppressor, SIRT5 maintains fatty acid oxidation and redox homeostasis by inhibiting dimerization of acyl-CoA oxidase 1, attenuating its function.[16] Consistently, in hepatocellular carcinoma, low SIRT5 expression is associated with increased acyl-CoA oxidase 1 succinylation and activity.[16] In acute myelogenous leukemia, glioblastoma multiforme, and certain other cancer types, isocitrate dehydrogenase gain-of-function mutants convert α-ketoglutarate into the oncometabolite R-2-hydroxyglutarate, which in turn inhibits α-ketoglutarate–dependent enzymes, including DNA and histone demethylases, thereby inducing epigenetic dysregulation.[7] Ectopic expression of SIRT5 reverses α-2-hydroxyglutarate–induced resistance to apoptosis in *IDH1* mutant glioma cells, impairing their growth.[17]

In an elegant new study published in this issue of *Gastroenterology*, Hu et al[6] characterize a novel tumor suppressor function of SIRT5 in PDAC. They show that SIRT5 levels are reduced in human PDAC, as well as in pancreatic tumors from an autochthonous mouse model. Low SIRT5 levels are associated with worsened mortality in