HHS Public Access

Author manuscript

J Natl Med Assoc. Author manuscript; available in PMC 2023 November 11.

Published in final edited form as:

J Natl Med Assoc. 2023 April ; 115(2): 164–174. doi:10.1016/j.jnma.2023.01.008.

Review of genetic and pharmacogenetic differences in cytotoxic and targeted therapies for pancreatic cancer in African Americans

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Literature review, writing and editing of the manuscript: GT, DR, EF, EA, JA, BH, RS, TG, SR Study Design: SR

DECLARATION OF COMPETING INTEREST

TG is a consultant for Pfizer Oncology and Tempus lab which may be a potential conflict of interest. SR received the Robert A. Winn Diversity in Clinical Trials Award sponsored in part by Bristol Myers Squibb Foundation. All other authors declare no conflicts of interest.

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer mortality and the incidence is projected to increase by 2030. Despite recent advances in its treatment, African Americans have a 50-60% higher incidence and 30% higher mortality rate when compared to European Americans possibly resulting from differences in socioeconomic status, access to healthcare, and genetics. Genetics plays a role in cancer predisposition, response to cancer therapeutics (pharmacogenetics), and in tumor behavior, making some genes targets for oncologic therapeutics. We hypothesize that the germline genetic differences in predisposition, drug response, and targeted therapies also impact PDAC disparities. To demonstrate the impact of genetics and pharmacogenetics on PDAC disparities, a review of the literature was performed using PubMed with variations of the following keywords: pharmacogenetics, pancreatic cancer, race, ethnicity, African, Black, toxicity, and the FDA-approved drug names: Fluoropyrimidines, Topoisomerase inhibitors, Gemcitabine, Nab-Paclitaxel, Platinum agents, Pembrolizumab, PARP-inhibitors, and NTRK fusion inhibitors. Our findings suggest that the genetic profiles of African Americans may contribute to disparities related to FDA approved chemotherapeutic response for patients with PDAC. We recommend a strong focus on improving genetic testing and participation in biobank sample donations for African Americans. In this way, we can improve our current understanding of genes that influence drug response for patients with PDAC.

Keywords

Pharmacogenetics$_1$; Disparities$_2$; Pancreatic cancer$_3$; UGT1A1$_4$; DPD$_5$; Equity$_6$

INTRODUCTION

In the United States, pancreatic ductal adenocarcinoma (PDAC) is the third and soon to be second leading cause of cancer death;[1] approximately 4% survive five years given 85% of patients have advanced unresectable disease at diagnosis.[2,3] Africa has the lowest age-standardized incidence rate (2.2/100,000) while Europe (7.7/100,000) and the Americas (7.6/100,000) have the highest rates worldwide.[4] However, in the United States, African Americans have a 50% – 90% higher incidence of PDAC and have a poorer prognosis compared to other racial groups.[5,6] These disparities are multifactorial and may reflect underlying differences in socioeconomic status and access to healthcare. Furthermore, chemotherapeutics such as gemcitabine and paclitaxel have been approved for PDAC treatment, yet responses are less than ideal.[5] This is particularly evident for African Americans, who show worse outcomes compared to Caucasians.[6,7] We propose that disparities in PDAC may also be a consequence of genetic variation resulting in variable (1) cancer therapeutic response (pharmacogenetics), (2) cancer predisposition, and (3) the unknown somatic mutational landscape of PDAC in African American limiting the benefit of druggable genes (precision oncology) in the group. According to Dere and Suto, pharmacogenetics is the study of individual genetic influence on drug response and pharmacogenomics studies the genetic influence of multiple mutations that concurrently influence a patient's therapeutic response.[8] This review will focus on improving the understanding of how genetics impacts PDAC drug metabolism, the efficacy

of therapeutically targeted germline and tumor mutations with consequential outcomes resulting in disparities.

METHODS

This narrative review included articles published from 1995 to 2022. The primary method was to find genes that interfere with drug metabolism of FDA-approved drugs. A PubMed search included the keywords: pharmacogenetics and pancreatic cancer. Next, searches of the name of each FDA-approved drug, toxicity, and African or Black was performed. Gene names found in studies were searched on PubMed using either “race” or “ethnicity” or “African” or “Black” as keywords. Some studies were found from the cited by or cited section from PubMed. The University of Alabama at Birmingham Cancer data analysis portal (UACLAN) was then used to identify whether genes found both in literature and database were significant for overall survival (OS) from PDAC.

Data availability statement

The data generated in this study are publicly available in UALCAN database [http://ualcan.path.uab.edu/analysis.html] and PubMed [https://pubmed.ncbi.nlm.nih.gov/]

RESULTS

Our review consisted of 51 peer reviewed studies that investigated the pharmacogenetics of cytotoxic therapies, therapeutics targeting cancer predisposition and DNA repair deficiency, and therapeutics targeting somatic mutations. The prevalence of these genes in African and European ancestral populations are outlined in Table 1.

Pharmacogenetics of cytotoxic therapies

Fluoropyrimidines: fluorouracil (5-FU and Capecitabine).—5-Fluorouracil is a cytostatic antimetabolite drug utilized to treat various solid tumors.[9] Capecitabine is an inactive prodrug of 5-FU that requires a 3-step conversion to 5-FU by carboxylesterase (CES), cytidine deaminase (CDA), and thymidine phosphorylase (TYMP) to become activated.[10, 11] The University of Alabama at Birmingham Cancer data analysis portal (UACLAN) showed that CDA expression is not statistically significant for OS.[12, 13] Allelic frequencies of CDA associated with decreased enzymatic activity are found in Table 1.

Dihydropyrimidine dehydrogenase (DPD) gene is encoded by DPYD which serves as the rate- limiting enzyme for metabolizing fluoropyrimidines.[14] Complete (homozygous) DPD deficiency is rare and can result in significant toxicities including myelosuppression, diarrhea, and mucositis.[9, 14] Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines categorizes these patients as poor metabolizers having two nonfunctional alleles or one nonfunctional allele plus one allele with decreased function. Partial DPYD deficient patients are intermediate metabolizers (one normal function plus either one nonfunctional or decreased function allele, or two alleles with decreased function), according to CPIC guidelines.[14] Approximately 3-5% of patients have partial DPYD deficiency and overdose can still occur in these patients.[14, 15]

The prevalence of DPD deficiency is more common in African Americans ranging from 4 to 12% compared to 3 to 5% in European Americans.[14, 16–18] Specific variants of DPYD vary between African and European Americans. According to CPIC guidelines, the DPD variant HapB3 with c.1129–5923C>G is found in 4.7% of Europeans and is the most common variant for decreased function among Europeans.[14] Offer et al. assessed circulating mononuclear-cell DPD enzyme activity in African American (n = 94) and European-American (n = 81) participants. The DPYD-Y186C variant was only identified in African ancestral populations and showed 46% lower DPD activity in carriers as compared with noncarriers.[17]

Genetic polymorphisms of thymidylate synthase (TYMS), are also associated with 5-FU toxicity. TYMS is involved in DNA synthesis and is inhibited by fluoropyrimidines. Inhibition of DNA synthesis eventually leads to cell death. Patients with a lower expression of TYMS mRNA (2R/2R or 2R/3R polymorphisms) experience more severe side effects because they are less able to inhibit the effects of 5-fu. Patients with higher TMYS expression (3R/3R) genotype experience less toxicity.[19] The prevalence of 2R is high in both European and African ancestral populations. Khushman et al compared genotypic differences of TYMS and discovered 28% of African Americans had the 2R/2R genotype which was marginally higher than European Americans at 24%.[18] Data from UALCAN demonstrated that TYMS expression level was significantly associated with survival for PDAC.[12, 13]

Irinotecan.—Irinotecan is a prodrug that kills cancer cells by inhibiting DNA topoisomerase 1.[20] Common toxicities after administration of irinotecan include neutropenia occurring in 20-54% of patients [21] and diarrhea occurring in 11-23%.[20–23]

Uridine diphosphate (UDP) glucuronosyltransferase (UGT) facilitates the glucuronidation of many drugs, including the active SN-38 (7-ethyl-10-hydroxycamptothecin), which subsequently increase water solubility. This increase in water solubility allows for the elimination of bilirubin and urine. Therefore, a decrease in the biologic activity of UGT can lead to irinotecan toxicity due to the accumulation of SN-38.[20, 22]

The UGTA1 allele is a subfamily of UGT with varying numbers of thymine adenine (TA) repeats on the promoter region. The wild type allele UGT1A1*1 has 6 TA repeats and is associated with normal function of the gene. Alleles with TA repeats higher than the wild type allele UGT1A1*1, are typically associated with decreased transcription levels, and subsequent lower activity as seen in UGT1A1*28 and UGT1A1*37 alleles with 7 and 8 TA repeats on their promotor region, respectively.[23, 24] These genes with lower activity have greater risk for dose-limiting toxicities. There are 3 UGT1A1 polymorphisms that have been widely studied and associated with toxicity: UGT1A1*28, UGT1A1*93, and UGT1A1*6.[21] The prevalence of UGT1A1*28 expression in African and European populations is 43% and 39% respectively, indicating lower gene activity in more patients with African ancestry.[21] An additional polymorphism significantly associated with toxicity include UGT1A1*93 found in 34% and 27% African and European populations, respectively. UGT1A*6 is commonly seen in the Asian population (15%) and less commonly in African (0.1%) and European (1%) ancestral populations.[21] Decreased enzymatic activity of UGT1A1

is the hallmark of Gilbert syndrome, causing mild unconjugated hyperbilirubinemia.[23] According to CPIC guidelines, UGT1A1*28/*28 and UGT1A1*6/*6 are the most common genotypes associated with Gilbert syndrome.[23] Package insert for irinotecan includes a recommendation for UGT1A1 testing.[25] Despite an association with increased toxicity, expression level for UGT1A1 was not significant for PDAC survival according to the UALCAN database.[12, 13]

Gemcitabine.—Gemcitabine (2'-deoxy-2',2'-difluorocytidine, dFdC) has variable responses ranging from lack of efficacy to severe cytotoxicity that may be attributed to variability in drug exposure and metabolism.[26] Several variants in genes directly involved in gemcitabine metabolism have been reported to impact gemcitabine response (examples are deoxycytidine kinase, DCK; cytidine deaminase, CDA; and transporters: SLC28A1, SLC28A2, SLC28A3, SLC29A1 (hENT1 expression), SLC29A2 (hENT2 expression), ABCB1, ABCC2, and ABCC10.[27–29] Fukunaga et al. evaluated the allelic frequencies of polymorphisms involved in gemcitabine metabolism.[27] From the 14 polymorphisms studied, 12 were seen in Africans and Europeans and 9 statistically significantly or highly statistically significantly varied between both groups. Statistically significant polymorphisms include: DCK 2190A>T, POLA2 2089G>A, SLC28A1 1543G>A and the highly significant polymorphs were- CDA 79A>C, CDA 208G>A, DCTD 315T>C, SLC28A1 1576T>C, SLC28A2 283A>C, TYMS 1494del.[27] Wong et al reviewed genetic polymorphisms with clinical relevance for cancer patients on gemcitabine therapy. In this study, the prevalence of CDA 79A>C (30-36% in Europeans and 4-10.8% in Africans) and CDA 435 C>T (30-32.5% in Europeans and 36% in Africans) were linked to lower progression free survival for patients receiving gemcitabine.[30] The CDA 208 G>A was linked to increased neutropenia and decreased clearance of the drug.[30]

Mohelnikova-Duchonova et al collected tissue samples from patients with PDAC who received surgical resection and found that higher expression of SLC281 was associated with worse OS.[31] Although POLA2 is primarily involved in DNA repair, it's knockdown increased the chemoresistance to Gemcitabine for patients with lung cancer[32] and it's expression level was significant for OS among patients with PDAC.[12, 13]

UALCAN data report overall expression levels of DCK, ABCB1, ABCC2, ABCC10, SLC28A1, SLC28A2, SLC28A3, SLC29A1, SLC29A2, CDA, and POLE are not significant for OS and race.[12, 13]

Nab-paclitaxel.—The combination of nab-paclitaxel with gemcitabine (GemNab) is a recommended first-line treatment option for patients with advanced or metastatic PDAC. Neutropenia, thrombocytopenia, and diarrhea are toxicities related to GemNab.[33] Several studies evaluated the presence of single nucleotide polymorphisms (SNPs) in the ATP Binding Cassette Subfamily B Member (ABCB transporters), and in the CDA genes in patients treated with gemcitabine or nab-paclitaxel chemotherapy and developing severe adverse effects. For instance, the association of hematological toxicity in patients with the CDA 79 A>C mutation.[33] Nab-paclitaxel can inactivate CDA, which results in inhibition of gemcitabine catabolism, leading to higher levels of gemcitabine and a higher response rate in the genetically engineered mouse models known as KPC models.[34] Prevalence of CDA

polymorphisms in African and European ancestral populations of CDA 79 A>C (Lys27Gln), CDA 208 G>A (Ala70Thr), CDA 435 C>T (Thr145Thr) are outlined in Table 1.

Polymorphisms in ABCB gene have been reviewed and correlated with diverse expression of efflux pumps in several tissue compartments and, as a result, modified drug levels.[35] In addition, ABCB1 polymorphisms have been related to hematological adverse effects in cancer patients receiving nab-paclitaxel.[36] Genes that code for solute carriers (SLCs) are linked to paclitaxel-induced cytotoxicity.[37] A subset of genes - SLC31A2, SLC43A1, SLC35A5, and SLC41A2 were shown to be associated with paclitaxel sensitivity and to regulate SNPs that were also linked to paclitaxel-induced cytotoxicity.[37] A population with Northern and Western European heritage from Utah, a Yoruba community in Ibadan, Nigeria, and an African American population from the Southwest of the United States were used in the study.[37] Increased expression of these three SLC genes, SLC31A2, SLC41A2, and SLC35A5, was linked to paclitaxel resistance in lymphoblastoid cell lines in this study.[37] The same study discovered a link between higher SLC43A1 expression and increased drug sensitivity.[37] The UALCAN database was utilized to evaluate the association between the expression of SLC31A2, SLC43A1, SLC35A5, and SLC41A2 in PDAC patients, and survival among different races.[12, 13] Decreased expression of SLC31A2, SLC43A1, SLC35A5 among Europeans and African Americans corresponded with increases in survival. For SLC41A2 gene however, an increased expression in Europeans led to a slightly shorter survival time whilst a decreased expression led to a much higher survival rate. African Americans, on the other hand, showed increased survival with increased expression and a decreased survival with a decreased expression. Europeans generally had a higher survival rate in comparison with African Americans across all four genes, highlighting disparities arising from genetic polymorphisms. The analysis of this data, however, showed no statistical significance.[12, 13] CYP2C8 is involved in paclitaxel metabolism, and UALCAN data showed overall expression was significantly associated with survival for PDAC.[12, 13] Compared to the wild type CYP2C8*1, CYP2C8*3, was linked to neuropathy as a result of clearance reduction. There is lower CYP2C8*3 allelic frequency in African Americans than European Americans.[38, 39] The CYP2C8*2 frequency was expressed in 18% African Americans and no Caucasians and is also associated with lower paclitaxel clearance.[38]

Therapeutics targeting DNA repair deficiency genes

Platinums (oxaliplatin/cisplatin).—Platinum agents such as oxaliplatin and cisplatin are cytotoxic chemotherapies used to treat a variety of cancers including lung, PDAC, and colorectal cancers. Platinum agents form covalent cross-links of platinum-DNA between the bases of damaged DNA. Once crosslinks are formed, DNA repair is prohibited eventually leading to cell death.[40] Efficacy of platinum agents are shown to be highly reliant on the inability of tumor cells to repair damaged DNA. Therefore, they are sensitive to cells with homologous repair deficiencies (HRD), including ATM, PALB2 and BRCA mutations.[40–42] The NCCN recommends combination regimens with platinum agents for those with HRD due to inherent oxaliplatin and cisplatin sensitivity.[43] HRDs are found in 5-9% of PDAC.[40] African Americans have significantly higher number of HRDs across multiple tumor types compared to other racial groups.[44] An analysis by Hsiao et al., showed the genes TP53,

R151, and SMG are most strongly associated with HRD predisposition and is common among African Americans, Caucasians, and Asians.[45]

Repair genes such as nucleotide excision repair (NER), base excision repair (BER), ECCR1, and ECCR2 are important biomarkers that influence the efficacy of platinum treatments.[41] High expression of these repair genes can also increase cisplatin and oxaliplatin resistance as they interfere with the DNA damaging mechanism of the treatments.[46, 47] Based on UALCAN data, ERCC1 and ECCR2 genes are not significantly associated with OS.[12, 13]

The difficulty in treatment with platinum agents is achieving little toxicity with an effective regimen and personalization of treatment. O'Donnell et al shown that Asian derived genes were the most sensitive while African derived genes were the most resistant to cytotoxicity from platinum agents.[48]

A study by Gao et al., investigated whole blood samples of 320 males to access racial differences in the expression of these biomarkers. Results demonstrated that the CC genotype of ERCC1 N118N (500C>T) was seen more frequently in African Americans at 76% compared to European Americans at 21% and TT genotype was seen more in European Americans at 30% compared to African Americans at 3%.[49] The study references that the TT genotype may reduce expression of ERCC1 and subsequently increase sensitivity to cisplatin, though a review by Amable (2016) reports this to be conflicting.[50] Further exploration on the connection between these repair genes and racial difference in treatment response is needed.

PARP inhibitors.—Poly (ADP-ribose) polymerase PARP inhibitors use multiple mechanisms such as trapping PARP-1 and PARP-2 on DNA at single stranded break sites to hinder appropriate repair of the damaged DNA. The detained repair mechanism will eventually kill tumor cells due to further compiling of damaged DNA.[51–53] Tumors that harbor a defect in HRD are particularly vulnerable to PARP inhibitors such as tumors that harbor BRCA-1 and BRCA-2 mutations.[54] In PDAC, BRCA-1 mutations have a 1% prevalence and BRCA-2 have a 5-10% prevalence.[54] Based on UALCAN data, expression levels of BRCA2 is statistically significant for OS, but not for BRCA1.

Olaparib is a PARP inhibitor approved for maintenance treatment of adult patients with deleterious germline BRCA mutated metastatic PDAC whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.[42] In a randomized, double-blind, placebo-controlled, phase 3 trial (POLO trial), maintenance Olaparib provided significantly longer progression free survival (7.4 months vs. 3.8 months) but not overall survival.[55] Subsequently, national guidelines recommend germline testing for all patients after a confirmed diagnosis of PDAC.[43, 56]

A retrospective analysis by Golan et al. examined the prevalence of BRCA mutations among African Americans with PDAC. This analysis geographically examined the first 2,206 patients with metastatic PDAC screened to enter the phase 3 POLO trial. African Americans had higher rates of newly identified germline BRCA mutations (10.7%) in addition to the highest prevalence in total population (13.8%) when compared to other racial

groups. Investigators noted potential disparities in genetic testing amongst racial groups. These results suggest further evaluation is needed with larger sample sizes.[51]

Other targeted therapeutics

Pembrolizumab.—Pembrolizumab is a PD-1 inhibitor which targets immune checkpoint proteins and has transformed the care of metastatic melanoma, non-small lung cancer, and many malignancies. However, results of clinical trials involving immunotherapy in PDAC have been disappointing.[57] The identification of subsets of patients who will positively respond to immunotherapies continues to be investigated. Pembrolizumab is FDA approved for patients with microsatellite instability-high (MSI-H) tumors.[58] Patients with mismatch repair deficiency (dMMR)/ MSI-H are most likely to have sustained clinical responses to immunotherapy.[59] dMMR and MSI-H mutations are rarely occurring in <5% of all diagnosed cancers and is the hallmark of autosomal dominant hereditary condition Lynch syndrome (LS).[60] In addition to being at high risk for colorectal and endometrial cancer, patients with LS have an 8.6-fold increase in developing PDAC.[61] Rosenblum et al. detected 1 in 200 African ancestral populations to harbor LS variants compared with 1 in 518 European ancestral populations.[62]

NTRK inhibitors.—Approximately 1% of solid tumor malignancies harbor NTRK fusion genes. They are extremely rare in PDAC and its incidence is < 1% in African and European ancestral patients with PDAC.[63] The NTRK1, NTRK2, and NTRK3 genes encode the receptors (proteins) TRKA, TRKB, and TRKC which are drivers of oncogenesis. NTRK fusion genes can be detected by DNA sequencing, RNA sequencing and plasma cell-free DNA profiling. Expression level of these genes are not significantly correlated with OS in PDAC based on data from UALCAN.[12, 13]

Entrectinib and larotrectinib are NTRK fusion protein inhibitors that are FDA approved with a tumor agnostic indication for metastatic cancers or unresectable cancers with NTRK gene fusions that have progressed or have no other alternative treatment options. In clinical trial cohorts (ALKA-372-001, STARTRK-1, STARTRK-2), entrectinib demonstrated an objective response rate (ORR) of 57% (95% CI, 43.2–70.8) and median duration of response (DOR) of 10.4 months (95% CI, 7.1–not evaluable).[64] A pooled analysis of three phase 1/2 clinical trials with larotrectinib in 153 evaluable patients demonstrated an ORR of 79% (95% CI, 72.0–85.0), 16% complete response (CR), and a median DOR of 35.2 months (95% CI, 21.2–not evaluable).[65]

There were few patients with PDAC that were studied in these pivotal clinical trials. Two of three patients with PDAC treated with entrectinib had a PR, and one patient with PDAC treated with larotrectinib had a PR. Although rare, testing for NTRK fusion genes should be performed on all patients with unresectable or metastatic PDAC as these agents have demonstrated promising response rate.

DISCUSSION

This review identified genetic mutations in African Americans that may affect toxicity and therapeutic response of cytotoxic and targeted therapies that are FDA approved for the

treatment of PDAC. The UALCAN database was used to ascertain if these genetic mutations were significant for OS.[12, 13] This database is publicly available and provides cancer genomics data to analyze genes of interest based on projects from The Cancer Genome Atlas (TCGA) and other projects. Genes associated with OS include TYMS ($p = 0.0052$), POLA2 ($p = 0.022$), CYP2C8 ($p = 0.027$), BRCA2 ($p = 0.027$), PALB2, and RRM1. Nonetheless, the low sample size of African Americans ($n = 6$) compared with Caucasians ($n = 155$) posed a limitation for properly stratifying racial differences in OS using this database. Furthermore, projects such as TCGA are important for developing therapeutics geared towards precision medicine. However, the small sizes of non-European samples limit generalizability of precision therapeutics conceptualized from the TCGA projects.[66]

Additionally, such small sample sizes also overlook diversities occurring within African ancestral populations and other racial groups. Categorizing all Black persons as a homogeneous group when collating cancer mortality data may mask significant differences linked to their ancestry as well as undermine the environmental and epigenetic risk factors associated with the disease.[67] For instance, a study by Pinheiro et al., 2016, demonstrated that Black people born in the United States had higher PDAC mortality rates as compared to Black people born outside the United States.[67] A subsequent study showed that PDAC mortality rates between 2012 and 2017 among African American males and females in Florida, Minnesota, California, and New York were higher than those of Afro- Caribbeans and Africans.[67] Afro- Caribbeans have PDAC mortality rates in between that of African Americans and Africans. Africans have the lowest PDAC mortality in comparison with other Black populations.[67] Additionally, Africa has the widest genetic diversity.[68] For instance, de Rocha et al., reported the allelic distribution of the DPD variant rs2297595-C to vary across Africa in 1% of west Africans, 6-10% East Africans and 12% South African Zulus.[69] Cancer research geared towards comparing mortality rates among Black people of different ancestry in the United States, could reveal significant variations that could lead to better prevention, control, and treatment options.[70]

Medical mistrust among African Americans plays a role in low participation in omics-based cancer research. Significant contributors to medical mistrust include the belief that the study will be financially profitable for researchers with little advancement to medicine, the possibility of negative side effects, and the uncertainty of who can access their personal information.[71] Added barriers include difficulties commuting to study location[71, 72] and establishing consistent communication with participants.[73] Study recruiters have approached these barriers with improved inclusivity efforts such as including the utilization of diverse health navigators and community health workers representing those communities being asked to participate, develop culturally competent clinical trial education, frequent appointment reminders, offer peer support, in addition to connecting the participants with other helpful resources.[74, 75] Furthermore, incorporating travel reimbursements, monetary incentives, culture competency training of medical staff, [74] along with the positive expectation of improving cancer treatments increase the likelihood of study participation.[71] With the continued proper intentionality during recruitment, the racial variability in genome-wide association studies is promising. Park et al., identified over 700 loci in genome-wide association studies that increase cancer risk, and 21 loci increase pancreatic cancer risk. Less than 1% of the 700 loci have been identified in African populations while more than 80%

identified in European populations.[76] Improving the sample sizes of African Americans and other minorities in biorepositories can lead to a greater understanding of pharmacogenetic differences and achieve an equitable distribution of care and outcomes for patients with PDAC.

Acknowledgments:

This research was made possible by Grant Numbers U54CA233396, U54CA233444, U54CA233465 from the National institutes of Health (NIH), National Cancer institute (NCI). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI. The final peer-reviewed manuscript is subject to the National Institutes of Health Public Access Policy.

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Table 1.

Racial frequency of genotypes that influence the pharmacogenetics and therapeutic targets of PDAC. This table demonstrates differences in allele frequencies between African and European ancestral populations and it is impact on enzymatic functional differences. These allele frequencies are associated with common drugs used to treat patients with PDAC and have implications on pharmacogenetics and therapeutic targets during treatment.

Genotype	Activity	Allelic frequencies (%)		Associated drug class
		African ancestry	European ancestry	
DPD deficient genotypes	Decreased Enzymatic activity	4-12%[16, 18, 77]	3-5%[16, 18, 77]	Fluoropyrimidines (5-FU and Capecitabine)
TYMS: 2R/2R expression	Decreased TS activity	28%[18]	23.8%[18]	Fluoropyrimidines (5-FU and Capecitabine)
MMR deficiency	Impaired DNA repair genes	9.6%[78]	10.4%[78]	Pembrolizumab
MSI	Impaired DNA repair gene	3.6-12%[79–81]	14%[79, 80]	Pembrolizumab
PALB2	Impaired DNA repair gene	6.6 Median TPM[12, 13]	5.5 median TPM[12, 13]	PARP-I
HRD: BRCA 1 mutation	Impaired DNA repair gene	3.54%[82]	2.15% Non-Ashkenazi 5.6% Ashkenazi[82]	PARP-I, Platinums (Oxaliplatin and Cisplatin)
HRD: BRCA 2 mutation	Impaired DNA repair gene	4.55%[82]	1.50% Non-Ashkenazi; 3.7% Ashkenazi[82]	PARP-I, Platinums (Oxaliplatin and Cisplatin)
ERCC1 mutation	Impaired DNA repair gene	73.5 TPM[1] 12, 13	63.8 TPM[12, 13]	Platinums
ERCC2 mutation	Impaired DNA repair gene	10.1 TPM[12, 13]	14.0 TPM[12, 13]	Platinums
UGT1A1*28 expression	Decreased enzymatic activity	13-43%[21, 83]	8-39%[21, 83]	Irinotecan
UGT1A1* 93	Decreased enzymatic activity	34%[21]	27%[21]	Irinotecan
UGT1A1*6	Decreased enzymatic activity	0.1%[21]	1%[21]	Irinotecan
POLA2 2089G>A	Gemcitabine resistance during Knockdown	18%[27, 32]	18%[27]	Gemcitabine
DCTD 315T>C	Gemcitabine pathway variant	48%[27]	25%[27]	Gemcitabine
SLC281 1543 G>A	Gemcitabine pathway variant	9%[27]	2%[27]	Gemcitabine
SLC281 1576 T>C	Gemcitabine pathway variant	0%[27]	47%[27]	Gemcitabine
SLC282 283A>C	Gemcitabine pathway variant	8%[27]	34%[27]	Gemcitabine
TYMS 149del (ttaaag)	Gemcitabine pathway variant	56%[27]	27%[27]	Gemcitabine
SLC 29A1 −1345 C>G	Transporters, increased gene activity *in vitro*	8%[30, 84]	0%[30, 84]	Gemcitabine
SLC 29A1 −1050 G>A	Transporter, increased gene activity *in vitro*	19%[30]	0%[30]	Gemcitabine
RRM1 −524 T>C	Decreased drug response	27%[30]	36%[30]	Gemcitabine
CDA −897 C>A	Reduced CDA activity *in vivo*		2% together[30]	Gemcitabine
CDA 79 A>C (Lys27Gln)	Decreased drug response	4-10.8%[30]	30-36%[30]	Gemcitabine, Fluorouracil

Genotype	Activity	Allelic frequencies (%)		Associated drug class
		African ancestry	European ancestry	
CDA 208 G>A (Ala70Thr)	Decreased CDA activity	12.5%[30]	0%[30]	Gemcitabine, Fluorouracil
CDA 435 C>T (Thr145Thr)	Lower response rates	35-36. 7%[30, 85]	30-32.5%[30, 85]	Gemcitabine, Fluorouracil
CYP2C8*3	Lower Paclitaxel Clearance	0-2[38, 39]	1-13%[38, 39]	Nab-Paclitaxel
CYP2C8*2	Lower Paclitaxel Clearance	2%[38]	18%[38]	Nab-Paclitaxel
NTRK genes	Fusion gene, oncogenic	0.34%[63]	0.28%[63]	NTRK fusion inhibitors

[1]TPM: Transcripts Per Million