A pilot study of Cancer Genome Profiling in the African American Population

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ABSTRACT

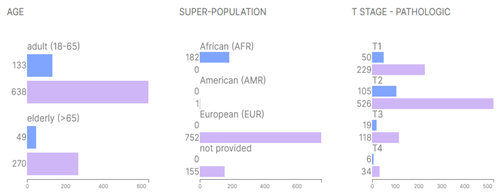
As an African American woman, it is imperative that I change the perception that we have on healthcare and the pharmaceutical industry. It is a common but respectable misconception that Medicine and research does not work in the African American population. Many of these misconceptions have developed over time from the medical mistreatment in diverse population, specifically African Americans. (T.S.E, Henriette Lacks etc.) Studies show that Breast and Ovarian cancer are two of the most prevalent cancers among women worldwide. African American woman have a lower incidence in both Breast and Ovarian cancers but have a higher mortality rate compared to their white counterparts. Genetics, Access to care, treatment options, and other healthcare disparities play a vital role in overall survival rates among this diverse population. While there has been research on both cancer types, there is limited data and research specially for African American women.

Keywords: Key words: Ovarian Cancer (OV), Breast cancer (BC) , Tuskegee syphilis experiment (T.S.E), Henrietta Lacks, Healthcare Disparities, Mortality, Genetics, and Diverse Populations

AIM / OBJECTIVE

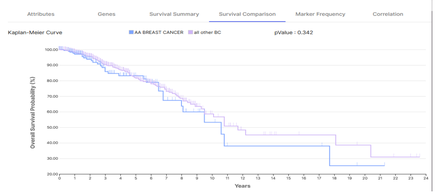
To gain better understanding of genomic landscape and expression profiles in Breast and Ovarian Cancer in the African American population and seek to identify biomarkers or potential targets for precision medicine to improve survival rates in diverse populations.

Fig 1. Sample size and variable for cohort



We generated two cohorts of patients that met a specific criteria. We used TCGA (The Cancer Genome Atlas) data sets to further specify our cohort studying BRCA (Breast Invasive Carcinoma) in Super Populations. Two cohorts were created, one excluding African Americans, and one cohort that only includes African Americans. (1)The cohort study is composed of a total of 1,090 patients, 182 African American Women and 908 for all other populations. We then compared the two cohorts (AA vs AO) to determine specific demographic information. The figures further explain specific demographics within the cohort regarding sample size, age, population and T-stage pathogenetic. (2)African Americans only account for 20.4% of the total cohort, showing initial diagnosis between the ages of 18-65. All other races account for the remaining 79.6%, showing initial diagnosis between ages 18-65. (3) The T-stage graph refers to the size and expansion of the initial tumor. Upon initial diagnosis both cohorts show stage T2, which means the tumor is more than 20mm but less than 50mm in size.

Fig 2. Survival Plot of cohort AA vs AO (BC)



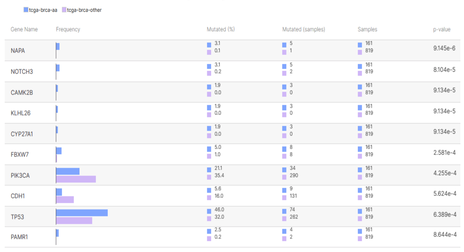
We examined comparatively survival rates of our cohorts which further confirmed our analysis. ICA cohorts determined the survival probability by calculating the number of subjects surviving by the total number of individuals who are at risk over a 24 year span. Though, African Americans represent only 20.4% of our total cohort, the survival rates among this population are significantly low compared to all other populations year by year. All other races show a max survival rate of over 23 years, while African American shows a max survival rate of 21 years. Further analyzing this data we discovered at 10.5 years, AA survival rate is at 45.6% while AO is at 56.7% P-value = not significant

Fig 3. Top Mutated genes in both cohorts

Gene	Mutation %	P-Value
BRCA1	**AA 3.1% , other 2.2%**	**0.5**
BRCA2	**AA 1.9%, other 2.6%**	**0.5**
PIK3CA	**AA 21.1% , other 35.4%**	**<0.001**
TP53	**AA 46%, other 32%**	**<0.001**

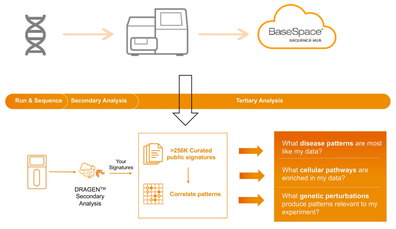
We examined somatic mutations in both the African American population and all other populations. We then conducted a search on marker frequencies and organized the data from the most frequent mutations to less frequent mutations. Marker frequencies allowed us to confirm the top mutation in both cohorts and also to understand the mutation percentages among each cohort. We found that BRCA1/2, PIK3CA and TP53 were the top genes mutated in both cohorts.

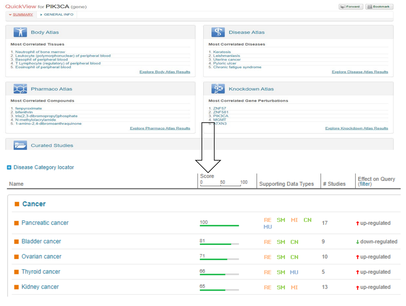
Fig 4. Genetic mutations frequently found in AA



We discovered common mutated genes in African American Women with high mutation frequencies. CAMK28, KLHL26 and CYP7A1 are only mutated in the African American population. NAPA,NOTCH3 and FBXW7 have higher mutation frequencies in AA, and less mutation frequencies in AO. PIK3CA, CDH1, TP53 and PAMR1 are mutated in both populations, however the mutation percentages are greater in all other populations. The seven notated genes are less studied genes and could be potential biomarkers for precision medicine in the African American population. However, PIK3CA, CDH1 and TP53 show a comparable percentage given the cohort variables. This graph shows a sample number of 161 AA, and 819 for AO.

MATERIALS & METHODS





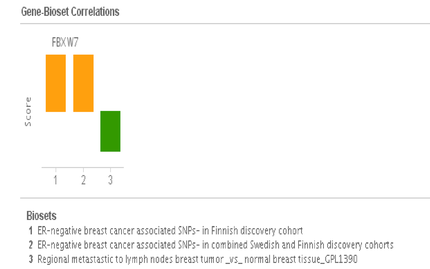
RESULTS

Our analysis confirmed the existing biomarkers, including BRCA1/2, PIK3CA, TP53 in Breast Cancer and their high frequencies and correlations within Breast Cancer cohorts of all races. Our analysis shows example of differences in existing biomarker (e.g. PIK3CA) in African American population which may indicate differences in response to targeted treatments. Our analysis suggests potential new biomarkers with higher occurrence in African American in Breast Cancer (e.g. FBXW7) which independent molecular and gene study suggested is highly associated with the disease and with potential treatment options including compounds and clinical trials. Our analysis also showed lower survival rate in other types of cancer within the African American population with fewer data and research available to guide similar analysis that we were able to perform on Breast Cancer.

Fig 5. Gene Expression VS mutation

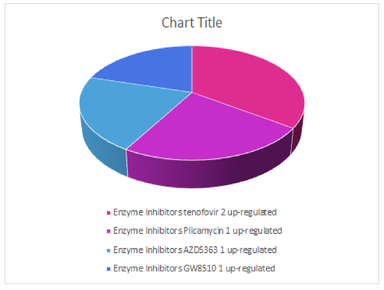
We explored the correlation between somatic mutations. Figure 5-A shows the positive correlation between PIK3CA and TP53 gene mutations. This is consistent in African American and in other populations. The correlation is a confirmation of the known connection between molecular drivers of cancer. PIK3CA is an oncogene, while TP53 is a tumor suppressor. Current understanding of cancer development suggests multiple drivers (oncogene plus tumor suppressor) in most growing tumors. We then further explored the correlation between gene expression and their mutations. Gene expression is usually driven by transcriptional changes, while mutations are from genetic changes. Therefore, it is unlikely there would be correlation due to different regulatory mechanisms. Figure 5-B shows the TP53 gene expression and mutations. The plot shows in the patients with TP53 mutations, some may have expression changes while there are no clear directions or correlations. This is the case for both African American and other populations. However, we saw some level of correlation in the gene PIK3CA specific to African American, as shown in Figure 5-C, that in the African American population, there seems to be more PIK3CA down-regulation, adding on to PIK3CA mutations. In this population, we have shown lower mutation frequency of PIK3CA, and with the more tendency of down-regulation of PIK3CA, it may suggest fewer occurrence of PIK3CA being the cancer driver, thus the treatment or therapies targeting PIK3CA may not be as effective or respond to the African American population than to other populations.

Fig 6. Potential Gene Mutations Worth Further Exploration (FBW7)



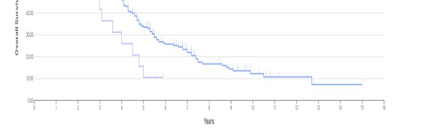
We further confirmed our analysis using Illuminas correlation engine. FBXW7 is a tumor suppressor that we have found to show frequent mutations in African American women.

Fig 7. Tenofovir (drug/ compound)



We then took a deeper look at lead compounds and drugs that currently target FBXW7. The given compounds/ drugs are highly correlated and shows up regulation. Confirmative analysis shows that FBXW7 has been linked to breast cancer, along with clinical trials that suggest this gene can be a target for therapeutic implications. We sought out to examine one drug/ compound that has been shown to have positive outcomes. Tenofovir is an antiretroviral medicine that is typically used for treatment of HIV and hepatitis B, but has proven to have tumoricidal effects on human cancer cells.

Fig8. Survival Rates In Cohort study AA vs AO (Ovarian Cancer)



We further did an Ovarian Cancer comparative analysis of the African American population and all others to see if the survival rates were similar or different to breast cancer survival rates. ICA cohorts determined the survival probability by calculating the number of subjects surviving by the total number of individuals who are at risk over a 16 year span. AA women (N= 55) survival rates are 6 years compared to all other races (N= 680) who have a 15 year survival rate, with the majority of non-Hispanic or Latino populations having a 5+ year survival rate. AA survival rate decreases to 51.8% at 3 years, while all other races are at 65.6% at 3 years. The P-value (1.966e-2) in comparison of survival rates in AA and AO is significant.

CONCLUSION

Understanding the genome profile of cancer in African American women will help in advancing precision medicine by identifying population specific changes and biomarkers, and by developing therapeutics based on the insights of the biomarkers. Our study shows a data driven approach in collating, analyzing and exploring genomic profile in Cancer in a subpopulation. With attention being made to more inclusive research and patient process, we expect more clinical and genomics data will become available in the research sector to enable this type of cohort study and with the tools we demonstrated it will be more effective in identifying new biomarkers and potential targets for therapies for diverse populations.

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