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EPIDEMIOLOGY

Assessing the effectiveness of the National Comprehensive Cancer Network genetic testing guidelines in identifying African American breast cancer patients with deleterious genetic mutations

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Abstract

Purpose Approximately, 10% of breast cancers are hereditary. Identifying women at high risk for hereditary breast and ovarian cancer allows for early detection, prevention, and individualized disease management for those diagnosed with breast cancer. There is limited data about breast cancer genetic risks among African Americans as the majority of the large studies have been conducted in European Americans. We examined the distribution of deleterious genetic mutations in African American breast cancer patients, and evaluated the effectiveness of the National Comprehensive Cancer Network (NCCN) guidelines for identifying African American women at high risk for deleterious genetic mutations.

Methods African American participants with breast cancer underwent an interview regarding health and family history, and a 30-gene saliva test. Medical records were accessed to determine whether participants had received prior genetic testing as part of usual care, results of previous testing, and cancer characteristics.

Results Two hundred and fifty participants were enrolled between February 2016 and May 2018. Twenty (8.0%) had a deleterious mutation in one of the 30 genes; *BRCA2* had the highest frequency (40.0%). 187 (74.8%) met eligibility for testing based on NCCN guidelines. Only 110 (58.8%) of participants eligible for genetic testing, according to guidelines, had received prior testing as part of routine care. Using the 30-gene test, we identified deleterious mutations in 17 of 187 (9.1%) of those who met NCCN criteria for testing, and three of 63 (4.8%) of those who did not meet criteria for testing nonetheless had a deleterious mutation associated with breast cancer.

Conclusions Our results indicate that a large proportion of African American breast cancer patients who meet criteria for genetic testing do not receive it as part of routine care. Even in women who do not meet testing guidelines, nearly 5% have a known deleterious mutation associated with breast cancer.

Keywords Breast cancer · Genetics · Deleterious mutation · African American · NCCN guidelines

Abbreviations

NCCN National Comprehensive Cancer Network
HBOC Hereditary breast and ovarian cancer
TNBC Triple-negative breast cancer
VUS Variants of undetermined significance

Introduction

Approximately, 10% of breast cancers are hereditary, with deleterious mutations in the *BRCA1* and *BRCA2* genes being responsible for a majority of the genetic predispositions [1, 2]. Genetic testing for hereditary breast cancer permits high-risk individuals to be identified. This then allows for the implementation of early detection with enhanced screening, pharmacological or surgical prevention, and individualized systemic therapy for those diagnosed with breast cancer [3–16]. The National

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Comprehensive Cancer Network (NCCN) has created testing guidelines to help identify individuals at risk for hereditary breast and ovarian cancer (HBOC) syndromes, or patients with a high probability of having a deleterious mutation in a HBOC-associated gene. These guidelines primarily depend on the age of onset of breast cancer, and family history of breast, ovarian, pancreatic, and/or prostate cancer. In addition, the current guidelines do not incorporate race, other than Ashkenazi Jewish race. The guidelines list numerous multi-faceted eligibility criteria, and therefore, may be tedious and time-consuming to implement in routine clinical practice. In addition, these guidelines were initially created when genetic testing was cost-prohibitive, and as such the guidelines needed to be restrictive.

There is a dearth of information about breast cancer genetic risks among African Americans as the majority of the large genetic studies have been conducted in European Americans [17–20]. This is despite the benefits of genetic testing, and the fact that African Americans present at a much younger age, have the highest death rates, and have higher rates of the most aggressive breast cancer subtype compared to any other racial group [21–24]. Even after controlling for the probability of having a deleterious mutation, African American women are less likely to undergo counseling for *BRCA1* and *BRCA2* testing [25]. The frequencies of deleterious germline mutations in the largest clinic-based cohort of prospectively ascertained African American breast cancer patients revealed that 68 deleterious mutations were found in 65 of 289 (22%) individuals. Deleterious mutations were seen in eight genes, with the majority in *BRCA1* and *BRCA2*, and the remaining in *PALB2*, *ATM*, *CHEK2*, *BARD1*, *TP53*, and *PTEN* [26]. These results indicate that a significant proportion of African American breast cancer patients and their families who are not referred for testing may have a missed opportunity for more individualized management. The racial disparity in breast cancer genetic studies has conceivably worsened the pre-existing outcome disparities, as breast cancer genetics is now critical in guiding management.

With advanced technologies, and the June 2013 Supreme Court ruling No. 12-398 in Association for Molecular Pathology versus Myriad Genetics, Inc. on *BRCA1* and *BRCA2*, which held that 'a naturally occurring DNA segment is a product of nature and therefore not patent eligible', genetic testing is now relatively inexpensive and more widely accessible [27]. In this research study, we sought to examine the distribution of deleterious genetic mutations in African American breast cancer patients, and to evaluate the effectiveness of the current NCCN guidelines at identifying African American women at high risk for deleterious genetic mutations.

Methods

Study design

Eligibility criteria for this research study included African American females diagnosed with any disease stage or clinical breast cancer subtype, age at least 18 years, and English-speaking. Participants were recruited from the St. Louis metropolitan area through referrals from physicians at the Alvin J. Siteman Cancer Center at Barnes Jewish Hospital and Washington University School of Medicine, breast cancer support groups, and community engagement using "snowball" sampling [28]. The study was approved by the Institutional Review Board at Washington University School of Medicine in St. Louis.

Participants provided informed consent and then completed a comprehensive interview regarding their personal health history and family history (Data Supplement 1–4). All participants also signed an authorization to release their medical records related to their breast cancer diagnosis and treatment, and provided a saliva sample for free research genetic testing through Color Genomics, Inc. Color Genomics provides physician-ordered, clinical-grade genetic testing direct to consumers. The genetic testing panel initially consisted of 19 genes associated with HBOC (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, *TP53*) and in June 2016, they expanded their panel to 30 genes associated with HBOC as well as the most common hereditary cancers such as colorectal, pancreatic and prostate cancer (genes added were *APC*, *MUTYH*, *MITF*, *BAP1*, *CDKN2A*, *CDK4*, *BMPR1A*, *SMAD4*, *GREM1*, *POLD1*, *POLE*). Nine participants completed the 19-gene panel while 241 completed the 30-gene panel. Research genetic results were shared with the research team and study participants were given the option to view their results. Complimentary genetic counseling with a board-certified genetic counselor was offered to all participants who completed testing. However, all participants who had a deleterious mutation identified were required to complete genetic counseling with the Color Genomics, Inc. genetic counselor prior to receiving their results.

The research team accessed participants' medical records to determine whether participants had received prior clinical genetic testing as part of usual clinical care, results of previous clinical genetic testing, stage of breast cancer at diagnosis, and whether participants had triple-negative breast cancer (TNBC). These data were analyzed in conjunction with the self-reported information provided in the research interviews.

Statistical analysis

Based on NCCN Guidelines Version 2.2017 for Genetic/Familial High-Risk Assessment: breast and ovarian, participants were categorized as to whether they met criteria for genetic testing or not. The proportion of participants who met the criteria for genetic testing and received genetic testing as part of their clinical care was determined. The deleterious mutation rate among all participants, those who met the NCCN criteria, and those who did not meet the criteria was also determined. χ^2, Fisher exact test, Student *t* test, or Wilcoxon test were performed as appropriate to compare differences in demographic variables and other patient characteristics between patients with a deleterious mutation and those without a deleterious mutation. Multivariable logistic regression was used to estimate the association between presence of a deleterious genetic mutation, variants of undetermined significance (VUS), and multiple predictors, including age of diagnosis, TNBC status, presence of bilateral breast cancer, family history of breast or ovarian cancer, and body mass index (BMI). All statistical analyses

Table 1 Characteristics of study population

Characteristic	Participants with deleterious mutation ($n=20$)	Participants without deleterious mutation ($n=230$)	*p* value
Age at diagnosis, mean (range), years	47.70 (35–61)	53.98 (27–84)	0.0018[d]
BMI, mean (SD)	36.69 (8.28)	32.95 (13.02)	0.0150[c]
Age at first live birth, mean (SD)	23.83 (5.79)	22.05 (5.74)	0.1100[c]
No. of live births, mean (SD)	2.22 (0.88)	2.43 (1.42)	0.7967[c]
Breastfed children			
Yes, *N* (%)	9 (50.00)	89 (44.28)	0.6400[a]
No, *N* (%)	9 (50.00)	112 (55.72)	
Triple-negative breast cancer			
Yes, *N* (%)	6 (31.58)	65 (28.89)	0.8042[a]
No, *N* (%)	13 (68.42)	160 (71.11)	
Bilateral breast cancer			
Yes, *N* (%)	5 (25.00)	18 (7.83)	0.0108[a]
No, *N* (%)	15 (75.00)	212 (92.17)	
Stage at diagnosis			
Invasive, *N* (%)	19 (95.00)	220 (96.07)	0.5741[b]
Non-invasive, *N* (%)	1 (5.00)	9 (3.93)	
Met NCCN criteria for genetic testing			
Yes, *N* (%)	17 (85.00)	170 (73.91)	0.4204[b]
No, *N* (%)	3 (15.00)	60 (26.09)	
Previous genetic testing			
Yes, *N* (%)	8 (40.00)	111 (48.26)	0.3138[a]
No, *N* (%)	12 (60.00)	119 (51.74)	
Family history of breast or ovarian cancer			
Yes, *N* (%)	11 (55.00)	124 (53.91)	0.9255[a]
No, *N* (%)	9 (45.00)	106 (46.09)	
Hormone replacement therapy			
Yes, *N* (%)	1 (5.26)	53 (23.14)	0.0840[b]
No, *N* (%)	18 (94.74)	176 (76.86)	

Due to missing information, one subject was excluded from analysis of stage at diagnosis, six were excluded from triple-negative breast cancer analysis, and two were excluded from hormone replacement therapy analysis. Thirty-one subjects who never had children were excluded from analyses of age at first live birth, number of live births, and breastfed children

SD standard deviation, *NCCN* National Comprehensive Cancer Network, *BMI* body mass index

[a]χ^2 test

[b]Fisher's exact test

[c]Wilcoxon test

[d]Student's *t* test

were performed with SAS version 9.4 for Windows (SAS Institute, Cary, NC).

Results

Between February 2016 and May 2018, 250 African American participants with a breast cancer diagnosis were enrolled to this study. Seven hundred and seventy-one eligible women were invited to participate; the participation rate was 32.4%. Data were not collected on those who declined study participation, as they did not sign informed consent. Participants had been diagnosed with breast cancer between 1979 and 2018. The median length of time since diagnosis was 2 years. The median age at diagnosis was 53.5 years (range 27–84 years). Median BMI was 31.2 kg/m^2 (range 17.7–62.8 kg/m^2). Seventy-one (28.4%) participants had TNBC, 23 (9.2%) had bilateral breast cancer, and 135 (54.0%) had a family history of breast and/or ovarian cancer (Table 1). To fully understand the demographics of participants, we obtained data on insurance and educational achievement. Only 6 (1.6%) participants were uninsured, and almost all (91.6%) had attained at least 12 years of formal education (completed high school).

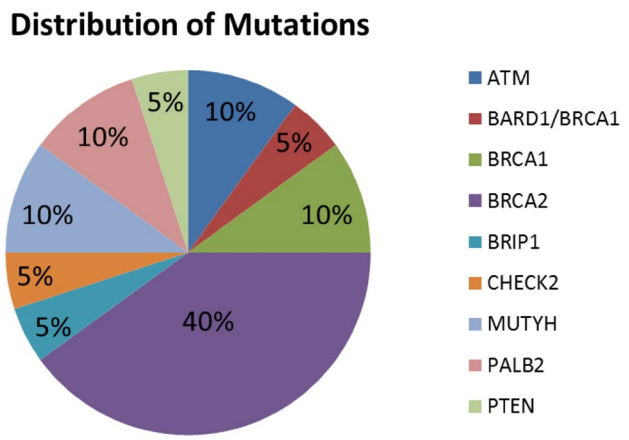

Fig. 1 Distribution of deleterious mutations in African American breast cancer patients ($n=20$). Names and distributions of twenty genes with deleterious mutations detected in African American breast cancer participants

Twenty (8.0%) of all 250 participants had a deleterious mutation in one of the 30 genes evaluated by Color Genomics, Inc. *BRCA2* deleterious mutations were seen in 3.2% of the overall study population, and observed in 8 (40.0%) of the 20 patients with a deleterious mutation, (Fig. 1). *BRCA1* deleterious mutations were observed in 1.2% overall, and in 3 (15.0%) of the 20 participants with a deleterious mutation. Patients with a deleterious mutation had a younger age at diagnosis, higher BMI, and higher incidence of bilateral breast cancer than those without a deleterious mutation.

Overall, 187 (74.8%) participants met eligibility for HBOC genetic testing based on NCCN Guidelines Version 2.2017, and 63 (25.2%) did not meet criteria. Only 110 (58.8%) of the 187 participants who were eligible for genetic testing had received prior testing as part of their routine clinical care; testing was confirmed by medical records for 105 of the 110 (95.4%). Seventy-seven (41.2%) participants who were eligible for HBOC genetic testing according to NCCN guidelines had not received it as part of their routine care. Testing rates were significantly higher in participants who were younger at diagnosis, and participants with a higher educational attainment (Table 2).

Table 3 lists the characteristics of participants with an identified deleterious mutation based on testing through Color Genomics, Inc. Deleterious mutations were identified in 17 (9.1%) of 187 participants who met NCCN criteria for HBOC genetic testing. Three (4.8%) among 63 participants who did not meet NCCN criteria also had a deleterious mutation identified, and one of the identified deleterious mutations was in *BRCA1*. The difference in mutation rates between participants who met NCCN criteria for testing, and those who did not meet NCCN criteria was not statistically significant ($p=0.42$). Six (7.8%) among the 77 participants who were eligible but had not received prior testing as part of usual care had deleterious mutations identified. Age at diagnosis (OR 0.95, 95% CI 0.91–0.99), and presence of bilateral breast cancer (OR 5.09, 95% CI 1.55–16.74) were

Table 2 Genetic testing rates in participants eligible for genetic testing according to NCCN guidelines

	N	Tested (CI)	Not tested (CI)
Eligible participants	187	58.82% (51.77–65.88%)	41.18% (34.12–48.23%)
Eligible participants diagnosed ≤ 45 years	59	81.36% (71.42–91.29%)	18.64% (8.71–28.58%)
Eligible participants diagnosed 46–50 years	30	60.00% (42.47–77.53%)	40.00% (22.47–57.53%)
Eligible participants diagnosed > 50 years	98	44.90% (35.05–54.75%)	55.10% (45.25–64.95%)
Eligible participants with less than high school degree	14	42.86% (16.93–68.78%)	57.14% (31.22–83.07%)
Eligible participants with high school degree	96	52.08% (42.09–62.08%)	47.92% (37.92–57.91%)
Eligible participants with college degree or more	76	69.74% (59.41–80.07%)	30.26% (19.93–40.59%)

CI confidence interval

Table 3 Characteristics of participants with a deleterious mutation

Age at diagnosis	TNBC	Bilateral breast cancer	Previous testing	Family history of breast or ovarian cancer	Gene	Mutation	VUS	Vus gene	BMI
Participants who met NCCN criteria for HBOC genetic testing ($n=17$)									
46	No	No	No	No	ATM	c.7998dupT (p.Met2667Tyrfs*4)	No	–	36.7
42	Unk	No	No	No	BRCA1	c.68_69delAG (p.Glu23Valfs*17)	No	–	35.7
35	Yes	No	Yes	Yes	BRCA1	c.3329delA (p.Lys1110Serfs*7)	No	–	21.9
48	Yes	Yes	Yes	Yes	BRCA2	c.2808_2811delACAA (p.Ala938Profs*21)	Yes	PMS2	35.2
36	No	Yes	Yes	Yes	BRCA2	c.9382C > T (p.Arg3128*)	Yes	MSH2	25.5
55	Yes	Yes	Yes	Yes	BRCA2	c.5616_5620delAGTAA (p.Lys1872Asnfs*2)	No	–	43.0
41	No	No	Yes	Yes	BRCA2	c.9382C > T (p.Arg3128*)	No	–	41.1
43	No	No	No	No	BRCA2	c.9253dupA (p. Thr3085Asnfs*26)	No	–	45.2
52	Yes	No	Yes	No	BRCA2	c.2957_2958insG (p.Asn986Lysfs*2)	Yes	PMS2	29.0
36	Yes	No	No	No	BRCA2	c.7254_7255delAG (p.Arg2418Serfs*2)	No	–	33.3
50	No	No	Yes	Yes	BRCA2	c.4876_4877delAA (p.ASn1626Serfs*12)	Yes	ATM	24.0
50	No	Yes	Yes	Yes	CHEK2	c.1502_1503dupAG (p.Glu502Argfs*12)	No	–	37.2
61	No	No	No	Yes	MUTYH	c.1187G > A (p. Gly396Asp)	Yes	NBN	31.6
47	No	No	Yes	Yes	MUTYH	c.1187G > A (p.Glys396Asp)	No	–	–
55	No	No	Yes	Yes	PALB2	c.3113G > A (p.Trp1038*)	No	–	35.2
48	Yes	No	No	Yes	PALB2	c.2411_2412delCT (p.Ser804Cysfs*10)	No	–	36.8
46	No	No	No	No	PTEN	c.1003C > T (p.Arg335*)	Yes	RAD51D	54.5
Participants who did not meet NCCN criteria HBOC genetic testing ($n=3$)									
60	No	Yes	No	No	ATM	c.7913G > A (p.Trp2638*)	Yes	PALB2	41.4
53	No	No	Yes	No	BARD1, BRCA1	c.266delC (p.Pro89Argfs*7) c.2457delC (p.Asp821llefs*25)	No	N/A	48.4
50	No	No	No	No	BRIP1	c.2992_2995delAAGA (p.Lys998Glufs*60)	Yes	MSH6, RAD51D	41.2

NCCN National Comprehensive Cancer Network, *HBOC* hereditary breast and/or ovarian cancer, *TNBC* triple negative breast cancer, *VUS* variant of unknown significance, *BMI* body mass index

associated with having a deleterious mutation (Table 4). VUS were observed in 22.4% of the overall population (56 patients) (data not shown). *BRCA1* and *ATM* genes had the highest frequencies of VUS (12.5% each). Only family history was associated with having a VUS (OR 0.44, 95% CI 0.24–0.83) (Table 4).

Discussion

Although deleterious genetic mutations occur in African American breast cancer patients at a similar frequency compared with other races and ethnicities, a large proportion of African Americans do not receive genetic testing. This represents an implementation failure for this group of patients. Our results are consistent with a previous report from a small registry-based cohort of African American breast cancer patients [29]. A report from a community-based cohort of predominantly European American breast cancer patients

Table 4 Odds ratios for presence of a deleterious genetic mutation and VUS in African American breast cancer patients

Covariates	Deleterious genetic mutation				VUS			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age at diagnosis	0.95 (0.91–0.99)	0.03	0.95 (0.91–0.99)	0.04	1.01 (0.98–1.04)	0.55	1.01 (0.98–1.04)	0.50
BMI	1.01 (0.99–1.04)	0.28	1.01 (0.98–1.03)	0.54	0.99 (0.96–1.02)	0.56	0.99 (0.96–1.03)	0.72
TNBC (Y vs N)	1.23 (0.44–3.42)	0.69	0.97 (0.32–2.89)	0.95	0.91 (0.47–1.79)	0.79	0.92 (0.46–1.82)	0.80
Bilateral (Y vs N)	4.71 (1.50–14.77)	0.01	5.09 (1.55–16.74)	0.01	1.03 (0.36–2.94)	0.95	1.13 (0.39–3.29)	0.83
Family history of breast/ovarian (Y vs N)	1.06 (0.40–2.77)	0.91	0.94 (0.34–2.60)	0.90	0.45(0.24–0.83)	0.01	0.44 (0.24–0.83)	0.01

Only mutations in genes that increase risk for breast cancer are included in this table

VUS variant of unknown significance, *TNBC* triple negative breast cancer, *BMI* body mass index in kg/m^2, *OR* odds ratio, *CI* confidence interval

at an increased risk of having deleterious genetic mutations, showed a testing adherence rate of 94% [30]. Furthermore, the results of this present study indicate that 4.8% of women who do not meet testing eligibility guidelines nonetheless have a deleterious mutation associated with breast cancer. Consequently, a large number of African American patients will have a missed opportunity for more individualized disease management. Increased uptake of testing in this population may help prevent lost opportunities for individualized management in those found to have deleterious mutations.

It is possible that the under-representation of African American patients in large-scale genetic studies will limit the validity of the evidence supporting the NCCN genetic testing guidelines in this specific population [17, 20]. For instance, the original studies identifying *BRCA1* and *BRCA2* as highly penetrant genes involved in HBOC syndromes were largely undertaken in individuals of European descent [1, 31–34]. Although, our observed mutation rate for those who did not meet NCCN guidelines was less than the 10% a priori mutation rate commonly used to suggest genetic testing, given the opportunity for individualized management and the wider availability of genetic testing, expanding the current guidelines may be warranted. A major obstacle to more widespread genetic testing has been the high cost of available panels. With technological advances, the cost of multi-gene testing has decreased dramatically, with expanded availability. As others have recommended, our results support expanding the current genetic testing guidelines immediately to include, at the very least, all patients diagnosed with breast cancer [35–37]. As the medical community considers larger scale testing, some issues need to be considered. First, this may inundate the current capability of genetic counseling services, and research on innovative genetic service delivery models will be necessary. The second issue is the downstream effect on family members of patients found to have deleterious mutations. Appropriate medical follow up and financial implications of risk-reducing surgeries will need to be considered. Lastly, the psychosocial and cultural implications of widespread testing are not known across different groups, but can be tested.

The results of this study, and others, report a high frequency of VUS in genes implicated in HBOC in African American patients [29, 38–41]. It is unclear whether these variants act to modify risk or disease aggressiveness. The consistently observed high frequency of VUS in African Americans is likely due to lack of robust data from genetic studies in this population. This points to the need for large-scale genetic research and routine testing to identify and properly classify genetic markers that can provide actionable information and improve preventive and clinical care in this high-risk population.

These results must be interpreted in the light of the study limitations. First, this is a single-institution study with a limited size; therefore, results may not be generalizable to a broader population. Without a comparison group, it may be difficult to draw conclusions on whether or not the proportion of African American women who underwent genetic testing would be different from other racial groups recruited through similar means. The observed mutation rate of 9.1% in participants who met criteria for genetic testing is very similar to the overall proportion of breast cancer that is hereditary in nature, thus, racial disparities in mutation rates are not evident in this study. Second, although these data show that a substantial proportion of African American patients eligible for genetic testing did not receive it as part of usual care, the specific reasons for this are beyond the scope of this study. Third, we acknowledge the possibility of selection bias. At the time of participation, the majority of participants were insured and had a high educational attainment. Fourth, since participants are all breast cancer patients, this study can only evaluate the effectiveness of guidelines for identifying African American breast cancer patients at high risk for deleterious mutations, and not for identifying high risk women from the general African

American population. Finally, although participants' medical records were accessed to complement the self-reported information provided in the interviews, a small proportion of records could not be obtained for verification. This may have led to recall bias for those few participants whose records were not available. Similarly, patients who participated may have been self-selected for familial HBOC syndromes and thus, results may not be generalizable.

In conclusion, results from this study indicate that a substantial proportion of African American breast cancer patients are not undergoing genetic testing even when eligible, leading to a lost opportunity for individualized management, and cascade testing for their relatives. Even in women who do not meet testing guidelines, nearly 5% have a deleterious mutation associated with breast cancer. Universal genetic testing of all breast cancer patients is simpler, will help close the racial gap and lead to increased knowledge of African American breast cancer genetics and improved clinical outcomes for all breast cancer patients and their family members.

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Compliance with ethical standards

Conflict of interest Foluso Ademuyiwa has served as an advisory board member for Eisai, Astra Zeneca, Jounce, Immunomedics, and QED Therapeutics. Foluso Ademuyiwa performs consulting for Cardinal Health, Best Doctors, Advance Medical Inc. Foluso Ademuyiwa has received institutional research funding from Polyphor, Pfizer, RNA Diagnostics, Immunomedics, Abbvie, and Seattle Genetics. Laura J. Bierut is listed as an inventor on Issued U.S. Patent 8,080,371,"Markers for Addiction" covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction. Patricia Salyer, Yinjiao Ma, Sherri Fisher, Graham Colditz, and Katherine Weilbaecher declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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