Ashkenazi Jews and Breast Cancer: The Consequences of Linking Ethnic Identity to Genetic Disease

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We explored the advantages and disadvantages of using ethnic categories in genetic research. With the discovery that certain breast cancer gene mutations appeared to be more prevalent in Ashkenazi Jews, breast cancer researchers moved their focus from high-risk families to ethnicity. The concept of Ashkenazi Jews as genetically unique, a legacy of Tay–Sachs disease research and a particular reading of history, shaped this new approach even as methodological imprecision and new genetic and historical research challenged it.

Our findings cast doubt on the accuracy and desirability of linking ethnic groups to genetic disease. Such linkages exaggerate genetic differences among ethnic groups and lead to unequal access to testing and therapy. (*Am J Public Health.* 2006;96:1979–1988. doi:10.2105/AJPH.2005.083014)

Throughout the 19th and early 20th centuries, race was widely presumed to have a biological basis and one that predisposed members to specific diseases.[1,2] Even after World War II, when the concept of race became more controversial, researchers continued to examine differences in disease susceptibility among racial and ethnic groups.[3] One persistent focus of researchers was on Ashkenazi Jews and their predisposition to autosomal recessive disorders, most notably Tay–Sachs disease.[4,5] Because these disorders were more prevalent among Ashkenazi Jews than others and often bore their own distinctive mutations, researchers concluded that the group was genetically unique.[4,6]

Over the past decade, new technologies developed through the coding of the human genome have led to increased genetic research that links racial and ethnic groups to specific diseases. Investigators maintain that these categories serve as a reliable tool for sorting patterns of human genetic diversity and that they will help both to identify the genetic basis of diseases and design more effective clinical interventions.[7–13]

Given past conclusions about the genetic uniqueness of Ashkenazi Jews, it is not surprising that genetic researchers continue to target the group. Nevertheless, in the case of breast cancer, scientific ideas that linked disease to ethnicity did not develop in linear fashion. In searching for breast cancer susceptibility genes in the early 1990s, researchers did not initially focus on Ashkenazi Jews. Only as a result of unexpected findings that followed on the discovery of BRCA1 did researchers turn their attention to the group.[14,15]

To understand the factors that led breast cancer researchers to link Ashkenazi Jewish identity to inherited disease susceptibility we conducted semistructured interviews with breast cancer and Tay–Sachs disease researchers. In analyzing our data, we sought to identify the strengths and limitations of genetic research that focuses on a single ethnic group, the meaning of race and ethnicity for researchers, and the public health implications for the targeted group and members of other racial and ethnic groups. We also explored historical scholarship on the Jewish Diaspora experience and scientific and demographic literature on founder populations to place these findings in a broader context. Although others have considered the broader public health consequences of linking race and ethnicity to genetic traits,[13,16–19] few studies have critically examined the process by which researchers make and advance associations between groups and genes.

METHODS

As part of a larger project on genetics, race, and ethnicity, we interviewed 30 genetic researchers (17 breast cancer researchers and 13 Tay–Sachs disease researchers) who were the first or last author of a publication that investigated genetic mutations in Ashkenazi Jews. To select the researchers, we combined the National Library of Medicine's Ovid MEDLINE (Available at: http://www.gateway.ovid.com; subscription only) search category "Jews" with "Breast Neoplasms/Genetics" (limited to 1997–2002) and "Jews" with "Tay–Sachs/Genetics" (without a time limit). After excluding review articles and authors not residing in the United States, the research team generated a list of 34 breast cancer and 21 Tay–Sachs disease researchers.

Methodologists acknowledge the difficulty in anticipating or justifying a necessary sample size for qualitative investigations. The sample size can only be determined in the course of data collection and analysis of the response to substantial issues of interest.[20–22] Sampling typically stops when redundancy or "theoretical saturation" has been achieved.[23] We contacted each researcher in the order in which Ovid MEDLINE generated the names within specialization (i.e., breast cancer or Tay–Sachs disease), until ongoing analysis indicated that a sufficient number of researchers had been interviewed and theoretical saturation had been achieved.

Each interview consisted of 1 hour of focused questions. Most were conducted over the telephone. The interviewee's verbal permission was obtained to audiotape the session. The interviews explored (1) how researchers described their selection of the disease and population; (2) how researchers portrayed the identification and recruitment of participants and their collection and use of DNA samples; (3) how researchers discussed social or ethical issues in their uses of ethnic categories; and (4) whether researchers described ethnic concordance and discordance with community organizations and research participants as affecting the research. The race and ethnicity of the researchers were

determined through self-report. The interviews were transcribed into computer files, coded, reconciled for discrepancies, and subjected to thematic analysis. This process allowed for the systematic identification of themes present in the researchers' responses and the specification of relationships among these themes and contextual factors. This qualitative research design discerns and describes the broad range of participants' experiences and perceptions. It does not provide estimates of the prevalence of the various phenomena.[24]

RESULTS

Tay–Sachs Disease and Ashkenazi Jewish Uniqueness

Scientific researchers have long viewed Ashkenazi Jews as a discrete group. Bernard Sachs, a physician practicing in New York City, first described Tay–Sachs disease, noting that all reported cases occurred in Jewish children.[25] Through the opening decades of the 20th century physicians widely believed the disease occurred predominately in Jews.[26] Although Tay–Sachs disease was occasionally reported in non-Jewish children, it, along with such other genetic diseases as Niemann-Pick and Gaucher, continued to be understood as part of a unique Ashkenazi Jewish genetic profile.[4,27,28] This understanding was further reinforced in the 1950s and 1960s when data collected from the newly established Sphingolipidosis Registry confirmed the diseases' significantly higher occurrence in Ashkenazi Jews.[6]

In 1969, several researchers observed that children with Tay–Sachs disease were deficient in the enzyme hexosaminidase A.[29,30] This finding led to a prenatal test for the disease as well as a test for heterozygote carriers. In 1971, Michael Kaback, a pediatrician at Johns Hopkins University, organized the first community screening program.[31] He contacted Jewish organizations in the Baltimore-Washington area and recruited a corps of volunteers who, in turn, recruited community members for genetic testing. The screening was typically conducted in Jewish communal institutions.[32] Similar programs in other cities soon followed, with members of the Ashkenazi Jewish community collaborating enthusiastically with researchers, who were often members of the community.[31,33,34] One interviewee recalled: "Here we have a population that is the subgroup, specifically concerned about health, well-organized, strong family values; we should be able to institute a screening program that allows them to plan to have children who are free of Tay–Sachs disease. It was just so obvious; and that arose from, I guess, my own family background and tradition." Other interviewees noted the importance of ethnic concordance and medical mission in producing trust between researchers and the community.

The impact of community screening was significant. By 1991, more than a million Jews from around the world had been screened for Tay–Sachs disease, leading to a more than 90% reduction in the disease within the group.[31,35] This result was a source of pride for researchers and members of the community and demonstrated the benefits of targeting and engaging ethnic groups in research on genetic diseases.

With the evidence that Ashkenazi Jews had a higher prevalence of Tay–Sachs disease and other genetic diseases came the search for a theory to explain the finding. Explanations included founder effect and selective advantage. Those proposing founder effects as the most likely explanation for Ashkenazi Jewish genetic distinctness pointed to the small size and subsequent growth of the population and the inability of researchers to identify a selective agent.[36–41] Researchers also asked how selective advantage could pertain only to Jewish populations and not to neighboring non-Jewish groups. Proponents of selective advantage argued that it was highly improbable that independent founder effects could account for the more than a dozen genetic diseases common in Ashkenazi Jews.[6,42] Whatever the explanation, both camps were convinced of Ashkenazi Jewish genetic uniqueness.[4]

The Search for Breast Cancer Genes

Despite an awareness of the link between certain genetic disorders and Ashkenazi Jews, researchers studying breast cancer genetics in the 1980s and early 1990s did not target the group. They believed that because breast cancer was clearly both a common and a multifactorial disease, it would be unlikely for any predisposing genes to segregate within specific ethnic or racial groups.[43,44] Moreover, epidemiological studies had not identified Ashkenazi Jewish women as having significantly higher rates of breast cancer.[45–47] Accordingly, researchers focused their work on families with multiple cases of breast cancer, constructing disease pedigrees of these families and then analyzing linkages to search for the location of possible cancer genes.[44,48,49]

With these methods, investigators from the University of California, Berkeley, led by Mary-Claire King, in 1990 located a region on chromosome 17 that appeared "to be the locale of a gene for inherited susceptibility to breast cancer in families with early-onset disease."[50(p1684)] The finding was based on the analyses of DNA samples from 23 cancer-prone White families across several generations. A total of 329 family members who participated were geographically dispersed, living in 40 states, Puerto Rico, Canada, the United Kingdom, and Colombia. Although this sample likely included some individuals of Ashkenazi Jewish descent, they were not so reported.[50]

The finding on chromosome 17 sparked other teams to search for candidate genes in this region, particularly genes whose molecular attributes suggested control of functions in cell development, cell repair, or hormone production.[51,52] In 1994, a group at Myriad Genetics (Salt Lake City, Utah), led by Mark Skolnick, isolated and sequenced one such gene, BRCA1. The Skolnick team identified 5 families with multiple cases of cancer; each family had a unique mutation in the BRCA1 gene.[53] Their samples were drawn largely from Mormon families, which reflected not a disproportionate amount of breast cancer in Mormons,[54] but instead the group's extensive genealogical records, which were linked to the Utah Cancer Registry and other databases.[55]

Once the BRCA1 gene was isolated, researchers faced an unanticipated challenge. They had expected to identify a small number of BRCA1 mutations that would allow them to easily estimate a mutation's penetrance and develop genetic tests and treatments.[56,57] It quickly became apparent, however, that BRCA1, because of its size and

complexity, was associated with a large number of highly dispersed mutations, many of which occurred only in single families.[57–59]

Another finding suggested a solution. In December 1994, a research team at McGill University, led by Steve Narod, identified 2 BRCA1 mutations shared among 8 families.[60] Four families carried the 185delAG mutation and another 4 the 5382insC mutation. The authors suggested that "these families were not known to be related, but haplotype analysis suggests that the carriers of each of these mutations have common ancestors."[60(p392)]

Investigators searched their records to learn whether other families with multiple cases of breast and ovarian cancer carried the same mutations. In July 1995, a National Institutes of Health team headed by Jeffrey Struewing screened the DNA of 24 families on the National Cancer Institute's Family Registry.[14] Ten of the 24 families carried a BRCA1 mutation and 3 of these families shared the 185delAG mutation. The Struewing team then announced a startling finding: "The three families . . . are not known to be related to each other but all are of Ashkenazi Jewish descent."[14(p3)] Simultaneously, the Narod team reported that all of its 8 families were also Ashkenazi Jews.[15]

Although neither team specified how it identified participants as Ashkenazi Jews, their findings led to a rapid redirection of BRCA1/2 research toward the group. For many researchers the possibility that the distribution of BRCA1 mutations might be similar to other Jewish genetic diseases now emerged. As one interviewee explained: "From that observation, [we] asked whether it could be a fairly common alteration in the Ashkenazi Jewish people in general and it has turned out to be . . . an entrée into . . . population-based research." Furthermore, if, as in the case of Tay–Sachs disease, "the majority of hereditary breast-ovary cancer families in [Ashkenazi Jews] can be attributed to a small number of mutations, our efforts to provide DNA-based predictive testing will be greatly enhanced."[15(p189)] In October 1995, the Struewing team analyzed stored DNA samples from Tay–Sachs screening programs and estimated that approximately 1% of Ashkenazi Jews carried the 185delAG mutation.[61] Two years later, with new samples Struewing and others estimated that approximately 0.4% of Ashkenazi Jews carried the 5382insC mutation.[62]

Still other findings reinforced this approach. In 1996, a second breast cancer susceptibility gene, BRCA2, was identified.[63] Several teams then reported a BRCA2 mutation, 6174delT, in Ashkenazi Jews.[64,65] Subsequent analyses of stored Tay–Sachs samples estimated a prevalence rate for 6174delT of approximately 1% among Ashkenazi Jews.[62,66] In total, it was estimated that 2% to 3% of Ashkenazi Jews carried 185delAG, 5382insC, or 6174delT.[62,66,67]

Researchers next turned to Ashkenazi Jews with unknown family histories of breast cancer to investigate the basic characteristics of BRCA1/2, including their molecular functions and the penetrance and prevalence of the mutations.[62,68–70] Breast cancer researchers now considered ethnicity as relevant as family history. The efficacy of this approach was further confirmed by the speed with which findings moved from laboratory to clinic.[71] In 1996, the Genetics and IVF Institute (Fairfax, Va) introduced the first genetic test for 185delAG, which targeted Ashkenazi Jewish women.[72] Later the same year, Myriad Genetics, which held patents on BRCA1 and BRCA2, introduced a test panel for all 3 "Jewish ancestral mutations."[72–74]

Tay–Sachs Disease as a Model for BRCA1/2 Research

Researchers hypothesized that if Tay–Sachs disease and BRCA1/2 were linked to the same genetically distinct population, existing collections of stored blood samples from Jews screened for Tay–Sachs carrier status could be used to quickly screen the DNA of thousands of Jews for BRCA1/2 mutations.[61,66,67] "When the BRCA gene was discovered," one interviewee explained, "it led us to start thinking about the 185delAG mutation. It led us because we had the technical capability . . . to test thousands of samples in a very limited time. . . . We had this large collection of patient samples from the Ashkenazi Jewish population. . . . We wanted to do a study to see what . . . the frequency of those alleles was in the Jewish . . . population."

Tay–Sachs screening programs also provided breast cancer researchers with a model for recruiting Ashkenazi Jews.[34] Like Tay–Sachs disease researchers before them, breast cancer researchers allied with Jewish community leaders and institutions. One National Institutes of Health team organized meetings in synagogues and community centers and advertised in Jewish newspapers. Although it explained that the research provided no direct benefits, 5318 members of the community participated. As one interviewee commented: "The Jewish community allowed us once again to take advantage of an historical accident . . . to get an answer that was not only valuable for all Jewish women who might carry a mutation but generally useful."

The community's positive response reinforced this approach. "The question," one interviewee noted, "was fundamentally a scientific question and the community was happy to contribute. . . . It was totally altruistic on the part of every single individual participant. Collectively, the community was saying we do this for ourselves, but the community was also saying we do it knowing that we provide information for the wide world."

In breast cancer research, as in Tay–Sachs screening programs, ethnic concordance and trust between researchers and the population facilitated recruitment. Interviewees reported that team members or the head of the program were themselves often Jewish and that they were the ones who spoke with community leaders. "We advertised widely in the Jewish community here," one interviewee explained.

> "I had my synagogue sisterhood pretest the instruments so I was pretty comfortable. We had a very large steering committee of interested rabbis and activists in the Jewish community to sort of help us frame it. . . .We basically had a campaign and enrolled Jewish community centers, a few public spaces, a few synagogues to allow us to do the study. And we had an outpouring of enthusiastic community support. . . . People just showed up, gave us their blood and gave us the answers, and we were scrupulously careful. Some of it is coincidence, because . . . in our little group of researchers . . . probably half of us were Jewish, so it didn't have the flavor of going into some extremely different community."

A few Jewish organizations were concerned about linking Ashkenazi Jews to a deadly disease.[75–80] Investigators responded, as one interviewee explained, by making it clear that

"this was not a finding that should be stigmatizing. In fact it was going to provide a benefit to the Jewish community." Another interviewee observed that prevalence of the mutations in Ashkenazi Jewish women was "just a biological fact. It's a historical fact. . . . Lack of awareness about the possibility of hereditary breast cancer in the Jewish population which . . . has enormous risk compared with other populations—maybe ten-fold higher of having a mutation—makes it rather disadvantageous to not talk about it."

Our interviewees acknowledged that linking hereditary breast cancer susceptibility to Ashkenazi Jews might carry social risks, such as employment or insurance discrimination. But they believed that the social risks, unlike the biological ones, were manageable. As one interviewee explained: "You wouldn't want somebody with a name like Cohen to have higher [insurance] rates just because they're clearly Jewish and are at greater risk for X, Y, Z, diseases, including breast cancer. But that's something you can get around. You can legislate against things like that."

Identifying Ashkenazi Jews

Researchers employed a variety of methods for identifying Ashkenazi Jews as possible study participants. Some relied on personal knowledge. "Initially," one interviewee recalled, "there was no systematic recording of religion or of ethnicity in that sense of the word. There were just families where I sort of knew many of the members individually, talking with them over the telephone and seeing them in the clinic and I just, I guess, knew they were Jewish." Others used participant self-identification: "I figured if you say you're an Ashkenazi Jew, then you are." Another concurred: "The inclusion criteria were what people called themselves." Or: "Everyone kind of knows what they are." Interviewees rarely challenged the validity of self-identification. "If they say they're Jewish and if they say all their ancestors are Jewish that will do it for me."

Some interviewees attempted to resolve problems of identification by pointing to the high likelihood that Jews living in North America were Ashkenazi. "When we asked people who expressed a Jewish religious preference where their families actually came from," one interviewee noted, "over 95% of them actually do come from that area that would be considered of Ashkenazi origin." Another interviewee insisted: "The truth demographically is that over 90% of Jews in North America are of Ashkenazi origin. . . . If they identify as Jewish, unless they specifically tell me that they are not Ashkenazi, they probably are, and I don't make a big deal of it." To researchers, these percentages made self-identification reliable. "Not knowing anything else, if you're just American and you self-identify as Jewish, you're overwhelmingly likely to be Ashkenazi."

Our interviewees also accepted the designation of Ashkenazi Jewish on stored samples that were applied by third or unknown parties. If a sample was labeled Ashkenazi Jewish, interviewees generally presumed it was. "At the time, there were samples that were from the cell bank repository that were labeled as patients of Ashkenazi background," one interviewee observed. "Supposedly somebody had already gone through and ascribed this patient as of Ashkenazi Jewish background." However, when asked how the original ascription was made, the same interviewee responded: "I have no idea." Another interviewee admitted: "I didn't do the defining. It was done for me. . . . I always get my samples from clinicians. [One clinician] had a screening program . . . and we used some of the leftover samples. They were coded in numbers but he knew which ones came from people who were of Ashkenazi Jewish descent."

Interviewees also relied on information from religious leaders. If a rabbi said participants were Ashkenazi, then they were. "We were able to get thousands of subjects," this interviewee recalled, "but it was mostly through a rabbi who was very close to the Ashkenazi Jewish population and so his identification was going to be very robust." Some interviewees attempted to verify self-identity by asking about the family's geographic origins, setting their own inclusion criteria. When asked about defining Ashkenazi Jews, one interviewee responded: "Just basically Eastern or Central European Jewish decent. When we are talking to somebody who relates a Jewish religious preference, we then ask them, sort of specifically, where their family came from, or at least as well as they can pin it down. . . . If they came from that sort of part of the world, we consider them to be Ashkenazi."

Some interviewees set more restrictive criteria: "Ashkenazi Jews are people whose 4 grandparents are Ashkenazi Jewish. If their 4 grandparents are not Ashkenazi Jewish, then we would characterize them as being of mixed ancestry." Others, however, were less concerned. "Sometimes I ask people," one interviewee explained. "Many people don't know, but basically people's ancestry is European or Russian or Israeli. If in doubt, I . . . include them. If only 1 of the relatives is Ashkenazi, I would still consider them Ashkenazi. . . . Even if they have 1 Jewish relative that has a European background from a genetic point of view, they're at risk." Thus, if a person identified herself as partly Jewish with a European ancestor, she would be classified as Ashkenazi. "Unless someone listed all 4 grandparents as being non-Ashkenazi, we included them as . . . Ashkenazi."

Founder Effects and BRCA1/2 in Ashkenazi Jews

To explain their findings, breast cancer researchers looked to Tay–Sachs and other Jewish genetic diseases. If BRCA1/2 mutations in Ashkenazi Jews were part of the same unique genetic profile as Tay–Sachs disease, then they must share the same genetic origin.[81] As one researcher stated, "the fact that certain Jewish communities can be characterized by the genetic diseases with which they are afflicted indicates a certain degree of genetic cohesiveness within the various Jewish ethnic groups, despite their long history of difficulties and threats to survival."

Although some geneticists working on Tay–Sachs and other autosomal recessive diseases continued to argue for selective advantage,[6,82–85] breast cancer researchers largely attributed Ashkenazi Jewish genetic uniqueness to founder effects.[86–88] As one interviewee explained, "It's a population in which there are founder mutations, meaning that there are about 3 mutations that are commonly found in Jewish women, so you have a large sample from which to work on a relatively common genetic background. It's an

interesting paradigm in which to work, because it's a founder effect."

As first formulated in the 1940s, the concept proposed that when geographic barriers restricted migration and increased endogamy in a population with few initial members, genetic drift could produce a distinct genetic cluster.[89] Although Ashkenazi Jews were neither geographically isolated nor few in number, geneticists substituted history for geography. With available historical demographic data, they argued that ghettoization and voluntary isolation were equivalent to geographic isolation, and that cataclysmic historical events, such as pogroms, had produced population contractions severe enough to facilitate genetic drift.[36,81,90,91] When, following these contractions, the surviving core of the Ashkenazi Jewish population expanded rapidly,[40] the resulting distinctive gene patterns spread through the population.[5]

DISCUSSION

Historical Challenges to Ashkenazi Uniqueness

The premise that Ashkenazi Jews represent a genetically unique population because of founder effects is historically problematic on 2 levels. First, it is based on demographic data that many scholars of Jewish history consider highly unreliable.[92–94] Second, recent historical analysis questions the degree to which the Ashkenazi Jewish population in the premodern period was isolated or the degree to which it underwent the extreme expansions and contractions that the theory requires.[95]

Historians of the Jewish Diaspora note that censuses from Central and Eastern Europe are incomplete and that surviving tax records are largely fragmentary and inconsistent.[92] Furthermore, such records are silent on the degree to which purported changes in population resulted from changes in birth and death rates as opposed to migration.[92,94,96] As a result, estimates of the Ashkenazi Jewish population in early European history have relied heavily on extrapolation from later written records.[94] The imprecision in such estimates,[93,94] however, is great, and many of them have been drastically revised (M. Stanislawski, PhD, oral communication, February 2001).

Recent historical studies also question how isolated Ashkenazi Jews were from surrounding Jewish and non-Jewish populations. The Diaspora experience was marked by high degrees of geographic mobility.[97] Jewish migrations to Europe were continuous, beginning even before the destruction of the Second Temple in 70 CE.[98] "By the time the Roman commander Titus leveled the Temple," one historian noted, "Jews abroad far outnumbered those dwelling in Palestine—and had done so for many generations."[98] Intermarriage and conversion were common in these communities, complicating Jewish identity.[99] Moreover, between the 14th and 16th centuries, as the result of wars, persecutions, and epidemics, Jews inhabiting diverse geographical regions migrated yet again, forming heterogeneous communities.[93,100] In some cases Ashkenazi and Sephardic communities mixed freely. In Amsterdam, for example, the first Jewish communities were composed of migrants from the Iberian Peninsula.[101,102] During the Thirty Years War (1618–1648), Jews from Germany, Poland, and Bohemia joined them.[103] Subsequently, some residents remained and others returned to their birthplace, making geographic distinctions even more tenuous.[102]

Recent reevaluations of demographic data also cast doubt on whether the Ashkenazi population underwent severe contractions and expansions. Although pogroms certainly killed large numbers of people, most massacres, like most wars, were local, affecting particular segments of the population. Even when thousands of Jews were slaughtered in the Ukrainian Chmielnitsky massacres in the mid–17th century, tens of thousands survived.[94] When stability returned to the region, Jewish migrants from other regions looking for economic opportunity joined this sizable population. Thus, the substantial population growth that followed reflected geographic mobility as well as increased birth rates.[94,104]

Genetic Challenges to Ashkenazi Uniqueness

Recent findings of 185delAG and 5382insC in non-Ashkenazi Jewish populations further challenge the idea of Ashkenazi Jewish genetic uniqueness. The 185delAG mutation has been identified in Jewish women of Greek, Indian, Iranian, Iraqi, Syrian, Turkish, and Yemeni origin.[105] One study of Moroccan Jewish women selected without regard to family history of cancer found the incidence of 185delAG to be 1.1%, approximately equal to that in Ashkenazi Jews.[106]

Researchers have also discovered the 185delAG mutation in numerous women who do not identify as Jewish or appear to have Jewish ancestry. One large study of Spanish women with breast cancer reported that the 185delAG mutation accounted for 16.7% of all mutations.[107] Other studies have found that the 185delAG mutation constituted 10.1% of all the BRCA1 mutations in Dutch women, 6.5% of mutations in German women, and 3.4% of mutations in Czech women.[108–110] In the United States, 185delAG has been identified as the most common BRCA1 mutation in a sample of Hispanic women in Los Angeles.[111] It has also been found in Hispanic women in Colorado, in Spanish Gypsies, and among South Indian women.[112–114] Overall prevalence data remain unknown because population-based studies have not been conducted in these groups.

The claim that 5382insC is an Ashkenazi Jewish mutation is even more problematic.[62,67,115] It has the largest distribution of the 3 "Jewish" mutations[116] in non-Jewish populations, especially in Central and Eastern Europe.[87,117–120] In Poland, a survey of families with breast or ovarian cancer reported that 5382insC represents 55.7% of the total BRCA1 mutations.[121] 5382insC was the most frequently occurring BRCA1 mutation in studies in Greece (45%), the Czech Republic (37.3%), Hungary (28.6%), and Germany (21.7%).[108,110,119,120]

Geneticists have offered 2 responses to these findings. Some have hypothesized ancestral links between non-Jewish mutation carriers and Ashkenazi Jews.[111] When the 185delAG mutation was found in Spanish Gypsies, researchers argued, without supporting evidence, that "the 185delAG mutation occurred on an ancestral haplotype that . . . had probably been transferred to Gypsies from the Jews, given that the Mediterranean countries were among the first countries in which the Gypsies settled."[122(p708)] After finding the 185delAG mutation in 6 non-Jewish

Americans of Spanish ancestry living in the San Luis Valley, Colorado, researchers asked carriers about possible Jewish ancestry.[114] Although none knew of a Jewish ancestor, a commentator hypothesized that "there is a high probability that they are truly descended from Marranos, Spanish Jews who pretended to convert to Christianity to avoid persecution."[123(p434)] When Indian researchers identified 2 sisters from Goa with the 185delAG, they suggested Jewish ancestry because "no such mutation could be detected from [the] North Indian population."[113(p184)] This type of reasoning makes the mutation itself a marker of ethnicity.

A second response asserts that mutations linked to Jews are, in fact, founder mutations linked to a neighboring ethnic group. When Hungarian and Polish investigators discovered a high frequency of 5382insC in Eastern and Central European populations, they labeled it a Slavic, not Jewish, mutation. "The geographic ubiquity and high frequency of the 5382insC," one Hungarian team observed, "are consistent with the suggested Eastern European origin of this mutation in the medieval period."[119(p738–739)] A Polish team insisted that because "Polish people are ethnically distinct,"[121(p685)] the 5382insC mutation had to be a Polish heritage mutation and should be included on a Polish screening panel. Thus, researchers compete over which ethnic group "owns" a mutation rather than consider the possibility that the mutation is shared among people who have lived in close proximity or that ethnic identity may be a less than reliable proxy for genetic risk.

Broader genetic studies suggest that ethnic groups seldom represent distinct genetic clusters.[124–126] A study of genetic variation in Iceland found that over the course of one thousand years "notable regional subdivision[s have occurred] in the Icelandic gene pool," despite the fact that it was settled by relatively few founders.[127(p93)] The study cautions that "for the purposes of association studies, Icelanders cannot be considered to be a single, randomly interbreeding population."[127(p93)]

In sum, human genetic diversity is continuous rather than interrupted.[3,128] The historical and geographic bridges that link populations to each other, not the gaps between them, are most significant. "Genetic discontinuities," 2 population geneticists have argued, "are generally not 'racial' or continental in nature but depend on historical and cultural factors that are more local in nature."[128(p1684)] Shared mutations among populations that have historically lived in close proximity are, thus, to be expected.

Problems With Self-Identification

Self-identification as a means of defining who is genetically an Ashkenazi Jew has several methodological disadvantages. Self-reported identity does not mirror genetic identity. The concepts of "situational ethnicity" and "plastic ethnicity," advanced by sociologists, recognize the fluidity of ethnic boundaries and a dependence on context in designating ethnic identification.[128,129] Self-reported identity incorporates social, cultural, and historical factors, rendering it unstable over time.[130] In a study with genetic microsatellites from 8 different populations, Wilson et al.[131] found that the categories generally used in reporting race and ethnicity did not accurately represent actual genetic clusters and that genetically inferred clusters derived without relying on ethnicity and geography were more reliable. Finally, Barnholtz-Sloan et al.,[132] in a case–control study of early-onset lung cancer, found that self-reported race, when compared with genotyping for "ancestry informative markers," was a less accurate predictor of genetic risk. They also found that such markers of ancestry did not correlate completely with self-reported race, and that significant overlap occurred within the racial and ethnic groups in their study.

Advantages to Population-Specific BRCA1/2 Research

BRCA1/2 research on Ashkenazi Jews has advanced knowledge of the genes and associated clinical consequences.[49,69,129,130,133] It has established the prevalence and penetrance of BRCA1/2 mutations among Ashkenazi Jewish women, clarified patterns of inherited susceptibility, and resulted in diagnostic and treatment benefits.[62,70,134,135] Ashkenazi Jewish women have access to an inexpensive screening panel (at a cost of $415 compared with $2975 for non-Ashkenazi Jewish women who do not have an identified familial mutation) and are more likely to undergo genetic testing than non-Ashkenazi Jewish women.[72,134,136–138] Testing access has crucial health implications because increased surveillance, prophylactic oophorectomies and mastectomies, and chemoprevention may reduce breast cancer risk in BRCA1/2 carriers.[49,133,139–141]

Disadvantages and Health Disparities

The disadvantages of concentrating BRCA1/2 research on Ashkenazi Jews have been largely unacknowledged. Whereas the assumption that Ashkenazi Jews represent a genetically unique population has provided a conceptual support for research on the group, it has limited the attention researchers have given to other groups. Such inattention risks creating health disparities because physicians become less likely to recommend, and individuals less likely to request, genetic tests or preventive treatment based on their group membership.[142,143] In the case of Tay–Sachs disease, an almost exclusive research focus on Ashkenazi Jews left other groups, including French Canadians who have a high prevalence of the disease, less well served. Screening programs have reduced the incidence of the disease among Jews in the United States, but the incidence among non-Jews has remained essentially the same for several decades.[31,144]

Research attention to BRCA1/2 in Ashkenazi Jews may well be generating similar disparities. A 2002 study found that Ashkenazi Jewish women with family histories of breast cancer were more than twice as likely as other women with a similar risk to undergo BRCA1/2 testing.[145] Another study found that Jewish women were almost 60% more likely to undergo counseling for BRCA1/2 than non-Jewish women with similar risk levels.[138] These differences likely reflect both physicians' increased readiness to recommend testing to Ashkenazi Jews and Ashkenazi Jewish women's increased awareness of their risk.[138,145]

These differences may also reflect the availability of an inexpensive BRCA1/2 test panel targeted at Ashkenazi Jewish women.[145] No similar panels have as yet been developed for other ethnic groups. In part, this is because of the fact that relatively little research has been conducted on the distribution of BRCA1/2 mutations in other groups,

especially at a population level. Research that has been conducted suggests, however, that the distribution of BRCA1/2 mutations in several other groups may also be dominated by a small number of distinct mutations,[146] including, in some cases, either 185delAG or 5382insC.[121] Such panels could serve as a less expensive preliminary test, allowing those women who test positive for an included mutation to avoid a more costly full gene test.

BRCA1/2 research not only presumes the assumption of Ashkenazi Jewish genetic uniqueness but also reinforces it. Ashkenazi Jews have been assigned specific genetic sequences, now widely discussed in terms such as Jewish ancestral mutations and Ashkenazi Jewish founder haplotype.[73,111,147–149] Yet breast cancer researchers did not discover "Ashkenazi Jewish mutations"; they discovered mutations in Ashkenazi Jews.

Conclusions

Our analysis recognizes the public health advantages of focusing genetic research on ethnic groups, highlighting important but largely unacknowledged public health disadvantages. Ethnic identity may be a weak proxy for genetic differences. New scientific findings about the widespread distribution of the 2 Jewish ancestral BRCA mutations in many other populations suggest that approaches that rely on ethnic identity to prioritize access to genetic testing and surveillance will contribute to health disparities among groups with similar levels of risk. Historical evidence about the extensive character of Jewish migration and the porous boundaries that separated Ashkenazi Jews from other Jewish and non-Jewish populations during the Diaspora challenges the power of founder effects as an explanation for gene distribution in Ashkenazi Jews. Moreover, establishing ethnic identity by self-report adds an additional element of unreliability to this process.

These findings are relevant to future genetic research. In the decade since the discovery of BRCA1/2, genetic researchers in other fields have relied on the perceived success of breast cancer investigators to turn their own research toward particular ethnic and racial groups. However, in accepting this model, there has been little discussion of whether the associated disadvantages are also likely to be replicated. Given the likelihood that such effects will recur, future studies that link genetic disease with ethnic identity should be closely scrutinized for their many consequences for all ethnic groups and for the quality of genetic research. ■

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S.I. Brandt-Rauf and S.M. Rothman originated the project and wrote the initial draft of this article. V.H. Raveis advised the design of the project's methodology and contributed to the writing of the article's Methods section. N.F. Drummond conducted original research and assisted with writing of the initial draft. J.A. Conte conducted interviews and reviewed existing literature.

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Verbal consent of all interviewees was obtained prior to each interview. The project was approved by the Columbia University Medical Center institutional review board.

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