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REVIEW ARTICLE

Disparities in Genetic Testing: Thinking Outside the *BRCA* Box

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A B S T R A C T

The impact of predictive genetic testing on cancer care can be measured by the increased demand for and utilization of genetic services as well as in the progress made in reducing cancer risks in known mutation carriers. Nonetheless, differential access to and utilization of genetic counseling and cancer predisposition testing among underserved racial and ethnic minorities compared with the white population has led to growing health care disparities in clinical cancer genetics that are only beginning to be addressed. Furthermore, deficiencies in the utility of genetic testing in underserved populations as a result of limited testing experience and in the effectiveness of risk-reducing interventions compound access and knowledge-base disparities. The recent literature on racial/ethnic health care disparities is briefly reviewed, and is followed by a discussion of the current limitations of risk assessment and genetic testing outside of white populations. The importance of expanded testing in underserved populations is emphasized.

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INTRODUCTION

It is startling to imagine that barely more than 10 years ago the notion of genetic testing for cancer predisposition was little more than that—a notion. The localization and cloning of a handful of genes in the 1990s, including the *BRCA1* (1994) and *BRCA2* (1995) tumor suppressor genes,[3,7,10,14] the *APC* (1991) gene,[16,21-24] and the DNA mismatch repair genes *MLH1* (1994),[2,6,19] *MSH2* (1993),[9,15] and *MSH6* (1995),[12,13,15] fostered the incorporation of molecular genetics into oncology care, but also introduced the troubling specter of cancer risk into the lives of individuals and families around the world (Tables 1 and 2). Miraculously, the results of a single blood test could quantify an individual's future cancer risk with remarkable accuracy and simplicity. Some maintained that such technology offered a sentence without a pardon, a diagnosis without a cure. Others feared that our very genes would become the platform for an insidious new genetic discrimination, with repercussions in health care, insurance coverage, and employment prospects. The future of cancer predisposition testing was, at its outset, unsure at best.

A decade later, the impact of predictive testing in cancer can be measured by the increased demand for and utilization of genetic services as well as in the progress made in reducing cancer risks in known mutation carriers. The most recent information from Myriad Genetic Laboratories (Salt Lake City, UT) includes data on more than 40,000 individuals who have undergone *BRCA1*/*BRCA2* DNA sequencing since it became commercially available.[30] Clinical research on *BRCA* mutation carriers has also been vigorous, with multiple founder mutations now recognized in various populations, as well as prospective and case-control evidence of risk modification through prophylactic oophorectomy[35-37] and bilateral mastectomy[40-43] showing cancer risk reductions on the order of 40% and 90%, respectively. The recent clinical guidelines from the US Preventive Services Task Force provide an excellent summary of this progress.[44]

Disappointingly, genetic testing for the mismatch repair genes *MLH1*, *MSH2*, and *MSH6* of hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) and the *APC* gene of familial adenomatous polyposis (FAP) has lagged behind that for *BRCA*, despite the life-saving benefit of colectomy in FAP and the long-term prospective follow-up data in HNPCC kindreds showing reduced cancer incidence[45,46] and survival and quality-of-life benefits[47] to regular colonoscopy and polypectomy. Equally concerning, differential access to and utilization of genetic counseling and cancer predisposition testing among underserved racial and ethnic minorities compared with whites has led to the recognition of growing health care disparities that are only beginning to be addressed.[48]

This review will explore two related areas of predictive genetic testing for cancer that have individually undergone extensive (health care disparities) and very limited (the expanding usage of cancer predisposition testing in the United States and worldwide) scrutiny. In briefly presenting the literature on disparities in genetic services utilization, we

Table 1. Characteristics of the Hereditary Breast-Ovarian Syndrome Predisposition Genes *BRCA1* and *BRCA2*

Characteristic	
BRCA1	
Location	17q21
Cloning date	1994[3]
BRCA2	
Location	13q12
Cloning date	1995[7]
Mutation prevalence estimates	
Ashkenazi Jewish ethnicity	≈1:40[5]
General population	≈1:500[11]
Strong family history	≈1:12[4]
Associated cancer risk[17-19]	
Breast	≈40%-80%
Ovarian	≈20%-40%
Prostate	≈3 (OR)
Pancreatic	≈2.5-3.5 (RR)
Other *BRCA1** or *BRCA2*†	≈2-4 (RR)

Abbreviations: OR, odds ratio; RR, risk ratio.
*Includes cervical, uterine body, and colorectal cancers, and lymphoma/leukemia.
†Includes prostate, pancreatic, stomach, and gall bladder cancers, and melanoma.

seek to summarize the contribution that the rapidly growing field of health care disparities research has made in cancer genetics and risk assessment. In discussing the current state of predisposition testing for the DNA mismatch repair genes *MLH1*, *MSH2*, and *MSH6*, we will highlight deficiencies in current testing practices and in the utility of predictive testing. Furthermore, we will present evidence demonstrating (1) that genetic testing disparities originate from the same social, cultural and economic forces that produce all health care disparities, (2) that disparities in genetic testing may be compounded by a decreased effectiveness of post-test risk-reducing interventions in underserved populations, and (3) that serious deficiencies exist in the utility of genetic testing in underserved populations as a result of limited testing experience in these groups, particularly in the mismatch repair genes associated with HNPCC. Ultimately, our message is a straightforward one: Increasing testing access and volume in racial/ethnic minority and underserved populations must be a national priority if mounting disparities in genetic testing utility and utilization are to be eliminated.

Table 2. Characteristics of the Hereditary Breast-Ovarian Syndrome Predisposition Genes *MLH1*, *MSH2*, and *MSH6*

Characteristic	
MLH1	
Location	3p21
Cloning date	1994[2,6]
MSH2	
Location	2p22
Cloning date	1993[3]
MSH6	
Location	2p16
Cloning date	1996[12,13]
Mutation prevalence estimates[15]	
Amsterdam criteria met	≈1:5
Amsterdam criteria not met	≈1:10
Associated cancer risk[16,20]	
MLH1/MSH2	
Colorectal	≈60%-80%
Endometrial	≈50%-60%
Gastric	≈10%
Ovarian	≈10%
Other*	≈1%-5%
MSH6	
Colorectal	≈40%
Endometrial	≈60%
Gastric	≈10%-15%
Ovarian	≈10%-20%
Other*	≈1%-5%

*Includes small bowel, brain, renal, and hepatobiliary tract cancers.

ORIGINS OF HEALTH CARE DISPARITIES

Health care in this country is neither distributed nor enjoyed equally. Disparities in the American health care system have been increasingly recognized in the last 20 years. The recent National Healthcare Quality and Disparities Report[49] revealed the magnitude of health care disparities in the United States and detailed the multifactorial origins of these inequities. Underserved cancer patients are confronted by access, treatment, and outcomes disparities much as their counterparts in other areas of the health care system. African American women have a higher mortality rate from breast cancer than white counterparts, despite having a lower incidence of disease.[50,51] This is due in part to socioeconomic and access-related delayed diagnosis, although lifestyle factors, belief systems, and biologic characteristics of tumors have also been implicated.[52-54] For colorectal cancer, disparities are equally discouraging.[55,56] The median age of colorectal cancer diagnosis for African American men is 5 years younger than for the white population (66 *v* 71 years) and 7 years younger for African American women (68 *v* 75 years). Age-adjusted mortality rates for cancer of the colon and rectum are nearly 40% higher in African Americans compared with whites, whereas Hispanics, Asian Americans, and Native Americans have rates 29% to 36% lower than whites. Yet for African Americans, recent declines in colorectal cancer incidence and mortality, praised as indicators of the success of cancer prevention efforts in screening and treatment, are only a fraction of those for white Americans.[57]

DISPARITIES IN GENETIC TESTING

In this setting, inequalities in genetic services utilization come as no great surprise. Soon after genetic testing for *BRCA1/BRCA2* became commercially available, Armstrong et al[58] found a strong negative association between nonwhite race/ethnicity and the use of *BRCA*-related services. The same group later reported that African American women were significantly less likely (adjusted odds ratio, 0.28; 95% CI, 0.09 to 0.89)) to receive genetic counseling for primary breast cancer prevention than white counterparts.[48] The implications of these disparities were reflected in the 2002 descriptive epidemiology of *BRCA* testing from Myriad Genetic Laboratories: Of the first 10,000 individuals tested who identified their race, fewer than 10% were from underrepresented racial/ethnic subgroups (Table 3).[4]

Knowledge-base and access-driven disparities in cancer-related health care have been explored extensively elsewhere, and will only be

Table 3. Characteristics of the Myriad Genetic Laboratories* *BRCA1/2* Testing Database (n = 10,000)

Characteristic	No.	%
Total population size	10,000	100
Sex, female	9,090	90.9
Age, years		
Median	49	
Range	6-97	
Race/ethnicity		
Western European	4,073	41
Ashkenazi Jewish	3,022	30
Central European	1,041	10
Latin American/Caribbean	229	2.3
Native American	218	2.2
African	163	1.6
Asian	112	1.1
Near/Middle Eastern	91	0.9
Deleterious mutation	1,720	17.2

NOTE. Adapted from Frank TS.[4]
*Salt Lake City, UT.

touched on here. Poor communication of family history, inaccurate risk perception,[48] and lack of awareness of genetic services contribute to a poor understanding and thus utilization of cancer genetic services,[59,60] particularly among racial/ethnic minorities where awareness of predictive genetic testing is reduced.[61,62] In contradistinction, greater medical knowledge base has been positively associated with increased motivation to undergo genetic counseling and testing and with patient-initiated inquiry and/or demand for services.[63-65] Thus, independent of actual need, those individuals who are aware of and ask for specialized genetic services are the most likely to receive them.

Underserved populations have also been shown to have poorer access to cancer services than white counterparts.[66,67] Highly technical services necessitating multiple office visits, extensive medical assessment, or primary care referrals like genetic counseling and testing are particularly vulnerable to access-related barriers, and financial restraints including lack of insurance, underinsurance, and incomplete Medicare/Medicaid reimbursements compound these barriers.[68] Access issues may also be magnified in semiurban or rural areas, where referral centers and professional services are less likely to be found.[69] In an effort to address some of these issues, the April 2005 Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) report[70] "Coverage and Reimbursement of Genetic Tests and Services" reinforced the need for universal coverage and reimbursement of genetic services to ensure equal access by all persons. Notably, the committee identified "significant barriers . . . limiting appropriate access," which the federal government could be "influential in minimizing or eliminating."

POST-TEST DISPARITIES

Access to genetic testing, however, does not guarantee that subsequent risk-reducing strategies are available to or pursued by high-risk underserved individuals. Racial/ethnic minorities experience greater barriers to entering cancer prevention trials than white counterparts,[71] despite initiatives from the National Cancer Institute and the National Institutes of Health (Bethesda, MD) to increase minority recruitment into clinical research. Outcomes disparities may also be a result of health care choices made by underserved persons after genetic testing is completed. Distrust of risk-reducing interventions coupled with greater reliance on faith and religion[72] may contribute to lower compliance with colonoscopy, mammography, and other preventive strategies.[49,73] Although limited information is available in this area, it is clear that the effectiveness (the real-life impact) of proven risk-reducing interventions will not attain the efficacy (the maximal theoretical impact) reported in recent prevention studies in underserved populations while the many complex disparities present in the American health care system persist. For example, despite equal access to medical oncology consultation, African Americans (the elderly in particular) with a newly diagnosed colorectal cancer have been shown to initiate and complete fewer courses of adjuvant chemotherapy than the white population. When causes were investigated, patient, hospital, and physician factors contributed more prominently to measured disparities than either socioeconomic or surgical outcome factors.[74] Thus, without comprehensive assessment and management strategies, access, and knowledge- and culturally based barriers to health care will almost surely lead to inferior health outcomes in high-risk minority populations.

TESTING THE UNDERSERVED: BEYOND *BRCA*

Even supposing equal access to risk assessment and genetic testing, nonwhite persons benefit less from these services. The reason for this may not be immediately evident, because one would expect that two individuals offered counseling and testing, despite racial or ethnic origins, should benefit equally. However, this is not the case.

Inadequate Risk Models

Risk assessment relies on predictive statistical models to estimate an individual's risk of either developing cancer or carrying a cancer-causing gene. For breast cancer risk assessment, the Claus,[75] Gail,[76] and BRCAPRO[77] models are widely used for this purpose, and in suspected HNPCC, a Mendelian model to predict *MLH1* and *MSH2* mutations (CRCPro) has recently been under development in the BayesMendel laboratory at The Johns Hopkins University (Baltimore, MD).[78] For underserved persons, the weaknesses in this design are two-fold. First, the majority of demographic and tumor-related data used to develop risk models comes from high-risk white families, meaning that their applicability in the nonwhite population may be reduced and their performance suboptimal.[79] Second, Mendelian models depend critically on accurate estimates of population-specific prevalence to estimate the probability of a particular high-risk genotype. The substantial impact of Ashkenazi ethnicity on BRCAPRO estimates is a direct reflection of the more than 10-fold increased prevalence of *BRCA* mutations in this ethnic group compared with estimates for the remaining US population. Without accurate estimates of mutation prevalence in minority subgroups, the reliability of these models is compromised.

Beyond reliability, the paucity of validated predictive models for HNPCC compared to breast cancer is no less frustrating a problem. Anywhere from 1% to 5% of incident colorectal cancer cases may be caused by germline mismatch repair enzyme mutations,[80] and when the high risks of endometrial (lifetime risk, 40%) and ovarian cancer

(lifetime risk, 10%)[81] for female mutation carriers are also considered, it is possible that more than 15,000 cancers per year in the United States are secondary to mutations in these genes (and many if not all are preventable with current technology). Could higher rates and earlier onset of colorectal cancer in African Americans be related to a higher prevalence of mismatch repair genes? Recent evidence has pointed to significantly higher rates of microsatellite instability in colorectal tumors from African Americans, suggesting a magnified contribution of HNPCC in this group.[82] Nonetheless, mutation prevalence estimates in this population are as yet unknown.

Risk assessment and model inadequacies aside, why do racial/ethnic minorities receive less benefit from testing? And moreover why do the true population prevalences of the *BRCA* and HNPCC mismatch repair genes continue to elude us?

Understanding Testing Benefits—And Lack Thereof

The answer to the first question is largely scientific. Because DNA sequence analysis relies on the comparison of a test DNA sequence to a standard (ie, the normal or wild-type human sequence), the determination of what gene sequence will serve as the standard is of critical importance. The pathogenicity of a deleterious mutation is determined when multiple affected individuals with a particular sequence change (ie, mutation) compared to the standard are identified. As more individuals with a particular mutation and a phenotype consistent with a deleterious mutation are discovered, the evidence for a pathogenic mutation further solidifies. The weakness of this approach becomes self-evident when the socioeconomically and racially skewed testing patterns in the United States are considered. Not only are the current standard cancer predisposition gene sequences based primarily on data gathered from Ashkenazi Jewish individuals (for *BRCA1* and *BRCA2*) and other white populations, but substantial genetic heterogeneity within African American and other nonwhite populations may further complicate this process.

Estimating Population Prevalence

To answer the second question, one must understand that the current inability to estimate population prevalence in nonwhite populations is less a function of science than of socioeconomics. Our limited knowledge of mutation frequencies is a direct reflection of the low volume of testing performed in underserved populations. For *BRCA* testing, the impact of this can be seen in the high rates of variants of uncertain significance and novel deleterious mutations found among African Americans.[8,14,83] High-volume testing in the Ashkenazi, on the other hand, has lead to the early identification of founder mutations and to more accurate estimates of the penetrance of various *BRCA* mutations in this ethnic group.[1,5]

In FAP, the literature on testing in nonwhite and non-Western populations is limited at best. Some attribute this to a decreased utility of testing for FAP in countries with limited resources, because of the rarity of this syndrome and the strong phenotype usually associated with classic FAP. Of course, this presupposes that the prevalence of mutations in nonwhite populations is equal to that of white populations, and that variants of this syndrome, such as attenuated FAP, are not more common. With expanded testing in Korean,[84] Czech,[85] Argentinian,[86] Singaporean[87] and South African black[88] populations, numerous novel mutations and phenotypic variations have been identified. Interestingly, whereas the common Western founder mutations at APC codons 1309 and 1061 are also found in most of these groups, no codon 1061 mutations were detected in the study of familial colorectal cancer from Singapore,[87] bringing to question population specific variability that is to date poorly defined.

Genetic testing for HNPCC has also been concentrated in white populations.[89] Using information from the recently unified InSiGHT database,[90] currently the single largest repository of mismatch repair enzyme mutation data in the world, we found that 73% of reported *MLH1* mutations were from American and Western European populations (Table 4). Only 11% of reports were from Asia, 3% from South American and Caribbean populations, less than 2% from African, and less than 1% from Native American or Middle Eastern populations. Although ascertainment bias may explain a large part of the Western European over-representation, the concerning fact remains that this worldwide database contains no more than a handful of reports on individuals from races and ethnicities who together represent more than 80% of the world's total population.

Because testing has been concentrated in Western European/white populations, the majority of identified founder mutations are in this group. The Finland I mutation, a 3.5-kb genomic deletion of *MLH1* exon 16, is thought to account for more than 50% of HNPCC in ethnic Fins.[25] Lynch et al[91] have traced an American *MSH2* founder mutation (a genomic deletion of exon 1-6) back 12 generations to its European ancestry. *MSH2* founder mutations have also been described in Newfoundland (A→T at nt943+3)[32] and in Ashkenazi Jews (missense mutation 1906G→C).[33] More recently, novel founder mutations have also been identified in Asiatic populations. Shin et al[27] have described mismatch repair gene founder mutations in a Korean HNPCC cohort, whereas Chan et al[26] have discovered a novel recurring 1.8-kb deletion of *MLH1* in persons from mainland China (Table 5).

Ultimately, the importance of identifying founder mutations in HNPCC can be best understood through the impact of the discovery of the Ashkenazi founder mutations on *BRCA* testing. With knowledge of prevalent population-specific mutations, at-risk individuals may be initially screened for the most common mutations. Unlike full DNA sequence testing, site-specific mutation screening is remarkably time and cost efficient and, depending on the prevalence of the founder mutations in question, may capture nearly 100% of mutation carriers in a particular racial/ethnic subgroup. In this setting, full-sequence testing would be reserved only for individuals who

Table 4. Frequency of Reported *MLH1* Mutation Studies by World Region from the InSiGHT Database[90] (n = 291)

	Reports			
	MLH1 (n = 291)		*MSH2* (n = 250)	
World Region	No.	%	No.	%
Western Europe	179	62	129	51
North America	34	12	22	9
French Canadian	1	< 1	4	1
Native American	1	< 1	0	0
Asia	31	11	14	5
Central/Eastern Europe	27	9	25	10
South America/Caribbean	9	3	9	4
Africa	4	1	14	5
Middle East	1	< 1	0	0
Australia, unidentified, other	4	1	39	15

Table 5. Founder Mutations in Hereditary Breast-Ovarian, Familial Adenomatous Polyposis, and Hereditary Nonpolyposis Colorectal Cancer

Founder Mutation	Population/Region
Hereditary breast-ovarian syndrome	
BRCA1	
185delAG	Ashkenazi Jewish[1,5]
943ins10	West Africa[8,10,14]
5382insC	Ashkenazi Jewish[1,5]
IVS13 + 1G>A	Africa[8]
BRCA2	
6174delT	Ashkenazi Jewish[1,5]
Hereditary nonpolyposis colorectal cancer	
MLH1	
3.5-kb deletion of exon 16	Finland[25]
Intron 5 splice site	Finland[25]
1.8 kb deletion of exon 11	China[26]
1757_1758insC	Korea[27]
2270insT	North Italy[28]
Intron 14 splice site	Denmark[29]
MSH2	
5kb deletion of exon 1-6	United States[31]
A->T at nt943 + 3	Newfoundland[32]
1906G>C	Ashkenazi Jewish[33]
MSH6	
1346T>C	Sweden[34]
2931C>G	Sweden[34]
651_652insT	Netherlands[38]
Familial adenomatous polyposis	
APC	
I1307K	Ashkenazi Jewish[39]

test negative for screening panels. Most American Jewish individuals undergoing *BRCA* testing today are first tested for the *BRCA1/2* Ashkenazi founder mutations (185delAG, 5382insC, 6174delT), and more than 90% of identified carriers are detected through this panel.[92,93] The efficiency and cost savings of this approach to mutation detection and cancer prevention cannot be underestimated.

SUMMARY AND RECOMMENDATIONS

Nearly 10 years after its commercial introduction, genetic testing for cancer predisposition has failed to achieve its full potential. Access and knowledge barriers continue to limit the use of this technology to the wealthy, the well insured, and the medically well informed. Despite major advances in prophylaxis, intensive screening, and chemoprevention, it is doubtful that underserved individuals receive the maximal efficacy of cancer prevention strategies. Perhaps most troubling, at the same time that highly concentrated testing for *BRCA* mutations in Ashkenazi Jews and other white Americans has produced a much greater understanding of mutation frequency and disease prevalence in these two populations, testing for mutations in the mismatch repair enzymes *MLH1*, *MSH2*, and *MSH6* of HNPCC has been underutilized and has remained localized to Western populations. This has limited the ability to estimate mutation prevalence and identify founder mutations for the various mismatch repair genes, particularly in underserved US minorities and in nonwhite populations worldwide.

Correcting disparities requires more than documenting that they exist. Recent work demonstrates that racially and culturally tailored medical interventions,[94] case management support for underserved individuals,[95] and federally-funded low-cost preventive health interventions can ameliorate health care disparities.[96] For genetic testing, the most important intervention to mitigate growing disparities is the expansion of testing to adequately sample underserved minority populations from the United States and abroad. Colorectal cancer and breast cancer will each afflict more than 1 million persons of every race and ethnicity worldwide this year.[97] As long as testing remains limited to Western, predominantly white populations, the preventive potential of genetic testing to reduce cancer incidence worldwide will not be realized.

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