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Tar Heel Footprints in Health Care

A periodic feature that recognizes individuals whose efforts—often unsung—enhance the health of North Carolinians

Kerry Crandall, MS, CGC

A seasoned genetic counselor at Mission Hospital's Fullerton Genetics Center in Asheville, North Carolina, Kerry Crandall has served in her current position for the past 19 years. In her daily activities, she provides pediatric genetic counseling, prenatal diagnosis counseling, hereditary cancer risk assessment, and general genetic counseling to patients and their families. In addition to her clinical commitments, Crandall also finds time to deliver educational presentations to a range of community members in Western North Carolina, including physicians, allied health professionals, local high school and college faculty and staff members, and the public. Ellen Boyd, MD, a clinical geneticist at Fullerton Genetics Center, said of Crandall, "[her] patients know that they are receiving the best of care and support when they have her. [She] is a great communicator. She empowers her patients and [their] families by providing them with information they need in an insightful manner, with compassion, and always with close follow-up."

In the early 1990s, Crandall began working with Boyd to establish the first genetic counseling program in cancer genetics in Western North Carolina. The company Myriad Genetics had just begun to offer testing of the *BRCA1* and *BRCA2* genes, which confer risk of breast and ovarian cancer, and Crandall took the initiative to apply for and receive a grant to provide *BRCA1* and *BRCA2* genetic testing for patients in the region. Boyd and Crandall also became active in providing enzyme replacement therapy for patients with lysosomal storage disorders by participating in clinical trials. As a study coordinator, Crandall has overseen numerous clinical trials and has worked alongside institutional review boards to better serve patients. Clinical trials of this nature are often conducted only at large academic research centers; by helping to bring these clinical trials to a community-based hospital, Crandall has allowed affected patients to receive services closer to home.

North Carolina is fortunate to have relatively good coverage of genetic services compared with other states. When Crandall began her career, the primary opportunities for genetic counseling were in either pediatric or prenatal settings. Now, however, many other opportunities exist, including cancer, research, and commercial genetic laboratories. As genetic testing becomes more widely used by primary care as well as specialty services, the need for skilled individuals who can communicate the results of genetic tests will continue to expand rapidly. Due to the constant growth in research findings and rapid advances in technology, genetic counseling is an ideal career for individuals who constantly want to learn. Crandall contends that genetic counselors have the unique opportunity to make a clear difference in the lives of patients through strong communication skills. Shearon Roberts, a fellow genetic counselor at Fullerton, agrees, saying of Crandall, "communication is the essence of our profession, and Kerry is a master." NCMJ

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ORIGINAL ARTICLE

The Relation of Race and Type of Health Insurance to Long-Term Risk of Mortality Among Lung Cancer Patients in Rural Eastern North Carolina

Samer E. Elchoufani, Jimmy T. Efird, Wesley T. O'Neal, Stephen W. Davies, Hope Landrine, Tithi Biswas

BACKGROUND Black patients with lung cancer have a higher mortality rate than do their white counterparts. Differences in insurance coverage, demographic characteristics, and treatment profiles may explain this disparity. The purpose of this study was to compare the long-term risk of mortality of black lung cancer patients with that of white lung cancer patients, by insurance type.

METHODS Patients who were diagnosed with lung cancer in Eastern North Carolina and treated at the Leo Jenkins Cancer Center between 2001 and 2010 were included in this study. A Cox regression model was used to compare the risk of mortality of black patients with that of white patients.

RESULTS A total of 2,351 lung cancer patients (717 black and 1,634 white) were treated at the Leo Jenkins Cancer Center during the study period. Independent of age and sex, black patients with lung cancer were observed to die sooner than their white counterparts (hazard ratio = 1.2; 95% confidence interval, 1.04–1.3; $P = .0070$). However, this difference was not statistically significant after controlling for and stratifying by insurance type.

LIMITATIONS Residual confounding and the misclassification of some variables could have biased estimated study effects.

CONCLUSION The racial disparity in lung cancer mortality observed in Eastern North Carolina is no longer apparent after health insurance type is accounted for.

Lung cancer is the leading cause of cancer deaths in North Carolina, with rates exceeding those reported nationally [1]. Furthermore, the lung cancer mortality rate per 100,000 population in North Carolina is higher among black patients than among white patients; in 2005, the rate for black men was 89.6, compared with 82.7 for white men, and the rate for black women was 45.5, compared with 35.7 for white women [2].

One possible explanation for the observed differences in mortality between black and white patients is unequal access to care [3-5]. A recent examination of lung cancer patients treated within the US Military Health System found that mortality rates for black and white patients were similar, suggesting that equal access to care may eliminate racial disparities in lung cancer mortality rates [6].

To our knowledge, a similar analysis accounting for differences in insurance type has not been conducted in a civilian population. The purpose of the current study was to determine the influence of insurance type on long-term risk of mortality among black and white lung cancer patients at a large tertiary referral hospital located in rural Eastern North Carolina.

Methods

Data collection. This study included patients who were evaluated and treated for lung cancer between January 1, 2001, and December 31, 2010, at the Leo Jenkins Cancer Center at East Carolina University. Study approval was obtained from the institutional review board at the Brody School of Medicine at East Carolina University.

Data were obtained from the Vidant Medical Center Cancer Registry, which includes patients seen at Vidant Medical Center, Brody School of Medicine, Physicians East, SurgiCenter, and other local physician offices. The registry follows standard data collection and validation procedures and has received the Commission on Cancer Outstanding Achievement Award from the American College of Surgeons.

The data we obtained included information on age, sex, race (self-reported), smoking status (self-reported), cancer stage and histology, and treatment history (surgery, chemotherapy, and radiation therapy). Only black and white patients were included to minimize the potential for residual confounding; approximately 1% of patients were of other races. Each patient's lung cancer was categorized based on pathology reports as belonging to 1 of 7 subtypes: squamous cell carcinoma (SCC); adenocarcinoma; non–small-cell lung carcinoma, not otherwise specified (NSCLC NOS); small-cell lung carcinoma (SCLC); large-cell neuroendocrine carcinoma (LCNEC); bronchoalveolar carcinoma; or other. Health insurance coverage categories were as follows: Medicare

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with supplemental insurance, Medicare without supplemental insurance, Medicaid, private insurance, and no insurance/self-pay. Smoking history was categorized as never, current, prior, or unknown/other (eg, smokeless tobacco use). Date of diagnosis was determined by the pathology report. Follow-up information concerning treatment, recurrence, and patient status was routinely collected. Patient status was determined at least annually by death certificates from county registrars, hospital records, the Social Security Death Index, and letters to primary care providers and/or patients.

Outcome. The study outcome was all-cause mortality. Long-term risk of mortality was computed from the date of diagnosis to the date of death. Patients who were still alive at the date of last contact were censored.

Statistical analysis. Categorical variables are presented as frequency and percentage; continuous variables are presented as the mean (plus or minus 1 standard deviation), median, and range. Statistical significance was tested using the Pearson's chi-square test for categorical variables and the Kruskal-Wallis procedure for continuous variables. Cumulative mortality percentages were computed using the Kaplan-Meier product-limit method. The log-rank test was used to compare the mortality of black patients with that of white patients. Cox proportional hazards regression models were used to compute hazard ratios (HR) and 95% confidence intervals (CI) for long-term mortality. Multivariable models included variables that have been previously reported to be associated with lung cancer mortality, regardless of their statistical significance in our dataset. These variables included age, sex, cancer stage, cancer histology, smoking history, surgery, chemotherapy, radiation therapy, type of health insurance (for pooled data), and 5-year period during which treatment was received (2001–2005 or 2006–2010).

Only a few values for insurance type were missing (n = 21). When values were missing, they were entered into the regression models as a separate category. Statistical significance was defined as $P<.05$. SAS software (version 9.3) was used for all analyses.

Results

A total of 2,351 lung cancer patients (717 black and 1,634 white) were treated at Leo Jenkins Cancer Center during the study period. Patient characteristics are stratified by insurance type in Table 1.

The median age of study participants was 67 years (range, 29–95 years). A total of 1,472 (63%) of the study participants were men; 879 (37%) were women. The most common histologic subtypes were SCC (31%), adenocarcinoma (30%), and NSCLC NOS (21%). The most common cancer stage was stage 4; specifically, there were 888 (38%) stage 4 cancers, 604 (26%) stage 3 cancers, 240 (10%) stage 2 cancers, and 619 (26%) stage 1 cancers. A total of 736 (31%) of the patients received surgical treatment, 1,062 (45%) received chemotherapy, and 976 (42%) received radiation therapy; some patients received more than one type of therapy. The median follow-up time was 9.2 months (interquartile range, 21 months). A total of 1,614 (69%) patients died during the study period.

An unadjusted Kaplan-Meier plot comparing mortality among black and white patients with lung cancer is shown in Figure 1. The median duration of survival was 11 months for black patients and 13 months for white patients (HR = 1.1; 95% CI, 1.03–1.3; log-rank $P = .013$). Adjusting for age and sex marginally increased the effect size and statistical significance of the result (HR = 1.2; 95% CI, 1.04–1.3; $P = .0070$). However, no statistically significant difference in mortality was observed between black and white patients in our multivariable Cox regression models after further adjusting for insurance type, clinical characteristics, and treatment (Table 2). Although a decreased HR (0.80) was observed for Medicaid insurance, the 95% CI spanned unity.

Discussion

Our results are comparable with those of a recent analysis of lung cancer mortality using data from the Department of Defense's Automated Central Tumor Registry [6]. This study found that all-cause mortality for black patients in the adenocarcinoma, SCC, and LCNEC groups was similar to that of white patients in these groups. Patients in the Department of Defense registry were treated within the US Military Health System, which provides equal access to medical care to all its beneficiaries. A retrospective case series review of lung cancer patients diagnosed at the Walter Reed Medical Center (which is part of the US Military Health System) also did not find any mortality difference by race [7].

The findings of our study closely match the results from a large (N = 76,086) cancer registry study of lung cancer patients in Florida who were diagnosed during the period 1998–2002 (6.7% of whom were black) [8]. In both studies, unadjusted mortality was significantly better in white patients with lung cancer than in black patients ($P<.02$). However, after accounting for insurance type and other relevant demographic, clinical, and treatment variables, there was no longer a statistically significant increase in the risk of death among black patients with lung cancer. The adjusted HR for the Florida study was 0.97 (95% CI, 0.94–1.01; $P = .151$), compared with an HR of 0.98 (95% CI, 0.88–1.1; $P = .77$) for the current study. Unlike our study, the Florida study did not provide results stratified by insurance type.

Several reports in the literature have shown that, compared with their white counterparts, black patients with lung cancer are diagnosed at a younger age, are diagnosed at a later stage of disease, and are less likely to receive standard treatment [3, 8-14]. However, we adjusted for clinical and treatment variables in our models. Our analysis also adjusted for, and stratified by, insurance status, which has been associated with several of the aforementioned factors. For example, patients with private insurance are more likely to receive diagnostic radiographic imaging and to undergo lobectomy for early-stage non–small-cell lung cancer than

are patients with other types of insurance [11, 15-17]. In addition, black patients are more likely than are white patients to have Medicaid or to have no insurance [18].

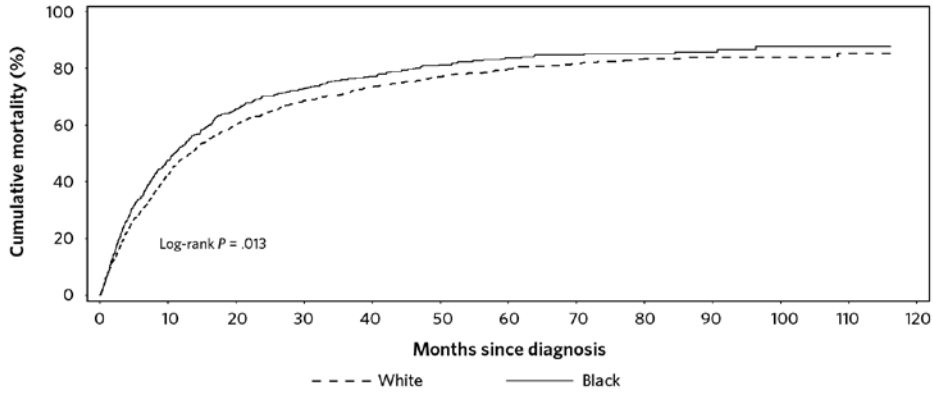
Strengths and limitations. There is a large black population in Eastern North Carolina that has historically experienced low socioeconomic position and discrimination. In 28 (97%) of the 29 counties in Eastern North Carolina, per-capita income falls below the national average of $27,915; in half of those 28 counties, per-capita income is less than $20,000 [19, 20]. Similarly, in 90% of the 29 counties in

TABLE 1.
Characteristics of Lung Cancer Patients Treated at Leo Jenkins Cancer Center From 2001 Through 2010, by Type of Health Insurance[a] (N = 2,351)

Patient characteristic	Medicare without supplemental insurance No. (%)	Medicare with supplemental insurance No. (%)	Medicaid No. (%)	Private insurance No. (%)	No insurance/ self-pay No. (%)	*P*-value
Overall	706 (30)	619 (26)	193 (8)	660 (28)	152 (7)	–
Age (years)						
Mean ± SD, median (range)	70 ± 8.3, 71 (43–95)	73 ± 7.0, 72 (43–92)	58 ± 8.4, 58 (41–81)	61 ± 9.4, 61 (34–93)	55 ± 7.1, 56 (29–72)	<.0001
Sex						
Male	458 (65)	389 (63)	90 (47)	416 (63)	105 (69)	<.0001
Female	248 (35)	230 (37)	103 (53)	244 (37)	47 (31)	
Race						
White	424 (60)	510 (82)	90 (47)	518 (78)	77 (51)	<.0001
Black	282 (40)	109 (18)	103 (53)	142 (22)	75 (49)	
Cancer stage						
I	193 (27)	177 (29)	46 (24)	183 (28)	16 (10)	<.0001
II	73 (10)	70 (11)	16 (8)	73 (11)	7 (5)	
III	184 (26)	147 (24)	44 (23)	175 (26)	48 (32)	
IV	256 (36)	225 (36)	87 (45)	229 (35)	81 (53)	
Histologic subtype						
SCC	245 (35)	204 (33)	52 (27)	175 (27)	40 (26)	.0022
Adenocarcinoma	192 (27)	176 (28)	62 (32)	212 (32)	47 (31)	
NSCLC NOS	139 (20)	123 (20)	39 (20)	144 (22)	50 (33)	
SCLC	84 (12)	69 (11)	21 (11)	73 (11)	8 (5)	
LCNEC	23 (3)	17 (3)	11 (6)	18 (3)	6 (4)	
Bronchoalveolar	14 (2)	11 (2)	4 (2)	16 (2)	0 (0)	
Other	9 (1)	19 (3)	4 (2)	22 (3)	1 (<1)	
Smoking history						
Never	54 (8)	61 (10)	6 (3)	69 (10)	6 (4)	<.0001
Previous	300 (42)	291 (47)	60 (31)	275 (42)	39 (26)	
Current	322 (46)	236 (38)	113 (59)	269 (41)	96 (63)	
Other/unknown	30 (4)	31 (5)	12 (8)	37 (7)	11 (6)	
Surgery						
No	516 (73)	425 (69)	134 (69)	395 (60)	128 (84)	<.0001
Yes	190 (27)	194 (31)	59 (31)	265 (40)	24 (16)	
Chemotherapy						
No	407 (58)	401 (65)	100 (52)	314 (48)	57 (37)	<.0001
Yes	299 (42)	218 (35)	93 (48)	346 (52)	95 (63)	
Radiation therapy						
No	422 (60)	400 (65)	89 (46)	385 (58)	74 (49)	<.0001
Yes	284 (40)	219 (35)	104 (54)	275 (42)	78 (51)	
Treatment period						
2001–2005	333 (47)	417 (67)	125 (65)	414 (63)	88 (58)	<.0001
2006–2010	373 (53)	202 (33)	68 (35)	246 (37)	64 (42)	

Note. LCNEC, large-cell neuroendocrine carcinoma; NSCLC NOS, non–small-cell lung carcinoma, not otherwise specified; SCC, squamous cell carcinoma; SCLC, small-cell lung carcinoma; SD=standard deviation.
[a]Category not shown: Patients (n = 21) for whom insurance information was missing.

FIGURE 1.
Unadjusted Kaplan-Meier Plot Showing Mortality of Black and White Lung Cancer Patients Treated at Leo Jenkins Cancer Center From 2001 Through 2010 (N = 2,351)



Eastern North Carolina, the proportion of the population that is black is higher than the national average of 13.1% [19, 20]. Reductions in per-capita income and/or increases in the proportion of the population that is black have been associated with corresponding increases in incidence rates of lung cancer, especially in female patients [21].

Our rural catchment area is unique in terms of the limited availability of health care resources in this region. For example, the recruitment and retention of physicians has been difficult in rural regions, and patients residing in these areas have less access to preventive health services than do residents of urban areas [22, 23]. Studies have also found rural residence to be significantly correlated with increased mortality in lung cancer patients [24, 25].

An additional strength of our study is that data were collected from a population-based cancer registry with a standardized data entry system and routine quality control. Furthermore, using a separate category for patients who had Medicare and supplemental insurance minimized misclassification of insurance type, since patients who had both Medicare and private insurance were not forced into one category or the other.

Detailed data were unavailable for some variables relating to smoking status (eg, quantity of cigarette consumption and duration of smoking) and insurance type (eg, length of coverage and crossover). Furthermore, we lacked individual data on socioeconomic position and occupation, and these variables could have influenced mortality. Some studies have found that socioeconomic inequalities affect the "timeliness and appropriateness of lung cancer staging and treatment" and subsequent mortality [15, 26]. We were unable to reliably estimate socioeconomic position using zip codes, because a large percentage of patients in the study region live in rural areas with postal box addresses. However, our inability to control for socioeconomic factors beyond insurance type likely did not seriously affect our findings, because patients in our catchment area are relatively poor, on average. A high percentage of both black and white patients have incomes that fall below the federal poverty guidelines.

Our study also had several other limitations. Cancer-specific death was not included in our database, so mortality may have been unrelated to malignancy. Race and smoking status were self-reported, and there could have been misclassification of this variable; for example, it is not clear at what point a patient was considered a prior smoker rather than a current smoker. Additionally, we cannot rule out the possibility that the study's power to detect racial differences was limited as a result of the relatively small sample of black patients, especially when patients were stratified by insurance type. The type of treatment was categorized as a binary variable and did not take into account dosing, length, or sequence of treatment. However, standard treatment protocols were used at our institution, and our analyses were adjusted for cancer stage and histology.

We considered missing values to be a distinct category, and they were entered into the regression models as a separate group rather than being imputed. We cannot rule out misclassification bias due to this categorization of missing values into a distinct group, but we did compare our results with an imputed complete dataset analysis (constructed by drawing residual errors from a normal distribution with a mean of zero and variance estimated by the residual mean square). Furthermore, we performed a complete case analysis with missing values excluded. Neither of those sensitivity analyses materially altered our results.

Although our analyses adjusted for demographic and other relevant variables, the nonrandomized, retrospective nature of this study means that unmeasured factors could have influenced our results. Retrospective studies are known to be susceptible to recall bias and to selection bias. Our results also could be due to chance, given the numerous comparisons that were performed. Lastly, some effect sizes were near unity and must be interpreted appropriately in a clinical context.

TABLE 2.
Adjusted Risk of Mortality for Black Versus White Lung Cancer Patients, Stratified by Type of Health Insurance (N = 2,351)

Type of health insurance	Adjusted HR (95% CI)[a,b]	*P*-value
All insurance types	0.94 (0.84–1.05)[c]	.30
Medicare without supplemental insurance	0.94 (0.77–1.1)	.51
Medicare with supplemental insurance	0.98 (0.77–1.3)	.88
Medicaid	0.80 (0.55–1.1)	.22
Private insurance	0.96 (0.76–1.2)	.76
No insurance/self-pay	0.97 (0.64–1.5)	.89

Note. CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, stage of cancer, histology of cancer, smoking history, surgery, chemotherapy, radiation therapy, and 5-year period during which treatment was received.
[b]Referent group was white race.
[c]Adjusted for insurance type.

Conclusion

Overall, black patients with lung cancer were observed to die sooner than their white counterparts in rural Eastern North Carolina, independent of age and sex. However, among patients with the same type of insurance, black and white lung cancer patients had comparable mortality after demographic characteristics, clinical characteristics, and treatment profile were controlled for. Future research with larger sample sizes is needed to confirm our findings in other rural and nonrural regions of North Carolina and to further explore the relationships between insurance coverage, risk factors, and access/utilization of care. NCM

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ORIGINAL ARTICLE

Community Perceptions of Genomic Research: Implications for Addressing Health Disparities

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BACKGROUND Increasing the engagement of racial and ethnic minorities in genomic research may help alleviate health disparities. This paper examines community perceptions of the relationships between race, genes, environment, and health disparities, and it discusses how such perceptions may influence participation in genomic research.

METHODS We conducted semi-structured interviews with 91 African American, Latino, and white lay community members and community leaders in North Carolina. Using constant comparison methods, we identified, compared, and developed linkages between conceptual categories and respondent groups.

RESULTS Participants described gene-environment interactions as contributing to group differences in health outcomes, expressed the belief that genetic predisposition to disease differs across groups, and said that social conditions trigger group-level genetic differences and create poorer health outcomes among African Americans.

LIMITATIONS Given the regional presence of major research institutions and the relatively high education level of many participants, this sample may not reflect the perspectives of those most disparately affected by health disparities.

CONCLUSIONS Members from multiple community sectors share perceptions and may respond to similar approaches when attempts are made to increase participation in genomic research. Researchers may inadvertently fuel the perception that health disparities experienced by minorities are rooted in the shared genomes of a particular group as distinct from those of other groups. The way researchers use race and ethnicity in recruitment, analysis, and communication of research findings inaccurately implies that there are genetic differences between races, when categories of social experience or ancestry may more accurately characterize health differences. Understanding these issues is crucial to designing effective community engagement strategies, recruitment plans, and messages about genomic research, which could ultimately help to lessen health disparities.

Technological advances have improved our ability to prevent, diagnose, and treat disease. Despite these advances, significant health disparities persist among racial and ethnic minorities [1]. These disparities have been linked to a variety of factors, including social and environmental inequalities and race-specific genetic variations [1-4]. Advances in genomics may allow us to disentangle and fully evaluate how genes and gene-environment interactions contribute to health [4]. In turn, this knowledge may provide strategies for addressing health disparities from a comprehensive perspective [3].

Progress in genomic sciences as a strategy to ameliorate health disparities is contingent upon members of diverse racial and ethnic groups engaging in the research process. Historically, however, research study populations have not reflected the diversity of those experiencing the diseases or conditions of interest [2, 3]. It is crucial that communities of color be engaged in genomic research in order for further advances to be made in personalized drug development, diagnostic and prognostic tools, and research into the effect of gene-environment interactions on health [2, 3]. Other advantages of community engagement in genomic research are that it facilitates an ethical and practical shift toward more participant-centered research practices and processes, and it allows us to consider the factors that influence people's willingness to engage in genomic research.

Previous studies have examined potential barriers to participation in genomic research. Although some studies have found that members of certain minority groups are hesitant to participate in population-based genetic research [5, 6], other studies have supported the contention that willingness to participate in research is the same across racial and ethnic groups, regardless of social class and knowledge [7-9]. Prior research with African Americans has examined how lack of familiarity with genetic concepts acts as a potential barrier to use of genetic services [10]. Although researchers have explored community perceptions of race and genetics [11, 12] and have looked for associations among race, genetics, and health outcomes [13], we know of no studies that have explored the public conceptualization of race (whether as a social or biological construct) and how it might shape understanding of and interest in genomic research.

Improving minority participation in genomic research requires a better understanding of how communities collectively view the social and genetic components of race and ethnicity, how those components interact to create

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differences in health outcomes, and how individuals weigh these issues when faced with opportunities to participate in race- and ethnicity-based genomic research. In this article, we report on findings from a qualitative study that examined individuals' perceptions of the causes of health disparities, and we consider the implications of those perceptions for genomic research.

Methods

We conducted in-depth semi-structured interviews with 91 lay community members and community leaders. Within minority groups, community leaders are central to information dissemination and health-related decision making [14]. Their voices are thus an important factor when members of these groups are evaluating opportunities to engage in genomic research that aims to address health disparities.

The interviews took place across a 22-county region in central North Carolina. Participants were recruited using purposive sampling based on self-identified race or ethnicity (African American, white, Latino), age (18–35 years, 36–65 years) and community status (lay, leader). Leaders included individuals working in or holding formal leadership positions across a range of community segments (clinics, grassroots organizations, media, education, etc) [15] and those in informal positions, such as neighborhood block captains or community activists. This study was approved by the institutional review board at the University of North Carolina at Chapel Hill (UNC-CH).

Recruitment. Recruitment was facilitated by regionally based community outreach coordinators who are part of the community research infrastructure of the North Carolina Translational and Clinical Sciences (NC TraCS) Institute, which is the administrative home of the Clinical and Translational Sciences Award (CTSA) at UNC-CH. To facilitate research linkages, each community site in the NC TraCS Institute maintains collaborative relationships with regional community-based organizations and clinical practices. Coordinators at each site contacted local agencies and clinics, regional community advisory boards, and a pool of community experts as recruitment sources. The coordinators then identified potential participants who met the inclusion criteria (age, sex, racial/ethnic category, community segment, and geographic location) and who agreed to be contacted by the study coordinator about possible participation. Latino interview participants were recruited by a community-based bilingual and bicultural research assistant, who made contact with organizations that serve the Latino community and asked for their aid in recruiting participants.

Interviews. Interviews were conducted by 3 trained research assistants who resided within the local communities. Interviews were held at community locations such as local libraries, community centers, and private offices. Latino participants had the option of completing their interview in English or in Spanish. For interviews conducted in Spanish, all study instruments were translated into Spanish using standard forward-and-back translation techniques [16] to ensure that materials were linguistically and culturally comparable to the original [17]. Interviews were audio-recorded and lasted 48 minutes on average (range, 35–75 minutes). Areas of inquiry included knowledge, beliefs, and experiences related to several topics: race and ethnicity, genomics and genomic research, the role of genomics in health disparities among diverse population groups, and beliefs about the benefits and harms of genomic research. As part of the interview, the terms *genetics* and *genomics* were defined for participants. For the purposes of this study, *genetics* is defined as the study of inheritance, or the way traits (like hair color or eye color) are passed down from one generation to the next. *Genomics* is a newer field that includes the study of all the genes in a person, as well as how those genes interact with each other and with a person's environment. After each interview, participants completed a brief demographic survey and received a $30 Visa gift card.

Data management and analysis. The audio files were professionally transcribed verbatim, and all identifying information was redacted. Transcriptions were imported into ATLAS-ti.v6.2, a computer program for managing text data. A 5-person team developed codes for conceptual categories by organizing the research questions into broad categories. Each code was assigned example text from the transcripts and rules for use to ensure appropriate and consistent application of the codes. Once the codebook was finalized, the research team coded transcripts in 2-person teams. Each team reconciled their application of the codes for each transcript and presented any challenges, with reconciliation, for review by the full team. Coding meetings were held on a weekly basis to ensure that the codes were being used appropriately across teams and to discuss any modifications to the codebook. A primary and secondary analyst then constructed matrices to identify, compare, and develop linkages between conceptual categories and respondent groups. Using constant comparison methods, thematic domains were delineated as the analysis of text data continued [18]. Demographic survey data was managed using Excel.

Results

Most lay participants (61%) were employed, 30% had a high school education or less, 76% had no history of clinical research participation, and approximately half (51%) were women. Among community leaders, 48% were African American, 55% were women, 73% had at least a college degree, and 34% had a history of clinical research participation (see Table 1). There was little variation in themes between responses from lay participants and responses from community leaders. Findings are presented across categories of race or ethnicity unless otherwise indicated.

The current study presents findings on 3 interrelated themes. First, we discuss participants' perceptions of the relationships between race or ethnicity, genetics and

genomics, and health outcomes. Second, we detail participants' understanding of gene-environment interactions by examining how they discuss racial and ethnic differences in socioeconomic and social contexts and by looking at what they say about the relationship of such differences to genetic predisposition. Finally, we consider how these perceptions can inform minority participation in genomics research that aims to improve health equity.

Race, ethnicity, genes, and health inequities. Respondents often used physical characteristics, such as differences in body type and hair texture, as evidence of genetic variation. Participants understood genetics as being related to traits that are passed down through families and that contribute to physical characteristics, frequency of disease, and predisposition to disease. Genetics is viewed as being largely unchangeable and leading to inevitable health outcomes, and it is credited with being the reason why family members often experience the same health condition. One Latino male leader described genetics as follows:

> Genetics is an inheritance from your family. For example, you have children and they can have your same eyes. . . . And diseases too, because they say "my grandmother had heart disease, my grandfather had diabetes," and you end up getting it until the third or fourth generation.

Genetics was seen as a key factor contributing not only to health outcomes but also to differences in predisposition across racial and ethnic groups. One African American male leader described this contribution by saying, "Genetics plays a large part in it. . . . Certain populations seem to be more susceptible to certain diseases." Similarly, a Latino male leader said, "I heard that the African race is more prone to disease, because of their genetic form." Genetic profiles that place an individual at risk for poor health outcomes were discussed as a tiered system; African Americans were seen as having the worst genetic predisposition to poor health, followed by Latinos, and then whites. Participants acknowledged that there are variations in disease outcome by racial or ethnic group; however, respondents only discussed disease differences that exist for racial and ethnic minorities, and all but one of the examples given were for disparities experienced by African Americans. Although this perception was present for all 3 respondent groups, the proportion of respondents indicating that genetic differences are an underlying cause for differences in disease outcomes was nearly twice as great among white respondents as among African American or Latino respondents.

Race, ethnicity, and gene-environment interactions. Participants were familiar with the concept of genetics; however, there was an overwhelming lack of familiarity with the term *genomics*. Most participants (84% of African American respondents, 81% of white respondents, and 76% of Latino respondents) had not heard of the term.

Although some of the terminology was unfamiliar, participants had clear concepts of how race and ethnicity drive and interact with differential social conditions. Race and ethnicity were described as being associated with differing cultural norms and behaviors and with the creation of differential conditions under which genetic expression occurs. Racial and ethnic groups were often described as differing in diet and levels of physical activity, both of which were said to contribute to differences in disease outcomes. Diet included the type and amount of food consumed and how food is prepared; African Americans and Latinos were perceived as choosing less healthy food items and preparation techniques. A white lay female participant offered her perception of how dietary differences contribute to differential health outcomes:

> I think we are all predisposed to certain diseases based on your race. . . . If you lived differently, then it doesn't have to affect your life. . . . Black people have [high] blood pressure, cut out fast food, cut out the chitterlings or whatever that's ethnically part of their diet, things that they have had in their history for years.

Although participants described differential health outcomes as largely attributable to social and cultural differences between racial or ethnic groups, participants also offered in-depth discussions of how each group's phenotypic expression (that is, what they look like) mediates the social conditions under which differential health outcomes occur. These social determinants included differential access to health care, education, fiscal resources, and even healthy food options. Latino respondents also cited language as a cause for differences, specifically in health outcomes, due to the inability of non–English speakers to access adequate or appropriate health care and challenges in communicating with health care providers. One African American male leader described the situation as follows:

> I think that by way of people not being in the same economic playing field as a lot of other ethnic groups, by them not having access because of economics, it leads people not to get early treatments, which leads to the progression of certain diseases, or getting a further developed disease that someone with insurance was able to get early treatment and be treated for certain things.

Interactions between genes and the environment were also described as creating racial and ethnic differences in gene expression based on where groups live, including both the physical living conditions and how "place" affects accessibility to health-promoting services. An African American lay female participant described this by saying:

> . . . on this side of the track has better stuff than on the other side of tracks. The one is getting better water, better meat, better vegetables. Their health is going to be better, their health is not going to decline as fast as the ones who is not getting those same things.

TABLE 1.
Demographic Characteristics of Study Participants

Demographic characteristic	Laypersons n = 47 No. (%)	Community leaders n = 44 No. (%)	Total N = 91 No. (%)
Self-identified race/ethnicity			
White	15 (32)	11 (25)	26 (29)
African American	16 (34)	21 (48)	37 (41)
Hispanic/Latino	16 (34)	12 (27)	28 (31)
Sex			
Male	23 (49)	20 (45)	43 (47)
Female	24 (51)	24 (55)	48 (53)
Mean age in years	37	44	40
Employment status			
Employed	27 (61)	36 (82)	63 (72)
Unemployed	9 (20)	3 (7)	12 (14)
Retired	3 (7)	3 (7)	6 (7)
Other	5 (11)	2 (5)	7 (8)
Level of education			
Some high school or less	8 (19)	2 (5)	10 (11)
High school graduate/GED[a]	5 (12)	3 (7)	8 (9)
Technical school	4 (9)	3 (7)	7 (8)
Some college	8 (19)	4 (9)	12 (14)
Completed college	10 (23)	14 (32)	24 (28)
Some graduate school	3 (7)	5 (11)	8 (9)
Graduate degree	5 (12)	13 (30)	18 (21)
Marital status			
Married	25 (56)	23 (52)	48 (54)
Separated	2 (4)	1 (2)	3 (3)
Divorced	4 (9)	8 (18)	12 (13)
Widowed	1 (2)	0 (0)	1 (1)
Never married	13 (29)	12 (27)	25 (28)
Income			
Less than $5,000	8 (19)	1 (2)	9 (10)
$5,000–$20,000	10 (23)	6 (14)	16 (19)
$20,000–$40,000	9 (21)	10 (23)	19 (22)
$40,000–$60,000	9 (21)	13 (30)	22 (26)
$60,000–$80,000	2 (5)	4 (9)	6 (7)
$80,000 or more	5 (12)	9 (21)	14 (16)
History of participation in clinical research			
Yes	7 (16)	15 (34)	22 (25)
No	34 (76)	28 (64)	62 (70)
Not sure	4 (9)	1 (2)	5 (6)
History of participation in genomic research			
Yes	2 (4)	5 (11)	7 (8)
No	43 (96)	37 (84)	80 (90)
Not sure	0	2 (5)	2 (2)
History of tissue or sample donation			
Yes	5 (11)	2 (5)	7 (8)
No	38 (84)	40 (91)	78 (88)
Not sure	2 (4)	2 (5)	4 (4)

Note. Some percentages may not add up to 100% due to rounding or to missing data.
[a]Has passed the General Educational Development test and received a Certificate of High School Equivalency.

African Americans were described as experiencing the poorest living conditions, Latinos were described as having somewhat better living conditions, and whites were described as living under the best conditions. African Americans were viewed as being more likely to live in conditions that exacerbate the expression of existing genetic predispositions to poor health outcomes. These living conditions were said to include the presence of toxins, insects, and proximity to industrial waste. A white male leader offered this explanation:

> A certain racial group maybe have a higher propensity for a certain disease, but if they have a healthier environment where they're eating healthier, it could lower the risk of heart disease or whatever. . . . On the other hand, if they genetically are prone to one certain disease, and there's nothing done to help that, and their environment is a poor environment where they may be putting toxins in their body, breathing toxins, drinking polluted water, I think that's definitely going to not only not help, but it's going to hurt. It may even bring that disease on earlier, and I think there's a difference in where racial groups tend to live. I would think that would have an effect on diseases and whether they may carry a genetic trait, but because of some of those disparities they may not be able to prevent them as best they could if they were in a more healthy environment.

Weighing engagement in genomics research and health equity. Given the cross-cutting belief that racial and ethnic groups are genetically and often socially distinct from one another, there are close ties between the factors that influence respondents' evaluation of genomic research and further perpetuation of the hierarchical structure respondents described. Not surprisingly, most African American and Latino respondents indicated concerns about research that aims to address health disparities (88% and 86%, respectively); however, most white respondents (81%) also cited concerns. Among those with concerns, the proportion of respondents whose concerns were directly tied to race was nearly twice as great among African American and Latino respondents as among white respondents. African Americans and Latinos spoke of mistrusting researchers and the government; these individuals also spoke of fearing medical abuses, the use of research to "promote" one race over another, genocide, and mistreatment or targeting of a particular race. Among one-third of Latinos, mistrust was closely tied to fears of deportation for family members who are undocumented immigrants. One African American female leader described historical and current concerns regarding this type of research:

> I think the fear is misusing the information; again, in our society we value different populations; the fear is that they could say, we only want 10% of this race to be born in a particular year because that is all we need or something. . . . The people that are doing the research, it is incumbent upon them to have the values that it's going to be done for good and not for abuse and for mistreatment of any race, one race versus another.

Similarly, a white female leader said:

> There's a long history of really bad practices . . . the history of Nazi Germany and the history of the Tuskegee experiments and the ways in which minority groups or people who are different . . . has the potential to reinforce stereotypes, to damage those people, to put them in situations where they're being exploited.

White respondents discussed race-related concerns regarding the use of genomics research to "mark" or to racially profile minorities. Instead of using research findings to address health disparities, this type of profiling could be used to reinforce stereotypes or to deny access to health insurance. A few white respondents also raised concerns that genomic research that aims to address health disparities may provoke race-related sensitivities, including elevated racial tensions, or may even result in a racial or ethnic group being blamed for certain health outcomes. One white male leader offered this perspective on concerns about genomic research that addresses differences in disease outcomes between racial or ethnic groups:

> The only thing I can think of is maybe identifying some inequities that are present, and that may cause maybe some racial tension—you know, for instance, if African Americans have a higher rate of heart disease, and if you're looking at genomics in that, that may be higher also because in general African Americans don't get promoted as quickly, live in poorer conditions, and a lot of that stuff I think we know already, but what I'm thinking in my head is there may be some tensions created when things like that are brought to light, and the more it's brought to light, I think the more we can help it, but it also may cause some tension.

Despite such concerns and the potential for harm, participants also identified potential benefits of genomic research. Each racial or ethnic group described the value of the anticipated knowledge to be gained through such research. New knowledge could provide a better understanding of the role of the environment in health, how diseases manifest, and prevention strategies, and this improved understanding could provide a basis for better medical care. Both African American and white respondents discussed the value of "helping certain races" or helping those most affected by health inequities. One lay white female respondent also discussed the value and the potential implications of genomic research that attributes disparities to social ills rather than to genetic differences:

> What would be really awesome is if they did research on everyone's genetics and found that we're much more alike than we are different inside our bodies. And so maybe people will have to face up to the fact that it's class and poverty that's causing higher rates of obesity, diabetes, heart disease, and almost any other disease you can mention in African Americans instead of the inverse, which I think is the scary side. I think finding differences could lead to race blame. I'm afraid of that.

Discussion

In this study, we explored community members' understanding of genomics and genetics, as well as their understanding of how these concepts relate to disparate health outcomes. Genetic researchers and social scientists have traditionally found it difficult to synergize biological and environmental explanations for health outcomes and health disparities. Interestingly, when considering determinants of health outcomes, community participants readily acknowledged the contributions of both biology and the environment, as well as the necessary interconnectedness between the two. Almost all participants had a clear and largely accurate understanding of genetics. Only a few respondents had ever heard the term *genomics*, but they largely endorsed the concept that interactions between genes and the social and physical environment contribute to group differences in health outcomes. They offered in-depth discussions of various social determinants of health, and they addressed the ability of those social determinants to create conditions that could affect gene expression and subsequently lead to health disparities. Given the prevailing use of labels to describe scientific work, researchers may sometimes be misled about community understandings of science and may fail to recognize that many scientific concepts are well understood by communities even though certain terminology may be unfamiliar.

Two main findings offer important insight for effectively engaging communities in genomic research in order to improve health equity. First, participants think that racial differences in physical appearance are evidence of genetic variation between racial groups, and this concept of race is part of their rationale for believing that racial and ethnic groups are genetically distinct. This belief prevails despite the fact that research has determined that there is significant genetic similarity between racial groups [19]. In fact, advances in research indicate that genetic differences in health have less to do with shared genomes among people with similar phenotypes, and more to do with shared geographic ancestry, which presents in a wide range of physical manifestations [20]. These findings are evidence that significant opportunities remain in translating clinical discovery to community understanding.

Second, individuals across racial and ethnic groups in our sample described a hierarchy of genetic predisposition (which mirrors social hierarchy) to explain poor health outcomes, primarily among African Americans. White respondents more frequently cited genetic differences as the basis for disparate health outcomes. Respondents viewed this greater genetic predisposition to disease as being triggered and magnified by exposure to worse social conditions, resulting in poorer health outcomes in African American communities. The idea of hierarchy along racial lines is not new, and historically it was used to justify the structure and enforcement of social inequalities [1, 21]. Although respondents did

not justify social inequality based on genetic inequality, participants did describe health disparities as being the result of genetic differences made manifest by social racialization. Although the perception of genetic differentiation by race is misconceived, interesting considerations are raised by the prevalence of this perception—particularly among those most often positioned at the top of the social hierarchy. In both the community and the clinical research enterprise, underlying assumptions of genetic predisposition may further perpetuate social inequality, undermine the need for genomics-based health disparities research, and hinder engagement by a broad spectrum of necessary community participants [3, 22]. The research enterprise also fuels the community perception that the gross health disparities experienced by communities of color are rooted in shared genomes that are distinct from the genomes of other racial and ethnic groups. Through their use of race and ethnicity in recruitment, analysis, and communication of findings, researchers often inaccurately imply genetic differences by race, when categories of social experience or ancestry may more accurately characterize differences in health.

Community participants expressed concerns and ideas about potential harms from genomic research that aims to address health disparities, including exacerbation of racial inequalities and misuse of information; these concerns and ideas are similar to those found in other studies [23-25]. Research that includes a racial component inevitably raises concerns regarding medical abuse or misuse of information, and such concerns are particularly salient for members of underrepresented and historically disenfranchised communities [7, 24, 26]. As the field advances, genomic researchers must recognize and attend to these concerns both in terms of how they conceptualize race and ethnicity and in how they discuss and operationalize individual and community-level protections [23]. Evidence supports significant genetic similarity between racial and ethnic groups, but prevailing social notions of race do not reflect this evidence; this suggests that communities and researchers may need to fully consider and interpret the individual and social harms of engaging in this type of research [27]. The differences in how groups in this study conceptualized harms and benefits suggest that Latinos may be more motivated than whites or African Americans to engage in research that is directly relevant to their immediate families as opposed to research that is designed to benefit the larger society. Researchers should consider different racial and ethnic groups' motivations for research participation, particularly how they evaluate benefits and harms. These issues are critical to the design of community engagement strategies, recruitment plans, and messages about research. Additionally, we found that, as in other studies, language barriers and fears of deportation remain a relevant concern in Latino communities [28].

These findings should be considered in the context of the study's limitations. We interviewed individuals within the central region of North Carolina, which is home to several major academic and private research institutions and organizations. Therefore the views expressed by participants in this study may differ from those of individuals in communities with less research saturation. As evidence of the ecologic context of research and higher education, many of our participants had at least some college education, even though we recruited across a variety of community networks. This population may not reflect the perspectives of those most disparately affected by factors that contribute to differences in health.

As the field of genomics evolves, scientists will better understand the potential uses of genomics to improve preventive, diagnostic, and therapeutic technologies. The challenge remains that racial and ethnic minorities experience disparate health outcomes yet are underrepresented in genetic and genomic research [2, 3]. To overcome this challenge and further minority engagement in genomic research, we will need to gain a better understanding of how community members conceptualize genetics, genomics, race, and ethnicity; what factors contribute to differences in disease experience; and what are their considerations when engaging in this type of research.

Initially, we recruited both lay community members and community leaders, and we expected some differences between these 2 groups in their level of familiarity with and perceptions of genomics. Despite stark differences in education and in history of clinical research participation, the lack of variation in responses between these 2 groups indicates that members from multiple sectors of the community share perceptions in this emerging field, and they may respond to similar approaches when attempts are made to increase participation in genomic research. Additionally, genetic and genomic researchers have the opportunity to more clearly consider the function of race and ethnicity in gene-based research, particularly when addressing health disparities. NCM

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POLICY FORUM

From Mendel to the Human Genome Project

Introduction

Like many of my contemporaries, I looked at the cover of this issue and opened the journal with just a bit of nostalgia, as well as trepidation. For me, genetics brings to mind the ingenious monk Gregor Johann Mendel and his experiments of crossbreeding hybrid peas in his garden. Genetics also evokes memories of an inspirational teacher who let his students catch hovering *Drosophilae melanogaster* and then assigned us the task of counting the number of white-eyed and red-eyed fruit flies in each generation to demonstrate single-gene inheritance. In college and medical school, I began to appreciate the strange beauty of the double helix and the mechanisms through which DNA directs the inner workings of each cell. When James Watson and Francis Crick untangled the helix into double strands of well-strung pearls with 4 variations—adenine, cytosine, guanine, and thymine—researchers thought they had unloosened the Gordian note of all time.

But not so fast. The double helix could be stained, colored, unwound, and isolated. First we sorted DNA into pairs of chromosomes, and then we began to see how chromosomes could be stuck together or pulled apart, resulting in deletions or duplications of entire chromosomes. In the twisting and spinning wild dance of replication, those ACGT base pairs could, and would, mix it up even more. Then our stains and microscopes got even better. Francis Collins led the Human Genome Project in its attempt to uncoil, unwind, and reveal the sequence of all of the genes packed into our chromosomes. This work began an ongoing investigation to determine what pieces, fragments, and sequences of which base pairs influence what traits, and when.

This issue of the NCMJ takes us further and wrangles our twisted genome to show that we can have base sequences in the right order yet with different expressions that can mean, literally, a difference of life or death. As we continue to explore the human genome, we often do not even know what we have discovered.

Genetics is not as simple as Gregor Mendel suggested, as we were bound to discover. Exposure, expression, and probability add to the crazy beauty—and mystery—of the genomic dance, one in which 4 partners create all the diversity of the world. NCMJ

Peter J. Morris, MD, MPH, MDiv
Editor in Chief

ISSUE BRIEF

Personalized Health Care in 2013:
A Status Report on the Impact of Genomics

Ralph Snyderman

This issue of the NCMJ describes the impact that genomics has had on the practice of medicine in the decade since the full sequencing of the human genome was completed in 2003. Specifically, it reports on how genomics is affecting health care delivery, describes the concept of personalized health care, and discusses the role that genomics plays in such care. The commentaries and sidebars that follow highlight the opportunities and challenges of bringing genomics into clinical practice. Reading these articles will hopefully give clinicians and others a better understanding of the benefits and limitations of genomic technologies. Emerging capabilities, resulting in part from genomic research, are providing an opportunity to move health care from a reactive, disease-focused model to one that is personalized, predictive, proactive, precise, and patient-centered. Genomics and related technologies have already changed many approaches to care, particularly in the field of oncology, and I believe they will help to transform our overall approach to the delivery of health care. With the rapidly accumulating capabilities being developed and the focus on patient-centered and personalized care, I expect that the practice of medicine will become proactive and personalized within the next decade.

On June 26, 2000, at a widely covered press conference at the White House, President Clinton announced the completion of a draft sequence of the human genome. The President predicted with great fanfare that decoding the human genome would lead to new ways to prevent, diagnose, and cure disease. The decoding of the human genome was touted to represent a new era of genetic medicine [1, 2].

Even before this extraordinary accomplishment, a new age of personalized medicine was being anticipated. Technological advances that were emerging during the latter part of the 20th century lent potential for a transformation in medical practice, which created optimism about the prospects for predictive and proactive care. This change was needed, as health care in the United States was becoming increasingly unaffordable; approximately 75 cents of every health care dollar was being spent on the treatment of chronic diseases [3]. One of the deficiencies in health care delivery has been its reactive focus on treating disease rather than preventing or effectively managing chronic diseases. It was hoped that a detailed understanding of the human genome might enable even more predictive and proactive approaches to health care.

As Chancellor for Health Affairs at Duke University in the latter part of the 1990s, I recognized emerging opportunities to abandon our reactive, sporadic, "one size fits all" approach to health care and instead adopt an approach that is proactive, strategic, and personalized. I firmly believed that the 21st century would herald a transformation in our approach to the practice of medicine. By the early 2000s, I was touting personalized health care as the second great transformation of medicine [4, 5], the first having been the introduction of science into the practice of medicine roughly a century before. In 2003 Duke created and launched one of the nation's first personalized health care programs, Duke Prospective Care, which we made available to all university employees [6, 7].

To understand the impact that genomics has had on today's health care, it helps to briefly consider the history of medicine [8]. Prior to the late 1800s, the practice of medicine was based on principles that had been formulated by Galen around 200 A.D. His "humoral imbalance" theory proposed that diseases were the result of imbalances of 4 basic humors: yellow bile, black bile, phlegm, and blood. Treatments were directed toward restoring the appropriate balance of the humors, and science played no role in this approach. Despite important advances in anatomy and physiology, science did not begin to influence the actual practice of medicine until the latter part of the 19th century. By 1850, experimental pathologists, including Carl von Rokitansky and Rudolf Virchow, had demonstrated that numerous diseases are associated with characteristic changes in organs and cells. Specific environmental factors, such as drinking water, were also shown to be associated with diseases, notably cholera. In the mid-1800s, Ignaz Semmelweis speculated that puerperal sepsis, "childbirth fever," was caused

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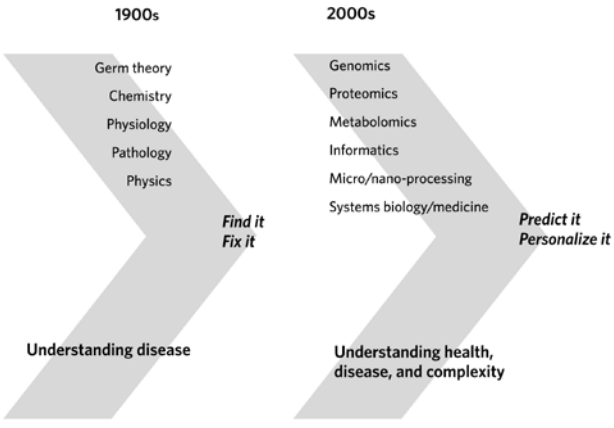
by an unseen particulate agent transmitted to mothers in childbirth by physicians who had performed autopsies on patients who had died from the disease. This concept of a transmittable disease-inducing agent flew in the face of the concept of humoral imbalances, and the idea of transmittable disease was met with scorn until microbiologists Robert Koch and Louis Pasteur identified specific microorganisms as causative agents of numerous complex diseases, including tuberculosis and rabies. When microbial factors were conclusively shown to be the cause of diseases, this new theory debunked the humoral imbalance theory as an underlying principle of medicine.

Medicine's First Transformation: A Scientific Basis for the Practice of Medicine

By the beginning of the 20th century, a congruence of scientific advances was poised to affect the practice of medicine. Major advances in chemistry and chemical synthesis allowed the development of specific therapeutic agents. The discovery of x-rays led to diagnostic imaging, and soon the concept of humoral imbalance was superseded by the concept of the pathophysiological basis of disease. Research and science became the drivers of medical advances (Figure 1). The Flexner Report of 1910 [9], which was funded and supported by the Carnegie Foundation, solidified the importance of scientific research to medical education and practice. Alexander Flexner decried the lack of a scientific basis for medical education and practice, and he proposed that US medical schools require that students be taught by faculty who were engaged in medical research and were practicing medicine in hospitals affiliated with the medical school. This model of basing medical education and practice on a foundation of science crystallized the first transformation of medicine.

FIGURE 1.
Scientific Basis of Health Care Transformations



Note. The sciences of the early 20th century enabled the identification of many disease mechanisms and causative factors. The science and technologies of the 21st century are enabling a dynamic understanding of health, the development of chronic diseases, and personalized health care. Source: Adapted from Snyderman [8].

The advances that stemmed from this transformation led to wondrous improvements in understanding and treating disease. What is now commonplace in medical practice would have been considered miraculous mere decades ago. However, an unforeseen consequence of focusing on mechanisms of disease was that medical practice became directed toward the treatment of established disease rather than toward prevention. An underlying concept of medicine is that disease is caused by an identifiable factor, and the role of the physician is to "find it and fix it." Similarly, a principle of research is to reduce complexity to a single measurable variable that can be studied experimentally. This reductionist approach is a magnificent way of learning many things, but it has limitations in dealing with conditions of great complexity, in which multiple factors affect outcomes. For example, the development of type 2 diabetes is dependent on a complex array of factors, both personal and sociological; thus it is not possible to fully understand the development of this condition or to devise effective treatments using a reductionist approach alone. Nonetheless physicians continue to be trained to identify the single most important underlying cause and to address that, rather than dealing with the complexity of chronic disease. In my view, this has resulted in our health care system being directed too much toward the treatment of disease events and not enough toward prevention, minimization, and management of disease [4, 5, 8, 10].

Role of Genomics and Related Sciences in Enabling a Second Transformation of Medicine

Scientific advances are now enabling a far more precise understanding of the mechanistic basis of disease. Germ theory, chemistry, physiology, pathology, and physics led to the first transformation of medicine, and now the emerging sciences of genomics, proteomics, systems biology, informatics, nanoprocessing, and digital technologies are providing capabilities that have initiated a second great transformation in health care delivery (Figure 1) [7, 8, 10-12]. Rather than relying on clinical or histopathological phenotypes, research is now defining diseases by their underlying mechanisms. Even more importantly, these new sciences have provided the technical capability to define the process of how diseases develop. Biological systems can now be studied dynamically through measurement of the activation or suppression of genes and metabolic pathways; the study and characterization of the circuitry involved in biological systems over time is called systems biology. The concepts of systems biology and their application to medicine are allowing the evolution of disease to be characterized and are making it possible to predict and track its development [8, 13, 14].

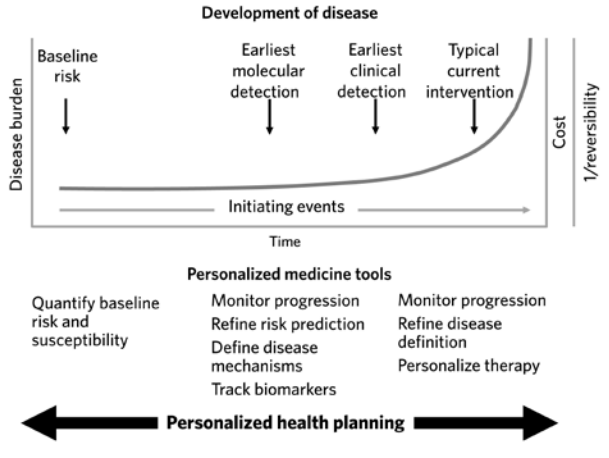
The concept that diseases result from the exposure of a host to a causative factor is too simplistic. Although the tubercle bacillus may be the "cause" of tuberculosis, the underlying health of the individual, his or her inherited

resistance, and the environment all play a critical role in the manifestation of the disease. The development of disease results from the dynamic interaction of the individual's inherited genetic background—which determines baseline susceptibilities—with the environment; baseline susceptibilities are modified over time by exposure to environmental factors that increase or decrease the likelihood that any given disease will develop. Disease may be initiated by a specific factor, such as a microbe or a toxin, or it may result from exposure to complex environmental factors, including diet, exercise, and stress. The latter may also enhance or diminish the individual's susceptibility to inciting agents. The reductionist approach to medicine unwittingly led to a disease-based health care system, but the systems biology approach, which recognizes the complexity of disease development, enables a dynamic and personalized health care model. With the ability to quantify an individual's baseline risk, to track whether disease is developing or regressing, and to understand the factors that mitigate disease, personalized health planning is possible for the first time in history (Figure 2). Personalized health care is proactive, accounts for the unique characteristics of the individual, and fosters enhancement of health as well as minimization of disease [4, 5, 7, 8, 10, 11]. Genetics and genomics provide an important scientific foundation for personalized health care.

Personalized Health Care and the Role of Genomics

Personalized health care is an approach to medicine that combines the concepts of systems biology, genomics, and other predictive technologies to create care that encourages patient participation and is personalized, predictive, and preventative. This approach is based on the understanding that susceptibility or resistance to various diseases depends on an individual's genomic inheritance and environmental exposure. Although many common diseases are based on Mendelian inheritance (eg, sickle-cell anemia, hemophilia, cystic fibrosis, Huntington disease), susceptibility to most chronic diseases results from more complex genetic inheritance [15-17]. An individual's genetic makeup and the impact of environmental factors, beginning in utero, determine a person's current clinical status and risks for future disease [18, 19]. Although an individual is born with a broad series of baseline susceptibilities and resistances to diseases, these susceptibilities and resistances change dynamically over the person's lifetime as a consequence of his or her exposures and actions. With this in mind, we can envision an approach to health enhancement and disease prevention or minimization that is based on how diseases actually develop. These concepts are the underlying basis of personalized health care, and the importance and limitations of genomics become apparent when viewed in this context.

FIGURE 2.
Inflection Curve of Disease Development



Note. Disease develops over time, and pathology accumulates subclinically until an initial clinical event signals its presence. As disease progresses, the cost of treatment increases and reversibility decreases. Available and emerging technologies enable early quantification of risk, measurement of disease progression, and early targeted intervention. These capabilities empower the development of personalized health care.
Source: Adapted from Snyderman [8].

Genomic analysis can aid in the prediction of baseline risks for certain diseases and may be able to help predict the course of disease [11]. This can be achieved by sequencing the whole genome or the exome and analyzing specific disease-associated variants, or by gathering information about which genes or gene products are specifically activated or suppressed in tissues of clinical interest [15, 20]. Baseline genetic analysis provides static background information regarding risk, whereas measurement of gene activation evaluates current activities. In a commentary in this issue of the NCMJ, Walters [21] notes that the field of epigenetics is now characterizing gene regulation as a consequence of environmental signals that impart rapid changes in gene expression, particularly during early stages of development. Genomics can also help to diagnose some diseases more precisely and can help to guide treatment. Thus genomics provides an important series of capabilities that allow personalized health care to continuously improve as technologies and clinical data provide more information. However, personalized health care is more than genomic medicine. To clarify this distinction, some definitions are needed [22].

Personalized health care is a coordinated, strategic approach to patient care that employs health care planning and appropriate predictive technologies—including, but not limited to, genomics—to customize care delivery across a continuum from health promotion to disease management.

Prospective health care and *P4 medicine* (predictive, personalized, preventative, and participatory medicine) are terms used in the description of personalized health care [8, 23].

A *personalized health plan* is a customized health plan that the provider and the patient develop together. It is a tool for coordinating and managing care for a distinct purpose (eg, health enhancement, primary prevention, or disease management). The plan includes an evaluation of the patient's

current health status, health risks, and susceptibilities, as well as shared goals to be met over a defined period of time. Progress is monitored by biomarkers or tracking tools that are incorporated into a therapeutic plan that is agreed upon by the patient and the provider.

Personalized medicine is the application of personalized medicine tools, whether genomic or not, to medical care. Nongenomic prediction tools include the Framingham coronary heart disease risk score and the Gail model for assessing the risk of breast cancer [10].

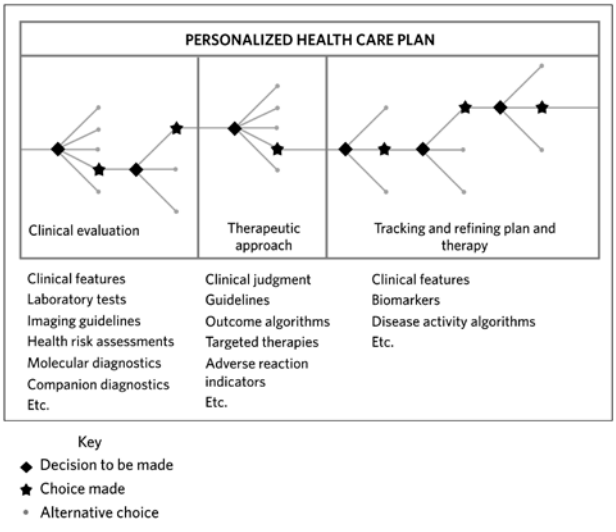
Precision medicine is the use of the full range of predictive technologies, including information from large databases, to diagnose and treat individual diseases. The terms *personalized medicine* and *precision medicine* are often used interchangeably [24].

Genomic medicine is the application of genomic tools to the practice of medicine. Genomic medicine is often incorrectly equated with personalized medicine, which has a broader definition. Genetic testing has already added to the value of newborn screening and has improved prediction of susceptibility to cancer, coronary artery disease, and other illnesses, and the impact of genetic testing on the practice of medicine will certainly increase in the future [15, 18, 19, 25].

Status of Genomics and Related Technologies in Personalized Health Care

Genomics and related testing, including gene expression and proteomic analysis, facilitate the personalization of health care in a number of ways. Specifically, such testing may make it possible to predict clinical risks, to diagnose disease, to identify disease mechanisms, to detect targets for individualized therapy, to track response to therapy, to predict drug metabolism, or to predict severe adverse outcomes. Personalized health planning can be thought of as a complex decision tree in which an initial clinical evaluation identifies goals to be met by subsequent therapeutic approaches (Figure 3). The development of therapeutic goals shared by the provider and the patient is based on an intense evaluation of the patient's current clinical status, using a broad array of diagnostic tools and approaches—both genomic and nongenomic. Based on the initial evaluation, diagnoses are considered and refined by further testing. In addition to providing a large array of diagnostic tools, genomic testing may be able to offer a far more precise diagnosis and definition of disease mechanisms and clinical risks. Similarly, genomic analyses can refine therapy selection on a mechanistic basis, help identify doses for certain therapies, and predict severe adverse outcomes. Once a therapeutic approach is undertaken, genomics and other predictive tools can help to track the progress of therapy and to inform new or additional therapeutic approaches (Table 1).

FIGURE 3.
Decision Tree Showing the Elements of a Personalized Health Care Plan for Treatment of a Disease



Note. This concept can also be used for primary prevention or health promotion.
Source: Adapted from Simmons et al [22].

The ability of genomics to add value to clinical care is dependent not only on the technology used to sequence genes but also on our understanding of the role of genetic variations in health and disease. The Human Genome Project, which was launched in 1990, enabled a new understanding of biology, evolution, anthropology, and definition of disease; it also identified therapeutic targets [15-17]. The fulfillment of the project's goals depended on unimaginable progress in gene sequencing, measurement of gene expression, analysis of gene activation, measurement of protein expression, and importantly, development of massive databases and analytical methods for relating sequence data to phenotypic outcomes. When Frederick Sanger first introduced gene sequencing in 1977, it allowed analysis by electrophoresis of approximately 10^2 channels at a time. Today, new optical methods allow roughly 10^9 templates to be measured simultaneously [16]. The field of next-generation DNA sequencing is a major new advance in sequence technology and has led to the establishment of a number of rapidly growing businesses [15-17, 20]. The cost of whole-genome sequencing has plummeted from more than $100 million in 2000 to about $5,000 today, and some predict that it may drop as low as $1,000 in the future [15].

Critical to understanding the impact of gene sequences on clinical manifestations is identifying haplotypes—genetic variants at a single locus reflecting linkage disequilibrium—and relating them to clinical manifestations. Such variants appear in "hot spots" on genes and can be measured as single-nucleotide polymorphisms (SNPs). It is estimated that fewer than 1,000,000 SNPs account for approximately 90% of genetic variation among humans, which simplifies the identification of disease mechanisms and individual susceptibilities [16]. Once specific SNPs are identified as being associated with a certain disease, tests can be developed to identify those SNPs, and it is no longer necessary to sequence large parts of the genome in order to diagnose

TABLE 1.
Capabilities and Tools Needed for Personalized Health Planning

Capability needed	Personalized medicine tools providing that capability
To quantify health risks	Health risk assessments
	Genomic predictors
	Single-nucleotide polymorphisms
	Gene sequencing
	Gene expression
To monitor disease progression	Biomarkers
To define disease mechanisms	Gene expression tests
	Proteomics tests
	Metabolomic profiles
	Clinical risk models
To select appropriate therapies	Clinical decision support
	Adverse outcome models
	Drug metabolism indicators
	Companion diagnostics
	Targeted therapies

that disease. SNP analysis has provided a quicker and less expensive way of identifying known genetic variants associated with a disease or with susceptibility to a disease. Direct-to-consumer testing for disease-susceptibility variants uses this technology [26, 27].

Unlike genomic sequencing or SNP analysis, which allows for the evaluation of an individual's genetic background, the identification of gene expression patterns is more targeted and determines which genes have been activated or suppressed in cells of interest: either cells from diseased tissue (ie, cancer cells) or cells that indicate a patient's response to a disease or to therapy. Microarray technology analyzes messenger ribonucleic acid from tissues, and gene expression patterns are identified. Complex algorithms can be developed to determine the relationship between patterns of gene activation and specific clinical issues, such as tumor aggressiveness, the likelihood of graft rejection, or the need for cardiac angiography [15].

Applications of Genomics to Personalized Health Care

Genomic analysis can be used to identify specific genetic variants associated with disease or disease risk. Gene sequencing is used not only to test for variants associated with known Mendelian diseases but also to identify individuals who have a high risk of developing a particular disease; for example, gene sequencing to look for mutations in the *BRCA1* and *BRCA2* genes can identify individuals with a strong susceptibility to breast and ovarian cancer [11, 15, 25]. Pros and cons of *BRCA* testing are discussed in the sidebar in this issue by Howard-McNatt [25]. Newborn screening for inherited Mendelian diseases, such as phenylketonuria and other metabolic disorders, has been available since the 1960s. As Sparks explains in her commentary [18], many newborn screening and diagnostic tests do not rely on genomics, but genomic technologies are nonetheless improving the clinical value of newborn screening. Prenatal screening in utero has also been greatly enhanced by genomic technologies, as Dickerson discusses in her commentary [19].

A major hope for the Human Genome Project was that whole-genome sequencing would lead to an understanding of the genetic basis of complex common diseases such as coronary artery disease, type 2 diabetes, and common psychiatric disorders. This hypothesis was tested in genome-wide association studies (GWAS) funded by the National Institutes of Health. The goal of such studies is to identify common variants associated with diseases; these studies are based on the premise that approximately 99% of genetic variance is due to common variants. For common diseases, many susceptibility alleles would be expected to have a small but ultimately important impact on disease development. To date, GWAS have identified loci associated with Crohn disease, type 1 and 2 diabetes, and adult macular degeneration. In each case, many loci have been identified, each contributing a small amount of risk, and studies have begun to improve our understanding of the underlying disease pathways [15-17]. In their commentary discussing genetic testing and obesity, Ng and Bowden [28] explain that genetic predisposition may play a role in the development of obesity; understanding this role could inform the treatment approach for specific individuals. Seyerle and Avery discuss the roles of next-generation sequencing and GWAS in personalized care in their commentary on genetic epidemiology [17]. In another commentary, Foreman and colleagues [20] explore the new world of massively parallel gene sequencing and describe the NCGENES initiative in North Carolina, which is studying the challenges of integrating genomics and clinical care. Whole-genome sequencing has already produced an abundance of apparently incidental findings that may have no clinical utility. In a sidebar, Krantz and Berg discuss how crowdsourcing can be used to determine the clinical relevance of incidental findings [29].

Genomic technologies have already begun to revolutionize approaches to cancer care by evaluating the clinical risks of breast cancer or helping to select targeted therapy. By defining the molecular pathways driving tumor growth, genetic technologies have identified drug targets, particularly protein kinases, and drugs that are able to specifically inhibit such drivers of disease are offering exciting new therapies for many forms of cancer. The ability to identify targets for therapies and to design diagnostic tests to detect the patients who are likely to respond to targeted therapy is revolutionizing cancer and its treatment (Table 2) [30, 31].

Genomic tests can also be useful in evaluating disease activity and aggressiveness and can thereby help to inform therapy. Oncotype DX offers 3 tests: an assay that uses a 21-gene ribonucleic acid (RNA) signature to predict risk of recurrence and to guide therapy for breast cancer; an assay that uses 12 genes to predict risk of recurrence of stage II or stage III colon cancer; and an assay that uses 17 genes to predict risk of recurrence and aggressiveness of prostate

TABLE 2.
Targeted Cancer Therapies

Goal	Therapeutic candidates
Block oncogene activation	Inhibitors of *BCR-ABL*, *c-KIT*, HER, *B-RAF*
Enhance tumor suppressors	Inhibitors of DNA methyltransferase, HDAC
Promote apoptosis	Inhibitors of *Bcl-2*; antisense IAPs
Inhibit angiogenesis	Inhibitors of VEGF, EGFR, Notch signaling
Abrogate limitless replication	Inhibitors of CDK, CHK, MTK
Inhibit invasion and metastasis	Inhibitors of TGFb, IGF-IR, FAK
Enhance immune surveillance	Immunomodulatory drugs

Note. CDK, cyclin-dependent kinase; CHK, checkpoint kinase; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; HDAC, histone deacetylase; HER, human epidermal growth factor receptor; IAPs, inhibitors of apoptosis proteins; IGF-IR, insulin-like growth factor receptor; MTK, mitotic kinase; TGFb, transforming growth factor beta; VEGF, vascular endothelial growth factor.
Source: Data are from the National Cancer Institute [30] and Medscape [31].

cancer. MammaPrint uses a 70-gene RNA signature to evaluate breast cancer. AlloMap molecular expression testing uses an 11-gene RNA white-blood-cell signature to evaluate the likelihood of heart transplant rejection, and Corus CAD uses a 23-gene RNA signature in circulating white blood cells to evaluate the risk of coronary artery disease [15].

Gene therapy, made possible through recombinant DNA technologies developed in the 1980s, has long offered hope for curing many diseases. Despite the unexpected difficulty of developing practical gene therapies, progress is being made—as Porada and colleagues discuss in their commentary [32]—and gene therapy is seen as a hope for curing many of the perhaps 10,000 human diseases that are caused by defects in a single gene.

Pharmacogenomics, which enables the identification of variations in drug metabolism as a consequence of inheritance, is discussed in detail by Jonas and Wines in their commentary [33]. Genomic testing is valuable in determining dosing levels for drugs such as warfarin (*CYP2C9*, *VKORC1*, *CYP4F2*) [33] and for predicting adverse events to the drugs abacavir (HLA-B*5701) and carbamazepine (HLA-B*1502). The efficacy of clopidogrel for coronary artery or peripheral vascular diseases can be estimated by analyzing *CYP2C19* [17, 33]. As Green describes in her sidebar [34], genetic testing is also finding variants of the cystic fibrosis gene (*CFTR*) that may guide the development and use of therapies that remedy the functional defect caused by a specific genetic variant.

Genomic research has begun to have an impact on medical care, to reveal the genetic basis of susceptibility to common diseases, and to better define disease mechanisms. The full impact of this research on clinical practice remains to be seen, but systems biology approaches—with next-generation sequencing, additional clinical studies (including observational studies), massive databases, and state-of-the-art bioinformatics—are expected to help revolutionize our understanding of human biology and disease. The tools derived from this understanding and the adaptation of such tools to the practice of medicine will continue to improve the power of personalized health care.

Direct-to-Consumer Testing

Many consumers have an interest in understanding their inherited disease risks. Several companies provide direct-to-consumer testing that measures an individual's genetic susceptibility to certain diseases. DNA from buccal swabs, for example, is analyzed by SNP analysis to detect variants associated with common and rare diseases. Although the accuracy of the measurements has not been problematic, the determination of disease susceptibility and the practical meaning of results have been troublesome, because we lack sufficient clinical data to allow for predictive validation [15]. These issues are discussed in the commentary by Adams and colleagues [26] and in the sidebar by Gulisano [27].

Ethical, Social, and Policy Issues Facing Genomic Medicine

To realize the full value of genomics for improving health care, major technical hurdles must be overcome so that we can validate the use of such technologies to accurately predict clinical outcomes. Clinical validation of genomic or other predictive tools often requires that vast amounts of data from many sources be aggregated and analyzed over a long period of time.

Resolving ethical, social, and policy issues is at least as important as overcoming technical hurdles. In her commentary, Tong explores the boundaries between personalized medicine and public health and explains the frameworks involved in genetic testing and treatment [35]. Other matters that need to be addressed are discussed by Dressler in her commentary [36]; these include how genomic tools are validated, what role the consumer plays in accessing genetic information, who pays for genetic tests, how providers and patients are educated to interpret genetic information, who owns genes or genetic information, and who has the right to access personal genetic information. Genomic and personalized medicine tools make possible a new approach to the practice of medicine. However, physicians and other health care providers must be trained and supported in this prospective approach to care; such training is discussed in the sidebar by Katsanis and colleagues [37]. The availability of clinical infrastructure—including electronic medical records, clinical decision support tools, and clinical training regarding the utility of genetics—will be essential. Reimbursement, patient privacy protection, and public acceptance also will need to be addressed to allow for full implementation [15, 35-37].

To sum up, genomics has already begun to affect health care, particularly by providing more accurate diagnoses and by identifying targets for therapy and selective therapeutics. In the future, genomics will play a greater role in facilitating

the transformation of care as it shifts from being disease-focused and reactive to being proactive and personalized. Equally important, genomics can enhance our understanding of who we are, where we came from, and, to a degree, where we are going. Many issues must be resolved in order to fully unleash the practical applications of genomic research, but the future will be exciting. NCMJ

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Pharmacogenomic Testing and the Prospect of Individualized Treatment

Daniel E. Jonas, Roberta Wines

Pharmacogenomics offers the hope of greater individualization of treatment. Therapies that exemplify the promise of pharmacogenomics include anticoagulation with warfarin and the use of antiplatelet medications (eg, clopidogrel) for secondary prevention after acute coronary syndrome. Good evidence of clinical utility must be obtained before pharmacogenomic testing is widely implemented.

The hope of pharmacogenomics lies in the possibility that we may be able to better individualize medical treatments—prescribing medications to those most likely to benefit and avoiding the use of certain medications in those most likely to be harmed by them [1]. In addition, when several medication options are available, pharmacogenomics could help us choose the one most appropriate for a particular individual.

Scientific advances in genome sequencing have resulted in a number of predictive genetic tests that are potentially useful for health care decision making. Such tests may predict risk for or susceptibility to future diseases in asymptomatic people (for instance, mutations in the *BRCA1* and *BRCA2* genes indicate a heightened risk of developing breast and ovarian cancer), or they may provide prognostic information for patients with a particular condition (for example, the Oncotype Dx test predicts the risk that breast cancer will recur). Genetic tests may also predict a person's response to medications (ie, pharmacogenomics) or to environmental factors (for example, nutrigenomics predicts responses to dietary factors).

For many practicing clinicians, the field of genomics is a "black box" plagued by uncertainty, hype, direct-to-consumer marketing, and little evidence of clinical utility. Many clinicians do not have the time or the tools to evaluate pharmacogenomic tests, and these tests are challenging to evaluate even for those who have a relatively detailed knowledge of genetics and related concepts [2].

Two types of drug therapy that exemplify the promise of pharmacogenomics are anticoagulation with warfarin and the use of antiplatelet medications for secondary prevention after acute coronary syndrome. Both types of therapy have large implications for population health. Warfarin is widely used to treat people with atrial fibrillation, deep venous thrombosis, pulmonary emboli, or artificial heart valves. Clopidogrel and other oral $P2Y_{12}$ inhibitors (eg, ticagrelor and prasugrel) are commonly used for secondary prevention after acute coronary syndrome.

Warfarin

In the United States, more than 30 million prescriptions are written for warfarin each year [3, 4], and of all the drugs in the modern medical formulary, warfarin remains one of the most challenging to manage. It is consistently one of the leading causes of adverse drug reactions leading to emergency department visits and hospitalizations, both in the United States and worldwide [5], and there are an estimated 7.6 adverse bleeding events for every 100 patient-years of treatment [6]. Warfarin has a narrow therapeutic window: Doses that are slightly too high can result in catastrophic hemorrhagic complications, whereas doses that are too low can result in thrombotic complications. As a result, specialized warfarin clinics are devoted solely to monitoring patients on this medication, and frequent monitoring of the patient's international normalized ratio (INR) is required; on average, such management requires 15 visits per year [7]. Further, individuals' response to warfarin and their dose requirements vary considerably.

Many genetic and clinical factors are associated with variation in warfarin dose requirements, including age, race, weight, height, smoking status, the use of other medications, and polymorphisms of the *CYP2C9*, *VKORC1*, and *CYP4F2* genes [8]. The *CYP2C9* and *VKORC1* genes, which encode for enzymes important for warfarin's site of action and metabolism (Figure 1), account for approximately 15% and 25% of the variation in warfarin dose requirements, respectively [8]. This finding has been replicated in observational studies of populations around the world [9, 10].

Several dose-calculation algorithms that combine clinical factors and genotypic information have been shown to accurately predict warfarin doses. In retrospective studies of patients receiving long-term therapy with stable doses

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Cystic Fibrosis:
A Model for Personalized Genetic Medicine

Deanna M. Green

Cystic fibrosis is the most common fatal autosomal recessive disease among whites, affecting approximately 30,000 people in the United States. It is a multisystem disease with morbidity and mortality resulting primarily from progressive pulmonary disease. Cystic fibrosis results from mutations in *CFTR*, a gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is an ion channel that regulates the movement of chloride and bicarbonate, and abnormalities in this protein can lead to problems with the secretion of salt and water in a variety of tissues. To date there is no cure for cystic fibrosis.

Because cystic fibrosis is genetic in nature, researchers have been able to focus on specific *CFTR* mutations that lead to specific changes in the CFTR protein. These genetic mutations can be separated into 5 categories, referred to as classes [1, 2]. Class 1 mutations result in premature termination of messenger ribonucleic acid (mRNA) and complete absence of the CFTR protein. Class 2 mutations result in defective processing of the CFTR protein; mutations in this class include the most common mutation, F508del. The defective protein produced by class 2 mutations is recognized as misfolded and is quickly degraded; thus it never reaches the cell membrane. Class 3 mutations cause defective protein regulation, often by means of reduced chloride channel activity. Such defects result in normal CFTR protein production but abnormal chloride channel transport. Class 4 mutations also involve defective conductance through the CFTR protein, which reduces the rate of ion flow and the duration of channel opening. Finally, Class 5 mutations result in appropriately folded CFTR proteins on the cell surface, but these proteins are significantly reduced in number. With these separate classes of genetic mutations, multiple opportunities have arisen to target the specific disease process.

Using high-throughput screening libraries, pharmaceutical companies have been able to identify numerous candidate compounds that can target specific mutations. Depending on which CFTR function they modulate, these compounds are referred to as *correctors* or *potentiators*. Potentiators promote effective chloride transport and can prolong opening of chloride channels. Correctors, however, improve CFTR processing and maturation in the cell, thus allowing the protein to be folded correctly and transported to the cell surface. Potentiators do not correct protein folding or transcription; rather, they target mutations that impair the function of a protein product that is already on the cell surface (Class 3, 4, or 5 mutations); in contrast, correctors are used to address mutations that result in protein products being trapped within the cell (Class 1 or 2).

The first potentiator to be successfully tested and to receive US Food and Drug Administration approval was ivacaftor. This molecule was found to be most effective in patients with the mutation G551D. In phase III clinical trials of subjects who had at least 1 G551D mutation [3, 4], ivacaftor significantly improved lung function as measured by forced expiratory volume in 1 second (FEV_1); this measure improved by at least 10.6% over a 48-week period. Subjects receiving ivacaftor were 55% less likely to have pulmonary exacerbations than those receiving placebo [3], and those receiving ivacaftor also gained more weight [3, 4].

Two other molecules that have been under study also fall into the category of correctors. One of these, VX-809,

of warfarin, such algorithms have explained more than half of the variation in dose requirements [8]. Despite this finding, randomized controlled trials have not yet shown that genotype-guided warfarin dosing improves clinical outcomes [11-14]. However, the trials conducted so far have been relatively small, single-center studies, and they were not designed or powered to evaluate health outcomes such as bleeding or thrombotic complications, nor to detect relatively small improvements in INR control or utilization outcomes. The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial [15]—a large, multicenter, double-blind, randomized trial that is currently ongoing—should help to clarify the clinical utility of genotype-guided dosing. The COAG study aims to enroll 1,200 subjects needing at least 3 months of warfarin therapy. Enrollment began in 2009, and results were expected after 4 years.

Having good evidence of clinical utility prior to widespread implementation of pharmacogenomic testing is important for several reasons. First, promoting the use of a test without evidence of clinical utility can be damaging for the field of pharmacogenomics; if the test is eventually shown not to be clinically useful, providers may become more skeptical of pharmacogenomic testing in general, which could substantially slow implementation of future tests that truly are useful. Second, time is a scarce resource for providers [16, 17], and a better alternative use of resources (ie, physician time, patient time, and reimbursements) would be to direct them toward things that have already been shown to have clinical utility—for example, screening for colorectal cancer or screening and behavioral interventions for unhealthy alcohol use.

Third, innovation and rapid diffusion of technology is a significant contributor to the high and rising cost of health care [18]. Indiscriminate dissemination and implementation of tests without evidence of clinical utility and cost effectiveness will further contribute to this problem. A high-quality cost-effectiveness analysis of genotype-guided warfarin

has been shown to correct the folding and processing of F508del-CFTR proteins in cells and to increase chloride secretion in bronchial cells by 14% [5]. In human trials, VX-809 when given alone has only been shown to result in a clinically significant decrease in sweat chloride but has not been effective for improving lung function or quality of life [6]. Due to this, phase III studies are now enrolling subjects with 2 copies of the F508del mutation to assess the combination of VX-809 and ivacaftor in terms of overall effectiveness on lung function and other endpoints.

The other corrector compound under study, ataluren, allows ribosomes to read through mRNA premature stop codons, resulting in the production of functional CFTR proteins in patients with specific class 1 *CFTR* mutations. Phase II studies of this drug showed promise, with ataluren increasing chloride conductance and FEV_1. However, phase III studies showed no significant improvement in any tested outcome, including FEV_1 [7, 8]. On later investigation, researchers found that aminoglycosides such as tobramycin, a medication that is commonly prescribed for cystic fibrosis, can interfere with ataluren at the ribosome [9]. These results will need to be investigated further.

In summary, cystic fibrosis is providing proof of concept that personalized medicine can be used to correct the base pathophysiology of a disease. Ivacaftor is the first drug of its kind to directly target the specific protein misfolding that leads to reduced activity of a protein. In the near future, physicians who treat patients with cystic fibrosis hope to add other medications to their arsenal that can directly combat the underlying defect of the disease. Thus, for any given mutation carried by a cystic fibrosis patient, we will have a drug aimed at that specific mutation. This therapy will reverse the dehydration in the lung and pancreas, in effect slowing the progression of disease. This type of therapeutic development provides promise for multiple other genetic diseases caused by protein defects, and it offers significant hope for the future of medicine. NCMJ

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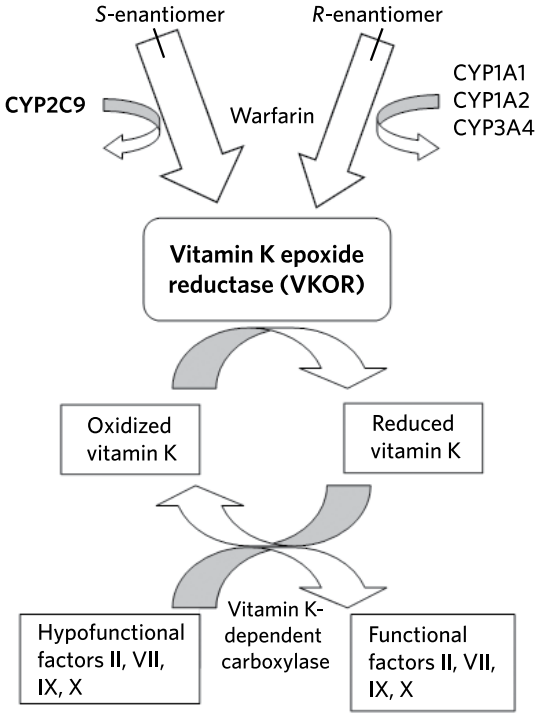
dosing concluded that, although such dosing is unlikely to be cost-effective for typical patients with nonvalvular atrial fibrillation, it may be cost-effective in patients at high risk for hemorrhage who are starting warfarin therapy [19]. Of note, the analysis was based on input from existing trials (which have inherent limitations, as noted above) and on outdated testing costs. The forthcoming results of the COAG trial and rapidly decreasing costs could change this cost-effectiveness balance.

Clopidogrel

In 2011 clopidogrel ranked seventh among the most prescribed medications in the United States, with a total of more than 28 million prescriptions [20]. This drug is commonly prescribed for secondary prevention after acute coronary syndrome. In 2012 the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) released guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction; these guidelines recommend dual antiplatelet therapy with aspirin and an oral $P2Y_{12}$ inhibitor—clopidogrel, ticagrelor, or prasugrel—for up to 12 months [21]. Until recently, only clopidogrel was available; ticagrelor and prasugrel were just approved by the US Food and Drug Administration (FDA) in 2011 and 2012, respectively. Another recent change is that generic clopidogrel became available in 2012, substantially reducing its cost, so it is now the preferred choice from a public health and cost perspective.

Clopidogrel is a prodrug that is transformed into its active form by several cytochrome P450 (CYP450) enzymes in the liver, one of which is CYP2C19. Variants of the *CYP2C19* gene have been associated with differences in the bioavailability of clopidogrel: CYP2C19*2 is the most common vari-

FIGURE 1.
Warfarin's Site of Action and Metabolism



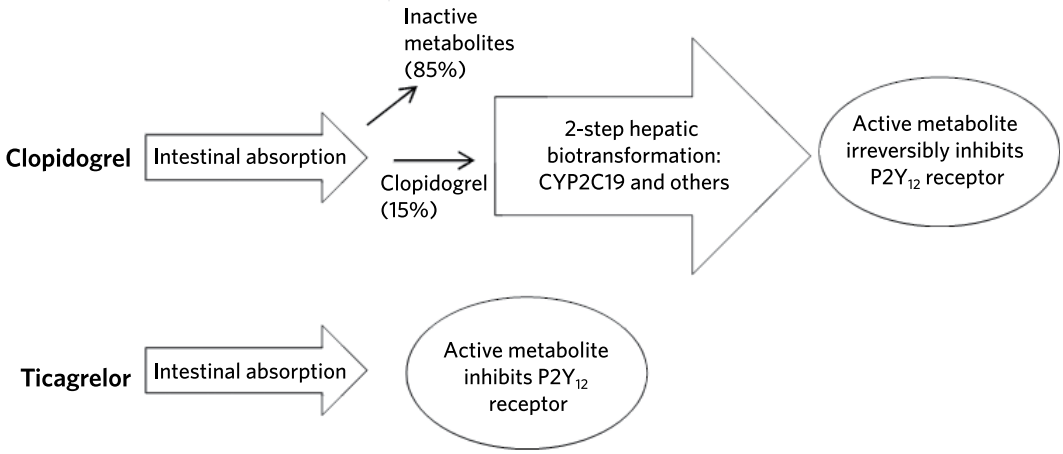
Note. Warfarin is biologically active in the liver, where reduced vitamin K is essential for converting clotting factors II, VII, IX, and X (as well as proteins C and S) into functional coagulation factors. Vitamin K epoxide reductase (VKOR) is a multicomponent enzyme system that regenerates reduced vitamin K. Warfarin produces its effect by inhibiting the VKOR enzyme complex. The S-enantiomer of warfarin is more potent; it is estimated to be up to 5 times more effective at inhibiting VKOR than is the R-enantiomer. The cytochrome P450 2C9 (CYP2C9) enzyme metabolizes S-warfarin; R-warfarin is metabolized by other cytochrome P450 enzymes (CYP1A1, CYP1A2, and CYP3A4).

ant allele, and CYP2C19*3 is a less common variant [22]. Individuals who carry 1 or 2 copies of these variant alleles may be intermediate or poor metabolizers of clopidogrel and may produce a smaller amount of the active form of the drug (Figure 2) [22-25]. In 5 of 7 cohort studies conducted in 2008 and 2009, the CYP2C19*2 variant was associated with an increased risk of cardiovascular events [26-33], leading to the conclusion that variant alleles may result in nonresponsiveness to clopidogrel and a subsequent increase in the risk of adverse outcomes.

Awareness of how genetic polymorphisms of *CYP2C19* can reduce clopidogrel's efficacy led to product label changes in 2009 and 2010 [34]. The current product label for clopidogrel [35] includes a boxed warning describing the increased risks of cardiovascular events among poor metabolizers; this label also notes that a genetic test is available to identify *CYP2C19* polymorphisms. However, there is no recommendation that prescribers pursue genetic testing of their patients. No rigorous studies have established a connection between use of a genotype-guided strategy and improved outcomes, and the ACCF/AHA guidelines explain that the clinical utility of genotypic testing has not been established [21]. Further, alternative hypotheses exist that may explain the link between *CYP2C19* variants and adverse outcomes; for example, the variant alleles may directly confer an increased risk of adverse outcomes, unrelated to clopidogrel metabolism.

As with genotype-guided warfarin dosing, pharmacogenomic testing to inform selection of a $P2Y_{12}$ inhibitor should have good evidence of clinical utility before it is widely implemented. We need randomized trials that compare clinical outcomes for patients who receive genotype-guided medi-

FIGURE 2.
Clopidogrel and Ticagrelor Pathways



Note. Clopidogrel is rapidly absorbed through the intestine. Approximately 85% of the administered dose becomes inactive and is eliminated, and the other 15% of the original dose goes through a 2-step biotransformation in the liver. Several cytochrome P450 enzymes—including CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5—convert clopidogrel to its active metabolite. The active metabolite irreversibly blocks the adenosine diphosphate receptor subtype $P2Y_{12}$, inhibiting platelet activation and aggregation for the lifespan of affected platelets (7–10 days). Ticagrelor is rapidly absorbed through the intestine with approximately 36% bioavailability. Hepatic activation is not necessary to produce the active metabolite that blocks the $P2Y_{12}$ receptor.

Pros and Cons of Screening for *BRCA* Mutations

Marissa Howard-McNatt

Estimates suggest that about 80% of breast cancers and 90% of ovarian cancers are sporadic [1]; only 5% to 10% of breast cancers are hereditary. Hereditary mutations of the *BRCA1* and *BRCA2* genes account for 60% of inherited breast and ovarian cancers [1]. According to data from the National Cancer Institute [2], the risk of a *BRCA2* mutation carrier developing breast cancer by age 70 years is 45%, and her risk of developing ovarian cancer is 11%–17%; *BRCA1* mutation carriers have a slightly higher risk of breast cancer (55%–65%) and a higher risk of ovarian cancer (39%).

Until recently, the management of breast cancers resulting from a *BRCA* mutation did not differ from management of sporadic tumors. However, genetic information is now important in planning surgeries and adjuvant therapies, and genetic testing for *BRCA* mutations is increasingly being used for risk assessment. This article will examine the pros and cons of such testing and discuss how it can affect patient care.

Genetic Consultation

In multidisciplinary breast centers, genetic counselors play a vital role by identifying and evaluating women who are at high risk for hereditary breast cancer syndromes. The US Preventive Services Task Force guideline on genetic risk assessment and *BRCA* testing strongly recommends that high-risk individuals be referred for genetic counseling and possible testing [3]. Genetic counseling and testing provide many benefits to the patient and to the health care team [1]. First, counseling and testing help to identify high-risk individuals who do not have cancer; these women will benefit from early screening and consultation. For a woman with a known cancer, counseling and testing may help her decide whether to undergo a bilateral mastectomy at the time of her cancer surgery, or whether to opt for careful surveillance of the remaining breast tissue. Finally, testing can alleviate the anxiety of not knowing one's carrier status.

The risks of genetic testing include the inability of such testing to detect all mutations, the unclear efficacy of some interventions, and the possibility of psychosocial or financial harm [1]. Genetic counselors can inform patients about Title I of the Genetic Information Nondiscrimination Act of 2008 [4], which provides protection against discrimination based on genetic information in health insurance underwriting decisions. However, that protection covers only group and individual health insurance; it does not apply to life insurance, disability insurance, or long-term care insurance [4].

Management

Women who test positive for a *BRCA* mutation have several options for reducing their risk of developing cancer. These include surveillance, chemoprevention, and surgical risk reduction.

For *BRCA* mutation carriers, early detection strategies include annual or semiannual clinical breast examination by a physician or allied health professional, annual mammography beginning at age 25 years, and/or annual breast magnetic resonance imaging (MRI) [5]; if both breast MRI and mammography are being performed, the breast MRI should be performed 6 months after the yearly mammogram. The benefit of a clinical breast examination is under debate, as such exams have not been shown to improve the rate of cancer detection. Nonetheless, patients say that they find the exam reassuring, and it gives the provider an opportunity to discuss the patient's care [6].

Mammography has been shown to decrease the breast cancer mortality rate; however, its sensitivity is estimated to be only about 36% in *BRCA1* or *BRCA2* mutation carriers [7]. In contrast, the sensitivity of MRI screening in women with a familial or genetic predisposition is nearly 80% [7, 8]. The pros of breast cancer surveillance with MRI are that it is noninvasive and it has no long-term side effects. The cons are that it has not been shown to reduce the risk of breast cancer–related death in *BRCA* mutation carriers, and it carries an increased risk of false-positive results, which can lead to additional imaging or biopsies.

Breast cancer chemoprevention is offered in the form of tamoxifen and raloxifene, with the latter being used for postmenopausal women. The Study of Tamoxifen and Raloxifene (STAR) [9] showed that these selective estrogen receptor modulators (SERMs) lowered the risk of developing invasive breast cancer by about 50%. However, SERMs

cation selection versus outcomes for patients who are all treated with clopidogrel. For example, the genotype-guided strategy could test everyone in that study group for *CYP2C19* polymorphisms and use ticagrelor instead of clopidogrel for poor metabolizers, because ticagrelor is not dependent on metabolic activation (Figure 2). Clopidogrel would be the default medication choice for those without variant alleles because of its well-established evidence of effectiveness [21], substantially lower cost, and slightly lower risk of minor bleeding [36]. NCMJ

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do not completely eliminate the risk of developing breast cancer, and data regarding their effectiveness in *BRCA* mutation carriers are limited.

Bilateral prophylactic mastectomy has been shown to reduce breast cancer risk in women with a family history of breast cancer. The risk reduction in *BRCA* mutation carriers has been shown to be 90% in women with intact ovaries and 95% in those who have undergone prophylactic oophorectomy [10]. Many women who choose bilateral mastectomy also opt for immediate breast reconstruction with implants or autologous tissue. The advantage of prophylactic mastectomy is that it greatly reduces the risk of developing breast cancer. The disadvantages include the need for extra surgeries with breast reconstruction, possible surgical complications (eg, bleeding and infections), and psychosexual concerns. However, studies have shown that most women are satisfied with their surgical choice and do not experience poor body image after surgery [11, 12].

In addition to prophylactic mastectomy, *BRCA* mutation carriers may consider prophylactic oophorectomy. Bilateral prophylactic salpingo-oophorectomy is associated with an 85% reduction in the risk of developing gynecologic cancer among *BRCA1* mutation carriers [13].

Breast specialists and genetic counselors play an important role in guiding patients with an increased risk for developing breast cancer through genetic testing and treatment options. There are pros and cons to each risk-reduction strategy, but the more informed a patient is, the better her outcome and overall satisfaction will be. NCMJ

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Educating Future Providers of Personalized Medicine

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No longer isolated specialties, genetics and genomics now span all fields of medicine. However, efforts to improve the genomic literacy of health care providers have struggled to keep pace with this change [1]. Canonical approaches to teaching genetics are not necessarily appropriate for the next generation of providers, who will be expected to implement genomic approaches in the clinic [2]. At the same time, patients increasingly have access to personal genomic information that has the potential to empower them to engage with clinicians and to collaborate on improving their health. Given this situation, how can we equip the provider workforce to meaningfully respond to patients' needs?

A cross-disciplinary team of faculty and staff members of the Duke University School of Nursing and the Duke Center for Personalized and Precision Medicine developed a formal genomics and personalized medicine curriculum for providers, which consists of 2 specialty electives designed for entry-level and advanced students in nursing and other health professionals. These interdisciplinary courses foster professional development and applied learning in key content areas. The focus of the courses is on clinical applications of genomics for the prevention, prognosis, and treatment of complex disease states; optional personal genome testing is made available through an online provider as an experiential learning tool. Overarching themes include ethical and social considerations relating to genome-based information and implications for personal health, public health, and public policy. The courses, which address all core competencies in genomics and genetics for nurses [3] and medical professionals [4] (eg, risk assessment, genetic testing and counseling, clinical management, and ethical implications), focus on underlying genomics concepts, communication with patients, and resources for evaluating technologies and calculating risk [1].

Rather than offering a traditional review of technologies within disease states (eg, cardiovascular risk, cancer, diabetes), the courses take a concept-based approach, discussing topics such as heterogeneity, oligogenicity, and gene-environment interactions. The courses also provide relevant examples from current literature. Classroom exercises build skills in evaluating the clinical validity and utility of genomic applications. Students emerge armed with real-world skills in using genomic applications and personalized medicine approaches, as well as an understanding of the implications of genomic technologies for society.

Students are given an opportunity to evaluate their own genomes and to gain personal experience with genomic testing through optional, subsidized personal genome testing integrated into the curriculum. Similar approaches have been used to educate graduate and medical students [5-9] and have led to improved learning outcomes [9]. Duke learners also are provided with mock genome profiles that they can substitute for, or use to supplement, their own profile. The personal genome platform serves as a touchstone throughout the courses as students explore different contexts of genomic information, from risk perception to ethical concerns.

To address concerns regarding the inclusion of students' personal genomes as an educational component [6, 10], the following measures were taken and reviewed with an external advisory board: confidentiality of participation; discussion of ethical, legal, and social considerations of direct-to-consumer genetic tests; a requirement that all instructors and students sign confidentiality statements; institutional review board assessment of social science research on the utility of personal genomes in the classroom; establishment of an external advisory board to handle unexpected stress or troubling outcomes; and provision of subsidized telephonic genetic counseling through a third party. The curriculum also establishes foundational principles before students receive their personal genome reports.

In the pilot offering, students unanimously reported that the experiential learning approach enhanced the lessons, noting the advantage of self-reflection within the classroom and acknowledging that both scientific and ethical concepts were reinforced with the personal

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genome reports. From an educational perspective, the personal genome testing provided an avenue for applied learning about genomic concepts and allowed for multiple embedded constructs to bridge and spark discussions. The genome platform sets a framework for evaluation of clinical validity and discussion of the personal and clinical utility of genomic tests, which fosters critical thinking and synthesis of concepts in personalized medicine. This approach cultivates a broad adaptive understanding of genomics and personalized medicine, beyond rote review of current technologies or disease-specific genome algorithms for care.

The challenges of translating genomic technologies into health care practice require novel approaches to educate existing and future health care providers. The future provider workforce must be armed with core principles of genomics, the ability to critically evaluate applications, and familiarity with the implications of genomic information in social and personal contexts. Experiential learning via a personal genome analysis can reinforce these concepts. Pedagogical approaches using personal genome testing of health care providers are likely to be beneficial when the focus of the course is on critical evaluation of dynamic concepts in human genomics. NCMJ

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Direct-to-Consumer Genomic Testing Offers Little Clinical Utility but Appears to Cause Minimal Harm

Stacie D. Adams, James P. Evans, Arthur S. Aylsworth

Direct-to-consumer genomic testing is available to anyone willing to pay for it. We investigated the reliability and reproducibility of such testing by sending DNA samples to 2 popular companies and by reviewing current literature on this topic. The concerns that were initially raised about direct-to-consumer genomic testing still seem valid.

With direct-to-consumer (DTC) genomic testing, an individual can send off a DNA sample, order tests, and receive results without an independent health care provider serving as an intermediary [1]. Some have hailed the availability of DTC genomic testing as a positive step that allows individuals to take charge of their health care; others point out that such testing can be unreliable, that the results can be misleading, and that such testing may cause more harm than good.

Since 2008, when *Time* magazine hailed 23andMe's DTC genomic testing as the invention of the year [2], this industry has expanded significantly. For $99, 23andMe now promises to deliver information regarding risk markers for 120 diseases; carrier status for 50 genetic disorders; 24 drug responses; and 60 traits, ranging from eye color and earwax type to muscle performance and reading ability [3].

Proponents of DTC genomic testing tout its potential to motivate lifestyle change and to increase vigilance for health conditions. Skeptics point out that existing data do not suggest that providing this kind of genetic risk information meaningfully affects a patient's lifestyle, and they note that increased vigilance is of questionable value when dealing with diseases that cannot be prevented.

In the early days of DTC genomic testing, there were concerns that the advertisements for such testing overstated the value of the testing, inappropriately suggested a deterministic relationship between genes and disease, and/or reinforced invalid notions about the relationships between diseases and ethnic groups [4]. As the cost of the services offered by these companies declines and the claims regarding these services increase, it seems reasonable to investigate what consumers may actually gain from such information. It also seems prudent to ask whether DTC genomic testing has provided the health care revolution that was predicted.

In 2008, we compared the results of DTC genomic tests provided by 23andMe and DeCODEme, which were 2 of the leading commercial suppliers of such testing at that time (S.D.A. and J.P.E., unpublished data). We purchased 2 kits from each company. DNA samples from 2 individuals were sent to both commercial laboratories for analysis, allowing direct comparison of 2 sets of results for the same DNA sample. No phenotypic information was provided to the companies. The DNA samples used were acquired by the International HapMap Project, which was launched in 2002 to identify "common patterns of DNA sequence variation in the human genome" (haplotypes) and to provide public access to that information [5]. HapMap samples are publicly available through the nonprofit Coriell Institute for Medical Research [6].

There were 14 health conditions for which both companies reported relative risk information. For 5 of these 14 health conditions—colorectal cancer, Crohn disease, heart attack, prostate cancer, and restless leg syndrome—one of the companies reported an increase in relative risk and the other company reported a decrease in relative risk (Table 1). The significance of relative risk changes was overemphasized, given that they were associated with very small changes in absolute risk. For example, one of the companies told both patients that their test results indicated a relative risk of 0.47 for celiac disease. With an absolute risk of 0.08%, however, this translates to an absolute risk reduction of approximately 0.04%. Even for conditions posing larger absolute risks, such as heart attack, the modest changes in risk represented by the 2 companies' relative risk estimates (0.83 and 1.18 for one patient in this analysis) were not meaningful enough to affect medical management.

We concluded that, although customers might find their risk profiles interesting, this information provides no guidance for physicians trying to make informed clinical deci-

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TABLE 1.
Estimates of Relative Risk From 2 Companies Performing Genomic Testing on DNA Samples From the Same 2 Individuals

	Relative Risk			
	DNA sample 1		DNA sample 2	
Condition	23andMe	deCODEme	23andMe	deCODEme
Age-related macular degeneration	0.62	0.25	0.62	0.25
Breast cancer	1.13	1.16	0.87	0.96
Celiac disease	0.47	0.38	0.47	0.24
Colorectal cancer	**0.99**	**1.15**	1.02	1.16
Crohn disease	**0.91**	**2.29**	0.56	0.88
Heart attack	0.99	0.87	**1.18**	**0.83**
Multiple sclerosis	1.37	1.52	2.69	2.41
Obesity	1.02	1.05	1.17	1.37
Prostate cancer	**1.03**	**0.85**	1.53	2.39
Restless leg syndrome	**0.75**	**1.60**	**0.75**	**1.06**
Rheumatoid arthritis	1.38	2.32	0.41	0.49
Type 1 diabetes	0.56	0.46	0.04	0.01
Type 2 diabetes	0.81	0.76	0.62	0.58
Venous thromboembolism	0.98	0.88	0.98	0.88

Note. Relative risk was reported to be increased by 1 company and reported to be decreased by the other company for 5 of the 14 health conditions for which both companies reported such information: colorectal cancer, Crohn disease, heart attack, prostate cancer, and restless leg syndrome. One sample had 4 discordant results and the other sample had 2 discordant results; the discordant relative risk values are in boldface type.

sions. The insubstantial magnitude of the risk information raised doubts about clinical validity. Moreover, there were sometimes substantial differences between the 2 companies in the level of risk reported, which calls into serious question the analytic validity of the findings.

A possible limitation of our findings is that these analyses were performed in 2008. However, the US Government Accountability Office (GAO) conducted a more extensive study in 2010, results of which were reported in testimony before members of the House of Representatives [7]. This study found similarly disturbing mismatches among the risk results provided by different leading DTC companies when identical samples were analyzed (Table 2).

Critics of DTC genomic testing have argued that companies' claims are misleading and could cause patients unnecessary worry or harm. The GAO study, which analyzed the results of 10 tests from 4 different companies, was particularly critical of the DTC genomic testing industry [7]. The following major concerns were raised in the GAO report: Some predictions of risk conflicted with the patient's known medical conditions (eg, a subject with irregular heartbeat was told that he was at decreased risk for developing such a condition); different companies made contradictory risk predictions for the same condition in the same patient (Table 2); the companies made misleading claims (eg, none of the companies was able to provide African American or Asian individuals with complete test results, although this limitation was not explicitly disclosed prior to purchase); and good-quality expert advice was lacking (follow-up consultations failed to provide the expert advice that had been promised) [7].

TABLE 2.
Contradictory Risk Predictions for Prostate Cancer and Hypertension Provided by 4 Different Companies Using DNA Samples From a 48-Year-Old Male Donor

	Risk prediction			
Condition	Company 1	Company 2	Company 3	Company 4
Prostate cancer	Average	Average	Below average	Above average
Hypertension	Average	Below average	Above average	Not tested

Source: This table is adapted from a report of a study by the US Government Accountability Office [8].

Furthermore, the GAO study found "10 egregious examples of deceptive marketing" [7], including claims that a consumer's DNA could be used to create a personalized supplement to cure diseases, claims that a company's supplements could "repair damaged DNA" or cure disease, and claims that testing could predict what sports a child would excel in. Finally, the report states,

> Perhaps most disturbing, one company told a donor that an above average risk prediction for breast cancer meant she was "in the high risk of pretty much getting" the disease, a statement that experts found to be "horrifying" because it implies the test is diagnostic.

Authors of a recent update on cardiovascular genomics concluded that "currently there are no clinically recommended genetic tests for many common forms of [cardiovascular disease] even though direct-to-consumer

Direct-to-Consumer Nutrigenomic Testing:
Is It Valuable in Spite of Its Limitations?

Monica Gulisano

Genetic testing is available for nearly 300 specific targeted mutations associated with various disorders [1]. Advances in genomic technology such as genome-wide association studies (GWAS) made possible the discovery of many such associations, and these advances have also ushered in an era of direct-to-consumer (DTC) genomic testing. Such testing is marketed directly to consumers, who can purchase it without any involvement on the part of their health care provider. There has been much discussion about regulation of such testing (and regulation of the marketing claims made regarding such testing), but DTC genomic testing is currently not regulated in the United States [2]. A 2008 survey [3] found that 23 companies were providing DTC genomic testing, and a 2012 review [2] found that 12 of those companies continued to offer such services.

Over the past decade, great advances have been made in discovering the genetic basis of monogenic diseases such as Tay-Sachs disease and cystic fibrosis, but finding meaningful associations between genetic variants and polygenic diseases such as diabetes, cancer, and cardiovascular disease is more difficult and will require more time. The clinical validity of currently available DTC nutrigenomic tests is limited, because the associations that have been discovered between gene variants and health conditions such as obesity and cancer are only small pieces of the puzzle; an individual's risk of disease ultimately results from the interaction of many genetic and environmental factors, only some of which are understood [2].

The idea of receiving nutrition recommendations based on one's unique genetic makeup is certainly attractive and can be perceived as empowering, especially in an age that calls for consumers to take charge of their own health. A recurrent marketing theme employed by companies that offer DTC genetic testing is to evoke a sense of empowerment in consumers by giving them genetic information; however, such marketing often fails to clearly disclose the lack of evidence for the tests' claims and the limitations in their ability to predict risk [4].

One of the presumed benefits of genetic testing is its potential to motivate lifestyle changes, although the ability of such testing to encourage healthy behavior is disputable [2]. Current research suggests that consumers believe that they will change their health behavior once they know their genetic test results. However, studies of actual changes in behavior after people receive the results of genetic testing have come to mixed conclusions. In a randomized trial of the use of personalized genetic risk counseling to motivate diabetes prevention [5], subjects were randomly assigned to receive genetic testing or no genetic testing. Those who had been tested were then ranked from highest to lowest risk, and those in the top and bottom quartiles were enrolled in a diabetes prevention program along with untested control subjects. Few significant differences were found in motivation, program attendance, and weight loss when the lowest-risk and highest-risk groups were separately compared with the control group [5].

One of the concerns surrounding DTC genetic testing is that it could cause consumers undue psychological stress and anxiety. However, studies that have investigated whether or not this is the case have not found data

genetic tests are being marketed to healthcare providers and the general public" [8].

In 2011, a survey showed that DTC genomic testing companies were offering testing for a host of mental health–related conditions—including alcohol dependence/abuse, autism, depression, nicotine dependence, schizophrenia, and smoking [9]—despite evidence that the markers being measured contribute only a small proportion of the genetic contribution to these conditions [10]. Although there seems to be strong public interest in testing for susceptibility to psychiatric disorders, little is known about the impact on individuals of receiving the results of such genetic tests [11]. Moreover, the low predictive power and uncertain clinical validity of DTC genomic testing for psychiatric disorders leads to significant difficulty interpreting such test results.

Further contributing to the potential for confusion among consumers are claims made by companies on their Web sites and in their marketing materials. The 23andMe Web site (https://www.23andme.com/) currently displays a link to a "life-changing story" about a woman who suffered from gastrointestinal symptoms for years before her doctor suggested DTC genomic testing, which revealed an elevated risk of celiac disease. This prompted her physician to obtain standard clinical testing, leading to a diagnosis of celiac disease in both the patient and her daughter. Such claims conflate marginally elevated risk assessment with diagnostic testing, the former being no substitute for appropriate clinical assessment and diagnostic evaluation.

Critics have worried that the confusion created by complicated risk profiles in the absence of proper genetic counseling may provoke unnecessary fear and worry in consumers. Current data, however, have not shown this to be a significant cause for concern. In a 2011 study, patients expressed no significant worries [12]. A more recent study showed that most consumers of DTC genomic testing services showed no difference in anxiety after long-term follow-up, compared with baseline, and 98.6% of respondents reported no test-related distress [13].

Nevertheless, geneticists are becoming aware of anecdotal incidents suggesting that some consumers may be

to substantiate that concern [6, 7]. This may be because consumers who purchase such tests tend to have high educational levels and knowledge of genetics [2].

Some companies claim to offer a genetically tailored diet plan and nutritional supplement recommendations that will protect against the diseases to which an individual is genetically predisposed and/or that will compensate for loss of function caused by a genetic variant. A study by the Government Accountability Office [8] failed to find support for these claims; instead, this study found that the advice offered usually consists of only standard sensible dietary suggestions and lifestyle recommendations.

The research community insists that current work in nutrigenomics is merely the tip of the iceberg and that it is still premature to determine the validity and utility of such testing. In the meantime, existing nutritional recommendations should be followed. For example, to decrease blood pressure and the risk of cardiovascular disease, diabetes, and certain cancers, patients should be encouraged to follow current evidence-based guidelines with regard to everyday eating and to consume a balanced diet—one containing a colorful and plentiful variety of vegetables and fruits; moderate amounts of lean animal and/or plant proteins, healthy fats, and whole grains; and appropriate calcium sources. Patients should also be encouraged to avoid consuming too many calories and to cultivate an emotionally healthy approach to eating. At the present time, personalized advice on how to accomplish these goals will be more helpful to patients than personalized genomic test results. NCMJ

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suffering as a result of DTC genomic testing, and there is certainly a potential for serious untoward incidents. 23andMe is now testing for the *APOE4* variant associated with increased risk for Alzheimer disease, as well as for several *BRCA1* and *BRCA2* mutations, which are associated with risk of breast and ovarian cancer. Reports of these test results are "locked," and there is genetic counseling information provided on the Web site, but all it takes to unlock these results is the click of a button. The Web site forums reveal that a number of individuals are concerned after learning that they are homozygous for the *APOE4* allele.

Positive outcomes from DTC genomic testing have also been reported. A small study carried out by 23andMe included 11 women and 14 men who had received an unexpected test result—the finding of a *BRCA1* or *BRCA2* mutation—and none of them reported more than transient moderate anxiety [14]. Furthermore, most of these individuals sought medical advice that resulted in confirmatory testing, risk-reducing procedures, screening of at least 30 relatives, and identification of 13 additional mutation carriers.

A major claim made by proponents of DTC testing is that simply knowing whether one is at increased risk for a particular condition may be enough to motivate significant lifestyle change. Some studies of DTC genomic testing customers have shown a trend toward both intended and actual behavior changes in individuals who learn that they may have a greater risk for conditions such as colon cancer [12, 15]. However, it is important to keep in mind that early adopters of DTC genomic testing services are likely to be among those most motivated to make health-related changes.

Those who work in primary care know that changes in patient behavior require more than just information, such as knowledge of cardiovascular disease risk factors or statistics regarding the impact of cigarette smoking on common health conditions. Although the notion of using genomic data to encourage preventive health strategies is appealing, early studies suggested that only a minority of consumers act on this information [16-20]. Furthermore, a primary care visit often includes collection of a family health history that identifies relatives with early heart disease or type 2 diabetes,

which will provide much more relevant data regarding relative risk for these genetically complex, multifactorial conditions than data obtained through current DTC genomic testing. A 2012 study [21] compared individuals who had been recently diagnosed with familial hypercholesterolemia through DNA testing with individuals who had no known genetic predisposition to cardiovascular disease (CVD) but who had a positive CVD-risk profile based on family history, cholesterol levels, and blood pressure. Those with positive findings on DNA testing had a higher perceived risk of CVD, but the 2 groups did not differ in the degree to which they attributed their risk to lifestyle or in their preventive behaviors [21].

The DTC genomic testing industry may expand in the future, but so far neither the benefits nor the risks have been as great as were initially predicted. In the future, North Carolina physicians will see more patients who want help deciding whether to pursue DTC genomic testing services, as well as patients who want advice regarding how to interpret their test results. At the present time, these results can generally be regarded as being largely of entertainment value. Only in rare cases will DTC genomic testing provide relevant health information to consumers, and it often produces data of uncertain validity. In our opinion, patients are currently better off spending their money on a gym membership (and then using it!) rather than parsing their genetic risks through DTC genomic testing.

The need for physician education is also a salient issue [22]. A survey of academic family physicians in the United States and Canada showed that a majority felt they were not knowledgeable about available genetic tests [23].

In summary, concerns regarding DTC genomic testing include both analytic validity and clinical validity. Currently, analytic validity is highly problematic—as illustrated by the fact that risk estimates from different companies for the same individual vary significantly, and the companies sometimes provide contradictory recommendations—which highlights the fact that no one yet understands how to validly interpret genomic data [24]. Clinical validity is also an area of concern, because the "risks" being reported are frequently insignificant, especially compared with the risk information that a physician can obtain by collecting a good medical and family history.

A central axiom of medicine is the admonition *primum non nocere* (first, do no harm). The wisdom of this insight remains instructive today, reminding us to remain cautious and vigilant in our treatment and testing, regardless of how superficially attractive DTC genomic testing may appear. NCMJ

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The NCGENES Project:
Exploring the New World of Genome Sequencing

Ann Katherine M. Foreman, Kristy Lee, James P. Evans

Massively parallel sequencing (MPS) is now a clinical reality, promising improved diagnosis, targeted therapies, and population-based screening. To realize the potential of genomics, we must learn how to apply this technology optimally. The NCGENES project is designed to address several challenges that must be overcome in order to integrate MPS into clinical care.

On April 14, 2003, the Human Genome Project was completed, resulting in a high-quality human reference genome and the promise of a new era of genomic medicine. Massively parallel sequencing (MPS), also known as next-generation (NextGen) sequencing, has made the rapid sequencing of vast quantities of DNA practical. The technology has transitioned rapidly to the bedside, where whole-genome sequencing (WGS) and whole-exome sequencing (WES) are now being pursued widely in a research context and are clinically available from a few laboratories nationally. WES and WGS have fueled excitement about the potential for improved diagnosis of genetic disease, targeted cancer therapies, and even population-based screening. Although the promise of genomics is great, its application presents a multitude of challenges, which stem from the massive amounts of heterogeneous data generated when a patient's genome is analyzed.

Ideally, the clinical implementation of genomic medicine will be guided by evidence-based best practices. The National Human Genome Research Institute, an institute of the National Institutes of Health, has developed the Clinical Sequencing Exploratory Research (CSER) program to investigate the optimal integration of MPS into clinical practice. The North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing (NCGENES) project, a grantee of the CSER program, is an effort to systematically study the most critical challenges in the integration of genomic medicine into clinical care.

The human genome is simply the total complement of DNA in a person. It includes *exons*—those parts of our genes that encode proteins—as well as noncoding *introns* and the regions of DNA between genes. The *exome* is the totality of those parts of our genome that encode proteins; it constitutes approximately 1% of the human genome [1]. Analysis of the exome is less costly than WGS (Table 1) and provides most of the clinically relevant information, because the vast majority of harmful variants or mutations that cause genetic diseases reside in the exome. Thus WES is currently used more often than WGS in clinical settings.

TABLE 1.
A Comparison of Traditional Sanger Sequencing, Whole-Exome Sequencing, and Whole-Genome Sequencing

Variable	Traditional Sanger sequencing	Whole-exome sequencing (WES)	Whole-genome sequencing (WGS)
Scope of test	1 gene or panel of genes for a specified phenotype	All protein-encoding genes	All protein-encoding genes and intervening DNA
Total number of variants	Few; dependent on the number of genes sequenced	~80,000–100,000	~3–4 million
Scope of results	Includes only information pertinent to gene(s) requested	Includes results pertinent to clinical indication and possibly significant incidental findings	Includes results pertinent to clinical indication and possibly significant incidental findings; higher likelihood of uncertain results
Turnaround time	~1–12 weeks	~10–15 weeks for targeted analysis; ~24–28 weeks for complete analysis	~12 weeks
Cost	~$500–$17,000, depending on the number of genes sequenced	~$4,500–$6,000	~$9,500

Note. WES and WGS are already cost-competitive with Sanger sequencing panels; however, the 3 types of sequencing differ greatly in the scope of testing and the number of resulting variants.

Genome-scale sequencing has been made possible through advances in technology that allow millions of sequencing reactions to occur simultaneously on a single microchip or flow cell—hence the term *massively parallel sequencing* (Figure 1). DNA derived from a blood sample

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Crowdsourcing to Define the Clinical Actionability of Incidental Findings of Genetic Testing

Matthew S. Krantz, Jonathan S. Berg

Genome-scale sequencing may soon be cheaper than targeted assays as a clinical diagnostic tool. However, these larger queries will turn up many incidental findings—that is, unanticipated information discovered during the course of testing. Implementation of genome-scale sequencing in the clinical setting will require novel methods for managing these incidental findings.

In order to grapple with our ever-changing knowledge of genetic disease and to make recommendations regarding minimal standards for reporting of incidental findings, a "binning" system for the management of such findings has been proposed; this system is based on both clinical utility and clinical validity [1]. Clinically actionable incidental findings (eg, Marfan disease) go into bin 1; these incidental findings are likely to be rare and would be reported to an individual because of high penetrance and the existence of evidence-based management recommendations. Incidental findings that have clinical validity but no clinical actionability go into bin 2; these findings require informed decision making on the part of the individual and would only be reported to the patient on request. In these cases, there may be a strong association between genotype and phenotype, but no immediate intervention exists; an example is *APOE* risk alleles that are associated with the onset of Alzheimer disease. As effective evidence-based interventions emerge for bin 2 variants, their classification will change. Finally, most genes currently have no known clinical significance. Variants of these genes go into bin 3, and these incidental findings would not be reported.

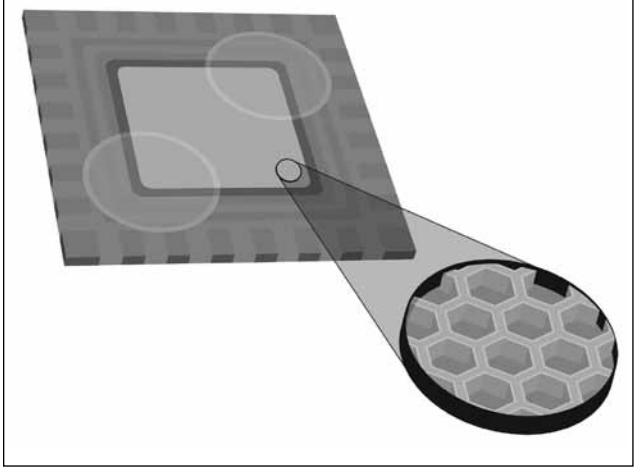
Although not strictly analogous, the bin 1 variants described above are similar to the incidental findings included on the minimal reporting list published by the American College of Medical Genetics and Genomics (ACMG) [2]. The ACMG working group that developed this list noted that their recommendations were hampered by lack of data on clinical utility and the need for a process by which recommendations could be updated regularly. The binning system described here tackles the lack of data on clinical utility and creates a process amenable to revision as new literature emerges.

So far, binning of genes has been provisional [3] and has been based on consensus among a small number of evaluators. In order to refine this approach into a more fully transparent, reproducible, evidence-based process, members of the North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing (NCGENES) team developed a semiquantitative metric that scores an incidental finding based on several key criteria: threat to health, chance of disease, efficacy of intervention, intervention acceptability, and knowledge base. This process yields a minimum total score of 0 (for genes with no known clinical relevance) and a maximum score of 15. A higher total score on this semiquantitative metric correlates with a greater degree of clinical actionability, which will hopefully allow us to

or saliva sample is sheared into fragments and processed to form a genomic "library." The processed fragments are loaded onto test chips for sequencing, and then each of the millions of sequenced fragments is mapped to the human reference genome, allowing assembly of an individual's genome. Once assembled, all variants from the reference sequence are interpreted with respect to whether they are innocent variations or whether they might cause disease. The magnitude of this task can be appreciated by noting that each person harbors approximately 100,000 variants that would be detected by exome sequencing. Most of these variants are innocuous, but a small minority might be responsible for disease. Identifying the few needles of clinically useful information in this haystack of data is a complex undertaking. Initial analysis is automated using computer software that classifies variants by type (eg, nonsense, missense, synonymous, or splice site variants). Interpretation is further aided by information such as how often a variant is found in the general population and prediction models that help assess the possible biological implications of variants. However, interpretation of a WES or WGS test still requires that experienced personnel spend substantial time combing through pertinent literature and databases to determine whether individual variants might be relevant to a patient's disease.

As is the case with any complex medical technology, the clinical potential of genomics cannot be fully realized until

FIGURE 1.
Massively Parallel Sequencing Involves the Use of Microchips That Can Perform Millions of Sequencing Reactions Simultaneously



set thresholds for determining placement of an incidental finding into bin 1, 2, or 3.

Reaching consensus regarding medical actionability will require multiple evaluations, and it is neither feasible nor desirable for a single working group to score all genome-scale incidental findings. Instead, having a robust number of evaluators will allow for greater diversity of opinion and expertise.

Crowdsourcing has been shown to be a powerful tool for answering scientific questions that require a wide array of input. Crowdsourcing employs distributed problem solving by engaging the public through open-source interfaces. Proteomics research has been accelerated by utilizing the collective intelligence of the crowd through the online game Foldit, in which players attempt to solve protein structures. Some compelling successes have been achieved using this approach; for instance, players modeled the crystal structure of the Mason-Pfizer monkey retroviral protease, which has provided insights that may be useful in the development of anti-HIV drugs [4].

Other areas of genetic research have also harnessed crowdsourcing. SNPedia is an online, open-access wiki project that allows users to input information about single nucleotide polymorphisms obtained from peer-reviewed journals into a computer-friendly format [5]. In another example of crowdsourcing, the Personal Genome Project aims to pair genomic and health data supplied by participants. The project is approved to study 100,000 participants and shares all information in the public domain, making it available for research [6]; to date, more than 1,800 people are enrolled. Although efforts are made to remove personal identifiers from the data, the Personal Genome Project operates under the premise of open consent, meaning that participants are not given promises of privacy, confidentiality, or anonymity.

We propose that the scoring of incidental findings using a semiquantitative metric could also be amenable to crowdsourcing. Defining medical actionability through crowdsourcing allows multiple annotators to provide scores for a gene-phenotype pair, and information can be updated as new evidence emerges. More genetic conditions will likely become medically actionable over time. It is essential, then, to choose an evaluation process that is highly adaptable to evolving medical research; crowdsourcing offers this flexibility. NCMJ

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we learn how to apply it optimally. This task is complicated by the limited scientific understanding of the impact of genetic variation on health. For the time being, WES will be most fruitful if it is performed in patients who are suspected of having a disorder that primarily arises from disruption of a single gene and who have defied diagnosis by standard means. Good candidates for WES include undiagnosed patients who exhibit a strong family history of the enigmatic disorder; those who appear to have a genetic disorder that can be caused by disruption of a variety of different genes; and those who exhibit complex patterns that are likely to result from a genetic disruption, such as developmental disorders or progressive neurological conditions. In the case of cancer, a strong genetic component to disease would be suggested by a young age at diagnosis or other unusual features (male breast cancer, for instance).

Even when several of these indicators are present, a more specific single-gene test or limited test panel will often be a more appropriate choice than WES or other broad, MPS-based genetic tests. For example, consider a 25-year-old woman who was recently diagnosed with bilateral renal cysts and whose family history includes a father who died of end-stage renal disease related to renal cysts; in this case, sequencing of the 2 genes responsible for autosomal dominant polycystic kidney disease, *PKD1* and *PKD2*, is likely to identify the underlying reason for the patient's disease more quickly and more cost-effectively than WES or WGS. MPS is likely to be more advantageous in cases of genetic heterogeneity, in which a patient's phenotype could be caused by a mutation in any one of a large number of genes. For example, more than 12 genes have been associated with long QT syndrome, and comprehensive testing for this condition using traditional sequencing can be a lengthy and costly endeavor.

NCGENES is seeking to define optimal applications of

WES by analyzing approximately 750 children and adults with suspected Mendelian genetic disorders who have eluded diagnosis by traditional means. Care has been taken to enroll participants with a variety of indications, including cancer, cardiogenetic diseases, neurodevelopmental disorders, and retinal diseases. Thus data from NCGENES will help to identify which types of patients are most likely to benefit from application of WES.

Costs of genomic analysis are expected to become comparable to the cost of single-gene tests in the near future. When that happens, there still may be compelling reasons to select a test with a specific focus rather than sequencing all of a person's genes. The breadth of information that WES yields will often result in false positives, identification of genetic variants of uncertain clinical significance (VUS), and incidental findings that are unrelated to the reason for ordering the test. These challenges must be understood before genome-scale sequencing can truly become a routine part of clinical care. In some circumstances, and for some patients, a traditional genetic test with a narrower focus will remain the best choice.

The chance of identifying a VUS increases with each gene analyzed, and identification of a VUS is virtually guaranteed when obtaining a genome-level test. The presence of a VUS essentially represents a potential false-positive result and can be confusing to patients and practitioners alike. Harm can ensue if a VUS is inappropriately treated like a positive finding; for example, follow-up of a VUS could prompt unnecessary screening or intervention, which exposes the patient to the risks of needless intervention and increases costs to the patient and the health care system. Even when providers appropriately recognize that medical decisions cannot be based on a VUS and offer genetic counseling, patients still may ascribe meaning to the variant, thus affecting their perception of their own health. In NCGENES, VUS are reported to participants only if they are considered a possible explanation for the participant's primary health concern; incidental VUS are not reported. The NCGENES team includes social scientists who will study the ethical and social implications of WES, including what impact, if any, the finding and reporting of a VUS has on participant perceptions of health compared with the impact of positive or negative diagnostic findings.

Incidental findings are not new in medicine; for example, unexpected tumors are sometimes identified on medical imaging. However, implementation of WES in clinical medicine invites incidental findings on a larger scale than has previously been seen in medicine. The majority of variants identified by WES or WGS will not be directly relevant to a patient's disease. Although the vast majority of these variants will have no clinical significance, it is important to recognize that a small portion of individuals undergoing WES will have incidental findings (ie, findings unrelated to the reason for sequencing) that have profound clinical importance. If variants influencing reproductive risk are considered (for instance, carrier status for recessive diseases such as cystic fibrosis or sickle-cell disease), then every person who has a WES or WGS test performed will have genetic variants identified that are clinically valid yet unrelated to the indication for testing and thus incidental to the purpose of the test. In an effort to begin to define the obligations of laboratories and clinicians, the American College of Medical Genetics and Genomics has published general guidelines regarding those genes that should be routinely examined for deleterious mutations when genome-scale sequencing is performed in a clinical context [2].

About 1% of individuals undergoing WES are found to have an unexpected mutation (ie, an incidental finding) that confers a high risk of severe disease that can be prevented or largely mitigated by medical intervention (eg, incidental discovery of a *BRCA1* mutation). Table 2 provides examples of such genes and the conditions they strongly predispose to when mutated. At the present time, this is a small group of genes, and it is recommended that the data of patients who undergo WES be examined for mutations in these genes in order to detect profound predisposition to preventable but

TABLE 2.
Examples of Medically Actionable Incidental Findings From Genetic Sequencing

Genetic syndrome	Genes that may have mutations	Likely adverse outcome if untreated	Typical intervention
Hereditary breast and ovarian cancer	*BRCA1, BRCA2*	Breast cancer	Prophylactic bilateral mastectomy or surveillance every 6 months alternating between mammogram and breast MRI
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	Colon cancer	Colonoscopy with removal of polyps every 12–24 months
Hypertrophic cardiomyopathy	*MYBPC3, MYH7, TNNT2, TNN13, TPM1, MYL3, ACTC1, PRKAG2*	Sudden cardiac death	Placement of implantable cardioverter defibrillator
Long QT syndrome	*KCNQ1, KCNH2, SCN5A*	Sudden cardiac death	Beta blockers and periodic ECG
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*	Myocardial infarction	Twice yearly cholesterol screening, with statins to be prescribed when hypercholesterolemia is documented

Note. ECG, electrocardiogram; MRI, magnetic resonance imaging.
These are examples of genetic conditions that are recommended to be reported as incidental findings if known disease-causing variants are identified in the genes listed. Such genes may also be candidates in the future for routine screening in the general population to prevent disease.

unexpected disease [2]. All NCGENES participants' exomes are analyzed for such variants regardless of the original indication for WES. If a mutation is found in one of these genes, results are returned to the research participant (or his or her parent in the case of minors). NCGENES participants with medically actionable incidental results will be interviewed about their experience of receiving such a result.

For most of the variants discovered through WES, the medical response is not clear. For example, carrier status for recessive diseases does not have direct relevance to an individual's health and may have little or no personal relevance if they have no plans for future children. On the other hand, mutations in the *PSEN1* gene cause a highly penetrant, early-onset form of Alzheimer disease, which is relevant to health; however, there are no known interventions that can modulate the disease outcome. How many of us would want to know that we were all but guaranteed to develop Alzheimer disease by age 65 years? Would we even want to be offered that type of information? NCGENES is seeking to answer these questions by finding out what other information in the genome (besides medically actionable and diagnostic information) is desired by patients who undergo WES.

To address these questions, adult participants in NCGENES are randomized into 1 of 2 groups. Individuals in the control group receive diagnostic results (ie, results related to the suspected genetic condition for which they were referred to the study) and medically actionable information. Those in the experimental group likewise receive diagnostic results and medically actionable information, plus they will be asked to decide whether they want various other categories of incidental information, such as carrier status for recessive diseases, and whether they want to know about variants that affect the risk of Alzheimer disease and other conditions [3]. By studying participants in the experimental group and the extent to which they seek such information, and by comparing the control and experimental groups with respect to their satisfaction with the decision to undergo WES and their personal perception of health, this study will help guide future decisions about how to handle non–medically actionable incidental findings that arise during clinical WES and WGS.

Genomic sequencing holds great promise and presents significant challenges in the clinical arena. These challenges are heightened with regard to genomic approaches to public health [4]. It is unlikely that individuals in the general population will benefit anytime soon from WES or WGS. However, one can readily imagine that it might be useful to screen members of the general population for mutations in carefully selected genes that confer a very high risk of severe but preventable or treatable disorders, such as colon cancer or breast cancer [4]. Additional studies to address the potential of such efforts are under way now at the University of North Carolina at Chapel Hill.

The world of genomics is moving quickly and will play a growing role in the care of patients. It is vital that we work together to define best practices for implementation of this new, promising, and highly complex technology. NCMJ

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Genetic Epidemiology:
The Potential Benefits and Challenges of Using Genetic Information to Improve Human Health

Amanda A. Seyerle, Christy L. Avery

Genetic epidemiology has the potential to significantly affect human health. This commentary examines major developments in the field's history, promising avenues of research, and possible challenges faced by genetic epidemiologists.

Understanding the distribution and determinants of human disease is increasingly a priority in an age of burgeoning health care costs and rising disease burdens. At the crossroads of genetics and epidemiology is the field of genetic epidemiology, which examines the role of inherited factors in disease etiology. Current public health benefits of genomics research are numerous, including an improved understanding of disease mechanisms [1], targeted cancer treatments [2], and better dosage regimens for pharmaceuticals [3]. However, to fully appreciate the current and future contributions of genetic epidemiology to improving human health, it is necessary to understand the major milestones in genetic epidemiology and the current challenges researchers face in the ongoing process of deciphering the human genome.

Genetic epidemiology is a relatively new field. It was first described by Neel and Schull in 1954 [4, 5], when molecular genetics was still in its infancy. Although direct measurement of genotypes was not possible then, genetic epidemiologists investigated the inheritance of disease by examining whether patterns of inheritance (eg, dominant, recessive, X-linked) were consistent with phenotype patterns observed in large families. For example, early segregation analyses of breast and ovarian cancer suggested a strong genetic etiology with an autosomal dominant mode of inheritance [6, 7].

Linkage analysis, the framework for which was first published in 1980 [8], was a natural extension of segregation analysis. Made possible by technological advances that allowed the direct measurement of genotypes, linkage analysis used populations of related individuals to assess the genetic basis of disease; this technique successfully identified the genes responsible for numerous monogenic disorders, including Tay-Sachs disease, Huntington disease, and cystic fibrosis [9]. On a population level, however, linkage analysis failed to make inroads into the identification of genes associated with complex chronic diseases. For example, genes shown via linkage to be associated with rare familial forms of breast cancer in specific families, including variants in the *GPT* and *ACP* genes, showed no association with breast cancer in the general population [10].

Limitations of linkage analysis led researchers to investigate other approaches to the identification of genes associated with complex diseases, including candidate gene studies. Candidate gene studies, which use a priori hypotheses to evaluate the evidence for association between the outcome of interest and variants in or near selected genes, became popular because they provided greater power for detecting associations for complex traits; they also could be performed in population-based cohort and case-control studies [11]. Despite leveraging biological knowledge, few candidate gene studies successfully identified associations. For example, a 2009 review of studies of candidate genes for obesity found that, of 21 genes examined, only 9 had been shown to have any association with obesity [12]. In addition, very few positive results were replicated in subsequent studies [13, 14].

Occurring in parallel with the rise in popularity of candidate gene studies was the sequencing of the human genome by the Human Genome Project (HGP); the first draft of the human genome was published in 2001 [15]. The HGP, which sought to catalog human genetic variation by identifying all human genes and sequencing the 3 billion bases in the human genome [16], has had a lasting influence on the practice of genetic epidemiology. A significant advance made possible by the HGP was the ability to conduct large-scale human genome studies, including genome-wide association studies (GWAS), which allow researchers to test associations between traits of interest and changes in a single base pair. Such changes, which are referred to as single-nucleotide polymorphisms (SNPs), are spaced throughout the

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human genome [17]. The availability of large-scale GWAS greatly increased the coverage of candidate gene studies, which typically evaluated a small number of SNPs in a handful of pre-specified genes. Using GWAS, genetic epidemiology has made significant progress in unraveling the genomic etiology of complex diseases. As of August 2013, GWAS had found more than 11,000 SNPs to be associated with one or more of a wide variety of diseases or risk factors [18].

Notably, GWAS often identify pathways that are largely ignored by candidate gene studies. One such example is the association between obesity and the *FTO* gene, which encodes a messenger ribonucleic acid (mRNA) demethylase [19] and was identified through a fused-toe phenotype in mice [20]. Although not a compelling candidate for an obesity gene, *FTO* was one of the first obesity loci identified by GWAS, and this finding has been successfully replicated across studies and populations [20-25]. Novel findings such as the *FTO* gene have also prompted new avenues of inquiry in obesity research, including closer examination of the relation between the control of energy expenditure and obesity [12]. This highlights the ability of GWAS to illuminate novel biological pathways underlying disease etiology.

Despite notable successes, genetic epidemiology has yet to fully elucidate the genetic basis of disease. With obesity, for example, studies have consistently suggested that a substantial fraction (16%–85%) of the variation in body mass index (BMI) is genetic in origin [26-31]. Although GWAS have identified 36 genetic regions associated with BMI, these regions only explain a tiny proportion (less than 2%) of the estimated heritability of BMI [32, 33]. One possible source of the missing heritability is gene-environment interaction [34]. In epidemiology, it is commonly understood that diseases are caused by both genetics and the environment; this is true even for monogenic disorders such as phenylketonuria (PKU). For example, a child who has the genotype for PKU will not develop the disease unless he or she is exposed to phenylalanine. In a population-wide context, studies of gene-environment interactions involve determining whether an environmental factor governs the variation in the magnitude of association between a genetic variant and a complex trait. Because environmental exposures are often more amenable to intervention than are genetic factors, gene-environment studies may offer the best avenue by which genomic research can contribute to improving public health; of course, these studies also help identify the missing heritability for complex diseases [17].

One promising area in which to study gene-environment interactions is pharmacogenomics, which involves examining the genomic underpinnings of drug response in order to better understand adverse drug reactions and to tailor individualized treatments [35]. As of 2011, there were 70 drugs for which the US Food and Drug Administration (FDA) had approved new labeling that includes information on genetic variants that affect the metabolism of the drug [17]. The classic example is warfarin, an anticoagulant used to prevent blood clots and embolisms. Today, genes encoding the VKORC1 and CYP2C9 proteins are routinely evaluated in clinical settings when warfarin dosage regimens are being assigned [3, 36, 37]. Similarly, the discovery of variants in the *CYP2C19* gene that reduce a patient's ability to metabolize clopidogrel prompted an FDA announcement warning that this drug, an anticlotting medication used to prevent stent thrombosis, may not be effective in patients with specific genetic variants [38]. In response to that announcement, companies have developed new drug therapies that work effectively in all patients, regardless of their *CYP2C19* genotype [38]. However, pharmacogenomic research needs to be expanded to examine diverse traits and to include racial and ethnic minorities. The inclusion of minorities is especially important because most pharmacogenomic research has examined populations of European descent, even though many genetic variants—including many of the clinically actionable pharmacogenetic SNPs—vary substantially in frequency in ethnically diverse populations [39].

When the human genome was first sequenced, many believed it would positively impact both medicine and public health. Warfarin and clopidogrel highlight the translational potential of genetic epidemiology research for improved patient care, but most of the findings in genetic epidemiology to date have not had a noticeable impact on public health. One reason for the perceived lack of impact is that many of the current benefits of genomic research are indirect. In 2011 the National Human Genome Research Institute published a perspective on genetic medicine, observing that "the most effective way to improve human health is to understand normal biology (in this case, genome biology) as a basis for understanding disease biology, which then becomes the basis for improving health" [1]. Therefore it remains difficult to fully ascertain the future promise of genetic epidemiology for the advancement of public health.

Equally important when assessing future contributions of genetic epidemiology is the realization that disease etiology is complex, and that genetic risk does not equate to genetic determinism. The complex relationship between genetics and disease poses an ethical dilemma for health care practitioners regarding what to tell patients about the results of genetic tests. Genetic tests may yield incidental findings in addition to the sought-after results, because it is often more economical to sequence the entire genome than to genotype only specific regions. For example, a test for the Huntington mutation could also yield results for Tay-Sachs disease, breast cancer, or hereditary hemochromatosis [40]. There is debate as to whether patients should be told about these incidental findings, which may be of potential medical value. Recently, the American College of Medical Genetics and Genomics (ACMG) published a set of recommendations that emphasize the need to alert patients to such incidental findings; these guidelines even outline how specific incidental findings should be handled [41]. However, the ACMG article also points out that for many genetic risk

variants there is insufficient data to make a clear recommendation [41].

Incidental findings are also problematic in research settings, and many large studies have performed extensive genotyping of study participants. For example, in 2012, the Electronic Medical Records and Genomics (eMERGE) Network—a collection of archives and biorepositories, some of which perform GWAS—identified a subset of genetic abnormalities about which data are sufficient to warrant informing patients of their test results. However, the decision of whether to inform patients of their results was left to the individual repositories [42].

Unfortunately, physicians and patients are not well-informed about how to interpret incidental findings [43]. Reporting these results will only be valuable when both the physician and the patient understand what the genetic information means and how it can be incorporated into clinical care [1].

Although genetic epidemiology is potentially beneficial, it is important to understand that the role of genetic epidemiology in medical care is largely undetermined, with a few notable exceptions. Even with advances such as the HGP, many important questions remain unanswered, including how the genome differs in diverse populations, how the environment affects the genome, and what role is played by epigenetics (the study of heritable mechanisms that alter gene expression without altering the underlying genetic sequence). Given these questions, it is not surprising that it could easily be 2020 or beyond before genetics has any significant impact on public health [1]. Even as genetic findings become more translational, the general public and even many health care professionals do not yet have sufficient knowledge to use genetic information effectively. Efforts to educate both patients and practitioners are therefore integral to realizing the full potential of this quickly advancing field, and this education should parallel current advances in genetic epidemiology. NCMJ

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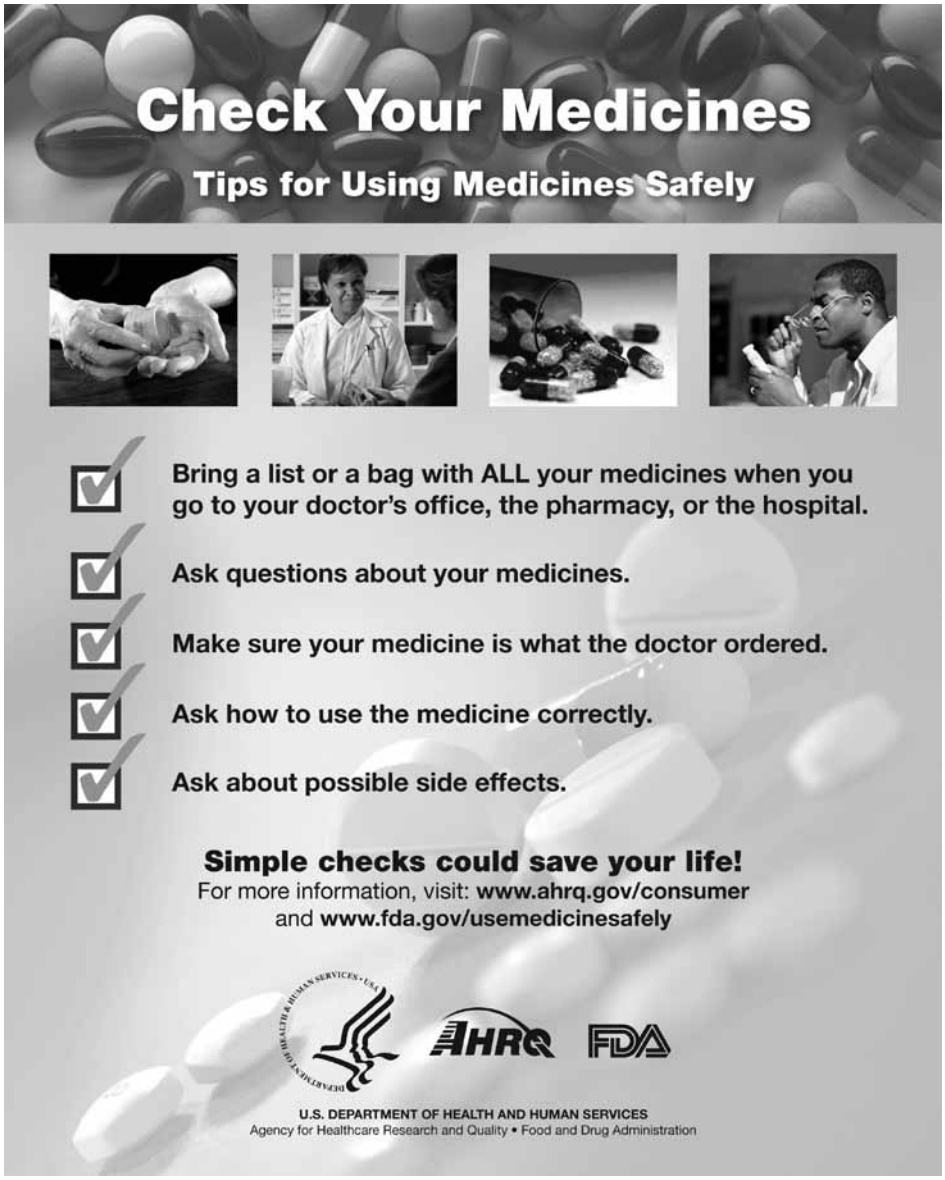

Integrating Personalized Genomic Medicine Into Routine Clinical Care:
Addressing the Social and Policy Issues of Pharmacogenomic Testing

Lynn G. Dressler

The provision of personalized genomic medicine presents significant policy challenges, such as ensuring equitable patient access to testing, preparing clinicians to manage genomic results, justifying test reimbursement, sharing genomic information for patient care, and protecting patients against misuse of genetic information.

Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?

T. S. Eliot, *The Rock* (1934)

Ten years after the completion of the Human Genome Project, we now have an incredible opportunity to apply the knowledge and technology gained from that effort. One of the most promising areas for translating genomic knowledge into routine clinical care is pharmacogenomics, which analyzes a patient's genetic makeup to predict responses to drug therapy. Pharmacogenomic testing can provide a path for the expansion of individualized genomic medicine to optimize a patient's health and can help to minimize the cost of care. However, implementing genomic testing to guide routine clinical decision making requires careful consideration of relevant social and policy issues, including the equitability of access to genomic tests and the preparedness of clinicians to use genomic information. These issues can either impede or facilitate successful integration of genomic information into clinical practice. They can also serve to drive public policy to support the implementation of such testing. Addressing these issues requires a transdisciplinary approach—one in which the goal is problem solving, rather than problem identification.

Clinical Utility of Pharmacogenomic Testing

Every individual inherits variations in DNA from each parent; these variations are passed down from generation to generation. When variations occur in genes that metabolize drugs, they can affect an individual's response to these drugs. By identifying these variations, pharmacogenomic testing can help to prevent or minimize toxic side effects and to maximize a drug's effectiveness. This information can be used to help guide clinical decisions—to choose a particular drug or drug dose, to select an alternate drug if one is available, or when no other drug is available, to carefully monitor drug response and provide supportive care to offset anticipated adverse events. Pharmacogenomic testing holds the promise of reducing health care costs (eg, by decreasing the number of hospitalizations for adverse drug events), avoiding unnecessary or ineffective therapy, and increasing patient adherence to drug therapy (because patients are more likely to comply with drug therapy that is effective and has minimal adverse effects). Although evidence-based data continue to be the most important factor influencing adoption of these tests in routine clinical practice [1], complex social and policy issues need to be addressed to ensure that all patients have the opportunity to benefit from clinically useful genomic tests (Table 1).

Consider the following clinical scenario:

A moderately overweight, 67-year-old white man with high blood pressure presents to his primary care physician with shortness of breath and a history of angina for the past 2 months. He is referred to a cardiologist and is seen in the cardiology clinic the following day, at which time cardiac catheterization is recommended. The cardiologist tells the patient that during the procedure it may be necessary to place a stent in his artery and to give him the antiplatelet drug clopidogrel. The patient is scheduled for a preoperative visit in 3 days. Although he has Medicare coverage, he is concerned about his finances, because most of the family's savings have been spent on treatment and care of his wife, who has multiple sclerosis. The couple may have to apply for Medicaid soon.

How can pharmacogenomics be clinically useful in this setting? Testing to help determine the patient's ability to metabolize clopidogrel may be helpful in this scenario. Clopidogrel is a prodrug that is converted to its active

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metabolite by the cytochrome P450 enzyme CYP2C19. Variations in the gene coding for the CYP2C19 enzyme can affect an individual's ability to activate the drug [2]. Up to 25% of white individuals in the United States have a variant allele that may result in reduced effectiveness of clopidogrel or drug failure, leading to stent thrombosis and risk of embolism [3]. Clopidogrel is one of several drugs that are required by the US Food and Drug Administration (FDA) to have a black-box warning recommending that patients undergo genetic testing before being given the drug (Table 2). If the patient has DNA variations that are associated with an inadequate response to clopidogrel, then the cardiologist can select appropriate alternate therapies, such as prasugrel or ticagrelor.

Dissemination of Information to Clinicians

For the patient mentioned above to benefit from *CYP2C19* testing, his clinicians must first be aware of the test and be prepared to utilize, interpret, and apply genomic test results to manage their patients. Numerous studies have indicated that physicians, pharmacists, and nurses do not feel well prepared to adopt and use pharmacogenomic tests [1, 4]. Clinicians need easy access to up-to-date, accurate information in order to determine the clinical usefulness and value of such tests for their practice and to decide whether and when to adopt these new tests. In 2009 the FDA recommended a change to clopidogrel's prescribing label to reflect recent publications identifying associations between *CYP2C19* variants and response to clopidogrel [5, 6]. Although clopidogrel is used in many settings, *CYP2C19* testing has value mainly for patients with acute coronary syndrome who are undergoing percutaneous coronary intervention (PCI) [2, 7].

The rapid pace of knowledge generation and the distillation of its clinical value require keeping careful track of the literature and evaluating its clinical utility—which many physicians do not have time to do. Fortunately, some resources can aid the clinician in making these assessments, including 2 efforts funded by the National Institutes of Health: the Pharmacogenomics Knowledge Base (PharmGKB) and the Clinical Pharmacogenomic Implementation Committee (CPIC). PharmGKB curates and synthesizes pharmacogenomic information in real time in a user-friendly database (http://www.pharmGKB.org). CPIC, a component of PharmGKB, consists of expert teams of clinicians who evaluate and publish guidelines for the interpretation and clinical application of pharmacogenomic test results [8]. Many of the CPIC guidelines relate to the drug-gene pairs associated with FDA black-box drug warnings (Table 2). However, additional resources for the clinician are needed. One option is to have point-of-care clinical decision support tools embedded in the electronic medical record (EMR); such tools can alert physicians to the existence of useful tests and can be systemized so that they are triggered at different points of care (eg, when the physician writes a prescription or when the pharmacist dispenses it) [9]. An in-house genomic medicine consultation service is another valuable resource [9]. Ideally, this service would be made up of an interdisciplinary team of experts who are available for education and for point-of-care evaluation and interpretation; these experts can work with a hospital's pharmacy and therapeutics committee as well as with clinicians, health information technology, and laboratories to provide tailored support services. Each of these efforts, however, depends on the efficient dissemination of accurate information to a network of clinicians. It is essential that education, training, and communication programs be tailored to the needs of clinicians at the local, regional, and state levels; that these programs be coordinated; and that they be developed for all clinicians to access and use.

Use of Electronic Medical Record Systems to Optimize Care

Consider a different scenario for the patient mentioned above. Instead of going to see his primary care provider and getting a referral, what if this patient suffers an acute episode at home? Now, rather than undergoing an elective procedure, he is rushed to the emergency department and admitted to the hospital for an emergency cardiac stent procedure. In this scenario, assume the patient's primary care physician knew about pharmacogenomic testing, had preemptively ordered a panel of tests during the patient's most recent annual visit, and already had the test result showing a *CYP2C19* variant associated with clopidogrel drug failure. Ideally, having interoperable EMR systems with a standard place for storing pharmacogenomic test results would allow the cardiology team to efficiently access this information at the point of care. The team could select an alternate ther-

TABLE 1.
Policy Issues Related to Genomic Testing

Information issues
Clinician awareness and preparedness
Dissemination of updated accurate information
Sharing of genomic information
Need for interoperable electronic medical record systems
Level of evidence needed for test approval, reimbursement, and endorsement
Resource issues
Assessment of clinical value added in order to justify expenditure for genomic testing
Reimbursement by health insurance providers
Appropriate economic models for assessment of impact of genomic testing
Social issues
Patient access and resources
Widening of the health disparities gap
Subgrouping, discrimination, and privacy concerns
Need for protections

apy, saving time and money by not ordering a test that had already been performed. Although there are federal incentives to implement an approved EMR system with interoperable capacity, in 2012 only 48.3% of office-based physicians in North Carolina reported having an EMR system that met basic criteria [10]. Pharmacogenomic test results, when they are available, are often buried in laboratory information and are not readily accessible for patient care. Cost, logistics, and lack of informatics technology support are significant barriers to the broad implementation and use of interoperable EMR systems. Additional incentives and support for such systems beyond what has already been established at the federal level [11] are needed to address this issue.

Level of Evidence Needed for Adoption and Reimbursement of Testing

Education, training, and EMR systems are insufficient to support the use of pharmacogenomic tests if there is variability in the levels of evidence needed for their approval, reimbursement, and endorsement. The Centers for Medicare & Medicaid Services (CMS) reimburse in the outpatient setting for *CYP2C19* testing and for each of the genetic tests mentioned in FDA black-box warnings (Table 2). Because third-party payers often follow the lead of CMS when making reimbursement decisions, CMS policy can have a significant impact on whether a test is covered. Although *CYP2C19* testing is strongly recommended by the FDA and is reimbursed by CMS for outpatients, some professional groups have not fully endorsed this test as a standard of practice [12].

Some of this variability may reflect the different thresholds of evidence and varying definitions of clinical utility sought by each stakeholder. Some of the variability also reflects the different sources of information that each stakeholder uses to make these assessments. The decisions made by CMS or professional groups, and the processes and policies that drive them, significantly influence clinicians who are considering whether to adopt new tests. Some clinicians will adopt tests early, some later, and some not at all [13]. A minimum level of evidence and consensus regarding the relevant criteria needed to satisfy definitions of clinical utility will promote more consistent assessment of genomic information.

Access to Care, Resource Allocation, and Health Disparities

In the first scenario for the aforementioned patient, the cost of testing (approximately $250–$350) would likely be reimbursed by Medicare, provided that the test was ordered in the outpatient setting and was clinically indicated (eg, related to a likely future PCI). CMS will not reimburse for preventive screening of the variant without medical necessity. Since the patient in this scenario could be considered to be at high risk for a subsequent PCI intervention, the test should be covered. However, if this patient were a Medicaid recipient, reimbursement as an outpatient would depend on where he was living, because the processes and sources of information for Medicaid reimbursement coverage decisions vary from state to state. To make things even more challenging, once the patient is admitted to the hospital, CMS reimbursement is based on the diagnosis-related group (DRG) code for the procedure, not for each individual test.

How can physicians and hospitals justify using limited health care resources to support pharmacogenomic testing? Data from my institution, regarding projected *CYP2C19* testing for inpatients undergoing a cardiac stent procedure involving clopidogrel, yielded the following conservative estimates of cost savings. For Medicare patients alone, cost minimization per year was estimated to exceed $500,000 (based on minimizing the length of the hospital stay and reducing 30-day readmission rates due to drug ineffectiveness). If these estimates and the evidence on which they are based are accurate, they support testing for all inpatients receiving cardiac stents.

A comprehensive economic analysis is understandably more complex. However, current economic models are insufficient to assess the potential impact of genomic testing, especially preemptive testing, which could affect an individual's health and associated health care costs over his or her entire lifetime [14]. Furthermore, by federal statute, CMS is currently not allowed to reimburse for preventive services unless authorized to do so by Congress [15]. Models for economic analysis, including the benefit of preemptive testing over an individual's lifetime, need to be developed and made accessible to members of Congress, physicians, and hospitals so that the impact of pharmacogenomic testing can be appropriately assessed.

A major concern related to the use of genomic information in health care is that it will exacerbate existing health disparities; this concern is especially relevant for states with large underserved populations, including North Carolina. The concern that testing will benefit only affluent patients and those with health insurance that covers the tests is borne out every day in other areas of health and genetics. As health care costs continue to grow and resources become even more limited, this continues to be a significant concern.

Subgrouping, Stigmatization, Discrimination, and Privacy

Although drug response can be related to a variety of nongenetic factors (eg, lifestyle, diet, cultural norms, environmental exposure, comorbid conditions, etc), the very nature of pharmacogenomic testing involves grouping patients based on genetic variations. Often these classifications or subgroups are associated with a particular ethnicity, ancestry, or geographic region of origin. Minimizing harm to already vulnerable populations can become even more challenging. When should markers of ancestry rather than race or ethnicity be used for testing decisions? When can ethnicity be useful?

To shed light on these issues, consider the drug carba-

TABLE 2.
Drugs with US Food and Drug Administration Black-Box Warnings Recommending Genetic Testing Prior to Use

Drug	Genetic test	Drug use for which test results are relevant	Implication of presence of genetic variant
Abacavir	HLA-B*5701 variant	First- or second-line treatment of HIV/AIDS	Potentially lethal hypersensitivity reaction
Carbamazepine	HLA-B*1502 variant	Epilepsy, bipolar disorder, and other applications in individuals of Han Chinese ancestry	Potentially lethal hypersensitivity reaction, especially in individuals of Han Chinese ancestry
Clopidogrel	*CYP2C19* variant	Antiplatelet therapy in patients undergoing percutaneous coronary intervention	Ineffective drug response; risk for stent thrombosis and other cardiac events
Codeine	*CYP2D6* variant	Pain management in children	Rare but potentially lethal response in children
Lenalidomide	Chromosome 5q deletion	Hematology, myelodysplastic syndrome, multiple myeloma	Chromosome 5q deletion indicates risk for high-grade toxicity
Tretinoin	PML/RARα fusion protein translocation	Oncology (multiple myeloma, acute promyelocytic leukemia)	Translocation predicts likelihood of drug response

Sources: PharmGKB Web site (http://www.pharmgkb.org/view/drug-labels.do) and US Food and Drug Administration Web site (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm).

mazepine, which is used for treating seizures and bipolar disease. Carbamazepine has an FDA black-box warning in its label that strongly recommends pharmacogenomic testing for the HLA-B*1502 allele in at-risk populations before prescribing this drug, as testing can predict potentially lethal hypersensitivity reactions. The variant allele HLA-B*1502 is associated with an increased risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in response to carbamazepine treatment [16, 17]. Both of these conditions can be fatal. In a case control study, 100% of the individuals with carbamazepine-induced SJS carried this HLA gene variant [16]. Although testing cannot predict with certainty which individuals with the HLA variant will develop or even die from SJS or TEN, it is clear that these individuals are at much greater risk for developing these potentially lethal reactions. Because the association between this gene variant and the hypersensitivity response is seen mainly in individuals of Han Chinese ancestry, testing and/or prescription of an alternative drug is advised for these individuals [17]. The test is not indicated for European Americans (whites) with no Asian ancestry. The benefit of knowing this information prior to using this drug is obvious, and one would hope that the information would be used appropriately; however, the opportunity for discrimination still exists, especially in situations where ancestry is assumed based on physical characteristics or surnames. Even without considering race or ethnicity, there is concern that genomic subgrouping may create new vulnerable populations.

Several federal and state laws are in place to minimize discrimination and misuse of information and to protect the confidentiality of genomic information and an individual's privacy. The Genetic Information Nondiscrimination Act of 2008 (GINA) [18] is a federal law prohibiting the use of genetic information, including family history, to discriminate against individuals in health insurance and employment [19]. Although GINA offers many levels of protection and has been enforced by courts, significant limitations exist. GINA does not apply to employers with fewer than 15 employees or to most military personnel [19]. Furthermore, GINA does not apply to life insurance, long-term care insurance, or disability insurance. Nonetheless, GINA is effective in minimizing misuse of genetic information.

The Health Information Portability and Accountability Act (HIPAA) provides privacy and security protections against unauthorized use or disclosure of personal health information, including genetic information [20]. HIPAA is not comprehensive protection, and many parts of this law are supplemented by GINA, especially in the employment setting. HIPAA applies to covered entities such as hospitals, health plans, and physician practices. HIPAA does not limit the disclosure of genetic information by insurers, nor does it apply to genetic information collected in some research settings, such as commercial industry [21]. The Americans with Disabilities Act of 1990 (ADA) [22] also provides some protection against discrimination on the basis of genetic information. In the employment sector, however, the protections offered when applying both the ADA and GINA are complex to interpret, especially regarding the language describing each law's protections for "asymptomatic individuals" compared with individuals "with manifest disease" [23]. In addition, many states have laws that address the use of DNA (eg, blood spot cards collected at birth) or in some way protect the confidentiality of genetic information or an individual's privacy. However, laws in different states vary a great deal in the protections they offer [24].

In conclusion, I want to emphasize that the use of pharmacogenomic testing to guide clinical care is not futuristic. This testing is already a reality, and assessment and application of genomic information will increasingly be an integral part of patient safety and quality of care measures. As the provision of health care transitions from a fee-for-service to a value-of-service environment, these assessments will become even more important. I have touched on only a few of the myriad policy questions and potential approaches to addressing them. Many other questions exist, and more will emerge as genomic information becomes a more routine part of medical care. Who should have access to genomic information, and when should incidental findings be communicated to patients? Who should oversee the quality of testing, control the approval process for drug and test devel-

opment, and give the pharmaceutical and biotechnology companies incentives to develop drugs and tests that target vulnerable populations, rare diseases, or resource-poor areas? As genomic medicine becomes integrated into our health care system, so too does the need to develop responsible policies and processes to address the associated social, economic, and information issues. NCMJ

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Update on Newborn Screening

Susan E. Sparks

Since phenylketonuria was first screened for in the 1960s, newborn screening has expanded to include more than 30 conditions. This commentary provides an update on newborn screening, including the follow-up of abnormal findings, the limitations of such screening, and the ethical questions that screening raises.

Newborn screening began in the 1960s as a way of detecting disorders that did not present with identifiable clinical features but that could be successfully treated if therapy was initiated early. Screening involves obtaining a sample of blood during the first 24 to 48 hours of life and looking for markers indicative of various disorders. A requirement of such screening is that each disorder being screened for must have a sensitive and reliable marker that can be detected by a simple, inexpensive test.

The prototype for newborn screening, which was also the first disorder to be screened for, is phenylketonuria (PKU), an inborn error of metabolism of the amino acid phenylalanine. Without treatment, PKU results in severe intellectual disability; however, if a phenylalanine-restricted, low-protein diet is initiated in the first few weeks of life, then intelligence remains normal or near-normal. PKU was initially screened for using a bacterial inhibition assay developed by Robert Guthrie [1], which relies on placing a blood sample on a plate with bacteria that cannot grow in the presence of high levels of phenylalanine. If there is too much phenylalanine in the sample, growth of the bacteria is inhibited, and the sample will appear to be surrounded by a "halo"—an area where there are no bacteria. The diameter of the zone with no bacterial growth is directly dependent on the amount of phenylalanine. If control amounts of phenylalanine are used in the same assay, then the amount of phenylalanine in the tested samples can be quantified. This method was soon applied to maple syrup urine disease (indicated by the detection of elevated leucine levels) and to homocystinuria (indicated by the detection of elevated methionine levels). In the 1960s, 37 states had laws supporting newborn screening for PKU.

In the 1990s, electrospray tandem mass spectrometry (MS/MS) methods were introduced into state newborn screening programs [2]. This methodology allows multiple analytes to be detected in a single blood spot sample. In addition to measuring levels of phenylalanine, leucine, and methionine, MS/MS can measure levels of other amino acids to identify certain urea cycle defects: citrullinemia, arginosuccinic aciduria, hyperargininemia, and the 3 types of tyrosinemia. An acylcarnitine profile performed by MS/MS also allows the detection of many organic acidemias, fatty acid oxidation defects, and other carnitine uptake and transporter defects.

All states now have laws mandating newborn screening. Each state independently determines which screening tests are done and what follow-up is provided [3]. In addition, states develop their own policies regarding sample collection, laboratory procedures, result reporting, and follow-up programs and education. Regarding consent for testing, most states have mandatory newborn screening with defined opt-out policies for parents [4].

Newborn screening has been extremely successful in improving the outcomes and decreasing the burden of PKU. With the expansion of newborn screening, however, states now vary significantly in terms of which disorders are screened for. In 1995 states mandated screening for an average of 5 disorders (range, 0–8); in 2005 this panel included anywhere from 4 to 45 disorders, depending on the state [5]. Because of this extreme variability, the Maternal and Child Health Bureau in the Health Resources and Services Administration of the US Department of Health & Human Services requested in 1999 that the American Academy of Pediatrics develop a national task force on newborn screening [6]. Subsequently, the Maternal and Child Health Bureau tasked the American College of Medical Genetics and Genomics (ACMG) with developing a process for standardizing state newborn screening programs, including deciding which conditions to include in the screening panel and providing guidelines for collecting and evaluating screening results [7]. The expert panel identified 29 core conditions and 25 secondary conditions that were to be included in a Recommended Uniform Screening Panel (RUSP). The Secretary of Health and Human Services endorsed the RUSP in 2010. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was also formed to pro-

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vide an evidence-based decision-making process for evaluating conditions that are nominated for inclusion in the RUSP [8]. In 2010 severe combined immunodeficiency and critical congenital cyanotic heart disease were recommended by the committee for inclusion in the RUSP and were approved by the Secretary of Health and Human Services, bringing the total number of conditions screened for to 31 (Table 1) [7, 9].

A majority of the disorders screened for require follow-up with confirmatory blood (biochemical) and/or genetic (molecular) testing by physicians who are experts in those disorders. In some states (including North Carolina), screening for cystic fibrosis actually involves genetic diagnostic testing as part of the screening process. In North Carolina, cystic fibrosis screening is a 2-tiered process. The first tier involves measurement of immunoreactive trypsinogen (IRT) levels. The 5% of samples with the highest IRT levels are then

TABLE 1.
Newborn Screening Panel: Core and Secondary Targets

Core panel				
Tandem mass spectrometry				
Acylcarnitines		Amino acids		
Disorders of organic acid metabolism	**Disorders of fatty acid oxidation metabolism**	**Disorders of amino acid metabolism**	**Hemoglobinopathies**	**Other disorders**
Isovaleric acidemia	Medium-chain acyl-CoA dehydrogenase deficiency	Phenylketonuria	Sickle-cell anemia	Congenital hypothyroidism
Glutaric acidemia	Very-long-chain acyl-CoA dehydrogenase deficiency	Maple syrup urine disease	Sickle-cell beta thalassemia	Biotinidase deficiency
3-hydroxy 3-methylglutaric aciduria	Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency	Homocystinuria	Hemoglobin SC disease (a variant of sickle-cell anemia)	Congenital adrenal hyperplasia
Multiple carboxylase deficiency	Trifunctional protein deficiency	Citrullinemia		Classic galactosemia
Methylmalonic acidemia caused by methymalonyl-CoA mutase deficiency	Carnitine uptake defect	Argininosuccinic acidemia		Hearing loss
3-methylcrotonyl-CoA carboxylase deficiency		Tyrosinemia type I		Cystic fibrosis
Methylmalonic acidemia caused by cobalamin disorder A or B				Severe combined immunodeficiency
Propionic acidemia				Critical cyanotic congenital heart disease
Beta-ketothiolase deficiency				
		Secondary targets		
Methylmalonic acidemia caused by cobalamin disorder C or D	Short-chain acyl-CoA dehydrogenase deficiency	Benign hyperphenylalanemia	Other variant hemoglobinopathies	Galactokinase deficiency
Malonic acidemia	Glutaric acidemia type II	Tyrosinemia type II		Galactose epimerase deficiency
Isobutyryl-CoA dehydrogenase deficiency	Medium/short-chain 3-hydroxy acyl-CoA dehydrogenase deficiency	Defects of biopterin cofactor biosynthesis		
2-methyl 3-hydroxy butyric aciduria	Medium-chain ketoacyl-CoA thiolase deficiency	Argininemia		
2-methylbutyryl-CoA dehydrogenase deficiency	Carnitine palmitoyltransferase II deficiency	Tyrosinemia type III		
3-methylglutaconic aciduria	Carnitine/acylcarnitine translocase deficiency	Defects of biopterin cofactor regeneration		
	Carnitine palmitoyltransferase IA deficiency	Hypermethioninemia		
	Dienoyl-CoA reductase deficiency	Citrullinemia type II		

Note. CoA, coenzyme A.
Source: Adapted from Watson et al [7].

subjected to a genetic testing panel that looks for more than 40 common cystic fibrosis mutations. An abnormal cystic fibrosis screening result is one in which 1 or 2 mutations are identified or the IRT value is greater than 175 ng/mL. If an abnormal result is found, a recommendation for confirmatory sweat testing is conveyed to the primary care provider.

Genetic testing is expected to become more commonplace in newborn screening in the future. This will require broader understanding on the part of providers, who may have to engage in potentially complicated and confusing discussions with parents about the newborn screening process and the test results. Research indicates that parents prefer that primary care physicians provide open, honest, informed communication about abnormal newborn screening results. Providers who avoid jargon, recognize parental distress, and encourage questions are rated higher. Knowing when to refer the newborn to specialists is also important [10].

Typically, laboratories relay newborn screening results to the primary physician within 2 weeks of receiving the sample. In North Carolina, results can also be accessed online through the newborn screening section of the North Carolina State Laboratory of Public Health (http://slph.state.nc.us/newborn/Reporting.asp).

The ACTion (ACT) sheets from the ACMG (http://www.ncbi.nlm.nih.gov/books/NBK55827/) are an excellent resource on newborn screening and abnormal screening results. Developed by an expert group with members from various specialties that deal with conditions involved in newborn screening, these sheets have been approved by the board of directors of the ACMG. For each marker, 2 items are provided: an ACT sheet, which describes the short-term actions a health professional should take in communicating with the family and initiating follow-up care of an infant who has screened positive for 1 or more conditions; and an algorithm, which presents an overview of the basic steps involved in determining the final diagnosis for the infant.

Although newborn screening is very effective, it does have limitations. Not all inborn errors of metabolism are included in the newborn metabolic screen, for a variety of reasons. In some instances, there is not an effective method of testing for a disorder using a blood spot sample; in other instances, the level of the metabolite does not differ between affected individuals and unaffected individuals. Another limitation is that screening may produce false-positive results (the screen is positive, but the individual does not have the disease) or false-negative results (the screen is negative, but the individual does have the disease). Because the goal of screening is to minimize the number of cases that are missed, false-positive results are very common; these results may lead to increased parental stress and may impair parent-infant bonding [11]. False-negative results are of even greater concern, because they mean that the screen failed to detect a condition for which early identification and treatment are crucial. Also, some diseases (including maple syrup urine disease, organic acidemias, and urea cycle disorders) may present clinically in the first couple of days of life, before the newborn screening results are available.

Some of the disorders currently screened for may not have clinical consequences. An elevated level of C5-OH acylcarnitine, which is the marker for 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency, can be detected in the blood spot of infants born to parents who may be carriers (or may have the disorder) but who have never had symptoms. While 3-MCC deficiency may be a common benign condition, identifying a baby as having 3-MCC deficiency may lead to unnecessary parental anxiety and inappropriate "labeling" of the baby.

In a 1968 report to the World Health Organization, Wilson and Jungner outlined 10 criteria that should be met prior to implementing screening for certain disorders [12]. Building on these criteria, the current Advisory Committee on Heritable Disorders in Newborns and Children has developed a process for determining which conditions should be added to the RUSP [8]. Specifically, a scoring system is used that assesses the magnitude and certainty of net benefit of screening (determined by reviewing the evidence in the literature and consulting experts). The committee also evaluates the feasibility of screening and the readiness of state newborn screening programs to adopt screening for the disorder.

Some disorders have been proposed to the Advisory Committee for which no good treatments are available, or for which only experimental treatments are available. Some of these disorders (eg, Krabbe disease, Duchenne muscular dystrophy, and fragile X syndrome) are currently included in pilot screening projects in some states. There is debate over the ethics of screening when the disorder has no proven treatment or cure (Krabbe disease), when disease onset is outside the newborn period (Duchenne muscular dystrophy), or when there are implications for additional family members (fragile X syndrome) [9].

There are additional concerns regarding newborn screening for cystic fibrosis. Unlike most screening tests, which require follow-up testing for diagnosis, the technology used for newborn screening of cystic fibrosis is a diagnostic test. Also, newborn screening for cystic fibrosis identifies not only affected individuals but may also identify carriers, who do not have the disorder, and there is the potential for confusion when relaying these results to parents [13].

Finally, there is debate over what to do with blood spot cards after screening has been completed. The federal regulatory standards of the Clinical Laboratory Improvement Amendments of 1988 require that results and cards be preserved for 2 years to allow for test verification and for quality improvement. How long the cards are stored beyond this period varies from state to state. A related issue is that only about half of states have laws addressing the use of residual sample on blood spot cards. Some states allow the blood to be used for public health and basic scientific research studies without requiring additional parental consent. This

practice is controversial, and legal disputes have occurred in several states [14].

As we celebrate the 50th anniversary of newborn screening, questions remain about how to maximize benefit and minimize harm [15]. While specialists will be primarily responsible for addressing these questions, primary care physicians also need to understand newborn screening in order to explain it to parents. As more disorders are added to the RUSP, physicians are more likely to be contacted with an abnormal screening result. Knowing how to approach these results and how to discuss them with parents will be crucial. Also, as genetic testing becomes more commonplace, newborn screening is increasingly likely to include use of diagnostic tests, so parents will need to be educated about the differences between screening tests and diagnostic tests. NCMJ

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An Overview of Prenatal Genetic Screening and Diagnostic Testing

Cheryl Dickerson

Although prenatal genetic testing has been available for more than 3 decades, the number of conditions that can be detected has increased exponentially over the past decade. This commentary describes currently available prenatal genetic screening and diagnostic tests and explores practical and social considerations related to prenatal testing.

Prenatal testing can involve either screening or diagnostic testing: *Screening tests* provide only a probability that the fetus is affected, whereas prenatal *diagnostic tests* can determine with near certainty whether a fetus has a particular condition. In some pregnancies, family history or parental age increase the chance that the fetus has a genetic condition, but most genetic conditions occur unexpectedly.

The first congenital conditions for which routine prenatal screening became available were Down syndrome (trisomy 21) and open neural tube defects such as spina bifida. Although these conditions have different etiologies, either can occur in any pregnancy, regardless of parental age, health, environmental exposure, or family history. Each year in the United States, approximately 1 in 2,950 babies is born with spina bifida [1] and approximately 1 in 700 is born with Down syndrome [2]. Most children with Down syndrome are born to women younger than 35 years, because women in this age group have the most pregnancies, but the chance of having a child with Down syndrome gradually increases with the age of the mother. Although there are myriad other genetic conditions that arguably result in more significant medical or developmental complications, the incidence of these other conditions is much lower; for instance, the incidence of spinal muscular atrophy is 1 in 10,000 births [3], and the incidence of Smith-Magenis syndrome is 1 in 25,000 births [4].

Following the introduction of second-trimester maternal serum screening for open neural tube defects and Down syndrome, additional screening tests became available for Down syndrome and other chromosomal aneuploidies, such as trisomy 18 and trisomy 13. These newer tests include first-trimester screening and noninvasive prenatal screening.

Maternal Serum Screening and First-Trimester Screening

Second-trimester maternal serum screening is available at 15–20 completed weeks gestation. In its current form, such screening uses the levels of 4 pregnancy-related hormones found in maternal blood and other variables, such as maternal age and race, to determine the probability that a fetus has open spina bifida, Down syndrome, or trisomy 18. First-trimester screening, performed at 11–13 completed weeks gestation, uses the levels of 2 pregnancy-related hormones found in maternal blood and variables such as maternal age and measurement of fetal nuchal translucency to arrive at probabilities that the fetus has Down syndrome or trisomy 18. (One laboratory that does first-trimester screening combines risk assessment of trisomy 18 with risk assessment of trisomy 13.) In a series of about 12,000 patients screened in North Carolina from 1978 to 1982, the detection rate for open spina bifida using maternal serum screening was found to be 83% [5]. For maternal serum screening and first-trimester screening, the detection rates for Down syndrome across all maternal ages are approximately 81% and 85%, respectively [6], whereas the detection rates for trisomy 18 across all maternal ages are approximately 60% and 90%, respectively [7, 8]. The false-positive rate for either type of screening for Down syndrome and trisomy 18 is typically 5% or less.

Ultrasound, Chorionic Villus Sampling, and Amniocentesis

If first-trimester screening or maternal serum screening yields an abnormal result with a specific risk assessment (eg, 1 in 100), then further evaluation is offered. How informative further evaluation is depends on gestational age, testing methodology, and the condition itself. A detailed anatomical ultrasound (level II ultrasound) can be performed as a screening procedure at 18–20 weeks gestation to look for anatomical characteristics of the condition in question. Approximately 50%–70% of fetuses with Down syndrome will exhibit one or more sonographic markers of the condition, and approximately 80%–90% of fetuses with trisomy 18 or trisomy 13 will exhibit one or more sonographic markers

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[9]. These sonographic markers can include variants such as echogenic intracardiac foci and choroid plexus cysts, as well as true malformations, such as heart or renal defects. Open spina bifida is detectable by level II ultrasound in approximately 90% of cases [10]. Diagnostic testing to confirm or rule out Down syndrome, trisomy 18, and trisomy 13 with greater than 99% confidence can be performed using chorionic villus sampling (CVS) or amniocentesis, both of which permit analysis of fetal chromosomes [11]. CVS is typically performed at 10–13 weeks gestation and involves obtaining an aspirated sample of the developing placenta. Amniocentesis is typically performed as early as 15 weeks gestation and involves obtaining a sample of amniotic fluid via needle aspiration. Amniocentesis also permits biochemical testing for open spina bifida, with a detection rate greater than 99% [10]. However, because CVS and amniocentesis are invasive procedures, there is a procedure-related risk for miscarriage; a retrospective cohort study published in 2006 found that the overall pregnancy loss rate for the 2 procedures was approximately 0.3% [12].

Noninvasive Prenatal Screening

Noninvasive prenatal screening, the newest addition to the prenatal testing menu, walks the line that has long separated screening from diagnostic genetic testing. There has been an effort for more than 2 decades to develop a reliable noninvasive test for the prenatal detection of genetic conditions. The presence in maternal blood of fragmented, cell-free fetal DNA (cfDNA), which constitutes approximately 3%–6% of the total cfDNA present in maternal blood [13], has allowed development of noninvasive prenatal screening for trisomies 21, 18, and 13. In addition, X and Y DNA fragments can be analyzed to screen for sex chromosome conditions such as Turner syndrome (45,X); such analysis also allows for prediction of fetal sex. Noninvasive prenatal screening laboratories have validated their methodologies in high-risk pregnancies, such as those of women who are 35 years of age or older, those in which there was an abnormal result on first-trimester screening or maternal serum screening, and those in which ultrasound identified one or more anatomical abnormalities associated with trisomies 21, 18, or 13. However, noninvasive prenatal screening will not be appropriate for average-risk pregnancies until further studies have been done.

Each laboratory that performs noninvasive prenatal screening reports its results slightly differently, but all quote high detection rates (greater than 99%) and low false-positive rates (generally less than 0.1%) for Down syndrome in particular [14]. The benefits of noninvasive screening include not just its noninvasiveness, but also its increased sensitivity and specificity compared with traditional first-trimester and second-trimester screening. However, false-positive results are still possible with noninvasive prenatal screening, so confirmation of abnormal results through CVS or amniocentesis is recommended. Also, such screening is not appropriate for other types of chromosomal abnormalities nor for single-gene conditions.

It is important to consider the positive predictive value (PPV) and the negative predictive value (NPV) of prenatal screening tests. PPV and NPV are influenced not only by the sensitivity and specificity of the test but also by the prevalence of the condition in the population being screened. It follows that more fetuses will be affected by a condition as the condition becomes more prevalent in a population, whereas fewer fetuses will be affected as the condition becomes less prevalent. For example, noninvasive prenatal screening has high sensitivity (greater than 99%) for Down syndrome in the high-risk population, but what is the chance that a positive screening result means that a fetus actually has Down syndrome? Although laboratories that perform noninvasive prenatal screening have not specified PPVs, I calculate the PPV for Down syndrome to be approximately 80% for 35-year-old pregnant women and 93% for 40-year-old pregnant women; this calculation assumes approximately 100,000 annual births to 35-year-old women and 20,000 annual births to 40-year-old women, based on averages calculated from 2011 US birth data compiled by the Centers for Disease Control and Prevention [15]. The PPV would be expected to be higher in 40-year-old women than in 35-year-old women, because approximately 1 in 70 mid–second trimester pregnancies of 40-year-old women is affected by Down syndrome, whereas this rate is only 1 in 250 among 35-year-old women. In contrast, the NPV of noninvasive prenatal screening for Down syndrome is very high (99.9%), because in most pregnancies the fetus does not have Down syndrome, regardless of maternal age.

Chromosomal Microarray

When prenatal genetic testing is desired for conditions not addressed by noninvasive screening, then it is necessary to perform CVS or amniocentesis. If there is a family history of muscular dystrophy, for example, the particular disease-causing gene mutation(s) present in the family must be known before prenatal testing is done, so that the results can be interpreted accurately. In the absence of this information, the wrong genetic test could be ordered, in which case there would be little or no promise of obtaining an informative result. Also, when a fetal sample is obtained through an invasive sampling procedure, which carries a risk of pregnancy loss, it is important that it be used appropriately.

The development of prenatal chromosomal microarray analysis has enabled screening of the fetal genome at a deeper level than other tests. Chromosomal microarray analysis involves testing chorionic villi or amniocytes for submicroscopic chromosome deletions and duplications that are below the limit of resolution of routine chromosome analysis [16]. Some submicroscopic deletion/duplication conditions cause anatomical malformations, so chromosomal microarray analysis can be helpful in making a diagnosis when ultrasound abnormalities do not fit any of the

recognized patterns of features described for more common conditions, such as Down syndrome or trisomy 18. If the fetus is chromosomally normal and appears sonographically normal but microarray testing reveals a less well-described microdeletion or duplication abnormality, or a variant of uncertain significance, then it can be difficult to predict postnatal morbidity, which can cause heightened anxiety for all involved. In addition, obtaining a normal result on chromosomal microarray neither rules out all genetic conditions nor negates the presence of sonographic abnormalities.

Parental Carrier Screening

The incidence of some genetic conditions is higher in certain ethnic groups: Sickle-cell anemia is more prevalent among African Americans, cystic fibrosis is more common among whites of Northern European decent, and Tay-Sachs disease is more prevalent among Ashkenazi Jews. Because these conditions are inherited in an autosomal recessive manner, carrier screening has been routinely offered to couples with these ethnic backgrounds to provide them with more accurate information about their chances of having a fetus affected by one of these conditions. When both members of a couple are found to be carriers of the same condition(s), prenatal diagnosis through CVS or amniocentesis can be considered. Expanded carrier screening for nearly 100 conditions has become available; however, the carrier detection rate for each condition varies with ethnicity and testing methodology. Also, the conditions for which carrier screening is available vary in their severity; some conditions cause significant medical or developmental complications, but other conditions are more benign or have onset in adulthood. Couples need to be aware of these important issues before proceeding with carrier screening [17].

Decision Making

Pregnant women accept or decline prenatal genetic screening or testing for varied and multilayered reasons. Some women consider the nature of the condition(s) being tested for and their perception of, or their personal experience with, the medical and/or developmental challenges the condition presents and how it will affect quality of life. Some take into consideration the availability of prenatal treatment and/or the accessibility of pediatric specialists during the newborn period. Some women are guided by faith; by the counsel of their spouse or partner, relatives, or close friends; or both. Some women want to avoid the risk for miscarriage associated with invasive procedures, whereas others believe that this risk is low enough to be acceptable. Some want to avoid the anxiety raised by uncertain or abnormal results, and others experience heightened anxiety in the absence of information.

Currently, fetal therapy is available for only a limited number of anatomical abnormalities, such as spina bifida [18]. Down syndrome, muscular dystrophy, fragile X syndrome, and thousands of other genetic disorders have no available prenatal treatment. Nontheless, prenatal genetic screening and testing can reassure parents that a pregnancy is at low risk of or is unaffected by a condition or set of conditions tested for—or it can give parents an opportunity to prepare (cognitively, emotionally, financially, and supportively) for the birth of a child who has a genetic condition. Whether termination of a pregnancy affected with a genetic condition is considered to be an acceptable option is a decision that ultimately rests with the pregnant woman and her family.

Understanding the benefits, risks, and limitations of prenatal genetic screening and testing is important for health care providers, laboratories, insurers, public policy professionals, and most of all, for pregnant women. Although the amount of genetic information that can be obtained about a pregnancy through screening and diagnostic testing will continue to increase, it will be up to each pregnant woman and her family to decide what they wish to learn. NCM

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Ethical Concerns About Genetic Testing and Screening

Rosemarie Tong

Many of the ethical concerns raised by genetic testing and screening relate to accuracy, cost, and confidentiality. Perhaps the most serious worry—one that is not without merit—is that the new genomics is a disguised version of the old eugenics. On balance, however, genetic testing and screening seem to be in society's best interests.

Today, people have unprecedented access to genetic information about themselves and, in some instances, others. Companies such as 23andMe (https://www.23andme.com/) give people access to their genetic profile without necessarily providing adequate means to interpret this information. The cost to complete the first sequencing of the human genome in 2003 was estimated at $2.7 billion (in Fiscal Year 1991 dollars) [1]. By June 2013, however, an individual could have his or her entire genome sequenced for $5,000 (a price that included an iPad containing the results), and some experts estimate that the price for whole-genome sequencing will drop to $500 in the near future [2]. People are now able to know a great deal about their present and future health status, but this knowledge is not without problems. Serious ethical questions surround both genetic testing of individuals and genetic screening of populations.

One of the main ethical issues surrounding genetic testing and screening is accuracy. Enormous and devastating consequences can result from receiving either a false-positive result (being told that you have a deleterious genetic condition when you do not) or a false-negative result (being told that you do not have a deleterious genetic condition when you actually do). Also, many people make decisions about whether to have a baby based on knowledge about the genetic condition of the fetus. A couple who are undergoing in vitro fertilization—who may have invested much time, physical and psychic energy, and money in this process—may decide to abort a fetus on what turns out to be a false-positive result for a particular genetic condition [3]. Similarly, it cannot be emphasized enough that women should not assume that they will not get breast cancer simply because they test negative for mutations in the *BRCA1* and *BRCA2* genes—only 5%–10% of all breast cancers are linked to such mutations [4]. The public needs to be repeatedly reminded that health status is not genetically determined in a simplistic way; for the most part, genes merely contribute to overall health. If an individual has the gene for Huntington disease, he or she will almost certainly develop this neurological disorder [5]. In contrast, a person may have multiple genes related to type 2 diabetes, but depending on his or her lifestyle choices, those genes may or may not be activated [6].

The high cost of genetic testing and screening is another source of concern. Genetic screening for the presence of *BRCA1* and *BRCA2* mutations and for conditions such as cystic fibrosis, Tay-Sachs disease, and Down syndrome ranges in cost from less than $100 to more than $2,000 [7]. In June 2013, Myriad Genetics had the exclusive right to test for *BRCA1* and *BRCA2* mutations, and the cost for this test was nearly $4,000 when a related genomic rearrangement test was included in the analysis [8]. Even if the cost of whole-genome sequencing drops from $5,000 to $500, an individual, institution, or organization still must bear the cost, and some people will also want follow-up tests to help their health care providers determine the subsequent course of treatment. Therefore, most health care ethicists recommend that genetic testing and screening be offered only to individuals who are at relatively high risk for a serious genetic disease. Requests for medically unnecessary genetic testing and screening should not be honored by health care professionals, even if patients threaten to get the information from other sources that may be less reliable [9].

In addition to expressing concern about the accuracy and cost of certain genetic tests, many health care ethicists and health professionals worry about the consequences if such tests were to become mandatory. For example, no one wants to repeat the poorly conceived and often misunderstood mandatory screening program for sickle-cell anemia that was instituted in the 1970s, especially given the mistrust that many African Americans already have of the health care system [10]. Sickle-cell disease is especially prevalent in the African American community; thus, when a relatively inexpensive test was developed in the 1970s that could iden-

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tify carriers for sickle-cell disease, laws were passed in many states that made testing mandatory for African American schoolchildren [11]. Unfortunately, some health care insurers rejected health insurance applications from individuals who were carriers of sickle-cell anemia, because they did not want to cover individuals whose children were likely to have the disease [11]. In addition, some employers refused to hire people who were carriers of sickle-cell anemia because they believed that these individuals would be too sick to work and/or that it would be too expensive to provide health care insurance for them [11]; these employers did not understand the difference between being a carrier of the disease and actually having the disease [12].

Maintaining confidentiality in genetic testing and screening is vital. Confidentiality is one of the foundations for a successful patient-provider relationship. Patients who cannot trust their health care providers to safeguard private information are not likely to reveal the information, thereby depriving themselves of good medical care [12]. In addition, patients sometimes ask their health care providers to withhold the results of genetic tests from family members or other intimates for fear of alarming or alienating them. But problems may arise when patients hide their genetic status from loved ones. Sometimes family members cannot make important life or medical decisions without the information that is being withheld from them. For example, a woman might want to know her future husband's Huntington disease status before agreeing to stand by him in sickness as well as in health, and before having children with him [13].

The Genetic Information Nondiscrimination Act of 2008 (GINA) does not provide health care professionals with definitive guidelines for balancing the need for patient confidentiality against the harm that could result from not disclosing the patient's genetic profile to family members and/or other intimates. GINA prohibits health insurers and employers from discriminating based on genetic information [14], but it remains silent about providing information to family members or intimates of the person with a genetic condition.

Perhaps the greatest concern about genetic testing and screening is whether it will lead to a program of eugenics aimed at eliminating those who are "unfit" and allowing only those who are "fit" to reproduce. Some health care ethicists and professionals fear that genomics will replicate the mistakes made by eugenics programs around the world during the first half of the 20th century. The eugenics programs that flourished in the United States from about 1890 to 1940 continued to operate in North Carolina until 1974. Between 1929 and 1974, North Carolina sterilized approximately 7,600 individuals who were deemed "feeble-minded or otherwise undesirable" [15]. Although the state officially apologized to the surviving victims of these involuntary sterilizations in 2003 and promised to make reparations [16], only recently did the state set aside $10 million to compensate these individuals [17]. An amount of $50,000 per victim has been suggested as an amount that would provide adequate compensation [17], but one wonders whether even several million dollars would adequately compensate someone who was denied the ability to procreate, sometimes without even being informed that he or she was being sterilized.

Because society has misunderstood and misapplied genetic information in the past, worries have arisen about the underlying motives for today's genomic medicine, but I believe there are important differences between eugenics programs of the past and today's genomic testing. Eugenics programs were based on very poor scientific evidence; for example, some proponents of eugenics believed that there were genes for criminality and promiscuity [18]. Eugenics also involved forced sterilizations—getting rid of undesirable people and sacrificing the individual for the supposed good of the group. In contrast, genomics is about controlling one's genetic destiny, choosing the kind of children one wants, and being as healthy and happy as possible [12]. Also, with today's genomic testing, every effort is made to be objective and to set aside assumptions about people's race, sex, ethnicity, and wealth.

Genomics enthusiasts often stress that the aim of reproductive genetic testing and screening is simply to inform prospective parents about the genetic health status of their future child, not to prompt prospective parents to select for only the best prodigy possible [19]. Nonetheless, a high percentage of parents do choose to abort a fetus if it tests positive for a serious genetic disease. Although people with Down syndrome can lead meaningful lives and report that they are happy [20], a 2012 analysis of 7 population-based studies and 9 hospital-based studies published between 1995 and 2011 found that 67% to 85% of women ended their pregnancy when they learned that the fetus had Down syndrome [21]. There is also evidence that a relatively high percentage of parents would consider aborting a fetus if it had a minor genetic defect such as myopia [22]; a propensity toward a disease such as obesity, which can be controlled by lifestyle adjustments beginning in early childhood; or Huntington disease, which has its onset quite late in life [23]. Lastly, in countries where there is a marked preference for boy babies over girl babies, some parents will abort a fetus if it is the "wrong" sex (ie, female). In both China and India, the sex ratio at birth is now 1.12 males for every female [24].

Many health care ethicists are troubled by the possibility that reproductive genetic testing could lead to elimination of undesirable fetuses, with prospective parents aiming to replace them with better or preferred children. A society in which prospective parents are under severe pressure to produce a perfect baby is one that probably has less tolerance for and acceptance of people who deviate from whatever is deemed "normal." As health care costs rise, some disability rights activists fear that rather than making reasonable accommodations for people with disabilities, societies will take the inexpensive way out and make it very difficult for

people to produce children who have mental or physical challenges [25]. Michael S. Lagan, a vice president of the National Organization for Rare Disorders, goes so far as to speculate that

> Eventually there will be discrimination against those who look "different" because their genes were not altered. The absence of ethical restraints means crooked noses and teeth, or acne, or baldness, will become the mark of Cain a century from now [12].

Although these problems are worth considering, indications are that better genetic testing and screening will increase rather than decrease people's freedom—that is, their ability to make autonomous decisions about their health and that of their children. Moreover, most people will not overreact after they see the results of their genetic tests. Rather, they will seek the help of health care professionals, who will do more targeted genetic tests and carefully explain to patients about their options [26].

However, one concern is the shortage of genetic counselors. In 2012 there were only 3,000 genetic counselors in the United States [27]. This small number of genetic counselors cannot be expected to answer the many questions people will likely have about their genetic test results, especially if use of such screening increases. Greater emphasis needs to be placed on increasing the number of genetic counselors, which could be accomplished in part by increasing their financial compensation. The few who are employed by genetic testing companies (about 9% of the 3,000) typically earn about $65,000 per year, which is at the high end of the pay scale [27]. Incorrectly interpreted genetic information is potentially harmful; by improving the quality of the interpretation of genetic test results, we are all more likely to benefit from this technology. NCMJ

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Gene Therapy:
The Promise of a Permanent Cure

Christopher D. Porada, Christopher Stem, Graça Almeida-Porada

Gene therapy offers the possibility of a permanent cure for any of the more than 10,000 human diseases caused by a defect in a single gene. Among these diseases, the hemophilias represent an ideal target, and studies in both animals and humans have provided evidence that a permanent cure for hemophilia is within reach.

Gene therapy, which involves the transfer of a functional exogenous gene into the appropriate somatic cells of an organism, is a treatment that offers a precise means of treating a number of inborn genetic diseases. Candidate diseases for treatment with gene therapy include the hemophilias; the hemoglobinopathies, such as sickle-cell disease and β-thalassemia; lysosomal storage diseases and other diseases of metabolism, such as Gaucher disease, Lesch-Nyhan syndrome, and the mucopolysaccharidoses (including Hurler syndrome); diseases of immune function, such as adenosine deaminase deficiency; and cystic fibrosis.

Although one might assume that the majority of these diseases could be corrected by simply providing an exogenous source of the missing or defective protein, this is not always the case. Even when the required protein can be purified or produced in recombinant form in sufficient quantities to be therapeutically useful, there is still the challenge of providing the missing protein, or replacing the defective protein, in a therapeutic fashion, which may require the delivery of the complex and often fragile protein to the precise subcellular location in which it is normally expressed. In addition, many patients suffering from a given genetic disease have never produced the specific protein in question, so their immune system has never "seen" this protein. Thus, infusion of the purified or recombinant protein could be followed by an immune response in which the cells of the immune system identify as a foreign entity the very protein that could treat the patient's disease; this immune system response can lead to loss of therapeutic benefit, despite continued protein infusions. Even in the absence of these immunologic hurdles, protein-based treatments can never cure the underlying disease. Rather, they require a lifetime of regularly spaced infusions to keep the disease process at bay. Even after years of treatment, the symptoms will return if the patient misses even a single dose of replacement protein, with potentially life-threatening consequences.

By providing a normal copy of the defective gene to the affected tissues, gene therapy would eliminate the problem of having to deliver the protein to the proper subcellular locale, since the protein would be synthesized within the cell, utilizing the cell's own translational and posttranslational modification machinery. This would ensure that the protein arrives at the appropriate target site. In addition, although the gene defect is present within every cell of an affected individual, in most cases transcription of a given gene and synthesis of the resultant protein occurs in only selected cells within a limited number of organs. Therefore, only cells that express the product of the gene in question would be affected by the genetic abnormality. This greatly simplifies the task of delivering the defective gene to the patient and achieving therapeutic benefit, since the gene would only need to be delivered to a limited number of sites within the body. Furthermore, if the gene could be specifically targeted to the organs that are most affected by the disorder, the risk of side effects from ectopic expression of the therapeutic gene would be avoided. Gene therapy, if targeted to the appropriate somatic cells, could thus promise permanent correction of the genetic defect following a single treatment. It is this promise that drives the myriad preclinical and clinical gene therapy studies for a wide range of diseases and disorders.

In most preclinical and all clinical gene therapy trials to date, the therapy has been performed on either children or adults, but it bears mention that many of the diseases being considered as candidates for gene therapy can be diagnosed early in gestation, making it feasible to treat the fetus in utero rather than waiting until after birth. Methods for accessing the human fetus are well established and clinically viable, and in utero stem cell–based therapies have been safely performed in the clinic for decades for a number of different diseases [1-3]. Performing gene therapy early in gestation would correct the defect prior to disease onset, allowing the birth of a normal, healthy baby who ideally would require no further treatments.

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In addition to the clinical advantages of such an approach, key differences between a fetus and an adult make the fetus a more suitable gene therapy recipient. For example, as a result of the active cycling of cells and the continuous expansion that occurs in all of the fetal organs throughout gestation, one can envision that initial transduction of even small numbers of target cells would lead to significant levels of gene-correction by birth. There are also immunologic advantages to performing gene therapy in utero, because exposure to foreign antigens during the period of early immunologic development can result in permanent tolerance if the presence of the antigen is maintained [4]. Over the past several years, we and others have demonstrated that it is possible to take advantage of the unique opportunities presented by the early gestational fetus to achieve significant levels of gene transfer to cells within several major organ systems following a single injection of vector [5-13], while simultaneously inducing immune tolerance to the vector-encoded transgene [14, 15]. Collectively, these findings provide compelling evidence that fetal gene therapy could represent a viable therapeutic option for diseases of multiple organs. Moreover, even if such therapy is not curative, the ability to induce lifelong tolerance would overcome the immune-related hurdles that currently hinder postnatal protein-based treatments. Despite its great promise, however, in utero gene therapy is still in the experimental stages, and carefully designed risk-to-benefit studies will need to be done in appropriate preclinical animal models before a therapy of this type could move into the clinical arena.

The Need for Better Treatments for the Hemophilias

Hemophilia A is caused by a defect in or deficiency of coagulation factor VIII. It is the most common inheritable coagulation deficiency, affecting about 1 in 5,000 males. Hemophilia B is far less common, only occurring in about 1 of every 30,000 male births; it is caused by a deficiency of or defect in coagulation factor IX. Roughly 60% of individuals with hemophilia A or hemophilia B present with the severe form of the disease (meaning they have less than 1% of the normal amount of clotting factor in their blood) [16]; these individuals experience frequent spontaneous hemorrhaging, leading to chronic debilitating arthropathy, hematomas of subcutaneous connective tissue or muscle, and potentially life-threatening internal bleeding. Over time, the collective complications of recurrent hemorrhaging result in chronic pain, absences from school and work, and permanent disability [17]. Current state-of-the-art treatment consists of frequent prophylactic infusions of plasma-derived or recombinant factor VIII or factor IX to maintain hemostasis. Although this treatment has greatly increased life expectancy and quality of life for many patients with hemophilia, this therapeutic approach is still far from ideal, because lifelong infusions are needed and the treatment is extremely expensive ($150,000–$500,000 per year). Even setting these shortcomings aside, factor replacement therapy is not available for approximately 75% of individuals with hemophilia worldwide, placing these patients at great risk of severe, permanent disabilities and life-threatening bleeding [18]. Even for patients with hemophilia A who are fortunate enough to have access to factor VIII and the means to afford prophylactic infusions, there is no guarantee of a life free from treatment complications. Approximately 30% of patients with severe hemophilia A develop inhibitory antibodies to the infused factor VIII protein, which greatly reduces treatment efficacy, increases morbidity and mortality, decreases quality of life, and can ultimately lead to treatment failure [19]. Although inhibitors are far less common in patients with hemophilia B [20], their formation can trigger severe immune responses, which can include anaphylaxis, placing patients in grave danger. Thus, there is a significant need to develop novel hemophilia therapies offering longer-lasting benefit or a permanent cure [21]. Gene therapy offers the promise of being such a treatment.

Hemophilia as a Paradigmatic Genetic Disease for Correction by Gene Therapy

Many diseases are being considered as candidates for correction with gene therapy, but several aspects of the basic biology and pathophysiology of hemophilia A and hemophilia B make them ideal targets [21-24]. First, although the liver is thought to be the primary natural site of synthesis of factor VIII and factor IX, neither factor needs to be expressed in either a cell-specific or a tissue-specific fashion to restore hemostasis. As long as the protein is expressed in cells that have ready access to the circulation, the protein can be secreted into the bloodstream and exert its appropriate clotting activity. Moreover, expression of this factor in other tissues of the body exerts no observable deleterious effects. This is in marked contrast to many other genetic diseases, which require that expression of the missing protein be exquisitely controlled, often with respect not only to cell type but also to a specific subcellular locale, in order for the protein to function correctly and to avoid deleterious effects. A second feature of hemophilia A and hemophilia B that sets them apart from many other diseases is that only a small amount of the missing clotting factors is required to achieve a pronounced clinical improvement. Indeed, raising the level of factor VIII or factor IX to even 3%–5% of normal would convert severe hemophilia A or hemophilia B, respectively, to a moderate or mild phenotype. Such a change would be expected to reduce or eliminate episodes of spontaneous bleeding and to greatly improve quality of life. Thus a marked clinical improvement would be anticipated in patients with hemophilia, even with the low levels of transduction that are routinely obtained with many of the current viral-based gene delivery systems. This reasoning prompted the American Society of Gene & Cell Therapy (ASGCT) to include the hemophilias on their list of the 10 diseases that hold the most promise as targets for viable gene therapy

products within the next 5–7 years (Table 1). This list was part of a "road map" the ASGCT provided to the director of the National Institutes of Health, Francis S. Collins.

To develop and test various gene therapy approaches for treating hemophilia A and hemophilia B, researchers have used several animal models, including dogs with congenital deficiency of factors VIII and IX [25], mouse models obtained by gene targeting and knockout technology [26, 27], and a line of sheep with a form of factor VIII deficiency that accurately mimics the human disease [28]. Marked therapeutic benefit has been obtained using a variety of vector systems in the murine model [29-33]. In dogs, phenotypic correction has been possible but has proved to be far more difficult than in mice [29, 30, 32-39]. In the sheep model, a single infusion of bone marrow stromal cells engineered to express high levels of factor VIII resulted in phenotypic correction and complete reversal of debilitating hemarthroses, but it also triggered the formation of inhibitors of factor VIII [40].

Despite these promising results in animal models, no clinical gene therapy trial has yet shown phenotypic or clinical improvement of hemophilia A in humans. Based on the disappointing results to date, there are currently no active clinical trials of gene therapy for hemophilia A, even though hemophilia A accounts for roughly 80% of all cases of hemophilia. Previous clinical gene therapy trials for hemophilia B were similarly disappointing with respect to clinical benefit [21, 41, 42]. However, a highly successful ongoing trial being conducted jointly by St. Jude Children's Research Hospital and University College London has recently highlighted the tremendous potential of gene therapy for the treatment of human hemophilia B [43]. In this trial, a single dose of a factor IX–encoding adeno-associated virus–based vector has resulted in expression of therapeutic levels of factor IX that have been sustained for more than 2 years, to date, in 6 adults with severe hemophilia B. The levels of circulating factor IX achieved with this approach, although not high, have enabled 4 of these 6 subjects to completely discontinue routine factor IX prophylaxis. The other 2 patients have not achieved complete independence from factor IX infusions, but this gene therapy–based treatment has allowed them to significantly reduce the frequency with which they need to administer prophylactic infusions [44]. These results represent a leap forward in the treatment and management of hemophilia B and make this an exciting time for the field of gene therapy. We eagerly await news on whether these groups succeed with their plans to adapt this strategy to the treatment of hemophilia A [45]. Even if this adeno-associated virus–based treatment approach does not prove to be fully curative, its ability to mediate long-term expression of factor VIII or factor IX should lessen disease severity, reduce health care expenditures, and dramatically improve the quality of life of patients with hemophilia A or hemophilia B, respectively. NCMJ

TABLE 1.
Disease Indications Identified by the American Society of Gene & Cell Therapy as Promising Targets for Gene Therapy

Leber congenital amaurosis
Adenosine deaminase severe combined immunodeficiency
Hemophilia
X-linked severe combined immunodeficiency
Parkinson disease
Age-related macular degeneration
Adrenoleukodystrophy
Thalassemia
Epstein Barr virus lymphoma
Melanoma

Source: Letter from the American Society of Gene & Cell Therapy (ASGCT) to Francis S. Collins, MD, PhD, director of the National Institutes of Health. January 6, 2012. ASGCT Web site. http://www.asgct.org/UserFiles/file/FinalSamulskiLettertoCollins.pdf. Accessed October 31, 2013.

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Is Genetic Testing of Value in Predicting and Treating Obesity?

Maggie C. Y. Ng, Donald W. Bowden

Obesity is a multifactorial disease resulting from the interaction between genetic factors and lifestyle. Identification of rare genetic variations with strong effects on obesity has been useful in diagnosing and designing personalized therapy for early-onset or syndromic obesity. However, common variants identified in recent genome-wide association studies have limited clinical value.

In the United States in 2009–2010, 35.7% of adults were obese, which is defined as having a body mass index (BMI) of 30 kg/m^2 or greater [1]. Concurrently, 16.9% of children and adolescents were obese, which is defined as being at or above the 95th percentile on the sex-specific BMI-for-age growth charts of the Centers for Disease Control and Prevention [2]. Obesity is a consequence of taking in more energy (through consumption of foods and beverages) than is expended (through exercise and other activities). Although the increasing prevalence of obesity is attributable in large part to the obesogenic environment and to lifestyle factors such as lack of physical activity and consumption of foods high in fat and sugar, individuals vary in their susceptibility to obesity, suggesting that genetic predisposition also plays a role. Family and adoption studies suggest that an estimated 20%–80% of population variance in BMI is due to genetic effects (ie, heritability) [3]. There is increasing interest in whether the genetic variants that have recently been associated with obesity are useful for predicting risk of obesity and/or for developing personalized therapy for obesity.

Identifying Genes Associated With Obesity

Both early rodent studies and targeted gene association studies in humans have identified rare genetic mutations associated with the development of early-onset severe obesity. The key features associated with these gene mutations (summarized in Table 1) can be found in the Online Mendelian Inheritance in Man database (www.omim.org), which catalogs diseases that have a genetic component and links these diseases to the relevant genes. Several of the genes associated with early-onset severe obesity belong to the leptin-melanocortin pathway, including the genes encoding leptin (*LEP*), leptin receptor (*LEPR*), melanocortin-4 receptor (*MC4R*), prohormone convertase 1 (*PCSK1*), proopiomelanocortin (*POMC*), single-minded homolog 1 (Drosophila) (*SIM1*), and brain-derived neurotrophic factor (*BDNF*). In addition to developing severe obesity at an early age, carriers of mutations in some of these genes also have intellectual disabilities and exhibit developmental delays, which suggests that there is an interplay between neurodevelopment and the hypothalamic functions of energy homeostasis and body-weight regulation.

The identification of genetic variants contributing to common forms of obesity has primarily been the result of recent genome-wide association studies (GWAS). The HapMap Project [4, 5] and the recent 1000 Genomes Project [6] have identified tens of millions of genetic variants, including single-nucleotide polymorphisms (SNPs) and copy number variations, and these studies have established patterns of chromosome structure in diverse populations. In GWAS, millions of these genetic variants in tens of thousands of individuals have been either directly genotyped or inferred from known patterns of chromosome structure using the HapMap and the 1000 Genomes data; GWAS have thus been able to test for associations between genetic variants and a variety of obesity-related traits. To date, at least 58 loci have been associated with various adiposity measures, including BMI, waist-hip ratio, percent body fat, subcutaneous fat, and visceral fat; these associations have primarily been made in individuals of European descent [7-9].

The first of these genetic loci to be identified is still the one most strongly associated with adiposity; it is located in intron 1 of the *FTO* gene on chromosome 16q12 [10]. Each copy of the risk allele is associated with a 1.2-fold increased risk for obesity and a 0.39 kg/m^2 increase in BMI in the general population [11]. The effect appears to be stronger (odds ratio = 1.67) in individuals with early-onset extreme obesity [12]. Association of *FTO* risk alleles with BMI is widely replicated across multiple populations, including Asians [13] and African Americans [14]. Overexpression or knockdown of Fto protein expression in mice leads to altered food intake, energy expenditure, body mass, and fat mass [15-17].

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TABLE 1.
Genes Implicated in Monogenic Obesity and the Traits Found To Be Associated With Them in Genome-Wide Association Studies (GWAS)

Gene symbol	Gene name	Phenotype	Associated traits
BDNF	Brain-derived neurotrophic factor	Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity (WAGRO) syndrome	Obesity, BMI, weight
CART	Cocaine- and amphetamine-regulated transcript	Severe obesity	
LEP	Leptin	Morbid obesity due to leptin deficiency	
LEPR	Leptin receptor	Severe obesity due to leptin receptor deficiency	Serum level of C-reactive protein, serum level of leptin receptor
MC4R	Melanocortin-4 receptor	Early-onset severe obesity	Obesity, BMI, waist circumference, height, serum level of HDL cholesterol
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	Early-onset severe obesity, hyperphagia, developmental delay	
PCSK1	Proprotein convertase subtilisin/kexin type 1 gene, or prohormone convertase 1	Early-onset severe obesity	BMI, serum proinsulin level, fasting serum glucose level (interaction with BMI)
POMC	Proopiomelanocortin	Early-onset severe obesity, adrenal insufficiency, red hair	Obesity, height
PPARG	Peroxisome proliferator-activated receptor gamma	Severe obesity, insulin resistance, lipodystrophy	Type 2 diabetes, fasting serum insulin level (interaction with BMI), plasma level of plasminogen activator inhibitor type 1
SIM1	Single-minded homolog 1 (Drosophila)	Early-onset severe obesity, Prader-Willi syndrome	

Note. BMI, body mass index; HDL, high-density lipoprotein.

A homozygous Arg316Gln mutation was identified in a family in which 9 individuals had a polymalformation syndrome characterized by growth retardation and developmental delay [18], suggesting that *FTO* plays a role in the development of the central nervous system and the cardiovascular system.

It is encouraging to note that some of the GWAS loci contain genes previously reported to be associated with monogenic obesity, including *LEPR*, *MC4R*, *PCSK1*, *POMC*, and the peroxisome proliferator-activated receptor gamma gene, *PPARG* (Table 1). This suggests that there is a wide spectrum of disease susceptibility; carrying highly penetrant rare variants of these genes leads to severe forms of obesity, while the common variants predisposes a person to more common forms of obesity. Additional GWAS loci—including neuronal growth regulator 1 (*NEGR1*), neurexin 3 (*NRXN3*) and SH2B adaptor protein 1 (*SH2B1*)—are expressed in the brain, which suggests that they may play a role in the neurological regulation of energy homeostasis.

In contrast, the genes and the respective causal genetic variants in many loci, particularly the novel ones, are unclear. The associated genetic variants are often located in noncoding or nongenic regions and are unlikely to be causal by themselves; rather, they are correlated with (ie, in close proximity to) unidentified causal variants. Studies in populations with different ancestries, and thus different genetic architectures, have revealed both shared and unique genetic susceptibility with varying effects; these studies may help to refine the location of causal genetic variants [19]. Analysis of the previously reported SNPs at *FTO* and *MC4R* has yielded consistent associations across East Asians, South Asians, Pima Indians, Hispanics, and African Americans. About half of the European-derived BMI variants are nominally significant ($P<.01$) in East Asians and African Americans, and additional variants have also demonstrated nominal significance in locus-wide analysis [14, 19]. Further bioinformatics analyses and functional annotation of coding variants [20] and noncoding variants may help to prioritize experimental validation of the putative functional variants.

Clinical Applications

There is increasing interest in the question of whether genetic findings can be applied in the clinical setting to improve risk prediction and facilitate personalized therapy for obesity. Despite the discovery of a large number of genetic loci, the effect size of each variant is modest. The most strongly associated variant at *FTO* only explains 0.34% of the phenotypic variance for BMI in the general population; summing 32 GWAS variants increases the explained variance to 1.45%, with each additional risk allele increasing BMI by 0.17 kg/m^2 [11]. Individuals carrying the lowest number of risk alleles have a BMI that is 2.73 kg/m^2 lower, on average, than those carrying the highest number of risk alleles [11].

The current set of identified common variants has poor specificity and poor sensitivity for predicting obesity in both cross-sectional and longitudinal studies. In the Atherosclerosis Risk in Communities (ARIC) study, the area under the receiver operating characteristic curve (AUC_{ROC}) for predicting risk of obesity using the demographic variables age and sex was 0.515, compared with the null value of 0.5 [11]. Addition of a genetic risk score based on 32 genetic

variants increased the AUC_{ROC} moderately in Europeans, to 0.575, but using the genetic risk score worked less well for African Americans, partly because of ethnic differences in effect size and allele frequencies of the tested variants [11, 21]. An analysis of the lifetime Northern Finland Birth Cohort 1986 showed that traditional risk factors—including parental BMI, birth weight, maternal gestational weight gain, and behavior and social indicators—had good predictive power for childhood obesity (AUC_{ROC} = 0.78); however, adding a genetic risk score based on 39 BMI-associated variants improved discrimination by 1% or less [22]. The lack of discrimination power for genetic variants is partly due to the small genetic effect, the use of surrogates rather than causal variants with larger effects, the presence of other unidentified common and rare genetic variants, and the lack of consideration of gene-gene and gene-environmental interactions. Clinical factors such as family history and birth weight are also influenced by genetic factors that contribute to the clinical prediction model.

Although the translation of genetic discovery into risk prediction is challenging at the population level, high penetrant variants associated with severe early-onset or syndromic forms of obesity may serve as a diagnostic tool and could assist in designing personalized therapy for individuals [23]. Mutations of the *MC4R* gene are most frequently found among children with nonsyndromic severe obesity, in whom the incidence ranges from less than 1% to 6% depending on nationality and variant [24]. These patients present with hyperphagia, severe hyperinsulinemia, tall stature, and high fat and lean mass. In patients with a syndromic form of obesity that is the result of single-variant mutations or large copy number variations—such as Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, Albright hereditary osteodystrophy, or WAGRO (Wilms tumor, aniridia, genitourinary anomalies, mental retardation, obesity) syndrome—obesity often coexists with intellectual disabilities or developmental delays [23]. Powerful and cost-effective tools to identify the mutations and structural variants of chromosomes include sequencing of genes known to have medical implications, surveying of all coding sequences in an individual's DNA using next-generation DNA sequencing, and using comparative genomic hybridization arrays. Screening of identified variants in family members also assists early diagnosis, which can allow clinicians to recommend preventive measures.

Only a few limited studies have examined the interaction between genetics and lifestyle and how this interaction affects risk prediction and therapeutic effects [25]. Nutrigenic studies have demonstrated that the Pro12Ala genetic variant in the *PPARG* gene interacts with fat intake and obesity, with free fatty acids acting as natural agonists of this transcription factor. A Mediterranean diet has been reported to be associated with reversal of the effect of increased weight in 12Ala allele carriers; this reversal was not observed with a conventional low-fat diet [26]. Other studies have demonstrated that genetic risk has a lower impact in physically active individuals than in people with an unhealthy lifestyle [27-29]. Studies of the effect of genetic risk variants on weight reduction following bariatric surgery have had conflicting results; those who have higher-risk genetic variants may or may not have lower weight loss after surgery [30, 31]. Long-term follow-up studies will be necessary to evaluate the genetic interaction with therapeutic outcomes.

Taken together, advancements in genetic discovery and technologies have improved our understanding of the biological basis of obesity. Genetic testing of patients with early-onset or syndromic forms of obesity and their families is recommended to facilitate early diagnosis and personalized intervention. Clinical geneticists and physicians will need to work together to explain patients' risk of obesity and to monitor their health. Cumulatively, the common genetic variants identified so far explain only a small proportion of the genetic contribution to obesity in the general population, and these variants exert differential effects in different populations. This limits their value in risk prediction compared with traditional clinical predictors, which can be measured easily and inexpensively. In the future, identifying additional genetic variants and understanding how they interact with lifestyle will improve the clinical applicability of these variants for risk prediction and personalized therapy. Overall, lifestyle modifications—including healthy diet and physical activity—remain the key to success in weight control, irrespective of an individual's genetic profile. NCMJ

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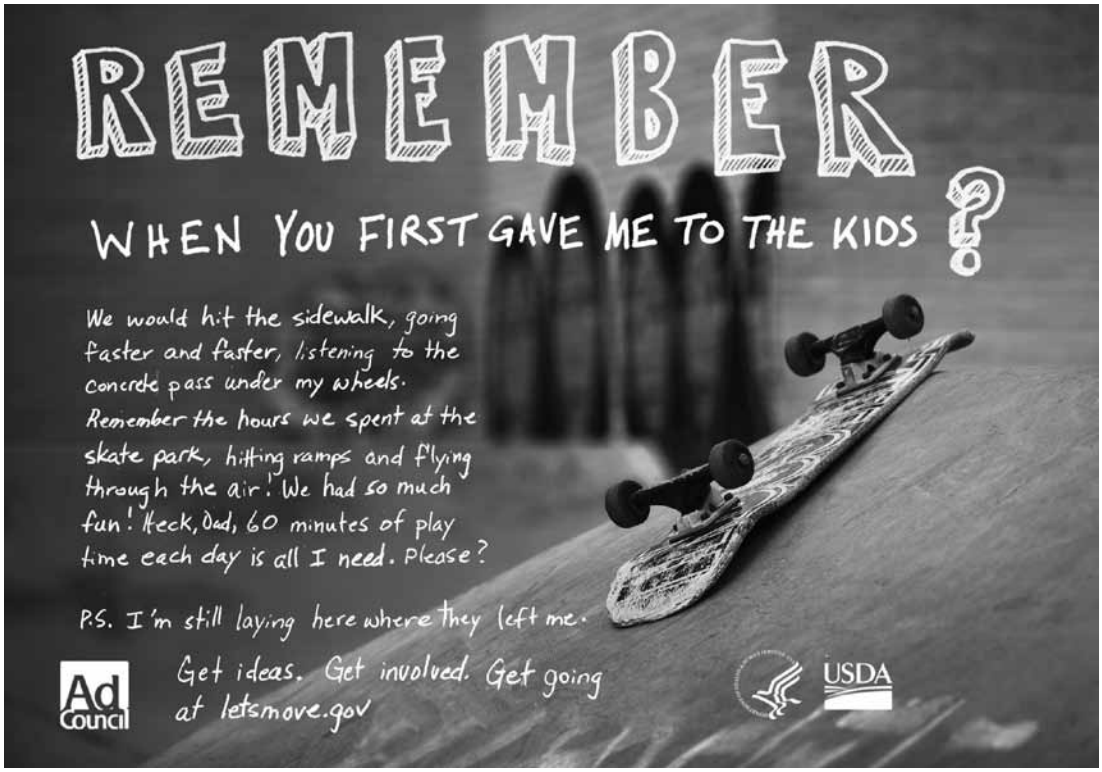

Epigenetic Considerations in Medicine

Dianne M. Walters

Epigenetic modifications are gene regulatory mechanisms that allow rapid adaptation to the environment. These mitotically stable and meiotically heritable changes are sensitive to environmental conditions especially during developmental periods, and they are essential to understanding how information in the DNA sequence is utilized. Recent research in this area has led to excitement and questions about medical applications of epigenetics.

Most common pathologies are complex, with multiple genetic and environmental factors contributing to disease etiology. Epigenetics is one mechanism through which gene-environment interactions occur. The term *epigenetics*—a combination of *epigenesis* (the study of embryological development) and *genetics*—was coined by Conrad Waddington in the 1940s to refer to gene-environment interactions during development that produce certain phenotypes [1]. The definition of epigenetics has changed as our understanding of genetics and molecular mechanisms has evolved, and today the term is commonly defined as the study of mitotically stable and/or meiotically heritable changes in gene expression without changes in DNA sequence [2]. Epigenetics arose to explain non-Mendelian inheritance and has sometimes been viewed as being in conflict with genetics, but epigenetics is actually complementary to genetics. Epigenetic modifications allow rapid adaptation to the environment and fine-tuning of genomic expression; thus epigenetics is essential to understanding how information in the DNA sequence is utilized.

Epigenetic Mechanisms

The most extensively studied epigenetic modification is DNA methylation, in which methyl groups are added to a region of DNA where cytosine nucleotides (C) are found adjacent to guanine nucleotides (G); such regions are known as CpG sites. Methylation is enzymatically mediated by several distinct DNA methyltransferases, which act to maintain existing marks through mitotic cell division, to preserve parental imprinting of genes, and to generate de novo methylation during development and in response to environmental conditions. CpG-rich regions, called CpG islands, are found in regulatory regions of approximately 70% of human genes, and methylation of these sites has traditionally been associated with silencing of gene expression [3] either through recruitment of histone deacetylases by methyl-CpG–binding proteins and chromatin compaction [4, 5], or by steric hindrance of transcription factor binding to promoter recognition sites [6]. Interestingly, the CpG density of gene promoters seems to inversely correlate with methylation status; in general, transcriptionally active genes have high-CpG-content promoters that are unmethylated and vice versa [3, 7], although some genes with methylated low-CpG-content promoters may still be activated by transcription factor binding in a tissue-specific manner [7]. This mode of regulation is thought to be important for somatic cell differentiation during development, so that specific genes are activated only during critical developmental periods. Unlike promoter methylation, CpG methylation within the body of genes correlates with a high level of gene expression, although the precise role of intragenic DNA methylation is incompletely understood.

Gene expression is also influenced by a number of chromatin structural modifications. The basic chromatin unit consists of 147 base pairs of DNA wrapped around a histone octamer; this unit is called a nucleosome. Nucleosome structure allows the entire genome to be compacted into the nucleus of a cell and regulates the extent to which transcription machinery has access to the DNA. This mode of transcriptional regulation involves post-translational covalent modification of the histone tails by specific enzymes. The most common modifications are acetylation and methylation, although numerous other modifications have been identified, including phosphorylation, ubiquitination, SUMOylation, citrullination, and adenosine diphosphate ribosylation. In general, acetylation is associated with DNA accessibility and transcriptional activity, whereas deacetylation is associated with transcriptional repression; histone methylation may be related to either activation or repression. These modifications alter the charge of the histone tail and therefore alter interactions with the DNA to allow nucleosome mobility and changes in DNA accessibility. Histone modifications can also affect higher-order folding

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of the chromatin through internucleosome interactions.

Another epigenetic mechanism involves noncoding ribonucleic acids (ncRNAs), which are key regulators of many cellular processes, including proliferation, differentiation, and apoptosis. The best-studied ncRNAs are microRNAs (miRNAs), which are 22-nucleotide sequences that bind the 3′ untranslated region of target mRNA. Binding of miRNA to its target leads to mRNA degradation or translational repression. Although mRNA silencing through this mechanism does not directly inhibit gene transcription, miRNAs prevent protein expression and are considered by many to be an epigenetic mechanism. Expression of miRNA is itself regulated by DNA methylation, in much the same way that methylation alters the expression of protein-coding genes. Alteration of DNA methylation patterns can thus be responsible for deregulation of miRNAs and can consequently alter the expression of target genes.

These epigenetic marks together compose the epigenome and work in combination to regulate genome-wide expression patterns throughout life. Epigenetics is critically important during the earliest stages of development and during differentiation of distinct cells and tissues. Epigenetic marks are replicated during mitotic cell division, with the result that cells of the same lineage will have the same epigenome and will express the same phenotype. Factors that alter the epigenome can therefore have lasting effects.

Epigenetic Gene-Environment Interactions

Epigenetic regulation is important from conception through adulthood; it first regulates gene expression in the generation of specific cell types, and it then ensures that cells maintain their differentiated state through cell division. The mitotic stability of epigenetic marks enables proliferating cells to maintain the same phenotype and function during growth, renewal, or healing processes. However, it also means that detrimental epigenetic marks will be carried to successive cell divisions. Because the epigenome can be altered by environmental factors, epigenetics is emerging as an etiological factor in a number of chronic conditions, including cancer, obesity, type 2 diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, chronic inflammatory diseases, and immune diseases.

The environment during embryogenesis is particularly important in establishing epigenetic marks, because reprogramming occurs shortly after fertilization and during germ cell differentiation. Although the mechanisms of methyl erasure and restoration are an active area of research, it is clear that several factors—including availability of methyl groups, exposure to environmental toxicants, and/or other stresses—can impact this process and can have effects well beyond the developmental period. The hypothesis that adult-onset diseases may have developmental origins is supported by studies of gestational exposures in both animals and humans. A number of environmental factors—including nutrition, toxicants, and stress—have been shown to have epigenetic effects [8]. In humans, prenatal exposure to famine was found to increase the incidence in adulthood of impaired glucose tolerance, obesity, coronary heart disease, lipid profile, hypertension, and schizophrenia, depending on gestational timing and the sex of the individual [9].

Although certain developmental stages represent particularly sensitive periods, epigenomic plasticity occurs in somatic cells throughout life. Epigenetic marks acquired over time may contribute to adult-onset diseases, especially age-related conditions, for which lifelong accumulation of epigenetic marks would be expected to increase risk. Most environmental epigenetic effects involve exposure of somatic cells, and these mitotically stable marks are passed down within a cell line. However, epigenetic states may be meiotically inherited from one generation to the next; this occurs when epigenetic marks are acquired during germline formation. Transgenerational inheritance of epigenetic marks is dependent on DNA methylation patterns that become programmed into the germline. Epigenetic inheritance occurs under normal circumstances in imprinted genes that express parent-specific methylation patterns. These genes are protected from reprogramming in the developing embryo. However, DNA methylation is erased and reestablished for most genes during primordial germ cell migration and gonadal sex determination. Thus, sex determination represents an exceptionally sensitive time period for epigenetic modification by environmental factors. One study uncovered evidence of transgenerational environmental effects in humans when preadolescent paternal smoking was found to be associated with greater body mass index in sons only, and paternal grandfathers' food supply was found to be correlated with grandsons' mortality risk [10].

Implications for Health Care

Recent research has improved our understanding of epigenetic mechanisms and has fostered both excitement and questions about the application of epigenetics to medicine. Epigenetic information has many potential applications in health care, including both therapeutic and diagnostic uses. Because the epigenome is responsive to environmental influences such as diet, prevention strategies are well recognized. Public health could also benefit from greater awareness of the effects of diet and lifestyle on chronic diseases such as obesity and type 2 diabetes, not only in the present generation but also in future generations. In addition, gene-specific alterations can potentially be used as biomarkers for diagnosis, classification, and prognosis; many studies are being carried out to explore possible uses of gene-specific alterations in cancer. Moreover, identification of developmental epigenetic changes that predispose an individual to late-onset diseases could facilitate early diagnosis, and preventive or therapeutic strategies could be implemented before these diseases present clinically. Since epigenetic changes tend to be reversible, there are also opportunities

for epigenetic drug development to restore healthy epigenetic states. However, safety and efficacy testing of such drugs may be complicated, because epigenetic modifications are tissue-specific.

Because epigenetics has the potential for medical applications, it raises a number of ethical issues [11], many of which are similar to the ethical issues associated with genetic information. Epigenetic analysis could generate a vast amount of sensitive information concerning the risk of developing chronic disease and the possible transmission of that risk to offspring, leading to privacy and confidentiality issues. There is also the potential for discrimination based on an individual's epigenetic information, both in employment and insurance settings. This is especially important for women of childbearing age, given the early developmental sensitivity of the epigenome to environmental exposures. Epigenetics also highlights the effects of inequality in living and working conditions; harmful exposures are associated with socioeconomic status, so certain populations may be at greater risk of epigenetic alterations. These and many other questions will need to be addressed as epigenetics becomes integrated into our health care system and medical knowledge base. Although the discipline of epigenetics is still in its infancy, advances in the field hold promise for improved human health. NCMJ

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Running the Numbers

A Periodic Feature to Inform North Carolina Health Care Professionals About Current Topics in Health Statistics

North Carolina's Genetic Counseling Program: Empowering Families with Genetic Knowledge

Every year in North Carolina, approximately 4,000 infants are born with major birth defects [1]. The overall risk that a baby will be born with a physical and/or mental disability is estimated at 3%–5% [2, 3]. Because many of these conditions are not detectable at birth, the percentage of affected individuals increases throughout childhood. For example, data from the National Health Interview Surveys, which are conducted by the Centers for Disease Control and Prevention, show that approximately 1 in 6 children aged 3–17 years had a developmental disability in 2006–2008 [4]. Because most of these conditions have at least some genetic basis, it is important that affected individuals and their families understand the role that genetics plays in the disease or disability.

The Definition Task Force of the National Society of Genetic Counselors' has stated that the genetic counselor's role is to help people "understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" [5]. This task force also notes that the genetic counseling process integrates 3 key elements: "interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; [and] counseling to promote informed choices and adaptation to the risk or condition" [5].

History

The North Carolina Division of Public Health has pioneered innovative statewide genetic services. The need for heightened public awareness of and increased access to genetic services in North Carolina was recognized almost 50 years ago, following the implementation in 1966 of a newborn screening program for phenylketonuria (PKU). The state's public health genetics program, established in 1970, was one of the first such programs in the nation.

One of the first actions of this new program was to develop a genetic services contract between the Maternal and Child Health Section of the North Carolina Division of Public Health and the Department of Pediatrics at the University of North Carolina School of Medicine. The purpose of the contract was to aid in the prevention of intellectual impairment by providing prompt follow-up when infants are identified has having PKU. During the early phase of the program, North Carolina began to develop additional connections among a variety of stakeholders, including experts in genetic health care, public and private agencies, educational institutions, medical schools, the state legislature, and public health programs.

With passage of the 1976 National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs and Genetic Diseases Act [6], North Carolina was able to obtain funding for a statewide public health genetic network. With this funding, the state hired 4 regional public health genetic counselors to provide genetic education, to serve as liaisons between communities and medical genetic centers, to provide genetic counseling, to receive referrals, and to coordinate satellite clinics. The ultimate goal of the statewide network is to enhance access to genetic resources for families across the state. These services are offered through the North Carolina Public Health Genetics and Newborn Screening Unit, which now

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includes the Newborn Metabolic Screening and Follow-up Program, the Early Hearing Detection and Intervention Program, and the Genetic Counseling Program. The mission of the North Carolina Public Health Genetics and Newborn Screening Unit is to help identify at-risk children and their families; to provide early diagnosis, intervention, and treatment; and to support prevention through increased awareness of and improved access to genetic services.

Organization of the Genetic Counseling Program

North Carolina's public health genetic counselors are employed by the Division of Public Health, Children and Youth Branch, and they are located in Asheville, Charlotte, Greenville, and Wilmington (see Figure 1). Genetic services at satellite clinics are provided through contracts with 5 medical centers across the state: UNC Hospitals, Wake Forest University School of Medicine, Fullerton Genetics Center/Mission Health, Brody School of Medicine at East Carolina University, and Carolinas Medical Center. The satellite clinics are coordinated by the public health genetic counselors, who work in conjunction with medical geneticists from the aforementioned institutions to provide clinical genetic evaluations. These clinics provide access to genetic services for families who otherwise might not receive such services.

Services

The main responsibilities of North Carolina's public health genetic counselors are to coordinate satellite genetic clinics, to provide genetic consultation services to families and health care professionals, and to increase public and professional awareness through education. Their specific roles include assisting with the coordination of satellite genetic clinics; offering professional consultation to help identify and refer patients in need of genetic evaluations; providing genetic counseling services to patients and their families; identifying educational resources related to specific genetic syndromes and offering those resources to families and health care professionals; making educational presentations on a variety of genetic topics; and helping to integrate genetic services into other public health programs throughout the state.

Figure 2 shows the 3 main types of services provided by the public health genetic counselors; these data come from quarterly reports of the North Carolina Genetic Counseling Program for the period 2009–2012. Educational activities accounted for 35.7% of all the services provided by

FIGURE 1.
North Carolina's Public Health Genetic Counselors and the Regions They Serve, 2013

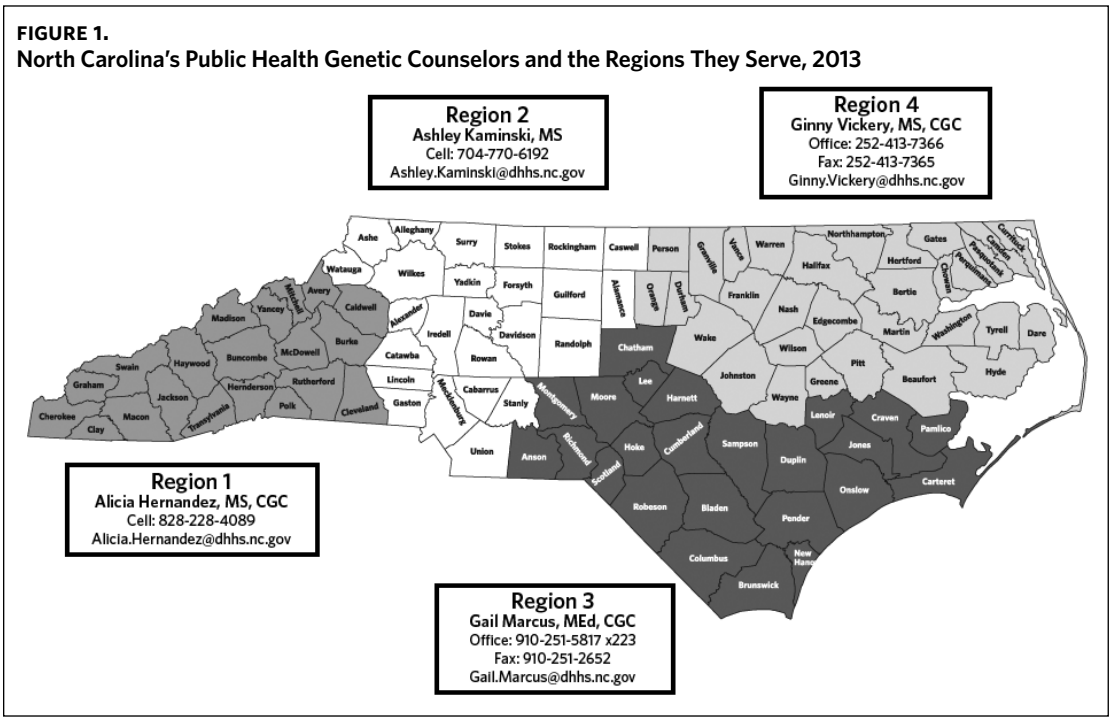
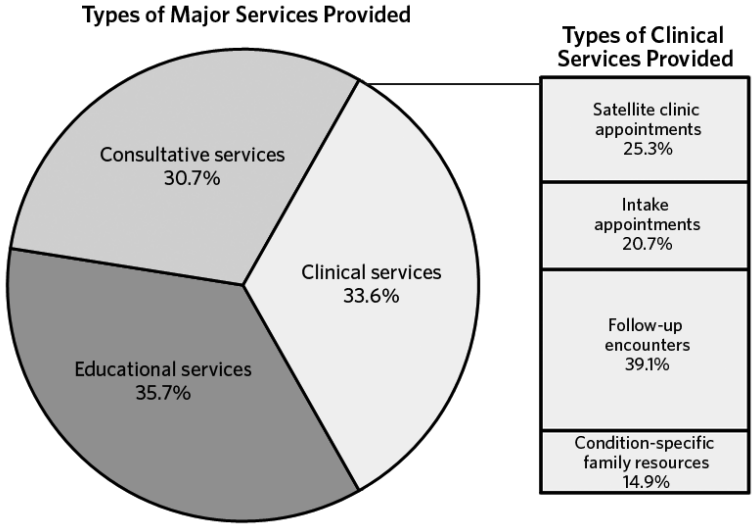


FIGURE 2.
Services Provided by North Carolina's Public Health Genetic Counselors, 2009–2012



Source: Data are from quarterly reports of the North Carolina Genetic Counseling Program, 2009–2012.

the counselors during the period 2009–2012, followed by clinical services (33.6%) and consultative services (30.7%). Figure 2 also includes a breakdown of the clinical services provided by the public health genetic counselors. The majority of clinical services were follow-up encounters (39.1%) and satellite clinic appointments (25.3%). Over the years, attendance at the satellite clinics has been very high, with the percentage of kept appointments consistently averaging more than 82%. The public health genetic counselors try to identify underserved populations that may benefit from the increased access provided by these satellite clinics.

Genetic counselors are also seeing increased uptake of their consultative services. Health care providers and early intervention program workers can seek guidance from public health genetic counselors regarding the appropriateness of possible genetic referrals, case management guidelines, and supportive technical assistance in ordering appropriate genetic testing and locating genetic services; they can also request information about specific genetic conditions. More families are being referred for genetic counseling appointments when they have known genetic diagnoses or risk factors that can be addressed by a public health genetic counselor. Counseling-only appointments do not require the services of a medical geneticist because testing is not being ordered; however, the genetic counselor may make testing recommendations to the referring physician. To enhance awareness of the Public Health Genetics and Newborn Screening Program, public health genetic counselors offer educational activities designed to engage a variety of audiences, including employees of local health departments, other public agency staff members, private medical providers, students, and the general public.

More information about genetic counseling services in North Carolina can be found at the North Carolina Department of Health and Human Services Web page (http://www.ncdhhs.gov/dph/wch/families/geneticcounseling.htm) and in the publication *North Carolina State Genetic Services: A Guide for Health Professionals* (http://www.ncdhhs.gov/dph/wch/doc/families/NC-StateGeneticServicesGuide-noCoverGraphic.pdf). NCMJ

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Acknowledgment

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Philanthropy Profile

Mobile Mammography:
Driving Preventive Care for Underserved Women

Since its inception in December 2007, the Kay Yow Cancer Fund has raised almost $8 million and has awarded grants totaling more than $2.7 million in support of cancer research and clinical trials of experimental drugs, and future research grants are currently under consideration. The fund was founded by its namesake, Kay Yow, a Hall of Fame women's basketball coach who led NC State to more than 700 wins and led the US Olympic team to gold at the 1988 Olympic Games in Seoul, South Korea; Yow was also inducted into the Naismith Basketball Hall of Fame and was the recipient of the first Jimmy V ESPY Award for Perseverance. Yow was first diagnosed with breast cancer in 1987, and she died of the disease in 2009.

Yow believed that her life was extended by her participation in experimental trials, and she appreciated her good fortune in being able to receive high-quality care from cancer specialists in the Triangle area. She wanted to give other cancer patients the same opportunity to access experimental drugs; in keeping with this wish, the majority of grants awarded to date by the Kay Yow Cancer Fund have gone to research projects coupled with clinical trials. The Kay Yow Cancer Fund partners with The V Foundation for Cancer Research and its scientific advisory board to solicit, review, and award research grants.

In 2012, however, the Kay Yow Cancer Fund decided to contribute to a new kind of venture. Joining forces with the Rex Healthcare Foundation, the Kay Yow Cancer Fund decided to support the Rex Healthcare Mobile Mammography Unit. Although this project is a departure from the organization's efforts to support cutting-edge research, the decision to participate in this project also stemmed from Yow's vision and mission for the fund. Nora Lynn Finch, president of the Kay Yow Cancer Fund and longtime friend of Yow, explained that Yow gave the board clear and direct instructions before her death: "Research for the cure. Research for drugs. Serve the underserved." The mobile mammography project was a way to fulfill the third prong of Yow's directive, so the fund's leaders were eager to become involved.

The Kay Yow Cancer Fund partnered with Rex Healthcare to acquire an advanced mobile mammography system for a mobile clinic. The mobile clinic, affectionately nicknamed "The Coach," is painted bright pink and features a towering portrait of Yow on its side. With the addition of this mobile clinic, Rex Healthcare's mobile mammography unit now includes 2 vehicles that canvas 17 counties in the Piedmont and Eastern regions of North Carolina. By traveling to local businesses, churches, schools, and civic groups, these vehicles remove the barriers of time, transportation, and resources that otherwise prohibit women from receiving these vital screenings.

Angela Harris, development officer for the Rex Healthcare Foundation, reported that the mobile mammography unit provided a total of 5,078 mammograms in 2012, with 1,952 of these mammograms being provided free of charge to women who did not have health insurance or who had prohibitively high deductibles. Mammograms are critically important because early detection of cancer greatly increases the chance of successful treatment—a fact that Yow understood well. Before her diagnosis in 1987, Yow's busy schedule caused her to delay seeing a doctor; after the team physician insisted, however, she finally underwent a mammogram. That mammogram was positive for a small mass, but thanks to its early detection, Yow was able to start treatment right away. Had she delayed her screening, the outcome might have been very different.

At the time of her diagnosis, Yow faced the difficult decision of whether to undergo treatment quietly or to go public with her battle. When Yow

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was first diagnosed in 1987, many still considered breast cancer to be a taboo topic, and most women chose to keep their struggles with the disease private. Yow had reasons to take her fight public. As Finch explains, "Kay was fine with people being private, but she knew that her purpose was higher than coaching basketball. Kay understood that her disease and battle provided an opportunity to serve others by taking her fight public." Today, great strides have been made in raising awareness about breast cancer—thanks to the efforts of Yow and organizations like the Kay Yow Cancer Fund and others—and each October a range of events and fundraisers are held in recognition of Breast Cancer Awareness Month.

Yow was open and public about her experiences from her first diagnosis; as time passed, her influence as a leader for the cause continued to grow. Finch believes that Yow really began to hit her stride in 1996, when both Yow and Finch served on the executive committee for the US Women's Open Golf Championship at Pine Needles Lodge and Golf Club in Southern Pines, North Carolina. That year a unique new model was employed to combine the tournament with a charitable cause, and the event was used to raise money for breast cancer research. According to Finch, the experience was instrumental for Yow because "it gave her the platform to articulate a message of women's golf, North Carolina, and breast cancer." Following that tournament, Yow established a number of annual events to raise money and spread awareness about the disease, including the Hoops 4 Hope NC State basketball game, the 4Kay Golf Classic, the Play 4Kay national initiative, and the 4Kay Run during the Women's Final Four.

The Rex Healthcare Mobile Mammography Unit is more than just a vehicle to deliver cancer screenings to the underserved; it is also one more way in which the Kay Yow Cancer Fund is raising awareness about breast cancer and the importance of mammogram screenings. "We get calls all the time from people who say 'I was driving down I-40 and saw the RV with Coach Yow on the side!'" says Susan Donohoe, Executive Director of the Kay Yow Cancer Fund. Rumbling across North Carolina, "The Coach" is a fitting tribute to Yow's larger-than-life legacy in the state. NCMJ

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Spotlight on the Safety Net

A Community Collaboration

Meeting the Perinatal Care Challenges of Eastern North Carolina

Improving the health of mothers and infants is an ongoing challenge throughout North Carolina, but the problems are particularly overwhelming in the eastern part of the state. The expansive area of Perinatal Care Region VI in Eastern North Carolina encompasses 29 counties and 22,000 annual births, 31% of which are to black mothers [1], and this region contains a disproportionate share of counties with the highest rates of maternal and infant mortality in North Carolina. Despite significant perinatal morbidity and mortality, and an epidemic of high-risk pregnancies, Region VI is predominantly supported by a single high-risk maternity clinic.

The Eastern Carolina University (ECU) High-Risk Maternity Clinic is the sole referral point for high-risk pregnancies in Eastern North Carolina. The clinic offers the services of board-certified maternal-fetal medicine specialists and accepts patients from all referral sources, regardless of a patient's ability to pay; the clinic also does not collect funds from uninsured women with household incomes lower than the federal poverty guidelines. The clinic cares for approximately 2,500 unique patients per year who have a variety of high-risk problems, including maternal complications such as hypertension, diabetes, obesity, HIV infection, and substance abuse; obstetrical problems such as preeclampsia, preterm labor, premature rupture of membranes, and multifetal gestations; and fetal complications, including congenital anomalies, aneuploidy, and growth restriction. The clinic offers prenatal care, education, management, and treatment. In addition to maternal-fetal medicine specialists, the clinic's ancillary staff includes perinatal nurse specialists, medical assistants, registered diagnostic sonologists, a certified dietitian and diabetes educator, and a licensed social worker.

The ECU High-Risk Maternity Clinic treats many patients who have only Medicaid coverage or who are uninsured. Despite the financial challenges of sustaining such a practice, the staff members of this clinic have managed to continue offering their outstanding services to women with high-risk pregnancies in Eastern North Carolina. In 2009 the North Carolina Child Fatality Task Force and its Perinatal Health Committee recognized the critical mission of this underfunded clinic and recommended that the North Carolina General Assembly appropriate state funds to support the clinic. The General Assembly agreed that the mission of the clinic was vital, and it initiated support through the Department of Public Health via the state's Title V Maternal and Child Health Services Block Grant. In the 2013 legislative session, the General Assembly appropriated $375,000 to support the clinic's work; this funding was part of an amendment to Senate Bill 402.

The need for a high-risk maternity clinic in Region VI is obvious, given the demographic characteristics of Eastern North Carolina, and there is also a powerful economic case for state support for this clinic. Despite its use of state funds, the ECU High-Risk Maternity Clinic actually saves the state money. An extremely premature infant is not only at high risk for severe morbidity or death, but the birth of such an infant is also enormously expensive for the state. An infant born at 24–26 weeks gestation may be hospitalized for 100–200 days, and the cost for such hospitalizations commonly reaches $250,000 [2]. This figure includes only the short-term cost of hospitalization; it does not include the decades of medical care that the state ultimately provides for children born prematurely,

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nor does it include the costs of educating these children in the state's public schools.

One example of the care provided at the ECU High-Risk Maternity Clinic is management of preeclampsia. Maternal-fetal medicine specialists and other clinic staff members regularly care for mothers with preeclampsia, and many of these mothers have had their pregnancies extended as a result of this care. By safely extending these high-risk pregnancies, the clinic offers infants a chance for survival with markedly reduced complications. Skillfully implementing these best practices also offers a tremendous return on investment. The ECU clinic has dramatically shifted the prematurity curve at this institution over the past 5 years. Extending 1 pregnancy from 24 weeks to 28 weeks saves $125,000 [2]. Data from ECU reveal that the clinic extends the pregnancies of 10 women with early-onset severe preeclampsia per year. This is just one area of care in which the ECU clinic is altering the perinatal landscape in Eastern North Carolina; other premature births are also being prevented.

The ECU High-Risk Maternity Clinic is committed to delivering high-quality care to a population in desperate need. The dedication and innovation of the staff members exemplify high-quality service, and the clinic has had a profound impact. Although the proportion of infants with a low birth weight has dropped in Eastern North Carolina, there is still much work to be done. Despite the challenges, staff members of the ECU High-Risk Maternity Clinic are in this fight for the long haul and are determined to win this battle. NCMJ

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Opioid Pain Control:
Safe or Effective?

Allan Zacher

To the Editor—I wish to compliment you on addressing the subject of chronic pain in the May/June 2013 issue of the NCMJ. This is a very appropriate and timely topic, but I would like to bring up an issue that state and federal agencies do not seem to be addressing.

The concept of evidence-based medicine has become one of the touchstones of modern medical recommendations. The idea is that there should be a high level of scientific support for a particular intervention or treatment before widespread use of that treatment consumes resources and potentially harms patients. In some areas this can be difficult; for instance, it is quite hard to find a study proving that parachutes are effective, compared to placebo. With regard to opioid treatment for chronic pain, however, not only have there been years of research, but the practice of using opioids to treat chronic pain has come under close scrutiny because there are so many adverse outcomes, including the potential for deaths due to opioid overdose. Indeed, the rate of death from opioid overdose now exceeds the rate of death from motor vehicle accidents.

There is basically no evidence supporting the use of opioids for chronic pain, despite such evidence being sought. Furthermore, most studies have compared opioids to placebo for relatively short periods of time, often 4–6 weeks; the longest study I am aware of lasted 12 weeks. There was a very good study by Eriksen and colleagues [1] that concludes, "it is remarkable that opioid treatment of long-term/chronic non-cancer pain does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity."

When are physician organizations going to start pointing to the emperor with no clothes and give voice to the lie, promulgated by drug companies, that these medications are safe and effective? This has created untold wealth for the drug companies and left a huge swath of death and disability, as well as destruction of lives due to iatrogenic addiction. It is time that medical societies begin practicing what they preach; they should not encourage expensive and dangerous interventions and treatments until there is evidence to support that they actually improve patients' lives. NCMJ

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Acknowledgment

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Health Care Costs Must Come Down

Ron Howrigon

To the Editor—There has been heated debate and discussion surrounding health care reform, the health insurance marketplaces, and what all of this will mean for the American people. There are wide-ranging opinions, including the belief that health care reform will solve all of our problems, or that the end is near and the whole system is going to implode. As a physician consultant with a master's degree in economics, I believe we are paying too much attention to the small details and not enough attention to the bigger picture.

What seems most obvious is that our health care delivery system is going to change. This country is spending too much money on health care, and it is impacting our economy and our state and federal budgets. In 1960, health care accounted for 5% of the gross domestic product (GDP), while defense spending accounted for 10% of the GDP. Now, health care is approaching 20% of the GDP, while defense spending is down to 5%. This trend cannot continue. If you do not believe me, consider the housing market over the last 20 years.

So, we know that health care costs must come down and that we cannot continue on the inflationary trend that we have experienced over the past 50 years. Knowing this, my main questions are: What will this mean for our health care delivery system and for those who provide and receive care? Also, will the Affordable Care Act help or hurt this process?

Unfortunately, when it comes to costs, I do not believe the Affordable Care Act will help to control costs. I just do not see how it is possible to add that many people to the roles of the insured, many of them subsidized by the federal government, and actually *reduce* costs. The argument is that by insuring these people, they will utilize less costly care, but I am not buying it.

If the Affordable Care Act does not control costs, what will happen? That remains to be seen. My biggest concern is that we will try to control costs by drastically reducing reimbursement to physicians. I dread the thought of a system in which everyone is insured but there are not enough doctors left to provide care. NCMJ

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