CDKN2A/p16 Genetic Test Reporting Improves Early Detection Intentions and Practices in High-Risk Melanoma Families

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Abstract

Genetic testing for melanoma has yet to enter routine clinical use because of the scarcity of available data on the effect of test reporting. A prospective study of 59 members of Utah *CDKN2A/p16* mutation–positive pedigrees was conducted to establish the effect of *CDKN2A/p16* genetic test reporting on melanoma early detection intentions and behaviors (total body skin examination and skin self-examination) in a high-risk population. Behavioral assessments were made at baseline, immediately after *CDKN2A/p16* test reporting and counseling, and at 1-month follow-up (42 participants). Baseline screening practices were poor relative to current recommendations, especially among participants without a personal history of melanoma. Changes from baseline practice were evaluated in three groups of participants (*CDKN2A/p16*$^+$ with history of melanoma, *CDKN2A/p16*$^+$ without melanoma history, and *CDKN2A/p16*$^-$). Across multiple measures, test reporting caused *CDKN2A/p16* mutation carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history, without decreasing compliance of the *CDKN2A/p16*$^-$ group. Compared with baseline, *CDKN2A/p16*$^+$ participants without a melanoma history reported greater intention to obtain total body skin examinations ($P < 0.0001$), increased intentions and adherence to skin self-examination recommendations ($P < 0.01$ and $P < 0.001$, respectively), and increased number of body sites examined at 1 month ($P < 0.002$); further, 55% reported adopting a new screening behavior at follow-up. Test reporting also improved skin self-examination adherence among *CDKN2A/p16*$^-$ participants ($P < 0.03$). The finding that *CDKN2A/p16* test reporting enhances compliance with early detection measures among *CDKN2A/p16*$^+$ participants without diminishing the compliance of *CDKN2A/p16*$^-$ participants suggests a favorable risk-benefit ratio for melanoma genetic testing in high-risk patients. (Cancer Epidemiol Biomarkers Prev 2008;17(6):1510–9)

Introduction

In the United States, an estimated 62,480 persons are expected to develop melanoma in 2008, and it is now the sixth and seventh most common cancer developed in men and women, respectively (1). An estimated 5% to 10% of melanomas are hereditary, and among melanomas having a hereditary pattern, an estimated 20% to 40% are associated with a pathogenic mutation in *CDKN2A/p16* (2, 3). Individuals in the United States who carry a *CDKN2A/p16* mutation have a 76% estimated lifetime risk of developing melanoma. Although the 5-year survival rate is 99% for localized melanoma, 5-year survival rates for regional and distant-stage diseases are 65% and 15%, respectively (1). Given the exceptionally high probability of developing melanoma in the *CDKN2A/p16* population and the poor prognosis of late-stage disease, it may be useful to identify and warn *CDKN2A/p16* mutation carriers of their high-risk status before the development of melanoma.

No published study has assessed the effect of genetic testing for melanoma on screening behaviors. Clinical genetic testing is routinely offered to high-risk breast cancer and colon cancer patients, and the favorable risk-benefit ratio of test reporting has been well documented (4-9). In contrast, genetic testing for melanoma has lagged behind, although the major predisposition genes for the three cancer syndromes were identified in very close proximity [*BRCA1/BRCA2* (10, 11), *MLH1/MSH2* (12, 13), and *CDKN2A/p16* (14, 15)] to one another. Variable penetrance estimates among different ethnic and geographic populations and known interactions with modifier genes have posed unique challenges for genetic counseling about *CDKN2A/p16* mutations. Penetrance estimates for *BRCA1/BRCA2* and *MLH1/MSH2* have ranged from 37% to 85% (16, 17) and from 38% to 78% (18-20), respectively, depending on whether studies have been population based or conducted with high-risk families. Estimates for *CDKN2A/p16* mutation penetrance have varied greatly (28-91%) depending on study design as well as ethnic background, regional UV

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intensity, and coinheritance of variants in MC1R (21-23), and these factors must be incorporated into risk assessment. Melanoma genetic testing has been considered controversial for additional reasons, including concerns that a report of a negative test result might lead to a false sense of security, that reporting positive test results might create psychological distress, and that genetic test reporting would not result in any advantage over counseling based on family history alone (24, 25).

Early detection of melanoma has dramatic potential to save lives because of the exceptionally good outcome for thin melanomas and poor prognosis for advanced melanomas (1, 26, 27). Skin screening examinations by medical professionals result in the identification of thinner melanomas (28, 29). It is also well established that the majority of melanomas are detected by the patients or their spouses (28, 30, 31). Indeed, such findings have led the American Academy of Dermatology (32) and GenoMel (an International Melanoma Genetics Consortium; ref. 33) to recommend that patients at risk for melanoma receive total body skin examinations (TBSE) at least annually and do skin self-examinations (SSE) monthly. These two screening strategies are the major components of early detection programs in melanoma. This report examines how *CDKN2A/p16* test reporting influences compliance with TBSE and SSE screening recommendations by evaluating the participants' intentions as well as actual reports of behavior 1 month later.

Patients and Methods

Study Population and Procedures. The studies were approved by the Institutional Review Board of the University of Utah (Institutional Review Board nos. 7916 and 13816). A total of 77 adult research participants from two large melanoma pedigrees enrolled in previous *CDKN2A/p16* identification studies (14, 34) had contributed DNA samples for research genetic testing. Each of these samples was subjected to genetic testing through a Clinical Laboratory Improvement Amendments–certified laboratory (Myriad Genetic Laboratories or Yale University School of Medicine DNA Diagnostic Laboratories), and the participants were offered the opportunity to receive these results. None of the participants were aware of their genetic status before their participation in this study. In previous communications with the melanoma research program (in-person clinic visits at the time of enrollment in the gene discovery study from 1986 to 1993 and again at the time of reenrollment between 2001 and 2005), all participants had received information about their elevated risk of melanoma based on family history as well as detailed verbal and written recommendations about photoprotection and screening. The participants' most recent counseling took place at the reenrollment clinic visit an average of 2.5 y (SD, 11 mo; range, 3.9-50.1 mo) before their genetic counseling appointment.

From May to November 2005, 64 (83.1%) of these individuals completed a baseline questionnaire and a genetic counseling and test reporting session (for genetic counseling protocol, see Supplementary materials). Of the eligible participants who did not participate in this study, seven expressed interest but were unable to participate or were not present at the clinic, two were out of the country for an extended period of time, one could not be located, one did not respond, and two declined to participate.

During predisclosure genetic counseling sessions, participants received melanoma genetics education and, after informed consent, were offered the opportunity to receive their genetic test result. After result disclosure, the meaning of the result was reviewed, and tailored screening and management recommendations were provided. All 64 participants elected to receive results, and 62 participants completed the immediate follow-up questionnaire. Of the 59 participants eligible for the follow-up study, 53 enrolled and 45 (76.3%) completed the 1-month follow-up questionnaire.

Measures

Demographics and Melanoma History. The participants completed standard demographic questions assessing age, gender, education level, marital status, and household income. We confirmed the melanoma history of each participant through the Utah Cancer Registry (a Surveillance, Epidemiology, and End Results Registry) and the Utah Population Database.

Genetic Testing Result. Sequence analysis showed two pathogenic *CDKN2A/p16* mutations in our study population: V126D and G-34T (in the 5′ untranslated region).

Behavioral Assessments. Data were collected at three time points: baseline reports of behaviors during the previous 6 mo, immediate postcounseling intentions, and, in the case of SSEs, 1-mo follow-up behaviors. Questionnaire items, response options, and order were designed to minimize participant effort while maximizing validity. First, the participants reported changes in behavior at the 1-mo follow-up in their own words before answering quantitative assessments to avoid potential response bias. Specifically, the participants were asked to indicate if they had made any new plans about screening behaviors following their genetic counseling session and, if so, to describe them.

Next, quantitative assessments of baseline screening behavior used both numerical (e.g., estimated number of SSEs in the past 6 mo) and verbal (e.g., weekly, once every few months) items to provide multiple assessments and to capture self-reports of screening behavior in ways that did not rely exclusively on the participants' ability to recall specific numbers of SSEs over a 6-mo interval. Additionally, comparative intention items were used in the postcounseling assessment for the same reason. Following the test reporting session, the participants were asked to report SSE intentions for the next 6 mo, first in verbal terms (e.g., about once a week or more, about once every 2-3 mo) and then relative to their current practice (1, much less than I have been doing; 3, about the same as I have been doing; 5, much more than I have been doing).

Finally, we examined multiple screening behaviors by assessing the reported receipt of professional TBSEs, frequency of SSE practice, and thoroughness of SSE and then evaluated each relative to recommendations made in the genetic counseling session (at least one annual TBSE, one monthly SSE, thorough and systematic SSEs). In particular, with respect to monthly SSEs, the participants were explicitly counseled that less frequent SSEs

might delay a diagnosis unnecessarily and that more frequent SSEs might diminish their ability to identify interval change in specific lesions.

Professional TBSE. The participants were asked at baseline whether they had received a TBSE in the last year and to indicate how many they had received in the last 5 y. Following test reporting, the patients indicated whether they intended to obtain a TBSE in the next year and their likelihood of obtaining TBSE in the future relative to current practice.

Frequency of SSEs. Items assessing adherence to recommendations for SSEs (both frequency and thoroughness) were adapted from Weinstock and colleagues (35). At baseline, the participants estimated the number of SSEs done in the last 6 mo and used verbal descriptors to characterize their behavior. The two question formats showed excellent correspondence and were converted to a monthly SSE average at baseline. At postcounseling, intentions to do SSEs were assessed with an absolute score based on verbal descriptors (e.g., once per month, every few months) and a separate rating of future intentions relative to baseline practice. At follow-up, the participants reported the number of SSEs done in the past month.

Thoroughness of SSEs. The quality of SSEs was assessed by (*a*) the participants' ratings of thoroughness; (*b*) the number and location of body sites examined from a checklist of 11 body sites, ranging from the scalp to the bottoms of the feet; and (*c*) the frequency with which another person was enlisted to help with the examination.

Results

Participant Characteristics and Demographics. Thirty (48.4%) women and 32 (51.6%) men were enrolled, with an average age of 46 y (SD, 16.13 y; range, 21-89 y). All participants were Caucasian and high school graduates; more than half (54.8%) had completed a bachelor's degree or higher. The median annual income was $50,000 to $59,999. The majority (79%) were married. Thirty-two (51.6%) received positive test results, and 21 (33.9%) had a confirmed personal history of one or more melanomas.

Because a personal history of melanoma was a strong predictor of the participants' baseline practice of screening behaviors, the participants were placed into three groups for analysis: (*a*) those with *CDKN2A/p16* mutation and no history of melanoma ($n = 14$; 22.6%), (*b*) those with *CDKN2A/p16* mutation and a positive history of melanoma ($n = 18$; 29%), and (*c*) those with neither *CDKN2A/p16* mutation nor a history of melanoma ($n = 27$; 43.6%). An additional group of three *CDKN2A/p16*$^-$ participants with a personal history of melanoma was excluded from the analyses reported here. Although this group is an important population to study, it was too small to yield statistically reliable conclusions. Table 1 presents demographic data for the three groups used in the analyses plus the excluded group. No significant difference was found among the three main groups on any demographic measure at baseline, nor was there any difference among groups in the proportion of participants completing the follow-up assessment [$X^2(59) = 1.37$; $P < 0.51$].

Overview of Analyses. As just noted, three groups of participants were retained for analysis: *CDKN2A/p16*$^+$ with no history of melanoma, *CDKN2A/p16*$^+$ with a personal history of melanoma, and *CDKN2A/p16*$^-$ with no history of melanoma. Repeated-measures analyses tested whether *CDKN2A/p16* result reporting led to significant differences from baseline in screening intentions and behavior among the three groups immediately following genetic test reporting and 1 month later. Importantly, for all analyses, there was no evidence of differential attrition at follow-up with respect to any baseline screening measure.

Professional TBSE

Low Baseline Frequency of Professional TBSEs. Through previous participation in our research program, participants had received strong verbal and written recommendations to have a TBSE at least annually based on their familial status. Despite these recommendations, only half (51.7%) of these high-risk participants reported obtaining a TBSE in the past year (Table 2). Participants with a personal history of melanoma were more compliant with TBSE recommendations (77.8%) than the *CDKN2A/p16*$^+$ and *CDKN2A/p16*$^-$ participants without a melanoma history (21.4% and 50%, respectively). Similar group differences were found for the average number of TBSEs in the past 5 years [$F(2, 55) = 10.89$; $P < 0.0001$], with participants with a melanoma history reporting 4.78 examinations compared with 2.57 for *CDKN2A/p16*$^+$ participants with no melanoma history and 1.98 for *CDKN2A/p16*$^-$ participants. There was no significant relationship between time since last clinic visit and baseline reports of TBSEs in either the past year or the past 5 years.

Genetic Test Reporting Increases Postcounseling Intentions to Obtain TBSEs. After genetic test reporting, the majority of participants indicated that they intended to obtain a TBSE in the next year (77.4%) or that they might do so (11.3%), representing a significant increase from baseline (Table 2). A repeated-measures analysis, done to compare each group before and after counseling, revealed a significant group-by-time interaction [$F(2, 54) = 7.17$; $P < 0.002$], such that the greatest increase, from 21.4% to nearly 100% ($P < 0.0001$), was found among *CDKN2A/p16*$^+$ participants with no history of melanoma. Among *CDKN2A/p16*$^+$ participants with a melanoma history, postcounseling TBSE intentions remained high (100%). Both *CDKN2A/p16*$^+$ groups reported significantly greater TBSE intentions than did the *CDKN2A/p16*$^-$ group [$F(2, 54) = 7.76$; $P < 0.001$]. However, TBSE intentions among *CDKN2A/p16*$^-$ participants also increased (from 50% to 65%; $P < 0.13$), revealing no trend toward reduced adherence. Significant increases in TBSE intentions relative to current practice were found for all groups (boldfaced values in Table 2).

Frequency of SSEs

SSE Adherence Metric Development. Initial examination of the SSE frequency data revealed several complexities. The baseline practice of SSEs was highly variable, ranging from 0 to 180 examinations in the past 6 months (see Fig. 1). Further, the meaning and desirability of an increase in the number of exams depended on how frequently the participants reported screening at baseline.

Table 1. Sample characteristics as a function of *CDKN2A/p16* status and melanoma history

	Carriers		Noncarriers	
	No melanoma history (n = 14)	Melanoma history (n = 18)	No melanoma history (n = 27)	Melanoma history (n = 3)
Age (y)	38.00 (14.61)	49.56 (14.05)	44.59 (14.37)	76.33 (14.84)
%Male	71	50	44	33
%Married	85.7	77.8	77.8	100
%Education >high school	92.9	82.2	81.5	33
Median income	$50,000-59,000	$60,000-69,000	$50,000-59,000	$30,000-39,000
No. confirmed melanomas		2.22 (1.26)		1.67 (1.16)

Specifically, although an increase in SSE practice by a participant who has not been conducting monthly self-examinations represents a desirable outcome, such an increase by a participant who is already conducting several such examinations represents an undesirable outcome. Therefore, to make the SSE frequency data interpretable, we created adherence metrics to capture the change in the direction of greater adherence (see below) and stratified some analyses by baseline screening status (underscreeners versus overscreeners) to examine the direction and magnitude of the changes in SSE frequency in each group.

Adherence at each assessment was judged relative to the recommendation of 1 SSE/mo in two ways. First, an average SSE adherence status for each group was calculated by applying a numerical scale to reported screening behavior at baseline and 1 month (underscreeners, <1 SSE/mo = −1; on-target screeners, 1 SSE/mo = 0; overscreeners, >1 SSE/mo = 1). Second, each participant was assigned a change-toward-adherence

Table 2. Baseline TBSE practice in the year before test reporting and in the past 5 y, as well as changes in absolute and relative TBSE intentions compared with baseline following genetic test reporting and counseling, in each group and in the total sample

	Carriers		Noncarriers	Total sample (N = 58)
	CDKN2A/p16$^+$ no melanoma history (n = 14)	*CDKN2A/p16*$^+$ melanoma history (n = 18)	*CDKN2A/p16*$^-$ no melanoma history (n = 26*)	
Baseline TBSEs				
Participants who received a TBSE in the past year at baseline, n (%)	3 (21.4)	14 (77.8)	13 (50)	30 (51.7)
Average no. TBSEs in the past 5 y	2.57	4.78	1.98	2.99
No TBSEs in the past 5 y at baseline, n (%)				
0 TBSEs	3 (21.4)	1 (5.6)	2 (7.7)	6 (10.3)
1 or 2 TBSEs	5 (35.7)	3 (16.7)	19 (73.1)	27 (46.6)
3 or 4 TBSEs	3 (21.4)	3 (16.7)	3 (11.5)	9 (15.5)
5 or 6 TBSEs	2 (14.3)	4 (22.2)	1 (3.8)	7 (12.1)
>6 TBSEs	1 (7.1)	7 (38.9)	1 (3.8)	9 (15.5)
Postcounseling TBSE Intentions				
Participants intending to receive a TBSE in the next year,† %	**97**‡	**100**	65	**83.1**‡
Intended TBSEs in future relative to current practice§	**4.29**‡	**3.33**‖	**3.52**¶	**3.64**‡

NOTE: Values in boldface indicate significant differences from baseline.

*One *CDKN2A/p16*$^-$ participant provided incomplete baseline data. As a result, the sample size in this group varies depending on which screening measure is considered.

†Values of 1 were given to participants who indicated that they intended to obtain a TBSE in the next year, whereas values of 0.5 were given to participants who answered ''maybe.''

‡$P < 0.001$.

§1, much less than I have been doing; 5, much more than I have been doing. Boldfaced values indicate that the group mean was significantly >3.0 (''about the same as I have been doing'') and thus represents a significant intention to increase TBSEs relative to current practice.

‖$P < 0.05$.

¶$P < 0.01$.

score that reflected movement from baseline toward the monthly standard. For example, a participant who reported changing from no SSEs at baseline to 1 SSE/mo received a change-toward-adherence score of +1 and a participant who reported moving from 4 to 2 SSEs/mo received a score of +2. In contrast, a participant who moved away from the target of 1 SSE/mo by increasing from 1 to 4 SSEs/mo received a score of −3 although he reported an increased number of monthly self-examinations.

Genetic Test Reporting Alters the Rates of Overscreening and Underscreening in Each Group

Baseline Rates of SSEs. Figure 1 displays the absolute number of SSEs per month at baseline, the intended frequency of SSEs after genetic test reporting, and the number of SSEs at 1 month for each participant in each of the three groups, with baseline underscreeners shown in red, baseline on-target screeners shown in green, and baseline overscreeners shown in blue. As shown in Fig. 1 and Table 3, the majority of participants were either overscreening [31% (mean, 10.60 SSEs/mo; SD, 10.54)] or underscreening [51.7% (mean, 0.23 SSEs/mo; SD, 0.24)] at baseline. As was the case with TBSEs, participants with a melanoma history reported more frequent SSEs (33% on-target screening, 44% overscreening) than did both groups of participants without a melanoma history [65% underscreening; $X^2(4) = 11.87$; $P < 0.02$]. As was the case for professional TBSEs, there was no relationship between time since last clinic visit and the reported practice of SSEs on any measure.

SSE Rates 1 Month after Genetic Test Reporting. Genetic test reporting resulted in a dramatic drop in underscreening from 51.7% at baseline to 15.4% at 1 month (Table 3). On-target screening doubled from 17.2% to 35.9%. However, overscreening also increased from 31% to 48.7%. The breakdown of adherence categories by group revealed some striking and significant changes. As shown in Table 3 and Fig. 1, among *CDKN2A/p16*$^+$ participants with no melanoma history, underscreening at baseline (64.3%) was replaced by on-target screening (20%) and overscreening (80%) at 1 month. Among *CDKN2A/p16*$^+$ participants with a melanoma history, the majority continued to practice either on-target screening (27.3%) or overscreening (63.6%). On-target screening among the *CDKN2A/p16*$^-$ participants increased from 15.4% to 50% following a negative genetic test result paired with counseling about the importance of continued SSEs.

Genetic Test Reporting Results in Movement toward Greater Adherence to SSE Recommendations. We next examined changes toward adherence in both postcounseling intentions and reported behavior at 1 month. Postcounseling intentions were highly correlated with reported practice of SSEs at 1 month across the sample ($r = 0.62$; $P < 0.0001$). As shown in Table 4, reporting test results to participants in the *CDKN2A/p16*$^+$ no melanoma history group led to a significant change toward intended adherence immediately following test reporting (mean, +0.78), and the magnitude of intended change was significantly greater in this group than in the other two groups [$F(2, 53) = 3.91$; $P < 0.03$]. These group differences were maintained at follow-up [$F(2, 36) = 12.97$; $P < 0.002$], with the *CDKN2A/p16*$^+$ no melanoma history group reporting a highly significant change toward adherence at 1 month (mean, +1.70). The *CDKN2A/p16*$^+$ melanoma history group showed no significant change toward intended adherence at postcounseling, but did show a significant change away from

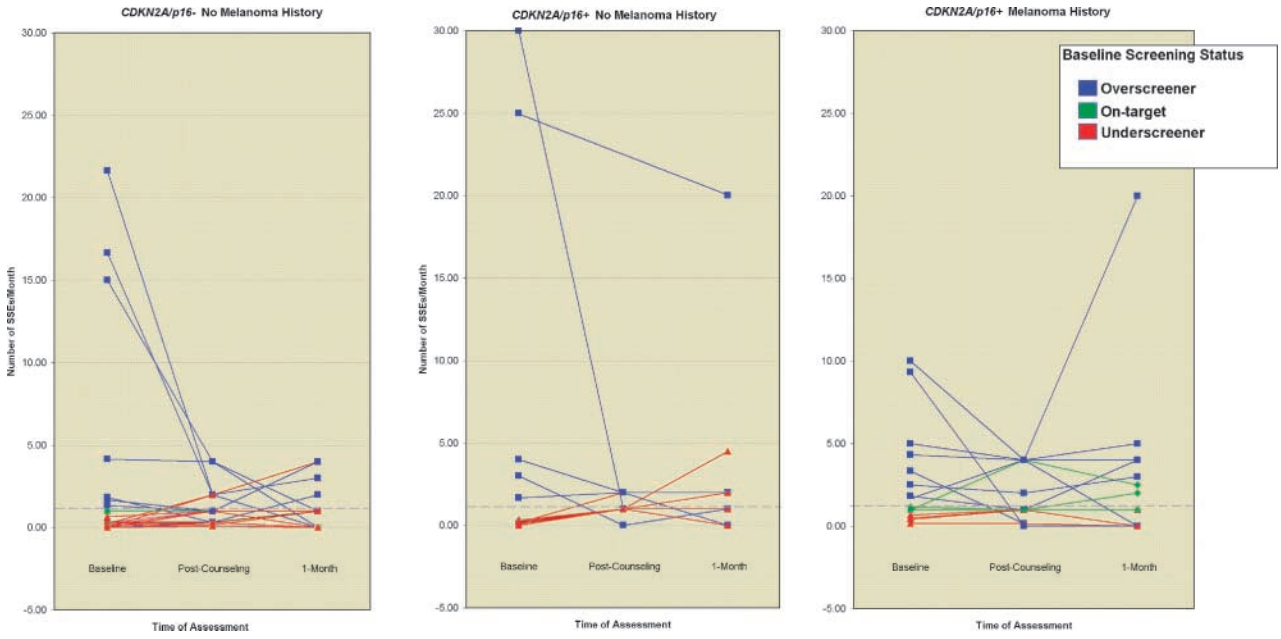

Figure 1. The absolute number of SSEs per month at baseline, the intended frequency of SSEs after genetic test reporting, and the number of SSEs at 1 mo for each participant in each of the three major groups. *Red*, baseline underscreeners; *green*, baseline on-target screeners; *blue*, baseline overscreeners. *Dashed line,* recommended practice of 1 SSE/mo.

Table 3. The number and proportion of participants who reported underscreening, overscreening, or on-target monthly SSEs and the resulting average SSE adherence status at baseline and 1 mo in each group and in the total sample

	Carriers		Noncarriers	Total sample
	CDKN2A/p16$^+$ no melanoma history	*CDKN2A/p16*$^+$ melanoma history	*CDKN2A/p16*$^-$ no melanoma history	
	n (%)			
Baseline screening status*				
Underscreeners	9 (64.3)	4 (22.2)	17 (65.4)	30 (51.7)
On-target screeners	0 (0)	6 (33.3)	4 (15.4)	10 (17.2)
Overscreeners	5 (35.7)	8 (44.4)	5 (19.2)	18 (31.0)
Average SSE adherence status†	−0.29	+0.22	−0.46	−0.21
Screening status at 1-mo follow-up				
Underscreeners	0 (0)	1 (9.1)	5 (27.8)	6 (15.4)
On-target screeners	2 (20)	3 (27.3)	9 (50)	14 (35.9)
Overscreeners	8 (80)	7 (63.6)	4 (22.2)	19 (48.7)
Average SSE adherence status†	**+0.80**‡	+0.55	**−0.06**§	**+0.33**‡

NOTE: Values in boldface indicate significant differences from baseline. Percentages may not sum to 100% due to rounding off.
*To be categorized as on-target, participants had to report conducting an average of 1 SSE/mo over the previous 6 mo at baseline. Underscreeners reported <1 SSE/mo; overscreeners, >1 SSE/mo.
†Underscreeners, −1; on-target screeners, 0; overscreeners, 1.
‡$P < 0.001$.
§$P < 0.05$.

adherence in the direction of greater overscreening at follow-up (see also Fig. 1). Finally, there was no evidence that *CDKN2A/p16*$^-$ participants reported changes in the direction of decreased adherence at either assessment (Table 4; Fig. 1).

Genetic Test Reporting Increases Intended and Reported Numbers of SSEs in Underscreeners. As a complement to the adherence analyses presented above, we examined changes from baseline in the absolute number of intended and reported examinations among underscreeners. As shown in Table 4, initial underscreeners showed significant overall increases in postcounseling SSE intentions [$F(1, 27) = 7.94$; $P < 0.02$] and reported numbers of SSEs 1 month following genetic test reporting [$F(1, 17) = 12.35$; $P < 0.003$]. A significant group-by-time interaction [$F(2, 17) = 6.74$; $P < 0.007$] indicated that the greatest increase was among underscreeners in the *CDKN2A/p16*$^+$ no melanoma history group who increased their practice of SSEs from once every 6 months to >2 in the month following genetic test reporting ($P < 0.0001$).

Virtually identical results were obtained for the relative practice measure (Table 4). The participants in all three groups reported intentions to increase their practice relative to baseline, with the greatest such increases reported by the participants with no melanoma history who received *CDKN2A/p16*$^+$ results [$F(2, 27) = 4.77$; $P < 0.02$]. As was the case for relative TBSE intentions, the group mean for underscreeners receiving negative *CDKN2A/p16*$^-$ test results was significantly >3.0, indicating an average intention to increase SSE practice, and only one *CDKN2A/p16*$^-$ participant in the total sample reported intentions to decrease SSE frequency. Taken together, these findings provide little to no indication of the development of a false sense of security among *CDKN2A/p16*$^-$ participants.

Genetic Test Reporting Reduces Intended, But Not Reported, Numbers of SSEs in Overscreeners. Immediately following genetic test reporting, overscreeners reported significantly decreased SSE intentions compared with baseline [$F(1, 13) = 11.07$; $P < 0.005$], with significant decreases among *CDKN2A/p16*$^+$ no melanoma and *CDKN2A/p16*$^-$ participants (Table 4). However, on the relative practice measure, no group mean was significantly different from 3.0, indicating intentions to continue baseline practice. At 1 month, none of the groups reported a significant change in the number of SSEs, and there were no significant differences among the groups.

Thoroughness of SSEs. Overall, participants with a melanoma history were more likely to report receiving assistance from another person [$F(2, 36) = 3.43$; $P < 0.05$]. There were no significant changes over time for any group in either thoroughness ratings or the frequency with which another person was enlisted to help with the SSE (Table 5).

Number and Location of Body Sites Examined. As shown in Table 5, genetic test reporting increased the number of body sites examined among *CDKN2A/p16*$^+$ participants with no melanoma history from 5.46 at baseline to 8.82 at 1 month [$F(1, 36) = 11.10$; $P < 0.002$; group-by-time interaction, $F(2, 36) = 7.70$; $P < 0.001$]. More detailed analysis indicated significant increases in the examination of the scalp, neck, shoulders, and legs in this group. There was no significant change in the *CDKN2A/p16*$^+$ melanoma history group (from 8.82 to 7.91). Although not significant, *CDKN2A/p16*$^-$ participants showed a trend toward a decrease in the number of body sites examined from 7.41 to 5.82 [$F(1, 36) = 3.83$; $P < 0.06$]. Internal analyses suggest that this downward trend seemed to be due to the inclusion of two participants who reported screening infrequently but thoroughly at baseline. Specifically, two *CDKN2A/p16*$^-$ respondents reported examining 10 of 11 body sites in each SSE, but conducting SSEs only once or twice in the 6 months before test reporting. Neither participant reported a SSE

at follow-up, resulting in a score of 0 sites. When the data were analyzed without these two participants, the mean values for the *CDKN2A/p16*$^-$ group were unchanged from baseline to 1 month (from 7.07 to 6.60 sites; $F < 1$, not significant).

Qualitative Reports of Adoption of New Behaviors at 1 Month. Qualitative reports of the adoption of one or more new screening behaviors at the 1-month follow-up were used to corroborate the reported changes in screening behaviors. These responses were coded by two independent raters with 98% agreement. Overall, 38.1% of participants reported adopting a new screening behavior in the month following test reporting. Of particular interest, 54.6% of participants without a personal history of melanoma who received a positive *CDKN2A/p16* test result reported adopting a new screening behavior, followed by 35% of participants receiving negative test results and 27.3% of *CDKN2A/p16*$^+$ participants with a melanoma history. There were no significant differences among the groups [$\chi^2(2) = 1.89$; $P < 0.39$]. The most frequent new screening behaviors listed were the conduct of more frequent or more

Table 4. Changes toward intended and reported adherence to monthly SSEs and changes in the absolute and relative intended frequency of SSEs immediately after genetic test reporting and at the 1-mo follow-up in each group and as a function of baseline screening status

	Carriers						Noncarriers		
	CDKN2A/p16$^+$ no melanoma history			*CDKN2A/p16*$^+$ melanoma history			*CDKN2A/p16*$^-$ no melanoma history		
	Baseline	Postcounseling	1 mo	Baseline	Postcounseling	1 mo	Baseline	Postcounseling	1 mo
Change toward adherence to monthly SSEs*		**+0.78** †	**+1.70** ‡		−0.04	**−0.45**§		+0.20	+0.15
Intended and reported number of SSEs per month									
Underscreeners‖	0.22	**1.11** †	**2.25** ‡	0.27	0.79	0.50	0.43	0.53	0.75
Overscreeners¶,**	15.12	**2.25** †	6.25	4.10	2.74	7.20	11.87	**2.47**§	2.00
On-target screeners ††	—	—	—	1.00	1.50	1.63	1.00	1.00	2.00
Intended SSEs in future relative to current practice ‡‡									
Underscreeners		**4.78** ‡			**3.75**§			**3.82** †	
Overscreeners		3.60			3.43			3.20	
On-target screeners		—			3.33			3.25	
Total sample		**4.36** ‡			**3.47** †			**3.63** ‡	

	Total sample		
	Baseline	Postcounseling	1 mo
Change toward adherence to monthly SSEs		**+0.26**§	+0.38
Intended and reported number of SSEs per month			
Underscreeners	0.34	**0.74**§	**1.18** †
Overscreeners	9.29	**2.53** †	5.58
On-target screeners	1.00	1.30	1.79
Intended SSEs in future relative to current practice			
Underscreeners		**4.10** ‡	
Overscreeners		3.42	
On-target screeners		**3.30**§	
Total sample		**3.76** ‡	

NOTE: Values in boldface indicate significant changes from baseline.

*Positive values indicate change in either direction toward adherence to the recommendation of 1 SSE/mo; negative values indicate a change in either direction away from the recommendation of 1 SSE/mo. Values in boldface are significantly different from 0 (no change).

†$P < 0.01$.

‡$P < 0.001$.

§$P < 0.05$.

‖Of the 30 underscreeners at baseline, 1-mo follow-up data were available for 6 of 9 participants in the *CDKN2A/p16*$^+$ no melanoma history group, 2 of 4 participants in the *CDKN2A/p16*$^+$ melanoma history group, and 13 of 17 participants in the *CDKN2A/p16*$^-$ group.

¶Of the 18 overscreeners at baseline, 1-mo follow-up data were available for 4 of 5 participants in the *CDKN2A/p16*$^+$ no melanoma history group, 5 of 8 participants in the *CDKN2A/p16*$^+$ melanoma history group, and 3 of 5 in the *CDKN2A/p16*$^-$ group.

**These results are likely to underestimate overscreening intentions immediately following test reporting. It is important to note that the highest score participants could receive at the postcounseling assessment was 4 SSEs/mo (intentions to practice SSEs once a week or more frequently). However, the results reported for significant decreases from baseline in intentions to practice SSEs remained the same when an analogous baseline SSE measure based on verbal descriptors was used to evaluate changes from baseline in postcounseling SSE intentions.

††Of the 10 on-target screeners at baseline, 1-mo follow-up data were available for 4 of 6 participants in the *CDKN2A/p16*+ melanoma history group and 3 of 4 participants in the *CDKN2A/p16*$^-$ group.

‡‡1, much less than I have been doing; 5, much more than I have been doing. Boldfaced values indicate that the group mean was significantly >3.0 (''about the same as I have been doing'') and thus represents a significant intention to increase SSEs relative to current practice.

Table 5. Changes from baseline to 1 mo in the reported thoroughness of SSEs in each group and in the total sample

	Carriers				Noncarriers		Total sample	
	CDKN2A/p16$^+$ no melanoma history		*CDKN2A/p16*$^+$ melanoma history		*CDKN2A/p16*$^-$ no melanoma history			
	Baseline	1 mo	Baseline	1 mo	Baseline	1 mo	Baseline	1 mo
Thoroughness of SSEs								
SSE thoroughness ratings*	2.67	2.61	3.23	2.77	2.38	2.25	2.71	2.50
No. body sites examined during SSEs†	5.46	**8.82**‡	8.82	7.91	7.41	5.82	7.26	7.26
Frequency of enlistment of another person's assistance in the conduct of SSEs§	1.91	1.91	2.82	2.27	1.77	1.47	2.10	1.82

NOTE: Values in boldface indicate significant changes from baseline.
*1, I did not pay close attention to my skin; 2, I casually checked my skin, taking a quick overall look; 3, I only looked at particular marks on my skin; and 4, I did a thorough skin exam.
†Participants used a checklist to indicate whether they had examined each of the following body parts when conducting a SSE: scalp, face, neck, shoulders, back, chest, arms, genitals, legs, feet, and bottoms of feet; they received a score of 1 for each of the 11 body parts checked.
‡$P < 0.01$.
§1, none of the time; 2, some of the time; 3, about half of the time; 4, most of the time; 5, all of the time.

thorough SSEs (26.2%), followed by reports of seeing a doctor more regularly for TBSEs (11.9%). Some respondents specifically noted that they had not adopted any new behaviors because they were already highly compliant with recommendations.

Discussion

This is the first study to prospectively characterize the effects of *CDKN2A/p16* genetic test reporting on screening intentions and behaviors among high-risk melanoma patients. The overall goal of this study was to evaluate the risks and benefits of *CDKN2A/p16* test reporting to assess the clinical utility of the test. The overriding conclusion is that *CDKN2A/p16* test reporting provides benefits to participants by enhancing adherence to recommendations for TBSEs and SSEs. There was little to no evidence for the development of a false sense of security among *CDKN2A/p16*$^-$ members of the families, and in fact, compliance with SSE recommendations increased in this group. Importantly, the benefits of test reporting were maintained at the 1-month follow-up, especially among *CDKN2A/p16*$^+$ participants with no melanoma history. Taken together with recent findings suggesting low overall levels of psychological distress among members of high-risk families anticipating information about the role of genetic factors in their family history of melanoma (36), these findings suggest a favorable risk-benefit ratio for performance of *CDKN2A/p16* genetic testing in appropriate high-risk melanoma populations. It will, of course, be important to determine whether these gains in screening intentions and behavior are maintained over time.

This study yielded novel and potentially useful data on the baseline practice of screening among high-risk melanoma patients. The study participants had been well informed on at least two separate occasions, both verbally and in writing, of their increased risk of melanoma based on family history alone. Despite this previous counseling, there was poor baseline compliance with TBSE and SSE recommendations. These findings are of great concern because they suggest that educating high-risk patients on the basis of family history alone is ineffective, particularly for individuals without a personal history of melanoma. In fact, because of the significant prior effort to educate this population about their risk, it is likely that baseline adherence in our sample exceeds adherence in the larger population of high-risk patients. Further investigation about how to best promote complete monthly examinations and annual TBSEs in high-risk patients is needed.

Across all of our multiple measures of adherence to TBSE and SSE recommendations, a clear and dramatic pattern emerged following genetic test reporting: *CDKN2A/p16* mutation carriers without a history of melanoma improved adherence intentions and behaviors to closely approximate the pattern seen in participants with a history of melanoma. Specifically, *CDKN2A/p16*$^+$ participants without a history of melanoma showed statistically significant increases in the intention to obtain an annual TBSE, in overall number and rates of SSE performance at 1 month, in changes toward adherence to the recommended monthly practice of SSEs, and in the number of body sites examined during SSE performance at 1 month. In each of these measures, the *CDKN2A/p16*$^+$ group without a history of melanoma initially showed values similar to the *CDKN2A/p16*$^-$ group and, following test reporting, showed values similar to *CDKN2A/p16*$^+$ melanoma patients. Furthermore, more than half of these participants reported the adoption of one or more new screening behaviors in the month following test reporting. Thus, one major goal of predictive genetic testing seems to have been reached—that of enhancing performance of early detection behaviors before the development of malignancy.

A major concern about the transition of *CDKN2A/p16* genetic testing into the clinical realm has been whether reporting of negative test status would result in a false sense of security in those individuals who still have a 1.7-fold increased risk for melanoma relative to the general population (24, 25, 37). Therefore, decreased compliance with TBSEs or SSEs following negative test reporting could pose a significant harm. There was only one

indication of a potential reduction among the *CDKN2A/p16*$^-$ participants: a nonsignificant downward trend in one of the three SSE thoroughness measures—the number of body sites examined during SSEs. In fact, following genetic test reporting, *CDKN2A/p16*$^-$ family members reported statistically significant increases in the overall rate of SSE performance at 1 month, and roughly one third reported the adoption of a new screening behavior.

Another major concern about reporting *CDKN2A/p16* test results is that *CDKN2A/p16*$^+$ patients will develop unhealthy behaviors related to the knowledge of their dramatically elevated risk. With respect to our data, we examined whether (*a*) genetic test reporting led to dramatic increases in overscreening and (*b*) genetic test reporting had a deleterious effect on the nearly one third of participants who were already overscreeners at baseline. Our follow-up data clearly indicated that the rates of overscreening increased in both *CDKN2A/p16*$^+$ groups but not to an excessive degree. This suggests that *CDKN2A/p16*$^+$ test reporting does not result in hypervigilance. Nonetheless, it will be important to understand the effects of overscreening behaviors on both mental health and melanoma detection.

Generalizing to Other Populations and Settings. It will, of course, be important to determine whether increases in screening behavior following *CDKN2A/p16* test reporting will be obtained in other populations and settings. In particular, it will be important to determine whether similar increases in adherence will be observed in clinical practice outside the context of a study setting such as ours. A few additional potential limitations of our study that may affect the generalization of the results are worth noting. First, our entire study population is derived from two large, very well-characterized pedigrees. Health behaviors among relatives may be correlated, leading to the potential for overestimation of the effect of the test reporting in such families. With respect to this possibility, we do note that there was substantial variation in baseline adherence to both professional TBSEs and SSEs, which suggests at least some degree of independence among individual family members in terms of adherence to medical recommendations. It will be important in future research to examine the pattern of screening behaviors before and after genetic test reporting among first-degree relatives and within households. Another important factor to consider is that genetic testing was a free benefit to participants in the present study. It is possible that patients who have made a personal financial commitment to paying for all or part of their genetic testing may show greater subsequent behavioral changes. If this is the case, the present results may underestimate patients' responses to test reporting, although such concerns should be balanced against the greater rates of uptake found when testing is provided at no cost.

Implications for Clinical Practice. Not all melanoma patients should receive genetic testing: only a small subpopulation (5-10%) of melanoma patients has a hereditary pattern suggestive of *CDKN2A/p16* mutation carriage. We have suggested a ''rule of threes'' for identification of appropriate testing candidates (38): (*a*) melanoma patients with two additional affected family members, (*b*) an individual with three primary melanomas, or (*c*) melanoma or pancreatic cancer patients with a total of three melanomas and pancreatic cancers combined in the family. Any first-degree relatives of established *CDKN2A/p16* mutation carriers are also testing candidates.

Conclusions

In summary, the individuals at highest known risk for development of melanoma are those who carry a *CDKN2A/p16* mutation. A clinical genetic test to identify mutations in this gene is currently available in Clinical Laboratory Improvement Amendments–certified (or otherwise qualified) laboratories, but before this investigation, the utility of the testing process had not been shown. The goal of cancer genetic testing is to identify high-risk patients so that prevention and early detection practices can be instituted before the development of malignancy. We have shown that reporting *CDKN2A/p16* test results to high-risk patients significantly improves their compliance with early detection recommendations, which supports similar findings for colon and breast cancer genetic testing. Further, in light of the poor baseline compliance with screening recommendations reported by high-risk familial melanoma patients, withholding test results may actually pose harm to this high-risk population. Thus, we have shown a direct benefit to carriers of the *CDKN2A/p16* mutation and a lack of significant risk to any of the groups tested. This favorable risk-benefit ratio leads us to recommend the transition of *CDKN2A/p16* genetic testing into clinical practice among appropriate high-risk members of the melanoma population, including those participants in research programs like ours who have not yet been notified of their mutation status (38, 39).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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