article

Impact of hemochromatosis screening in patients with indeterminate results: The hemochromatosis and iron overload screening study

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Purpose: Assess the quality of life impact of receiving indeterminate test results for hemochromatosis, a disorder involving *HFE* genetic mutations and/or elevated serum transferrin saturation and ferritin. **Methods:** The study sample was from the Hemochromatosis and Iron Overload Screening Study, a large observational study of hemochromatosis among primary care patients in the US and Canada using *HFE* genotype and serum transferrin saturation and ferritin screening. Study subjects included 2,304 patients found with hemochromatosis risk of uncertain clinical significance. Assessed was SF-36 general health and emotional well-being before screening and six weeks after participants received their test results. Health worries were assessed after screening. **Results:** Of the study subjects, 1,268 participants (51.5%) completed both assessments. Compared to normal controls, those with *HFE* mutations or elevated serum transferrin saturation and ferritin levels of uncertain significance were more likely to report diminished general health and mental well-being, and more health worries. These effects were associated with participants' belief of having tested positive for hemochromatosis or iron overload. **Conclusion:** Notification of indeterminate results from screening may be associated with mild negative effects on well-being, and might be a potential participant risk in screening programs for disorders with uncertain genotype-phenotype. ***Genet Med* 2006:8(11):681–687.**

Key Words: *Hemochromatosis, screening, acceptance, ethics, primary care, HEIRS*

Routine screening for genetic-based disease is increasingly possible for many diseases and disorders, offering a means to detect latent risk for disease long before clinical expression and allowing primary prevention.[1,2] Hereditary hemochromatosis (HH) is an example in which this opportunity is offerred.[3–5] HH is a blood disorder associated with mutations in the *HFE* gene[6,7] that occurs in 1 in 227 Caucasians.[8] It is a serious health concern but is easily detected through genotypic testing, or phenotypic testing. The risk of biochemical iron overload can be predicted by genotype and gender.[9] Male C282 years homozygotes have the highest risk of iron overload (88%).[10] Survival is dependent on the prevalence of cirrhosis which is low in population screening studies (1–4%)[11,12] but as high as 15% in referred patients.[13,14] Patients with cirrhosis have a 5.5-fold relative risk of death compared to the noncirrhotic hemochromatosis patients.[15,16] HH can cause other complications such as primary liver cancer, diabetes mellitus or other endocrinopathy, arthropathy, cardiomyopathy, and reduced longevity,[17,18] but timely treatment can prevent many of these complications.[19] Routine screening for genetic disorders is controversial. For HH, as well as for other diseases, negative effects from screening have been discussed[20–22] such as stigmatization,[23,24] the anxiety of being found with genetic risk for disease,[25–28] and knowing that one needs long-term treatment. These risks however must be weighed against the potential benefits of disease prevention[29] and might be deemed acceptable, especially if steps are taken to reduce distress through routine genetic counseling.

However, the potential for a favorable risk/benefit ratio from screening appears to not apply to a potentially large proportion of screened individuals found to have "indeterminate results." For genotypes or phenotypes with an uncertain (yet believed nontrivial) relationship to disease, it would be difficult to genuinely reassure patients or to provide specific recommendations for surveillance. Moreover, it is uncertain how patients may react to notification of indeterminate test results and therefore how to weigh

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this potential risk against the potential future benefit of knowing one has a genetic mutation that has received some research interest. For some, the knowledge of having uncertain risk with no recommended treatment for prevention could be distressing or even misunderstood, especially if risk counseling is not offered. The option of simply not notifying patients of results for indeterminate genotype risk is problematic as they may have family members with higher risk *HFE* genotypes; and because a lack of scientific evidence about *HFE* genotype risk does not imply an absence of risk, only a limitation of knowledge. These issues deserve attention in the general medical literature because indeterminate genotype and phenotype risk groups can be found much more frequently than groups clearly linked to increased disease risk (e.g., homozygosity). To address a gap in the literature on the extent that indeterminate results are worrisome or distressing, we collected questionnaire data in a large population-based observational study of HH screening in US and Canada. We assessed the impact of notification of *HFE* genotypes of indeterminate HH risk or elevated iron values below an alert threshold on subjects' perceived general health status, psychological well-being, health worries, and overall views on genetic testing.

METHODS AND MATERIALS

Subjects were participants of the Hemochromatosis and Iron Overload Screening (HEIRS) Study, a large observational study designed to evaluate the prevalence, risk factors, and potential clinical, personal and societal impact of HH and iron overload. The HEIRS study screened SF and TS levels, and the *HFE* C282 years and H63D alleles in a multi-ethnic sample of 101,168 adults, aged 25 years and older from five field centers in North America. Recruitment occurred in primary care clinics and offices, clinical laboratories, and health plan memberships. Study materials were available in English, Spanish, Vietnamese, and Mandarin by recruiters fluent in these languages at selected field centers. Laboratory testing was performed in a central laboratory (University of Minnesota Medical Center, Fairview, Minneapolis, MN). Participants were asked to complete a questionnaire prior to screening and after they had received their screening results. A central coordinating center (Wake Forest University, Winston-Salem, NC) conducted the data management and analysis. Details of the study design, laboratory testing, data management and analysis are described elsewhere.[30,31] The study was approved by the Institutional Review Boards at each field center, the central laboratory and the coordinating center.

Results of the HEIRS screening test were mailed to all participants, and those who were homozygous for the *HFE* C282 years mutation or had serum transferrin saturation and ferritin values that exceeded study thresholds (TS >50% for men or >45% for women and SF >300 μg/L for men or >200 μg/L for women) were invited to attend a comprehensive clinical evaluation. The present study was limited to 1,712 participants randomly selected from the population of 40,075 HEIRS participants who did not meet criteria for the clinical evaluation but who had *HFE* genotypes (C282 years/+, C282 years/H63D, H63D/H63D, or H63D/+) believed to confer a low but uncertain risk for HH, or an "alert value" of serum transferrin saturation and/or ferritin that was above or below the middle 95% of the US population distribution as measured by the National Health and Nutrition Examination Survey III thresholds for iron overload, but did not exceed the study thresholds stated above. Additionally, a sample of 592 controls without known or suspected *HFE* genes and no blood iron alert level, was randomly selected among the field centers and frequency matched to the age and gender distribution of the pool of other participants not eligible for the comprehensive clinical evaluation. Thus, none of the 2,304 study participants had serum transferrin saturation and ferritin levels suggesting possible iron overload nor did they have significant genetic risk for HH based on C282 years homozygosity. A synopsis of HEIRS screening results letters for the indeterminate *HFE* risk and control groups is presented in Table 1. These study participants were sent a follow-up survey by mail that included the SF-36 general health and mental well-being scales as well as measures assessing attitudes toward genetic screening health worries, and perception of test result approximately one week after results notification. To increase survey response rates, a follow-up mailing was sent to nonresponders approximately one month after the initial mailing. Some field centers with lower response rates also contacted nonresponders by phone or in person or offered incentives for survey completion.

Self-report measures

Prior to screening, data were collected on date of birth, gender, and race/ethnicity, language preference, general mental well-being and perceived general health. For language preference, seven race/language categories were created by combining and collapsing race, ethnicity and preferred language categories: 1) English-speaking Caucasian; 2) English-speaking African-American; 3) English-speaking Asian or Pacific Islander; 4) English-speaking Hispanic; 5) Non-English-speaking Asian; 6) Non-English-speaking Hispanic; and 7) other (including English-speaking multiple races, non-English-speaking African-American, non-English-speaking Caucasian, and all American Indian or Alaska Native). Educational attainment was collected on the post results survey and categorized as "less than high school diploma," "high school diploma," "some university, college or vocational training," "Bachelor's degree," or "postgraduate training."

Perceived general health and general mental well-being were assessed with the SF-36[32] scales. Scale scores were calculated using published algorithms[33] and change scores from baseline to follow-up were used as dependent variables. Attitude about genetic testing was assessed by level of agreement to the statement "Genetic testing to find out about disease risk is a good idea." Responses ranged from 'strongly agree' to 'strongly disagree' on a 4-point Likert scale. For analysis, this variable was dichotomized as either 'agree' or 'disagree.'

Health worry (e.g., feeling upset, sad or anxious about your test results) was assessed using nine items adapted from the Core Items of the Cancer Genetics Studies Consortium.[34] An-

Table 1
Screening result groups

HFE status	Phenotypic result	Key messages	Advice (abbreviated)
+/+	No *HFE* (mutations No iron alert	No genetic variations, and "your iron tests are within the usual range"	"You are *welcome* to share this info with your MD"
+/+	No *HFE* mutations. Iron alert	No genetic variations; "you do not have the type of iron levels that we are investigating in this study. However, the result of at least one of your iron tests was outside the usual range"	"We *suggest* that you share this info with your MD"
C282Y/+, H63D/H63D, or C282Y/H63D	*HFE* mutations No iron alert	"Iron tests are within the usual range"; you have "one or more" genetic variations that "may slightly increase your risk to develop iron overload in the future"	"We *encourage* you to 1) share" results with your MD 2) "talk to a genetics counselor about the risk to your family members"
C282Y/+, H63D/H63D, or C282Y/H63D	*HFE* mutation Iron alert	"You do not have the type of iron levels that we are investigating in this study. However, the result of at least one of your iron tests was outside the usual range"; you have "one or more" genetic variations that "experts are not sure exactly how much these changes increase your risk to develop iron overload in the future"	"We *recommend* that you 1) "share results with your MD" 2) "talk to a genetics counselor about the risk to your family members"
H63D/+	*HFE* mutation No iron alert	"Your iron tests are within the usual range"; "you have a variation in one of the genes that has been observed in people with iron overload. However, this variation is also very common in healthy people"	"You are *welcome* to 1) share" this info with your MD"and 2) "discuss with MD the possibility that others in your family could be at risk"
H63D/+	*HFE* mutation Iron alert	"You do not have the type of iron levels that we are investigating in this study. However, the result of at least one of your iron tests was outside the usual range"; "you have a variation in one of the genes that has been observed in people with iron overload . . .. It is unlikely the genetic variation identified is contributing to the iron test results that are described above"	"We *recommend* that you 1) share this information with your MD" and 2) "discuss with MD the possibility that others in your family could be at risk"

swers ranged from 1 to 4 where 1 = Never, 2 = Rarely, 3 = Sometimes, and 4 = Often. Because the response distribution was extremely skewed, we created a dichotomous scale such that participants who answered 'Sometimes' or 'Often' to at least 1 of the 9 questions were categorized as 'worried'. Perception of genetic test result status was measured from responses to three questions asking if participants believed they had: No hemochromatosis gene abnormalities; an abnormality in just one gene; an abnormality in both genes; unsure about HH abnormality in 1 or 2 genes; or no HH abnormalities.

Data analysis

Analysis-of covariance and logistic regression models were created to test effects of the specific letter sent and the potential mediating variables on study outcomes. Participants were included in the analysis if they had a value for each variable used in the multivariable logistic regression analysis. The dependent variables included change in levels of SF-36 GH and MWB, attitudes about genetic testing, and health worries, and were adjusted for screening assessment values for: race/preferred language, age, gender, educational attainment, preferred language, SF-36 general health and mental well-being scores (follow-up – baseline value), and attitude toward genetic testing. The health worries scale was administered only after tests results were known and thus was not modeled as change from screening assessment.

RESULTS

Overall, of the 2,304 subjects, survey data were returned or collected on 1,268 participants sampled (51.5%), 130 participants did not have information on the four outcomes and 12 additional participants were diagnosed with iron overload prior to their participation in HEIRS and were thus excluded. Predictors of not returning a survey, examined from initial screening data were male gender, nonwhite race/ethnicity, clinical site, and younger age which were statistically significant at the $P < 0.05$ level. Participant characteristics not statistically associated with survey return were type of result letter received (and thus indeterminate *HFE*/iron overload type) and perceived health score. Table 2 pre-

Table 2
Characteristics of the Study Sample

Variable	Total[a]	Letter			
		Genetically normal w/o iron	Genetically normal w/iron	Genetically abnormal w/o iron	Genetically abnormal w/iron
N	1,125	296	157	341	331
Age Mean (SD)	49.7 (13.2)	48.5 (12.5)	48.9 (14.5)	51.2 (13.1)	49.5 (13.1)
Blood iron mean (SD)					
Transferrin saturation	28.2 (14.0)	27.9 (8.3)	22.9 (16.1)	29.8 (8.3)	29.3 (19.8)
Serum ferritin	142.5 (189.9)	108.7 (91.9)	190.5 (266.5)	124.2 (98.7)	168.9 (261.9)
Gender N (%)					
Female	795 (71.2%)	233 (79.3%)	119 (77.3%)	209 (61.8%)	234 (70.9%)
Male	321 (28.8%)	61 (20.7%)	35 (22.7%)	129 (38.2%)	96 (29.1%)
Race N (%)					
Non-hispanic white	708 (62.9%)	138 (46.6%)	73 (46.5%)	244 (71.6%)	253 (76.4%)
Black	152 (13.5%)	58 (19.6%)	34 (21.7%)	39 (11.4%)	21 (6.3%)
Hispanic/English-speaking	30 (2.7%)	4 (1.4%)	6 (3.8%)	11 (3.2%)	9 (2.7%)
Hispanic/non-English-speaking	85 (7.6%)	24 (8.1%)	11 (7.0%)	24 (7.0%)	26 (7.9%)
API/English-speaking	62 (5.5%)	36 (12.2%)	18 (11.5%)	3 (0.9%)	5 (1.5%)
API/non-English-speaking	38 (3.4%)	21 (7.1%)	5 (3.2%)	6 (1.8%)	6 (1.8%)
Other/Unknown	50 (4.4%)	15 (5.1%)	10 (6.4%)	14 (4.1%)	11 (3.3%)
Education N (%)					
<HS	116 (10.4%)	31 (10.5%)	37 (17.4%)	22 (6.5%)	36 (11.0%)
HS graduate	221 (19.8%)	64 (21.7%)	33 (21.3%)	67 (19.7%)	57 (17.4%)
Some college	389 (34.8%)	96 (32.5%)	60 (38.7%)	114 (33.5%)	119 (36.3%)
Bachelor's degree	169 (15.1%)	49 (16.6%)	17 (11.0%)	59 (17.4%)	44 (13.4%)
Post-graduate training	223 (20.0%)	55 (18.6%)	18 (11.6%)	78 (22.9%)	72 (22.0%)
Health status					
General health mean (SD)	64.3 (22.8)	65.7 (21.1)	58.9 (24.3)	66.3 (22.3)	63.7 (23.8)
Mental well-being mean (SD)	80.8 (16.7)	81.5 (16.3)	80.8 (16.4)	81.9 (17.0)	79.0 (16.8)
Attitude on genetic testing agree or strongly agree N (%)	793 (70.5%)	204 (68.9%)	107 (68.2%)	246 (72.1%)	236 (71.3%)

[a] Number of HEIRS participants without C282Y homozygosity and without significantly elevated TS/TF levels.

sents the demographic characteristics of study participants. Subjects had a mean age of 50.3 (± 31.2) years and were predominately female (73%). Approximately 61% self-identified as non-Hispanic White, 14% as Black, nearly 11% as Hispanic (75.4% non-English-speaking), and nearly 10% as Asian/Pacific Islander (40.7% of these were non-English-speaking). Most (89%) reported completing at least high school, and approximately 70% completed some college. At the time of the follow-up survey, the mean SF-36 general health score and mental well-being scale scores were 64.3 and 80.8, respectively, out of a possible 100 (perfect health). Approximately 70% of subjects agreed that "genetic testing to find out about disease risk is a good idea."

Table 3 shows responses for the mediating variable of the participant's perception of whether or not he/she had hemochromatosis. Approximately 92% of respondents who received a letter indicating that they had no abnormal test results ('normals') believed that they were free of hemochromatosis. In contrast, only 63% of those who were told they had both an *HFE* gene abnormality and iron "alert value" believed they did not have hemochromatosis. Similarly, *uncertainty* about having hemochromatosis rose from 5.4% among those with normal results to 19.5% in those with both gene and iron abnormalities.

Adjusting for model covariates of age, race, gender, educational attainment and baseline values of the relevant outcomes, analysis of variance and logistic regression (data not shown) showed that the screening result letter group was not associated with perceived general health ($P = 0.74$) or attitudes

Table 3
Perception of having hemochromatosis score by screening results letter: Percent response distribution

		Hemochromatosis[a] perception		
Letter	N	0	1	2
HFE genes normal without iron alert	289	93.4	4.5	2.1
HFE genes normal with iron alert	150	74.0	18.0	8.0
HFE genes abnormal without iron alert	321	75.1	15.3	9.7
Genetically abnormal with iron alert	316	64.2	18.7	17.1

[a] Hemochromatosis belief: 0 = I do not have hemochromatosis; 1 = I am not sure if I have it; 2 = I have hemochromatosis.

about genetic testing ($P = 0.38$) and was statistically associated with health worry ($P < 0.001$) with the percentage of persons classified as "worried" ranging from 22% of normal controls to 40% of participants with *HFE* mutation(s) and an "alert value."

Table 4 presents the final analysis of variance model and logistic regression (adjusting for age, race/ethnicity, education, initial screen value of the outcome variables) for mean change in SF-36 general health and mental well-being scales and attitude about genetic testing. After considering mediators of hemochromatosis perception and extent of *HFE* gene abnormality (e.g., no *HFE* mutation; "low-risk *HFE* mutation group"; H63D carrier), the results letter group did not significantly predict changes in any of the outcome variables from prescreening to postresult. However, belief by participants that they had HH or had any *HFE* mutation, was associated with poorer outcomes in general health and mental well-being compared to those who perceived no abnormality. Participants' belief that they had any *HFE* mutation was also associated with attitudes about genetic testing such that those who were unsure if they had HH were less likely to view genetic testing positively than those who erroneously concluded they had HH (52% vs. 80% and 73% for participants who are sure that they do or do not have HH, respectively).

Table 4 also presents the results for self-reported health worry self-reported after receiving screening results. As with the other outcomes, belief that one had HH, or had any *HFE* mutation was significantly associated with increasing level of health worry, while screening results letter group was not associated with belief score.

DISCUSSION

In this large multi-site study of HH screening and detection, participants with low or indeterminate risk *HFE* genotypes and/or iron "alert values" had reduced general mental well-being and increased health worry relative to controls with normal iron levels and no *HFE* mutations. Thus, our findings contribute to the literature on the impact of genetic screening on psychological well-being of patients with no prior knowledge

Table 4
Change in well-being and attitudes about genetic testing during the pre- and post-screening period, and level of health worries

	General Health[a]		Psychological Well-being[a]		Genetic Test Attitude[b]		Health Worry[c]	
Characteristic	(PR-IS)	*P*-value	(PR-IS)	*P*-value	% Agree	*P*-value	%Worried	*P*-value
Letter group		0.597		0.900		0.564		0.154
wt/wt without iron	–7.73		1.81		69.3		21.1	
wt/wt with iron	–8.41		3.45		68.8		31.7	
HFE mutation without iron	–6.23		2.34		72.2		34.2	
HFE mutation with iron	–6.38		1.31		71.3		40.4	
Perceived hemo		0.029		0.016		0.001		0.001
0 = no	–4.93		4.30		72.7		26.8	
1 = not sure	–7.04		2.81		52.3		45.3	
2 = yes	–9.59		–0.43		79.8		57.3	
Perceived gene		0.426		0.082		0.001		<0.001
0 = no gene abnormality	–5.96		3.86		71.8		21.8	
1 = uncertain	–8.31		1.42		57.9		42.2	
2 = one gene abnormality	–7.62		3.97		81.7		37.9	
3 = two gene abnormalities	–6.87		–0.34		64.7		66.0	

[a] Linear regression, post-screening result (PR) value adjusted for age, race, gender, education and prescreening (IS) value of dependent variable.
[b] Logistic Regression, PR value adjusted for age race, gender, education, and IS value of dependent variable.
[c] Logistic Regression adjusted for age, race, gender, education, and IS value of general health.

of possible risk by focusing on those with low or indeterminate-risk. Effects of HH screening on well-being and worry in this risk group appear to be mediated by the extent that the participant believed their test results indicated they had HH or iron overload. Letter group, per se, was not associated with adverse well-being or worry. The overall decline in SF-36 general health and mental well-being scores from initial screening (baseline) to postresults follow-up was relatively modest, approaching a one-half standard deviation threshold for a minimal important difference held by some.[35] Approximately twice as many participants who perceived presence of hemochromatosis reported health worries than those who concluded that they did not have this disorder (26.8 vs. 57.3%). The effect on health worries was most closely associated with the participants' belief about the number of *HFE* mutations detected. The implication of these findings is that, when screening results are vague or indeterminate regarding risk of disease, people may conclude that they have an abnormality that threatens their health and, as a result, feel less well and worry more. As persons with such results may be viewed as not belonging to a clearly defined risk results group they might not be offered counseling. It is not known whether provision of genetic counseling would have alleviated this distress. In HEIRS, in the absence of knowledge about the impact of screening on well-being, none of the participants with detected abnormal *HFE* genotypes were provided follow-up medical evaluation or face-to-face genetic counseling. Numerically, some 23,695 HEIRS participants were discovered to have combinations of *HFE* alleles associated with indeterminate risk, or 10 times more likely than finding cases with *HFE* alleles viewed as clearly high-risk in this population. The requirement of genetic counseling would be a large undertaking and must be carefully weighed in study designs in the decision of whether to inform patients of indeterminate risk.

Many previous screening studies for iron overload have only notified affected individuals, thereby removing the problem of communicating uncertain risk status. Conventionally, patients aren't informed of trivial results because these results can cause only negative effects, such as stigmatization and anxiety, as mentioned above, without producing the possible gains that can result from treatment.[36] This conventional approach recently, however, has been challenged as paternalisitic, and may introduce other problems[37,38] such as withholding information pertinent to participants and families that in the future may be more clearly understood and acted upon to promote health. Some persons may want this knowledge even though there are no benefits presently available, or even if they know, perhaps as a result of researchers having informed them, that being informed may do harm. The ethical argument in favor of disclosing such results even when they risk harm is respect for patient autonomy. For participants who want to be informed of indeterminate results, it may be that, as with nontrivial risks, prior discussion of both the possible (nontrivial or trivial) findings and how persons could be prone to reacting in either case with alarm to this finding could reduce these risks. In this regard, however, there are sparse data in the literature whether genetic counseling can alleviate stress in such situations. Studies have shown marked anticipatory anxiety among those awaiting test results for various conditions or disease predispositions,[39–43] though fewer have found evidence of significant psychological symptoms or emotional upset after testing, even for those found to be carriers.[44,45–48] To date, most of the literature on pre- and post-genetic testing-related distress had focused either on those who knew of increased risk (e.g., for hereditary cancers or Huntington disease) prior to testing,[49] or on those found to have possibly increased fetal risk during pregnancy.[50] Given that in the future, population screening for many late-onset disorders may reveal more genotypes with low or unclear risk than those clearly associated with disease, it is important to understand how people perceive and react to this type of result.

Our findings indicate that more research is needed on how participants perceive their results when screening for a variably expressed adult-onset genetic disease reveals mutations that may or may not confer a disease risk, and whether potential adverse effects of such results on perceived well-being and on health worries are transient or persistent. Informed consent documents for many genetic tests have specifically addressed the possibility of getting a result with unclear clinical significance; either because a particular mutation has not been reported before (as in *BRCA1* or *BRCA2*) or because there is inadequate information about genotype/phenotype correlations for specific alleles or allele combinations (as in *CFTR).* Some consent documents also point out that there may be insufficient evidence to make clear recommendations about surveillance or prevention strategies if mutation(s) are found, or raise the possibility that testing could cause psychological distress or health worry. Finally, studies are needed to determine whether patients who desire to be informed of trivial risks, and are so informed have any risk for subsequent emotional harm or have enhanced relationships with the researcher or health care provider.

Although HEIRS provided a rich source of data to conduct this study, some limitations should be noted. First, with a survey response rate of 51% there is a possibility of response bias and that the actual proportion of HEIRS participants with "indeterminate" results who experienced a decline in well-being or health worry would differ from our study sample. This could occur if the majority of nonrespondents were either psychologically healthier or sicker than those who did respond. Another limitation is that our measures of well-being were necessarily brief and did not include specific measures of psychological distress, such as anxiety or life outlook that might have been affected more or less than measures of general health. Future studies might seek to better quantify if and how health worries affect daily life to better define the full impact that screening results may have on the participant. Lastly, we do not know if the changes we observed were transient or longer lasting. We will be assessing this, as well as the relationship between results and subsequent health behavior and attitudes about genetic screening, with data collected from a one-year follow-up survey.

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