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Authors
McLaren, Christine E
Fujikawa-Brooks, Sharon
Chen, Wen-Pin
et al.

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Longitudinal Assessment of Air Conduction Audiograms in a Phase III Clinical Trial of Difluoromethylornithine and Sulindac for Prevention of Sporadic Colorectal Adenomas

Christine E. McLaren,1,2 Sharon Fujikawa-Brooks,2 Wen-Pin Chen,2 Daniel L. Gillen,3 Daniel Pelot,2 Eugene W. Gerner4 and Frank L. Meyskens, Jr.2

Abstract

A phase III clinical trial assessed the recurrence of adenomatous polyps after treatment for 36 months with difluoromethylornithine (DFMO) plus sulindac or matched placebos. Temporary hearing loss is a known toxicity of treatment with DFMO, thus a comprehensive approach was developed to analyze serial air conduction audiograms. The generalized estimating equation method estimated the mean difference between treatment arms with regard to change in air conduction pure tone thresholds while accounting for within-subject correlation due to repeated measurements at frequencies. Based on 290 subjects, there was an average difference of 0.50 dB between subjects treated with DFMO plus sulindac compared with those treated with placebo (95% confidence interval, −0.64 to 1.63 dB; \( P = 0.39 \)), adjusted for baseline values, age, and frequencies. In the normal speech range of 500 to 3,000 Hz, an estimated difference of 0.99 dB (−0.17 to 2.14 dB; \( P = 0.09 \)) was detected. Dose intensity did not add information to models. There were 14 of 151 (9.3%) in the DFMO plus sulindac group and 4 of 139 (2.9%) in the placebo group who experienced at least 15 dB hearing reduction from baseline in 2 or more consecutive frequencies across the entire range tested (\( P = 0.02 \)). Follow-up air conduction done at least 6 months after end of treatment showed an adjusted mean difference in hearing thresholds of 1.08 dB (−0.81 to 2.96 dB; \( P = 0.26 \)) between treatment arms. There was no significant difference in the proportion of subjects in the DFMO plus sulindac group who experienced clinically significant hearing loss compared with the placebo group. The estimated attributable risk of ototoxicity from exposure to the drug is 8.4% (95% confidence interval, −2.0% to 18.8%; \( P = 0.12 \)). There is a <2 dB difference in mean threshold for patients treated with DFMO plus sulindac compared with those treated with placebo.

Removal of adenomas found during screening sigmoidoscopy or colonoscopy may prevent colorectal cancer (1), the second most common cause of cancer deaths in the United States (2). Difluoromethylornithine (DFMO) has been identified as a potent inhibitor of intestinal and colon carcinogenesis in animal models, especially in combination with nonsteroidal anti-inflammatory drugs (3–5). DFMO and the nonspecific nonsteroidal anti-inflammatory drug sulindac also interact additively to prevent the growth and viability of human colon cancer cells (6). Results of a phase III clinical chemoprevention trial showed the efficacy of a low dose of DFMO plus sulindac, at a dose one half the usual therapeutic dose. In the population of individuals at moderately high risk for sporadic adenomas, 41% of subjects receiving placebos developed recurrent adenomas compared with 12% of subjects receiving DFMO plus sulindac. There was a marked reduction in the recurrence of all adenomas in subjects receiving DFMO plus sulindac (70% decrease relative to those receiving placebo), advanced adenomas (92% decrease), and recurrence of more than one adenoma (95% decrease; ref. 7).

Temporary hearing loss is one of the known toxicities of treatment with DFMO (8–13). One study reported permanent hearing loss with higher doses than used in the current trial (14). In the phase III clinical chemoprevention trial conducted by Meyskens and colleagues, self-reported hearing changes were not significantly different between the two groups. Although no evidence of a decrement in the normal speech range was documented, serial audiograms suggested a possible effect across a broader range of frequencies tested that was...
reversible in some cases (7). The details of the audiologic studies and comprehensive analyses are reported here. The statistical issues that have been addressed include the need for (a) appropriate adjustment for known sources of variation in hearing; (b) application of the generalized estimating equation (GEE) approach to the data to take into account the correlation between values across frequencies for individual subjects, hearing thresholds measured in left and right ears, and age adjustment; (c) estimation of the differences in hearing thresholds between final and baseline values and between frequencies; and (d) evaluation of the effect of treatment with DFMO plus sulindac on hearing loss.

Materials and Methods

Study design

This study was a randomized, double-blind, placebo-controlled trial to test whether the combination of a low dose of DFMO plus a low dose of sulindac reduces the recurrence of colorectal adenomas detected by standard colonoscopy. The trial involved seven clinical sites in the United States. The human subjects committee at each site approved the study protocol and written informed consent was provided by all patients before enrollment. Quality control to promote uniform practice and protocol compliance included meetings before enrollment and site inspections during and after the trial. An independent Data and Safety Monitoring Board reviewed the safety and efficacy data twice yearly.

Recruitment and study population

Eligibility required patients of ages 40 to 80 y with a history of ≥1 resected adenoma of at least 3 mm within 5 y before study entry. Patients with ≥20 dB sensorineural hearing loss above age-adjusted norms (15) assessed by pure tone audiometry at any frequency in the normal hearing range were ineligible. Additional eligibility criteria are reported elsewhere (7). A screening colonoscopy within 6 mo of study entry was done, and all polyps were removed and pathologically examined. Before randomization to the agents, screening was done and included baseline history, physical examination, pure tone audiometry, and laboratory evaluations for baseline hematologic, renal, and hepatic status. A 1-mo placebo run-in period was used to assess compliance. To be randomized, participants had to show 80% adherence to the 1-mo run-in medication. Three years after randomization, colonoscopies were done. Gastroenterologists associated with the trial performed all study colonoscopies.

Safety evaluations were done at return visits after the run-in and at 3, 6, 9, 12, and every 6 mo through the end of the study. Pure tone audiograms were done at 18 and 36 mo after randomization, or off study, and repeated 6 mo later. Compliance with the protocol, including in-person and telephone visits, study medication, and blood draws, was monitored throughout the duration of the study.

Hearing assessment

Air conduction pure tone thresholds were obtained by audiologists using standard clinical protocol. Frequencies tested were 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. The interoctave frequencies of 3000 and 6000 Hz were added to the usual clinical practice to capture changes at these critical frequencies (16). For audiometric testing, 6-dB steps were specified in the protocol as this has remained a standard since 1959 (17, 18). All audiograms were evaluated for change in thresholds by the study audiologist.

Study treatment

DFMO was given orally at a single daily dose of 500 mg, and sulindac was given orally at a single daily dose of 150 mg. The dose intensity of DFMO was estimated as the proportion of full dose that a participant took during the trial. The randomization used a blocked design and was stratified by clinical site and on the basis of the use (defined as ≤81 mg daily or ≤25 mg twice weekly) or nonuse of low-dose aspirin at study entry.

Statistical analysis

A total of 375 subjects were randomized. Of these, 290 participants had baseline and at least one repeat air conduction audiogram available for analysis. For pure tone thresholds, summary statistics were computed at each frequency for two treatment groups. Consistent with the approach taken in previous investigations, the average of pure tone threshold values from left and right ears was used for graphical and numerical analyses (13, 19, 20). For a given frequency, the available value was used if the threshold value was present for one ear but missing for the other ear. For each treatment group, box plots were constructed to illustrate the variability in thresholds at each frequency and at each test time. For adverse events reporting, the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 were used. A description of these criteria is available online (5). The relative risk of hearing loss of at least 15 dB in any frequency across the entire range tested in the DFMO plus sulindac group versus that of placebo was assessed by log-binomial regression. The likelihood ratio test P value is reported. The estimated attributable risk from exposure to the DFMO plus sulindac was calculated as the difference in the proportions of subjects in the two groups who experienced hearing loss of at least 15 dB in any frequency. The two-sample test of equality of proportions was applied and the 95% confidence interval (95% CI) for the difference in proportions was calculated. Similarly, the relative risk of hearing loss of at least 15 dB in the DFMO plus sulindac group at two consecutive frequencies versus that of placebo was assessed by log-binomial regression.
Imputation and smoothing for missing threshold values

For some subjects, not all frequencies had decibel values recorded for one or both ears. Inspection of the data showed that although the research protocol specified that measurements were to be taken at 3,000 and 6,000 Hz, pure tone thresholds were missing for both ears at 3,000 Hz for 33 of 290 subjects and at 6,000 Hz for 36 of 290 subjects. If threshold values were missing for both ears, multiple imputation was used to estimate the average at that threshold. Multiple imputation with the regression method was applied to impute 10 values for each missing threshold value (SAS 9.1, PROC IM). Locally weighted scatterplot smoothing (Lowess) was used to reduce within-subject variation across frequencies. Generalized cross-validation criterion was used to select subject-specific smoothing parameters (21). In addition, the profiles of smoothed values were examined graphically per subject by treatment group.

Multiple linear regression

For each frequency (250-8,000 Hz), multiple linear regression analysis was applied with the observed pure tone threshold from the 18-mo or end-of-treatment audiogram as the outcome variable and predictors including baseline threshold value, age group (decade), and treatment group. When the end-of-treatment audiogram was available, it was used as the outcome variable for the analysis. In most cases, the end-of-treatment audiogram was obtained at ~36 mo. Otherwise, the threshold values measured at the 18-mo visit were used. Models with interaction between treatment, age group, and use of low-dose aspirin at study entry were considered. For the outcome of hearing thresholds, at each frequency the estimated mean difference between treatment groups and 95% CIs were computed from models adjusted for baseline hearing threshold and other covariates.
Generalized estimating equation

In the audiology monitoring process, several pure tone tests were done across a range of the frequencies. For analysis, previous studies have used either multiple regression analysis (11, 13) or repeated-measures ANOVA (12, 22–26). In contrast, to take into account the correlation between values across frequencies for individual subjects, the GEE method was applied with subjects as clusters, an exchangeable correlation structure, and a normal link function. The outcome variable was pure tone threshold, measured at the 18-mo or end-of-treatment audiogram. Predictors included baseline threshold value, age group (decade), quartile of dose intensity, frequency, and treatment group. Models were examined that contained variables representing interactions between age groups, treatment groups, and frequencies, where frequencies were grouped into three levels: low (250-500 Hz), medium (1,000-4,000 Hz), and high (5,000-8,000 Hz). The estimated mean difference between treatment groups and 95% CIs were computed from GEE models adjusted for baseline hearing threshold and other covariates. To examine goodness-of-fit of the GEE models, the marginal $R^2$ was calculated (27, 28). Results from the 10 separate GEE models were combined (29).

Recovery from treatment

To examine recovery from treatment, mean pure tone thresholds at baseline were compared with those obtained from retesting at least 6 mo after treatment was stopped. The mean (±SD) of the duration of the follow-up to the date of the end of therapy was calculated. For individual participants, the presence of clinically significant hearing loss was defined as sustained threshold elevations of at least 15 dB above baseline at any frequency on both end-of-treatment and posttreatment audiograms. The proportion of patients with clinically significant hearing loss was computed for each treatment group.

Results

Descriptive and graphical results

Each of the 375 subjects enrolled in this phase III clinical trial had baseline audiograms done. Of these, 290 participants had repeated air conduction audiograms available for analysis (Table 1). At baseline there was no significant difference in average pure tone threshold for left and right ears (score statistic $P = 0.82$), and thus the average of pure tone threshold values from both ears was used for graphical and numerical analyses. Shotland and colleagues (30) present gender-specific tables of 95th percentiles for age-adjusted air conduction pure tone thresholds, adjusted up to the nearest 5-dB increment. The values are adapted from information published by Morrel et al. (15). For any 2.5-year age range, they represent hearing levels in decibels in which at least 95% of the population have equal or better hearing. For each participant, values recorded at baseline were compared with age-adjusted air conduction pure tone thresholds for 500, 1,000, 2,000, and 4,000 Hz (15, 30). There were 33 of 151 (21.2%) in the DFMO plus...
sulindac group and 30 of 139 (21.6%) in the placebo group with hearing worse than the 95th percentile for at least one of these four frequencies.

For each treatment group, the subject-specific differences between pure tone thresholds (final − baseline) are presented as box plots in Fig. 1. Frequencies are plotted on a log10 scale. To conform to clinical practice, positive values on the vertical axis indicate hearing loss, and negative values indicate hearing improvement. Shown in reverse of the usual orientation, the box stretches from the 25th to the 75th percentile. The median is shown with a line across the box, and the mean is indicated with an asterisk. The audiogram values were not corrected for age.

Figure 2 displays traditional audiograms of the median threshold values at baseline and at 18 or 36 months for the DFMO plus sulindac group (n = 151) versus placebo (n = 139). Comparison of the median values is shown by age group (Figs. 3 and 4). There were 42 of 151 (27.8%) subjects in the DFMO plus sulindac group who experienced clinically significant hearing loss, defined as at least a 15-dB hearing loss from baseline in any frequency across the entire range tested, compared with 27 of 139 (19.4%) of subjects in the placebo group. The estimated attributable risk of ototoxicity from exposure to the drug is 8.4% (95% CI, −2.0% to 18.8%; binomial test P = 0.12).

There were 14 of 151 (9.3%) in the DFMO plus sulindac group and 4 of 139 (2.9%) in the placebo group who experienced at least 15-dB hearing reduction from baseline in two or more consecutive frequencies across the entire range tested (χ² test P = 0.02). The unadjusted relative risk of hearing loss for the DFMO plus sulindac treatment group was 3.2 (95% CI, 1.09-9.55) relative to that of placebo.

Comparison of pure tone thresholds across frequencies

Multiple linear regression analyses for each frequency showed some evidence of interaction between treatment and pretreatment use of low-dose aspirin at 2,000 Hz but not for other frequencies. For the regression models with main effects of threshold, age group, and treatment group, Table 2 gives parameter estimates and 95% CIs for predictors. These analyses were based on the average threshold measured in left and right ears, without imputation for missing values. For frequencies of 250 to 2,000 Hz and 4,000 Hz, data from the entire cohort of 290 subjects were analyzed. Threshold data were analyzed from 257 subjects measured at 3,000 Hz, 254 subjects measured at 6,000 Hz, and 288 subjects measured at 8,000 Hz. Parameter estimates for variables representing age group and treatment with DFMO plus sulindac indicate the estimated mean difference in pure tone threshold compared with that of the reference...
group. Adjusted for baseline hearing threshold and age, 95% CIs for mean hearing thresholds include zero for each frequency. Thus, there was insufficient evidence of a difference in mean hearing threshold between treatment groups for each frequency. However, statistically significant hearing loss was experienced for patients who were 60 to 80 years of age, compared with those who were 40 to 50 years old. For example, on average, subjects who were 70 to 80 years of age experienced 5.3-dB greater hearing loss at a pure tone frequency of 2,000 Hz, compared with the youngest group of patients and adjusted for baseline audiometry values and treatment.

As described previously, for each subject multiple imputation was applied to impute threshold values missing from both ears at the same frequency. Data from the cohort of 290 were analyzed using the GEE method applied to each of 10 individual data sets. Dose intensity did not add information to models containing main effect predictors. For models including baseline threshold value, age group, treatment, an eight-level categorical variable representing frequency, and treatment by frequency interaction, no significant interactions were found. The distribution of score statistic P values, ordered from lowest to highest, was 0.158, 0.275, 0.276, 0.296, 0.316, 0.326, 0.355, 0.436, 0.465, and 0.515. Thus, for the GEE models of main effects, results from the 10 data sets were combined to estimate parameter values and 95% CIs (29). As displayed in Table 3, on average, subjects in the DFMO plus sulindac group did not have statistically significantly greater hearing loss than those in the placebo group. The estimated mean difference in hearing thresholds was 0.50 dB higher in those taking DFMO plus sulindac than in those taking placebo (95% CI, −0.64 to 1.63 dB; P = 0.39). For the placebo group, the estimated means (95% CI) are as follows: baseline, 25.3 dB (23.5-27.2); 18 months, 26.1 dB (24.3-28.0 dB); 36 months, 27.6 dB (25.7-29.5 dB); and follow-up, 29.8 dB (27.7-31.9 dB). Within the normal speech range of 500 to 3,000 Hz, on average, subjects in the DFMO plus sulindac group experienced 0.99 dB greater hearing loss than the subjects in the placebo group (95% CI, −0.17 to 2.14 dB; P = 0.09).

### Recovery from treatment

There were 122 of 290 (42.1%) of subjects with follow-up audiometry measurements made at least 6 months after treatment was stopped. The mean time of the follow-up exam was 2.14 (±1.26 SD) years after treatment was stopped. On average, thresholds measured in the DMO plus sulindac group were 1.08 dB greater than for patients in the placebo group (95% CI, −0.81 to 2.96 dB; P = 0.26), adjusted for baseline values, age, and differences between frequencies. Relative to thresholds measured at the end of treatment, the adjusted mean difference in hearing thresholds was 0.79 dB (−0.94 to 2.53 dB; P = 0.37). There were 42 of 122 (34%) of participants who sustained threshold elevations of at least 15 dB above baseline at any frequency on both end-of-treatment and post-treatment audiograms; 25 of 63 (40%) in the DFMO plus sulindac group as compared with 17 of 59 (29%) in the placebo group. These proportions were not statistically significantly different (χ² test P = 0.21). The estimated relative risk of clinically significant hearing loss in patients treated with low doses of DFMO plus sulindac was 1.6 (95% CI, 0.96-2.62) relative to those taking placebo, adjusted for age and pretreatment thresholds at each frequency.

### Table 2. Multiple regression parameter estimates and 95% CIs for model predictors based on observed hearing thresholds for the average of left and right ears

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>250</th>
<th>500</th>
<th>1,000</th>
<th>2,000</th>
<th>3,000</th>
<th>4,000</th>
<th>6,000</th>
<th>8,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>4.582</td>
<td>3.987</td>
<td>2.777</td>
<td>2.593</td>
<td>2.145</td>
<td>4.208</td>
<td>2.745</td>
<td>4.106</td>
</tr>
<tr>
<td>Baseline</td>
<td>(1.84-7.33)</td>
<td>(1.35-6.62)</td>
<td>(0.49-5.07)</td>
<td>(0.02-5.17)</td>
<td>(−0.55-4.84)</td>
<td>(1.10-7.31)</td>
<td>(−0.72-6.21)</td>
<td>(0.53-7.68)</td>
</tr>
<tr>
<td>Age group 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[60, 70] y</td>
<td>1.695</td>
<td>1.232</td>
<td>1.095</td>
<td>2.813</td>
<td>3.307</td>
<td>2.403</td>
<td>3.582</td>
<td>3.768</td>
</tr>
<tr>
<td>Age group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[50, 60] y</td>
<td>−2.44-2.99</td>
<td>−2.60-2.85</td>
<td>−2.49-2.19</td>
<td>−1.53-3.77</td>
<td>−1.64-3.83</td>
<td>−2.84-3.47</td>
<td>−1.28-6.57</td>
<td>−0.96-6.27</td>
</tr>
<tr>
<td>Age group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[40, 50] y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFMO plus</td>
<td>0.808</td>
<td>0.596</td>
<td>1.076</td>
<td>1.056</td>
<td>1.455</td>
<td>0.365</td>
<td>0.694</td>
<td>0.186</td>
</tr>
<tr>
<td>sulindac (n = 151)</td>
<td>(−0.66-2.28)</td>
<td>(−0.87-2.06)</td>
<td>(−0.19-2.34)</td>
<td>(−0.38-2.49)</td>
<td>(−0.08-2.99)</td>
<td>(−1.34-2.07)</td>
<td>(−1.26-2.65)</td>
<td>(−1.77-2.14)</td>
</tr>
<tr>
<td>Placebo (n = 139)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Comparison reference groups were age group 1 [40, 50] y and placebo treatment group.
Discussion

Treatment groups were similar with regard to time between randomization until performance of the outcome audiogram. Based on the new quantitative evaluation of pure tone audiograms, mean hearing thresholds did not differ between those treated with DFMO plus sulindac or placebo for each frequency. Adjusting for baseline threshold, age, and frequencies, the average difference of 0.50 dB between treatment groups was not statistically significantly different from zero (95% CI, −0.64 to 1.63 dB; \( P = 0.39 \)) and was less than the instrument error of +5 dB. Similarly, in the normal speech range of 500 to 3,000 Hz, there was no significant difference in mean hearing thresholds (\( P = 0.09 \)). Models showed no significant association between dose intensity and hearing thresholds. Hearing loss was not a function of increasing dose intensity. Of 290 subjects, 122 had follow-up air conduction testing at least 6 months after stopping treatment, and the mean difference between treatment groups in average hearing threshold was 1.08 dB (95% CI, −0.81 to 2.96 dB; \( P = 0.26 \)), adjusted for baseline values, age, and differences between frequencies. There was a mean difference of 0.79 dB (−0.94 to 2.53 dB) between treatment groups relative to thresholds measured at the end of treatment (\( P = 0.37 \)).

Analyses were done using the GEE method. Advantages are that unbalanced data can be analyzed; an empirical sandwich estimator criteria is applied to model the error structure; and the GEE model is relatively insensitive to possible misspecification of the covariance structure as compared with the general linear mixed model (31). This procedure fits a population-averaged response as a function of covariates without explicitly accounting for subject to subject heterogeneity. The regression coefficients have interpretation for the population rather than for any individual. The population-averaged response for a given covariate value is directly estimable from observations without assumptions about the heterogeneity across individuals in the parameters, and thus parameters are in this sense one step closer to the data than subject-specific parameters (32).

Table 3. Parameter estimates and 95% CIs from GEE models applied to hearing thresholds for the average of left and right ears measured in 290 subjects, with multiple imputation for missing thresholds

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% confidence limits</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.811</td>
<td>−0.864, 2.486</td>
<td>0.343</td>
</tr>
<tr>
<td>Smoothed baseline</td>
<td>0.837</td>
<td>0.797, 0.877</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age [70, 80) y</td>
<td>4.766</td>
<td>2.436, 7.096</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age [60, 70) y</td>
<td>2.949</td>
<td>1.140, 4.757</td>
<td>0.0014</td>
</tr>
<tr>
<td>Age [50, 60) y</td>
<td>0.912</td>
<td>−0.733, 2.558</td>
<td>0.277</td>
</tr>
<tr>
<td>Age [40, 50) y</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DFMO/sulindac</td>
<td>0.498</td>
<td>−0.636, 1.632</td>
<td>0.389</td>
</tr>
<tr>
<td>Placebo</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Discussion of Potential Conflicts of Interest

Frank L. Meyskens and Eugene W. Gerner are co-founders of Cancer Prevention Pharmaceuticals. No other potential conflicts of interest were disclosed.

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Participating Institutions and Investigators

Chao Family Comprehensive Cancer Center, University of California Irvine, CA: Frank L. Meyskens, Jr., M.D. (Principal Investigator); Gregory Albers, M.D.; Sharon Fujikawa-Brooks, Ph.D.; Philip M. Carpenter, M.D.; Daniel L. Gillen, Ph.D.; Christine E. McLaren, Ph.D.; Daniel Pelot, M.D.

Arizona Cancer Center, University of Arizona, AZ: Eugene W. Gerber, Ph.D.; Steven Goldschmid, M.D.; Peter Lance, M.D.

Denver Department of Veteran Affairs Medical Center and University of Colorado: Dennis J. Ahnen, M.D.

Department of Veterans Affairs Long Beach Healthcare System, CA: Jayashri Kidao, M.D.

Kaiser Permanente, Sacramento, CA: Michael J. Lawson, M.D.

Loma Linda University, CA: John McCracken, M.D.

University of Michigan, Ann Arbor, CA: D. Kim Turgeon, M.D.

University of Kansas, Kansas City, CA: Curt H. Hagedorn, M.D.

VA Loma Linda Healthcare System, CA: Ronald Griffer, M.D.

References


