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Data generated by the genome-wide association studies of bipolar and schizophrenia from the Genetic Association Information Network (GAIN) were used for the analyses described in this article. The data were obtained from the database of Genotype and Phenotype (dbGaP) found at <http://www.ncbi.nlm.nih.gov/gap> through dbGaP accession numbers phs000017.v3.p1 and phs000021.v2.p1 for bipolar and schizophrenia, respectively.

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REFERENCES

1. Ober C, Tan Z, Sun Y, Possick JD, Pan L, Nicolae R, et al. Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. *N Engl J Med* 2008;358:1682-91.
2. Moffatt MF, Kabisch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470-3.
3. Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, et al. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. *Am J Hum Genet* 2009;84:581-93.
4. Sleiman PM, Flory J, Imielinski M, Bradfield JP, Annaiah K, Willis-Owen SA, et al. Variants of DENND1B associated with asthma in children. *N Engl J Med* 2010;362:36-44.
5. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006;38:904-9.
6. Clarke GM, Carter KW, Palmer LJ, Morris AP, Cardon LR. Fine mapping versus replication in whole-genome association studies. *Am J Hum Genet* 2007;81:995-1005.
7. Souness JE, Rao S. Proposal for pharmacologically distinct conformers of PDE4 cyclic AMP phosphodiesterases. *Cell Signal* 1997;9:227-36.
8. Boswell-Smith V, Spina D, Page CP. Phosphodiesterase inhibitors. *Br J Pharmacol* 2006;147(suppl 1):S252-7.
9. Rudd RM, Gellert AR, Studdy PR, Geddes DM. Inhibition of exercise-induced asthma by an orally absorbed mast cell stabilizer (M & B 22,948). *Br J Dis Chest* 1983;77:78-86.

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Ineffectiveness of telephone-based environmental control intervention to improve asthma outcomes

To the Editor:

Current guidelines recommend testing for allergic sensitization (skin or blood tests) for all patients with persistent or uncontrolled asthma and environmental control education for those patients with positive test results.¹ Practical barriers to following this recommendation include cost, additional visits, and possible need for specialist referral. The purpose of our study was to test a relatively undemanding, convenient, and inexpensive means to fulfill this

recommendation in a large health plan without the need for a physician's office visit or specialist referral. Reports of improved asthma outcomes using telephone interventions^{2,3} supported a telephone-based intervention for this study.

Asthmatic patients aged 18 to 56 years who had not seen an allergist in the prior year were identified from Southern California Kaiser Permanente (SCKP) administrative data. Automated telephone calls using speech-recognition technology⁴ were made to randomly selected eligible patients until study recruitment was complete (see below). On the call, the Asthma Control Test (ACT) was administered, as previously reported,⁴ and patients with uncontrolled asthma (ACT score <20) were asked whether they would be interested in participating in the study. Study participation was confirmed on a follow-up "live" telephone call, at which time a baseline ACT score was obtained, and consent forms approved by the SCKP institutional review board were completed by mail.

Consenting patients were randomly assigned to the intervention or control group. All study patients were advised to contact their regular physician regarding their uncontrolled asthma. The control group did not receive any further interventions. The intervention group was asked to go to any Kaiser laboratory to obtain an allergy blood test for aeroallergens (Cap RAST to a panel of selected tree, grass, and weed pollens; mold spores; dust mite; and cat and dog dander). Patients were advised of their specific sensitivities by mail, and all allergic patients were sent written (Kaiser Permanente's "Controlling Asthma Triggers") and video (American Academy of Allergy, Asthma & Immunology's "Environmental Control Measures") environmental control information regarding pollen, mite, mold, pet dander, tobacco smoke, and other irritants. Patients in the intervention group were called 1 month after they were sent environmental control information to be sure they received the information, to reinforce the advice, and to answer questions.

Study patients were called 6 months after entering the study by research personnel blinded to study group to complete a follow-up ACT test and to determine whether participants had made any changes in their home environments ("Have you made any changes in your home environment in response to any of the information you have received during this study?"). Control patients might have made environmental changes randomly or in response to being told on the screening or baseline call that their asthma was not well controlled, but they did not receive any specific environmental control information during the study. Administrative data information (asthma hospitalizations, emergency department visits, oral corticosteroid dispensings, and number of short-acting β -agonist canister dispensings) were obtained for the 6 months before and 6 months after entry into the study for study patients (intervention and control), as well as 6 months before and after telephone ACT completion by patients who did not enter the study.

Power analysis for this study was based on unpublished data from our San Diego Kaiser Permanente patients who completed the ACT administered on 2 occasions 3 months apart by automated telephone calls using speech-recognition technology. Patients with uncontrolled asthma (ACT score <20) on the first call were advised to contact their primary care physician. Of 167 patients with uncontrolled asthma on the first call, 60% continued to have uncontrolled symptoms on the second call. We thus assumed that 60% of our control patients would continue to have uncontrolled asthma with the same intervention (advice to contact

TABLE I. ACT results in study patients

ACT parameter	Baseline		6 mo		6-mo Intervention	
	Intervention (n = 149)	Control (n = 151)	Intervention (n = 126)	Control (n = 111)	Made changes (n = 30)	Did not make changes (n = 96)
Mean (SD)	16.5 (4.5)	17.3 (4.7)	18.1 (4.4)	18.2 (4.4)	19.5 (3.5)	17.7 (4.5)
Percentage uncontrolled (ACT score <20)	73.1*	60.9	52.4	56.8	40.0	56.3
Mean (SD) change from baseline	—	—	1.6 (4.4)	0.7 (4.4)	2.5 (4.3)	1.3 (4.4)
Percentage increase from baseline by ≥ 3 (ACT minimal important difference ⁵)	—	—	40.5	33.3	50.0	37.5

* $P = .02$ versus control patients at baseline. No other significant differences between groups were seen at either time period.

their primary care physician). The study was powered to provide 80% power (2-tailed $P = .05$) to detect a clinically meaningful 33% decrease in follow-up uncontrolled asthma by ACT score (the primary outcome variable) from 60% in the control group to 40% in the intervention group, which was 100 patients per group. We planned to enroll 150 patients per group to account for the expected dropout rate of about 30% we have experienced in prior telephone surveys. The study was approved by the SCKP Institutional Review Board.

While identifying the 300 study participants with uncontrolled asthma (ACT score <20), automated telephone calls during recruitment identified 623 patients with uncontrolled asthma who chose not to participate and 1909 patients with controlled asthma (ACT score ≥ 20) who were ineligible. The 300 study participants were randomized to the intervention group (n = 149) and to the control group (n = 151); the groups did not differ significantly by age or sex (data not shown). Allergy blood tests were completed by 117 (78.5%) of 149 intervention patients, of whom 72 (61.5%) had positive test results. More patients in the intervention group than the control group continued to have uncontrolled asthma on their baseline telephone call ($P < .05$, Table I).^{5,6} It is not clear why 27% of intervention patients and 39% of control patients had improved to controlled status on their baseline ACT from uncontrolled status on their screening ACT, although being told on the screening call of their uncontrolled status might have played a role by encouraging improved medication adherence or medical attention. No other significant differences between groups in ACT scores were seen at baseline or at 6 months or in changes between baseline and 6 months (Table I). Restriction of the analyses to intervention patients who completed the blood test or to allergic patients did not change the results (data not shown). There were also no significant differences between the intervention and control groups in the proportions of patients who reported making home environmental changes during the study (23.8% vs 25.2%, respectively). Intervention patients who reported making environmental changes had better outcomes than those who did not report making such changes (Table I), but the differences did not reach statistical significance.

There were no significant differences between the intervention and control study groups regarding asthma hospitalizations or emergency department visits, any oral corticosteroid dispensings, or high short-acting β -agonist canister dispensings in the 6 months before or after entering the study (Tables II and III). Patients with controlled asthma not in the study did have less evidence of prior and subsequent medical use compared with patients with uncontrolled asthma not in the study ($P < .01$, Tables II and III).

The purpose of this study was to test an environmental control intervention for asthma that did not require a physician's office

TABLE II. Administrative data markers of uncontrolled asthma in patients in the study 6 months before and 6 months after study initiation*

Parameter	Group	
	Intervention	Control
Asthma hospitalization or ED visit†	(n = 139)	(n = 139)
Before	2.9%	2.9%
After	4.3%	2.9%
Any oral corticosteroid dispensing‡	(n = 131)	(n = 134)
Before	22.9%	20.1%
After	17.6%	20.9%
SABA ≥ 7 §	(n = 131)	(n = 134)
Before	6.1%	9.0%
After	9.2%	6.0%

ED, Emergency department; SABA, short-acting β -agonist canisters.

*There were no significant differences in results between intervention patients versus control patients.

†Only patients with continuous enrollment during the 6 months before and 6 months after study initiation were included in these analyses.

‡Only patients with pharmacy benefits during the 6 months before and 6 months after study initiation were included in these analyses.

§This SABA cutoff was based on a previously validated β -agonist long-term control scale.⁶

visit. We are reporting the negative results because we believe it is important to report what does not work to facilitate the design of interventions that will work. Actually, certain aspects of this strategy did work. We were able to identify by means of automated telephone technology patients with uncontrolled asthma who would subsequently manifest significantly more impairment and risk indicators of uncontrolled asthma over the following 6 months compared with patients with controlled asthma. A majority of intervention patients did complete their blood tests, and the majority of these patients had evidence of allergic sensitization. In addition, there was evidence of improvement in asthma control in both the intervention and control groups (Table I).

However, the intervention was not strong enough to induce intervention patients to make more home environmental changes than control patients, and therefore it is not surprising that asthma outcomes did not improve significantly more in intervention patients than in control patients. It is potentially encouraging that intervention patients who reported making changes appeared to do better than those who did not report making changes, but these differences were not statistically significant in this subgroup analysis, and even if significant, such improvement could not be definitively attributed to the intervention (versus, for example,

TABLE III. Administrative data markers of uncontrolled asthma in patients not in the study during 6 months before and 6 months after recruitment

Parameter	Group	
	Uncontrolled	Controlled
Asthma hospitalization or ED visit*	(n = 547)	(n = 1750)
Before	2.9%	0.9%†
After	1.6%	1.7%
Any oral corticosteroid dispensing*‡	(n = 523)	(n = 1683)
Before	17.8%	10.5%†
After	17.2%	11.7%†
SABA ≥7*‡§	(n = 523)	(n = 1683)
Before	6.7%	2.0%†
After	6.3%	3.5%†

ED, Emergency department; SABA, short-acting β -agonist canisters.

*Only patients with continuous enrollment during the 6 months before and 6 months after study recruitment were included in these analyses.

† $P < .01$ in patients with controlled asthma not in the study versus those with uncontrolled asthma not in the study.

‡Only patients with pharmacy benefits during the 6 months before and 6 months after study recruitment were included in these analyses.

§This SABA cutoff was based on a previously validated β -agonist long-term control scale.⁶

other characteristics of patients who make changes). It is not certain what more would need to be done for a successful intervention, but possibilities include the following: (1) taking into account a history-RAST correlation to determine individual patient relevance of the allergic sensitization; (2) a more tailored environmental control education program based on a patient's specific sensitization and environment; (3) a more individualized environmental control education program, taking into account the patient's total asthma state (severity, control, and treatment); (4) 1 or more in-person sessions to optimize information transfer and bidirectional communication; and (5) home visits.

Further studies will be necessary to determine which of these or other aspects of an environmental control intervention (eg, targeting patients who express a willingness to make changes) would successfully improve asthma outcomes in allergic patients. However, considering the role allergens can play in asthma and the ameliorative effect of environmental control,¹ the economic and human costs of uncontrolled asthma, and the expense and possible side effects of medications, such interventions would certainly be worth pursuing.

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REFERENCES

- Expert Panel Report 3: guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-S138.

- Donald KJ, McBurney H, Teichtahl H, Irving L. A pilot study of telephone-based asthma management. *Aust Fam Physician* 2008;37:170-3.
- Patel RR, Saltoun CA, Grammer LC. Improving asthma care for the elderly: a randomized controlled trial using a simple telephone intervention. *J Asthma* 2009;46:30-5.
- Schatz M, Zeiger RS, Drane A, Harden K, Cibildak A, Oosterman JE, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol* 2007;119:336-43.
- Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009;124:719-23.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol* 2006;117:995-1000.

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IL-4 receptor α polymorphisms are predictors of a pharmacogenetic response to a novel IL-4/IL-13 antagonist

To the Editor:

Evidence from genomic research, *in vitro* cell signaling, and animal studies strongly implicates the IL-4/IL-13 pathways in the pathogenesis of allergic asthma.¹⁻⁷ However, there are limited data on pharmacologic modulation of these pathways. We performed a descriptive pharmacogenetic analysis using data from an early phase II mechanistic trial of the drug pitrakinra, a novel IL-4/IL-13 dual antagonist, in patients with allergic asthma (ClinicalTrials.gov identifier NCT00535431).⁸ Pitrakinra is similar to the native IL-4 molecule, although specifically designed with 2 amino acid changes (R121D/Y124D), rendering it an effective competitive antagonist of IL-4 receptor α (IL-4R α).⁸ Pitrakinra reduces late-phase responses to inhaled antigen based on phase II clinical studies to date,⁸ and genomic DNA samples were obtained from 29 participants in this clinical trial. In addition, we obtained DNA from 23 cynomolgus monkeys from preclinical antigen-challenge studies, in which monkeys were treated with an IL-4/IL-13 antagonist similar to pitrakinra and with the same mechanism of action.⁹ We hypothesized that single nucleotide polymorphisms (SNPs) in the gene encoding IL-4R α (*IL4RA*) would predict treatment response in the human studies and that there would be a similar effect of *IL4RA* gene variation in nonhuman primates.

The protocol and results of the early phase II trials have been reported previously and are described in brief below.⁸ The primary clinical outcome was change in late-phase antigen response to inhaled allergen challenge in patients with asthma. Acute and late-phase responses were measured at screening and after 4 weeks of twice-daily therapy with nebulized pitrakinra or placebo. After allergen challenge, FEV₁ was measured over a 10-hour period to assess late antigen response (LAR; 4-10 hours). The outcome for this genetic analysis was the ratio of LAR after 4 weeks of treatment with either placebo or pitrakinra compared with baseline levels. Therefore an increased LAR ratio corresponds to a reduction in late-phase FEV₁ response to antigen after treatment or an improvement in lung function relative to baseline measurements.

Pharmacogenetic analysis was performed on genomic DNA from predominantly non-Hispanic white (83%) male (63%) subjects with asthma randomized to placebo (n = 14) or pitrakinra (n = 15) with complete data on the primary outcome. We selected 14 *IL4RA* tagging SNPs and 3 nonsynonymous amino acid coding changes from the HapMap CEU reference