Heritability of Chronic Obstructive Pulmonary Disease and Related Phenotypes in Smokers

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Rationale: **Previous studies of chronic obstructive pulmonary disease (COPD) have suggested that genetic factors play an important role in the development of disease. However, single-nucleotide polymorphisms that are associated with COPD in genome-wide association studies have been shown to account for only a small percentage of the genetic variance in phenotypes of COPD, such as spirometry and imaging variables. These phenotypes are highly predictive of disease, and family studies have shown that spirometric phenotypes are heritable.**

Objectives: **To assess the heritability and coheritability of four major COPD-related phenotypes (measurements of FEV_1, FEV_1/FVC, percent emphysema, and percent gas trapping), and COPD affection status in smokers of non-Hispanic white and African American descent using a population design.**

Methods: **Single-nucleotide polymorphisms from genome-wide association studies chips were used to calculate the relatedness of pairs of individuals and a mixed model was adopted to estimate genetic variance and covariance.**

Measurements and Main Results: **In the non-Hispanic whites, estimated heritabilities of FEV_1 and FEV_1/FVC were both about 37%, consistent with estimates in the literature from family-based studies. For chest computed tomography scan phenotypes, estimated heritabilities were both close to 25%. Heritability of COPD affection status was estimated as 37.7% in both populations.**

Conclusions: **This study suggests that a large portion of the genetic risk of COPD is yet to be discovered and gives rationale for additional genetic studies of COPD. The estimates of coheritability (genetic covariance) for pairs of the phenotypes suggest considerable overlap of causal genetic loci.**

Keywords: missing heritability; pleiotropy; pulmonary function; imaging phenotypes; chromosomal partition

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Novel estimates of heritability for chronic obstructive pulmonary disease and four lung function–related phenotypes are estimated using a population-based dataset and compared with pedigree-derived estimates.

What This Study Adds to the Field

We present heritability estimates of emphysema for the first time. This study suggests that a large portion of the genetic content of chronic obstructive pulmonary disease is yet to be discovered and gives rationale for later genetic studies for chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and has recently risen to become the third leading cause of death in the United States. Although cigarette smoking is the most important risk factor for the development of COPD, only a small proportion of smokers develop clinically significant COPD. In family studies, it has been shown that the risk of COPD is approximately two to three times higher in smokers who have a first-degree relative affected by COPD (1). This suggests that genetic factors play an important role in development of COPD. The best known genetic factor linked to COPD is a deficiency of the serine protease α_1-antitrypsin (encoded by *SERPINA1*), which occurs in 1–3% of patients with COPD (2). Recently, genome-wide association studies (GWAS) have revealed various common variants in several genetic loci that are associated with COPD susceptibility including *CHRNA3/CHRNA5/IREB2* (3), *HHIP* (4), *FAM13A* (5, 6), and a chromosome 19q region near *CYP2A6* (7). However, similar to other common nonmendelian diseases, these genetic variants account for a small percentage of the heritability in COPD-related phenotypes, which has been estimated in previous twin studies and family studies to be 20–40% for spirometric phenotypes, such as FEV_1 and FEV_1/FVC (8, 9), and even higher, 50–60%, for smoking behavior phenotypes (10, 11). Rare variants may be related to the substantial undetermined heritability because not all rare variants are tagged by GWAS chips. Another explanation is that the heritability is not missing but hiding (12). Recently, Yang and coworkers (12, 13) proposed a method of estimating the total amount of phenotypic variance captured by all single-nucleotide polymorphisms (SNPs) on GWAS commercial genotyping arrays using unrelated individuals. They estimated that about 45% of the phenotypic variance of human height could be explained by all the SNPs genotyped for GWAS. Their approach showed a nearly 10-fold increase from the 5% explained by published and validated individual SNPs in GWAS for height (14–16). Their method can be extended to multiple phenotypes to determine pleiotropy (17) by estimating coheritability between pair of phenotypes. Pleiotropy is said to be present when two or more phenotypes share some causal loci.

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TABLE 1. DESCRIPTIVE STATISTICS OF THE STUDY POPULATION USED FOR HERITABILITY ESTIMATION

Variable	Non-Hispanic White Mean ± SD (Sample Size)	African American Mean ± SD (Sample Size)
Age, yr	61.97 ± 8.79 (n = 6,415)	54.45 ± 7.08 (n = 2,792)
Male, %	52.27% (n = 6,415)	56.20% (n = 2,792)
Body mass index	28.69 ± 6.09 (n = 6,415)	29.09 ± 6.71 (n = 2,792)
COPD cases, %	47.32% (n = 5,354)	31.78% (n = 2,152)
Current smokers, %	39.52% (n = 6,415)	81.12% (n = 2,792)
Pack-years of smoking	47.59 ± 26.14 (n = 6,415)	38.41 ± 21.87 (n = 2,792)
Height, cm	169.90 ± 9.43 (n = 5,978)	171.33 ± 9.67 (n = 2,792)
FEV_1, % predicted (post-bronchodilator)	72.99 ± 26.03 (n = 6,398)	81.57 ± 23.64 (n = 2,756)
FEV_1/FVC (post-bronchodilator)	0.64 ± 0.17 (n = 6,398)	0.72 ± 0.14 (n = 2,756)
% Emphysema	7.46 ± 10.42 (n = 5,777)	3.72 ± 7.44 (n = 2,514)
% Gas trapping	24.51 ± 20.60 (n = 5,385)	16.89 ± 17.49 (n = 2,192)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

By using Yang's method in the Genetic Epidemiology of COPD (COPDGene) Study population of approximately 10,000 subjects, we report heritability estimates of spirometric phenotypes (post-bronchodilator FEV_1 and FEV_1/FVC), chest computed tomography (CT) scan phenotypes (percent emphysema and percent gas trapping), and COPD disease status. Because COPD is defined based on reductions in FEV_1 and FEV_1/FVC (FEV_1 <80% of predicted and FEV_1/FVC <0.7), heritabilities of these two phenotypes were adjusted for study ascertainment to predict population heritability. Prebronchodilator FEV_1 and FEV_1/FVC are highly correlated with post-bronchodilator measures and our estimations show that they have very similar heritability estimates. Therefore, we only report post-bronchodilator FEV_1 and FEV_1/FVC in this paper. Genomic partitioning of the heritability to the separate autosomes shows the distribution of causal variants over the genome, and also enables us to account for any population substructure in the sample (18). We therefore estimated the heritability of two phenotypes (FEV_1/FVC and percent emphysema) in non-Hispanic whites (NHW) for each of the autosomes (nonsex chromosomes), the sample size being too small to partition the heritability for the African American (AA) sample. Finally, we estimated the percentage of the overall heritability that can be explained by four previously reported GWAS SNPs (3–6).

METHODS

Sample

COPDGene is one of the largest cohorts of well-characterized smokers for respiratory disease research, including 10,192 current and former smokers with airflow obstruction ranging from none to Global Initiative for Chronic Obstructive Lung Disease stage 4 (very severe) COPD. The study design of COPDGene has been reported previously (19). Briefly, both NHW subjects and AA subjects were included between the ages of 45 and 80 with at least a 10 pack-year smoking history. Exclusion criteria included pregnancy, history of other lung disease except asthma, prior lobectomy or lung volume reduction surgery, active cancer undergoing treatment, or known or suspected lung cancer. After data cleaning, 6,678 individuals from the NHW and 3,300 individuals from the AA population with complete genotypic data remained. All of the subjects were not knowingly related to each other. The sample is enriched for COPD subjects by design.

Genotyping was performed on the Illumina OmniExpress platform (Illumina, San Diego, CA). We excluded SNPs that have minor allele frequency less than 0.01 and Hardy-Weinberg equilibrium P value less than 10^{-8} using PLINK (20). Only SNPs located on the autosomes were used. After filtering, 664,892 and 663,347 autosomal SNPs were retained for analysis in the NHW and AA population, respectively.

Phenotypes

COPDGene subjects underwent extensive phenotypic assessment, including spirometry (pre and post bronchodilator) and chest CT scans (inspiratory and expiratory). Spirometry, chest CT scans, and smoking phenotypes were considered as continuous variables, whereas COPD disease status was a binary outcome in the analysis. Prebronchodilator spirometric phenotypes are highly correlated with post-bronchodilator measures and our estimations show that they have very similar heritability estimates. Therefore, we only report post-bronchodilator FEV_1 and FEV_1/FVC in this paper.

Spirometric measures of lung function were performed before and after the inhalation of 180 μg (two puffs) of albuterol, according to American Thoracic Society criteria (21). Volumetric chest CT acquisitions were obtained at full inspiration (200 mA), and at the end of normal expiration (50 mA). Quantitative image analysis to calculate percent emphysema and percent gas trapping was performed using 3D SLICER (http://www.slicer.org/). Percent emphysema was defined as the total percentage of both lungs with attenuation values less than −950 Hounsfield units on inspiratory images, and percent gas trapping was defined as the total percentage of both lungs with attenuation values less than −856 Hounsfield units on expiratory images.

TABLE 2. HERITABILITY ESTIMATES

Phenotypes	NHW N	NHW Heritability (SE)	AA N	AA Heritability (SE)	Wald P Value*
FEV_1, % predicted†	6,128	38.4% (5.7%)‡	2,756	50.9% (13.5%)‡	0.395
FEV_1/FVC†	6,128	37.3% (5.7%)‡	2,756	46.6% (13.9%)‡	0.538
Log of % emphysema	5,777	28.2% (6.0%)‡	2,514	31.3% (14.5%)‡	0.849
Log of % gas trapping	5,385	24.0% (6.4%)‡	2,192	27.9% (14.9%)‡	0.808
COPD disease status†	4,929	37.7% (7.4%)‡	2,152	37.9% (20.4%)	0.992
Body mass index	6,145	18.7% (6.0%)	2,792	29.0% (12.8%)	0.469
Height	6,145	59.4% (5.6%)‡	2,792	45.5% (13.5%)‡	0.341

Definition of abbreviations: AA = African American; COPD = chronic obstructive pulmonary disease; NHW = non-Hispanic white.

*Wald test for the comparison of heritability estimation between NHW and AA.

† After ascertainment adjustment, heritability of FEV_1 is still 38.4% and FEV_1/FVC is 37.0% in NHW. In the AA population the adjusted heritability of FEV_1 is 51.0% and FEV_1/FVC is 49.4%.

‡ LRT P value for testing heritability different from zero passed threshold 0.05.

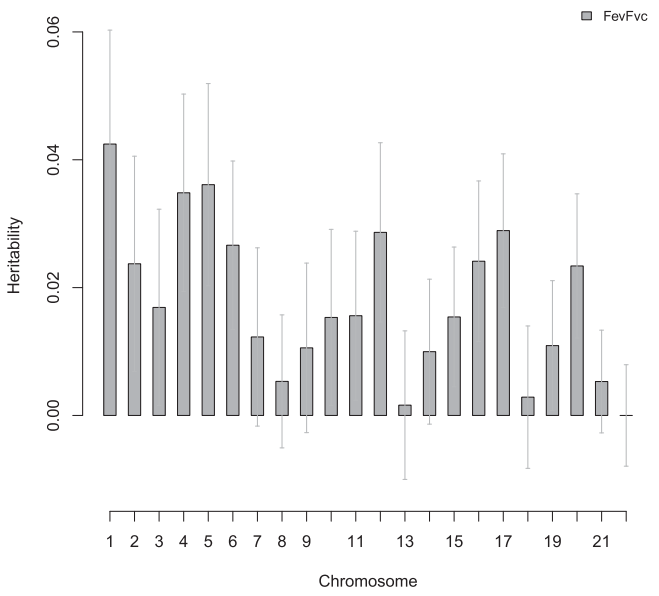

Figure 1. Chromosomal partition of phenotypes FEV_1/FVC in non-Hispanic white sample. Error bars are the standard error for each estimate.

Statistical Methods

Heritability and genetics relationship matrix estimation. We calculated a genetic relationship matrix (GRM) using SNPs from all of the autosomes. The GRM uses SNP data to measure the relatedness between each pair of individuals in our sample. This GRM replaces the known information about relatedness found in pedigrees. Heritabilities for continuous and binary outcomes were estimated using the software package GCTA developed by Yang and coworkers (13). Heritability of disease status was estimated using a liability model as illustrated previously (22, 23).

To determine whether the distribution of genetic variance differs by chromosome, and to account for the effects of population stratification, we first calculated the GRMs from the SNPs separately on each autosome. We then estimated the genetic variances for all 22 autosomes in a joint analysis using a linear mixed model. In this model, the heritability of each autosome is just the ratio of its genetic variance to the overall phenotypic variance. We used one representative spirometric phenotype, FEV_1/FVC, and one CT scan phenotype, percent emphysema only in NHW sample because of the small sample size in AA (18).

To quantify the effect of population substructure, we estimated the genetic variance for each autosome in a separate analysis. Using these estimates of the genetic variance, we calculated the autosome-specific heritabilities in two ways: using the jointly estimated genetic variances (h^2_{joint}) and using the separately estimated genetic variances (h^2_{sep}). The joint estimates, h^2_{joint}, can be viewed as adjusting for genetic variation on other chromosomes (i.e., the effect of population substructure). The estimated h^2_{sep} does not take population substructure into account. We then regressed the difference in the two estimates of the genetic variances, jointly and separately, on the length (in mega–base pairs) of the corresponding chromosome. The regression slope can be attributed to population stratification because longer chromosomes are likely to have more ancestry informative markers, assuming that the ancestry informative markers are randomly distributed across the genome (18).

Heritability that can be explained by the four previously reported GWAS SNPs was calculated by comparing the genetic variances estimated with and without using the four SNPs as covariates.

Adjustment for ascertainment. When the proportion of cases and control subjects are not a random sample from the general population, the sample heritability needs to be adjusted to estimate general population heritability. The adjustment for ascertainment is a straightforward extension of the approach used to estimate heritability from dichotomous data using the threshold model. We first express heritability in the sample (h^2_s) as a function of population heritability (h^2). Because h^2_s can be estimated from the data, h^2 is therefore determined if the sampling fractions (prevalence in the population and in the sample) and thresholds to define cases are known.

In COPDGene, disease status is defined by two phenotypes: an individual is a case when post-bronchodilator FEV_1 is less than 80% predicted and post-bronchodilator FEV_1/FVC is less than 0.7. Although slightly more complex, the general approach for ascertainment correction extends readily when disease status is defined using two variables. See the online supplement for a detailed derivation.

Genetic covariance. The estimation of the genetic covariance between two phenotypes can be seen as an estimation of covariance between multivariate traits within a linear mixed model framework (24, 25). We parameterized covariance structure of Y_1 and Y_2 to be

$$\begin{aligned}\text{Cov}(Y_{1i}, Y_{2j}) &= \sigma_{g_{12}} K_{ij} + \sigma_{e_{12}} K_{ij} \\ \text{Var}(Y_t) &= \sigma^2_{g_t} K + \sigma^2_{e_t} I, \quad t = 1, 2\end{aligned}$$

where $\sigma^2_{g_1}$ and $\sigma^2_{e_1}$, $\sigma_{g_{12}}$, and $\sigma_{e_{12}}$ are the genetic and environmental variances and covariances, with i and j indexing subjects and t indexing traits, and K is the GRM. Each parameter was estimated using a maximum likelihood method (26). The genetic correlation coefficient is defined as follows:

$$\rho = \frac{\sigma_{g12}}{\sqrt{\sigma^2_{g_1}}\sqrt{\sigma^2_{g_2}}}$$

RESULTS

Heritability Estimation for COPD-related Phenotypes

The COPDGene Study enrolled a total of 10,192 smokers. After phenotypic exclusions and genotyping quality control, we started with a total sample of 9,978 individuals with full genotypes including 6,678 NHW subjects and 3,300 AA subjects. All of the individuals within each racial group were used to calculate race-specific genetic relationship coefficients based on previously filtered autosomal SNPs. To avoid inflation caused by closely related individuals, we selectively excluded one of any pair of individuals with an estimated relationship greater than 0.025 (corresponding to the relationships of third or fourth degree of relationship) to maximize the remaining sample size. A total of 6,415 NHW individuals and 2,792 AA individuals remained for genetic relationship coefficient calculations and for various descriptive statistics generation (Table 1). Percent emphysema and percent

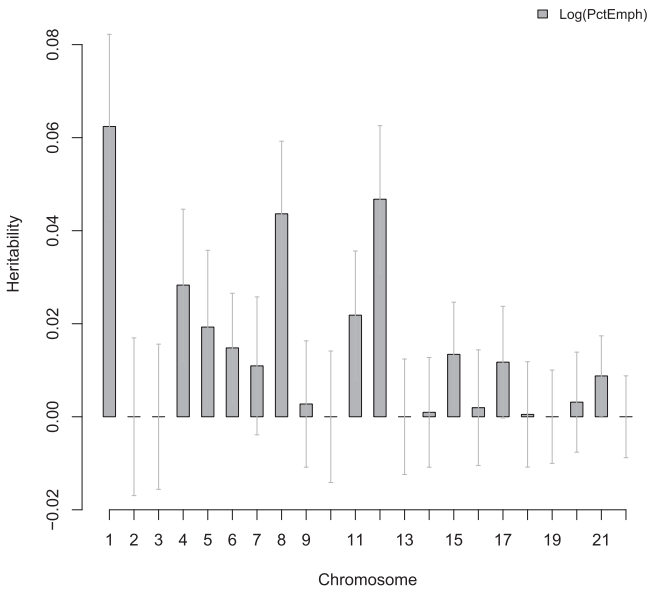

Figure 2. Chromosomal partition of percent of emphysema in non-Hispanic white sample. Error bars are the standard error for each estimate.

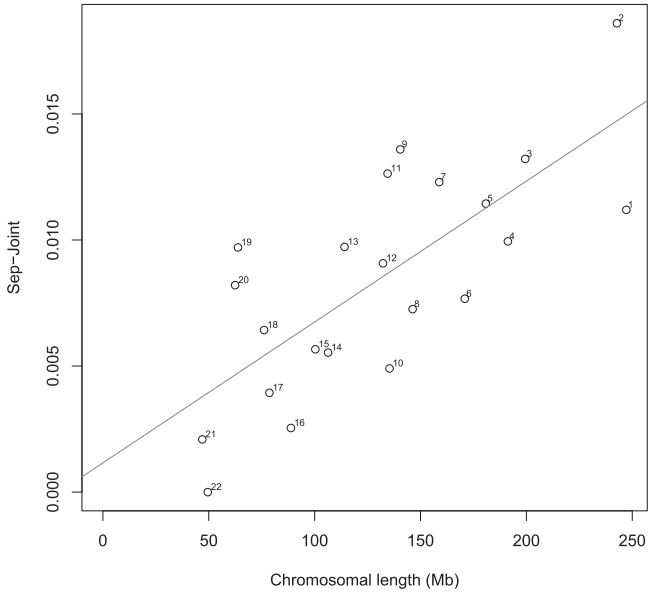

Figure 3. Variance caused by cryptic relatedness and population stratification. Shown is the difference between the estimates of variance explained by each chromosome by the separate (Sep) and joint analyses for FEV_1/FVC. Numbers next to each *dot* are the chromosome numbers. *Straight line* is the regression line (difference between analysis separately and jointly regressed on chromosomal length.)

gas trapping were log-transformed to achieve normality. Phenotypes used for estimation are standardized residuals after adjusting age, sex, age^2, age $\times$ sex (i.e., interaction between age and sex), and age^2 $\times$ sex. We also estimated heritability adjusting for smoking by including pack-years and current smoking as covariates. No obvious outliers (larger than $\pm$6 standardized residuals) were found. We found substantial differences in the AA and NHW samples. On average, individuals in the AA sample were younger than in the NHW sample, and the AA sample contained more current smokers but fewer COPD cases. Consistent with the larger fraction of control subjects in the AA sample, the mean values of the spirometric phenotypes in the AA sample were higher than the NHW sample, and the mean of the CT scan emphysema and gas trapping phenotypes was lower. We address this point in comparing the estimated heritabilities from the two racial groups.

The results of heritability estimation are displayed in Table 2. We estimated the heritability of FEV_1 to be 38.4% in the NHW population and 50.9% in the AA population. For log percent emphysema and log percent gas trapping, the estimated heritabilities are lower and have higher standard errors compared with FEV_1 and FEV_1/FVC. Among the five phenotypes (COPD disease status, and four COPD-related phenotypes) the ranking of the heritability estimates are the same between two populations (i.e., FEV_1 is the most heritable phenotype and percent of gas trapping is the least heritable). Heritability estimates in the AA population were generally higher than the NHW population. FEV_1 shows the greatest difference, with an increase from 38.4% in the NHW population to 50.9% in the AA population. To determine whether heritability estimates for well-studied anthropometric characteristics were consistent with other reports, we estimated the heritability of height and body mass index in our cohort. The heritability of height in our cohort was about 60% in NHW, similar to prior estimates (12). The heritability estimates for body mass index were much lower, 18.7% in NHW and 29% in AA, which are also similar to estimates from three combined population-based GWAS (18).

Using the likelihood ratio test, we tested whether each estimated heritability estimate is significantly different from zero. In the NHW population, genetic components of all phenotypes except for body mass index were significantly different from zero; however, in the smaller AA population both body mass index and COPD disease status did not have statistically significant genetic components. Although the heritability estimates were generally higher in the AA, based on a Wald test we found the heritability estimates between NHW and AA were not statistically significantly different from each other.

Our results adjusting for current smoking and pack-years of smoking are shown in Table E1 in the online supplement. The effect of adjustment is negligible for the imaging phenotypes in AA. In both populations, COPD disease status and spirometric phenotypes showed around a 5% drop in heritability after smoking adjustment, although this drop is well within the standard errors. Therefore, for the remainder of the paper we use estimates unadjusted for smoking variables.

Because our sample is enriched for COPD cases, defined by FEV_1 less than 80% predicted and FEV_1/FVC less than 0.7, we adjusted the estimates of FEV_1 and FEV_1/FVC for ascertainment. In both populations ascertainment adjustment had little effect on heritability estimates. The heritability of COPD disease status was estimated to be 37.7% under a liability scale assuming 10% prevalence in the NHW population and 37.9% in the AA population assuming the same prevalence, with higher prevalence assumptions leading to higher heritability estimates.

Genome Partitioning of the Heritability

Chromosomal heritabilities (Figures 1 and 2) of both phenotypes significantly correlate with chromosomal length. Although chromosome 1 has the highest heritability for both phenotypes, the standard errors were very large. We found that the

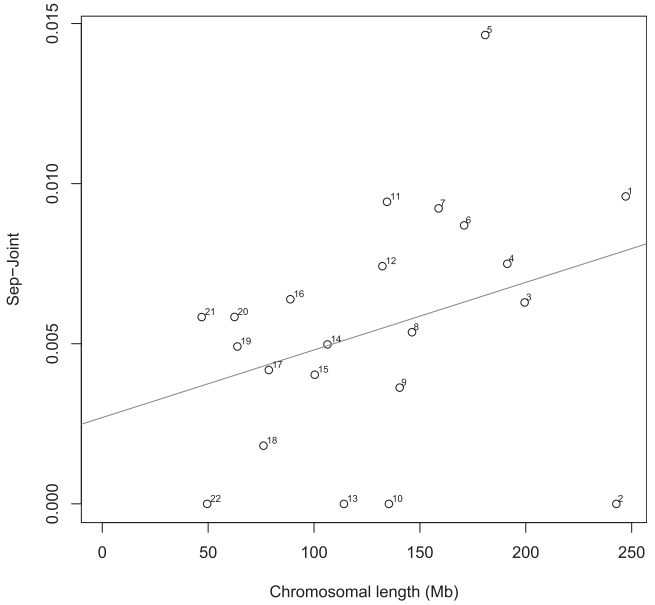

Figure 4. Variance caused by cryptic relatedness and population stratification. Shown is the difference between the estimates of variance explained by each chromosome by the separate (Sep) and joint analyses for percent of emphysema. Numbers next to each *dot* are the chromosome numbers. *Straight line* is the regression line (difference between analysis separately and jointly regressed on chromosomal length.)

TABLE 3. GENETIC CORRELATION COEFFICIENT ESTIMATES FROM NON-HISPANIC WHITE (ABOVE THE MAIN DIAGONAL) AND AFRICAN AMERICAN (BELOW THE MAIN DIAGONAL) SAMPLES

	FEV_1	FEV_1/FVC	Log of % Emphysema	Log of % Gas Trapping
FEV_1	—	0.889	−0.626	−0.844
FEV_1/FVC	0.797	—	−0.818	−0.877
Log of % emphysema	−0.573	−0.725	—	0.903
Log of % gas trapping	−0.855	−0.696	0.814	—

TABLE 4. GENETIC COVARIANCE ESTIMATES FROM NON-HISPANIC WHITE (ABOVE THE MAIN DIAGONAL) AND AFRICAN AMERICAN (BELOW THE MAIN DIAGONAL) SAMPLES

	FEV_1	FEV_1/FVC	Log of % Emphysema	Log of % Gas Trapping
FEV_1	—	0.336 (0.052)	−0.205 (0.044)	−0.247 (0.047)
FEV_1/FVC	0.394 (0.122)	—	−0.264 (0.048)	−0.261 (0.049)
Log of % emphysema	0.233 (0.106)	0.260 (0.115)	—	0.245 (0.053)
Log of % gas trapping	−0.293 (0.109)	−0.253 (0.115)	0.245 (0.122)	—

SE is given in parentheses.

proportion of estimated heritability attributed to population structure across the whole genome is minimal: 0.88% and 0.56% for FEV_1/FVC and percent emphysema, respectively (Figures 3 and 4).

Comparison with Known COPD-associated Variants in NHW Population

To quantify the effect of known COPD-associated variants on the results, we considered four SNPs that have previously been shown to be associated with COPD in NHW: (*1*) rs7671167 in *FAM13A* on chromosome 4; (*2*) rs13180 at the chromosome 15 locus (*IREB2/CHRNA3/CHRNA5*); (*3*) rs7937 at the chromosome 19 locus (*RAB4B/CYP2A6*); and (*4*) rs7655625 near *HHIP* on chromosome 4 ($r^2 = 0.96$ with rs13118928). We used these SNPs as covariates in the model when estimating heritability of FEV_1. In the NHW population, when compared with the results without including the known associated variants, the overall estimated heritability of FEV_1 dropped from 38.4–35.4% indicating 7.8% (3%/38.4%) of the original heritability can be explained by these four SNPs, which is in line with an estimate of approximately 5–10% of variance explained by the previous GWAS (7). With the liability scale, heritability of COPD disease status decreases to 34.2% from 37.7% when the four GWAS variants are included in the model.

Estimated Genetic Correlation Coefficients

In both populations, genetic correlations were all greater than 0.5 (in magnitude) suggesting considerable overlap of the genetic content between the four major COPD-related phenotypes that were analyzed (Table 3). Consistent with intuition, genetic content of lung function and CT scan phenotypes were negatively correlated. Interestingly, although heritability estimates vary between the two racial groups, genetic covariance estimates are similar across populations (Table 4).

DISCUSSION

Issues of missing heritability have been widely discussed in light of the fact that the many genetic variants discovered by GWAS for complex traits can only explain a small portion of the total estimated heritability (27, 28). One of the explanations is that some causal variants have such small effects that they cannot pass the stringent significance threshold used in GWAS. Therefore, variation that is based only on significant SNPs cannot explain all of the heritability. Yang and coworkers (12) developed a method to estimate heritability using all SNPs within a GWAS. In this paper we estimated heritability based on their method in a population of smokers from the COPDGene study, and we also estimated coheritability for COPD status and four major phenotypes. To our knowledge, these are the first estimates of heritability and coheritability for COPD or lung function–related phenotypes using a population-based dataset.

In our GWAS cohort, spirometric phenotypes have higher heritability estimates than chest CT scan phenotypes in NHW and AA samples. There are several possible explanations for the slightly lower heritability estimates of imaging phenotypes compared with spirometric phenotypes. It is possible that the specific imaging phenotypes that we analyzed have higher measurement errors because of technical issues. It is also possible that the imaging phenotypes have lower genetic contributions than spirometric phenotypes. Assessment of additional CT imaging phenotypes is required to resolve this issue (29). Heritability estimates are generally higher in AA sample than in NHW sample, especially spirometry phenotypes, although the differences in the heritability estimates were not statistically significant. Although we cannot rule out the possibility that there is a greater contribution from common genetic variants to these phenotypes in AA, we have low power to detect this because of the small sample size of the AA.

Generally, the previously reported COPD GWAS SNPs account for approximately 8% of the heritability in the NHW population. It was of interest that results for FEV_1/FVC were very similar to FEV_1 for both populations, because more GWAS associations have been found for FEV_1/FVC than for FEV_1 in general population samples (30).

Our basic approach to estimation of heritability assumes that the phenotypes are polygenic (i.e., there are numerous causal genetic variants spread throughout the genome). This explains the dramatic difference between our estimates and the heritability attributed to a small number of SNPs identified as statistically significant in GWAS studies. This is likely because many associated SNPs have either smaller effect size or low minor allele frequencies that typical GWAS studies have been unable to detect. The current analysis indicates that there are considerable genetic components for five major COPD-related phenotypes, and between phenotypes there is substantial genetic overlap. Of interest, chest CT scan phenotypes, which have not been explored before, were shown to have a modest, but statistically significant genetic component. Our estimates of heritability for spirometric phenotypes are consistent with results from previous family-based studies in the literature. Further analysis with denser genetic content can be performed to search for the location of causal variants underlying complex traits like COPD.

Author disclosures are available with the text of this article at www.atsjournals.org.

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ONLINE DATA SUPPLEMENT

Heritability of COPD and Related Phenotypes in Smokers

Jin J. Zhou, Michael H. Cho, Peter J. Castaldi, Craig P. Hersh, Edwin K. Silverman and Nan M. Laird

Ascertainment Adjustment

In the following derivation we express the sample heritability, h_s^2, by the population heritability, h^2. Then population heritability can be found by inverting the expression.

First we calculate phenotypic variance in the sample. For a random variable Y
$\text{var}(Y \mid sample) = \text{E}(Y^2 \mid sample) - \text{E}(Y \mid sample)^2.$
Based on statistical theory we have
$$\begin{aligned}\text{E}(Y \mid Sample) &= \Pr(Y < t \mid sample)\text{E}(Y \mid Y < t) + \Pr(Y > t \mid sample)\text{E}(Y \mid Y > t) \\ &= P\text{E}(Y \mid Y < t) + (1-P)\text{E}(Y \mid T > t)\end{aligned}$$
where $P = \Pr(Y < t \mid sample)$.
Mean value of Y above and below threshold are
$$\text{E}(Y \mid Y < t) = -\frac{\sigma^2 z}{K} + \mu, \text{ and } \text{E}(Y \mid Y > t) = \frac{\sigma^2 z}{1-K} + \mu.$$
where z is the height of normal curve $N(\mu, \sigma^2)$ at threshold *t* and $K = \Pr(Y < t)$.
Therefore,
$$E(Y \mid sample) = \theta\sigma^2 z + \mu \qquad (2)$$
where $\theta = \frac{1-P}{1-K} - \frac{P}{K}$. By the same logic we have
$\text{E}(Y^2 \mid sample) = \theta\sigma^2 z(t+\mu) + \sigma^2 + \mu^2.$
The variance of Y in the sample is then
$\text{var}(Y \mid sample) = \theta\sigma^2 z(t - \mu - \theta\sigma^2 z) + \sigma^2.$ (3)
Obviously if there is no ascertainment, i.e. $P = K(\theta = 0)$, the mean and variance in the sample reduce to population mean and sample variance.

Now we calculate genetic variance in the sample. Provided that
$Y \sim N(\mu, \sigma^2), g \sim N(0, \sigma_g^2)$, and $Y = g + e$, Y and g follow a bivariate normal distribution with $\text{cov}(Y, g) = \text{var}(g)$. The genetic mean in the sample is then
$$\begin{aligned}\text{E}(Y \mid sample) &= \Pr(Y \mid sample)\text{E}(g \mid Y < t) + \Pr(Y > t \mid sample)\text{E}(g \mid Y > t) \\ &= P\text{E}(g \mid Y < t) + (1-P)\text{E}(g \mid Y > t).\end{aligned}$$
Taking advantage of the conditional mean $\text{E}(g \mid Y) = h^2(Y - \mu)$, the mean of the genetic value when the corresponding phenotypic value is less (greater) than the threshold is
$$\text{E}(g \mid Y < t) = \frac{h^2\sigma^2 z}{K} E(g \mid Y > t) = \frac{h^2\sigma^2 z}{1-K}.$$
Therefore
$\text{E}(g \mid sample) = h^2\theta\sigma^2 z.$
Genetic variance in the sample is then determined by the equation
$\text{var}(g \mid sample) = h^4\theta\sigma^2 z(t - \mu - \theta\sigma^2 z) + h^2\sigma^2,$
utilizing the conditional variance $\text{var}(g \mid Y) = h^2(1-h^2)\sigma^2$.

Finally heritability estimated in the sample is

$$h_s^2 = \frac{\text{var}(g \mid sample)}{\text{var}(Y \mid sample)} = \frac{1 + h^2\theta z(t - \mu - \theta\sigma^2 z)}{1 + \theta z(t - \mu - \theta\sigma^2 z)} \quad (4)$$

Equation (4) is equivalent to the heritability on a liability scale when assuming standard normal distribution of the phenotypes[29]. Given population mean, variance and prevalence or threshold, population heritability can be calculated by inverting the equation. If threshold is defined and P is known, the population mean and variance can be found using equation (2) and (3) by certain root-solving algorithms such as the Newton-Raphson algorithm.

Table S1. Heritability Estimates (after adjusting for pack-years and current smoking status).

Phenotypes	NHW		AA		Wald P-value
	N	Heritability (SE)	N	Heritability (SE)	
FEV_1, % predicted	6128	33.21% (5.65%)	2756	45.79%(13.35%)	0.386
FEV_1/FVC	6128	32.27% (5.65%)	2756	41.15%(13.77%)	0.551
Log of % Emphysema	5777	23.27% (5.92%)	2514	32.06%(14.55%)	0.576
Log of % Gas Trapping	5385	20.14% (6.34%)	2192	27.54%(14.96%)	0.649
COPD disease status[#]	4929	33.67% (7.33%)	2152	32.31%(20.00%)	0.949

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Dr. Hersh reports grants from National Heart Lung and Blood Institute, during the conduct of the study; grants from National Heart Lung and Blood Institute, grants from National Institute of Nursing Research, grants from Alpha-1 Foundation, personal fees from Novartis, personal fees from CSL Behring, outside the submitted work; .

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Michael
2. Surname (Last Name): Cho
3. Date: 26-June-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jin Zhou

5. Manuscript Title: Heritability of COPD and Related Phenotypes in Smokers

6. Manuscript Identifying Number (if you know it): Blue-201302-0263OC

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
National Institutes of Health	☑	☐	☐	☐		

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Alpha-1 Foundation	☑	☐	☐	☐		
Merck	☐	☑	☐	☐		

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Cho reports grants from National Institutes of Health, during the conduct of the study; grants from Alpha-1 Foundation, personal fees from Merck, outside the submitted work; .

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

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1. Identifying information.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): nan
2. Surname (Last Name): laird
3. Date: 27-June-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: jin zhou

5. Manuscript Title: Heritability of COPD and Related Phenotypes in Smokers

6. Manuscript Identifying Number (if you know it): Blue-201302-0263OC

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. laird has nothing to disclose.

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3. Relevant financial activities outside the submitted work.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Peter
2. Surname (Last Name): Castaldi
3. Date: 25-June-2013

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jin Zhou

5. Manuscript Title: Heritability of COPD and Related Phenotypes in Smokers

6. Manuscript Identifying Number (if you know it): Blue-201302-0263OC

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Castaldi has nothing to disclose.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jin
2. Surname (Last Name): Zhou
3. Date: 25-June-2013

4. Are you the corresponding author? [✓] Yes [ ] No

5. Manuscript Title: Heritability of COPD and Related Phenotypes in Smokers

6. Manuscript Identifying Number (if you know it): 201302-0263OC

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? [ ] Yes [✓] No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? [ ] Yes [✓] No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? [ ] Yes [✓] No

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Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Zhou has nothing to disclose.

Evaluation and Feedback

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1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

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3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence,or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Edwin
2. Surname (Last Name): Silverman
3. Effective Date (07-August-2008): 26-June-2013

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Jin Zhou

5. Manuscript Title: Heritability of COPD and Related Phenotypes in Smokers

6. Manuscript Identifying Number (if you know it): Blue-201302-0263OC

Section 2. The Work Under Consideration for Publication

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Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	☐	☐	☑	NIH		×
1. Grant	☐	☐	☑	COPD Foundation	The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, and Sunovion.	×
						ADD
2. Consulting fee or honorarium	☑	☐	☐			×
						ADD
3. Support for travel to meetings for the study or other purposes	☐	☑	☐	NIH		×

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ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
3. Support for travel to meetings for the study or other purposes	☐	☑	☐	COPD Foundation	The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, and Sunovion	×
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☑	☐	☐			×
						ADD
5. Payment for writing or reviewing the manuscript	☑	☐	☐			×
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	☑	☐	☐			×
						ADD
7. Other	☑	☐	☐			×
						ADD

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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Relevant financial activities outside the submitted work

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Relevant financial activities outside the submitted work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	☑	☐	☐			×
						ADD
2. Consultancy	☐	☑	☐	GlaxoSmithKline AstraZeneca		×
2. Consultancy	☐	☑	☐	Merck		×
						ADD
3. Employment	☑	☐	☐			×
						ADD
4. Expert testimony	☑	☐	☐			×
						ADD
5. Grants/grants pending	☐	☐	☑	GlaxoSmithKline		×
						ADD
6. Payment for lectures including service on speakers bureaus	☐	☑	☐	GlaxoSmithKline AstraZeneca Merck		×
						ADD
7. Payment for manuscript preparation	☑	☐	☐			×
						ADD
8. Patents (planned, pending or issued)	☑	☐	☐			×
						ADD
9. Royalties	☑	☐	☐			×
						ADD
10. Payment for development of educational presentations	☑	☐	☐			×
						ADD
11. Stock/stock options	☑	☐	☐			×
						ADD

ICMJE Form for Disclosure of Potential Conflicts of Interest

12. Travel/accommodations/ meeting expenses unrelated to activities listed**	☑	☐	☐			×
						ADD
13. Other (err on the side of full disclosure)	☑	☐	☐			×
						ADD

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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