Association Between the MUC5B Promoter Polymorphism and Survival in Patients With Idiopathic Pulmonary Fibrosis

Anna L. Peljto, DrPH
Yingze Zhang, PhD
Tasha E. Fingerlin, PhD
Shwu-Fan Ma, PhD
Joe G. N. Garcia, MD
Thomas J. Richards, PhD
Lori J. Silveira, PhD
Kathleen O. Lindell, PhD
Mark P. Steele, MD
James E. Loyd, MD
Kevin F. Gibson, MD
Max A. Seibold, PhD
Kevin K. Brown, MD
Janet L. Talbert, MS
Anna L. Peljto, DrPH

Importance Current prediction models of mortality in idiopathic pulmonary fibrosis (IPF), which are based on clinical and physiological parameters, have modest value in predicting which patients will progress. In addition to the potential for improving prognostic models, identifying genetic and molecular features that are associated with IPF mortality may provide insight into the underlying mechanisms of disease and inform clinical trials.

Objective To determine whether the MUC5B promoter polymorphism (rs35709590), previously reported to be associated with the development of pulmonary fibrosis, is associated with survival in IPF.

Design, Setting, and Participants Retrospective study of survival in 2 independent cohorts of patients with IPF: the INSPIRE cohort, consisting of patients enrolled in the interferon-γ1b trial (n=438; December 15, 2003–May 2, 2009; 81 centers in 7 European countries, the United States, and Canada), and the Chicago cohort, consisting of IPF participants recruited from the Interstitial Lung Disease Clinic at the University of Chicago (n=148; 2007–2010). The INSPIRE cohort was used to model the association of the MUC5B genotype with survival, accounting for the effect of matrix metalloproteinase 7 (MMP-7) blood concentration and other demographic and clinical covariates. The Chicago cohort was used for replication of findings.

Main Outcomes and Measures The primary end point was all-cause mortality.

Results The numbers of patients in the GG, GT, and TT genotype groups were 148 (34%), 259 (59%), and 31 (7%), respectively, in the INSPIRE cohort and 41 (28%), 98 (66%), and 9 (6%), respectively, in the Chicago cohort. The median follow-up period was 1.6 years for INSPIRE and 2.1 years for Chicago. During follow-up, there were 73 deaths (36 GG, 35 GT, and 2 TT) among INSPIRE patients and 64 deaths (26 GG, 36 GT, and 2 TT) among Chicago patients. The unadjusted 2-year cumulative incidence of death was lower among patients carrying 1 or more copies of the IPF risk allele (T) in both the INSPIRE cohort (0.25 [95% CI, 0.17-0.32] for GG, 0.17 [95% CI, 0.11-0.23] for GT, and 0.03 [95% CI, 0.00-0.09] for TT) and the Chicago cohort (0.50 [95% CI, 0.31-0.63] for GG, 0.22 [95% CI, 0.13-0.31] for GT, and 0.11 [95% CI, 0.00-0.28] for TT). In the INSPIRE cohort, the GT and TT genotypes (risk for IPF) were associated with improved survival compared with GG (hazard ratios, 0.23 [95% CI, 0.10-0.52] and 0.48 [95% CI, 0.31-0.72], respectively; P<.001). This finding was replicated in the Chicago cohort (hazard ratios, 0.15 [95% CI, 0.05-0.49] and 0.39 [95% CI, 0.21-0.70], respectively; P<.002). The observed association of MUC5B with survival was independent of age, sex, forced vital capacity, diffusing capacity of carbon monoxide, MMP-7, and treatment status. The addition of the MUC5B genotype to the survival models significantly improved the predictive accuracy of the model in both the INSPIRE cohort (C=0.71 [95% CI, 0.64-0.75] vs C=0.68 [95% CI, 0.61-0.73]; P<.001) and the Chicago cohort (C=0.73 [95% CI, 0.62-0.78] vs C=0.69 [95% CI, 0.59-0.75]; P=.01).

Conclusions and Relevance Among patients with IPF, a common risk polymorphism in MUC5B was significantly associated with improved survival. Further research is necessary to refine the risk estimates and to determine the clinical implications of these findings.

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lar adhesion molecule 1, and interleu-
kin 8 have been shown to be associated
with poor outcomes in IPF, and when
combined with clinical features, these
plasma proteins predict mortality in IPF.\(^8\)

Rare mutations in \(SFTPC, SFTPA2,\)
telomerase reverse transcriptase
(\(TERT\)), and telomerase RNA com-
ponent (\(TERC\))\(^9-11\) have been associated
with development of pulmonary fibro-
sis. Recently, a common polymor-
phism in the promoter of a mucin gene
(\(MUC5B\)) has been found to be asso-
ciated with an increase in risk of de-
veloping both familial and sporadic IPF
in an allele dose-dependent man-
ner.\(^12,13\) While \(MUC5B\) expression in the
lung was 14.1 times higher in patients
with IPF, the \(MUC5B\) promoter poly-
orphism was associated with up-
regulation of this transcript only in un-
affected participants.\(^12\)

The objective of the current study
was to determine whether the \(MUC5B\)
gene ID: 727897; http://www.ncbi.nlm
.nih.gov/gene/727897) promoter poly-
orphism (rs35705950), previously re-
ported to be associated with the
development of pulmonary fibrosis, is
associated with survival in IPF.

**METHODS**

**Study Cohorts**

The study was approved by the hu-
man use committees of National Jew-
ish Health, the University of Colorado
Denver, and the University of Chi-

The INSPIRE cohort (derivation
cohort) consists of study participants
who were enrolled (December 15,
2003–April 12, 2006) in the interferon-
\(\gamma\)1b IPF clinical trial and provided writ-
ten informed consent.\(^14\) INSPIRE co-
hort participants were treated with
concomitant agents if they met strict cri-
teria for progression of disease.\(^14\) Par-
ticipants with available genetic and
clinical follow-up data from the IN-
SPIRE study were included in this
study. Participants in the derivation set
were followed up from randomization
until death or study termination (a
maximum of approximately 3 years af-
after randomization). Vital status was as-
essed through a combination of pa-
tient/family/caregiver contacts and use
of death registries (where permitted).
Despite early termination of the study,
assessable data (including vital status)
were obtained for 99% of study pa-
tients, including all of the 438 pa-
tients in the current analysis.\(^14\)

The Chicago cohort (validation co-
hort) consists of IPF participants who
were recruited from the Interstitial Lung
Disease Clinic at the University of Chi-

cohort for validation.

No patient was dually enrolled in both
cohorts; however, all patients in the
INSPIRE cohort were included in a re-
cent publication that demonstrated an
allele dose-dependent relationship be-
tween a common polymorphism in the
promoter of a mucin gene (\(MUC5B\)) and
the risk of developing IPF.\(^12,13\) All analy-
ses of both cohorts were performed
anonymously. Both cohorts consisted of
participants who were considered to be
unrelated on the basis of self-report.

**Genotyping of MUC5B rs35705950**

For the INSPIRE cohort, genotypes of
the \(MUC5B\) SNP rs35705950 were de-
termined using Taqman genotyp-
ing.\(^12,13\) For the Chicago cohort, geno-
typing was performed using the Sequenom iPLEX-Gold assay.

**MMP-7 Analysis**

The plasma concentration of MMP-7
was determined by enzyme-linked im-
munosorbent assay in the INSPIRE co-
hort following manufacturer (R&D Sys-
tems) instructions and as previously
reported.\(^8\)

**Statistical Analysis**

The primary analysis tested for an
association of the \(MUC5B\) polymor-
phism with survival using Cox propor-
tional hazards models (Kolmogorov-
type supremum tests did not indicate
significant departures from the propor-
tional hazards requirement for the
\(MUC5B\) genotype variable in either the
INSPIRE [\(P=.40\) or Chicago [\(P=.10\)]
cohorts). The model was developed
within the INSPIRE cohort by includ-
ing the \(MUC5B\) genotype and then using
a stepwise backward elimination pro-
cess based on the Akaike information
criterion to select among potential covar-
iates (sex, age, smoking status, baseline
diffusing capacity of carbon monoxide
[DLCO], baseline forced vital capacity
[FVC], and interferon-\(\gamma\)1b treatment)
for inclusion in the final model. Be-
cause of power considerations, only
main effects were considered. The same
model was then fit within the Chicago
cohort for validation.

In a secondary analysis, the MMP-7
variable was added to the final survival
model for the INSPIRE cohort to deter-
mine whether the \(MUC5B\) polymor-
phism was significantly associated with
survival in addition to the previously re-
ported effects of MMP-7.\(^8\) In prelimi-
nary analyses of MMP-7, evidence ex-
isted of a threshold effect on survival.
Accordingly, MMP-7 was modeled as a
binary variable categorized at the first
quartile (<5.7 ng/mL vs \(\geq\)5.7 ng/mL).
An additive genetic model was used for
the genotype in all survival models, con-
sistent with previous findings.\(^12,13\) Any
patient receiving a lung transplant dur-
ing follow-up was censored at trans-
plant date in the analysis.

A Wald \(\chi^2\) test was used to test for
association of covariates with sur-
vival, for which a 2-tailed \(P<.05\) was
considered significant. Survival analy-

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PREDICTION OF SURVIVAL IN IDIOPATHIC PULMONARY FIBROSIS

Table 1. Clinical and Demographic Characteristics of the Cohorts

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>INSPIRE (n = 438)</th>
<th>Chicago (n = 148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of follow-up, median (IQR), y</td>
<td>1.6 (1.2-2.1)</td>
<td>2.1 (1.1-3.9)</td>
<td>.25</td>
</tr>
<tr>
<td>Deaths, No. (%)a</td>
<td>73 (17)</td>
<td>64 (43)</td>
<td></td>
</tr>
<tr>
<td>Transplant events, No. (%)</td>
<td>7 (2)</td>
<td>10 (7)</td>
<td>.003</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>115 (26)</td>
<td>35 (24)</td>
<td>.58</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>66.6 (7.54)</td>
<td>69.0 (8.75)</td>
<td>.005</td>
</tr>
<tr>
<td>Ever smokers, No. (%</td>
<td>312 (71)</td>
<td>96 (72)</td>
<td>.93</td>
</tr>
<tr>
<td>FVC, mean (SD), L</td>
<td>2.9 (0.76)</td>
<td>2.5 (0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FVC, mean (SD), % predicted</td>
<td>72.2 (12.37)</td>
<td>64.5 (18.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DLCO, mean (SD), mL/min/mm Hg</td>
<td>47.3 (8.89)</td>
<td>46.2 (17.92)</td>
<td>.51</td>
</tr>
<tr>
<td>DLCO, mean (SD), % predicted</td>
<td>12.5 (4.40)</td>
<td>10.7 (4.51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMP-7, median (IQR), ng/mL b</td>
<td>7.8 (5.7-11.0)</td>
<td></td>
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</tr>
</tbody>
</table>

**MUC5B genotype, No. (%)**
- GG 148 (34) 41 (28)
- GT 259 (59) 98 (66)
- TT 31 (7) 9 (6)

**Abbreviations:** DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; MMP-7, matrix metalloproteinase 7.

 ses were performed using SAS, version 9.3 (SAS Institute Inc), and the Cox proportional hazards models were applied using the SAS PHREG procedure.

The area under the receiver operating characteristic curve (AUC) was calculated at 100-day intervals for the final, adjusted model in each cohort (with and without the MUC5B genotype covariate). In addition, the integral of time-specific AUC measures (C statistic) was calculated as an overall measure of the predictive value of these nested models. We used a bootstrapping procedure with 10,000 samples to calculate 95% confidence intervals for the C statistic within each cohort. We used a permutation test to assess the difference between C statistic values for the nested models in each cohort. For this purpose, we used 10,000 permutations of the genotype values, with respect to the rest of the data set, to calculate empirical P values. All C statistic calculations were performed using R, version 3.0.0, packages “risksetROC” and “boot.”

RESULTS

Study Cohorts

There were 438 patients from the INSPIRE cohort and 148 patients from the Chicago cohort included in the analysis (eFigure). The demographic and pulmonary function characteristics of participants in the cohorts were clinically similar; however, participants in the Chicago cohort were older and had more physiologically advanced disease compared with the INSPIRE cohort (Table 1). The Chicago cohort also had a longer period of follow-up (median, 2.1 years) than the INSPIRE cohort (median, 1.6 years), which contributed to the larger number of deaths among the Chicago participants (Table 1).

The observed similar frequencies of the MUC5B polymorphism minor allele (T) among the INSPIRE and Chicago cohorts (37% and 39%, respectively) were similar to what has been observed in IPF. The MUC5B polymorphism did not meet the expectations of Hardy-Weinberg equilibrium (HWE) (P < .001) for either cohort, indicating its likely role as a true risk allele, as previously reported.

**MUC5B rs35705950 Genotype and Survival**

The unadjusted 2-year cumulative incidence of death was lower among patients carrying 1 or more copies of the IPF risk allele (T) in both the INSPIRE cohort (0.25 [95% CI, 0.17-0.32] for GG, 0.17 [95% CI, 0.11-0.23] for GT, and 0.03 [95% CI, 0.00-0.09] for TT) and the Chicago cohort (0.50 [95% CI, 0.31-0.63] for GG, 0.22 [95% CI, 0.13-0.31] for GT, and 0.11 [95% CI, 0.00-0.28] for TT). In the single-variable proportional hazards model, INSPIRE participants who were heterozygous and homozygous for the minor allele (GT and TT) were at lower risk of mortality compared with participants with the GG genotype (hazard ratios [HRs], 0.52 [95% CI, 0.34-0.78] and 0.27 [95% CI, 0.12-0.60], respectively; P = .001) (Table 2 and Figure 1). A similar association of the polymorphism with survival was observed in the Chicago cohort, wherein HRs for participants with the GT and TT genotypes were 0.49 (95% CI, 0.30-0.79) and 0.24 (95% CI, 0.09-0.63), respectively (P = .004) (Table 2 and Figure 2). These associations were also significant after independent adjustments for age, sex, smoking history (ever vs never), baseline FVC, and baseline DLCO. Within the INSPIRE cohort, the HR for the MUC5B genotype also remained unchanged (and significant) after independent adjustment for interferon-γ1b treatment (treatment vs placebo); HRs for the GT and TT genotypes were 0.48 (95% CI, 0.31-0.73) and 0.23 (95% CI, 0.10-0.53), respectively (P < .001).

After including all relevant variables (sex, baseline FVC, and baseline DLCO) in a final model, the MUC5B genotype remained a statistically significant predictor of survival. The adjusted HRs for survival associated with the GT and TT genotypes were 0.48 (95% CI, 0.31-0.72) and 0.23 (95% CI, 0.10-0.53), respectively.

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0.64-0.75) and C=0.68 [95% CI, 0.61-0.73], respectively) for the INSPIRE cohort. This result was replicated in the Chicago cohort (C=0.73 [95% CI, 0.62-0.78] and C=0.69 [95% CI, 0.59-0.75], respectively). The increase in the C statistic value was statistically significant in both the INSPIRE (P<.001) and Chicago (P=.01) cohorts, suggesting that the MUC5B genotype improves the predictive accuracy of the model.

In the secondary analysis, the observed association between the MUC5B promoter polymorphism and survival was explored after accounting for the effect of MMP-7, which has recently been reported as prognostic in IPF. Matrix metalloproteinase 7 was significantly associated with survival when added to the final model for the INSPIRE cohort. The hazard was 2-fold higher for patients with MMP-7 levels of 5.7 ng/mL or higher than for patients with MMP-7 levels of less than 5.7 ng/mL (HR, 2.06; 95% CI, 1.05-4.07; P=.04) (TABLE 3). However, the HR for the MUC5B genotype remained constant and statistically significant, suggesting that the MUC5B promoter polymorphism explains a portion of the variation in survival among IPF participants beyond that explained by MMP-7 levels.

No significant association between treatment and survival was observed in the INSPIRE cohort (eTable 1), and none of the genotype groups was associated with improved survival in the treatment stratum compared with placebo. However, exploratory analyses showed evidence of a possible interaction between interferon-γ1b treatment and MUC5B genotype. When stratified by treatment group, the effect of the genotype appeared to be stronger in the treatment group than in the placebo group. For the GT and TT groups, the unadjusted HRs were 0.75 (95% CI, 0.35-1.63) and 0.56 (95% CI, 0.12-2.65), respectively, among the placebo group and the unadjusted HRs were 0.44 (95% CI, 0.27-0.71) and 0.19 (95% CI, 0.07-0.50) among the treatment group. In post hoc analyses, the interaction was not statistically significant (P=.07) when added to the final survival model (eTable 2).

**DISCUSSION**

These findings suggest that the common polymorphism in the promoter of MUC5B (rs35705950), previously reported to be strongly associated with the development of familial interstitial

<table>
<thead>
<tr>
<th>Table 2. Survival Analysis Models of MUC5B</th>
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<tr>
<td>Model</td>
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<tr>
<td>Univariable MUC5B genotype</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>GT</td>
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<tr>
<td>TT</td>
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<tr>
<td>Adjusted MUC5B genotype</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>GT</td>
</tr>
<tr>
<td>TT</td>
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<tr>
<td>FVC</td>
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<tr>
<td>DLCO</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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</table>

Abbreviations: DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; HR, hazard ratio.
MMP-7, ng/mL findings are consistent with previous studies showing improved survival in IPF. These results suggest that the IPF phenotype is heterogeneous and consists of at least 2 clinical subtypes that are, in part, separable by the MUC5B genotype. This would imply that the IPF phenotypes associated with other genetic and/or environmental risk factors (separate from the MUC5B promoter polymorphism) have poorer prognosis and possibly different pathogenic mechanisms. If there are several genetic variants associated with survival in IPF, it is conceivable that the MUC5B variant and less severe pathological changes in familial interstitial pneumonia, as well as another report of slower decline in FVC for patients with IPF. This study is, to our knowledge, the first to demonstrate that a genetic variant is associated with survival in IPF.

While the minor (T) allele is the risk allele for development of IPF, it is also the minor allele that confers a survival advantage among patients with IPF. These results suggest that the IPF phenotype is heterogeneous and consists of at least 2 clinical subtypes that are, in part, separable by the MUC5B genotype. This would imply that the IPF phenotypes associated with other genetic and/or environmental risk factors (separate from the MUC5B promoter polymorphism) have poorer prognosis and possibly different pathogenic mechanisms. If there are several genetic variants that lead to lung fibrosis, it is conceivable that the genotype-phenotype relationships are also unique and, consequently, give rise to specific, gene variant-directed clinical outcomes.

However, it is important to consider how and under what circumstances the promoter polymorphism of MUC5B might create a survival advantage in patients with IPF. Although individuals with the MUC5B promoter polymorphism could present earlier in the course of disease (lead time bias) or have preferential loss of sicker participants (survivor bias), these explanations are unlikely. In this study, patients with IPF with or without the MUC5B promoter polymorphism presented at similar ages and with similar degrees of lung impairment (Table 4). Moreover, the 2 cohorts in this manuscript are representative of physiologically mild (INSPIRE) and moderate (Chicago) stages of IPF, suggesting that the MUC5B polymorphism may be associated with outcome at different stages of disease. Previous findings indicate that patients with IPF have enhanced mucous production regardless of the MUC5B promoter genotype.12

Table 3. Survival Analysis Model in INSPIRE Cohort, Adjusted for MMP-7

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-7, ng/mL</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5.7</td>
<td>1 [Reference]</td>
<td>.04</td>
</tr>
<tr>
<td>≥5.7</td>
<td>2.06 (1.05-4.07)</td>
<td></td>
</tr>
<tr>
<td>MUC5B genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>1 [Reference]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GT</td>
<td>0.46 (0.30-0.70)</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>0.21 (0.09-0.49)</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>0.55 (0.34-0.89)</td>
<td>.01</td>
</tr>
<tr>
<td>DLCO</td>
<td>0.89 (0.85-0.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 [Reference]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.25 (0.12-0.53)</td>
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</table>

Abbreviations: DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; MMP-7, matrix metalloproteinase 7.

Although the specific mechanisms that convey the observed survival advantage to patients with the MUC5B promoter polymorphism are not yet apparent, enhanced mucosal host defense, reduction in infectious complications, a beneficial drug response, and a potential dual role for MUC5B in wound repair should all be considered. Regardless of the mechanism, the results suggest that patients with IPF with the MUC5B promoter polymorphism may represent a pathogenically distinct disease entity that incorporates both a significantly higher predisposition to disease and a significantly longer survival. It is conceivable that specific pharmacologic agents may work well in a subset of patients with IPF who are separable by genomic and biochemical markers. The findings of this study suggest that there may be value in measuring the MUC5B polymorphism in future clinical therapeutic trials.

It may also be useful to assess whether future prognostic models that
incorporate MUC5B and other molecular features have the potential to affect clinical care of patients. The clinical-radiographic-physiologic scoring system as well as a simpler index including pulmonary function and, most recently, a model that incorporates sex, age, FVC, and DLCO have all been found to be predictive of mortality to some extent. Additional studies have evaluated change in pulmonary function indexes over 6- to 12-month periods in IPF and have concluded that the decline in FVC is predictive of survival. Although these clinical assessments of IPF are modestly successful in correlating measures of disease severity with eventual mortality and potentially allow better staging of patients with IPF, they do not approach the predictive accuracy required to guide personalized management. In particular, these approaches cannot predict which patients, despite similar clinical presentations, will have a better or worse clinical outcome, a task that is necessary because of the variable and unpredictable course of the disease. Moreover, these approaches have limited utility because they focus on measures of disease severity (ie, FVC and DLCO) to predict future disease progression. Given that the addition of MUC5B resulted in relatively small gains in predictive accuracy in patients with established disease, it is premature to consider routine clinical genotyping of patients with IPF. However, there may be value in assessing scoring systems that use the potential predictive value of MUC5B combined with other genetic and molecular factors to predict prognosis in patients with subclinical and early-stage disease, before a notable decline in lung function is observed. This is especially important because there are currently no IPF pharmacological therapies approved for use in the United States, and opportunities for early genetic counseling or lung transplantation may be a patient’s only recourse. Recently, several other genetic loci have been identified as risk factors for fibrotic lung disease. Future studies are needed to determine whether these loci account for the apparent phenotypic heterogeneity and have added predictive value for survival in IPF that could be used to develop improved scoring systems.

Although the MUC5B polymorphism did not meet the expectations of HWE, this was not an unexpected finding and is not likely to bias the results of this analysis. Previous studies have reported similar observations among patients with IPF. In the study by Seibold et al, the minor allele frequency among patients with IPF was very similar to those observed in this study (38% compared with 37% for INSPIRE and 39% for Chicago), while the frequency among controls was reported to be much lower (9%) and consistent with HWE. In addition, it has been shown that these departures from HWE in the cases but not controls are consistent with the disease model wherein the minor (T) allele is associated with disease. Regardless, the findings presented here are robust to departures from HWE because a genotype-based test of MUC5B was used as opposed to an allelic test, which does assume HWE.

This study had several limitations. First, although analyses in both cohorts were well powered to detect the association of genotype with survival, the relatively low numbers of events in each cohort led to wide confidence intervals for the estimated HRs. Larger samples would be needed to obtain a more precise estimate of the HRs for the MUC5B genotype.

Second, while there was not statistically significant evidence of an interaction effect between the MUC5B genotype and interferon-γ1b treatment, it is possible that a true interaction exists that this study was not powered to detect. This would imply that the strength of the association between genotype and survival is dependent on interferon-γ1b treatment. However, if there was a true

<table>
<thead>
<tr>
<th>Table 4. Patient Characteristics by MUC5B Genotype</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td></td>
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<tr>
<td>Deaths, No. (%)</td>
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<tr>
<td>Transplant events, No. (%)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>FVC, mean (SD), L</td>
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<tr>
<td>FVC, mean (SD), % predicted</td>
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<tr>
<td>DLCO, mean (SD), mL/min/mm Hg</td>
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<tr>
<td>DLCO, mean (SD), % predicted</td>
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<tr>
<td>MUC5B Genotype</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>GT</td>
</tr>
<tr>
<td>TT</td>
</tr>
<tr>
<td>Abbreviations: DLCO, diffusing capacity of carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; MMP-7, matrix metalloproteinase 7.</td>
</tr>
<tr>
<td>aMMP-7 and treatment data unavailable for Chicago cohort.</td>
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</table>

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interaction effect, replication of the strength of the association between genotype and survival within the Chicago cohort would not have been expected, since none of these patients were treated with interferon-γlb. Further studies would be needed to determine whether an interaction effect exists between the MUC5B genotype and other clinical treatments. Nevertheless, this emphasizes the need to account for genotype in clinical trials and prediction models of IPF.

Third, this study used all-cause mortality as the primary end point, as opposed to IPF-related mortality, to maintain generalizability and comparability across cohorts since cause of death information was not complete for both cohorts. Among the INSPIRE patients, 66 of the 73 deaths were confirmed to be IPF related and 7 (2 GG and 5 GT) were possibly or definitely unrelated to IPF. This should have little effect on the results of this study because the vast majority of patients with IPF die within a relatively short period owing to the nature of the disease.

Fourth, data for additional genetic markers and serum biomarkers that have been reported to be associated with outcome in IPF were not available for these cohorts. More comprehensive predictive models may be developed by including these biomarkers and other genetic risk factors.

Idiopathic pulmonary fibrosis is etiologically heterogeneous and biologically dynamic, and sequence changes in MUC5B, transcriptional signatures in the fibrotic lung,\textsuperscript{2,28} and serum biomarkers, including chemokine ligand 18, KL6, SFTPA, SFTPD, MMP-7, intercellular adhesion molecule 1, and interleukin 8, are potential predictors of disease activity and outcome in patients with IPF.\textsuperscript{6,8,29} Further study is necessary to refine the risk estimates and to determine the research and clinical implications of these findings.

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Author Affiliations: Departments of Epidemiology (Drs Peljto and Fingerlin) and Biostatistics (Drs Zhang and Fingerlin), School of Public Health, Department of Medicine, School of Medicine (Ms Murphy and Drs M. I. Schwarz and D. A. Schwartz), University of Colorado Denver, and Departments of Biostatistics (Dr Silveira) and Pathology (Drs Brown and D. A. Schwartz and Ms Talbert), National Jewish Health, Denver; Department of Medicine, University of Chicago (Dr S Ma and Noth), and Institute for Personalized Respiratory Medicine, Department of Medicine, University of Illinois at Chicago (Dr Garcia), Chicago; Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Drs Rich-Kos; Lindell, Gibson, and Kaminski, and Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee (Dr Steele and Loyd and Ms Markin); InterMune, Brisbane, California (Drs Kosen and Seiwert).

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICJME Form for Disclosure of Potential Conflicts of Interest. Drs Seibold and D. A. Schwartz have filed a patent for MUC5B genetic variants, methods, and compositions for risk prediction, diagnosis, prognosis, and treatment of pulmonary disorders. Drs Kosen and Seiwert are employee shareholders of InterMune Inc, which is pursuing a license to the aforementioned patent, and have filed patents on use of peripheral blood biomarkers in IPF. Dr Noth has contracts for clinical trials with Boehringer Ingelheim, Sanofi, and Medgenix; has served on the speakers’ bureau of GlaxoSmithKline; is a consultant to Boehringer Ingelheim and ImmuneWorks; and has patents related to gene expression profiling and plasma proteins. Dr Kaminski is a consultant to Sanofi, InterMune, Stemedica, Celgene, Promedior, and Vertex; is a recipient of investigator-initiated research grants from Gilead, Celgene, and Centocor; and has a patent on use of peripheral blood biomarkers in IPF. No other disclosures were reported.

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The intellect has little to do on the road to discovery. There comes a leap in consciousness, call it intuition or what you will, and the solution comes to you and you don't how or why.

—Albert Einstein (1879-1955)