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Pharmacogenetics and interstitial lung disease

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Purpose of review
Interstitial lung disease (ILD) is comprised of a heterogeneous group of disorders with highly variable natural histories and response to therapies. Pharmacogenetics focuses on the variability in drug response because of the presence of genetic factors that influence drug metabolism or disease activity. In this article, we review relevant drug-specific and disease-specific polymorphisms that may influence therapeutic response, and then highlight a recently identified drug–gene interaction in patients with idiopathic pulmonary fibrosis (IPF).

Recent findings
The emergence of high-throughput genomic technology has allowed for identification of gene polymorphisms associated with susceptibility to specific disease states, including IPF and several connective tissue diseases known to cause ILD. IPF risk loci span a diverse group of genes, while most associated with connective tissue disease are critical to immune signaling. A recent pharmacogenetic analysis of patients enrolled in an IPF clinical trial identified a variant within *TOLLIP* to be associated with differential response to *N*-acetylcysteine therapy.

Summary
Though few pharmacogenetic investigations have been conducted in patients with ILD to date, ample opportunities for pharmacogenetic exploration exist in this patient population. Such exploration will advance our understanding of specific ILDs and help usher in an era of personalized medicine.

Keywords
connective tissue disease, idiopathic pulmonary fibrosis, interstitial lung disease, pharmacogenetics

INTRODUCTION

Pharmacogenetics, the study of variability in treatment response because of an individual's genetic constitution, traces its origins to the mid-20th century [1,2]. Pharmacogenomics, often used interchangeably with pharmacogenetics, focuses on how a drug influences gene expression across the entire genome [1,3]. Whereas pharmacogenomic investigation provides valuable mechanistic insight and facilitates the development of novel therapies, pharmacogenetic investigation identifies individuals predisposed to benefit or harm from a particular therapy and, therefore, serves as a lynchpin of personalized medicine.

Pharmacogenetic investigation requires one or more genetic biomarkers with which to stratify a population to test for differential drug effect. Single nucleotide polymorphisms (SNPs) serve as the most commonly utilized pharmacogenetic biomarkers, but larger structural variants, including insertions, deletions, copy number variations and inversions have also been explored [4–6]. The frequency of gene variants can vary substantially across genetic ancestral groups, and needs to be taken into account during the study design phase of pharmacogenetic investigation. Pharmacogenetic biomarkers are chosen because of a plausible influence on a drug's pharmacokinetics – distribution, elimination, absorption, and metabolism – or pharmacodynamics – modulation of a disease-causing or disease-palliating molecular pathway [3].

Within pulmonary medicine, pharmacogenetic investigation has shed light on important drug–gene interactions among individuals with asthma [7–10] and chronic obstructive pulmonary disease [11–13]. Less is known about the role pharmacogenetics

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KEY POINTS

- Pharmacogenetic investigation has the potential to guide therapeutic selection in patients with ILD.
- Polymorphisms within genes critical to drug processing or disease activity represent relevant genetic biomarkers with which to conduct pharmacogenetic investigation
- N-acetylcysteine may be an effective therapy for genetically predisposed individuals with IPF.

plays among patients with interstitial lung disease (ILD). This paucity of data stems from multiple factors. First and foremost is the phenotypic heterogeneity of the disease processes that comprise ILD. Despite shared clinical, radiographic, and pathologic features, the natural history of individual ILDs, along with their response to therapy, varies widely [14–19]. Also contributing is the low overall disease incidence of ILD, estimated to be 30/100 000 in the United States. [20] Together these factors have restricted therapeutics research to only the most common ILDs, including idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated ILD (CTD-ILD).

Despite these challenges, opportunities abound for pharmacogenetic discovery in patients with ILD. Easily acquired blood samples along with paired clinical data from patient registries and clinical trial datasets provide the components necessary to explore clinically relevant drug–gene interaction in this patient population. In this review, we highlight drug-specific polymorphisms known to influence pharmacokinetics or dynamics and provide an overview of polymorphisms associated with specific ILDs that may influence therapeutic response. We then review past pharmacogenetic testing performed in patients with IPF and highlight a recently identified drug–gene interaction in this population.

DRUG-SPECIFIC PHARMACOGENETIC BIOMARKERS

ILD etiology guides therapeutic selection in this patient population. ILDs characterized predominantly by inflammation, including most CTD-ILDs, are often treated with immunomodulatory compounds, such as corticosteroids, azathioprine, mycophenolate mofetil, and tacrolimus. The antifibrotic agents pirfenidone and nintedanib were recently approved for the treatment of IPF, which represents a fibrotic-predominant process. These therapies also hold promise for patients with systemic sclerosis, a connective tissue disease (CTD) in which fibrosis predominates, and are under investigation.

Although the aforementioned therapies have unique mechanisms of action, all undergo extensive hepatic processing and may, therefore, be influenced by polymorphisms within genes involved in this process. Of particular importance are variants within genes encoding hepatic cytochrome p450 protein superfamily, uridine 5'-triphosphate glucuronosyltransferases, N-acetyltransferases, and sulfonyltransferases [21]. Because the role each of these enzymes plays in drug metabolism has been extensively characterized, their genetic structure and functional polymorphisms are well documented. Drug-specific polymorphisms with potential pharmacogenetic relevance are outlined below.

Corticosteroids

After the binding of corticosteroid to the glucocorticoid receptor, this complex is transported into the nucleus of the cell where it inhibits transcription of proinflammatory genes and induces transcription of anti-inflammatory genes [22]. Corticosteroids are commonly used as an adjunct to other immunomodulatory therapies in patients with CTD-ILD [23]. Polymorphisms within *NR3C1*, which encodes the glucocorticoid receptor, have been associated with increased glucocorticoid sensitivity in healthy adults and corticosteroid dependency in children with inflammatory bowel disease [24,25]. Additionally, polymorphisms within *CRHR1*, encoding the corticotrophin-releasing hormone receptor, *STIP1*, encoding an adaptor protein within the intracellular glucocorticoid receptor heterocomplex and *TBX21*, encoding a transcription factor that influences T-lymphocyte production, have been associated with differential inhaled corticosteroid responsiveness in patients with asthma [26–28].

Azathioprine

A prodrug of mercaptopurine, azathioprine inhibits B and T lymphocyte production through disruption of DNA synthesis. Azathioprine is commonly used to treat a wide variety of autoimmune conditions, including ILD associated with rheumatoid arthritis (RA) [29], Sjogren's disease [30], systemic sclerosis [18,31,32] and myositis [33–35]. To become the metabolically active mercaptopurine, azathioprine requires activation by the enzyme thiopurine methyl-transferase (TPMT). Polymorphisms within *TPMT*, the gene encoding the TPMT enzyme, have been shown to modulate drug bioavailability and adverse event risk, including bone marrow toxicity and gastrointestinal intolerance [36,37]. Such findings have led to consensus statements across multiple specialties that offer practice guidelines

based on *TPMT* genotype testing [38–41]. Genes encoding other enzymes critical to azathioprine processing, including aldehyde oxidase and xanthine oxidase, also offer potential for pharmacogenetic investigation in ILD, as polymorphisms within these genes have been linked to differential azathioprine response among individuals with inflammatory bowel disease [42].

Mycophenolate mofetil

Like azathioprine, mycophenolate mofetil is commonly used to treat CTD-ILD and has been shown to preserve lung function in this population [43–45]. Mycophenolate mofetil is rapidly converted to mycophenolic acid (MPA), which then blocks B and T-lymphocyte proliferation through selective inhibition of inosine monophosphate dehydrogenase. Polymorphisms within inosine monophosphate dehydrogenase have been shown to markedly reduce the in-vitro antiproliferative effects of MPA [46] and have the potential to influence drug response. MPA is subsequently inactivated by hepatic UDP-glucuronosyltransferase (UGT). Polymorphisms within *UGT1A9* have been associated with a significant increase in UDP-glucuronosyltransferase activity, thereby reducing the amount of circulating bioactive MPA [47]. Although these polymorphisms still have unclear clinical consequences, further investigation is warranted.

Tacrolimus

A calcineurin inhibitor used most often to prevent solid organ transplant rejection, tacrolimus has also been shown to slow pulmonary function decline and improve outcomes in patients with myositis-associated ILD [48–50]. Polymorphisms within cytochrome p450 genes *CYP3A5* and *CYP3A5* have been shown to influence the bioavailability of tacrolimus [51]. Absorption of tacrolimus may also be influenced by the presence of polymorphisms within the *MDR1* gene, which encodes a cellular efflux pump protein [52].

Pirfenidone and nintedanib

These antifibrotic agents were recently approved in the United States for the treatment of patients with IPF after phase 3 clinical trials demonstrated efficacy in the slowing of pulmonary function decline [53–55]. Athough its exact mechanism of action remains incompletely characterized, pirfenidone has been shown to reduce human fibroblast proliferation and myofibroblast differentiation through attenuation of transforming growth factor-β expression (TGF-β) and downstream signaling pathways [56,57]. Polymorphisms within TGF-β have been linked to an increased risk of pulmonary fibrosis in patients with sarcoidosis and liver fibrosis in those with hepatitis C and alcoholic abuse [58,59], raising the question of whether pirfenidone may differentially affect patients with IPF carrying these polymorphisms.

Nintedanib attenuates myofibroblast proliferation through inhibition of receptors for fibroblast growth factor (FGFR) and platelet-derived growth factor [60]. Polymorphisms within several fibroblast growth factors and platelet-derived growth factor have been linked to various types of cancer, including colon [61], breast [62] and thyroid [63]. Whether the presence of such polymorphisms in patients with IPF would affect nintedanib efficacy remains unknown. A complete list of drug-specific biomarkers with potential pharmacogenetic relevance is shown in Table 1.

DISEASE-SPECIFIC PHARMACOGENETIC BIOMARKERS

The emergence and rapid expansion of high-throughput genomic technology has led to the identification of many novel genetic loci associated with specific disease states. Based on the assumption that genes at these loci contribute to disease onset and/or activity, polymorphisms within these genes have the potential to influence the pharmacodynamics of therapies used to treat the disease [64].

Idiopathic pulmonary fibrosis

Within ILD, IPF remains the best characterized to date. Among individuals with familial interstitial pneumonia (FIP), the heritable form of IPF, rare mutations within genes involved in surfactant production, [65–69] and telomere stability [70,71] were the first gene variants to be identified in IPF. More recently, two groups identified rare mutations in *RTEL1*, which encodes an important regulator of telomere elongation, to be associated with FIP susceptibility using whole-exome sequencing [72▪,73▪]. Mutations within *PARN*, which encodes an exoribonuclease involved in mRNA processing, was also found to segregate with FIP using this approach [73▪]. The rare nature of these mutations will likely limit their utility in pharmacogenetic modeling, but similar effects along shared pathways may allow for aggregation of certain mutations to generate larger cohorts.

Among patients with sporadic IPF, numerous genetic and genomic investigations have identified common gene variants associated IPF susceptibility

Table 1. Drug-specific polymorphisms with potential pharmacogenetics relevance

Drug	SNP	MAF[a]	Chromosome	Gene	Protein	Reference
Corticosteroids	rs860457	0.22	5	*NR3C1*	Glucocorticoid receptor	[24]
	rs6190	0.01				
	rs1876828	0.09	17	*CRHR1*	Corticotropin-releasing factor receptor 1	[26]
	rs242941	0.32				
	rs4980524	0.39	11	*STIP1*	Stress-induced phosphoprotein 1	[27]
	rs6591838	0.24				
	rs2236647	0.44				
	rs2240017	0.05	17	*TBX21*	T-box transcription factor TBX21	[28]
Azathioprine	rs1800462	<0.01	6	*TPMT*	Thiopurine S-methyltransferase	[37]
	rs1800460	0.01				
	rs1142345	0.04				
	rs55754655	0.11	2	*AOX1*	Aldehyde oxidase 1	[42]
	rs4407290	0.04	2	*XDH*	Xanthine dehydrogenase	[42]
Mycophenolate mofetil	rs11706052	0.05	3	*IMPDH2*	Inosine-5′-monophosphate dehydrogenase 2	[46]
	rs6714486	0.07	2	*UGT1A9*	UDP-glucuronosyltransferase 1–9	[47]
	rs17868320	0.02				
Tacrolimus	rs776746	0.38	7	*CYP3A5*	Cytochrome P450 3A5	[51,52]
	rs2740574	0.23	7	*CYP3A4*	Cytochrome P450 3A4	[51]
	rs1045642	0.39	7	*MDR1*	Multidrug resistance protein 1	[52]
Pirfenidone	rs3917165	0.05	14	*TGFβ3*	Transforming growth factor β-3	[58]
	rs3917200	0.15				
	rs1800471	0.05	19	*TGFβ1*	Transforming growth factor β-1	[59]
Nintedanib	rs351855	0.3	5	*FGFR4*	Fibroblast growth factor receptor 4	[61]
	rs2981582	0.4	10	*FGFR2*	Fibroblast growth factor receptor 2	[62]
	rs6554162	0.41	4	*PDGFRA*	Platelet-derived growth factor receptor α	[63]
	rs1800812	0.28				

MAF, minor allele frequency; SNP, single nucleotide polymorphisms.
[a]Based on 1000 Genomes Project data (www.1000genomes.org). Actual MAF will vary depending on ancestral background of study population.

(Table 2) [74–81,82▪,83–85]. The short arm of chromosome 11 has received considerable attention, as two genes strongly associated with IPF susceptibility, *TOLLIP* and *MUC5B*, reside at this locus [74–76]. *TOLLIP* encodes Toll-interacting protein, which acts to inhibit Toll-like receptor (TLR) signaling. Several TLRs are active in the lung, including TLR2 and TLR4, and have been shown to be vital mediators of the innate and adaptive immune response [86–90]. *MUC5B* encodes a highly glycosylated protein that contributes to airway mucus production and also functions to maintain immune homeostasis [87,91,92]. In addition to their association with IPF susceptibility, two SNPs – rs5743890 within *TOLLIP* and rs35 705 950 within *MUC5B* – are associated with differential survival [74,93].

Additional loci linked to IPF by genome-wide association study (GWAS) and other genetic investigations, include MDGA2 [74], SPPL2C [74], MAPT [76], LRRC34 [76], FAM13A [76], DSP [76], OBFC1 [76], MUC2 [76], ATP11A [76], DPP9 [76], TERT [76,77], IL-8 [78], IL1RN [79,80], TNF-α [80], HLA-DRB1 [81], HSP70 [82▪], and CDKN1A [83]. Although identification of these variants has advanced our understanding of how IPF develops, few have been shown to predict survival. The highly variable natural history of IPF, whereby some patients remain stable over many years, others progress steadily and some die from rapidly progressive disease, suggests that some genes may contribute to disease onset whereas others contribute to disease progression [94–96]. Indeed, several polymorphisms associated with disease activity, but not susceptibility, have been identified within TP53 [83], TLR3 [84], and TGFB1 [85].

Connective tissue disease-associated interstitial lung disease

Although several GWAS have been conducted in patients with CTD, none have been performed

Table 2. IPF-associated polymorphisms with potential pharmacogenetics relevance

SNP	MAF[a]	Chromosome	Gene	Protein	References
rs5743894	0.2	11	*TOLLIP*	Toll-interacting protein	[74]
rs5743890	0.1				[74]
rs7144383	0.13	14	*MDGA2*	MAM domain-containing glycosylphosphatidylinositol anchor protein 2	[74]
rs17690703	0.2	17	*SPPL2C*	Signal peptide peptidase-like 2C	[74]
rs35705950	0.38	11	*MUC5B*	Mucin-5B	[74–76]
rs1981997	0.17	17	*MAPT*	Microtubule-associated protein tau	[76]
rs6793295	0.32	3	*LRRC34*	Leucine-rich repeat-containing protein 34	[76]
rs2609255	0.26	4	*FAM13A*	Protein FAM13A	[76]
rs2076295	0.54	6	*DSP*	Desmoplakin	[76]
rs11191865	0.45	10	*OBFC1*	CST complex subunit *STN1*	[76]
rs7934606	0.52	11	*MUC2*	Mucin-2	[76]
rs1278769	0.2	13	*ATP11A*	Probable phospholipid-transporting ATPase IH	[76]
rs12610495	0.34	19	*DPP9*	Dipeptidyl peptidase 9	[76]
rs2736100	0.43	5	*TERT*	Telomerase reverse transcriptase	[76,77]
rs4073	0.34	4	*IL-8*	IL-8	[78]
rs2637988	0.47	2	*IL1RN*	IL-1 receptor antagonist protein	[79]
rs419598	0.28	2			[80]
rs1800629	0.22	6	*TNF-α*	Tumour necrosis factor	[80]
rs3135388	0.2	6	*HLA-DRB1*	HLA class II histocompatibility antigen, DRB1–1 β chain	[81]
rs2075800	0.46	6	*HSPA1L*	Heat shock 70 kDa protein 1-like	[82▪]
rs2227956	0.01	6			[82▪]
rs1043618	0.22	6	*HSPA1A*	Heat shock 70 kDa protein 1A	[82▪]
rs1061581	0.41	6	*HSPA1B*	Heat shock 70 kDa protein 1B	[82▪]
rs733590	0.47	6	*CDKN1A*	Cyclin-dependent kinase inhibitor 1	[83]
rs12951053	0.06	17	*TP53*	Cellular tumour antigen p53	[83]
rs12602273	0.07	17			[83]
rs3775291	0.28	4	*TLR3*	Toll-like receptor 3	[84]
rs1800470	0.41	19	*TGF-β1*	Transforming growth factor β-1	[85]

MAF, minor allele frequency.
[a]Based on population of reference cited. Actual MAF will vary depending on ancestral background of study population.

in specifically in patients with CTD-associated ILD. But because immune-mediated mechanisms are believed to be responsible for ILD development in these patients, polymorphisms associated with specific disease states may serve as relevant pharmacogenetic biomarkers (Table 3). Among the best-characterized CTDs is RA. In 2010, investigators conducted a GWAS meta-analysis in over 12 000 RA cases that confirmed known susceptibility loci at *PTPN22, CTLA4, TNFAIP3,* and *CD40*. This study also identified SNPs within *IL6ST*, *SPRED2*, *RBPJ*, *CCR6*, *IRF5*, and *PXK* to be novel risk loci and SNPs within *IL2RA, CCL21,* and *AFF3* to be novel risk alleles within known risk loci [97].

GWAS in other CTDs have also demonstrated a strong association between disease susceptibility and polymorphisms within genes involved in immune signaling. A GWAS conducted in over 2 000 patients with systemic sclerosis identified several risk loci within the major histocompatibility complex (MHC) on chromosome 6 and at *CD247*, *IRF5,* and *STAT4* [98]. MHC SNPs have also been strongly associated with disease susceptibility in patients with poly and dermatomyositis, as have risk loci at *PLCL1, BLK,* and *CCL21* [99,100]. Substantial overlap in risk loci exists between the aforementioned CTDs and patients with Sjogren's syndrome, which can result in several types of lung disorders, including ILD. In a GWAS of patients with Sjogren's syndrome, risk loci were again identified within MHC genes, along with *IRF5, BLK,* and *STAT5*. A novel risk locus was also was identified at *IL12A* [101]. Because the overwhelming majority of SNPs associated with CTD lie within genes critical to immune signaling, such polymorphisms have a high potential to influence the response to immunomodulatory therapy.

Table 3. CTD-ILD-associated polymorphisms with potential pharmacogenetics relevance

CTD	SNP	MAF[a]	Chromosome	Gene	Protein	Reference
RA	rs2476601	0.1	1	PTPN22	Tyrosine-protein phosphatase nonreceptor type 22	[97]
	rs11676922	0.49	2	*AFF3*	AF4/FMR2 family member 3	
	rs3087243	0.44	2	*CTLA4*	Cytotoxic T-lymphocyte protein 4	
	rs934734	0.52	2	*SPRED2*	Sprouty related, EVH1 domain-containing protein 2	
	rs13315591	0.1	3	*PXK*	PX domain-containing protein kinase-like protein	
	rs874040	0.033	4	*RBPJ*	Recombining binding protein suppressor of hairless	
	rs6859219	0.18	5	*IL6ST*	IL-6 receptor subunit β	
	rs26232	0.29	5	*NREP*	Neuronal regeneration-related protein	
	rs3093023	0.47	6	*CCR6*	C–C chemokine receptor type 6	
	rs6920220	0.22	6	TNFAIP3	Tumour necrosis factor α-induced protein 3	
	rs10488631	0.13	7	*IRF5*	Interferon regulatory factor 5	
	rs951005	0.14	9	*CCL21*	C–C motif chemokine 21	
	rs706778	0.44	10	*IL2RA*	IL-2 receptor subunit α	
	rs4810485	0.25	20	CD40	Tumor necrosis factor receptor superfamily member 5	
SSc	rs2056626	0.37	1	CD247	T-cell surface glycoprotein CD3 zeta chain	[98]
	rs3821236	0.25	2	STAT4	Signal transducer and activator of transcription 4	
	rs6457617	0.47	6	*HLA-DQB1*	HLA class II histocompatibility antigen, DQ β 1 chain	
	rs4959270	0.45	6	IRF4	Interferon regulatory factor 4	
	rs12537284	0.16	7	IRF5	Interferon regulatory factor 5	
	rs10515998	0.06	18	CDH7	Cadherin-7	
Myositis	rs6738825	0.45[b]	2	*PLCL1*	Inactive phospholipase C-like protein 1	[99]
	rs2736340	0.36[b]	8	*BLK*	Tyrosine-protein kinase Blk	
	rs951005	0.21[b]	9	*CCL21*	C–C motif chemokine 21	
	rs32552080	0.21	6	HLA-DRB1	HLA class II histocompatibility antigen, DRB1–14 β chain	[100]
SS	rs10553577	0.3	2	*STAT4*	Signal transducer and activator of transcription 4	[101]
	rs485497	0.54	3	*IL12A*	IL-12 subunit α	
	rs6579837	0.12	5	*TNIP1*	TNFAIP3-interacting protein 1	
	rs112357081	0.59	6	*HLA-DRA*	HLA class II histocompatibility antigen, DR α chain	
	rs3757387	0.54	7	*IRF5*	Interferon regulatory factor 5	
	rs2736345	0.36	8	*BLK*	Tyrosine-protein kinase Blk	
	rs7119038	0.18	11	*CXCR5*	C–X–C chemokine receptor type 5	

RA, rheumatoid arthritis; SS, Sjogren's syndrome; SSc, systemic sclerosis.
[a]Based on population of reference(s) cited. Actual MAF will vary depending on ancestral background of study population.
[b]Based on MAF reported by 1000 genomes project (www.1000genomes.org) as no study population frequency reported.

DRUG–GENE INTERACTION IN PATIENTS WITH IPF

The first suggestion of drug–gene interaction in patients with IPF was reported as secondary analyses of a GWAS [74] and survival analysis [93]. DNA samples from patients enrolled in the 'Anti-Coagulant Effectiveness in Idiopathic Pulmonary Fibrosis' trial [102] were among those used to conduct our group's recent GWAS. Post hoc analysis of this cohort (reported in the supplement) showed possible interaction between warfarin therapy and the *MUC5B* promoter polymorphism, though the small sample size precluded formal interaction testing. It was observed that among genotyped trial participants, more deaths occurred in those with the polymorphism who received warfarin compared with placebo (6 warfarin vs. 1 placebo), suggesting a possible interaction.

In their survival analysis of the *MUC5B* promoter polymorphism [93], Peljto and colleagues used DNA samples collected from patients enrolled in 'The INSPIRE Trial: A Study of Interferon γ-1b for Idiopathic Pulmonary Fibrosis' [103]. These authors showed that the survival benefit associated with this polymorphism was stronger among those receiving interferon γ-1b compared with placebo. Although formal interaction analysis failed to cross the significance threshold ($p_{interaction} = 0.07$), it did raise

the question of whether this therapy may have been more efficacious in those carrying the polymorphism. The authors did point out however that the survival benefit observed with the polymorphism in the INSPIRE cohort would not be expected in the University of Chicago replication cohort if this benefit was due solely to drug–gene interaction.

In December 2015, our group published the first dedicated pharmacogenetic investigation conducted in patients with IPF to date [104▪▪]. This was performed using paired genetic and clinical data from patients enrolled in the 'Effectiveness of Prednisone, Azathioprine, and *N*-Acetylcysteine in Patients with Idiopathic Pulmonary Fibrosis' (PANTHER) clinical trial [19,105]. Common SNPs within *TOLLIP* and *MUC5B* were genotyped and tested for interaction with trial interventions, including N-acetylcysteine (NAC) monotherapy and combination therapy with prednisone, azathioprine, and NAC, using a composite end point of death, transplantation, hospitalization and ≥at least 10% decline in forced vital capacity.

Using a multivariable Cox proportional hazards model, we identified significant interaction between NAC monotherapy and rs3 750 920, a coding SNP within exon 3 of *TOLLIP*. Genotype-stratified

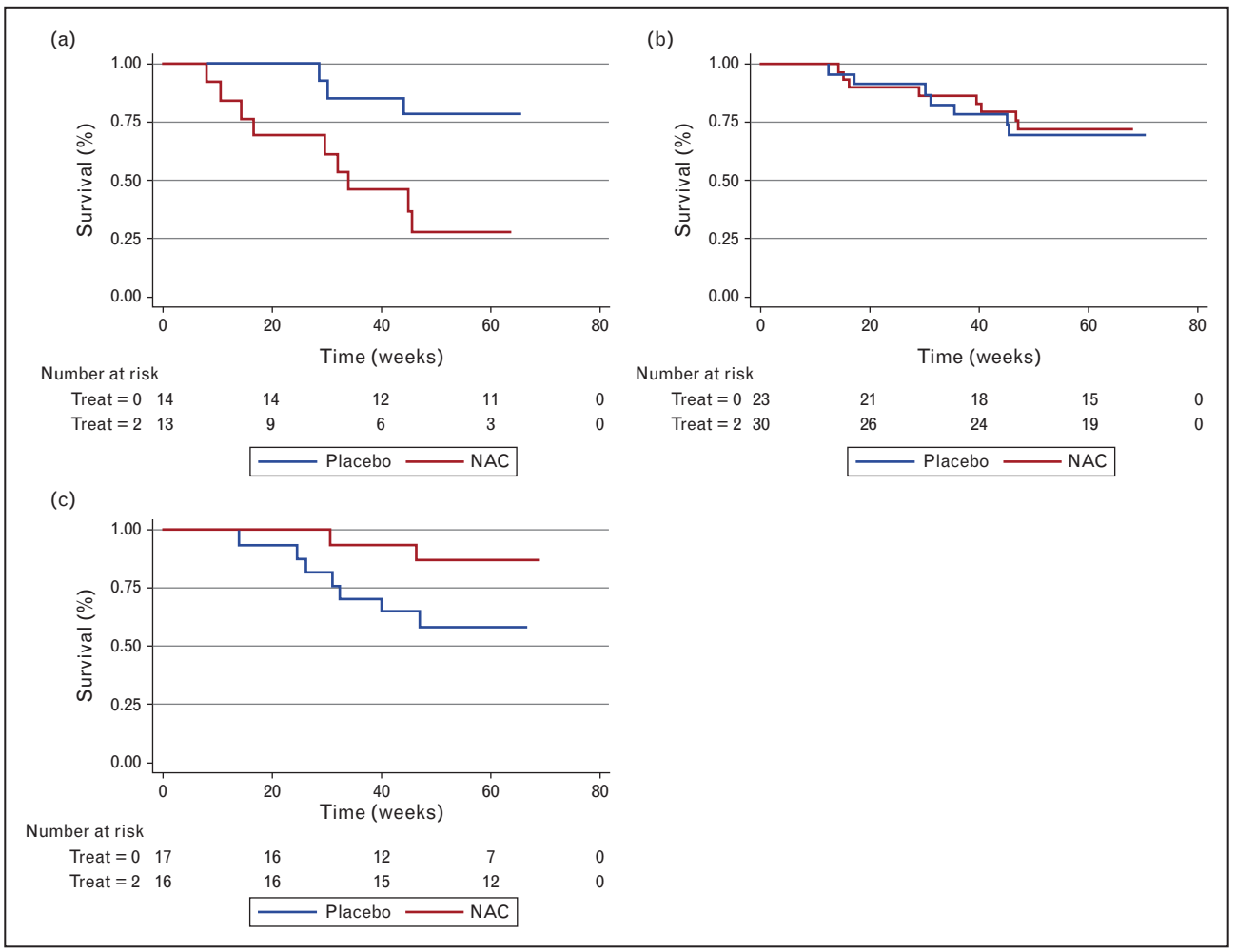

FIGURE 1. Composite endpoint-free survival between NAC and placebo groups after stratification by rs3750920 (TOLLIP) genotype. In those with a CC genotype (a), NAC therapy is associated with worse survival than placebo ($P_{logrank} = 0.01$; hazard ratio, 3.23; 95% confidence interval, 0.79–13.16; $P = 0.10$). In those with a CT genotype (b), survival is similar between groups ($P_{logrank} = 0.82$; HR 0.76; 95% CI 0.27–2.19; $P = 0.62$). In those with a TT genotype (c), NAC therapy is associated with improved survival compared with placebo ($P_{logrank} = 0.06$; HR 0.14; 95% CI 0.02–0.83; $P = 0.03$). Multivariable Cox regression models adjusted for age, sex, FVC (percentage predicted), and diffusion capacity of the lung for carbon monoxide (percentage predicted) at time of study enrollment. Reproduced from [104▪▪] with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; NAC, N acetylcysteine.

Kaplan–Meier curves and Cox models were constructed (Fig. 1) and showed that those with a CC genotype had an increased composite end point risk whereas those with a TT genotype had a decreased risk. Sensitivity analysis showed that the increased risk among those with a CC genotype was driven primarily by forced vital capacity decline events, whereas the decreased risk associated with the TT genotype was consistent across all end points. These findings were then replicated in an independent IPF cohort of patients followed at the University of Chicago and enrolled in the INSPIRE clinical trial.

This study had several limitations, including its post hoc, exploratory design and small sample size (<50% of PANTHER participants consented to genetic analysis). Despite these limitations, this study again raised the question of whether NAC may be an efficacious therapy for some patients with IPF and supports the pursuit a genotype-stratified NAC clinical trial. Furthermore, it highlighted the importance of pharmacogenetic investigation in patients with IPF, and ILD in general, and underscored the need for biospecimen collection in this patient population.

CONCLUSION

As medicine strives to usher in an era of personalized medicine, extensive pharmacogenetic investigation will be necessary to make this goal a reality. Prospective, randomized, genotyped-stratified clinical trials have already been conducted in patients with asthma [106,107], and provide a template for implementation in ILD. Prior to formal testing in clinical trials, drug–gene interaction must first be identified using paired DNA and clinical data from patient registries and completed clinical trials. Patient and provider education will be paramount in this endeavor, as biospecimens will be needed for such work and should be collected from as many patients as possible. Equally important will be a coordinated effort among ILD centers, not only to ensure robust pharmacogenetic testing, but to also expand clinical trial access to patients with less common ILDs.

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Conflicts of interest

J.M.O.is currently receiving a grant from the American Thoracic Society and Boehringer Ingelheim outside the submitted work. I.N. is currently receiving a grant from the NIH and HLR outside the submitted work. He has received honoraria from Boehringer Ingelheim, Gilead/perceptive, Sunovion, PILOT CME and Genentech outside the submitted work. He reports a patent TOLLIP in IPF that is pending, a patent PBMC expression signature in IPF which is pending and patent Plasma proteins in IPF that has been issued. F.J.M. is currently receiving a grant from NIH outside the submitted work. He has received nonfinancial support from Bayer, Centocor, Gilead, Promedior. He reports honoraria from Ikaria, Genentech, Nycomed/Takeda, Pfizer, Vertex, American Thoracic Society, Inova Health System, MedScape, Spectrum Health System, University of Texas Southwestern, Stromedix/Biogen, Axon Communications, Johnson & Johnson, Genzyme, National Association for Continuing Education, Boehringer Ingelheim, Veracyte, Academic CME, UNITY Forest, Janssens, GSK, Nycomed/Takeda, Actelion, Amgen, Astra Zeneca, CSA Medical, Ikaria/Bellerophon, Forest, Merck, Pearl, Roche, Sudler & Hennessey, American College of Chest Physicians, CME Incite, Center for Healthcare Education, Inova Health System, Miller Medical, National Association for Continuing Education, Paradigm, Peer Voice, Projects in Knowledge, St. John's Hospital, St. Mary's Hospital, University of Illinois Chicago, Up To Date, Wayne State University, Grey Healthcare, Merion, Informa, Annenberg, Theravance outside the submitted work.

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