Purpose of review
A number of recent studies have explored the possibility to apply personalized medicine to interstitial lung diseases (ILDs), particularly idiopathic pulmonary fibrosis (IPF), the most common and deadly of the idiopathic interstitial pneumonias. In our review, we summarize and discuss the most recent literature on personalized medicine in IPF as well as hypersensitivity pneumonitis and sarcoidosis, with emphasis on patient subgroups for which a personalized approach to disease prognostication and management may become a reality in the near future.

Recent findings
Most of the studies that have explored the applicability of personalized medicine to ILDs have been conducted in patients with IPF. Such studies have suggested the existence of several distinct disease subgroups defined by similar genetic profiles, molecular pathways, exposures and individual lifestyles. Personalized medicine in hypersensitivity pneumonitis is in its infancy. The development and applicability of personalized medicine to sarcoidosis, on the other hand, remains problematic for several reasons, including the lack of a diagnostic gold standard, the highly variable and unpredictable disease course, particularly across patients of different ethnicities, the poor correlation between disease activity and disease severity and the lack of a validated management algorithm.

Summary
A number of distinct patient subgroups have been identified in ILDs. Although available data need to be validated longitudinally, the possibility to study homogeneous groups of patients may allow prediction of disease behavior and response to treatment with dramatic clinical implications.

Keywords
hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, interstitial lung disease, personalized medicine, sarcoidosis

INTRODUCTION
Interstitial lung diseases (ILDs), also referred to as diffuse parenchymal lung diseases, are a large and heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis, often sharing similar clinical, physiologic and radiological features. A broadly used classification categorizes ILDs as idiopathic interstitial pneumonias (IIPs), of which idiopathic pulmonary fibrosis (IPF) is the most common and severe; diseases related to connective tissue disease (CTD-ILDs), drug intake and occupational and environmental exposures and sarcoidosis [1]. Despite a steadily growing interest and clinical research in ILDs, patient management remains suboptimal, mainly because of the limited knowledge of disease pathogenesis and the highly variable and unpredictable disease course [2].

Personalized medicine is a medical approach that emphasizes the customization of healthcare, with all decisions and practices being tailored to individual patients [3]. The first step in personalized medicine is the identification of biological markers (e.g. biomarkers), which, broadly speaking, can be defined as measurable factors – most often proteins, found in blood, body fluid or tissue but which can be also physiological measures such as forced vital capacity (FVC) or imaging measures – that carry...
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A growing body of evidence suggests that patient genetic make-up may be important in treatment decision-making by defining subgroups of patients who share specific pathogenetic profiles and are therefore more likely to respond to a given therapy.

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Current clinical prediction models [14,15] identify those at an increased risk of mortality, but fail to predict disease progression, as measured by pulmonary function decline [16**,17*]. These realities make IPF a frustrating disease for patients and clinicians alike, and have led to substantial investigation aimed at identifying subgroups that display differential outcomes and treatment response. Such investigation forms the backbone of personalized medicine in IPF, which aims to optimize disease prognostication and management by incorporating environmental, phenotypic and biomarker data into risk stratification models and treatment algorithms. Below are examples of promising subgroups for which personalized medicine may soon become a reality.

Gastroesophageal reflux/hiatal hernia subgroups

Gastroesophageal reflux (GER) is among the most commonly encountered comorbid conditions in patients with IPF and represents a potential cause of IPF via alveolar injury from aspirated stomach contents [18*]. Although estimates vary, GER has been described in up to 87% of individuals with IPF using 24-h esophageal potential of hydrogen monitoring [19]. Asymptomatic GER and nonacid GER are also common in IPF [19,20*], complicating the manner in which GER is diagnosed and prevalence determined. In addition to GER, a large minority of patients with IPF also suffer from a hiatal hernia, which may exacerbate GER and further contribute to microaspiration [21,22].

GER is typically treated with antacid therapy, including proton pump inhibitors and histamine-2 blockers. Data regarding the benefit of such therapy are conflicting and currently limited to retrospective analyses [23,24,25**]. Although initial studies suggested improved outcomes in those treated with antacid therapy [23,24], a recent posthoc analysis of pooled IPF clinical trial datasets failed to replicate these findings and demonstrated an increased incidence of pulmonary infections [25**]. Formal testing of antacid therapy is underway in a phase II clinical trial titled ‘Pilot Trial of Omeprazole in Idiopathic Pulmonary Fibrosis (PPIPF)’ (NC02085018). Although the results of this investigation will no doubt be informative, the concern remains that acid blockade fails to prevent the aspiration of stomach contents, irrespective of content acidity. As such, the mechanical correction of GER is also under investigation in a phase II clinical trial, titled ‘Treatment of IPF with Laparoscopic Anti-Reflux Surgery (WRAP-IPF)’ (NCT01982968). In addition to laying the foundation for larger, phase III trials, these investigations will begin to delineate whether such
interventions benefit IPF subgroups with comorbid GER and hiatal hernia.

**Airway microbiome subgroups**

Microbes have long been implicated in the pathogenesis of IPF. Early studies suggested a potential role for several human herpes viruses, as these were found in higher proportions of individuals with IPF than control individuals [26–31]. Whether such viruses lead to the alveolar injury characteristic of IPF remains unclear, however. Recent investigations of the lower airway microbiome have shed light on bacterial pathogens as well. Molyneaux et al. [32] demonstrated a more than two-fold higher bacterial burden in the bronchoalveolar lavage fluid of patients with IPF compared with control individuals. Furthermore, increasing bacterial burden predicted both pulmonary function decline and death in this IPF cohort. In a similar investigation, Han et al. [33] showed that the presence of *Streptococcus* and *Staphylococcus* species predicted IPF progression and reduced progression-free survival. These findings, in addition to a recent randomized placebo-controlled trial showing that cotrimoxazole may improve survival in IPF [34], support an upcoming, phase III multicenter clinical trial titled ‘Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis’ (CleanUp) (NCT02759120). This trial will not only determine whether antimicrobials represent an efficacious adjunct to antifibrotic therapy in IPF, but will also allow for the testing of such therapy in prespecified, microbiome-derived subgroups.

**Genetic subgroups**

Although environmental risk factors have long been known in IPF, genetic risk factors have only recently begun to be delineated. Genome-wide association studies identified single nucleotide polymorphisms (SNPs) across multiple loci to be associated with IPF susceptibility [35,36]. Several SNPs are located on the short arm of chromosome 11, within *MUC5B* and *TOLLIP*, both of which play vital roles in airway host defense [32,37–39]. A recent investigation by Fingerlin et al. [40**] identified an additional novel locus within human leukocyte antigen (HLA) complex, underscoring the potential role that impaired host defense plays in IPF pathogenesis. In addition to their association with IPF susceptibility, SNPs within *MUC5B* and *TOLLIP* have also been linked to differential survival, though the strength of association varies depending on the cohort under consideration [36,41–43]. A recent pharmacogenetic investigation [44**] also showed that a common SNP within *TOLLIP* may also modulate the response to N-acetylcysteine therapy, an antioxidant commonly used to treat IPF before a phase III clinical trial failed to demonstrate efficacy [45]. Although such outcome analyses are novel, they are reliant on SNPs linked to IPF susceptibility. Given the aforementioned heterogeneity in IPF natural history, a genome-wide investigation aimed at identifying SNPs specifically linked to IPF outcomes would greatly enhance our ability to incorporate genetics into risk stratification models. Such work would also synergize with current gene expression work aimed at predicting mortality [46], and allow for the testing of IPF-specific therapies in cohorts genetically predisposed to a poor outcome.

**HYPERSENSITIVITY PNEUMONITIS**

Hypersensitivity pneumonitis is an ILD triggered by inhaled antigens, with multiple known causative agents. Recently Cramer et al. [47] studied the risk of hypersensitivity pneumonitis among pigeon breeders in a retrospective study and identified an adjusted hazard ratio of 14.36 (95% confidence interval 8.10–25.44) for hypersensitivity pneumonitis and other ILDs for pigeon breeders. Although still rare, this finding suggests that protective measures should be considered among pigeon breeders to minimize antigen exposure.

Diagnosis of hypersensitivity pneumonitis can be challenging, with wide variability in clinical, radiographic and pathologic findings and a possible initiating antigen identified in only around 50% of cases [48,49]. To aid diagnosis of hypersensitivity pneumonitis, Johannson et al. [50*] have proposed clinical prediction models (cross-validated C-statistic 75.2–78.0) incorporating only clinical and radiographic features including age, history of down feather and/or bird exposure and the presence of ground-glass opacity and mosaic perfusion on chest computed tomography. A group of patients with chronic hypersensitivity pneumonitis develop progressive fibrosis with associated morbidity and mortality. Long et al. [51] have identified that baseline serum levels of YKL-40, a chitinase-like protein mainly secreted by macrophages, neutrophils and epithelial cells, were significantly higher in patients with chronic hypersensitivity pneumonitis than healthy controls, and patients who progressed or died had higher baseline YKL-40 levels than those who remained stable and survived. This finding requires external validation; however, it suggests that serum YKL-40 may have utility as a prognostic biomarker in hypersensitivity pneumonitis patients.

The standard of care for chronic hypersensitivity pneumonitis is antigen removal and corticosteroids; yet, the antigen may not be identified and patients...
may continue to progress or have corticosteroid related side-effects. Alternative evidence-based therapeutic approaches are therefore required. Morisset et al. [52] performed a retrospective multicentre study of the cell cycle inhibitors mycophenolate mofetil (MMF) and azathioprine (AZA). Longitudinal trajectories in lung function were analyzed prior to, and after treatment initiation. Both treatments were generally well tolerated. No change in lung volumes (FVC) was identified; however, there was an improvement in gas transfer (diffusion capacity of the lung for carbon monoxide) of 4.2% (P < 0.001) after 1 year of treatment. These retrospective data are supportive of the need for prospective randomized clinical trials to study the long-term efficacy of MMF and AZA in chronic hypersensitivity pneumonitis.

In patients with advanced, chronic hypersensitivity pneumonitis, lung transplantation may be considered; however, data on outcomes following transplantation have been limited. Kern et al. [53] performed a single centre retrospective analysis of all patients undergoing transplantation with a diagnosis of hypersensitivity pneumonitis. Thirty-one individuals with hypersensitivity pneumonitis had undergone transplant, with the diagnosis made only at explant in five cases. At 5 years, posttransplant survival was 67% (compared with 49% in a group of patients with IPF). In two patients, a recurrence of hypersensitivity pneumonitis in allograft was identified, demonstrating the need for vigilance for ongoing antigen exposure and disease recurrence following transplantation for hypersensitivity pneumonitis.

**SARCIOIDOSIS**

Sarcoidosis is a systemic granulomatous disorder with a wide-ranging pattern of presentation and severity [54]. Although the cause of the disease remains unknown, a large body of evidence indicates that susceptibility to sarcoidosis is genetically determined [55]. The disease, however, is not caused by defects in a single major gene or chemical pathway; instead, it results from a complex interaction between environmental/infectious agents and multiple genes, some with a major disease effect, but many with a relatively minor effect [56]. Genetics is also believed to contribute to the highly variable clinical manifestations and prognosis of sarcoidosis [56].

Consistent with the concept that sarcoidosis granulomatous inflammation results from an abnormal immune response to persistent antigenic stimuli, several HLA alleles have been associated with the disease [55]. However, there is a considerable variability in the alleles that are associated with increased disease risk or ‘protection’ across different ethnicities, which makes the personalization of genetic susceptibility/protection very challenging at this moment. There is one situation, however, in which a genetic association is robust across different populations, and is practical and clinically relevant. This is the HLA-DRB1*0301 (DR3) association with Löfgren’s syndrome, an acute and almost invariably benign form of sarcoidosis that manifests with fever, bilateral hilar lymphadenopathy and erythema nodosum with or without periarticular inflammation of the ankles [57]. Notably, approximately 50% of individuals who present with Löfgren’s syndrome but do not carry the DR3 allele experience persistent disease and a less favorable outcome [57].

Recent studies have highlighted the potential of immune mediators and immunogenetics in determining disease development and behavior, and guiding treatment in sarcoidosis. Levin et al. [58] genotyped a large population of African American patients (n = 1277) and matched controls (n = 1467), and found that, consistent with previous findings among individuals of European descent [57], carriage of the HLA-DRB1*0301 allele is associated with a resolving disease course. Owing to the high likelihood of experiencing a self-limiting disease course, treatment may be contraindicated in sarcoidosis patients carrying the HLA-DRB1*0301 allele. Fischer et al. [59] recently performed the largest sarcoidosis case–control study to date. In the screening step, they genotyped a European cohort of 1726 patients and 5482 controls using the Illumina Immunochip SNP array, whereas multiple European cohorts and one African American cohort were used for replication and subgroup analysis. They identified novel disease susceptibility loci with genome-wide significance at 12q24.12 (ATXN2/SH2B3), 5q33.3 (near IL12B), 4q24 (MANBA/NFKB1), 2q33.2 (FAM117B) and 1p31.3 (IL23R) along with three independent signals in the HLA region. Notably, this study suggests a significant genetic overlap between sarcoidosis and other immune-mediated inflammatory disorders, thus providing hypotheses for novel therapeutic targets.

As with other ILDs, the main goal of personalized medicine in the management of sarcoidosis is the identification of biomarkers to predict disease behavior and response to treatment. Indeed, it is well known that a person’s genes influence his/her responses to drugs, both in terms of therapeutic effect and adverse effect. Testing leukemia patients for their thiopurine S-methyltransferase (TPMT) status is one of the most common examples of treatment being tailored to match patients’ genetics [60]. In sarcoidosis, TPMT genotype may potentially affect response to thiopurines such as azathioprine and methotrexate, two commonly used second-line
steroid-sparing agents [61,62], although this has never been formally addressed in adequately powered clinical studies. Patients who experience disease progression despite (or intolerable side-effects from) conventional therapy are usually treated with antitumor necrosis factor (TNF) monoclonal antibodies, especially in organ-threatening or life-threatening disease [63]. Wijnen et al. [64] evaluated the contribution of TNF-α G-308A genotype to response to anti-TNF-α treatment in 111 patients with refractory sarcoidosis. They observed that individuals homozygous for the G allele were more likely to respond to anti-TNF treatment (either infliximab or adalimumab) compared with carriers of the AA or GA genotype. Personalized prescribing has the potential to revolutionize the landscape of sarcoidosis treatment; at present, however, there is very limited evidence for it to be applied to clinical practice [65].

The development and applicability of biomarker tools to sarcoidosis remains problematic for several reasons, including the lack of a diagnostic gold standard; the highly variable mode of presentation, manifestations and outcome; the poor correlation between disease activity and disease severity; and the lack of a validated management algorithm [66]. As such, the added value of biomarkers over the standard clinical assessment in patients with sarcoidosis remains to be established.

CONCLUSION
Over the past few years, genetic and molecular approaches have improved dramatically our knowledge of the genetic heterogeneity of ILDs, particularly IPF. These studies have suggested the possibility to stratify patients on a pathway-specific basis, thus allowing for the testing of therapies in more homogeneous cohorts. Disease prognostication and management will also benefit from incorporation of environmental and phenotypic data into risk stratification models and treatment algorithms. The importance of personalized medicine in ILDs remains to be established and much work is needed to prospectively validate available data. If successful, however, this approach has the potential to transform the diagnosis, classification and management of these challenging diseases.

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Conflicts of interest
The remaining authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- - of outstanding interest

17. This study shows that models for time to respiratory hospitalization or death, or death alone display acceptable discriminative performance, whereas clinical prediction models poorly predict functional disease progression in IPF.

This study suggests that baseline gender, age, physiology stage predicts death or lung transplantation but not the rate of future pulmonary function decline.


A recent guideline document that provides evidence-based recommendations on pharmacological interventions for IPF.


This retrospective study confirms that abnormal gastro-oesophageal reflux is highly prevalent in patients with IPF and suggests a role for pathological gastro-oesophageal reflux in the development of the disease.


This posthoc analysis of the placebo groups of three trials of pirfenidone suggests that antiacid therapy may not be beneficial in patients with IPF and may actually be associated with an increased risk of infection in individuals with advanced disease.


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