Review

Idiopathic Pulmonary Fibrosis
Time to get personal

Theodoros Karampitsakos[1], Serafeim Chrysikos[1], Vassilios Tzilas[2], Katerina Dimakou[1], Demosthenes Bouros[2], Argyris Tzouvelekis[2,3]

[1]5th Department of Pneumonology, General Hospital for Thoracic Diseases "SOTIRIA", Athens, Greece
[2]First Academic Department of Pneumonology, General Hospital for Thoracic Diseases "SOTIRIA", Medical School, National and Kapodistrian University of Athens, Athens, Greece
[3]Division of Immunology, Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece

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Correspondence:
Argyrios Tzouvelekis MD, PhD
Division of Immunology
Biomedical Sciences Research Center
"Alexander Fleming"
34 Fleming street, Vari, 16672, Athens, Greece
E-mail: argryios.tzouvelekis@fleming.gr

SUMMARY
Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and debilitating disease of unknown etiology. Median survival after diagnosis ranges from 3 to 5 years. The clinical course of the disease is highly heterogeneous and unpredictable. Despite this heterogeneity, the two novel compounds, pirfenidone and nintedanib, are administered uniformly to patients with IPF with little correlation to inter-individual differences. Personalized medicine refers to a medical model aiming to determine disease susceptibility, tailor the ideal treatment, predict and improve outcome according to individuals' molecular and environmental profile. The conceptualization of precision medicine dates back to the era of Hippocrates, the father of western medicine, who first coined out the term "idiosyncrasy" to describe the individuality in the clinical course of the disease. Compared to oncology, precision medicine approaches in IPF have significantly lagged behind. Disease management and prognostication is still based on functional and physiological parameters, which present with several caveats and provide no mechanistic insights. This short review article summarizes the current state of knowledge in the prognostic and therapeutic field of IPF, highlights the most recent findings and addresses the pressing need to integrate molecular biomarkers in the everyday clinical practice.
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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) represents a devastating chronic lung disease of unknown origin, characterized by the complex interaction of environmental, immunologic, genetic and epigenetic factors[1-6]. Median survival after diagnosis ranges from 3 to 5 years[7]. The clinical course of the disease is highly unpredictable and heterogeneous[8]. Based on current functional and physiological indices, patients are categorized into three distinct patterns of disease progression: slow progressors, rapid progressors and patients with relative stability interposed by periods of rapid acceleration named acute

exacerbations[8-10]. Until recently, lung transplantation was the only approach that could prolong patients' survival. To this end, two novel compounds (pirfenidone and nintedanib), able to reduce the rate of progression, represent the pharmaceutical treatment approved for the disease[11,12]. These compounds are administered uniformly to patients with IPF based on diagnosis and with little correlation to inter-individual differences[13].

Personalized medicine dates back to the times of Hippocrates who stated that ''It's far more important to know what person the disease has than what disease the person has" and refers to a medical model aiming to determine disease susceptibility, tailor the ideal treatment, predict and improve outcome according to patients' molecular and environmental profile[14,15]. However, it was not until the 19th century that significant progress has been achieved, as Reuben Ottenberg reported the first known blood compatibility test in 1907. The past 2 years precision medicine initiatives have drugged much of attention[13]. Unfortunately, personalized medicine approaches in IPF have significantly lagged behind[16,17]. In the past few years, several conventional therapeutic regimens led to fatal-side effects[18]. To this end, there is an amenable need for the identification of distinct endotypes and application of targeted therapeutic approaches on a pathway-specific basis. This short review article summarizes the current state of knowledge in the prognostic and therapeutic field of IPF and presents ways to optimize the use of precision medicine in the everyday clinical practice by providing realistic answers to fundamental questions.

WHICH IS THE CURRENT STATUS USED IN THE EVERYDAY CLINICAL PRACTICE FOR TREATMENT STRATIFICATION AND PROGNOSTICATION?

Despite disease heterogeneity and complexity, pirfenidone and nintedanib are currently administered uniformly to patients irrespective of endotypes[13,19-21]. Clinicians usually choose the compound that is theoretically best tailored to the individual patient, according to comorbidities and risk of adverse events. With regards to comorbid conditions including lung cancer, pulmonary hypertension and gastroesophageal reflux, the ideal approach remains to be elucidated and consensus task forces are greatly anticipated[16,22-26].

Prognostication is solely based on functional and physiological parameters. Currently, forced vital capacity (FVC), diffusion capacity for carbon monoxide (DLCO) and 6-minute walking test(6MWT) are the main prognosticators used in the real life setting[6,27-29]. GAP (Gender, Age and Physiology variables) score and composite physiologic index (CPI) are the two most reliable risk-stratification algorithms[30,31]. However, these parameters present with significant caveats including technical variabilities, overestimation of FVC in patients with combined pulmonary fibrosis and emphysema (CPFE) and erroneous interpretations of 6MWT due to myoskeletal and heart related comorbities[28,32-34]. Finally, all these parameters provide no mechanistic insights.

WHY PERSONALIZED MEDICINE APPROACHES FOR IPF HAD SIGNIFICANTLY LAGGED BEHIND IN THE PAST?

IPF is a relatively 'newly introduced' disease. Wiliam Osler first coined out the term ''chronic interstitial pneumonia" almost a century ago; yet, in this case fibrosis was unilateral[35]. The pathologic term ''usual interstitial pneumonia (UIP)" was introduced by Averill Liebow in 1968[36]. Until the past few years, IPF was an underecognized entity and considered as an end stage lung disease with no effective treatment. Thus, precision medicine approaches have focused on identification of compounds for more common diseases, including anti-IL-5 (mepolizumab), anti-IgE (omalizumab), anti-IL-13 (lebrkizumab and tralokinumab) treatment for asthma and PD-1/PD-L1 inhibitors (nivolumab and pembrolizumab) and compounds targeting EGFR mutations (erlotinib, gefitinib, afatinib) for non-small cell lung cancer[17,37-39].

COULD GENETICS AND EPIGENETICS CONTRIBUTE TO PERSONALIZED MEDICINE APPROACHES? (Table 1)

Common or rare variants have been associated with nearly half of IPF cases[40-42]. Intriguingly, a common variant located in the putative promoter region of the MUC5B gene (rs35705950) conferred risk for pulmonary fibrosis development, but has also been associated with better prognosis[43-57]. Similarly, a toll interacting protein (TOLLIP) functional variant (rs5743890) was found protective against fibrosis development but was also associated with increased mortality among individuals affected[16,46]. Another single nucleotide polymorphism (SNP) within TOLLIP (rs3750920) was able to stratify patients with IPF based on treatment response to N-acetylcysteine[58,59]. A

TABLE 1. Main biomarkers investigated in IPF and their potential clinical utility in the context of personalized medicine.

Field	Biomarker	Potential clinical utility	Reference
Genetics	MUC5B	Disease susceptibility	(45)
	TOLLIP	Disease susceptibility, treatment responsiveness	(46)
	TLR3	Disease prognosis	(60)
	Telomeres/Telomerase	Disease susceptibility	(66, 67)
	HLA(DRB1*1501), (DQB1*0602)	Disease susceptibility	(62)
	Surfactant proteins	Disease susceptibility and prognosis	(76)
Epigenetics			
	CDKN1A/ p21waf1/cip1 and Fas	Disease diagnosis	(87)
	let-7d, miR-21, miR-154	Disease diagnosis	(88, 89, 92)
Genomics			
	miR-29	Disease diagnosis, therapeutic target	(95)
	52-gene-signature T-cell co-stimulatory Pathway	Disease prognosis	(101, 119)
Proteomics			
	CCL-18, CXCL13, MMP-7 SP-D,CA 19-9,CA-125	Disease prognosis	(114, 117, 118, 127)
	LOXL2	Disease prognosis, therapeutic target	(103)
	Galectin, CTGF, IL-13, NOX1/NOX4, SHP	Therapeutic targets	(106-108) (102, 110)
3D			
Pulmospheres	3D spheroids of cells from biopsy	Treatment response	(128)

CA: carbohydrate antigen or cancer antigen, CCL: Chemokine (C-C motif) ligand, CDKN1A: Cyclin Dependent Kinase Inhibitor 1A, CTGF: connective tissue growth factor, CXCL: Chemokine (CXC-motif) ligand, Fas: Fatty acid synthase, HLA: human leukocyte antigen, IL: interleukin , IPF: Idiopathic pulmonary fibrosis, LOXL: lysyl oxidase like-protein, miR: microRNAs, MMP: Matrix Metalloproteinase, MUC: Mucin, NOTCH: Neurogenic locus notch homolog protein, NOX: NADPH oxidase, SHP: Src homology region 2 domain-containing phosphatase, SP: surfactant protein, TLR: toll-like receptor, TOLLIP: Toll-interacting protein.

functional variant (Leu412Phe, TLR3 L412F) of toll-like receptor 3 (TLR3) has been also reported as a marker of rapidly progressive disease in patients with IPF[60]. Furthermore, loss of-function mutations in a TLR3 agonist (ELMOD2) have been associated with familial IPF susceptibility[61,62]. Short leucocyte telomere length has been also associated with worse survival in IPF[63-66], while patients with telomerase mutations were more prone to complications due to nephrotoxic immunosuppressants and to post-transplantation hematologic complications, maybe owing to reduced bone marrow reserves[67-74]. Several other mutations in genes have been suggested as biomarkers including mutations associated with surfactant proteins[15,75]. Interestingly, patients carrying SFTPA2 mutations had also an increased risk of developing lung cancer[22,76,77].

With regards to epigenetics, application of high-throughput screening methods identified differentially methylated and expressed genes including TOLLIP, NOTCH1, Thy-1, CDKN2Ap14ARF and SHOX2 homeobox family gene in patients with IPF[78-86]. Histone demethylase and deacetylase inhibitors have been suggested as novel therapeutic targets for a subset of patients[22,87]. Finally, both downregulated and so called "anti-fibrotic" (let-7d, miR-29) and upregulated (miR-21, miR-154) have been considered major orchestrators of pulmonary fibrosis[88-93]. Interestingly, mir-29 has exhibited in vivo therapeutic

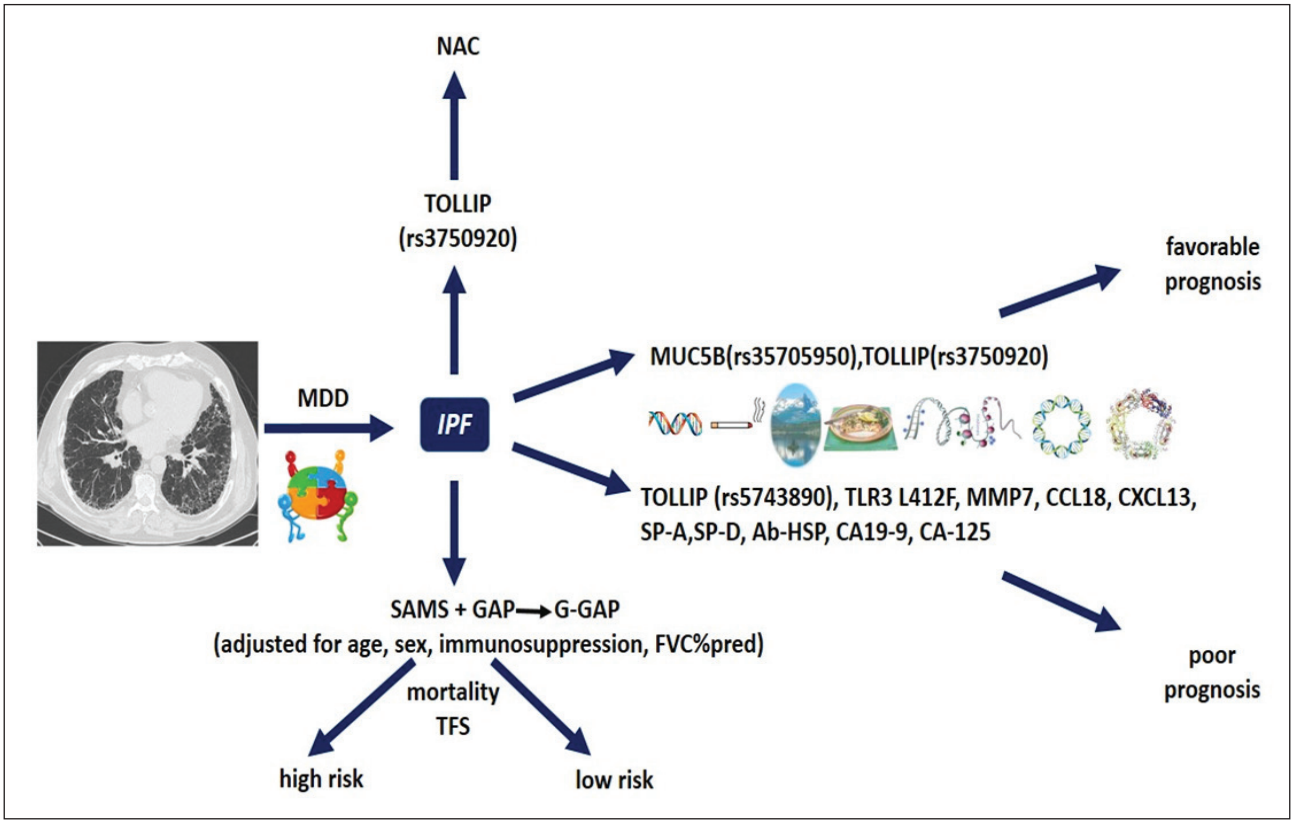

FIGURE 1. Figure 1 depicts main applications of personalized medicine in patients with IPF. A single nucleotide polymorphism (SNP) within TOLLIP (rs3750920) was able to stratify patients with IPF based on treatment response to N-acetylcysteine. Patients with specific SNPs (MUC5B rs35705950, TOLLIP, rs3750920) present with a survival benefit. Several other biomarkers depicted in the figure have been associated with poor prognosis. Finally, combination of a genomic risk scoring system (Scoring Algorithm for Molecular Subphenotypes; SAMS) and GAP score after adjustment for several parameters, was able to discriminate patients into two risk groups with regards to mortality and transplant free survival.

benefits in several models of pulmonary fibrosis and is currently entering the pipeline of clinical trials; yet, caution is demanded as such trials exhibit several risks including the risk of carcinogenesis[94-97].

TIME TO GET PERSONAL? MAIN LESSONS FROM PERSONAL "OMICS" PROFILING (Table 1)

Kaminski and Selman distinguished patients with IPF into rapid progressors and slow progressors based on genomics[2,98-100]. In a follow-up study, a 52-gene outcome-predictive signature including genes involved in "The costimulatory signal during T cell activation" Biocarta pathway (CD28, ICOS, LCK, and ITK) discriminated patients into two groups with significant difference in transplant-free survival (TFS)[101].

Proteomics technology led to the identification of several novel therapeutic compounds, currently used in clinical trials including inhibitors of LOXL2, CTGF, IL-13, galectin, NOX1/NOX4, and SHP[96,102-110]. Moreover, several biomarkers validated in independent cohorts, including MMP-7, CCL-18, CXCL13 and MMP-degraded extracellular matrix proteins, have been identified through proteomics[9,111-113]. In particular, increased MMP-7 values have been associated with poor prognosis[77,114-116]. Increased levels of circulating chemokine ligand 18 (CCL18) and chemokine (C-X-C motif) ligand 13 (CXCL13) were also likewise predictive of IPF progression[101,117,118].

WHAT HAS BEEN RECENTLY ADDED TO THE FIELD?

Significant progress has been achieved in the context of personalized medicine during the last year. A genomic risk scoring system (Scoring Algorithm for Molecular

Subphenotypes; SAMS) ,able to discriminate patients into two risk groups with regards to mortality and transplant free survival, has been recently published[119]. These findings provide evidence that integration of genomic data into prognostic algorithms encompassing demographic and functional data significantly improves the prediction of outcome compared to GAP index alone and address the need for more complex criteria than conventional demographic and physiologic parameters in studies investigating therapeutic effect[15,120-126].

Moreover, the recently published PROFILE study is the largest prospective analysis of serum biomarkers in IPF. Three epithelium derived biomarkers (CA19-9, CA-125 and surfactant protein D) were able both to discriminate stable from progressive IPF and identify patients at increased risk of mortality[127]. No studies had previously identified CA19-9 as a biomarker of IPF progression or CA-125 as a dynamic IPF biomarker, in the past. Furthermore, this study validated that high concentrations of baseline surfactant protein D and MMP 7 can be used to distinguish individuals with disease from controls and predict outcome. These results are of paramount importance, as they could demonstrate a crucial role in an effort to streamline clinical trial designs and even assess treatment response based on biomarkers.

Towards the direction of assessment of treatment response, another recent study reported that 3D pulmospheres (spheroids composed of cells from primary lung biopsy) predicted responsiveness in antifibrotic compounds and thus the most beneficial anti-fibrotic drug for every patient as individual. However, a major caveat is the fact that pulmospheres were obtained via video-assisted thoracic surgery (VATS)[128]. Obtaining tissue to form 3D pulmospheres with less invasive methods such as cryobiopsy could play a cardinal role in personalized medicine approaches in the future.

FUTURE PERSPECTIVES AND CONCLUDING REMARKS

Despite recent discoveries on disease pathogenesis and treatment, IPF still represents an incurable disease. Application of precision medicine could predict responsiveness in available compounds and lead to efficacious treatments for specific IPF endotypes, like mepolizumab and omalizumab in asthma and novel regimens in lung cancer. Ideal application of personalized medicine involves a '' two-way process". This process includes 1) extremely precise diagnostic tests and biomarkers able to determine whether patient may benefit from an intervention or not and 2) the therapeutic intervention itself. Several future challenges remain to be addressed for the successful application of this "two-way process" including the following:

Diagnostic tests: Advances in computational power and medical imaging (i.e. microCT) are paving the way for personalized medical approaches considering and combining patient's anatomical profile along with physiological and genetic features[129,130].

Pharmacogenetic approach: Implementation of biomarkers and pharmacogenetic approach into future clinical trials is crucial, given the robust information we have gained during the past years from biomarkers including MUC5B, TOLLIP, MMP-3, MMP-7, CXCL13, lysyl oxidase homolog 2, periostin, heat shock protein 70 and type V collagen[9,40,129,130]. A number of such studies (PROFILE, COMET, LGRC, the European IPF network registry) have already been organized[111,131-133].

Therapeutic interventions: Studies using lung-targeted therapies including clinical studies for the role of aerosolized thyroid hormone administration in patients with IPF are greatly anticipated[134].

Targeted approach for comorbidities: Clinical trials targeting comorbid conditions including gastroesophageal reflux, lung cancer and pulmonary hypertension are also of paramount importance. To this end, studies for proton pump inhibitors in IPF present with conflicting results and there is caution for their use mainly due to the subsequent alteration of lung microbiome. The role of lung-gut axis in this context deserves further investigation[135,136]. The results of a phase II clinical trial for laparoscopic anti-reflux therapy in IPF will address whether this intervention is only a trigger for acute exacerbation or beneficial for a subgroup of patients[137]. Furthermore, there is a pressing need for Consensus Task Force addressing the ideal diagnostic algorithm and chemotherapeutic regimen in patients with IPF and lung cancer[138,139]. Finally, studies for antifibrotics plus a vasodilator or even tyrosine kinase inhibitors alone for patients with IPF and pulmonary hypertension are anticipated.

Collectively, from FDA's vantage point, the era of precision medicine has already arrived. In 2010, FDA announced the "Regulatory Science Initiative" highlighting personalized medicine as a key priority area and since 2011, approximately one-third of files, submitted for compounds waiting for approval, included some type of genetic or other biomarker data. However, personalized medicine in IPF had lagged behind. Thus, there is a pressing need

to enrich former president's Obama precision medicine initiative with diseases including IPF, which accounts for the same number of deaths with breast cancer in the USA and is the non-cancer lung disease with the gravest prognosis[22,140]. It's upon clinicians' and researchers' hands to persuade the scientific and political community that IPF should be launched into the same trajectory as many types of cancer.

ΠΕΡΙΛΗΨΗ

Ιδιοπαθής Πνευμονική Ίνωση: Ώρα για εξατομικευμένη προσέγγιση

Θεόδωρος Καραμπιτσάκος[1], Σεραφείμ Χρυσικός[1], Βασίλειος Τζίλας[2], Κατερίνα Δημάκου[1], Δημοσθένης Μπούρος[2], Αργύριος Τζουβελέκης[2,3]

[1]5η Πνευμονολογική Κλινική Νοσοκομείο Νοσημάτων Θώρακος ΝΝΘΑ «ΣΩΤΗΡΙΑ», Αθήνα, [2]Α' Πανεπιστημιακή Πνευμονολογική Κλινική, ΝΝΘΑ «ΣΩΤΗΡΙΑ», Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα, [3]Ερευνητικό Κέντρο Βιοϊατρικών Επιστημών «Αλέξανδρος Φλέμινγκ», Αθήνα

Η Ιδιοπαθής Πνευμονική Ίνωση (ΙΠΙ) είναι μία χρόνια, προοδευτικά εξελισσόμενη πάθηση άγνωστης αιτίας. Η μέση επιβίωση κυμαίνεται μεταξύ 3 και 5 ετών. Ωστόσο, η κλινική πορεία της νόσου είναι εξαιρετικά ετερογενής και απρόβλεπτη. Παρά την ετερογένεια στο προφίλ των ασθενών, τα δύο νέα φάρμακα, η πιρφενιδόνη και το nintedanib, χορηγούνται χωρίς ιδιαίτερη διάκριση ανάμεσα στους ασθενείς με ΙΠΙ. Η εξατομικευμένη/προσωποποιημένη ιατρική αναφέρεται σε ένα ιατρικό μοντέλο ικανό να διαπιστώσει την πιθανότητα νόσησης από ένα νόσημα, να βοηθήσει στην επιλογή της βέλτιστης θεραπευτικής προσέγγισης αλλά και να επιχειρήσει να προβλέψει την έκβαση του ασθενούς βάσει του μοριακού/περιβαλλοντικού/ατομικού προφίλ του. Η ιδέα της εξατομικευμένης προσέγγισης άρχεται από την εποχή του Ιπποκράτη, του πατέρα της δυτικής ιατρικής, που πρώτος χρησιμοποίησε τον όρο "ιδιοσυγκρασία" για να περιγράψει την ιδιαιτερότητα που παρουσιάζει κάθε ασθενής στην κλινική του πορεία. Σε σχέση με την ογκολογία, η εξατομικευμένη ιατρική στην ΙΠΙ δεν αναπτύχθηκε αντίστοιχα. Η αντιμετώπιση και πρόγνωση της πάθησης εξακολουθεί να βασίζεται σε λειτουργικές, φυσιολογικές παραμέτρους, οι οποίες συνοδεύονται από πολλά μειονεκτήματα και δεν παρουσιάζουν ιδιαίτερη συσχέτιση με παθογενετικούς μηχανισμούς. Η συγκεκριμένη βιβλιογραφική ανασκόπηση παραθέτει τις νεότερες εξελίξεις σχετικά με την πρόγνωση και θεραπεία της ΙΠΙ και τονίζει την αδήριτη ανάγκη ενσωμάτωσης μοριακών βιοδεικτών στην καθημερινή κλινική πράξη.

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