Suggestions for improving clinical utility of future guidelines for diagnosis and management of idiopathic pulmonary fibrosis: results of a Delphi survey

To the Editor:

Medical guidelines on diagnosis and management of relevant diseases aim to make recommendations for clinical practice while standardising patient care. However, evidence-based guideline development is laborious and challenging, the recommendations require nuanced wording, and the optimal approach remains controversial.

In December 2019, an international working group of interstitial lung disease (ILD) experts from 14 European countries and North America debated whether the current clinical practice idiopathic pulmonary fibrosis (IPF) guidelines [1] are informative and clinically useful. The 3rd International ILD Summit (ISILD-3) in Erice, Italy, addressed evolving clinical and research topics. Guideline-related issues were discussed to identify ways in which future guideline formulation in ILD might be optimised. Difficulties in the generation of accurate and applicable guideline recommendations raised questions that were further explored and assessed among ISILD-3 participants by an electronic survey in January 2020.

The objective was to identify opportunities to improve future international guidelines from a clinical expert point of view, with some of the participants having been involved in previous and current guideline development. Two series of questions were formulated from the previous discussion and selected by a core committee (co-authors). The first series addressed general questions about guidelines (questions 1–9), with the second addressing questions specific for IPF or other ILD guidelines (questions 10–14). All 64 ISILD-3 participants were invited to complete the survey using the *SurveyMonkey* platform. Response options included "yes", "no", "no opinion" and comments. 60/64 (94%) of the ISILD-3 participants completed questions 1–9 and 55/64 (86%) completed questions 10–14. Participant views are summarised in table 1. An agreement of 70% or more was defined as consensus *a posteriori*. Consensus was evaluated for "yes", "no" and "no opinion".

More than 70% of ISILD-3 participants endorsed: 1) piloting of recommendations in clinical practice to identify and minimise ambiguity; 2) provision of the minimum information needed by patients to ensure patient participation in decision making; and 3) routine updating of guidelines to incorporate significant developments. Piloting of the recommendations in future clinical practice guidelines before publication might provide useful insights and identify weaknesses within smaller groups of patients and community physicians. However, the feasibility of accomplishing this in a timely manner and applicability to other regions are of potential concern. Input from 4–5 representative community pulmonologists as external reviewers during the peer review process could increase the clinical usefulness of future guidelines. The ISLD-3 participants reinforced the need for unambiguous and clear statements, with a critical attention to wordsmithing, particularly for recommendations. Additionally, guideline questions need to be carefully formulated. Recommendations include varying strengths. As in many rare diseases, the evidence base for most IPF-related key clinical questions is weak, resulting in recommendations based on low quality evidence with low confidence in the effect estimates. While this is articulated in the written document, the message may not be clear to the general and broad audience. Conditional or weak recommendations may be interpreted as equipoise, allowing for flexibility depending on local expertise, preference and resources. Of note,

@ERSpublications
Evidence-based guideline development is challenging. Implementation can be suboptimal. A Delphi survey among clinical experts evaluated possibilities to improve clinical utility and implementation of IPF and other ILD guidelines. http://bit.ly/3avcOug

Cite this article as: Funke-Chambour M, Albera C, Bendstrup E, *et al*. Suggestions for improving clinical utility of future guidelines for diagnosis and management of idiopathic pulmonary fibrosis: results of a Delphi survey. *Eur Respir J* 2021; 57: 2004219 [https://doi.org/10.1183/13993003.04219-2020].

TABLE 1 Survey questions for refined guidelines

Survey questions	Survey result	Comments from individual participants
1) Should guidelines include recommendations for different levels of expertise?	Yes 48% No 42% No opinion 3% Other 7%	Guidelines might address different levels of expertise to determine to what extent a patient can be evaluated and treated from a general pulmonologist and at which point a referral to an expert centre should be considered. A two-level guideline would avoid opposing recommendations within two separate guidelines.
2) Do expert centres need recommendations to evaluate key risk/benefit issues?	Yes 65% No 23% No opinion 7% Other 5%	In general, guidelines in respiratory medicine are made to serve the general pulmonologist and the non-expert centre, but different levels of recommendation might be included and criteria for referral to an expert centre could be defined. Formulation of key risk and benefit issues might be useful to allow uniform guideline application. Adaptation of guidelines to countries where prescription and coverages of costs is only authorised by ILD experts or to other countries where it can be made by general pulmonologists needs to be considered.
3) Should recommendations be piloted in clinical practice to identify ambiguity?	Yes 77% No 10% No opinion 10% Other 3%	Guidelines need unambiguous and clear statements, with a critical importance of wordsmithing because of the potential of unintended ambiguity. Guidelines could be tested in a protected setting before implementation into clinical routine (*e.g.* routine practice by a small group of clinical teams).
4) Would concurrent Delphi exercises ensure that guidelines capture real world issues?	Yes 53% No 25% No opinion 17% Other 5%	Current challenge to develop valid guidelines is the low level of evidence but for rigid guidance a high level of evidence is required. The necessity of adherence to the standards of IOM has been discussed. A compromise might be combining GRADE system and the expert opinion approach. Routine Delphi survey in a smaller group might allow to test relevance, acceptance and application of guidelines in different countries and cultures.
5) Should key guideline discussion be made electronically and not in face-to-face discussion at major meetings?	Yes 22% No 60% No opinion 17% Other 1%	Group discussions have been conducted during major annual meetings (*e.g.* ATS and ERS). Vocal group discussions might be penalising (*e.g.* for individuals with English not being their first language, less outspoken, less comfortable in disagreeing). Electronic formulation allows time for reflection and possibility for all to pronounce their point of view. The Delphi process approach may provide opportunities for more equal contribution by participants by removing potential barriers.
6) Should guidelines include recommendations on minimum information needed by patients to ensure patient participation in decision making?	Yes 75% No 18% No opinion 7% No other	Minimal information might be provided to patients to allow informed participation in decision making. The patient should be informed whether the result of an intervention would change treatment approach and outcomes. Individual morbidity and mortality for any planned intervention would be important information for patients.
7) Should guideline membership include fair representation of experts with regard to age, race and gender?	Yes 65% No 22% No opinion 10% Other 3%	Various countries/regions and equal gender distribution of guideline committee participants should be considered and involved as they have been historically underrepresented. No opinion mainly was for the age factor, which might be in conflict with expertise increasing with experience.
8) Are routine guideline updates necessary to take aboard major new information?	Yes 93% No 5% No opinion 2% Other 1%	New published studies continuously add knowledge (*e.g.* cryobiopsy), which justify regular updates. Not updating guidelines would be a possibility if patients are sent to expert ILD centres instead.
9) Should patient involvement be more rigorous, with views obtained from patient groups?	Yes 60% No 20% No opinion 20% No other	Several guidelines committees have included patients from patient advocacy groups on guidelines committee. The way to select a representative of the majority of patients needs to be chosen.
10) Should separate diagnostic criteria for a definite diagnosis and a working diagnosis be formulated?	Yes 71% No 27% No opinion 2% No other	Integration of histopathology in lung biopsy will lead to the highest confidence in diagnosis, but risks associated with obtaining the lung biopsy or patient preferences/desires are limiting factors.

Continued

TABLE 1 Continued

Survey questions	Survey result	Comments from individual participants
		The Pulmonary Pathology Society did not affirm histopathological diagnosis as a separate confirmation of UIP. Most care givers prescribe antifibrotic therapy without requesting SLB if a provisional diagnosis or "working diagnosis" of IPF can be made with a high likelihood (>70%). A working diagnosis would help patients to receive treatment in countries where IPF diagnosis according to international guidelines is required. Diagnosis should be made following discussions by a highly experienced multidisciplinary team to increase diagnostic confidence.
11) Should the formulation "conditional recommendations" be replaced by "case by case evaluation"?	Yes 69% No 18% No opinion 7% Other 6%	"Conditional recommendation" represents a source of confusion for practitioners.
12) Should decision for SLB be taken by ILD centres?	Yes 96% No 2% No opinion 2% No other	SLB decisions should be made ideally, when possible, at ILD centres with multidisciplinary discussion. Evaluation at an expert centre before surgical biopsy is not geographically possible in some regions, but it could have been a conditional positive recommendation (with a strong recommendation made in discussion unless there are major geographical barriers).
13) Should the role for BAL for diagnosis of non-IPF be clarified?	Yes 80% No 16% No opinion 4% No other	In the latest version of the guidelines literature research limitation excluded important BAL studies. This led to a weak recommendation with diverging opinions and re-evaluation of this diagnostic tool including all existing evidence has been suggested.
14) Should recommendations for progressive-fibrosing ILD be included in IPF guidelines?	Yes 42% No 56% No opinion 2% No other	The discussion was whether IPF guidelines should include all progressive fibrosing disease or focus on IPF. Inclusion might lead to additional confusion.

Presented comments were made by individual participants and do not necessarily reflect general opinion of all ISILD-3 (3rd International ILD Summit) participants. ILD: interstitial lung disease; IOM: Institute of Medicine; ATS: American Thoracic Society; ERS: European Respiratory Society; UIP: usual interstitial pneumonia; SLB: surgical lung biopsy; IPF: idiopathic pulmonary fibrosis; BAL: bronchoalveolar lavage.

"conditional" has been replaced by "suggestion" in the new guidelines for hypersensitivity pneumonitis, and hopefully this eliminates the confusion caused by the term "conditional" in the IPF guidelines [2].

Moreover, the need to adhere to the Institute of Medicine (IOM) standards has been intensively discussed. Adherence to robust methodology reduces the inherent problem with guidelines derived from expert opinion, *i.e.* conflicts of interest, reinforcement of existing practices and exclusion of different views. However, the strength of the methodology of IOM standards may also be their weakness with regard to clinical applicability and implementation. A suggested compromise was to complement the IOM system with expert opinion drawn from clinical experience, *e.g.* the Delphi process, which helps to systematically converge expert opinions. The incorporation of the Delphi approach and testing of recommendations before implementation might increase relevance, acceptance and application of guidelines in different countries and cultures. Using the Convergence of Opinion on Recommendations and Evidence (CORE) process, a Delphi-like process yielded consensus-based recommendations that were highly concordant with recommendations for IPF diagnosis using IOM-adherent methodology [3]. Recently, the CORE process has been utilised by experts to formulate suggestions about pulmonary rehabilitation during the COVID-19 pandemic [4] and is receiving increased attention in respiratory medicine [5].

A strong call for integration of patients' desires was raised. A minimum level of information needs to be provided to ensure patient participation in decision making. The amount and type of information provided by the physician could be defined within official guidelines and might include, for example, risks for procedures and for not performing them.

Guidelines should be routinely updated to incorporate significant developments and follow a structured approach [6]. Timely integration of new data should serve to optimise and standardise the approach to diagnosis and treatment of patients with IPF and other ILDs.

Consensus was reached (⩾70% of ISILD-3 participants) on the following topics: 4) the formulation of separate diagnostic criteria for a definite diagnosis and a working diagnosis; 5) the referral of patients to ILD centres for decision on surgical lung biopsy (SLB), and 6) the need for further characterisation of the diagnostic role of bronchoalveolar lavage (BAL).

The proposal of a working diagnosis was welcomed by many of the ISILD-3 participants. Most clinicians prescribe antifibrotic therapy without requesting SLB if a provisional diagnosis or "working diagnosis" of IPF can be made with an acceptably high likelihood (>70%) [7]. Although integration of histopathology from lung biopsy will lead to the highest diagnostic confidence, the risks associated with biopsy and patient preference/desire are limiting factors. A working diagnosis helps patients to receive treatment in countries where IPF diagnosis according to international guidelines is required for drug funding. In all cases, diagnosis should be made following discussions by a highly experienced multidisciplinary team to increase diagnostic confidence.

The ISILD-3 participants suggested referral of patients to ILD centres for decision on SLB where cases can be reviewed *via* multidisciplinary discussion. Evaluation at an expert centre before SLB is not feasible in some regions, but the working group considered multidisciplinary discussion prior to SLB an important component of clinical care. Alternative ways, *e.g.* virtual counselling or discussion (eMDD), as currently tested in ongoing studies [8], may provide future possibilities for expert centre evaluation.

The need for further clarification of the diagnostic role of BAL was emphasised. In the latest version of the IPF guidelines, literature research excluded important BAL studies. This led to a weak recommendation with diverging opinions; re-evaluation of this diagnostic tool including all existing evidence has been suggested. Meanwhile, two recent systematic reviews found that, for example, BAL lymphocyte percentage is increased in hypersensitivity pneumonitis compared to IPF and sarcoidosis, although an optimal diagnostic threshold could not be identified [9, 10]. Prospective studies to standardise the role of BAL in ILD diagnosis are needed.

The limitation of this statement relates to the bias of experts who attended ISILD-3, with predominantly European and 12% North American representatives. This document constitutes a perspective of these clinical experts and do not reflect the standpoint of other groups involved in guideline development, such as methodologists.

We hope that discussions arising from ISILD-3 will inspire future clinical practice guideline developers to establish recommendations that are easy to interpret and implement, and have a meaningful impact for our patients with IPF or other ILDs.

Manuela Funke-Chambour[1], Carlo Albera[2], Elisabeth Bendstrup[3], Ulrich Costabel[4], Jan C. Grutters[5], Sergio Harari[6], Kerri A. Johannson[7], Michael Kreuter[8], Irina Strambu[9], Carlo Vancheri[10], Francesco Varone[11], Patrizio Vitulo[12], Wim A. Wuyts[13], Fernando Martinez[14,16] and Ganesh Raghu[15,16], on behalf of Erice participants

[1]Dept of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [2]Dipartimento di Scienze Mediche, Università di Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza – Molinette, Turin, Italy. [3]Dept of Respiratory Diseases and Allergology, Aarhus University Hospital, Aarhus, Denmark. [4]Center for Interstitial and Rare Lung Diseases, Ruhrlandklinik, University Hospital Essen, Essen, Germany. [5]ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, The Netherlands. [6]University of Milan, Dept of Medicine, Division of Internal Medicine, Division of Pulmonary Disease, Ospedale San Giuseppe MultiMedica IRCCS, Milan, Italy. [7]University of Calgary, South Health Campus, Calgary, AB, Canada. [8]Center for Interstitial and Rare Lung Diseases, Thoraxklinik – University Hospital Heidelberg, German Center for Lung Research, Heidelberg, Germany. [9]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania. [10]AOU "Policlinico Vittorio Emanuele", Catania, Italy. [11]Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy. [12]IRCCS ISMETT, Palermo, Italy. [13]Unit for Interstitial Lung Diseases, Dept of Respiratory Medicine, University Hospitals Leuven, Leuven, Belgium. [14]Weill Cornell Medicine Pulmonary and Critical Care Medicine, New York, NY, USA. [15]Center for Interstitial Lung diseases, Depts of Medicine; Laboratory Medicine and Pathology (adjunct), University of Washington, Seattle, WA, USA. [16]Co-senior authors.

Correspondence: Manuela Funke-Chambour, Inselspital, Pulmonology, Bern University Hospital, University of Bern, Bern 3010, Switzerland. E-mail: manuela.funke-chambour@insel.ch

Received: 16 July 2020 | Accepted: 9 Dec 2020

The Erice participants: Carlo Albera (Italy), Goksel Altinisik (Turkey), Kjetil Ask (Canada), Elisabetta Balestro (Italy), Elena Bargagli (Italy), Elisabeth Bendstrup (Denmark), Marialuisa Bocchino (Italy), Francesco Bonella (Germany), Martina Bonifazi (Italy), Giulia Cacopardo (Italy), Maria Rosaria Calvello (Italy), Diego Miguel Castillo Villegas (Spain), Ulrich Costabel (Germany), Vincent Cottin (France), Bruno Crestani (France), Manuela Funke-Chambour (Switzerland), Jack Gauldie (Canada), Peter George (UK), Jan C. Grutters (the Netherlands), Sergio Harari (Italy), Gisli Jenkins (UK), Keri Johannson (Canada), Mark Glynne Jones (UK), Nicolas Carlos Kahn (Germany), Meena Kalluri (Canada), Michael Keane (Ireland), Maria Kokosi (UK), Michael Kreuter (Germany), Donato Lacedonia (Italy), Brett James Ley (USA), Marlies Sandra Lourens Wijsenbeek (the Netherlands), Fabrizio Luppi (Italy), Toby Michael Maher (UK), Georgios Margaritopoulos (UK), Fernando Martinez (USA), Jellerindert Miedema (the Netherlands), Nesrin Mogulkoc Bishop (Turkey), Maria Molina Molina (Spain), Philip Molyneaux (UK), Julie Morisset (Canada), Stefano Palmucci (Italy), Mauro Pavone (Italy), Ganesh Raghu (USA),

Elisabetta Renzoni (UK), Luca Richeldi (Italy), Alfredo Sebastiani (Italy), Jacopo Simonetti (Italy), Paolo Spagnolo (Italy), Giulia Maria Stella (Italy), Martina Sterclova (Czech Republic), Irina Strambu (Romania), Sara Tomassetti (Italy), Nazia Chaudhuri Toner (UK), Sebastiano Emanuele Torrisi (Italy), Elisavet Tsitoura (Greece), Haluksaban Turktas (Turkey), Argyrios Tzouvelekis (Greece), Claudia Valenzuela (Spain), Ada Vancheri (Italy), Carlo Vancheri (Italy), Francesco Varone (Italy), Patrizio Vitulo (Italy), Athol Wells (UK) and Wim Wuyts (Belgium).

Conflict of interest: M. Funke-Chambour reports grants from Roche, grants and personal fees for advisory board work from Boehringer Ingelheim, outside the submitted work. C. Albera reports personal fees for advisory board work, consultancy and steering committee work from Roche, MSD and Bayer, personal fees for advisory board work and consultancy from Boheringer Ingelheim, Fibrogen and GSK, grants from Roche and Boheringer Ingelheim, during the conduct of the study. E. Bendstrup reports grants, personal fees and non-financial support from Boehringer Ingelheim and Hoffmann la Roche, outside the submitted work. U. Costabel reports personal fees for consultancy and lectures, and non-financial support from Boehringer and Roche, personal fees for consultancy from Fibrogen, Pliant Therapeutics and Bristol-Myers Squibb, personal fees for lectures from AstraZeneca and Novartis, outside the submitted work. J.C. Grutters has nothing to disclose. S. Harari reports personal fees for lectures and advisory board work from Roche, grants and personal fees for lectures and advisory board work from Actelion and Boehringer Ingelheim, outside the submitted work. K.A. Johannson reports personal fees, non-financial support and other (advisory board work) from Boehringer Ingelheim, personal fees from Hoffman-La Roche Ltd, Blade Therapeutics and Theravance, grants from The Chest Foundation, University of Calgary Cumming School of Medicine, UCB Biopharma SPRL and Pulmonary Fibrosis Society of Calgary, personal fees and non-financial support from Three Lakes Foundation, outside the submitted work. M. Kreuter reports grants and personal fees from Boehringer Ingelheim and Roche, personal fees from Galapagos, outside the submitted work. I. Strambu reports personal fees for advisory board work and lectures from Boehringer Ingelheim, personal fees for lectures from Roche Pharma, AstraZeneca and Novartis, personal fees for investigation work from Galapagos, outside the submitted work. C. Vancheri reports grants and personal fees from Roche and Boehringer Ingelheim, outside the submitted work. F. Varone reports personal fees from Boehringer Ingelheim and Roche, outside the submitted work. P. Vitulo has nothing to disclose. W.A. Wuyts reports grants from Roche and Boehringer Ingelheim, outside the submitted work (paid to institution). F. Martinez reports personal fees for advisory board work, non-financial support for travel and other from AstraZeneca, other (steering committee work and publication) from Afferent/Merck, personal fees for advisory board work, data monitoring committee work, steering committee work and lectures, non-financial support for travel and other (publication) from Boehringer Ingelheim, other (teleconference without compensation) from Bristol Myers Squibb and twoXR, other (travel support) from Chiesi, personal fees for lectures and non-financial support for travel from Canadian Respiratory Society, CME Outfitters, Inova Fairfax, MDMagazine, NYP Methodist Hospital Brooklyn, Miller Communications, National Association for Continuing Education, Novartis, Peer View, Rare Diseases Healthcare Communications and WebMD/MedScape, personal fees for advisory board work and non-financial support for travel from CSL Behring, Sanofi/Regeneron, University of Birmingham Alabama, Sunovion and Teva, personal fees for lectures from Dartmouth University, France Foundation, New York University, Rockpointe Communications and Vindico, personal fees for advisory board work from Gala, Pearl and Verona, personal fees for data monitoring committee and advisory board work, and non-financial support for travel from Genentech, grants, personal fees for advisory board, data monitoring committee and steering committee work, and non-financial support for travel from GlaxoSmithKline, other (steering committee without compensation) from Nitto, personal fees for steering committee work and non-financial support for travel from Patara/Respivant, personal fees for educational activities from Physicians Education Resource and UpToDate, personal fees for steering committee work from ProMedior, other (data monitoring and steering committee without compensation) from Biogen, non-financial support (steering committee) from Veracyte, non-financial support for travel and in-kind study support from Zambon, non-financial support (consultancy and in-kind study support) from ProTerrix Bio, personal fees for consultancy from IQVIA, Raziel and Abvie, outside the submitted work. G. Raghu reports personal fees and other (consultancy) from Boerhinger Ingelheim, Roche, Respivant and Veracyte, other (consultancy and data monitoring committee work) from Avalyn, other (consultancy) from BMS, Biogen, Blade Therapeutics, Bellerophan, Fibrogen, Gilead, Genentech, Nitto and Promedior, and grants from NIH, outside the submitted work.

References

1 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis: an Official ATS/ERS/JRS/ALAT Clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
2 Raghu G, Wilson KC, Bargagli E, *et al.* Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.
3 Wilson KC, Schoenberg NC, Raghu G. Idiopathic pulmonary fibrosis guideline recommendations need for adherence to institute of medicine methodology? *Ann Am Thorac Soc* 2019; 16: 681–686.
4 Spruit MA, Holland AE, Singh SJ, *et al.* COVID-19: Interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated international task force. *Eur Respir J* 2020; 56: 2002197.
5 Wilson KC. Consensus-based recommendations in respiratory medicine. *Eur Respir J* 2020; 56: 200288.
6 Vernooij RWM, Alonso-Coello P, Brouwers M, *et al.* Reporting items for updated clinical guidelines: Checklist for the Reporting of Updated Guidelines (CheckUp). *PLoS Med* 2017; 14: e1002207.
7 Walsh SLF, Lederer DJ, Ryerson CJ, *et al.* Diagnostic likelihood thresholds that define a working diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; 200: 1146–1153.
8 Wijsenbeek M, Bendstrup E, Valenzuela C, *et al.* Design of a Study Assessing Disease Behaviour During the Peri-Diagnostic Period in Patients with Interstitial Lung Disease: The STARLINER Study. *Adv Ther* 2019; 36: 232–243.
9 Patolia S, Tamae Kakazu M, Chami H, *et al.* Bronchoalveolar lavage lymphocytes in the diagnosis of hypersensitivity pneumonitis among patients with interstitial lung disease: a systematic review. *Ann Am Thorac Soc* 2020; 17: 1455–1467.
10 Adderley N, Humphreys CJ, Barnes H, *et al.* Bronchoalveolar lavage fluid lymphocytosis in chronic hypersensitivity pneumonitis: A systematic review and meta-analysis. *Eur Respir J* 2020; 56: 2000206.