



This is a repository copy of *Granulomatous–lymphocytic interstitial lung disease : an international research prioritisation.*

White Rose Research Online URL for this paper:  
<https://eprints.whiterose.ac.uk/183312/>

Version: Published Version

---

**Article:**

Hurst, J.R., Abbas, S.H., Bintalib, H.M. et al. (27 more authors) (2021) Granulomatous–lymphocytic interstitial lung disease : an international research prioritisation. *ERJ Open Research*, 7 (4). 00467-2021.

<https://doi.org/10.1183/23120541.00467-2021>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial (CC BY-NC) licence. This licence allows you to remix, tweak, and build upon this work non-commercially, and any new works must also acknowledge the authors and be non-commercial. You don't have to license any derivative works on the same terms. More information and the full terms of the licence here:  
<https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>



# Granulomatous–lymphocytic interstitial lung disease: an international research prioritisation

Copyright ©The authors 2021

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact [permissions@ersnet.org](mailto:permissions@ersnet.org)

Received: 15 July 2021  
Accepted: 18 Sept 2021

To the Editor:

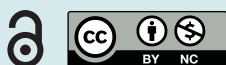
Granulomatous–lymphocytic interstitial lung disease (GLILD) has been defined as “a distinct clinico-radio-pathological ILD [interstitial lung disease] occurring in patients with CVID [common variable immunodeficiency disorders], associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded... usually seen in the context of multisystem granulomatous/inflammatory involvement” [1]. The immune and inflammatory complications of CVID such as GLILD are important and associated with reduced survival [2]. However, as a rare manifestation of a rare disease, the scientific understanding and evidence basis to inform effective diagnosis and management of GLILD [3] are limited. There are challenges with the definition of GLILD presented above and the terminology more widely of ILD in people with CVID, which requires further consensus. In this manuscript, we use the term GLILD to describe the heterogeneous ILD seen as part of multisystem immune dysregulation in a substantial minority of people with CVID. A recent international survey of clinicians found little uniformity in diagnostic and therapeutic interventions, identifying an urgent need for new evidence to support consensus guidance [4]. In 2019, the European Respiratory Society (ERS) established a Clinical Research Collaboration to address GLILD (eGLILDnet) [5]. eGLILDnet aims to promote the exchange of research ideas among clinicians and scientists in order to plan, conduct, evaluate and publish clinical and translational studies. Better evidence to diagnose and manage GLILD requires new multicentre research and to this end, we have conducted and here report the results of an international research prioritisation exercise in GLILD. This was a partnership between multiprofessional clinicians and people living with GLILD.

This research prioritisation exercise was based on methodology developed by the James Lind Alliance (JLA) but was not an official JLA process and did not include the final workshop stage (the final ranking was based on voting as described further below). We created an online survey using SurveyMonkey in nine European languages, open between 12 August and 14 September 2020. Dissemination of the survey was assisted by the ERS, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) and the European Society for Immunodeficiencies (ESID). Clinicians were invited to provide the link to patients. The survey asked participants what questions they had about the diagnosis, treatment, follow-up and scientific understanding of GLILD. All responses were translated into English for processing.

Each individual response was separated (participants were allowed to submit more than one response in each category), given a unique number and grouped into six broad categories: diagnosis, treatment, follow-up, scientific understanding of GLILD, other aspects on GLILD and responses that were out of scope.

Next, within each category, questions and statements were grouped into themes, and a short summary was developed. The narrative summary was used to develop specific overarching questions and recommendations for development of consensus resources. Members of the eGLILDnet Steering Committee reviewed the responses and confirmed that all the original comments had been captured.

This process generated a list of seven suggestions for resource development and 27 research questions. From our knowledge of the literature, including a recent systematic review [3], none of the 27 questions had already been adequately addressed and, therefore, all 27 questions went forward to the final prioritisation.



Shareable abstract (@ERSpublications)

**The first ever research prioritisation exercise in GLILD: this survey identified areas of interest in the diagnosis, treatment and management of GLILD, which can be used as a roadmap for future research** <https://bit.ly/3nVuzti>

**Cite this article as:** Hurst JR, Abbas SH, Bantalib HM, *et al.* Granulomatous–lymphocytic interstitial lung disease: an international research prioritisation. *ERJ Open Res* 2021; 7: 00467-2021 [DOI: 10.1183/23120541.00467-2021].

In this final stage, respondents could vote for  $\leq 10$  of the 27 questions they most preferred to see answered. The questions were provided in both lay and technical language, again using SurveyMonkey. The survey was available in Dutch, English, German, Italian and Spanish (the surveys from the first round that generated the most frequent responses). Dissemination of the final survey was facilitated by ERS, ESID and IPOPI, together with a direct e-mail to respondents who had left contact details in the initial survey. The survey was open between 1 December 2020 and 20 January 2021. At closure, each question was ranked separately by the number of votes it received from 1) patients and carers, and 2) clinicians. A final joint list, with equal weight given to clinician and patients responses, was created by taking the average of the two ranks and ordering these.

In total, 252 people from 48 countries registered on the survey. 135 people from 33 countries left one or more questions or statements (the other 117 just left contact details). Of those leaving responses, 77 (57%) were female, 55 (41%) were male and the remainder did not respond or preferred not to say. 89 (66%) were aged 30–49 years and 39 (29%) were 50–69 years old, with fewer younger, older or preferring not to say. 23 (17%) were people affected by GLILD or carers, 41 (30%) were immunology physicians, 51 (38%) were respiratory physicians and four (3%) were allied health professionals. The five commonest countries were the UK (n=24), Spain (n=19), Germany (n=12), the Netherlands (n=12) and Italy (n=11), together accounting for 58% of respondents. There were 699 individual responses made, originally submitted in the Diagnosis (n=169), Treatment (n=187), Management (n=144), Science (n=128) and Other categories (n=70).

The 699 responses could be summarised as seven areas for resource development and 27 research questions that went forward to voting. The areas for resource development included suggestions to develop consensus diagnostic criteria for GLILD; consensus protocols for adults and children with GLILD that cover screening, diagnosis, treatment and follow-up; and to develop educational resources for patients and multiprofessional clinicians to help raise awareness of GLILD. There was also the suggestion to review the terminology of GLILD and ILD occurring in COVID.

Of the 269 people voting in the research prioritisation stage, 114 (42%) were female, 154 (57%) were male and the remaining participant left the question blank. 145 (54%) were aged 30–49 years and 101 (37%) were 50–69 years old, with fewer younger, older or preferring not to say. 47 (17%) were people affected by GLILD or carers, and 222 (83%) were clinicians: 53 (24% of clinicians) primarily worked in immunology whilst 169 (76% of clinicians) primarily worked in respiratory or internal medicine specialties. The five commonest countries were Italy (n=34), the UK (n=28), Spain (n=23), the Netherlands (n=12) and Switzerland (n=11), together accounting for 39% of respondents.

The results of the research prioritisation are reported in table 1, ordered by overall rank but also indicating rank by patients and clinicians separately. The number of votes cast for questions varied between 36 and 177. Because of the relative preponderance of respiratory clinicians over immunologists, we also analysed the data by first giving equal weight to respiratory and immunology preferences in the clinician group, then combining this with the patient rank. This analysis did not affect the top eight ranks (data not shown).

We have conducted and report the first ever research prioritisation exercise in GLILD. Importantly, our results give equal weight to the voice of clinicians and those affected by GLILD.

The three top ranked questions, addressing the role of corticosteroids and alternative regimens as first-line treatment in GLILD, would best be answered by a randomised trial of watchful waiting *versus* intervention in newly diagnosed patients with GLILD, with intervention randomised to corticosteroids or an alternative regime, and with weaning according to a pre-defined protocol. The eGLILDnet consortium will now work towards designing and conducting such a study. It is notable that questions directly affecting treatment decisions were prioritised over diagnostic and basic research. However, since all our questions received votes, all of these areas may still be considered relevant for further research.

In addition to prioritising research questions, the process generated seven areas for resource and/or consensus development. These included the need to revisit the definition and diagnostic criteria for ILD in COVID in general (and GLILD in particular), and tools to support research (such as standardised radiology reporting and a database), clinical practice (including diagnostic criteria and protocols for both adults and children), and educational resources for patients and clinicians. The eGLILDnet collaboration will work with partners to address these.

The strengths of our approach were the wide international engagement, and a prioritisation process giving equal weight in the final prioritisation list to patients and clinicians.

TABLE 1 Top research priorities with equal weight given to patient and clinician preferences, and separately for patients and clinicians

Overall rank	Patient rank	Clinician rank	Priority
1	1	1	Do corticosteroids or an alternative agent have the best risk–benefit to induce remission in adults with GLILD?
2	2	4	Do corticosteroids or an alternative agent have the best risk–benefit to maintain remission in GLILD?
3	6	2	In newly diagnosed GLILD, is first-line treatment superior to watchful waiting?
4	4	5	Are there specific risk factors in CVID for developing GLILD?
5	3	8	What is the optimal screening approach to detect incident cases of GLILD in people with CVID?
6	9	6	Are there specific pathological endotypes of GLILD with different natural history and treatment responses?
7	13	3	What is the value of a lung biopsy in the work-up of a patient with suspected GLILD?
8	7	11	What is the value of antifibrotic drugs such as pirfenidone and nintedanib in treating GLILD?
=9	9	14	Are there specific genetic endotypes of GLILD with different natural history and treatment response?
=9	11	12	Develop a discovery biomarker programme on blood and BAL to assist diagnosis and management of GLILD.
11	4	20	What is the benefit of a higher <i>versus</i> lower trough immunoglobulin replacement target in GLILD?
12	11	15	What is the value of CT-PET in the work-up of a patient with suspected GLILD?
13	8	19	Is GLILD a pathogen-driven local manifestation of a systemic immune dysregulation?
=14	15	18	Is immunosuppression for GLILD associated with increased risk of infection?
=14	26	7	What is the value of BAL in the work-up of a patient with suspected GLILD?
16	18	16	What is the value of blood or other biomarkers in the work-up of a patient with suspected GLILD?
17	25	10	Do higher or lower dose corticosteroids have the best risk–benefit to induce remission in GLILD?
=18	13	23	What is the role of B-cells in the pathogenesis of GLILD?
=18	15	21	Is GLILD an intrinsic dysregulation of the adaptive immune system?
=18	20	16	What is the optimal first-line treatment of GLILD in children?
=18	23	13	Which type of lung biopsy has the most favourable risk–benefit?
=18	27	9	What is the value of blood or other biomarkers in assessing disease activity?
23	15	24	What is the value of bone-marrow transplantation in the treatment of GLILD?
=24	18	27	Which epigenetic modifiers contribute to the manifestation of GLILD?
=24	20	25	What is the value of thoracic MRI in the work-up of a patient with suspected GLILD?
=24	23	22	What is the outcome of lung transplantation for GLILD?
27	20	26	Develop a health-status questionnaire to assess burden in GLILD

GLILD: granulocytic–lymphocytic interstitial lung disease; CVID: common variable immunodeficiency disorders; BAL: bronchoalveolar lavage; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance imaging.

Limitations include the potential loss of nuance when summarising the original 699 statements, although the process was overseen by the eGLILDnet Steering Committee. To prevent loss of detailed remarks, the anonymised responses to all questions are available for interested researchers on request to the steering committee. It is notable that for some questions, there was significant disparity between patient and clinician preferences (with clinicians ranking questions around diagnostic investigations higher). We used a modified version of the JLA methodology, without the final workshop, and other methods of research prioritisation are available [6].

It is now up to the clinical and research community, working with patients, funders and the pharmaceutical industry, to develop studies to address these questions and improve the care and lives of those living with GLILD.

John R. Hurst <sup>1</sup>, S. Hamza Abbas<sup>1</sup>, Heba M. Bantalib <sup>1</sup>, Tiago M. Alfaro <sup>2</sup>, Ulrich Baumann<sup>3</sup>, Siobhan O. Burns<sup>4,5</sup>, Alison Condliffe<sup>6</sup>, Jesper R. Davidsen <sup>7</sup>, Børre Fevang<sup>8,9</sup>, Andrew R. Genney<sup>10,11</sup>, Filomeen Haerynck<sup>12</sup>, Joseph Jacob <sup>1,13</sup>, Stephen Jolles<sup>14</sup>, Olivia Lamers<sup>15</sup>, Anne Bergeron<sup>16</sup>, Marion Malphettes<sup>17</sup>, Véronique Meignin<sup>18</sup>, Cinzia Milito<sup>19</sup>, Tomas Milota<sup>20,21</sup>, Martine Pergent<sup>22</sup>, Antje Prasse <sup>23,24,25</sup>, Isabella Quinti<sup>19</sup>, Elisabetta Renzoni<sup>26</sup>, Anna Sediva<sup>20,21</sup>, Daiana Stolz<sup>27</sup>, Bas Smits<sup>28</sup>, Friedolin Strauss<sup>29</sup>, Annick A.J.M. van de Ven<sup>30,31</sup>, Joris van Montfrans<sup>30,31</sup> and Klaus Warnatz<sup>32,33</sup>

<sup>1</sup>UCL Respiratory, University College London, London, UK. <sup>2</sup>Unit of Pneumology, Coimbra Hospital and University Centre, Coimbra, Portugal. <sup>3</sup>Paediatric Pulmonology, Allergy and Neonatology, Hanover Medical School, Hannover, Germany. <sup>4</sup>Institute of Immunity and Transplantation, University College

London, London, UK. <sup>5</sup>Dept of Immunology, Royal Free London NHS Foundation Trust, London, UK. <sup>6</sup>Dept of Infection, Immunity and Cardiovascular Diseases, University of Sheffield, Sheffield, UK. <sup>7</sup>South Danish Centre for Interstitial Lung Diseases (SCILS), Dept of Respiratory Medicine, Odense University Hospital, Odense, Denmark. <sup>8</sup>Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Oslo, Norway. <sup>9</sup>Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway. <sup>10</sup>Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK. <sup>11</sup>Paediatric Immunology, Great North Children's Hospital, Newcastle upon Tyne, UK. <sup>12</sup>Dept of Pediatric Pulmonology and Immunology, Jeffrey Modell Foundation Diagnostic and Research Centre, PID Research lab, Ghent University Hospital, Ghent University, Ghent, Belgium. <sup>13</sup>Centre for Medical Image Computing, University College London, London, UK. <sup>14</sup>Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK. <sup>15</sup>Dept of Parasitology, Leiden University Medical Center, Leiden, The Netherlands. <sup>16</sup>Université de Paris, Hôpital Saint-Louis, AP-HP, Pulmonology Dept, Paris, France. <sup>17</sup>Immunology Dept, Inserm U1126, Hôpital Saint-Louis, APHP, Paris, France. <sup>18</sup>Dept of Pathology, Hôpital Saint-Louis, APHP, Paris, France. <sup>19</sup>Dept of Molecular Medicine, Sapienza University of Rome, Rome, Italy. <sup>20</sup>Second Faculty of Medicine, Charles University, Prague, Czech Republic. <sup>21</sup>Motol University Hospital, Prague, Czech Republic. <sup>22</sup>International Patient Organisation for Primary Immunodeficiencies, Brussels, Belgium. <sup>23</sup>Dept of Pulmonology, Hannover Medical School, Hannover, Germany. <sup>24</sup>DZL BREATH, Hannover, Germany. <sup>25</sup>Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany. <sup>26</sup>Interstitial Lung Disease Unit, Royal Brompton Hospital/Imperial College London, London, UK. <sup>27</sup>University Hospital Basel, Clinic of Respiratory Medicine and Pulmonary Cell Research, Basel, Switzerland. <sup>28</sup>Dept of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, The Netherlands. <sup>29</sup>dsai e.V. Patientenorganisation fuer angeborene Immundefekte, Schnaitsee, Germany. <sup>30</sup>Dept of Internal Medicine and Allergology, University Medical Centre Groningen, Groningen, The Netherlands. <sup>31</sup>Dept of Rheumatology and Clinical Immunology, University Medical Centre Groningen, Groningen, The Netherlands. <sup>32</sup>Dept of Rheumatology and Clinical Immunology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. <sup>33</sup>Center for Chronic Immunodeficiency, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany.

Corresponding author: Heba Bantalib ([heba.bantalib.20@ucl.ac.uk](mailto:heba.bantalib.20@ucl.ac.uk))

Provenance: Submitted article, peer reviewed.

Acknowledgements: We thank all those who took part in the survey, and staff at the European Respiratory Society, the European Society for Immunodeficiencies and the International Patient Organisation for Primary Immunodeficiencies for their help and support in disseminating the surveys.

Conflict of interest: J.R. Hurst reports grants, personal fees and nonfinancial support from pharmaceutical companies that make medicines to treat respiratory and immunological diseases outside the submitted work. S.M. Abbas has nothing to disclose. H.M. Bantalib has nothing to disclose. T.M. Alfaro has nothing to disclose. U. Baumann has nothing to disclose. S.O. Burns reports personal fees from CSL Behring, Baxalta US Inc., Biotest, the European Union, the National Institute of Health Research, UCLH and GOSH/Institute of Child Health Biomedical Research Centers, and CSL Behring, outside the submitted work. A. Condliffe has nothing to disclose. J.R. Davidsen has nothing to disclose. B. Fevang has nothing to disclose. A.R. Gennery has nothing to disclose. F. Haerynck has nothing to disclose. J. Jacob reports personal fees from Boehringer Ingelheim, Roche and GlaxoSmithKline, outside the submitted work. S. Jolles has nothing to disclose. O. Lamers has nothing to disclose. A. Bergeron reports grants from SOS Oxygene, personal fees from Takeda, and personal fees from AstraZeneca, Pfizer, MSD, Gilead and Enanta, outside the submitted work. M. Malphettes has nothing to disclose. V. Meignin has nothing to disclose. C. Milito has nothing to disclose. T. Milota has nothing to disclose. M. Pergent has nothing to disclose. A. Prasse reports personal fees from Boehringer Ingelheim, Roche, Novartis, Chiesi, Pliant and AstraZeneca outside the submitted work. I. Quinti has nothing to disclose. E. Renzoni reports grants from Boehringer Ingelheim, and lecture fees from Boehringer Ingelheim and Roche, outside the submitted work. A. Sediva has nothing to disclose. D. Stolz reports grants from AstraZeneca AG, Curetis AG and Boston Scientific, and payment for lectures and/or advisory boards from AstraZeneca AG, Novartis AG, GSK AG, Roche AG, Zambon, Pfizer, Schwabe Pharma AG, Vifor AG, Chiesi AG and MSD, outside the submitted work. B. Smits has nothing to disclose. F. Strauss has nothing to disclose. A.A.J.M. van de Ven has nothing to disclose. J. van Montfrans reports having participated in an advisory board for Takeda during the conduct of the study. K. Warnatz reports grants from Bristol Myers Squibb outside the submitted work.

Support statement: This study was supported by the European Respiratory Society. Funding information for this article has been deposited with the Crossref Funder Registry.

### References

- 1 Hurst JR, Verma N, Lowe D, *et al.* British Lung Foundation/United Kingdom primary immunodeficiency network consensus statement on the definition, diagnosis, and management of granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract* 2017; 5: 938–945.
- 2 Resnick ES, Moshier EL, Godbold JH, *et al.* Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012; 119: 1650–1657.
- 3 Lamers OAC, Smits BM, Leavis HL, *et al.* Treatment strategies for GLILD in common variable immunodeficiency: a systematic review. *Front Immunol* 2021; 12: 606099.
- 4 van de Ven AAJM, Alfaro TM, Robinson A, *et al.* Managing granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency disorders: e-GLILDnet international clinicians survey. *Front Immunol* 2020; 11: 606333.
- 5 Hurst JR, Warnatz K, ERS eGLILDnet Clinical Research Collaboration. Interstitial lung disease in primary immunodeficiency: towards a brighter future. *Eur Respir J* 2020; 55: 2000089.
- 6 Nyanchoka L, Tudur-Smith C, Thu VN, *et al.* A scoping review describes methods used to identify, prioritize and display gaps in health research. *J Clin Epidemiol* 2019; 109: 99–110.