James Lind Alliance refreshed top 10 CF research priorities: A summary of the topics raised in the underlying questions

This document has been produced to give an accessible summary of the topics raised in the underlying questions in the JLA refreshed CF research priorities announced in 2022.

We strongly recommend review of the full list of the underlying questions for more information. This is available on the CF research priority refresh page of James Lind Alliance website.

Background

In November 2022 a refreshed top 10 of CF research priorities was announced. These were identified in a partnership between Cystic Fibrosis Trust, University of Nottingham and the CF community, and facilitated by the James Lind Alliance (JLA) team at the National Institute of Health and Care Research (NIHR).

Information on the process to refresh the CF research priorities first identified a JLA Priority Setting Partnership (PSP) in 2017 is available on the project website (questioncf.org), the JLA website and Cystic Fibrosis Trust website.

A part of this process was to group together related, 'underlying' questions into 'umbrella' questions that were voted on to identify the top 10 refreshed research priorities. (The wording of the underlying questions are as submitted by participants to the project surveys).

Summary of the topics raised in the top 10 JLA refreshed CF research priorities

Q1 What options are available for those not able to take current CFTR modulators (including rarer mutations, not eligible and unable to tolerate)?

Topics included in the underlying questions:

Approximately 10% of people with CF are unable to benefit from CFTR modulator medicines. The topics included: 1) Extending the use of CFTR modulators for other mutations or for those with limited response; 2) New CFTR medicines for the 10%; 3) Alternative ion channel medicines, support for people unable to access modulators, and 4) Accelerating the process for new medicines. Respondents also commented on groups that might benefit from this research, including those: unable to access the medicines or unable to tolerate them; ineligible due to genotype, explicitly mentioning those with class 1 / nonsense mutations; and ineligible for other reasons eg pregnant or post-transplant.

Previous PSP[1]? New question
Proportion of underlying questions from lay respondents[2]: 63%
CF priority refresh ID[3]: C2

1 In the first survey of the priority refresh project, participants were asked to review the top 20 CF research priorities identified in 2017, and were also invited to submit new questions.
2 People from the CF community and CF professionals were invited to participate and information on interests in each question are included.
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Q2 What is the best way to diagnose lung infection when there is no sputum eg children and those on modulators?

Topics included in the underlying questions:

Traditionally, sputum samples have been used to diagnose the type of organism present in lung infections. However, as lung health improves with modulators and in young children, there is little or no sputum produced. The topics included: 1) How to detect and monitor infections: without sputum, alternatives to cough swab, using remote monitoring; 2) How to obtain sputum;3) Preventing and monitoring colonisation of bugs; 4) best way of interpreting the microbiome, and 5) What does it mean if culture/cough swabs show the absence of infection. The groups of people explicitly mentioned include people with milder disease, adults and children on Kaftrio, and babies and children – the latter specifically relating to alternatives to cough swabs.

Previous PSP[1]? - New question
Proportion of underlying questions from lay respondents2: 38%
CF priority refresh ID[3]: R3

Q3 How can we relieve gastro-intestinal (GI) symptoms, such as stomach pain, bloating and nausea?

Topics included in the underlying questions:

Gastro-intestinal (GI) symptoms of CF can range from bloating and stomach cramps to intestinal blockages. They can prevent people with CF getting the calories they need, be extremely painful, embarrassing and disrupt day to day life. The topics included: 1) What causes GI symptoms such as constipation, diarrhoea, wind and stomach upsets, 2) How do food and Creon interact and how to prevent problems with digestion; 3) How to manage long term GI issues and GI co-morbidities (eg colorectal cancer, celiac disease, IBD, SIBO, etc); 4) How to fix CF bloating (including comments on its effects on mental wellbeing and body confidence), and 5) How to accelerate research.

Previous PSP[1]? Number 2 in previous top 20
Proportion of underlying questions from lay respondents[2]: 89%
CF priority refresh ID[3]: GI5

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Q4 How do we manage an ageing population with CF?

Topics included in the underlying questions.

As people with CF are now living longer, questions about the impact of age on CF and risks of developing age-related conditions were mentioned. The topics included: 1) What causes cardiovascular disease (where stroke was mentioned specifically) and what were the risks of developing them, particularly for people taking Kaftrio; 2) Distinguishing between CF symptoms vs symptoms of getting older; 3) Effects of CF and CF related co-morbidities as people get older; 4) Effects of getting older on CF and CF related co-morbidities; 5) Managing CF physiotherapy with increasing age, and 6) Revised expectations of living longer on health, support and education.

Previous PSP[1]? Number 16 in previous top 20
Proportion of underlying questions from lay respondents[2]: 69%
CF Priority refresh ID[3]: Ag1

Q5 Is there a way of reducing the negative effects of antibiotics eg resistance risk and adverse symptoms in people with CF?

Topics included in the underlying questions:

People with CF are susceptible to developing lung infections requiring anti-infective medicines, including antibiotics. These medicines often carry risks of side effects, and antimicrobial resistance (AMR) has developed against some of them. The topics included: 1) How to reduce AMR, for those taking (antibiotics) for many years and when there are a lack of new medicines available and 2) Understanding how, why and how much (dosage) antibiotics are prescribed and the side effects they cause.

Previous PSP[1]? Number 9 in previous top 20
Proportion of underlying questions from lay respondents[2]: 100%
CF priority refresh ID[3]: I6

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Q6 What are the long term effects of medications in CF (including CFTR modulators)?

Topics in the underlying questions:

Most of the medicines taken in CF are long term therapies, this includes the new CFTR modulator drugs as well as traditional treatments such as long term antibiotics, mucolytic therapies and aids to digestion. The topics included: 1) What are / are there any long term effects of CFTR modulators ('all of them, not just Kaftrio'), where some specifically mentioned side effects, and 2) What are their (CFTR modulators) effects on body composition in the long term.

Previous PSP[1]?: This question was two questions merged "What are the long-term effects of medications for CF?" (C1) and "What are the long-term effects of CFTR modulators?" (TT17)*. C1 was included in the original PSP top 20 at number 19. TT17 is a new question. All of the underlying questions relate to TT17, as no new underlying questions were asked on C1 in the priority refresh project.

Proportion of underlying questions from lay respondents[2]: 56%
CF priority refresh ID[3]: C1 / TT17* (This question is a merge of two questions)

Q7 What are the effects of modulators on systems outside the lungs such as pancreatic function, liver disease, gastrointestinal system, bone density etc?

Topics included in the underlying questions:

The main focus of the effectiveness of CFTR modulators is on the lungs as this is the main cause of morbidity and mortality for people with CF. CF also affects many different parts of the body outside of the lungs and there was interest in how CFTR modulators affect these. The tissues/organs/body systems raised in the underlying questions include: 1) Gut: alteration of mucus flow, effects of CFTR modulators (with children explicitly referenced); 2) Pancreas: effects of modulators on pancreas, on both exocrine (digestive-juicing producing) and endocrine (hormone producing) functions; 3) Bone: impact of CFTR modulators and whether any changes are reversible; 4) Liver: impact of CFTR modulators on development of liver disease, on other CF symptoms and vice versa, and 5) Effects of CFTR modulators on sinuses, eyesight (including cataracts), heart, sweat chloride.

Previous PSP[1]? New question
Proportion of underlying questions from lay respondents[2]: 31%
CF priority refresh ID[3]: C14

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Q8 What are the effective ways of simplifying the treatment burden of people with CF?

Topics included in the underlying questions:

People with CF have to carry out many treatments on a daily basis which is time consuming and impacts on daily life. Over three quarters of underlying questions were related to changes due to taking CFTR modulators. The topics included: stopping or adjusting amount/duration of specific therapies such as 1) Inhaled therapies such as mucolytics and antibiotics, 2) Creon, 3) Airway clearance treatments, and 4) Physiotherapy.

Other questions about modulators included: 5) How do treatments change with age; 6) Effects of modulators on energy balance, and 7) prioritisation of therapies.

CF professionals raised questions such as: 1) Reducing clinic frequency 2) Adherence to treatment, 3) Support people with CF require from MDTs, and 4) Whether new care plans are needed.
Underlying questions that didn't explicitly mention CFTR modulators include: 1) How to simplify (eg simplify delivery) or reduce treatment plans; 2) Can treatments by combined; 3) What do treatments do, and 4) Improvements in the development of inhaler systems to reduce the time required/speed up their delivery.

Previous PSP[1]? Number 1 in previous top 20
Proportion of underlying questions from lay respondents[2]: 43%
CF priority refresh ID[3]: A6

Q9 Can genetic therapies (such as gene editing, stem cell and mRNA technology) be used as a treatment for CF?

Topics included in the underlying questions:

The aim of CF genetic therapies is to allow the production of a working CF protein within the lungs of people with CF. This would lead to an improvement in symptoms for all people with CF, including those who cannot benefit from or tolerate CFTR modulators such as Kaftrio. The topics in the underlying questions included whether genetic therapies could be beneficial for people with CF; whether it was being used already, and what progress had been made so far.

The underlying questions also included a range of different descriptions of genetic therapies from: DNA / chromosome therapies, gene therapy, gene editing and CRISPR Cas9 technology, RNA therapies; to stem cell / regenerative cell therapies. Expectations on their effects ranged from 'treatments', 'lasting change' and making the condition 'so mild it is no longer necessarily fatal' to 'cure'. 11/38 underlying responses explicitly mentioned cure.

Previous PSP[1]? New question
Proportion of underlying questions from lay respondents[2]: 82%
Priority refresh ID[3]: Genetic[1]

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Q10 Is there a way of preventing CF diabetes (CFD) in people with CF?

Topics included in the underlying questions:

CF diabetes (CFD) is a distinct form of diabetes unique to people with cystic fibrosis. Having CFD can lead to people having a poorer lung function than other people with CF and, ultimately, shorter lives. Underlying questions included whether CFD could be prevented, and the role of CFTR modulator therapy on delaying or preventing the development of CFD.

Previous PSP[1]? Number 5 in previous top 10
Proportion of underlying questions from lay respondents[2]: 50%
CF priority refresh ID[3]: DM3

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