[Researcher\_1] 0:05

There we go. So there'll be four kind of parts to this to this discussion, we'll start off with some demographics. So we get a bit of an idea of who we all are, we'll have a look into the current practice, the unmet needs and the TPP, kind of elicitation section, and then some of the reflections on the patient focus group that we did earlier in the year just to go and try and get some feedback on what the patient's had said from their perspective. So just to start off with, we'll do a round of introductions, I'll go through mine in a kind of way just to give you an idea of what we're looking for. But so the job role years of experience the region in which you work, or the hospital setting, and then your exposure or interaction with people with CF, so where you fit along the pathway. So I'm [Researcher\_1] , I'm a research methodologist at the Newcastle MIC. And so far, my exposure or interaction with people with CF is largely on this project, but I have done similar projects working with long-term issues in the past. So, [CFG2\_1 ], could you start us off, please? Yeah.

CFG2\_1 1:19

And so Hi, I'm [CFG2\_1 ] . I'm a CF consultant where I work at the adult CF centre. So, by background obviously, I've been looking after patients with CF clinically for going on far too long as I've done two CF fellowships before this post. But I've also dated my PhD and did a five year research fellowship and academic post So my entire PhD was about infection, inflammation and biomarkers and looking at pulmonary exacerbation. So that's whilst I'm back doing full time clinical, that's one of my big kind of clinical and research interests.

[Researcher\_1] 2:02

Thank you, [CFG2\_1 ]. [CFG2\_2]

CFG2\_2 2:06

Yeah, thank you. I'm similarly I'm a consultant in paediatric cystic fibrosis. I've been involved in CF for about 22 years and as a consultant for 15 years. And my main interest really is the clinical side of determining whether infections are clinically significant for patients or not, and whether or not they need treatments. And that's always been challenging in CF, I think is more challenging now with with modulators coming for many of our patients. Also got a background in research. So that's, that's my synopsis.

[Researcher\_1] 2:59

Wonderful, thank you [CFG2\_2]. [CFG2\_3].

CFG2\_3 3:05

My name is [CFG2\_3], I'm a paediatric cystic fibrosis nurse. The main hospital that I feed into is. But I also work within the community. I've been in this particular job for 13 years, and I work with children and young people every day.

[Researcher\_1] 3:23

Thank you very much, [CFG2\_4].

CFG2\_4 3:30

I'm [CFG2\_4] . I'm a physiotherapist.. And so I've worked in CF, probably guess now for sort of 15 to 16 years now across a few different centres. And obviously, my interest in and this is as the person who gets the samples quite often or not as the case may be. And so yeah, so that's my interest, obviously, in this area.

[Researcher\_1] 3:59

Thank you [CFG2\_4]. [CFG2\_5].

CFG2\_5 4:03

Hi, . I'm the Lead CF pharmacist at adult CF Centre. So [CFG2\_1 ]I've been working in this centre for about 12 years now. I've done my independent prescribing qualification, so I prescribe pretty much almost every day for people with CF. And my involvement, I guess is in both the inpatient and the outpatient setting in terms of dealing with medicines, mainly really, I guess, you know, with our people with CF.

[Researcher\_1] 4:39

Thank you very much, [CFG2\_5]. [CFG2\_6].

CFG2\_6 4:43

I'm [CFG2\_6]. I'm a senior biomedical scientist in the microbiology department. I look after all the respiratory specimens from CF patients in addition to that also all the specimens from the critical care patients. I'm also heavily involved in the local transplantation programme, where we have what we think is probably a unique system of what might be termed synergy testing to guide perioperative antimicrobial therapy if the patient so do go ahead with transplantation.

[Researcher\_1] 5:14

Wonderful. Thank you very much, [CFG2\_6]. So I think that's everyone there, we've got a good idea of what everyone's doing. It's good to see that we've got a good a good spread of, of job roles as well. So I think we have a few clinical consultants, we have physios, we have pharmacist, biomedical scientists and nurses. Is there anyone else involved in the sort of care team for CF patients that is missing from this group?

CFG2\_1 5:42

We have a much bigger MDT. And it's how much you want to in terms of infection management, probably we've got most of the people represented, but we do have dietitians, social workers, youth workers. There's a lot of other people as part of our team, but I guess some of those are probably more involved in other parts of CF rather than infection and medication delivery per se.

CFG2\_2 6:05

Yeah, I was wondering about specialists cystic fibrosis microbiologist, but some of you might wear that hat already. But say something like and that leads, you know, would be our CF microbiologist of choice, who we often ask whether whether or not a particular result is clinically likely to be clinically significant or not.

CFG2\_1 6:34

Yeah, we have our microbiologist who comes to all of our MDTs. And I think quite a lot of the centres around the UK have a dedicated microbiologist who clinical microbiologist, who comes to their MDTs or provides input so somebody from that group would be quite good.

[Researcher\_1] 6:50

All right, brilliant. Thank you very much. It's good to know what voices we've got and which voices we haven't, you know, just moving forward and to get a good idea of what there is. So moving on to the kind of current practice at the moment. Can maybe someone can start us off and I'm not really quite sure the order in which a patient with CF might present to you guys but what what is the kind of current practice for diagnosing a pulmonary infection or an exacerbation in cystic fibrosis?

CFG2\_1 7:17

So I'll do adults, it is different than paediatrics, if that's alright with you [CFG2\_2], because it is it's although it's becoming closer now with modulators but... so we diagnose infection in two different ways. One is looking for acute exacerbation, as you said, and change from baseline. And the other one is our more routine screening of infection, even when patients are clinically well. So sometimes clinical symptoms and microbiological sampling are not always hand in hand. So that's one thing I guess that's important, and that's a big question that we've been debating recently is - what action we take, do we treat the patient or do we treat the sample? and that can be a really big discussion sometimes... In terms of diagnosing exacerbations, the standard line is there is no definition of a pulmonary exacerbation in cystic fibrosis, there are Fuchs criteria and God knows how many but essentially, most of us are just clinically looking at 'are they off from their baseline', being it more symptomatic, deterioration in weight or nutrition, increasing in sputum production, check radiological changes, lung function changes. It's a kind of jigsaw puzzle of different things. And it will depend a lot on the patient's severity of disease and their age, which of those things is most important. In most cases, we'll be making antibiotic treatment decisions before we see acute samples. So we might be able to get acute at the moment, acute virology back very quickly, but in terms of microbiology, bacterial culture, we will be making the antibiotic decisions based on previous samples, not the acute ones at that stage.

[Researcher\_1] 7:53

Thank you very much. Does someone else want to lead us on the on the paediatric side perhaps?

CFG2\_2 9:16

So I could comment on page. So we do similar so we get cough swab samples on our babies and young children. regularly, every clinic visit, every six to eight weeks, more frequently in young babies soon after diagnosis. And there are some pathogens that we grow on those that we would treat regardless of symptoms. Right, rightly or wrongly. I think I think for some of those pathogens, there's good evidence and for some not so good evidence. And then again, like [CFG2\_1 ]said, with the With a pulmonary exacerbation, we'd be looking to get samples. But again, we don't generally get those results back. until quite a way into the treatment of the exacerbation.

[Researcher\_1] 10:14

I think we have we have a section obviously later on about the unmet needs, but it sounds like that the empirical use of antibiotics is one that seems to be up there pretty high. And this waiting for, for culture and so on. But we'll definitely get back to that. I think. Obviously, we have a few different roles involved here. Is there anything that's a sort of, you know, your day in and day out standard practice? And where does it become a bit more variation based on the patient? Or the individual that you're seeing there in front of you? What's the kind of what's the what's the standard procedure in a day when you're looking at diagnosing pulmonary infection or exacerbations? And what's the sort of patient variation side of this? Does anyone want to start us off maybe, [CFG2\_3]?

CFG2\_3 11:03

Well, obviously I see babies from three weeks old, right up into, you know, teenagers that are going to be transitioning. And you're going on for the babies, what the parents are telling you about how they are, how they're presenting ... with the teenagers, obviously, they'll be speaking, and like the consultants said, you'll be looking at everything nutrition, lung function in the older children who can do it, doing a cough swap. Sometimes we try and get an induced sputum because often children don't expectuate easily at all. So that can be difficult. And if we really want to get to the nitty gritty of it will some children will be referred for bronchoscopy, but we'll have done other things first. Some centres do cough plates. I don't tend to, but I know [city] Children's Hospital, they use cough plates as well for getting results. But yeah, it's similar to what the others have said already. It's a group of things that we do to try and determine whether or not they've got an exacerbation or not.

[Researcher\_1] 12:10

Where do most patients present? Is it usually with you guys in secondary care setting or in a CF clinic or is in the GP, or A&E? how does that work?

CFG2\_1 12:21

Our patients don't go to GPs, pretty much ever. They are... I've seen some good national data suggesting that certainly in the adult population, we're seeing a few more present through a&e Recently, but I suspect that's more related to lack of primary care and out of hours cover. So people are just directed into A&E, if they you know, if it's Saturday afternoon, or Sunday evening or whatever, because 24 hour CF cover is there. But it's sometimes remote and not always local to the patient. So unstable patients would have to go to their local emergency department, for example, some one presentation with that station is coughing up large amounts of blood, particularly in adults. So in that situation, you would, of course, advise to patients go to a&e, but most of the time the patients phone us and tell us they don't feel so good, or the parents phone and say something's not right. And then we see them in clinic. And we have the capacity to see people very quickly in clinic if we need to.

[Researcher\_1] 13:20

And do you think? Sorry. Go ahead.

CFG2\_3 13:22

No, I was just gonna say So my role is a little bit different. Because I'm based in the community quite a lot. I'll review them at home straightaway. So they'll phone me, and then it'll be a home visit. And if they need to be brought to clinic sooner, I'll facilitate that if necessary.

[Researcher\_1] 13:31

Is that the same for you, [CFG2\_4]? Is that how it works?

CFG2\_4 13:45

Oh, sorry, I thought my mic wasn't on then. Yeah, so I tend to see people in clinics mostly. So we're doing a few home visits from a physio perspective, to see if nurses that would see more of our adult patients at home on a home visit. So yeah, again, similar to what other people have said, CF people access us much more readily than any other health care providers. You know, and that's quite often the best way of managing them, you know, in a non emergency situation. So yeah, very much the same.

[Researcher\_1] 14:21

As an open question, do you think that they're coming to you specifically with CF related issues? Or are they things that maybe, they use you kind of as a GP, in some ways? Yep, nodding all around. Okay, good.

CFG2\_1 14:34

Our colleagues describe us as GPs, but for a very specialised group of patients. We are trying to work on that in adults, because we're increasingly being asked things that are actually outside our field of expertise, and we're trying to direct people to the true experts in that area, if we can.

[Researcher\_1] 14:54

Okay. And you think do you know what the reasons are behind that? What do you why do you think the patients that you see to use come to you, particularly is it rapport? Or is it ease of access?

CFG2\_1 15:06

ease of access. We've trained them that way from a young age. Like they must let us know. So they do. And I think it's also to be fair to them that being a relatively rare disease in the grand scheme of things they've encountered a lot of people over the years who don't understand their disease, particularly well, understand the medications they're on. And they find that quite difficult. So they would rather talk to someone who does understand their disease.

[Researcher\_1] 15:33

Yeah, I think I'm sure [Facilitator\_1] , can chip in as well there. But from the patient side of things, I think we've heard similar, similar accounts, where if it's not the person that they used to, then they have to describe their entire CF history to someone and it gets a bit tedious, and they're not quite sure if they've understood properly. [CFG2\_5] from a pharmacy side of things, is it all dispensing? Is that all done through secondary care? Or is it GPs as well? Is there anything in in that?

CFG2\_5 16:02

Well, I can speak sort of specifically to Wales, but the way that drugs work in Wales is very different to the way it works in England. So not specific to antibacterials per se. But for example, in England, my understanding is that a lot of the more specialist medicines have been repatriated into secondary care. We've still got some quirks in Wales, whereby some of the nebulizers, some of the mucolytics and the antibacterial nebulizers, we have shared care agreements for, so we would ask the GP would you be happy to prescribe dornase or Toby NEBS for this patient? And sometimes they say yes, and sometimes they say no, so it's a real mixed picture in Wales. Similar to a lot of the rest of the UK, we have homecare provision for both ongoing treatment, so the modulators, the inhaled antibiotics, we also have home care provision for pre prepared IV antibiotics. So that might be something that we might either look to do the entirety of a course of IV antibiotics at home, or we might bring someone into hospital and start their course of antibiotics and then send them home. And the other thing, I guess, from our perspective, is that we actually cover quite a large geographical area. So the concept of somebody who lives five miles away from the hospital coming up to see us for a clinic review, or, you know, to pop in is very different from someone who lives in, we have got some people who live in the very far west of Wales. So, as everyone was talking earlier on, I was just thinking a little bit about, i wonder whether geographically for some centres. If you cover a large geographical area, whether that adds an added complexity into both the diagnostic and the treatment pathway, and things like do you drive? Have you got someone that can bring you? Is there public transport, that sort of thing?

[Researcher\_1] 18:06

Sounds like the network might be quite important there of access. Sorry, go ahead, [CFG2\_1 ].

CFG2\_1 18:13

I was just going to say that we've been talking about that a lot actually, in terms of our samples, because now samples are precious in the CFTR modulator world. We've been doing more induced few times, but also for the spontaneous sputums, we've been finding that our patients that are particularly far away. You can post sputum and a lot of centres are doing that. But we know that that may delay the time from patients to processing. And obviously, if you can get it processed quicker, that will be better. So we've been working with our microbiologist to try and set up exactly that some kind of network where samples can go more locally. And then either the initial processing be done locally or the samples and then transferred properly through microbiological channels rather than in the post. But that's definitely something that we've had more problems with recently, I think. And it definitely GP samples are very difficult, because they're often lost in transit and sometimes even become inappropriately labelled. So that's much tougher for patients to use primary care.

[Researcher\_1] 18:13

Absolutely. [CFG2\_4], you got a hand up?

CFG2\_4 18:19

Yes, I was gonna say we've got very much the same experience here. So through the pandemic, we started set up a postal sputum system and got very much less samples and before Kaftrio rollout as well. So, you know, at the time when you would expect more samples to come back, and having said that since Kaftrio, we've been doing more induced sputum, more cough swabs, and even our induced sputum approach at the moment, isn't always productive. And you know, there's plenty of times we've spent that that time to sort of try and get the sample with hypertonic saline, you know, at decent strengths and volumes and still to no avail. And so yeah, so a different way of having a way to sample or a way to view would be great.

[Researcher\_1] 20:13

[CFG2\_6], do you have any insights in terms of where the samples are coming from from from your lab side?

CFG2\_6 20:19

Right. Yeah, now we, we cover quite a large geographical area. So there's a bit of an issue in it. We have a couple of outreach clinics who do regularly send us specimens. However, the issue here is they do not always send us specimens. They, sometimes the specimens are referred to the local centres, where the staff are not appropriately trained in CF microbiology. And also, these local centres also don't have the appropriate culture media, particularly with regard to things like ntms and Burkholderia. I'm sorry, sorry. Yes. Go on. Sorry.

[Researcher\_1] 20:58

I was gonna say is it is it largely sputum cultures, or sputum samples that you receive? are there any other samples that come in?

CFG2\_6 21:06

Raw from here from the outreach clinics, it's normally a cough swabs which aren't ideal. We know we we've done a lot of work to prove that both Cough, cough swabs and cough plates are inferior specimen types to sputum, but it's obviously more, they find it easier to send us those specimens.

[Researcher\_1] 21:26

Thank you [CFG2\_6]. I think there's a bit of nodding there when we mentioned about cough swabs and cough plates not being quite as up to the task, which leads us quite nicely on to the kind of confidence that that you, you guys have in the tools that are available to make a diagnosis of infection or an exacerbation? So if we have to go through those, what are the sort of common diagnostics that are used? How often are they used? Which ones are the kind of routine ones and which ones aren't necessarily standard? And what's your kind of confidence in the use of those tools? I'll just leave it open to start with.

We'll go for [CFG2\_4], because I think you mentioned that you receive some samples or not. So let's go. Let's go with you to start with.

CFG2\_4 22:12

Yeah so, very much physio perspective is cough swabs are next to useless, unless you have no other way of obtaining anything. Yeah, sputums obviously, if we can get a decent, visible, nice green bit of sputum, we would know that that was a good sample. Our induced sputums, like I say, are now we're getting much more salivary secretions coming back, rather than, you know, your classic CF sputum previously. And so again, we do find it quite difficult at the moment when patients are saying they'd like to stop certain antibiotic treatments because they haven't grown Pseudomonas in the last year, but they've only got negative cough swabs as opposed to sputum samples. And so we're very much trying not to make a call on a cough swab, you know, and to obtain a sample in whatever way we can to be able to make that that decision. So yeah, really, I suppose we're believing a sputum results over anything else. And again, rarely would we do bronchoscopy in adults. And on the occasions that we may well have to do that, again, you know, quite often there isn't a lot of microbiology that comes back from that. So yeah, I suppose orders would be cough swabs are next to useless as I say, and sputum is our gold standard.

[Researcher\_1] 23:46

Thank you very much. I'm like, does anyone have anything else to add there? [CFG2\_1 ], you've unmuted?

CFG2\_1 23:49

No, I was gonna say, I totally agree. I hate cough swabs. But unfortunately, it was something that as adults we never had to worry too much about. But we do a lot now. I guess we feel the same, We do induced sputums. And it isn't always productive. Putting them through a full CPAP seems to help sometimes. So we have resorted to that if needs be. I think we've definitely bronched more patients in the past couple of years, than I've ever done in adults before. And that's mainly been around NTm. Because we're really... it's particularly around stopping treatment for things like abscessus, you really want to be clear. And so I think around NTm, we may well be doing more bronchoscopies for either diagnostic purpose or stopping treatment because it's so critical to so many things. We've been doing a bit more sinus sampling, actually. And that's been somewhat more productive, sort of right in terms of patients. And that has helped us for example, with making some of those Pseudomonas decisions because if they're still got Pseudomonas in their sinuses, then you will, you would lean towards potentially continuing with their in house Pseudomonas therapy in totality because even if it cleared it, it's likely to re-seed. So that's something that we have been finding has been helpful, because it's not pleasant for the patient, but it's not terrible. And it's better than bronchoscopy. And we've actually got a lot of patients even on modulators, who've still got ongoing sinus symptoms. So actually, they're really quite reasonable to use those sinus samples to help us and there's so much research about upper airway versus lower airway. But in clinical practice, sometimes it's just nice to get an idea of anything so that you can have a reasonable informed discussion with the patient about where to go. And are we've got a biobank here. So we're not part of the repository, but we've got our own biobank. So we've also been getting saliva samples. We're thinking about doing throat swabs as well, and just storing some of those samples away for some more research. So we can maybe correlate that with what we've got just trying to think about samples that are easier for us to get and less invasive from a patient point of view.

[Researcher\_1] 26:00

[CFG2\_3], obviously, with a paediatric kind of focus, and as you say, more in the community sort of setting. Do you think the tools the diagnostics or you use differ based on how you how they're being used or where you're using them?

CFG2\_3 26:13

Yeah, I mean, we use a cough, we use cough swabs a lot, on babies, it's an induced cough swab, so you know, will touch the back of the throat. And then in children that can cough, we will use that. It's very difficult to get sputum from them, we will do some nasal swabs sometimes, I've not heard of sinus swabs. I don't know how, how that works. But it sounds like it wouldn't be well received in children, but I might be wrong. And we can get saliva samples as well, if necessary. It's hard, really, because they hate having them done. And they will do them, once they know that, you know, they can cough on them, and it's not going to hurt then they'll cooperate. I'm not sure what else we use. So it does work for us. And we do obviously pick up Pseudomonas and the other bugs. So, yeah, we use them a lot.

[Researcher\_1] 27:07

There's a follow up question for that one. But just before we jump on to that one, are there any other diagnostics or things that are used? Maybe not so routinely? So I think there was a mention of Bronhoscopy that was used occasionally or more recently now, but in terms of imaging, perhaps, or any other sort of tests that are used, perhaps not quite so routinely?

CFG2\_1 27:26

I guess in adults, we do chest X-rays, and CTs pretty willy nilly in this situation, certainly, with X-rays will do if anyone's more symptomatic mainly, partly to diagnose infection, but also to make sure that it's not anything else as the cause for their symptoms like a pneumothorax. And we provide a pretty low threshold for CT in an adult population. Just because it gives us better imaging, particularly of atypical infections like fungus, or NTm. And sometimes it's helpful for us just to get an idea of the trend of this sort of serial images. So CT will use quite a lot, not necessarily as a diagnosis, but to guide treatment, and to give us an idea of if we're on the right track with what we're doing.

[Researcher\_1] 28:14

So would you incorporate that into a patient's sort of standard check-up? Or is it a bit less likely than that?

CFG2\_1 28:22

In all honesty, we try and avoid radiology if we can because of radiation. So we'll do it if people are symptomatic or unwell. CT-wise, we try and get a baseline on all of our new transitioning patients just so we've got an idea of what their lungs look like. And then other than that, it's just guided by clinical need essentially. So if a chest X-ray looks very abnormal, and need to understand it better, if they have been treated well for bacterial infection, but are not improving in the way you would hope, so then you're looking for other types of organisms. Or we've got some patients who just clinically are deteriorating. And you're just trying to understand if there's anything else going on, on top. And we use it I guess, for disease staging, because FEV1 is not the best way of looking at extent of structural lung disease in all patients so equally in patients with really good lung function. So it gives us a better idea of what the extent of their structural lung damage is.

[Researcher\_1] 29:21

In terms of something like spirometry, I think we didn't actually mention that, but it's not used in any way as a sort of diagnostic, that'll give you an indication of infection? is that sort of more common than a cough swab or...? Yeah, no?

CFG2\_1 29:37

you'd be doing most of it together and most of our patients have got home Spiro in an adult population. So they check their own lung function. We're part of Project Breathe. So we've got patients who are giving us Fitbit data, lung function, weight, you know, cough scores, all sorts of things, but most of the time someone signs up and they say they're unwell. Obviously, we try and arrange review, but also if they've got home spirometry get them to do a lung function. But even before Kaftrio, what we were seeing was, people could feel very unwell and their lung function wouldn't necessarily have dropped to reflect that. At the same time you see patients whose lung function has dropped, but they feel absolutely fine. And you're kind of trying to work out what the cause of the drop in lung function is. So it's a useful tool, and we will always do it and we do it a lot. But you can't on its own. It's not a way of making a diagnosis, you need other information to go with.

[Researcher\_1] 30:33

Absolutely. We've touched on it a little bit in and out i think. But what what sort of adaption or compromise does the clinical care team need to take on board in regarding the sort of detail or the information that they can gain from the test that they used? Is there sort of a patient acceptability or a preference that impacts on what clinical diagnostic tests you would use for that particular patient? How much are you willing to sort of compromise on perhaps the information that you gain in order to promote acceptability? Or to ensure that you're getting a sample at all?

CFG2\_2 31:13

I think we, I think we have to do what's practicable. So if you wanted the best possible sample, then you might do a six lobe, Broncbo-alveolar lavage. But you can't do that every visit. It's very invasive. time consuming. We don't have the resources to do it. You know that there are potential complications of the procedure. So so so yeah, so certainly in peads we compromise with with with cough swabs unless we can get sputums or induced sputum. So and again, kids don't like doing induced sputums too often. But we would certainly aim to do an induced sputum once a year if we could. In most patients, but you know, doing cough swabs, we're aware that as everyone said, they're not very sensitive. And probably studies which suggest only a third as sensitive as a sputum sample, at best. So whilst we do pick up things, like Pseudomonas from time to time, we worry about all the times we're getting false negatives.

[Researcher\_1] 32:20

And [CFG2\_4] is that same for you. Do you think in terms of patient acceptability? Youre on mute there sorry. alright.

CFG2\_4 32:29

Yeah, I mean, the least invasive is obviously a patient's preference, and cough swabs, you know, are more tolerable, but, you know, depending, again, we've got variability between our patients as to how tolerable they are. And what I sort of have noticed is that we start once we've started floating the idea of induced sputums in clinics, people tend to be able to then cough something up. And sometimes, you know, the thoughts of having to go through an induced sputum does the job. And but yeah, I think people we've sort of seemed to notice, I suppose in our clinics is that people think that they're non-productive. But then when you actually go through, you know, an airway clearance cycle with them or give them some hypertonic saline. Actually, there is quite a bit of secretions there. It's just having the time. And the engagement, really, to see that through

[Researcher\_1] 33:35

[CFG2\_1 ], you've got something to add?

CFG2\_1 33:36

No, no, I was just going to say I think the other thing we've noticed with our adults, and actually we had a great conversation with our paediatric colleagues about it. Is that what they perceive to be sputum has changed, so they're telling you they're non-productive because what they're producing is white or not as thick and sticky, but it's still sputum. So it's also a bit of education to the patients that actually something that looks fairly innocuous to them is actually still sputum and it's worth sending.

[Researcher\_1] 34:06

So there's been quite a bit of a discussion about modulators or Kaftrio. What were the signs and symptoms for a patient presenting with infection before and after the sort of wide widespread use of modulators? Go on [CFG2\_2].

CFG2\_2 34:29

So, CF used to be easier as a clinician, I think. So somebody would come in, they were ill. They were more productive, their sputum had gone, gone green, or brown. Their oxygen saturations might have might be a bit lower than their baseline, lung function might have dropped. And we'd be confident they had an exacerbation. We'd put them on antibiotics and and they'd get better and if they didn't, we thought about aspergilusm or mycobacterium, or other atypicals... now on modulators I must say in paeds, it's rare that they're getting exacerbations. But if but if they do, it just seems totally different. And, and it's really difficult to know if what we've regarded as CF pathogens that we're picking up is still actually the driver of clinical symptoms or not, or just incidental findings. So we're all a bit at sea now in poeple that are on modulators, knowing actually what the right thing to do is. And there's loads of research needed to help us with that.

[Researcher\_1] 35:49

[CFG2\_1 ]?

CFG2\_1 35:49

I was gonna say, I totally agree, I think, you know, we've realised that the respiratory symptoms that used to be the predominant way that patients themselves would recognise exacerbations before that, you would often see tiredness, lethargy, reduced exercise tolerance, and then the chest symptoms would come and then the lung function would drop... So people were used to that as their pattern. That's not the pattern anymore, because often the chest symptoms don't change, we have seen that some of the systemic symptoms stay. So they do notice that they're maybe just got a bit less energy, or they're a bit not quite on their baseline. And we've had a whole load of people who phoned us and go, I don't really know if I'm ill. But I don't feel quite as well as I did last week. And we're trying to kind of go, have you gotten, you know, at the same time, I think what we've seen in adults, we're definitely seeing loads less exacerbations, and lots more people who are more clinically stable, and therefore either having oral antibiotics, rather than coming in for admission. And that's something which is good. But we're a little bit worried that we've got a few patients who are having quite a lot of oral antibiotics, who may be actually might benefit from more aggressive treatment, because they don't feel that ill. That's an, it's a more difficult discussion to say, I want you to come into hospital... We're definitely giving shorter courses. So even if people do feel ill, they're picking up much more quickly. So we're definitely seven to 10 days is probably enough for a lot of our patients now rather than the full two weeks. It's a tricky one, we were having a whole massive conversation this morning, just like you said [CFG2\_2] about haemophilus because we never used to see haemophilus in adults. And we've seen quite a lot more of it. And I'm not completely convinced it's a pathogen, I suspect they're just not growing as much Pseudomonas. So I'm just seeing haemophilus that's always been there. And we have this sort of circular conversation going well, were they ill? is this new? Should we give something? Should I say? Those are the kinds of conundrums particularly that we're seeing where you're going? Well, I don't know if this is just actually reflecting their normal flora, rather than actually being a pathogen and all the things we used to use to assess that aren't quite as reliable as they once were.

[Researcher\_1] 37:57

[CFG2\_6], have you noticed something similar from the microbiology side of things, from the lab?

CFG2\_6 38:03

Well, what we're now sort of noticing is, there's no difference in the pathogens, but the macro, microscopic appearance of the sputum from CF patients is completely different. All it was pre- days of the modulators. Now the sputum you get from the standard patient, we have far fewer the, you know, sort of very thick, typical green specimens that we used to get regularly. We don't, i haven't noticed any change in the frequency of isolation of typical CF pathogens.

[Researcher\_1] 38:39

No change in the sort of colony forming units or the No, no,

CFG2\_6 38:44

not at all. No. Okay.

[Researcher\_1] 38:46

And then from a pharmacy side, is there changes in the we've mentioned shorter courses for antibiotics and so on. What have you sort of noticed, [CFG2\_5]? You're on mute, by the way?

CFG2\_5 38:57

Yeah, sorry. I, I guess just sort of reiterating what other people have said. And so just going back to the previous conversation, I know when [CFG2\_4] was speaking there about induced sputums and patient acceptability. I'm certainly not an expert. It's not my field, but my understanding is that the physio team here have got various options that they can offer to the people we look after as to how we go about doing an induced sputum. So apologies, I've gone off to the on a slightly different question. But that's very much I think, part of offering what's acceptable to someone or, you know, best compromise, I guess.

[Researcher\_1] 39:37

Okay. And have you noticed anything different in the pharmacy or prescribing side of things, with the introduction of modulators?

CFG2\_5 39:47

Well, yeah, I mean, I think there's all sorts of things. It's affected and we're still learning I think so. We're very much what people are needing to do in terms of airways clearance has changed and therefore they have been and quite a lot of discussions between us and the people we look after about, can we stop various airways clearance, salt tablets, you know that that's changed since Kaftrio came along. So the need for people to have significant doses of salt replacement has certainly changed, in some people. And I think we have a real mixed bag in that I think some people, as [CFG2\_4] was saying earlier are perhaps less keen to be carrying on with some of their other treatments, some other inhaled antibiotics if they can, which, which is it, you know, sometimes a conundrum in itself. But yeah, it has certainly changed things. And an equally we've had people who've had slightly off topic, but their bowel symptoms have perhaps been quite different, having gone on to the modulators, so they might be better or worse. So you know, from a medicine perspective, you could argue that there may have been a change in what laxatives we're needing to use for people.

[Researcher\_1] 41:02

In terms of antibiotic susceptibility testing, is any of that done? kind of angled towards [CFG2\_6] and perhaps, [CFG2\_5], but open to everybody as well?

CFG2\_6 41:12

Well, we, we are using the current CF trust guidelines, we do susceptibility testing yearly. Unless the patient has deteriorated significantly, we know that this diffusion testing is completely unreliable. So it's just used as a guide. It's just used for records effectively, when we do have this additional system, we have the patients in there particularly dire state where we do go on to do that we term our synergy panels.

[Researcher\_1] 41:45

So what are these? Are these all culture? Or is there something else in the there?

CFG2\_6 41:49

right, essentially, it's basically culture, yes, where we grow the organism, purify them, and then challenge them against ... against various agents, and both initially single and double and if necessary, triple combinations, to see if we can get any match over what sort of the kills all of the patients organisms. Now this is done in predominantly in the pre transplant setting. But it's also done in the case of a patient who was particularly ill and current therapy doesn't seem to be working.

[Researcher\_1] 42:27

Is that widely, the use case for everybody else as well? No, [CFG2\_1 ]'s saying no. How do you do that?

CFG2\_1 42:34

I have used [CFG2\_6]s approach because when I was in [city], we did use that approach. And we actually our pre-transplant patients went to [city]. So synergy testing can be helpful clinically, especially in tricky pre transplant cases where perhaps your antibiotic options are limited, sometimes by intolerances and allergies. So actually having a combination that you might be able to put together of things that they can tolerate. It's sometimes more effective. And but Yeah, certainly we barely do sensitivity testing, maximum about once a year, the same as [CFG2\_6], and I know some centres continue to but yeah, it's just occasionally it's helpful to give you an idea of whether it's the same bug and that's maybe something that moving forward. Is it a new pseudomonas, or was it their original Pseudomonas that might be helpful, but with other ways of doing strain typing, kind of sensitivity is probably outpaced by newer modalities now for that.

[Researcher\_1] 43:36

Thank you, [CFG2\_1 ]. Does anyone have any more comments on antibiotic susceptibility testing?

CFG2\_2 43:42

Yes, so we get, we get we do just yearly in our patients with chronic pseudomonas. If we get a new Pseudomonas in anybody, which obviously happens in peads, probably more more than in adults. Then we get susceptibility testing on that first isolate. And then other organisms like Haemophilus and staph and things we routinely get, you know, a limited susceptibility testing on those isolates as well.

[Researcher\_1] 44:13

I imagine obviously, with culture as the basis, these even with antibiotic susceptibility testing been in place there's a bit of a delay between when antibiotics are administered and when you get these results back. Well, I guess my kind of question is how do you assess if a treatment is effective

CFG2\_1 44:32

I get better! ... To be fair, this is giving me PhD nightmares. But this is pretty much what we looked at. The reality is that clinically we kind of give a multi-dimensional assessment where we go, how's their weight, their nutrition, their lung function, their respiratory symptoms, their inflammatory markers, all of those things and you put all the bits of the jigsaw together and say, Are they better than before or not? But there are all sorts of ways of measuring that if you get into the research world, and the things that are not standard clinically, but usually is to some degree clinical judgement, and you just look at everything. And each day, I think they're getting better.

CFG2\_2 45:25

What we don't know is whether they've got better anyway, a lot of the time. And the other thing we look for is whether that whether the organism is being cleared, so particularly Pseudomonas eradication, we will look hard at the end of that course within an induced sputum to see if we've got reasonable evidence that it's been eradicated. But again, any sample even from an induced sputum is never going to be 100% sensitive. So we do what we can.

[Researcher\_1] 45:52

kind of blending in a little bit, maybe into the TPP side of things now, but how long would you wait on antibiotics? If you knew you could get a test within X amount of time? Would you wait on that? Or would you still be dispensing empirically?

CFG2\_5 46:11

I guess it would depend on how unwell someone is. Yeah.. I think maybe.

CFG2\_1 46:16

it's pretty unusual for us to wait for the sputum in a exacerbation setting, in serial monitoring setting, or general decline, we're not quite sure what's going on, then we might wait for the sputum samples, but someone's clinically unwell, then you treat them anyway.

[Researcher\_1] 46:16

Thank you very much for that. I wanted to ask a little bit about the cost side of things. What are the economic side the major economic costs in the in the pathway for CF infection? And exacerbation? Do you know what they might be?

CFG2\_1 46:58

I'm gonna hide under the desk, because [CFG2\_5] dispenses the antibiotics that [CFG2\_1 ]prescribes.

CFG2\_5 47:03

I was just thinking slightly laterally and thinking actually, some of the really expensive antibiotics that we use, possibly now pale into comparison with the cost of the CFTR modulators. So they are considerably more expensive. From a drug perspective, certainly, there's a massive range of costs. So some of the newer anti-Pseudomonas that have come onto the market, more recently, are very much more expensive, but we've equally got some old antibiotics, which are widely produced by loads of different generic manufacturers. The cost has come down, you know, significantly. So I guess from my area of work drugs, certainly there's, there's a massive range in terms of what a cost of treatment might be.

[Researcher\_1] 48:00

And what about in terms of say person time? I think [CFG2\_3] , you mentioned you have call outs to people's homes, and so on, what what are the kind of what are the costs sort of implications of that? Do you think?

CFG2\_3 48:12

Well, yeah, it's in buying time, isn't it and then fuel prices getting there, time spent at their family home? The equipment that you need, so the cough swabs need to be bought, or the plates... what else do we have? And then just all the equipment that you buy, say for a clinic setting? So your lung function, spirometry? What else have we got that's expensive?... I'm just trying to think of all of the things I have to order. Yeah, just sputum collection pots. So all of those consumables really, as well as time. Yeah.

CFG2\_4 48:51

Yeah, time is quite a big issue from a physio perspective, again, is that you, it used to be that you'd hand someone a pot on the way into clinic, it would be full by the time they left. Whereas now, you know, we're spending quite a significant amount of time, you know, up to an hour, or an hour and a half, with people to sort of develop the induced sputum side of things and to do some airway clearance to receive that same... Well, I say the same, not even the same sort of sample you would have had previously. So again, physio time, I would say in terms of pursuit of samples, is an increased cost for sure.

[Researcher\_1] 49:32

And [CFG2\_6], from the lab side of things, where are the costs there?

CFG2\_6 49:37

recently, it's basically media and identifications. I mean, we produce most of our media in house and I think we do everything apart from our Berkaderia media we produce it as produced in house here, the only other real costs are the identifications and we do everything by MALDI-Tov

[Researcher\_1] 50:01

Okay, thank you very much. Who pays for all the tests? That might be a hard a difficult one. Sorry.

CFG2\_1 50:10

It depends where you are. That's what I'm just thinking.. because CF care is funded differently in each of the four UK nations. So that's important and also within different centres. The way that funding splits between direct clinical care versus microbiological care versus radiological is complicated. There is funding comes into the CF centre, some places, it's then allocated to different departments like we will give X to microbiology and Y there, others that's absorbed within the general microbiological budget and as part of their funds... so it's almost impossible to know. And we look at the spreadsheets quite a lot. And I still don't actually know the answer to that question.

[Researcher\_1] 51:02

Do we think that that's good in a way that we don't really have to be concerned too much about what the individual cost of everything is? Or is that a concern in the background? Really?

CFG2\_3 51:15

Sometimes that's a concern, you know, if you're wanting to buy nebulizers, to treat nebulized antibiotics, so for example, in [county], my manager is quite good. I can just buy e-flows or, you know, get up to date equipment, where's my colleague who works in [county], she's not allowed to get anything. So that's because of her manager and her CCG. So there is cost implications that we have to think about and I think depending on which area are in as to how difficult it is to purchase what you need.

[Researcher\_1] 51:48

You're nodding along there [CFG2\_2]?

CFG2\_2 51:53

Yeah, my long experience working in the NHS is it's horrible to hear things like [CFG2\_3] saying there were an individual's care will depend on what postcode they're in, and that, you know, sadly, that happens. And we're all aware it happens. But it's really sad. And we don't want it to happen. But the other thing I would say about is, we generally don't ask too many questions. So I wouldn't go to my microbiology lab and say, did we pay you for this? I wouldn't ask that question. No, it happens and I'm happy.

CFG2\_1 52:27

Exactly. And [CFG2\_5] can probably talk about this better than me. The other thing we've realised with the postcode lottery is that that's also about drugs coming on to formularies in different parts of the country. And for us, for example, we've got some patients in England and some in Wales. So we can prescribe certain things to our English patients that we can't prescribe to our Welsh patients. And some things I can prescribe to my [city] patients, but I can't prescribe to my [city] patients, because they're not coming from us directly. So we're having to they're being locally prescribed or dispensed and that particular area is not on board with that. Vitamins at the moment is one of them. But there's all sorts of things along those lines like nebulized antibiotics and other things that can become a problem.

CFG2\_2 53:13

Yeah, we get charity funding for things like E-flows. So we struggled to get E-flows funded in [trust], but fortunately, charities support that buys them and then we loan them to families.

CFG2\_1 53:24

And I think that's something definitely in terms of drug development, that that's really important to think about. Because certainly when you talk to some of the scientists, they're thinking very much about how they will deliver it, but not the logistics of like the you can design ahead for but actually, how did the person get the machine that that connects to and who pays for it and who pays for the servicing? And, you know, for example, we've got certain nebulizers where if you lose that antibiotic, you can keep the nebulizer but if you have to come off that particular antibiotic, then you lose that nebulizer. And these are things that are very complicated, and do require a bit of thought in terms of translating something new into actual clinical practice.

[Researcher\_1] 54:10

And [CFG2\_6], from your side of things, who pays you?

CFG2\_6 54:12

Yeah it's just a central funding for us, Yeah.

[Researcher\_1] 54:25

Well, I think this is quite a good conversation. So we'll move on to the sort of unmet diagnostic needs and the TPP kind of elicitation side. So what we're trying to get here is what are the what are the unmet needs in CF infection and exacerbation? Not necessarily related directly to diagnostics, it can be a pathway issues or as we said, you know, equity of care, time to results to get some samples back. What are the kinds of unmet needs at the moment?

CFG2\_2 54:54

I'd like to know what is normal flora in a person with CF in their airway, when they don't have an exacerbation, when they're well, and when when they don't need to be treated. Because I think that's a massive unknown, and would help us then make decisions when we get results later.

CFG2\_1 55:16

Yeah. I think that's huge. And also the difference between culture and non-culture based. So particularly with the microbiome stuff, you get an idea, there's a lot of stuff down there that we don't see. And then we randomly do see it in culture and treat it. And actually it was there all along. So that's a, an interesting divide between what we can know what we do know. And then how does that determine it. And I guess if I put my inflammation hat on, the other thing is whether just bacterial diagnosis alone is sufficient, or whether you actually then want some idea of disease activity as a consequence. So in all the levels of inflammation in the lungs actually rising as a consequence of that bacteria, which might help you understand whether it's just sitting there or is actually driving any active process at the time. And we are incredibly bad at the moment at measuring that and we don't have very good tests. So, you know, that would help us put the bacteria into more context, I think in terms of what it's actually doing in the lungs.

[Researcher\_1] 56:17

This is colonisation versus infection, is it?

CFG2\_1 56:20

Yeah.

[Researcher\_1] 56:20

Yeah, good look, solving that one. So in terms of other unmet needs, it's generally this kind of an opportunity to air out your gripes. You know, we won't be going back to your bosses or anything like that. As I said, we are independent, which is good to know where we're kind of like, if you're nitpicking the pathway, what is it that could be done better? Do you think? [CFG2\_4]'s show Oh, go on. Go ahead. Alright. Sorry. Everyone's gone. We'll start with [CFG2\_5], and then [CFG2\_2] and then [CFG2\_4], there we go.

CFG2\_5 56:56

Just sort of coming maybe from a more pharmacy angle. So apologies. I think timely tobramycin levels might be nice. Again, I think it depends where you are geographically in which lab you send them to, you know, could we do something that wasn't from a venous sample? Could we turn them around in a different way? And then the other thing, I was just thinking, I'm not quite sure how far it's got around the country. But looking at that, and I apologies, I can't remember the mutation, but the genetic mutation that means that you handle Aminoglycosides differently, and you might be more at risk of toxicity? I know, that's something that we've started thinking about a little bit recently. But I don't think certainly in [city], we've got to the point where we're routinely able to maybe send people for that testing. So yeah, sorry, from a more of a pharmacy perspective that rather than a diagnostic per se,

[Researcher\_1] 57:52

that's very good. And it's diagnostic, at some way level anyway, with the opposite is something that the genomic laboratory hub would do, is it? Who would do something like that? Yeah.

CFG2\_2 58:05

We do them all in [city]. So are 240 network, children, young people attending our service, we get [city] genetics lab to look for that mitochondrial mutation. We've only found one of our 240 Young people has it.

[Researcher\_1] 58:22

That's potentially worth it, Is it? Given the possible impact? Yeah,

CFG2\_2 58:27

yeah. So we would avoid using aminoglycosides in that young person. Wherever possible.

[Researcher\_1] 58:35

And, [CFG2\_2], did you have something to air out there as well?

CFG2\_2 58:39

Yeah, I was just gonna say, it'd be really nice to have rapid, so faster than culture diagnostics, with the quantitative elements. So knowing roughly how much of the organism was there, would be helpful as well.

CFG2\_4 58:59

I think sort of home based monitoring would be useful. I know, obviously, we've all gotten very much more remotes, and virtual in our management of patients. So something that potentially patients could carry out a test at home, which give a results that they could then bring along with their FEV1 to a virtual clinic would be useful. Obviously, the quality of that results would would be in question potentially, but that may well be, you know, the first first sort of line of monitoring for then, further, you know, testing to be done from their

[Researcher\_1] 59:39

[CFG2\_1 ], are you're going to mention breathe?

CFG2\_1 59:41

but no, actually. I think that's where they're going. I think having actually done some of this when I was in [city] and Randox have a chip that can do this, not at home, but you can do it. There's a lot of this available in virology at the moment, not so much in bacteriology. But it is possible to do some of this, I think my, the important point with that would be the sensitivity and the specificity to make sure that we don't see so many false positives, because that causes a huge amount of anxiety for patients. So a false positive Pseudomonas would be huge for a patient who doesn't have Pseudomonas previously. So I think it's important to think about the patient impact of those kinds of tests. And I guess, rapid diagnosis is really good, as serial monitoring is also helpful. So if someone had known pseudomonas, being able to check it at home and see if it's gone, would be quite nice. But I would worry a little bit about the anxiety induced in someone picking that up themselves for the first time, without a clear safety net of who would act on that if they did it. And what the plan would be to, as we've seen regularly with COVID, that some of those more point of care tests require that some kind of secondary line of validation, and being clear that what that secondary line of validation would be so that you don't act on things that actually, you know, or have patients act on things that might end up not being quite right. But I mean, I think that would be nice. In adults, it used to be something we weren't bothered about, because we had so many sputum samples and so much growth that it didn't really worry us. But now, we probably are more concerned about picking things up quickly. And I think [CFG2\_5]'s got a really good point. It's about at this point, also our antibiotics strategy, so not just the result, but what you actually do as a consequence of that result, because our standards of care are woefully out of date. And we keep asking for them to be updated. And we understand the limitations of that. But it leaves us somewhat knowing that practice is varying extensively across the country, and there's not limited research, for example, we're seeing most eradication, what's the right regime, how many samples do we need to send? How long should we be treating for? when do we stop do it? There's a lot of stuff that the research we've got is pre-CFTR modulator. So we don't know how applicable it is to our current population. And then you're trying to make antibiotic decisions without really an evidence base to support you. And as [CFG2\_5] said, we've got a lot of patients in adults with significant complications with aminoglycosides. Over the years renal failure, dialysis, significant hearing impairment, and you look at our younger population, and think I don't want to do that to them. And I don't want to undertreat, but equally, I don't want to overtreat patients who are going to live for much longer. So I think that's important to us. And our dosing strategies as well. We've been looking at that as patients age, that the traditional CF doses don't work well in people who are 86 years old. And we're finding that what we're doing is dramatically different. And we don't really have any guidance on that at the moment. So if you were testing a new drug, I'd certainly be thinking about testing it in a broad age range, both kids and adults, but also the older adults, because that's coming back to us quite a lot. And by older, unfortunately, we are talking in 40 Plus, but it is a group that's important. And it's just being aware that that's the future of CF care, isn't it? And that we need to make sure what we do is suitable for that ageing population.

[Researcher\_1] 1:03:24

Absolutely. Thank you, [CFG2\_1 ]. [CFG2\_3], obviously, your pathway or your care pathway is slightly different to some of the other people in the CF team. And what are the unmet needs for you, do you think? What are the unmet needs at the moment what what is missing from the pathway?

CFG2\_3 1:03:41

I suppose, as the as the others have said, it is speed of diagnosis really, about what they might be growing, because we do treat based on their symptoms. I don't know, I was imagining something like you know, and you do test the pH of the stomach, and you dip, dip it in, and it changes colour. It'd be nice if you just cough on something and it would change colour and tell you what, you know what bug it was, that would be perfect, and how easy that will be to do or not. But, you know, parents could say, well, I've done I've coughed on this, and I've got staph, and that would help you make the decision. I know you won't be coming up with something like that. But I was just imagining it. Speed I think.

[Researcher\_1] 1:04:26

Okay, well, I mean, it's not it's not beyond the realms of possibility. I mean, there are breath analysis techniques that do this kind of stuff. And obviously, everyone's had a lateral flow test now, haven't they? And you could easily do that against one specific bug. So that it doesn't sound completely unreasonable. Really. Thank you for that. And [CFG2\_6] from the lab side of things, what was the what are the issues there?

CFG2\_6 1:04:50

Ideally, a more rapid method of speciating new isolates of Burkholderia, becuase currently we're isolating new Burkholderia... Yeah, it's one of the things where the MALDI-TOF falls down, it's unable to speciate them adequately and it's sort of sort of three weeks down the line before we get the result back from the reference centre.

[Researcher\_1] 1:05:12

I think you mentioned Burkholderia before at the start didn't you? what are the issues there at the moment? What's the story?

CFG2\_6 1:05:21

Well, it's highly transmissible. And if a patient becomes colonised this with acertain mutation, they are ineligible for transplantation.

[Researcher\_1] 1:05:31

So yeah, of course, that's the one. Does anyone have any other comments to make at the moment about unmet needs

CFG2\_2 1:05:40

mycobacteria. Current current kind of culture based techniques are slow, often in getting us a result. And it can take ages to get any kind of sensitivity for what it's worth, to microbial sensitivities. So I think, better, faster identification of worrying mycobacteria, like mycobacterium abscessus, would be helpful.

CFG2\_1 1:06:14

Even with whole genome sequencing, as [CFG2\_6] said, for NTm, that still involves going to reference laboratories. So even if the actual test is rapid, the logistics of getting what you've got to the right person slows it all down. And that won't give him sensitivity testing. So you don't have to wait, even when you know when it is, you still have to wait. And certainly in TB, they've moved really far forward with this now, so it would be quite nice to see similar with NTm.

[Researcher\_1] 1:06:43

And so if we were to imagine ourselves, as you know, maybe advising NICE or maybe advising a commissioning group. And these kinds of issues were coming up, how do you think we might address some of them? So I've been trying to note them down as we go along. So what is normal flora in CF? I think was the question asked by [CFG2\_2], how would you go about addressing that? How would you find an answer to it?

CFG2\_2 1:07:17

I really don't know. [CFG2\_1 ]PhD might help us.

CFG2\_1 1:07:24

Yeah, I guess we would go for lots and lots and lots of serial samples, oh, longitudinally over a long period of time.

[Researcher\_1] 1:07:31

So this would be a clinical trial, or probably, observational?

CFG2\_1 1:07:36

observational, but with lots and lots and lots of samples over a long period of time, because the few studies that have been of this, from a microbiome point of view show that there is relatively stability, stability in people's microbiota, despite IV antibiotics and other things happening, but also that knowing what the baseline is really gives you a much better idea of whether they really deviated from that when they become more unwell. So I think it would unfortunately, just mean, lots of samples, which would probably mean, a patiently acceptable non-invasive way of getting a sample that they can do at home, rapidly and potentially the test at home and report back or somehow get back to I mean, biobank, and the repository is one solution, but you're going to want samples over I don't know, relatively long periods of time, frequently. And then if you're looking across the age ranges, you'd need suitable cohorts so that you had enough five year olds to decide what's roughly normal for a five year old, and then what's roughly normal for a 50 year old. And so you'd really need pretty much everyone with CF, probably to be contributing.

[Researcher\_1] 1:08:47

Did you get that [Facilitator\_1]? Right, well set that up next week. And in terms of the segmented, longitudinal coverage, the do we think that this might also help with that problem that we had with inflammation and the colonisation versus infection sort of questions? Yep... So we need a big, big old study. Okay. [CFG2\_3], you were unmuted for a second, there. Did you have something to add?

CFG2\_3 1:09:24

Oh, no. I was just wondering if we could use the registry to get some of that information every year. There seems to be more questions added. And there's going to be a registry meeting. I think next week. But I just wondered if you could get some information that way over a long, long period. I don't know what the question would be. But you've got a cohort of 10,500/ People already on the registry.

[Researcher\_1] 1:09:52

Thank you very much. I'm moving on to... equity of care came up I think for quite a few people. Obviously, it's a broad question, but how would you address equity of care? What is it that needs to change and make that kind of more equitable in a way? Is it the guidelines? Is it the funding streams, the method of funding? How would you address that?

CFG2\_2 1:10:22

I think it's to do with NHS in the Four Nations having the same funded standard of care for everybody. So I think that's probably got to come from government, or NHS England. Yeah.

CFG2\_1 1:10:44

If you can persuade NHS across the four nations and get them to agree on that, I'd be amazed. But I think it is having a good standard of care or a good guideline always helps, and is sometimes easier than sorting all these funding streams. But we've always been so lucky, and CF to have a really good, this is what your care should look like. And this is who should be in your team. And that's helped us be better than many other areas of medicine. And we're kind of held up as they aren't you all amazing in CF and you've got this working. But actually, what we've got is all the people at the moment, but we don't quite know how we should be using all the people and what's the right thing to do. So I think if you've got a good standard of care, you'd probably then find that the funding falls alongside it. Because certainly, for example, in Wales, they're very keen on 'well what should you be doing?' What's the CF trust say? you're always going to have local variation. But if you've got somebody very clearly going, this is the standard, you should be holding yourself to, you know, the laboratory standards, for example, adhere to really well across the country. And that's part of it, and then it's actually trying to engage, make sure that when these things are created, people from all four of the nations are involved in their creation, and somebody did admit to me the other day that they didn't know how CF care was funded in Wales. As our medical association, I suggested that it might be nice to know how it was in the different countries.

[Researcher\_1] 1:12:19

Absolutely. We talked a little bit about time to results. And was it a tobramycin that you mentioned, [CFG2\_5]?

CFG2\_5 1:12:28

I think just just from a local perspective, so we're part of a health board and our CF service, and the ward is based in one of the hospitals. And the laboratory that deals with our tobramycin levels is based in the other hospital, which is not very far away, it's four or five miles away. But you could assume that if you happen to be in the other hospital for whatever reason, and were on tobramycin, for whatever reason, there's a good chance you'd get your tobramycin level back the same day, usually with ourselves, not always, but usually it's the following day, by the time it comes back. So you have to factor in the logistics of that. And you have to work out when the sample needs to get to the lab, what time does the transport go from one site to another. And I'm only talking on a very local basis. But I can imagine perhaps for the areas of the country where they have a large geographical variation that I can imagine they would have the same issues. So it doesn't cause us huge problems by and large. But how much nicer would it be if you had that back just those few hours earlier? And I guess, you know, have we got constraints on the weekend as well, in terms of what we can do when, you know, certainly not so much a tobramycin. But with things like sirolimus, which is an anti rejection drug locally, they only run those on certain days, I assume, because in the lab, you know, you can't just run them willy nilly, you have to have a panel that you do them against or, you know, however they run them. So I'm sure there must be other people who are came across similar problems.

[Researcher\_1] 1:14:18

Do you think how would you address the issue then? Is it is it that you need more transport between the one hospital and the other? Or is it that you need that same capability in your half the hospital? What do you think the answer would be?

CFG2\_5 1:14:31

I mean, it could be either, but I think, you know, thinking even further afield, we have quite a lot of the people that we look after who do their own antibiotics at home. And some of those do them in west Wales and some of them do them in mid Wales. And actually for them that's even more challenging because they may live two or three hours away from us. So the way that we do levels for those people, by and large as they then end up having to come back to us on day 8 or whatever to have that sample taken. So even on a broader sense being able to get things into a lab in [county] or [county], and over to the central lab in [city], who I understand I think do the tobramycin levels for pretty much all the health boards in Wales, that has its own added logistics that's even more challenging. But in all honesty, I don't know enough about what the limitations and practicalities are of how you actually run that in a lab. And I guess if we had someone involved who was from the microbiology labs or the TDM, labs, they might be able to explain better about perhaps why you can't just do those at the moment, wherever you want to.

[Researcher\_1] 1:15:46

[CFG2\_6], I think you've said that quite a few of your samples came in from across the [region of England]? Do you have much issue with sort of transport and logistics side? Or do they come to you relatively quickly?

CFG2\_6 1:15:56

It's interesting that this problem has already been raised with tobramycin we have exactly the same problem and [city]. Tobramycin levels almost exclusively taken at one centre and have to be transported over the city to be tested elsewhere. Now, the centre where they are actually taken does have does have the facilities to test them. However our blood sciences colleagues refuse to do so... So there's there is always a delay in testing while specimens are transported over the city, and that can cause problems, particularly specimens taken, you know, sort of late evening later on... and that will obviously mean at least a 12 hour hiatus before the specimens are actually tested.

[Researcher\_1] 1:16:43

And that refusal [CFG2\_6] from from the centre is that based on, ownership or funding...?

CFG2\_6 1:16:52

They allege they are too busy. Right, that we're just, you know, this would just entails but putting specimens onto their onto their tracking system, which would take no time whatsoever.

[Researcher\_1] 1:17:03

See, there's a lot of issues then with with movement of samples between centres. Sounds like, okay,

CFG2\_3 1:17:09

Just just to chime in. Sorry... Would there be any utility almost in having like almost like a whole monitor then like blood glucose monitor for tobramycin, the equivalent of finger prick, and it comes out with a number that the patient then reports in some kind of portal or something, I don't know.

CFG2\_1 1:17:30

If it could be done, it would be amazing. I mean, when you see what's starting to happen with the immunosuppressive levels, and they're increasingly being done on finger prick samples, which are posted to transplant centres, there's Azol sensitivities and levels of anti-fungals that can be done that way at the moment, it's fingerprick in a post, so there will be a delay. But it Yeah, I don't know how uncomplicated or complicated it would be. But to some degree, that's almost better than diagnosing because you've already made a treatment decision, you're treating the patient and that is making sure that treatment is safe and effective.

CFG2\_2 1:18:13

It's not just tobramycin levels it's amycasin levels we currently send from [city] to [city] be assessed and that those levels can take a long time to come back. I haven't had a patient recently needing amycasin but it's two to three days sometimes.

CFG2\_1 1:18:32

[city] might do most of the country because [country] to [city] and was like that just we couldn't get them done on the island of Ireland at all, which is crazy.

CFG2\_5 1:18:41

I think [city] do their own amycasin. I'm not aware that we send our amycasin to [city], but I guess if it's three days, that's a long time to wait isn't it to know are we getting the levels right and are we are we giving somebody too much? You know, I think it would make you feel I'd make me feel a little bit uncomfortable I gues, but the pharmacists are always worried about things aren't they? So that's fine.

[Researcher\_1] 1:19:09

[CFG2\_6], you got something to add there have you?

CFG2\_6 1:19:11

Yeah, we do our own amycasin testing in [city] we obviously have the same exactly the same issue as we have with the tobramycin levels.

[Researcher\_1] 1:19:21

When we're thinking about the sort of test characteristics in this realm of exacerbation and infection in CF, what are the kind of test characteristics do you think that the most important so in terms of say, you know, the scope or the test performance accuracy, we've mentioned a little bit about sensitivity and specificity. The cost, the time to results, the type of sample that you might be using, who performs the test. You know the kind of design features and interconnectivity with the patient management systems. What are the what are the kind of top three characteristics that you think are important for a test coming into diagnosis of infection in CF, this kind of area, maybe we'll do a bit of a round table thing just to get everyone's views. [CFG2\_4], do you want to start off?

CFG2\_4 1:20:11

accuracy. Top, obviously. And then I suppose specificity, isn't it after that, and speed will be my next. Top three, essentially. Yeah.

[Researcher\_1] 1:20:26

It might be a silly question. But why is accuracy top?

CFG2\_4 1:20:29

And we can't make a decision unless you confident in your result can you? You've got to delay treatment in order to sort of follow that up with subsequent results. If you're not sure whether of the accuracy.

[Researcher\_1] 1:20:47

ok. [CFG2\_3]?

CFG2\_3 1:20:50

For children, non-invasive, I think, if we can, that'd be really important. And then obviously, I agree, accurate results. That's that's important as well.

[Researcher\_1] 1:21:02

Sorry, for those that are coming at the end. It's always one of those things where someone's already said all the things you wanted to say, [CFG2\_2]?

CFG2\_2 1:21:12

Yeah, I agree. It's, it's, it's accuracy in terms of is this is this test, clinically, clinically relevant, and helping me with my treatment decisions? So having got the result of this test, am I further along knowing whether or not I need to change this person's treatment or not?

[Researcher\_1] 1:21:39

It's that action on result that's important? do you think? yep. [CFG2\_1 ]?

CFG2\_1 1:21:45

Yeah thanks. So I'm just thinking go back to the real basics of what we teach our medical students, the ideal test is, will it change your clinical management? And that's the key isn't it? Because you would never ask a patient to do a test, just for the sake of getting information, the aim would be that you would change their management based on it. So accuracy, reliability, and reproducibility. And then patient acceptability, which will obviously vary depending on the patient and the age of the patient, I guess. And speed is important, but to some degree, I'd rather have a test that takes 24 hours, but I can act on it, than one that takes one hour, but I don't know if it's wrong or right.

CFG2\_5 1:22:35

Yeah, I'm just reflecting on that. I think actually, I think I agree with that. I think that speed sounds like a great idea, doesn't it? But if you then have to do another test to be certain of the result, actually, perhaps if you can wait a little bit longer, as long as it's not too long, then maybe that's the most important thing.

[Researcher\_1] 1:22:58

[CFG2\_6]?

CFG2\_6 1:23:00

accurate information initially. We always get large number of specimens that turn up. This isn't just a problem with CF, it's across the board, where we aren't given the appropriate information. And this is particularly significant for CF sputum specimens that turn up without the relevant information, the inappropriate culture media will be put on, and reports and everything else following on from that will be delayed.

[Researcher\_1] 1:23:29

And do you think without naming any names? Are there any particular culprits?

CFG2\_6 1:23:37

I'm sure they will be.

[Researcher\_1] 1:23:40

Fair enough, samples coming in, say from the GP or someone who's not necessarily accustomed to doing these kinds of sample types more often is that where you find that there's more issues?

CFG2\_6 1:23:53

To be honest, the chest clinics are the worst offenders, who should know better.

CFG2\_1 1:23:57

yeah, I think it's because to be fair, in the interest of efficiency, for example, our nurses and physios sometimes print out everyone's sputum sample request, prior to them coming. So they just write CF sputum surveillance or something, because and that's just logistical, because we only have one printer, and everything's electronic. And if you try and do it at the time, then you hold the whole clinic up. So there are sometimes it's not intentional, and I hope that we do ethically. But I do know that for example, from a standard clinical review, sometimes things are done in preparation or done by someone who hasn't actually seen the patient and they're just they're trying to get the flow through. I know our physios have talked a lot about induced sputum and trying to make sure that they recording all the information for you, [CFG2\_6], that it is an induced sputum and how precious it is, and exactly what they've done and given to the patient in order to get it, so that you can put that into context.

[Researcher\_1] 1:24:56

[CFG2\_6], was there anything you wanted to say?

CFG2\_6 1:25:01

No, that was that was just that was an error?

[Researcher\_1] 1:25:04

Yeah. Fair enough. Well, I was wondering if it is it something that you know, could the form be better? Or is it? Is it purely something outside of that? Do you think?

CFG2\_6 1:25:17

Well, we have a combination here both of forms and electronic ordering. It's, you know, I think it's just what happens on the day basically.

[Researcher\_1] 1:25:26

Okay. So one part of the discussion that came up there a little bit was about if the accuracy was good enough, the time to results can be more flexible, which I think we could very, very lightly touched on right at the start was how long can we wait? How long can you wait for a result that you're happy with? Compared to say, something you could get instantaneously? That might give you an idea, but perhaps you can't act on entirely? [CFG2\_5], what would your views be from a pharmacy perspective?

CFG2\_5 1:26:05

I don't know, I suppose, trying to think from a realistic perspective, I imagine that it's going to be in an ideal world, what you could hope for, it's going to be very different if it's something that's like a slow growing NTm compared with a fast growing bacteria. Sorry, I'm not I'm not sure I've got a proper answer to that really sorry, I let someone who is brighter than me come up with something.

[Researcher\_1] 1:26:31

I don't think that's the reason is a very, very tough questions.

CFG2\_2 1:26:37

I would say in a person with cystic fibrosis, on a modulator. So you're less worried about them, Who presented in clinic with cough, say, and you did a near patient test that told you they had respiratory syncytial virus and no major bacterial pathogens, then I could be confident enough to potentially send them home without giving them a course of oral antibiotic, rightly or wrongly, and not every CF clinician would agree with me probably. But I think in someone on a modulator I'd be comfortable with that. Whereas currently, I probably send them home on an oral antibiotic and wait three days for the culture results to come back. And then I may or may not draw that course of antibiotics to a close if, if the culture is negative. But of course, the culture is not 100% sensitive. So it's, yeah, this is an art rather than a science probably at the moment.

CFG2\_1 1:27:39

Definitely our, I guess the counter to that is that, that will be great. What we could do is do more what GPs do, which is you could get the test. And if you could have a reliable test within 24 hours, send them away with their prescription for their antibiotics, but tell them not to get it. And then they can get it or not, which GPs use all the time don't they for various particularly Paediatrics and, you know, if you within this timeframe take it if not, if things don't improve. And I think on the whole, CF patients as well, even if they are very unwell and come in, it's not rare, but it's less common, that they crash in. And they need to be admitted straight from clinic, it's more often that they phone and then they come to clinic, and then you perhaps arrange for them to come in the next day or the day after or wherever. So that speed is perhaps less of a problem for us because we have more control over our own beds. We have more control over when people come in. And we try to protect our patient's autonomy around that as well. So the clinic tests will be great in terms of does this person need something today? But actually, if you've already decided they need to come then you've got a little bit more of a window to decide what you do, I guess?

[Researcher\_1] 1:28:57

[CFG2\_4] you got your hand up there?

CFG2\_4 1:29:00

Yes, I suppose it depends, doesn't it on what bacteria or what? Whether it's microbacteria, whether it's bacteria we're looking for. So know, one example we've had recently is we had a patient admitted to hospital for two weeks, was sending our regular sputum samples. They'd been discharged home at the end of a two week IV admission and their last sample that we sent grew Pseudomonas at the end of the IV antibiotics, and at which point obviously, they'd gone home. We hadn't, you know, test dose them. This was a new Pseudomonas growth. So we'll be starting eradication therapy. So again, there was that delay to get them back to clinic to test dose with inhaled agents. So I suppose yeah, I suppose I'm thinking along the lines of a new Pseudomonas like that you want to action a bit quicker, you don't want to be waiting around and the same way as you maybe can afford to in in other situations. So yeah, I suppose that's something we've noticed our turnaround since COVID, from lab results has been a lot slower. I don't know if that's across the board. But yeah, we're noticing more and more that potentially people admitted, we don't know results from admissions until after they've gone. So again, the clinic ones are subjected to the same sort of delays.

[Researcher\_1] 1:30:24

Obviously, in an ideal world, a test would be 100% accurate, and we'd be happy to rely on it all the time. But that's not obviously the case. What if the balance is between sensitivity and specificity? And which one's more important? So we're talking? Should we be having a test where everyone who is positive definitely has a condition that needs to be tested? Or do we want to have one where everybody who tests negative can be left alone? You know, that they're perfectly fine? There's a little bit of a balancing in there. So do you think it's, it'd be better to say, bring more people in with a potential exacerbation knowing or infection knowing that some of them might not actually have anything? Or is it better to get the majority of people who have an infection, but we might miss one or two of them using this test? But do you think the balance is? [CFG2\_3]?

CFG2\_3 1:31:22

Not Really, I'd have to think about that for a bit longer.

[Researcher\_1] 1:31:34

that's okay. This this is like really deep into into diagnostics here, [CFG2\_5]?

CFG2\_5 1:31:40

I was just wondering, does it matter what the consequence of whatever you're looking for is? And that, so that might be either clinically or could that mean that that might impede your chance of having a transplant later on? Or might it depend on the person that's in? so if you're immunocompromised, you know, maybe knowing whether you've definitely got something or or not, is of a different clinical consequence than somebody else? Maybe. So maybe it depends on what you're trying to find.

[Researcher\_1] 1:32:21

Does anyone have anything more they want to add?

CFG2\_2 1:32:25

I kind of feel that knowing someone's definitely clear of something is is really helpful in CF. And what I worry about with diagnostic tests, increasingly with, PCR techniques, and all of this is, is that we might have a danger of being oversensitive, and worrying about all sorts of things that actually aren't clinically relevant. So I suppose I'm worried I'm worried about over-sensitivity really.

[Researcher\_1] 1:33:05

Do you think there's much use in like combination testing, say, if one test rules out this, but another one can maybe rule in something else, and you kind of get a balance by doing multiple tests? I guess that kind of addresses what you were mentioning there about over-sensitivity, if one test says you might have something and then you do a follow up test, and that says the same thing, you might be more inclined to agree with it. If it says something different, you might go back and readjust what you think the kind of combination of tests might be that you'd be confident in?

CFG2\_2 1:33:40

That can be helpful, but at any test where you have to speak to a family and say, We found something on this cough swab, we're not sure what it is, we're going to run some more tests, it creates anxiety for the family. And yeah, so you kind of want your first test that you do to give you a reliable, as reliable an answer as possible. And then you can make the phone call and have the plan all in one episode. Wherever possible. I think that's much easier for families and for the people who have CF, I think that's my perspective from from my angle as a carer.

CFG2\_1 1:34:27

from a patient perspective, that's the question, isn't it? Is it better to know that you don't have something X or Y, so you don't have Pseudomonas? But I can't 100% tell you what you do have, for example, is that more anxiety inducing, or saying, Well, I think you've got pseudomonas. But, that might not actually be true. And that might be worse actually, because then you're kind of opening a lid on something that carries a lot of connotations, whereas being able to be clear about, like [CFG2\_5] said, the really Important things. Most people would be pleased to know they didn't have that, and then would bear with you while you say, but it could be x, y, or Z or, you know, these other things it could be. And we suggest you up your airway clearance and do this and give a plan. And I guess maybe that actually is. And I think we've seen that was COVID, Haven't we, people just want to know they don't have it. They're slightly less worried about what they do have. But they want to know, it's not that. And I guess maybe that would be something that's worth asking the patients actually as to what they would rather in that situation, and what they would feel more comfortable with.

[Researcher\_1] 1:35:39

absolutely. And then that leads us quite neatly into the final part of our discussion for the last few minutes. So we did a similar thing, not the exact same kind of questions. But similar thing with with patients earlier in the year, which which [Facilitator\_1] helped put together, I think [Researcher\_2] was in there as well. So I wanted to share some of these feedback with you guys, and just trying to get a bit of a, you know, your views or your discussion on that. So we we did the top three kind of characteristics, the similar kind of thing that we did with you guys, we actually came up with five in the end. So the ones that came up were accuracy was the first one because they wanted to be confident that they were getting the right treatment. It sounds broadly similar to what you guys have said here, time to results was very important to them, because they were quite concerned about empirical antibiotic use. And I think this has came up, perhaps more so with the modulators as well, that the they're a bit more concerned about being given antibiotics all of the time, the speed in which it takes to do the test. So one of the things that came up quite a bit in that discussion was the kind of impact on the patient's lives themselves. And there's a quote that I've used far too many times now, which from one of the patients that which was CF is like having another full time job. And that kind of gives you the sense of the amount of time and the amount of brain kind of capacity and the, as you say, worry and anxiety that goes into all of this kind of stuff. So I think the speed, the impact it has on their daily routine was quite important to them. To go hand in hand with that is convenience as well, that was another one. So a lot of them preferred to have something that would be done at home where it wasn't reliant upon coming into the clinic, or it wasn't reliant upon going into a GP or so on, something they could do at home. And something that wasn't necessarily done every single day, where it wasn't sort of regimented on them that they had to do this, you know, twice a day, or three times a day, or whatever that might be. And of course, acceptability. And that one was a bit more varied. I think in the response, as we've kind of discussed here, what people are accepted, or find acceptable is quite varied. So some people were discussing that they'd much rather have something like, what did we say this at the start, like a nasal swab, or a sinus sampling or something rather than doing well, bronchoscopy or throat swab or so. But some people were very much against, say, blood testing, which others found would be quite acceptable. I mean, they sound fairly similar to what you guys were thinking, Do you think? Does that all make sense? That's what you've seen in your practice, as well as what the patients are reflecting back to you?

Yeah. Okay, that's good. It's good to know that everyone's on the same page. The other thing that we discussed briefly was, what the impact, sorry, what the percentage impact is on decision making between the clinician or the clinical care team and the patient themselves. There was a lot of variability in this, as you might expect. So some of them were saying, oh, you know, I've been doing this for years. It's sort of it's 50:50. I say this, they say that, and we're all happy on the same page. Others, especially the ones that were parents of young children with CF, they were saying they didn't, you know, they're a bit kind of swamped, and they're underwater, and they don't really know where they are. And so they were much more happier to take a backseat and let the clinical care team make the decisions and then work that into them as it goes. So obviously, I've made a mistake here in telling you what their answers were before asking you what you thought felt, but what do you think the impact is in what's the kind of percent split between decision making in patients and clinicians? What do you kind of find in your practice? [CFG2\_4], should we start with you?

CFG2\_4 1:39:26

Yeah, so again, I think it depends on the type of treatment or the you know, what it is you're treating again, and again, the consequences. And I know specifically, the discussions that I have with people around nebulizer use, and it's very much again, in the case of new pseudomonas, that we're very, you know, strongly saying that this is something that you should do, in order to eradicate, but then having said that, in those who are chronically colonised, not exacerbating haven't had samples for a while, and have stopped taking the medication. It's quite often, you know, a different decision or a different sort of more collaborative approach of okay, well, we'll keep an eye on things, if things change, we'll change the approach. And so again, I think it varies. I mean, it's always collaborative, clearly, especially in adult care. But then the strength of the message, I suppose, varies depending on the consequences of, you know, treatment or not treatment, going forward.

[Researcher\_1] 1:40:35

And [CFG2\_1 ], do you find that's the same in adults, as well? that kind of back and forth.

CFG2\_1 1:40:42

Yeah, I think so, I think probably, I've always worked on the principle that I will outlay the options, and [CFG2\_5] will laugh, because I've often got Plan A to Z for some of our patients. So this is what we could do. This is what we would suggest you do or what we feel is the best course of action. And this is why, but it's up to you. And you need to make the final decision. Because in adults, particularly, they just won't do it. Unless they're happy and feel that it's a decision that they made the final and sometimes that's very nice middle grounds, like saying that inhaled antibiotics, were suddenly happy to carry on on a month on month off, but they wouldn't want to do something continuously. So if you give them options, people will usually find something that works for them. Teenagers is a slightly different level of conversation. And we do anything from you will do this, to which they don't. But sometimes that's what you end up. Don't do anything, as long as you understand what the consequences of not doing anything are. And I guess for me, we work quite a lot on patient leadership and things. For me, it's just making sure patients understand what could happen if they do X. And what might happen if they do what I just say they are prepared for those, and then they can hopefully make that decision for themselves.

[Researcher\_1] 1:42:02

Great. Thank you, [CFG2\_1 ]. [CFG2\_3] iand [CFG2\_2], from a more paediatrics kind of side of things. What are your views on the kind of patient or family and clinician split?

CFG2\_3 1:42:15

I suppose, in paediatrics, it depends on the age of the child. So I think when they're younger and their babies, then I think it's the health professionals sort of telling you what they feel should be done. But then as as they get older, like [CFG2\_1 ] said, the teenagers, then you're definitely sharing their decision making because they're not going to always do what you tell them to do. So it's better to work with them. I mean, we work with families, when the children are much younger, but I think they perhaps listen to us a bit more, the parents. perhaps be more inclined to do what we suggest.

[Researcher\_1] 1:42:57

That's similar for you [CFG2\_2], is it?

CFG2\_2 1:43:00

Yeah, I agree with everything else we've said. It's in very young, recently diagnosed babies. Parents, in my experience, generally just want you to tell them what they need to do that, that they're coming to terms with, with this new condition. And they don't want to know all about the uncertainty of whether or not flu crops is a good idea what the evidence is for flu clucks. What is the evidence for a two week course oral antibiotic, they just want what, you know, what is what is standard care? Tell me what to do, and I'll do it, kind of thing in general. And then as they get more used to living with cystic fibrosis, I think, many of them will be able to deal more with some of the uncertainties and we'll be able to share some more of the uncertainties with them about well, actually, this is what we tend to do. But actually there isn't that much evidence for it. But they don't like to hear that at the time of diagnosis.

[Researcher\_1] 1:44:10

No, that's probably understandable. I think

CFG2\_1 1:44:12

Weirdly, our late adult diagnoses are the same. I had one this morning. She was like, just what do I need to do? Just tell me because you just haven't got the headspace to cope with the complexities?

[Researcher\_1] 1:44:24

Absolutely. We're coming up to the end of our time, I was gonna open the floor. [Facilitator\_1]. [Researcher\_2], do you have any questions that you'd like to add at the end? I think we have covered a good amount.

[Facilitator\_1] 1:44:37

Yeah, I don't think I've got questions. But I have got a long list of notes where you have said things that we've heard from the patient community through our focus groups, directly related to the TPP project, but also in focus groups discussing other aspects of, of their care, you know, detection and monitoring. [CFG2\_1 ] you said about, you know, the information going to parents, you know, if it's the first time that they've told you that they're growing something, and the anxiety around that has definitely been bought up. Yeah, the things like, you know, the use of antibiotics, but also the use of X rays and CTs, you know, say, as people are living longer, there's definitely things that they're starting to think about, you know, they're thinking about their longer term health, when perhaps they haven't been thinking about that before. Combining nibs, [CFG2\_5], you said about the Toby sampling, again, that's come up in conversations, you know, the the distress of one trying to get a blood sample, try having to return to hospital to do a blood sample, when you're trying to do high move IVs in the first place, getting a right amount of sample waiting for the result, or you're getting a call back saying, Sorry, that sample what we didn't quite get enough blood and we haven't been able to do the sample, and you're hanging on that result to do your next round of IVs. And knowing that if you don't get it, everything's going to fall out of sync. And you've tried got to try and pull it back to getting your IVs done in the hours that you've worked out, fit into your life. So yeah, there's a lot of distress around that. Yeah, say just so much better. There's so many notes that I've written down where everything you've said has resonated with those conversations.

[Researcher\_1] 1:46:32

That's a really good, that's really good thing to end on. I think, one question that we usually finish up on somewhere in the last minute, is there anything that you feel is important to tell us about diagnosing CF infection or exacerbations that we haven't touched upon? Is there anything that you sort of came into this thinking? Oh, this? Yes, I definitely need to mention this, and it just hasn't been able to come up, there hasn't been an opportunity to for it? No, we're all pretty happy. Everything was well covered. All right, fantastic. Well...

[Facilitator\_1] 1:47:00

Sorry. Can I just ask something in it from the last focus group, we had the clinic one, we I asked about the combination of testing. So if people felt that one test perhaps didn't give all the information they wanted, if you were able to have several of the easier tests that came together, in combination, a maybe gave you a bit more reliable result, as a as an overall picture, like a puzzle coming together that could give you a bigger picture. How would you feel about that, as opposed to relying on the results of a single, accurate test that could be difficult to get takes a long time for a result?

CFG2\_5 1:47:50

Does it depend on how you take that test? Like if you've got lots of little tests that give you a bigger picture? Can you still take one blood sample or one sputum sample or one whatever sample? Or do you need to take five or six different ones? And do you take them all at the same time? Or do you have to do them at different points in time? I imagine the acceptability for some of that will depend on what the answer to that is.

[Facilitator\_1] 1:48:20

Yeah, I think there was some thought around, say, like urine sampling for Pseudomonas might give you an indication, alongside nasal sampling, alongside resting heart rate, yeah, which is what people have reported noticing a difference, which could be picked up automatically on their smartwatches or Fitbit or something like that. And each of those things, say, coming together to form a picture that might present an alert and like almost like an early alert system.

CFG2\_1 1:48:59

I mean, I guess that's what project breathe just doing the alert is coming to us very soon. I guess we don't make clinical decisions in isolation, we always look at the whole picture. So having a better picture is better. As [CFG2\_5] said, it's then if you're going to have a better picture, that it's the right picture, because heart rate is something that we've looked at, I'm waving my Apple Watch around that, you know, patients report that consistently. But those are perhaps the things that you would need the evidence to say, really getting into my PhD things. This was what we were looking at as if we did everything, actually, some of the things that come out as important are perhaps not the things that we've traditionally accepted, and also the things that we think are important, are perhaps not important to the patient. So if you came up with a combo test, you'd probably need some research to say well, what's actually important in terms of say identifying infection, what correlates with you Micro tests, but also, which of those is important to the patient as well? And how early would they want to know that? So anything is possible. It's just trying to find that lovely, nice middle ground, isn't it in terms of what you can do, I guess it comes back to our false positive, false negative thing. But actually, if you can, therefore, be not just clear about what you haven't got, but potentially steer you in the direction as to what you have. That would potentially help people would need to feel more reassured.

[Researcher\_1] 1:50:34

Thanks. Thank you very much for that. And thank you for that question as well [Facilitator\_1]. We're slightly over so we'll let everyone get off. But thank you very much for joining the focus group. I've certainly got a lot out of this. This has been fantastic. I'm sure the rest of the team have as well. But I hope you guys have have enjoyed the conversation.

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