1st WG Regulatory Meeting 2025: Minutes

WG Leads

Klaus Pantel, Ariane Hallermayr, Remond Fijnemann

Meeting Minutes / questions to the Speakers & Discussion

Welcome and introduction by the WG

Klaus Pantel

Good afternoon, everybody. It's really my pleasure to welcome you all here to the regulatory working group of the European, the good vibes to society, and I know that some of you who are not here are probably already on vacation, but I guess we still have a lot of people interested in the LBS and the regulatory working group. And I would like to thank also. Svenja and Josef Vaas, who is new here in our administration, who have helped together with Raymond and many others to prepare this meeting today for the next couple of hours and uh. Those of you who live in a hot office like me, you know, I mean, please. Uh, be sure to refresh. Uh, before you started during the meeting, you hear everything about the climate catastrophe. I'm not sure whether that's already the case, but at least the north seems to be the New South. That's at least my feeling so with these stupid words. I would like to hand over to Raymond. I think it's veneer. And please let us know what is the agenda for today that everybody got and then we can get started.

Remond Fijneman

So I think the agenda for today was sent around maybe good to mention in addition, also Ariana, who worked on this session and. In this particular session, I will kick off actually building upon where we left November 27 in Barcelona when we had the workshop on the regulatory group and then Ariana, you will present on MRD in Germany. And I think then there's a presentation by babies from Sysmex and Christina Michler. Who's doing climate sorry. Can someone do a bit of time management, in particular that that we do not go overtime on the on the first part so so please keep track there. So yeah, if you could do that. That would be great. Then I will. Try to share some slides and see how that works. What's happening?

1st Presentation by Remond Fijneman, PhD (Translational Gastrointestinal Oncology group, The Netherlands Cancer Institute); Title: How to visualize the complexity and diversity of biomarker implementation in Europe

Ariane Hallermayr

Now we can see your slides, but not in presenters mode or just regular PowerPoint.

Remond Fijneman

Yeah. So I'm. Trying to get this organised. She's right. Now.

Klaus Pantel

Yes, perfect, good.

Remond Fijneman

And then I get in trouble only seeing. Part of it, OK. So I do not see you anymore. So please once in a while, give the sign of life. That will be very helpful. And it's important to say that this part of the session was prepared by. Dan from the. Book who's joining me here now? Felesky hotel. And Paul on the list. And I hope. Well, Paul is travelling at the moment. I hope he is at some point back in time to take over. I think he is in the call, but if not. So Paul, you let us know when the latter part you can handle it or that we should handle it from here. So maybe a very. General remark on the Working group regulatory, we pursue the overarching goal of driving implementation and the introduction of liquid biopsy assays into routine clinical practise. That's a great goal to have in mind. But building upon the workshop that we had end of November in Barcelona, I think well, one way that I left that meeting was besides that it was a very interesting and enthusiastic meeting. I think the feeling I took home was also things are really complex. But we did. Try to formulate the number of action items at a time. One is that we fall off writing a position paper to increase the knowledge and awareness about the current hurdles and gaps in the biomarker implementation process. And actually this is the key topic of this part of today's session. And just to mention some of the other action items that we. Tried to compose following that meeting is to see whether we should install expert review teams, whether we should provide recommendations for guidelines. Whether we should seek the dialogue with and ask advice from the EMA to formulate the best practise regulatory framework for EU biomarker regulatory acceptance and implementation to seek endorsements by medical professional societies like ESMO but also on the national level. And to seek dialogue with and ask advice from EU Member States National Regulatory Authority. This, but I think this was put on paper. A bit narrow. We should frame this European countries who need their national regulatory authorities and from there formulate the best practise frameworks for biomarker regulatory acceptance and implementation. And although these. That the bullets are not a key topic of today, they will briefly return in some of the slides that I want to share with you. So. Maybe you were all there in November and then this is repeating the slides that were shown. But I think for today's discussion, it's helpful to at least go through them again once more. So what are the show stoppers of European

biomarker implementation? And so at the time, but also in the way that our thinking frame may evolve and position the problem, it's good to start with something that is in place and that is drug development and approval. From discovery in the lab to preclinical development to formulation in a way that drugs can be administered to patients. To clinical research in its phases 1-2 and three to evaluation and approval, the steps to adoption, bringing drugs to the patients is the steps that are needed. For the drug development at approval. And so here, there's always a disease and a specific condition that you want to treat. You have thought about the outcome measures like overall survival and importantly for today's discussion, there are authorities that are able and will take the responsibility to. Evaluate the drugs and to give some to our authorised to give some kind of approval and of course on the European level, that's the EMA on the Dutch national level. Those are instances as CBG, commissive ordering Chinese Midler. Sea bomb, the government, etcetera. And so the point that we wanted to make at the time is that European and national authorities define the rules and what makes Europe different from the US is, to some extent maybe to a large extent, solidarity aiming for. Healthcare for all, rather than best care for some who can afford it. But of course, when you work from solidarity, you need to think through. Who? When you are able to reimburse some drugs so you have to think of the predefined criteria. But once those predefined criteria are there, pharma knows what studies to design. Knows that there are authorised regulatory bodies who can evaluate and approve the drugs and in this way, even though laborious, there is a structured introduction and there is a path forward to reimbursement of the medication and to adoption of the drugs. Access to the patients. So in this complexity. There are steps that are taken by the EU. And there are steps that are taken on the national level, and I think at the time I gave this example, which I never checked, but I just got it by asking check GPT. But there are some aspects that are variable in the different columns. If you start at Emma and FDA and you look at the focus, the focus is on safety, on efficacy and at the EMA, on quality. But when you look at cost that is not assessed. By the EMA. In the end, the EMA will make sure that there is marketing authorization. When it comes to cost, you can see that this is relevant to the different nations in Europe, and that there's variability in what is important or less important in terms of the cost, but also in terms of whether you're addressing an unmet need. And in how evidence is being generated? And I think this aspect of diversity among countries is something that we hope to get back on later on also for the biomarker implementation path. So when you now put the drug development pipeline next to. That of the. Biomarkers. There's lots of resemblance starting from biomarker Discovery assay development, analytical performance test characteristics, clinical performance, clinical research in terms of prospective and interventional. Trials evaluation and approval and adoption, and what we aim to do are things like determining prognosis, for instance, in the case of MRT testing or treatment response monitor. Where the outcome measures can be in terms of the tests, the sensitivity, specificity, positive and negative predictive value. But when we get to the questions regarding evaluation and approval, in particular when the biomarkers are not predictive biomarkers, when the biomarkers are not connected. To medication use. Then there is a problem. Basically there there's a lack of systematic structured way, so the predefined test requirements for a clinical application are basically not there. And as a consequence, because they are not there, it's very, very difficult, nearly impossible to design a study where you, As for instance A biomarker company would have the purpose of showing that your test. Can't stand the the the the questions at hand and and can be evaluated and when meeting the requirements should be approved. So this authorised regulatory bodies are basically lacking and so the consequence is what we are doing today and what we're doing today. Is basically apply or you can

instead of apply when you shoot opportunistic introduction ad hoc in hospitals or in regions of Europe where in. A partly non evidence based manner, biomarkers can be introduced and this is the type of anarchism that I'm afraid we are heading to. But it would be nice if we can avoid it. Who can define the test requirements for prognostic air response monitoring biomarkers? And this was 1. Of the questions I think posed end of November in Barcelona and one of the discussion points, or actually lots of the discussion was about what ELBS can and would like to do. ELBS is a fantastic public private. Society with lots of CTD, DNA and other liquid biopsy expertise. And and we can have a voice and we have projects and initiatives that where we put together the experts in terms of what test requirements should be met for applications like MRD testing or like response monitoring. So getting back to one of the action items, something maybe not for today, but something to think about in this context is, is this the context where expert review teams should be put together to provide recommendations for guidelines? The other is who can and evaluate well, who can evaluate and approve the biomarkers at the time I made a little joke, I turned Emma into the necessity of an EB A so not a European medicine agency, but the European biomarker Agency. Someone actually mentioned this to the EU and they were immediately. Allergic to a new institution? So I'm I'm. I'm not going to do that again. I'm not putting on paper that we should install the EBA, but to some extent I think we need to find a mechanism. Where. Preferably in context of Emma, there is a biomarker department understanding the needs of biomarkers that are not related to the drugs. So somehow we need. To seek the dialogue with and ask advice from the EMA, we need to formulate the best practise regulatory framework for EU biomarker regulatory acceptance and implementation. So this is also one of those action items that needs to be followed up upon. Now, Doug. Is leader of the coin initiative in the Netherlands. Coin stands for circulating tumour DNA on the road to implementation. And this was a project that has been around for quite a few years. It united basically lots of the CF DNA experts in the Netherlands. It's connected to the CF DNA day where we now actually see participation from Belgium and. Germany. But it's good to think about how. Each and every one of us from our countries where we are based. Whether it's useful to unite the CFD DNA experts and think how things are organised in our countries in terms of the path to reimbursement and how biomarker testing in the end. Practically can be offered to patients. So on the national level as well as on the European level, but also on the national level, it's important to seek endorsement by medical professional societies. To seek the dialogue with and ask advice from the European national regulatory authorities, but also on the national level, formulate a best practise regulatory framework for national biomarker regulatory acceptance and implementation and a system in which there is a national gathering, maybe even a national society, connected to elbs. Could be a mechanism to stimulate this? So zooming out, what are the key questions for the biomarker implementation? Well, is it safe? Is it useful? Is it affordable, accessible, available? When we ask the question, is it safe? We think in terms of pre analytical and analytical test performance and how a test performs in clinical samples. When we asked the question whether it's useful, we are discussing basically clinical utility should not only be clinically applicable, but should also gain health at acceptable cost. And that is also that part of is it affordable, accessible, available meaning what is the regulatory path to reimbursement and how do you arrange to test adoption in routine clinical practise? When you don't think of the the. Aspects that are more on the European level, like ivdr. Versus the aspects. That are more on the national level. Which and how our health insurance companies paying for a test? For instance, you can see here part of the complexity of these different questions based on the different organisational levels. And so that's. This long introduction, but basically recap of where we left in November. Leads to the question if we want to

achieve these things, maybe one of the first steps to do is to really have a position paper, a position manuscript that clarifies demonstrates how we can visualise this complexity and diversity of biomarker implementation in Europe. And So what we want to discuss today is how can we get to such a position paper and what we propose to do is to use the introduction that I just gave as a backbone to a manuscript. But what we need is kind of a table in which we succeed to really visualise the complexity and the diversity in each of the different settings that we are working in. So Paul, I'm hope you're still on board. Where are you? Paul, are you still travelling or Are you ready to take over?

Paul van der Leest

Yeah. My apologies, Damon. I'm still on the road, so if you can can have this part please, and I will join you. For the discussion later.

Milena Cavic

Good.

Remond Fijneman

And that can help me out here as well. So the idea is to write the position paper but it should contain something like a table in which we touch upon the different features that matter to biomarker. And so in general, well, the problem is that the way we are moving forward today, it will result in unequal access to innovative diagnostics. So for instance, we already mentioned US cancer patients have access to CTD, DNA testing, of course with the site remark when they. Have the financial means to pay for it. But today. EU cancer patients don't, or at least don't, in a structured manner, have access to CTD DNA testing. Why not? Well, part of it just explained. It leads to the unregulated integration of CTD DNA testing in routine clinical practise and it. Stimulate inequity. We will at the moment see ad hoc locations in Europe where CTNA testing is offered and maybe several of you do offer ctna tests to patient. But it actually contributes to in equity instead of equity. So the goal of the position paper is basically to highlight the current trajectory, to show the existing gaps in the biomarker implementation process across Europe. And the way to do that is to identify the key barriers that hinder adoption in. Europe and in the EU Member States. And so the approach is to conduct a survey and assess the implementation status with you in the call here. And and see where each and every one of us is in this process. And then we want to analyse the survey results and pinpoint the critical factors for successful biomarker integration. Now the way that we thought of building up the survey, but this is open for debate. Is to basically follow a little bit this biomarker path from discovery to implementation, but to focus the questions on general well in addition to some of your details where you're located and and institution etcetera, but then to focus on. Generally, could biopsy information on pre analytical analytical perform? On questions regarding clinical performance, approval and adoption. So we will take them now 1 by 1 and again asking you afterwards on feedback, what things are missing, whether you feel where we can adapt or improve such a survey. So when it comes to the general liquid biopsy information, of course we can apply liquid biopsies in various ways can be applied in context of different tumour types. It can be applied in terms of different clinical applications like MRD testing like gene mutation profiling like response monitoring. So how is it used? In clinical practise. And then we have questions about the performance evaluations. So what are the criteria for the performance of the biomarkers that you use?

And in the labs were CTD, DNS tested. What are the accreditation requirements for these labs you complement me later.

Klaus Pantel

Yeah, but.

Remond Fijneman

And and then in terms of the reimbursement, is the test reimbursed, do you have your local budget for a sequencing test? And then locally you succeed to squeeze in CTD DNA testing in your own local budgets, no need to inform specifically any health insurance? Company or the government? Or do you have a structured way in which really city DNA test as a CT DNA test is covered by insurance companies or by governmental funding? Moving to pre analytical analytical performance, how? How do you know? How do you decide which test is suited for the purpose that you're using it for? Or have in mind? And are the pre analytical requirements standardised? What are the predefined analytical? Performance criteria. When is the test good enough? What in terms of asset performance validation and then in terms of technical performance or reference standards that you use and related to the clinical applicability? Other things to come to mind than to explain this further.

Daan van den Broek

Oh, I think I think a lot of labs will be will have an accreditation and then basically that's your background against which you do this. Just to explain a little bit more on what you can make this really difficult or just think about what's being done in in really day practise.

Remond Fijneman

They're regarding clinical performance. How to assess the clinical utility? What are the clinical performance criteria? When do you? When do you consider or decide that there are sufficient clinical utility? Is it necessary to have a randomised controlled trial or do you deal with real world data? Regarding the type of data accuracy of the data, the outcome that's measured and whether cost effectiveness analysis are done or not. And regarding health, technology assessment is that the necessity for the cost effectiveness or not? And when you do it in, in which context is this done? This is done simply by looking on a per test basis or do you take the clinical component where the patient is in the journey? Into account? Or do you take the whole patient journey into account? Regarding approval, when can an SEC be used in clinical practise? Which performance criteria must an assay meet to get approved? How is approval granted? Who is entitled to approve? We are looking forward to whether you have answers here. This is where in the Netherlands we have challenges I guess to come up with clear answers.

Daan van den Broek

Absolutely.

Remond Fijneman

UM. And then the reimbursement in clinical practise, so if there is approval, does that truly lead to reimbursement in your setting in your environment or not? Adoption, if there is an assay that is approved, who can use it? Is this adoption regulated? Is it offered in all hospitals to all patients in your country or is it just a few hospitals? So in that respect is equal access to biomarkers? The shirt. And reimbursement in clinical practise is the reimbursement. So the fact that the test is reimbursed A requirement for adoption, in other words, if it's not reimbursed for definition, you cannot offer it to the patients or other ways in which to circumvent this in in clinical practise. In your environment. I think this is where I would like to stop. And would like actually to stop sharing if because otherwise I don't see anyone. I would very much to like to have your feedback on how to get to this position paper and in particular. Pillar. Yeah, your thoughts about filling in a survey that's relates to a table for which the key purposes basically to show the complexity and the diversity today and use it then for our further agenda trying to smoothen the path. So. Implementation of the biomarkers.

Daan van den Broek

Yeah, I think it's good to emphasise that the questions are not aimed at we've we've already been been filling it in and I think it's especially interesting and and relevant to also say, OK, I don't know or it's not there. So it's not to. Get answers on. What should be? There, but it's really the the, the, the, the situation at this moment to really get more insight in, OK, what's lacking, what can we learn from other countries, what are the options and what are the challenges?

Klaus Pantel

Yeah. Thank you very much really for this clear presentation. And I fully endorse that we should really make a survey and also start writing a position paper. I just saw that nature has a new journal starting next year. It's called nature health, and they already asked for submissions this year. This could be an interesting candidate journal. But of course there are also others. I definitely think that the liquid biopsy or the biomarker field in general is definitely a field of great interest. And uh, I think that uh, all your points that you raised in your talk and are also applicable to other fields of biomarkers. I mean this. So I guess that you know that we have a good use case with liquid biopsy, but I guess that it could even draw a broader attention in the field, huh? I mean, there's no question. About it and I can only say that I fully also support the statement that if there's no clear road map, it is very risky for companies to invest in this field. I mean, imagine you would have no road map for clinical drug discovery. I mean, you know, you would not. Take $1 billion and just use it. You know the way you can. So I think that in the drug development, there's a clear sequence of events and things that need to be fulfilled that you have outlined very nicely here. And I guess in the biomarker or diagnostic development, it's indeed there is a lack of such a structure. This is one of my comments, so I think very welcome. The second comment is. I love the European biomarker agency and I love it even more that people didn't like it. So. So you made a good point. Obviously all all good ideas were disliked in the beginning, Lemon. So don't don't worry. But but I think I mean one could also talk with EMA. I know for example like the German Minister of Health has one agency that is taking care of all the grants or things like that. So I think that some of these agencies have also possibilities to outsource certain tasks you know, so you may not get such a beautiful name. But, but you may be in business if you talk to these, let's say, key agency, you know. So that's also something, I mean, they can get the light. I don't care, right, as long as, I mean we we contact them and find out what kind of let's say flexibility there is really you know no this was the two points but but I

would really like to open the discussion. As you said, uh. Are there any other points that, uh you would like to raise now? And please, Raymond, take over the discussion.

Remond Fijneman

Trying to look around, who wants to give some feedback? But I so I agree with you completely clause. And I think if there is a position paper, it helps actually as a pull back to be able to explain clearly and to to use it as the backbone in the discussions with the different agencies. UM. And whether it's an EBA or not, I don't care as long as someone really takes the responsibility to get the the the path streamlined for biomarkers like it has been for the for the drug development. So that's I think the key component. But. So.

Klaus Pantel

You speak up.

Remond Fijneman

Because I cannot see exactly who may have raised a hand or something like that.

Patrizio Giacomini

I I I don't.

Speaker

But.

Patrizio Giacomini

Know how to raise my hand?

Remond Fijneman

Are you doing well? I see your hand raised, Patricio, because you have recently done a survey, actually. So I was actually curious about your feedback and experience.

Patrizio Giacomini

Yes. So I mean that that is exactly my comment I shared with you the questions. I don't know whether you had the the chance to go through and maybe 20 to 30% of the questions that you wanted to ask in the next survey have already been address. By the survey of the European Union biopsy society that we have put together with the ensuring and Ellen Heights, so the survey is now closed, we got more than 100 response, far more than 100 respondents, and next week we will start to elaborate. So maybe I mean I I have to check with Ellen the head, but I'm sure that we can share the the result, the pertinent results with the relevant results. Of the survey to have a kind of a of a starting point to formulate even more detailed replies. On the specific topics, so I think I think we are in business for that. We have a coverage all over Europe. We do have a mailing list in case we want to involve other experts. For and I well, by the way, I'd like to thank Arianne because Arianne was involved in this and she suggested some

of the questions that we've been asking. So I mean, as you say, the European with biopsy society works very well because we are a real group.

Remond Fijneman

And that would give her a kick start a teacher. So that would be great. And and apologies that some of the questions will be overlapping with questions that basically people just replied to. But I am afraid that that's redundancy. We will try to keep it limited, but it will not be completely eliminated.

Patrizio Giacomini

I I said, I think we're done. This is not is not an issue. I mean it, it is possible now. I mean it is the topic that is totally different than the answer they was saying that determining what's going on in Europe. In this case, we will ask more what would do you think.

Klaus Pantel

Gee, yeah.

Patrizio Giacomini

That it is necessary to do next to want to have City settled.

Klaus Pantel

Yeah. Yeah. I also think it's complimentary and thank you Patricio and Ariana and everybody who worked on that survey. Hundreds of feedbacks, that's actually good. I'll, I'll I like. That cool, young Gee, I see you.

Yong-Jie Lu

Yeah, I just know it's it's clearly and I totally agree and I support for this. Yeah, the position paper and also the survey. And also there's a lot of the good idea in there and my is it one comment is that because it's a liquid. I'll say it is one in vitro diagnosis device devices and there are some Europeans individual device and the approval. The procedure I'm just thinking is that maybe we we can think. As well, how? How that can be linked to? Yet to this the liquid biopsy?

Klaus Pantel

Very good, absolutely. MHM. Good point. I see Milena. I see the hand that is from Elena.

Milena Cavic

Yes. Hi, hello. Sorry, I'm also in route. I if you can see me, I'll switch the around. So thank you very much for this meeting and I think we touched upon a lot of interesting topics that we will be discussed in Barcelona and and I thank Raymond for also including the non EU Member States voice which we also discussed. I think it's important because we will have more countries of course on the route to implementation of. All the things that we talked about, which are not currently Member States and I think we need to at least address it if we are going to write in the position paper, the point of view of these countries as well, I would be happy to collaborate with you on that we can. To the point of view of

Serbia as a representative of these countries, but of course I would like to make an overview of all the countries that are either on the white list or entering EU Member States and or other countries, as well as the specificities, as we highlighted in the meeting, are that we need to be compliant both with. Our national legislative, but also with the EU Member State legislative. So it's a little bit different than for the countries we're currently in the EU, I think. There are many important aspects to address, both for research for research which will be translated into the clinic. And it's a start. It's a very complex topic and it will of course depend on many national factors, but I think we can digest it. We've said multiple times. This is a very good group and we all have direct information from all of these countries for the implementation. So I'll be happy. And we will help out if if it's needed. I mean if you are taking on this voice as well, if it's only going to be focused on the EU Member States, then of course. It might be a little bit different, so just wanted to say that we we are really.

Klaus Pantel

Ohh you're you're very you're very welcome. Melina. You're very welcome. I think. I mean, for those who do not know Melina, she's from Serbia. And I think that we you're very welcome also to look at these. You know, states that may become a member sooner that are really part of our community. So you're very welcome. Absolutely.

Remond Fijneman

Yeah, and I think.

Milena Cavic

Perfect. Then we have the negative to collaborate with. The society the Scientific Societies collaborated with researchers and clinicians, so the EA, TR and the ESMO affiliated National Societies, we formed an intersociety working group this year and I think this approach, which we also discussed during the Alps meeting works because then you have the national Scientific societies. Pushing towards the government to hear the scientific voice.

Speaker

Sure. So.

Christine Mißler

Then.

Milena Cavic

That's the approach that we are currently doing in Serbia and they are listening to us. This is a very good step.

Klaus Pantel

Very good.

Remond Fijneman

Other remarks or questions. Otherwise, will now I'm going to ask you a question. You have a biomarker that's not a liquid biopsy but a tissue biomarker. Do you encounter similar problems?

Wilma Mesker

Yes, yes, it's uh. Well for that tissue biomarker I have contact with the. Uh, the European Society for uh pathology, of course. And well. Yeah. Let me tell you that I did so many attempts. Uh, to have it implemented in the TNM classification, which is now accepted, but the direction of the of the ESP even advised me to write an article about all the attempts I performed to have it finally implemented. In the in the TNM classification, it's well, I don't know if I'll if I will do it, but when I hear this presentation, I think it's worthwhile. Yeah.

Klaus Pantel

Very interesting. Absolutely we can. We can learn from each other. We can learn. So learn from long journeys to make a short on the future, yeah.

Christine Mißler

I could.

Wilma Mesker

I could write it down, I mean and and and and, well, let you know what steps I've taken to bring it that far. But it takes, well years.

Klaus Pantel

M.

Wilma Mesker

Now.

Remond Fijneman

Paul. Your your you see, you see more relaxed than than than driving at the moment. Were there aspects? If you want to further highlight or explain the next steps that are coming up.

Paul van der Leest

Yes, I'm here now. Now I think you explained it really well. This was indeed what we're what we have been talking about and we prepared the the questionnaire for so maybe indeed the next steps is that we would like to to if if there's any more comments on the on the on the survey, we would like to adjust it a bit and and. And on doctor's suggestions. And then send it out as soon as possible to give you the opportunities as well to to fill it in so we can collect this overview and then we will analyse the results of course and and try to implement this in the position paper which we are currently drafting. So yeah, if you have any suggestions, any comments please let us know. And then we we tried to to accommodate this as soon as possible.

Remond Fijneman

OK. Thanks. And and as soon as possible, we'll still be after summer holidays. I hope Paul because you're close to and that's probably many already in summer season.

Paul van der Leest

Probably I'll have some holidays here.

Milena Cavic

Yeah.

Remond Fijneman

If there are no more comments, remarks, feedback at this point in time. I think we can move on. Ariana, do you want to? Starts on the MRD part in Germany.

2nd Presentation by Ariane Hallermayr, PhD (MGZ Munich, Germany) + Nikolas von Bubnoff, PhD (Universitaetsklinikum Schleswig Holstein, Germany); Title: Project concept – MRD detection in CRC stage II patients to guide adjuvant treatment (Model in Germany)

Ariane Hallermayr

Yes, perfect. Thank you. Also, since we moved the meeting, actually Nicola Nicolas is here now as well. So we just spontaneously decided to do the presentation together as most of the part of specifically the clinical part. His background just for regarding the background of this presentation now. And so we started an initiative initiative originating also out of Alps where we plan our plan set up a project how we want to introduce MRD detection into clinical practise in Germany. And today we would like just to get you also into the loop loop. What is going on here? So just share my screen. Can you see the screen already?

Christine Mißler

Yes, yes.

Ariane Hallermayr

OK. OK, perfect. So I guess when I would directly like like to give over to Nicholas to present the. Background here. Let's see. It's working. Yes. OK, Nicholas.

Nikolas von Bubnoff

Hi, Anna. Hi everybody. Great to be here with you. So background of our use case is the observation that for localised colorectal cancer, adjuvant chemotherapy is not strictly done because uh we. Effect. Business is limited to high risk patients and currently these high risk patients are identified based on clinical criteria. For example, AT and MT4 perforated tumour, Ilios emergency surgery or less than 12 notes that during surgery. Dissected, and this is a very unprecise stratification of patients and we know

that for that reason in stage 2 colorectal cancer only less than 5. Percent of the patients receive adjuvant chemotherapy, so there's no strict recommendation in stage 2 and currently there's no biomarker that allows us to predict which patients have a high relapse risk. And this is the background for this use case because we know already from previous studies. That patients that after surgery they have MRD are that patients that are ctna positive, they have extremely high risk of relapse which you see on the on the next slide.

Ariane Hallermayr

At home.

Nikolas von Bubnoff

And with the hazard ratio of 18 and we know that this is not only the case for stage 2, this is also the case for stage 3. So this is a very parallel situation and this was the background for for a clinical trial that was started seven years ago by by Jeannie Thai and this is. A trial that is called dynamic trial. It has been presented with A5 year year update last year at ASCO and has been published in in the New England Journal. And if you go to the next slide, you can. See the trial design, which is very straightforward but very important to to to very carefully and analyse what what is studied here. So the the treatment stratification is based upon ctna positivity after completion of surgical treatment. So ctna. Positive patients receive accurate treatment and CT negative patient. And observation and this is randomised in a 2 to one fashion to standard management. So the actual treatment decision is based on conventional uh criteria. That means that in in the CTD and our guided guided management arm, the patients that are negative. And not receive excellent treatment. And so this is the trial design and on the next slide you can see the outcome. The outcome is that in the experimental arm where negative patients didn't receive atrovent treatment. There was a reduction of chemotherapy from 28 to 15% of patients that received chemotherapy without compromising the uh recurrence. Free survival, which you can see on the on the right hand side. That means that for CTD net negative patients you can you can leave. Without chemotherapy, without affecting the outcome of these patients, and you can see also the numbers below that couple of. Markov and so you can see that in the city guided management arm it was 300 patients and it was starting with 150 patients in the compared to in the standard management and and what we I don't know what is on the next slide is OK, but I can say that.

Ariane Hallermayr

Already the summary.

Nikolas von Bubnoff

The last ASCO a couple of weeks ago, we follow up study was presented also by Jeannie Thai. The Dynamic free study and this was a study that analysed. Intensifying intensifying treatment for stage 3 colorectal cancer patient and that was extremely interesting for the positive patients for the high risk patients that were not addressed in this study that I've shown you in in and in this study came out that it intensifying the treatment and positive patients does not. Improve the outcome, but what you see is that 60% of the patients have a clearance. The citation and clearance, irrespective of the treatment and these patients have an extremely good. Outcome and the uh the clearance dependent on the post surgical ctna burden. So patients with a high ctna burden have a lower probability of CTD neck clearance

which would be for for the monitoring aspect. This is not now uh directly affecting our use case but another application that would be extremely important to also look at the. CTD and a clearance with a hazard ratio of 11. So that was also a very strong effect. But now the the the idea behind the use case. We now have a situation where we have a biomarker that this identifies patient subpopulation with a hazard ratio of 18. So this is a dream situation and so our idea is that if we you know if we use that biomarker for clinical treatment. Verification. We have a reduction of cost. We have a reduction of toxicity and we have no decrease in in in the outcome probability. So there are in, in our view there's a clear evidence to transfer this biomarker into clinical application and and for. Purpose. We need a situation where we have reimbursement and reimbursement and where where we have standardised analytic analytical criteria because we, uh, it's absolutely critical that we are sure that we have a high analytical sensitivity and specificity. And this is where Ariana comes in now.

Ariane Hallermayr

Yes. No, we also still have here some real world world data, making it reasonable on for our use case I think, but really for CC stage 2. UM around 20% of all CC patients have the stage and Nicholas summarised this data also that those would be around 420 patients per year and 9:00. And and around 10% of all those CC stage 2 patients would be treated with adjuvant chemotherapy and for our use case, actually we really want to go into the direction of de escalation in case of CTD and a negativity post surgery. And now we're really I come in the if we want to do MRD diagnostics and clinical practise, it is very critical to fulfil several or. Necessary quality quality parameters. And we looked into the details, what was done during or within the dynamic trial because they got actually those very good results and they did initially targeted sequencing on the DNA isolated from FP tissue in 15 frequently mutated genes and colorectal cancer. Here's the detailed achieved panel, they and. Prized and for MRD detection, they uh, performed the tumour informed analysis of minimum one variant per patient using safety technology. However, within the study details, at least in the method section, I couldn't find any details regarding the limit of detection what they achieved, but rather they did statistical testing. To compare always the patient to a control cohort to identify is the variant detected or not and is the patient every positive or negative and based on this uh patients were stratified for or against at even chemotherapy. Since such a individual lies. Approach or patient specific approach based on tissue testing and then designing an essay for the specific variant the patient has is probably a little bit difficult. In routine diagnostic we we would suggest really to analyse the. The E DNA from the same 50 genes they evaluated during the dynamic trial using an NGS based approach and for MRD detection. We still would do tumour informed analysis but analyse just the identical gene panel with the high sensitivity and specificity for the detection of the T DNA. And. We the analysis should be performed by accredited laboratories reaching for this method a limit of detection of OH point, 1% variant and leaf frequency for individual variants. Yes, I think that's it. So within the project proposal, we would like to submit a grant proposal actually to the INNOFORM. UM, it's a German, yeah. I don't know how to say possibility to get funding for such model projects prior to introduction into clinical practise and there we would like to really focus on the health services model and and for this use case we would like to recruit. CSC, Stage 2 patients perform for those patients post surgery, ctna analysis in three different laboratories or yeah sites in Munich and Liebeck and Briston. Specifically all. Reaching the defined quality parameters for cDNA or MRD analysis and based on the MRD detection results and either it is decided for deescalation or adjuvant chemotherapy. But so far at the moment we are really very much in the beginning and in

the concept phase. However, we would like to submit this proposal still. Within this year, to get on with this project, yes. And here's just an overview of the people who are involved or were involved until now and and who are working on this, yes. Thank you very much. Are there any questions or maybe we can have a some discussion on this?

Barbara Behrens

Other.

Remond Fijneman

Zillion questions go ahead because second car should go first.

Barbara Behrens

OK. Bye. Bye. Bye. How Arianna. Thank you very much. This is a very interesting project. My question is in principle. I know that since long time this circulate study is is done by Professor Fulbright and this is a huge study. I haven't followed up about. The outcome of this study, but in principle this is very similar to what you're planning now, right?

Ariane Hallermayr

So I think, Nicholas, you would probably a better reply or response here.

Nikolas von Bubnoff

The interesting thing about the circulate study is that the circulate study will primarily test the effect of chemotherapy in CTD net positive versus negative phase.

Barbara Behrens

OK, OK.

Nikolas von Bubnoff

And, UM, uh. Unfortunately the recruitment is stopped right now because, UM, the BMBF has not. Uh has not agreed for further funding, at least now, which would be really bad. But uh for that. For that reason, there's currently no no enrollment in this in this study. But this is, you know, the circular study principally addresses the.

Barbara Behrens

Right, yeah. OK.

Nikolas von Bubnoff

Effect of chemotherapy and positive. Patients. So this is something that also the dynamic free study does not address. The Dynamic Free Study address is the same thing. But in stage 3, so these.

Barbara Behrens

Yeah. The the escalation. So they are they are looking.

Nikolas von Bubnoff

That would be perfectly complementary, and so we hope very much that circulate will proceed enrollment sometime.

Barbara Behrens

At the escalation. OK. OK. Yeah. OK. Thank you. Thank you very much.

Ariane Hallermayr

And I I and I also think for our idea of this enough for project. We would really appreciate or the goal would be really to have a model how this can be implemented into clinical routine based on the data that is available already and. Actually, the effectiveness or usefulness of MRD detection rather than I am getting new data on this, it's more like is it practical.

Barbara Behrens

To OK. Yeah, where I would think that above of oh point 1% might already be.

Ariane Hallermayr

Yeah. Cortana lies.

Barbara Behrens

A bit too high. Maybe so. If you look into the details of the T data, which has been done by PQS, we have seen those data in detail. Then you have several patients being far below, oh, point 1%.

Ariane Hallermayr

But for individual variants, or if multiple variants are tested. So for the individual position of each variant.

Barbara Behrens

I think for the multiple. So the the the mutation will be higher.

Ariane Hallermayr

Yeah, so here I was talking about the very not the multiple variants, but really for each individual position, if multiple variants are detected, the ctna level would be still lower.

Barbara Behrens

OK, OK.

Remond Fijneman

So I like the example a lot.

Ariane Hallermayr

Yes, Raymond, yes.

Remond Fijneman

For the type of discussions from our working group SO1 aspect is there's this beautiful randomised controlled trial in Australia. A fantastic result comes out. And the Dutch oncologists, when they saw the title of the paper, they were completely happy. And they thought, wow, we can, we can now use cDNA to guide. Treatment decisions and then they started to read the paper and they concluded, oh, this is interesting. In the Netherlands, apparently. We are. So they tell me I'm not an oncologist. They are already a little bit more reluctant. To offer chemo and so basically they said the population described in the Australian study who is now being with health chemo. Does not get chemo to begin with in the Netherlands, at least to a large extent, and what it learned me and all of us, I guess, is how can we transpose? Beautiful. Randomised controlled trials that are run in different areas of the world, whether it's Australia or Japan or in Europe or in the US, how can we use those data where we of course see that there is value to the use of the biomarker but apply it. To our national or local health care system and to the standard of care that's being offered. So in that respect, when you propose to run the study that you have in mind, do you want to run it as a study of let's include an X number of patients? In in in, in One Direction? Or is it a randomised controlled trial? How do you, in the end evaluate the outcome compared to the current standard of care? So how do you? How do you envision that for this study?

Ariane Hallermayr

So I I think it's a very, very, very good question since we are still in really in the beginning of planning, I think we don't have precisely decided yet or Nicolas, do you have already something in mind because you will be anyways the lead.

Nikolas von Bubnoff

I mean all these points are very valid, and I'm also aware that the study has been received also with intense discussions in this and you know in in the.

Ariane Hallermayr

Year.

Nikolas von Bubnoff

Yield and this is affecting a population of patients that is approximately, you know 10% or slightly below 10% of stage 2 patients. It's approximately 25% or even 30% in stage 3. So this is a significant subpopulation that we do not. Stratify right now and therefore in Germany it's I can tell you that less than 10% of stage 2 patients receive treatment at all. So we currently do not, uh recommend absolute treatment in in at least in patients but do not have clinical risk factors. So this you are completely right, but at the same time you know the A patient that has biomarker positivity. We don't know what to do with these patients, but a patient that is negative and that does not have at T4 tumour. Because in T4 the difference is there is a slight difference, but in patients without clinical risk. Photos and velocity DNA negative. I would like to know if I'm negative because then you would be absolutely sure that you can omit atrovent treatment and on the other side in patients that are cDNA positive without doubt you

should go for aspirin treatment. But. You are right, we cannot say whether this treatment certification really helps the patients that are seated in a positive that's that's correct. So there's, there's still some, you know, a little bit fuzzy situation. But still I think the the information would be absolutely important to know in in Stage 2, if you are positive or negative. So if you are belonging to the 10% positive patients for for whom you would go for uterine treatment. Or for the 90% negative where you have, you know you know can safely omit chemotherapy. So I think this is a biomarker. I mean we use a lot of biomarkers with less clinical information capability compared to this one that are reimbursed.

Remond Fijneman

No. And.

Nikolas von Bubnoff

You know, the control arm is 150 patients, so if you go to the commands and bound is also in Germany and ask for, you know reimbursement level say no no way this is uh too small study and uh you know if you go to the UM to the uniform and then we also have the opportunity to. To increase the evidence.

Remond Fijneman

Yeah, this is what I mean. If there's internationally so much evidence from large trials, including over thousands of patients and there's on the stage 2 setting, there's probably 7 trials or so ongoing in the world. Several of those will have their results in the coming years. Those data should feed. Into the local setting that you have at hand, and that should also help the people who perform health technology assessments to judge. How many patients is really concerns and how much then for those patients and the benefits there, whether that weighs or does not weigh against the the cost of the total cost then of the testing that's done?

Nikolas von Bubnoff

Absolutely. This is something that you will also have as an added value, cost effectiveness evaluation. So how many costs do you save? UM&UM, how many toxicity do you? Uh, do you have less? And also we can build up the infrastructure of the processes and you know the the hardware, the platforms that we can use for such an implementation. I think this is also very strong point because we don't have any. Harmonisation in Germany. There are currently activities also by Alps to to reach harmonisation, but I think this would be a perfect use case also to come into a situation where we, where we have harmonised. Platforms across institutions where we know that we can use these platforms for clinical stratifications as well.

Remond Fijneman

And then Arianna, the second question that I had relates to a discussion already partly ongoing and that is what is the sensitivity of the test that is needed. So basically you're saying we're looking for minimal residual disease.

Patrizio Giacomini

MHM.

Remond Fijneman

But what is the limit of detection that is required? And I think this is part of what the helps community, but also from projects like item ID and I guess clouds you you may add some comments here. But it would be great if from those initiatives. We basically put some guidelines out there where we say if this is the clinical application, then this is really the recommended. Test requirements that are needed or, and of course those are very different for the MRD testing than for the gene mutation profiling than for the response monitoring. But I could imagine in particular for the for the MRD detection that that Friday mid will offer more. Insights etc.

Klaus Pantel

Yeah, maybe I can start with the answer. I mean, you're absolutely right, Raymond, that it's really the goal of our EU guide MD project to find out which tests is required or which sensitivity is required or which tests could be also more. We had a long discussion about that. Our IMC meeting in Nice, uh, very interesting. Also this Charles Swanton and others, you know, working in the field for a long time. I guess at present we cannot really say what is required, you know, is it 0.100.1 or shall we spend even wants to have less than one parts per million you know or is there really a certain biological limit, let's say if you you may get 10. Percent false negatives, no matter what technology you use, because maybe some of these minimal visual diseases are not shedding because they're dormant cells sleeping somewhere or whatever, you know. So I guess this is still a question that is out there. I guess the colon study in a certain way is very nice and you know that they're very supportive. But what I also understood now after many discussions and not only today, is that the CDC stage 2 case is a little bit tricky because you have many patients that don't need chemo anyway. So you can say yes, I did not had a disadvantage of not giving a chemo, but now we come back to the numbers that Nicolas already mentioned and that's why in our discussion with the healthcare pay us, they also said already well you need higher numbers you know because the. Effect size might be not really too big, you know, and so I think that's why asking for a larger study is using a very good idea and then using it also to harmonise the. The detection and setting up maybe eqa and whatever you have, you know it's it's a good idea. But but I would definitely say that at present the jury is still out. What kind of sensitivity also in what tumour type it might be also different in different tumour types. Is needed for detecting MRD and for making a clinical decision on it. So maybe you can detect the last piece of DNA, but it may not make really change your final decision. All these questions are still out there. The only thing we know today is that we do not catch all relapses by any tests. Yet, but maybe this is just. Something you will never do. I think there's no biomarker test that is 100% precise, right? So maybe this striving for perfectionism is leading to, yeah, not not the best. I guess it's an academic wish, but sometimes it can be. Not so prohibitive. Hmm.

Ariane Hallermayr

But I think also what I I would like to add is with this this occasion on this project we would really like to introduce already a use case and not because the data is so promising and not wait for the perfect method, but really go with what we have at the moment. Another thing I would like to add and correct. Sorry clause I forgot got to add Hamburg on. Our slide, so we of course, uh, all this initiatives with discussing with the health care providers came originally from Hamburg and we will would do of course

analysis also in Hamburg. But we are still in the beginning and I put it. Up very quickly, so of course Hamburg and Clouds are involved as well in this project.

Klaus Pantel

No, thank you, Ariana. I think I like the project from the beginning a lot because de escalation is certainly something I mean and and not using chemotherapy where it's not useful. It's certainly something important we know also in breast cancer that we overtreat patients tremendously because we don't know exactly which one. Needs treatment, right? So so overtreatment in the age of empathetic. Is is also a big issue in other tumour types so so I think it is a very important question, yeah. And actually for the patients, I mean, we always say that even the prognostic marker, I think that Wilma mentions the TNM, even prognostic information for patients who have, for example, an oestrogen resident positive tumour and who never know whether they are, you know, free or free labs for the next 20 years. I mean, if you would have a test that could tell them, OK, you are safe, right? I mean, even if it's only prognostic, so to say. Right. I mean is something very valuable for patients, I mean, yeah.

Speaker 13

Cool.

Nikolas von Bubnoff

Just a very brief comment so. So my feeling is as you already discussed that only you know the observation that we can do a, you know kind of a controlled escalation and justifies clinical application. And I think we should also include. Patient perspective in this project, because this is also affecting. UM, you know the uh, uh, psycho, oncological burden that patients in an utterance situations have, and we might also think about maybe also including dynamic monitoring of cDNA positive patients because of the problem with the dynamic free study the subsequent study. Was that, uh, the escalation of treatment in CTD and a positive patients was not specified. And also not randomised, so this is a very unsafe message for for the escalation of cDNA positive patients and therefore we we are really in need also to to increase information about these patients, what kind of treatment did these patients? Receive and what treatment is possibly correlated with with reduction of relapse risk in sitting in a positive space. So this is something that we could also think about to. Root in. In this use case.

Klaus Pantel

Yeah. And in the positive patients, Nicolas, it may also depend on the level of ctna or the level of tumour burden, right? So so there are many questions, but we could address them very nicely in such a study. We have to look a little bit at the watch. You have 45 minutes were left. Raymond. You asked me to, you know, careful.

Remond Fijneman

I think it's time for the next topic, yes.

Speaker

Good, good.

Remond Fijneman

It's time to. Hand over to appearance and Christine Michelle for. Their work on current efforts by bio Deutschland in liquid biopsy reimbursement so.

3rd Presentation by Barbara Behrens, PhD (Sysmex, BIO Deutschland) and Christine Mißler, PhD (Berlin Partner für Wirtschaft und Technologie GmbH, BIO Deutschland); Title: Current efforts by BIO Deutschland in Liquid Biopsy Reimbursement

Barbara Behrens

Perfect. Hi. Thank you very much that you invited us to talk a little bit about our project. I'm for us, it's the very first time to be here and let me share my screen. No. Can you see my screen?

Daan van den Broek

Yes.

Ariane Hallermayr

No, not yet. Not yet.

Remond Fijneman

You may have to press the share. Do you did you press the share button below this blue thing?

Barbara Behrens

Ah, maybe not. Let me check. Did I? No, I didn't press this blue thing. No. Now I did it.

Remond Fijneman

We can see it.

Barbara Behrens

OK. And this is the presentation.

Ariane Hallermayr

Mode, yes.

Barbara Behrens

Perfect. OK, so I'm yes, I'm. I'm here for the very first time. So I try to put something together, which is of of value for for you and I will start with the discussion or with the with the presentation and Christine

Missler. Will take. I'm from. I'm Barbara Behrens from Sussex Deutschland. And I'm responsible for the medical science at sysmex. Christine is from Berlin, partner, and she will introduce herself as soon as she starts. And we have the consumer from emptyset. I think Ariana knows him very.

Patrizio Giacomini

Hello.

Barbara Behrens

Well, and he will. He will support us in the discussion. So hmm. Doesn't want to change. OK, let me first introduce you briefly into bio Deutschland, because this is the organisation we are representing today. So bio Deutschland is an independent German biotech organisation representing companies and organisations in the biotech area in Life sciences and in the bioeconomy sector. And Budokan is promoting the interests of their members nationwide as well as globally. And the overall goal is to transfer biology into industrial usage and in order that you can better understand the activities which we have studied in the task force, let me briefly explain the special situation of the German healthcare system in two slides. So the Ministry of Health in Germany. Delegates the decisions to the. Medical self governance. This is called GBA and it's a joint federal committee. This GBA consists of 13 member 13 delegates, 3 independent antennas sent by four groups. This is the public health insurer funds. The German hospital organisations, the regional organisations. And their roof organisation of the physicians? And then the equip has already been mentioned here. It's the Institute for Quality and Efficiency in the German healthcare system, and the GBA is using them to check the evidence and the efficacy of medical measures and then decide on reimbursement. Yes or no. And we have three different reimbursement paths in Germany and the main two, I will very briefly explain, it's in the inpatient setting and in the outpatient setting in the inpatient setting, we have flat rates per patient per disease and. Treatment and in Case No reimbursement is available, you can apply for a new application. This is a new diagnostic and treatment option. However the likelihood for a positive decision is less than 5%. And meaning that if liquid biopsy is done in the inpatient setting, the costs for the liquid biopsy are eating up the lump sum for the patio. In the outpatient setting, we have special codes. They are called EBM codes for different services for the legally patients and geocodes for the privately insured patients. And then we have the cross-sectional care. This is a real specialty, which is very complicated, rarely done and I don't wanna I I really. Want to leave this out today? And we are working in the task force liquid bulbs at bio Deutschland. This is a group of liquid bulbs experts coming from companies which are members of the new Deutschland organisation, and our goal is very similar to what has been introduced by you already. Our goal is that liquid bulbs is recognised as a new diagnostic standard. Included into indication related. Applications in the EBM code and we want to achieve a uniform quality standard. This has already been mentioned by you before for routine use and we want, of course achieve adequate renumeration for the practitioners and the laboratories and the manufacturers, because only then this will be done in. A high quality. Let's look at the current status in Germany for the reimbursement, which is really not satisfying at all. There are only a few EBM codes available in the so EBM code means outpatient setting. They are for non small cell lung cancer and Mamma carcinoma. And they do not cover the costs of the analysis at all, and there is no reimbursement for colorectal cancer. And currently the EBM codes are only for companion diagnostic. There is no reimbursement in the inpatient setting as EVM codes can only be used in the outpatient setting, which leads in the practical use to very strange workflows that

patients are let out of the hospital for half a day. Then the the blood is taken, the analysis is. Somehow done and then patients come back into the hospital. So this this is then delays of course in the analysis are are a consequence. This and as the codes are not cost covering and high quality and sensitive, liquid biopsy analysis is cost intensive. Platforms are used with low quality and for instance for ESL One mutation, oncologists are surprised that the years. Or one mutations are so rare in their path. So thus we need improved quality controls and more and higher reimbursement codes for high quality and sensitive analysis. So we really need and additionally an expansion of the applications at least for companion diagnostic for corrective cancer and as the next step. For minimal residual disease, which is of high importance, I see this exactly as you see it and for monitoring. So in a nutshell in. Now. In a nutshell, the current reimbursement situation in Germany ignores the potential. Here you can see the available EBM codes in the outpatient setting. And as said, uh already, it's only for non small cell lung cancer only for Mamma carcinoma and only for companion diagnostic and the amount which is paid ranges from 260 to €725, which is of course. Not cost covering because, UM. Ohh whoops, this is. Strange here, I did something wrong, so let me let me show this here the there is a reimbursement example which is done by Professor Malcolm Barboza, which is presented by professor logo labou at the Vision 0 Berlin. Summit. And here you see that digital PCR, the EBM code covers €350 and their own calculation is €637.00. So it's about double the price the own costs than the reimbursement and it's even worse in. NGS, there are the EVM codes. Uh. They all added up. Come to €815.00 and the own cost calculation is 3 times higher. So the current reimbursement system is far away from being cost covering. Sorry, the animation was not perfect here, so let's go back to the. Presentation. This is in in contrary very different in the molecular testing in tissue. Here the code in Chapter 19.4 of the pathologists is sufficiently reimbursed for the NTS panels with up to €250. However, it clearly states in the preamble. That analysis of cell free DNA is. Included and the question is now or was now for us in the Georgian organisation. How can we change this so we have a real specialty for the German reimbursement system, which is strictly regulated first before we could do any application we needed to know to whom to address the official? Dedication to the GBA. Or the evaluation committee, which in Germany is called Bezier Ausmus so, and this to whom to address the the application is based on the fact whether liquid biopsy is judged as a new method or a new service. So to get this answer. We had to do another official application first, which we had to do to the evaluation committee. And and this uh application is called request for information. So we addressed the question whether they see NGS based liquid biopsy as a new method or a new service. And UM, as this was a very important application for us, we really wanted to fine tune the content of this application and we organised 3 online roundtables with high-ranking German liquid bulbs. Experts with oncologists, pathologists, clinical lab doctors, doctors, human geneticists and, of course, Professor Panther was part of this round table discussions and we got from all of them very high high level information and input. So this changed. Our idea that we with which we started for the application dramatically because we had started first, the discussion with the wish to receive a general code for all cancer entities like in tissue testing. However, the discussion with the experts, they convinced us. That we need to concentrate on the entities with highest existing evidence and consider all current national and international guideline proposals. So we ended up with somehow a restriction, so we ended up with the following content. We applied for Ng. Liquid Panel sequencing limited. To advanced non small cell lung cancer, colorectal cancer and Mama carcinoma. And then the limitation from the guidelines for initial molecular diagnosis and follow up for the therapy adaption in case of tissue shortage under time pressure in case unreasonableness for patients or clinical

contraindications. If only bone metastasis could be biopsied in the event of high expected heterogeneity and for efficiency reasons. And we. Really, with Bleeding Heart said. OK, we do not want to include minimal residual disease and monitoring into this application. So our objective then was to get an EBM code in the outpatient setting that allows the physician to perform a validated. Palsy panel in the above clinical or in the described clinical situations. This application and was uh done by garden health and they were sitting from the very beginning in the driver's seat and the application was done on March 15th, 2024 and the the veterans also had in principle only six month time to give us an. Answer It took ten months until the Garden Health received the answer on November 14th in 2024. And the answer was it's a new service, meaning that we could avoid the equip and the DBA and address the next application to the to the Alsos, again to the counselling. The committee so this application, the name of this application is. We wanted the start of counselling for an EBM code. This is how I try to translate. It to translate it and we address this application again to the evaluation committee and this application could now no longer be done by a company. This had to be done by a a medical society or an association, and the association who applied for us. Was the bio Deutschland organisation and the the submission was done personally or the application was personally brought from from your Deutsch. And the beginning of February 2024 to the committee. UM the the application at a glance, so it was not. The content was not so much different from our first application. It was more detailed in describing the clinical evidence and describing the already existing. Of these, and if you want, we can go through it in detail. It's just written here. So the indications are again non small cell lung cancer, correct and cancer and breast cancer in stage 3B and four, which does not mean that if we get an EBM code. That this will be this restricted to what we have applied for, it could be broadened from from the evaluation. Committee. The target group is patients in the event of initial diagnosis and recurrence or treatment failure. The test is an NGS analysis from plasma, so we are only talking about CT DNA, not about CTC's for predictive mutation detection. The specialists in the laboratory pathology laboratory. Medicine and human geneticists. They do this in Germany. The liquid biopsy and the requested service was inclusion of the predictive CT DNA testing as a code and the opaque in the EBM code. And the in the described patient population comparable to what is available already in tissue, the benefit we see and we described it, it's better, it's faster, it's safer therapy decision with high acceptance for more patients and the scientific basis, the basis of course were studies. Which we had in which we could include however they wanted us to only include 55 publications and highlight them, which is of course not so much to really highlight all all available evidence. And now we need patience, because in principle they have two years time to to to decide on whether liquid biopsy will get an EBM quote or not. The the the Evaluation Committee is kind. Of a a. Black box. They are not so much. Talking to us, however, all the signs we see seem to be the chief, and now I would like to hand over to Christina. She will present our activities, which we do as kind of lobby work to to support the. Christina, I will. I will kick you through the through the.

Christine Mißler

Slides. Yeah. Thank you very much. Yeah. Barbara, I told you. What? What? Uh, the liquid biopsy group does. Uh, concretely, for for the reimbursement of like liquid biopsy. But additionally we also, yeah. This we also yeah, have some information for for the for the people for for different uh yeah people and. One thing you see here we we have two liquid biopsy brushes, 1 published in 2022 and one in 2024. There you can get in general over. You quality aspects are discussed. Also regulatory issues and national

and international initiatives are mentioned and you also find a list of stakeholders in science and industry. It is focused on Germany and so it's in German. But nevertheless I will post the link. Into the chat. And when we look at the second slide. But we are also organising events. One digital event was in 2021, but we had also, yeah, a session at the Deutsche Deutsche Biotechnology ataga. And we also have a LinkedIn group where we publish news. Regarding liquid biopsy. Until now we are approximately 160 members and now I will post the link for the UM yeah, for the focus booklets and also the LinkedIn group. If someone of you is interested then join us. Yeah, and this is uh, yeah. And uh. One side of uh of the focus booklet where uh, you can see what? Yeah, is discussed there, but you can also take the link from the from the chat. Yeah. So then, Barbara, you you take again?

Barbara Behrens

Yeah. I could do this. Yeah. We in. In principle, we we have the same idea as you have in the else. We are preparing a position penning paper in in German language with the idea to inform politicians and health insurers. About the possibilities of liquid biopsy. And yeah, and just in order to to accompany the application because we we have recognised that the politicians who will partly have to decide on whether or not a liquid biopsy will be will will get. A reimbursement or not, they are not sufficiently in the loop and and we want that pay organisation support us as well. So for this reason we try to develop in understandable language the the possible hurdles, how these hurdles can be overcome, and the benefit of liquid biopsy for patients. If this is ruled out in the board routine. And that's it. What what we currently do and what I wanted to share with you.

Klaus Pantel

Thank you very much. Uh, Barbara, this was uh, very informative. Uh. I mean, be cross our fingers of course, because that would be a big I mean advance, you know, for us at least here in Germany because you also make it very clear that if the method is not reimbursed. That's a reasonable way. It's also a kiss of death, right? I mean, so, so definitely. No. No, very, very good. And I think everybody else understood that things in Germany are complicated. So. But you explained it very, very well. I mean just not nice.

Barbara Behrens

I I try to I'm I'm not a real specialist in reimbursement in in, in Germany but I I try to learn a lot and yeah So what what what what? What for me is really striking is that. There are partly uh platforms used in Germany with very low uh sensitivity and that even oncologists where I know they are very well, well known, well known oncologists, breast Mama carcinoma specialists they are. The prized that they only have years are one positivity in their patient cohort of 10% and if we ask them so. But what what? Which technology is your pathology is is your pathologist using? They don't know this. They don't know this and and and and they don't care because they. Have the opinion that they get good quality and I think this is something so this educational background is something I I think which is of highest importance to spread this into the world because then if not, people will think that liquid.

Klaus Pantel

Absolutely.

Barbara Behrens

Topsy is not good. No, it's just the technology which is used, which is maybe not good, yeah.

Klaus Pantel

So. It's a very important point. I see Nicholas here.

Nikolas von Bubnoff

Thank you so much. That was really interesting. And my question for you is so. It's it's very good to see that it might be possible in the future to to have reimbursed liquid biopsy in patients as you said for non small cell lung cancer, colorectal cancer and breast cancer in in in that Special Situations which are of clinical relevance. So if you don't have tissue, if the tissue is old. If you have time pressure and as you said so this is exactly the setting that we have in patients that we that we deal with in molecular to mobile settings with the broad coverage of of entities in very difficult treatment situations with patients that have, you know undergone 3 or 4 or 5. In lines of treatment, do you envision that it might be possible to also, you know, include molecular to mobile patients with that new service regulation in the future irrespective of the entity, because we want in, in Germany, we want to do a. UM, uh prospective evaluation in order to uh, you know, to, to demonstrate that for these patients we have benefits if we use liquid biopsy also in terms of turn around time for. Example and in patients where we have a shortage of of tissue, do you think that it's possible or do you think that before you do this you should have more evidence and we we should be you know get together and create this evidence?

Barbara Behrens

And. So the uh, let let's say this in in principle in the very beginning our idea was we we just. Go to the uh, the veterans, Alsos and tell them you know what, you just delete this one sentence in the in the code for the pathologist, that liquid bulbs is not allowed and we are fine and the and. And then we started the discussion with all the expert and then said, you know what? And we are very sure that this will not. Be successful, so please try to limit this and we limited this. However, and this is how the application is phrased. However, this does not say that the the the veterans also will not decide that it makes sense to just delete, delete the sentence you know. So it's open for them to broaden the the the application and we of course hope that. This will happen. However, we don't know because our we we have talked, of course, uh to help ensure. And their fear is that there will be a cost explosion and and for this reason they somehow want to limit this in the very beginning. So we have to be patient. And of course, in order to we are now this positioning paper. Will be for minimal residual disease and and for and. And will include monitoring as well and we have thought about whether we will include medical economic evaluations, however. We were told don't do this, they will not trust you anyway because everybody comes and says, you know what, if we do this then we will save costs and this is never true. So don't, don't, don't go this route. So you know it's open. We hope that we will get an EBM code. We hope that. That this will already be broadened, but we think that if we have 1 foot in the door, this was our, this was our intention to have one foot in the door to open this can of worms and then we hope that. Yeah.

Speaker 13

Yeah, maybe I can also comment on that because I think also it is really good to be within this application as specific as possible, because otherwise all your evidence is somehow, yeah, diluted. But

this of course does not says that there will be a. Thought now approach later on and in addition I just like to tell, at least in Germany, it is possible that you can hand in some assumption of costs to the health insurances. This is, we know, a lot of work because it has to be per patient. But if there is an evidence that liquid biopsy will give an added value, and if this for example supported by by uh by medical guidelines, this might be a way also to say to health insurance companies. It's really a need for for. Yeah, for liquid biopsy. And this will also help the application. You have to say, well, it's valid or it's really an added value for patient care. So it's in German cost to the health insurance companies.

Klaus Pantel

Yeah, maybe I can add also one comment. I mean I should say that after the vacation, we will have the first meeting of our new patient advocacy group in the LDS.

Barbara Behrens

Ah.

Klaus Pantel

I I I think if I would be a patient advocate, you know I would say maybe one reason to do this because I don't like to have the tissue biopsy. I prefer to have a blood draw. And I must really say that if I would be a cancer patient and you would give me the possibility to decide between needle biopsy of my lung or a blood draw. I mean, I I think that 10 out of nine patients will have the blood draw, right. So I think that in our German system, we are still a little bit backwards regarding the patient. Will we always write that down in our grant applications and grant calls and every society is saying, yeah, the patient will the patient will we have to include the patients. But I personally feel that if he if he really take it serious, the patient will. You know, I think also the refusal of a patient to have a tissue biopsy as first diagnosis could be an important case. And I know that oncologists don't like that. I always get criticised when I say that because sometimes people say yeah, but if you recommend the wrong thing to the patient, but then we come back to the either you believe on the liquid biopsy thing or not, right. If you're a non believer then the patient is anyway lost, you know. So I think that and believing has also to do with quality and that's also something you mentioned, Barbara, very nice. Lastly, that we have to, I mean we can really work together out some very nicely to make the education you know, make clear that you only get real good results if you use the right technologies, right for the right questions. And I think this is also something we could do very nicely. Together, because I definitely think so that. You know the money for reimbursement should be not the argument at the end of the day, yeah. So definitely I I guess there is still a lot of education done and I would definitely pledge to include the patients you know, in into this I mean. Come on. I mean, they are the ones that have no conflict of interest. They want to have the best, best diagnosis and the best treatment, huh?

Nikolas von Bubnoff

That should be case.

Klaus Pantel

The reason why the reason why little biopsy is more advanced reimbursed in the US is really because the tissue biopsy is so expensive in the US Sir, the needle biopsy costs you easily 10/5 or $10,000, right. So that has really, I mean propelled the interest in liquid. Biopsy 2, you know. So yeah.

Remond Fijneman

If I make comments. I think two things, one on the patients and one on the on the Nice presentation from Barbara regarding the patients. I think one of the challenges in Europe is that the patients will ask for a test that is not available in our healthcare system. So the patients are I think better and better informed and enthusiastic the risk. Is that they are more enthusiastic than is realistic. So yes, we definitely should make use of the patient voice. And at the same time it's it's we and the studies that we evaluate and perform that should guarantee that what we offer suits the purpose and to have a realistic story on what we can but also on what we cannot detect. So that's that's beyond believing that's actually. Data and and evidence that we can put on the table. But then making use of the patient voice I think is is very valuable, but I have already and I'm not going to elaborate on it now, but I have seen over enthusiastic patient situations that could work actually against the introduction of the liquid biopsy. Testing. So we need to take it step by step and do it in a in a sensible. Way. Regarding question to Barbara, so in your. Work. It's really a great example. Again in terms of the challenges to reach out to the right regulatory authorities and how actually the authorities themselves are still a bit in the dark and asking, you know, when these new applications come up. In which box to put them basically so it's good to have. You bio Deutschland and other efforts paving the path, but then imagine you're successful and and imagine you're successful in Germany. How can the people in? The Netherlands, in Poland, in Denmark, in Spain, Italy. How can they use? The facts that you paved the path in Germany and say, oh, look at Germany here, it's it's granted. Do you see any mechanisms where we can make use of the successes from one country to another?

Barbara Behrens

So we try to make use a bit in our position paper to point on the United States and say and say look at the United States and we thought that in Italy the the reimbursement of liquid biopsy. Better and some steps before us, so we try to point on those countries and say, you know what, we in Germany we don't want. To be the the. The latter ones, and we don't we we need to show our innovativeness. Hey, let's go this step. So and I'm. Maybe it's I. I think it says so. So these applications. Actions are I think they are public, so in principle what we have written in these in these applications is something and the evidence is something which might be used in other countries as well because we are not only focusing on German publications, we are focusing on worldwide. Applications ensuring the clinical evidence and. I think that that that's it. However, every every reimbursement system, they are so diverse and so specific that yeah, I know that in Germany they are looking too nice. So what is done in UK is something which is of high value, something which is done in Spain. Spain, you know it's it's, it's, it's different and the the, the, the higher regulated and the more the more difficult it seems to be to to to get some reimbursements the the the more important it is for the germ. For for the reimbursement system.

Klaus Pantel

So I think that what you say, Barbara, is UM, there is a bit of, let's say pressure that that, that, that be done you know by.

Barbara Behrens

Yes, yes.

Klaus Pantel

Not maybe saying a company that that it's maybe labs and bio dodge not I mean could be you know some non for profit organisations that could really I mean bring this information together and say here listen you know I mean it's really already accepted in AB and C and. I mean, yeah, why? Why not in our country, right. And if there would be a mechanisms like that, that would be actually nice. Of course it would be also fantastic if there would be a mechanism in the European Union. Let's say, if you have something reimbursed in two or three countries, I mean that, that there would be some kind of process.

Barbara Behrens

Yeah. Yep.

Klaus Pantel

Initiated, but I think that's not the case yet. Yeah.

Barbara Behrens

So the question is, uh, as soon as in case we are, umm successful. And in case it's introduced in the germ reimbursement system after one or two years, we might check with the health insurers. How did this did this somehow does this have?

Speaker

MHM.

Barbara Behrens

Any influence on the on the costs for one patient and is it maybe less expensive since or is it more expensive and so if it's not more expensive and if patients are satisfied, then maybe this is something. Which in other countries could be used as an as an as an example.

Klaus Pantel

Yeah. And also I think measure really the the patient side definitely you know, yeah, about.

Barbara Behrens

Yes, the so. So in Germany the patient.

Klaus Pantel

Quality of life and and things like that, yeah.

Barbara Behrens

Patient voice is very important in Germany, yeah.

Klaus Pantel

Yeah, very good to. To measure that too. Cool. Very good. We have 7 minutes left. Raymond uh, Ariana Nicholas. Whoever is the boss here today, please. I think that.

Remond Fijneman

Wants to drop a question or remark.

Ed Schuuring

Just a small remark, I'm sorry I I I joined 30 minutes later, so I hope my question is not really referring to what you already discussed, but here we're talking quite a lot on the on the cost of the tests, reimbursement of the test.

Klaus Pantel

Yes. Yeah.

Ed Schuuring

Thing. But we also should I think be clear that the effects on treatment developments and the costs for the treatments are that are coming up from these diagnostic assays are should also be included in the calculations. So changing based on an essay that that there isn't, that there will be less treatment or more treatment or whatever, also affects the costs. And I think we should take into account that we don't talk only to the insurance companies about the cause of the test, but we talk about the process.

Barbara Behrens

So. Or the yeah, the cost per patient per per patient process in principle? Yes, exactly, I agree.

Remond Fijneman

Hmm.

Klaus Pantel

Absolutely no. That's very important. I I guess Barbara made a remark regarding that they that they didn't include that and there were it was recommended not to be included because the healthcare companies, at least in Germany here that all the time and then they have also clever mathematicians. Who? Who then say, OK, if you don't get this treatment, you get another treatment and maybe that's even more expensive. And so I guess that. Am I? I really think it's a very important point, Ed and I. I also like the idea to, once it should be accepted, to have an evaluation period, maybe of two years and and and really do them. The calculations are called growth, life measures and what so on. And and and get really some good, uh feedback on that, yeah.

Daan van den Broek

Mm-hmm.

Barbara Behrens

That's because we only could do a theoretical model that has not been shown and we we thought that this theoretical model is not trusted. With the enough so we we need to show the real, the real life.

Speaker

No.

Remond Fijneman

Yeah, yeah, but then the reference too nice, for instance, makes sense, I guess, because I think in the UK they have started. Liquid biopsy testing and nice will be involved in evaluating and so more data will be coming.

Klaus Pantel

Yeah, yeah.

Remond Fijneman

Up. In conjunction with that, it would be. Good to be able to use those models in the settings of the different countries with their own specific variables in the care setting. So I think that's in that respect the the yeah, the health economics across the patient journey.

Klaus Pantel

MHM.

Remond Fijneman

It will matter a lot, but it's also a complex 1 to to take it from a model indeed, like a technical model. To the real clinical practise, but maybe this is a topic close area that that we should touch upon in in one of the future meetings on this working.

Klaus Pantel

It's very good. No, I think if we can learn from the experiences in the different states, you know and and and bring this experiences together that, that that is very, very good, absolutely. Cool. So who's writing the position paper now, Raymond? During the vacation time?

Remond Fijneman

Always in the lead this session was important. On the one hand to inform you and on the other hand, to build upon the table that we will use and that will be sender oh follows there again but.

Yong-Jie Lu

Good.

Ariane Hallermayr

Yeah.

Remond Fijneman

We're aiming for September to send this around in the survey and then take it from there.

Paul van der Leest

Yes, that sounds sounds like a good. Planning.

Klaus Pantel

Great, excellent. And if you want me, uh, at at a certain time point to check with nature. Let me. Know. Hmm. Cool.

Remond Fijneman

Yeah, let's discuss clause. I think it's so there can be one or two or three options that we have in mind, but it's good to learn from the possibility that you mentioned.

Daan van den Broek

Yeah.

Speaker

Yeah.

Klaus Pantel

Cool. Great. Well, I think it was a very fruitful meeting. Thanks a lot. And I guess most of you will go on vacation soon. So I wish everybody a nice summer vacation. Don't get sunburned, huh? So, but enjoy. Relax and come back full of. And ideas? So all the best to.

Ariane Hallermayr

You OK? Thank you. Thank you. Bye bye.

Milena Cavic

Right.

Barbara Behrens

OK.