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ELBS Regulatory Meeting – minutes // 07.2023

WG leads: Ariane Hallermayr, Klaus Pantel
Speakers: Rodrigo Toledo (Spain), Stefano Indraccolo (Italy), Ariane Hallermayr (Germany)

1) Discussion on Impulse Presentations

Overview of Liquid Biopsy Reimbursement Landscape - Spain:

Stefano Indraccolo: I believe you mentioned you set up the Guardant CDx LB test in Barcelona. Does this mean you run the test directly in the labs? believe in Italy it is set up in a way that Guardant offers this assay through Myriad. This is their commercial strategy in Italy. But apparently in Spain it is possible to run the test in the lab?

Rodrigo Toledo: Yes, this is correct**.** Guardant has signed a contract with one Spanish institute *VHIO*, here in Barcelona. This was a complete tech transfer. There is a very well regulated core facility here that is ISO certified, etc. They provide genomic analysis for clinical trials (not research based). Guardant transferred all technology for the G 360 to this core facility. They have the same model for the Royal Marsden Hospital in the UK.

Klaus Pantel: And the funding for the tests comes directly from Guardant? Or form other sources?

Rodrigo Toledo: No, it is different local funding's or pharma funding.

Leandro Lo Cascio: Do you know if the generated data stays in Spain or whether it is transferred to the US? Where is this data stored?

Rodrigo Toledo: That is a great question, which I cannot answer directly.

Leandro Lo Cascio: I am asking simply as here in UK there is quite some discussion on exactly this topic. On whether the patient genetic data is staying in the UK or is it transferred outside.

Rodrigo Toledo: I can definitely get this information for you. Just to clarify, I was showing these specific examples to share that despite the lack of public funding, hospitals and researchers are finding ways to integrate LB. We cannot get stuck and wait for reimbursement.

Klaus Pantel: I absolutely agree, we definitely need to focus on intermediate ways of financing. Similarly after the Herceptin trials and approval of Herceptin itself, there were not many laboratories doing HER2 fish analysis. So for 4 – 5 years Roche was supporting a few labs in Germany doing these analysis. Many pathology labs were not well equipped to do the testing at that point in time and Roche supported the diagnostics before the system was geared up to take over. There a quite a few examples of these intermediate funding's in the past covering assays that are now clinical routine.

Overview of Liquid Biopsy Reimbursement Landscape - Italy:

Klaus Pantel: I completely agree that the role of the patient organizations could be a significant one, since they have the most independent role as a stake-holder. I could imagine that governments and policy makers would listen to patients even more than to researchers and companies.

Rodrigo Toledo: How is the setup in Italy, where are the patient samples sent for analysis? Are they analyzed locally or at core facilities?

Stefano Indraccolo: I can speak for the Veneto region. We have one regional laboratory reference center. We provide local hospitals or researchers with Streck tubes on our own budget and then there is a network of deliveries amongst the hospitals. Logistics are not a problem. We offer two possibilities 1) patients can come to our local blood drawing point and get their blood drawn on site 2) blood is drawn in their hospital and then shipment to our center. We provide the analysis as digitally signed reports to the doctors that requested them. This is true for all patients except those that go through a molecular tumor board. These are special cases/ rare tumors – for those requests it is not directly requested by a medical oncologists who takes care of the patients but through the MTB. Molecular results are then provided to the MTB, the MTB meets and makes a clinical recommendation to the medical oncologists who is in charge of the patient.

Yong-Jie Lu: A quick question to you both. All coverage that has been discussed so far is for ctDNA based assays. I am just wondering whether there is any coverage for CTC tests (e.g. CellSeatrch)? In the UK these assays are used but not funded through government.

Stefano Indraccolo: As far as I know, there is currently no reimbursement for CTC tests.

Rodrigo Toledo: Similarly, in Spain, the funding is only research based.

Klaus Pantel: In Germany it is a little different. We have an additional private health insurance sector in addition to the public one and these insurances sometimes cover CTC analysis, depending on the clinical question (e.g. HER2 and PDL1 presentation).

<u>Overview of Liquid Biopsy Reimbursement Landscape - Germany:</u>

Stefano Indraccolo: You mentioned the possibility to request individual test for specific questions. Which would be the reimbursement fees there? Would this be aimed at comprehensive genomic profiling of cfDNA or a specific test?

Ariane Hallermayr: So far, this is aimed at targeted variant detection, as companion diagnostic, to define actionable variants. However, you can also issue these individual requests for other tumor types in which LB is not currently reimbursed. I believe most initial requests are rejected. However, if there are more and more requests coming in, at a certain point this changes and health insurances start to reimburse. But I am not aware of any case of monitoring or MRD in which this was successful yet.

Rodrigo Toledo: Again, I am curious to know when we talk about these tests. Do you know where they are mainly performed? In house, in reference centers? Is there a difference between public and private insurance?

Ariane Hallermayr: In our case, as a diagnostic lab, the samples are analysed in house. I don't think there are huge reference centers yet in which large amount of LB samples are being processed. However, there are of course companies such as Foundation Medicine who offer commercial tests in their own labs. Yet, I believe most tests are being performed in diagnostic labs. We have blood collection tubes ready to be shipped upon request by the physician. They collect the blood, fill in the request form and send it back to us for analysis. In our case we have only in house developed tests.

Stefano Indraccolo: I can add regarding Italy, we also have public and private insurance sector. The private patients can access comprehensive genomic profiling on tissue and plasma by paying. Some hospitals offer this service (mainly private hospitals). At this point Foundation Medicine is the leading company in charge of this. In both cases the patient goes to the hospital, sees an oncologists, blood is drawn and sent (I guess to Germany) for analysis as Foundation Medicine has a big European laboratory in Germany. The medical Dr. gets results in 10-12 days, makes a report and this is discussed with the patient. The second company trying to get into play here is Guardant Health. They are big in the US and now they are working in Europe through Myriad, which is well known for their MRD testing. This mainly applies to the private sector since for public hospitals there is always a concern related to where the genetic data is stored in the end. On which servers (European/US).

Klaus Pantel: What is your experience, Ariane, how many samples from privately insured patients do you receive?

Ariane Hallermayr: It is still a small number. I think the balance is about 50/50 from public to private, but the total amount of samles is still low, about 1 -2 samples per month. This is of course increasing the cost for us because we try to keep turn-around time short (results latest in 2 weeks). Recently, I am receiving more samples in which the patients actually requested the analysis from their physicians. It seems as though the oncologists do not often offer these LB tests to their patients, maybe because they do not want to burden them with tests they may have to pay out of pocket.

Klaus Pantel: This is super interesting and it comes down to the question who do we need to Convince? The patients, the clinicians? Both? Is it a matter of education? Is it a matter of believing in the analysis? Do they hesitate regarding the cost? How many patients and doctos really know about this?

Nikolas v. Bubnoff: I think the problem is not patients or doctors. If you tell both parties about the possibility of a non-invasive way of response evaluation etc. the argm,ents in favour are very easy to communicate. About 90% of patients and doctors I talk to are very enthusiastic about this possibility. The problem is really the communication of the usefulness, availability, and then reimbursement. To communicate the benefit of LB is not the difficulty but we are so slow to generate clinical evidence to show that clinical decision making can be based on LB studies.

Klaus Pantel: So how can we speed that up?

Nikolas v. Bubnoff: In situations where we have clear evidence that clinical decision making is in fact supported by LB analysis my suggestion would be to directly contact the specialists (tumor entity wise) and to talk to them and also to involve professional societies (ADO – dermatology etc.). To really approach them and discuss the evidence and how we could make use of this. This way, we could find a joint way forward, I believe the societies at least in Germany would be open to this.

Klaus Pantel: What role could ELBS play in this? To somehow speak with a common voice in Europe?

Nikolas v. Bubnoff: Yes, absolutely. Since this is an independent group of experts ELBS would be perfectly suited to moderate and communicate for this mission.

2) Possible Ideas for the Regulatory WG

Ariane Hallermayr: It might be a good idea to have a request form for patients and oncologists as a small public health study. A small initial study on European level to identify common problems.

Rodrigo Toledo: I agree, mapping the landscape to guide the next actions and find out who do we need to convince would be beneficial. This is a good way to learn and understand what is going on, where there is progression, where are the gaps. This is a lot of work but not costly and provides useful information. We could circulate the questions internally in each country but would need to unify them beforehand to really assess the landscape of different countries.

Timm Greve: As a mid-term suggestion, would it make sense to approach specific health insurance companies to have a more direct influence? Maybe we could at least manage to have some insurance companies reimbursing these analysis for special settings.

Klaus Pantel: Good idea. In Germany we have another instrument, which are specific contracts with selected health insurance companies. The lung cancer network in Germany has really started that way when they were looking for NGS refunding for tissue analysis in the beginning. They had deals with major health insurance players.

Nikolas v. Bubnoff: regarding the special medical groups, we have the ADO meeting in Hamburg in September. Maybe we could set up a meeting with the committee to set up a road map. This would be a great way to start.

Klaus Pantel: Then lets start to organize this that would be great. It is a limited number of tumors (mostly melanoma) and the number of people involved are not infinitive. Sometimes it makes sense to start "smaller" and create a good model.

Timm Greve: A quick question to all, are you aware of the recent Hanse Merkur LB initiative? They started a big initiative for everybody to pay 20 Euro a month and receive one free LB test. If they get a hit an additional PET scan and other services are included. What is the thought here?

Ariane Hallermayr: This is for screening?

Timm Greve: Yes.

Klaus Pantel: In principle this is not a bad idea, however, it might be trouble in progress. There was no interaction with an independent consortium to provide guidance on which assay to choose. In principle it is great to hear about innovative approaches to financing these analysis but then the test itself should keep the promise. Otherwise there is big disappointment and it could be detrimental for the LB field.

If we as an ELBS interact with these stakeholders in an independent way, this would be our strength. Rather than a single company or site which has a large commercial interest. We include different backgrounds and countries and could contribute to common guidelines which would then need to be integrated into national guidelines. Publishing guidelines in itself does not help. They are not automatically taken up by national bodies and integrated into practice. This is something we need to actively do.

Stefano Indraccolo: Absolutely, and sometimes it takes years between the publication of guidelines and the implementation on the national level. For example the ESMO guidelines on NGS were published in 2020 and the Italian government took them into consideration and integrated parts of them into health care services in 2023. And this most likely took quite a lot of behind the scenes work to accomplish and convert a paper into a change in practice. I think this last mile is

the most difficult one.

Personally, I have seen quite a bit of practice changing data in the GI field. I am wondering whether it would make sense to get in touch with the medical society's toward the end of the running trials. Within the trials there are no problems, the test are covered. In the US, this might lead to the approval of a companion diagnostic. In Europe the situation might be different. Here, we generally have more freedom in this sense of testing and taking the next steps takes longer. In terms of colorectal cancer I am sometimes wondering how much more evidence needs to be generated to convert these many, many excellent studies in high impact journals into a change in clinical practice. To enable reimbursement of a LB test to find MRD or in metastatic colorectal cancer to treat resistance mechanisms (KRAS BRAF, etc.). In my discussion with top oncologists of the field, they say in their view, LB analysis is closer to clinical practice in mCRC patients which have initially been treated with anti-EGFR inhibitors and have become resistant to the therapy than the use of LB in stage II CRC in adjuvant setting. The reason being that in case of stage II CRC, there is a fear of false negative results which could lead to under-treating the patient who could later claim this was malpractice. In the mCRC setting LB would then be used to either check for resistance mechanisms in blood, which is easier in in the metastatic setting than tissue, or to determine a therapeutic window for re-challenging with anti-EGFR therapy (could be when e.g. KRAS mutations are cleared from blood).

Klaus Pantel: Absolutely. False negatives are dramatic in these situations. But this might be one of the promising future clinical scenarios. We could try to asses which of these scenarios most clinical oncologists can agree upon.

Ariane Hallermayr: In our lab the most requests we get out of the tests that are not reimbursed yet, are also stage II CRC MRD detection. And then of course ESR1 mutation testing in BCa. It makes so much sense to test but the price is expensive.

Klaus Pantel: I am sure, if we make a list of these applications, it will a list of 5-6 specific applications. We could then think of the way to approach the exerts and see if they agree that this field is already as far to ensure clinical decision making or what kind of trial would be needed? With this information we could go to specific medical societies and say – these are the applications of interest and we could have a focussed discussion, not a general LB discussion.

Ariane Hallermayr: Great, them we might start a survey following the meeting and collect this information to get these indications down. And then follow up on a harmonized European request of how information distribution on LB issues is working so far. To really assess what oncologists and patients want. One additional idea for later on would be to initiate cost-effectiveness analysis on LB analysis in these specific clinical settings to collect actual data on this. This could then be used to increase pressure on healthcare providers and policy makers for reimbursement.

Klaus Pantel: Sure, we have a health economy group here at the UKE. Once we have specific Applications we could ask them to become involved.