Molecular Markers in Lung Cancer: Who To Test & What to Test For? (Part 6)
with Drs. Charles Rudin, Alice Shaw, David Spigel, & Glen Goss
Implementing Molecular Markers in a Network/Health Care System
by Dr. Glen Goss

Dr. West: Hello everyone -- I’m Dr. Jack West, medical oncologist and founder and CEO of the Global Resource for Advancing Cancer Education, or GRACE. We’re going to continue with the next of our program “Molecular Markers in Lung Cancer: Who to Test and What to Test For?”. I was joined in this program by Dr. Charlie Rudin at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore, MD; Dr. Alice Shaw, Assistant Professor and thoracic oncologist at Massachusetts General Hospital and Harvard Medical School in Boston, MA; Dr. David Spigel, Thoracic Oncologist and Director of Clinical Research in the Lung Cancer Program at the Sarah Cannon Cancer Center in Nashville, TN, and Dr. Glenwood (Glen) Goss, Chair of the Lung Cancer Committee of The National Cancer Institute in Canada and Professor at the University of Ottawa in Ontario, Canada.

So I’d like to turn, before we get into the question and answers, to Dr. Goss talking about the feasibility of doing this kind of work across a platform, potentially even national policies, and you can speak to how you’ve approached that.

Dr. Goss: Yes, Jack thank you for inviting me to be a member of the panel, it’s been an extremely interesting afternoon, I have to say.

I’ve been asked to speak on the feasibility of integrating molecular markers across comprehensive healthcare systems, intersection of benefit with cost. Now in the medical literature there’s not a lot that has been written on this. There may be in the financial literature but I’m not familiar with it, but in the medical literature there hasn’t been.

If anybody is interested in this topic, what I would suggest you do is look at the article, it’s the Lancet Cancer Commission that was published in Lancet Oncology in September of 2011, so last year, and it’s a getting together of all the great minds in oncology to come up with some common themes, etc.

I’m going to just talk in general about some cancer care cost first and that is in 2008, the worldwide cost of cancer attributable to disability and premature death was about 895 billion; that’s not actual care cost, that’s got nothing to do with care,
that’s just the effect on society. It’s also estimated that the efficacy rate of drugs is about 50%, that takes all stages into consideration and all tumor types. For instance, the last six weeks of life patients often get many anti-cancer drugs that are actually of no benefit whatever to the patient. So about 50% of all drugs delivered don’t do any good to the patient. This annual waste from misdiagnosis and mistreatment accounts for about $350 billion.

Turning from the worldwide view to the US vision, the US Federal Government spent in 1990 about 27 billion dollars on cancer care, by 2008 it was 90 billion and by 2020 it’s going to be 157 billion. So, over a period of 30 years there’s been a 600% increase in the amount of money that is being invested in cancer care in the US, that’s a huge amount of money and a huge increase.

Opposed to that, in the private sector in 2009, US personalized medicine market was estimated as being about 232 billion and is expected to grow annually at about 11% to 450 billion by 2015, which we know is only in 2-3 years from now. So, it’s not that as society we cannot afford the current cost, we can, there’s absolutely no doubt, it’s just a question of setting our priorities, what we want to pay for and what we don’t.

But we certainly cannot afford that incremental cost on an ongoing basis, there has to be a ceiling to that. And that’s where this personalized meds and molecular profiling of patients and their tumors comes into play.

This is a slide that has been shown in various forms by all the speakers today, but I’d like to make a few points which have already been made in our discussions. One is that not all of these targets are “druggable” at the moment. For instance, the biggest chunk there, which is KRAS is not druggable and we’ve discussed that.

Not all of these targets are going to be important, that’s the other thing. Although there are now drugs for a lot of these targets, a lot of these drugs are only available in clinical trials. So what I’m trying to do is I’m trying to temper patients’ expectations by saying ‘Look, even though we can do the molecular profiling, we don’t have the answer even if we do necessarily get your molecular profile’ although with time increasing number of patients are being able to be treated or put on a trial where they would appear to be active treatment.

To start with the US, the US have been the world leaders in this molecular profiling of lung cancer and of other tumors. The two big and earliest promoters of this outside of Harvard and Baltimore have been the Lung Cancer Consortium, which Charlie has spoken about, and the Memorial Sloan-Kettering, where they have been genotyping all their tumors since January 2009 and they have looked at 7 genes in 14 mutations.
Now the important point about this is that at last year’s presentation, when Mark Kris presented the Lung Cancer Consortium data, he said that only 13% of patients were actually found...an active treatment was found for them [1:44:40] despite the fact that they were profiled. So I want you to remember that number of 13% because it’s going to come up again later in my talk.

This snapshot, this is one of the multiplex profiling. I put this up just to inform people that you can detect these mutations in a very small amount of DNA, as little as 5% of DNA, so we don’t need a lot of tissue actually to do this molecular profiling but we do need tissue, as has been clearly made earlier on.

When you speak to medical oncologists in academic meetings they will tell you that we can profile a hundred tumors for $200 alright? And if you speak to scientists they would say ‘Oh well the price is coming down and we are soon going to be able to do genotyping on thousands of genes, at $50, the price is coming down’. So what I did was, I got my research assistant to find a few places and asked her to try and price this in real terms.

So, I’m not picking at Vanderbilt at all because this is probably true of most of the places where they provide this technology. So at Vanderbilt this is what you get with snapshot, these are the genes, the eight genes, and those are the mutations that they look for as listed on the slide.

But this is the cost, this is the actual cost. So if you’re a patient at Vanderbilt and your tumor is going to be genotyped with snapshot, it costs you $1400. Vanderbilt will do the same genotyping on somebody who is not at the center for $1700. Now if you batch them, so if you’re a physician who has multiple lung cancer patients and you can batch them – and I think this scenario is remote, it’s not common – you can get it for $1600 for five patients, if you are at the VU, but if you’re outside of VU, it costs you $2000. This gives you an idea of the actual cost to the patients. It’s somewhere around $1500-$2000 to have your tumor typed for eight genes. So that’s about the cost.

Well what about in other jurisdictions outside of the U.S.? What are they doing? In the UK in 2011, which is approximately two years after the U.S. started their endeavor, so in 2011 the UK Technology Strategy Board and two big pharma companies have funded an exercise where they are going to genotype 9000 patients in seven medical centers.

These patients are going to be genotyped for free. This incorporates all tumors and these are the mutations that they are going to be looking at. And as you can see, most of those mutations, there were actually drugs in particular cancers for those mutations. So if you have a wild-type KRAS, then colorectal cancer, there’s appropriate treatment for you, if you have an EGFR mutation, non small cell lung
cancer. So they have chosen pretty conservatively and quite carefully that panel of genes.

In France, a network of 28 hospitals linked across France, the National Cancer Institute and the Ministry of Health have funded a genotyping exercise which involves the genes listed there. And it costs about nine million dollars a year of public money and they believe that they are going to save many, many more millions of dollars if they do this.

In Canada, led by the Ontario Institute of Cancer Research in the Princess Margaret Hospital, five cancer centers, including my own, have done a feasibility study where we have looked a hundred patients, and what we have done is we have compared two systems. So we have compared the sequenome system with the Pax biosystem and looked for validation across both systems. And what we have screened for is 238 mutations in 19 oncogenes. And one of the feasibility metrics was to be able to deliver results in 21 days. So that has been accomplished.

On the initial 15 patients there were actionable mutations in 57% of patients. That was pure serendipity because that rate has fallen to 12%, which is exactly the same as Mark Kris’s 13% in the Lung Cancer Consortium, so actionable mutations, somewhere between 10% and 15% currently.

Now, that is obviously going up in places like MGH I’m sure it’s higher than that by now, but that in the general public is about what you get. As a result of this we are now going to enroll 500 patients on another study looking at 25 oncogenes and genotyping them. And on this occasion we want to get the molecular profiling into electronic medical records.

This is an issue in Ontario because of the legislation and that’s why this study is so important. It’s got to do with privacy legislations and this whole area around genotyping and the legislation around it. So this is a pilot study to see if we can deliver that.

This is my final slide. What are the advantages of molecular profiling or biomarker driven cancer treatment? Well, the first is, we avoid time wasted on drugs that are not effective, and patients are not subjected to toxicities of non effective treatments.

Secondly, in general, the new generation of targeted agents have fewer side effects than our older chemotherapy. So you are saving toxicity, you are delivering more effective treatment and you are not creating toxicity in patients that are not going to benefit.
This improves health outcomes and because of the size of clinical trials – and this has been alluded to both by David and a number of you – the cost of clinical trials is hopefully going to fall.

The additional spending; so this is the theory, that the additional spending on innovative targeted medicines will be offset by savings made from more effective and tailored strategies. So that’s on the plus side. On the minus side, or the disadvantages are that number one, we have not had a lot of validation. So a lot of the biomarkers that are being tested for and patients being put on treatment for have not been properly validated.

Also, the regulatory agencies have not come out clearly on what they want. They have come out on individual biomarkers and they have written quite extensively on what they consider a minimum standard for biomarkers but they haven’t addressed this issue that we are all subjected to on a daily basis and that is multiple biomarkers within a single screening profile. So then we need some guidance on that.

And then in lung cancer there is nearly complete absence of evidence from randomized controlled phase three trials supporting the utility of a particular marker. To date, as far as I am aware, there is no trial that has randomized patients based on a marker rather than on treatment.

The other issue that we need to address is the issue that has been alluded to by all the speakers and that is the analytical validity of the test that we’re doing. What I mean by that is, you can send the same lung cancer to one institution and that institution will report the tumor as being EGFR positive and you can send that tumor to another institution and the patient will be reported as EGFR negative.

Now this cross validation, and not a lot of it is being done, but when you do it – and I have been involved in two studies where this has been done – you’ll find this incompatibility of results.

So we need the test to be validated, analytically validated and to be robust. And then using those tests we need to design the validation clinical trials and that’s the way we have to move forward.

**Dr. West:** Well thank you. I want to pull back and ask in general question. You brought up a big issue, and that’s cost.

We are hearing more about it, we didn’t used to think about it and the general rule about oncology was that it’s inelastic, that we don’t really factor in costs. We can’t because the stakes are so high. It’s becoming harder to not think about it and it’s
being published more about and it is being talked more about, both in the general press, in the lay press, and in our own meetings.

The question is, these tests have costs and the drugs are costing more and more. As clinicians, is it our role to even think about this or must we divorce ourselves from that entire process and say we have to do what’s best for our patients and not factor-in cost to society? It’s a hard one.

**Dr. Spigel:** Well, none of us like talking about cost with the patient when it comes to trying to help them. I think the best argument, one of the best arguments that can be made for all of this that we’re doing from a cost perspective is – and Charlie alluded to this with that study – is avoiding what could be an expensive therapy in someone that is not going to benefit from it.

We’ll pick on Tarceva for the moment. So a drug that can cost anywhere from $1500 to $3000 a month for a patient or an insurer, you know, not giving them that drug when they don’t have the target that that drug was designed to inhibit. So there are cost savings there. And I do believe what Glen was saying in that there are all these downstream savings that hopefully can occur because you’re not giving patients carbo/Taxol and gem and Taxotere because maybe they are staying on a drug like Xalkori for a year and a half.

Now you can make an argument aren’t you just deferring or delaying those costs because those same patients are going to get Carbo/taxol or Alimta or whatever down the road, but my sense is probably the duration on those therapies won’t be the same as if they got it first line. But cost is always a nightmare and as technologies advance, the company X, Y or Z has a new panel that can be done for a little bit less or a little bit more, and who’s going to pay for that?

I just recently sent Alice a sample from a patient, where it was a ROS testing. Alice has one of the few centers in the country that offers it. But, and Glenn brings up the point, what are you are going to do if that result’s positive anyway?

So this was the long discussion with a patient. The tests, not to pick on Mass General, I thought it was very reasonable cost, it was something that was much lower than that, it was actually a few hundred dollars -- $600. I had a discussion with a patient about the small chance that that would be positive and if it were positive, I don’t know that I could get her access to Xalkori but maybe I could steer her towards the clinical trial that had a drug -- a next generation ALK inhibitor. And with that discussion she was willing to pay out of pocket that cost to have the testing then.
And in similar conversations I’ve had with patients, they’ve been willing to do that. But most patients cannot afford this extensive testing. So I don’t know if we have the answers on that.

Dr. Shaw: In the ALK world in particular it’s a big issue because unlike the mutation testing that we’ve talked about, EGFR and KRAS and PI3Kinase, where you can kind of batch it on, do it sort of in a multiplex way, ALK and ROS and RET, there are all these individual FISH tests, and the way Xalkori is approved of course in conjunction with the diagnostic that’s approved by the FDA, and so depending on the insurer they can insist that that FDA approved kit be used.

Now the estimated cost for doing that type of testing then comes out to anywhere between $1000 to $1500 per patient. So if you think about an ALK patient and frequency being, say, 5% in our population, that means we have the screen 20 patients or pay perhaps $20,000-$30,000 to identify one ALK positive patient, and that cost has come up many times when we have met with other oncologists, especially from out of this country, who think about those costs and just think there is no way they or us actually, can really manage costs like that. Like you were pointing out, we don’t screen most of the patients in this country and if we did, and we had to pay $20,000 to find one ALK positive patient, it would be…formidable.

Dr. West: Yeah, these are issues that we are having to wrestle with. In addition to wrestling with just the cancer we now have the financial thorniness of it.

Dr. Goss: So to try and answer your original question, I think as physicians our primary responsibility always is to our patients. But on the other hand, society can’t do this without physician help and input. So we have a responsibility to our societies to provide some leadership and some advice on how best to move forward. So in our individual practices we have to do what’s best for our patients. As societal animals we have to try and find a way to deliver the best possible care of the most reasonable cost. I think that is a societal responsibility that we have.

Dr. West: People added some questions, and my apologies to the online audience that we will not be able to get to everyone’s questions.

So one is the issue of reflex testing in early stage patients. The NCCN guidelines are for advanced disease and that’s where we have it tested. Are you doing, do you recommend mutation testing in earlier stage patients, and how would you use that information now? I open up to anybody who would speak to it.

Dr. Rudin: So I can certainly speak to what we do. We are not doing it and we are not pursuing it because we would not use that information to inform treatment decision. As has been pointed out, EGFR mutation in that context, it’s not so clear that they should get Tarceva. And in fact, for those patients who are appropriate
for standard chemotherapy in the post surgical setting, we would recommend chemotherapy regardless of the mutational status. So we are actually not doing that.

Having said that, if and when those patients recur, we certainly want to know their mutational status, so we often go back and look at those in retrospect, but we are not doing it reflexively except in advanced stage disease patients, at least at our institution.

**Dr. West:** Other comments?

**Dr. Spigel:** Yeah, I think that’s the right answer. You are aware of the CAP IALSC guidelines, they are supposed to address this issue, it’s supposed to come out any day now, they had a public comment period in the last month and they are going to address this very issue. So we have reflex testing at our center, but trying to limit that the patients with only advanced disease. I think ideally if a patient, when they recur, you want a new biopsy anyway, probably, to see if the tumor maybe has a different genotype than what they were diagnosed with.

**Dr. Goss:** I don’t think there’s anything wrong testing this conceptually in the form of a clinical trial -- that’s fine. But I’m in agreement with Charlie and with David that in the adjuvant setting there is no role for it at the moment.

**Dr. West:** Well, I think that part of the problem is once you have that information it sometimes leads you to bad decisions. That’s my concern about it.

Final question, and you alluded to this, if somebody recurs, you’re going to want tissue. In fact I think we could probably all agree that it would be most valuable to have the tissue at that time of recurrence and not just rely on their surgical biopsy material from two years ago anyway because of the sense that tumors change over time.

That leads to the question of serial biopsies, which we haven’t talked much about. We’re really talking…the strongest toehold we really have on this is early at the time of first diagnosis. I know that at Mass General you are routinely at least trying to get biopsies. Can people speak to your perceptions now about risk vs. benefit of repeat biopsies and what do you actually do with that information if you have it.

**Dr. Shaw:** So, at our institution we do routinely perform repeat biopsies, but primarily in the context of acquired resistance to Tarceva and Xalkori. For example, of course if we have someone who has relapsed, we to go back to the surgical specimen unless it’s exhausted or not available. But in the context of acquired resistance we definitely want to be re-biopsy people and we direct patients to clinical trials based on those results.
Dr. Spigel: I think it comes down to either you have a trial that’s looking at re-biopsy -- you are looking for a resistance patterns. But really, are you going to do something with that information? I’m fortunate to be at a centre that has a very large phase one program, so it’s easy for me to have a conversation about how that could lead us to steering towards one of 70 clinical trials that might make more sense than just picking one out of a hat.

But I think if a patient doesn’t have ready access to act on that information from the doctor, I’m not sure how helpful it will be right now. I mean, I think it’s ideal, but I’m not sure from other than an academic standpoint, it would help patients who don’t have access to clinical trials.

Dr. Rudin: I think Glen made a very important point earlier about the relative perspective of this from patient perspective vs. physician. As doctors we are taught ‘first do no harm’ -- you know, really don’t do things if it’s going to be potentially dangerous unless it’s really going to influence your care.

But I think patients who have advanced lung cancer are willing to take risks that are going to be potentially informative for them in terms of guiding future therapies. And I think increasingly, at centers like...up in Boston certainly, and the other great example of this I think is the BATTLE trial that was done at MD Anderson, patients are willing to do this and I think we need to listen to our patients.

Dr. West: That I agree with, I think that makes sense. We haven’t really talked about risk, actual risk of the biopsies, and I think our perception is that it’s pretty minimal. Occasionally people will have a pneumothorax and need to be hospitalized with a chest tube but that tends to be the extent of it. It’s not zero.

And the other rule that we have right after ‘above all do no harm’ as the first rule of medicine is, you know, a lot of us are taught, if it’s not going to change your management, don’t do a test. And I think that’s right now the thing that we struggle with: How much do we invest in “this could be useful in the future even if you can’t use it now”. that’s I think a challenge.

Dr. Goss: And hopefully in the future, these newer technologies, like circulating tumor cells and circulating DNA will be developed to a degree where we have confidence in them and can base our testing on them.

Dr. West: That would be amazing.

Dr. Goss: And then patients will not have to be biopsied.

Dr. West: Well, I want to thank our panelists and I want to thank the LUNGevity Foundation for our partnership with them that made this program possible. So thanks very much and have a good night everyone.