Personalized Cancer Genomics: The Road Map to Clinical Implementation

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. The promise of personalized medicine has now been around for some time but growth in this field is now rapidly gaining momentum. By using information from an individual's genome, transcriptome and proteome, a customized management plan maybe tailored for each individual.

In the April 2012 issue of *'Clinical Chemistry',* Dr. George Yousef, an Associate Professor from the Department of Laboratory Medicine and Pathobiology at the University of Toronto provided his perspective on a study performed by University of Michigan team that utilized a comprehensive sequencing strategy to obtain multi-molecular level data that are then integrated to answer the question of eligibility of metastatic cancer patients to enter certain clinical trials.

Dr. Yousef is our guest in this podcast. Doctor, in the last few years, we've started to hear a lot about personalized medicine or personalized healthcare, which probably have different meanings for different people. So, how would you define personalized medicine and how significant is it in patient management?

Dr. George Yousef: Well, in the broad term, personalized medicine can be defined as utilizing the genetic makeup of an individual to accurately plot the course of an illness and consequently to kind of customize or tailor the patient management plan to fit the specific needs of this individual patient, and this should have impact on both, the patient and the healthcare system.

So, if we look at the patient, we will enable the patient to have his disease detected early to get the right treatment at the right dose. On the other hand, if you look from a health system perspective, this personalized medicine approach will be reflected in a significant saving and more efficiency because you will reserve treatment only for a sub-group of patients who are likely to respond to this particular treatment.

Also, you will reserve intensive follow-up and adjuvant treatment only for patients who really need it. Those are the patients with a known or predicted aggressive disease.

Bob Barrett: But now this approach is really already been used in our current management system. For example, the hormonal receptor status in breast cancer and other

predictive markers like KRAS mutations for metastatic colon cancer. So, what is new about this and what makes it such a hot topic in recent years?

Dr. George Yousef: You are absolutely right. The concept of personalized medicine has been there for a while. As you mentioned, there are few examples of a personalized approaches that rely on a single molecule to kind of sub-stratify or classify a patient.

But what happened in recent years is that we witnessed a new revolution in the concept of personalized medicine and this, in my opinion, came because of three main factors.

Number one is the completion of the human genome project. So, now we have all the players identified, and this is our golden chance to understand the interaction or the cross talk between them. How do they interact together to produce the disease phenotype?

And number two is the invention of what we call high-throughput molecular technologies. These are the techniques that allow the simultaneous analysis of hundreds or even thousands of molecules in the same time. Examples would be micro-array analysis, mass spectrometry and others.

So, this allowed us to have or to generate an enormous amount of information and subsequently, a significant acceleration in biomarker discovery.

Finally, this was coupled by unprecedented advances in bioinformatics and computer abilities that allowed an accurate assessment of all these hundreds of thousands of molecules and to study the interactions between them. These three factors together kind of trigger a new era when we are at the verge of having a revolution through personalized medicine.

Bob Barrett: Well, that sounds very impressive but we've been hearing about this revolution towards a new era of personalized medicine for number of years now, we haven't really seen it translated into clinical practice. There are some exceptions but the patient management strategies in many diseases like cancer and diabetes are more or less the same. How can you explain that?

Dr. George Yousef: Well, this is a very interesting question. I agree with you, there was an initial period of enthusiasm. Everyone was expecting an eminent revolution over

the way that we practice medicine but then after this exciting discovery phase, we started to realize that this transition from bench to bedside is actually a multi-step process and it's more complicated than previously thought; and this is for a number of reasons.

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Now, think about it. After the exciting discovery, we need to extract and focus on what we call clinically meaningful or informative molecules out of this ocean of millions of molecules that we produce in our discovery phase, and this is a tedious process.

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The second is that we need to translate these informative molecules into a clinically formed test into a clinical test. This test should be affordable, should be standardized and should be done within a reasonable timeframe, that's completely different from the research setting when we don't care about all these factors.

Another serious aspect that needs time to assess is how much more information these molecules provide that are beyond what we already have using the routine lab test. So, for example, it doesn't make sense for me to have a test that's a couple of thousand dollars in cost that will not produce much more information compared to what we can have just through the regular microscope.

So, what I feel is that we are moving in the right direction, but we need to understand that this is a multi-step process. We need first to be patient, to complete our analysis and assessment, and we also need to be realistic. It's not going to be an eminent revolution but rather complementary steps to be added to our current management system for cancer patients step-by-step.

Bob Barrett: Okay doctor. Last year, the group from the Michigan Center for Translational Pathology at the University of Michigan published a feasibility study that utilizes comprehensive sequencing in order to redefine the eligibility criteria for a clinical trial. How successful do you think this approach would be?

Dr. George Yousef: Well, I'm glad you mentioned this because this is an excellent example to show how can we translate the research setting into a molecular test that is clinically informative. So, what happened to this group is that they focused on a specific question, that's the eligibility criteria for enrolling the patients to clinical

trail, and here's the surprise: they found that a patient for example, with a melanoma has a rare mutation, so he is eligible to be enrolled into a colon cancer trial.

That's something unique. This is a new perspective because we're used to classify patients or to enroll patients into clinical trials based on the organ. So, we have a clinical trial for colon cancer, clinical trial for lung cancer etcetera but now maybe it's the time to enroll patients into clinical trials based on the behavior of the tumor rather than the location.

Another interesting aspect is that they managed to focus only on a subgroup of what we call clinically actionable or clinically informed molecules, so that the test can be done at a reasonable price of about $5000 and in a reasonable timeframe, so that it can be useful to the patient and this is exactly, what we need, one specific question that is addressed in a practical way each time.

Bob Barrett: Well, you mentioned the cost for a moment there, but don't you think molecular testing will be much more expensive than our regular testing especially when using these highly advanced technologies like second-generation sequencing and mass spectrometry. Do you see the cost as real obstacle towards the implementation of molecular techniques?

Dr. George Yousef: Well, I agree with you that the cost is an important consideration. These are tests that are about a few thousand dollars per test on average but on the other hand, we have to think about it in a different perspective because yes, the initial investment for the infrastructure and implementing these technologies is going to be more expensive. But on the other hand, once this is established, the running cost will be significantly lower, especially when these tests becomes more popular and more routinely used.

Another factor that you should think of is the cost-effectiveness. So, yes we do have a test that will cost $5,000 but the results of this test might lead to savings of $50,000 on average. This is the average cost for treating metastatic cancer patient to chemotherapy. So, if the patient is not eligible and is not likely to respond to this particular treatment as indicated by this test, that will save us much, much more money compared to the price of the test. So, cost-effectiveness is very important in this regard.

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Bob Barrett: Well, listening to what you're saying, implementing that molecular medicine should bring about some ethical issues and concerns. Do you agree with that?

Dr. George Yousef: I definitely agree. There are some ethical dilemmas that we have to deal with, with the implementation of this personalized medicine approaches, especially with using the high-throughput technologies.

So, for example, what kind of information are we going to convey to the patient? Is it just information that's related to his current illness? How about if we discover, like incidentally, that this patient is at risk of another disease in the future, would we be able to tell the patient this information? How about other family members who might be at risk? Are they eligible to have a look at the test results and know if they are at risk of this disease? Same thing for employers, for insurance companies.

So, it's not an easy task but this wouldn't hold my emphasis toward personalized medicine approaches. So, in my opinion we need a multidisciplinary team, a team that has lawyers, doctors, lab-scientists and patient representatives to develop a standard of practice that deals with these ethical issues and identify all the pros and cons.

In this case, the patient will have a chance to write or sign an informed consent with previous knowledge of what exactly does this mean.

Bob Barrett: Well, finally Dr. Yousef, let's look ahead. What do you think the future of this field is going to be?

Dr. George Yousef: In my opinion, we are on the right track, but we need to be number one; patient. This is a multi-step process that will take time for the assessment of the clinical significance of these tests. We need to take out time for the standardization of these tests and we need to be realistic in our expectations.

So, in the future, I guess we need to focus only on one question at a time. So, the way I see it is that molecular medicine or personalized medicine will be implemented step-by-step slowly to compliment rather than replace the current management system of cancer and other diseases.

Bob Barrett: Dr. George Yousef is an Associate Professor from the Department of Laboratory Medicine and Pathobiology

at the University of Toronto. He's been our guest in this podcast from *'Clinical Chemistry'*. I'm Bob Barrett. Thanks for listening.

Total Duration: 13 Minutes.