Glaucoma Hot Topics Panel

Eytan Z. Blumenthal, MD[1], Maria Francesca Cordeiro[2], Leopold Shmetterer[3], Hana Levkovitch Verbin[4], Alon Harris[5].

[1]Department of Ophthalmology, Rambam Health Care Campus, and the School of Medicine, Technion Israel Institute of Technology, Haifa, Israel.

[2]Department _____, Institute of Ophthalmology, Faculty of Brain Sciences, University College London, London, UK

[3]Department _____, Singapore Eye Research Institute, Lee Kong Chan School of Medicine, Nanyang Technological University, Singapore

[4]Clinical Department and School of Continuing Medical Education, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[5]Department _____, Indiana University School of Medicine, Indiana, USA

Correspondence to: Eytan Z. Blumenthal, MD
                      Department of Ophthalmology
                      Rambam Health Care Campus
                      P.O.B. 9602, Haifa, 31096, Israel

                      Tel: 972-4-777-2668
                      Fax: 972-4-777-2142
                      E-mail: eytan@blumenthal.org.il

MODERATOR: Good day to you all. In the next 45 minutes, we'll try to break down two topics of interest for which there is no known solution or perfect answer, and we'll do it in a slightly different way. We'll start with the first topic for debate, and when we have are two speakers, one will take an optimistic approach, and the second a pessimistic approach.

Topic 1: Medical Treatment of Glaucoma 5 and 15 Years from Now

Our first topic is "Medical treatment of glaucoma 5 and 15 Years from now: New compounds, delivery methods, rejection of current options, and revolutions." So let us be optimistic during the initial talk.

THE OPTMIST: Hopefully longer. What's possible in 5 years, what's possible in 15 years? In the next 5 minutes, I'll quickly cover drug delivery. I may even cover neuroprotection, and then I'll talk about what will happen during the next 10 years.

So, the onset of intravitreal injections has driven a real change in the way things are done in medical retina. What about in glaucoma? You've probably all seen this, phase 2B, I think. This is the bimatoprost intracameral technology that is similar to Ozurdex. That trial is on-going, we don't know the results yet.

This is the other technology that Allergan recently acquired, the bimatoprost ring. I don't know if anyone in the audience has used it. This technology has a slow depot, Again, it's bimatoprost, and it sits on the eye like this.

This is the microneedle injection. Again, this is a medical retina advance, so this uses triamcinolone, and is a suprachoroidal injection. So expectations for the future, supposedly, are that all these patients who are noncompliant with daily drops may be able to benefit from instilling devices like this.

The punctal plug delivery system recently completed phase 2 trials. Again, I don't know the results, but it's an option. One that definitely isn't going ahead is the Ocusert, although those of us who used it found it very useful for certain patient types.

Neuroprotection. We need to move on from just IOP. I think everyone's in agreement with this statement. What is available? Well, VISUfarma has developed Coenzyme Q10, a mitochondrial targeting agent which is topically delivered. This is an in-vivo experimental work that my group published, and we believe potentially there is an indication for Coenzyme Q10 in glaucoma.

Other things to look at are drugs that are already used in conditions like Alzheimer's disease that target beta-amyloid. Again, we've published on some of these drugs, such as the abeta-antibody and Congo red, which stop the beta-amyloid fibrils from curling up together.

We recently showed that brimonidine actually has an effect on the beta-amyloid pathway; putting forward the idea that brimonidine used in glaucoma may be useful for treating Alzheimer's disease.

In Italy, which seems to be a hotbed of neuroprotection, nearly all of these drugs shown here are going through some sort of trial. Again, there are other agents which are not targeting IOP, and I've just ran out of time for my talk on DARC, because one of the things these new drugs needs is a way of quickly assessing whether they work.

Ocular gene therapy, where are we? These are possible ocular targets in glaucoma for gene therapy, with more and more coming through, and the strategies, obviously, are all at a very early stage. SiRNA is perhaps the most promising.

What about optic nerve regeneration and RGC regeneration? The jury is still out on that one. There was a very good commentary the other day on optic nerve regeneration; very few axons were found to extend outside of the brain, and a suggestion is that barriers to regeneration are even more important for glaucoma.

THE PESSIMIST: I just heard that "The Optimist" was saying terrible things about me. So, anyway, I would like to start out by saying something about hurdles blocking innovation in glaucoma and why I adopted a pessimistic view, which is in reality, rather realistic, or just slightly pessimistic.

One of the hurdles is definitely that the disease process is inadequately understood, and we have some fundamental questions that we are unable to answer, one of the very fundamental questions being, where does the disease start? A second very fundamental question asks what is the relation between changes in the anterior and posterior segment that we see in glaucoma? We have very few clues about this.

The second reason why I'm quite pessimistic is the history of treating neurodegenerative disease. You know that in the brain, the field of neuroprotection began a long time ago, in the 1980s. Now, approximately 35 years later, the clinical success of neuroprotection is not very exciting. Let's put it this way.

It might be a little bit easier, though, in the eye than in the brain, because we have better surrogate outcomes, and we are a little bit brighter than the brain people. Nevertheless, it is still extremely challenging.

The third reason why I'm a little bit pessimistic is that prostaglandins work pretty well. I mean, they really are sort of a gold standard, and if you look into other treatment areas, you hardly find something that is as effective as prostaglandins and as well tolerated. This is really something very exceptional. Most people benefit from prostaglandins in terms of IOP lowering, and most people tolerate these drugs pretty well.

The fourth reason being, who shall pay in the time of generics? Nowadays, around the world, prostaglandins have become extremely cheap. I'm not even talking about beta receptor antagonists. And generally, if you want to go into new drug areas, what will enter the market could be quite expensive, and this is simply related to the enormous financial burden invested in bringing a novel therapy to the market.

It will not be easy to convince the payers to accept a novel therapy if it is not revolutionary. If there is a total revolution, this might be different. But if it is just, let's say, a little bit of improved pharmacokinetics or something like that, it will be very difficult to convince the authorities to invest enormous sums.

Now we come to the final question, perhaps the most important: is there a clinical need to do so? Concurrently, I would like to point out an excellent recent review article by Remo Susanna and a group of very well-known glaucoma experts who ask the question, why do people still go blind from glaucoma?

I think one of the key issues is that glaucoma remains often undiagnosed. Any type of new therapy will not help people who are undiagnosed. At least from my point of view, this is maybe the major challenge we currently face in glaucoma. I am not talking about Third World countries, but about developed countries. All the epidemiological studies that were done either in Greece or in the UK, or that we ran in Singapore, indicate that more than 50% of glaucoma cases are undetected.

Of interest, we run a diagnostic retinopathy screening program that relies on fundus photography. It is amazing how many cases of undiagnosed end-stage glaucoma we detect that were previously undetected. So as with any type of new treatment, it will not help those patients who are as yet undetected, and I'm not talking about the situation in third world countries where this is even more of a problem.

Next, of course, glaucoma is still improperly treated. But what the authors mean here is not that we don't have good treatment options, but that too many people lack access, or are not taking these medications.

This is in fact a major problem, and I know how it is with my mother-in-law, how difficult it is to get her to take her medication. My mother-in-law is particular in some respects, but I'm not so sure she's particular in that respect.

I think it is one of the major challenges we generally have that we know how to treat many, many diseases. The same is true for diabetic retinopathy. But we have big problems translating this treatment optimally into the patients who are in the age range that need this treatment.

This is also related to a lack of compliance. Another challenge is that, even if we have better treatments available than we do nowadays, it's still a big problem how to convince patients to take their prescribed medications and to improve adherence, because even with better treatments, and even assuming we have true neuroprotective treatments available, we will still be faced with the problem that many patients will, for whatever reason, not take their medication.

So I think when we talk about novel treatments, we also have to be very clear if we will have good screening. If all the patients will have success to and will take the currently available medications, I think the vast majority of cases of blindness could be avoided.

MODERATOR: As usual, the truth probably lies somewhere in the middle. We can take three comments or questions. Let's start with the panel.

COMMENT: I just want to add that these three points are actually very similar to any chronic disease. Some patients are undiagnosed, some patients, like in diabetic or hypertension or any chronic disease are not properly treated, and some don't take their prescribed drugs. Still, there is a lot of innovation in other fields, and I'm sure we are also in a field where we are going to see dramatic innovation. So I'm optimistic.

THE PESSIMIST: May I answer on this? I think there are some issues where our field is different. One thing is that glaucoma is non-symptomatic. This makes the number of undiagnosed patients much higher than in other diseases. The second point that is problematic is that public awareness of glaucoma is relatively low as compared, for instance, to brain disease, diabetes and hypertension.

The third thing is I agree with you is innovation, but we also have to be clear that for the vast majority of glaucoma patients, there are good treatments available, which is not true for many other diseases. For instance, if you look at Alzheimer's disease, public awareness is much higher. It is symptomatic, because patients realize they have the disease at relatively early stages, but the problems they face have no treatment.

THE OPTIMIST: So I want to give an optimistic angle to your pessimistic view. I think the question was what one felt would happen in 5, 10 and 15 years. I'm not sure you've answered that. I think what you've done is say: "Because of these drawbacks, I'm giving up on 5 and 15 years altogether." But even the most pessimistic of the pessimists would have to agree that something might happen, and even concerning the issues you raise, is it not possible that the future might improve the ratio of undiagnosed and improperly treated patients?

The lack of compliance is already addressed by suggesting other ways of drug delivery. So many of the points you raise are currently being addressed. This may not produce an ultimate solution yet, that which, I agree with you, is still lacking. But in 5 or 15 years, the three issues you raised may actually receive answers originating from innovation being looked at now.

LAST COMMENT: My comment is going to be a bridge to the next topic, because I think all these comments have one common denominator, and that is trying to tailor a specific diagnosis to a specific treatment, which I think is part of the problem.

Topic 2: Will personalized medicine be commonly used in glaucoma five years from now?

MODERATOR: Lets now proceed to the second topic, "Will personalized medicine be commonly utilized in glaucoma five years from now? If so, what and how?" And by "personalized", I mean that we will tailor different treatments to suitable patients.

THE OPTIMIST: I received from the Moderator the optimistic view, are we going to use personalized medicine in 5 years from now?

Before I answer I will explain why I am indeed optimistic, I would like to start by giving a brief presentation about what is personalized medicine. In fact, a recent synonym would be "precision medicine".

So by talking about personalized medicine, we are actually talking about tailoring the medical treatment and prevention, not only medical treatment but also prevention, to fit the genetic as well as additional characteristics of the individual patient. With this approach, we have the potential to tailor therapy to the best individual response and highest safety margin to ensure better patient care. This may allow us to provide our patients with earlier diagnosis for many diseases, to conduct a risk assessment and to receive optimal treatment. This, of course, will improve health care and lower healthcare costs.

Now, let's move on to a somewhat different term, which is actually very similar to personalized medicine, what we now call "precision medicine". The goal of the precision medicine initiative is to move beyond personal treatment and to develop a systematic plan for all illnesses, including, of course, eye diseases.

So the focus is to identify which approaches will be most effective for which patients based on genetic factors, which may be the most important, but also to take into account environmental and lifestyle factors.

Pharmacogenomics is a crucial part of precision medicine. It's the study of how genes affect a person's response to any particular drug. This field combines pharmacology and genomics. For the pharmacologist, the primary goal of pharmacogenetics is to develop more effective, safer, medications and dosages. It's not just the medication, but also the individualized dose that makes a difference, taking into account the patient's genetic background. This important goal was recently recognized as part of the new U.S. Precision Medicine Initiative announced by President Obama in 2015.

Hence, I am optimistic about precision medicine or personal medicine in light of all the promise for improving many aspects of health and health care in the next 5 years, because this way of thinking will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease like glaucoma will work better in each individual patient.

This is in contrast to a one-size-fits-all approach, which I'm going to talk about more in relation to glaucoma. Advantages and advancements in genomics, coupled to data science and machine learning, hold promise in providing better approaches for our patients.

Just to give you one example that we all know, is blood transfusion. We do not just take blood from a donor and transfuse it to a recipient. We measure and examine blood markers, biomarkers, and then we arrive at a match. This is actually what we want to achieve for each patient, for each disease.

So lets return to precision medicine in glaucoma. First of all, why do we need it? Why is it that what we are doing right now is not good enough? It is because glaucoma is a very common disease, approach almost 10% of the elderly population, and this is without taking into account ocular hypertension. So for many patients we need to rely on risk calculators so that we will be able to treat the patient based on his/her own individual risk profile.

We would all like to be able to predict progression. We would like to know how frequently should we follow-up the patient in clinic, and how frequently should we perform imaging and visual fields. We want to tailor and individualize target intraocular pressure that best reflects the patient's oveall risk, and most important, we would very much like to tailor treatment ojn an individual basis.

This process is relevant not only to glaucoma, and not only in respect to treatment, it's also about being able to predict that patient's risk of progression, and communicate how frequently should that patient return for their regular eye examination.

So right now we prescribe medication by trial and error, based on our patients' comorbidities. If, for example, they suffer from a lung disease, we are in all likelihood not going to prescribe a beta blocker. We also prescribe based on efficacy, side effects, cost and compliance. But in fact, most of us would prescribe, as the first drug

of choice, a prostaglandin analogue, but perhaps this is not the way to go. What we actually need is a genetic profile to guide us towards the optimal medical therapy for any patient with glaucoma.

In addition, prior to glaucoma surgery, we may want to use genetic markers to predict the response to antifibrotic agents, like 5-fluorouracil or mitomycin-C.

So where are we headed in 5 years, based on what we currently know? Let us begin by taking a brief pause from the field of glaucoma and talk about oncology. Personalized medicine is actually already here. We know that in oncology, therapy is prescribed based on specific genetic mutations, a very common and successful approach in oncology. Looking back 20 years, the first papers about personalized medicine in oncology began to appear. Within 10 years the treatment of cancer changed dramatically. This analogy places us in a very optimistic scenario regarding glaucoma.

So far, more than 70 genes were identified that are associated with glaucoma, although most of them are related to the infantile and congenital subtypes. However, some of them are also associated with high-tension and normal-tension glaucoma. Further genetic studies have identified polymorphisms, such as the LOXL1, related to exfoliation syndrome. In many studies linkage is used, such as in GWAS approaches to identify novel risk genes for elevated intraocular pressure; as well as additional alleles of genes already identified.

When we relate to intraocular pressure, there is significant potential, because intraocular pressure is a complex trait determined by multiple factors, including aqueous outflow, uveoscleral outflow, trabecular outflow and episcleral venous pressure. It appears that multiple interventions may be found that hold potential in treating glaucoma.

We currently already have at our disposal a comprehensive diagnostic test, the genetic eye disease panel, which includes all the genes known to harbor mutations that cause inherited retinal degeneration, optic atrophy and early-onset glaucoma. This new test can be used in a clinical setting. It is not comprehensive nor is it specific for glaucoma, but in five years it is very likely that dramatic developments will occur.

There are studies regarding lifestyle, including smoking, physical activity and weight loss, which are also relevant for precision medicine. Lastly, two relatively new papers suggest that we can gain knowledge by using certain statistical techniques. One of them is the "Kalman filtering" algorithm that can dynamically determine what additional information and measurements we need, based on prior data and measurements obtained in the past for an individual patient. This approach may also help us to adjust and tailor the frequency of follow-up recommended.

We also have a lot of advancements and new data regarding steroid-induced glaucoma; new genes and alleles that may tell us who is likely to respond to steroids by a meaningful elevation of intraocular pressure, and who is likely not be affected.

In summary, I believe that in 5 years, personalized medicine will be used in clinical decision-making for individualizing the treatment regimen, based on which disease related factors can be influenced, and based on the genetic profile of the patient, an assessment of risk, as well as other factors.

MODERATOR: Thank you very much. We will now conclude with a pessimistic approach which we hope will leave room for at least some progress.

THE PESSIMIST: While my slides are being set up, we can jump straight to my last slide, I fully agree with what was already said. I remain optimistic about tailored medicine, but no way in 5 years. In my opinion… no way.

We are dealing with a complex multifactorial disease. Yes, trying to tailor specific risk factors to treatment and produce better outcomes is what we all want. However, we need to understand that the wide variability seen in response to any therapy depends on multiple factors: age, nutrition, health status, environmental exposure, epigenetic factors, concurrent therapies, adverse drug reaction profile and more.

Yes, it will do wonderful things. We can decrease health care costs and wasteful spending, achieve better responses and provide wider safety margins. But boy, do we have work. Yes, genetics certainly unraveled several distinct genes, especially in relation to primary congenital glaucoma, and more recently glaucoma risk alleles, modification of were demonstrated to have an effect on the age of the onset of certain types of glaucomas. So, yes, this is great news about the future of tailoring treatment in glaucoma based on genetic factors.

But again, I would like to remind you all that all we have right now at our disposal is the ability to lower intraocular pressure. If I take the example of an "old horse" that we've used in glaucoma these past decades, Timolol, it has been shown as less efficacious in black patients compared with nonblack patients. This might very well be the case with many of the new glaucoma medications that are either on the market or as yet undiscovered.

Regarding the genetic and pharmacogenomics worlds, which were just described, I would like to jump straight to an example: beta blockers are metabolized by the cytochrome P450 enzyme with CYP2D6. We know about poor metabolizers who consequently show excessive beta blocker blockade of heart rate and higher plasma Timolol concentration. So, yes, gene encoding beta adrenergic receptors or the ADR are polymorphic, and ADR genes have a complex role in ciliary body. There's a lot of good things we can accomplish if we take beta blockers for examples, but no, I don't think it will be ready in 5 years.

Take covariates in the IOP response to topical beta blockers, another avenue for personalization. For example, drug binding to melanin within ocular tissues. Again, Timolol has been shown to be less efficacious in black patients compared to nonblack. Again, while we are immersed in a wonderful world trying to benefit from pharmacogenomics, and take a closer look at drug metabolism in respect to controlling IOP via genetic factors, we learn that race, as well as perhaps central corneal thickness are perhaps all inter-related? Well, how do we go about it? We will have to develop mathematical models. Maybe they will be able to assist us along the lines of genetics.

It's been shown that there is value in analytical assessment for diseases based on discrete risk factors. Taking into account the heterogeneous nature of glaucoma necessitates a complex mathematical approach to characterize the delicate interplay between progression and risk assessment of specific factors.

This is a very complex task. I know it because I have been working with mathematical models for the past eight years. You first have to understand the measurements. Then you have to understand the main questions. You have to study the anatomy and the physiology of the system. You have to formulate a precise question to start with. You have to develop appropriate mathematical models, and then combine these models with experimental data.

Following is an example which is useful, but only in the early stages. In my area of research, I look at how different pressures affect the lamina cribrosa. I look at the intraocular pressure but then factor in the retrolaminar pressure as a surrogate for intracranial pressure. We can learn from the model that different responses exist in different individuals as to what affects the ocular blood flow to the optic nerve. Is it the IOP, which in many cases appears to have a stronger effect than actual changes of the retrolaminar pressure? These are the kind of analyses that a model can help us with.

Here is another example. If you look at oxygen saturation, you can appreciate that the clinical data shows that higher levels of oxygen venous saturation in glaucomatous individuals might exceed the levels found in healthy individuals. If you analyze this within the context of a mathematical model, you can hypothesize that this is the result of cell loss, which causes a lowering of metabolic demands in the tissue, which ultimately leads to higher venous saturation in the diseased eye.

By actually creating a model and looking at model predictors, one finds that determining the metabolic demands necessary to stimulate the level of oxygen venous saturation that was measured clinically can confirm that the increase in oxygen venous saturation is indeed secondary to cell loss in primary open-angle glaucoma, but apparently, this is not the case in normal tension glaucoma. These examples teach us how mathematical modeling can be used for distinguishing and then tailoring therapies for specific classes of glaucoma patients.

So we can also rely on glaucomic, defined as theintegrated use of multiomics and system science approaches towards rational discovery, development and tandem applications of diagnostics and therapies for glaucoma specifically, and, more broadly, for personalized visual health.

A complex disease like glaucoma is perhaps best conceptualized as a syndrome displaying a common clinical endpoint but with a vastly heterogeneous molecular underpinning and host-environment interactions.

So, bringing this dilemma to closure, individual medicine, certainly, we all want to see it happen. We all need it, certainly in glaucoma. We can improve management by tailoring, using genetic profiles, mathematical modeling, and by using racial profiles. The future application of this profiling could lead to fewer return office visits.

Certainly, the FDA is certainly in with us. The FDA has outlined steps needed in order to integrate biomarker information for clinical use in drug development, a more efficient use of healthcare dollars. All of this sounds wonderful.

Individual medicine, however, in precision medicine, as my optimistic counterpart so nicely defined it for us, will cost millions of dollars and require Congress to approve such funding over multiple years.

Technology for sequencing large amounts of DNA of individual patients is expensive and time-consuming. Hence, a cost-benefit analysis with economic modeling is needed to demonstrate and measure the health benefits and long-term cost savings stemming from walking down this path towards improved treatment outcomes, thereby decreasing disease morbidity.

Another scientific challenge that we have is which genetic markers are the most clinically significant for altering disease outcome? Genetic markers will need to be tested and validated. Could this be achieved within five years? I doubt it.

MODERATOR: Thank you Dr. Pessimist. Do we actually need personalized medicine? Do we want it? To try and answer these two fundamental questions, please allow me to do a "metaphoric visual field test" to each and every one of you in the audience in order to check if you have a huge scotoma in the center of your visual field, whether you are seeing "the forest" or "the trees"? Stop and think for 5 seconds, do I actually need personalized medicine in the clinic? And then please allow me to share with you a few examples that are perhaps so obvious that you'll say, "Wow, maybe I do have a scotoma."

Number one, when a new patient walks into my clinic with a pressure of 27, should I treat conservatively, or perhaps skip the entire medication stage and head straight to surgery? If only I could know whether medication would lower pressure adequately, and whether a trabeculectomy is going to succeed or fail? Perhaps I would be wise to go directly to a tube?

It appears that at least one person in the audience listened and outsmarted me just now: "You think we have a scotoma? You have a much larger one". "I actually want to know if the patient sitting in front of me is going to go blind during their lifetime, because if they're not, we can certainly save a lot of burden, time, apprehension, money and side effects."

These are just a handful of fundamental "personalized medicine" questions that we're so accustomed to walking around that we forget that they're sitting right in front of us, huge hot potatoes. Hopefully we'll get some answers in the future to the really basic questions related to treating glaucoma.

COMMENT: First, I agree with what the pessimist said that achieving this in 5 years appears hopeless. I would like to tell you two stories, one related to drug development and one unrelated. In 1989, I traveled with my parents for 3 weeks to Germany. We spent half the time in East Germany, and the other half in West Germany. In both countries my father met ministers with whom he negotiated. None had any idea that in October 1989 the Wall separating the two Germanys would fall. So predicting what will likely happen in the future often ends up as a futile exercise.

The second story relates to drug development. When complement factor 8 was identified as a major risk factor for having AMD as well as geographic atrophy, and we thus realized that the complement system plays a major role both conditions, similar questions were raised, For instance, will there be a treatment for geographic atrophy in the very near future? Everybody was extremely optimistic and consequently the pharma industry invested a lot of money into this. Now, 5 years

later, many are frustrated because we have no treatment available, and all the trials came back negative.

So one really needs to be extremely careful in committing to any kind of prediction, because such matters are, to a large degree, very unpredictable.

COMMENT: I would like to respectively disagree. The analogy of the Berlin Wall falling down is completely opposite to the way we, as doctors, were taught to look after our patients. By saying we cannot predict, you risk losing the major advancement in the field of oncology that successfully learned how to use markers to predict who will benefit from cancer therapy. In the same way, I think it's important to realize that just because we haven't advanced in this area recently, there is no reason to assume that this stagnation will be maintained in the future. Nothing of what you have said made me change my mind about this. I remain optimistic.