Interview

An interview with Lawrence Lesko for *Personalized Medicine*

Lawrence Lesko speaks to Sarah Miller, Commissioning Editor

Lawrence Lesko currently serves as Professor of Pharmaceutics and Director of the Center for Pharmacometrics and Systems Pharmacology at the University of Florida College of Pharmacy at Lake Nona in Orlando (FL, USA). This appointment followed his retirement in July 2011 after 16 years as Director of the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the US FDA. While at the FDA, Lesko led the advancement of personalized medicine, through the update of existing drug labels with new genetic information and the development of the Voluntary Genomic Data Submission Program. Lesko has published more than 200 peer-reviewed manuscripts, is a frequent invited national and international speaker, and is the recipient of multiple awards for his achievements relating to clinical pharmacology and personalized medicine.

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■ **How did you become involved in the field of personalized medicine?**

I got involved back in the 1970s, when I was involved in individualization of drug therapy at the University of Massachusetts Medical Center (MA, USA). We had a program there called therapeutic drug monitoring and, while we weren't using genetics at that time, we were optimizing the doses of a whole menu of drugs mainly using blood drug concentrations.

Somewhere around 1980 we became interested in acetylation, which is a well-known genetic polymorphism. We began offering a testing service called 'isoniazid acetylation phenotyping', which was a simple process: we collected urine specimens over 6 h and then measured the ratio of acetyl isoniazid to free isoniazid, and the metabolic ratio was a phenotypic measurement of the genetic variability of *N*-acetyltransferase. That was really the beginning of getting involved with personalized medicine for me: we were using the phenotypic information much like genetic tests are used today to personalize anti-tuberculosis treatment with isoniazid using the acetylation ratio as a way to decide whether a higher or lower dose of the drug should be given to patients, to make sure that the disease was in check and that patients would not be susceptible to any serious adverse events.

We were also applying acetylation information to other acetylated drugs that the

patient might be taking. For example, if they were taking isoniazid for tuberculosis, they may also be taking procainamide, a widely used antiarrhythmic drug in the 1980s. Because patients would also polymorphically acetylate procainamide, we would use isoniazid phenotyping, which correlated with procainamide phenotype, in order to figure out the right dose. For me, phenotyping was a natural extension of therapeutic drug monitoring.

Let's fast-forward to my work at the US FDA, which played an important part in my getting involved in personalized medicine: it was right around 2000–2001 and we received a letter at the FDA sent from a high-ranking industry official. The letter was specifically addressed to Dr Janet Woodcock, who was the Director of the Center for Drug Evaluation and Research at that time. The letter stated that industry would like to perform more exploratory genomics; that is, collect and analyze DNA in their clinical trials. However, the industry was concerned that they, or the FDA, wouldn't know exactly what that information would necessarily mean. The industry spokesperson said that industry was concerned that the FDA was not ready to review this technology and correctly interpret the genomic information. The industry was concerned that reviewers would overreact and ask them to do more work, or misinterpret the data, which would somehow hurt drug development programs.

So, Dr Woodcock and I met. She said that we really needed to incentivize personalized medicine, and as a result I was able to lead the way at the FDA in developing the Voluntary Genomic Data Submission Program, which was a big success in my opinion. It encouraged industry to start submitting exploratory genetic data informally – or unofficially, if you will.

We then began to look at updating labels of marketed drugs, such as warfarin and irinotecan, with genetic information. There were many well-characterized CYP450 enzyme polymorphisms and we wanted to demonstrate a way to translate genetic knowledge to labels, and then subsequently to patient care – although this was, at that time, a small step in the grand scheme of things.

So that was how I originally got involved in personalized medicine at the FDA, and over the next 10 years following that initial letter from the industry spokesperson, we continued to develop policies, guidelines and recommendations for industry for developing personalized medicines.

■ You have been leading the University of Florida's new Center for Pharmacometrics & Systems Pharmacology for just over a year, where you are involved in developing a new graduate training program. What motivated you to become involved in this new role?

The Center for Pharmacometrics and Systems Pharmacology is the newest center at the University and the program is for student and graduate student training, offering PhDs, post-doctoral fellowships and faculty training, so it's pretty educationally diverse. There were really four reasons for me to get involved with the University of Florida College of Pharmacy.

First, I had been at the FDA for 20 years and I started to feel like I was in the twilight of my career, but also that I had enough years in front of me to do something new and reach one more worthwhile professional goal. Also, the thought of retirement was really scary! So I started to think about opportunities. I like building things – programs, organizations and businesses. It's what I've done for my whole career and I felt it was a good time to hand over my responsibilities as Director of the Office of Clinical

Pharmacology to somebody who could take the Office to the next level with their own imagination and ideas. Fortunately, I hired the right people during my time of being Office Director; in fact, I hired individuals with the long-range goal of having one of them replace me and one of the individuals that I hired in 2008 – Dr Issam Zineh – is my replacement at the FDA and I'm delighted because I recognized his leadership ability and his expertise in personalized medicine 4 years ago when I first met him.

Second, I learned a huge amount of science and medicine while at the FDA, as you can imagine, and really felt this passion to share that knowledge with the next generation of clinician–scientists, graduate students, fellows and faculty who are just starting their careers. I thought the University of Florida would be very unique in having someone like me to share that knowledge in terms of drug development and regulatory science, and personalized medicine.

Third, I hired a lot of scientists at the FDA (we went from approximately 25 to 165 reviewers in the Office of Clinical Pharmacology from 1995 to 2011) and I always felt that graduate education and postdoctoral training needed some fresh ideas. So I thought the Center at the University of Florida would be a good training ground for me to try out some of those new ideas I have for graduate education that revolve around having individuals coming out of academia better prepared for their work in drug development and regulatory science.

My vision for the Center is an educational program that is orientated towards problem-solving and not necessarily performing research in name only. The problems that we focus on here at the Center are, in a sense, 'large' problems; things that could have a high impact on drug development and public health. We also emphasize what I felt was missing in education – the 'soft skills'; for example, the ability to look at a situation and say "I can see what the question is", or, "I know how I'm going to plan to use my quantitative tools and I know who else I have to get involved to solve the problem." This is because everything we do in drug development and regulatory review is now multidisciplinary, and so soft skills such as critical thinking, communication, team work and understanding the other stakeholders in the scientific innovation

adoption chain are all part of the training program we're setting up at the University of Florida.

Fourth and finally, why the University of Florida? Well, it's a fresh new campus and program in Orlando, FL, USA, often called the Lake Nona or Medical City campus, and it was exactly what I was looking for. I thought it would allow those of us in the Center and on campus to develop new scientific ideas in the early phases of drug development where creativity and innovation are most possible. The opportunity was initially state-funded with a very nice administrative support structure, both within the University and on the campus itself.

I think the expectations of advanced education, especially in personalized medicine, have also changed significantly; certainly my own expectations have. I recently tried to articulate this, particularly with respect to medical school education, in a recent article written with my colleague, Dr Julie Johnson [1]. The educational structure hasn't changed since the discovery of the DNA double helix, but the research funding environment has changed quite a bit. I think more and more employers (whether they are industry, academia, the FDA or other government agencies) are looking for people that can solve problems and identify issues, rather than people who are very good in a specialized, minutal technology area of research.

■ **In your opinion, what role do agencies such as the FDA have to play in the development & delivery of personalized healthcare, & what changes need to be made to accommodate the growth of genomic medicine?**

I have always felt that the FDA has to be a leader of industry in the development and delivery of personalized medicine, not a follower as some people perceive. The roles of the FDA and other agencies, such as the EMA, are huge. They don't do much research themselves, but they do cause a lot of research to be done, primarily by industry.

In terms of drug and diagnostic codevelopment for personalized medicine, regulators set the expectations for the pharmaceutical industry and manufacturers of companion diagnostics, which is

the commercial door to the marketplace. Leadership by the FDA and other agencies in this context means that they have to interpret their regulations, which are generally broad, in a way and context of how therapies are different today compared with 20 years ago with regard to individualization. Regulations are hard to change; however, the FDA has flexibility in interpreting them, meaning they can be interpreted to enable and promote personalized medicine.

The FDA also set policies, all of which are going to have an impact on the development of personalized medicines, whether it is about how to oversee and regulate diagnostics, or what the threshold is for evidence of benefit for codeveloped drugs.

Furthermore, regulatory agencies create guidance for industry, which is also very important. During my years at the FDA we wrote many guidance documents on codevelopment of companion diagnostics, clinical pharmacogenomics and clinical pharmacology related to early drug development. Overall, that is how the FDA can show leadership in influencing the development of personalized medicines.

In terms of the delivery of personalized medicine, which is a little trickier as there are so many other partners in this adoption chain, the FDA can play their part by updating labels with pharmacogenomics evidence when appropriate, as with warfarin, clopidogrel, cisplatin and many other drugs with genetically updated labels. The language used in the labels is going to influence the delivery of personalized medicine, and this has been challenging for assuring the uptake and adoption of the information. However, while good drug labels are important, there's a lot more that contributes to adoption of genomic medicine beyond the labels or the FDA itself.

■ **Which areas of healthcare do you feel genomic medicine will impact the most?**

This is a sort of pecking order or hierarchy of opportunities, with some good news and bad news.

Number one on the 'good news' list is the obvious: serious and life-threatening diseases in which somatic or acquired mutations play a major role. I find it interesting that these are generally diseases in

which the cells of humans play a host role; whether this is as the ‘host’ of a tumor or an infection. These are the areas that I think will be at the forefront for the next decade, as we gain a better understanding of somatic mutations in cancer and infectious diseases and their response to medicines, like we now know for spontaneous clearance of the hepatitis C virus (and its response to treatment) and the ‘host’ *IL28B* genotypes, for example.

What’s also coming up fast in the hierarchy of personalized medicine is treating the underlying cause of genetically based diseases; those with clear genetic defects that you can correct or clear up are going to be another big area impacted by genomic medicine. This is evidenced clearly by a recent approval by the FDA in January 2012; Kalydeco™ (ivacaftor; Vertex Pharmaceuticals, Inc., MA, USA) that was approved for patients with the G551D mutation of cystic fibrosis. The drug helps improve the function of defective CFTR protein and thins the thick mucus that builds up in the lungs of cystic fibrosis patients.

Last on my pecking order or hierarchy for impact of personalized medicine are going to be the ones everyone is hoping for: chronic complex diseases such as Parkinson’s disease. I think the focus of genomics here will be different. Usually when you think of genetic diseases, the focus is on correcting the result of a genetic defect, and even finding a cure. However, in Parkinson’s and other complex diseases I don’t expect we’re going to have cures; rather, what we’re trying to do is find targeted therapies that can halt disease progression, so it’s a different mindset or context for genomics compared with other disease types in healthcare.

With other diseases such as diabetes, with millions and millions of people affected and many of them not treated correctly, we don’t have a clue about all the genetic underpinnings of the disease. Where genetics come into play in diseases such as diabetes is not finding cures or preventing the disease, but finding the right drug combinations to use in subgroups of patients to maintain normal blood glucose, which I think is going to have a huge impact on diabetic complications.

The bad news is the cost of some of these personalized medications. For

example, the treatment of cystic fibrosis with Kalydeco is close to US\$300,000 per year, and patients have to take it for their entire lives.

■ **What do you feel have been the most significant developments in the field of personalized medicine in the last 10 years, & has progress been as you would have expected?**

It’s actually gone faster than I would have thought back in my days doing therapeutic drug monitoring with isoniazid phenotyping! What I think people forget is that Watson and Crick first published the famous paper describing the double helix structure of DNA back in 1953, which isn’t that long ago. In the past 60 years, we have been connecting all of that knowledge about DNA to diseases.

Some of the most significant developments for me have been, obviously, in cancer. We’ve seen many cases, such as in multiple myeloma with the new drug, Kyprolis™ (carfilzomib; Onyx Pharmaceuticals, Inc., CA, USA), where response rates are significantly enhanced, and in some pediatric leukemias such as acute lymphoblastic leukemia, where survival rates of 90% or more have been achieved. This hasn’t happened in all cancers though – in others (e.g., metastatic [late-stage] prostate cancer) we’ve seen lifespans extending by just months. However, I think when you look at diseases or therapeutic areas collectively, cancer is where we’ve seen the most significant and translatable research in the field of personalized medicine, with infectious diseases very close behind that.

What’s happened in personalized medicine is that technology has outpaced everything else in the adoption chain. Everyone seems to have the Kindle® eReader now, but one of the first Ereaders in the market was introduced by another company 6 years ago and never took off with customers. The lesson from this is that when technology is developed too quickly and the infrastructure for its use isn’t in place, it dies on the vine; the same applies to some genetic technologies. For me this has been the problem: we continue to move over the horizon with new genomic technologies, which is okay, but it’s illogical to begin introducing genetic tests into a healthcare system that’s not yet built to accept it.

Overall, I think the most significant developments have been in measurement technology, diagnostic test development and clinical applications in the areas of oncology and infectious disease. In my mind, the progress to date has been remarkable given where we were 60 years ago – just figuring out that DNA has a double helix structure. I think we're going to see a lot of new applications in the future, too. What's also significant in this field is how quickly people have got on board the train, so to speak. The awareness level of personalized medicine has shot up like a rocket. I would say that in 2000 when I was at the FDA there was very little knowledge and interest in the pharmaceutical and regulatory enterprise about personalized medicine. Ten years later it's in everyone's speeches, all of the pharmaceutical company chief executive officers are talking about it and the biomedical literature is full of new articles about genetic medicine. I think that this is also a significant development because it will spur people on as far as greater awareness of personalized medicine goes.

■ You have previously voiced your opinion that the genomics revolution could take 60 years to fully unfold [101]. What, in your opinion, would the state of play be in 60 years time if the genomic revolution is fulfilled – how would it differ from today?

Let's benchmark: the notion of inherited genetic differences was recognized as early as the 1860–1870s; Watson and Crick discovered the double-helix structure of DNA in 1953; and 2012 – where are we today? Healthcare today is waiting for something 'big' to happen. You have a symptom, you go to a doctor, you get a diagnosis, you have an overt disease and then you get treated. It's a model that's very good with acute disorders – for example, a sinus infection or headache. Where it's not so good is with chronic disorders, such as Alzheimer's disease, diabetes and hypertension; we try to treat those diseases, but not very successfully in many cases.

So what happens in 60 years? It's 2072 and I think everyone will have a better appreciation of the benefits of genomics; they will be asking: "What are my risks of disease, particularly for hereditary disease,

and what am I going to do about it?" I think we're going to see a better integration of early disease detection thanks to genomic screening tests and we're going to have biomarkers as 'reporters' of something going wrong in a patient – for example, using protein biomarkers in the blood, not just genomics. I particularly liked Eric Topol's book *The Creative Destruction of Medicine* [2], which kind of has this same theme: an integration of monitoring sensors and devices that can look at your blood pressure minute to minute and monitor your clinical reactions to interventions very quickly.

However, I think what will also be available in 2072 that's not available now is the combination of getting the benefits of genetics or genomics with that of other nongenomic interventions. I think we're going to have more connections between genomic variability and lifestyle; genomics and compliance with medications; and better known relationships between genomics and obesity, smoking and exercise – I think all of these lifestyle factors will be personalized. We're beginning to see the tip of the iceberg now: we're beginning to ask questions such as "Given my genetic makeup, can you pick the best diet for me that would evade or reduce the risk of a disease? Can you personalize an exercise program or any other nondrug modality that, combined with my genomic risks, would give me the best opportunity to avoid a disease or, if I get a disease, to treat it optimally?"

I can also easily imagine a device worn like a wristwatch in 2072 that has data-capturing algorithms that allow me to monitor my health and make informed decisions on the fly by just looking at my wristwatch – a bit like my dive computer at the moment that is very informative about my dive profile when I go underwater.

In 2012 medicine is basically treating symptoms or altering the progression of disease, but I think the future is being able to say: "You are cured." It's going to be like acute infections at the moment, which we cure with antibiotics; in 2072 we are going to be able to cure diseases that are currently called chronic complex diseases based on fundamental concepts of genomics.

Related to this, I think the ENCODE international collaboration project [102] at the University of California, Santa Cruz

(CA, USA) is interesting. It is basically an encyclopedia of functional DNA elements and they've done a better job than ever before of connecting genes with actions at the protein and RNA levels, and other regulatory elements that subsequently connect that with diseases. I think that project could be a little like the discovery of the double helix, in that the achievement can be hailed as entering a new phase in our fundamental understanding of the 'blueprint of life'. ENCODE gave more meaning to the helical structure of DNA, just as its discovery in 1953 provided greater understanding of how our cells manage genetic instructions.

■ **What are the main obstacles to be overcome over the next few decades in personalized medicine?**

I can think of four main obstacles. Number one is the science itself: underpinning everything such as genetic testing and diagnostics is an understanding of molecular science and how to connect genetic differences with the overt phenotype we call 'disease'. There's going to be a lot of links between those connections. Understanding the fundamental mechanistic science is going to be crucial, and in order to do so we're going to have to figure out how to process huge amounts of genomic and clinical data and derive useful information from their relationships. We're at that point now in personalized medicine where we don't have too little technology – we have too much. I think the underlying science – both understanding pathways mechanistically, then the connection between genetic variability and disease and then figuring out how to derive useful or actionable information from that huge dataset – is a number one priority.

Number two, once you've figured all that science out, you've got to develop a drug and a companion diagnostic (codevelopment) to leverage the information. I think today's strategies for doing that are hugely inefficient and more costly than anyone is going to be able to accept economically in the future. Development strategies for drugs and companion diagnostics have to change and become more efficient in order to keep costs manageable. These will change according to changes in government policies such as those of the FDA and EMA. Guidance and guidelines for

industry can recommend new opportunities for different and more efficient development strategies. For example, could you imagine an increased use of *in silico* clinical trials, as opposed to conducting real clinical trials? Will we soon be at a place where we can design our trials on the computer and conduct them just like how they design and test drive cars and airplanes? Getting to that is not going to be without obstacles.

A third obstacle is really the healthcare system *in toto*. What I'm thinking about here are administrators: hospital administrators who negotiate and administer third-party payers. In the current personalized medicine construct, there is rarely a comparative-efficacy evaluation built into the programs. That's really a crucial point because hospital administrators are looking at opportunity costs: how else could I use that money than for personalized medicines? Let's use the cystic fibrosis example. If I'm going to reimburse an individual patient US\$300,000 per year, partially or in full, so that I can relieve their ability to accumulate mucus and suffer less from pulmonary exacerbations, how else could I use US\$300,000 to benefit society as a whole? I think questions like that are going to be big obstacles for personalized medicine so we need to build in comparative intervention assessments to a greater degree in personalized medicine, so that the people who make decisions are not paying others to figure out opportunity costs and pushing back from adopting personalized medicine.

The fourth obstacle is the whole ecosystem of operation for mainstreaming personalized medicine: how do you operationalize and achieve personalized medicine? I have a mental image of a drug company and a diagnostic company developing a product, but what happens between the upstream codeveloped product and the downstream delivery of clinical value to the patient? Who has to get on board to buy into this value chain to make that drug and companion diagnostic of value to the patient? There are many people in that chain who must also benefit in order to support the delivery of personalized medicine: the first stop would be the FDA who approves the drug and diagnostic; second would be the insurance companies that provide reimbursement; third would be the physician who has to order the test and prescribe the drug;

and fourth would be the patient who has to agree to be tested and comply with the treatment regimen. Each of these stakeholders is going to have their own view of value, costs, benefits and risks of adopting personalized medicine. I think people need to sit down and analyze that ecosystem operationally and figure out who is going to benefit, and who isn't, and address those potential weak links in the value chain. Obviously companies will benefit, but will physicians benefit? Do they know if and which patient will benefit? I'm not sure they do; that depends how much pain is involved in adopting personalized medicine relative to the current standard of care. Once all of that has been figured out, the next step is incentivizing the process; to grease the wheels and solve the operational issues.

■ **What shorter-term actions can be taken to facilitate the translation of personalized medicine into practice?**

In technology and personalized medicine, which itself is technology- or diagnostic test-based, we tend to always look for new discoveries. However, in the short term, we have to find ways to use the easy stuff: what we currently know. We need to focus more on applications and less on discovery, all things being equal. Take warfarin, for example: why aren't we using *CYP2C9* and *VKORC1* genotyping yet as the standard of care? Article after article shows their clinical utility, testing is relatively cheap, the evidence for testing is fairly strong and it's recommended in the FDA label; however, not much is happening in adoption by physicians. So first I think we need to focus on the evidence. Good evidence is better than waiting for perfect evidence, and warfarin is a good example of where good, if not perfect, evidence is plentiful. Naysayers are saying let's get the randomized trial done on warfarin genetic testing; we might have that in 10 years time, although I doubt it, but I think we have good-enough evidence already, and we should move forward on adoption in the short term.

In addition, the FDA drug labels are critical in personalized medicine, but only if the information included is clear and actionable. Too many labels have genetic information, but they are not necessarily informative to compel prescribers to act on that information.

The third short-term action to get on board with, and this is happening now, is regarding preemptive genotyping. People are now figuring out that it's a lot easier to have the genetic information in a medical record when a doctor needs it so that when physicians are prescribing a drug they don't have to wait 2 weeks to get a result back from the lab. So I think the combination of electronic health records and preemptive genotyping is within our grasp right now to move personalized medicine a step further.

I also think we have to incentivize physicians. I don't think that physicians, except maybe oncologists and those in specialized medical centers, realize the benefits of personalized medicine to them, not necessarily to their patients, as individuals in the value chain. Physicians currently see a huge upfront cost to adopt a genetic test not unlike the cost of adopting electronic health records; it requires a change in their whole practice routine; and they only have 15 minutes to see a patient, which makes change challenging. I can see physicians saying: "I realize the benefits of personalized medicine, I get it, but it's not worth my time, cost and pain to implement it in my primary care practice." So I think we have to do what we usually do in the USA: provide government incentives. What we could say to physicians in this case of personalized medicine is that we'll reimburse 50% more for every patient treated under Medicare and Medicaid if you do a genetic test that improves drug efficacy or safety. And if you don't, we'll actually penalize you by cutting the reimbursement rate by 50%. Moves like that would get personalized medicine moving in the short term.

My final short-term target is patients themselves. I'm somewhat amazed that by and large patients don't expect more of healthcare. When a patient goes to a doctor who writes out a prescription, every patient expects to get better. When a patient goes into a hospital they expect to come out without a serious adverse event. All of the studies that have been done to date show that adverse events are a problem; however, when the public reads that 1.5% of the population experience these reactions, they don't think that it's going to happen to them. So, I think there's a need for greater patient education and demand – a demand for better care for their money. It's a bit like buying any household product: you

wouldn't buy a refrigerator that only works 50% of the time and be happy about it, so I think patients should look at medicine as a commodity and say: "I need to get better return on my money for this medicine!"

■ **Do you have anything else you would like to discuss or any concluding comments?**

This kind of relates to my last comment about patient demand for personalized medicine. We need to find more ways of getting people experienced in having their DNA collected and make them part of the overall process. We know that biobanks are coming up, such as at the Coriell Institute for Medical Research (NJ, USA) and other places where people can volunteer to participate in personalized medicine studies. I would say that more than 80% of people who get involved in giving their DNA become activists for personalized medicine. It's the age-old theory of education and knowledge transfer: if you're active in the process you're going to be much more engaged than if you're sitting passively in the sidelines waiting for something to happen. Students don't learn as well if they sit in a classroom and listen to lectures. Courses in several medical schools, such as at Vanderbilt University (TN, USA) or Stanford University (CA, USA) allow students the opportunity to collect their own DNA and have it analyzed by a commercial laboratory as part of learning. While not without controversy, both institutions have implemented precautionary measures to avoid ethical concerns.

From that medical school experience, which has been, in balance, a positive one, you can make the case for direct-to-consumer genetics. I've always liked consumer genetics, if it's done right with the necessary precautions. I said as such while I was at the FDA. What consumer genetics, or any other equivalent means of engaging patients as partners in personalized medicine research can do, is create a database large enough to find meaningful relationships between genetic variability and diseases. There's something really important about 'power in numbers' and it links back to education and the article I wrote with my colleague

Dr Julie Johnson about the importance of it [1]. Education of not only physicians, but also patients, is not the be-all and end-all, but it's an important step in the value chain.

I've actually had my DNA analyzed twice, at least partially, and at two different institutions. I know many of my risk propensities and I love it both as a clinician-scientist and as a patient. I've had my DNA done for diseases that might have hereditary components and I actually found the results to be very similar between the two providers. I found the results very interesting and have used them in my personal healthcare, primarily for both helping my physician to select a drug and also in selecting a dose, and I think it's fabulous! My doctor didn't think so at first, but I thought it was great. So I'm a believer in personalized medicine because I've had my DNA tested and I used the information. I know what it can inform and I'm using it in decision-making whenever I can. I think all of us who promote personalized medicine need to do that.

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