June 2015 Issue | Edgar Staren, MD, PhD, MBA

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Welcome to *Functional Medicine Update* for June 2015. This is the second in our series on functional medicine approaches to oncology and cancer therapy, and I think you're going to find this issue is a very nice next step taken from our first issue that talked about patient management issues and use of integrative care. This month we're going to focus on how genomics get built into this whole approach towards the emerging 21st century model of cancer care and how it relates to improving quality of life, and also improving patient outcome. And we can have no better guest to do that than our clinician/researcher of the month this month, Dr. Edgar Staren.

So without further ado, let's move into our discussion with Dr. Staren.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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We are once again in our series on the developments in cancer and how functional medicine and the field of cancer genomics is interfacing in the development of this 21st century evolution of the field with our extraordinary research and clinical expert Dr. Edgar Staren. Let me just give a quick introduction to Dr. Staren. We could probably take the whole of the interview to fully do justice to his background. I think he is the perfect person to really bring us into the 21st century in this discussion with his background, which has touched upon every aspect in the evolution of cancer care, from being an oncological surgeon to being an expert in chemotherapy to being a PhD in immunology and now the evolution of immunotherapy, and now making transitions as a leader in the area of cancer genomics, and his recent appointment now as the CEO of the Advanced Individual Medicine and Analytics Group that has been

born out of the Translational Genomics Research Institute, which as many of you know was kind of a spin-off from the government genomic deciphering project under Francis Collins. Jeff Trent was the Director of Science under Dr. Collins in the NIH deciphering of the human genome reported in 2000, and Dr. Trent then moved on into the Translational Genomics Research Institute. And now Dr. Staren is a collaborator in bringing this new revolution in cancer genomics into the fore. I think you can see just from that brief introduction the breadth and the depth of Dr. Staren in the field.

Dr. Staren, thank you once again for being what you are and in the field and also for spending the time with us on Functional Medicine Update.

ES: Well, Jeff, thank you so much for that most kind introduction and it really is a privilege to be with you here today.

JB: Maybe the way that we could start is if you could give a quick review. You've got just such a wonderful family and a tremendous past history of engagement, and your own personal story is, I think, really important for people to understand as it relates to your connection to the whole field of cancer care. When we hear your story, it reminds us that we carry along with our genes our experience in life, which often becomes our epigenetic modifier or modulator of what we do and I think your story is fascinating.

ES: Well thank you, Jeff. It's my pleasure to do so. I first and foremost am very proud to be a husband, father, and—what you don't know—is most recently a grandfather. My oldest and his wife just gave birth to twins, here, a week and a half ago, and so that's a pretty exciting deal. My mother used to say if she had knew it was that good she have done that first. That's our first encounter, there, and I'm sure that's true.

When the Doctor Becomes the Patient: Significant Lessons Learned From a Cancer Diagnosis

I am a surgical oncologist and was a very busy practicing surgeon. I did 400+ oncology cases per year, and was very much involved in academic leadership positions as an associate dean as well as a department chairman and a founding director of a cancer institute. Subsequently, as you indicated, I moved more into the full-time executive positions as the Chief Medical Officer for Cancer Treatment Centers of America and led one of the hospitals as a CEO of our western regional facility. And most recently, over the last now year and a half, I have moved into a number of positions and finally as the CEO for Ashion Pain Management and Advanced Individual Medicine.

But—I have said it on a number of occasions—despite that rather diverse and lengthy experience in health care, perhaps the most significant learning lesson for me, was now approximately 10 years ago when I was diagnosed with cancer and had a diagnosis of a very aggressive sarcoma in my leg, and remember all too well when after a biopsy which was presumed to take out a benign lesion I got a phone call from my partner. I remember distinctly being in the driveway, just pulling in with my wife and two youngest kids in the back seat, where my partner said, "Ed, I need you and Lisa to come on into the office so we can talk." Well, I've given that same preface before to patients and so I knew what that meant and I said, "PK, I'm hearing that we have some bad news," and he said, "Yes, Ed. It's a cancer and it's a bad one." Which it was. I knew enough about statistics to now know that based on the size and what I found out to be the histology indicated that my survival was not good, and as we all know, when you talk about survival and cancer it's in large numbers of people, but on the individual basis it's either zero or 100 percent. But that being the case, my expected five-year survival was 30 percent and I remember looking

in the back seat and seeing my then little four-year-old daughter and wondering if I was going to get to see her be five.

That was a huge lesson of the impact that patients go through, but more than that, in very short order I recognized the problems that patients have told me about for years but I didn't realize how acutely they were in place, and that is the day after surgery I was in the hospital and ended up having severe pain from an excision of this lesion and asked the nurse for a pain medication. She said, "Dr. Staren, I'm sorry, it's only been three hours." And I remember thinking how goofy that was and how the pain was really starting to get pretty severe and I said, "Well, please call the resident and see if they can come on up and write me an order to change so I can get something." And she said, "I'm sorry, Dr. Staren, they are in a level one trauma and not available." And I said, "Please call my partner"—who had done the surgery—and of course he was down in the emergency room, too. The point being is that no one was available and I sat there in progressively increased pain, and you have to remember I'm the director of the cancer center, the chairman of surgery, this was my department. I mean, this lady worked for me. And I'm thinking how silly this was, and particularly knowing that there was no good physiologic reason why I shouldn't get any pain medication, but our patients don't know that. They think, "I'm having pain and they're not giving me a pain medication. There must be something wrong with me because there is no reason why these healthcare professionals would want to do something purposefully that was going to hurt me and so I must be the problem."

Well, shortly thereafter I also realized the poor way we were dealing with—in addition to pain management—nutritional support, psychosocial support, rehabilitation, and it was a turning point in my professional career: to recognize that in an organization where we thought we were doing mind/body/spirit approach, in fact what we were doing was providing excellent state-of-the-art traditional care, but we were encumbering that with very poor delivery of support services, which ultimately contributed, in an enormous manner, to making that state-of-the-art traditional care successful. And it is really what led me to CTCA, to an organization that approaches medicine in an integrative manner, and a continued quest for a true focus on personalized medicine, which has led me to the position I'm in today.

JB: You know, I'm just sitting here and I've had the privilege of hearing your story before, but every time you relate it, it comes with such deep compassion and deep humanness that it gives me gooseflesh. It's a very, very powerful story, and one that I can just feel—vicariously—how it's one of those transition points in your life that has now influenced, in a positive way, so many thousands of other people as it relates to the bringing of your skill and professional talent probably into a different realm of application (a broader realm of application). It's magnificent that you've given yourself the freedom to tell that story because it's very powerfully motivating and energizing. So, thank you.

ES: Thank you, Jeff, very much.

JB: I just finished having the privilege of watching The Emperor of All Maladies public television program with Siddhartha Mukherjee, and the excellent historical review. I think that that six-hour program hopefully will be a teaching tool for every person that's going in to some part of the field of cancer therapy because I think it's such a tremendously well done historical review of how we got to where we are and where we can be going. But you, in your experience, are a person who has chronicled so much of this change in cancer therapy and how we view cancer and how we treat it, I'd love to get—if it's not asking too much—maybe your snapshot review of the evolution of the field in your years of

experience. It must be quite remarkable for you to look back in your career and see how things have changed.

Diagnostics & Therapeutics: The Evolution of Cancer Care

ES: It is, Jeff. The episode that I personally went through is one of those classic personal tragedies that I think turns into personal blessing. I guess every life event has that potential and I feel very blessed to have been given my health back, albeit with some of the sequelae of treatment that are not insignificant in and of themselves. It's a different subject, but it certainly speaks to that whole global and long-term influence of cancer both on the individual and how it impacts on family and society, etc. But it has been remarkable what we have had in a relative blink of an eye in history in terms of changes on both the diagnostic and the therapeutic side of cancer, and it's not as if we haven't known about cancer for an incredible period of time, but to be able to do something about it is really relatively recent. I look at the evolution of cancer care specifically such that in the 20th century it was really based on kind of microscopic observation. We would end up looking at the patient and see that they ended up having a large tumor and perhaps by examination only you would identify that they had lymph nodes involved, or they had evident signs indicating that they had metastatic disease. But it was based on that observational activity that treatments were indicated, and as you well know, during that period of time it was pretty much a coin toss on what the impact of treatment would be, and there are those that believe that in as many circumstances harm was delivered by virtue of the treatment rather than help. It was not intentional harm, of course, but it was based on ignorance.

As we progressed we moved more into microscopic, inclusive of even advanced microscopic immunohistochemical analysis and such that made progress from a diagnostic standpoint, and certainly improved our ability to be able to treat based on that diagnostic standpoint. But while progress was made, it really wasn't a change in the paradigm. We simply were continuing in the little bit more sophisticated manner that observation on large numbers of people based on rather crude assessment tools and taking that information and applying, again, relatively crude therapies. But it's within, now, the 21st century that we've taken what I think initiated in 1971 with the National Cancer Act, where both funding and authority was put in place to understand cancer, to understand the molecular basis behind what caused cancer to occur and therefore translate that information into specific therapies that could be dedicated towards the individual cancer. We can and probably should talk in a little bit more detail how that has progressed—that molecular understanding—and has allowed us to truly translate into personalized medicine approaches for the individual patient. It's been a remarkable transition in a relatively short period of time.

The Business of Cancer Management

JB: I want to move into this discussion with you as it relates to the molecular biology of cancer and how that relates to cancer genomics, but before I take that step—because I know that's going to open an extraordinary landscape of expertise that you have, and insight—I'd like to bear on one other part of your expertise and that's this management part. The business of cancer management is a very complex business, from the diagnostics to the treatment to the patient management issues. It's a very, very complex, multi-headed field, and it requires probably a very unique way of managing the complexity when it delivers down to the patient, which for them is just "get me well, make it simple, and hopefully I can manage through the process." You've been really a master in developing management concepts and building teams. Tell us a little bit about what your thoughts are in the organizational structure of

managing this multi-headed hydra in ways that make sense.

ES: Well, thank you for asking. I believe that at the end of the day, while we pay lip service to it, it is not entirely true that attention has been paid to the patient as the focus of care. We end up having multiple constituents in health care, particularly in the United States, that attend to multiple needs, and that includes of course the patient, but also the doctor, the pharmaceutical companies, the provider at their health system or hospital level, and of course the payers. There are conflicting interests in those participants, and it's easy to forget that patient in that kind of an approach. One of the things that has been my focus has always been the patient-centric approach, and our chairman at Cancer Treatment Centers of America has a quote that says it is always and only about the patient. It's really easy to forget that, but if you constantly put that in your mindset and put the others all to the side, at the end of the day water does reach its level and patients then become empowered to be a participant in their care. What I mean by that is that if you end up focusing on the patient, what you focus on is what the patient values, and you'll find that there is lots of attention paid to things that they don't value, and which cost a lot of money.

Patients don't particularly care about going into a medical system or a hospital that ends up having a six-story marble façade with fountains and all the other effects. Talking with patients one-on-one, they tend to view that as rather imposing, foreboding, and perhaps intimidating at best. And it costs a lot of money. Well, what do patients tell us that they want? They want to come into a warm environment that feels more as if they were at home, that they end up being welcomed and embraced, that their name is known—that they're not a number—so that they end up having that personal-type of an approach. Two, patients want to be informed. There is a wealth of information available because of the internet, but it's also very confusing. When a patient ends up coming in with a three-inch stack of papers that sounds good, but much of that will be redundant and, worse, conflicting information, and so while that would seem to empower a patient it often confuses them, and without being paternalistic it is important to provide information, in terms the patient understands, that is credible information so that they can then determine—based on what's available, both on the diagnostic side and on the treatment side—what they view as important and then be a participant in saying, "That's the type of care that I want." So that they are much more inclined to engage actively in that care, have their emotions and therefore their immune system and their endocrine system all as active participants in support of that successful therapy and outcome.

JB: Oh boy, that is a real major paradigm-shift concept. I know you have in excess of more than one hundred publications in the medical scientific literature. A number of those are on metric evaluation of quality of life-related issues in the cancer patient. One always asks the question: Is there a correlation or any connection between quality of life experiences in cancer care versus quantity of life in terms of outcome variables? You've done a masterful job of really looking at these quality of life issues across a range of different types of cancer. I presume the takeaway you've gotten from that research is very consistent with what you've just said?

Evaluating Quality-of-Life Issues in Cancer Patients

ES: Yes, it is. And first of all, Jeff, I'm so grateful for your most kind compliments to my contribution to medicine and the literature, but this audience probably is aware of all of your contributions. You've been a hero of mine—I will say that unabashedly—on the contributions that you've done for so many years and,

frankly, have been a stimulus for me to do much of this work, so I want to openly say thank you and acknowledge all the work you've done. But with that in mind, you're spot on: the work and global analyses of multiple cancers, as well as diving down more specifically into individual cancers, shows a clear correlate with not just satisfaction with addressing issues concerning quality of life—in other words, pain management, rehabilitation, management of fatigue, nausea, etc. All of those end up not only having an impact on a patient's satisfaction, but many studies, from not just Cancer Treatment Centers of America where much of the work I was involved in and we're speaking about, but institutions across the country have been regularly reporting, now, improvement in actual survival, and these are in some of the largest journals by some of the largest institutions. So it is one that the message is getting out objectively and the good news is that that small bell in the distance has now become a resounding bell among all of the institutions across the country, recognizing that they must provide this integrative type of approach and addressing these quality of life issues because it is going to make a difference not just in the satisfaction of the patient but it's actually going to make a difference in their life.

JB: So that obviously bears very directly on the framing of cancer care from a broader perspective than just dealing with the cellular lesion. Some people call that integrative care or comprehensive care. You've been a pioneer in that. What kind of push-back, or what kind of resistance or challenges does one encounter when you start widening the playing field, so to speak, in terms of comprehensive cancer care?

ES: You know, it's interesting: people get entrenched in what they were trained to do. That seems counterintuitive because we're also trained that medicine increases rapidly and, you know, the statistic that I was always quoted when I was in medical school was that medicine was doubling in knowledge base every seven years and now people suggest that that's every three to five years and that number continues to decrease. Therefore, if you don't engage in ongoing, continuing learning and have an open mind to that learning, you are destined to be treating patients far less than optimally, and in fact, maybe more stated, incorrectly.

Concepts that now are coming forward that make sense, but have always been out there in the distance include this whole concept of systems biology. And again, Jeff, you've certainly been a pioneer in this area, but it speaks to the concept that an individual disease, and particularly chronic diseases, of which cancer is more regularly being classified, are not isolated to that particular cell or organ, but there are impacts from the entire and multiple systems across our body that need to be addressed to optimally treat that particular disease process. It makes complete sense. We certainly recognize that on the benign side our bodies have systems interactions and networks, if you will. Why wouldn't we think that that would not make sense with regard to disease processes, and therefore our approaches to address those disease processes need to be similarly systems based?

JB: Oh boy. We're really talking about the evolution of this 21st century medical paradigm, which is just so exciting to be living through this period where we move from disease as kind of a fixed independent entity to this concept of network and systems thinking and some of the fundamental changing the soil in which the cells reside which then creates the outcome of their phenotype. This is a really powerful paradigm shift.

ES: Well, if I might interject just to piggyback on that a little bit. When we think of cancer, and it's obviously been the focus of my professional career and especially since I've had a personal experience with it, which, by the way, we've all had. Mine was me, but I daresay there's not a family that has not

been touched closely and so it really impacts on all of us in a deep manner, and it's a disease that is particularly onerous. You know, you talk about various chronic diseases such as heart disease, and you think, "Well, maybe I could have impacted that, you know, by adjusting my diet, etc.," But then you move into areas for which traditionally we have thought that you might not impact on, and certainly cancer would be to the extreme in that: "Well, gosh, I didn't do anything to cause this." Well, I think the good news on that—on that glass-half-full-glass-half-empty approach—is that increasingly, with a systems approach, we recognize that we can actively impact before the disease occurs. That with lifestyle approaches, we can do our utmost within a range of possibilities—and it would be great to talk about that a little bit—but to understand where that range is by now increasingly available testing opportunities that we can follow along our lives and optimize our lifestyle to avoid those diseases in the first place, and should it be after the fact and the disease has occurred, maximally intervene in a therapeutic manner against those particular chronic diseases. It's an amazingly exciting time, and as you said, a true paradigm shift.

JB: Well, I want to move to that question, but before we move there I want to take a step in between, which is to come back and revisit this discussion of cancer genomics and the life of a cell, to use a Lewis Thomas aphorism. As we know, in the whole field of cancer therapy we've gone through the development of surgical techniques and the development of chemotherapeutic techniques, and then we saw the development with taxanes of some interesting approaches towards modulating specific genotypic expression patterns that are associated with malignancy, and then we had this remarkable breakthrough with HER2 receptor and Herceptin, which was really a paradigm-shifting concept.

Cancer Genomics and the Age of Immunotherapy

Right on the heels of that was Gleevec that got into some concepts of being more targeted therapies that made remarkable progress in patients. And now we're moving into the age of immunotherapy, of which your background, and training, and your PhD work certainly gives you some really important insight into, and how this all interfaces—all of this—with the modulation of genes and genetic susceptibility factors. That then leads into where we are with next gen sequencing and how important that's going to be in both understanding of propensity towards cancer, or let's call it risk factors, and also how to manage individual forms of cancer knowing that each form of cancer carries with it its own unique genetic signature. Tell us a little bit about—now with your new role as the CEO of the Individual Medicine and Analytics Group at Ashion—how you see this cancer genomics playing out in the development of cancer therapy.

ES: Well, you know the good news is that we've been dancing around this for a long period of time. Much of my work has focused on breast cancer, and I think that that's a good example of where this evolution is occurring. If we think about it, it's not as if we haven't been engaging in personalized medicine approaches for some period of time. Really it was in the early '70s that first reports came back with regard to tamoxifen specifically being an important therapeutic intervention against the estrogen receptor in breast cancer. There have been great advances since that time addressing the estrogen/progesterone receptor, and you mentioned Herceptin and we'll get to that in a moment. But parallel to that, of course, you address the issue of taxanes and such.

If I think about it, during the course of my career, we really had 20, 30, maybe 40 chemotherapies over all available that we would alter the number within a particular group, then we would alter the administration, the dose, the timing, etc., but consistent with that paradigm being the same there wasn't

huge advances. Then along comes this concept of molecular classification rather than thinking about tumors based on their organ of origin. I think about some of the early work within the hematological malignancies that has been at the forefront of molecular separation of different cancers—the leukemias and the lymphomas—and how that information was utilized to engage in therapy. I ended up having a picture of a couple of lymphomas that if you looked at by histology you would think they were from exactly the same patient, whereas if you looked at their molecular panel they are radically different and clearly would warrant different interventions. Well, in the area of breast cancer, we've done the same thing. We've gone from having, "This is a ductal carcinoma and a lobular carcinoma" to at least four different subtypes, each with multiple subtypes within and with characteristic molecular abnormalities, and what we're finding is—as you mentioned—one of the keys ends up being a marker that HER2/neu, which is part of the HER family of course, of tyrosine kinase activity, and being able to inhibit that particular receptor when it is present on cancers (and which occurs 15 to 20 percent of the time) and the remarkable effect that an anti-HER2/neu therapy or Herceptin has in and of itself and how additive that can be to those state-of-the-art traditional chemotherapies that we've had available for such a long period of time.

What's exciting to me is that what we're seeing in breast cancer we are seeing across the board in other cancers. And to also follow up, you mentioned Gleevec. I think that that's the perfect example of how this whole concept of genomic therapy—of personalized medicine—has changed our thinking of organ-based therapy. You end up having, with Gleevec or imatinib, a therapy which is targeted at two tumors that could not be more diverse: chronic myelogenous leukemia as well as the GIST tumors (the gastrointestinal stromal tumors). They could not be more diverse. No one would think, at first glance, that it would be appropriate to give a similar therapy to a patient that ends up having a tumor in the lining of the stomach as you would give to someone with a leukemia, yet because of their commonality of this particular molecular marker, we do just that, and we've gone from a tumor that was close to uniformly fatal (that being CML) to one that has an 80+ percent response rate. We've gone from a tumor such as GIST, that ends up being a highly aggressive tumor with really minimal therapeutic opportunities to one where that is really the first line therapy for the same kinds of reasons.

To me the exciting thing is how much we still don't know. There is a great example in that continuing evolution. You mentioned immunotherapy. I grew up with metastatic melanoma being a tumor that we were excited about response rates of 15 or 20 percent, and that was with some immune potentiating agents, such as IL-2 and interferon. But if you looked at the chemotherapy approaches, which were the standards of care, you'd have response rates (no cure, but simply response rates), which was the summary of both a partial response and one that at least by imaging therapy had the tumor going away, of 10 or 15 percent at best. To now, with some of these targeted molecularly-based therapies having 80-plus percent response rates, and even for metastatic cases, which were by definition incurable before, patients that are actually being cured. It's mind-boggling to be able to think that that's happened in this short space of one's lifetime.

JB: I'm reminded, as you're talking, of one of your more recent publications in the Annals of Surgical Oncology in 2014. The paper is titled "Initial Experience with Genomic Profiling of Heavily Pretreated Breast Cancer Patients."[1] Obviously these are women who have already been through the standard treatment of choice and have not been successful. The conclusion that you have in that paper I think is a watchword to all of us who are not every day, like you, following the progress that is being made. I'd just like to quote from the conclusion of the paper (I know you probably want to comment on it): "Almost all advanced breast cancers possess at least one well characterized genomic alteration that might be

actionable at the clinical level. Further, in most cases a plausible argument can be advanced for the potential biologic and clinical relevance of FDA-approved anti-neoplastic agent not currently indicated in the treatment of breast cancer." Now that is one powerful statement. Maybe you want to comment on it. I think it's really, really insightful.

ES: Well, first of all, I'm honored that you read my paper, so thank you for doing so. It turns out to be, I believe, the critical statement, and there are several points that can be made from that. One, this field is advancing rapidly and so clinicians, to meet the needs of their patients, need to—in an ongoing manner—educate themselves as to these changes. It's difficult to do, but it's a mandate. Two, we need to be, as a healthcare organization—and I refer to that being the providers, the pharmaceuticals, all of us—need to engage cooperatively to make sure that we're sharing information to get that out there as promptly as possible because at the end of the day these are life-saving opportunities, and if that's your mother, you want that therapy available yesterday, and it's a tragedy to think that there would be a molecular opportunity identified and that we delay in the delivery of a therapy that can make a difference to that patient simply because of bureaucracy or ignorance, and so I feel that there is an ethical responsibility to stay on top of this in a rapid manner. But what we are seeing also is that today what we have available ends up growing rapidly. There are 200 drugs actively being pursued in the FDA pipeline that are targeted therapies that can be difference-making to those patients, and so there must be a facile mechanism for those drugs to become approved—to reach that FDA approval—so that clinicians feel comfortable in applying that therapy to their patients, and also with the confidence of knowing that the providers are going to be reimbursed for that, because those drugs do cost money and so in the interest of the patients we need to have a facile mechanism in place to ensure the delivery of those important therapies.

JB: In a recent issue of Time magazine, the cover was a photograph of two women, both of whom had glioblastoma brain cancer, one living in North Dakota and the other living in Virginia.[2] The woman in North Dakota was being treated by standard of care at the local oncology center of excellence in her area, but because it was not a large teaching and research-based center, she didn't have access to clinical trials for some of the more in-development drugs, whereas the woman in Virginia had access to a large metropolitan research-based oncology center and so she had access to these different clinical trials. The argument was posed, in this particular discussion in the magazine, that for the woman who was being treated in North Dakota, that there would be some reticence there to do genomic screening because it would raise questions from that data that probably couldn't be answered because the person would not have access to some of these experimental drugs and be part of a clinical trial, whereas in the other center, genomic evaluation of the tumor would be more frequent and probably even routine. So there are some really interesting questions about when is it appropriate to start using genomic analysis of tumors in directing therapy. Where do you think we are on that continuum?

ES: I think it's a moving target and that's the way it will probably be for some time. But I do think that we do have some fairly concrete groups that we can suggest that genomic testing should be performed on. It certainly is appropriate in those patients that end up being refractory to first line therapy or therapies, so those that have already been well-defined by standard guidelines—those that are refractory to those therapies—those patients are clear indications. Those patients that end up having known highly aggressive tumors and for which the choice of therapies are quite limited. Some examples of that: pancreatic cancer is one that certainly falls into mind as a strong candidate therein; those patients that end up having assessment of their tumors and for which there are no identified biomarkers that would help to guide

therapy would be an excellent group that would be indicated for genomic testing; and then those that are rare cancers, for which there are not clearly defined therapies and, in the cases that therapies have been proposed, that they've been poorly successful—adrenocortical cancer is a great example of that one. Those four, right now, are the ones that we look at as the most likely candidates for genomic testing, but it's fair to say that that's going to be a moving target, and the reason for that is that as therapies become available and are shown to be dramatically better than what had been available as the previous therapies, the indications for genomic evaluation will change.

If you look at lung cancer as an example, in 1980 the classic definition of lung cancer was adenocarcinoma, squamous carcinoma, and neuroendocrine carcinomas; that was how we categorized it. Shortly thereafter—certainly by 1990—we ended up having at least one molecularly based target—that being EGFR. Thereafter, that continued to increase, where today, over 50 percent of lung cancers end up having a molecular target for which there is a possible therapy. And in fact for some of the subgroups, targeted therapies are actually being recognized as the first line approach, so rather than going through the patient having the "standard" chemotherapies and then, when they become refractory to those, a molecularly based targeted therapy is recommended. In some of the subtypes of lung cancer, targeted therapies are first line. Therefore one could argue that at the very least genomic testing of a number of genes is going to be first line in lung cancer, and in the very near future it's probable that even large panels will be first line for lung cancer, and as lung cancer goes, I believe the rest of the cancers are going to follow.

Cancer and Personalized Prevention

JB: That was a very, very remarkably succinct and insightful response. Thank you. I think everyone who heard that had an ah-ha. That was a great summary of a tremendous amount of information. Well, we've got one last thing that I said I'd come back to and I would feel remiss if we didn't spend a moment having you give a comment to it and that's the concept of early assessment and—I guess you would call it—personalized prevention. You know, one of the things I took away from The Emperor of All Maladies public television show with Dr. Mukherjee is the comments of many experts in the field—the cancer researchers who have been legendary in their contributions to the evolution of the understanding of cancer and its therapy, virtually unanimously came to the same point, and that is prevention trumps anything else. If you could really think of ways of quantifying prevention at the individual level, that would be the biggest breakthrough. They use smoking as an example—you know, look at the effects that anti-smoking had on reduction of lung cancer; I mean, it trumps all therapeutics in terms of its importance to public health and individual health as well. Where are we in the quantifying early assessment and biomarker area, leading into the development of a personalized chemoprevention program for cancer?

ES: There are a couple of questions in there and the first one is the approach and then where are we at. There have been a number of things that have occurred of late and certainly this is an area that you are so knowledgeable in, Jeff. People talk about how much there should be a responsibility to oneself on their own actions and their own health support. There are societal implications and the like. The one that has become acutely mind-changing for me is the whole epigenetic concept. I'm going to get back to the focus of your question, but I think this introduction is relevant for the audience, and that is that if you think that your actions impact only on you, then it's a little more difficult to be critical and say, "Well, they've made their choice and, you know, they're not taking good care of themselves, they're not decreasing their stress, they're not eating well, they're smoking, they don't exercise, etc." But when you realize that, in fact, your actions that address epigenetic changes are actually showing to be heritable—that your

bad decision to smoke may impact on your grandchildren—it really changes your mindset on the rightness or wrongness of some of your activities. I want to at least introduce that concept to some of the thinking with regard to how we monitor our own activities and what we can do about it.

I look at a genomic analysis in a manner that ends up being a framework of possibilities. In other words, it gives us a range, if you will, of the likelihood or the lack of likelihood of developing a particular disease or having a particular malady, etc., but it is not as if we are defined to have that occurrence, and we can certainly modify the likelihood of that occurrence by the actions that we take. A very simple example would be out of the disease realm, and that is if someone ends up having a genetic pattern such that they are a remarkable athlete—they end up having the ability to run fast, jump high, etc., maybe this person has the capacity to be a remarkable basketball player, as an example—but if they did not exercise the activities to optimize that opportunity that they are genetically given, it's not likely they are going to make a basket. Certainly if they are not practicing, exercising, eating well, etc., they're not likely to be in the NBA. Well, taking that to the extreme, someone that is predisposed, if they end up smoking, having exposure to noxious gases and a whole host of others that might predispose to lung cancer, they have maximized their likelihood of what would be their genetic likelihood of developing that disease. And we are increasingly showing that with a genomic analysis we can predict for the likelihood of a multiplicity of diseases, but then the importance of the wellness part of it is monitoring, in an ongoing manner, proteometric measures, metabolomic measures in some of the more in depth, monitoring how well we're doing with regard to prevention of those particular predisposed disease entities.

As you know, Jeff, Leroy Hood is a hero of mine and certainly, you know, I think you think the same way, not presupposing. He's a remarkable individual and his proposed 100K study to look at where individuals fall within that range of an initial analysis, which would include genomic analysis and then doing ongoing monitoring of those patients to determine where they are at and the likelihood of developing those diseases, I believe is a critical way of the future and speaks to this whole concept of personalized wellness approaches to taking care of individuals and certainly bodes very well for the likely success of human beings being able to be empowered to impact on their own health and how that will impact on society going forward.

JB: I'm almost breathless from the breadth and the depth of information that you have shared with us in this last 50 minutes. It's been truly remarkable. It takes a person who thinks broad and digs deep to be able to concisely summarize and to articulate as clearly as you have the range of information that you've shared with us. I think this is one of those empowering moments. I'm convinced that everyone who listens to this—they'll take away a little bit of a new resolve in their lives as it relates to what can be done and where they need to keep their eyes open and their minds clear because we are at the threshold of a great paradigm shift that you've guided us to.

Dr. Staren, I want to thank you. I know your time is very precious, but we've appreciated every moment you've shared with us and we look forward to following your work and hopefully have a chance to check back in. I think what you're doing now with individual medicine and the analytics that will support it is truly going to move the health of not only our country but the world forward very dramatically, so thank you.

ES: Thank you, Jeff. It's really been my privilege.

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