July 2015 Issue | Thomas Brown, MD, MBA

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Welcome to *Functional Medicine Update* for July 2015. This is the third and the final of our three-part series on functional oncology and I think we're very privileged to have Dr. Tom Brown as our clean-up hitter in this three-part series. I think you will find Dr. Brown's insight, experience, and vision as to where this field is going to be extraordinarily important, both from a mindscape way and also from a clinical utility way. So with that, let's move to our discussion with Dr. Brown.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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I'm very happy to say that not only do we have an extraordinary treat with our clinician/researcher this month, but also I'm a little bit parochial in that we have an expert who is actually local to our area—Seattle, Washington—who I believe, as of 2013 when he came to join the Swedish Cancer Institute as its new Executive Director, brought a tremendous expertise to the community and really poised this area to continue to be a development center of excellence in the area of cancer therapy.

So let me say a little bit about who you're going to be hearing from, Dr. Thomas Brown. Dr. Brown, when he chose to take this responsibility as the Swedish Cancer Institute new Executive Director, brought a tremendous background. He came from the University of Arizona, where he served as a professor of medicine and their Chief Operating Officer at the University of Arizona Cancer Center. Prior to that he was a professor and vice president at the University of Texas MD Anderson Cancer Center, and while on the faculty at Duke University, he led the development of a multidisciplinary gastrointestinal cancer program and a regional, community-based clinical trial consortium.

He also holds a Master's in business administration from Rice University, and was a graduate of the Medical College of Virginia. He completed his internal medicine residency at the University of Florida

and his fellowship in medical oncology at Johns Hopkins in Baltimore. His clinical practice and research focus has been on therapeutic development in gastrointestinal malignancies. His professional and academic interests include healthcare policy and international healthcare delivery systems, and he served on numerous institutional and national/international committees and boards, and among numerous honors I think one that stands out is he was selected as a Jones Scholar while at Rice University and was selected also for inclusion in the Best Doctors in America since 1998. So that's quite a portfolio and I probably just tipped the touch of the iceberg of the many things that Dr. Brown has accomplished in his years of service.

We were very fortunate to have Tom as a presenter at our Thought Leaders Consortium in 2014 in collaboration with Lee Hood's Institute for Systems Biology. Tom laid out to the audience, during his presentation, a really wonderful vision of where cancer therapy is going and what the status of cancer research and development is in the global community and also specific here to what's going on in Seattle at Swedish.

The Incidence of Cancer is Increasing

Tom, it's with great privilege that we want to thank you for giving your time to Functional Medicine Update and bringing your wisdom and insight to us. Recently in Lancet—I think this was the March 21st issue in 2015—there was an editorial that was titled "Cancer: The Elephant in the Room," in which they really went back and reviewed what is the status of cancer incidence in the United States and the world at large, and where are we heading, and reviewed or reflected on the Bailar and Smith paper that appeared many years ago that said that we were losing the war on cancer, but now there is evidence to suggest that we're making some progress. It's still—according to this editorial—an elephant in a room that requires more and more understanding and appreciation and respect for what's happening.[1] Can you kind of tell us what is going on in the field of cancer incidence and therapy in terms of its prevalence and concern today?

TB: Well, Jeff, first of all good morning and it's a pleasure to be speaking with you today. The overall perspective in terms of the challenge that cancer represents I think is best thought of in terms of the evolving demographic. That is, cancer is—in many ways—increasing in prevalence. The outlook for many cancers, though, is improving, even cancers with advance stage. Of course part of what has happened over the recent decades is that illnesses that have tended to be major public health issues (certainly in the realm of infectious diseases and more recently in the realm of cardiovascular diseases) have had an increasingly more positive outlook. Certainly in the case of infectious diseases there have been major strides over the decades and that has led to an aging demographic where cancer has, in many ways, become one of the major public health issues, if not the major public health issue, and this is playing out not only within the United States, but on a global level and obviously it's an emerging issue in the developing world. So I would agree that cancer and the resources that are deployed to address the cancer challenge are, as you say, the elephant in the room in many respects.

JB: Kind of fueling this discussion—maybe even bordering on debate—is a recent paper by Tomasetti and Volgelstein that has gotten quite a bit of press, I think both in the medical world and maybe even in the healthcare consumer world, and that was the publication recently that suggested that cancers really are all spontaneous and it's just kind of the Monte Carlo bad luck of the draw—there's really nothing that one can do in terms of modulating, to any great extent, the appearance of cancer; these just appear statistically

randomly. That caused quite a bit of controversy in the literature. I'm sure you're familiar with this paper and the argument.[2] Do you have a thought about that whole concept?

TB: Well, I think that it's clear, based on the available evidence, that there are both important biological factors as well as important environmental factors that lead to cancer risk and to cancer. I think you would agree that there is no debate in certain realms with regard to certain environmental factors, for example tobacco, tobacco products, the impacts of unhealthy diets (whether one is talking about a high fat diet or other examples). And of course conversely the positive impact that activities such as exercise can have on both cancer incidence and the outcome of cancer interventions once cancer is diagnosed. Those examples are but a few salient examples amongst many examples of how there are certainly events—whether environmental or biological—that impact cancer risk/cancer occurrence and the outcomes once one is diagnosed with cancer, so I think that would be a clear objective statement against the notion that this is simply a matter of random chance.

JB: So when one is—as you are—in a position of managing a very complex, multi-headed organization in the Swedish Cancer Institute, how do you balance the obvious primary focus, which is therapeutic intervention needs, against this concept of prevention, which obviously is another part of the story that relates to these induced forms of cancer from various environment and lifestyle factors?

Practicing Personalized Medicine in a Large Cancer Center

TB: I think, Jeff, that really brings us into the notion of what many refer to as personalized medicine. Some others use terms such as targeted therapy or precision medicine, amongst other labels. We prefer the term personalized medicine because it has the dual connotation—the double entendre, if you will—of on the one hand caring for the whole patient and their family, their support group, and then on the other hand, addressing the individual biologic parameters that are at the core—the mechanism—of carcinogenesis, so that those two concepts are not contradictory in any way. They are integrated and they address not only the issues that relate to treating existing cancer, but—from our perspective—both the caring for the whole patient as well as attending to the biological phenotype or fingerprint of one's cancer or the patient themselves. Those issues relate not only to the management of active cancer, but to the entire arc of experience that one might have with regard to cancer, to include early diagnosis, screening, prevention. So again, we consider those two concepts inexorably linked, as one might observe in the world around us.

JB: Well on the side of good news—and there is, fortunately, I think, good news in this whole area that we're talking about—I recently read this paper that appeared in the Lancet titled "40-Year Trends in the Index of Survival for All Cancers Combined and Survival Adjusted for Age and Sex for Each Cancer in England and Wales, 1971-2011: A Population-Based Study," and one of the summary statements, which I think is very encouraging, and I quote: "These findings support substantial increases in both short-term and long-term net survival from all cancers combined."[3] In this case, this was done in the British Isles in England and Wales. I believe that this data also translates over the United States as well. So that sounds very encouraging. Are we moving, with this improved survival, to cancer as another form of chronic disease? Are we seeing the transition?

With Improved Survival Rates, Is Cancer Becoming a Chronic Disease?

TB: I think as a practicing medical oncologist I have observed over the recent decades, as have my colleagues, that it is becoming more and more common to have people with active cancer that is incurable living for extended periods of time. Of course, the focus for those individuals is that they have as normal a quality of life as possible. So the number of people who are living under those circumstances as opposed to succumbing to the cancer in a short period of time is increasing. And yes, in many disease types the notion of advanced cancer as a chronic illness is a reality. A common example would be either a metastatic breast or a metastatic colon cancer, where it is not unusual for patients to live for many years even though their diseases are incurable. And it's not unusual, increasingly, to see cancer patients who succumb to illnesses that are not related to the cancer and not related to the therapy for their cancer. Clearly that's somewhat of a victory. I think that all of us would agree that the best way to cure cancer is to not develop it in the first place and therefore the emphasis on population health, on wellness, on prevention as well as screening and early detection, remains so important. We are making very considerable advances in both the management of potentially curable cancer once it is diagnosed as well as the long-term management of advanced cancer, but our collective desire would, of course, be to prevent cancer as much as possible.

JB: I had the good fortune of being one of the people that sat for three nights in a row so six hours over those three days show of The Emperor of All Maladies, Dr. Siddhartha Mukherjee's literation of his book in a TV special format. I found it an extraordinarily well done public information series. Of course I love the book, too. I was worried that I was going to be disillusioned when I saw the video portrayal, but I thought it was very, very well done. One of the things that struck me was this inflection point that is occurring right now in understanding cancer at the cellular and molecular level and at the immunological level and the development of this cancer atlas, which seems like it is a very big step forward in us getting our arms at least around the landscape of cancer. Could you tell us a little bit about that?

TB: There's no question that the revolution in cellular biology that began in the 1950s with Watson and Crick and then subsequently has evolved in what some consider a very slow manner but it's been a very impressive manner to where we are today, which is understanding, in many instances and in the case of cancer, understanding the details of the molecular mechanisms that take one from a normal cell to a cell with uncontrolled growth. To understand the gene-related steps, whether it be mutations within the DNA sequence or abnormalities in the RNA expression or resultant abnormalities in protein expression, mostly in all cases ending in some perturbation of protein expression, these steps are being understood in the context of both carcinogenesis (what leads to the causation of cancer) and then likewise into possible interventions that might overcome those abnormal steps. And for many, this is still seen as the future. The reality is—to use the hackneyed expression—the future is now, in that we have real-life examples of where this type of information leads to practical steps in the management of our cancer patients.

JB: Being one arm's length away from really understanding what I'm seeing because I'm still on a learning curve, when I look at this cancer atlas, which has really started to catalogue specific genotypic mutations that are associated with specific kinds of cancer, the list looks very, very long, but it appears as if there are specific genotypes, certain mutational frequencies that are much more prevalent than others, which—then—probably is where a lot of the action must be going on as it relates to development of new therapeutic agents that would modulate those specific hotspots. Has this concept really started to pan out as we start seeing how this leads into personalized cancer care?

Classifying Cancer by Organ Site is Becoming an Outdated Concept

TB: Absolutely, and as you've heard me say before, Jeff, I think the best way to reflect on these changes is to look at how cancer in general has been classified or categorized over the many decades. So how have we generally approached our patients? We have generally approached them by the organ site of origin. We've organized patients, basically, on whether they have colon cancer or lung cancer or breast cancer. And I do feel that within the next 10 to 15 years we will be looking back at that lengthy period of time somewhat quizzically and thinking that it was interesting that we were treating patients based on that type of organ-of-origin classification as opposed to looking at the unique molecular phenotype or molecular fingerprint of one's tumor and ultimately at the person themselves. Again, one might have a patient with so-called colon cancer who has a molecular phenotype or molecular fingerprint to their tumor that is very similar to someone who has clinical lung cancer, so that increasingly we're being focused on the common mutations, the common changes in protein expression, the common epigenetic changes, the common immune-related dysregulation that might characterize a certain tumor or set of tumors as opposed to the organ site of origin, and that's the true revolution in the way that we think about cancer.

JB: Yes, I think that you explained that very, very clearly and it seems that that is a huge paradigm shift, a huge move forward in, as you said, personalization, precision, however you want to term that. I saw a paper just recently in the Journal of the American Medical Association that was titled "Association of Type and Location of BRCA-1 and BRCA-2 Mutations with Risk of Breast and Ovarian Cancer."[4] For me this was a very interesting article because I'd actually never thought about the diversity of different mutations that can occur within the genes that regulate BRCA-1 and BRCA-2 expression, and that they may have different penetrants into disease and they may have different therapeutics for their management depending on where those mutations occur within BRCA-1 and 2. This is just an example of a more general theme. Am I heading in the right direction in the way I'm interpreting this article?

Germ Line Mutations versus Somatic Changes: An Important Distinction

TB: Right, well, part of what you're touching on, though, is a very important subject for clinicians to reflect on, and that is we have gene alterations, mutations, and other molecularly based changes that occur in germ line tissue that is, by definition, inherited at some level, and then we have the similar changes that can occur in somatic tissue or non-germ cell tissue, and, for example, tend to happen in tissues that then become cancerous, effectively being associated with the patient's tumor, which is more often than not a set of somatic changes, non-germ-cell changes, as opposed to germ line changes. I think that what we will increasingly see is some convergence of those two variants. And another way of expressing that is those who are familiar with the role of genetic counselors know that genetic counselors, almost by definition, spend the majority of their time addressing issues for patients and their families related to germ line molecular perturbations, for lack of a better euphemism. Increasingly, though, I believe—certainly this is gradually becoming the case at the Swedish Cancer Institute—the genetic counselors will also become involved in working in a multi-disciplinary team fashion with patients and their families along with the provider team in addressing non-germ-line molecular perturbations. So that, again, it's important to recognize the current division between germ line molecular-based events and somatic non-germ-line molecular-based events.

JB: So when we take a lot of these discoveries and advancements in understanding about the molecular and cellular etiology of cancer and we translate it over into how does this drive new potential therapeutics, it appears as if we come back—in part, at least—to the immune system, saying, "Well, if there are ways that we could alert, activate, or mobilize the immune system to recognize the friends from the

foes more effectively, and we could activate the cataloguing of immune cells for immunotherapy in such a way as we can induce their activity against the right cells that we might have a whole new breakthrough in cancer therapy. What's the status right now as we see this advancing frontier of consideration?

Immunotherapy is One of Many Active Therapies in Current Cancer Treatment

TB: Well, there's no question, Jeff, just as there has been a renaissance in what's viewed as targeted therapy or molecularly target-based approaches, there has been a long-awaited, foreseeing of immunotherapeutic approaches. That's no accident. Much of the understanding of molecular biology has, as its endpoint, the understanding of proteomic changes that are tied to changes in DNA and RNA, thus it's not surprising that that clarity in terms of mechanistic changes that lead to cancer has also informed immunotherapeutic approaches. It is also true that as we find more effective systemic therapies that are not immune-based that allow for lowering of the tumor volume, that in theory at least, immunotherapy becomes an even more attractive approach to addressing low residual volume disease, something that we all recognize occurs naturally when one's immune system can often manage low volumes of malignant cells. So, again, I think that the evolution in our understanding of the human genome and the related RNA protein and epigenetic changes has informed immunotherapeutics to some degree, but also the proliferation is not an exaggeration. The proliferation of active therapies in advanced cancer have opened the door, so to speak, to the role of immunotherapy in terms of addressing lower volume disease.

JB: So it sounds like the toolkit is expanding for the field of oncology, and we didn't really even talk yet about advances being made in surgical oncology, which are tremendous advances there for debulking tumors and getting rid of cancer at the organ, tissue-specific level. So if we go back to this inflection point that you and I were discussing earlier, which is starting to look at the unique genetic personality of tumors versus just their histological definition of their site of origin and their grading in terms of staging, how is the insurance industry, Medicare, the government viewing next-gen sequencing and actually getting this information that starts our information moving forward in this direction?

TB: Well, of course, it is a rapidly evolving field in terms of the science, and in fairness to everyone I think first of all something we haven't talked about is the acculturation that is necessary amongst providers, amongst physicians. This is a very different way of thinking about illness and of thinking about therapeutic opportunities for patients, so it's not surprising that the traditional reimbursement system has likewise had challenges in figuring out how to reimburse. Initially reimbursement has been—and to some degree is still being done—on the basis of individual mutations that might have a code and a charge attached. As we enter into organized panels, there are actually codes that have been produced for certain panels, really based on panel size. But in general the federal system, CMS, does not yet have charges attached to those codes. I do believe that probably within the next 6 to 12 months this will be evolving. On the one hand, third party payers are somewhat concerned about the proliferation of this type of testing. I think, though, that as the field unfolds that we're finding it is an opportunity to, again, focus—target—the way we approach patients, both in their evaluation and in the use of specific therapies. I believe that in the relative short run we'll find that the molecular phenotyping of tumors and of the patient themselves will lead to greater value in healthcare. Now that's arguably a hypothesis at this point, but I'm very optimistic about this revolution in the molecular understanding of carcinogenesis as leading to a more value-oriented approach to cancer care.

JB: You said something there that I had never thought about that I think is quite fascinating as it relates to

these panels that associate themselves across a number of different genes, and that leads one to start thinking about moving away from the one-disease-one-drug mentality into a systems biology thought about cancer, because now we have multiple drugs often being used for the management of cancer like we do with HIV or with Hep C. It's not like a one-hit treatment because of the complexity of these conditions, so we're moving from what may be the foundation of the ICD-9 codes and considering independent diseases that all had singular etiologies and have one drug to treat them to a new model that's really a systems-based model that's going to require not only a lot of revolutionary thinking, but also procedural organization delivery in terms of how this gets translated into patient management and reimbursement. Am I far away from what's happening or is that part of the story?

Incorporating Data from Genomic Arrays into Clinical Workflow is a Challenge

TB: No, Jeff, you're right on the mark. For example, we're using a highly actionable, meaning that the gene alterations that we're looking at (the mutations) have practical steps in terms of commercially available therapies or therapies that can be used off-label for the set of gene alterations that we're looking at in our panel at the Swedish Cancer Institute. We're currently using a panel of 68 gene alterations. We're about to go to a panel of more than 160 gene alterations. There are other commercially available panels that are at least twice that size. The point is that ultimately—and again, in the not-too-distant future—we're likely to be using, routinely, whole exome sequencing, where one is looking at the broad array of active regions in the human genome, and in addition looking at the downstream expression that results from those changes in DNA, so looking at RNA expression or RNA sequence changes, and in turn looking at the further downstream protein changes that include epigenetic changes, and we haven't gotten into other areas, like biome changes that can occur in areas like the intestinal tract, etc. So there is gradually, then, a proliferation of data that needs to be put into context, and obviously in some ways it's the task of finding the needle in the proverbial haystack and there's only one way to do that in an organized and disciplined manner, and that is with sophisticated IT informatics platforms. Over time, these platforms need to be integrated into the standard work flow, and what I mean by that is into the standard electronic medical record. That is the challenge, because as our audience knows, providers are increasingly tasked with a range of responsibilities that include activities tied to direct medical care, but also activities that are more distant, tied to things like reimbursement or other regulatory issues. And it's imperative, as the data analysis becomes more challenging, to have this incorporated into the EMR through decision-based tools—that is, tools that enable decision-based medical practice, incorporated into the normal workflow. There are examples of these tools emerging. Clearly, on the one hand, one has to organize the complex medicine that is coming from the patient who is sitting in front of you. One the other hand, you have to put that individualized information in the context of the medical literature's whole and the context of the experience of other similar patients. Again, there are tools that are emerging to facilitate that process.

JB: That was a beautiful summary explanation for a very complex area, which I'm sure we could have spent hours talking about and we still wouldn't have had a complete answer but that was a wonderfully succinct summary. I'd like to ask one last closing question which I believe is probably on the minds of a lot clinicians as it relates to patient management in the oncology area. This really comes out of a recent Time magazine article in April 2015.[5] The cover issue was about the juxtaposition of two women of about the same age who had the same diagnosis of cancer—a glioblastoma. One was in a more rural area of the country (I think it was North Dakota, actually) and was being seen at the regional medical center there in North Dakota, and the other woman with glioblastoma was in a more metropolitan area that had

access to a large cancer research teaching and therapy center. The question that was raised in the article—I mean, there were several questions, but one that I think that was the dominant question—was is there an advantage if you are close to a major metropolitan center where you have access to not only genomic profiling but also, then, experimental drugs and drug trials that are ongoing that might have new therapeutics that are related to your specific mutational type of issue—does that give competitive advantage to individuals that are in centers where that type of research is going on, or is it just asking questions for which you have no answer that produces anxiety and so it's better not to ask the question as it relates to genomic profiling? That was kind of the theme of the article. Do you have an opinion as to how we're managing this issue?

Key Challenge to Modern Healthcare: Access

TB: Well, Jeff, you're touching on a subject that for me, personally, is one of the key challenges of modern healthcare, whether one is talking about within the United States or globally, and that is access. And the point I would like to make—you were framing this rhetorically in the context of geographic distance—I would argue that yes, geographic distance can impact access so that the short answer to your question is yes, there is some advantage to being close to an urban location where you are more likely to have tertiary quaternary centers that offer these higher level technologies. On the other hand, as you and I know there are socioeconomic barriers that may have nothing to do with geography. You might be living within an urban center but still not have access to a certain level of expertise or the nurturing supportive care that is required because of issues that relate to lack of insurance, or lack of other resources (transportation, etc.). So that these wonderful technologies can be available to us, but they might as well be nonexistent if there isn't the attendant access for the individual patients. So I think this is very important as we roll out new advances in healthcare and in the case of cancer care to be sure that we're working on a population-based approach that addresses both metropolitan areas as well as rural areas, and obviously—again—this is another very complex subject that has rather complicated solutions. One of the things that we are striving for in our personalized medicine program is to provide at least universal access within our patient population, so that there aren't defined financial barriers to accessing this technology. It's being done in the context of an IRB-approved protocol. We're attempting to translate the consent forms in the common non-English-based languages that are found in our immediate population. So again, I think that access, which can come in many forms, not just geographic distance but can come in the form of socioeconomic barriers, is a key issue.

JB: Thank you. That was a very, very important and moving discussion for us all to consider. Thank you very much. I guess I do have one other quick last question and that has to do with your view as to whether you feel this technology that we're seeing emerge to quantitate things that were previously only qualitatively understandable, as we get deeper drilling into genomic aspects, whether this technology can find a potential application as we move forward in its understanding and in the informatics area and its analysis into the quantitation of prevention as to really precisely designing personalized prevention programs as well as personalized treatment programs. Do you see this as something down the road in our future?

TB: Well, Jeff, as you know from my earlier comments and also from earlier discussions that you and I have made, I feel very strongly about this point. There are many who think of molecular phenotyping of tumors and of patients as being primarily directed at selecting a particular therapeutic intervention, usually a drug—an agent—whether it be an immunotherapeutic agent or a more traditional molecularly

targeted agent. But the truth is there is ample evidence now that this molecular phenotyping can be just as importantly applied to the areas of cancer control, so we're talking again about early diagnosis, prevention, and screening. And effectively assessing risk, whether inherited risk in the context of germ line changes or acquired risk in the context of non-germ line mutations that occur that might lead to either a defined risk of cancer or clearly to the emergence of cancer through a pre-malignant condition. So yes, I feel that this type of molecular fingerprinting, as the lay expression is often applied, will apply to the entire arc of cancer experience to include simply assessing population risk, and this is where the value proposition is for this approach, and there's an interesting contradiction in this in that on the one hand we're increasingly talking about population health (wellness on a population basis), but the way this is being applied is by recognizing the individuality that expresses itself through unique biologic changes in an individual and in an individual's tumor, and through that individualized understanding, be more effective in the way we apply resources to the entire population.

JB: Well, Dr. Thomas Brown, I can't thank you enough and I think the Swedish Cancer Institute and Seattle and the local environment is very fortunate to have you as the executive director of the institute. Your vision and this broad landscape that we've had the privilege of discussing with you demonstrate both breadth and depth. It's been a really exciting conversation for me and I'm sure all of our listeners are taking away a lot of news-to-use. Thank you so much for your vigilance and your leadership and we look forward to following what's going on with you and the institute and thank you for the time you spend with us today.

TB: Well, Jeff, thank you and thank you for what you do. Thank you very much. It's been a pleasure.

JB: I appreciate it

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