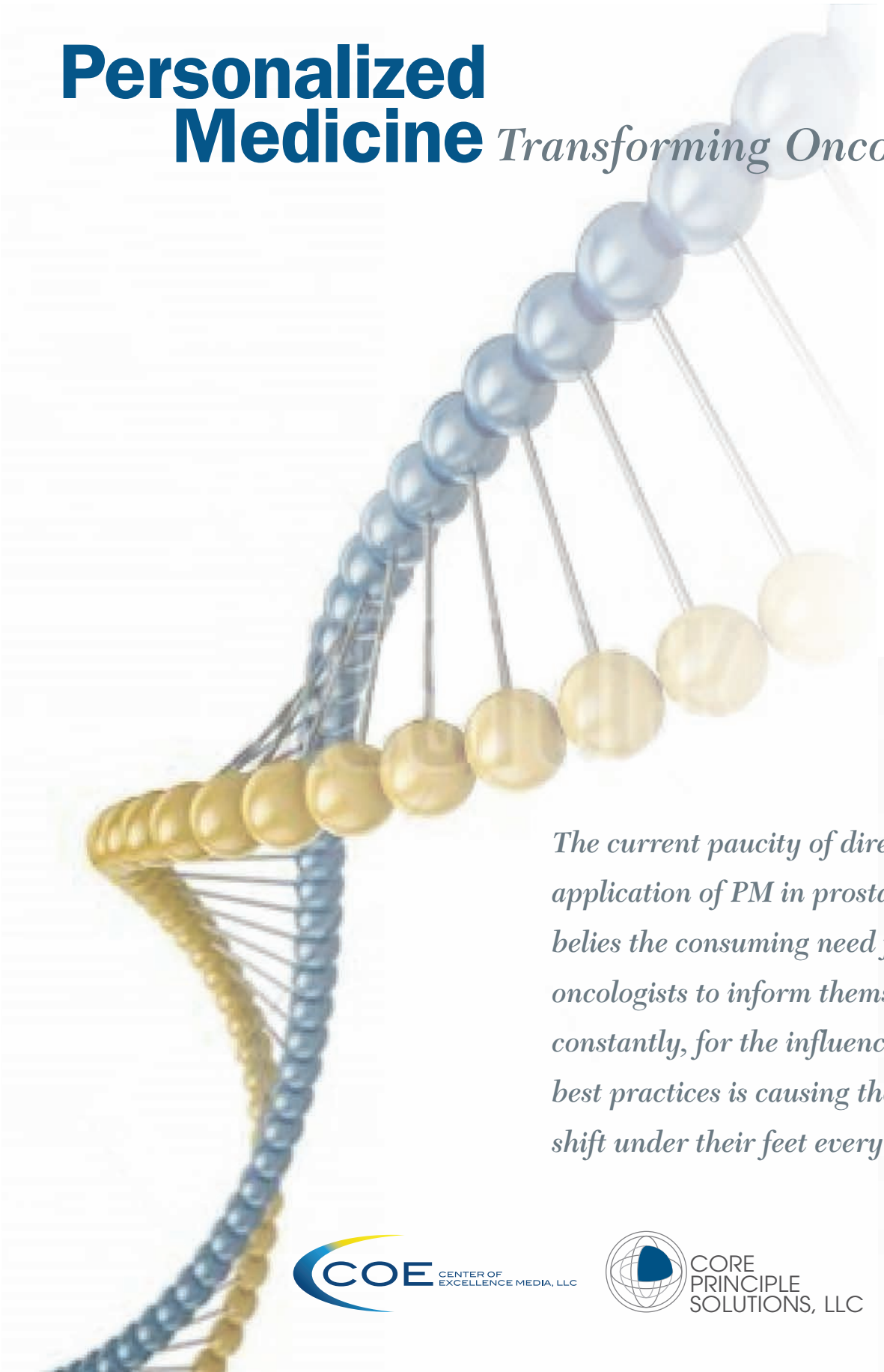
Personalized Medicine *Transforming Oncology*



The current paucity of direct application of PM in prostate cancer belies the consuming need for oncologists to inform themselves constantly, for the influence of PM on best practices is causing the ground to shift under their feet every moment.

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RATIONALE

This article is offered as a primer to oncologists, oncology nurses, oncology pharmacists, payers, and other healthcare professionals on the much anticipated tenets of personalized medicine in prostate cancer.

DISCLOSURE

The opinions expressed in this primer are those of the author and faculty and do not necessarily represent the views of Center of Excellence Media, LLC, Core Principle Solutions, LLC, or the Global Biomarkers Consortium.

WHITE PAPER AUTHOR

Robert E. Henry	Strategic Editor, *Personalized Medicine in Oncology*

FACULTY

A. Oliver Sartor, MD	C.E. and Bernadine Laborde Professor of Cancer Research Tulane University School of Medicine Medical Director, Tulane Cancer Center
Gary M. Owens, MD	President, Gary Owens Associates

PERSONALIZED MEDICINE AND PROSTATE CANCER:

An Interview With Dr Oliver Sartor

Robert Emmett Henry, Strategic Editor

In June and July of 2011, *Personalized Medicine in Oncology (PMO)* had the opportunity to interview Dr Oliver Sartor, Medical Director of the Tulane Cancer Center, on the arrival of personalized medicine (PM) in the clinical cancer environment. We discussed what it is, how much and how limited has been its impact on the clinical treatment of prostate cancer in particular, and what constitutes its governing dynamics. The goal of the discourse was to help frame the expectations of practicing oncologists, their patients, and indeed all stakeholders involved in the process of care for prostate cancer. We engaged in a lively exchange of ideas, facts, and strategic considerations that provides a snapshot in time for the reality of PM, the perceptions surrounding it, and the prospects it holds for improving survival, time to progression, health-related quality of life (HRQoL), and value.

The interview yielded its desired goal: a clinically practical and practicable overview, comprehensive in scope, on the extent to which PM is part of the clinical armamentarium in the war against prostate cancer. The fact is that PM remains largely an unrealized dream for cancer in general, and to a very high degree for prostate cancer, where PM has yet to break through many barriers to its implementation. PM relies strongly, but not exclusively, on biomarkers, and few exist for prostate cancer. That does not mean that PM is not actively entering on the scene of prostate cancer, rather that it is doing so in an iterative fashion, with incremental improvements gradually reshaping the clinical strategic picture of this cancer. By way of example, nomograms have added real value in this field, and the ability to risk stratify patients by optimally utilizing conventional factors has contributed to progress in the field. During this transition era – a neither-fish-nor-fowl point in prostate cancer where treatment is moving toward personalization but still remains largely confined to conventional practices – the need for clarity of vision is particularly acute as clinicians look to avoid intellectual and procedural chaos. For despite the leanness of PM in prostate cancer, the process of conversion to it has begun, and woe to the clinician who suddenly falls behind amidst the avalanche of information that is amassing. Given the sometimes stark distinctions between personalized and non-personalized medicine, we sought to demonstrate the confluence of forces relevant at the clinical flash point. The refuge of the practitioner from chaos in this ill-defined milieu is the experience and clinical wisdom of a leading researcher with two qualities. First, this expert will have been through disruptive innovation countless times before and is familiar with the process of adaptation. The second quality is what William F. Buckley, Jr referred to as "the jeweler's eye":

The fact is that PM remains largely an unrealized dream for cancer in general, and to a very high degree for prostate cancer.

knowing the line between cutting edge and bleeding edge, and how to accentuate the former and avoid the latter. To these ends we sought out Dr Sartor and charted a coherent guide to the beginning of an era.

The good news is that PM is clearly on the march and is destined to prevail in prostate and other cancers. This requires continual readjustment of the clinician's approach to risk assessment, diagnosis, treatment, supportive care, and follow-up and engagement of stakeholders contiguous with the clinical oncologist on three fronts: patients and their caregivers, payers, and the increasingly complex laboratory infrastructure that is constructing the PM edifice. The current paucity of direct application of PM in prostate cancer belies the consuming need for oncologists to inform themselves constantly, for the influence of PM on best practices is causing the ground to shift under their feet every moment. PM is already awash in an information explosion. This necessitates a razor-sharp focus on those areas of PM relevant to the clinician – either directly or obliquely – and conversely knowing what is beyond the clinicians' need-to-know. Time-consuming granularity of detail will derail the oncologist's quest for the clinical storehouse of knowledge that can be put to work in the burgeoning field of PM in prostate cancer, categorizing what elements of it are in place and the red herrings that have failed to achieve the evidentiary validation required of sound medicine.

Today's oncologist faces a field both informed and blurred by the isolated successes of the phenomenon that is PM.

Today's oncologist faces a field both informed and blurred by the isolated successes of the phenomenon that is PM. Breakthroughs in diagnosis, predictive modeling, and drug treatments are transforming some cancers from deadly, acute disease states into chronic ones. They exist more as metaphors for the research and treatment of the other cancers than guides for current application there. The difficulties lie in the exquisite complexity of the human physiology and correspondingly complex field of biological therapies, replete with surprising obstacles to predictability and replication of diagnostic tests that continue to frustrate experts in the vital fields of laboratory and pathology science.

All this comes down to the awareness that rhetoric is not a consumable therapeutic regimen, and that the applause that accompanied the initial PM breakthroughs also distracts from the immense body of hard work by researchers and clinicians alike. Both are eager to apply PM principles to a needy patient population, but they receive practical lessons in intellectual humility by the biological and chemical realities demanding specific execution of the premise that PM exists to fuse treatment to an individual's need for it – and equally important, to rule out patients from treatment options they are physiologically incapable of benefitting from.

The preventing of waste usage of biologicals, surgical procedures, and all other intervention draws us to the important matter of the financial aspect of PM – in this instance, value obtained by blocking access to care that cannot help a specific patient. Value, not quality, governs all healthcare, even if quality is the prominent desired component of value. The pursuit of pure, undiluted quality, however, is an impossibility, a contradiction of the fundamental admixture of forces that make healthcare feasible, which is the balance of cost, quality, and access. Failure to simultaneously manage the cost of care, or ac-

cess to it, while achieving quality (effectiveness and safety) is tantamount to a chess strategy based entirely on offense while leaving one's queen unguarded. The participants to the medical frontier that is oncology PM are obligated by sheer force of this "Iron Triangle" of healthcare to pursue quality only insofar as it is affordable and accessible – the alternative being a fantasy scenario where researchers devise cures requiring resources so great as to make them affordable only to the wealthiest of the wealthy. Indeed, the resources needed to accomplish the PM conquest of prostate cancer would exceed even that bankroll. Rather, the bulwark of the entire healthcare system is needed to supply the energy and systems for the measured, sustainable advance of innovation.

Pursuing the financial aspect of PM further, the actual healthcare model that makes PM innovation feasible turns out to be wellness-based healthcare: the cycle of prevention, intervention, and innovation. While value-based practices balance cost, quality, and access to funnel resources to where they will do the most good, the wellness paradigm provides its own form of resource allocation efficiency by ensuring that individuals avoid disease wherever possible in the first place. This avoids overconsumption of resources, which in turn preserves them for innovation, the products of which must be used only according to best practices (eg, according to guidelines and value). This calls up healthcare disparities reform, the branch of epidemiology devised to ensure that patients with identical conditions do not receive unequal treatment due to unscientific utilization criteria (eg, a happenstance condition of the immediate availability of hospital beds resulting in excessive and unnecessary use of them; or an excessive number of surgeons leading to unnecessary surgical procedures; or availability of nearly appropriate generic drugs being substituted by a pharmacy benefit for a branded drug that is actually appropriate for the patient's condition). PM, the high point of cancer care and carrying with it a high price tag, is seen to possess qualities that attenuate its empiric costs. Furthermore, the other efficiency measures of healthcare disparities reform, value-based resource allocation and wellness-based healthcare, are all available to help make PM interventions financially feasible. These measures, however, do not self-actuate: they require systems to bring them into practice across all stakeholder levels. These are the healthcare delivery components upon which rest the hopes for being able to carry out the promise of PM in oncology by ensuring its value and not relying just on the compelling force of its quality.

PM must meet the value test or wait until conditions have been devised that make it financially sound. Simply put, PM must demonstrate value. We discussed with Dr Sartor the premise of PM – the right drug for the right patient – as the basis for the affordability of targeted biological drugs and their corresponding diagnostic tests that qualify patients to receive them. The process of PM in prostate cancer is highly dependent on predictive modeling that exists to save lives and money. A primary example in prostate cancer is nomograms. Dr Michael Kattan of the Cleveland Clinic has been involved in their invention and refinement.[1] They represent the picture of PM progress in the field of prostate cancer as well as anything. So too are the drugs emerging to broaden pharmacotherapeutic options beyond docetaxel, including abiraterone, denosumab, alpharadin, sipuleucel-T, and cabazitaxel.

Predictive modeling ensures that precious time is not lost by putting patients on a regimen without knowing first if it will benefit them. The

costs saved in avoiding follow-up tests, palliative care, and ultimately by using the correct pharmacotherapeutic regimen for that individual contribute to the financial feasibility of targeted biological therapy.

As was stated in a previous article in *PMO* on the matter of affordability of PM-based therapies, "life will find a way": viz, if a targeted therapeutic agent is worth using, stakeholders will devise methods to achieve this essential condition of value. Innovation is disruptive by its very definition, and we can expect that PM will change the entire landscape of the healthcare system. Thus researchers and clinicians heroically blaze a trail in search of improved outcomes without up-front assurances. It is the desperate condition of the disease that propels them forward, determined to land on their feet.

A Payer's Perspective on Personalized Medicine and Prostate Cancer:

New Treatments, Personalized Medicine, or Both?

Gary M. Owens, MD

In this issue of *Personalized Medicine in Oncology*, the subject of personalized medicine and its applicability to the diagnosis and management of prostate cancer is extensively reviewed in an interview of Dr Oliver Sartor by Robert Henry. As it pertains to personalized medicine and prostate cancer, Dr Sartor notes: "We're at the beginning of this era, certainly not toward the end, and as we approach many patients in prostate cancer, we don't have nearly that degree of specificity. We still look at a patient and wonder, if I give you this drug, is it going to help you or not?"

Why is this important for payers? Among men, cancers of the prostate, lung, and colorectum account for 52% of all newly diagnosed cancers. Prostate cancer alone accounts for 28% (217,730) of incident cases of cancer in men.[1] With prostate cancer representing more than a quarter of all newly diagnosed cancers and with the wide range of therapeutic options at each stage of disease, the choices of therapy and the associated cost of these therapies is a significant area of focus for payers. Furthermore, with the aging baby boomer population, prostate cancer prevalence is expected to continue to rise. It is for these reasons that prostate cancer is a major issue for payers. But the incidence and prevalence of prostate cancer alone is not the sole driver of increasing cost for this disease.

As just one example of how important this area is becoming, let us look at a significant recent change. In 2010 and 2011 we have seen an increase in the number of treatment options for advanced prostate cancer. The *New York Times* notes in an article dated June 27, 2011, that the cost of treating metastatic castration-resistant prostate cancer has increased dramatically in the last year. In the past 15 months, 3 new drugs that extended the lives of prostate cancer patients in clinical trials have been approved by the Food and Drug Administration, and several other promising medicines are in clinical trials. However, the article goes on to note, "the price of these drugs has already stirred concerns about the costs of care among patients, providers and insurers." For example, Provenge costs $93,000 for a course of treatment, while Zytiga costs about $5000 a month. Another of the new drugs, Jevtana, costs about $8000 every 3 weeks. "With other pricey drugs on the way," said Joel Sendek, an analyst at Lazard, "we could be talking easily $500,000 per patient or more over the course of therapy, which I don't think the system can afford, especially since 80 percent of the patients are on Medicare."[2]

There are many themes running through this transition to PM in oncology, some of them specific to prostate cancer, others to the entire gamut of cancers, still others specific to each individual cancer. For instance, Dr Sartor makes it clear that prostate cancer is the most heterogeneous of cancers. Many of these cancers need no treatment at all, and others are fatal regardless of the therapies currently administered. With this wide range of tumor nuances, targeting them will be more challenging than ever, making the research and clinical application of PM in prostate cancer particularly challenging.

The first lesson of PM in cancer is to resist the urge to conclude that PM is already in widespread practice. It is not. PM is only beginning, and much of cancer therapy is still being practiced according to pre-PM clinical strategies be-

Let us place these new therapies in context with the clinical state-of-the-art today. In the interview, Dr Sartor clearly points out: "We need biomarkers that can say 'You are an ideal candidate for our therapy X, you are an ideal candidate for therapy Y, and you unfortunately will not benefit from this therapy.' We don't know what patient is going to benefit most from the new vaccine, sipuleucel-T. And that is the dividing line between personalized medicine and today's medicine. Once we categorically know that a patient has asymptomatic metastatic castrate-resistant prostate cancer, we do not know how to predict responses within that category. We are still practicing medicine largely in a pre-personalized medicine paradigm."

As I reviewed the interview, I began to speculate on the following scenario: What if I were forced to choose between new therapeutic agents for the treatment of advanced prostate cancer or technological advances that will ultimately improve the process of care to make better use of existing therapies? Which would I choose? While the lure of newer and potentially better drugs is certainly there, if forced to make a choice now, I would opt for the latter. Ultimately it is my belief, and also the belief of many of my managed care colleagues, that more might be gained from improving care, managing patients to guidelines, and using information from genetic and molecular diagnostics to better guide our choices of interventions.

Fortunately, I don't have to make that choice. In this interview, Dr Sartor eloquently states: "As the progress in this field occurs, I predict we're going to have rapid progress over the next decade and even more. The practicing clinician is going to have to be alerted and made aware of the opportunities for targeted therapy, the opportunities for linkage between molecular diagnostics and therapeutic choice that help to drive patient care. This is a very bright field, an evolving field that is good to be involved in from a communication perspective." It will be precisely this type of information about what works and on whom and ultimately about what is cost-effective that will guide us to make appropriate therapeutic choices in the future. The reality is that we will be able to have it both ways. New therapeutic options will continue to be developed in parallel with genetic and molecular tests that can help guide therapeutic options. It is my hope and the expectations of many payers that the next decade will see this rapid progress of personalized medicine in prostate cancer "catch up" to the therapeutic options and ultimately guide both the clinician and the payer about how application of this technology can improve the care choices that are needed along the path to better outcomes. By using that information, coupled with appropriate application of new drugs and technology, we can improve the level of care for prostate cancer patients. All of the stakeholders in the system, managed care organizations, physicians, manufacturers, and patients (to name only a few) need to work together and use technological, humanistic, and process improvement solutions to accomplish this goal.

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cause research has not yet unlocked the mysteries that enable PM management specific to most aspects of cancer. Applying this principle to highly heterogeneous prostate cancer underscores this fact. Framing our expectations for PM in cancer must start with the acknowledgement that we know little rather than celebrating what we have discovered to date. Resisting the urge to oversimplify the status of PM in cancer care punctures the notion that we can extrapolate the experiences involving the interaction of genomics, tumor landscape, and other PM elements in one cancer to others. Only empirical research will show which PM rules of engagement will apply across the board and which will remain localized. Assume nothing – except that we have a long way to go before we enter the new era of PM in oncology. At present we are only knocking on its door and occasionally slipping through it. It is because the results of these forays into clinical success are so brilliant that we are already committed to the full-scale attack on the domain of cancer by mastering the technique across all cancers.

We turn now to the discussion between the Strategic Editor of *Personalized Medicine in Oncology*, Robert Henry, and Dr Oliver Sartor.

Robert Henry We are talking with Dr Oliver Sartor, Medical Director of the Tulane Cancer Center, on the intersection of personalized medicine and the process of care for prostate cancer. To start things off, there tends to be an oversimplified view of the presence of personalized medicine in cancer – or even the notion that personalized medicine is a separate way of dealing with cancer apart from conventional treatment paradigms.

Dr Sartor I certainly agree with that. I think personalized medicine is a goal, not necessarily a reality. We're becoming better at stratifying patients, in predicting the overexpression of HER2/neu in breast cancer, the presence of the Philadelphia chromosome, the *bcr-abl* oncogene to predict Gleevec responses – even, to a more surprising degree, the ability to sequence things like EGF receptor and predicting responsiveness to certain agents.

We're at the beginning of this era, certainly not toward the end, and as we approach many patients in prostate cancer, we don't have nearly that degree of specificity. We still look at a patient and wonder, if I give you this drug, is it going to help you or not?

Robert Henry In the meantime, how can we help frame the expectations of oncologists and help them sharpen their acumen? Just how distant are the NCCN guidelines from providing a precise, granular guide to the practice of personalized medicine in oncology?

Dr Sartor Actually, it isn't bad. It simply reflects the science that we have available now. As we gain insights into the disease, we are able to modify therapies in a more favorable manner, and this has become relatively routine in certain cancers.

In prostate cancer we haven't really reached that point. We have broad risk stratifications. We have low, intermediate, and high risk and we have a very low risk category as well, but we don't do a molecular test to be able to say, "Ah, you are the type of patient that will benefit from X, Y, or Z." We are using the traditional parameters of PSA and Gleason score in a clinical setting, the ones we have used for some time, to choose therapies that are best for the patient. But we still have a huge amount of heterogeneity within each of our risk categories. And even though we apply, for instance in high-risk localized disease, utilization of radiation, hormonal therapy is appropriate. And we still have many patients who are cured and some patients who are not.

The ability to predict effectively those patients who are not going to be cured and to add in an additional therapy that enhances their cure rate is still a bit of a dream rather than a reality today.

Robert Henry The challenge to establishing cancer biomarkers is surprisingly formidable. There has not been a major cancer biomarker discovered in many years. One would expect greater headway being made in this area.

Dr Sartor It's interesting, though I think that might be a little bit pessimistic. We have learned how to use better the biomarkers that we have, even though we're still using the same ones. I'm a prostate-focused physician, and PSA is a biomarker that's been around since the late 1980s, originally described as being potentially helpful in terms of predicting response and progression among those patients with prostate cancer after various treatments.

We understand its significance in various states to a greater extent than we used to. For instance, consider the expectations after radical prostatectomy. We now make treatment decisions solely on rise in PSA after radical prostatectomy. I will make recommendations for what we call salvage radiation therapy simply on a change in PSA. Nothing else. No bone scan, no CAT scan, no effect of patient symptoms. Just the PSA will drive me to a treatment decision. I think that's a piece of progress.

We also understand better the limitations of PSA. I was talking to one of my fellows and posed the question, "Would you rather have a PSA response, a 90% decline in PSA that lasts for 1 month, or a 1% decline in PSA that lasts for 10 years?" And what we have is a limitation on the interpretation of PSA response. Your PSA response is only 1 parameter, but the durability of that response is a whole separate parameter, and the ability for progression-free survival to be assessed is distinct from what happens with PSA as a monolithic end point.

Robert Henry So the challenge is to make that understood and put into a systematic methodology by the practicing oncologist. Which brings up the matter of increasing specialization in oncology. The era of general oncology is coming to a close, owing to the sheer force of knowledge and nuance. Could you describe this process in regard to prostate cancer?

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Dr Sartor I think that as we look at specialization within oncology, it becomes increasingly necessary. When we have a disease like prostate cancer that is incredibly heterogeneous, we also have the opportunity for having it misunderstood.

I'm fond of saying that any statement about prostate cancer that is monolithically made is probably wrong. People say prostate cancer is a dangerous disease. Well, of course, that's wrong. And we have people say that prostate cancer is a disease that old men will die with, not of. I say, well that's a dangerous statement, because we know that it kills about 30,000 people a year.

It's actually the second-leading cause of death from cancer in American men. Yet its incidence-to-mortality ratio is the lowest – or the highest, since it's mortality, high in that case meaning good. You have a lot cases and few deaths. It's the best of any of our major cancers.

We just are multiplying our knowledge at a rate that is becoming hard to handle. I view increasing specialization as inevitable, and I regard the increased knowledge that will be necessary

in order to make optimal decisions as something that will increasingly play within the purview of the oncologic specialist.

Robert Henry I think about the growth of highly specialized knowledge and the emergence of new specialists within the field of informatics and others involved in the processing of genomics/tumor data. There is a rise in infrastructure and personnel, in the volume of biological and genetics knowledge under examination. Is the immense diversity of tumor landscape and genetics also driving the need for such specialization?

If there is a weak link in the chain here at present in PM in oncology, might it be the difficulty in validating the biomarkers?

Dr Sartor I think it's a combination of factors. As we move forward, the ability to generate the new knowledge is going to be dependent on those in informatics and other specialties. We have 7 prostate cancer genomes that have been published in *Nature*[2] recently, and the information from 1 patient was 99 billion base pairs of sequencing information. So a hundred billion, just as a rough number, of base pair knowledge is incorporated into that experiment.

I don't see that being clinically relevant within the near-term future, but that type of information is going to be necessary to make the progress in prostate cancer that we need to make. It may be that these more discovery-oriented experiments are going to move into a greater translational era. By that I mean that if we find 3800 mutations within the genome and discover that 18 of them are particularly informative, then we'll devise testing for those 18 that can be performed in a more consistent manner.

I do believe we'll become increasingly personalized, although I think that today's promise of personalization, for instance in prostate cancer, is not nearly as high as we would like. As we move forward into the future, we're going to come closer to our goals, and then the knowledge required from an individual physician is going to have to be greater and greater. And it's not just happening in prostate; it's happening for all cancers. That is why I think that inevitably we will have a greater degree of specialization among our oncologists.

Robert Henry One of the areas I am interested in your thoughts on is the reliability of biomarkers. If there is a weak link in the chain here at present in PM in oncology, might it be the difficulty in validating the biomarkers?

Dr Sartor It's a process like any process, and it requires reliability, context, and repeatability. When you begin to look at these new diagnostic biomarkers, they are actually similar in a way to new pharmaceuticals. They can't be done in just one lab. To be valid, it has to be reproducible when run through a variety of laboratories, or at least laboratories that are accessible to a large number of people. From my perspective, if you don't have a valid biomarker, you may not have a valid targeted therapy: the two go hand in hand.

Robert Henry The fact that validated biomarkers are scarce makes the progression into personalized medicine a much more arduous process than it otherwise would be and complicates the understanding of what is meant by personalized medicine. The term *personalized medicine* might connote to some a new, distinctly ordered process of practicing medicine, a brave new world of medicine quite detached from conventional medicine, and from what you are describing, that would be a false dichotomy. I wonder if you could help us clarify what personalized medicine means by providing us with your

own definition of it. What is personalized medicine and what is it doing differently in the treatment of prostate cancer?

Dr Sartor I would describe it as being able to evaluate individual patients in individual treatment decisions. We're at a point now in prostate cancer, my area of expertise, where that degree of personalization is not really possible. But I do regard this as something that is continuing to change, and the science of prostate cancer is proceeding rapidly now, as is the implementation of new therapies.

You're probably aware that we have 4 new FDA-approved therapies since March 2010: sipuleucel-T, cabazitaxel, denosumab, and abiraterone. Each of these is tailored for a disease state. The asymptomatic, metastatic castrate-resistant prostate cancer for all patients with the sipuleucel-T, are they patients with post-docetaxel progression in metastatic castrate-resistant prostate cancer for both the cabazitaxel and abiraterone? We're stratifying our patients, dividing them into prognostic categories, but it's not truly personalized yet.

We need biomarkers that can say "You are an ideal candidate for our therapy X, you are an ideal candidate for therapy Y, and you unfortunately will not benefit from this therapy." We don't know what patient is going to benefit most from the new vaccine, sipuleucel-T. And that is the dividing line between personalized medicine and today's medicine. Once we categorically know that a patient has asymptomatic metastatic castrate-resistant prostate cancer, we do not know how to predict responses within that category. We are still practicing medicine largely in a pre-personalized medicine paradigm.

Robert Henry So for purposes of practical implementation, personalized medicine does not exist as an overlay on top of NCCN guidelines or as a separate set of guidelines for prostate cancer.

Dr Sartor Correct. I think that as personalized medicine techniques become developed, they should be incorporated into the guidelines rather than exist as a separate set of guidelines, a separate kind of therapy for prostate cancer.

Robert Henry You regard it therefore as an iterative process, amenable to augmenting rather than reinventing.

Dr Sartor Yes.

Robert Henry To the extent that personalized medicine is incrementally moving into prostate cancer treatment, is it showing up in localized, regional, or widely metastatic disease: the early, middle, or late stage of prostate cancer?

Dr Sartor It's all about tumor stratification. When somebody comes to me newly diagnosed, I evaluate about 7 variables pretty quickly. What is their PSA, Gleason score, clinical stage, age, comorbidities, and percentage of their cores that are positive? Are we talking about 12 cores being taken and only 1 core positive? Are we talking about 12 cores being taken and 12 cores positive, and of the cores that are positive, how much of a particular core is positive?

By using those factors, and some people would add in prostate size in order to be able to calculate PSA density, you can create a low-, intermediate-, and high-risk category or very low-risk category for individual patients.

Now interestingly, the comorbidity assessment is something that we're not terrifically good at. For prostate cancer, we have to know for the early stages how long the patient is expected to live in order to determine whether there might be benefits from treatment because it can be a slow-growing disease. What that means is that we would not expect patients who have a short life expectancy to benefit from therapy, whereas those with a long life expectancy very well may benefit.

To make it simple, the 99-year-old man in a

nursing home and the 48-year-old marathon runner are not necessarily going to be treated the same way, even if their cancer is the same.

The mixing of age comorbidities with the prognostic factors attached to the prostate cancer is part of what we do to "personalize it." But it's really not to the point yet where we're perfect, and I'm hoping we'll continue to do better.

Robert Henry Which helps me understand your answer to my question, What is personalized medicine? You are saying it is sometimes experienced as an iterative process yielding increasingly positive results from existing procedures as our handling of them improves, and that it can appear abruptly in other instances with the discovery of a new biomarker and companion biological treatment.

Would you regard the Gleason score as more of a prognostic factor than a predictive factor?

Dr Sartor I think this is a matter of terminology. The Gleason score is prognostic, and it also can be predictive of certain events. We've published studies in which high-risk scores are associated with shorter hormonal responses, etc. But as we look at the Gleason score, we realize there are groups of patients who have higher-risk disease, some of whom respond very well to therapy, and some of whom don't. It's an important prognostic variable, but it doesn't really get us, in my opinion, to the personalized state.

Robert Henry How does the heterogeneity of the prostate cancer patient provide a means of profiling these patients?

Dr Sartor In my opinion, there is no disease that we deal with that is more heterogeneous than prostate cancer. Some of these patients have totally indolent disease that will pose no risk during their lifetime. The fact is, that's probably the majority of prostate cancers that exist today. And some patients have vicious aggressive disease where death is almost inevitable.

A 60-year-old man in the United States has somewhere between a 30% and 60% probability of harboring prostate cancer. Those data are derived from autopsy series in which men have died from other causes. The prostate is removed, it's thin sliced, it's sectioned, and it's looked at carefully through a microscope to determine if there's any incidence of cancer.

So why don't we say, 50% of men age 60. And that doesn't mean that 50% of these men are going to die. The number of men who are going to die is only about 3%, so the vast majority of men who have evidence of this cancer are not at risk in their lifetime, whereas other people have Gleason 8-9 metastatic disease. I saw a poor fellow recently whose PSA had gone from 0.2 to 188 within the space of 6 months. That's a cancer whose kinetics are deadly. Unfortunately he's doing very, very poorly as we speak.

So the heterogeneity in prostate cancer is huge, associated with kinetics that are great, kinetics that are poor, and our ability to risk stratify only partly takes that into account today.

Robert Henry To look at personalized medicine conceptually, what is its potential to aid amidst this kind of heterogeneity?

Dr Sartor To me it's all about risk stratification right now. I can usually discriminate between those cancers that are dangerous and not dangerous. Or you might consider Larry Klotz's criteria for surveillance. He has 98% survival from his cohort at about 8 years of follow-up simply by observing patients and intervening only for those individuals who he believes are at high risk for progression. If I reported 98% survival at 8 years for any treatment approach that we do, that would be applauded. That's certainly worth recognizing.

So we do have the ability to create risk stratifications that are sensitive enough and good enough that we can achieve correct results the

vast majority of the time. But we are still not at the personalized point of looking at patients within that category and say, "You are more likely to progress, and you are unlikely to progress." What we really need to do is treat aggressively and approach patients with surveillance. So these full abilities to risk stratify are still elusive, and we're continuing to work on them.

Robert Henry When you evaluate the research concerning personalized medicine in prostate cancer and other cancers, has there been a surprising advance or a particular disappointment – and what would you say are the reasons for that advance or that disappointment?

Dr Sartor I think the advances in breast cancer stand out, where the ability to molecularly recognize and stratify patients has made great progress. In prostate cancer we are behind, and because prostate cancer disease kinetics are slower as a whole, we also are behind in terms of evaluating adjuvant therapies. Therapies that are standard in breast cancer are, in prostate cancer, still not unequivocally effective or noneffective – the trials haven't sufficiently matured.

So prostate cancer is a bit of a disappointment in that I feel like we're behind other cancers in some ways, but it's not just due to lower funding. Of course, higher funding would always help, but because the disease changes more slowly and the outcomes are slower, it takes more time in prostate cancer to get the type of results that are considered to be reliable.

When we're looking at end points in the trials, our primary focus is on survival. And if you want to do a trial that evaluates survival in early-stage prostate cancer, then it's going to last a minimum of 10 years in order to be informative. So that's an area in prostate cancer that is particularly challenging. It's a slower moving disease and the trials take longer to evaluate.

Robert Henry Let's examine the etiological implications of personalized medicine. To start off, it helps to get an idea of how old the idea of personalized cancer medicine is. Did it begin with the understanding that all cancers don't emerge from a single bad seed but are organ or tissue based?

Dr Sartor I think the roots go back a long, long time. While it's hard to pinpoint an exact date, physicians have always had this sort of dichotomy between the patient that needs to be treated and the knowledge derived from the field of study.

I think the advances in breast cancer stand out, where the ability to molecularly recognize and stratify patients has made great progress.

When I'm in my office, I'm surrounded by textbooks and articles and the Internet today, all of which feed me information, and there's a hierarchy of information there. There's the finding of what happens in a mouse that is inconsequential to the treatment of my patient. I'm not going to take a mouse study and immediately extrapolate it to my patient in the clinic. That's just too great an extrapolation – perhaps even worse, an in vitro experiment in a cell. These are often provocative experiments, but they don't change the way I practice clinical medicine. And then we have the case report, which is always interesting. But of course, they are anecdotal: if the clinician had told us a story about another patient, it might not have happened in the same way. Retrospective case reviews allow us to review what happened to a series of patients. A prospective trial follows patients prospectively under certain prespecified conditions. Sort of our gold standard is the prospec-

tive randomized trial. As we move up this hierarchy of information, I have more confidence in being able to tell my patient, "I think this is a good idea for you and here's why."

As we are going historically through this same process of moving from our field of knowledge to the individual patient, we have been practicing some degree of personalized medicine for a long time, and we're better at it today because of our prognostic markers and our ability to risk stratify.

The path to progress involves making refinements to our risk stratification schemes and becoming more and more personalized in our therapy.

Michael Kattan has made nomograms popular. These are a way of improving clinical judgment by saying, for example, a patient with 3 positive biopsies with a Gleason 7 disease, treated with surgery when the PSA was 14.3, has a 79% chance of no PSA recurrence after 7 years. That quantitation of knowledge is an important step forward because it goes beyond what our clinical judgment can do. Now we are really taking an individual patient and inserting his information into a database and comparing quantitatively how he would do relative to others who've had similar disease states. That's a step toward personalization, an important step, but it's not really quite there yet.

Robert Henry Is staging, which is now very much taken for granted, an early form of personalization?

Dr Sartor It is. Do you know in prostate cancer that this staging is less important today than ever? What do we use? We use what I've heard about the risk categories, the low-, intermediate-, and high-risk categories. I didn't talk about their stage, although staging is embedded within those categories. If you have metastatic disease, you don't fit into this category. This low, intermediat, and high risk fits patients with localized disease. But as we look forward, we know that we're going to have staging as a background measure. But there is going to be much more to treating the patient than just the clinical stage. That's just one-on-one.

And for prostate cancer, whether you are T1c, meaning you are nonpalpable PSA elevated, or T2a, which would mean that you have a small palpable lesion, really is pretty much inconsequential. Both of these patients can be low-risk patients. The stage is not the important variable. If you have a Gleason 8 T1c, PSA of 4.5, that is a high-risk patient by virtue of the Gleason score, but if you have a Gleason 6 T1c, PSA 4.5, that is a low-risk patient. So the Gleason score is the trump card here, not the clinical stage.

The path to progress involves making refinements to our risk stratification schemes and becoming more and more personalized in our therapy. But within each risk stratification category, we still have a fair amount of heterogeneity that presents the challenge which, in my opinion, is where we have the real opportunities for improvement.

Some of these little Gleason 6s may actually have danger associated with them, and it may be because when the biopsy is performed the whole prostate is not utilized as a target for the biopsy; you just do the posterior portion. And so there is sampling error that may account for some of the Gleason 6s that do worse than others, because sampling the wrong part of the prostate would prevent finding the bad tumor. In fact, if you have a Gleason 6 on biopsy and you take out the prostate, step section the whole gland and look at it under a microscope, you

probably will be upgraded 30% to 40% of the time. The cancer in the prostate will be worse than initially suspected. Sampling errors are an important issue that plays into this role.

Robert Henry Would techniques like PET scanning or even measurement of circulating tumor cells help make therapy recommendations more personalized than before?

Dr Sartor Not today. The PET scans for prostate are, perhaps disappointingly, not FDA approved for reimbursement through Medicare, so we don't utilize PET scanning. At the same time, there is some experimental PET scanning coming that looks quite interesting and that may be able to add additional risk stratification information.

Further, if we look at novel forms of MRI, there appears to be information that can discriminate between various categories in patients within a single risk category. So for instance, you can take your low-risk patients and put them into higher or lower categories potentially based on an MRI spectroscopy result.

This is where the field is evolving, to become better at predicting prognosis, because once you understand the prognosis then you can also make treatment decisions a little more effectively.

Robert Henry Yes. Relevance based on risk. Are gauging the performance status and determining overall patient health comorbidities key elements in personalizing the appropriate care?

Dr Sartor Absolutely. Again, this is part of a risk stratification variable. Do you want to talk about the 7 variables that I try to evaluate in each new prostate cancer? Age and comorbidities are right up there at the top, because if we don't know the age and comorbidities of the patients, it's almost impossible to make good treatment decisions – getting back to that 48-year-old marathon runner and the 99-year-old nursing home patient. The same disease gets treated in a different manner.

Robert Henry Is age as relevant a feature in personalized medicine as it was in the past?

Dr Sartor It is, but I think we're also a little smarter about the way we look at age. There's chronologic age and there's physiologic age. I know some 70-year-olds who are creeping around and barely making it from the bedpan to the breakfast table, and there are other 70-year-olds who are out running marathons. There's a lot of heterogeneity within an age group. I think that life expectancy rather than age per se is the important variable. That piece of information is needed to make good treatment decisions.

Robert Henry And issues of ethnicity, family history, and genetic risk factors?

Dr Sartor Absolutely. They're relevant, and I simplified things when I said "7 factors." I recently went through risk stratification in my typical way with a patient, and I forgot to ask about family history, and he reminded me. He said, "My father died of prostate cancer, and I really don't want to undergo that." So family history influences decisions.

We're not perfect at understanding how aggressiveness of prostate cancer is transmitted from generation to generation. But certainly when we have a patient whose father died of prostate cancer at age 61, it's a different scenario than if there were no family history; and we may interpret data differently for a patient whose father had prostate cancer and died of his congestive heart failure at age 98. This does play a role in the way we approach patients, but quantitating that role and fully understanding it is something that we are working towards.

Robert Henry Recently ASCO President Dr George Sledge stated that cancers increasingly will be treated – not just researched – on a molecular basis rather than as organ-based diseases. It

would seem that the present level of sophistication in personalized medicine will not permit that.

Dr Sartor I agree with Dr Sledge that we're beginning to shift into where we're going to be characterizing tumors on their molecular and genetic characteristics. But while we are making small strides in this direction, I don't think we are really there yet. For most of the solid tumors we don't have a well-characterized genetic signature that we can use in treatments. We know that solid tumors as a whole have a high degree of genetic heterogeneity, even though they defy clear-cut ranking.

Robert Henry How can this translate into a formula for the clinicians not deeply involved in research? Is it in any way practical for them to regard cancer as a tissue-based rather than an organ-based disease?

Dr Sartor What we're really talking about here is knowledge that is relevant at this point to research and development. We have been able to define certain mutations – KRAS, certain cell membrane–based proteins, etc – that seem to suggest a certain therapeutic modality. But we are a long way right now from being able to say we have truly shifted into a molecularly characterized disease classification. For now, we are organ-based, and we are going to make headway essentially one item at a time with the new molecular diagnostics that are evolving. When we look at the ALK-EMLK4 alterations in non–small cell lung cancer – that's only about 4% to 7%, but that's a very critical 4% to 7%, and that leaves the remainder of the non–small cell lung cancers molecularly very heterogeneous – we see that there is going to be very slow progress, but progress we have to keep track of.

Robert Henry It sounds like this leaves much of personalized medicine in the researcher's corner rather than the clinician's corner.

Dr Sartor There is certain utility in knowing the mutations of EGFR in selected tumors. In my area of expertise, prostate cancer, it is not at that point yet where any form of molecular characterization of tumors is useful in terms of making therapeutic decisions.

Robert Henry Would you characterize this information as something we should alert clinicians to, and that Dr Sledge's comment is relevant to a clinician from that standpoint, even if it is a step away from being de rigueur?

Dr Sartor Yes, I think it's something they should be cognizant of, part of the ceaseless process of keeping up with the literature in order to understand the advances in the field and how they translate into clinical practice. But I think we have to stop short of saying that we have moved to a molecular-based system of cancer classification in therapeutics. We are beginning that process but have a long way to go.

Robert Henry How much of this will ultimately matter to the practicing oncologist? What is the "need-to-know" when it comes to the specifics of the different kinds of diagnostic assays?

Dr Sartor This is actually the critical question, because each category of therapy is going to be dependent on *validated* assays. You can't give Herceptin without understanding the expression of HER2/neu. You can't give an alpha inhibitor in an appropriate way without having assays that pick up the information pertinent to therapeutics. They go hand in hand. I think clinicians need to be aware of the diagnostics, given their therapeutic implications. They have to order the right test.

Robert Henry Because personalized medicine has many moving parts, it becomes imperative for the clinicians to stay in front of information relevant to their operations and avoid digressions into lab-oriented or research-intensive details.

Dr Sartor I think that is one of the reasons why this targeted approach to personalized therapy is going to be important from a clinical perspective. As the progress in this field occurs, I predict we're going to have rapid progress over the next decade and even more. The practicing clinician is going to have to be alerted and made aware of the opportunities for targeted therapy, the opportunities for linkage between molecular diagnostics and therapeutic choice that help to drive patient care. This is a very bright field, an evolving field that is good to be involved in from a communication perspective.

Robert Henry As you're talking, I'm seeing this process of care take shape as an art: there is no painting-by-numbers here. The nuances in cancer diagnosis and treatment make it an extraordinary art. Collecting and making sense of the variables is, you're right, getting exponentially difficult and complex.

Dr Sartor Actually, I would like to think it's a science, but I'm fond of the quote, "I love evidence-based medicine, but there's not enough evidence to go around for every patient I treat." I'm encountering patients right now who have been exposed to cancer therapies for which we have absolutely no reporting data.

I have a patient today going on protocol who has progressed despite docetaxel, cabazitaxel, and abiraterone, and there's absolutely nothing written about such a patient. No guidelines in the literature are telling me what I should do or what I shouldn't do, so now I make decisions with very imperfect knowledge. Am I going to practice evidence-based medicine? How can I? There has never been a patient reported in the literature with this particular combination of treatments.

Robert Henry It's a humbling sort of thing, and it reminds what Dr John Laragh said in a press briefing at the New York Academy of Sciences about 18 years ago, just prior to the release of the JNC VI guidelines for hypertension. Dr Laragh, who is distinguished for his co-discovery of the role of the renin angiotensin aldosterone system (RAAS) in the etiology of hypertension, stated, "Risk factors are a measure of our ignorance, not our knowledge, and therefore we shouldn't get parochial about it and rule out examination of alternative schools of thought."

I'm encountering patients right now who have been exposed to cancer therapies for which we have absolutely no reporting data.

Dr Sartor I think we have to be pretty humble, because each time we think we're perfect, I promise you we're not. Even though we're gaining knowledge almost in an exponential fashion, the application of that knowledge is far from what we hope to achieve at some point in the future. It's that constant evolution and that constant challenge that makes medicine so fascinating. And as you have the patient who comes to us, it's really a privilege that they give to us to be able to be responsible for their care. You face immense challenges making that transition from a scientist to a physician, and yes, we are scientists. We do understand our literature, but then we're humbled by how much we don't know. And making those decisions is the challenge and art of this, and we're always going to need that when it comes to patient care.

Robert Henry I would welcome your impressions about the environment in which we're pursuing this new medicine. You mentioned that PET scans weren't approved by Medicare for prostate imaging. Healthcare must satisfy a triad of criteria: clinical, business, and policy.

Those are the hubs or the spokes to the wheel, the healthcare sectors. Is the environment in which personalized medicine and research in prostate cancer are being pursued conducive to and facilitating the advances, the leads you're trying to pursue, or is the pursuit of quality getting increasingly difficult?

Dr Sartor We're facing almost unprecedented cuts in the basic sciences for the type of research in prostate cancer that I think will lay the foundation for the next clinical advances. I have a significant concern about our funding for basic research in the United States. And since we traditionally have been the leader, I'll globalize that statement to say I have significant concerns about funding basic research – the new knowledge that comes from our basic and translational scientists that lays the foundation for our next clinical progression – particularly that which is applicable to prostate cancer.

The clinical trials are proceeding reasonably well right now. The ability to accrue to trials is better than ever before.

The clinical trials are proceeding reasonably well right now. The ability to accrue to trials is better than ever before. But I think there are going to be new challenges because of the multiplicity of new therapies and because we have been using overall survival as an end point for a number of years. But now that we have docetaxel, sipuleucel-T, cabazitaxel, and abiraterone, all of which have been shown to prolong survival, doing survival end point trials is going to be evermore challenging.

That is good news for our patients, but it's a challenge for our progress, and we're going to have to learn how to sequence and combine agents in new ways. That presents challenges to companies who quite frankly work in fairly monolithic scenarios: my drug or no drug, my drug or a generic drug. But as we move forward, my drug needs to be combined with your drug, and we've got to create partnerships to make that happen. Those barriers exist from a business perspective, one of what you call the hubs of medicine, and that business perspective is very real.

Robert Henry Yes, transparency is a very scarce commodity, and approaching medicine without regard for the context of financial, business, and policy considerations is unrealistic.

How are guidelines and visualization of personalized medicine techniques helping clinicians understand their practical application?

Dr Sartor I agree to the importance of graphics in understanding complex medical processes. I do like the algorithm that's been laid out by the NCCN. I think that is a dynamic system for updating treatment algorithms that incorporates information in a pragmatic way as it becomes available. If it's not in NCCN, you have to wonder how relevant it really is. There are other guidelines committees – the ASCO guidelines have been promulgated, the AUA guidelines in certain areas have been promulgated. I think the NCCN gives sort of an algorithmic approach that is followed better than anybody's. I would point people there if they were looking for treatment choice algorithms.

Robert Henry Has personalized medicine accelerated the role of patient-reported outcomes (PROs) in prostate cancer?

Dr Sartor Patient-reported outcomes is an area that is getting considerable attention, and it goes hand-in-hand with personalized medicine. The development of new drug strategies for prostate cancer may be predicated on the PROs. Survival as an end point is increasingly

difficult as a primary end point as we have more and more agents that prolong survival. And so the question is, how do you bring new therapeutics to the market? There are some trials right now that are moving through the PRO process that are accruing using PROs.

The true merit of a therapeutic is that you either live longer or better, or both. Simply put, the patient needs to feel, function, and survive longer and better. And feeling better and functioning better are linked to PROs, and we need to be better at using them. This is an area of active research. There has been nothing in the last decade that has been approved for prostate cancer involving PROs. The last one was in 1997. I was principal investigator on that trial, involving cyclic AMP, and it was pure PROs as a method for success or failure of the trial.

Robert Henry The picture of personalized medicine becomes clearer as you speak – a gradual, iterative process with many faces, some objective and others subjective and, well, personal. Looking at the technical, statistical side once again, what is needed to improve the validation of diagnostic tests in prostate cancer?

Dr Sartor First of all, there must be repeatability and the ability to perform quality control in the assay that yields a high degree of reproducibility, not only within a laboratory but between the office and a lab. But most importantly, the demonstration of the validation of a test is showing its clinical utility. We can all do a test – the question is whether it is better or worse than what we currently have on the market. And if a test is going to be valid and an improvement, then unequivocally we need to compare it to the best standard currently used by clinicians and show that this is a better test. And many studies have failed to show an improvement in comparison to the best tools that clinicians use today.

Robert Henry Will genomics, proteomics, and metabolomics become a regular part of the day-to-day activities of the practicing oncologist?

Dr Sartor Yes, because they become clinically relevant. I'm not saying that we're all going to become genomicists. But we're going to have to have a better working knowledge of all the new technologies that are applied to cancer treatment, because those newer investigations provide potentially important information on prognosis and therapeutic response. What clinicians have to know is how to benefit their patient with the latest knowledge. As this body of knowledge changes, they must adopt it and become more proficient at the newer terminology and these newer fields of medicine.

I just spent a ridiculous part of my weekend working on alpha-particle radiobiology because suddenly I need to understand the radiobiology implications for clinical practice. I need to understand the limitations and advantages of new therapeutic advances. In order to do that I have to understand biology in a context I never understood before. And that's actually exciting for me. I love to learn. And if I learn things that benefit my patients, it becomes very pragmatic and important for me to learn that topic. I think most oncologists are similar: they want to understand how they can make their patients better, and that's the bottom line.

Robert Henry Yes, oncology has drawn out the need to understand things in a highly encyclopedic fashion concerning the governing dynamics of the disease's biology, the pathophysiologies involved, and its treatment. Are community-based cancer centers going to be able to keep up with the academic research centers in this iterative process?

Dr Sartor Actually, the community oncologists are very involved in the research. They may tend to be a little more pragmatic in their out-

look than the research centers – there is a knowledge-for-knowledge-sake atmosphere in the academic community. But when that knowledge becomes relevant to patients, the community oncologists are hungry for that information. The knowledge is making its way to them through the usual suspects: the journals, meetings, seminars, CME courses. Now of course, we have more things to add to that. I just finished up a podcast. We didn't used to do podcasts, but I do now. The access to the information is there for the community doctors, and they are making their way to it.

Robert Henry How has predictive modeling changed over the past 5 years in prostate cancer?

Dr Sartor It has gotten incrementally better. Again, for example, consider the work by Michael Kattan and his nomograms. There has been increased acceptance of nomograms and an increased number of variables that have been added to them to give them more robust and repeatable characteristics. There have been alterations in end points about what the nomograms can predict. Each of these advances is important to keep in mind as we bring new diagnostics into the field, because we have to improve upon the current nomograms if we're going to make an impact in the field.

Robert Henry Clinicians have to prioritize diverse end points in their treatment strategies: survival, time to progression, supportive care, health-related quality of life (HRQoL), and other outcomes goals and measures. Do you expect PM to make its principal contributions in terms of any particular cancer stages or end points?

Dr Sartor The ultimate impact we would like to have is on survival, and this is going to be predicated on really good PM markers as a real distinction between those patients who do or do not have the marker. Time to progression should be viewed as an intermediate end point that may or may not be important. It can be important, particularly for people who have no evidence of disease, but their time to progression means that they'll be undergoing additional therapies. Supportive care is going to be important, and HRQoL is certainly related to supportive care. As to the other end points and goals, they involve everything from tumor response rate, which is another measure of efficacy, to the PROs where people have better pain relief, longer pain relief, pain relief that requires less opioid use – there are a variety of PROs that feed into the PM approach. We have to get past where we are to that set of markers that changes the way we practice.

Robert Henry Are you experiencing or do you predict that there will be a greater degree of patient interaction and engagement in prostate cancer, especially given the nascent phase of personalized medicine?

Dr Sartor There are different ways to view that question: either a population or personal basis. I have long incorporated patient preferences into my treatment algorithms. Particularly when you look at the NCCN, you may see that there are several appropriate choices for each disease state. And that is why I think that communication between the patient and the physician is crucial, that helping the patient understand the potential toxicities, benefits, and risks of each therapy is going to be the essence of a patient-doctor communication that drives decision making. The bottom line is that patients should be involved. There may be certain circumstances where alternative therapies are not well developed, but that still needs to be communicated to the patient, for it provides some sort of limitation to the choices that the patient should be making.

Robert Henry How is PM expanding physi-

cians' understanding of the disease process due to the targeting it entails? Is it replacing a pragmatic approach to treatment with a biologically informed approach to etiology and pharmacodynamics? Historically primary care physicians expressed little interest in drug mechanisms of action or the specifics of disease etiology, favoring the conclusions of research. As PM moves into the process of care, this must change.

Dr Sartor Yes, and it will. But I think that in the past we have had a little better handle on the disease than some people might perceive. I will say that this is true in prostate cancer in particular, because for many, many years we really didn't have chemotherapy, which is sort of the prototype treatment for cancer. What we had were hormonal therapies. And with hormonal therapies you actually have rather exclusive pharmacodynamic feedback. If I give an agent that is supposed to suppress testosterone, I can measure testosterone and find out if I was successful or not. And then there are older data that show if you have elevations in some of your adrenal androgens, you were more likely to develop resistance, causing you to pay attention to adrenal androgens. This is a way of personalizing medicine before it was a sort of buzz word.

Clearly as we go forward we will have to adapt to a new environment – one where the degree and detail of the diagnostic tests are dramatically increasing and the therapies are more and more targeted for very specific populations. We are in the transition zone. But we have understood how to do this thing before; now it is just becoming much more sophisticated.

Robert Henry This degree of biological knowledge tends to vary across specialties. Internists and other primary care physicians often had no idea *how* a beta-blocker worked. They didn't care to know the why, but rather the what – the results. At the end of the day, the patients did well on them so they prescribed them, a sort of anonymous-black-box approach to this.

Dr Sartor Most oncologists are interested in pathophysiology. It's been part of our training; we learn about pathways. But what we've learned in the past is only part of what we're going to learn in the future. I'm positive we are going to be more focused on the pathways and diagnoses in order to practice medicine as well as we can.

Robert Henry And that is the impact of personalized medicine at work. Related to this is the tradition of off-label usage in oncology, practiced here more than in any other area of medicine, with the possible exception of AIDS. The practice of pushing the envelope and going off-label is coming to a screeching halt when you use biologicals.

I'm positive we are going to be more focused on the pathways and diagnoses in order to practice medicine as well as we can.

Dr Sartor It is. I think that this propensity for off-label usage developed because many of the drugs we used in the past, chemotherapy drugs in particular, were only applicable to the diseases beyond the clinical trials. For example, take carboplatin. You could go from disease to disease because platinum would bind with DNA. But as you go to a HER2-targeted antibody, you can't just start using it in everybody who has every disease – you have to have a rationale. And that physiological fact is going to tie us in the future much closer to the indications, as will the expense.

Robert Henry Right, science-for-science's sake is out of the picture. The drug has to get its job done and demonstrate value: cost, quality,

and access. Then too there is danger in undocumented, unvalidated use of powerful biological agents, which demand targeted use. It struck me that the long-standing tradition in oncology of the use of drugs for unapproved indications has changed along with the technology, and because of it, and this amounts to a culture change.

Dr Sartor Agreed.

Robert Henry Now for a deceptively elementary question: do you categorize prostate cancer as an acute or chronic disease?

The truth is that most decisions in cancer are not of an emergency nature. It's better to be thoughtful than urgent.

Dr Sartor It's a chronic disease, though there can be acute decision points in the process of a chronic disease. But nevertheless, it's a chronic disease, and I think it's best approached in a measured and thoughtful way. I think, too, actually the patients feel rushed into a decision, they hear they have cancer, they feel that if they don't make a decision today that it's going to be problematic. The truth is that most decisions in cancer are not of an emergency nature. It's better to be thoughtful than urgent. And that's true in almost all cases of prostate cancer.

Robert Henry My reason for this question involves payers – private, and Medicare – and the way in which they are set up to be supportive or unsupportive of the treatment of *any* chronic disease as opposed to acute diseases. In a separate communication I am considering writing an article that would be titled: "Should Medicare and Health Plans Recuse Themselves From Management of Chronic Diseases?"

Dr Sartor I like the question. If we're running a for-profit health plan, we often have a responsibility toward shareholders that may or may not be in the patient's best interests. I've learned from long experience that many insurance companies really do attempt to do the right thing and make the decision that is in the patient's best interest. But I also know that there are many circumstances when that is not true. And I am supportive of guidelines. But sometimes when you have point A and point B, it would be better for a patient to go to point B, but that may not fit a general guideline even though it serves that individual patient.

I will give you a perfect example. I recently had a patient taking zoledronic acid, which can be associated with an acute phase reaction with fevers and flu-like symptoms. I gave it to this gentleman, and he had the worst case I have ever seen in my entire life. He was nearly hospitalized as a consequence of an adverse drug event. There was an alternative medication that had actually been shown to be superior, and when I filed, the insurance company denied my ability to administer this alternative medication. And even when I appealed it, they still were denying coverage for it. Now, that is bad medicine. If I had given the patient what the insurance company wanted, it would have resulted in a decrement in his quality of life and a poor decision-making process on my part. Yet the appropriate decision, laid out in peer-reviewed literature and supported in a prospective randomized trial, was denied by the insurance company. Now that is as irritating as it can get.

Robert Henry Yes, it cries out for an oversight mechanism to ensure that clinical reality triumphs by allowing physician discretion. The fact that abuses done in the name of individual physician discretion have wasted resource utilization does not mean we can dispense with it. What I find disturbing is that, even though in-

surance companies or Medicare usually comply with good medical practices, they can still possess the power to block them and indeed oppose medical guidelines when they choose to. Systems changes are in order to ensure that payer/Medicare control over resource management does not devolve into a blatant bureaucratic takeover of clinical practices with obstinate, supply- or cost-driven coverage decisions that fly in the face of patient health. This cannot continue, especially given the nuances of cancer care. It is certainly antithetical to personalized medicine. Perhaps the question becomes, "Is the payer model compatible with personalized medicine requiring individualized physician discretion?"

Dr Sartor Clearly work must proceed in earnest on that front. Medicine is not a cut-and-dried process, and bowing to systems instead of having systems serve the patient by accommodating physician discretion is naive, counterintuitive, and unhealthy. And it won't save money by attempting to oversimplify healthcare resource utilization – it just pushes off health problems until they become extremely expensive to treat, or impossible to treat successfully.

Robert Henry In what ways is health information technology facilitating the uptake of PM?

Dr Sartor It's that very fact of having knowledge at your fingertips that is facilitating its assimilation into practice. Lectures that were once available only by physically attending them are now available on the Internet. The information is now retrievable when you want to retrieve it and are ready to retrieve it. All this is changing the way clinicians learn, in a very positive way; I'm embracing the concept.

Robert Henry How are the cancer associations facilitating the acceptance of PM into clinical practice?

Dr Sartor ASCO is asking permission of their lecturers to webcast their presentations. I always do, though there are those who do not, or who make them available only to small groups – perhaps for proprietary reasons, perhaps because their findings haven't yet been published in the peer-reviewed literature, or for other reasons. Our largest organizations are embracing new technologies, particularly webcasting and the retrievability of abstracts. I'm on the ASCO abstracts practically every day. There is a treasure trove of information.

Robert Henry The epidemiology of cancer, in particular the population-based healthcare needs involved in the graying of America, is about to intersect violently with the eroding viability of certain stakeholder groups, especially oncologists. The ASCO Workforce Committee issued a report in 2007 that projected a massive shortage of oncologists by the year 2020, precisely when the boomers would need them more than ever.[3,4] What interests me is this collision of forces, where the complexities of PM in oncology demand an oncologist's hands-on expertise – not a nurse or PA instead of an oncologist – and yet there arises an epidemic shortage of oncologists precisely at a moment of intense population-based prevalence of cancer. Simply put, PM needs oncologists, not just nurses and PAs. Is there anything, to your knowledge, that is being done to reverse this disastrous trend?

Dr Sartor It's a good question, but I don't really know the answer. That would imply that there would be more training slots available, more opportunities for appropriate training – and the truth is, I don't know.

Robert Henry I once asked Dr Sam Silver what he considered to be the cause of this shortfall, and he immediately replied, "The failure to reward oncologists for their cognitive services."

Dr Sartor That's a great statement. I must admit that I feel the same. I go through what I

do, and how many years it has taken me to become good at what I do, and then I look at the reimbursement that is received. I am paid very similar to a family practitioner treating hypertension. If I were a lawyer, I hate to say it, but I would be one of those very high-priced lawyers because of my expertise, my focus, and my ability to solve complex problems in the world in which I work. But in medicine the cognitive aspects are really undervalued, and what you do as a specialist physician, unless you do a procedure, is in my opinion grossly undervalued by our society. Yet, it's also not. When you look at cancer centers, they are a huge magnet for philanthropy, and people who have cancer value very much what oncologists do and are willing to give gratefully for advances in the field. But the reimbursement systems we deal with are not nearly as quick to be grateful.

Robert Henry Yes, the healthcare system's financial model is antiquated and oriented to acute care rather than chronic care, toward rewarding procedures rather than strategic management of diseases. It's hard to change the tires on a Formula 1 racing car going 180 miles an hour, which is what the healthcare system is trying to do.

Dr Sartor It's all very rapidly evolving, but nobody is trying to figure out how to pay more for cognitive services because everybody is trying to find ways to pay less for healthcare. And in part I do understand that. When we look at the costs of many of the new therapies, they're really staggering. So even as we contemplate the problem of certain areas of under-reimbursement, there are other areas where there is over-reimbursement. At ASCO I was one of the speakers providing a wrap-up, The Day in Review, and I reviewed the genitourinary highlights. Everybody talked about everything – except for costs.

And the cost is a very important part of what we do, and there has to be a very careful balance here. Because if you mandate lower costs, then you remove some of the incentives that drive creative people's effort. And when you take away some of the reward, you diminish some of the risk-taking by people who have to make decisions about how to allocate capital and how to make investments. I think one of the reasons we are making progress is that we have had an era where people had been willing to make investments: the NIH made investments, private groups made investments, the biotech industry made investments. And if we stimulate that effort, we will stimulate the rate of progress. But at the same time, we have to make sure we don't get greedy. And I am concerned that there has been greed, and I think that has the potential for huge backlashes which can diminish the rate of progress.

Robert Henry It seems that what is needed most are leadership and the establishment of unity between the three sectors of the healthcare system we discussed earlier: clinical, business, and policy. Together they must look past the short-term financial picture. The "next quarter-itis" mindset often frightens stakeholders into doing what is best for the next quarter financial report, instead of laying the foundation for dealing with the real costs in healthcare: chronic diseases.

Dr Sartor Yes, and I think sometimes managers get criticized for that, because they're the ones there where the rubber meets the road. But the real culprits are the investors. By way of example, if you go to the *Wall Street Journal*, it isn't just about the next quarter report, it's also about the *expectations* of that upcoming quarter. We've reached a point where the people providing the capital so that these business enterprises can grow and prosper are so demanding that they are

no longer interested in what you did last quarter, they only care about what you're going to do next quarter before it even occurs! To me it's largely madness. Managers are obsessing over finances precisely because the investors are driving them to this fever pitch.

Robert Henry Yes. The curious irony here is that unlike any other industry, healthcare requires maturity on the part of investors so that they don't make unsustainable demands on the very industries that they're trying to profit from.

There is an interesting side to new drug development costs that I encountered while I was chairing the Pharmaceutical, Biotech, and Medical Device Summit this year at the 8th Annual World Health Care Congress. One of the speakers, Dr Vicki Seyfert-Margolis of the FDA, is very involved in genomics and biologics and looking to facilitate their development. She pointed out that the cosmic costs of launching a new drug – now averaging over 1.3 billion dollars, which includes failures – could be reduced greatly by transparency between researchers, because many researchers are replicating one another's mistakes, causing far too many drugs to fail in phase 3 and so incurring disastrous financial losses. Obviously there is the need to protect proprietary interests, but she is trying to work out processes for a certain measure of transparency appropriate to biologicals. This follows a whole new set of dynamics, and the old rules of engagement are simply not working out. As costs for R&D are becoming unsustainable, we have to adapt and devise new systems to ensure that progress needed for personalized medicine can continue.

Dr Sartor I find companies to be overly secretive. Again, this may be driven not so much by the companies' basic premises or cultures, but by the investors. I do not want to seem apologetic for the high price of medicines, but it is a fact that it takes a lot of money to research and develop and bring to market these drugs. Looking at the drug development process from the regulatory framework, if there could be a way to diminish risk even a little bit, I think that would be a positive step toward maintaining the progress required for the advance of PM in oncology. So there are opportunities for investors, companies, and regulators to get better at providing the conditions essential for innovation that is value based.

The cost of medicine is the issue that I think is going to become a national debate tomorrow even more than today.

The cost of medicine is the issue that I think is going to become a national debate tomorrow even more than today. So if you look at sipuleucel-T, $93,000 will be the charges to the administering physician or group – $93,000. The question is, can we afford as a country the ability to deliver all of these therapies to our patients?

There's a flip side to that. If the research is going to be intensive and expensive, are investors going to have an appropriate return for the risks that they take? Somehow there has to be a balance. If you price drugs at a point where there is no return on investment for those who fund the research necessary to make the knowledge, then you have put forth the scenario where our goose lays no more golden eggs.

Robert Henry That's right. The end of R&D based on cost-minimization policies.

Dr Sartor But if you decide that costs are going to continuously escalate and that rates of return will be attractive, then can our society afford to pay for all the advances that we fund?

Robert Henry Or phrased another way, we come face to face with lambda: how much society decides it is going to pay for an incremental advance in outcomes. Are we willing to give up a little bit more of our gross domestic product in order to improve health outcomes? There's the intriguing thing, the lambda. And who controls that lambda? That's a very inchoate process. To be blunt, who speaks for what society wants in medicine? And who has no right to assume this? The decision, I think, should be shared multilaterally, representing all stakeholders who make healthcare possible.

Are we willing to give up a little bit more of our gross domestic product in order to improve health outcomes?

Dr Sartor There is more still. We end up spending a huge amount of our GDP, and I'm speaking from a United States perspective, with no better outcomes than countries that spend much less of their GDP. We have made our therapies more expensive.

I'll mention proton beam as being a case in point where an incremental possible advance – which incidentally has never been shown in a randomized trial in prostate – costs many-fold more than therapies that we are currently widely utilizing. If we adopt proton beam as a standard – and there is no reason we should at this point because of the lack of randomized trials – then we would escalate vastly the cost of care with only the possibility of incremental benefit.

Robert Henry So value again shows itself as the holy grail of healthcare in general and personalized medicine in particular: the balance of cost, quality, and access determines what is feasible versus what is a pipe dream. Are there groups within the cancer societies that are providing the kind of oversight and guidance to help steer physicians away from counterintuitive practices? This is almost a first cousin to the epidemiological discipline of healthcare disparities research/reform. We waste immense resources due to erratic care of different patients with identical conditions, depending on where they happen to live and who happens to be treating them. So in regard to the uptake of new technologies based on incremental possible advance, is there good oversight? Is the American Cancer Society, is ASCO, up to the challenge of ensuring value-based, patient-centered, wellness-based care? Is that what NCCN guidelines are for? I have purposely packed a lot of qualifiers of best practices into this question, because achieving the high road of medicine entails all of these and doubtless other measures as well.

Dr Sartor Well, yes and no. There's a lot of yes and no here, because even as we move to better guidelines, the guidelines don't necessarily change behavior, and underlying our system of medicine in the United States is a substantial profit motive for a huge number of practitioners, hospitals, for-profit hospitals. They're in the business of maximizing profits, not following guidelines, and that's something our country has to come to better terms with.

Robert Henry And the price for the consequent inefficiencies is coming due – "under the lash of necessity," as George Will likes to put it. Reluctantly we are coming to terms with that. Let's hope they are terms that are good for medicine.

Well, as Bette Davis said in the movie classic, *All About Eve*, "Fasten your seatbelts – it's going to be a bumpy night!" I want to thank you very much for a stimulating discussion and for the penetrating perspective you have provided

us in the advance of prostate cancer care into the personalized medicine era.

Dr Sartor It was my pleasure as well. Thank you for an engaging and provocative discussion. I look forward to continuing our dialogue.

Robert Henry I am certain our readers will look forward to it as well.

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