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Supplement to
The American Journal of Managed Care

A Vision of the Future of Healthcare: An Exclusive Q&A With John M. Harris

In an exclusive interview, *The American Journal of Managed Care* discussed trends in managed care with John M. Harris, MBA, director of Veralon, a managed care consultancy firm. Harris has over 25 years of experience in managed care consultancy, working with providers, payers, hospitals, physicians, and other stakeholders.

Q: How do you see the Affordable Care Act changing the healthcare landscape?

A: The Affordable Care Act, in a number of ways, has sparked this more competitive healthcare environment that we are in. By putting the critical mass of Medicare behind new payment models, it is driving providers to pay attention and change, and payers tend to follow what Medicare does in terms of new payment models. So, one thing it has done is to create critical mass for change that makes providers actually take notice and make changes. The other thing that the Affordable Care Act did is that the insurance exchanges

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Leveraging Real-World Data to Advance Patient Care: A Q&A Session With Joshua Ransom, PhD

In an exclusive interview with *The American Journal of Managed Care*, Shyft Analytics Product Launch Director Joshua Ransom, PhD, discussed trends in the use of real-world data analytics in managed care, healthcare, and the life sciences industry. With Shyft Analytics, he is developing a new software-as-a-service platform for analysis of real-world patient data. Dr Ransom has a background in genetics and molecular biology. He also serves as co-director of the National Association of Managed Care Physicians' Medical Directors Genomics, Biotech, and Emerging Medical Technologies Institute.

Q: How is big data analysis in healthcare today different from the late 1990s, with analysis of observational data using systems like Archimedes?

A: What I see as different this time has everything to do with empowering individuals with clinical or business questions as well as hypotheses, by creating platforms that allow these

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created an efficient individual market for health insurance; and what that has done is driven providers and payers to compete in ways that they haven't before, or haven't as much before, in providing care in a cost-effective way that satisfies consumers because those consumers are choosing individual plans with often narrow networks of providers providing the care. In that way, the Affordable Care Act has sparked both the competition in value-based payments, as well as competition where individuals are choosing their health plans, and are willing to trade off and choose narrower network plans with lower prices, and that is forcing a lot of new competition.

Q: How have trends in healthcare affected insurers, physicians, and patients?

A: Healthcare had traditionally been a part of the economy where there was not a lot of competition. For a number of reasons, competition was blocked in healthcare. Patients didn't have enough information to make judgements about what was good or bad in terms of the care that they might receive. Insurers, by covering a lot of the costs of the care, took away any price sensitivity that patients might have. Physicians tended to focus on providing care in a way that they were accustomed to, rather than in a way that might be more convenient or effective or appreciated by patients.

Q: How are health coaches in certain managed care practice models changing the healthcare industry, and how is the role of mid-level and supplementary providers changing the healthcare industry?

A: One of the things that has changed in healthcare is that there is less of a rigid commitment to traditional models of care. As the market has become more competitive, the providers have thought of different ways of meeting patient needs, and health coaches or nurse practitioners, and physician assistants are examples of people, other than the physician, meeting the patient's needs. If you ask a primary care physician whether they need to be the one providing the services that they are providing to patients, many of them will say that somewhere between a half and 90% of what they do could be provided by someone else with less training. So when there is economic pressure on the cost of that care, or potential shortages of physicians, other models with other providers meeting some of the needs that physicians used to meet become more viable approaches to providing care. Health coaches are the more extreme example of that, and nurse practitioners are a more long-standing and accepted example.

Q: What are your perceptions of mobile health apps as they currently exist, and how might they evolve as the industry changes?

A: If you think about the ways apps change our lives and make things easier to do, whether it's banking, getting an Uber, or communicating with each other, as consumers get accustomed to using these convenient tools, for healthcare to stay stuck in the mindset that you can't use any of those approaches is kind of crazy. But healthcare has traditionally stuck with more traditional models of communication and interaction, so I think the apps that allow for communication are an obvious way that apps will change healthcare delivery. But in addition to that, apps collect data and can use that data to assess how a patient is doing. For instance, using a mobile device to collect data on activity is critical to managing people's chronic illnesses.

Q: What do you see as some of the major benefits and drawbacks to consumers and managed care in these disruptive changes that are occurring in the healthcare industry?

A: Any time an industry is disrupted, usually it is to the benefit of consumers. Consumers are seeking lower cost, greater convenience, and more thoughtful approaches to meeting their needs. These disruptive innovators are very focused on what the consumer wants and needs. The traditional providers are struggling with how to keep up with that and how to secure their position in the market and meet patient needs in an effective way. Some more innovative incumbent providers may embrace these technologies and embed them within their care delivery system. Others will resist them and will probably see patients steered away from them because they are not participating in or using those tools effectively.

Q: Some people have called the current shift to accountable care organizations (ACOs) “old wine in new bottles” because many current ACO strategies were implemented in the past. Is the current ACO model a big enough change, or will larger change be necessary; and what is the gap that large managed care organizations need to recognize?

A: I think that accountable care, as it has been put forward by Medicare and the Medicare Shared Savings Program, is a step in a long transition, and you can already see Medicare’s track 3 and next-generation ACOs as further steps to have a more thoughtfully managed set of services for patients. The original Medicare ACO was set up with lots of patient choice because they were trying desperately to avoid having patients complain that they couldn’t go to see their doctor. The later models are starting to limit that patient choice and support better-coordinated, closed systems of care, where all of your information is available and we avoid patients taking their X-ray from one provider to another—having a nice, closed, fully integrated system, with a single IT system supporting it. In the long run, that is probably the type of healthcare delivery system we are going to have, where people choose a specific system of care, which includes specific hospitals and physicians, and that they get a very coordinated set of services from that system of care—and that is a big change for us. We used to have a system, and still to a degree do, where patients can go anywhere and to any provider, but we have learned that there are significant sacrifices in that wide-open system because there is a real benefit to having all of the data available, and in place and coordinated among the providers in a detailed, thoughtful way. That is extremely hard to accomplish in disparate organizations but easier to accomplish within closed systems of care.

Q: Some health specialists are likely to be particularly resistant to accountable care models and other changes in healthcare provision and reimbursement. Which providers are likely to be more or less amenable to change over time?

A: I think some of these changes are very hard for physicians. When they trained to be physicians, they believed that they would be independent, have their own practice, and be in charge of all important decisions. The new model that they are being asked to participate in is one that is team-based, where they work with other healthcare professionals in a very thoughtful way, where technology is supporting them and where their role may be more about their technical expertise than their being the chief. That is a hard transition for a lot of physicians because it wasn’t what they signed up for. More recently trained physicians are more prepared to be part of the team, more prepared to use information technology, more prepared to think about the quality and cost factors that the payers are concerned with, and I think are better positioned to succeed in this new environment. Is that all good? Some of it is good. However, there will be nostalgia from both physicians and patients for the old days, when a doctor had a personal relationship with a patient and showed up at the hospital bed when the patient wasn’t doing well and saw them in the supermarket and asked how they were doing. We are in an environment where there is so much information, and data, and expertise that a physician needs.... It is unreasonable to expect physicians to succeed in the complex environment we have now without the support of a team and effective information technology.

Q: What is the role of change in reimbursement, and how is that likely to factor into change in the provision of healthcare?

A: New payment models allow and encourage providers to focus on the total cost of care in ways that the old payment models didn’t. It was not uncommon 10 or 20 years ago for a physician to say, “All I’m supposed to worry about is what the right care is. I’m not even supposed to know the cost of the care that I’m prescribing.” That sounds a little quaint now, but that used to be how physicians thought about it. You could argue that being responsible stewards of healthcare spending is one of the things that physicians ought to be doing. These new payment models move away from fee for service, which encouraged less coordinated care and more volume because one would only get paid if one provided a service. That is not to say that the new models are flawless. They have significant flaws as well and are likely to lead to their own sets of problems, but they will likely help reduce excess spending in areas where it can be reduced. The example we’re seeing of that now is bundled payments for things like joint

replacements or other conditions where, when physicians in hospitals start to pay attention to the costs, as well as the quality of the patient experience, they've said, "For these hip replacements and knee replacements, the patients don't need to go to a nursing home nearly as much as they have. We ought to send people home for home care instead of to a nursing home." That ends up being cost saving and something that patients are much more satisfied with.... Is that really difficult for skilled nursing facilities because they are losing volume and struggling to compete? Yes, it is a big, earth-shaking change for nursing facilities; but it is an example of how these new value-based payments can change how care is delivered, both on quality and on cost.

Q: We have seen a flurry of mergers across all businesses in the past year, and certainly that is affecting health-care as well. What is this portending?

A: The big question to ask when you see the mergers is, are these organizations merging to be able to be big enough to make the changes—to do the innovations that will allow them to succeed in the long run—or are they merging just to try to have enough market share to fight the innovations? I think what we would hope to see is that the providers and payers are merging to be able to invest in the technology they need to drive change, to be able to support organizations that would have been too small to drive change, to actually be able to drive change, and to have large enough integrated provider networks to be able to meet the needs of a significant population. It is important that these mergers provide a large enough network to a large enough population to succeed as a provider network meeting the needs of a full population. Is the goal just to get large enough to negotiate better prices and to fight change, or is it going to support the transformation, the new technologies, the new innovations that will lead to a much better set of services for consumers that really meets their needs in the long run? ●

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individuals to ask their question of the data. In this new era, that person does not necessarily have to be a programmer or statistician. Instead, they can now use a guided system to derive a preliminary answer to their question using real-world evidence (RWE), and then focus their organization's experts on promising leads.

Q: How do you balance the user interface design that is easy to use with the control you can have with direct programming of some of these systems?

A: It is a huge undertaking because there is a continuous push by the medical and research community to use scientific advances to more granularly define patient diseases. There is no single or standard answer. I can tell you what we are trying to do is create a system that is reusable and extensible; to more efficiently define and standardize, where possible, while still accounting for the differences in process and focus between life sciences organizations. A flexible system with a more natural language approach might help a user identify a definition for patients with diabetes using natural grammar. For instance, I might write, "I want 2 occurrences of type 2 diabetes at least 30 days apart, but no more than 180 days apart." Also, when I say "type 2 diabetes," it is a code that means—from a US standpoint—ICD9, but also takes into account other coding systems, like SNOMED or MedDRA. We are on the cusp of combining common data models with a more natural language approach to provide a guided experience. The user knows what the question is, but now you can have an analytic framework to guide you through what that means exactly, and advise you on how to approach the data analysis.

Q: How does the 21st Century Cures Act factor in with real-world data and novel clinical trial designs, and what are some of the likely early applications of novel statistical computer models?

A: It is still in such early days. I think it really is going to be more of an evolution than a revolution. With that said, there are certain mandates coming from places like the 21st Century Cures Act (pending passage through the Senate) that start an 18-month long clock on pharma/biotech looking at frameworks for reevaluations and label changes using additional RWE and patient-reported outcomes data to support their submissions. But also, the FDA is saying publicly that they are going to be (at some level) expecting either a plan on how life sciences manufacturers propose to leverage post-marketing surveillance, or other evidentiary data to justify their submissions about what the underlying unmet need in the patient population is. That is a potential game-changer. Life science and healthcare companies know that there is so much potential insight locked up in these real-world datasets that is too tantalizing and valuable not to pursue. There is also risk for manufacturers not to be a part of owning the story. For example, some principal investigator, who has run a low power, 30-person trial, publishes the trial, creating a huge risk for the manufacturer. The manufacturer, in turn, has to try to figure out how they can respond, and (instead of spending years running another trial) an observational data set allows them at least a first response to say either, "Wait, we are not able to reproduce the observed effect in a much larger population," or, "There is something here, we have to look into this and consider how best to discuss the new

information with the physicians, regulators, and payers about an appropriate response, maybe even indication/label changes.”

Q: What are the likely first applications of real-world data in research and practice?

A: I think we have already seen some things come out. For managed care, healthcare is in an interesting period right now. There are certain diseases with near-simultaneous launches that are allowing managed care to conduct comparative data analysis where there won't be prospective head-to-head comparative effectiveness research. A managed care company evaluating a manufacturer's new product might say, “Okay, we are willing to give you a chance, and we may even give you a formulary position, but we expect that your drug will perform as promised if we are putting you in a preferred formulary position versus your competitors. We want the best medications for our members.” Manufacturers will have to evaluate pay-for-performance contract approaches more in the United States, and I expect this to continue to gain traction.

Q: With regard to pay for performance, is it a bigger challenge to analyze the data, or is it a bigger challenge to make all of those disparate datasets work together and to organize all of the data?

A: My strong supposition is that if there is going to be a single place where RWE stumbles, it will be on data completeness for now—many medically relevant events happen outside the observation of electronic medical records or claims data: everything from minor injuries to administration of over-the-counter pain medications. Any place where there is a gap, there is an inherent bias in numbers. There are biases from certain types of physicians who are not coding and providing complete information about their patients. These gaps create inherent biases that we cannot completely correct for, statistically. We cannot fully know how that impacts the biases in the datasets. Depending on how we fill in the gaps in the data to generate more complete datasets, then analysis will become the bigger issue—seeing how the signals are changing over time, in real-time. It also becomes a technological issue as we move towards more of the real backbreaker: genomic data. Right now, the standard benchmark for the bigness of big datasets is moving from astronomy to genomics. Every patient having 50 gigabytes of raw sequencing data for their genome is going to be an interesting set of technological challenges, and coming from the world of genetics, I would say we are not that far away from genomics hitting the medical mainstream. The costs have come down enough where it is going to become, not a cost barrier, but a technology and personnel capability bottleneck. There's also a significant statistical challenge. We're finding that the statistical methods traditionally used in the life sciences have been stretched to their limit when dealing with large datasets, and

we're getting extremely low *P* values for effects due to the noise inherent in evidentiary data. This has led to several fields requiring a finding of “significant” on multiple independent data sources prior to proceeding under the assumption that it is an actual significant finding. Because of an accumulation of these effects, we're going to see the need for devoted life sciences analytics platforms emerge over prior, non-standardized ad hoc solutions.

Q: How do you see real-world data changing managed care, the provision of care, and the whole healthcare arena in the next 10 to 15 years?

A: I think we are already seeing some problems emerge, where you hear the medical directors talk about how they have 5 new genetic tests per week coming across their desk. You have a potential of 20-25,000 genes in the human genome, not counting all of the gene isoforms. The amount of information is going to be overwhelming. That amount of information is going to require a much heavier reliance on technology and decision support tools to help them in their evaluation because it is too much for our physicians, our medical directors, and even the scientists who are studying these genes. For instance, there are nearly 2000 articles on a single gene called *MYC* every year; for scientists to stay up-to-date on just 1 gene, they have to spend a couple dozen hours a week just reading the papers that come out that week to stay on top of everything. Multiply that by 20-25,000 potential genes; it is going to require better leveraging of technology to pull out perspective and insight in order to make the best decisions for patients.

Q: What are the most important challenges in leveraging real-world data right now?

A: It comes back to data standardization, and across-the-board standards. We have seen a need for people who are thinking about this as setting up a process that is cross-functionally integrated across multiple independent groups. That means setting up processes and governing councils, and thinking about data analysis in a way that brings together many different stakeholders to come up with a corporate-wide definition of the patient cohort and outcomes of interest. Pick your favorite disease, say type 2 diabetes. How are we, as an organization, going to define this? What labs, diagnoses, drugs, and events we determine means that we, as an organization, trust that a patient in the data actually has this condition, rather than another, similar condition. If a user wants to go into the system and make a tweak for herself to compare a slightly different population, that's fine, but we need to all start from a common ground, so that we are at least working from some universal, institutional truth. Across datasets, it is too easy to get lost, and the provenance of everything the user did must be documented. It is all about transparency and reproducibility. •

Understanding the Role of NOACs in Atrial Fibrillation Treatment: A Q&A Session With Noel Boyle, MD, PhD

At the 2015 National Association of Managed Care Physicians Fall Managed Care Forum, *The American Journal of Managed Care* discussed the era of novel oral anticoagulants (NOACs) with Noel G. Boyle, MD, PhD, professor of medicine at the UCLA Cardiac Arrhythmia Center.

Q: Dr Boyle, what is the history of oral anticoagulants in the treatment of atrial fibrillation?

A: Warfarin has been around since the late 1950s and was used right up until the first NOAC was approved in 2010, as it was the only option. Over the last 5 years, a total of 4 NOACs have been approved. All of these agents are approved by the FDA and shown by major studies published in the *New England Journal of Medicine* to be equivalent or noninferior to warfarin. We now have multiple choices; indeed, it has been described as a new era in anticoagulation for managing patients with atrial fibrillation who are at risk of stroke.

Q: What are the main points about the efficacy and safety of NOACs in reducing the absolute risk of stroke and in comparison with warfarin?

A: The NOACs have turned out to be very safe to date. In the major trials, all have been shown as noninferior to warfarin, and in fact, some of them are actually statistically superior to warfarin in reducing the risk of stroke. Indeed, they have a lower risk of bleeding, and particularly a statistically significant lower risk of intracranial bleeding. Now we have many, many more options to offer the patient. Another particular benefit of these drugs is the very quick onset of action; they are fully effective within about 3 to 5 hours, compared with warfarin, where it can take several days to achieve therapeutic levels. They have an almost 1-dose-fits-all rule, but not quite, as they all need to be adjusted based on the creatinine clearance and some other factors in other patients, but there is minimal dose adjustment to be done compared with warfarin. In addition, these drugs have a safety profile that is certainly equivalent, and maybe even superior to warfarin in terms of bleeding. However, this does not mean that we are or should be ready to discard warfarin. We have 60 years of experience in using this drug. We know it is very effective. It rarely causes serious problems, other than bleeding if it is very supratherapeutic. We have a reversal agent for warfarin—vitamin K—and (except for 1 NOAC, for which a reversal agent was approved in October 2015 by the FDA), there are no reversal agents for the other NOACs at present. Another major factor is the cost of these drugs. In general terms, you can think of 1 month of warfarin as costing the same

as 1 day of a NOAC drug, so that is a huge differential in cost; certainly this a major issue for patients paying out of pocket, although many of the drug companies have discount programs for self-pay patients.

Q: What do the results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study indicate about the use of rate control versus rhythm control and the role of anticoagulation?

A: The AFFIRM study compared a rate control strategy with a rhythm control strategy. The study was published in the *New England Journal of Medicine* in 2002. The basic finding was that there was no difference between the 2 strategies in terms of survival or also in terms of stroke. To understand this, however, you need to look at the data carefully. Many patients assigned to a rhythm control strategy had their anticoagulation stopped if they had electrocardiograms recorded showing sinus rhythm. In the trial there was a trend towards a higher rate of stroke in the rhythm control group, likely because they or their doctors stopped their anticoagulation too early. For patients going for cardioversion, there is a consensus that if it is very clear that a patient's atrial fibrillation has been there for less than 48 hours—and often this is something we can only establish with a very careful history—then you can proceed to anticoagulate the patient and perform cardioversion. If there is any uncertainty about the duration of atrial fibrillation, then the options are to proceed with transesophageal echocardiogram and cardioversion or cardioversion following a month of anticoagulation. We now have data for 2 NOACs showing that it is also safe to cardiovert these patients after a month of use of these particular NOACs.

Q: With regard to guidelines, there is now a statement regarding shared decision-making between the patient and physician in deciding whether to use NOACs. What other fundamentals can you comment about in deciding whether to use a NOAC?

A: I think the key here is that the patients be educated on the benefits and risks of warfarin versus the benefits and risks of the NOACs, and also cost is not a factor that can be ignored. However, warfarin must still be considered as the gold standard. If there is a benefit for the patient in terms of the NOACs, then that should be clearly explained. We provide all of our patients with the American Heart Association patient information sheets on warfarin and the NOACs. I think it's important that we emphasize—except for 1 agent, which has an approved reversal agent—that none

of the other NOACs currently have reversal agents. The convenience of the NOACs, however, remains a very important factor for many patients. I think the fact that they don't need to come in for regular blood tests with the NOACs is a very important factor for many patients. An additional feature that physicians are very aware of is the drug interactions with warfarin. It is very important that physicians be aware that the NOACs also have significant drug interactions, and often that has been minimized in the promotion of these drugs. There are significant drug interactions with either P-glycoprotein and CYP3A4 inhibitors and inducers. For instance, the CYP3A4 inducers, such as rifampicin and anti-epileptic drugs, as well as the CYP3A4 inhibitors such as macrolide antibiotics, antiviral drugs, antifungal drugs, and antiarrhythmic drugs, all have major drug interactions with the NOACs.

Q: What are some of the differences between pivotal trials in terms of the kind of bleeds that occurred predominantly and the comparative bleed rates versus warfarin?

A: All of these trials actually showed lower bleed rates than warfarin, both for major bleeding and particularly for intracranial hemorrhage. All NOACs had a statistically significant reduction in intracranial hemorrhage. That has been the major fear factor of physicians for decades in use of warfarin—the risk of intracranial hemorrhage. It is very reassuring to see that all of these drugs had lower risk of major hemorrhage and equivalent or lower risk of major bleeding when compared with warfarin.

Q: What do you see as the future of NOACs and their expansion into treatment of other major conditions in which patients are currently only eligible for warfarin therapy?

A: I think the major advantage of these drugs for the patients is that they do not require testing, and that they have fewer interactions than warfarin. A major advantage for the doctors is how quickly these agents are effective. Once you give a dose of these drugs, anticoagulation is effective within 3 to 5 hours versus 3 to 5 days with warfarin. It may certainly facilitate early discharge in many patients, compared with having to wait for a therapeutic international normalized ratio (INR). There is no doubt that many patients prefer these drugs because of these issues, and that hopefully would tend to increase the compliance with these drugs. Of course, the concern is that we still don't have any qualitative measure of the efficacy of these drugs. We usually can't be certain that the patient has been taking them because we don't have an equivalent test to the INR that is reliable for these drugs. So, for example, for a patient coming in for cardioversion who has been taking a NOAC, we really have to rely on a very, very convincing history of patient compliance to feel safe and confident in proceeding with cardioversion.

Q: What are some important points to remember about the safety of NOACs?

A: It is important to remember that while these drugs have significant numbers in clinical trials of 15,000 to 20,000 individuals, when these drugs go into mass usage as oral anticoagulants, they are going to be used by millions of patients. There is always the potential for unforeseen side effects over time. In the trials, patients were followed for 2 to 3 years, but for most patients with atrial fibrillation, these are going to be lifetime drugs—they may be taking these drugs for decades. Postmarketing monitoring is going to be very important for all of these drugs so that we keep a close watch for any unanticipated effects or other potential side effects that could be serious over time. ●

Evolving Treatment for Chemotherapy-Induced Nausea and Vomiting: A Q&A Session With Susan Urba, MD

The *American Journal of Managed Care* interviewed Susan Urba, MD, professor of internal medicine in the Division of Hematology and Oncology at the University of Michigan and a member of the National Comprehensive Cancer Network (NCCN) Antiemetic Guideline Committee. Dr Urba also directs the Symptom Management and Supportive Care Program at the University of Michigan.

Q: What kind of methods do you use to determine which patients are candidates for aprepitant and some of the other high-cost medications in controlling chemotherapy-induced nausea and vomiting (CINV)?

A: Up until now, we have not had any choice because the main recommendations have been, for a long time, serotonin antagonists, a neurokinin-1 (NK-1) receptor antagonist, and dexamethasone. So, we have not had too many choices at all in the category of NK-1 receptor antagonists. Now we have a new option, rolapitant, as well as a new combination product that involves a new treatment called NEPA (netupitant and palonosetron), and now olanzapine also, which has just been added to the guidelines. Rolapitant has not yet been approved, although it is going to be released within the next few days. Over the coming year or two, we will see if we find benefits to one more than the other. However, as far as we can tell, the treatments certainly seem relatively equal.

So, right now, treatment choice will probably be cost driven, as far as which option we choose.

Q: What is the role of atypical antipsychotics in the management of CINV?

A: Regarding the use of atypical antipsychotics for nausea and vomiting, the main one that has been tested is olanzapine. It has been tested in a situation in which it was compared with aprepitant, which is one of the NK-1 receptor antagonists, and results showed that it was equally effective in complete response for controlling nausea and vomiting, meaning no vomiting and no use of rescue medication. It was about the same as aprepitant, but it was better at controlling long-term nausea—days 3 through 5 after chemotherapy. It was seen that control of nausea in that period was actually better than the aprepitant, so since that time, the NCCN Antiemetic Guideline Committee has added the use of olanzapine, in combination with two other medications that it was tested with, for reasonable control for the highly emetogenic chemotherapy.

Q: How has the emergence of targeted therapies changed the need for CINV treatment, given that more emetogenic regimens that include traditional drugs, such as the platinating agents, are in some cases being replaced by targeted treatments?

A: I think, in general, the chemotherapy agents have tended to be more emetogenic than the targeted agents. The targeted agents range anywhere from pretty well tolerated to having the possibility of lots of side effects, but it is not always nausea and vomiting. Some of them are inflammatory issues, and you have to watch labs carefully, but I wouldn't say that the targeted agents have particularly increased our need for antiemetics. In fact, some of the targeted agents fall within the low to moderate emetogenicity category.

Q: What are some of the ways that you prevent CINV?

A: It is all about prevention. When you write for chemotherapy, you always need to write for an anti-nausea recommendation. There are 3 main drugs from the antiemetic groups. The antiemetic therapy must be given on the day of therapy, and typically medications are administered 2, 3, and 4 days after the chemotherapy.

Q: How is olanzapine in the prevention of CINV affecting prescribing of the NK-1 antagonists?

A: So far, the news is relatively late breaking, and olanzapine has relatively recently been added to the guidelines. I don't think too many people have used it yet as primary prevention, other than if they were participating in the studies that would have generated

this recommendation. I think up to now, it has been used more as a rescue agent, where if patients were given other preventive medications and then did not do very well, then they would be given olanzapine as one of the possible rescue agents. So I think in the next year or two, we are going to see more people using it upfront for prevention.

Q: What are some of the possible benefits of rolapitant over aprepitant?

A: That will also be determined in the future because they have not been compared in a head-to-head trial of rolapitant versus aprepitant, so we are sort of extrapolating from the various studies that were done. What we can notice is that rolapitant is a very long-acting agent and it binds very strongly to its receptors. It does not interfere with or is not metabolized along the particular pathway that aprepitant is, and therefore there might be the possibility of less drug interactions. I think as time goes on, we are going to have to really ask ourselves that question. We have not had the chance to yet because we have not had access to it, but those are some of the potential ways. And then, of course, cost will have to factor in here, but I imagine the company will try to be as competitive as possible.

Q: Are there any basic pharmacology data that you are aware of in receptor binding or design of rolapitant that might suggest it could have an advantage over the existing agent, aprepitant?

A: I think it does not interact with the CYP3A4 pathway as much as aprepitant does—that is where some of the interactions that we have to look for with aprepitant may be less of an issue with rolapitant. Having said that, I don't think of aprepitant as being a very difficult drug to use. I don't think of a lot of different drugs that it would interact with—maybe just a few, so that difference may not be very substantial in practice.

Q: On the contentious issue of medical cannabis, does that have a role in the treatment of CINV?

A: It is not part of any guidelines for prevention or necessary rescue. Marinol (dronabinol) is part of the rescue on the list of drugs, however. If the patient is having severe breakthrough nausea and vomiting, that is one to try. Marinol does contain one of the active agents of cannabis, so that is about as close as it is going to come to being in guidelines. Having said that, are there occasional patients who have resistant nausea and vomiting who may end up on medical cannabis? Yes, but they really need to be very carefully screened.

Q: Regarding coverage issues with the long-acting serotonin antagonists, has there been any role for the shorter-acting serotonin antagonists like ondansetron, with several daily doses as an off-label use in patients who do not have coverage for some of the longer-acting serotonin antagonists?

A: I have not found that the insurance companies will cover one versus another in that group. The ones they seem to be resistant to are the transdermal treatments. Granisetron comes in a transdermal patch and that is more expensive. Sometimes when I have tried to prescribe it, they have said, “No, the patient must first show that they have failed a good attempt at using oral ondansetron or granisetron.” I think the transdermal systems are the more expensive ones that they balk at. I know that at my university, I have been allowed to prescribe any of the serotonin antagonists, but it is with preference. I think usually one of the pharmaceutical companies will negotiate with the pharmacy to try to have a high-volume discount, so if we all use one rather than another, perhaps we can get a better price for that hospital—and we are all

about saving money. But if for another reason I really thought that one antiemetic was better than another, typically the hospital will let me use it, at least for those drugs that are on formulary.

Q: How do you see treatment of CINV changing in the future?

A: I think we continue to look at guidelines. I think we continue to encourage people to use them. We are always looking at this big issue of cost, which is getting worse and worse, so I am not surprised that the approach with olanzapine was used—trying to find a less expensive drug. Some studies have been done looking at metoclopramide to see if that could be substituted for other things, so I think one of the things in the future is really looking at cost containment. And, for the day 2, 3, and 4 when we have typically used serotonin antagonists, there was a meta-analysis that showed that for some patients, dexamethasone alone may be enough. If we are aware of that and just prescribing enough therapy to get good treatment to the patient, but not to have the cost too high, that is where we have to look. •

Managing the Costs of Care in Oncology: Results of the *Genentech Oncology Trend Report*

Several trends, including mergers and acquisitions, increasing out-of-pocket costs, decreasing reimbursement, and next-generation tests, challenge stakeholders in the oncology marketplace.

At the 2015 National Association of Managed Care Physicians Fall Forum, Dale Evans, MD, director of medical affairs and payer support for Genentech, discussed the highlights of the latest *Genentech Oncology Trend Report*. Each year, this trend report incorporates perspectives from various stakeholders in the oncology field, including managed care professionals, specialty pharmacies, oncology practice managers, oncologists, and employers. Genentech has been publishing the *Genentech Oncology Trend Report* for the past 7 years, over which time Dr Evans has managed the development of the report in cooperation with a third-party communications firm, Emron.

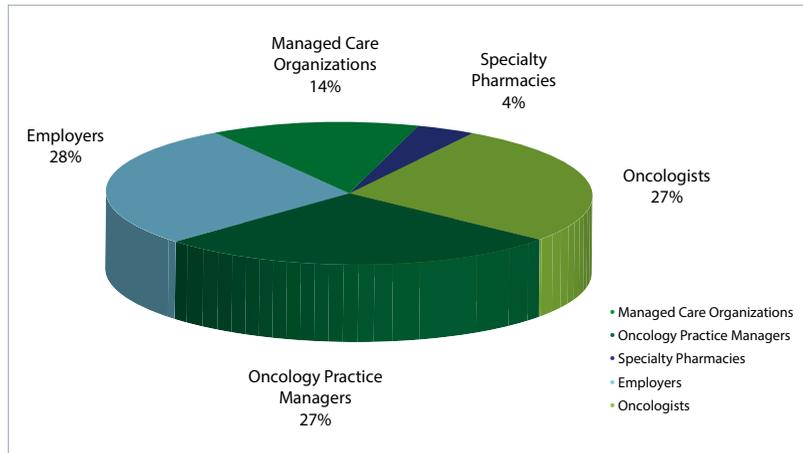
Each year, Emron develops the survey with help from an editorial board of oncology leaders. Because the report is developed by an outside consultant by surveying a sample of professionals, the opinions contained in the report do not necessarily reflect those of Genentech. The report includes opinions obtained from 5 different types of stakeholders: managed care organizations (MCOs), specialty pharmacies, oncologists, oncology practice managers, and self-insured employers. These stakeholders are recruited through the Internet; results were obtained in 2014 from May to September.

Survey Participants

Most of the 105 MCO stakeholders who participated in the survey were regional or state organizations. Average MCO membership was 2.3 million covered lives under the medical benefit and 1.6 million covered lives under pharmacy benefits. Among the 30 surveyed specialty pharmacy stakeholders were 13 pharmacy benefits managers, 8 independent specialty pharmacies, and 9 others. Survey results included the opinions of 200 oncologists, with community practice oncologists accounting for almost half of the group (49%). Academic oncologists accounted for 30% of oncologist participants, and the remaining surveyed oncologists were hospital-based physicians. All 201 surveyed employer organizations were self-insured entities that make benefits determinations and establish and pay for their own claims (**Figure 1**).

Genentech designed the 2015 report to follow several marketplace trends, including adoption of guideline- and pathway-based care; management of cancer drug cost, revenue, coverage, and access; practice consolidation, workload, and staffing; palliative and advanced care planning; pharmacogenomics; population health management; and health information technology (HIT). With the growth of smartphone-based mobile health applications, HIT has grown to encompass trends in mobile technologies as they relate to health management.

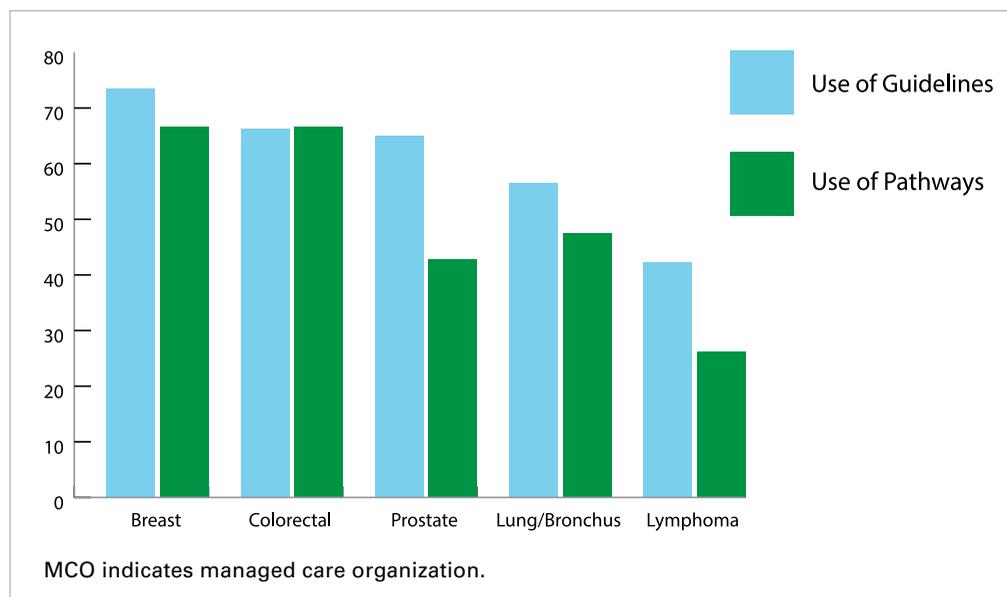
Figure 1. Stakeholders Surveyed



Guidelines, Pathways, and Patient-Centered Medical Homes

In response to a question about the 3 most pressing challenges facing MCOs today in oncology management, MCO respondents identified balancing treatment standardization with personalization, advanced care planning, and developing equitable provider payment alternatives to fee-for-service. Treatment standardization encompasses guidelines and care pathways, and, indeed, MCOs are using guidelines and pathways of care to manage oncology treatment at an increasing rate. For example, the use of pathway-based care grew from 31% of plans in 2013 to 40% in 2014. Most often, guidelines and pathways focus on the most common cancers, including breast cancer, colorectal cancer, prostate cancer, lung and bronchus cancer, and lymphomas (Figure 2). Guidelines and pathways are more commonly adopted in these con-

Figure 2. Use of Guideline- and Pathway-Based Care by MCOs



ditions than in other less common oncologic conditions.

Guidelines are more generalized than treatment pathways; thus, guidelines are more often used than pathways—although use of both types of standardization methods is growing with time. Despite the growing reach of guideline- and pathway-based care, according to Dr Evans, full adoption has not yet occurred because “as physicians, we usually practice what we learn in medical school until we retire.” Oncologists report using guidelines in about two-thirds (65%) of cases and pathways in half of cases. In order of preference, oncologists use guidelines developed by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and internally by their specific institutions. Hospitals and cancer centers are the most likely organizations to use internally developed guidelines.

Of the MCOs that pay for physician consultations, payments may be in the form of individual bonuses or physician bonus payments. Of payer-provider initiatives in 2014, one of the most common initiatives was measurement of the cost effects of treatment pathways on care, followed by investigation of patient-centered medical homes (PCMHs) across the provider network. Third, MCOs made a priority of measuring the clinical impact of treatment pathways on patient care and health outcomes. Pathways are an important trend in oncology care and a critical component of collaboration between MCOs and provider networks.

Beyond treatment standardization, broader adoption of the PCMH model of care is another key trend in the oncology landscape. MCOs report that the most common type of PCMH is organized around the care of a primary care physician. Oncology medical homes, in which care is organized around the oncology specialist, account for a smaller proportion of PCMHs.

Managing Oncologic Drug Costs

Cancer drug management is another key trend in cancer care that Genentech tracks in its

Managing Oncologic Drug Costs

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Continued on page 11

annual report. According to the 2015 publication, 12% to 13% of MCOs reimburse providers through global payments, risk sharing, or value-based/quality initiatives. These new provider payment models are poised to grow in coming years; more than one-third of MCOs are currently investigating new payment options and 7% to 20% of plans are undertaking pilot programs for the various payment models.

Drug acquisition processes in oncology care vary across providers. Community-based oncology practices predominantly cling to the traditional “buy-and-bill” model, in which the practice purchases medication from a distributor and bills patients for the medications under a medical benefit. Conversely, a small but growing proportion of community-based practices (13%) obtains medications through specialty pharmacies.

Nearly two-thirds (62%) of oncology practice managers expected growth in the cost of oncologic therapies between 2013 and 2014; 18% did not expect any increase or decrease in drug-related costs, and 15% projected a decrease in costs related to oncologic pharmacotherapy. Of the managers who expected a decline in drug-related costs, common reasons cited for the projected cost drop included lower patient volume, a greater proportion of commercially insured patients, more treatments sourced through hospitals, more white bagging and reliance on specialty pharmacies, direct contracting of payers with infusion centers, payer restrictions on renegotiation of purchase contracts, and practice reorganization.

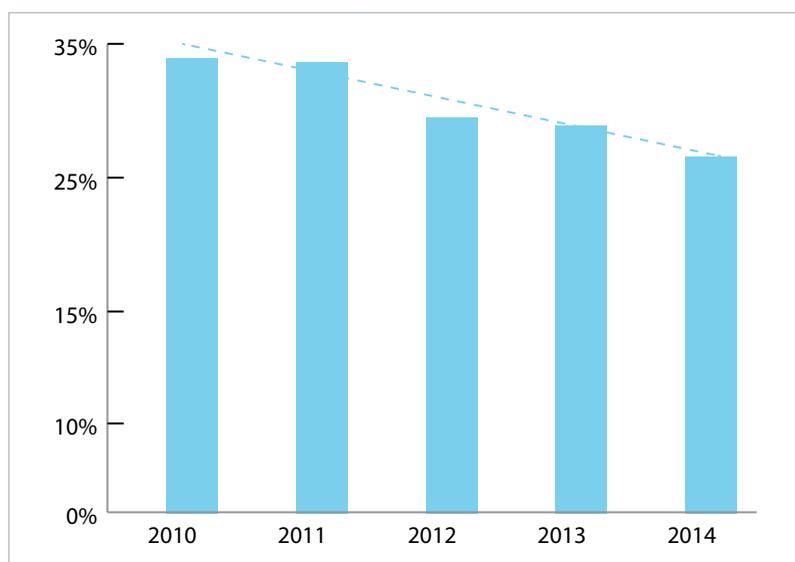
Declining Margins on Oncologic Drugs

Concurrent with the projected rise in the cost of oncology drugs, approximately half (49%) of oncology practice managers reported a decrease in drug margins, with just over 1 in 4 managers (27%) reporting the decreases over the prior year as slight. Tracked over multiple years, however, the trend toward falling drug margins has continued year after year since the Genentech oncology survey began tracking this metric. To manage this threat to revenue, oncology practice managers report using several strategies, including maximizing the value of group purchasing organization contracts (often through affiliated hospital systems), reducing drug waste, introducing a robust precertification/predetermination process, and finding the most inexpensive drug sources. In addition, oncologists will often attempt to reduce the cost of existing medications by enrolling patients in clinical trials whenever possible.

Rising Out-of-Pocket Costs

As the margins on dispensing and providing oncologic agents have fallen, the out-of-pocket (OOP) costs to patients have escalated. Specialty pharmacies, office practice managers, oncologists,

Figure 3. Percentage of Patients Able to Pay All Out-of-Pocket Costs for Oncologic Therapy Over Time



and employers all rated increasing OOP costs as 1 of the 3 most pressing challenges in the provision of oncology care in 2014, with specialty pharmacies, office practice managers, and oncologists all rating OOP costs as the most pressing issue. In fact, the only group for whom rising OOP costs was not among the top 3 most pressing challenges was MCOs.

The Affordable Care Act (ACA) has substantially changed the type of insurance that oncology patients have. In the roughly 18 months since its implementation, more than two-thirds (70%) of office practice managers have seen an increase in the proportion of patients with high-deductible commercial plans. In fact, Genentech itself was affected by this shift. Dr Evans noted, “Genentech went to a higher deductible plan last year. We have had that experience directly.”

In addition to the growth in high-deductible insurance plans, even in the era of the ACA, some patients remains without insurance. A substantial proportion (43%) of oncology practice managers reported difficulties in verifying insurance benefits for patients, which may be related to the complexity and variety of plans available under the ACA. The lag time between plan enrollment and a patient’s visit to the provider has been an issue with benefits verification.

Over the last 5 years, the Genentech trend report has tracked the percentage of patients who could pay their OOP costs, as reported by oncology practice managers. With rising OOP costs, the percentage of patients who could pay all OOP expenses has fallen from 34% in 2010 to 30% in 2014 (Figure 3).

“This is part of reimbursement uncertainty for oncology practices,” explained Dr Evans. To help manage this trend, oncology practices are making private arrangements and setting up payment plans with patients, billing patients and requiring full payment

before ordering the next cycle of drug therapy, and enrolling patients in drug manufacturer rebate programs. Although these rebate programs are available, only slightly more than half (56%) of patients meet the requirements for reimbursement under manufacturer programs.

Supply Issues in Oncology Therapy

Drug shortages remained an important issue in 2014. Almost one-third (32%) of oncologists noted an increase in drug shortages during 2014 and reported an economic impact of those drug shortages on oncology practices. Close to half of oncologists (45%) believed drug shortages led to detrimental clinical effects on patient care, specifically in relation to unavailability of older generic drugs and infused medications.

Oncologists are coping with drug shortages mainly by changing the standard of care. This was the strategy employed in more than two-thirds (68%) of cases. Alternatively, oncologists reported switching from an oral drug to alternatives (if available), delaying the start of treatment, temporarily suspending chemotherapeutic treatment regimens, checking on the availability of specific drugs before developing treatment plans, borrowing from or lending drugs to hospitals, sequestering drugs for specific patients, and sequestering supplies of generic drugs vulnerable to product shortages.

Mergers and Acquisitions

One of the most dominant trends in oncology business management is broad-scale mergers of oncology practices. According to Dr Evans, “Whether community-based, hospital-based, or academic- or medical center-based, a large percentage of all of these practice types are considering joining or combining with another practice, integrating with or entering into a joint venture with a hospital, or selling their practice to a hospital.” This trend points to a future marked with “upheaval and reorganization in the oncology practice area for a long time to come.”

Predominant reasons for mergers and reorganizations, as reported by oncology practice managers, included improving oncologist productivity and withstanding the implications of healthcare reform. MCOs are managing the shift from community-based to hospital-based oncology care in a variety of ways. Within hospital systems, MCOs are setting up utilization management review requirements, including prior authorization and precertification rules; moving infusion services to 340B payments (in hopes that hospitals will pass the savings along to MCOs); and promoting community hospital settings where appropriate. MCOs are also attempting to improve reimbursement for oncology practices in a number of ways by providing recommendations for oncologists to find the most cost-effective site of care, entering risk-sharing arrangements with providers, and trying to create member awareness through case management.

Oncology Care Workload and Staffing

Regarding oncology care workloads, Dr Evans said, “Every year, oncologists say they are working harder and it is more difficult. However, looking at hours worked, the number of hours has not changed.” The increased workload on oncologists comes from another area: increasing demand for continuous patient communication through e-mail, phone, and electronic media. Other new demands on community practices include quality reporting requirements and increased documentation using electronic health records (EHRs).

Although these EHR systems have been touted as sources of increased efficiency, Dr Evans noted, “Electronic health record implementation challenges are substantial.” The net result is increased hiring of staff, including nurses, pharmacists, advanced practice providers, medical assistants, and medical scribes. In addition, practices are cross-training staff to serve in more roles, adjusting practice hours, and scheduling more time for patient visits. “They hope to gain efficiencies from full implementation of electronic health record systems,” concluded Dr Evans.

Palliative Care and Advanced Care Planning

In the area of advanced care planning, little has changed over time, unfortunately. The percentage of oncologists discussing advanced care planning with all patients, regardless of the stage of cancer, remains at just 28% of oncologists, with 44% discussing advanced care planning only with patients with advanced disease or short life expectancy and 20% discussing end-of-life issues only with patients with metastatic disease. “Of course,” explained Dr Evans, “all oncologists should be discussing advanced care planning for all of their patients. The needle has moved very little on this.”

The top MCO initiatives for palliative care and advanced care planning include creation of new palliative care benefits and palliative care teams. MCOs are beginning to expand payments to hospitals for the development of survivorship care plans. Of the 200 oncologists surveyed, 4 in 10 are creating survivorship care plans for at least some of their patients and nearly 1 in 4 (23%) create a plan for all of their patients with cancer.

Common templates for survivorship care plans include those developed by ASCO (40%), followed closely by those developed through NCCN (38%), with a minority of providers basing care plans on recommendations developed by the American Cancer Society (22%) or through independently developed institution-specific templates (21%).

Managing the Cost of a Growing Range of Next-Generation Tests

MCOs are struggling to manage payments for a broad and expanding array of molecular and biomarker tests. Part of the reason for these difficulties is attributable to the traditional model of oncologic care, in which MCOs did not manage lab tests at all. Almost 1 in 4 plans (24%) have already developed review protocols

for new molecular and biomarker tests, whereas more than one-third (34%) of plans are developing strategies to develop and manage testing platforms and laboratories.

Currently, 27% of plans require prior authorizations for biomarker testing, 22% restrict drug costs by limiting treatment to patients with favorable laboratory results, and 21% restrict testing coverage based on evidence. As precision medicine grows, two-thirds of oncologists report an increase in referrals of patients for molecular and biomarker testing and more than half (52%) of oncologists refer patients for genetic counseling on a regular basis. Whole genome sequencing remains less common, with only 1 in 4 oncologists referring patients for these more comprehensive tests. Although most (65%) of these tests are currently administered through payer-approved commercial laboratories, a growing range of precision medicine tests are performed within oncology practices as desktop machines become more widely available. Almost 1 in 4 (24%) oncologists report having some type of in-practice laboratory.

Regarding the cost-effectiveness benefits of molecular testing and biomarker testing on treatment decisions, most (70%) oncologists rate the benefits of these tests as moderate to significant, while whole-genome sequencing is rated as slightly less beneficial: approximately one-third of oncologists rates these tests as providing moderate to significant cost-effectiveness on treatment decisions.

Employer Health Initiatives

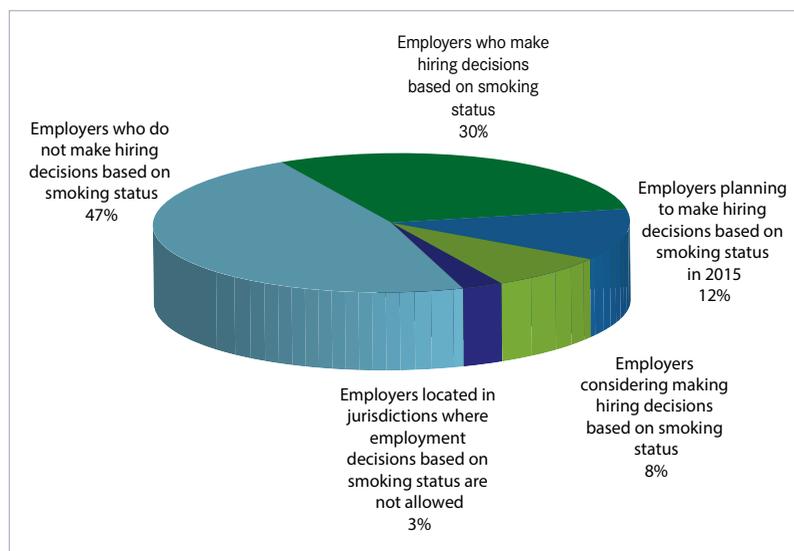
Employers are increasingly attempting to control the costs of care and the impacts of those costs on their businesses by providing health risk assessments and incentives for lifestyle changes in employees. About half (49%) of employers offered health risk assessments and lifestyle change programs in 2012; now, more than two-thirds (67%) offer such programs. Monetary incentives for participation in these employer-based lifestyle improvement programs are offered by more than three-fourths (76%) of employers who have health risk/well-being assessments.

Smoking cessation is another important part of employer-initiated lifestyle health improvement programs. Two-thirds of employer-based insurers offered incentives for smoking cessation in the 2014 survey, and where it is not prohibited by law, almost one-third of employers screened prospective recruits for tobacco use as part of hiring decisions (Figure 4).

Novel Digital Approaches

EHRs and mobile health applications are an important and growing trend in oncology management. More than three-fourths (76%) of oncology practice managers had EHR systems

Figure 4. How Smoking Status Affects Hiring Decisions for Employer-Based Healthcare Plans



in place in 2014, and mobile health applications were offered by over half of MCOs. Currently, these applications are used for finding a physician or a pharmacy. Alternative patient visits through telehealth consults are covered by relatively few (10%-11%) MCOs, although this consultation service is poised for growth.

Key Trends

Important trends in oncology for 2015 include increased OOP costs for patients, lower reimbursements, and a growing movement toward standardization of care through guidelines and clinical pathways. Oncologists face many challenges in caring for patients: growing demands on their time through increased expectations on communication, drug shortages, and financial uncertainty. A growing number of practices are merging to help negotiate more favorable terms with manufacturers and MCOs. Although most of these trends in oncology practice place more restrictions on the practice of oncology, stakeholders hope to realize efficiencies through effective use of technology to minimize costs and maximize the quality of care for the patients they serve. ●

Reference

Genentech. *Genentech Oncology Trend Report: Perspectives From Managed Care, Specialty Pharmacies, Oncologists, Practice Managers, and Employers*. 7th ed. South San Francisco, CA: Genentech; 2015. <http://www.genentech-forum.com/annual-genentech-oncology-trend-report>. Accessed November 23, 2015.

Opportunities for Improving VTE Management Through Guideline-Based Care

Through appropriate use of risk-scoring algorithms and by standardizing diagnosis and treatment, managed care professionals can improve outcomes in the management of venous thromboembolism (VTE).

Optimizing the management of VTE is an important priority for managed care plans in an era of greater cost containment. In a presentation at the National Association of Managed Care Physicians meeting, Darrell W. Harrington, MD, FACP, professor of medicine at the David Geffen School of Medicine, University of California, Los Angeles, discussed current and novel management strategies in the prevention and management of VTE events. Dr Harrington focused on updated evidence-based strategies, translation of evidence-based strategies into clinical practice, appropriate use of diagnostic strategies for VTE management, and opportunities for improving diagnostic strategies, including realizing efficiencies in diagnosis.

VTE is fundamentally a continuum of thrombotic processes that range from deep vein thrombosis (DVT) to pulmonary embolism (PE) and its sequelae. The thrombotic process may begin in any extremity of the upper or lower limbs, or even the brain. From these sites, clots may migrate to the pulmonary vasculature, resulting in a PE. Like cancer and atrial fibrillation, the incidence and prevalence of VTE is expected to rise over the coming decade¹⁻⁷ (Figure^{5,6}).

Much of this growth in VTE relates to environmental factors, such as increased prevalence of obesity. Currently, approximately 1 million VTE events occur in the United States each year. Of the 1 million cases of VTE, most are DVTs. However, DVTs are not benign and are associated with a substantial increased risk of

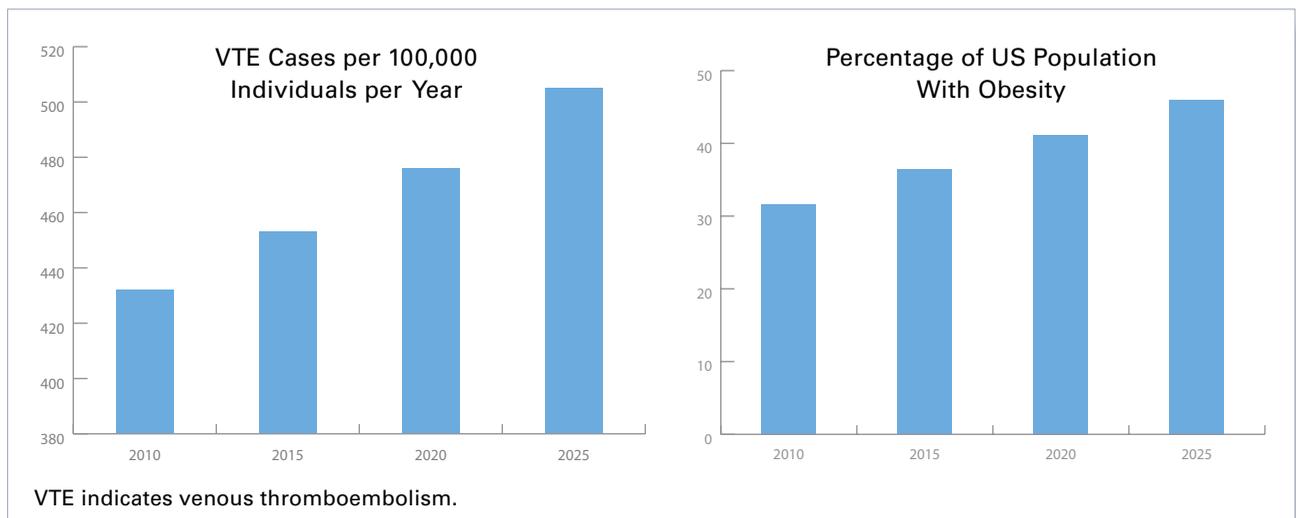
mortality. In fact, 6% of patients with a DVT will die within 1 month of diagnosis, and 12% of patients will develop a PE over the same timeframe.¹⁻⁶

In addition to increasing the risk of mortality, VTE is a chronic, recurring disease state. Regarding this long-term risk, Dr Harrington noted, “Whether a patient is followed for 2 years or 10 years, up to one-third of patients will have a recurrence of VTE.” VTE prophylaxis remains underused in the United States, and adherence to evidence-based practice guidelines is poor. An estimated 40% to 55% of orthopedic surgeons, and 50% to 60% of internists and hospital physicians are nonadherent to evidence-based VTE prophylaxis guidelines.^{5,8-10}

The multinational ENDORSE study was a cross-sectional worldwide study to estimate VTE prophylaxis rates internationally. Researchers examined patients in medical and surgical settings and determined whether patients were eligible for VTE prophylaxis based on 8th American College of Chest Physicians (ACCP) guidelines. More than half (52%) of hospitalized patients were at risk for VTE, and surgical patients were at even greater risk, with nearly two-thirds (64%) of these patients at high risk for a thromboembolic event.¹¹

Researchers determined whether patients had clear indications for VTE prophylaxis based only on IA or IB recommendations. In other words, Dr Harrington noted, this was a clear case of “I will sue you if you don’t do this’ guideline recommendations.” More than half of patients (59%) in surgical settings, and well over one-third (40%) of patients in medical settings did not receive VTE prophylaxis. “This is probably the biggest opportunity for improving outcomes in patients,” concluded Dr Harrington.¹¹

Figure. Projected VTE and Obesity Rates Through 2015^{5,6}



Aspirin Inappropriate for VTE Prophylaxis in the Joint Replacement Setting

According to Dr Harrington, the most important change in recommendations between the 8th and 9th versions of the VTE guidelines was the addition of a strong recommendation against the use of aspirin. The reason for this change was a closer look at the data in an important trial known by the acronym PEP, or Pulmonary Embolism Prevention trial. This study of approximately 17,000 patients was initially misinterpreted by the authors of the 8th ACCP guidelines because they hadn't yet read the full trial.¹²

Although results in the pooled analysis of the PEP trial indicated a benefit for the use of aspirin for VTE prophylaxis, this benefit was completely driven by events prevented in patients who had experienced hip fractures, which accounted for only about 4000 patients in the study. For the remaining patients, aspirin had no benefit. "There was zero benefit for aspirin versus placebo," stated Dr Harrington. "There is no effect on total VTE events and no effect on total mortality rates or on fatal mortality rates in patients undergoing elective joint replacement."¹²

By the release of the 9th ACCP guidelines, authors had recognized their erroneous interpretation of the PEP study and changed a strong recommendation for the use of aspirin to a strong recommendation against the use of aspirin as VTE prophylaxis. According to Dr Harrington, "Aspirin could be somewhere in the guidelines, but it should not be an option alongside other main-line evidence-based strategies."^{3,4}

Classifying Patients at High Risk for VTE

Another important part of appropriate VTE prophylaxis is the selection of patients using evidence-based risk-scoring algorithms. Several algorithms are commonly used, including the PADUA and CAPRINI scores. The PADUA score may be the most appropriate scoring system for identification of patients at high risk of VTE because it has been shown to classify approximately 40% of patients in a typical hospital setting at high risk—roughly the same proportion of patients who were at high risk of VTE in the ENDORSE study and other large randomized controlled trials.^{11,13}

According to Dr Harrington, for most medical centers, approximately 40% of patients have a high risk of VTE. "Unless you practice at a center with a high burden of severe illness, if 80% to 90% of patients at your center are receiving VTE prophylaxis, it is likely that too many patients at your center are receiving VTE prophylaxis."¹¹

Choice of Anticoagulant Therapy

According to Dr Harrington, "There are very few absolute contraindications to VTE prophylaxis, with one being a history of a true anaphylactic reaction to anticoagulant treatment, active bleeding, or having received thrombolytic therapy within the prior 24 hours. Other potential interactions may be regarded as precautions."^{3,4}

The choice between low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) has been the subject of heated controversy in cardiovascular medicine. Less nursing time is required to administer once- or twice-daily LMWH versus the 3-times-daily UFH, but, Dr Harrington noted, "There is not a lot of data to show superiority of LMWH over UFH."^{3,4}

There are no strong recommendations in medically ill populations for continuing prophylaxis once patients leave the hospital, with the possible exception of patients at very high risk of VTE events, especially patients with cancer.^{3,4}

The most important change in recommendations between the 8th and 9th versions of the VTE guidelines was the addition of a strong recommendation against the use of aspirin.

The Role of Graduated Compression Stockings and Mechanical Devices

In a class 2C recommendation (a weak recommendation with moderate-quality evidence), the current ACCP guidelines do recommend the use of mechanical thromboprophylaxis with graduated compression stockings or pneumatic compression devices for acutely ill, hospitalized medical patients at risk of thrombosis who are currently bleeding or are at high risk for major bleeding. It is important not to extrapolate this recommendation to patients who are not at high risk for major bleeding and patients who are not currently bleeding. In many cases, the harm of using mechanical VTE prevention alone likely outweighs the benefits.³

With respect to the use of graduated compression devices for prophylaxis of VTE, Dr Harrington advises against them because of data from a trial showing not only that these mechanical devices do not work in preventing VTE events, but also, that they cause harm in the form of an approximately 5% risk of skin injury. Dr Harrington recommends against the use of mechanical devices as monotherapy. "Use of any of these mechanical devices for VTE prophylaxis is not data driven and may cause harm."¹⁴

Estimating Bleeding Risk and Knowing When to Use Advanced Testing

Just as patients may be classified according to their risk of VTE, other risk-scoring tools are available to estimate the risk of bleeding in patients who are potential candidates for anticoagulant therapy. These risk-scoring methods are important for responsible use of pharmacotherapy when balancing the risk of an intervention with the benefits of therapy for a given patient.³

Electronic health record (EHR) systems are critical in the process of standardizing treatments and using risk-scoring algo-

gorithms appropriately as part of an overall clinical decision-making process. However, these algorithms are not perfect. Risk-scoring algorithms should be used in combination with what is known about the patient's pretest probability of developing a VTE event. Researchers have studied the reliability of risk-scoring algorithms using computed tomography angiography (CTA) and other methods.³

In patients who have a low probability of developing a VTE before a test, the negative predictive value of risk-scoring algorithms is excellent, with a 96% to 97% chance of confirming that a patient does not have a VTE. However, in patients with a high pretest probability of having a VTE, the reliability of risk-scoring algorithms falls dramatically. In these patients, risk-scoring algorithms miss VTEs in 40% of patients. Consideration of pretest probability is crucial to accurate diagnosis.^{3,15}

A useful strategy for saving costs and reducing unnecessary testing in patients with VTE is appropriate use of the D-dimer test. If CTA is necessary in a patient, a D-dimer test is warranted. If the test result is negative for D-dimer, VTE can be ruled out, and the patient is spared invasive and expensive testing with CTA. If managed care companies were to incorporate D-dimer testing before CTA, it would not only save costs but also eliminate the need for invasive testing in many patients. Encouraging D-dimer testing before CTA is an important consideration for any managed care organization or hospital system hoping to improve the quality of VTE care.^{3,15}

PEs: When to Treat, Where, and for How Long

Another important consideration in the treatment of DVT is the timeframe of the event. In patients with a high likelihood of having a PE, starting anticoagulant therapy early—in some cases, even in the absence of a definitive PE diagnosis—can help prevent morbidity and mortality. In fact, noted Dr Harrington, “If, in these patients, anticoagulant therapy is initiated within 3 hours, you can actually prevent death.” In the treatment of patients with a suspected PE, guidelines continue to recommend against using thrombolytic therapy, except in cases of hemodynamic instability or an iliofemoral clot.³

In selecting patients who are candidates for home therapy, the HESTIA criteria are a set of 11 risk factors, the presence of any one of which renders a patient ineligible for home treatment. “If you have any of the 11 criteria, you go to the hospital,” stated Dr Harrington. By applying HESTIA and other risk-scoring algorithms, it may be possible to increase the percentage of patients receiving outpatient PE management.^{3,16}

For virtually all patients, 3 months of therapy is an appropriate duration of outpatient thromboprophylaxis. In some situations, such as thrombophilia or malignancy, longer treatment durations are more appropriate.³

Novel Agents

Discussing novel oral anticoagulants (NOACs), Dr Harrington advised against thinking of these agents as a monolithic group. “When people hear about how these drugs work, they want to put all of the drugs into the same class,” he said. “In fact, these drugs have very specific FDA approvals and are not interchangeable.”¹⁷

NOACs are a major advance in the management of VTE, with predictable pharmacokinetic and pharmacodynamic characteristics, and multiple phase 3 trials show lower rates of bleeding with NOACs than with warfarin. Standardizing the management of VTE is a key area in which managed care can make a difference for patients, reducing VTE-related morbidity and mortality, improving patient outcomes, and simultaneously reducing the costs of care.¹⁷

Take-Away Points

The management of VTE relies on several fundamental approaches that may improve care while simultaneously reducing cost. These simple but important changes to processes include:

- Requiring VTE risk assessment using the CAPRINI score (or another algorithm); preferably with documentation integrated into EHRs
- Requiring D-dimer testing before physicians resort to CTA. A negative D-dimer test will eliminate the need for CTA, reducing cost and the risks of unnecessary CTA testing
- Notifying physicians that aspirin alone for VTE prophylaxis should not be used in patients undergoing hip or knee replacement
- Avoiding use of mechanical devices for VTE prophylaxis in the absence of anticoagulant therapy
- Avoiding use of thrombolytic drugs for treatment of a PE
- Standardizing posttreatment outpatient VTE prophylaxis for the vast majority of patients to a duration of 3 months

By implementing these changes, managed care organizations can help standardize the treatment of VTE. Through a standardized VTE management protocol, healthcare professionals may more easily identify and protect patients at high risk for DVTs, and treat PE events appropriately when they do occur. Through treatment standardization and simple implementation of evidence-based rules, managed care professionals can partner with health systems to improve outcomes for at-risk patients. ●

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Novel Oral Anticoagulant Agents in Atrial Fibrillation: New Indications and Approvals

Noel G. Boyle, MD, PhD, of the UCLA Cardiac Arrhythmia Center and Ronald Reagan UCLA Medical Center in Los Angeles, California, discussed effective anticoagulation strategies for stroke prevention in patients with atrial fibrillation (AF) at the 2015 National Association of Managed Care Physicians Fall Forum. Dr Boyle discussed recent FDA approvals for the prevention of stroke, including the novel oral anticoagulants (NOACs) and medical devices, as well as the appropriate use of these therapies for treatment in a manner consistent with guidelines.

Four NOACs have been approved in the past 5 years. In addition to these pharmacologic therapies, 2 medical devices have been approved for reduction of stroke risk in patients with AF. These include the Watchman device (approved March 13, 2015) and the Lariat device (approved in 2006 as a class II medical device).¹⁻³

An estimated 15% of all strokes are attributable to AF, with that proportion approaching one-third (30%) of patients in elderly individuals. In more than three-quarters (80%) of patients, these emboli originate in the left atrial appendage (LAA). Although LAA closure devices may be used in some patients, these

devices have certain technical limitations and are associated with intraprocedural and postprocedural complications.²⁻⁴

In pharmacologic therapy, improving adherence with warfarin therapy and international normalized ratio monitoring remains an important priority. However, direct thrombin inhibitors and factor Xa inhibitors have been demonstrated to be equivalent to warfarin with fewer side effects and drug interactions. In large phase 3 clinical trials, treatment with NOACs for prevention of stroke has proven to be at least as effective and as safe as warfarin. The cost of NOACs and the lack of reversal agents (with 1 exception) are important considerations in therapeutic choice.⁵

In general, NOACs have a rapid onset of action of 2 to 4 hours, with effects dissipating rapidly 12 to 24 hours after administration of a dose. Because of this rapid dissipation of the anticoagulant effects of NOACs, warfarin may be preferable clinically in patients who have difficulty maintaining adequate adherence. However, although NOACs generally have fewer drug interactions than warfarin, it is important to be aware of possible interactions with CYP3A4 inducers and inhibitors (Table¹).⁶

Use or nonuse of NOACs also affects patient eligibility for certain medical procedures. In patients who have received more

Table. Selected Medications That May Interact With NOACs¹

CYP3A4 inhibitors	CYP3A4 inducers	P-glycoprotein inhibitors
Ketoconazole	Rifampin	Ketoconazole
Itraconazole	Carbamazepine	Itraconazole
Ritonavir	Phenytoin	Ritonavir
Clarithromycin	St. John's wort	Clarithromycin
Erythromycin		Dronedarone
Fluconazole		Verapamil
Atorvastatin		Quinidine
Digoxin		Digoxin

NOAC indicates novel oral anticoagulant.

than 3 weeks of therapy with 2 specific NOACs, cardioversion may be performed, but NOAC treatment should be stopped for 48 hours or more before surgery if the patient has a major bleeding risk and for 24 hours or more before surgery if the bleeding risk is minimal.⁵

Because NOACs are generally excreted through the kidneys—but to varying degrees—renal function must be assessed regularly with all agents, and dose reductions should be performed if renal function is compromised. Until recently, none of the NOACs was indicated for use in patients with a creatinine clearance lower than 15 mL/min or in patients undergoing hemodialysis. However, 1 NOAC has recently been approved in patients undergoing hemodialysis.^{5,6}

Although warfarin remains an important treatment in the management of AF, the improved safety profile and superior efficacy of NOACs over warfarin is well documented in pivotal trials.

NOACs have a growing range of indications as oral anticoagulants, but warfarin remains the only anticoagulant indicated for use in patients with mechanical heart valves. However, pending the results of ongoing postmarketing registries and studies, more information on the safety and efficacy of NOACs in certain high-risk populations will become available.^{5,6}

In 2014, the American Heart Association, American College of Cardiology, and Heart Rhythm Society (AHA/ACC/HRS) jointly published guidelines for the management of AF, and in 2015, the European Heart Rhythm Association (EHRA) released practical guidance for the use of NOACs. These guidelines emphasize the importance of the risk stratification CHA₂DS₂-VASc score as a

useful assessment tool for estimating stroke risk in patients with AF. Also emphasized is the importance of shared decision making between the patient and physician in treatment with NOACs.^{5,7}

Ongoing controversies with NOACs include selection of patients for therapy based on comorbidities and the severity of AF. In the Asymptomatic AF and Stroke Evaluation in Pacemaker Patients (ASSERT) study, patients with asymptomatic AF who had experienced a prior stroke and had been implanted with a pacemaker were assessed with continuous monitoring equipment for the hazard

ratio of stroke or systemic embolism in the 6 minutes after an episode of AF. Results indicated a 2.5-fold greater risk of stroke or systemic embolism during the 6 minutes. Considering that the median duration of subclinical AF averages 4.2 hours and that most strokes in the ASSERT study were not temporally related to an episode of AF, subclinical AF may simply function as a risk marker for stroke in most patients—no causal relationship between paroxysmal episodes of AF and stroke has been established.⁸

Because nearly one-third (30%) of patients in the ASSERT trial who experienced a systemic embolism or stroke had AF that was detected only after the event, the ASSERT study showed that the relationship between AF episodes and stroke is not as strong as was once thought. This finding resulted in new concerns about performance of cardioversion in patients with an AF episode of fewer than 18 hours' duration. Previously, in these patients, physicians believed anticoagulant therapy was unnecessary. However, because AF episodes are detected only after a stroke in 30% of cases, cardioversion of patients who are not receiving anticoagulation may place these patients at increased risk of stroke.⁸

Other studies in the acute management of AF are ongoing. An important in-progress study, STROKE-STOP, will answer further questions about AF. The researchers randomized in a 1:1 ratio 25,000 patients with an average age of 75 to 76 years to receive screening for AF or no screening. Of the roughly 12,500 participants randomized to the screening arm, about half (n = 6496) opted to receive screening with a handheld electrocardiogram (ECG) device for 1 minute each day over 2 weeks. Of these patients, the ECG device identified AF in 11% of patients, of whom 3% had newly diagnosed AF. Results of this in-progress study are expected in 2018.⁹

As answers to questions about the use of NOACs in certain populations of patients with AF are clarified through clinical trials, and as the use of existing agents expands, it is important for managed care professionals to be aware of new populations who

are eligible for NOAC therapy. Although warfarin remains an important treatment in the management of AF, the improved safety profile and superior efficacy of NOACs over warfarin is well documented in pivotal trials. The expansion of indications for the use of these novel agents in new patient populations is an important clinical development. ●

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