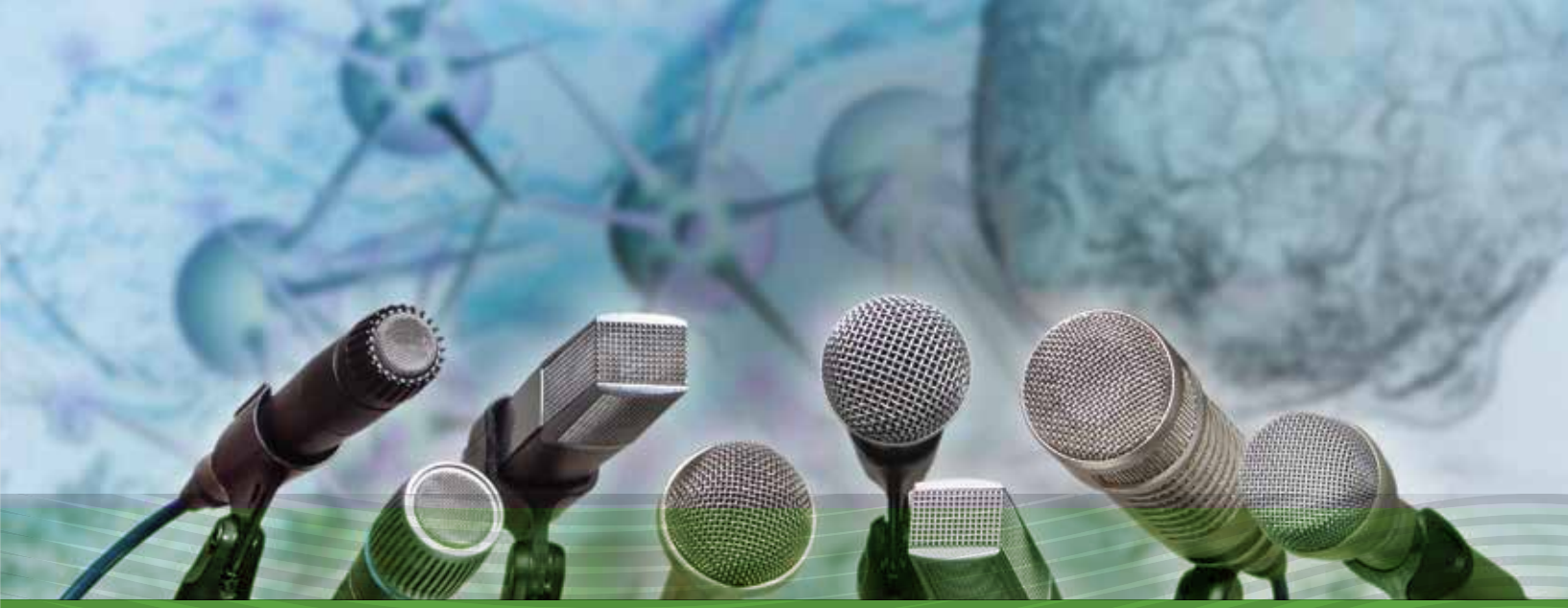
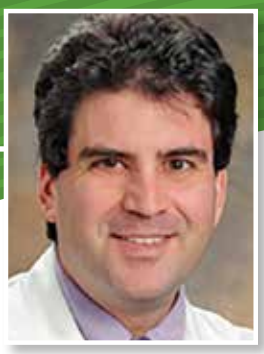


Interview with Dr. Kevin Knopf
Medical Oncologist and Hematologist



Kevin Knopf

Kevin Knopf, MD, MPH, is a Staff Oncologist and a Visiting Senior Research Scientist with Evidera and is a practicing oncologist in San Francisco, California. He is the Director of the Hematology and Oncology Clinic at St. Luke's Hospital, Associate Clinical Professor at Dartmouth Medical School, and the Medical Director, Cancer Commons. Dr. Knopf is the Co-Editor of the Journal of Community and Supportive Oncology and on the editorial boards of Value Based Cancer Care and the Journal of Managed Care Pharmacy, in addition to an Ad Hoc Reviewer for the Journal of Clinical Oncology and the Journal of Clinical Genitourinary Cancer. Dr. Knopf received his medical degree from the University of California – San Francisco School of Medicine, and his oncology training was completed at the National Cancer Institute in Bethesda, Maryland. He also has a background in epidemiology and health economic modeling.

This interview was conducted by Noemi Muszbek, MA, MSc, Senior Research Scientist, Modeling and Simulation, Evidera.

There have been many advances in oncology in the last few years, including immunotherapies such as checkpoint inhibitors and biomarkers. How do you see the immune-oncology products affecting the treatment landscape?

From my perspective as a clinician, it is always the art of picking the therapy that is most likely to work for each patient. For both immunotherapy and targeted therapies, we are trying to find biological targets that will predict a priori how the therapies are going to work. For example, we know that smokers are more likely to respond to immunotherapy in lung cancer than nonsmokers. Previously, before we had the EGFR assay to predict response to tyrosine kinase inhibitors (TKIs), we knew nonsmokers would be more likely to respond to specific drugs than smokers. So, we are looking for markers or predictors, whether it is mutational status or mutational burden or other measurable indicators, and in a clinical setting, it then becomes the art of discovering which predictive markers are the most reliable in deciding a treatment path for each individual patient.

Right now, immunotherapy is being given to many patients and we are only seeing some of them respond. For those who do, it is wonderful and we are seeing durable responses where we were not previously, such as in metastatic melanoma. But there is a lot of information coming at the individual clinician and processing all of that information to figure out the best predictive markers for any one given patient from large trials is a challenge which clinicians face.

Clearly, the development of these immunotherapies are very promising to certain groups of patients. What role do you think chemotherapies and TKIs will play?

I think everybody is very excited about immunotherapy because it's a new class of agent, and we're seeing responses where we hadn't before, but it does not work for everyone. Chemotherapy, therefore, still plays a very important role in treating many types of cancer. Right now there are maybe five or six major histologies that we see day-to-day that do not have any immunotherapy indication for them. Targeted therapies are also extremely important for many types of cancers. For example, currently we have different treatment options for both renal cell cancer and kidney cancer, so sequencing the therapies, when and when not to use immunotherapy is a challenge for the average clinician to figure out. For example, in lung cancer, immunotherapy has a very big role in squamous cell cancer and adenocarcinoma, but in the adenocarcinomas found in nonsmokers, we're much more likely to be using TKIs, first line and second line, before we get to immunotherapy.

"One important aspect of these value frameworks being successful will be more dialogue between the different stakeholders in the healthcare system."

As advances are made, there are more options for patients, but with more information becoming available all the time, choosing the right therapy for each patient is more challenging for clinicians. Biomarkers, companion diagnostics, precision genomics - these are all much more important in day-to-day clinic work than they used to be. This makes it more important than ever for clinicians to continue educating themselves on the latest information. The amount of information the average clinician needs to know to practice effectively is increasing year by year.

Biomarker research, then, is key?

Yes. In the U.S., one issue that we are facing more and more is balancing the cost of therapy versus the efficacy. The therapies can be very expensive, and so we are looking for ways to make sure that we can get the right therapy to the right patient, and get it paid for by the insurance companies. At the same time, there is concern about total cost of cancer care.

The development of value frameworks, which help assess different therapies in different populations, could be a valuable tool to clinicians, in addition to payers, in making treatment decisions. Do you see this as a benefit to clinicians?

Yes, to a degree, but this is different in the U.S. than in Europe where we have to deal with six or seven different payers, each with their own set of rules and developing their own value frameworks. I would say nine out of ten clinicians are not thinking too much about the cost of the therapy but rather focusing on choosing the right therapy for their patient. Some physician groups are forming larger groups and becoming part of accountable care organizations, which will take on risk like cost of medicines, diagnostic imaging, therapeutic imaging, etc., that will then need to be part of a framework. Then, someone within each organization will need to understand this framework very well so that the organization can be financially solvent, while ensuring clinicians can continue to provide optimal care to their patients. So, I think that the value framework is going to have an increasingly important role for anybody practicing in any part of oncology - medical radiation, surgery, pathology, diagnostic imaging – and we will see a lot of opportunities and challenges facing us in the next couple of years within the value framework.

One important aspect of these value frameworks being successful will be more dialogue between the different stakeholders in the healthcare system. Right now clinicians seem to be in one part of an organization and administration is in another part. Everybody needs to have a seat at the table, with open and honest dialogue about what the trade-offs are going to be. We are all potential patients, so that triumvirate of clinicians, administration, and patients is a good place to start. Many physicians are not used to thinking about economic trade-offs, so it's important to have economists involved, as well as pharma because they want to be able to cover the cost of innovating for new drugs. To make these future frameworks effective, there needs to be more cross-talk and cross-pollination of ideas.

So, I think there are more challenges and pressure on the clinicians right now, but the positive thing is that we have much more dialogue about these things than we did a decade ago.

How do you think individual clinicians or the larger clinician organizations should balance the cost and value of the different treatments?

It's very challenging, especially when you have large fully capitated healthcare systems, academic medical centers, large multi-specialty group organizations, and individual physician practices in the mix. I think from a patient and societal perspective, the balance is between how you spend the healthcare dollar and what you get for that dollar. So, in economic terms, we want to eliminate options where cost minimizations clearly show you should not pursue a treatment. The challenge will be in the cost-effective domains where trade-offs need to be made between side effects versus cost, quality of life, and/or length of life. These decisions have to be made fairly high up in healthcare organizations, but there have to be many people at the table, including clinicians, patients, and finance people to decide how to make the right decisions. In the U.S., Medicare will probably force the issue for the private payers as they switch away from fee-for-service oncology and average sales price methodology to MACRA (Medicare Access and CHIP Reauthorization Act) and other newer methodologies. I think the patient has to always come first, and we always have to do the right thing for the patient, but as we lay out what the exact right thing for the patient is from the clinician and patient's perspective, we'll have to align the financial incentives so that we can still keep delivering optimal healthcare.

Many of the value frameworks would like to incorporate more than just cost effectiveness, efficacy, and safety and also look at need, severity of the disease, and the patients' perspective. From a practicing clinician perspective, what would you find most useful for value frameworks to take into consideration?

I think clinicians in the U.S. are most comfortable talking about quality of life, because we know toxicities and we know which of the therapies have which side effects. So, whenever we have a patient/physician interaction, part of the interaction is assessing the patient's quality of life. We have economic ways of turning quality of life into cost utility functions, but I think it is crucial to understand and appreciate that quality of life is extremely important to patients. In my field, medical oncology, we have three goals: cure, prolong survival with quality of life, and palliate. Patients, especially those with incurable cancers, are not just concerned with how long they live, but also what their quality of life will be. I think there is more of a focus on quality of life, and I think that will continue.

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Cost will always be a big part of the equation though.

Definitely, and part of that is because now in the U.S. there is a lot more press about the cost of some therapies and of how much things cost in general in healthcare. It is more in the public eye, and oncology is a perfect place to start to have more dialogue about this, because we are always making those trade-offs between quality of life and quantity of life for patients who have an incurable cancer.

What would increase the acceptance of the economic argument or the economic issues for clinicians?

I'm not really sure. Some physicians do not want to think that way, and others, with some economic or social policy experience, are very interested. I expect there will be some doctors within every health organization who have an interest in this and will be the stewards for the others in the group. I imagine some oncologists will become experts in the value of cancer care and will form working groups to talk about how value propositions can be implemented in clinical care. There is a movement happening already. The number of articles about cost effectiveness has risen dramatically in the past five years compared to the five previous years. We just want it to happen in the right way and that patients get the right treatment at the right time in a cost-effective way.

You are the director of Cancer Commons, a non-profit network of patients, physicians, and scientists focused on knowledge sharing to get the best possible outcomes. How do you see the relationship between patients and clinicians changing in the future, especially with the increase of available information?

Cancer Commons (www.cancercommons.org) is a completely not-for-profit organization in Silicon Valley. There is a patient-facing side where patients can ask how

"Patients will be better informed about their treatment options, and clinicians will have to be better prepared to respond."

they should treat their cancer and a doctor-facing side where doctors can collaborate around complex clinical issues. One of the changes I see in the next five years is that patients in states with electronic health records will have access to their health information in ways they never have before. The patient will be much more involved in their care, asking the doctors more questions, and seeking out the best treatment for their cancer in different ways. Organizations like Cancer Commons are in response to that, allowing patients a resource to get their questions answered as best as possible from knowledgeable sources. Patients will be better informed about their treatment options, and clinicians will have to be better prepared to respond.

There is a growing effort to collect, combine, and analyze data, such as ASCO's CancerLinQ. Do you see real-world evidence helping clinicians in your decision making?

Real-world evidence is great because we're prescribing drugs based on clinical trials that were done with certain types of patients, and then in the real world, we have to figure out if our patient matches the patient in the clinical trial. There is a scarcity of real-world evidence trials, so having retrospective data sets to analyze or a series of real-world trials with economic and quality of life endpoints might help fill that gap. We know that we do not always get the same results in the real world compared to clinical trials, but we don't know why some patients in the clinical trials and some of our patients are outstanding responders to certain agents. Data will help answer that question, as will the movement in precision oncology. I think both of these things are very promising to improve quality of care.

What advantages and risks do you see in the use of real-world evidence?

The advantages are that it is real and most patients are treated in community settings, not in rarified settings. Most patients have real-world comorbidities or other issues not accounted for in clinical trials. Clinical trials can underrepresent patient populations. For example, a large proportion of our patients are over the age of 70, but they are underrepresented in clinical trials. Having real-world evidence would help us treat specific patient populations and select the best therapies. The risks are the same as in any sort of analytic framework - does what you're getting from the analysis match the person before you? I also think the risk of overfitting data is there, so results of analyses from real-world data will have to be interpreted with the same caveats as those from clinical trials. Overall, there is a lot of good that comes from real-world evidence, and potentially a little harm.

Lastly, why do you think oncology drugs in particular are singled out of all the expenditures in healthcare?

I think oncology is an interesting use case because we have had a lot more drugs approved in the past 10 years than prior. We have made a lot of progress in oncology in large part because the molecular biology revolution of the 1970s allowed us to understand much more about how cancer behaves, so we have a lot more targets than we did before. There are a lot more drugs available, and this brings the economic issues to the forefront. Also, with the speed of new drug options becoming available, it is harder to find the value proposition compared to other therapeutic areas where new options come more slowly. There is also a lot more media coverage about the cost of oncology treatments than ever before, which increases public awareness.

Hopefully, the establishment of value frameworks and the new developments we just discussed, such as big data, precision oncology, etc., will provide help in the assessment of value. I see a lot of opportunity in the area of oncology coming our way in the next several years.