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Highlighted below are recent stories from *Oncology Fellows* that addresses the problem of bias, medical ethics, and complex surgeries.

Do you have a story or experience that could benefit your colleagues? Contact Anthony Berberabe (aberberabe@onclive.com) for author guidelines. If your story is published, we provide a $500.00 honorarium.

Is Anchoring Bias a Real Phenomenon?
Two case reports illustrate the challenges of anchoring bias, which occurs when a physician locks onto a clinical diagnosis too early, often by basing those decisions on information provided by another physician.

Weighing Medical Ethics in Pediatric Oncology
When "doing no harm" means not trying an experimental drug therapy, which may prolong a patient's suffering, despite the patient and family's wishes. It is a thorny issue made especially complicated when treating pediatric patients.

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Grant Opportunity

American Cancer Society Supports Early Career Clinicians' Move into Clinical Science
The American Cancer Society has launched a new grant program to support early career clinicians aiming to become clinician-

Watch your inbox for our *Oncology Fellows* e-newsletter— written for fellows, by fellows. Send an email request to Tony Berberabe (**aberberabe@onclive.com**) to receive your copy.

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Keeping Ahead of Oncology's Advances Requires Vigilance

Aditya V. Shreenivas, MD, MSCR
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IT IS DIFFICULT TO stay up-to-date with the changing treatment paradigm in hematology-oncology. This field is rapidly evolving, and the explosion of information is too much to handle sometimes. Fellows in training are generally expected to stay abreast of current treatment modalities and breakthrough research, but doing so is slowly becoming a challenge for all of us. It is important to note that in 2017, the FDA issued 58 new approval notifications in hematology-oncology, much more than in any other field of medicine.[1] According to an estimate from a PubMed search, more than 1.17 million articles have been published in the field of oncology over the past 10 years. Jeremy Warner, MD, MS, published a review in 2015 noting that PubMed contains more than 2.7 million articles filed under the Medical Subject Heading "neoplasms." He also observed that the number of articles published in oncology was much higher than that of other medical fields like cardiology and endocrinology.[2] These observations are a testament to the explosion of data in the field of cancer medicine.


Aditya V. Shreenivas, MD, MSCR

The constant interplay of research between the disciplines of oncology, molecular biology, genetics, and bioinformatics have made this a complicated field. Although medical research data are now readily available online to both physicians and patients, it is often a challenge to glean relevant information from them. As physicians, it is very important for us to develop skills to determine what is important in the context of clinical care. It is also essential for us to pay adequate attention to rapidly evolving guidelines in oncology for the benefit of our patients. But this is a Herculean task.

Methods of Staying Current

There are several ways to tackle the problem of information overload. I think the most important way to stay up-to-date is to develop a habit of continuous learning. We should make every effort to block out a specific time each day to catch up on reading, even if it's just 30 to 45 minutes. For trainees, I believe reading about different topics each day or the literature around a case presented in clinic would be ideal.

We should also take a cue from lawyers—unbelievable, I know. A lawyer friend told me that group discussions are a common practice in law school and are quite helpful in preparing students for tough internal examinations. Group discussions are a great way of improving understanding of a subject. It also helps us identify our shortcomings and weaknesses in a short span of time. Routine peer-to-peer interaction can be a useful way of staying abreast of changing guidelines and cutting-edge research.

If you ask senior oncologists, they will probably tell you to read top peer-reviewed journals, such as the *New England Journal of Medicine*, the *Journal of Clinical Oncology (JCO)*, and *Blood* to stay current in hematology-oncology. Although there is no question about the accuracy and quality of data available in these journals, it is a challenge to follow all the relevant information on different disease subtypes. Hence, it is important to carefully choose and pay »

attention to landmark studies that have led to new drug approvals or are changing treatment strategies.

Listening to podcasts from the *JCO* is another easy way of keeping informed if you don't always have the time to read journals. National meetings like those hosted by the American Society of Clinical Oncology, the American Society of Hematology, and the American Society of Blood and Marrow Transplantation are an important source of updated information for most of us. These meetings give us an opportunity to interact with experts and obtain firsthand information about breakthrough research in our field. Prioritize listening to the keynote presentations if your time is limited at these meetings. These presentations are practice changing, and their findings are fair game for future board examinations. Board review lectures are also a great resource and highlight the most recent and clinically relevant data.

Another way to stay up-to-date is by creating email notifications on PubMed for topics of interest so that every time a new article on a specified topic is published, an email notification will be sent to your inbox, and you can quickly read the article on your mobile device.

Burden of Taking 2 Board Examinations

Hematology-oncology fellows, unlike their counterparts in cardiology, nephrology, rheumatology, and endocrinology, have to pass 2 boards after graduating, which adds more stress to their lives post fellowship. According to the American Board of Internal Medicine's 5-year report of first-time test takers, the average board passing rate for hematology has been one of the worst among all specialties of medicine.[3] Although board pass percentages have started to improve, it will be interesting to see whether the trend continues.

Not to sound cynical, but there can be only 2 explanations for this trend: Either test takers are becoming smarter or the test itself is becoming easier. Honestly, I feel we are better prepared for these examinations than our predecessors because of increased awareness and easy access to board review materials these days. I guess it's also reasonable for some of us to schedule these examinations at our convenience and not take both boards in the same year if we feel that our preparation is suboptimal. Fellows should also take in-training examinations very seriously. These may help us identify areas that need our special attention and time. Results from some studies have also shown that they remain a great predictor of hematology-oncology certification examination scores and are probably more accurate than a program director's assessment of our medical knowledge.[4]

Apps for the Future

The incorporation of medical decision-making tools and computer applications into clinical practices has signaled a major revolution in medicine. Oncologists already use mobile apps like the National Comprehensive Cancer Network Guidelines App, UpToDate, and Medscape as convenient sources of information and to streamline treatment algorithms of disease subtypes. Mobile apps and clinical vignette modules can also be upgraded to take advantage of better graphics and animations, to enhance physician engagement with their patients, and to make learning more fun. Animation-enhanced learning can be introduced to educate physicians about specific diagnostic, treatment, and follow-up scenarios. All these ideas, if implemented in a better way, could benefit all of us.

There is an urgent need to develop better learning tools for trainees to not only stay up-to-date but to also excel in this field. As future hematologist-oncologists, we are obligated to provide the best care possible to our patients and stay informed. ■

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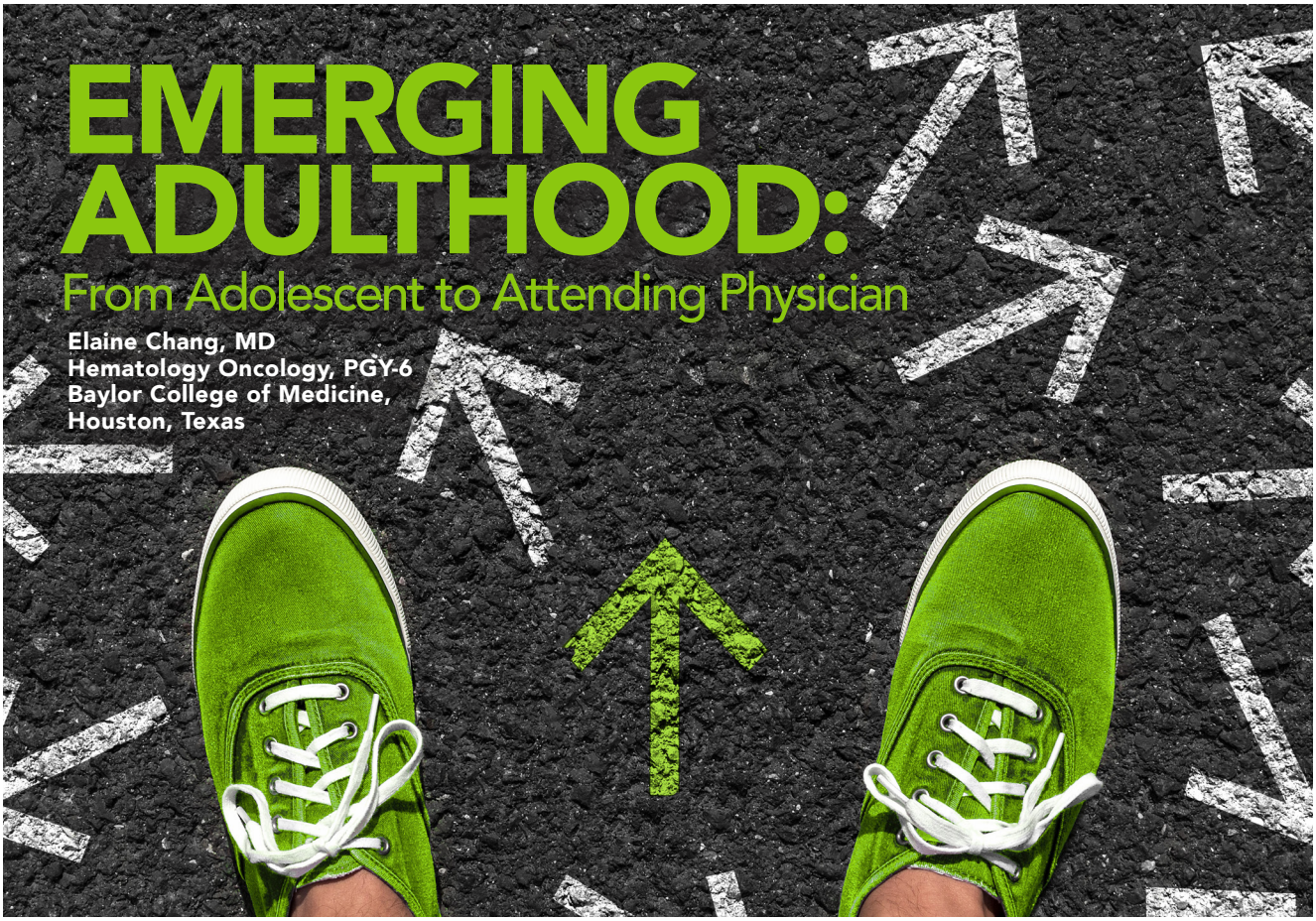

EMERGING ADULTHOOD:

From Adolescent to Attending Physician

Elaine Chang, MD
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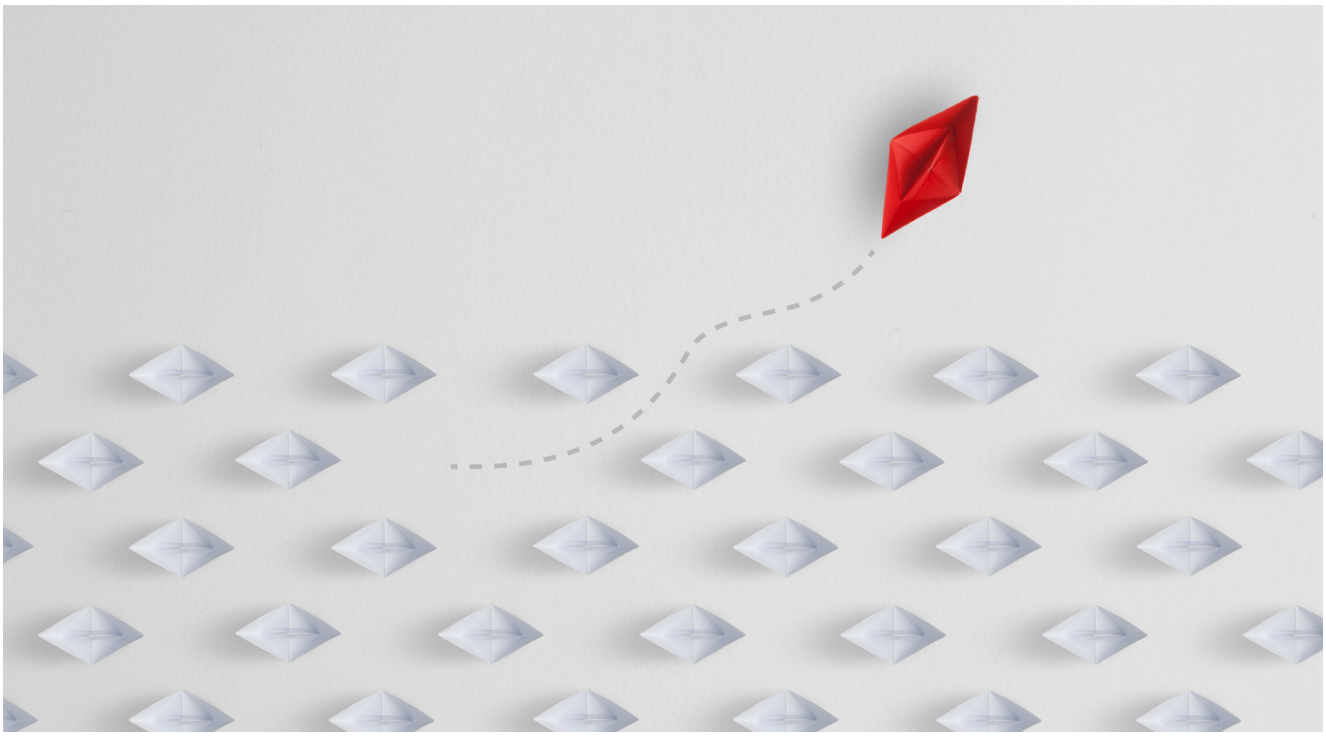
What do you want to be when you grow up?
It was a common question to be asked as children, as soon as we learned the meaning of the words "job" and "work." By the time I graduate from high school, I am answering earnestly, "I want to be a doctor." I am blissfully unaware that no one at age 18 has any inkling of what that means. And so emerging adulthood begins, as described by Jeffrey Arnett in 2000, pertaining to young adults between 18 and 25 years of age who do not have children, do not live in their own home, or do not have sufficient income to become fully independent.[1] It is the period of time when adolescents become adults by exploring the seemingly endless possibilities of life directions.

What do you want to be when you grow up? In college, my understanding of this mysterious guild guarded by the Hippocratic Oath does not grow much. I know that I want to help people, change the world, and have enough money for a comfortable lifestyle. Medicine still seems like a great career to accomplish those goals.

What do you want to be when you grow up? In medical school, I still want to help people and change the world; but in the meantime, I need to study, study, study; then choose a residency; and then match. I keep my head in the books because fear of failure is always crouching at the door. Selfishly studying sucks out the sense of personal achievement and feeds professional burnout, especially when nostalgia for the college days, when I used to help people in tangible ways, hits. I console myself and strengthen the delayed gratification muscle: "It's just temporary. Study now, so you can be a better doctor and help people more effectively in the future." Even after I start rotating wards and studying is no longer occupying the majority of my days, I'm at the bottom of the totem pole and not sure how to navigate my role. Confidence and the sense of personal achievement are at all-time lows. By the time I graduate with my medical degree, I begin to wonder, "When am I ever going to graduate from emerging adulthood and reach adulthood?"

Elaine Chang, MD

What do you want to be when you grow up? I want to help people, and as an intern, I finally can. Those moments, I think "I've finally arrived." My new goal is to be a *competent* physician. Being a consistently excellent physician seems like an unrealistic goal on most days. I'm just trying to survive, like Cosette sweeping the floor, singing "Castle on a Cloud."[2] »



Who am I? What is my calling? "You will find truth more quickly through delight than gravity. Let out a little more string on your kite," says Alan Cohen, author of inspirational and work/life balance books.

The only way to stay afloat is to figure out what my superiors want of me. But I start learning to tell stories, narratives that illuminate different perspectives of familiar situations faced by the medical trainees; that acknowledge and interpret the challenges common in our interactions with our colleagues, patients, and society; that absorb and interpret experiences in a way that shapes our character and how we see our role in the world.[3-7] Stories become a modality for discernment: "Of all the things I do, which things matter? Which threads do I want to keep and weave into the narrative of my life? How do these threads give me hope for a meaningful future?"

What do you want to be when you grow up? Having miraculously survived internship, I am now a resident applying for hematology-oncology fellowship, after meeting several admirable attendings and thinking to myself, "They are great people. I want to be that efficient and effective, influence medical students and residents, practice fantastic communication skills, and show compassion to patients and colleagues." By now, I've been in a rigorous academic environment for 20 years. The atoms of academic curiosity make up the air I breathe and are embedded in every cell of my soul, becoming the framework for an academic career.

What do you want to be when you grow up? Fellowship is like intern year all over again—in other words, survival mode. Two years pass, I'm in 26th grade, and oops, I realize the feeling that I'm Cosette hasn't left me, that I'm sweeping the floor, but I am increasingly urged to straddle 2 worlds, as well-intentioned superiors admonish me, "Start building your castle now. How many floors? How many staircases? What color walls?" as the adult questions percolate in a befuddled puddle in my mind. Do I want to join a group private practice and have a comfortable lifestyle, with time to be a human being outside of medicine, but stoop to conniving business relationships and grovel for referrals? Do I want to stay in academics, preserving my naïve, idealistic self who doesn't have to plot shrewd business moves, but remain under the mercy of institution politics? Do I want to spend my days being creative, asking questions and designing research studies to answer them, but under the gun of submitting grants every 6 weeks? And then there's industry—I don't know much about that aspect of the medical world, but I'm pretty sure I don't want to travel that much.

I begin to realize that we have stereotypes of all these careers, and we're expected to apply for jobs based on these skewed stereotypes. Additionally, we are trained to be perfectionists and excel at everything—teaching, clinical acumen, communication, research—just like Cosette is certainly trained to sweep, wash dishes, do laundry, scrub the floors, and more.

Does it come down to "just do/pick something?" Maybe there is no wrong choice. My theory is that many of us make decisions based on the stereotypes of these careers and the stories we tell about ourselves. We develop an identity as an altruistic person, and the only way we can be in underserved care is to stay in academia. Or we develop an identity as an

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The medical journey is like a labyrinth. The farther we go, the more choices we encounter.

altruistic person, but we have too much debt, so we need to go into private practice, and we tell ourselves we'll make up for it in the future by donating to worthy causes. Or we develop an identity as a smart person who thrives during tumor board discussions, and we get on the academic clinician-educator track. Or we develop an identity as a smart person who wants to leave a mark forever on medical history, and we jump on the academic physician-scientist track.

Maybe we need to start telling more nuanced stories about ourselves and these careers. We need altruistic, pragmatic people in industry, committed to the delivery of effective drugs to people in need. We need creative clinicians in communities everywhere, willing to use their brains in applying evidence-based medicine to each patient individually, rather than universally or blindly following heuristic techniques. We need business-minded entrepreneurs in global health who can negotiate, forecast, and lead within cost-effective, sustainable growth models.

Many of us may feel like we don't have stories to tell. Where do we find the setting, the characters, and the storyline? We need to reach down into our memories, search for, and reflect upon:

- The people with whom we enjoyed working with or the patients we have enjoyed helping
- Our favorite transferable skills
- The working conditions that enabled us to work at our top form and effectiveness
- The organizations most in line with our mission or purpose in life

As Andrew Delbanco[8] writes in *The Real American Dream: A Meditation on Hope*:

> At the heart of any cohesive culture is a story that gives it hope, a story that helps us overcome the lurking suspicion that all our working and getting and spending amounts to nothing more than fidgeting while we wait for death. Hope depends on finding some end to be pursued more extensive than merely instant desire…Without it, we are, as the anthropologist Clifford Geertz has put it, "a kind of formless monster with neither sense of direction or power of self-control and a chaos of vague emotions." ■

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Personalized Medicine in a Time of Depersonalized Patient–Doctor Relationships

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I EAGERLY AWAITED THE next patient to be put into a room. I had reviewed his large pile of medical records the night before and knew he was coming in to potentially enroll in a phase I/II clinical trial that was evaluating a new drug in patients with a specific actionable mutation. His tumor had developed this alteration as his metastatic disease worsened, which had already progressed through multiple lines of prior therapy. He came to us as a last resort.

As I walked into the room and greeted him and his wife, I vaguely caught a sense of anxiety but ignored it because I had more important things to discuss. After taking a history, which I already knew from the night before and upon finishing a complete physical exam, I launched into my usual sequence of discussion. I spoke about the natural history of this cancer type and what our trial entailed. I discussed that we didn't know if this treatment would work or not, but the preclinical data were encouraging, and we were enrolling patients to determine dose and toxicity. I then went on to discuss the adverse effects (AEs) that we had seen thus far and, finally, ended with the overall poor prognosis of this disease. I then stated that if the treatment did not have the effect we were hoping for, altruistically enrolling into this trial could potentially help another patient in the future.

The patient nodded silently throughout my rehearsed monologue. His wife frantically wrote down notes without making eye contact, and I noted that her face was flushed and she was almost in tears. When asked if they had any questions, they both appeared overwhelmed, so I walked out of the room, passively stating that I would be back with the attending physician after we discussed his case. The patient ultimately enrolled onto our trial but over time, he progressed and died.

I reflect on this and similar patient interactions that I have encountered throughout my fellowship. On the one hand, I am on the cutting edge of research and have the opportunity to enroll patients into clinical trials involving experimental therapies, often stating that we are giving "tomorrow's cure today." I do believe that the future of oncology is now, and in my lifetime, I hope to see cancer cured.

On the other hand, I failed to truly recognize and understand the patients whom I treated. Somewhere during my short career, I had lost the ability to build genuine relationships with the person sitting in front of me. Sure, I knew everything about their oncologic history and the mechanisms behind tumorigenesis. I worked hard and

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long hours making sure each patient was properly cared for. I monitored for toxicities and managed AEs. But I knew nothing about a patient's background, family, or values. I desensitized myself from my job. I later learned that this particular patient drove several hours to receive his treatment and had been laid off from work because of missed time. He had young children at home who did not know about his diagnosis or prognosis. His wife was barely able to cope with the unfortunate turn of events that had destabilized their livelihood, yet the patient remained stoic as a way to cope with his crumbling world.

Gagandeep Brar, MD

I think this apathetic mentality develops as a coping method for oncologists when frequently exposed to death and dying. After all, we are people, too, each with set limitations of what we can psychologically handle. It is easy to keep patients at a distance and close ourselves off to feeling emotion when they die. It is overwhelming to open ourselves unconditionally and feel the effects of mortality on a regular basis. I used to think that oncologists were the "angels of death," as patients often succumbed to their disease. I thought our role was simply to prolong life and, oftentimes, prolong suffering. This detachment led me astray from what my true focus should always have been—to help a person in need.

Learning from this case, we need to remember that building sincere and genuine patient–doctor relationships is just as important as treating their illness. We have a unique opportunity for a complete stranger to put their life in our hands, and we have the ability to provide comfort, hope, and assurance in a time of fear and doubt for a patient and their family. It isn't easy, but remember that we are allowed to grieve. It's not a failure or a fault to incorporate compassion with professionalism. Take time to get to know your patient and remember their life as they are. We treat people, not ID numbers.

Rachel Naomi Remen, MD, clinical professor of family and community medicine, University of California, San Francisco, School of Medicine has said: "The expectation that we can be immersed in suffering and loss daily and not be touched by it is as unrealistic as expecting to be able to walk through water without getting wet…We burn out not because we don't care but because we don't grieve." ■

For more timely and practical articles, go to onclive.com/link/2375.

Steady Increase in Liver Cancer Death Rates Observed in Adults Aged 25 and Older

Tony Berberabe, MPH

A NATIONAL CENTER FOR HEALTH Statistics (NCHS) briefing stratifies liver cancer mortality by sex, ethnicity, and age for adults aged 25 years and over. Overall, death rates increased significantly for both sexes, with death rates for men 2 to 2.5 times the rate for women from 2000 through 2016. The news for non-Hispanic white, non-Hispanic black, and Hispanic adults is not good, either, with increased liver cancer death rates reported for these populations. However, liver cancer deaths declined for non-Hispanic Asian or Pacific Island (API) adults during the same time period.[1,2]

Specifically, liver cancer death rates for adults aged 25 and over increased 43%, from 7.2 per 100,000 US standard population in 2000 to 10.3 in 2016. Age-adjusted death rates for liver cancer increased 43% for men (from 10.5 to 15.0 per 100,000) and 40% for women (from 4.5 to 6.3) (**Figure 1**). When ethnicity was considered, the age-adjusted death rate increased for non-Hispanic white, non-Hispanic black, and Hispanic adults but decreased for non-Hispanic API adults (**Figure 2**).

When particular age groups are stratified, Jiaquan Xu, MD, author of the data brief, said that among patients aged 55 to 64 years, liver cancer death rates rose from 2000 through 2013. Since 2013, the rate remained stable until 2016, the last year that records were available.

"If we look at the age group [of] 45 to 54 [years] from 2000 to 2005, the rate has increased, but from 2005 through 2012, the rate has remained stable. Further, since 2012, it has decreased by about 20%. That looks like a good sign for the younger age group," said Xu, an epidemiologist at NCHS.

Jiaquan Xu, MD

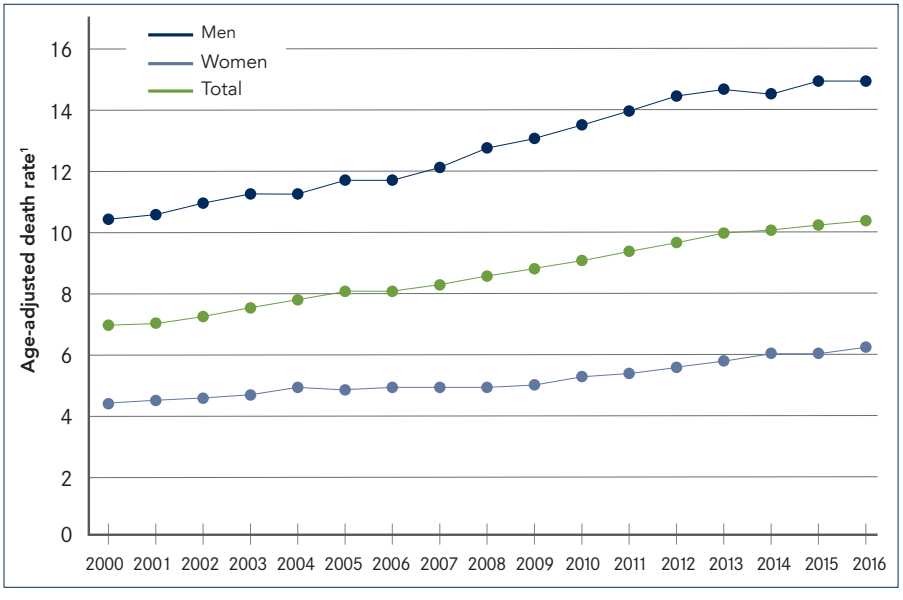
For adults aged 65 to 74, the rate increased 7% from 2000 to 2008 (from 18.7 to 20.0 per 100,000) and 37% from 2008 to 2016 (from 20.0 to 27.3). The 2000-2016 rate increased 35% (from 29.8 to 40.2) for adults aged 75 and over. The liver cancer death rate was the highest for adults aged 75 and older, followed by age groups 65 to 74, 55 to 64, 45 to 54, and 25 to 44 years.

Although the non-Hispanic API group had the highest liver cancer death rates during 2000 to 2014, among the 4 races and Hispanic-origin groups, this group experienced the only decrease (22%), from 17.5 in 2000 to 13.6 in 2016. For Hispanic adults, the liver cancer death rate increased 27%, from 11.5 in 2000 to 14.6 in 2016, surpassing the rate for non-Hispanic API adults that year.

In 2016, Washington, DC, had the highest age-adjusted liver cancer death rate (16.8 per 100,000 US standard population), and Vermont (6.0) had the lowest rate. "When we look at liver cancer among non-Hispanic blacks, the death rate for liver cancer seems to be rising. Given the population of the Washington, DC, area, that could be 1 of the factors that led to the higher rate," Xu said.

Behind Washington, DC, age-adjusted death rates for liver cancer among adults were highest in Louisiana (13.8), Hawaii (12.7), and Mississippi and New Mexico (12.4 each) in 2016. The 5 states with the lowest age-adjusted liver cancer death rates were Vermont, Maine (7.4), Montana (7.7), and Utah and Nebraska (7.8 each). ■

Figure 1. Age-adjusted Death Rates for Liver Cancer Among Adults Aged 25 and Over, By Sex: United States, 2000-2016



[1]Deaths per 100,000 US standard population aged 25 years and older.
Source: National Center for Health Stastics, National Vital Statistics System, Mortality.

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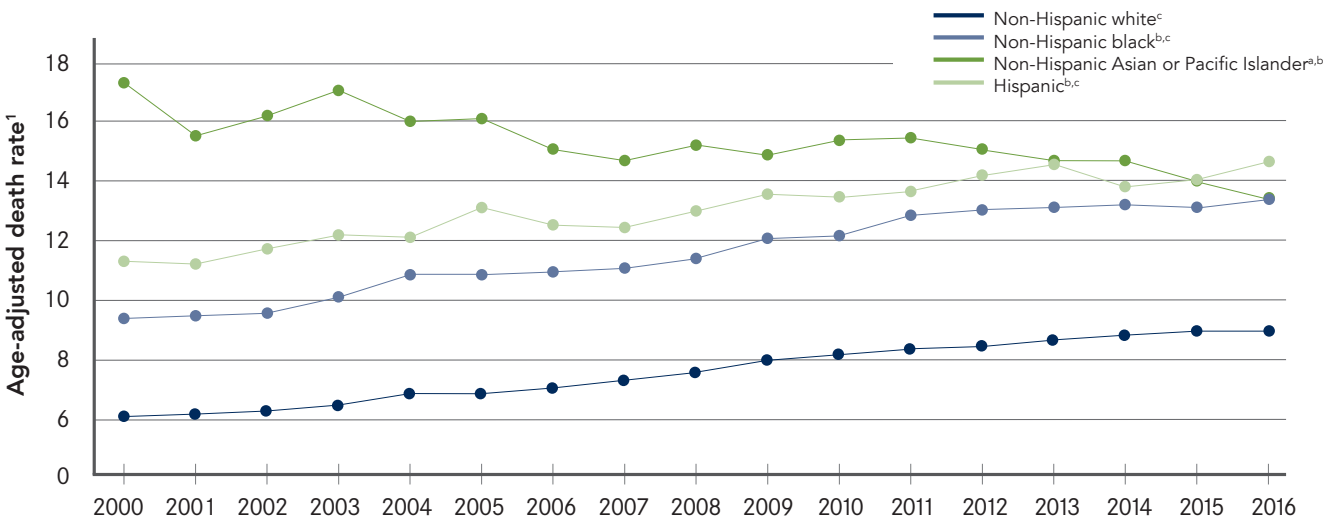
Figure 2. Age-Adjusted Death Rates for Liver Cancer Among Adults Aged 25 and Older, by Race and Ethnicity: United States, 2000-2016



[a]Significant decreasing trend for non-Hispanic Asian or Pacific Islander adults from 2000 to 2016 (P <.05). [b]Significantly higher compared with non-Hispanic white adults throughout the period (P <.05). [c]Significant increasing trend from 2000 to 2016 (P <.05). Deaths per 100,000 US standard population aged 25 years and older.

Should Fitness Trackers Be Used to Assess Performance Status in Patients With Cancer?

Tony Berberabe, MPH

USING WEARABLE ACTIVITY MONITORS may eventually supplement standard assessments of performance status (PS) and functionality that could inform clinicians, especially because objective evaluation of PS is difficult to determine. Patients spend most of their time outside of the clinic, self-report to providers, and undergo changes throughout treatment. Findings from a recent study at Cedars-Sinai Medical Center (CSMC) in Los Angeles, California, demonstrated the feasibility of using these wrist-worn devices to correlate with Eastern Cooperative Oncology Group (ECOG) PS and Karnofsky PS (KPS) scales.[1] PS is affected by bias, resulting in patient activity being over- or underreported, which can affect short- and long-term treatment plans and clinical trial eligibility.[1]

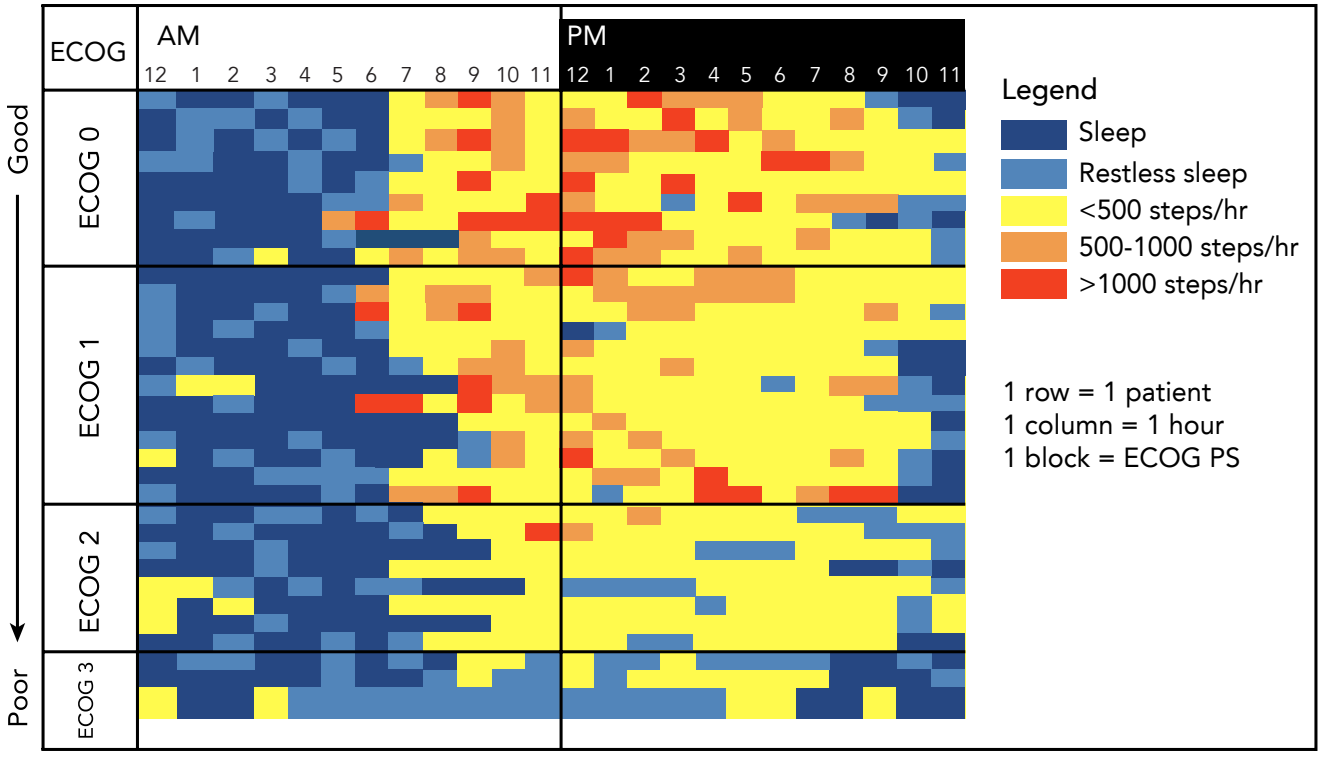
Gillian Gresham, PhD

"Before we can ask if these devices can change practice or replace these standard assessments, we need to determine if it's feasible for the patient to use them, [and] to wear them, and if there are any challenges with their use," said Gillian Gresham, PhD, lead author and postdoctoral student at CSMC. "After establishing short-term feasibility, we can begin to explore whether these measurements correlate with standard assessments, patient-reported outcomes, and predict clinical outcomes," she added.

Additional objectives of the study included measuring patient reported outcomes (PROs). "We were able to correlate PROs such as improved physical functioning, better pain tolerance, improved sleep, and lower levels of depression with increased activity, as measured using the devices," Gresham said.

Thirty-seven patients (20 men) with stage IV or unresectable advanced stage III cancer agreed to participate in the single-center, single-cohort study that evaluated the Fitbit Charge HR device to measure daily activity. Patients of varying ECOG PS and KPS ratings participated, with participants agreeing to wear the Fitbit for 3 consecutive clinic visits over 2 weeks, in which ECOG PS and KPS were assessed. Associations between metrics (steps, distance, and stair climbing) and PS, clinical outcomes (adverse events [AEs], hospitalizations, and survival), and PROs were determined. »

Figure. Heat Map of Average Activity Intensity for Each Patient Over a 24-hour Period, as Measured by a Wearable Activity Monitor and Sorted by ECOG PS Categories.



ECOG indicates Eastern Cooperative Oncology Group; hr, hour; PS, performance status.
Source: Gresham G, Hendifar AE, Spiegel B, et al. Wearable activity monitors to assess performance status and predict clinical outcomes in advanced cancer patients. *Digital Medicine*. 2018;1(27):1-8. doi: 10.1038/s41746-018-0032-6. To view a copy of this license, visit creativecommons.org/licenses/by/4.0/.

Median age was reported as 62 years (range, 34-81). At baseline, patients' ECOG-PS scores were 0 (24%), 1 (35%), 2 (24%), or 3 (16%). The majority of patients were diagnosed with gastrointestinal cancer (n = 27) and had stage IV disease (n = 34). There were 2 patients with locally advanced stage IV pancreatic disease and 1 patient with stage IIIB endocervical serous carcinoma.

The highest correlations were observed between average daily steps and both PS scores. Each 1000 steps/day increase was associated with reduced odds for AEs (odds ratio [OR], 0.34; 95% CI, 0.13-0.94), hospitalizations (OR, 0.21; 95% CI, 0.56-0.79), and hazard for death (hazard ratio [HR], 0.48; 95% CI, 0.28-0.83). On average, patients walked about 3700 steps, or 1.7 miles, a day, climbed 3 flights of stairs daily, and slept 8 hours/night as measured by their wearable device (**Figure**).

Although the device doesn't measure heart rate the same way electrocardiograms do, it estimates heart rate by measuring blood flow through pulse readings. "We lined up measurements of the heart rate at a specific time in the clinic and matched it during the time that the patients were wearing the Fitbit and looked at the comparison of those 2 findings for each clinic visit," said Gresham. "They were very closely related. That was encouraging but warrants further investigation."

The investigators were, however, intrigued by the poor correlation between sleep quality and duration (as measured with the device), said Gresham. "I think we need more granular-level data with regards to sleep," Gresham said. "[Although] Fitbit has improved its sleep recording quality since we completed the study, it opens up a new and interesting facet of research," she said. "It also highlights the importance of the patient's voice in their management, and is an example of how a patient's perception of their sleep quality may not always match what is measured. Perhaps in this case, quality does not mean quantity."

Using the device did allow patients to engage more with their physicians, according to the authors. Patients could discuss symptoms, provide information about their level of activity, and ask questions that providers don't usually get a chance to talk about with the patient. "It's a way to engage both with the patient and providers—something that I think is highly valuable in patient care," added Gresham.

The device data also revealed interesting details about the patients' daily lives that may not always be apparent during clinic visits, according to Gresham. For example, an older patient appeared frail during clinic visits, and scored a lower PS rating. The investigators found that after a week of wearing the Fitbit, the patient averaged almost 15,000 steps a day. "It turns out, this particular

Patients wore the Fitbit Charge HR for 3 consecutive clinic visits. Some patients took full advantage of the mobile technology, and others just used the device as a wristwatch.

patient was probably one of the most active patients we followed…and they didn't just start walking more steps because of the study…they said it was part of their daily routine. These observations suggest that the use of devices can help inform and even change the course of treatment decisions and importantly, help inform treatment decisions in the future. It also reminds us that assessments should not be made based solely on age or physical appearance, but on a patient's overall activity levels and functionality."

The data collected by the devices can be used to fill in the gaps between clinic visits, said Gresham. "Throughout their care, we're seeing that performance status assessments tend to be rather static and are often missing from the patient medical chart. We can now detect changes in real time by anticipating potential [adverse] effects or try to intervene a little bit sooner if complications or adverse events occur. It also allows for the patient to self-monitor themselves and notify their care team if there are changes to their usual activity levels."

Data were collected through the device's online dashboard, and each patient was provided an anonymous, de-identified email account that was used to register the Fitbit, access their activity data, and receive email summaries of weekly activity levels. Investigators observed a range of attitudes towards the devices. Some patients "explored the technological abilities of the device, and others just wore it like a watch," Gresham said.

The data collected by devices like these could give oncology fellows access to information that they otherwise would not have had before, said Gresham. "Currently, along with the enterprise information services department here at CSMC, we're working to integrate the wearable data into the patient's medical chart," she said. "The more knowledge that can be gathered about the patient beyond the clinic assessment could give the fellow an idea about the patient's daily routine, levels of activity, and the patient's standard for normal."

In the long term, the data can be tracked from initial diagnosis, treatment, potential cure, and recurrence. The fellow has a way to monitor the patient, especially for patients who might have difficulty going to the clinic for various reasons such as socioeconomic or reliable transportation, she added.

The findings provide new information regarding the use of an emerging technology in cancer clinical settings. The incorporation of wearable activity monitors to correlate with functional and clinical outcomes are only beginning to be reported, according to the authors.

It is not clear whether activity monitor data can replace ECOG-PS or KPS assessments, but they can provide supplemental data for current functionality tools. Not only were step counts and other activity metrics correlated with PS, but they also provided a more detailed and continuous account of patients' activity levels with the added benefit of being recorded in the patients' free-living environments.

> **"The device allowed for even more physician–patient engagement… something that I think is highly valuable in patient care."**
>
> —GILLIAN GRESHAM, PHD
> CEDARS-SINAI MEDICAL CENTER

In the future, Gresham said the investigators would like to see if the data could be used as stand-alone functional outcomes to evaluate the impact of a particular intervention or treatment on the patient's daily activity. "Like patient reported physical function and activities of daily living, frailty status, or provider assessed performance status, we would like to see 'activity,' as something clinicians can use to assess a patient's functionality. Maybe some day in the future, we can incorporate physical activity recommendations or 'activity prescriptions' into the routine care of patients with the goal of improving health outcomes," she said.

Gillian Gresham completed this work under the supervision of Steven Piantadosi, MD,PhD, Curtis Meinert, PhD, and Arvind Shinde, MD, MBA, MPH (senior author of the paper). ■

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Optimal Sequence Strategies Explored for Relapsed/Refractory Myeloma

Angelica Welch

INITIATING TREATMENT FOR RELAPSED/refractory multiple myeloma requires a clear plan that is guided by the patient's history of treatment, according to Sagar Lonial, MD.

In a presentation during the 2018 Pan Pacific Lymphoma Conference, Lonial, professor and chair of the Department of Hematology and Medical Oncology at Emory University School of Medicine in Atlanta, Georgia, and chief medical officer of the Winship Cancer Institute of Emory University, discussed optimal sequencing techniques for patients with relapsed/refractory myeloma.

Sagar Lonial, MD

The so-called players in the treatment of patients with relapsed/refractory myeloma fall into 2 categories, Lonial explained—older agents and new novel ones. Older therapies include bortezomib (Velcade), lenalidomide (Revlimid), carfilzomib (Kyprolis), and pomalidomide (Pomalyst). Newer agents are ixazomib (Ninlaro), entinostat (not yet approved), elotuzumab (Empliciti), and daratumumab (Darzalex), with many others on their heels, Lonial said.

An ongoing debate revolves around treatment at relapse. Lonial noted that although some experts theorize that biochemical relapse is sufficient evidence to initiate therapy, he prefers to wait and assess. "There is a huge controversy on this issue, but I come down on the side of observation for patients with asymptomatic biochemical relapse. Just because a patient has a protein, [that] doesn't mean you have to feel obligated to jump in and do something," he explained.

When considering treatment, Lonial said, clinicians should look at 3 factors, which are related to disease, treatment, and the patient.

Disease-related factors include presentation of indolent or aggressive relapse, genetics of relapse, level of tumor burden, and Multiple Myeloma International Staging System stage at diagnosis.

Treatment-related factors are prior agents used, progression on an immunomodulatory agent or proteasome inhibitor, maintenance, toxicities experienced, cardiac dysfunction after treatment, chronic obstructive pulmonary disease, and duration of prior therapy.

Patient-related factors involve prior illness, comorbidities, renal insufficiency, hepatic involvement, frailty, and patient preference.

"One of the things that we struggle with at our center is that patients come from 2 to 4 hours away, so if you have a choice between something oral versus something that is intravenous that needs weekly therapy, that may change your decision making," Lonial explained.

Once a treatment course is chosen, clinicians must assess the landscape. Most of the action currently involves randomized phase III trials, which break down into 2 groups. The first group, which focuses on patients who

received lenalidomide plus dexamethasone in the control arm, consists of the ASPIRE trial with carfilzomib, TOURMALINE-MM1 with ixazomib, ELOQUENT-2 with elotuzumab, and POLLUX with daratumumab.

ASPIRE and TOURMALINE-MM1 partnered lenalidomide and dexamethasone with proteasome inhibitors, whereas ELOQUENT-2 and POLLUX used immunotherapy. All 4 trials were identically designed, Lonial said, but differed in size. Additionally, regarding progression-free survival (PFS), very few patients had prior lenalidomide with dexamethasone. Moreover, none were refractory to lenalidomide plus dexamethasone. "That is important because many of our patients are progressing on lenalidomide maintenance," Lonial said. "How relevant are these trials to the patient you have sitting in your office who is progressing on lenalidomide maintenance?"

> **"It is important to have a plan in terms of how you approach relapse. Make sure you know what patients are progressing on, and use that information to guide where you are going next."**
>
> — SAGAR LONIAL, MD
> EMORY UNIVERSITY SCHOOL OF MEDICINE AND WINSHIP CANCER INSTITUTE

The second group of studies involves patients who received bortezomib and dexamethasone as the control arm—ENDEAVOR, PANORAMA, and CASTOR, as well as a trial of bortezomib plus dexamethasone with or without elotuzumab.

"Most of us have patients who are progressing on maintenance therapy in one form or another," Lonial said. "What you are going to do next may depend on what they are immediately coming off of."

Some questions and challenges remain, Lonial said: what to do for patients progressing on lenalidomide, the limitations in proteasome inhibitor dosing, and data with pomalidomide-based treatments in early relapse.

Considering some of the recently presented data, Lonial explained how these regimens might fit into treatment for patients with relapsed/refractory disease.

Findings from the international, open-label, randomized, phase II ELOQUENT-3 trial (NCT02654132) showed that adding elotuzumab to pomalidomide and dexamethasone reduced the risk of disease progression or death by 46% compared with pomalidomide and dexamethasone alone.[1]

This phase's primary endpoint was investigator-assessed PFS. Investigators reported at the 2018 European Hematology Association Congress that the median PFS was 10.3 months (95% CI, 5.6-not evaluable) with the elotuzumab combination compared with 4.7 months (95% CI, 2.8-7.2 months) with pomalidomide plus dexamethasone (HR, 0.54; 95% CI, 0.34-0.86; $P = .0078$). The secondary endpoint objective response rate was 53% (95% CI, 40%-66%) with elotuzumab compared with 26% (95% CI, 16%-40%) in the control arm (odds ratio, 3.25; 95% CI, 1.49-7.11; $P = .0029$).

"The median PFS of elotuzumab plus pomalidomide and dexamethasone was on par with daratumumab plus pomalidomide and dexamethasone, suggesting that if they get daratumumab earlier, perhaps elotuzumab plus pomalidomide and dexamethasone could be a good salvage," Lonial said.

Findings from the phase III OPTIMISMM study presented at the 2018 American Society of Clinical Oncology Annual Meeting showed a median PFS of 11.20 months with pomalidomide, bortezomib, and dexamethasone compared with 7.10 months with bortezomib and low-dose dexamethasone alone (hazard ratio [HR], 0.61; 95% CI, 0.49-0.77; $P < .0001$).[2] These findings suggest that the combination of pomalidomide, bortezomib, and dexamethasone may be a new standard of care in patients with relapsed/refractory multiple myeloma with prior exposure to lenalidomide.

New agents on the horizon include venetoclax (Venclexta), selinexor, and B-cell maturation antigen–directed chimeric antigen receptor T cells, such as bb2121. These therapies hold great opportunities for durable responses, Lonial said.

Overall, Lonial advised taking a standard approach to the management of early relapse and having a plan for managing first and second relapse. "It is important to have a plan in terms of how you approach relapse. Make sure you know what patients are progressing on, and use that information to guide where you are going next," he said. "If a patient is progressing on lenalidomide maintenance, I tend not to use lenalidomide as part of my salvage therapy and think about a proteasome inhibitor or pomalidomide as a partner." ■

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Investigator Discusses Combination Potential in Hodgkin Lymphoma

Tony Hagen

IMMUNE CHECKPOINT INHIBITORS HAVE scored impressive hits against Hodgkin lymphoma (HL) in recent years, but there remains a need for a more complete victory over this disease, Stephen M. Ansell, MD, PhD, told a gathering at the 2018 Pan Pacific Lymphoma Conference in Maui, Hawaii.

"We're learning lessons from the biology of Hodgkin lymphoma. That gives us opportunities to do things—to create combinations that will benefit patients," said Ansell, chair of the Lymphoma Group at Mayo Clinic in Rochester, Minnesota.

Stephen M. Ansell, MD, PhD

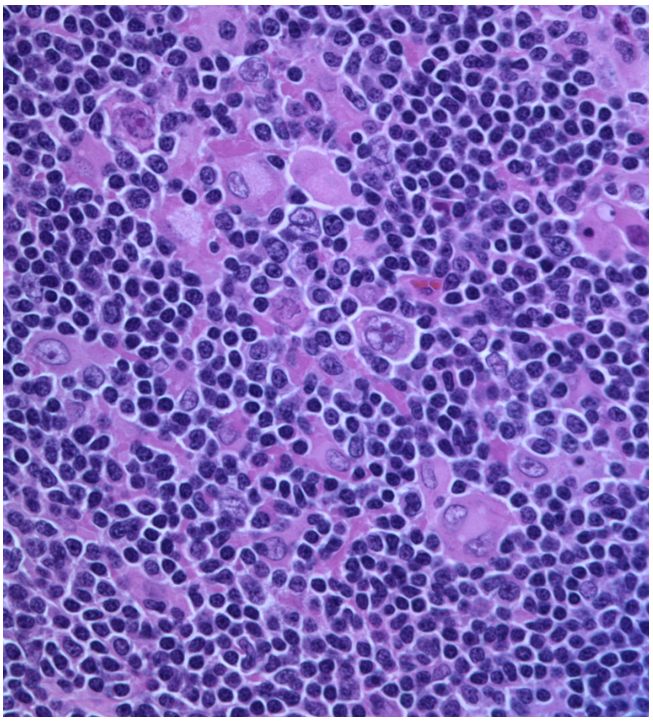
He discussed the efficacy of PD-L1 blockade in HL, patient treatment that has encouraged him to look for deeper solutions, alternative drug combinations that seem to be making headway, and potential avenues of discovery for the future.[1]

Ansell cited the case of a patient with HL who called him one night to announce that his treatment with nivolumab (Opdivo) was working. The patient had, among other symptoms, lymphadenopathy, and he explained that his armpits no longer itched. Sure enough, it turned out that his HL was on the retreat, but after a 2-year course of treatment, the disease was not completely gone. After an interim, he went back on the drug, and his progress has seesawed since.

"As an immunologist, I was super disappointed," Ansell said. It was clear that despite efficacy of treatment, the immune cells were not demonstrating sufficient immunological memory. "If you really have an immune system that saw something it didn't like, it would create memory cells, and every time it saw that antigen, it would go nuts and focus in and kill it right away." Another thing Ansell found disturbing: It appeared that patients would have to be treated throughout their lifetimes.

In a review of the evidence for nivolumab as checkpoint inhibitor therapy, Ansell cited the single-arm phase II CheckMate 205 trial for relapsed/refractory (r/r) classic Hodgkin lymphoma (cHL), which after a median follow-up of 18 months demonstrated an overall response rate (ORR) of 69% (95% CI, 63%- 75%), a median duration of response of 16.6 months (95% CI, 13.2-20.3 months), and median progression-free survival of 14.7 months (95% CI, 11.3-18.5 months).[2]

He also discussed the KEYNOTE-087 single-arm phase II study of pembrolizumab (Keytruda) for r/r cHL, in which the agent achieved an ORR of 69.0% (95% CI, 62.3%-75.2%) and a complete response rate (CR) of 22.4%



Hodgkin lymphoma can be subclassified into 4 pathologic subtypes based upon Reed–Sternberg cell morphology.

(95% CI, 16.9%-28.6%). Thirty-one patients experienced a response ≥6 months.[3]

Results of both trials contributed to the notion that a new paradigm had been achieved in treatment of cHL. "What's disappointing here is [that] it's not really a plateau," Ansell said. "Patients are slowly progressing, telling us we did something right." However, the problem isn't solved, he said.

The phase I JAVELIN study tested avelumab (Bavencio) as a selective binder to PD-L1 in r/r HL. The ORR for all 31 patients was 41.9%, and partial response (PR) was 25.8%, Ansell noted. The median time to response was 1.5 months (range, 1.4-6.2 months).[4] "Overall, you can tell that the majority of patients are benefiting. I'm not sure whether you're seeing a different outcome whether you block on the ligand side or the receptor side," he said.

Reed-Sternberg cells tend to be surrounded by macrophages that overexpress PD-L1 and interfere with effector cells that mount an immune response. "[However,] a number of patients have a copy number gain or an amplification of the locus, resulting in overexpression of PD-L1 and PD-L2, but that actually is associated with responses. It does tell us that these very high PD-L1–expressing patients are the ones who have the greatest degree of benefit," Ansell said.

"PD-L1 is actually shed and secreted into the bloodstream, and so you can have an effect at a distant site from this high PD-L1 expression. It might be important not only

to block PD-L1 at the tumor site but in the macro environment, too," he added.

This has been attempted by combining the immune checkpoint inhibitors nivolumab and ipilimumab (Yervoy). In CheckMate 039, this resulted in an ORR of 74% (n = 23) and a CR rate of 19% (n = 6).[5] "But does that really look different than nivolumab [action] alone? It'll take a randomized trial to show that. There may be some modest increment in benefit," Ansell said.

Another improvement on checkpoint blockade has been attempted through brentuximab vedotin (Adcetris) with nivolumab as salvage therapy. "You're hoping for an immunological cell death, which means that as the cell dies, it releases neoantigens that are then mopped up by macrophages and dendritic cells and shown to the immune system. That whole process is inhibited by PD-L1 expression. If you could prevent that, you could get a nice 2-for-1 where you increase death, increase antigens, and increase tumor cell activation and have a better result," Ansell said. Via this method, Diefenbach et al achieved an ORR of 100% (n = 12) and a CR of 66% (n = 8).[1] More time is needed to see whether these responses are durable, Ansell said.

> **"We're learning lessons from the biology of Hodgkin lymphoma. That gives us opportunities to do things—to create combinations that will benefit patients."**
>
> — STEPHEN M. ANSELL, MD, PHD
> MAYO CLINIC

Using PD-L1 blockade at the start of treatment also has potential. "There are data that show you can do that successfully. Is getting PD-1 blockade at the same time as chemotherapy the answer? It might be, but I think we're going to need randomized studies to prove that," Ansell said.

The use of bispecific antibodies has also brought promising results, he said. In targeting CD30 with AFM13, a bispecific anti-CD30/CD16A antibody construct, Rothe et al achieved what Ansell called modest responses: In the phase I study, 28 cHL patients achieved a PR of 12% and stable disease (SD) of 50%. With higher doses, the PR and SD rates improved to 23% and 54%, respectively.[1]

Finally, triggering macrophages to recognize tumor cells and break them apart may be another way to evoke a more complete response. However, this process is inhibited by CD47 binding to signal regulatory protein alpha (SIRPα), a regulatory membrane glycoprotein. In an attempt to wake up macrophages so that they behave toward tumor cells like "bar bouncers," Ansell is participating in a phase I, open-label, multicenter study to evaluate the safety and tolerability and identify the maximum tolerated dose of TTI-621, a soluble recombinant fusion protein consisting of the CD47 binding domain of human SIRPα linked to the Fc region of human IgG1, in patients with r/r lymphomas.[6]

"Can we tell you this is an effective therapy in Hodgkin lymphoma? Not yet, but getting the innate immune system to work with the adaptive immune system is 1 of the ways, and there are now trials moving forward," Ansell said. "Bispecific antibodies and macrophage-directed approaches, I think, are going to be the future in combinations as we go beyond immune checkpoint therapy." ■

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19TH ANNUAL **INTERNATIONAL LUNG CANCER CONGRESS**

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With Time, Translational Research Becomes Standard of Care in NSCLC

Lisa Astor

MOLECULAR PATHOLOGISTS HAVE HELPED advance translational research significantly for lung cancer over the past 10 years, and nowhere is that more obvious than in *EGFR*-mutant non–small cell lung cancer (NSCLC), according to a keynote address by Frances A. Shepherd, MD, FRCPC, OOnt, OC, during the *19th Annual* International Lung Cancer Congress®.

Frances A. Shepherd, MD, FRCPC, OOnt, OC

"Our translational research has really been translated into standard of care," said Shepherd, the Scott Taylor Chair in Lung Cancer Research at the Princess Margaret Cancer Centre and a professor of medicine at the University of Toronto in Ontario, Canada, and a 2016 Giants of Cancer Care® (Lung Cancer) awardee. "We've learned so much, and our translational molecular pathologists have helped us so much."

Broader *EGFR* Testing Could Guide Treatment Decisions

It has become standard of care for patients with NSCLC harboring *EGFR* mutations to be treated with an EGFR tyrosine kinase inhibitor (TKI) in the first-line setting, because EGFR-targeted therapies have shown superiority over chemotherapy in this patient population. Recent advancements have also shown that increased information from the pathologist regarding specific *EGFR* mutations can help oncologists decide which therapy to give each patient.

The second-generation EGFR inhibitor afatinib (Gilotrif) was approved in 2013 for the treatment of patients with metastatic NSCLC with exon 19 deletions or exon 21 L858R substitutions. The approval was expanded in January 2018 to include uncommon *EGFR* alterations, including L861Q, G719X, and/or S768I, based on results from the LUX-Lung trials.

Afatinib demonstrated significant benefit over chemotherapy in patients with exon 19 deletions in pooled analyses from the LUX-Lung 3 and 6 trials. In the LUX-Lung 3 trial, the median overall survival (OS) was 33.3 months with afatinib compared with 21.1 months with pemetrexed/cisplatin chemotherapy (hazard ratio [HR], 0.54; 95% CI, 0.36-0.79; $P = .0015$); in LUX-Lung 6, the median OS was 31.4 months with afatinib versus 18.4 months with gemcitabine/cisplatin (HR, 0.64; 95% CI, 0.44-0.94; $P = .023$).[1]

In the LUX-Lung 7 trial, however, patients with *EGFR*-mutant advanced NSCLC demonstrated modest improved survival with afatinib compared with gefitinib (Iressa). Patients with exon 19 deletions, specifically, had a median OS of 30.7 months compared with 26.4 months with gefitinib (HR, 0.83; 05% CI, 0.58-1.17; $P = .2841$).[2] Although the OS benefit was not found to be statistically significant and the toxicity profile of afatinib is more difficult, Shepherd noted that in fit patients with exon 19 deletions, she will prescribe afatinib. For less fit patients, she recommended gefitinib.

In updated results from the ARCHER 1050 trial presented at the 2018 American Society of Clinical Oncology Annual Meeting, dacomitinib, another EGFR TKI, showed improved OS compared with gefitinib in patients with treatment-naïve *EGFR* exon 19 deletion or exon 21 L858R mutations.[3] Dacomitinib, which was granted a priority review by the FDA in April 2018 for this setting, demonstrated a median OS of 34.1 months compared with 26.8 months with gefitinib (HR, 0.760; 95% CI, 0.582-0.993; 2-sided *P* = .0438). The OS benefit was particularly significant among patients with exon 21 L858R mutations specifically, with a median OS of 32.5 months with dacomitinib versus 23.2 months with gefitinib (HR, 0.707; 95% CI, 0.478-1.045; *P* = .0805).

Responses to afatinib were also seen in patients who had point mutations or duplications in exons 18 through 21 in the LUX-Lung trials. Of 38 patients in this group, 27 responded to treatment and demonstrated a median OS of 19.4 months (95% CI, 16.4-26.9 months), whereas patients with exon 20 insertions (n = 23) had a median OS of 9.2 months (95% CI, 4.1-14.2 months), and just 2 patients had objective responses.[4]

Shepherd explained that patients with exon 20 insertions had the worst prognoses compared with more common *EGFR* mutations, and most of these insertions were not responsive to EGFR TKIs. "Initially, we were only testing for [exons] 19 and 21," she said. "Now we have much broader EGFR panels, and so our pathologists can guide our therapy and help us select the appropriate TKI."

Don't Stop Testing at 1 Mutation

It may be important to know about comutations in addition to *EGFR*, Shepherd added. For example, comutation of the *EGFR* and *TP53* genes frequently occurs and may help predict which patients will transform to small cell lung cancer (SCLC).

A prospective analysis of 65 patients with *EGFR*-mutant lung adenocarcinoma that had transformed into SCLCs that were resistant to EGFR TKIs revealed that patients harboring completely inactivated *RB1* and *TP53* had a 43-fold greater risk of transforming to SCLC (relative risk, 42.8; 95% CI, 5.88-311).[5] Shepherd noted that patients known to be at increased risk of transformation can be watched more closely.

The *TP53* comutation also serves as both a prognostic and predictive biomarker in *EGFR*-mutant NSCLC, because patients with *EGFR* and *TP53* comutations have a worse prognosis than *TP53* wild-type patients and demonstrate worse progression-free survival (PFS) on EGFR TKIs (HR, 1.74; *P* = .06). Additionally, patients with *TP53* comutations had a shorter time to development of central nervous system metastasis (HR, 1.43; *P* = .25).[6]

"[Even though] we have no treatment strategy to apply to *TP53*/*EGFR*-mutant tumors…we might screen more frequently for brain metastases; we might biopsy earlier for SCLC transformation. We might learn something," Shepherd said.

Resistance to EGFR TKIs and Improved Detection

Molecular pathologists play a crucial role in determining mechanisms of resistance to EGFR TKI therapy, Shepherd said: "Resistance—this is where molecular pathologists have to be our friends for sure."

Although T790M is the most common resistance mutation, appearing in approximately 60% of patients, it is far from the only mechanism of resistance. However, third-generation EGFR TKIs have shown sensitivity to T790M, and osimertinib (Tagrisso) received FDA approval in 2017 for the treatment of patients with *EGFR* T790M–mutant NSCLC who progressed on an EGFR TKI, based on results from the phase III AURA3 trial.

In addition to demonstrating a PFS benefit for osimertinib over chemotherapy in patients with *EGFR* T790M mutations, the AURA3 trial also demonstrated that early clearance of plasma *EGFR* mutations could be used as a predictor of response to osimertinib. In an AURA3 analysis led by Shepherd, patients who demonstrated shedding of *EGFR* mutation in the peripheral blood had worse PFS compared with nonshedders (8.3 vs 14.0 months) and worse objective response rates (68% vs 75%).[7]

Additional genomic aberrations could be found in the peripheral blood, and Shepherd noted that there was no improvement in PFS with the detection of *TP53* mutations in plasma (HR, 1.17; 86% CI, 0.78-1.76). "Technology has advanced so much that we can even do next-generation sequencing on little peripheral blood samples," Shepherd commented. ■

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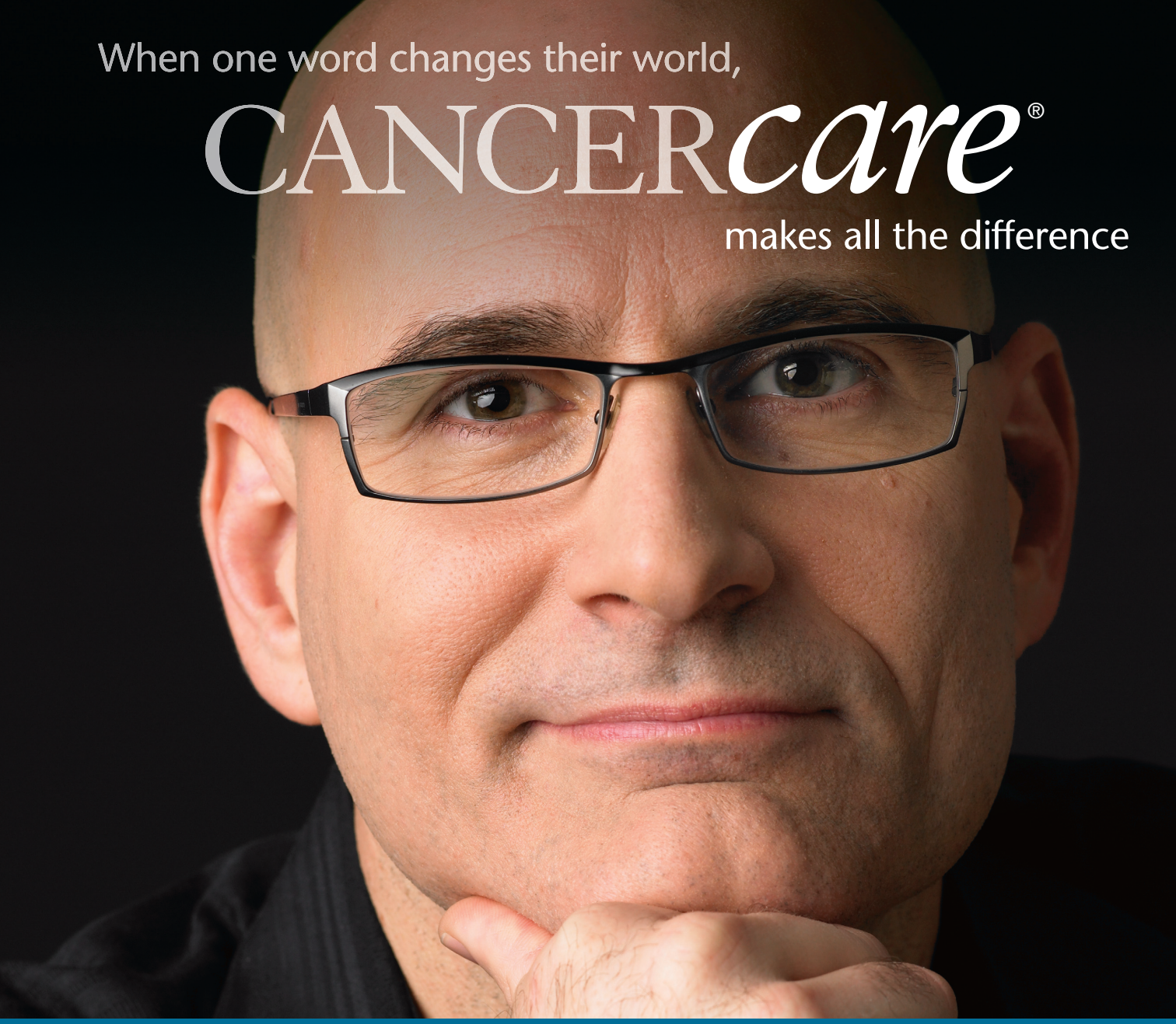

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