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The Screen Steals the Show – A Review of the New Apple Series 4 Watch

By Dieter Bohn@backlon
Photography by Vjeran Pavic.

The greatest Apple product comeback story of the past few years has, without a doubt, been the Apple Watch. Launched with great fanfare four years ago, the initial version tried to do way too much with way too little, and it had confusing software to boot. Worst of all, it was unclear what the original Apple Watch was even for. No single thing stood out.

Then Apple did what Apple often does: iterated, refined, and fixed. But as much as there were software and hardware improvements to the Series 2 and Series 3, the most important refinements were to the Apple Watch’s purpose. It gained clarity. It was for fitness and notifications. Eventually, when it was ready, Apple added better connectivity.

Now, with the Series 4, Apple is iterating again. And, importantly, it’s learned how to iterate the product’s hardware and its purpose at the same time. The Series 4 has finally achieved something like the original goal of the Apple Watch. It’s not quite a do-anything computer on your wrist, but it can be different things to different people now.

With apologies to the new iPhones, the Apple Watch Series 4 was the most impressive thing Apple announced last week. After using it for the past week or so, I think it lives up to the hype.

GOOD STUFF
- Great battery life
- Huge, beautiful screen
- Health-tracking features, not just fitness

BAD STUFF
- No always-on screen option
- Complication options can be confusing

Before we get too far, we should talk pricing. This Watch is not especially cheap. The smallest, least expensive model comes with GPS and Wi-Fi and costs $399. But if you start piling on the upgrades, you can quickly jack up the price to something that feels exorbitant, especially if you’re upgrading from a Series 2 or Series 3. It’s $29 more for the larger size, $100 for LTE compatibility (plus $10 per month or so from your carrier), and the stainless steel models are $200 more (and only come with LTE). Add in Apple Care, and you can end up spending a lot — though it’s nothing like the wild “Edition” prices of yore. (Don’t even get me started on the Hermès model.)

THE LARGER SIZES DON’T FEEL THAT MUCH BIGGER THAN THE OLDER MODELS

The two new sizes are 40mm and 44mm, but they really don’t feel that much bigger on your wrist than the old sizes. I was using the 42mm Series 3 and the 44mm size is only subtly bigger, but it’s also subtly thinner. To me, it feels about the same, but I think the trade-off of size for thinness is worth it. I suspect the same will be true for people who prefer the smaller size, but my recommendation is to go to a store and try one on before buying.

I’m really happy — and impressed — that Apple managed to make existing Watch bands fully compatible with the new sizes. Even my old third-party bands fit seamlessly into the new Watch body.

Things look different when the screen turns on. The screen on the Series 4 is just incredibly good. Apple says it’s 30 percent bigger, which is one of those specs that’s easy to just sort of pass over when you read it. But 30 percent is a lot, and you absolutely notice it right away.

It’s still OLED so the blacks are truly black and blend into the watchface glass. But if you pick a full-screen watchface, you’ll see that the screen also goes closer to the edges of the Watch than before, including the rounded corners.

The overall effect makes the square display on my Series 3 look dumpy and cramped by comparison — even though, until last week, it was arguably the best smartwatch screen on the market. As John Gruber writes, “The Series 4 displays take up so much more of the face of the watches that the new 40mm watch’s display is larger than the display on the old
Beyond the size and the screen, there are a few other subtle exterior differences to note about the hardware. The rear of the Watch is now ceramic instead of metal to allow for a better wireless signal. If you spring for the LTE model, the garish red dot on the digital crown has been replaced with a much more subtle red ring.

The microphone has been moved between the two buttons so that it's further away from the speaker to help reduce echo in calls. The speaker has been boosted to provide more volume. It really is way louder, and I haven't heard any distortion during phone calls.

Last year’s Apple Watch had some issues with LTE at launch, though Apple fixed it up fairly quickly. This year, I haven’t had any major problems with LTE. In fact, several people I called with the Watch simply didn’t believe I wasn’t on a phone. It sounds good, and the louder speaker means you can hear it without holding the thing next to your ear.

But it does take the Watch a minute (sometimes two) to switch on LTE and get connected. That’s not radically worse than what happens when you pull your phone out of airplane mode, but on the Watch, it’s always a little less clear what’s happening and why when data is not coming in.

On the inside, there’s a faster S4 processor, a W3 chip (which is just Apple’s W2 chip with Bluetooth 5.0 support), and an accelerometer and gyroscope that are able to take samples of your movements more often (which is how Apple was able to add the new fall detection feature). Apple’s also tied haptics to the digital crown, so when you spin it, you feel little ticks that precisely correlate to what’s happening on the screen. It’s completely unnecessary but pretty neat.

BATTERY LIFE HAS BEEN STUPENDOUS

Last but certainly not least: the battery size is about the same. Battery life on the Series 4 is as good or better than on the Series 3 Watch. Apple claims 18 hours of regular use or six hours of outdoor workouts. I haven’t done a six-hour outdoor workout (and I don’t plan to), but my testing shows the battery life far exceeds Apple’s own claims.

I took the Watch off the charger on Saturday morning and wandered around Oakland for four hours while disconnected from my phone. I used LTE for maps, a couple calls, and GPS for tracking my outdoor walk “workout.” I was still at 50 percent at the end of that day, and I didn’t get below 20 percent by the end of my lazy Sunday (which also involved an hour or so of GPS tracking and some LTE data).

The battery life is so good that I wish Apple gave me an option for an always-on ambient screen, maybe by turning off some radios. Alas, you still have to turn your wrist to see the time.
Maybe the most interesting change, though, is how Apple is more clearly separating out health features from the fitness stuff. There are a few new features in watchOS 5 and the Series 4 that are designed to help you detect health problems, not just encourage you to close those activity rings or run a marathon.

That's interesting because it more explicitly positions the Apple Watch as a device that can help detect health problems, making it something that people who can't exercise that much might be more interested in. Apple, as always, is very careful to not cross the line into making actual health claims about its new features. It's careful to say that the Watch can detect things like irregular heartbeats, not that it will.

**THERE'S A BIG DIFFERENCE BETWEEN “TRACKING YOUR FITNESS” AND “MONITORING YOUR HEALTH”**

watchOS 5 is able to detect low heart rate now, in addition to high heart rate. Later this year, Apple will add detection for irregular rhythms and provide notifications for them. The big new feature on the Series 4 is that it can take an electrocardiogram (EKG) using electrodes built into the back of the Watch and the digital crown. It can then send a PDF of your results to your doctor. I wasn't able to test that as it is coming later this year. Both irregular heartbeat detection and the EKG features have been granted “de novo” classification by the FDA, and that distinction is important, as Angela Chen explains: It's important to understand that the FDA has “cleared” both apps, but that's not the same as “approving” them. There are usually three ways to get the FDA involved in a new project, according to Jon Speer, co-founder of Greenlight Guru, a company that makes quality management software for medical device companies. The most advanced is FDA approval, which is done only for Class III products, or technologies that might have higher risk but also a higher benefit. (Think: implantable pacemakers.) Approval is the gold standard, and companies need to do a lot of testing to receive this designation.

**The Apple Watch is in Class II. For Class II and Class I, the FDA doesn't give “approval,” it just gives clearance.**

Another new feature exclusive to the Series 4 is hard fall detection, thanks to a new 800Hz accelerometer and gyroscope that can that can measure up to 32 G-forces. The Watch should be able to tell if you’ve had a spill and ask if you’d like to call emergency services. If you don’t move for a full minute after falling, it can do that automatically and also send a message to your emergency contact. Apple is turning it on automatically for users who tell the Watch they’re over age 65, and it’s making it an option for younger users as well.

I've tried to trigger it without hurting myself and I haven't been able to, which I suppose is a point in the Watch’s favor. (My tests were far from scientific; I was just hurling myself at the couch.) Apple says that to build its fall detection algo-

So throwing yourself into bed after a long day shouldn’t trigger it, but a fall from a ladder or tripping over a curb and flailing your arms as you hit the ground might. Again, Apple’s health claims are not that the Watch will detect these falls, but simply that it could.

A lot of people were really excited about Walkie Talkie mode, but after testing it, I don't think it's especially compelling. Unlike those classic Nextel Push-to-Talk phones, Walkie Talkie mode on the Apple Watch is essentially just a FaceTime Audio call with a button you press to talk and little beeps and visual indicators to tell you if it's your turn.

When you send the first message, you have to wait for a connection to be made, and then it's just tapping the screen and talking. The connection stays active until a few minutes after the last person finishes speaking. It's neat, but it doesn't feel as instant as a true PTT system. I also had connectivity problems with it, but that may have just been OS launch-day overloading.

That said, it's silly fun to push the big yellow button with your nose when it's your turn to talk. I strongly recommended it. (If it becomes a thing, I want to make sure I get full credit for coining the term “nose calls.”)

Siri on watchOS 5 is still Siri. There's a new feature that lets you simply lift your wrist and start taking instead of pushing a button or saying “Hey Siri,” and it works really well. The Siri shortcuts you set up on your iPhone should also work from your Watch, too. Siri still feels super unreliable, though.

Siri gets especially fussy when you have a spotty connection. Too often, when I wanted to ask a question, I’d be met with a “hang on…” message, followed by a “I’ll tap you when I’m ready” message, followed by an interminable wait during which I’d forget whatever it was I needed Siri for.

One last little watchOS 5 thing I must mention: you can open links to webpages now, too, which is kind of fun. Articles you click on get put into readability mode, so you don't have to worry too much about ads or bad layouts on your Watch. Hooray for the web!
Studies show that physicians weigh many factors in considering when to retire. Of course, how financially secure they feel is part of the decision. However, since physicians are among the highest paid workers in the U.S., with median* salaries over $208,000, finances aren’t as much an issue, as they are to the average worker. It turns out that, after putting so much time and dedication into their careers, it’s difficult for physicians to know when to retire.

Financial Security

Naturally, physicians want to wait to retire until they feel financially secure. But, in a survey of physicians commissioned by Comp Health, 83 percent said they felt prepared financially, or had a plan in place and were confident their plan would make them financially secure at retirement age. Other studies confirmed their financial security. They are concerned about possibly having to scale down their lifestyle, but as a group, physicians feel financially prepared. So, the decision is about much more than money.

Joy of the Job

The fact is, most physicians are passionate about their jobs, even late into their careers, and they feel that they are still able to make valuable contributions, according to a survey by Physicians Practice. They put a lot of effort into their education and acquiring skills through the years, and they don’t want to leave that behind. The survey contacted physicians in family practice, emergency medicine, psychiatry, OB/GYN and surgeons. Many said they would miss the social aspects of work, of interacting with their co-workers and patients. The Comp Health survey revealed that as they worry about staying competitive, they’re also concerned about being bored in retirement, of losing their sense of purpose and becoming depressed.

Hard to Keep Up

Yet, physicians find that it’s hard to keep up on all the advancements and changes in medicine, according to an article in Wall Street Physician. As they get older, their health declines, as does everyone’s health, and they may find that they’re slower and suffer greater fatigue than in earlier years, simply from the rigors of the job. In the Physicians Practice survey, 51 percent said they’d like to transition to part-time hours before retiring completely. Available data, though, from the American Medical Association of physicians who are active in their fields, doesn’t distinguish between full-time and part-time work. So, it’s tough to tell how many physicians actually work part-time before they retire.

Looking for Balance

The shortage of physicians has caused most to work long hours throughout their careers, missing out on many aspects of their non-work lives. As they reflect on this, many say if they had it to do over, they would insist on more work/life balance. They recognize that if they retired, they’d have the time to spend with family and to take up hobbies.

Average Retirement Age

Physicians in the Physicians Practice survey said they’d like to work until age 68. A 2016 report by the American Academy of Family Physicians found that, between 2010 and 2014, primary care physicians retired at an average age of 65. They found no difference between those who worked in various areas of the country or in other medical specialties. In the general U.S. population, people say they hope to work until age 65, but the average age for retirement is 63. So, physicians are working longer than the average American.

Length of Career

After four years of college, another four years of medical school, and between three and seven years spent in internships, depending on their chosen specialty, it takes between 11 and 16 years to become a full-fledged physician. Assuming that they entered college at age 18, this means that they begin their solo careers between the ages of 29 and 34. Therefore, assuming that he or she retires at the age of 65, the average length of a physician’s career is between 31 and 36 years.

* A median salary is the midpoint in a list of salaries for one occupation, with half earning more and half earning less.
Your One-Stop, See-All Practitioner in the Arctic and Antarctic

Forget choosing between sprawling city hospitals and small boutique clinics, subways compared to streets, ambulances versus Uber versus your own speeding automobile. When you’re cruising in the Arctic and Antarctic, the nearest hospital is a long way off, and in terms of the health care, everyone has access to the same kind – and the same person. During her voyage around the Arctic archipelago of Svalbard, Dutch polar cruise doctor Lauke Bisschops told us all about her experience treating injuries, illnesses, and a surprising lack of sea sickness.

What did you do before signing on as an Arctic cruise doctor?

I was an emergency physician for six years, and I’m currently in residency to become an elderly care physician. This is a medical specialty that only exists in the Netherlands. The physician tries to maintain and improve the quality of life for elderly people and chronic patients. I think my combination of emergency and elderly care, which mostly involves treating common complaints, is particularly useful on this ship. I know what to do in case of an emergency, and I also know how to treat everyday ailments.

What are the everyday Svalbard ailments you’ve treated so far?

Mostly small problems: colds, stomach aches, minor injuries from the movement of the ship – if you’re reading this and you’re on your own polar cruise, keep your hands away from the doors! I only had one seasick patient, which was a surprise. Luckily all the patients I saw could be treated on the ship. Plancius has a well-equipped clinic with enough medication and supplies to treat most anything. I’ve also seen quite a few people who just wanted something checked out, something I don’t even need my stethoscope for.

So nothing serious has happened? No frostbite, no Arctic yeti attacks?

Not yet, but then the cruise isn’t over! One woman did give me a scare recently. She looked like she might be having a heart attack, but after careful examination I saw it was something benign. In a situation like this, you get very focused. You realize you’re a long way from a hospital. My ER experience helps me stay calm and do what I have to do. Knowing what is happening and reacting on time is very important when you’re this far from help.

Is being a sailing Svalbard doctor all that you expected?

I expected to be outdoors as much as possible, and so far I haven’t been disappointed. I did not, however, expect to love the sky, clouds, and water so much. Sometimes it’s like you’re not even looking at the sky, but some kind of abstract painting. I have never seen anything like it in the world outside of an Arctic cruise. Standing on the bow of the ship as we sail between the icebergs, watching another ship disappear into the mist – these things make me feel like a real explorer.

Are there perks to being an Arctic doctor, apart from the lack of seasickness?

I have a special place on board. I’m not a crew member and I’m not a passenger, but I’m a bit of both. So I get the best of both. Beside my tasks as a doctor, I also help on the gangway and do other things, such as watching for polar bears. I love doing that, but I’m not very good at it. The guides and crew, especially Captain Alexey, are amazing at it. Real experts at spotting wildlife.
What's been your most memorable Svalbard moment so far?
Easy, seeing my first polar bear. It's amazing to see how big and powerful they are. I have seen them so much on television, and now to see them in real life is something I thought I was never going to experience before starting this job. And again, the sky and the clouds. I think I've taken at least a hundred pictures of just the sky.

In your experience, is it easy for a doctor to make friends in the Arctic?
Actually, I've made friends with most of the expedition guides and plan to stay in contact with them. One of the guides is also from the Netherlands, so we'll definitely see each other. I also plan to stay in touch with some of the crew from the ship. Visiting these people will not be easy, as almost all of them live and work in other places all over the world, but I'll chat with them on WhatsApp or Facebook – once I'm back in a part of the world that has internet, that is.

Why Svalbard? Why not St. Barts or the Mediterranean?
I love to see a variety of places. This year I've already gone to Tanzania, the Philippines, and Honduras to travel and work as an expedition doctor. But the polar regions are, for me, more special. They are one of the last places on Earth where humans are not dominating the environment, but visiting it. The experience of an “unspoiled” place makes me feel small and realize what we are doing to the planet. And hearing lectures about the melting ice and seeing the struggling wildlife makes me realize we can't ignore the fact that climate change is happening right now, not at some vauge future date. I think anyone who sees what it's like here would feel the same.

Would you ever sign on for another cruise? Is there an Arctic Doctor: Part Two?
How about Antarctic Doctor: Part One? In December I'm going on an Antarctic cruise for the first time. For me this is a great way to explore, practice my profession, and meet people from all over the world who are as excited about these places as I am. When Oceanwide asked me if I wanted to work on another cruise, I didn't hesitate for a minute. I'd already heard so many stories about how amazing the nature was in Antarctica. I feel privileged to get this opportunity.

And in Antarctica you'll cross the Drake Passage, which is known for its rough seas – and hence, seasickness

Then I'll make up for the seasickness I'm not treating right now!
Stop the Money-Shaming in Medicine

By James M. Dahle, MD

There is a taboo in medicine. It is becoming less prominent, but it still exists. You’re not supposed to talk about money. Not how much something costs a patient, not how much you get paid, not how you invest, and certainly not about the freedom from medicine that financial independence can bring.

This first shows up as you are applying to medical school. You don't want anyone writing a letter of recommendation or heaven forbid an admissions committee to get even a whiff of an idea that you might actually want to receive a paycheck for practicing medicine at some point down the road. It is reinforced throughout medical school and residency and persists throughout your career in interactions with your peers, your professional colleges, your board certification organization charging you thousands to take an online test, and your hospital.

Meanwhile, the business world and particularly the financial services world views you as a whale, ready to be harpooned. And all these little doctors in their own little silos who “love science and just want to help people” are taken advantage of one by one. It pisses me off.

But you want to know what makes me even madder? When I see doctors “money-shaming” each other. Reinforcing this taboo that you can’t talk about or even learn about business or finance because it’s “filthy, dirty money” and you’re a “bad doctor” to think about it. Let me give you an example.

PIMD Gets money-shamed

Passive Income MD wrote a blog post a while back about how he is financially free from medicine. I read the post and thought, “That’s great. Now he can practice medicine if and how he likes. He’ll be a better doctor and take better care of people. Or, if he wants, he can get out of medicine and do something else that he finds more fulfilling. If he practices less or stops altogether, it allows the services of other doctors to be more in demand, keeping salaries high for everyone.

How wonderful!”

Well, his post gets picked up by Doximity and shared. That’s wonderful too. I love it when my stuff gets shared with a larger audience, and I’m sure PIMD does too. There really is (almost) no such thing as bad publicity in this business. So I saw it in the email that Doximity sends out every now and then and took a look at some of the comments below his post.

Most were very supportive, until I ran into one written by a psychiatrist, published under his real name (which I’ll leave out as it really isn’t relevant to my point):

Why did you go into medicine in the first place? It sounds like to get rich. Congratulations. Patients were a lousy revenue stream, too much maintenance. So you are free from an opportunity to do work that actually relieves suffering, and if you are half-as clever financially as you claim to be, you could have made a good living at. You are free from having to do the hard work of medicine. After practicing for 40 years, I still value using my competence to lighten the burden of disease on my fellow human beings, more than the fact I make a good salary doing so. You could have made more money if you had started with an MBA and a Law degree, and skipped the fake wanting to practice medicine. You are free from medicine, from hard work, from dealing with truly heavy responsibilities. Your narcissism is normative in American society. You are free giving, and free to take all you want. Enjoy! You exploited the profession, and now you can live the hedonism that is the core of your value system.

Hey kids! Get off my lawn! Seriously though, other doctors read this comment and say to themselves, “Self, be sure you don’t talk about money or financial independence to any of your colleagues because some of them are going to react like this.”

To the psychiatrist’s credit, he returned later down in the comments section and left a bit of an apology and a more nuanced, less inflammatory explanation of his views on the subject.

Stop money-shaming!

I call this sort of thing “money-shaming,” and I want you to quit doing it. Some of us are more altruistic than others. That’s always been the case. And there is someone more altruistic than you are. You're a family doc working for $180K? Great. There’s a classmate down the road who is a pediatrician making $150K. And one who went into the military and worked for $120K while being deployed all over the world taking care of those defending your freedom. And someone else who works 3 days a week in the homeless clinic for a pittance. And someone who spends their vacation time in Co-
But the truth of the matter is that very few of us are willing to practice medicine for free. Especially on a full-time basis. In fact, it turns out that most of us wouldn't be practicing as much as we do now if it wasn't for the money. I have surveyed many groups I have talked to. I ask them if they'd report to work tomorrow if I wrote them a check for $10 Million today. They almost all say yes. But when I ask them if they'd be working less in a year (fewer shifts, shorter days, fewer patients per day, less call etc), they almost all raise their hand. My conclusion? Most doctors are working, at least partially, for financial reasons.

Why should that be a surprise? And why would it be a bad thing? Adam Smith pointed out centuries ago that, in general, we benefit each other and society as a whole as we pursue our own self-interest. That's capitalism. And it has led to the greatest increase in freedom, wealth, and humanity that this planet has ever seen. Nurses get paid. Teachers get paid. Garbage men get paid. Judges get paid. Politicians get paid. Uber drivers get paid. That doesn't diminish the value of the work they do. There's a reason it's called “work”–because they have to pay you to do it.

In fact, I would argue that the MOST selfless and altruistic doctors among us are the ones who are financially independent and still practicing because they love it. I would love to shorten the average time period between when a doctor comes out of residency and when she can practice merely because she loves it. But even then, I don't expect her to work for free.

Celebrate the financial success of your colleagues
So my challenge to you is that rather than money-shaming your colleagues, you celebrate their successes. What a difference between going to FinCon (a conference of financial bloggers where you are invited to give a talk and everyone celebrates your achievement because you doubled your income) and a medical conference (where financial or business topics are generally given short shrift)!

When we start talking about paying off our student loans and our mortgages and avoiding whole life insurance and becoming millionaires and becoming financially independent then we'll all, doctors and patients alike, be better off. If nothing else, at least a lot of salesmen masquerading as financial advisors will be driven out of business.

James M. Dahle is the author of The White Coat Investor: A Doctor's Guide To Personal Finance And Investing and blogs at the White Coat Investor. He is the creator of Fire Your Financial Advisor!, a high-quality 12 module course with a little over 7 hours of videos and screen-casts, a pre-test, section quizzes with answer explanations, and a final exam. The goal is to take a high income professional from square one, teach them financial literacy and help them write their own financial plan.

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Life starts all over again when it gets crisp in the fall.
-F. Scott Fitzgerald
value in one's own self a mantra and I even managed to convince my mother to serve as a volunteer teacher, a concept that was not easy for her to consider. To her surprise, she became an exceptional teacher in addition to being an amazing mother. Many years later, in honor of my mother, I established the annual "G. Shahin Award" through the Duval County Medical Society, which serves to recognize those residents and fellows who publish the most impactful scientific articles of the year.

My reasons behind becoming a physician
I knew early in life that I wanted to be a physician. My grandfather was a pharmacist, and my aunt and uncle were both physicians. I was fascinated very early on to observe the impact that doctors had as healers in people's lives. Despite my keen interest in pursuing medicine as a career, my plan to attend college and go to medical school was not exactly an easy journey. Frankly, most girls got married and had children after high school whereby they were dependent on their husbands to provide for them and their families. There was no doubt in my mind that I needed to take a different path. Realizing that pursuing this goal meant I would most likely have to seek education outside of Iran, I participated in a countrywide academic competition in hopes of obtaining a foreign exchange scholarship.

I earned this opportunity at the age of 16 when I received an "American Field Service Scholarship." This award entitled me to be a guest of an American family for one year and to finish my high school education in the United States. I accepted this invitation with a great deal of enthusiasm. This trip was an opportunity for me to walk away from the traditional life path in my homeland and move towards an exciting new adventure where I was the ultimate arbiter of my future. I will never forget my first impressions of New York City, where I was first exposed to the incredible diversity of cultures, colors, accents, outfits, and opinions that were all intertwined within the society. The common thread, however, was clear: despite the seeming diversity on the surface, there was a deep underlying appreciation of individual freedom that permeated this society. Ultimately, the scholarship and year abroad ended and I was able to return home and to begin pursuing...
my medical training. Later, my husband and I came to the United States for our postgraduate training. While in the U.S., we were blessed to have our two sons, both of which have also chosen to pursue medicine as careers.

**Living through the Revolution**

In 1979, upon invitation from Shiraz University, my husband and I returned to Iran to start our professional academic careers. We were both very excited to return to the city of Shiraz as it was the setting for so many fond memories that we shared from our medical school days. Our return home, however, was challenging to put it lightly. When we arrived, there was clear evidence of civil unrest and not long after our return, the revolution began. Living through the revolution was a humbling experience. Life became an exercise in balancing between survival and adhering to our principals. I tried to focus on my work and my patients but the environment we were working under became intolerable so I felt no choice but to resign from the University system. In search of an alternative, my husband and I became the driving force behind establishing an eighty-bed private hospital staffed with ten other American board-certified physicians from varying specialties. When I look back, I can proudly say that I was successful in bringing together a multidisciplinary team of physicians in order to care for some of the most neglected patients in our city. I can confidently state that establishing that hospital was the greatest joy in my professional life.

Despite the remarkable professional success that both my husband and I experienced, the gradual loss of personal freedoms as the revolution continued began to have an unbearable impact on our everyday life. It was clear that - despite our best attempts - practicing medicine and living our lives with autonomy and freedom was not going to be tolerated by the government. Thus, our departure became inevitable. It is interesting to look back and reflect on how readily one is willing to trade comfort and wealth for safety and freedom.

**Our return to the United States**

Ultimately, we were able to make our way back to the United States where Jacksonville, Florida became our second home. The University of Florida was willing to support my request for permanent residency. The community of Jacksonville embraced my family and I for which we are most grateful. I have been fortunate to have a life that is filled with both incredible adventures and challenging experiences. My outlook has been to try to extract lessons and inspirations from both the good and the bad.

I currently hold the position of Professor and Chair of the Department of Pathology and Laboratory Medicine at the University of Florida College of Medicine - Jacksonville. Despite the considerable time that being a department chair requires, I am firmly committed to teaching the next generation of pathologists to which I serve as Director of our Cytopathology and Breast Pathology Fellowship Training Programs. In addition, I am the Medical Director of UF Health Jacksonville Laboratories and the Director of UF Health Breast Center.

Both of our children are now physicians, as well. My eldest son, Ali, is a urologist who works with my husband, Dr. Ahmad Kasraeian, at their private practice: Kasraeian Urology. My youngest son, Sina, found his calling in medicine as well, and is an outstanding orthopedic surgeon.

Personally, I have immersed myself in community affairs that are close to my heart. Perhaps the many years of feeling homesick and away from my country is what drew me to helping Northeast Florida’s indigent population. I became the founding member of We Care Jacksonville for which physicians volunteer to treat the underserved. At the first event of this organization, I was proud to open up my home to hold the inaugural fundraising dinner. Similarly, I directed “The Physicians Talent Show” at the Florida Theater where physicians were able to showcase their talents in benefit of a worthy cause. Funding generated through these efforts went to providing free medications to those in need. I have also served as a founding board member of the I. M. Sulzbacher Center for the homeless, where my family and I had the opportunity to cook and serve more than 400 people. In addition, I have

My husband, Dr. Ahmad Kasraeian, and I at Shiraz University School of Medicine in Iran, while we were students.

My husband and I in Italy during our breast cancer symposium in 2000.

Family photo with my husband, Dr. Ahmad Kasraeian; my youngest son, Sina, and his wife, Haley, and their two dogs; my oldest son, Ali, and his wife Addie, my grandson, Alik, and their dog. (photo credit to Sarah Hedden)
served with Volunteer Jacksonville, American Cancer Society, and the Duval county Medical Society to name a few.

My experience at the University of Florida
I have remained a loyal subject to the mission of the University of Florida and have tried my best to stay focused on issues that matter most to the profession of medicine. Aside from being Chair of the Department of Pathology and Laboratory Medicine, I was privileged to serve as the first Assistant Dean for Research. During my tenure, I focused on building the infrastructure of our IRB and solidifying the Office of Research Affairs on the Jacksonville campus. I additionally founded the "UF Association of Professional Women in Jacksonville" with the goal of supporting equality and inclusion at the work place. Among the many roles that I have played, the one that I enjoy the most has been my contribution as a teacher and a patient advocate. I strive to bring attention to women's health issues, particularly breast cancer.

Breast cancer remains a major public health problem across the globe. This is a complex array of diseases with no single cause or cure. Like a silent enemy, breast cancer presents itself in a variety of forms and shapes and can strike at different times and in different places. The best approach has been to focus on individualized therapy to which I have established the first breast health center in the North Florida region at UF Health Jacksonville.

Access to breast health care and optimal approaches to breast cancer detection and therapy are a global challenge. This challenge is one requiring a worldwide collaboration among those who have the power to implement change. Simply put, we need to do better! Whenever a patient comes to us for the first time with an ulcerated breast mass too far advanced for us to help, it is a failure of the medical community as a whole. As physicians, health care providers and educators, wherever we are, we need to deliver an enhanced quality of care that our patients so rightly deserve. To this end, my dream is to build a comprehensive breast health center in our community for our medically underserved population that currently have no place to go.

My efforts so far have been focused on advancing “Global Breast Health Education.” There is no doubt that up to date knowledge about breast cancer for both physicians and the public are the keys to early breast cancer detection and better outcomes. During my career, in January 1995, I founded The Breast Journal. This physician focused scientific publication is an internationally recognized reference for providing the latest information about breast cancer. In February of the same year, I started the inaugural “Multidisciplinary Symposium on Breast Disease.” Now in its 24th year, this symposium has crossed the borders of the United States and has provided multidisciplinary scientific information across the globe. In Rome and Paris, their governments issued special stamps in recognition of our symposium and Komen Italia - as an affiliate of the Susan G. Komen Foundation - was established. Three years ago, I was honored at the American Embassy of Rome, during the 15th year anniversary of Race for the Cure in Rome, Italy for my initiation of these efforts.

Our symposium in Cairo, Egypt resulted in illuminating the pyramids in pink during our symposium and the first Race for the Cure was held in that region of the world. In Saudi Arabia, our symposium was the first of its kind to freely talk about breast cancer and formed the foundation for the establishment of their first ever breast center. Offering “The Public Forum: What Everyone Should Know about Breast Health” is another example of service to the community to enhance breast health literacy among the public. This has been an annual event for the past 20 years and is our signature event during October Breast Cancer Awareness month.

One-on-one patient education about the nature and extent of their disease and providing patients with different options for therapy has been a unique service that we provide. “The Breast Pathology Consultation and Second Opinion Ser-
vice” has served our community by allowing us reduce the number of unnecessary mastectomies and minimize over-diagnosis and overtreatment of patients with breast disease.

**Contributions to breast cancer research**
I strived to change the culture of Pathology from passive interpreter of tissue biopsy samples to active partners in clinical care. Since 1984, I have been able to expand the Department of Pathology and Laboratory Medicine by establishing a newly designed laboratory, increasing the number of faculty and residents, establishing new fellowships and introducing new and emerging technologies. Introduction of a Fine Needle Aspiration Biopsy Clinic and a Tumor Analysis Laboratory resulted in our ability to assess the status of hormone receptors in aspirates. This was instrumental in the foundation of a national clinical trial to start pre-surgical chemotherapy in breast cancer patients. In addition, I was able to define the cytomorphology of high-risk premalignant breast disease and establish a cytologic grading system named the “Masood Cytology Index.” This index was the only surrogate endpoint biomarker that opened the window of opportunities to be used in National Cancer Institute (NCI) funded chemoprevention trials. Defining cytomorphology as a morphologic breast cancer risk predictor resulted in the honor of being named as one of the Top 20 Most Influential Oncology Professors in the world in 2012.

In addition, I have established the International Society of Breast Pathology, authored three books, contributed to several book chapters, editorials, commentaries and over 120 scientific publications, and served on several scientific and national organizations across the world. I have been a frequent speaker at local, national and international meetings and have traveled to 55 countries, including visiting professorships at Institute of Curie in Paris, France, where I collaborated with the senior cancer specialists identifying genetic and cellular changes that proceed breast cancer. In addition, I have been fortunate to receive numerous local, national, and international scientific and community service awards during my professional life.

**The challenges**
The numerous adversities and successes that I have faced in my personal and professional life have no doubt helped to shape who I am today. Being taken seriously as a foreigner and a woman is not always a foregone conclusion. It is because of the many challenges I have faced that I strive to live my life with courage and compassion so that others may draw strength from my story. In light of the many professional accolades, as I reflect back, my most important accomplishment has been my family and raising my children into two highly regarded physicians in our local community.
Health care systems are eager to adapt to newer technology and widespread network options, all in the name of giving patients the best possible care. However, this comes with a price: more outlets for hackers to breach valuable data. Although data breaches in the retail and banking sectors have received massive coverage, the health care sector has not received the same kind of attention.

Consider that in 2017:
• There were 477 health care breaches reported to the U.S. Department of Health and Human Services or the media (nearly 5.6 million patient records were affected).
• Augusta University Medical Center was hit with two phishing attacks,
• A UC Davis Health employee’s choice to respond to a phishing email with login credentials compromised health information for nearly 15,000 patients.

As technology evolves, so do hackers. In 2015, insurance group Anthem suffered what was believed to be the largest breach of a health care company to date: more than 37 million patient records — including names, Social Security numbers, birthdays, addresses, email and employment information, and income data — were exposed.

Medical data is big business as records can fetch top dollar on the black market — up to $500 per patient. The information in stolen medical records is used to buy medical equipment or drugs — either of which can be resold — or to file bogus claims with insurers. Further, medical records lack the kinds of safeguards as credit cards or banking materials as they cannot be canceled.

Whether used in a secure or open location, mobile devices such as smartphones and tablets can offer hackers backdoor access to a medical group’s network. Medical devices that use the internet, network, or Bluetooth connectivity have proven revolutionary for the health care industry, but because they may not have been network-ready originally, they do not have the kinds of security protections to ward off hackers.

The HIPAA Breach Notification Rule requires covered entities to notify patients when there is a breach of their EPHI. The Breach Notification Rule also requires entities to promptly notify the Department of Health and Human Services (HHS) and issue a notice to the media if the breach affects more than 500 individuals. Breaches affecting fewer than 500 individuals must be reported using the Office for Civil Rights’ (OCR) web portal (the OCR only requires these reports to be made annually).

However, compliance is not enough. HIPAA incentivizes health care providers to adopt secure networks by imposing large fines on providers who suffer breaches of protected health information due to a cyber attack. The cost and consequences of a breach fall on the entity, rather than the attacker. Memorial Healthcare System (MHS) paid the U.S. Department of Health and Human Services (HHS) $5.5 million for violations of HIPAA’s Privacy and Security Rules. In addition to massive fines and penalties for violations, the settlement process and implementation of a corrective action plan are extremely costly, time-consuming, and stressful.

How can the health care industry protect itself:
• Vendors should install security patches on a more widespread basis for machines that record data such as CT scanners.
• Old or unpatched operating systems should be upgraded so that medical facilities are less vulnerable to attacks.
• Networks should be segmented, or divided into subnetworks, to make them more secure.
• Health care groups must implement bring-your-own-device policies — such as allowed/banned apps and acceptable-use rules — for mobile devices like smartphones and tablets.
• Increase employee training to reduce the concern that employee negligence will contribute to or result in a security breach.
• Data should be backed-up regularly, encrypted, and safeguarded with multi-factor authentication.
ARTICLES IN THIS ISSUE

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• CME: Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?
3 - From the CEO's Desk: Lipstick On A Pig?

5 - CME: Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?
I’m sitting at Gate 34 at the airport in Austin, TX. My flight is delayed and I don’t know when I’m going to get on this plane. I’ve been on the road for work for a week, the 2019 budget is due, and I need to write this article. I’m a little stressed… …and my stress level is 1/10th of what you as a physician deal with on a daily basis.

As the CEO of the Duval County Medical Society (DCMS), it is my honor and privilege to serve on the Board of the American Association of Medical Society Executives. In this capacity, I am able to work with Executives from the American Medical Association, State Medical Associations, and County Medical Societies across the United States.

This week, this group has been meeting to share best practices in helping our members reduce stress and return to the joy of medicine. The LifeBridge Physician Wellness Program offered by the DCMS is a nationally recognized best practice. I was happy to share the successes of our program in working with many physicians to cope with stress, burnout and the myriad of issues physicians deal with on a daily basis.

However, I was equally concerned to hear about the impact of a recent article on KevinMD entitled Physician Wellness Programs are Lipstick on a Pig, which is causing a stir in the physician community.

The article posits that Physician Wellness Programs don’t do anything to actually help physicians. It says that the problem is solely burdensome regulation, cumbersome electronic health records, and a system that abuses physicians.

I disagree. Those concerns are specifically why LifeBridge is different than other programs, and why the DCMS is taking a leading role in reducing physician burnout.

LifeBridge is a free, confidential service which provides any DCMS member access to a counselor for up to six free confidential sessions per calendar year. Our program is approved by the Florida Board of Medicine and does NOT create any medical record. Utilization of the program will not be reported to your insurance, your program is approved by the Florida Board of Medicine and does NOT create any medical record. Utilization of the program will not be reported to your insurance, your employer, the Medical Society, or the Board of Medicine. Sessions are conducted in person in one of several convenient and private locations throughout the city.

If you are experiencing stress or burnout… or even if you are concerned that you might be at the early stages of burnout; if you are dealing with stressful times in your household; if you are concerned that you may want to leave medicine because you’ve lost the joy; if any of these scenarios apply to you, PLEASE, do what so many of your colleagues have done and take advantage of this free resource.

Lipstick on a pig?

This is more than someone telling you to be mindful while still holding you accountable for a never-ending deluge of digital paperwork. This is the opportunity for you to truly take the time to focus on your own well-being. But what about all of that burdensome regulation? Until that goes away, I’ll always be stressed at work.

This is where the power of being involved in organized medicine truly matters. The DCMS has a number of delegates who are actively involved in the Florida Medical Association (FMA) and the American Medical Association (AMA). Both of these groups are relentlessly working to help guide the ever-changing healthcare landscape to be less burdensome on physicians.

They are also constantly vigilant in protecting physicians from regulations which would do real harm to physicians. A very recent example was the Proposed CMS Rule which would “simplify” E/M codes for physicians, but also reduce reimbursement for a majority of those codes. The AMA, FMA and DCMS all came out strongly in opposition to this proposed rule, with hundreds of member physicians submitting comment to modify the proposed rule.

For 165 years, the DCMS has been fighting for the physicians of Jacksonville and we’ll continue to fight for you every day. All that I personally ask in return is that you continue taking care of the health of our community… and that starts with yourself.
Progress in the management of metastatic breast cancer in 2018:

Is a cure in the horizon?

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent’s Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “Progress in the management of metastatic breast cancer in 2018: Is a cure in the horizon?” authored by Gerardo Colón-Otero, MD, which has been approved for 1 AMA PRA Category 1 credit. For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Gerardo Colón-Otero, MD, Professor of Medicine, Mayo Clinic College of Medicine, Vice-Dean, Mayo Clinic School of Medicine, Dean, Florida Campus, Mayo Clinic School of Medicine.

Objectives:
1. List the drugs approved over the last six years for the treatment of metastatic breast cancer.
2. Describe the biomarkers used for the selection of treatments for patients with metastatic breast cancer.
3. State the names of promising new drugs currently being evaluated for the management of metastatic breast cancer.

Date of release: Oct. 1, 2018    Date Credit Expires: Oct. 1, 2020    Estimated Completion Time: 1 hour

How to Earn this CME Credit:
1) Read the “Polypharmacy; A Case-based Primer on the Practice in the Geriatric Population” article.
2) Complete the posttest. Scan and email your test to Kristy Williford at kristy@dcmsonline.org.
3) You can also go to www.dcmsonline.org/NEFMCME to read the article and take the CME test online.
4) All non-members must submit payment for their CME before their test can be graded.

CME Credit Eligibility:
A minimum passing grade of 70% must be achieved. Only one re-take opportunity will be granted. If you take your test online, a certificate of credit/completion will be automatically downloaded to your DCMS member profile. If you submit your test by mail, a certificate of credit/completion will be emailed within four weeks of submission. If you have any questions, please contact Kristy Williford at 904-355-6561 or kristy@dcmsonline.org.

Faculty Disclosure:
Gerardo Colón-Otero, MD reports grant/research support from Novartis to Mayo Clinic for Investigator Initiated Trial.

Disclosure of Conflicts of Interest:
St. Vincent’s Healthcare (SVHC) requires speakers, faculty, CME Committee and other individuals who are in a position to control the content of this educational activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly evaluated by SVHC for fair balance, scientific objectivity of studies mentioned in the presentation and educational materials used as basis for content, and appropriateness of patient care recommendations.

Joint Sponsorship Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of St. Vincent’s Healthcare and the Duval County Medical Society. St. Vincent’s Healthcare designates this educational activity for a maximum of 1 AMA PRA Category 1 credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.
Abstract

Progress in the management of breast cancer over the last 40 years has resulted in a decrease in breast cancer mortality and morbidity. Major advances include the significant prolongation of life in patients with HER2 positive subset breast cancers and the addition of multiple new agents for the treatment of the most common type of breast cancer, namely the Estrogen Receptor (ER) positive subtype. The identification of the BRCA genes as the main causes of inherited breast cancer, and the identification of drugs that are particularly effective in these subset of patients has also resulted in improved outcomes. Recent findings suggest that checkpoint inhibitors have significant synergism with chemotherapy in the neo-adjuvant setting. Immuno-conjugate drugs for the triple negative breast cancer sub-group are showing significant activity in the refractory setting. The authors predict that the effective personalized combination of these targeted treatments will likely result in cure of the majority of metastatic breast cancer patients in the next 15 years.

Introduction

It has been 40 years since the United States Food and Drug Administration (FDA) approved tamoxifen, an oral medication that targets the estrogen receptor which is expressed in over 80 percent of breast cancer cases. Since then, over a million women in the United States (U.S.) in the prime of their lives have succumbed from metastatic breast cancer. Over the past five years, there has been a marked acceleration in drug development against cancer propelled by advancements in basic science, particular molecular biology. A total of eight new targeted drugs against metastatic breast cancer have been FDA approved over the last six years, which is more than the number of drugs approved over the preceding 30 years (Table 1).

Table 1: Timeline of the development of new agents for the treatment of breast cancer since 1977

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
<th>Mechanism of action/Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>1977</td>
<td>Competitive inhibitor of ER/ER positive</td>
</tr>
<tr>
<td>Exemestane</td>
<td>1999</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>2000</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>2002</td>
<td>Competitive inhibitor of ER/ER positive</td>
</tr>
<tr>
<td>Letrozole</td>
<td>2004</td>
<td>Aromatase inhibitor/ER positive</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>2006</td>
<td>monoclonal antibody against HER2/HER2 positive</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2007</td>
<td>tyrosine kinase inhibitor of HER2/HER2 positive</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2012</td>
<td>mTOR inhibitor/ER positive</td>
</tr>
<tr>
<td>TDM-1</td>
<td>2013</td>
<td>immuno-conjugate binds to HER2/HER2 positive</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>2013</td>
<td>monoclonal antibody against HER2/HER2 positive</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>2016</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Neratinib</td>
<td>2017</td>
<td>tyrosine kinase inhibitor of HER2/HER2 positive</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>2017</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>2017</td>
<td>Cyclin kinase inhibitor/ER positive</td>
</tr>
<tr>
<td>Olaparib</td>
<td>2018</td>
<td>ARP inhibitor/BRCA mutated</td>
</tr>
</tbody>
</table>

Breast cancer is the most common cancer in women in the U.S. with more than 240,000 cases per year and over 40,000 deaths per year. Data has shown significant heterogeneity among individual breast cancer cases, particularly in the metastatic setting, which significantly contributes to the almost universal development of treatment resistance and eventual patient’s demise. Despite this, there are multiple reasons to be optimistic, including the fact that new drugs with new mechanisms of action are being developed. It is important to understand the data on recently approved drugs and promising new agents against metastatic breast cancer. The data on these agents suggest that the elusive goal of achieving cures for the majority of patients with metastatic breast cancer may be within reach in the next 15 years.

Recent progress: A look into a promising future

Estrogen Receptor positive disease

The discovery of tamoxifen and the aromatase inhibitors led to a marked improvement in the outcome of patients with metastatic ER positive breast cancer. The m-TOR
inhibitor everolimus received FDA approval in 2012 based on the results of the BOLERO2 clinical trial which showed a significant prolongation of progression free survival in the group treated with exemestane and everolimus compared with exemestane as a single agent. The last few years have seen the introduction of cyclin kinase inhibitors (palbociclib, ribociclib and abemaciclib) which nearly doubled the time before progression in the upfront and second line setting treatment for metastatic ER positive breast cancer in combination with anti-estrogen treatments. There will likely be development of additional combinations for the treatment of metastatic ER positive breast cancer and the identification of the mutations associated with drug resistance. The discovery of the Estrogen Receptor activation mutations (ESR1 gene mutations in the ligand binding domain) and their associated resistance to aromatase inhibitors will likely lead to the personalized initial treatment of ER positive metastatic breast cancer and the selection of the estrogen receptor degrading inhibitor, fulvestrant or other anti-estrogen agents, over the aromatase inhibitors in this subset of patients. The ISPY 2 trial showed marked improvement in pathological complete remission (pCR) with the upfront neoadjuvant addition of pembrolizumab to paclitaxel (an increase in pCR from 19 percent to 39 percent) in ER positive HER2 negative tumors. These results suggest that the early incorporation of pembrolizumab and paclitaxel in the neo-adjuvant (upfront) treatment of patients with locally advanced ER positive breast cancer will likely result in improved outcomes. Studies incorporating all of these agents may be feasible given the differences in toxicities associated with these agents. It is likely that these new combinations may result in a greater percentage of patients with metastatic ER positive breast cancer achieving long term control of their disease if not cures.

HER2 amplified breast cancer
Up to one in every four women with breast cancer will harbor tumors with amplification of the HER2 gene. These patients used to have the poorest prognosis among all breast cancer subsets, even worse than that of the triple negative subset, until the introduction of trastuzumab. Trastuzumab is a monoclonal antibody that targets the HER2 protein and which was shown to significantly improve survival among patients with HER2-amplified metastatic breast cancer. The level of improvement by the addition of trastuzumab to chemotherapy was so significant that it resulted in outcomes that were similar to that of patients with metastatic ER positive HER2 negative tumors, the subset with the best prognosis. The subsequent addition of pertuzumab to trastuzumab and chemotherapy in patients with metastatic HER2 positive breast cancer in the Cleopatra trial, led to further significant improvements in overall survival. The subset of HER2 amplified breast cancers with increased infiltration of lymphocytes in the tumor had the best response to the combined monoclonal antibodies treatment with up to 40 percent of these patients been free of tumor progression at five years, which represents a remarkable achievement. These findings suggest the possibility of significant synergism between combined monoclonal antibodies and checkpoint inhibitors and implies that this combination could potentially lead to a cure for the majority of these patients. The development of the immune-conjugate TDM-1, led to significant improvements in progression free survival and overall survival in the second line setting as compared with the combination of lapatinib and capecitabine. The development of new, more effective tyrosine kinase inhibitors (neratinib and pyrotinib) is likely to even further improve these outcomes. The newer tyrosine kinase inhibitors are showing significant clinical activity against metastatic disease involving the brain, a common complication in the HER2 positive breast cancers seen in up to 50 percent of these patients. The newer immune-conjugate, trastuzumab deruxtecan, has been associated with over 60 percent response rates in patients who failed trastuzumab, pertuzumab and TDM-1. These levels of activity are likely to translate into significant improvements in overall survival when these agents are used in the upfront setting. Finally, the checkpoint inhibitor pembrolizumab has shown significant activity with a 15 percent response rate in patients who failed multiple previous systemic treatments including trastuzumab, when added to trastuzumab treatment. Given this finding, one could predict significant synergism of pembrolizumab when given in the upfront setting in combination with chemotherapy and dual HER2 inhibition with pertuzumab and trastuzumab. It is quite likely that combination treatments that incorporate the novel tyrosine kinase inhibitors with the newer immuno-conjugates and
checkpoint inhibitors will potentially lead to long term control or cure in a significantly higher percentage of patients with metastatic HER2 amplified breast cancer.

**Triple negative Breast Cancer**

Tumors that do not express ER and Progesterone Receptor (PR) and do not have amplifications of the ERB2 (HER2) gene (called triple negative breast tumors) have the worst prognosis. These tumors are more common in younger patients, in patients with germline BRCA1 mutations, and in African American, Hispanic and Native American subjects. Standard of care for these patients consists of systemic chemotherapy, with most patients eventually progressing and dying from their disease. In 2018, olaparib, a Poly (ADP-Ribose) Polymerase (PARP) inhibitor, became the first drug approved for the treatment of metastatic breast cancer in patients with germline BRCA mutations and HER2 negative metastatic breast cancer including triple negative breast cancer, given the findings of greater response rates with less toxicity than single agent chemotherapy. Based on the results of the use of these agents in BRCA mutated high grade serous carcinomas of the ovaries, tumors that are genetically similar to triple negative breast cancer, it is likely that the use of these agents as maintenance therapy earlier in the management of metastatic BRCA mutated triple negative breast cancer will likely translate into even greater benefit. Talazoparib is another PARP-inhibitor that will likely be approved for breast cancer in the near future based on the results of the phase 3 EMBRACA trial that showed a significantly higher response rate and duration of treatment response as compared with chemotherapy.

Immuno-conjugates are another promising new treatment for metastatic triple negative breast cancer. These agents consist of a monoclonal antibody targeting a protein expressed by the triple negative breast cancer cells, attached to a chemotherapeutic agent. Three of these agents are currently undergoing phase 3 clinical trial evaluations and are likely to be approved for clinical use in the near future. Glaebatumumab vedotin targets the transmembrane glycoprotein NMB (osteoactivin) which is expressed in over 25 percent of breast cancers. A 30 percent response rate was observed in a phase 2 trial of refractory triple negative breast cancer. A phase 3 trial of glembatumumab versus capecitabine is currently underway. Ladiratuzumab vedotin targets the LIV-1 transmembrane protein that is expressed by over 90 percent of breast cancers. A 25 percent response rate was observed in 63 patients with metastatic breast cancer who had failed median of four prior chemotherapies. Sacituzumab govitecan is an immuno-conjugate of an anti-TROP-2 antibody linked to SN-38 which is the active metabolite of irinotecan. TROP-2 is a surface glycoprotein expressed in over 90 percent of breast cancers. A 34 percent response rate was observed in 110 patients with metastatic breast cancer who had failed two or more previous chemotherapies. The toxicity profile of PARP inhibitors, checkpoint inhibitors, and the immune-conjugates suggest that combination treatment with these agents may be feasible and could possibly be synergistic. If so, this may translate into significant improvement in overall survival and potential cures.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Breast cancer subset</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrotinib</td>
<td>HER2 positive</td>
<td>TK inhibitor HER2</td>
</tr>
<tr>
<td>Trastuzumab deruxtucan</td>
<td>HER2 positive</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Sacituzumab govitecan (Immu-132; anti-Trop-2)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Glaebatumumab vedotin (anti-GP-NMB)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Ladiratuzumab vedotin (anti-LIV-1 with MMAE)</td>
<td>triple negative</td>
<td>immuno-conjugate</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>triple negative</td>
<td>PD1 monoclonal AB</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>BRCA mutated</td>
<td>PARP inhibitor</td>
</tr>
</tbody>
</table>
Conclusion

Over the last six years, new agents have been approved for the treatment of breast cancer than over the preceding 35 years, a result of amazing advancements in molecular biology over the last decade. Currently, at least seven agents with promising preliminary results will likely become FDA approved over the next few years. The expansion of knowledge of the causes of tumor resistance to targeted agents will translate into the development of new agents that could bypass the resistance mechanisms. It is hoped that these developments will translate into cures so that the untimely loss of over 40,000 women in the prime of their lives per year in the U.S. alone can be prevented.

References

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A Conversation with Natalie MacLean, Wine Writer

By Wendy Michaels

LoveToKnow Wine had the pleasure of interviewing Natalie MacLean, author of Red, White, and Drunk All Over, a book for both wine experts and beginners alike. MacLean offers her expertise and insight in this informative and entertaining book. Grab a glass of your favorite wine and learn more about the author, her website and her book.

Could you tell our readers a little bit about your book, Red, White, and Drunk All Over?
I take my readers behind the scenes of the international wine world, exploring its history, visiting its most evocative places and meeting its most charismatic personalities. For example, while tasting sensuous pinot noir in the ancient cellars of Burgundy, I discover the mysterious tenets of biodynamic viticulture from the tiny, ferocious Lalou Bize-Leroy, part-owner of France's acclaimed Domaine de la Romanée-Conti. I work in a couple of wine stores to figure out how people can find the right bottle when faced with thousands of them. And I wade into a famous feud between Robert Parker and Jancis Robinson, two of the world's best-known wine critics to determine what those scores out of 100 really mean.

Is your book best suited for beginners or can all levels of wine lovers gain something from it?
I hope that the book will appeal to two groups. One is beginners who are just starting to learn about wine and who will pick up a lot of tips from this book but won't find it intimidating. The other group includes those who are already knowledgeable about wine, but will enjoy reading all the inside stories about people in the international wine world. And if you're buying gifts for these people in your life, you can get a lot of your shopping done in one swoop.

Red, White, and Drunk All Over
The book is also ideal for those who are part of a wine club, since it can give them new ideas for tasting themes and discussions. It's also good for members of book clubs who would enjoy a good glass of wine as they discuss this book and their favorite wines or most memorable bottles. In fact, I've included tips on how to set up an informal wine tasting with friends at home.

My book will also be useful to those thinking of traveling to a wine region: they could either read it before going or while there. That's especially true for anyone visiting one of the famed wine regions I describe, such as California, Burgundy or Champagne. Those who prefer to be armchair tourists, with a good glass in hand, can journey vicariously with me. And finally, I think my book would make a great hostess gift for a dinner party or holiday gathering. Instead of agonizing over which bottle to bring when your host has probably already chosen the wines anyway, why not bring this book? It's a great conversation piece that will make you look cultured but with a great sense of humor.

Why did you write this book?
Although I've been exploring my passion for wine in the articles I write for magazines and newspapers, I knew that writing a book would allow me to dig even deeper, meet more fascinating people, travel to more interesting places and even spend more time thinking about just what makes us so crazy about wine.

What is the hardest food to pair with a wine? Any tricky ones?
Although I addressed general food-and-wine matching principles in the hard cover edition, I decided to focus on five foods that are toughest on wine: salads and vegetables, spicy dishes, take-out and frozen food, cheese and chocolate. So many readers have asked me about these particular pairing challenges that I thought it deserved its own chapter. As a determined hedonist, I won't admit that there's any food that can't be paired with some wine. The guidelines for pairing wine with difficult food are the same as those for traditional wine-friendly dishes: harmonize your flavor, texture and weight.
Beyond this, there are some specific tips to keep in mind with each of these groups. For example, my theory is that green food and green wine go together. So veggies dance with wines that have herbal, grassy aromas, such as New Zealand Sauvignon Blanc. In fact, if there were an award for “Veggie Wine of the Century”, it would go to this one. Not only does it have complementary aromas of asparagus and canned peas, but it also has bright citrus notes that complement most vegetables. You’ll find the real meat of the discussion in the book.

**Do the old rules of wine matching still apply (red wine with red meat, white wine with white meat)?**

Those are good guidelines and starting points, but food and wine have both changed so much that the key is to experiment.

How did you develop your interactive food-and-wine matcher? Tell us about it. We particularly love the ability to click for recipes that have a complimentary ingredient from the search as well as find your wine reviews for the recommended wines.

Creating this tool also stems from the many questions about food and wine matching that I received from readers of my e-newsletter. I wanted to make the suggestions fast and simple, and to use the technology available to me.

**What can people expect if they sign up for your free newsletter?**

Every month, I e-mail more than 80,000 wine lovers my top wine picks, tips on matching wine with food, choosing from restaurant lists and cellaring wine. On my web site, I’ve also posted more than a thousand links to vintage charts, wine accessories, food-matching advice, wine region tour guides, producers and retailers, clubs and courses, industry jobs and my favorite wine books and movies.

**What if a visitor can’t find a particular food or wine in your matching database? Is there a way for people to contact you?**

Sure! They should e-mail me via my web site, www.nataliemaclean.com and I’d be happy to suggest a match for them … and then I’ll add it to the matcher.

**What is your favorite type of wine, and why?**

The one someone else buys for me! Seriously, I do love Pinot Noir for its seductive aromas and flavors and the way it pairs with so many dishes. That’s why chapter one is all about Pinot.
Many people who love the fall season flock to the Northeastern U.S. to see the colorful autumn leaves. However, Georgia is actually one of the most underrated fall foliage destinations in the country! This state is packed with beautiful and accessible state parks with plenty of trees and wide-open spaces to take in all those vibrant reds, oranges, yellows, and browns. These are our nine favorite places to embrace the colors of the season and see the fall foliage in Georgia.

**Cloudland Canyon State Park, Rising Fawn**
Cloudland Canyon is a wonderful Georgia destination at any time of year, but its colors really come alive in fall. There are some great hiking routes here, as well as mountain biking trails that allow you to view the fall foliage while also getting some excellent exercise. The Five Points Recreation Area has single-track trails that are fun and challenging for mountain bikers. For hiking, the West Rim Loop offers amazing views of the canyon, is moderately difficult, and is about five miles in total length. There are some yurts here that you can rent out for a glamping weekend among the fall foliage.

**Piedmont Park, Atlanta**
While many of the best views of fall foliage require a trip out to one of Georgia's state parks, you can see some really beautiful colors right here in the city of Atlanta. Head to Piedmont Park to see the city's stunning architecture next to the beautiful leaves turning from green to red, orange, and yellow. There are some nice paved trails for walking your dog and going for runs here, as well as a large off-leash dog park for your pup to run and play. Atlanta is sometimes referred to as the "city of trees," which should tell you that there are lovely spots all over town to snap photographs and relax among the natural beauty.

**Tallulah Gorge State Park, Tallulah Falls**
Tallulah Gorge is always a stunning and impressive park to visit, but you're really missing out if you haven't seen it in the fall. It's a very popular canyon to visit in the Southeast and allows you to hike along the rim to see colorful oak and maple trees. If you're up for a longer hike, stop by the visitor center early in the morning to get a permit to hike down to the gorge floor. This is an ideal place for hiking and also whitewater kayaking. In November, the water here is released from the dam, creating some intense Class IV and Class V rapids. Therefore, it's best to leave these adrenaline-boosting waters to the true experts.

**Brasstown Bald, Near Blairsville**
Brasstown Bald is a famous mountain in North Georgia that offers dramatic views of the fall foliage. It's also the highest peak in the state. If you're up for a challenge, hike the Arkaquah Trail to the top, which involves a steep initial incline and traversing ridge lines. You'll be rewarded with lovely views of the colorful leaves in fall, as well as the nearby farms down below.

**Red Top Mountain State Park, Cartersville**
If you're coming from Atlanta, it's an easy drive of less than an hour to reach Red Top Mountain State Park. Here you can see Lake Allatoona surrounded by all of the beauty of fall colors. The Hill Loop is a great trail to see the lake and forest with all of its colors on foot or on a bike. You can also get some nice views of the lake from the Homestead Trail, which is about a 5.5-mile hike.

**Black Rock Mountain State Park, Clayton**
Black Rock Mountain's summit stands at approximately 3,640 feet, and you can get incredible views of the fall foliage from up here. One recommended fall foliage hike is the James Edmond Backcountry Trail, which has a few primitive campsites available to stay overnight in a tent. This is a loop trail that extends a little over seven miles and takes you to the top of Lookoff Mountain. For a shorter hike, try the Tennessee Rock Trail, which is about 2.2 miles long and has great views too.

**Yonah Mountain, Near Helen**
Yonah Mountain is located near the town of Helen, Georgia and offers some excellent hiking opportunities to see fall foliage. The Yonah Mountain Trail extends about 4.4 miles round trip and is moderately difficult. Dogs are allowed on the trail, so bring your pup along to enjoy the crisp, cool weather. You can start your fall foliage journey from Chambers Mountain Road south of Helen and reach the summit in about 2.2 miles. Views from the trail are gorgeous, but don't get too close to the drop-offs at the top because they can be dangerous. You can also set up a tent at the summit of Yonah Mountain or at base camp, and primitive campsites are first-come-first-served. While in the Helen area, you can visit the Unicoi State Park and Lodge, which offers lovely views of the colorful leaves and even zip lines to take you to the top of them. There's also a fun Oktoberfest celebration that takes place in Helen every fall, so plan to refuel with tasty German brats and beer after your time among the trees.
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I am a sucker for restaurants that offer small plates; not only does it help with my indecisiveness, but it also gives me a better feel for the place when I get to try a wide variety of their dishes. The restaurant hidden in the very back of Riverside Liquors on King Street had a menu that intrigued me, so we decided to give it a shot.

I heard about Riverside Liquors from friends before and have walked past it hundreds of times while visiting other local businesses in the area. It took me 3 years to go inside and try it, but I am glad we finally did. I had an assumption that it would be dive bar-ish but was pleasantly surprised by the atmosphere. There was a casual, classy vibe and I really liked that there weren’t any TVs. Although I tend to stick to beer, because we were in a liquor store, I felt compelled to order a cocktail. All of the cocktails on their drink list sounded appealing. As a sucker for tequila, I ordered a “sidekick” ($8) and my husband ordered a “new fashioned” ($8). Both were great.

Absolutely everything on the menu sounded delicious, so we really had to reign in the number of small plates we ordered. After staring at the menu for 10 minutes, checking out the specials on the board, we exercised self-control and narrowed it down to 4 items to start with (because hey, you can always order more). The dishes we chose were the fig & olive tapenade ($8), chorizo stuffed dates ($7), beet salad ($7), and the stuffed poblano ($11).

The tapenade was a stack of cream cheese, olives, and figs, drizzled with honey and served with warm house-made bread. The brininess of the olives, the sweetness of the figs/honey, and the creamy cheese all worked together in perfect harmony. As a carboholic, I could have used more bread.

Dates are one of my favorite small plate menu items and theirs were great. The spice of chorizo inside the sugary date and the saltiness of the bacon wrapping the date made for a delicious sweet and savory bite.

I try to incorporate a salad in most meals and I was impressed with the flavor packed in Riverside Liquors’ beet salad. I was surprised that the salad didn’t have any lettuce, but once I took the first bite I didn’t miss it at all. There were so many textures—tender beets, crunchy walnuts, creamy goat cheese, and crisp green onions. I wish they sold the bacon vinaigrette in bottles!
The stuffed poblano had great Mexican flavors. It was a surprisingly light dish and not greasy at all. The taste of the pepper was there without the heat. There was a good cheesy stretch to each bite of meat and rice. The lime crema added freshness as well.

As we were getting ready to cash out, we were chatting with the bartender (Dan was awesome) about my love of tequila and he asked if we wanted to try another cocktail - a spin on the "last word" ($12), using Mezcal instead of gin. It was a beautiful cocktail and great way to finish our meal.

Riverside Liquors is located at 1251 King Street.
Real Estate investing is a fantastic source of passive income and one of the best ways to build your wealth over the long run, especially if you’re entrepreneurial minded.

I mean, wouldn’t it be fantastic to live off the monthly rental collected from your properties? And real estate investing can be done without a significant level of savings.

The advantages of real estate are many: the passive cash flow, the tax benefits, the leverage, the capital appreciation on the long run or the hedge against inflation.

However, real estate investing is not something you can just improvise. It definitely has a learning curve. Finding the best deals, assessing the investment opportunities, negotiating the financing, concluding acquisitions, all of that can be a bit overwhelming.

**How have I built this shortlist?**

In order to go straight to the very best Real Estate investing books, here’s the process I’ve followed:

- I have selected the books on Amazon that are relevant to Real Estate investing
- I eliminated those with reviews below 4 stars or low numbers of reviews (such as all the cheap of free e-books)
- That list of books has then been cross-referenced with other leading websites for the books they reference under Real Estate investing (Entrepreneur.com, businessinsider.com, inc.com, forbes.com)
- I finished by establishing the shortlist and wrote the independent reviews below taking into account book content, site reviews and above all user reviews

So here are the Top Real Estate Investing books you can find:

**CRUSHING IT IN APARTMENTS AND COMMERCIAL REAL ESTATE**
*How a Small Investor Can Make It Big,* by Brian H Murray

Brian Murray is a real life example of someone who started from scratch and built a multi-million dollar real estate company (Washington Street Properties) out of sheer determination and passion. Crushing it in Apartments and Real Estate is a rough guide to real estate investing, with a very effective approach to finding and financing commercial property.

It will teach you how to grow your portfolio on your own, taking from Murray’s own experience. He shares with us a lot of real-time stories about his own path to success.

Contents of the book: Mastering the fundamentals, bootstrapping it, exploiting Home field advantage, picking the best battleground, finding the right property, analyzing properties, structuring deals creatively, working with banks, running your real estate as a business, adding value, lowering the rents and leasing it up, creating a factory, being passionate and having a purpose, buying and holding, striving for balance, keep learning and getting started.

**THE BOOK ON RENTAL PROPERTY INVESTING**
*How to Create Wealth and Passive Income Through Intelligent Buy and Hold Real Estate Investing!* by Brandon Turner

Brandon Turner is the co-host of the BiggerPockets with Joshua Dorkin, a successful podcast featuring interviews with investors of various backgrounds, niches and experience levels.

This Book on Rental Property Investing addresses everything you need to know to get started. It will even give you clear game plans on how to make $1,000,000 dollars through rental properties.

Readers appreciate the fact that the content is readily actionable for new and active real estate investors.

Starting with the reasons why you should love rental properties, the author goes on to give us the five keys to rental property success.

He gives us four sample plans, and explains who the ten members of your real estate team should be. Analyzing a rental property, investing while living in an expensive area, or types of rental properties are also topics he covers.

And oh yes, never forget that real estate boils down to just three things location location location.

Brandon Turner explains how to find rental properties, which ones make the best rentals and how to submit an offer. He covers negotiation, financing, how to get your loan approved, and goes on to reveal the full due diligence process.
After closing the deal, you will need to start managing your rentals, that’s also covered in the book in an entire Chapter.

To conclude, if you want to build cash flow through rental properties, you should seriously consider this book.

THE MILLIONAIRE REAL ESTATE INVESTOR
by Gary Keller and Dave Jenks

The cover of this book says "Anyone can do it.... not everyone will.... will you?".

The Millionaire Real Estate Investor enjoys amazing ratings on most websites. It is a handbook that is very researched and takes its insights from interviews with 100 millionaire real estate investors who have made it and acquired considerable wealth through real estate investing.

The strategies described by Gary Keller will inspire you to start investing.
The first part of the book is about charting the course, while the second part looks at the four stages of a successful strategy:
• Think a million (the spiritual journey of wealth building)
• Buy a million (the five models of millionaire investor)
• Own a million (the seventeen issues of own a million)
• Receive a million (achieve $1 million in annual cash flow)
Part Three is about putting it all together, establishing you base camp and establishing a financial track to run on.

THE ABCS OF REAL ESTATE INVESTING
The Secrets of Finding Hidden Profits Most Investors Miss (Rich Dad Advisors) by Ken McElroy

This ABC outlines the steps you need to take to achieve financial independence via real estate passive income.
Ken McElroy has close to 30 years experience at at a multi-family asset and property management firm that has purchased well over $400 million in properties in the past years.

The book is published by Rich Dad Advisors, a company set up by the famous Robert Kiyosaki. Inside, Ken McElroy shares his technique for assessing a property’s value, how to perform research or how to setup a team.

Whether you are an aspiring real estate investor or a pro, this book is full of actionable insights, being the fruit of years of experience from an industry veteran.

THE BOOK ON INVESTING IN REAL ESTATE WITH NO (AND LOW) MONEY DOWN
Real Life Strategies for Investing in Real Estate Using Other People’s Money by Brandon Turner

Brandon Turner’s book challenges the idea that having little or no capital will prevent you from becoming a real estate investor. Having no cash should not be a deterrent.

The author is also the co-host of the well known Biggerpockets podcast, in which he challenges people to step beyond the hype and gives them real life examples and strategies that they can start applying.

It all starts with the mindset, and being convinced that a lack of funds is not an obstacle. There are many strategies that can be applied creatively.

This book will teach you:
- the art of creative real estate investing, with four basic rules
- how to invest in owner occupied investment properties, and the corresponding loans
- how to work with partnerships
- how to get home equity loans and lines of credit
- strategies for using hard money
- how to raise private money to fund your deals
- lease options, what they are, the risks and drawbacks
- seller financing, how to find some
- real estate wholesaling
- creative combinations

Build a Rental Property Empire
The no-nonsense book on finding deals, financing the right way, and managing wisely by Mark Ferguson

In this book, Mark Ferguson goes into all the details of successful real estate investing strategies. Finding the best deals, acquiring the properties, managing them. It is all covered, in a simple, direct and clear to understand writing style.

The author is a long time Real Estate investor but also the creator of the Investformore.com website, enjoying a huge online following and visitors counted in millions.

Aside from his realtor business, Ferguson has built for himself a group of 16 properties from which he extracts a yearly income of $90,000, so his advice and strategies are firsthand.

This book will teach you:
- why real estate can make you richer than stocks
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