DEEP MEDICINE

HOW ARTIFICIAL INTELLIGENCE CAN MAKE HEALTHCARE HUMAN AGAIN

ERIC TOPOL

With a foreword by
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chapter one

INTRODUCTION TO DEEP MEDICINE

> By these means we may hope to achieve not indeed a brave new world, no sort of perfectionist Utopia, but the more modest and much more desirable objective—a genuinely human society.
>
> —Aldous Huxley, 1948

"You should have your internist prescribe anti-depression medications," my orthopedist told me.

My wife and I looked at each other, bug-eyed, in total disbelief. After all, I hadn't gone to my one-month post-op clinic visit following a total knee replacement seeking psychiatric advice.

My knees went bad when I was a teenager because of a rare condition known as osteochondritis dissecans. The cause of this disease remains unknown, but its effects are clear. By the time I was twenty years old and heading to medical school, I had already had dead bone sawed off and extensive reparative surgery in both knees. Over the next forty years, I had to progressively curtail my physical activities, eliminating running, tennis, hiking, and elliptical exercise. Even walking became painful, despite injections of steroids and synovial fluid directly into the knee. And so at age sixty-two I had my left knee replaced, one of the more than 800,000 Americans who have this surgery, the most common orthopedic operation. My orthopedist had deemed me a perfect candidate: I was fairly young, thin, and fit. He said the only significant downside was a 1 to 2 percent risk of infection. I was about to discover another.

After surgery I underwent the standard—and, as far as I was told, only—physical therapy protocol, which began the second day after surgery. The protocol is intense, calling for aggressive bending and extension to avoid scar formation in the joint. Unable to get meaningful flexion, I put a stationary bicycle seat up high and had to scream in agony to get through the first few pedal revolutions. The pain was well beyond the reach of oxycodone. A month later, the knee was purple, very swollen, profoundly stiff, and unbending. It hurt so bad that I couldn't sleep more than an hour at a time, and I had frequent crying spells. Those were why my orthopedist recommended antidepressants. That seemed crazy enough. But the surgeon then recommended a more intensive protocol of physical therapy, despite the fact that each session was making me worse. I could barely walk out of the facility or get in my car to drive home. The horrible pain, swelling, and stiffness were unremitting. I became desperate for relief, trying everything from acupuncture, electro-acupuncture, cold laser, an electrical stimulation (TENS) device, topical ointments, and dietary supplements including curcumin, tart cherry, and many others—fully cognizant that none of these putative treatments have any published data to support their use.

Joining me in my search, at two months post-op, my wife discovered a book titled *Arthrofibrosis*. I had never heard the term, but it turned out to be what I was suffering from. Arthrofibrosis is a complication that occurs in 2 to 3 percent of patients after a knee replacement—that makes the condition uncommon, but still more common than the risk of infection that my orthopedist had warned me about. The first page of the book seemed to describe my situation perfectly: "Arthrofibrosis is a disaster," it said. More specifically, arthrofibrosis is a vicious inflammation response to knee replacement, like a rejection of the artificial joint, that results in profound scarring. At my two-month post-op visit, I asked my orthopedist whether I had arthrofibrosis. He said absolutely, but there was little he could do for the first year following surgery—it was necessary to allow the inflammation to "burn out" before he could go back in and remove the scar tissue. The thought of going a year as I was or having another operation was making me feel even sicker.

Following a recommendation from a friend, I went to see a different physical therapist. Over the course of forty years, she had seen many patients with osteochondritis dissecans, and she knew that, for patients such as me, the routine therapeutic protocol was the worst thing possible. Where the standard protocol called for extensive, forced manipulation to maximize the knee flexion and extension (which was paradoxically stimulating more scar formation), her approach was to go gently: she had me stop all the weights and exercises and use anti-inflammatory medications. She handwrote a page of instructions and texted me every other day to ask how “our knee” was doing. Rescued, I was quickly on the road to recovery. Now, years later, I still have to wrap my knee every day to deal with its poor healing. So much of this torment could have been prevented.

As we’ll see in this book, artificial intelligence (AI) could have predicted that my experience after the surgery would be complicated. A full literature review, provided that experienced physical therapists such as the woman I eventually found shared their data, might well have indicated that I needed a special, bespoke PT protocol. It wouldn’t only be physicians who would get a better awareness of the risks confronting their patients. A virtual medical assistant, residing in my smartphone or my bedroom, could warn me, the patient, directly of the high risk of arthrofibrosis that a standard course of physical therapy posed. And it could even tell me where I could go to get gentle rehab and avoid this dreadful problem. As it was, I was blindsided, and my orthopedist hadn’t even taken my history of osteochondritis dissecans into account when discussing the risk of surgery, even though he later acknowledged that it had, in fact, played a pivotal role in the serious problems that I encountered.

Much of what’s wrong with healthcare won’t be fixed by advanced technology, algorithms, or machines. The robotic response of my doctor to my distress exemplifies the deficient component of care. Sure, the operation was done expertly, but that’s only the technical component. The idea that I should take medication for depression exemplifies a profound lack of human connection and empathy in medicine today. Of course, I was emotionally depressed, but depression wasn’t the problem at all: the problem was that I was in severe pain and had Tin Man immobility. The orthopedist’s lack of compassion was palpable: in all the months after the surgery, he never contacted me once to see how I was getting along. The physical therapist not only had the medical knowledge and experience to match my condition, but she really cared about me. It’s no wonder that we have an opioid epidemic when it’s a lot quicker and easier for doctors to prescribe narcotics than to listen to and understand patients.

Almost anyone with chronic medical conditions has been “roughed up” like I was—it happens all too frequently. I’m fortunate to be inside the medical system, but, as you have seen, the problem is so pervasive that even insider knowledge isn’t necessarily enough to guarantee good care. Artificial intelligence alone is not going to solve this problem on its own. We need humans to kick in. As machines get smarter and take on suitable tasks, humans might actually find it easier to be more humane.

AI in medicine isn’t just a futuristic premise. The power of AI is already being harnessed to help save lives. My close friend, Dr. Stephen Kingsmore, is a medical geneticist who heads up a pioneering program at the Rady Children’s Hospital in San Diego. Recently, he and his team were awarded a Guinness World Record for taking a sample of blood to a fully sequenced and interpreted genome in only 19.5 hours.[1]

A little while back, a healthy newborn boy, breastfeeding well, went home on his third day of life. But, on his eighth day, his mother brought him to Rady’s emergency room. He was having constant seizures, known as status epilepticus. There was no sign of infection. A CT scan of his brain was normal; an electroencephalogram just showed the electrical signature of unending seizures. Numerous potent drugs failed to reduce the seizures; in fact, they were getting even more pronounced. The infant’s prognosis, including both brain damage and death, was bleak.

A blood sample was sent to Rady’s Genomic Institute for a rapid whole-genome sequencing. The sequence encompassed 125 gigabytes of data, including nearly 5 million locations where the child’s genome differed from the most common one. It took twenty seconds for a form of AI called natural-language processing to ingest the boy’s electronic medical record and determine eighty-eight phenotype features (almost twenty times more than the doctors had summarized in their problem list). Machine-learning algorithms quickly sifted the approximately 5 million genetic variants to find the roughly 700,000 rare ones. Of those, 962 are known to cause diseases. Combining that information with the boy’s phenotypic data, the system identified one, in a gene called ALDH7A1, as the most likely culprit. The variant is very rare, occurring in less than 0.01 percent of the population, and causes a metabolic defect that leads to seizures. Fortunately, its effects can be overridden by dietary supplementation with vitamin B6 and arginine, an amino acid, along with restricting lysine, a second amino acid. With those changes to his diet made, the boy’s seizures abruptly ended, and he was discharged home thirty-six hours later! In follow-up, he is perfectly healthy with no sign of brain damage or developmental delay.

The key to saving this boy’s life was determining the root cause of his condition. Few hospitals in the world today are sequencing the genomes of sick newborns and employing artificial intelligence to make everything known about the patient and genomics work together. Although very experienced physicians might eventually have hit upon the right course of treatment, machines can do this kind of work far quicker and better than people.

So, even now, the combined efforts and talents of humans and AI, working synergistically, can yield a medical triumph. Before we get too sanguine about AI's potential, however, let's turn to a recent experience with one of my patients.

"I want to have the procedure," my patient told me on a call after a recent visit.

A white-haired, blue-eyed septuagenarian who had run multiple companies, he was suffering from a rare and severe lung condition known as idiopathic—a fancy medical word for "of unknown cause"—pulmonary fibrosis. It was bad enough that he and his pulmonologist had been considering a possible lung transplant if it got any worse. Against this backdrop he began to suffer a new symptom: early-onset fatigue that left him unable to walk more than a block or swim a lap. He had seen his lung doctor and had undergone pulmonary function tests, which were unchanged. That strongly suggested his lungs weren't the culprit.

He, along with his wife, then came to see me, very worried and depressed. He took labored, short steps into the exam room. I was struck by his paleness and look of hopelessness. His wife corroborated his description of his symptoms: there had been a marked diminution of his ability to get around, to even do his daily activities, let alone to exert himself.

After reviewing his history and exam, I raised the possibility that he might have heart disease. A few years previously, after he began to suffer calf pain while walking, he had stenting of a blockage in his iliac artery to the left leg. This earlier condition raised my concern about a cholesterol buildup in a coronary artery, even though he had no risk factors for heart disease besides his age and sex, so I ordered a CT scan with dye to map out his arteries. The right coronary artery showed an 80 percent narrowing, but the other two arteries were free of significant disease. It didn't fit together. The right coronary artery doesn't supply very much of the heart muscle, and, in my thirty years as a cardiologist (twenty of which involved opening coronary arteries), I couldn't think of any patients with such severe fatigue who had narrowing in only the right coronary artery.

I explained to him and to his wife that I really couldn't connect the dots, and that it might be the case of a "true-true, unrelated"—that the artery's condition might have nothing to do with the fatigue. His underlying serious lung condition, however, made it conceivable that the narrowing was playing a role. Unfortunately, his lung condition also increased the risk of treatment.

I left the decision to him. He thought about it for a few days and decided to go for stenting his right coronary artery. I was a bit surprised, since over the years he had been so averse to any procedures and even medications. Remarkably, he felt energized right after the procedure was done. Because the stent was put in via the artery of his wrist, he went home just a few hours later. By that evening, he had walked several blocks and before the week's end he was swimming multiple laps. He told me he felt stronger and better than he had for several years. And, months later, the striking improvement in exercise capacity endured.

What's remarkable about this story is that a computer algorithm would have missed it. For all the hype about the use of AI to improve healthcare, had it been applied to this patient's data and the complete corpus of medical literature, it would have concluded not to do the procedure because there's no evidence that indicates the opening of a right coronary artery will alleviate symptoms of fatigue—and AI is capable of learning what to do only by examining existing evidence. And insurance companies using algorithms certainly would have denied reimbursement for the procedure.

But the patient manifested dramatic, sustained benefit. Was this a placebo response? That seems quite unlikely—I've known this man for many years, and he tends to minimize any change, positive or negative, in his health status. He seems a bit like a Larry David personality with curbed enthusiasm, something of a curmudgeon. Ostensibly, he would be the last person to exhibit a highly exaggerated placebo benefit.

In retrospect, the explanation likely does have something to do with his severe lung disease. Pulmonary fibrosis results in high pressures in the pulmonary arteries, which feed blood to the lungs, where the blood becomes oxygenated. The right ventricle is responsible for pumping that blood to the heart; the high blood pressure in the arteries meant that it would have taken a lot of work to force more blood in. That would have stressed the right ventricle; the stent in the right coronary artery, which supplies the right ventricle, would have alleviated the stress on this heart chamber. Such a complex interaction of one person's heart blood supply with a rare lung disease had no precedent in the medical literature.

This case reminds us that we're each a one-of-a-kind intricacy that will never be fully deconvoluted by machines. The case also highlights the human side of medicine: We physicians have long known that patients know their body and that we need to listen to them. Algorithms are cold, inhumane predictive tools that will never know a human

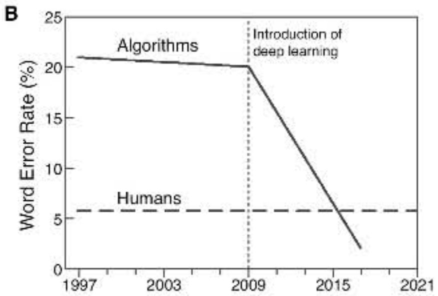

Figure 1.3: The increase in machine AI accuracy for image (A) and speech (B) interpretation, both now exceeding human performance for narrow tasks in labeled datasets. Sources: Panel A adapted from V. Sze et al., "Efficient Processing of Deep Neural Networks: A Tutorial and Survey," *Proceedings of the IEEE* (2017): 105(12), 2295–2329. Panel B adapted from "Performance Trends in AI," *Word Press Blog* (2018): https://srconstantin.wordpress.com/2017/01/28/performance-trends-in-ai/.

The deep learning examples are narrow: the depression predictor can't do dermatology. These neural network algorithms depend on recognizing patterns, which is well-suited for certain types of doctors who heavily depend on images, like radiologists looking at scans or pathologists reviewing slides, which I call "doctors with patterns." To a lesser but still significant extent, all clinicians have some patterned tasks in their daily mix that will potentially be subject to AI algorithmic support.

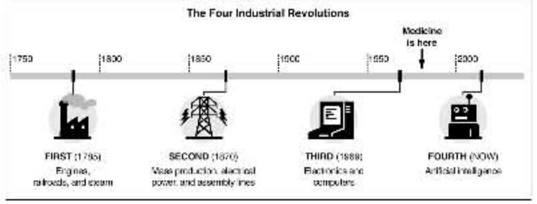

Figure 1.4: The four Industrial Revolutions. Source: Adapted from A. Murray, "CEOs: The Revolution Is Coming," *Fortune* (2016): http://fortune.com/2016/03/08/davos-new-industrial-revolution.

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We're early in the AI medicine era; it's not routine medical practice, and some call it "Silicon Valley–dation." Such dismissive attitudes are common in medicine, making change in the field glacial. The result here is that although most sectors of the world are well into the Fourth Industrial Revolution, which is centered on the use of AI, medicine is still stuck in the early phase of the third, which saw the first widespread use of computers and electronics (Figure 1.4). That MP3 files are compatible with every brand of music player, for example, while medicine has yet to see widely compatible and user-friendly electronic medical records exemplifies the field's struggle to change.

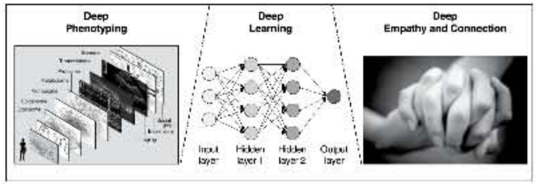

Figure 1.5: The three principal components of the deep medicine model. Source (left panel): Adapted from E. Topol, "Individualized Medicine from Prewomb to Tomb," *Cell* (2014): 157(1), 241–253.

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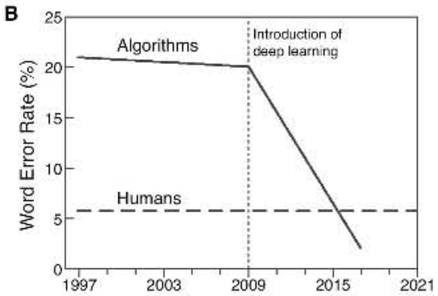

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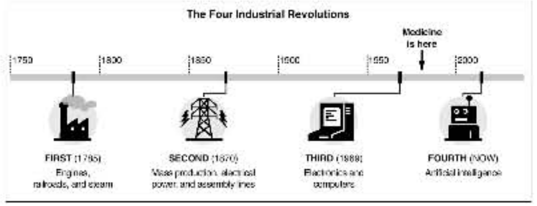

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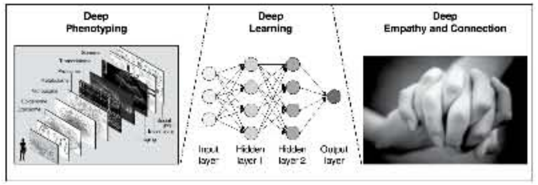

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By every metric, the amount of money spent on healthcare has exploded. Yet, even with all the employment in the sector and all the money expended per person, the time spent between doctors and patients has steadily dwindled, whether for office visits or in the hospital. Doctors are much too busy. The exorbitant charge of almost $5,000 for a day in the hospital might only include a few minutes of your doctor coming by to visit (for which there's another charge). Consumed by patient care, physicians were passive while major new changes took hold in the business of healthcare, including electronic health records, managed care, health maintenance organizations, and relative value units. Now, the highest-ever proportion of doctors and nurses are experiencing burnout and depression owing to their inability to provide real care to patients, which was their basis for pursuing a medical career.

What's wrong in healthcare today is that it's missing care. That is, we generally, as doctors, don't get to really care for patients enough. And patients don't feel they are cared for. As Francis Peabody wrote in 1927, "The secret of the care of the patient is caring for the patient."[5] The greatest opportunity offered by AI is not reducing errors or workloads, or even curing cancer: it is the opportunity to restore the precious and time-honored connection and trust—the human touch—between patients and doctors. Not only would we have more time to come together, enabling far deeper communication and compassion, but also we would be able to revamp how we select and train doctors. We have prized "brilliant" doctors for decades, but the rise of machines will heighten the diagnostic skills and the fund of medical knowledge available to all clinicians. Eventually, doctors will adopt AI and algorithms as their work partners. This leveling of the medical knowledge landscape will ultimately lead to a new premium: to find and train doctors who have the highest level of emotional intelligence. My friend and colleague, Abraham Verghese, whom I regard as one of the great humanists of medicine, has emphasized these critical points in the foreword of the book, which I hope you have taken the time to read carefully. This is what deep medicine offers.

To develop the conceptual framework of deep medicine, I'll start with how medicine is practiced now and why we desperately need new solutions to such problems as misdiagnosis, errors, poor outcomes, and runaway costs. That, in part, hinges on the basics of how a medical diagnosis is made today. To understand the reward and risk potential of AI, we will explore the AI precedents, the accomplishments ranging from games to self-driving cars. Of equal, and perhaps even greater, importance will be an exploration of AI's liabilities, such as human bias, the potential for worsening inequities, its black-box nature, and concerns for breaches of privacy and security. The transfer of tens of millions of people's personal data from Facebook to Cambridge Analytica, who then used AI to target individuals, illustrates one critical aspect of what could go wrong in the healthcare context.

Then we're ready to move on to the new medicine that will integrate the tools of AI. We'll assess how machine pattern recognition will affect the practice of radiologists, pathologists, and dermatologists—the doctors with patterns. But AI will cut across all disciplines of medicine, even "clinicians without patterns" and surgeons. One field that is especially in urgent need of new approaches is mental health, with a profound mismatch of the enormous burden of conditions like depression and the limited number of trained professionals to help manage or prevent it. AI will likely prove to have a critical role in mental health going forward.

But AI, and specifically deep learning, won't just affect the practice of medicine. In a complementary way, it will also transform biomedical science. For example, it will facilitate the discovery of new drugs. It will also extract insights from complex datasets, such as millions of whole genome sequences, the intricacies of the human brain, or the integrated streaming of real-time analytics from multiple biosensor outputs. These endeavors are upstream from the care of patients, but catalyzing advances in basic science and drug development will ultimately have a major effect in medicine.

AI can also revolutionize other aspects of our lives that are, in one sense or another, upstream from the clinic. A huge one is how we eat. One of the unexpected and practical accomplishments of machine learning to date has been to provide a potential scientific basis for individualized diets. That's conceivably an exciting advance—the idea of knowing what specific foods are best for any given person. We can now predict in healthy people, without diabetes, what particular foods will spike their blood sugar. Such advances far outstrip whatever benefits might accrue from following a diet for all people, such as the classic food pyramids, or fad diets like Atkins or South Beach, none of which ever had a solid evidence basis. We'll review that fascinating body of data and forecast where smart nutrition may go in the future. Many of these at-home advances will come together in the virtual medical coach. It most likely will be voice mediated, like Siri, Alexa, and Google Home, but unlikely to remain a cylinder or a squiggle on a screen. I suspect they're more apt to come in the form of a virtual human avatar or hologram (but simply text or e-mail if one prefers). The virtual medical coach is the deep learning of all of one's data, seamlessly collected, continuously updated, integrated with all biomedical knowledge, and providing feedback and coaching. Such systems will initially be condition specific, say for diabetes or high blood pressure, but eventually they'll offer a broad consumer health platform to help prevent or better manage diseases.

All this potential, however, could be spoiled by misuse of your data. This encompasses not just the crimes we've seen all too much of so far, such as cybertheft, extortion (hospitals having their data held for ransom), and hacking, but the nefarious and large-scale sale and use of your data. The new, worrisome, unacceptable wrinkle could be that insurance companies or employers get hold of all your data—and what has been deep learned about you—to make vital decisions regarding your health coverage, your premiums, or your job. Avoiding such dreadful scenarios will take deliberate and intense effort.

This book is all about finding the right balance of the patients, doctors, and machines. If we can do that—if we can exploit machines' unique strengths to foster an improved bond between humans—we'll have found a vital remedy for what profoundly ails our medicine of today.

I hope to convince you that deep medicine is both possible and highly desirable. Combining the power of humans and machines—intelligence both human and artificial—would take medicine to an unprecedented level. There are plenty of obstacles, as we'll see. The path won't be easy, and the end is a long way off. But with the right guard rails, medicine can get there. The increased efficiency and workflow could either be used to squeeze clinicians more, or the gift of time could be turned back to patients—to use the future to bring back the past. The latter objective will require human activism, especially among clinicians, to stand up for the best interest of patients. Like the teenage students of Parkland rallying against gun violence, medical professionals need to be prepared to fight against some powerful vested interests, to not blow this opportunity to stand up for the primacy of patient care, as has been the case all too often in the past. The rise of machines has to be accompanied by heightened humaneness—with more time together, compassion, and tenderness—to make the "care" in healthcare real. To restore and promote care. Period.

Let's get started.

chapter nine

AI AND HEALTH SYSTEMS

> The nurses wear scrubs, but the scrubs are very, very clean. The patients are elsewhere.
>
> —Arthur Allen

A few years ago, on a warm sunny afternoon, my ninety-year-old father-in-law was sweeping his patio when he suddenly felt weak and dizzy. Falling to his knees, he crawled inside his condo and onto the couch. He was shaking but not confused when my wife, Susan, came over minutes later, since we lived just a block away. She texted me at work, where I was just finishing my clinic, and asked me to come over.

When I got there, he was weak and couldn't stand up on his own, and it was unclear what had caused this spell. A rudimentary neuro exam didn't show anything: his speech and vision were fine; muscle and sensory functions were all okay save for some muscle trembling. A smartphone cardiogram and echo were both normal. Even though I knew it wouldn't go over too well, I suggested we take him to the emergency room to find out what the problem was.

John, a Purple Heart–decorated World War II vet, had never been sick. In fact, we had previously enrolled him in our Wellderly genomics sequencing research program at Scripps Research for people age eighty-five and older who had a remarkable health span, never had a chronic illness, and weren't taking medications like statins for high cholesterol or other chronic conditions. Only in recent months had he developed some mild high blood pressure, for which his internist had prescribed chlorthalidone, a weak diuretic. Otherwise, his only medicine over the years was a preventive baby aspirin every day.

With some convincing he agreed to be seen, so along with his wife and mine, we drove over to the local ER. The doctor there thought he might have had some kind of stroke, but a head CT didn't show any abnormality. But then the bloodwork came back and showed, surprisingly, a critically low potassium level of 1.9 mEq/L—one of the lowest I've seen. It didn't seem that the diuretic alone could be the culprit. Nevertheless, John was admitted overnight just to get his potassium level restored by intravenous and oral supplement.

All was well until a couple of weeks later, when he suddenly started vomiting bright red blood. He was so unwilling to be sick that he told his wife not to call Susan. But she was panicked and called Susan anyway. Again, my wife quickly arrived on the scene. There was blood everywhere, in the bedroom, in the living room, and bathroom. Her father was fully alert despite the vomiting and a black, tarry stool, both of which were clear indications that he was having a major gastrointestinal bleed. He needed to go to the ER again. At the hospital a few hours later, after an evaluation and a consultation with a GI specialist, an urgent endoscopy showed my father-in-law had esophageal varices that were responsible for the bleeding.

To do the procedure of localizing the source of bleeding, John was anesthetized and given fentanyl, and when he finally got to a hospital room in the evening, he could barely say a few words. Soon thereafter he went into a deep coma. Meanwhile his labs came back: his liver function tests were markedly abnormal, and his blood ammonia level was extremely high. An ultrasound showed a cirrhotic liver. We quickly came to the realization that the esophageal varices were secondary to end-stage liver disease. A man who had been perfectly healthy for ninety years all of a sudden was in a coma with a rotted liver. He was receiving no intravenous or nutritional support, but he was receiving lactulose enemas to reduce his blood ammonia level from the liver failure. His prognosis for any meaningful recovery was nil, and the attending doctor and the medical residents suggested that we make him a do-not-resuscitate order.

Arrangements were made over the next few days for him to come to our house with hospice support, so he could die at home. Late on a Sunday night, the night before we were to take my father-in-law home to die, my wife and daughter went to visit him. They both had been taught "healing touch" and, as an expression of their deep love, spent a few hours talking to him and administering this spiritual treatment as he lay comatose.

On Monday morning, my wife met with the hospice nurse outside the hospital room. Susan told the nurse that, before they went over the details, she wanted to go see her father. As Susan hugged him and said, "Dad, if you can hear me, we're taking you home today." John's chest heaved; he opened his eyes, looked at her, and exclaimed, "Ohhhh-hhh." She asked him if he knew who she was, and he said, "Sue."

If there was ever a family Lazarus story, this was it. Everything was turned upside down. The plan to let him die was abandoned. When the hospice transport crew arrived, they were told the transfer plan was ditched. An IV was inserted for the first time. The rest of the family from the East Coast was alerted of his shocking conversion from death to life so that they could come to visit. The next day my wife even got a call on her cell phone from her father asking her to bring him something to eat.

My lasting memory of that time is taking John on a wheelchair ride outside. By then he'd been in the hospital for ten days and, now attached to multiple IVs and an indwelling Foley catheter, was as pale as the sheets. Against the wishes of his nurses, I packaged him up and took him in front of the hospital on a beautiful fall afternoon. We trekked down the sidewalk and up a little hill in front of the hospital; the wind brought out the wonderful aroma of the nearby eucalyptus trees. We were talking, and we both started to cry. I think for him it was about the joy of being alive to see his family. John had been my adopted father for the past twenty years, since my father had died, and we'd been very close throughout the nearly forty years we had known each other. I never imagined seeing him sick, since he had always been a rock, the veritable picture of health. And now that he had come back to life, compos mentis, I wondered how long this would last. The end-stage liver disease didn't make sense, since his drinking history was moderate at worst. There was a blood test that came back with antibodies to suggest the remote possibility of primary biliary cirrhosis, a rare disease that didn't make a lot of sense to find in a now-ninety-one-year-old man (the entire family had gotten to celebrate his birthday with him in the hospital). Uncertainties abounded.

He didn't live much longer. There was debate about going to inject and sclerose the esophageal varices to avoid a recurrent bleed, but that would require another endoscopy procedure, which nearly did him in. He was about to be discharged a week later when he did have another bleeding event and succumbed.

PREDICT, PREDICT, PREDICT

What does this have to do with deep changes with AI? My father-in-law's story intersects with several issues in healthcare, all of them centering on how hospitals and patients interact.

The most obvious is how we handle the end of life. Palliative care as a field in medicine is undergoing explosive growth already. It is going to be radically reshaped: new tools are in development using the data in electronic health records to predict time to death with unprecedented accuracy while providing the doctor with a report that details the factors that led to the prediction.[1] If further validated, this and related deep learning efforts may have an influence for palliative care teams in more than 1,700 American hospitals, about 60 percent of the total. There are only 6,600 board certified palliative-care physicians in the United States, or only 1 for every 1,200 people under care, a situation that calls out for much higher efficiency without compromising care. Less than half of the patients admitted to hospitals needing palliative care actually receive it.[2] Meanwhile, of the Americans facing end-of-life care, 80 percent would prefer to die at home, but only a small fraction get to do so—60 percent die in the hospital.[3]

A first issue is predicting when someone might die—getting that right is critical to whether someone who wants to die at home actually can. Doctors have had a notoriously difficult time predicting the timing of death. Over the years, a screening tool called the Surprise Question has been used by doctors and nurses to identify people nearing the end of life—to use it, they reflect on their patient, asking themselves, "Would I be surprised if this patient died in the next twelve months?" A systematic review of twenty-six papers with predictions for over 25,000 people, showed the overall accuracy was less than 75 percent, with remarkable heterogeneity.[4]

Anand Avati, a computer scientist at Stanford, along with his team, published a deep learning algorithm based on the electronic health record to predict the timing of death. This might not have been clear from the paper's title, "Improving Palliative Care with Deep Learning," but make no mistake, this was a dying algorithm.[5] There was a lot of angst about "death panels" when Sarah Palin first used the term in 2009 in a debate about federal health legislation, but that was involving doctors. Now we're talking about machines. An eighteen-layer DNN learning from the electronic health records of almost 160,000 patients was able to predict the time until death on a test population of 40,000 patient records, with remarkable accuracy. The algorithm picked up predictive features that doctors wouldn't, including the number of scans, particularly of the spine or the urinary system, which turned out to be as statistically powerful, in terms of probability, as the person's age. The results were quite powerful: more than 90 percent of people predicted to die in the following three to twelve months did so, as was the case for the people predicted to live more than twelve months. Noteworthy, the ground truths used for the algorithm were the ultimate hard data—the actual timing of deaths for the 200,000 patients assessed. And this was accomplished with just the structured data in the electronic records, such as age, what procedures and scans were done, and length of hospitalization. The algorithm did not use the results of lab assays, pathology reports, or scan results, not to mention more holistic descriptors of individual patients, including psychological status, will to live, gait, hand strength, or many other parameters that have been associated with life span. Imagine the increase in accuracy if they had—it would have been taken up several notches.

An AI dying algorithm portends major changes for the field of palliative care, and there are companies pursuing this goal of predicting the timing of mortality, like CareSkore, but predicting whether someone will die while in a hospital is just one dimension of what neural networks can predict from the data in a health system's electronic records.[6] A team at Google, in collaboration with three academic medical centers, used input from more than 216,000 hospitalizations of 114,000 patients and nearly 47 billion data points to do a lot of DNN predicting: whether a patient would die, length of stay, unexpected hospital readmission, and final discharge diagnoses were all predicted with a range of accuracy that was good and quite consistent among the hospitals that were studied.[7] A German group used deep learning in more than 44,000 patients to predict hospital death, kidney failure, and bleeding complications after surgery with remarkable accuracy.[8] DeepMind AI is working with the US Department of Veterans Affairs to predict medical outcomes of over 700,000 veterans.[9] AI has also been used to predict whether a patient will survive after a heart transplant[10] and to facilitate a genetic diagnosis by combining electronic health records and sequence data.[11] Mathematical modeling and logistic regression have been applied to such outcome data in the past, of course, but the use of machine and deep learning, along with much larger datasets, has led to improved accuracy.

The implications are broad. As Siddhartha Mukherjee reflected, "I cannot shake some inherent discomfort with the thought that an algorithm might understand patterns of mortality better than most humans."[12] Clearly, algorithms can help patients and their doctors make decisions about the course of care both in palliative situations and those where recovery is the goal. They can influence resource utilization for health systems, such as intensive care units, resuscitation, or ventilators. Likewise, the use of such prediction data by health insurance companies for reimbursement hangs out there as a looming concern.[13]

Hospitals are the number one line item of healthcare costs in the United States and account for almost one-third of the $3.5 trillion annual expenditures. While personnel are the biggest factor driving their costs, the need to avoid hospitalizations, whether the first or a readmission, has taken center stage for many AI initiatives. Economics play a major role here, since readmission within thirty days of hospitalization may not be reimbursable. There are concerns, and indeed some debate, as to whether trying to restrict hospitalizations would have an adverse effect on patient outcomes.[14]

Multiple studies have taken on the challenge of predicting whether a hospitalized patient will need to be readmitted in the month following discharge from a hospital, particularly finding features that are not captured by doctors. For example, a study conducted by Mount Sinai in New York City used electronic health records, medications, labs, procedures, and vital signs, and demonstrated 83 percent accuracy in a relatively small cohort.[15] A much larger set of 300,000 patients was used to train and validate the DeepR Analytics DNN,[16] which compared favorably to other efforts, including DoctorAI[17] and DeepCare. This objective is being pursued by many start-up companies and academic centers, along with AI for case management. Notably, Intermountain Healthcare, University of Pittsburgh Medical Center, and Sutter Health are among first movers working on implementation of such algorithms.

Among the bolder objectives is to predict disease in patients without any classic symptoms. A group based at Tsinghua University in Beijing took data from more than 18,000 real-world EHRs to accurately diagnose six common diseases: hypertension, diabetes, COPD, arrhythmia, asthma, and gastritis.[18] Using solely eighteen lab tests, certain conditions, such as kidney disease, could be accurately predicted by a DNN in a large cohort of nearly 300,000 patients followed over eight years.[19] The Mount Sinai group studied EHRs from 1.3 million patients to predict five diseases—diabetes, dementia, herpes zoster (also known as shingles), sickle cell anemia, and attention deficit disorder—with very high accuracy. Preventing these diseases would require two variables to be true: that such algorithms using EHRs, lab tests, and other data survive further testing, showing that they can indeed predict the onset of these diseases, and that effective

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Prediction	N	AUC	Reference
In-hospital mortality, unplanned readmission, prolonged LOS, final discharge diagnosis	216,221	0.93[*] 0.75[~] 0.85[#]	Rajkomar et al., Nature NPJ Digital Medicine, 2018
All-cause 3-12 month mortality	221,284	0.93[^]	Avati et al., arXiv, 2017
Readmission	1,068	0.78	Shameer et al., Pacific Symposium on Biocomputing, 2017
Sepsis	230,936	0.67	Horng et al., PLOS One, 2017
Septic shock	16,234	0.83	Henry et al., Science, 2015
Severe sepsis	203,000	0.85[@]	Culliton et al., arXiv, 2017
C. difficile infection	256,732	0.82[++]	Oh et al., Infection Control and Epidemiology, 2018
Developing diseases	704,587	range	Miotto et al., Scientific Reports, 2018
Diagnosis	18,590	0.96	Yang et al., Scientific Reports, 2018
Dementia	76,367	0.91	Cleret de Langavant et al., J Internet Med Res, 2018
Alzheimer's disease (+ amyloid imaging)	273	0.91	Mathotaarachchi et al., Neurobiology of Aging, 2017
Mortality after cancer chemotherapy	26,946	0.94	Elfiky et al., JAMA Open, 2018
Disease onset for 133 conditions	298,000	range	Razavian et al., arXiv, 2016
Suicide	5,543	0.84	Walsh et al., Clinical Psychological Science, 2017

AUC: area under the curve, a metric of accuracy, LOS: length of stay, N: number of patients (training + validation datasets), [*]in-hospital mortality, [~]unplanned readmission, [#]prolonged LOS, [^]all patients, [@]structured and unstructured data, [++]for U of Michigan site

Table 9.1: A sample of fifteen studies using AI to predict clinical outcomes.

THE HEALTHCARE WORKFORCE AND WORKFLOW

There are many uses of AI for hospitals and health systems that extend well beyond predicting death and major outcomes. By 2017, healthcare became the number one US industry by total jobs for the first time, rising above retail.[21] More than 16 million people are employed by health services, with well over 300,000 new jobs created during calendar year 2017 and again in 2018. Almost one of every eight Americans is employed by the healthcare industry.[22] Projections from the US Bureau of Labor Statistics for the next ten years indicate that most of the jobs with the highest anticipated growth are related to health, including personal care aides (754,000), home health aides (425,000), physician assistants (40,000), nurse practitioners (56,000), and physical therapy assistants (27,000). Because human resources are by far the most important driver of healthcare costs, now exceeding $3.5 trillion in the United States per year, you can imagine that people are thinking about how AI can automate operations and alleviate this unbridled growth and related costs. As Katherine Baicker of Harvard put it, "The goal of increasing jobs in health care is incompatible with the goal of keeping health care affordable."[23]

Some economists have suggested that the growth of new job types in healthcare will match or exceed the rate at which AI can replace them. But Kai-Fu Lee, a leading authority in AI, thinks otherwise: "It will soon be obvious that half our tasks can be done better at almost no cost by AI. This will be the fastest transition humankind has experienced, and we're not ready for it."[24]

Hospitals, clinics, and health systems employ people to abstract their medical records to come up with the right billing codes for insurers, and they employ significant numbers of dedicated personnel for payment collection and claims management. The American Academy of Professional Coders has more than 175,000 members with an average salary of $50,000 to do medical bill coding. It is remarkable that the cost of doing the billing for a visit with a doctor in the United States is over $20, or 15 percent of the total cost. It's even worse for an emergency room visit, as the cost of billing accounts for more than 25 percent of the revenue.[25] Overall, in the United States, more than 20 percent of healthcare spending is related to administration.[26] Manual, human scheduling for operating rooms or staffing all the inpatient and outpatient units in a hospital leads to remarkable inefficiencies. Much of the work that attends to patients calling in to schedule appointments could be accomplished with natural-language processing, using human interface as a backup. Algorithms are already being used at some health systems to predict no-shows for clinic appointments, a significant source of inefficiency because missed appointments create so many idle personnel. Even the use of voice assistants to replace or complement nurse call buttons in hospitals by Inovia's AIVA may help improve productivity.[27]

All these operational positions await AI engagement and efficiency upgrades. Some efforts are being made already. One example is Qventus, which uses multimodal data —from the EHR, staffing, scheduling, billing systems, and nurse call lights—to predict proceedings in a hospital's emergency department, operating rooms, or pharmacy. The company claims to have achieved a marked reduction in patients falling in a hospital,[28] the percentage of patients who leave the emergency room without being seen, and the time it takes for a doctor to see a patient.[29] Companies such as Conversa Health, Ayasdi, Pieces Tech, and Jvion are also using AI to take on these logistical tasks, along with many unmet needs for improving efficiency and patient engagement.[30]

How AI can ease medical workflow is exemplified by a program that MedStar Health, the largest health system in the Washington, DC, region, has initiated in its emergency rooms. The typical ER patient has about sixty documents in his or her medical history, which takes considerable time for clinicians to review and ingest. MedStar developed a machine learning system that rapidly scans the complete patient record and provides recommendations regarding the patient's presenting symptoms, freeing doctors and nurses to render care for their patients.[31] Another example is AI automation of medical images, which isn't simply about reading MRIs. The FDA-approved Arterys algorithm called Deep Ventricle enables rapid analysis of the heart's blood flow, reducing a task that can take an hour as blood is drawn and measured by hand to a fifteen-second scan.

Marked improvement in the workflow of medical scans is starting to take hold. Using deep learning algorithms for image reconstruction, multiple reports have indicated the time requirement for acquiring and processing the scans has fallen, improving the quality of the images produced, and substantially reducing the dose of ionizing radiation will become possible. When such improvements are implemented, this may well be one of the first ways we'll see AI promoting safety, convenience, and the potential to lower cost.[32] Another is with radiotherapy for cancer. Researchers at the University College London and DeepMind used an automated deep learning algorithm to markedly accelerate the segmentation processing of scans, achieving similar performance to experienced radiation oncologists for patients with head and neck cancer with remarkable time savings.[33] The use of deep learning algorithms for image segmentation has considerable promise to improve both accuracy and workflow for scans, compared with our prior reliance on traditional algorithms and human expert oversight.

Better prediction of an important diagnosis in real time is another direction of AI efforts, as we've seen, and this issue is of huge importance in hospitals, as one of the major challenges that hospitals face is treating infections that patients catch while hospitalized. Sepsis, a deadly infection common in hospitals, is responsible for 10 percent of intensive care unit admissions in the United States. Treating it costs more than $10 billion per year, and treatment often fails: sepsis accounts for 20 to 30 percent of all deaths among hospitalized patients in the United States. Timely diagnosis is essential since patients can deteriorate very quickly, often before appropriate antibiotics can be selected, let alone be administered and take effect. One retrospective study by Suchi Saria at Johns Hopkins Medicine used data from 53,000 hospitalized patients with documented sepsis, along with their vital signs, electronic medical records, labs, and demographics, to see whether the condition could be detected sooner than it had been. Unfortunately, the accuracy of the algorithm (ROC ~.70) was not particularly encouraging.[34] A second deadly hospital-acquired infection, *Clostridium difficile* or *C. diff*, is also a target of AI. The data to date look a bit more positive. *C. diff* kills about 30,000 people each year in the United States, out of more than 450,000 patients diagnosed.[35] Erica Shenoy and Jenna Wiens developed an algorithm to predict the risk from 374,000 hospitalized patients at two large hospitals using more than 4,000 structured EHR variables for each. Their ROCs were 0.82 and 0.75 for the two hospitals, with many features that were specific to each institution.[36] With automated alerts to clinicians of high *C. diff* risk, it is hoped that the incidence of this life-threatening infection can be reduced in the future.

Preventing nosocomial infections, which one in every twenty-five patients will acquire from a caregiver or the environment, is also an important challenge for hospitals. For example, we know that lack of or suboptimal handwashing is a significant determinant of hospital-acquired infections. In a paper titled "Towards Vision-Based Smart Hospitals," Albert Haque and colleagues at Stanford University used deep learning and machine vision to unobtrusively track the hand hygiene of clinicians and surgeons at Stanford University hospital with video footage and depth sensors. The technology was able to quantify how clean their hands were with accuracy levels exceeding 95 percent (Figure 9.1).[37] Such sensors, which use infrared light to develop silhouette images based on the distance between the sensors and their targets, could be installed in hospital hallways, operating rooms, and at patient bedsides in the future to exploit computer vision's vigilance.

Indeed, machine vision has particular promise for deep learning patterns in the dynamic, visual world of hospitals. The intensive care unit is another prime target for machine vision support. Reinforcement learning has been used as a data-driven means to automate weaning of patients from mechanical ventilation, which previously has been a laborious and erratic clinically managed process.[38]

Surveillance videos of patients could help determine whether there is risk of a patient pulling out their endotracheal (breathing) tube and other parameters not captured by vital signs, reducing the burden on the nurse for detection. The ICU Intervene DNN, from MIT's CSAIL, helps doctors predict when a patient will need mechanical ventilation or vasopressors and fluid boluses to support blood pressure, along with other interventions.[39] Another CSAIL algorithm helps determine optimal time of transfer out of the ICU, with the objective of reducing hospital stay and preventing mortality.[40] Other efforts centered on the ICU reduce the burden on the nurse by automated surveillance with cameras or algorithmic processing of vital signs.

We're still in the early days of machine vision with ambient sensors, but there is promise that this form of AI can be useful to improve patient safety and efficiency. Another common hospital task that machine vision will likely have a role in changing is placing a central venous catheter, commonly known as a central line, into a patient. Because these lines are so invasive, they carry a significant risk of infection and complications such as a collapsed lung or injury to a major artery. By monitoring proper technique, with respect to both sterile conditions and line placement, safety may improve. Operating rooms could change as machine vision systems continuously track personnel and instruments along with workflow.[41] Prevention of falls in the hospital by cueing into risky patient movements or unsteadiness is also being pursued with AI vision.

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genetic discrimination by employers and health insurers, and even that remains incomplete, as life insurance and long-term disability plans can discriminate based on genetic information. And, although the Affordable Care Act made provisions for excluding preexisting conditions for coverage considerations, that isn't set in stone, as the Trump administration has made clear.[49] Along these lines, risk prediction, by individual, is the next frontier of concerns that remain to be addressed.

Perhaps less pernicious but still worrisome is reliance on "wellness" programs, which most medium to large employers in the United States have, despite the fact that, overall, they have not been validated to promote health outcomes. Typically, a wellness program combines step counting, weight and blood pressure readings, and cholesterol lab tests, as well as some incentive for employees to participate (such as a surcharge on an employee's contribution to the cost of insurance). But wellness is poorly defined, and the cost effectiveness of such strategies has been seriously questioned.[50] One way such programs could be improved, however, is through the use of virtual medical coaches, which could gather and make use of far more granular and deeper information about each individual. Here again is the concern that employers, through their insurance providers, could use such data to financially disadvantage individuals, which could be a major disincentive for patients to use such technology.

Looking overseas, one relatively small insurer that has been gaining some experience with more comprehensive data is Discovery Limited, which originated in South Africa but is also now available in Australia, China, Singapore, and the UK. Its Vitality program uses a Big Data approach to capture and analyze physical activity, nutrition, labs, blood pressure, and, more recently, whole genome sequences for some individuals. There have yet to be any publications regarding the betterment of health outcomes with this added layer of data, but it may represent a trend for insurers in the future.

MEDICAL AI AT THE NATIONAL LEVEL

AI in medicine hasn't attracted quite the same level of attention or ambition as AI for global military, cyber, and superpower dominance, about which Vladimir Putin declared, "Whoever becomes the leader in this sphere will become the ruler of the world."[51] The goal is better health and lower cost for citizens, not world dominance. It is still happening around the world. Canada has been an epicenter for deep learning, with Geoffrey Hinton and colleagues at the University of Toronto, and the dozens of former students who now have prominent AI leadership roles at Google, Uber, Facebook, Apple, and other leading tech companies. Hinton believes that AI will revolutionize healthcare, and his company Vector is using neural networks for the massive datasets throughout hospitals in Toronto. His Peter Munk Cardiac Centre is focused on cardiovascular care, using AI to actualize remote monitoring of patients. Deep Genomics, started by Brendan Frey, one of Hinton's students, is using AI for genomic interpretations.[52] These are just a few of the AI healthcare initiatives and companies in Canada.

It's likely the big changes in AI medicine will take hold far more readily outside the United States, and countries like India and China are particularly likely to be prominent first movers. India has a doctor-to-patient ratio of only 0.7 per 1,000 people, which is less than half that of China (1.5) and substantially less than that of the United States (at 2.5). The ingenuity in AI in India is reflected by companies like Tricog Health for cloud-based heart condition diagnosis, Aindra Systems for automated detection of cervical cancer via path samples, Niramai for early breast cancer detection, and Ten3T for remote monitoring. The pioneering work at the Aravind Eye Hospitals, the largest eye care network in the world, in collaboration with Google, was the basis for deep learning algorithms to detect diabetic retinopathy—a condition for which more than 400 million people are at risk but the majority of whom are not getting screened.[53]

But it's China that seems positioned to take the lead in AI for medicine. So many important factors line up: unparalleled quantity of data collection (citizens cannot opt out of data collection), major government and venture fund investment, major AI programs at most of the big universities, and a very supportive regulatory environment.[54] Beyond all these attributes, there is the need. As Lin Chenxi of Yitu, a Chinese medical image recognition company, put it: "In China, medical resources are very scarce and unequally distributed so that the top resources are concentrated in provincial capitals. With this system, if it can be used at hospitals in rural cities, then it will make the medical experience much better."[55] There are only twenty eye doctors for every million people in China, recapitulating the general trend for the country, where the proportions of various specialists to the population as a whole are one-third or less the proportions found in the United States. China is using more than 130 medical AI companies to promote efficiency and expand access in its healthcare system.[56]

Behind all this is major support. In 2018, the Chinese government issued its manifesto to become the world leader in AI, making the endeavor its own version of an Apollo 11 moon shot.[57] Although there has been a talent gap between China and the ancestries. If all members of the species had comprehensive data in such a resource, with their treatments and outcomes, this would enable AI nearest neighbor analysis to find "digital twins." These are individuals who most resemble, by all demographic, biologic, physiologic, and anatomic criteria, the person at risk or with a new important diagnosis. Knowledge of outcomes from twins would enable better prevention or treatment of the individual and the next generation. The likelihood of assembling such a resource for the world's population is very low, especially impaired by concerns over privacy, data security, and cross-cultural sharing considerations. But we are seeing this at a smaller scale, with efforts such as Tempus Labs in cancer (Chapter 7). It's a think-big scenario to imagine what awaits us in the longer term for all medical conditions without geographic boundaries. But even if the odds are low now, I hope recognition of the possibilities will help make those odds better. As soon as patient outcomes are shown to be unequivocally improved by having digital twins inform best treatment, it is likely there will be substantial commitments across health systems to develop and prioritize such infrastructure.

With this review of the opportunities at the level of healthcare systems, it's time to turn upstream—to the discovery side of drugs and the science that leads to better treatments and mechanistic insights about health and disease. AI is beginning to have a big impact there, too, which over time may further improve the outcomes and efficiency of medical practice.