Translating technology into the clinic

March 7, 2019

Massachusetts Institute of Technology

AI Powered Healthcare

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- How AI could bring big savings to the health insurance market
- Natural language tools helping to address physician burnout
- A new pediatric AI outperforming junior doctors

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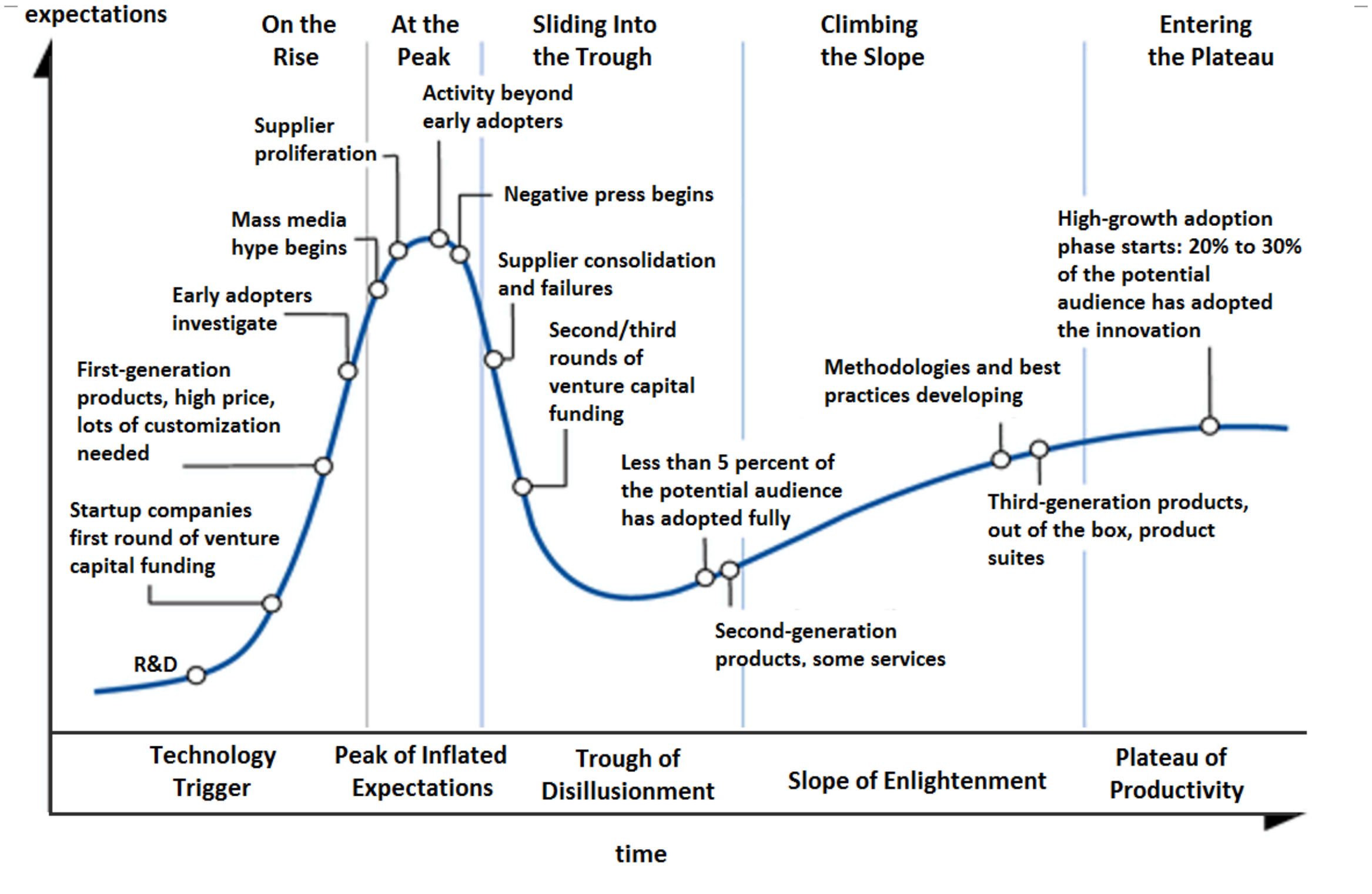
The Hype Cycle

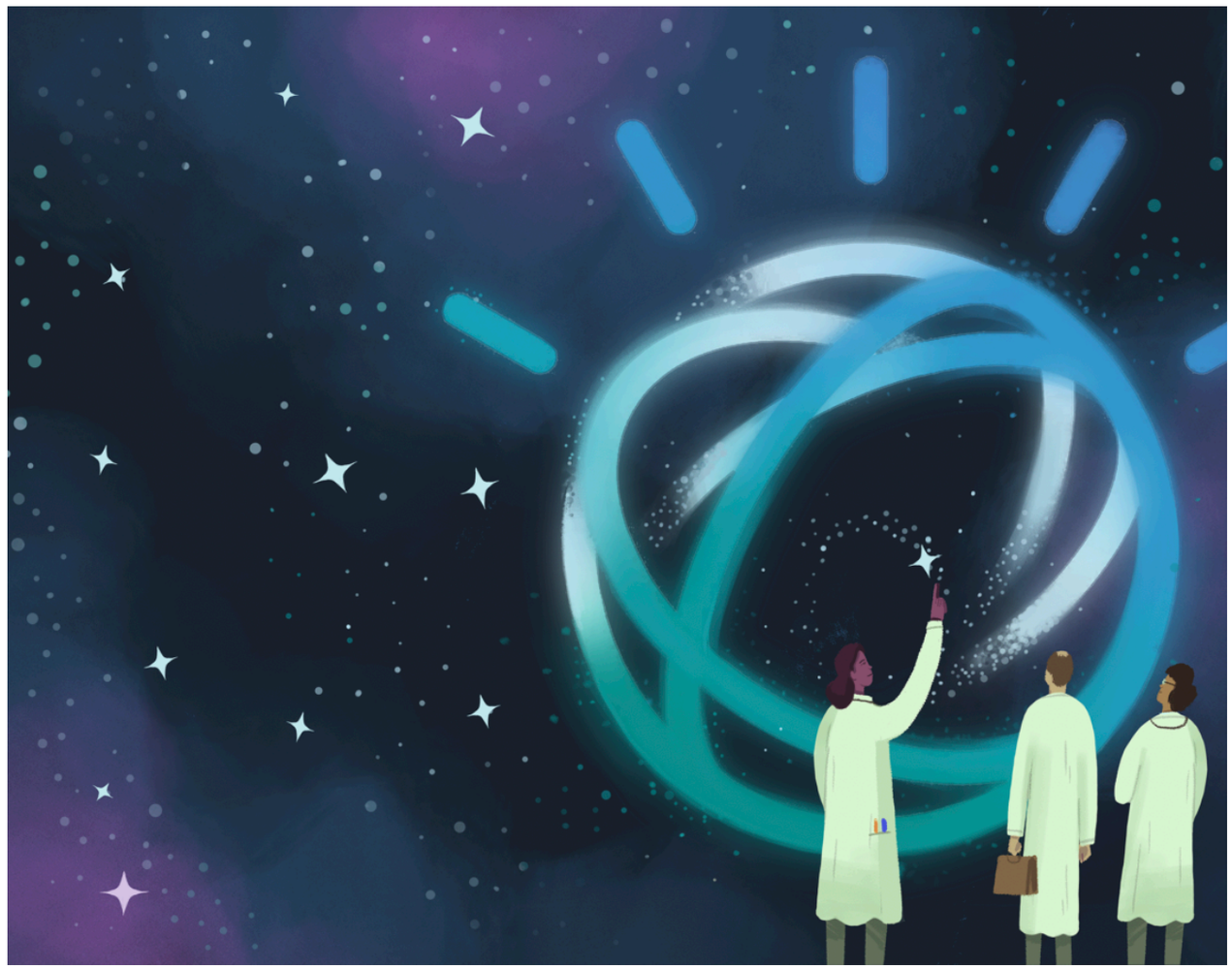


A Cautionary Tale

IBM pitched its Watson supercomputer as a revolution in cancer care. It's nowhere close

***By* Casey Ross @caseymross *and* Ike Swetlitz @ikeswetlitz**
September 5, 2017

STAT



- Watson for Oncology uses the cloud-based supercomputer to digest massive amounts of data — from doctor's notes to medical studies to clinical guidelines.

https://www.statnews.com/2017/09/05/watson-ibm-cancer/

Watson's problems

- "Breathlessly promoting its signature brand — Watson — IBM sought to capture the world's imagination, and it quickly zeroed in on a high-profile target: cancer.
- … isn't living up to the lofty expectations IBM created
- … still struggling with the basic step of learning about different forms of cancer
- Only a few dozen hospitals have adopted the system
- at foreign hospitals, physicians complained its advice is biased toward American patients and methods of care
- hasn't published any scientific papers demonstrating how the technology affects physicians and patients
- its treatment recommendations … are based exclusively on training by human overseers, who laboriously feed Watson information about how patients with specific characteristics should be treated. … those human operators are a couple dozen physicians at … Memorial Sloan Kettering Cancer Center in New York. **Doctors there are empowered to input their own recommendations into Watson, even when the evidence supporting those recommendations is thin**
- most stunning overreach is … [the] claim that Watson for Oncology, through artificial intelligence, can sift through reams of data to generate new insights and identify … "even new approaches" to cancer care. STAT found that **the system doesn't create new knowledge** and is artificially intelligent only in the most rudimentary sense of the term. [5]

Watson's problems (continued)

- Hospitals pay a per-patient fee … , and ranges between $200 and $1,000 per patient
- **At hospitals that don't link it with their medical records, more time must be spent typing in patient information.** [She] spends about 90 minutes a week feeding data into the machine
- the results for a 73-year-old lung cancer patient were underwhelming: **Watson recommended a chemotherapy regimen the oncologists had already flagged**
- the background information Watson provided, including **medical journal articles, was helpful**, … [b]ut the system did not directly help him make that [treatment] decision, **nor did it tell him anything he didn't already know**
- **IBM has not exposed the product to critical review by outside scientists or conducted clinical trials to assess its effectiveness**

- "Artificial intelligence will be adopted in all medical fields in the future," said Dr. Uhn Lee, who runs the Watson program at Gachon University Gil Medical Center in South Korea. "If that trend, that change is inevitable, then why don't we just start early?"

Watson's MD Anderson experience

- The MD Anderson alliance was essentially the early face of Watson in health care. … But the project disintegrated amid internal allegations of overspending, delays, and mismanagement. In all, MD Anderson spent **more than three years and $60 million** …
- The cancer hospital's first major challenge involved getting the machine to deal with the **idiosyncrasies of medical records**: the acronyms, human errors, shorthand phrases, and different styles of writing. "Teaching a machine to read a record is a lot harder than anyone thought," she said. Her team spent countless hours on that problem, trying to get Watson to extract valuable information from medical records so that it could apply them to its recommendations.
- Chin said her team also wrestled with **deploying the system in clinical practice**. Watson, even if guided by doctors, is as close as medicine has ever gotten to allowing a machine to help decide the treatments delivered to human beings. That carries with it thorny questions, such as how to test the safety of a digital treatment adviser, how to ensure its compliance with regulations, and how to incorporate it into the daily work of doctors and nurses.
- "Importantly," Chin said. "How do we create an environment that can ensure the most important tenet in medicine: **Do no harm**?"
- Finally, the project ran into a bigger obstacle: Even if you can get Watson to understand patient variables and make competent treatment recommendations, how do you get it access to enough patient data, from enough different sources, to derive insights that could **significantly advance the standard of care**? Chin said that was a showstopper.

https://www.statnews.com/2017/09/05/watson-ibm-cancer/

Computerized Physician Order Entry (CPOE)

- A study led by David Bates, MD, Chief of General Medicine at Boston's Brigham and Women's Hospital, demonstrated that **CPOE reduced error rates by 55% —** from 10.7 to 4.9 per 1000 patient-days. Rates of **serious medication errors fell by 88%** in a subsequent study by the same group. The prevention of errors was attributed to the CPOE system's structured orders and medication checks. Another study conducted at LDS Hospital in Salt Lake City by David Classen, MD, demonstrated a **70% reduction in antibiotic-related ADEs** after implementation of decision support for these drugs.
- CPOE has paid other dividends. **Length of stay at Wishard Memorial Hospital in Indianapolis fell by 0.9 days**, and **hospital charges decreased by 13%** after implementation of CPOE. A study at Ohio State University also identified substantial reductions in pharmacy, radiology and laboratory turn-around times, as well as a reduction in length of stay in one of the two hospitals studied.
- Research estimates that implementation of CPOE systems at all non-rural U.S. hospitals **could prevent three million adverse drug events each year**.

https://www.leapfroggroup.org/sites/default/files/Files/2018%20CPOE%20Fact%20Sheet.pdf

CPOE Benefits

- Prompts that warn against the possibility of drug interaction, allergy or overdose;
- Accurate, current information that helps physicians keep up with new drugs as they are introduced into the market;
- Drug-specific information that eliminates confusion among drug names that sound alike;
- Improved communication between physicians and pharmacists; and,
- Reduced long-term healthcare costs.
- — https://www.leapfroggroup.org/sites/default/files/Files/2018%20CPOE%20Fact%20Sheet.pdf

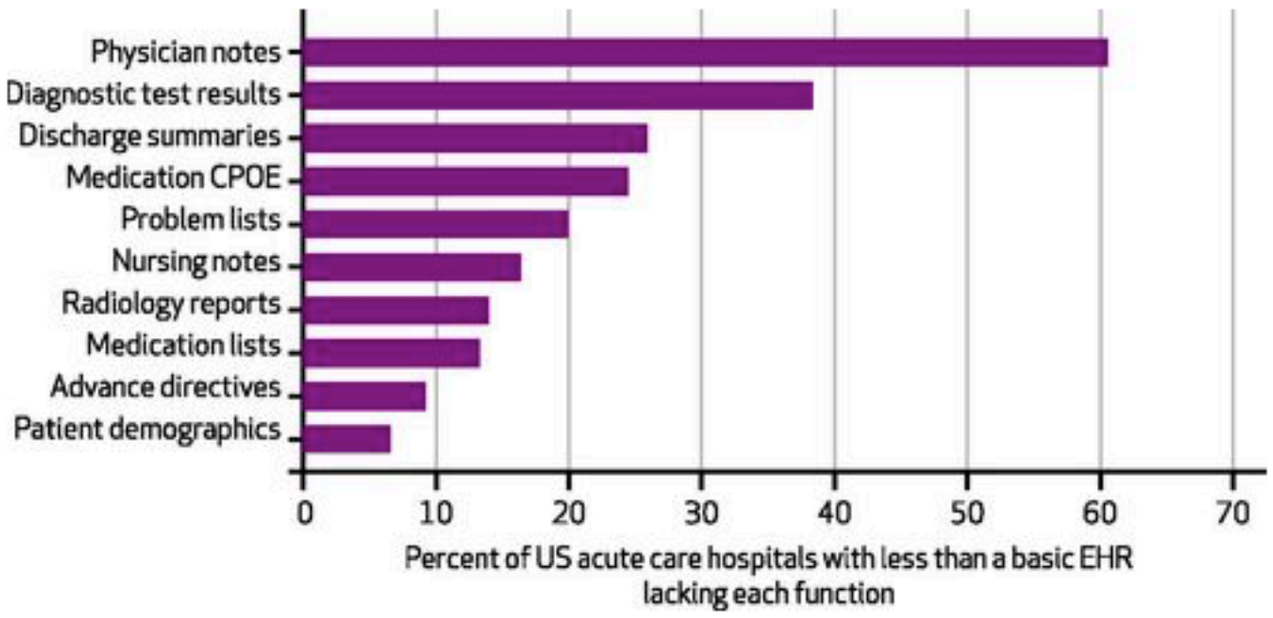
- *Potential future benefits: ML to learn drug-drug interactions*
  - *Identify occurrences in patient notes, reports*
  - *predict from drug class, patient conditions using past data and models*

Adoption of CPOE

- Institute of Medicine (National Academy of Medicine) called for universal adoption of CPOE by 1999.
- "… the CPOE products available as of 2006 represent only a second generation technology', characterized by many limitations. … CPOE adoption in urban hospitals will not reach 80% penetration until 2029."

https://libres.uncg.edu/ir/uncg/f/E_Ford_Predicting_2008.pdf

- **Exhibit 3** Prevalence Of Functions Not Yet Adopted Among Hospitals With Less Than A Basic Electronic Health Record (EHR) System



SOURCE Authors' analysis of American Hospital Association Annual Survey–IT Supplement data, 2014. NOTE CPOE is computerized provider order entry.

CPOE Effect on Pharmacists

- The pharmacists at both the short-term and long-term-CPOE sites spent more time on distributive tasks and less time on clinical tasks … pharmacists at the long-term CPOE site spent a statistically significant less amount of time on clinical tasks
- utilization of CPOE places new burdens and challenges on the pharmacists
- [a] study found that physicians were spending over twice the amount of time on EHR and desk work than on direct clinical face time

Table 3. Average time (min/hr) spent by hospital staff pharmacists on activities

Activity	Mean ± *SD*			*p*-value*
	A: Non-CPOE Hospital	B: Short-term CPOE Hospital	C: Long-term CPOE Hospital	
Clinical[φ]	6.55 ± 6.40	4.95 ± 4.15	3.79 ± 4.91	.0046
Administrative[§]	5.55 ± 6.76	5.59 ± 6.04	8.15 ± 8.31	.0337
Order Entry[&]	29.62 ± 11.24	17.44 ± 10.73	10.27 ± 8.88	< .0001
Order Verification[#]	0.88 ± 1.77	13.93 ± 8.50	16.60 ± 9.63	< .0001
All Other Distributive Tasks[δ]	13.60 ± 10.04	15.86 ± 8.38	19.66 ± 8.42	.0002
Distributive Tasks (Combined)	44.11 ± 9.87	47.23 ± 8.43	46.53 ± 9.17	.0850
Miscellaneous[€]	3.78 ± 4.64	1.54 ± 3.20	2.23 ± 3.51	.0011

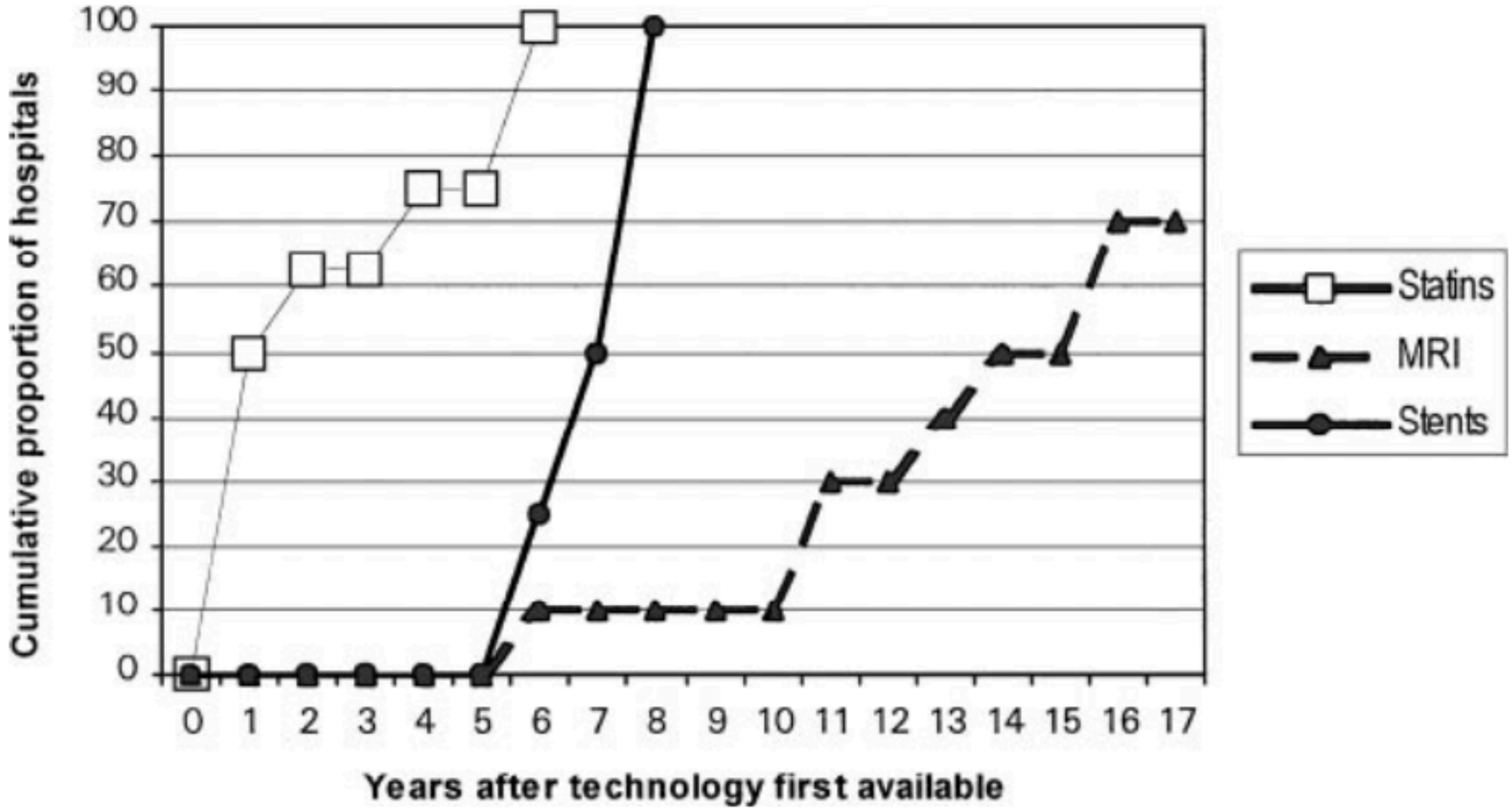
Note. CPOE = computerized provider order entry; Minutes may not equal to exactly 60 due to rounding to second digit after decimal; *p-value calculated by ANOVA - a value of <.05 is considered statistically significant; [Φ] Tukey's test performed to test statistical significance between each site; A to C was significant; [§] Tukey's test performed to test statistical significance between each site; no direct comparisons were significant; [&] Tukey's test performed to test statistical significance between each site; A to B, A to C, and B to C were all significant; [#] Tukey's test performed to test statistical significance between each site; A to B and A to C were significant; [δ] Tukey's test performed to test statistical significance between each site; A to C and B to C was significant; [€] Tukey's test performed to test statistical significance between each site; A to B and A to C was significant

Lewing, B. D., Hatfield, M. D., & Sansgiry, S. S. (2017). Impact of Computerized Provider Order Entry Systems on hospital staff pharmacist workflow productivity: A three site comparative analysis based on level of CPOE implementation. Journal of Hospital Administration, 7(1), 1–8.

Diffusion of New Medical Technologies

- The selected technologies had markedly different diffusion curves.
  - Statins diffused rapidly soon after launch.
  - Coronary stents were initially used 6 years after first availability, but within 2 years all responding hospitals reported using them.
  - MRI scanners were initially purchased 6 years after first availability with a subsequently slow rate of diffusion, and are still absent from some hospitals.
- Influences on the adoption of each technology were different.
  - Commercial marketing was reported as a major influence on the diffusion of statins but not at all on MRIs.
  - Cost impact was a major negative influence on the diffusion of MRI scanners and statins,
  - whereas enthusiastic individuals were key to the diffusion of stents.

Booth-Clibborn, N., Packer, C., & Stevens, A. (2000). HEALTH TECHNOLOGY DIFFUSION RATES. *Intl. J. of Technology Assessment in Health Care*, *16*(3), 781–786.



*Year 0 = year of first availability (England)

How to assure quality?

- Problem of bias in published reports: only successful studies get published
  - Multiple testing by groups unknown to each other will yield *some* positive results

The Importance of Potential Studies That Have Not Existed and Registration of Observational Data Sets

John P. A. Ioannidis, MD, DSc

main analyses would require little time, yet prep

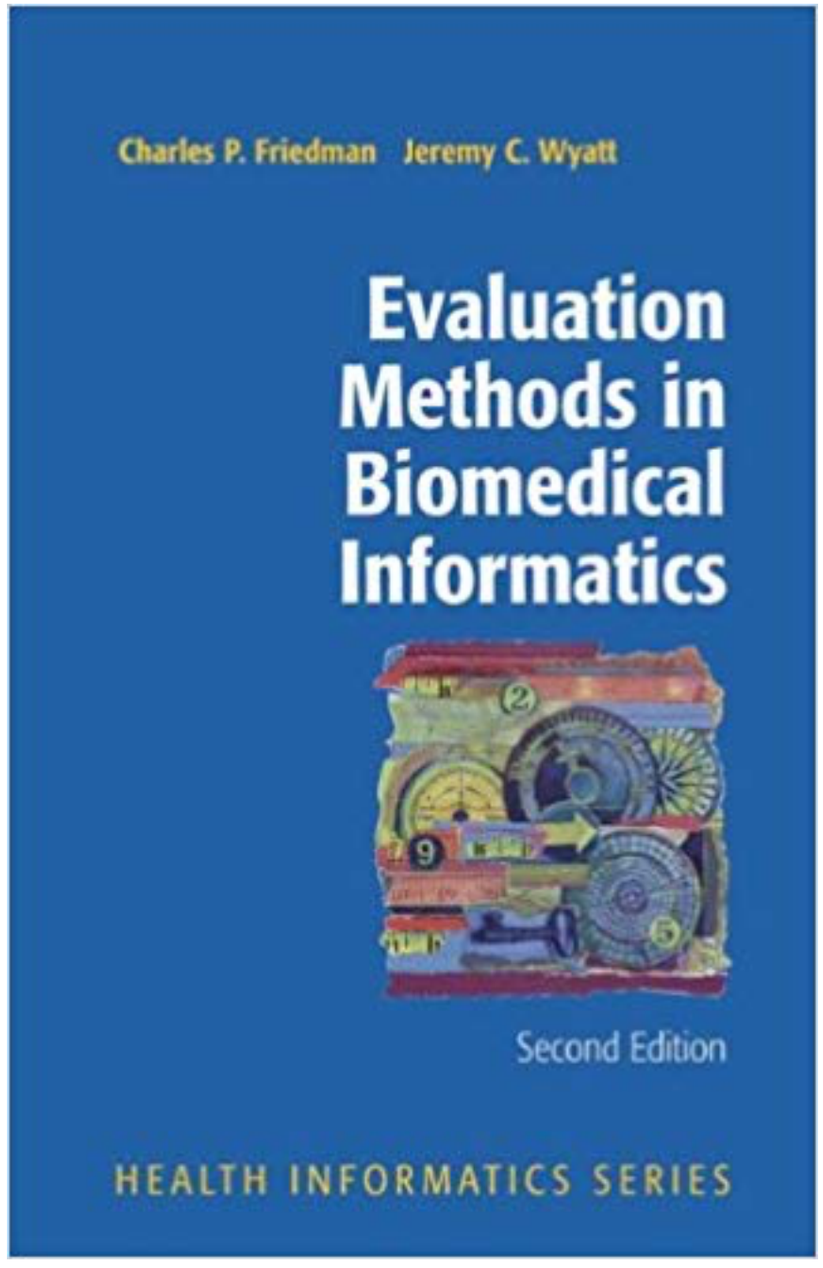
- Well-known inability to replicate large fraction of biomedical (and other) studies
- Require replication of studies in more than one data set—Drazen, NEJM

Ioannidis, J. P. A. (2012). The Importance of Potential Studies That Have Not Existed and Registration of Observational Data Sets. JAMA : the Journal of the American Medical Association, 308(6), 575–576. http://doi.org/10.1001/jama.2012.8144

Replication study type	Example study	Utility of replication study design
Exact (or close) replication	A laboratory study of the usability of a specific CPOE system is repeated in a different laboratory using the exact same protocol and system	High fidelity replications test the validity of an earlier study
Partial replication	A clinical trial of a CPOE system is repeated using the same system in a similar clinical environment, using an identical implementation strategy, and enrolling comparable groups of patients and clinicians	Modest level fidelity replications test the validity of an earlier study when it is not possible to undertake high fidelity studies
Conceptual replication	Following a trial of a CPOE system in a clinical setting that shows mortality effects, the general hypothesis that all CPOE systems increase mortality rates is tested by using a different CPOE system, with a different implementation strategy, clinical setting and research subjects	Conceptual studies test the generalizability of past results, by sharing common hypotheses but using different clinical settings or methods
Quasi replication (partial)	To test the impact of implementation strategies on mortality rates after a particular CPOE is trialed, the same CPOE system is now tested in a comparable setting, but use a different implementation strategy	Quasi-replications seek to extend earlier experiments by including novel elements or hypotheses to build on the prior work, not just replicate it
Quasi replication (conceptual)	With evidence that CPOE use is associated with mortal- ity changes, researchers test if this is generalizable to other system classes. They test the hypothesis that many clinical systems can affect mortality rates with an experiment using electronic health records and measuring mortality effects	The lowest fidelity form of replication, these studies help test the generality of prior results, but do not allow strong conclusions when their results conflict with earlier studies

Suggestions for Biomedical Informatics

- Friedman and Wyatt
  - very detailed analysis and caution
  - e.g., evaluation by different groups from developers
- Staged evaluation
  - Regression testing as program is improved
  - Automated search for inconsistencies
  - Retrospective review, judged by clinicians
  - Prospective review, judged by clinicians
  - Prospective controlled trial: answer, outcome
  - In both the retrospective and the prospective trials, the computer's performance should be compared to the performance of unaided clinicians, preferably by a panel of experts blinded to which decision maker they are evaluating.



Szolovits, P., & Pauker, S. G. (1979). Computers and clinical decision making: Whether, how, and for whom? (Vol. 67, pp. 1224–1226). Presented at the Proceedings of the IEEE, IEEE. http://doi.org/10.1109/PROC.1979.11437

HEALTH IT ANALYTICS
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January 08, 2019

By Jennifer Bresnick

FDA Tackles Artificial Intelligence with New Software Review Plan

The FDA is speeding up its regulatory processes to accommodate the new realities of the artificial intelligence ecosystem.

FDA Approach to Regulating AI-based “devices”

- Clearance for class III medical devices—those subject to the highest level of regulatory control—typically requires sponsors to submit clinical data supporting their tech, Allen said, so officials have clear proof of the safety and efficacy of the device. Devices with no legally marketed, substantially equivalent predicates are also automatically classified as class III, regardless of the risk they pose.
- “This could have been the pathway for artificial intelligence algorithms,” Allen wrote. “However, the FDA has recently revamped the de novo request process, which allows the developer of a low- to moderate-risk device without a predicate to submit a request to the FDA to make a risk-based classification of the device into class I or II.”
- Once that de novo request is granted, the device can then serve as a predicate for 510(k) premarket approval of similar devices in the future, which is how a good chunk of AI software has been approved to date.

https://www.radiologybusiness.com/topics/policy/how-fda-will-regulate-ai-related-medical-devices

FDA Regulation of AI & ML-based CDSS

- Software Precertification (Pre-Cert) Pilot Program
  - model that offers more flexibility and faster, iterative review processes
  - establish processes for software as medical device (SaMD) technologies, which may include software functions that use artificial intelligence and machine learning algorithms
- evaluated across five major domains:
  - product quality
  - patient safety
  - clinical responsibility
  - cybersecurity responsibility
  - proactive culture
- So far, approved mainly image interpretation applications; expectations:
  - Imaging Analytics and Pathology
  - Natural Language Processing and Free-Text Data
  - Clinical Decision Support and Predictive Analytics
  - Cybersecurity and Ransomware

Companies that received FDA approval for AI algorithms in 2018

https://hackernoon.com/demystifying-the-current-upward-trend-in-fda-approvals-of-medical-devices-using-artificial-cb9cc18d175

FDA-Approved AI Algorithms for Clinical Applications

IMAGEN

- The **OsteoDetect** software is a computer-aided detection and diagnostic software that uses an artificial intelligence algorithm to **analyze two-dimensional X-ray images for signs of distal radius fracture**
- The company submitted a retrospective study of 1,000 radiograph images that assessed the independent performance of the image analysis algorithm for detecting wrist fractures and the accuracy of the fracture localization of OsteoDetect against the performance of three board certified orthopedic hand surgeons.
- Imagen also submitted a retrospective study of 24 providers who reviewed 200 patient cases
- Both studies demonstrated that the readers' performance in detecting wrist fractures was improved using the software, including **increased sensitivity, specificity, positive and negative predictive values**, when aided by OsteoDetect, as compared with their unaided performance according to standard clinical practice.
- The FDA reviewed the OsteoDetect device through the De Novo premarket review pathway, a regulatory pathway for some low to moderate risk devices of a new type

FDA-Approved AI Algorithms for Clinical Applications

- The **IDX** software is designed to **detect greater than a mild level of diabetic retinopathy**, which causes vision loss and affects 30 million people in the US. It occurs when high blood sugar damages blood vessels in the retina
- The program uses an AI algorithm to analyze images of the adult eye taken with a special retinal camera. A doctor uploads the images to a cloud server, and the software then delivers a positive or negative result
- The FDA recently cleared AI-based software to help **detect stroke**
- The FDA based its decision on data from a clinical study of 900 diabetes patients' retinal images collected from 10 primary care sites. Here, the rate at which IDx-DR was able to correctly identify more than mild diabetic retinopathy was 87.4 percent, while images with mild or lesser diabetic retinopathy were correctly identified 89.5 percent of the time.

FDA-Approved AI Algorithms for Clinical Applications

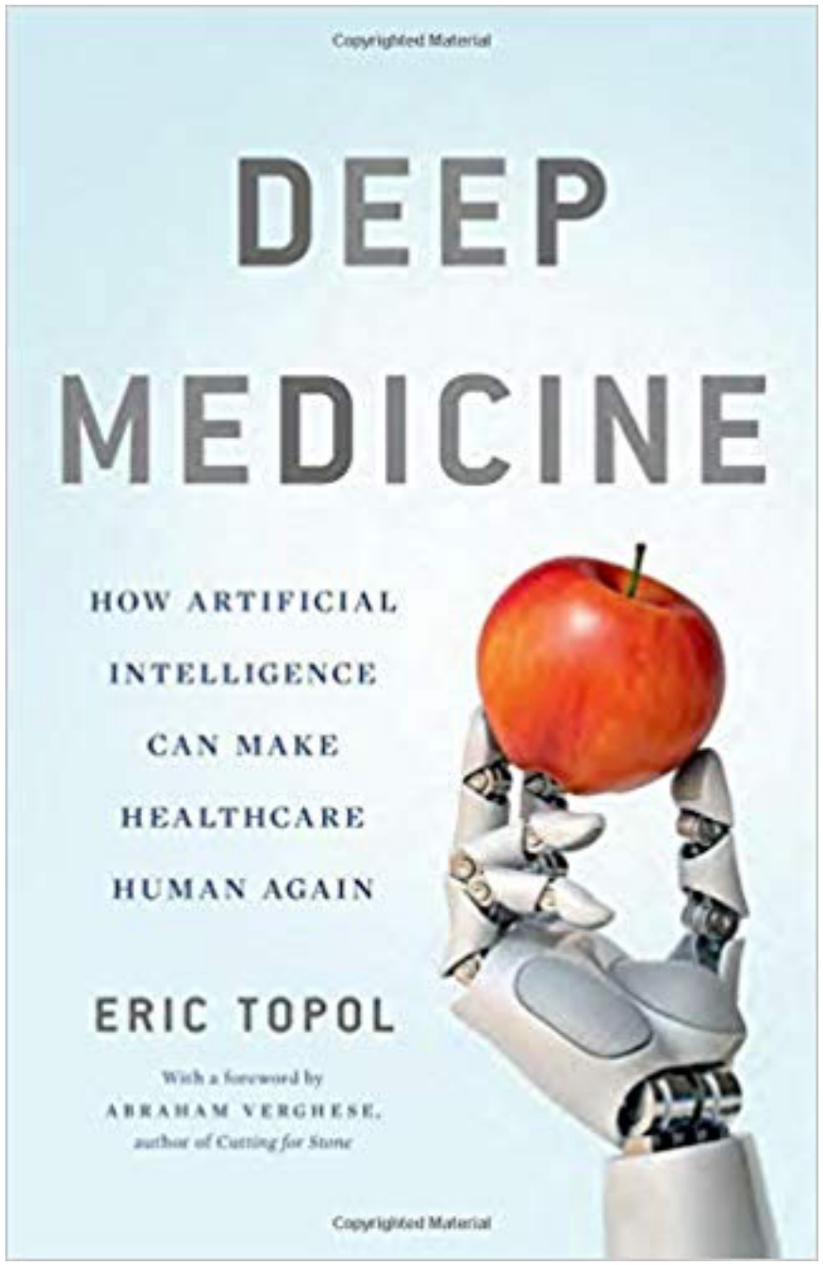
Viz.ai

- **Viz's** first product is designed to help in that race against time by automatically **analyzing CT scans of ER patients**. The company has trained machine-learning algorithms similar to those that an iPhone uses to spot cats in your photos to **detect blockages in major brain blood vessels**
- The company submitted a retrospective study of 300 CT images that assessed the independent performance of the image analysis algorithm and notification functionality of the Viz.AI Contact application against the performance of two trained neuro-radiologists for the detection of large vessel blockages in the brain. Real-world evidence was used with a clinical study to demonstrate that the application could notify a neurovascular specialist sooner in cases where a blockage was suspected

FDA-Approved AI Algorithms for Clinical Applications

ARTERYS

- In Feb 2018, FDA issued its fifth 510(K) clearance for **Arterys,** an AI-based, cloud medical imaging software. helps clinicians **measure and track tumors** or potential cancers, and easily apply radiological standards. The initial deep learning workflows will be for liver MRI, and CT scans, as well as for lung CT scans
- The software uses deep learning to automate the segmentation of lung nodules and liver lesions, with accuracy equal to segmentations performed manually by experienced clinicians. The clinician has the capability to edit these automated segmentations, so they always remain in control
- 510(K) approval through comparison of software identification and measurement of lesions to expert-assessed images and showing excellent correlation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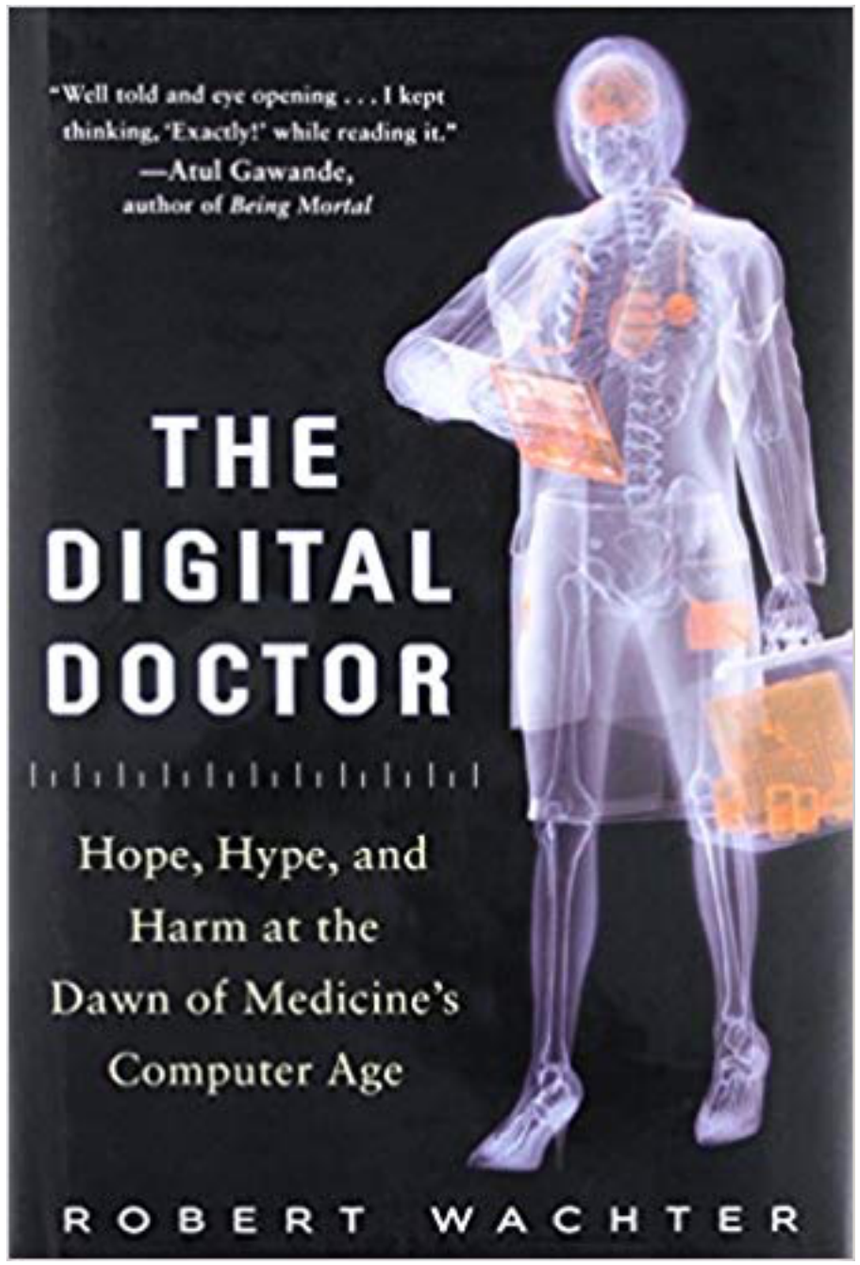
"Well told and eye opening . . . I kept thinking, 'Exactly!' while reading it."
—Atul Gawande,
author of Being Mortal
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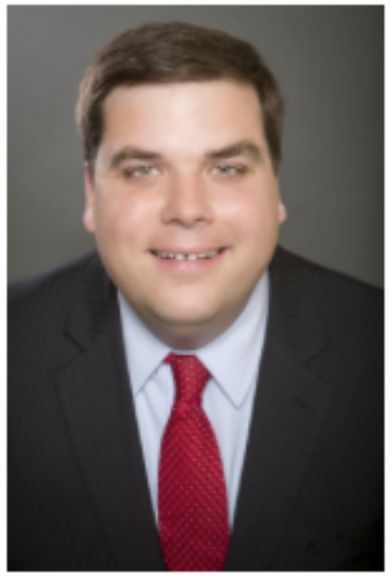

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http://researchfaculty.brighamandwomens.org/briprofile.aspx?id=807