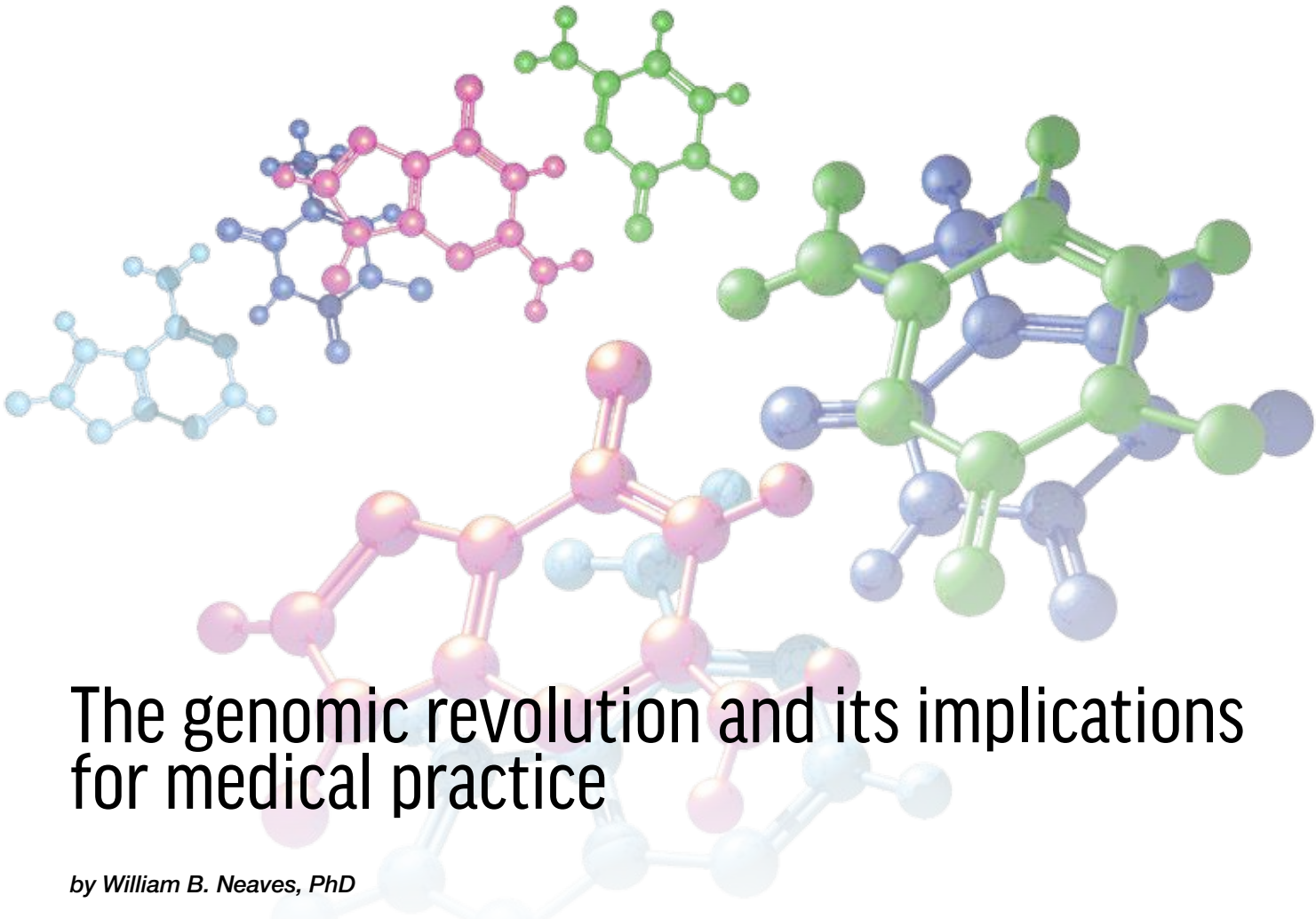

The genomic revolution and its implications for medical practice

by William B. Neaves, PhD

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The future of medicine as a public good has never appeared brighter. Affordable sequencing and interpretation of individual human genomes can now yield insight into diseases that should enable prevention as well as precise intervention. Digital technologies, robotics, and algorithmic approaches to evidence-based medicine will make individualized health care more accessible and effective. At the same time, the future of the medical profession has never been so difficult to predict.

As the genomic revolution unfolds, clinically actionable data will multiply exponentially. How can physicians adapt? Democratization of medical knowledge available through the Internet is empowering patients to take charge of their health care. What value do physicians continue to add? Medical expertise will someday reside in digital surrogates on smartphones. Will people still need doctors?

A challenge to the traditional doctor-patient relationship is reflected in genome-based medicine. Early last decade, at the beginning of the Genome Era, the biomedical community referred to the dream of basing diagnosis and therapy on a patient's sequenced genome as personalized medicine. Later, many began dubbing it individualized medicine, and in 2015, then-President Obama popularized it, calling it precision medicine. Now it is called accurized medicine.

Will doctors in the 21st century practice precision medicine so that patients do not perceive it as impersonalized medicine? Can doctors do it better than the digital surrogates that threaten to replace them?

The antecedents of the genomic revolution remind us where we've been, and the first applications of genomic medicine show where we're going.

Where we've been

For more than a century, medicine has benefited from precision enabled by knowledge of an individual patient's genes. Nobel Laureate Karl Landsteiner introduced the concept of precision medicine a century ago when he classified patients into four blood antigen phenotypes that result from a diploid combination of three different alleles

Karl Landsteiner at work in a laboratory.
Photo by ullstein bild/ullstein bild via Getty Images

(a, b, and o) at a single gene locus.[1] Landsteiner's success in making blood transfusions safe pointed the way to gene-based medicine, but further progress was slow.

Not until late in the 20th century did knowing what alleles are present at a gene locus enable physicians to avoid pharmaceutical drugs that can produce devastating effects. The drug 6-mercaptopurine helped most children with acute lymphocytic leukemia, but killed a small number of patients. Studies revealed that approximately 0.3 percent of children have a mutated gene for thiopurine methyltransferase; they cannot metabolize 6-mercaptopurine and will likely die if given it.[2] Today, children with acute lymphocytic leukemia are routinely genotyped to determine if they should not receive the drug.

Similar pharmacogenetic success stories include screening patients for mutations in the RYR1 calcium-channel gene to avoid anesthetic-induced malignant hyperthermia, and detecting high risk CYP2B6 genotypes that could compromise an HIV patient's metabolism of efavirenz, a commonly used reverse-transcriptase inhibitor.

In the last decade of the 20th century, physicians began using genes to determine who would benefit from taking a specific drug—not just who should avoid it. It has long been known that κ-opioid analgesics achieve only limited pain relief in most people. Men do not benefit from the drug, and only some women experience effective analgesia. The melanocortin-1 receptor mediates κ-opioid analgesia, and research has shown that only women with two mutated alleles at the receptor gene locus experience robust analgesia when treated with the drug.[3] Hence, genotyping the melanocortin-1 receptor identifies those women for whom κ-opioid drugs such as pentazocine will provide adequate pain relief.

The drug gefitinib inhibits elevated tyrosine kinase activity associated with specific mutations of an epidermal-growth-factor receptor gene. Approximately 10 percent of patients with non-small-cell lung cancer carry one or more of these specific mutations, and they benefit dramatically from gefitinib, but for the remaining 90 percent gefitinib does nothing.[4] Patients with this type of lung cancer are routinely genotyped to determine if gefitinib will successfully treat their disease.

Gene-based medicine changed how we think about diseases. If the diagnosis of disease is the first step to effective therapy, physicians increasingly think more in terms of causes than symptoms. For almost a century after Rudolph Virchow described a patient with "white blood" in 1845, leukemia was thought to be a single disease.[5] During the 20th century, leukemia was classified according to the course of the disease (acute or chronic), and the type of cell giving rise to the malignancy (lymphocytic or myelogenous). Leukemia is now known to result from a multitude of pathogenic mechanisms, many involving chromosomal translocations and gene fusions.[6]

Chronic myelogenous leukemia results from a chromosomal translocation that disrupts the normal DNA

sequence of the gene for the growth-promoting enzyme tyrosine kinase. The constitutively expressed, and overly active, enzyme causes cancerous proliferation of the affected cells. The drug imatinib binds to the active site of the altered tyrosine kinase and blocks its ability to promote abnormal cellular growth.[7] Although imatinib can also bind to normal tyrosine kinase found in white blood cells lacking the chromosomal translocation, it does no apparent harm to healthy cells, and avoids the devastating side effects associated with non-specific chemotherapeutic agents traditionally administered to cancer patients. Imatinib has achieved the holy grail of the pharmaceutical industry by knocking out cancer cells while leaving healthy cells alone. Even though it resulted from a narrow focus on only two gene loci, it exemplifies the kind of precision expected to come from whole-genome sequencing.

The examples of genotyping allow for a radical departure from the one-size-fits-all pharmacology of the 20th century.

Where we're going

Gene-based medicine at the end of the 20th century relied on genotyping individual loci or small sets of loci known to be associated with a disease, so-called candidate genes. Compared to sequencing whole genomes, focusing on candidate genes had many disadvantages by excluding other genetic loci from consideration, and causing unexamined loci of potential clinical relevance to be missed. It ignored portions of a gene that may be biologically significant, i.e., promoters and untranslated regions. As knowledge of the number of potentially relevant genes increased, genotyping candidate genes became as costly as whole-genome sequencing.

Sequencing a whole human genome for the first time occurred in 2001, the year Victor McKusick MD (ΑΩΑ, Johns Hopkins University, 1946) predicted that "comprehensive DNA sequencing of the genome" would exert an influence on medicine "fully as great as was that of Andreas Vesalius' '*de corporis humani Fabrica*'" published in 1543.[8]

Assembling and interpreting the sequence data required another two years. It was a triumph of intellect and technology that will forever stand as a major landmark of biomedicine, comparable to Gregor Mendel's discovering the gene in the mid-19th century, and Watson's and Crick's revealing the molecular structure of DNA in the mid-20th century.

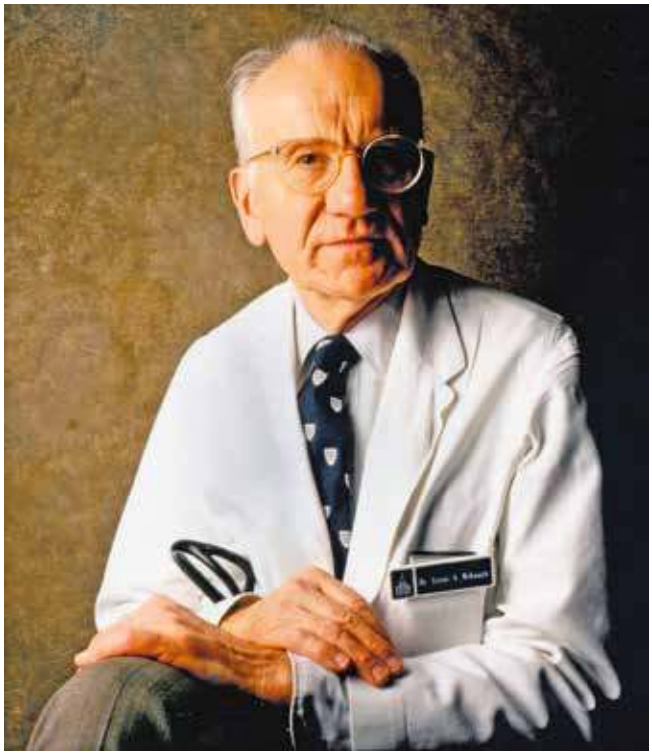
The feasibility of sequencing whole genomes inspired visions of a new era in medicine when diagnosis and therapy could rely on discerning all the genes, alleles, and

Rudolph Virchow, MD. Credit: Bettmann / Contributor

mutations in an individual patient. But whole-genome sequencing of individual patients was still a distant dream, primarily because the expense of sequencing individual genomes made it economically impractical.

In 2008, the cost declined to the point that the utility of whole-genome sequencing in individual patients could be explored. The Genome Center at Washington University compared a leukemia patient's genome with her cancer's genome and found 10 mutations that may have caused her cancer, or promoted its progression.[9] Eight of these mutations had never before been linked to her type of cancer, and they became potential targets for developing new therapies. This landmark demonstration ushered in a new, more productive era of genome-based medicine that will revolutionize how medicine is practiced.

Only at the end of the first decade of the 21st century were patients finally treated on the basis of sequencing their whole genomes. At a cost of $100,000 each in 2009, the Baylor College of Medicine Genome Center sequenced the genomes of 14-year-old fraternal twins suffering from dopa-responsive dystonia.[10] The twins were being treated with L-dopa, but tremors, awkwardness, and spasms



Victor Almon McKusick, MD (1921 – 2008), widely regarded as the father of clinical medical genetics.
Photo by: Universal History Archive/UIG via Getty Images/Universal

Stephen Kingsmore, MD, DSC, director, Rady Children's Institute of Genomic Medicine. Courtesy of Rady Children's Institute of Genomic Medicine

persisted. Whole-genome sequencing identified mutations that decreased a cofactor required for the synthesis of serotonin in addition to dopamine. By supplementing L-dopa therapy with a serotonin precursor significant clinical improvements were documented in both twins.

The work of the Baylor team with the Beery twins was the first peer-reviewed report of direct alteration in clinical management based on whole-genome sequencing of individual patients. When the paper appeared in June 2011, the cost of sequencing a patient's genome had decreased to $10,000. As the cost subsequently fell into the $1,000 range, whole-genome sequencing became an increasingly affordable way to seek clinically actionable information.

In September 2014, Stephen Kingsmore's team at Children's Mercy Hospital (CMC) in Kansas City reported the first cost-effective use of whole-genome sequencing in treating individual patients.[11] They had sequenced the genomes of 44 infants in the neonatal intensive care unit at CMC. Using a rapid sequencing process that is completed, analyzed, and interpreted within 24 hours, they diagnosed the illness in 28 of the 44 cases.

Kingsmore's team was able to recommend treatment changes in 14 cases. They found a mutation linked to an overactive immune response that was injuring an infant's liver and spleen. The genome-based diagnosis resulted in treatment with immunosuppressive drugs, and the baby was able to go home in good health.

In October 2014, Kingsmore's team launched a large-scale clinical trial to sequence whole genomes of many hundreds of sick infants. The project at CMC was the first of four newborn-sequencing studies to receive FDA approval, and it is funded by a multimillion-dollar grant from the National Institutes of Health. By the end of 2014, Kingsmore could sequence whole genomes at a cost of less than $700 each, using the latest Illumina technology.

Early in 2015, positive results were reported in a phase I clinical trial of a new therapy for metastatic melanoma based on whole-genome sequencing of patients and their tumors.[12] Sequencing a patient's normal genome, and tumor genome, is the first step in determining if the cancer cells harbor actionable mutations that provide opportunities for targeted therapy. Comparison of matched genomes from a patient's normal, and cancerous, cells facilitates identifying driver mutations for therapeutic targeting.

Many clinics still sequence only the DNA from a patient's tumor cells without also sequencing DNA taken from a patient's normal cells. Omitting comparison of genomes from a patient's tumor and normal tissue makes it difficult to judge which mutations should be targeted for therapy.

Also in 2015, a team in the United Kingdom reported comparison of whole-genome sequences from subpopulations of cancer cells in individual tumors.[13] They found that most cells in a tumor carried the same mutations driving early cancerous growth, but subpopulations of cells carried additional mutations that could compromise the efficacy of therapy. This raised the possibility of using stratified therapy to target both the widely shared driver mutations, and those found only in smaller subpopulations of tumor cells.

How many genomes must a genome-sequencer sequence to treat a patient precisely? Fortunately, the cost of genome sequencing continues to fall.

John Porter making the first Bible reading in the crypt of old St. Paul's Cathedral, London, 1540. Three Lions / Stringer

Implications for medical practice

With whole-genome sequencing on the verge of becoming as ubiquitous as the routine clinical chemistry profile, physicians face exponential increases in the mass of medically relevant new information patients will expect them to master. Physicians already confront a challenge similar to that experienced by priests during the Reformation, and the emergence of genomic medicine will only exacerbate the problem.[14]

Before the Reformation, the church and its priests monopolized religious knowledge. Producing a single copy of the Bible required a year's effort by a scribe with goose quill and vellum sheets. Only ordained priests had custody of hand-copied Bibles, and laypeople depended on priests to reveal the contents. Priests enjoyed a position of power and prestige.

In the second half of the 15th century, Gutenberg invented the moveable-type printing press, and used it to mass-produce Bibles, an act that triggered many unintended and unimagined consequences. One was the Reformation, which shook the foundations of the church, and changed forever the relationship between laypeople and priests.

By the end of the 16th century, ordinary people could afford a printed Bible, and those who were literate could read it for themselves. The information monopoly of the priesthood disappeared, and the profession had to find new ways to add value to the lives of parishioners. In post-Reformation Europe, it became much harder for priests to know more than laypeople.

Fast-forward half a millennium, and consider the parallel between priests during the Reformation and doctors today. Formerly ignorant patients are empowered by digital technology that gives them access to the latest medical information. Now, it is smartphones rather than the printing press, but the threat to professional hegemony is the same. For physicians in the 21st century, the challenge will be to know at least as much about diagnostics and therapeutics as their digitally facile patients.

At the very least, a physician must ferret out all that is known about the patient's condition, bring it together at the crucial moment, and reach an informed conclusion about what is best for the patient. The massive amount of clinical data for each patient in the emerging age of genomic medicine already far exceeds the capacity of human memory. First and foremost, a physician must become adept in using the best tools information technology has to offer.

The platform of this tool kit is a mental prosthesis.[14] We depend on mental prostheses to acquire, organize, and understand the meaning of data. The essential mental prosthesis is a portable device connected to an interactive network, and equipped with software that exercises logic in locating, assembling, and interpreting information specific to a physician's professional requirements.

Last decade, the physician's mental prosthesis was a

National Human Genome Research Institute technician prepaes DNA for sequencing using a hand-held pipette.
Photo by Maggie Bartlett/MCT/MCT via Getty Images

wireless laptop linked to searchable databases. Inevitably, the size of the device diminished and portability improved. Popular options now include digital tablets and smartphones.

A few doctors who are early-adopters already use optical head-mounted displays. Eventually, a physician's wearable technology may be surgically implanted and invisible to the patient—an integrated extension of the practitioner's intellect and senses.

How will such mental prostheses change medical education and clinical practice? Will unaided memory maintain the significance it now does? What about correlative thinking?

Software in digital devices already retrieves, organizes, and interprets relevant information as the patient encounter unfolds. Computer screen warnings flash if the doctor attempts to prescribe an unconventional therapy.

Where will these trends lead? Might medicine be practiced by robots? Already, robots are replacing certified nursing assistants in elder care. Robots are proving to be good listeners whose undivided attention comforts dementia patients.[15]

Could individual patients rely on a medical app in their smartphones? In his 2015 book about patient empowerment in the 21st century, Eric Topol, MD, (AΩA, University of Rochester School of Medicine and Dentistry, 1979) envisioned a new era of medicine "powered by unplugged digitization, with the smartphone as the hub," and he devoted a chapter to "My (Smartphone) Doctor."[16]

Could Dr. Siri be your personal physician? The feature would use a natural language interface and digital biomonitors to record symptoms and vital signs. It would interrogate the individual's electronic medical records, including the patient's sequenced genome. It would retrieve relevant clinical information from Web databases and the Cloud. It would determine the most probable diagnosis. It would answer questions, make recommendations, and prescribe therapy. Dr. Siri would return personalized responses unique to the individual.

The business world is ready to help people serve as their own physicians. Early in 2015, *Nature* published a story about the high level of commercial interest in selling diagnostic tests to consumers—i.e., patients—and eventually, direct marketing of therapies based on whole-genome sequencing.[17] A company in California, 23andMe, has sold sequence analysis and SNP genotyping to the public since the last decade. In February 2015, it became the first company to receive FDA approval for a genetic test marketed directly to consumers, not physicians—a test for mutations that cause a rare disease called Bloom syndrome.[18]

IBM and Memorial Sloan Kettering announced a collaboration in 2013 to use IBM's trademarked "cognitive computing technology," known as Watson, to assemble information about individual patients, correlate it with published research and outcomes in similar patients, and list treatment options with the highest probability of success.[19] Watson's data mining capability enables it to stay abreast of the latest medical advances reported in scientific journals and medical meetings. Because Watson relies on cognitive computing, it continually learns from its operations, and improves the relevance of suggested treatment

options for individual patients.

Memorial Sloan Kettering, a partner in Watson's development, says, "The tool is designed to help oncologists anywhere make the best treatment decisions for their individual patients."[20] Watson for Oncology is a companion of the Watson Health Cloud, and IBM says of the latter, "It will empower individuals to understand more about themselves. And, it will help doctors, researchers, and insurers make better, faster, and more cost-effective decisions."[21] IBM envisions a much larger universe of Watson clients than practicing oncologists—a universe that includes people who have cancer, people who think they might have cancer, and people who fear they might get cancer.

The intersection of genomics and digital technology bodes well for the health of individuals, but it has stimulated commercial and personal interests that threaten to marginalize physicians.

Doctors in the 21st century cannot practice medicine without digital devices and software powerful enough to make genomics actionable for their patients, who have devices that provide access to the same information in a highly personalized way.

References

1. Owen R. Karl Landsteiner and the First Human Marker Locus. Genetics. 2000;155: 995–8.

2. Weinshilboum R. Thiopurine pharmacogenetics: Clinical and molecular studies of thiopurine methyltransferase. Drug Metab Dispos. 2001;29: 601–5.

3. Mogil J, Wilson SG, Chesler EJ, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci USA. 2003;100: 4867–72.

4. Lynch TJ, Bell DW, Sordella R, et al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. N Engl J Med. 2004;350: 2129–39.

5. Major RH. Classic Descriptions of Disease. Springfield (IL): Charles C. Thomas. 1948.

6. Look AT. Oncogenic Transcription Factors in the Human Acute Leukemias. Science. 1997;278: 1059–64.

7. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344:1031–7.

8. McKusick VA. The Anatomy of the Human Genome: A Neo-Vesalian Basis for Medicine in the 21st Century. JAMA. 2001;286:2289–95.

9. Ley TJ, Mardis ER, Ding L, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. Nature. 2008;456: 66–72.

10. Bainbridge MN, Wiszniewski W, Murdock DR, et al. Whole-Genome Sequencing for Optimized Patient Management. Sci Transl Med. 2011;3:87re3: 1–6.

11. Reardon S. Fast genetic sequencing saves newborn lives. Nature. 2014;514: 13–4.

12. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348: 803–8.

13. McGranahan N, Favero F, de Bruin EC, et al. Clonal status of actionable driver events and the timing of mutational processes in cancer evolution. Sci Transl Med. 2015;7:283ra54: 1–11.

14. Neaves WB. Leaping beyond the genome—what lies ahead? CAP Today. 2002;16(7): 54–64.

15. Aronson L. The Future of Robotic Caregivers. New York Times; July 20, 2014. http://www.nytimes.com/2014/07/20/opinion/sunday/the-future-of-robot-caregivers.html.

16. Topol E. The Patient Will See You Now: The Future of Medicine Is in Your Hands. New York: Basic Books. 2015.

17. Hayden EC. Gene-testing firms set sights on drug development. Nature. 2015;520: 597–8.

18. Kroll D. FDA approves 23andMe Gene Carrier Test. Forbes; February 19, 2015. http://www.forbes.com/sites/davidkroll/2015/02/19/fda-okays-23andmes-direct-to-consumer-gene-carrier-testing-starting-with-bloom-syndrome/.

19. Hempel J. IBM's massive bet on Watson. Fortune. 2013;168(6): 80–5. http://fortune.com/2013/09/19/ibms-massive-bet-on-watson/.

20. Memorial Sloan Kettering website. Memorial Sloan Kettering trains IBM Watson to help doctors make better cancer treatment choices. https://www.mskcc.org/blog/msk-trains-ibm-watson-help-doctors-make-better-treatment-choices.

21. IBM Watson website. Discovery Advisor—Engagement Advisor—Watson Health Cloud—Watson for Oncologists. http://www.ibm.com/madewithibm/watson/?r=lob&s=2&S_PKG=-&ct=C34403YW&jm=-&S_TACT=C34403YW&iio=CHQ&cmp=C3440&cr=google&cm=k&csr=Capabilities+-+Watson_BR&ccy=us&ck=ibm%20watson%20cognitive%20computing&cs=b&cn=Cognitive_BR&mkwid=smBK8KjUo-dc_80679237256_432t5q28552_.

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