Opinion Paper

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Diagnostics 4.0: the medical laboratory in digital health

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Abstract: During recent years, the digital revolution has changed the face of societies including industrial production, economies and peoples' social lives. From these changes we may extrapolate the developments that digitization of health care will bring to medicine in general and laboratory medicine in particular. Disruptive technologies will fundamentally change the way laboratory tests are going to be ordered, carried out and interpreted in the future, and test results from various sources need to be curated to be of added value for the patient's condition. Wearables and implantables will quantify the concentrations for an unknown number of laboratory parameters, and the data will be stored in cloud services at the fingertips of the patient as the sovereign of his/her health care data. A 24/7 online availability of health services will strengthen predictive medicine and may enable a vastly improved preventive health care that is supported by deep-learning algorithms for clinical decision-making not only on behalf of the physician, but also the empowered patient (e.g. health bots). This will likely shift the current role of Laboratory Medicine as a central provider of diagnostic information from a "hidden champion" towards a higher visibility redefining the patient-physician-laboratory relationship. For example, accessing digital health data will allow Laboratory Medicine to more efficiently contribute to the medical dialog than is often the case today. From this perspective, this will require major readjustments in the way we execute our profession, and it will also need new concepts of education and continuous professional development.

Keywords: digital health; digitalization; health bot; Laboratory Medicine.

Background

Digitization has started to change health care in general, and it will change diagnostics and Laboratory Medicine in particular. This short paper makes the argument that the future development of Laboratory Medicine may be extrapolated from developments that – as a principle – can be witnessed in many other areas of the economy and society when challenged by disruptive technological changes.

"Creative destruction" is a technical term coined by the Austrian economist Joseph Schumpeter in the early 1940s in macro-economies [1, 2]. It describes the overthrowing of an existing (and working) system with a new one having the potential to replace it. Triggers typically are quantum leaps in technology serving as disruptive elements to set off the fundamental changes [3]. Between disruptive events, an increased sophistication advances existing technology until the next cycle of creative destruction. The sequence of the industrial revolutions that started in the 19th century with the steam engine is a prime example for Schumpeter's hypothesis.

The revolutions

Specifically, the first industrial revolution brought mechanization through the invention of the steam engine with the result of enhanced productivity that ended human labor, e.g. in the textile industry. In the second revolution, electricity and the electrical motor abolished the dependency of a direct force transmission from the power source using belts and gears that were still required during the steam engine age. This allowed setting up machinery in a decentralized, compact fashion and enabled automation as well as smaller and more efficient production plants, e.g. in the automotive industry. Following the 1970s, the third industrial revolution eventually brought mass computerization to manage complex manufacturing processes, automation and eventually miniaturization. Here, for the first time non-physical, i.e. the intellectual human labor of

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a society based on the provision of services was increasingly to be replaced by machines. One could argue that the ultimate sophistication step in the mass computerization age has been the invention of the smart phone, although these were not overly successful prior to the release of Apple's iPhone in 2007 [4]. This device was the first to combine a personal telecommunication device running on a fully functional computer operating system with a revolutionary user interface to allow an intuitive Internet access while synchronizing with the owner's personal electronic devices and services. In a historic misjudgement, the then market leader predicted that the expensive iPhone would be a massive failure eventually leading to Apple's demise [5]. It appears very clear now that the iPhone has tipped the smartphone towards being a major disruptive element and trigger in the digitalized era. These devices now connect "human affairs" with the digital world and the cyber networks of devices representing the Internet of Things (IoT), e.g. vehicles, home appliances, personal electronic assistants, sensors and actuators [6, 7]. Indeed, IoT devices are uniquely identifiable through their embedded computing system, linked through IP addresses and can connect without human interference. Within a decade, approximately 6 billion smartphones were operational globally representing the preferred communication platform technology. Between 2016 and 2017 there has been an increase of 31% of devices with online capabilities totalling 8.4 billion. In the near future of the fourth revolution, approximately 30 billion devices have been predicted to communicate inside the IoT. In developed countries, most individuals are expected to possess 1000–5000 personal devices constantly exchanging data through the IoT [8–10]. Taken together, cyber-physical systems (mechanisms controlled by computer-based algorithms that are tightly integrated between the Internet and its users) and the IoT, cloud computing, deep machine learning and artificial intelligence are a reality or are expected to become one in the near future.

Industry 4.0 is the name for the current trend of automation and data exchange in manufacturing technologies [11–13]. The term was originally coined in a German working group mandated by the German government to explore the potential of digitalization and includes cyber-physical systems, the IoT, cloud computing and cognitive computing [14]. One major characteristic of industry 4.0 is the immediate flow of information in real-time and the potential to react to changes without delay. Together with clear and standardized processes, e.g. in manufacturing, the potential to make real time changes in any process has tremendously increased productivity. It is obvious, how these IT technologies and IoT infrastructures will

influence individual health perspectives and will impact medicine and medical workflows in general.

The disruptive scenario

Worldwide, health care expenditures account for 6–11% of the global GDP. Ten percent of these costs are believed to be due to inefficiencies. Industrial Internet adaptations directly impacting on clinical and operational inefficiencies that are estimated at \$430 bn per year are expected to lower costs at approximately \$100 bn per year explaining the rapidly growing interest in the potential of digitalization in medicine. Therefore, it appears feasible to draw parallels to the changes the digital era has already brought in the realms of industry and economy. For example, consider the largest automotive people transportation company in the world: Uber does not possess a single car. Consider the largest "hotel chain" in the world: founded in 2008, AirBNB, does not own a single hotel, but – with 3000 employees – provides accommodations in 81,000 cities in 190 countries with millions of over-night stays [15]. A very visionary account of evolutions in the digital age was recently been given by Jeremy Rifkin in his book "The Zero Marginal Cost Society ..." [16]. Accordingly, we might speculate that the biggest medical providers of the future may not own or run their own hospitals. Instead, they will integrate billions of personal devices and components of the IoT that are monitoring and recording human physiology data points, vital signs and possibly live biochemistry data. These are continuously monitored and streamed to personal data clouds alerting the individual or health care professionals at early signs of illnesses or pathological conditions in real time, thereby opening the possibility to a preventive medicine prior to the onset of disease. The professional and economic perspectives of dealing with clinically healthy individuals in addition to the traditional patient are staggering.

Analytics in Diagnostics 4.0

At present, transdermal diagnostic measurement of what we call "wet lab laboratory parameters", i.e. in the blood through wearable devices are not feasible in a relevant diagnostic setting. However, in-patient monitoring by means of implantable diagnostic devices is actively being developed by nanotechnology. For example, intensive research explores the long-term biocompatibility of derivatized surfaces as a prerequisite for an extended use

of implantables, and first technical solutions have been reported recently [17, 18]. Specifically, carbon nanotubes (CNTs), graphene nanoflowers and other technologies allow the immobilization of probing molecules and have been used successfully in the design of various laboratory tests for real time analysis (cited in [18–22]). Self-assembling aptamers for the probing of biological fluids have been demonstrated to specifically capture and measure small molecule therapeutic drugs present in biological fluids in low nanomolar concentrations [23–25]. Microfluidic biosensors can be manipulated, and their data integrated instantly [26].

Such scenarios obviously have several important implications for “Laboratory Medicine as we know it” particularly in an ambulatory setting, where individuals will monitor health parameters and biomarkers from various sources and have these data uploaded through communication devices to a service – not necessarily a medical institution equipped for integrating personal healthcare data from different diagnostic modalities on a broad scale. Hence, the findings from regular medical laboratory testing (with its vast availability of general and specialized tests) will appear side by side with the data from “patient-near” or even a future “in-patient” mobile health testing to be integrated into electronic health records. Furthermore, test results for the same parameter will have different origins: they will stem from medical central laboratories, pharmacies, from professional POCT instruments, simple home-testing devices or may come from other sources. It is hard to imagine that mobile health devices can substitute the vast test portfolios of a professional medical laboratory in the near future. Instead, such mobile health related to the laboratory may first comprise basic parameters indicating imminent systemic dysfunctions like an acute coronary syndrome, kidney failure, severe metabolic dysfunction and endocrinological derailment or an acute systemic inflammation to direct – in its wake – a more elaborate testing performed by the clinical laboratory. Today, modern wearables directly record physical activity, blood pressure or heart rate through routine applications, and manufacturers are seeking certification of their wearables for clinical monitoring. As a first example, Apple’s iWatch has received FDA approval as a medical device to monitor ECG on September 12th, 2018.

Traditionally, the trigger for laboratory testing is the diagnostic question asked by the patient’s physician. However, in the scenarios detailed, the medical laboratory will not be the only source of *in-vitro* diagnostic information. Specifically, the future patient will collect medical data from various sources and different proficiencies outside the direct patient-physician dialog, entirely,

thereby also affecting the position of laboratory medicine in the diagnostic process. In conclusion, we will see a decentralization in this data acquisition (i.e. the actual analytical test and generation of the test result) together with a centralized data processing and management (i.e. the cloud services) prior to any clinical decision support (i.e. by health care professionals). As the sovereign of his data – and in the center of all interactions within the health system – the patient will recognize the specialization and skills of laboratory medicine. Thus, questions regarding the clinical interpretation of biomarker results – particularly in complex constellations – may be increasingly addressed to the medical laboratory as the provider of the core diagnostic data.

Medical proficiency in Diagnostics 4.0

The power of laboratory medicine as a medical profession lies in the combination of analytical and medical interpretation and requires access to the patient’s clinical context information. However, today’s daily experience usually is that – beyond the request for analysis – little or no useful information with respect to clinical context accompanies the sample that reaches the laboratory. This reduces diagnostic laboratory findings to technical results and falls short of their potential medical value. A digitalized health care environment that allows access to real-time clinical context information in electronic health (care) records will provide new diagnostic opportunities for the laboratorian.

Next to improved diagnostics in the classical disease management, digitalized health care holds yet another promise of enormous proportions: where broad-scale and constant monitoring is possible, disease prevention and earlier diagnosis of disease, i.e. prior to an onset of clinical symptoms immediately become growing issues. It may be argued that with a wide-spread participation, a reliable assessment through monitoring devices and apps together with online response management may improve the efficiency of health care.

On the other hand, any health economic benefit of such predictive testing must be weighed against the (considerable) additional expense of monitoring and testing a presumed healthy population instead of the individuals with a symptoms-based increased prevalence of a suspected disease, only. For laboratory medicine, this would constitute a new approach/role in medicine requiring increased emphasis on rule-out strategies, e.g. based

on quantitative laboratory values within a given reference range or an individual biological variation [27, 28]. The analytical costs eventually associated with massive predictive diagnostics may be difficult to calculate, but they likely could be very cheap on a per-parameter basis as compared to today. Also, individuals aggregating their health data through a subscription to a predictive diagnostic service offered by a large provider, may not even represent a heavy burden on a public health care system altogether. Indeed, the analytical costs of predictive diagnostics could become a “marginal cost” position, when embedded in related IT, data storage and other individual subscription services. To integrate laboratory test data from various sources into an individual’s electronic laboratory record will create new challenges for laboratory medicine, e.g. regarding preanalytics, analytical quality and commutability or the timely context of those test results. Only where the analytical data from different sources are commutable irrespective of their provenance or can be harmonized, they will be safe-to-use and support clinical decision-making in the diagnostic or preventive setting.

Also, the commutability of cumulative laboratory results within an electronic health record is a prerequisite to warranting cost reductions. Otherwise, it may be difficult for physicians in a clinical situation to interpret and use previous results and to abstain from ordering “a new set of tests”. To contribute to such harmonization issues in eHealth and mHealth structures, Laboratory Medicine will have to develop new approaches to quality assessment in the era of Diagnostics 4.0.

Medicine has been lagging behind in the digital revolution for several reasons, one concern being that the physician-patient privilege requires absolute shielding of all data from being examined and communicated outside the doctor’s office. In the digital era, such concerns are increasingly being questioned, and patients have been more open. It could also be argued that generations that share their entire identities online are not opposed to share their individual big data including their health files, if there is a benefit associated with it. In essence, medicine has to adapt to new rules made by the patient and his/her peers. On the other hand, the physician-patient privilege protects the patient’s personal rights and safety within the confines of medicine, e.g. to shield the patient from discrimination and harm, and the respective legislations are tight in most countries. However, in a health care environment, where personal health data are acquired, managed, stored and retrieved outside the medical arena, patient rights are impossible to enforce fully and will be replaced – in part – by consumer protection rights, i.e. at an inferior level.

Patients and bots

Currently, there are approximately 300,000 health apps of different clinical utility available. Of those, medical chatbots categorize patients’ clinical symptoms using AI-powered algorithms to suggest differential diagnoses in an automated fashion. As IoT devices, these apps function without direct human interaction. For example, the German start-up Ada Health founded in 2011 [29] has more than 4 million users in 130 countries and is considered a market leader in this field. Ada’s database includes more than 7 million assessments made over the years on the basis of its algorithm and an extensive and growing medical library. Clinical symptoms, previous conditions, e.g. diabetes, and individual health observations are being processed online to result in differential interpretations following which the users get advice to consult a doctor. As the medical term “diagnosis” is a professional right reserved to a physician, the company issues the algorithm’s interpretations with limited advice (and strong disclaimers). Ada also keeps a history of the clinical symptoms of the user during the different logins as a follow-up longitudinal personal record. Similarly, the Babylon health bot [30], a speech-controlled health bot from the UK with 150,000 registered users provides an additional feature: members can pay a monthly subscription rate for the additional access to a 12 h/day, 6 days/week online-referral to a physician specialist based on the kind of symptoms evaluated by the health bot’s algorithm. As a last example, Mediktor [31] will identify a wide range of physician specialists and serves as a portal to mediate the respective online contacts to doctors. Based on the result of its assessment of the clinical symptoms or their severity, users are advised to self-referral to a hospital. Where costs for medical consultations apply, these can be billed through the user’s account. Diagnostic laboratory information so far has not found its way into these algorithms, but it can be safely assumed that the future Diagnostics 4.0 will not stop at storing individual’s cloud files or at tapping databases from various sources for a later interpretation by a laboratory professional. Diagnostic algorithms developed through deep machine-learning programs will eventually interpret individual results, once key issues in biomedical informatics processing technologies have been solved. First models have been introduced already, where sets of laboratory parameters support differential diagnosis and clinical decision-making in specific diseases like COPD or cardiovascular conditions [32, 33].

While health bots provide some first guidance for an individual seeking medical advice, they are not yet sufficient substitutes for professional diagnostic use. The

providers emphasize that the actual visit to the doctor's office is not to be preplaced by their service. On the other hand, the clinical disclosures given by the user during each health bot visit would provide additional information to a certified professional electronic health record also managing other diagnostic data sources (e.g. Radiology, Human Genetics, Histopathology, Microbiology, etc.). Indeed, they would add structured clinical information that is missing from many patient records today and would support the diagnostic accuracy and relevance of laboratory findings.

Digital twins and avatars

Within Industry 4.0, manufacturing processes have been successfully streamlined using “digital twin” technology that represents a digital model simulating the operation, e.g. of a power plant or an engine prior to its physical realization. An important aspect in this concept is that the digitalization allows for building and *in-silico* testing of optimized work processes and production [34, 35]. In medicine, the analog has been termed “Avatar”, “digital clones” or “digital patient”. Here, the accumulation of individual eHealth and mHealth data aim at the generation of a virtual copy of an individual or as a model to simulate disease or treatment results [36, 37]. Thus, avatars will create predictive models of the expected health trajectory for an individual, so that warnings can be issued prior to systems failures and clinically apparent disease in metabolic disorders, cancers, etc. [38, 39]. So far, the simulation of human health condition through advanced mathematical modeling has been pursued for non-invasive monitoring of body functions and activities in health care and education [40–42]. The Apple iWatch is the first wearable approved as medical device to convey these data. Beyond these realizations, the incorporation of complex laboratory diagnostic results and big data is the central objective for mathematical understanding and modeling the development and progress of human disease [37].

Summary

The future relationship between the laboratory, the referring physician and the patient will be greatly affected in digital health. Traditionally, the laboratory is eclipsed by the physician dealing with the patient. Usually, the diagnostic results are conveyed exclusively by his doctor, and while the laboratory is a hidden champion in the overall

process, it is not visible to the patient. Without medical context, the full virtue of the diagnostic laboratory information cannot be appreciated by the patient resulting in a less-than-optimal value for him. With the future health care models leading to a democratization of medical data, the patient will “shop” his data for the best information value available. With a broader access to medical records, the linear axis patient- physician-laboratory will shift into a triangular one in Diagnostics 4.0. Laboratory Medicine should consider such a development early.

Also, the multitude of sources of health care data will require a proficiency shift of Laboratory Medicine that will be less defined by the analytical skills in diagnostic testing rather than its competence to integrate data and to interpret them in a synopsis with the clinical context data in a very timely fashion. The promise of improved medical interpretation is an intensified dialog/consultation with the treating physician as well as with the patient that can be expected to increase the efficiency of laboratory diagnostics during the clinical decision-making process in general.

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References

- Schumpeter JA. Capitalism, socialism and democracy (1949). London: George Routledge & Co., Taylor and Francis Group, 1976.
- Creative destruction. Wikipedia, the free encyclopedia. https://en.wikipedia.org/wiki/Creative_destruction.
- Rahman AA, Hamid UZ, Chin TA. Emerging technologies with disruption effect: a review. *Perintis eJournal* 2017;7:111–8.
- YouTube. Steve Jobs – iPhone Introduction in 2007 (Complete). <https://www.youtube.com/watch?v=9hUlxyE2Ns8>.
- YouTube. Ballmer Laughs at iPhone. https://www.youtube.com/watch?v=eywi0h_Y5_U.
- Främling K. Tracking of material flow by an Internet-based product data management system. *Tieke EDISTY Magazine* 2002;1:24–5.
- Huevio E, Grönvall J, Främling K. Tracking and tracing parcels using a distributed computing approach. In: Solem O, editor, *Proceedings of the 14th Annual Conference for Nordic Researchers in Logistics (NOFOMA'2002)*. Trondheim, Norway, 2002:29–43.

8. Sarma S, Brock DL, Ashton K. The networked physical world. MIT Auto-ID Center White Paper. Cambridge, MA, USA: Massachusetts Institute of Technology, 2000.
9. The difference engine: “chattering objects” Economist 2010. https://www.economist.com/blogs/babbage//2010/08/internet_things.
10. US Energy Information Administration 2017. How many meters are installed in the United States and who has them? <https://www.eia.gov/tools/faqs/faq.php?id=108&t=3>.
11. Industry 4.0. Wikipedia. https://en.wikipedia.org/wiki/Industry_4.0#cite_note-2.
12. Lasi H, Kemper HG, Fetteke P, Feld T, Hoffmann M. Industry 4.0. *Bus Inf Syst Eng* 2014;6:239–42.
13. Hermann M, Pentek T, Otto B. Design Principles for Industrie 4.0 Scenarios. In: 49th Hawaii International Conference on System Sciences. Piscataway, NJ, USA: IEEE, 2016. DOI: 10.1109/HICSS.2016.488.
14. Kagermann H, Wahlster W, Helbig J, eds. Recommendations for implementing the strategic initiative Industry 4.0: Final report of the Industrie 4.0 Working Group. 2013.
15. Airbnb. Wikipedia, the free encyclopedia. <https://en.wikipedia.org/wiki/Airbnb>.
16. Rifkin J. The Zero Marginal Cost Society: the internet of things, the collaborative commons and the eclipse of capitalism. New York: St. Martin’s Press, 2014.
17. Daniel KD, Kim GY, Vassiliou CC, Galindo M, Guimaraes AR, Weissleder R, et al. Implantable diagnostic device for cancer monitoring. *Biosens Bioelectron* 2009;24:3252–7.
18. Carrara S, Ghoreishizadeh S, Olivo J, Taurino I, Baj-Rossi C, Cavallini A, et al. Fully integrated biochip platforms for advanced healthcare. *Sensors (Basel)* 2012;12:11013–60.
19. Taurino I, Magrez A, Matteini F, Forró L, De Micheli G, Carrara S. Direct growth of nanotubes and graphene nanoflowers on electrochemical platinum electrodes. *Nanoscale* 2013;5:12448–55.
20. Taurino I, Magrez A, Matteini F, Cavallini A, Forró L, De Micheli G, et al. High-performance multipanel biosensors based on a selective integration of nanographite petals. *Nano Lett* 2014;14:3180–4.
21. MacKay S, Wishart D, Xing JZ, Chen J. Developing trends in aptamer-based biosensor devices and their applications. *IEEE Trans Biomed Circ Syst* 2014;8:4–14.
22. Schwartz JJ, Thompson JD, Bajaj VS. Aptamer-based sensors, implantable devices and detection system. US patent publication 20160278638, 2016. <https://patents.google.com/patent/US20160278638A1/en>.
23. Baj-Rossi C, De Micheli G, Carrara S. Electrochemical detection of anti-breast-cancer agents in human serum by cytochrome P450-coated carbon nanotubes. *Sensors (Basel)* 2012;12:6520–37.
24. Aliakbarinodehi N, De Micheli G, Carrara S. Enzymatic and nonenzymatic electrochemical interaction of abiraterone (antiprostata cancer drug) with multiwalled carbon nanotube bioelectrodes. *Anal Chem* 2016;88:9347–50.
25. Aliakbarinodehi N, Jolly P, Bhalla N, Miodek A, De Micheli G, Estrela P, et al. Aptamer-based field-effect biosensor for tenofovir detection. *Sci Rep* 2017;7:44409.
26. Zhang YS, Busignani F, Ribas J, Aleman J, Rodrigues TN, Shaegh SA, et al. Google glass-directed monitoring and control of microfluidic biosensors and actuators. *Sci Rep* 2016;6:22237.
27. Carobene A, Braga F, Roraas T, Sandberg S, Bartlett WA. A systematic review of data on biological variation for alanine aminotransferase, aspartate aminotransferase and γ -glutamyl transferase. *Clin Chem Lab Med* 2013;51:1997–2007.
28. Aarsand AK, Røraas T, Bartlett WA, Coşkun A, Carobene A, Fernandez-Calle P, et al. Harmonization initiatives in the generation, reporting and application of biological variation data. *Clin Chem Lab Med* 2018;56:1629–36.
29. Ada Health. www.ada.com. Accessed: October 2018.
30. Babylon Health. www.babylonhealth.com. Accessed: October 2018.
31. Mediktör Health. www.mediktör.com/corp/. Accessed: October 2018.
32. AlinIQ. www.corelaboratory.abbott/int/en/offerings/brands/aliniq. Accessed: October 2018.
33. Pacific Knowledge Systems <http://pks.com.au/>. Accessed: October 2018.
34. Tao F, Cheng J, Qi Q, Zhang M, Zhang H, Sui F. Digital twin-driven product design, manufacturing and service with big data. *Int J Adv Manuf Technol* 2018;94:3563–76.
35. Brown SA. Principles for developing patient avatars in precision and systems medicine. *Front Genet* 2016;6:365.
36. Iansiti M, Lakhani KR. Technology: the truth about blockchain. In: HBR.org, January/February 2017.
37. Okun S, Wicks P. Digital me: a journey towards personal health and thriving. *Biomed Eng Online*. <https://hbr.org/2017/01/the-truth-about-blockchain>. Accessed: October 2018.
38. Diaz V, Viceconti M, Stroetmann V, Kalra D. Roadmap for the digital patient. http://www.vph-institute.org/upload/discipulus-digital-patient-research-roadmap_5270f44c03856.pdf. Accessed: October 2018.
39. The virtual physiology Human (VPH) Institute. <http://www.vph-institute.org/discipulus.html>. Accessed: October 2018.
40. My Health Avatar. www.myhealthavatar.eu. Accessed: October 2018.
41. Medical Avatar. www.medicalavatar.com. Accessed: October 2018.
42. Body Interact. <https://bodyinteract.com/>. Accessed: October 2018.

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