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1 Personalized medicine

1.1 Introduction

Everyone is different. Each person represents a unique combination of genomic, demographic, developmental, occupational, and environmental factors. This also means that treatment challenges for every person are not the same.

Traditional medicine is based on the application of protocols. If a given therapy was observed to be successful for a group of people in a randomized controlled trial (RCT), then traditional medicine concludes that the treatment should work for all patients. Although this assumption works in general, with recent scientific advancements, it has become clear that there are situations where the assumptions fail because of the following reasons.

First, traditional approaches do not account for the ethnic heterogeneity of patients. The risks for developing many diseases vary across ethnic groups. In addition to disparities in disease risk across races and ethnicities, there are also survival disparities across different racial groups (e.g., 5-year survival rates among those with breast cancer) [1–4].

Second, the one-protocol-to-heal-them-all approach does not necessarily account for confounding factors, such as race, age, gender, body mass index, socioeconomic status, or even birth month [5–8]. Protocols impose an "if-else" rule-based approach, which usually depends on the observation of laboratory tests and the response of the patient to the treatment. In addition, most clinical protocols are based on initial RCTs. However, in order for an RCT to be adequate, all possible confounders need to be identified *a priori* before the randomization occurs. If one confounder variable is missing during the randomization step, then the results of the RCT would not generalize to those groups.

Third, there is a diversity of patients' responses to treatment. A higher response rate to the treatment for a group of people may also be associated with increased toxicity for the other. This basically means that even if a given treatment helps some people or subpopulation of the study, the treatment may be harmful to another subpopulation.

There is also the issue of adherence to the treatment regime. Certain patient populations do not believe in taking prescription medications because of ideological reasons (e.g., those adhering to the scientology religion do not believe in taking prescription medications). Therefore, RCTs may exclude these individuals because they are not willing to cooperate with the treatment protocol. However, in some cases, these individuals still enter hospitals and seek medical care. If this patient

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subpopulation has never participated in any clinical RCTs, it may be difficult to determine whether the treatment would be effective among this patient population. They are essentially an unstudied patient population. These constitute some of the very important and critical challenges faced by personalized and precision medicine in the twenty-first century.

An important concern is that many clinical trials are not representative of the diversity that exists in human populations. For example, Kwiatkowski et al. [9] studied ethnic and gender diversity in 304 publications between 2001 and 2010 and found out that in 277 treatments and 27 prevention trials, over 80% of participants were white and nearly 60% were male. Another study by Chen et al. [10] pointed out that the percentage of reporting minorities from five major studies in literature varied between 1.5% and 58.0%, and only 20% of papers in high impact factor oncology journals detailed the results broken down by each separate ethnic group. There is an ongoing effort to encourage minorities to participate in random clinical trials [11]. However, this is a challenging area because researchers must overcome years of mistrust generated by a system that has often been discriminatory toward minority populations [12]. To conclude, efforts need to be made to redesign clinical trials to reflect the diversity of the patient population treated in the clinic and to address issues pertaining to individuals themselves instead of populations as a whole.

The aforementioned challenges with traditional approaches in medicine show an emerging need for developing more customizable treatments based on the "true" patient [13], which would be more fit to a given patient, instead of focusing on general outcome statistics [14]. Schork [15] reported that somewhere between 1 in 25 and 1 in 4 (25%) patients are actually receiving benefit from taking some of the most popular drugs in the United States. For example, statins, which are prescribed to lower cholesterol, were said to benefit only 1 in 50 patients.

As in personalized medicine, there are no historical data for each of the patients; therefore, recent efforts focus on tailoring treatment to a given set of characteristics of the patient rather than to the entire individual as a whole. Precision medicine is about giving the right patient the right drug in the right dosage at the right time [16]. Tailoring a therapy based on the observation of the context of the patient allows therapy adjustments down to a fine-grained level of detail. The hope is that this would improve the prognosis and reduce costs of the treatment.

In recent years, there has been a noticeable increase in interest on the implementation of precision medicine programs. The "All of Us" initiative was launched in the United States in 2015 with the aim to recruit at least one million individuals with diverse lifestyles, environments, and biology to create a database for scientific analysis that is open to researchers around the world. Similar programs, but on a smaller scale, were also launched across the globe: Australia, Belgium, Canada, Estonia, France, Israel, Japan, Korea, Luxembourg, Singapore, Thailand, and the United Kingdom [17]. Much of the effort is taken to create as accurate data as

possible, including multiomic data, i.e., genomic, proteomic, transcriptomic, epigenomic, microbiomic, and other information. The combined data could be analyzed to search for patterns for common diseases. By combining knowledge about the patient, not only disease prognosis could be predicted, but also its susceptibility of the disease and the patient's response to certain treatments. This research could lead to an improvement in the health and outcome of the patient.

Similarly, an individualized approach can support better understanding of genetic factors for rare diseases. A rare disease is defined by the Food and Drug Administration (FDA) as a disease, affecting fewer than 200,000 people in the United States (≥0.06%). The FDA has identified a total of 7,000 diseases meeting these rare disease criteria, many of which have no known treatment.[1] Understanding molecular mechanisms in different diseases could create a better classification of diseases. This can allow researchers to repurpose existing drugs used for treating one disease for treatment in another [18].

The volume of health care-specific data is increasing. The number and amount of publicly available data sets is rapidly growing. The Database of Genotypes and Phenotypes offers access to both publicly available and restricted individual level data [19, 20]. The Gene Expression Omnibus created in 2000 stores more than 40,000 data sets with 1,200,000 of samples by 2018 [21–23]. Creating repositories with collected biological samples (biobanking) as well as the integration of multiple types of data (multiomics) has provided different sources of information. This multiview approach could allow better understanding of mechanisms of diseases.

With a growing number of publicly available patient data, there is an emerging need to implement novel techniques for data analysis. With recent advances in machine learning, deep learning becomes widely used in biomedical sciences [24]. Another technique that has become more popularly applied to bioinformatics is biclustering [25]. This data mining technique can be used to identify subgroups of patients with specific characteristics [26, 27]. With the recent progress in the field and development of sophisticated and accurate methods that can extract informative patterns, a step was made toward finding explanation for diseases [28–31].

In the subsequent parts of this chapter, we provide a very brief introduction into different techniques and their applications to personalized medicine.

1.2 Three-dimensional printing

Printing in 3D, which is a process of building a 3D object layer by layer based on a computer model [32], has already allowed rapid prototyping and customization in manufacturing, designing, and production of parts for automation or components

1 www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-disease-day-2019.

for construction. This technique was invented in the early 1980s by Charles Hull and called "stereolithography." The exact processes of 3D printing differ and depend on the material used, device, speed, or resolution [33].

One of the first reported applications of 3D printing in medical domain was the development of prosthetics and dental implants [34]. Since then, 3D printing has made a great impact on medicine by allowing the development of customized bones, ears, cells, blood vessels, tissues, or even organs. This area of application is called bioprinting. Three-dimensional printing has also allowed the emergence of multiple personalized medical devices as well as drug development.

In this part, we overview the recent applications of 3D printing technology in medicine.

1.2.1 Medical 3D bioprinting

Enabling 3D printing of biocompatible materials could be considered a recent breakthrough in regenerative medicine. The integration of multiple technologies from biomaterial sciences, engineering, cell biology, medicine, and physics has allowed to deliver synthetic cells or tissues, including a multilayered skin, bone, or even heart [35, 36]. This provides a technique for the creation and development of cells or even organs in biosynthetic materials, which could be later transplanted to patients. With high need for tissues and organs for transplantation, biocompatible materials could be used as a potential alternative. The implantation of cells or organs that would mimic the native ones in both geometry and cell distribution has been sought for over a decade. The rejection rate might be minimized by using cells from the donor's own body, which could serve to create a replacement organ [33, 37].

A typical process of 3D bioprinting begins with imaging of the damaged tissue, choosing the design (biomimicry, self-assembly, or minitissue building blocks), selecting the material (the most popularly used materials are synthetic or natural polymers or decellularized Extracellular matrix (ECM)) and cells, bioprinting, and application, which either could be in vitro or may require some maturation in a bioreactor before it could be transplanted [36].

1.2.2 Medical devices

The personalization of the medical devices has played a great role especially in cases where the patient is expected to be wearing a device for an extended period. One of the success stories of the application of 3D printing in health care is manufacturing hearing aids. The process of fitting the right hearing aids used to be handcrafted and

was very lengthy. In the situation where a millimeter of difference in the design of a device could cause discomfort to the patient, 3D printing comes with the perfect aid. By imaging, a device could be perfectly fitted to the patient, which greatly shortens the process and improves the comfort [33].

Another example of using a personalized device for improving health care is the Invisalign® aligner [38]. The set of orthodontic devices allowing a gentle adjustment of teeth location has proven to successfully help thousands of patients without the necessity to wear visible braces.

The development of personalized masks for acne treatment is another interesting application of 3D printing. By taking a digital image of a patient's face, a mask is manufactured, which allows to dissipate the solution evenly on the skin of the patient [39].

1.2.3 Anatomical models for surgery planning

What is even more promising is that computer models can be printed using 3D printers, which could increase the success rate of very complex surgeries. In this way, the surgical removal of tumor from involved organs could be practiced in a simulator as needed before the actual procedure, without any harm to the patient. Similarly, vascular modeling may enable cardiac surgeons to implant stents customized to the patient. A digital model of the blood vessels can serve to design the stents of the proper construction: size, shape, and bendability. The stent could be later printed and implanted to the patient with greater success rate than the conventional ones and decrease rejection rate [31].

1.2.4 Medication manufacturing

One of the latest trends in using 3D printing for biomedicine is the development of targeted drugs or those with different release times. The first 3D-printed drug called Spritam® was approved by the FDA in 2015. The drug offers treatment for seizures in epilepsy [39].

A 3D-printed drug has been successfully used as a patch for the prolonged release of anticancer drug in pancreatic cancer treatment [40]. This allows the drug to reach desirable concentration at the tumor sites, in contrast to traditional chemotherapeutic drugs, which are poorly soluble in aqueous media.

There is ongoing research on creating multidrug pills. Those personalized pills would substitute multiple pills administered to a patient with a single personalized pill. Patients would no longer need to remember the dosages of different drugs, e.g., two pills of one drug three times per day and one pill of another drug twice a day.

Instead, a simplified pill would be administered, and all the required doses would be released automatically. This should improve the car by minimizing the mistakes of the patients, such as taking too much pills of a first drug or missing another [33].

1.3 Holography and personalized medicine

Holograms have been popularized in science fiction and often consist of a 3D image that interacts with a user when triggered (e.g., when an individual walks up to a kiosk). But what are holograms, and how can they be used to advance personalized medicine? Holograms are 3D images that are formed by the interference of light beams from a laser or other coherent light source [41]. Holography is the science and study of making holograms.

So how can holograms be used in personalized or precision medicine? By definition, holograms are made through the interference of light beams that produces an image. Holographic sensors are sensors that change color based on the angle of light that refracts from the structure. They consist of 3D analyte nanostructures. When the light diffracts from these nanostructures, one can learn something informative about what is taking place [41].

1.3.1 Holographic sensors and point-of-care testing

For example, there are colorimetric urine tests that measure pH, protein, and glucose in patients' urine. A smartphone algorithm was also developed to quickly read the results of these colorimetric tests and to detect important color changes in the urine in response to the test [42]. This would be especially useful for those that are color blind and unable to read the color change results themselves.

Colorimetric tests are an emerging area of point-of-care medicine [43]. These tests have been suggested as proof of concepts for blood-based biomarker tests for psychiatric diseases [44]**.** They could be used to detect if a patient is having a chemical imbalance crisis event, which is important in psychiatric disease treatment. These point-of-case colorimetric tests could also be used to detect if patients are taking their prescription medications (drug adherence) or using illicit substances [45]. Biometric holography can also be used to detect chemoresistance among patients [46].

Environmental exposures, such as exposure to DDT (an insecticide used to reduce the mosquito population), could also be monitored via colorimetric tests, which have been described as early as the 1940s [47] but are gaining more traction recently [48]. These colorimetric methods would be very useful in the future to help quantify the number and kinds of environmental exposures. A recent study on prenatal exposures found that at least 219 distinct environmental exposures have been studied in the literature with regard to their prenatal effects [6]. Therefore, methods

are needed to easily identify if individuals have been exposed to these various exposures, and if so, to what extent.

1.3.2 Holographic sensors and surgery

Microsoft has developed a new HoloLens in which researchers are developing methods in the surgical context. Holographic methods can be used to detect and clearly delineated cancerous from noncancerous tissue. However, it is often difficult to implement these methods in the surgical context because of surgeons' reliance on their natural eyesight to make important delineations that may not be captured by current digital methods. Therefore, rather than fully replacing a surgeon's eyesight with a digital headset, researchers are beginning to use Microsoft's HoloLens to augment the surgeons natural eyesight without fully replacing their eyes to help in delineating cancerous from noncancerous tissue [49]. These methods are still in their nascent stages, and much work is required in this area to make these methods applicable and usable in the clinical setting.

1.4 Robotics

One of the areas used to be thought of as science fiction and has now become a reality is robot-assisted surgery. Over 1.75 million robotic procedures have been performed in the last 14 years in the United States only [50].

Robotics can improve health care by supporting aid at minimal invasive surgeries. Robotic arm could be much more precise than a human hand and better control surgery instruments. It also does not transmit tremors manned surgeries. This allows for more precise operations, smaller incisions, and decreased loss of blood. As the results of postsurgery complications risks are usually decreased, hospitalization shortened and recovery process speeded up.

One of the robotic devices that have already become established is the *da Vinci* robot by Intuitive Surgical. The robot, operated from the console, was approved by the U.S. FDA for performing different complex medical surgeries that support gynecology, urology, and other disciplines. It is commonly used worldwide for prostatectomies and gynecologic surgeries. Similar devices are also developed by other companies.

Intensive work is also being done on remote surgeries, which could be performed by a skilled specialist from any place in the world. According to *PC Magazine*, the first successful remote operation on a human using 5G network was performed in China.[2] The surgeon who was located over 1,800 miles from the operating room implanted

2 https://www.dailymail.co.uk/health/article-6821613/Surgeon-performs-world-remote-brain-surgery-patient-1-800-MILES-AWAY.html.

deep brain stimulation device to a patient suffering from Parkinson's disease. With the rapid development of 5G mobile network, such surgeries may become more popular and improve local health care, especially in cases when transportation of the patients is unsafe or expensive.

Although the progress in robotics is clearly visible, multiple challenges still remain. A nonnegligible number of surgical complications were observed. Among over 1.75 million of robotic-assisted surgeries performed between 2000 and 2013, among 10,624 reported adverse events, 144 deaths, 1,391 patient injuries, and 8,061 device malfunctions were reported [50].

1.5 Computer modeling

One of the ways how recent technologies change reality is computer modeling. In the recent years, simulation has moved far beyond classic approaches for visualizing large data sets [51]. Digital models of certain organs or tissues acquired using visualization techniques, such as CT, MRI, X-ray, or ultrasound, could be used as simulators, which can be used to train future generation of surgeons. Similarly, performing a procedure on a real patient is no longer the only way that surgeons may learn their profession. The 3D-printed physical models of real organs may serve as a great educational tool for surgeons.

Visualization technologies bring also a deeper insight into the actual nature of a particular disorder. Creating a digital model of an actual organ of a patient may allow to better understand the nature of a particular disorder. Different reparative procedures could be compared, and thus the optimal procedure or treatment could be adjusted to the patient. Digital copies of the organ may also be shared and discussed by a group of physicians.

Another area of interest is modeling a patient within the health system. With digitalization, electronic health records were introduced in multiple providers across Europe and the United States. The major aim of the systems was storing patients' data in digital forms, which included all procedures, physicians' notes, and laboratory results. With the expansion of data mining and machine learning, electronic systems became invaluable sources of information. Unfortunately, the systems were not designed for this purpose, and the extraction of data is sometimes challenging. Different approaches are made to better understand the interaction of patients with the health care. For example, by modeling trajectories of patients for different diseases, groups with different survival chances may be extracted, which could be later used for targeting similar patients with different treatments [52].

1.6 Hybrid operating room

The way that surgeries are performed has significantly changed over the last few years. With access to more advanced technologies, diagnostics, and imaging,

increasingly complex procedures are performed and—what is even more spectacular—are successful in delivering the proper care to the patient.

In this section, we start with a short overview of a modern surgical theater, which is called a hybrid operating room (OR). We also highlight some of the recent advances in techniques of extended reality and the ways that it has started to be adapted in operating theaters. A more thorough information on hybrid OR could be found in Chapter 7 of this book.

1.6.1 Hybrid OR

The quality of surgeries is continuously increasing, thanks to the better training of the surgeons, as well as the investments in facilities by hospital stakeholders. Combining a traditional OR with interventional suite with advanced imaging and visualization creates a space for more advanced surgeries. This facility, usually operated by an interdisciplinary team of clinicians, is also called a hybrid OR.

Hybrid ORs are modern spaces that facilitate state-of-the-art equipment, allowing image-guided or minimal invasive procedures or even open procedures. Instant access to C-arms, CT, or MRI devices during the procedure allows constant monitoring of the state and instantaneous adjustment during the procedure. This is especially valuable for providing the best care for patients undergoing cardiac or neurovascular procedures.

The flexibility offered by hybrid ORs is not limited to cardiac or neurosurgeries. With access to such advanced facilities, the facilities can also provide support for ER, laparoscopic, orthopedic trauma surgeries, and many others.

1.6.2 Augmented, virtual, and extended reality (AR/VR/XR)

Virtual reality (VR) and augmented reality (AR) technologies, collectively called extended reality (XR), have been in development and use since the 1990s but have recently become much more affordable and much easier to work with, and developing software for these applications has become easier as well. Because of this, there is a boom in new XR applications, and there is a fast growth in adoption across many fields, including health care, data visualization, gaming, architecture, and training and maintenance within many fields. Within health care, some applications fit within the broader topic of personalized medicine.

The difference between VR and AR lies in the relationship between the computer-generated virtual experiences and the real world. In VR, a user is completely immersed in a virtual world. Typically, this is achieved by wearing a head-mounted display capable of stereographic image projection that completely blocks out the user's view of the real world. Two well-known systems of this type are the HTC Vive and the Oculus Rift. Interaction with the virtual world typically involves two handheld

controllers that the user manipulates. The application can completely control the world that the user sees and interacts. In AR systems, the user wears a headset with a see-through projection screen, sometimes in the form of what looks like glasses. The computer-generated imagery is projected into the user's eyes from this screen and overlaid on top of the user's view of the real world. In contrast to VR, AR allows the user to navigate and interact with the real world while viewing computer-generated imagery.

The following are some examples of surgical XR applications. Other examples of how personalized medicine could be used for a hybrid OR may be found in Chapter 7 of the book.

1.6.3 VR for visualization and assessment of mitral valve geometry in structural heart disease

In this small study, the SyGlass[3] VR application is evaluated as a tool to assist in the modeling and measurement of mitral valve (MV) geometry [53]. The long-term goal of the project is to develop an easier and faster method for evaluating the MV geometry of a patient with MV anomalies. There are two common MV anomalies, each addressed by a different surgical procedure. The geometry of the MV determines which procedure should be used, and the echocardiogram that is used to image the valve is performed at the beginning of the patient's time in the OR. Thus, there is a need for a quick and easily learned method to analyze the patient's MV geometry in the OR.

Conventionally, interactive 3D modeling of the MV in echocardiography involves visualizing and interacting with the valve in a volume-rendered image and a series of cross-sectional planes on a standard 2D computer display. Although this is a state-of-the-art method, it requires a sophisticated 2D-to-3D mental integration step to identify and measure individual components of the MV, it is time consuming, and it requires specialized training. By contrast, the SyGlass application presents a 3D volume of the MV in VR, which allows for much more natural perception of and interaction with the 3D structure. The user can look around naturally to get different views of the MV, yielding very rich depth and structural information. They can hold a virtual marker tool in their hand and reach out naturally to line it up precisely in space with the portion of the MV they intend to mark for specifying its geometry.

This preliminary study suggests that the use of SyGlass for MV measurement has reproducible high accuracy, and it is quick. If further study confirms these findings, this method could be performed on site in the OR to help make a quick decision about which surgical procedure to implement for the patient.

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3 syglass.io.

1.6.4 3D-ARILE by the Fraunhofer Institute for Computer Graphics Research IGD

The 3D-ARILE system[4] is an experimental AR system meant to assist in the surgical removal of a sentinel lymph node after the excision of a malignant melanoma tumor. A near infrared-activated dye is injected in the lymph node, and a custom 3D NIR-sensitive camera tracks its location in space. The surgeon wears a custom AR headset that interacts with the 3D camera to collect information about the lymph node's position in space and then presents an image of the lymph node to the surgeon, overlaid on the patient's body. The surgeon can change her move, and the overlaid lymph node image maintains its proper representation in space. Because AR allows the surgeon to view the virtual lymph node image overlaid on the real-world image of the patient, she has a more natural 3D view of the lymph node and can work directly on the surgical site without having to change her view to an external monitor. This promises greater accuracy and speed during the tumor excision.

1.7 Summary

For the last couple of years, personalized medicine has made enormous progress to deliver better, faster, and more customizable treatment to multiple patients. By taking an individualized, nonstandard approach, better fitting solutions could be proposed to the patients, and thus the time and cost of providing improper treatment could be saved.

Multiple advances were adapted in health care throughout the last decade. The progress was observed in imaging (e.g., more precise 3D images of organs, and emergence of sophisticated extended reality devices), prosthetics, orthodontics or orthopedics (3D-printed implants), drug design and transplantation (3D bioprinting), and modeling vessels or organs. The advances in robotics have started to allow fully remote surgeries, which will become even more popular with the implementation of 5G network across the countries. Hybrid ORs, which are becoming more popular in the modern hospitals, have already allowed clinicians to perform very advanced medical procedures. The progress in robotics justify thinking of unmanned (i.e., fully autonomous) surgeries in the future.

Personalized medicine cannot be narrowed down to a specific method or application. It should be considered as a multidisciplinary approach, which puts the health of the patient in the first place and offers advanced options for the recovery in modern facilities. This shift in approach from "follow the protocol" to individualized therapy requires a holistic approach, which will simultaneously consider the nature

4 www.fraunhofer.de/en/press/research-news/2017/november/ar-glasses-help-surgeons-when-operating-on-tumors.html.

of the patients' problems and previous expert knowledge on treatments that could be helpful for the particular person.

In this book, a closer look into multiple areas of personalized medicine is taken. With this short introductory, we overviewed some of the most interesting applications of personalized medicine. The more detailed information on the selected techniques could be found in the subsequent parts of this book.

1.8 References

[1] Amorrortu, Rossybelle P, et al. "Recruitment of racial and ethnic minorities to clinical trials conducted within specialty clinics: an intervention mapping approach." *Trials* 19 (2018): 115.
[2] Burroughs, Valentine J, Randall W. Maxey, Richard A. Levy. "Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment." *Journal of the National Medical Association* 94.10 Suppl (2002): 1.
[3] Settle, Kathleen, et al. "Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients." *Cancer Prevention Research* 2.9 (2009): 776–81.
[4] Wikoff, William R, et al. "Pharmacometabolomics reveals racial differences in response to atenolol treatment." *PloS One* 8.3 (2013): e57639.
[5] Boland MR, Shahn Z, Madigan D, Hripcsak G, Tatonetti NP. "Birth month affects lifetime disease risk: a phenome-wide method." *Journal of the American Medical Informatics Association* 22 (2015): 1042–53.
[6] Boland MR, et al. "Uncovering exposures responsible for birth season–disease effects: a global study." *Journal of the American Medical Informatics Association* 25 (2017): 275–88.
[7] Boland MR, Kraus MS, Dziuk E, Gelzer AR. "Cardiovascular disease risk varies by birth month in Canines." *Scientific Reports* 8 (2018): 7130.
[8] Boland MR, Kashyap A, Xiong J, Holmes J, Lorch S. "Development and validation of the PEPPER framework (Prenatal Exposure PubMed ParsER) with applications to food additives." *Journal of the American Medical Informatics Association* 25 (2018): 1432–43.
[9] Kwiatkowski, Kat, et al. "Inclusion of minorities and women in cancer clinical trials, a decade later: have we improved?" *Cancer* 119 (2013): 2956–63.
[10] Chen Jr, Moon S, et al. "Twenty years post-NIH Revitalization Act: enhancing minority participation in clinical trials (EMPaCT): laying the groundwork for improving minority clinical trial accrual: renewing the case for enhancing minority participation in cancer clinical trials." *Cancer* 120 (2014): 1091–6.
[11] Hamel, Lauren M, et al. "Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer." *Cancer Control* 23 (2016): 327–37.
[12] Durant RW, Legedza AT, Marcantonio ER, Freeman MB, Landon BE. "Different types of distrust in clinical research among whites and African Americans." *Journal of the National Medical Association* 103 (2011): 123–30.
[13] Boland MR, Hripcsak G, Shen Y, Chung WK, Weng C. "Defining a comprehensive verotype using electronic health records for personalized medicine." *Journal of the American Medical Informatics Association* 20 (2013): e232–8.
[14] Lu, Yi-Fan, et al. "Personalized medicine and human genetic diversity." *Cold Spring Harbor Perspectives in Medicine* 4 (2014): a008581.
[15] Schork, Nicholas J. "Personalized medicine: time for one-person trials." *Nature News* 520 (2015): 609.

[16] Roberts, Jason A, Anand Kumar, Jeffrey Lipman. “Right dose, right now: customized drug dosing in the critically ill.” *Critical Care Medicine* 45 (2017): 331–6.
[17] Ginsburg, Geoffrey S, Kathryn A. Phillips. “Precision medicine: from science to value.” *Health Affairs* 37 (2018): 694–701.
[18] Schee Genannt Halfmann S, Mählmann L, Leyens L, Reumann M, Brand A. “Personalized medicine: what’s in it for rare diseases?” In: Posada de la Paz M, Taruscio D, and Groft S, eds. *Rare Diseases Epidemiology: Update and Overview. Advances in Experimental Medicine and Biology*, Vol. 1031. Switzerland: Springer, 2017.
[19] Mailman, Matthew D, et al. “The NCBI dbGaP database of genotypes and phenotypes.” *Nature genetics* 39 (2007): 1181.
[20] Tryka, Kimberly A, et al. “NCBI’s database of genotypes and phenotypes: dbGaP.” *Nucleic Acids Research* 42 (2013): D975–9.
[21] Clough, Emily, Tanya Barrett. “The gene expression omnibus database.” *Statistical Genomics*, pp. 93–110. New York: Humana Press, 2016.
[22] Edgar, Ron, Michael Domrachev, Alex E. Lash. “Gene expression omnibus: NCBI gene expression and hybridization array data repository.” *Nucleic Acids Research* 30 (2002): 207–10.
[23] Wang, Zichen, Alexander Lachmann, Avi Ma’ayan. “Mining data and metadata from the gene expression omnibus.” *Biophysical Reviews* 11 (2019): 103–10.
[24] Ching, Travers, et al. “Opportunities and obstacles for deep learning in biology and medicine.” *Journal of the Royal Society Interface* 15 (2018): 20170387.
[25] Xie, Juan, et al. “It is time to apply biclustering: a comprehensive review of biclustering applications in biological and biomedical data.” *Briefings in Bioinformatics* 1 (2018): 16.
[26] Orzechowski, Patryk, Krzysztof Boryczko. “Propagation-based biclustering algorithm for extracting inclusion-maximal motifs.” *Computing and Informatics* 35 (2016): 391–410.
[27] Orzechowski, Patryk, Krzysztof Boryczko, Jason H. Moore. “Scalable biclustering—the future of big data exploration?” *GigaScience* 8 (2019): giz078.
[28] Gusenleitner, Daniel, et al. “iBBiG: iterative binary bi-clustering of gene sets.” *Bioinformatics* 28 (2012): 2484–92.
[29] Orzechowski, Patryk, et al. “Runibic: a bioconductor package for parallel row-based biclustering of gene expression data.” *Bioinformatics* 34 (2018): 4302–4.
[30] Orzechowski, Patryk, et al. “EBIC: an evolutionary-based parallel biclustering algorithm for pattern discovery.” *Bioinformatics* 34 (2018): 3719–26.
[31] Orzechowski, Patryk, Jason H. Moore. “EBIC: an open source software for high-dimensional and big data analyses.” *Bioinformatics* (2019): btz027. https://doi.org/10.1093/bioinformatics/btz027.
[32] Sachs, Emanuel, et al. “Three dimensional printing: rapid tooling and prototypes directly from a CAD model.” *Journal of Engineering for Industry* 114 (1992): 481–8.
[33] Ventola, Lee C. “Medical applications for 3D printing: current and projected uses.” *Pharmacy and Therapeutics* 39 (2014): 704.
[34] McGurk M, et al. “Rapid prototyping techniques for anatomical modelling in medicine.” *Annals of the Royal College of Surgeons of England* 79 (1997): 169.
[35] Kolesky, David B, et al. “3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs.” *Advanced Materials* 26 (2014): 3124–30.
[36] Murphy, Sean V, Anthony Atala. “3D bioprinting of tissues and organs.” *Nature Biotechnology* 32 (2014): 773.
[37] Cohen, Daniel L, et al. “Direct freeform fabrication of seeded hydrogels in arbitrary geometries.” *Tissue Engineering* 12 (2006): 1325–35.
[38] Wong, Benson H. “Invisalign A to Z.” *American Journal of Orthodontics and Dentofacial Orthopedics* 121 (2002): 540–1.

[39] Konta, Andrea, Marta García-Piña, Dolores Serrano. “Personalised 3D printed medicines: which techniques and polymers are more successful?” *Bioengineering* 4 (2017): 79.
[40] Yi, Hee-Gyeong, et al. “A 3D-printed local drug delivery patch for pancreatic cancer growth suppression.” *Journal of Controlled Release* 238 (2016): 231–41.
[41] Yetisen AK, Naydenova I, da Cruz Vasconcellos F, Blyth J, Lowe CR. “Holographic sensors: three-dimensional analyte-sensitive nanostructures and their applications.” *Chemical Reviews* 114 (2014): 10654–96.
[42] Yetisen AK, Martinez-Hurtado JL, Garcia-Melendrez A, da Cruz Vasconcellos F, Lowe CR. “A smartphone algorithm with inter-phone repeatability for the analysis of colorimetric tests.” *Sensors and Actuators B: Chemical* 196 (2014): 156–60.
[43] Vashist SK, Luppa PB, Yeo LY, Ozcan A, Luong JH. “Emerging technologies for next-generation point-of-care testing.” *Trends in Biotechnology* 33 (2015): 692–705.
[44] Guest FL, Guest PC, Martins-de-Souza D. “The emergence of point-of-care blood-based biomarker testing for psychiatric disorders: enabling personalized medicine.” *Biomarkers in Medicine* 10 (2016): 431–43.
[45] Argente-García A, Jornet-Martínez N, Herráez-Hernández R, Campíns-Falcó P. “A solid colorimetric sensor for the analysis of amphetamine-like street samples.” *Analytica Chimica Acta* 943 (2016): 123–30.
[46] Choi H, Li Z, Sun H, Merrill D, Turek J, Childress M, Nolte D. “Biodynamic digital holography of chemoresistance in a pre-clinical trial of canine B-cell lymphoma.” *Biomedical Optics Express* 9 (2018): 2214–28.
[47] Stiff HA, Castillo JC. “A colorimetric method for the micro-determination of 2, 2, bis (p-chlorophenyl) 1, 1, 1 trichlorethane (DDT).” *Science* 101(1945): 440–3.
[48] Ismail HM, et al. “Development of a simple dipstick assay for operational monitoring of DDT.” *PLoS Neglected Tropical Diseases* 10 (2016): e0004324.
[49] Cui N, Kharel P, Gruev V. “Augmented reality with Microsoft HoloLens holograms for near infrared fluorescence based image guided surgery.” In: *Molecular-Guided Surgery: Molecules, Devices, and Applications III*. Vol. 10049, p. 100490I. International Society for Optics and Photonics, 2017.
[50] Alemzadeh, Homa, et al. “Adverse events in robotic surgery: a retrospective study of 14 years of FDA data.” *PloS One* 11 (2016): e0151470.
[51] Orzechowski, Patryk, Krzysztof Boryczko. “Parallel approach for visual clustering of protein databases.” *Computing and Informatics* 29 (2012): 1221–31.
[52] Beaulieu-Jones, Brett K, Patryk Orzechowski, Jason H. Moore. “Mapping patient trajectories using longitudinal extraction and deep learning in the MIMIC-III Critical Care Database.” *Pacific Symposium on Biocomputing* 23 (2018): 123–132.
[53] Aly HA, et al. “Virtual reality for visualization and assessment of mitral valve geometry in structural heart disease.” *Circulation* Suppl. (in press).