**Going Digital: A Survey on Digitalization and Large Scale Data Analytics in Healthcare**

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**Abstract**—We provide an overview of the recent trends towards digitalization and large scale data analytics in healthcare. Both are instrumental in the dramatic changes in the way healthcare will be organized in the future. We discuss the recent political initiatives designed to shift care delivery processes from paper to electronic, with the goals of more effective treatments with better outcomes; cost pressure is a major driver of innovation. We describe newly developed networks of healthcare providers, research organizations and commercial vendors to jointly analyse data for the development of decision support systems. We are addressing the trend towards continuous healthcare where health is monitored by wearable and stationary devices; a related development is that patients increasingly take responsibility for their own health data. Finally we discuss recent initiatives towards a personalized medicine, based on advances in molecular medicine, data management, and data analytics.

**Keywords**—Big Data, Healthcare, Personalized Medicine

I. INTRODUCTION

Data has always been the basis for a scientific approach to healthcare: diagnostics are supported by physiological measurement, laboratory data and diagnostic imaging; the analysis of treatments and the effects of potential disease causes are based on clinical and epidemiological studies. Study design and data acquisition used to be the main challenges whereas data volume and data management have not been major problems. We expect that this will change rapidly as new sources of healthcare data become increasingly relevant. The generated data sets are high-dimensional and abundant; the sheer amount is simply exploding. In the same sense as “digitalization” stands for the digital presence of citizens, services, and “things” in general, the term “digital health” is associated with the wealth of health-related data becoming available in digital form. The management and the analysis of this data with the goal of gaining insights and making insights actionable is sometimes referred to as Healthcare Big Data. Whereas the term “Big Data” might quickly fall out of fashion, the underlying issues and technological challenges covered in this paper most likely will not.

Driving forces for this change include a number of recent political initiatives designed to shift care delivery processes from paper to electronic, with the goals of more effective treatments with better outcomes; cost pressure is a major driver of innovation. One example is the Health Information Technology for Economic and Clinical Health Act (HITECH Act) in the U.S. The focus of the HITECH Act is the meaningful use of an interoperable electronic health record (EHR), enabling the exchange of information across institutions. The overriding goals are that each involved healthcare professional should have complete patient information, that patients are treated by the best available institution for their problems, that medical research results can have more immediate impact, and that overall effectiveness is increased. In the context of these initiatives, large volumes of data will be collected and many improvements in healthcare will be based on the analysis of this data, with improved outcome at manageable cost as main goals. As a precondition to realizing the full potential, fundamental changes in the healthcare system might be required and data privacy, data ownership and data security issues must be resolved.

“Variety” and “volume” are the Big Data aspects most relevant to healthcare. Variety means that detailed information about an individual must be available to personalize recommendations and interventions, such as lifestyle recommendations, alarms, reminders, preventive measures, screenings, referrals, and treatment recommendations. Key issues are, first, how detailed knowledge can be acquired, managed and stored, second, how the “intelligence” comes into the system and, third, how recommendations should be optimally communicated to stakeholders.

Volume is important to gain valid insights and actionable solutions from healthcare data. If data on many individuals is collected, one can perform statistical analysis, data mining and train machine learning systems.

Overriding issues in all developments are data privacy, data security and the questions of viable business models, reimbursement models and legal certainty.

The goal of this paper is to provide an overview of how digital health is affecting the future of healthcare and the expected changes are dramatic. The paper is written for the interested reader with limited prior exposure to healthcare issues and contains six major sections—organized along the digitalization sources—which describe different digitalization and analytics trends in some detail.

In the next section we consider the digitalization process within the clinic. As mentioned, many advances in clinical data management are based on a broader adoption of the electronic health record (EHR), which is the main driver for
a digitalization of the clinical information systems. The EHR can improve patient safety and can increase transparency and accountability. Implementing EHRs faces challenges, mostly associated with the additional efforts and costs and the fear that the center of attention might move away from the patient to the IT system. We also focus on the clinical data situation: what type of data is typically available and how it is documented and organized. We discuss the importance of shared terminologies and how clinical data can be used for modeling and improving decisions. We address some issues with working with clinical data, in particular data security and data privacy.

Clinics increasingly collaborate with university institutes with analytics competencies and with commercial vendors in digitalization and Big Data projects. In Section III, we describe a few specific projects. We also discuss some of the statistical issues that arise in integrating observed data from different sources, such as various biases, the issue of hidden confounders and batch effects. Another important issue is the representation of the temporal aspects of patient data.

Payers, registries and national health systems, as in the U.K., have long collected healthcare related data across clinics. A novel development in recent years is that clinics are increasingly required to report data for purposes like quality control and policy development. Much can be gained if data can be exchanged between different care venues, as for instance in integrated care. Health information exchange (HIE) encompasses all activities towards a mobilization of digital healthcare information across organizations within a region, community or hospital system [5]. We discuss data privacy, de-identification and the U.S. HIPAA regulations. These topics are covered in Section IV.

Healthcare becomes increasingly patient-centered and patients want to get in charge of their own health and their own health data. Families want to keep health profiles and make them accessible to authorized care givers, like their family doctors. This is supported by a number of evolving cloud-based offerings. One can envision new IT platforms as basis for a revolution in healthcare management, supporting both a patient-centric and a data-centric view. Also, there are patients with one or several serious, sometimes chronic, diseases who want to interact with a social community of patients with similar problems. Social media used by these patients may provide insights into drug effectiveness, drug side effects and can be useful for the detection and the tracking of infectious disease. Health data is even made available directly by the patients for research and other uses via platforms like PatientsLikeMe. We discuss these developments in Section V.

Another big digitalization trend is increasing data capture during the course of everyday activities. Smart phones can collect fitness and health related data via internal or external sensors. This data can be analyzed by the patient via platforms and apps or it can be sent to the health provider. Over a patient’s lifetime large amounts of personal data will be collected and data analysis offered as a service by platform operators. In addition to wearable devices, ambient sensors will play a role, in particular for the care of the elderly. There is an ongoing effort to “shift care to the left”: to identify risk and intervene before disease develops. This trend often manifests itself in the broader application of predictive models and highly targeted testing to individuals and an increasing emphasis on prevention rather than diagnosis and treatment. These developments are discussed in Section VI.

Finally, there is an increasing trend towards personalization in healthcare (i.e., more precise and personalized care) partially but not solely driven by the lower cost and increasing availability of molecular data in form of genomic (including whole genome), proteomic and metabolic profiles. The analysis of germline DNA characterizes disease predispositions whereas the analysis of somatic cancer DNA and RNA characterizes the disease. Treatment decisions are increasingly made based on complex molecular patient profiles, which comes at an increased level of complexity that easily overwhelms the decision maker. Large-scale analytics becomes even more relevant since the personalized decision rules themselves might be derived from large sets of data, in line with the trend towards an evidence-based medicine. This is the topic of Section VII.

Section VIII summarizes the developments with an attempt of an evaluation and a discussion of opportunities and threats.

In this paper we focus primarily on the situation in the U.S. The main reason is that the U.S. is ahead in digitalization and large scale data analytics in general and also in particular with respect to Big Data in healthcare. Another reason is that the U.S. has the largest healthcare market worldwide. We will highlight the situation in other countries when relevant, in particular some of the developments in the U.K. are highly innovative and demonstrate opportunities in a national healthcare system.

II. DIGITIZING HEALTHCARE DATA

A. Motivation

Healthcare is a large and complex enterprise that is relevant to essentially every person on the planet. The digitalization of healthcare data in a manner that is easy for computers to utilize is important to support the delivery of care through data visualization, collaboration and clinical decision support as well as a variety of forms of models. Of course traditional operational reporting and analysis are important as well. Recently, the concept of a “learning healthcare system” has been popularized [6]. In a learning healthcare system data harvested from the care process is continuously analyzed and used to create insights into how the care delivery process should evolve.

When data are digitized we can create new and useful ways to display and visualize these data, which has the potential to provide better insights into a patient’s status and optimistically better decisions [7]. Another important application for digitized healthcare data is clinical decision support (CDS). CDS systems combine the data with clinical knowledge to provide patient specific suggestions at the appropriate time in the care process. These systems have been demonstrated to improve the quality, safety and efficiency of care though these benefits have not been universally observed [8], [9]. Lack of complete, timely and correct data frequently underlies the failure to achieve these benefits.

A few authors have attempted to characterize the ways that health systems hope to take advantage of analytics. Bresnick
and colleagues for example, found the following ways that healthcare systems are interested in applying data analytics [10]:

- Identifying at-risk patients
- Tracking clinical outcomes
- Performance measurement and management
- Clinical decision making at the point of care
- Length of stay prediction
- Hospital readmission prediction

The goal of the latter is a reduction of costly penalties for hospital readmissions, which were introduced by Medicare under the 2010 Patient Protection and Affordable Care Act (ACA). Insurance companies have started to use data analytics to identify likely patients which resulted in a 40-50% reduction in readmissions for patients with congestive heart failure [11].

Another study identifies the following uses for analytics [12]:

- Analytics-based drug discovery processes
- Identification of better and safer therapies
- Optimal clinical trial designs and patient recruitment
- Evidence-based medicine to integrate clinical expertise and research results to support the best decisions about patient care, often at the point of care
- Protocol-based medicine that draws on research results to identify best practices for specific conditions, medical histories and patient populations
- Personalized medicine that blends diverse data sources, including genetic profiles, with historical clinical data to lead to personalized

These are mixes of descriptive tasks, prediction tasks and prescriptive tasks [10].

**Descriptive analytics** is a classical data mining task and extracts human understandable information from data in form of simple rules (association rule mining) or in visual form (visual analytics) [13]. Often the results are presented as a report. Typical projects might be to identify areas for improvement on clinical quality measures or on specific aspects of care. It is important to note that the human is in the loop and draws conclusions based on the findings [10].

For **predictive analytics**, traditional statistical methods or machine learning can be used. The task might be to forecast the volume of future procedures, diagnoses, or outcomes. Other tasks are patient condition monitoring with different alarm functions. The application of predictive models typically requires a robust and high-quality infrastructure, which enables real-time data processing. “Medical devices must be fully integrated to provide up-to-the-second information on patient vitals to improve safety, while alerts and alarms have to be developed and presented to clinicians without hopelessly disrupting their workflows or annoying them into ignoring critical warning” [10]. The good news is that confounding factors, as long as their statistical properties do not change, can be ignored in pure prediction problems; on the other hand a predictive model trained in one clinic might not work well in another clinic.

**Prescriptive analytics** encompasses the ability to recommend actions and to answer “what if” type of questions. Whereas a predictive model might recommend an action that is “typically” performed for a patient with particular properties, a prescriptive analysis would be able to prescribe an action that would lead to best outcome. “Prescriptive analytics doesn’t just predict what’s likely to happen, but actively suggests how organizations can best take action to avoid or mitigate a negative circumstance” [10]. The requirements on data quality and system robustness is even greater than with predictive analytics. In particular, a prescriptive analysis requires a careful analysis and consideration of hidden confounders. Prescriptive analytics has been called “the future of healthcare Big Data … the healthcare industry has an enormous opportunity to take advantage of these decision-making abilities” [10].

B. **The Electronic Health Record**

For decades, much of what was documented about a patient was in paper format and collected in a folder that was physically moved across the clinical departments and was eventually filed. Today, patient data is increasingly recorded and stored in an electronic form, the electronic health record (EHR) [14]. The EHR has potential to improve patient care through analysis and decision support while at the same time improving the quality of the data documented. In its most basic form, an EHR consists of the same paper documents except that they are scanned and stored digitally. Of course this does little to support analysis or clinical decision making. In more advanced systems, all text is machine readable and portions of the data are increasingly stored in structured form that is described semantically and easily accessible to algorithms and analytic tools. As we will discuss in Section [IV], the HITECH Act has stimulated increased use of the EHR in both hospitals and ambulatory practices across the U.S [15], [16], [17]. Meaningful use, as defined by HITECH, requires both the capability and actual use of the EHR to perform functions such as electronic prescribing and ordering of tests, electronic access of test results, medication alerts, computerized systems for tracking lab tests, implementations of medical guidelines. In some countries, the EHR is standard (e.g., in the Netherlands, New Zealand, Norway, Sweden and the U.K.), whereas countries like the U.S. and Germany have lagged. Surveys found that, despite much broader adoption over the last several years, U.S. physician enthusiasm for EHRs has not improved in the last 5 years [18]. The authors attribute the physician’s lack of enthusiasm to doctors not seeing enough benefit from the EHR and that EHR products do not deliver all necessary functionalities, being difficult to use, and not being interoperable with each other. In addition, there are worries about data leakage. which are increasing in frequency [19], and compliance with regulations.

C. **Structured Data Capture**

EHRs can only achieve their full potential is time and cost associated with data capture from clinicians can be kept under control. While a good deal of clinical data can be captured from other venues such as laboratory or radiology systems or from devices (e.g. vital signs, ventilators), a significant amount of data must be entered by providers. Because of the time and effort required for providers to capture structured data, they
often question if there is sufficient value to warrant the impact on productivity [20], [21]. Contemporary EHRs are estimated to require an additional 48 minutes per day, much of which is devoted to documentation [22], [23].

In addition to direct entry by providers or their surrogates, structured data can be derived from unstructured data including free text, images and other signals. Radiology involves the acquisition, analysis, storage and handling of radiological images and certainly involves huge amounts of data, in particular when the analysis involves time, as in angiography, or all three spatial dimensions, as in whole body screening. Pathology involves the analysis of tissue, cell, and body fluid samples, typically via microscopic imaging. As pathology is increasingly digitized, increasing amounts of digital data is generated and needs to be handled and stored. In many cases, the raw data are images, e.g., from radiology or pathology, and a medical specialist interprets the images and describes the findings in a written, free-text or unstructured report but algorithms can increasingly be applied to extract structured data directly from the images themselves.

Both researchers and commercial developers have devoted considerable effort to improve the efficiency of structured data capture and some hope that Natural Language Processing (NLP) will obviate the need for structured data capture but progress has been incremental. While there is progress in focused areas, NLP of clinical texts is notoriously difficult. Some of the reasons are that texts are ungrammatical, contain short phrases, non-standardized and overloaded abbreviations and employ an abundant use of negations and lists. Structured reporting, where the text is generated automatically and the physician simply enters keywords and short pieces of text, would be a great advance, but is currently not the standard [24], in part because it is typically more time consuming for the provider. Nevertheless, written text is a major medium: The exact numbers vary, but a significant proportion of the clinically relevant information is only documented in textual format. Besides radiological and pathological reports, medically relevant textual sources are reports from other departments, notes, referral letters and discharge letters.

Another issue is that the structured data entered by providers or extracted from text needs to be represented such that it can be “understood” by a computer, in other words healthcare system needs to be able to communicate effectively and in the same agreed upon formalized “language”. Some languages are essentially simple taxonomies and vocabularies and are the basis for standards used in the billing process, such as ICD for diagnosis, CPT for procedures, and SNOMED codes for diseases or conditions. For medications, there is the National Library of Medicine’s RxNorm, the National Drug Code (NDC) system. This variation means that using the data often requires mapping or translation between coding systems which usually are necessary for a particular application.

D. Coding and Coding Systems

Healthcare is complex and healthcare data has to represent an extensive array of data: there are hundreds of thousands of clinical concepts that have to be represented. In order to accommodate this scale and simplify representations, coding systems have been adopted for clinical concepts. The concept of heart failure for example can be represented in the International Classification of Disease Version 9 Clinical Modification as “428.0”. This approach facilitates using keyword value approaches to representing data. Unfortunately, there are multiple coding systems for most clinical concepts so heart failure can also be represented by I50 (ICD-10), 16209 (DiseaseDB), D00633 (MESH), 42343007 (SNOMED) and others. Even more unfortunately, a good deal of data are coded using idsyncratic clinical codes that are unique to a specific healthcare delivery system. This variation means that using the data often requires mapping or translation between coding systems which usually requires substantial human effort and, in some cases, a specific data model.

E. Data Silos

Another barrier to utilizing clinical data are the ubiquitous clinical data silos. In addition to the fragmentation of a patient’s data across various participants in the healthcare ecosystem each medical department has historically had its own department-specific database and reporting system and only a portion of that information is integrated into the EHR [29]. Before a provider sees a laboratory test result displayed in their EHR for example, the data has traveled along a complex and convoluted path to get there: Laboratory instruments themselves are sophisticated computing and data management systems that then pass data through laboratory instrument management systems and potentially laboratory information system, through
an interface engine and eventually to the EHR. Each phase supports specific data management and monitoring tasks and adds and loses pieces of data \[30\]. Another issue is that each data silo might code information differently and building wrappers for the purpose of data integration is anything but simple. These challenges are the basis for the recent preference for integrated EHR platforms which share a common database across many departments which largely eliminate the data silos inside an organization. In fact healthcare organizations have often accepted lesser functionality in order to achieve this benefit.

Figure 1 shows some of the clinical data silos and a typical patient story.

**F. Clinical Data Integration Efforts**

Some providers may have implemented a separate research data system such as i2b2 \[31\] or tranSMART \[32\]. The systems extract clinically relevant information from the EHR and from other clinical resources and databases and integrate them into the research database. A research database can be a great resource for data analytics project. Unfortunately, installing a research database project can be extremely demanding since it might need to access data that is in the data silos of the different departments. As discussed these databases might all have different structures and use different terminologies.

In contrast to clinical data, billing data —in part because of its simplicity and in part out of necessity— is consistently structured and is often part of a research database. Unfortunately, it does not contain much of the clinically relevant information and may not accurately and fully reflect clinical reality. Providers may not be as careful in recording administrative data believing it is not critical to be exactly correct or, in some cases, billing data may coded to maximize reimbursement rather than to most accurately reflect the patient’s clinical status.

**G. Privacy Protection and De-identification**

De-identification is the process used to prevent a person’s identity from being connected with information. Common uses of de-identification include human subject research for the sake of privacy for research participants. Common strategies for de-identifying data sets are deleting or masking personal identifiers, such as name and Social Security Number, and suppressing or generalizing quasi-identifiers, such as date of birth and zip code. Concepts are k-anonymity, l-diversity, epsilon differential privacy, differential identifiability coarsening, imputation, and data swapping \[33\]; appropriate patient consent may reduce the need for de-identification \[34\].

De-identification is difficult for clinical data in general but particular difficult for textual data since a personal identifier might appear unexpectedly in the middle of a text and for genomic data, considering that a person’s genetic profile is unique.

**III. MOBILIZING DATA IN A TRUSTED NETWORK**

Integrated care is a worldwide trend in healthcare focusing on more coordinated and integrated forms of care provision and may be seen as a response to the problems associated with the fragmented delivery of health in many countries. Integrated care —as some other forms of alliances and inter-clinical collaborations— permits the integration and evaluation of data from several sources, which makes sense for many reasons. First, the patient sample size simply is larger if compared to a single clinic. Second, patients may stay for more problems within an integrated care system and for a longer time spam, possible all their life; thus data on a particular individual is more complete.

In this section we describe representative projects where clinic networks team up with research centers—which provide expertise in data analytics, machine learning, and medical informatics—to explore the potential of clinical data analytics. The long-term vision behind these and similar projects is a system where patient data is analyzed online, and research insights rapidly becomes common practice, resulting in best care for each patient.

**A. The Pittsburgh Health Data Alliance**

The Pittsburgh Health Data Alliance is a collaborative Big Data effort involving Carnegie Mellon University (CMU), the University of Pittsburgh (Pitt) and the University of Pittsburgh Medical Center (UPMC). It is financed by the latter but all three institutions contribute grant funding \[35\].
The stated goals are characteristic for similar projects: Primarily they seek to analyze and make use of the massive amount of data generated in their health care system, including EHR patient information, diagnostic imaging, prescriptions, genomic profiles, insurance records, and data from wearable devices. The results could support the development of evidence-based medicine, and lead to the augmentation of disease-centered models with patient-centered models of care. The vision is a data-driven medicine based on a large sample of patients, which will assess an individual’s disease risk and make personalized recommendations for treatments. Other intended outcomes are spinoff companies and promotion of economic development in the region [36].

The CMU plans to develop an automated patient diagnosis system, which is also the goal of many similar research efforts. Based on automatically retrieved symptoms and lab findings the system searches medical literature and analyzes patient data to provide possible diagnoses. To refine the diagnosis additional tests might be requested.

The role of Pitt’s Center for Commercial Applications of Healthcare Data (CCA) is to develop new technology for potential use in commercial theranostics, combining diagnostics with therapy, and imaging systems for patients and doctors.

UPMC Enterprises leads the efforts to turn these innovative ideas into for-profit startup companies.

A concrete collaboration is the early detection of disease outbreaks, e.g., by tracking of over-the-counter medication sales. Involved are the “Real-Time Outbreak of Disease Surveillance” (RODS) Laboratory at Pitt and the “Event and Pattern Detection” (EPD) Lab at CMU’s Heinz College.

Being one of the first sizeable Big Data projects in healthcare, the effort attracted the interest of a number of IT companies, which supplied high-performance database platforms, business intelligence solutions, and interpretability platforms for integrating patient records. In general, there is an increasing care provider demand for Big Data functionalities in clinical information systems and vendors have to adapt to these needs. In fact, considering the dramatic changes expected in healthcare, in which IT is expected to play a major role, many IT vendors are actively exploring future business opportunities.

B. The Mayo Project

A collaborative effort between Mayo Clinic and several departments at the University of Illinois is part of a large federal grant for the support of medical research by Big Data [37]. The collaborative effort involves the Institute for Genomic Biology, the Department of Computer Science, the Coordinated Science Laboratory, the College of Engineering and the National Center for Supercomputing Applications (NCSA). The effort includes the setup of a new Center of Excellence for Big Data Computing and a network to move and share the data between researchers building on the Campus Advanced Research Network Environment (CARNE), which had been created with the goal of providing unrestricted high-speed access to off-campus locations for specific research purposes. A major project is the Knowledge Engine for Genomics, or KnowEng[1].

C. Neonatal Intensive Care at Kaiser Permanente

This is an early project that demonstrated the potential of Big Data in intensive care. In current medical practice, newborns are typically taken to the neonatal intensive care unit (NICU) if the mother’s temperature rises above a threshold because this may signal an increased risk of neonatal sepsis, a bacterial blood infection[38]. Kaiser Permanente has used data analytics to develop the interactive and online “Newborn Sepsis Calculator” that determines the probability of neonatal sepsis, allowing the care team to better determine which babies to evaluate and treat for infection [39].

D. Indiana Network for Patient Care

The Regenstrief Institute was an early advocate for clinical data interoperability based on information standards and leveraged that work to enable health information exchange both regionally and nationally. Regenstrief investigators implemented the Indianapolis Network for Patient Care (INPC) in 1995 with the goal of providing clinicians with data necessary for patient diagnosis and treatment at the point of care. In 2016, over 100 hospitals, thousands of physician practices, ambulance services large local and the state public health departments, regional laboratories and imaging centers, and payors participate in the INPC. The federated data repository stores more than 4.7 billion records, including over 118 million text reports from almost 15 million unique patients. The data are stored in a standard format, with standardized demographic codes, laboratory test results are mapped to a set of common test codes (LOINC) with standard units of measure and medications, diagnoses, imaging studies, report types are also mapped to standard terminologies. The flows of data that enable the INPC support results delivery, public health surveillance, results retrieval, quality improvement, research and other services. Building on this experience, Regenstrief investigators have informed the development of the nationwide health information network program now called the eHealth Exchange (“Exchange”).

The INPC data has been utilized by Regenstrief for many Big Data studies and projects including:

- The OMOP (Observational Medical Outcomes Partnership [40] and the subsequent OHDSI (Observational Health Data Science and Informatics) [41] projects to utilize Big Data understand methodological approaches to using large scale observational data using drug safety as an example
- As part of ConvergeHEALTH, an effort spearheaded by Deloitte that aims to offer comprehensive data sharing among key organizations. Deloitte has an analytics platform that allows hospital systems to compare results from tools designed to study certain patient outcomes: their OutcomesMiner tool helps users explore real-world outcomes for sub-populations of interest
- The Merck-Regenstrief Institute “Big Data” Partnership – Academic-Industry Collaboration to Support Personalized

[1]http://www.knoweng.org/
with properties and problems X, procedure Y is typically done. The outcome is not always well documented; readmission within a certain period of time (typically a month) is sometimes taken for a negative outcome. Alternatively one might define a hospital stay of more than a certain number of days as a negative outcome, where the threshold is DRG-specific. In some cases, for example after a kidney transplantation or mastectomy, the patient is closely observed, potentially over lifetime, and outcome is monitored.

Another important issue, and in particular with prescriptive modeling, is that the temporal order of events needs to be documented in the data. To analyze of the causal effects of a decision and to optimize decisions, it is important to know which information was available to the decision maker at the time of decision. At the current status of documentation, reconstructing the temporal order of events can be difficult.

The project addresses two use cases in detail. The first concerns nephrology. Kidney diseases cause a significant financial burden for the health system. The aim of this work is to systematically investigate drug-drug interaction (DDI) and adverse drug reactions (ADR) in patients after renal transplantation and to realize an integrated decision support system. The use case is particularly interesting since longitudinal data from several decades are available and since outcome is usually reported. First ILDS results are reported in [43].

The second use case concerns breast cancer, which is one of the most common malignancies in women. Relevant events are screening, diagnosis, therapy and follow-up care.

Of special interest here is the determination of risk factors, the evaluation of the therapy and the prediction of side effects. The integration of genome information in clinical decision support is sometimes referred to a clinicogenomics.

F. Similar Initiatives and Projects

In the US and in other countries many similar initiatives have been started or are in the preparation phase.

The Dartmouth Institute, Dartmouth-Hitchcock, Denver Health, Intermountain Healthcare, and the Mayo Clinic are the founding members of the “High Value Healthcare Collaborative (HVHC)”, which is a collective of close to 100,000 physicians and close to 10 million patients across the U.S. In an early project, HVHC found strikingly different costs and processes for total knee replacements among four hospital sites, with one site performing significantly better than the others [44]. Subsequently, this site’s best practices were shared with the other three and all four could reduce their lengths of stay for knee-replacement procedures by a full day [45].

The University of Michigan has announced a large Big Data Science Initiative targeting health, in the context of mobility and wearable devices [45].

The University of Washington Tacoma have developed the “RiskO-Meter” using data analytics. It provides a risk score to clinicians and patients to predict the return of congestive heart failure patients to the hospital within the critical 30 day readmissions window [47].

Penn Medicine, part of the University of Pennsylvania Health System, is working on a Big Data project to develop predictive analytics to diagnose deadly illnesses before they occur. The
backbone is a homegrown enterprise data warehouse, called Penn Data Store. An example is the prediction of a danger of severe sepsis, which relies on analysis of six vital sign measurements and lab values. The model takes into account more than 200 clinical variables and enables Penn Medicine to detect 80 percent of severe sepsis cases within 30 hours of the typical onset of symptoms [45].

Deep Learning is one of the most exciting developments in machine learning in recent years with stunning successes in a number of applications. One of the driving forces is DeepMind, a London based company owned by Google. DeepMind Health is a project in which UK NHS Medical Data are analyzed. The agreement gives DeepMind access to healthcare data on more than a million patients [49]. A first outcome is the mobile app Streams, which presents timely information that helps nurses and doctors detect cases of acute kidney injury. By comparing patients’ information with millions of other cases, the app might be able to predict that they are in the early stages of a disease that has not yet become symptomatic. Additional test can then be run to determine if the prediction is correct.

Two other notable Deep Learning efforts are Deep Genomics\textsuperscript{2} and Entlitic\textsuperscript{3}. Considering the overwhelming success of Deep Learning in image analysis, one can expect that many companies will follow. One of the first approaches for using Deep Learning (more specifically recurrent neural networks) to model the sequential decision processes in clinics is described in [43].

G. Comments on the Value of Big Data Studies

An interesting question is: what is the value of an observational Big Data study versus classical randomized controlled trials (RCT). Prospective RCTs are often cited as the gold standard for evidence since by a careful study design, effects of hidden confounders can be minimized. In contrast, a Big Data analysis will mostly concern observational studies (cohort studies, case-control studies) whose conclusions are considered by some to be less reliable. Here, hidden confounders might produce correlations, independent of a causal effects. Confounders are variables that both influence decisions (or disease causes) and, at the same time, outcome. Multivariate models should be considered where predictors contain all variables that were used in decision making. Unfortunately, some of these variables might not be available for analysis, such as patient symptoms and patient complaints, which both are often not well documented.

Another issue are hidden disease causes. Even with all advances in diagnostics, we are still very far from being able to completely describe the health status of an individual. Technically, the health status of a patient consists of many dimensions and only some of these dimensions (i.e., some infections, some cancer types) can be inferred by specific diagnostic tests. In Big Data analysis one is partially doing “new medicine”, i.e., one might address disease causes that might not have been identified as such, or might be composed of sub-causes. Since the model then implicitly needs to learn information on the latent causes from observed proxies, the models often become high-dimensional, and their predictions become difficult to analyse, although there predictive performance might be excellent. This is an effect observed in a multitude of predictive machine learning applications in and outside of healthcare. Overall, this can mean that clear hypotheses might not be formed in the process, which is contrary to healthcare tradition and some cultural change might be required. Latent causes might be the reasons why a medication sometimes seems to work and sometimes not. The Big Data perspective is: If there are hidden causes they might be reflected by the many observed dimensions.

Other issues are related to data collection which might introduce various forms of biases. An example are batch effects, which might happen in the merging of data from different institutions, but which can be eliminated by a careful statistical analysis [50], [51].

But RTCs also have their shortcomings, in particular due to the way patients are selected for a study and due to the small sample size. RTCs are often done in relatively healthy homogeneous groups of patients chosen to be healthy except for the condition of interest and free of common diseases like diabetes or high blood pressure and neither extremely young or old [52]. If patients have several problems, treating them as if they are mutually independent might be bad in general, and information on treatment-treatment interactions might not be easily assessable through RTCs. Also, interplay between diseases like hypertension, high cholesterol and depression might not become apparent in RTCs. Since patients are difficult to recruit in general, and the management of clinical studies is costly, sample size is often small. For the same reasons, findings need to be general and not personalized and there are long delays until a result is certain and can become clinical practice.

Big Data analyses, in contrast, consider data from a large variety of patients and potentially can draw conclusions from a much larger sample. They are based on the natural population of patients, and can conclusions can potentially be personalized. For instance, with depressed diabetic patients, one would want to compare hospitalization rates between those taking antidepressants and those who were not, to determine if more patients should receive psychiatric treatment to help them manage their health. Currently such studies involve great efforts. In the future these questions could be answered by a simple database query [53].

A final point is that we don’t yet know if physicians are willing to accept evidence from Big Data studies. We will discuss an example for the case of breast cancer in Section VII. A predictive or prescriptive analysis might output a ranking or prioritization of options based on many patient dimensions and the ranking might be pattern based and not always easy to interpret. It remains to be seen if the medical profession will accept these aspects of a Big Data decision support system.

\textsuperscript{2}http://www.deepgenomics.com/
\textsuperscript{3}http://www.enlitic.com/
IV. OUT WITH THE DATA

A. Introduction

In this section we focus on data that is leaving the clinic systems, i.e., data that is accessible to the payers, data that is collected in registries and data that is reported to healthcare agencies. Payers have a unique longitudinal view on patients and can perform statistical analysis on treatment efficiencies and outcome, for the detection of fraud, and for the optimization of their offerings. Registries are a valuable source for epidemiological research. We will discuss Health information exchange (HIE), which refers to various activities around the mobilization of healthcare information electronically across organizations [5]. Data reported to healthcare agencies can be used for quality control and for policy optimization. As an example of the latter, we discuss the HITECH act, which is an attempt to improve the clinical system in the U.S. by encouraging an adoption of the EHR and its meaningful use via incentive programs. Finally, we discuss privacy and data safety issues.

B. Data Accessible to Payers: Billing Data

The most common situation where data is leaving the clinic is when claims are filed with a payer, e.g., a health insurer or a health plan. Depending on the particular reimbursement rules in place, payers see data of varying levels of detail, quality and biases and claims data may not fully reflect a patient’s burden of illness [54], [55]. While the appropriateness of billing data to clinical research is often debated, many, many studies have used these data to guide clinical care, policy and reimbursement.

Claims data provides a holistic view of the patient across providers for a specific period of time and claims data permits a patient centric view on health. Claims data also provide direct and indirect evidence of outcome, e.g., by analyzing readmissions. There are also increasing opportunities in analyzing differences in costs or quality across providers.

Payer organizations are increasingly interested in understanding their customers, in this case their patients. Surveys, questionnaires, call center data, and increasingly social media including tweets and blogs, where patients are sharing their experiences, are analyzed for gaining insights to improve quality of services and to optimize offerings.

A major concern is the detection and prevention of abuse and fraud. Healthcare fraud in the U.S. alone involves tens of billions of dollars of damages each year [56] and fighting fraud is one of the obvious activities to immediately reducing healthcare costs. Note that some forms of fraud actually do not only harm the payer but directly the patient (e.g., by unnecessary surgery) [57], [58]. Naturally there is a grey zone between charging for justified claims on the one side and abuse and fraud on the other side. Certainly, billing for services never provided, e.g., for fictitious patients or deceased patients, is clearly fraud, but the change of a diagnosis can arguably medically be justified or, if unjustified, simply be done to justify a more expensive treatment (upcoding).

A 2011 McKinsey report discussed that fighting healthcare fraud with big data analysis can be quite effective [2]. Activities in this area focus on the detection of known fraud patterns, the prioritization of suspicious cases for law enforcement agencies as well as the identification of new forms of fraud. A successful approach has been to generate statistical models of clinical pathways and best practices and to detect abnormal claims (against the population) or suspicious temporal changes in charging patterns within the same provider. In addition to analyzing billing, one can analyze different kinds of provider networks, where nodes are the providers and the links are common patients, analyzing homophily or “guilt by association” patterns. Another measure is the black listing of providers. Most commercial systems use a combination of different strategies [56]. Despite all these efforts, and mostly due to the fragmentation in the system and a huge grey zone, it is estimated that only a few percentage of the fraud actually occurring is currently being detected.

C. Registries

Disease or patient registries are collections of secondary data related to patients with a specific diagnosis, condition, or procedure. There exist registries for dozens of problems, the best known ones are cancer registries, which have become an invaluable tool for understanding and detecting cancer within the U.S. but also on many other countries.

Population-based cancer registries regularly monitor the frequency of new cancer cases (so called incident cases) in well-defined populations. The basis are case reports collected from different sources, e.g., treatment facilities, clinicians and pathologists, and death certificates. If an unexpected increase of cases can be observed in registries, hypotheses about possible causes are generated. Hypotheses are then investigated in a second step by collecting more detailed data and performing further analysis. Registry data is critical to determining the location of geographic and temporal cancer clusters and it can be used for the development and tracking of the most effective therapies and treatments. Population based registries can also monitor the effects of preventive measures. Public health officials use the data to make decisions on research funding and educational and screening programs [59].

In contrast to population registries, hospital cancer registries are traditional means for research within a clinic or a clinic system using more detailed data about diagnosis, therapy and outcome. As in the more recent Big Data projects discussed in the last section, the data is used for the development of decision support systems, to determine optimal treatments, and for planning therapies.

The quality of the conclusions that can be drawn from cancer registries critically depend on the completeness and the quality of data. Both might improve through the adoption of the EHR: Stage 2 of the HITECH act calls EHR reporting to cancer registries to support comparative effectiveness research. In October 2012, the University of Kentucky launched a first U.S. working model for EHR reporting of cancer cases to a state’s cancer registry [59].

An important aspect is to guarantee that the electronic data transfer is safe and that proper precautions and safeguards have

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1 http://www.nih.gov/health/clinicaltrials/registries.htm
been implemented. If only summaries are reported, HIPAA violations (see Section IV-C) can be avoided. Note that with registries one obtains in-use data and one needs to be aware of possible confounders distorting the analysis (see Section III).

D. HIE

Health information exchange (HIE) refers to various activities around the mobilization of healthcare information in digital form and across organizations [3]. It is intended to regulate the electronic transfer of clinical and administrative information across diverse and often competing health care organizations [60]. HIE is also useful to public health authorities to assist in analyses of the health of the population

The Health Insurance Portability and Accountability Act (HIPAA) provides strong protections for the privacy and security of personal health information by also acknowledging that data needs to be exchanged across organizations within a region, community or hospital system [61], [62].

Several organizations have emerged to support the health information exchange efforts, both on independent and governmental/regional levels. These organizations develop and manage a set of contractual conventions and terms and develop and maintain HIE standards.

There are two main models for HIE data architectures. In a centralized HIE there is a central (or master) database which holds a complete copy of all of the records of every involved patient. In a federated HIE each health care provider is responsible for maintaining the records of their individual patients and are responsible for data availability and common data standards.

Patient consent can be managed by an opt-in approach or an opt-out approach. In opt-in, a patient is not automatically enrolled into the HIE by default and generally must submit written permission for their data to be exchanged. In opt-out, patients give implicit consent when they agree to use the services of a health care provider who is submitting data into an HIE. In this latter model a patient can request to opt-out of the HIE, generally with a written form.

One major goal is a nationwide health information network that will allow physicians quick access to their patients’ medical histories without compromising their privacy. In addition the data can be used to support the learning healthcare system and provide data for Big Data analysis [6], [63].

E. Care.Data

The U.K. has a national health system (NHS), which attempts to address many of the problems associated with the fragmented systems in the U.S. and in many other countries. A program called care.data was announced by the Health and Social Care Information Centre (HSCIC) in Spring 2013. The care.data program is advertised to integrate health and social care information from different sources to analyze benefits and potential shortcomings of the NHS [64]. The data could be used in anonymized form by health care researchers, managers and planners, but also by parties from outside the NHS such as academic institutions or commercial organizations.

Stated goals of the project were

- to better understand diseases and develop drugs and treatments,
- to understand patterns and trends in public health and disease to ensure better quality care,
- to plan services that make the best of limited NHS budgets,
- to monitor the safety of drugs and treatments,
- and to compare the quality of care providers in different areas of the country.

Regardless of the question if the program was managed well or not, the experience shows which type of acceptance problems projects like these can encounter. An opt-out model was implemented where individuals were being informed that data on their health may be uploaded to HSCIC unless they objected, but the opt-out option was unclear. It was seen as a major problem that it was impossible for a patient to determine what the data will be used for, i.e., it was impossible to limit the use only for medical research by excluding insurance companies and pharmaceutical industry. Another issue was that the data was pseudonymized, i.e., a unique identifier was used and the re-identification might be easy. People were worried that data was made accessible to consulting companies like McKinsey or PWC as well as pharmaceutical companies, like AstraZeneca. There was also concern that the police could access the data.

In October 2014 the program was review by the Cabinet Office Major Projects Authority and it was concluded that the it had “major issues with project definition, schedule, budget, quality and/or benefits delivery, which at this stage do not appear to be manageable or resolvable”.

F. Incentive Programs

The wording is dramatic: Some argue that healthcare is undergoing the most significant changes in its history, driven by the spiraling cost of care, shifting reimbursement models, and changing expectations of the consumer. Reforming the health system to reduce the rate at which costs have been increasing while sustaining its current quality might be critical to many industrialized countries. An aging population and the emergence of new, more expensive treatments will accelerate this trend.

It has been argued that by far the greatest savings could be achieved by population wide healthier lifestyles, which would largely prevent cardiovascular diseases and chronic conditions like diabetes. Chronic conditions account for an astounding 75% of healthcare costs in the U.S. [65], [66]. There is some hope that the proliferation of fitness and health apps might be greatly beneficial to population health.

Population health management tries to improve the situation by different measures as a value based reimbursement system causing providers to change the way they bill for care. The goal is to align incentives with quality and value. Instead of providers being paid by the number of visits and tests they order (fee-for-service), their payments are increasingly based on the value of care they deliver (value-based care). For those providers and health systems that cannot achieve the required
scores, the financial penalties and lower reimbursements will create a significant financial burden.

An important instrument in the U.S. is the HITECH act. The Health Information Technology for Economic and Clinical Health Act, abbreviated HITECH Act, was enacted under the American Recovery and Reinvestment Act (ARRA) of 2009. Under the HITECH Act, the United States Department of Health and Human Services (HHS) is spending several tens of billions of U.S.-dollars to promote and expand the adoption of health information technology to enable a nationwide network of electronic health records (EHRs). This can then be the basis for informed population health management and for improving health care quality, safety, and efficiency, in general.

The general goals are to improve care coordination, reduce healthcare disparities, engage patients and their families, improve population and public health, by ensuring adequate privacy and security.

The implementation is in three stages. An organization must prove to have successfully implemented and used a stage for a minimum of time before being able to move to a higher stage. If stages are successfully reached financial incentives in Medicaid and Medicare are being paid. If stages are not reached, financial penalties can be implemented in both systems.

In Stage 1, the participants do not only need to introduce an EHR but also need to demonstrate their meaningful use. The core set of requirements include the use computerized order entry for medication orders, the implementation of drug-drug, and drug-allergy checks, the implementation of one clinical decision support rule and protect electronic health information (privacy & security).

Stage 2 introduces new requirements, such as demonstrating the ability to exchange key clinical information between providers of care and patient-authorized entities electronically. Health information exchange (HIE) (see Section [III]) has emerged as a core capability for hospitals for stage 2.

Stage 3 of meaningful use is shaping up to be the most challenging and detailed level yet for healthcare providers. Among the elements are additional quality reporting, clinical decision support and security risk analysis. The Stage 3 rule lists clinical decision support as one of the eight key objectives. Unlike the Stage 1 which required one clinical decision support rule, Stages 2 and 3 specifically require the use of five clinical decision support interventions.

There has been criticism of HITECH related to the increased reporting burden and the focus on reporting requirements and not on outcomes.

The HITECH act provides many opportunities for data mining and text mining, for example in the development of certified tools which provides evidence that a provider is fulfilling the various meaningful use criteria.

Other incentive programs have been put in place as well. For example the Centers for Medicare & Medicaid Services (CMS) provide incentives via the Hospital Readmission Reduction Program (HRRP). Incentives are paid if patients are not admitted to the same clinic within 30 days of release.

The New York State Department of Health has instituted the Delivery System Reform Incentive Payment Program (DSRIP: http://www.health.ny.gov/health_care/medicaid/redesign/docs/dsrip projectfactsheet.pdf) with the goal of transforming NY Medicaid healthcare delivery to reduce avoidable hospitalizations by 25%. More than $8 Billion will be paid out in incentive and infrastructure payments to 25 Preferred Provider Systems (PPSs) provided they meet this ambitious goal in 5 years.

The 25 PPSs are each geographically-local networks of varying size (from 100+ to near 500+) different medical entities of varying sizes (hospitals, physician practices, imaging centers, SNFs, rehab, hospice, etc.) who would normally compete for patients, but have voluntarily come together to form trusted health networks (i.e., a PPS), and have agreed to share patient data and coordinate patient care to improve patient care and experience through a more efficient, patient-centered, and coordinated system. The PPSs have “signed up” for different targeted programs (e.g., targeting mental health, fetal-maternal health, diabetes, pediatric asthma, etc.) depending on community health assessments they performed in their area.

Although population health management might seem to be slow moving and bland if compared to the more visible precision medicine initiatives, it has recently been argued, that the impact of the former might me dramatically greater, if one looks at the current state of the art [67], [68]. Looking at diabetes, precision medicine may help a few scattered patients in the right clinical trials to tackle their Type 1 diabetes, but it may not prevent the 28 percent of undiagnosed Type 2 diabetics from experiencing adverse effects from a lack of treatment the way a robust risk stratification and predictive analytics program might.

G. Data privacy, De-identification and HIPAA

Data breaches in the medical industry happen more often than expected [11]. A wake-up call was the February 2015 cyber attack on Anthem Health, which affected the personal information of 78.8 million people. Health care information has considerable value in the back market. Since, in general, even a major data breach does not affect revenue, organizations have few incentives to invest in digital security; thus, regulations are introduced to encourage security measures.

The storage, access and sharing of medical and personal information of any individual is addressed in the HIPAA Privacy Rule. The HIPAA Security Rule outlines national security standards to protect health data created, received, maintained or transmitted electronically. The latter is also known as ePHI (electronic protected health information) [69].

The HITECH Act supports the enforcement of HIPAA requirements by introducing penalties of health organizations that violate HIPAA Privacy and Security Rules. Any company that deals with protected health information (PHI) must ensure that all the required physical, network, and process security measures are in place and followed.

V. THE PATIENT IN CHARGE

Patients become more active in taking charge of their own health and by doing so they leave traces that can be analyzed to better understand population health and health concerns. On the down side, public traces can also be used to the patients’ disadvantage and there is an increasing worry about bullying patients.
A. Leaving Traces

Web-based search is part of nearly everyone’s life and is also the preferred venue to find out about one’s health issues. Health related research often starts with Wikipedia, which is frequently consulted on health issues by both patients and health professionals. Wikipedia is undoubtedly an important source of information although quality issues have been raised [70]. There are a number of health specific portals (e.g., netdoctor, healthline, Yahoo Health, WebMD, whatnext.co and RevolutionHealth), some of which are managed by leading healthcare providers such as the Mayo Clinic and the Cleveland Clinic.

Other web services help patients find the right provider for their problems. Among them are commercial resources like Healthgrades and ZocDoc as well as government resources such as Medicare’s Hospital Compare site. One can observe an increasing willingness to “shop for health” leading to the question of which company would become the Amazon of healthcare.

As the general population, patients are increasingly active in social networks like Facebook and various blogs. In addition there are a number of social network services addressing specific health issues [71]. The motivation is obvious: Patients with the same problems want to communicate and exchange information. Problem-specific communities are organized by commercial and noncommercial web portals and special services can be provided to these groups by third parties.

B. Analyzing Traces

Statistics on anonymized search query logs and traces in social media can be analyzed to inform public health, epidemiologists and policy makers, and can support the early detection of epidemics, the analysis and modeling of the flow of illness and other purposes [72]. Infodemiology is a new term standing for the large-scale analyses of anonymized traces and can potentially yield valuable results and insights that address public health challenges and provide new avenues for scientific discovery [72].

A widely discussed example is the analysis of search query logs as indicators for disease outbreaks. The idea is that social media and search logs might indicate an outbreak of an infectious disease like a flu immediately, including detailed temporal-spatial information of its spread. Previously, such outbreaks might go unnoticed for days of even weeks. But models have proven difficult. Google flu for example, predicted well initially but the fit was very poor later [73], [74].

Another application is the detection of adverse drug reactions, which could be improved by jointly analyzing data from the U.S. Food and Drug Administration’s Adverse Event Reporting System, anonymized search logs and social media data [72]. The analysis of patients’ traces has increasing importance in pharmacovigilance, which concerns the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.

Still there is little experience yet in the quality, reliability and biases in data generated from Web query logs and social network sites and conclusions should be drawn with great caution [75], [76].

However, the same traces, when re-identified, can be aimed at making inferences about unique individuals that could be used to infer patient’s health status. Many dangers are associated, e.g., with social scoring in healthcare. Reference [72] reports on a Twitter suicide prevention application called Good Samaritan that monitored individuals’ tweets for words and phrases indicating a potential mental health crisis. The service was removed after increasing complaints about violations of privacy and imminent dangers of stalking and bullying. As pointed out by [72], health issues can also be inferred from seemingly unrelated traces. Simply changing communication patterns on social networks and internet search might indicate a new mother at risk for postpartum depression.

Another issue is that some companies are working together with analytic experts to track employees’ search queries, medical claims, prescriptions and even voting habits to get insight into their personal lives [72]. Although HIPAA legislation forbids employers to view their employees’ health information, this does not apply to third parties. A company which received public attention is Castlight, which gathers data on workers’ medical information, such as who is considering pregnancy or who may need back surgery [5]. Castlight’s policy is to only inform and advice the individuals directly and only report statistics to employers.

These issues are increasingly addressed by regulators, e.g., in the US by the Americans with Disabilities Act (ADA) and the Genetic Information Non-Discrimination Act (GINA). [72] points out the technical difficulties in protecting the citizens against violations, in the face of powerful machine learning algorithms which can “jump categories”: Machine learning can enable inferences about health conditions from nonmedical data generated far outside the medical context [72].

C. PatientsLikeMe

An openly commercial social network initiative is PatientsLikeMe [78], [79] with several hundred thousands of patients using the platform and addressing more than a thousand diseases. The majority of users have neurological diseases such as ALS, multiple sclerosis and Parkinson’s, but it has been moving into AIDS and mood disorders [80], [81].

PatientsLikeMe is not merely a chat board with self-help news but also collects quantitative data. It has designed several detailed questionnaires it circulates regularly to its members. For example, epileptics can enter their seizure information into a seizure monitor. It has a survey tool to measure how closely patients adhere to their treatment regimen, but also scans language in the chat boards for alarming words and expressions. PatientsLikeMe offers different services. For example, it created a contrast sensitivity test with the Massachusetts Eye and Ear Hospital for people with Parkinson’s and the hallucinations that come with mood disorders. The stated goal is the realization of a learning health care system.

The business model of PatientsLikeMe is not based on advertising. Instead, the company has based its business model

\[\text{http://www.castlighthealth.com/}\]
around aligning patient interests with industry interests, i.e., accelerated clinical research, improved treatments and better patient care. To achieve these goals, PatientsLikeMe sells aggregated, de-identified data to its partners, including pharmaceutical companies and medical device makers. In this way, PatientsLikeMe aims to help partners in the healthcare industry better understand the real-world experiences of patients as well as the real-world course of disease. Some of PatientsLikeMe’s past and present partners include UCB, Novartis, Sanofi, Avanir Pharmaceuticals and Acorda Therapeutics.

D. Managing Your Own Data

Consumers might not only want to research their health issues and communicate with others, but also possibly manage their own data.

If patients take responsibility for their own data, they must be able to store, manage and control the access to their data. By nature, this would overwhelm the patient’s capabilities and commercial and noncommercial services realize some of necessary functions. The core is a personal health record (PHR) which is a patient centered assembly of all personal health information.

Among the earliest offerings is the Microsoft HealthVault, which addresses consumers who want to manage their own or their family’s health. The HealthVault permits the storage and consolidation of a patient’s life health information and permits the patients to give access to this information to selected parties. For example, the HealthVault keeps digital records of children’s immunization records or a user’s medical imaging results and displays them to authorized parties whenever wanted. Doctors can send data and files right into an individual’s HealthVault account. The site lets the users generate letters that the user can give to their healthcare professionals, outlining instructions and security and encryption details. As discussed in the next section, a lot of healthcare and fitness related data are produced by mobile devices and services like the HealthVault offer convenient functionalities for managing, storing and analyzing those data. The World Medical Card and WebMD also has related services.

Naturally, due to privacy issues and their distributed nature, PHRs are difficult to use as part of an analytics project; nevertheless the rich information in a PHR can be used in a personalized advisory and alarming system.

VI. CONTINUOUS HEALTHCARE

With the tremendous growth in prevalence and the technological progress mobile devices have made recently, the disruptive potential of mobile health and more general technology enabled care is frequently discussed. A new generation of affordable sensors is able to collect health data outside of the clinic in an unprecedented quality and quantity. This potentially enables the transition from episodic healthcare, dominated by occasional encounters with healthcare providers, to continuous healthcare, i.e., health monitoring and care potentially anytime and anywhere! Continuous healthcare certainly has the potential to create a shift in the current care continuum from a treatment-based healthcare to a more prevention based system. At a first glance this seems like a distant goal but many health problems can be prevented by a healthy lifestyle and the early detection of disease onset, in combination with early intervention. However, the full potential remains to be unlocked as a 2012 Pew Research Center study about mobile health reveals. While about half of smartphone owners use their phone to look up health information, only 1 in 5 smartphone users own a health app. Currently this exciting field is in a flux and opportunities, challenges and crucial factors for the widespread adoption are discussed in current research.

A. Technological Basis

The technological bases of mHealth includes smart sensors, smart apps and devices, advanced telemedicine networks such as the optimized care network and supporting software platforms. There is a broad range of new devices that have entered the market: smartphones, smart watches, smart wrist bands, smart head sets and Google Glass, among others. In the future, patient-consumers might use a number of different devices that measure a multitude of different signals: “headsets that measure brain activity, chest bands for cardiac monitoring, motion sensors for seniors living alone, remote glucose monitors for diabetes patients, and smart diapers to detect urinary tract infections”. This possibility has led to development of so called Body Area Networks (BANs) another form of technological enabler are sensors that measure physiological signals, physical activities, or environmental parameters and come along with an internet like infrastructure. BANs are used to monitor cardiac patients and help to diagnose cardiac arrhythmias. Add-ons to mobile devices such as lab-on-a-chip technologies are particular interesting technologies and might represent a new form of point-of-care devices. Reference presents a laboratory-quality immunoassay that can be run on a smartphone accessory and reference presents a 3D printed attachment for a smartphone for the detection of sickle cell disease. Especially for developing countries with a limited infrastructure the potential of such technologies is huge.

From an engineering perspective, this is equivalent to condition monitoring and predictive maintenance, enabled by smart sensors, connectivity and analytics — a combination often referred to as the internet of things (IoT). By measuring and aggregating the signals of many different persons, machine learning algorithms can be trained to detect e.g. anomalies and unexpected correlations that generate new insights. Again open source initiatives such as the Open mHealth initiative are important enablers that could pave the way to overcome the data integration challenge.

B. Selected Use Cases

1) Disease prevention: Smartphones are increasingly being used for measuring, managing and displaying health and

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6http://www.optimizedcare.net/
7http://www.openmhealth.org/
lifestyle related parameters such as weight management, physical activity, smoking, and diabetes among others. Improving lifestyle and fitness of the general population has the potential to reduce healthcare costs dramatically and thus this type of health monitoring might have dramatic positive impact on population health and health cost reduction. In a recent scientific statement, the American Heart Association (AHA) reviews the current use of mobile technologies to reduce Cardiovascular Diseases (CVD) risk behavior [93]. CVD continues to be the leading causes of death, disability and high healthcare costs [93] and is thus a prime example for investigating the potential of mHealth technologies to reduce CVD risk behavior. The work investigates different tools available to consumers to prevent CVD ranging from text messages (e.g. smoking cessation support), wearable sensors, and other smartphone applications. While it becomes quite clear that more evidence and studies are needed that investigate the effectiveness of these technologies, the results can be seen in a way that mHealth in CVD prevention is starting to achieve promises. Finally, the AHA strongly encourages as future direction to conduct more research in this direction in order to create further evidence.

2) Early detection: Many diseases can be treated best when discovered early and before they cause serious health consequences. Early detection can happen at the population level or at the individual level. Reference [83] highlights an early warning system for disease outbreaks caused by illness related parameters such as environmental exposure or infectious agents. On the individual level, the previously mentioned Body Area Networks represent a major enabler for early detection of abnormalities. So-called smart alarms can be understood as another form of early detection on the individual level. Smart alarms cover a range of applications and especially the elderly can profit from it. It ranges from monitoring heart activity, breathing, and potential falls [90].

The company AliveCor is offering a mobile ECG that is attached on a mobile device (either smartphone or tablet). The attached device creates an ECG that is then recorded via an app. The ECG is cleared by the FDA and can also detect atrial fibrillation a leading cause of mortality and morbidity. AliveCor states the device has been used to record over five million ECGs. The ECGs are used to train a machine learning algorithm to detect the previously mentioned anomalies such as atrial fibrillation.

3) Disease Management: Healthcare costs can be reduced when the patient can be monitored at home instead of in the clinic and if physicians can optimize care without the need to call in the patients for a medical visit. Some hospitals and clinics collect continuous data on various health parameters as part of research studies [11]. Especially the management of chronic diseases can benefit from continuous healthcare. In a recent review [94] the authors screen systematically for randomized clinical trials that give evidence about better treatment adherence when using mHealth technologies. The type of applications range from simple SMS services to video messaging with smartphones to other wireless devices. They conclude that there is without doubt high potential for these technologies but as the evidence in the trials was mixed, further research is needed in getting better understanding in improving usability, feasibility, and acceptability.

4) Support of translational research: With hundreds of millions of smartphones in use around the world, the way patients are recruited to participate in clinical studies might change dramatically. In the future patients might be able to decide themselves if they want to participate in a medical study and they might be able to specify how their data will be used and shared with others.

Major research institutions have already developed apps for studies involving asthma, breast cancer, cardiovascular disease, diabetes and Parkinson’s disease. One interesting use case in that space is the control of disease endpoints in clinical trials with mHealth technologies. As a concrete example Roche developed an app to control or measure the clinical endpoints of Parkinson disease [9]. The app, which complements the traditional physician-led assessment, is currently used in a Phase I trial to measure in a continuous way disease and symptom severity. The app is based on the Unified Parkinson’s Disease Rating Scale (UPDRS) which is the traditional measurement for the disease and symptom severity. The test which takes about 30 seconds investigates six endpoint relevant parameters such as a voice test, balance test, gain test, dexterity test, rest tremor tests and postural tremor.

The Clinical Trials Transformation Initiative [10], an association representing diverse stakeholders along the clinical trial space works on the next generation of clinical trials. Recently, the initiative has launched a mobile clinical trials program to investigate how mobile technologies and other off-site remote technologies can further facilitate clinical trials.

C. Implications for the clinical setting and doctor’s offices

Some hospitals and insurers have already recognized the willingness of patients to use telemedicine services [95] and thus are offering video consultations – a contemporary “house call” – to patients via Skype and other internet conferencing systems. “In the way that video calls and instant messaging revolutionized the way people communicate with others, now health systems are exploring how e-health consultations for routine ailments can relieve the pressure on primary care systems that are functioning beyond capacity,” Blumenthal writes [11]. Some patients find these e-visits to be cheaper and more convenient. About 55% of patients recently asked in a survey would send a photo of their skin to a dermatologist for consultation [11]. Researchers say more evidence is needed to understand if virtual medical visits will actually reduce costs or improve health outcomes. But the demand among patient-consumers is there and some large insurers have begun to pay for these virtual consultations [11].

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8http://www.alivecor.com/

9http://www.roche.com/media/store/roche_stories/roche_stories-2015-08-10.htm

10http://www.ctti-clinicaltrials.org/

11http://www.pwc.com/us/en/health-industries/healthcare-new-entrants/assets/pwc-hri-new-entrant-chart-pack-v3.pdf
D. Regulatory implications

The recent growth and increased popularity of mHealth applications in combination with questions of regulatory oversight of these has created a sphere of action where many different stakeholders have to align with each other. The continuous healthcare ecosystem has brought together stakeholders that were previously more or less unconnected and now have to interact. For instance in the US, certain app developers have suddenly to deal with premarket notification or so-called 510(k) clearance processes from the FDA. The driving question here is which type of mHealth applications fall under FDA’s jurisdiction over medical devices. Indeed different classifications of "mobile medical applications" and according FDA guidance now exist, but they still seem to be a moving target.

While the FDA wants to ensure to take care of their public health responsibility to oversee the safety and effectiveness of medical devices (including also certain types of mobile apps), some politicians and industry representatives are afraid that innovation is hampered by regulatory oversight. However, first warning letters to doctor’s had to be sent out where mobile medical apps showed unexpected behavior and another case revealed that about 52 adverse event reports were generated for one specific diabetes app within two years [96]. This supports the fact that further intensive dialogue between stakeholders is needed. [96] describe in detail the challenges that come along with the regulation of mHealth technologies and provide potential alternative regulatory scenarios.

E. Selected Projects

Many different projects have been started involving clinics, research institutes and technology providers. In a recently started pilot between the MD Anderson Cancer Center and Polaris Health, Apple watches will collect data from breast cancer patients [97]. The Apple watches will capture behavioral data that could affect the outcomes of treatment. According to a Polaris statement, data to be collected includes side effects, information about sleep behavior, levels of physical activity, and patient mood that could affect patients’ treatment and outcomes. Researchers will combine this information with electronic health record data from the patients and health data of other breast cancer patients to create new insights.

Another example shows the potential for developing countries. Medic Mobile [13], a non-profit technology company has developed a software platform that is used in 23 countries in Africa, Latin America, and Asia to improve care in rural areas. The use cases of the platform range from antenatal care, childhood immunization, disease surveillance, and drug stock monitoring. For antenatal care the organization report on their homepage that approximately 500,000 people have been covered in the countries Bangladesh, Kenya, and Nepal. Over 1.800 community health workers are using their smartphones to register women in a central database once they are pregnant. Automated text messages are sent to organize appointments and health workers can register any potential danger signs.

Japan Post one of Japan’s largest insurers join forces with IBM and Apple to address issues of an aging generation [98]. They will be designing app analytics and cloud services around the iPad to help to connect millions of seniors with their families but also to healthcare services. The project will help Japan Post, which already has a massive Big Data-style collection of health care information, to both know more about its customers and to improve the health and wellness of its seniors, thus allowing customers to live potentially longer, healthier and more independent.

Communities have been established that even try to put their lives into data. The Quantified Self movement [99] uses sensors to put a person’s daily life into data by self-tracking biological, physical, behavioral or environmental signals. The community is supported by a company of the same name [10].

F. Conclusion

In conclusion, the potential benefits of continuous healthcare are tremendous. Of course many challenges remain: will it be possible to solve major issues with data privacy? Will it be possible to maintain population interest in the long run or are health apps just a temporary phenomenon? Will there be reimbursement structures for mHealth? How many enterprises will find long term sustainable business models? Will we overcome the data integration challenge such that we can bring clinical meaning to digital health data?

VII. GETTING PERSONAL

A. Precision Medicine is Changing Healthcare

Maximizing the positive effect of a healthcare intervention and concurrently minimizing adverse side effects has always been the dream of individualized healthcare. Over the last decades it became clear that this goal cannot be achieved with insights from conventional studies alone, which have been focusing on empirical intervention efficacy and side effects in large patient study groups. The reason is that, due to the biological diversity of individuals, environment and pathogenesis, any incident of a complex disease is like no other. This leads to the “n=1” principle, meaning that therapy should be tailored to the patient’s individual characteristics, realizing, what has been called, precision medicine [11]. In this article we will use the term precision medicine interchangeably with personalized or individualized medicine. Precision medicine refers to the idea to customize healthcare — with medical decisions, practices, and procedures being tailored to similar patient groups or even to the individual patient. Many times molecular patient or disease characteristics are the basis of a patient or patient group characterization.

Without question, the most important milestone for the realization of a personalized medicine was the publication of the reference sequence of the human genome about 15 years ago [101], [102]. In the following years, the patient’s and the disease’s genomic profile supplemented with other molecular and cellular data became the basis for a dramatic progress in

12https://medicmobile.org/
13http://quantifiedself.com/
14Another term sometimes used is the “unique disease principle” [100].
the understanding of the molecular basis of disease. But the impact of this knowledge is not limited to the understanding of the genome, the healthy biological function or the malfunction in a disease: As new analytical methods like next generation sequencing (NGS) and new proteomic platforms bring cost down, in the near future, molecular data will increasingly become part of clinical practice.

The main goal must be the connection of data to clinically relevant and usable information. The more data is available the more complex phenomena and less strong associations can be discovered and validated. As a matter of fact, research and clinical applications go along with a huge increase in the volume and variety of data available to characterize the physiology and pathophysiology: In personalized medicine one needs to learn from large sets of high-dimensional data to develop new insights, e.g., in genome-wide association studies (GWAS), and many patient dimension need to be known, stored and handled in the future to realize the full potential of precision medicine in clinical practice. The vision of a real time personalized health care is the rapid and real-time analysis of biomaterials obtained from the patients based on newest research results in a network of research labs and clinics.

By far the greatest efforts in precision medicine have been devoted to cancer (oncology), but precision medicine becomes increasingly relevant to other medical domains, e.g., the central nervous system (e.g., Alzheimer and Depression), immunology/transplant, pre-natal medicine, pediatrics, infectious diseases and cardiovascular.

B. Understanding Disease on a Molecular Level

Much attention in recent years has been focusing on the genetic cause of disease.

Monogenetic disorders with a high penetrance have been linked to mutations of single genes in inherited genes. The causative genes of most monogenic genetic disorders have now been identified.

Monogenetic diseases are relatively rare and attention has shifted largely to complex diseases: Most common diseases, including most forms of cancer, are based on an interaction of several factors including a number of inherited genetic variations, one or several mutations acquired during cell life time, as well environmental factors. Consider, for example, that worldwide approximately 18% of cancer deaths are related to infectious diseases. Due to the complex interplay of several factors, these diseases show, what has been termed, “missing heritability”.

Insights into inherited genetic cell disorders are obtained from germline DNA, typically obtained from blood cells. Genome wide association studies (GWAS) examine the correlation between germline genetic variations and common phenotypic characteristics, such as breast cancer. With next generation sequencing (NGS) there is potential to decode the complete genome for costs in the order of a few hundred U.S. dollars. This is expected to increase the insight into which diseases can be explained by genetic variance and could revolutionize molecular medicine for some diseases.

Additional genetic variations of interest are those acquired during the lifetime of somatic cells, which comprise all cells that form an organism’s body, excluding the germ cells. As genetic alterations accumulate, the somatic cell can turn into a malignant cell and form a cancerous tumor. Genetic profiles (mutations and amplifications) of somatic cancer cells are obtained from analyses of tumor biopsies. Their distinct mutation and gene amplification pattern is linked to many clinically relevant characteristics, such as prognosis or therapy response. In some cases the tumor is easily accessible, however in other cases like tumors or metastases of certain organs (e.g. brain, liver, lung) a biopsy is not standard of care. In those cancer patients the access to the material, from which the genomic information could be obtained is difficult. Recently, novel methods have been developed that permit the analysis of alternative sources of tumor material, such as circulating tumor cells (CTCs). These are cancer cells that have shed into the blood stream from a primary tumor. CTCs can constitute seeds for subsequent growth of additional tumors (metastasis) in distant organs, triggering a mechanism that is responsible for the vast majority of cancer-related deaths. CTCs thus could be considered a “liquid biopsy”. Also circulating tumor DNA (ctDNA) was found to resemble the tumors genomic profile, being useful for cancer detection and prediction of therapy efficacy.

The transcription of RNA from DNA is called gene expression. This step plays a crucial functional role, because RNA is translated directly into functional proteins. Furthermore RNA has regulatory functions, of which many are not yet understood. In some cancers such as breast cancer the expression of few genes has already been proven to be of great clinical relevance such as estrogen receptor and the HER2 oncogene. With methods becoming available, that give access to genomewide gene expression analyzes whole gene expression profiles have been used to characterize cancer diseases. Transcriptomics is the study of transcriptomes (RNA molecules, including mRNA, miRNA, rRNA, tRNA, and other non-coding RNA), their structures and functions. DNA microarrays (which, despite their name, really test for RNA) and RNA-seq (RNA sequencing) can reveal a snapshot of RNA presence and quantity cellular activities at a given moment in time: From RNA levels one can conclude which proteins are currently being generated in a cell, however not, whether these proteins have functional role in the cell, the organ or the disease.

Whereas the genome contains the code, the proteins are the body’s functional worker molecules. Several methods like immunohistochemistry, and enzyme-linked immunoassays (ELISA) are used in clinical practice. In research and recently also in clinical tests, mass spectroscopy is used to determine many proteins in a tissue, opening this field for high throughput and big data approaches. Increasingly also protein microarrays are used as a high-throughput method to track the interactions and activities of many proteins at a time as well.

While the transformation of genetic information into functional proteins is well researched with regard to clinical relevance, other „omics“ fields are yet to be implemented into scientific and clinical models. Epigenomics, Metabolomics and...
Lipidomics are three further levels of systems biology which might be unraveled by big data analyses. Epigenetic changes modify genes on a molecular level, that expression is altered and becomes more difficult. Metabolomics concerns chemical fingerprints that specific cellular processes leave behind, in particular, the study of their small-molecule metabolite. Lipidomics focuses on cellular lipids, including the modifications made to a particular set of lipids, produced by an organism or system.

The environment is increasing the number of possible interactions that play a role in the etiology (i.e., disease cause) and pathogenesis of a disease. The exposome encompasses the totality of human environmental (i.e., non-genetic) exposures from conception onwards, complementing the genome. For example, scientists believe that, for most people, Alzheimer’s disease results from a combination of genetic, lifestyle and environmental factors that affect the brain over time. Less than 5 percent of the time, Alzheimer’s is caused by specific genetic changes that, by itself, virtually guarantee a person will develop the disease.

As a medical field, molecular medicine is concerned with the molecular and genetic problems that lead to diseases and with the development of molecular interventions to correct them. A better understanding of the underlying molecular mechanisms of diseases can lead to great advances in diagnostics and therapy. In particular, cancer subgroups can be determined by omics profiles and the most effective treatment with smallest adverse effects can be determined for each subgroup. This concept is at the center of precision medicine.

To give insight in what is clinically relevant today let’s look at the concrete example of breast cancer. Molecular techniques have both changed our understanding of the basic biology of breast cancer and provide the foundation for new methods of “personalized” prognostic and predictive testing. Several molecular markers are already established in clinical practice such as high penetrance breast cancer causing genes (BRCA1 and BRCA2). Also the characterization of the tumor is driven by molecular markers such as estrogen receptor, progesterone receptor and a genetic alteration, the HER2 amplification. All of these characteristics are well known from times before high throughput molecular analysis or the achievement of genomewide data approaches. The biological signal of those markers were all strong enough to be discovered each at a very early time. Now, more than 15 years after the primary publication of the human genome all different levels of biology (DNA, RNA, Protein, Epigenetics, miRNA, …) can be analyzed in a reasonable amount of time revealing much more detailed and comprehensive insight into the biology of a cell including single gene functions and pathways as an interaction of whole groups of proteins and regulatory mechanisms. The Cancer Genome Atlas for example was one of the first big data analyses, which compared the genetic information of the tumor with the genetic information of the blood on a large scale for each single of the three billion base pairs. This project could, for the first time describe systematically, which genes will mutate in the course of the pathogenesis of a healthy mammary cell to a breast cancer cell.

C. Molecular Diagnostics and Therapy

In molecular diagnostics “biomarker” refers to any of a patient’s molecules that can be measured to assess health and can be obtained from blood, body fluids, or tissue. Biomarkers are of central importance and biomarker testing is at the center of personalized medicine and are specific, e.g., to DNA, RNA or protein variations. Biomarker tests may also test if certain proteins may be overactive, in particular if they help to promote cancer growth. A companion diagnostic is a diagnostic test (biomarker) used as a companion to a therapeutic drug to determine its applicability, e.g., efficacy and safety, to a specific patient. Companion diagnostics are co-developed with drugs to aid in selecting or excluding patient groups for treatment with that particular drug on the basis of their biological characteristics that determine responders and non-responders to the therapy.

A therapy may be based on the identification of a molecule (a drug target), often a protein, whose activity needs to be modified by a drug. Pharmaceutical research tries to find drugs, so called targeted drugs that bind to the harmful protein with the goal of making it less harmful. Targeted drugs are typically small-molecule drugs (ligands).

Targeted therapy is one of the newest categories of cancer drugs and there are a number different strategies. For example, antibodies might be generated (so called monoclonal antibodies) which are man-made versions of large immune system proteins that bind to very specific target proteins on cancer cell membranes. Some targeted drugs block (inhibit) proteins that are signals for cancer cells to grow. Drugs called angiogenesis inhibitors stop tumors from making new blood vessels, which greatly limits how big they can grow. Immunotherapy is treatment that uses the body’s own immune system to help fight cancer, e.g., uses the patient’s immune system to attack those cells. For example the protein HER2 is a member of the human epidermal growth factor receptor family and its overexpression plays an important role in certain forms of breast cancer. HER2 is the target of the monoclonal antibody trastuzumab.

D. Implementing Precision Medicine

Precision medicine in the post-genomic era faces many challenges. The implementation of precision medicine will require changes and improvements on many levels. Fields, that have to be concerned with reach from technology development (one genome can comprise up to 400GB of data) over social and ethical challenges to legal implications and the need

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10http://www.genome.org/27541319
11http://www.mayoclinic.org/diseases-conditions/alzheimers-disease/basics/causes/con-20023871
12Reality is even more complex: there is even heterogeneity within a particular tumor. The hypothesized cancer stem cell model asserts that within a population of tumor cells, there is only a small subset of cells that are tumourigenic (able to form tumours). These cells are termed cancer stem cells (CSCs), and are marked by the ability to both self-renew and differentiate into non-tumourigenic progeny (cancer stem cell model). In the natural selection in cancer model, one assumes a process of natural selection within a given tumor which also would explain why cancer is so difficult to fight: a treatment might eliminate one strain giving room for another strain to develop.
19http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/
for large scale educational programs for patients, physicians, researchers, health care providers, insurance companies and even politicians [114]. The abundance of data and possibilities to connect information now and in the future raises the question, whether current rules for intellectual property, reimbursement and personal privacy have to be adapted to regulate the problems and chances that come with the changes of personalized medicine. Regulatory authorities have already acknowledged those challenges and released a report (“Paving the Way for Personalized Medicine: FDA’s role in a New Era of Medical Product Development.”) [115]. In this report the FDA described a plan, how to integrate genomic medicine into clinical practice and drug development. Steps to implement precision medicine include the development of regulatory scientific standards, research methods, reference material and other tools [115]. Implementing and even commercializing precision medicine will demand new standards with regard to protection of patients and the patient’s family’s privacy. Questions arise especially for healthy individuals who have genetic predisposition for a disease or patients who have a genetic alteration (either germline or somatic) and who are thought to be non-responsive to standard treatments. Until a clear benefit for those persons is established, this data will have to be protected. In some cases the person, for which the molecular data is created, might not want to know the complete extent of an interpretation of those results. The Genetic Information Nondiscrimination Act (GINA) was passed in this context. It aims at the reduction of the fear of patients who are participating in genetic research. It has to be clear, that a patient’s genomic information will not be misused by employers, insurers or other stakeholders. Recently in cancer patients sequencing the full patient’s and tumors genome has become closer to standard healthcare, with a firsts insurer covering the costs of such a test [20].

E. First steps towards an “n=1”-medicine by big data approaches

Dramatic improvements in the quality and speed of genomic sequencing and analysis as a clinical diagnostic tool for individual patients combined with the innovations propelling immuno-oncology are paving a new era for truly personalizing the treatment of cancer. At the heart of this new hope is the newfound ability to rapidly identify and target tumor cells with specific DNA mutations unique to each cancer patient. The products of mutated genes encoding altered proteins are so-called “neoepitopes” and serve as the molecular address to direct and redirect immune cells for killing and to procure long term immunity. Neoepitopes are defined as unique mutations found specifically in a patient’s tumor (not normal tissue) that can be targeted by the immune system to attack the tumor with minimal off target toxicity. Also it is highly unlikely that the same neoepitopes occur in other patients, and if so only in small group of patients. Therefore a possible treatment of neoepitopes with a medicine that is manufactured real-time is a real-life example of “n=1” medicine [116], [117].

Identifying neoepitopes for each patient is made possible by high-throughput whole genome or exome sequencing and by the direct comparison of abnormal tumor DNA with each patient’s own normal DNA. The former widens the search for drugable targets (neoepitopes) in the >99% of the genome deemed untargetable or unimportant by panel sequencing. The latter reduces the significantly high false positive error rates associated with tumor-only sequencing techniques [118]. Precision in individualizing treatments targeting neoepitopes further requires confirmation of the expression of mutated genes, thus avoiding another potential pitfall of false positive errors, and the potential for the altered protein to induce immunogenicity. As an example, an expressed neoepitope, once confirmed to be presented to immune effector cells such as cytotoxic T-cells by antigen presenting cells, is a molecular address that may be delivered by an immunogenic vehicle, much like vaccination against a pathogen. One such vehicle is the adenovirus which may be engineered to express within its DNA many neoepitopes, and upon injection, can locally infect dendritic cells which then present an identified neoepitope to the immune effector cells. Despite great promise, the use of adenovirus or any other foreign delivery vehicles remains hindered due to the pre-existence or the induction of neutralizing antibodies against them by the patient’s immune system. This limitation has been overcome by engineered adenoviruses which are capable of safely vaccinating and re-vaccinating against hundreds of neoepitopes and tumor associated antigens despite pre-existing immunity against adenovirus [119]. Remarkable results have thus far been published demonstrating the delivery of tumor associated antigens by this engineered adenovirus in a cohort of late-stage colorectal cancer patients [120]. A more recent development has been the engineering and application of T-cells and NK-cells that express antibodies on their surface as part of a “chimeric antigen receptor” (CAR) for direct targeting of tumor cells expressing their cognate antigens. One particular approach, an off-the-shelf human NK cell line dubbed NK-92, is engineerable to produce innumerable CARs. These cells are now being engineered to produce CARs (dubbed taNKs) targeting neoepitopes discovered to be expressed by individual cancer patients’ tumor cells, thus harkening a novel, truly personalized immunotherapeutic approach to fight cancer. For this and many other reasons, the discovery of neoepitopes has the potential to be a watershed moment in the war against cancer. These examples show, that the implementation and utilization of the immune systems includes yet another layer of data, giving first examples of true n=1 medicine. One of the challenges with neoepitope discovery and targeting will be the management of Big Data: teraFLOPS of compute resources in a cloud environment to generate terabytes of sequencing data. Including whole genome and/or whole exome sequencing, RNA sequencing and molecular modeling of immune presentation of neoepitopes. To meet the demands of heterogeneity, analysis and long term storage of data from multiple biopsies for each patient is a further challenge. These activities require compute and storage under HIPAA, and high-speed and large-bandwidth connectivity for transiting sequence data from sequencing labs to supercompute/cloud environment rapidly such that derivation and delivery of neoepitope targeting
platforms is enabled in actionable time for each patient. These challenges require significant infrastructure and resources, but are overcome in private, dedicated Big Data supercompute clouds interconnected by dedicated fiber infrastructure capable of transporting terabytes of data at terabits per second. The latter are implemented for the benefit of financial trading markets, and now have been retrofitted to meet the needs of sequencing analysis and neoepitope discovery.

**F. Big Data in Research**

The aim is to use the newly gained insight into etiology, pathogenesis and progression of diseases for novel treatments and prevention. Large international consortia have been built over the last years including not seldom hundreds of thousands of individuals to compare genetic and environmental information of healthy individuals with diseased patients. Several of those consortia have built super-consortia merging data and biomaterials of several large scale consortia together. One example is the OncoArray Network[21], in which more than 400,000 individuals are genotyped for more than 570,000 genetic variants. Diseases included in this effort are breast cancer, ovarian cancer, colon cancer, lung cancer and prostate cancer. The studies conducted with this data are called “genome wide association studies (GWAS)”. They examine the correlation between germline gene variations and phenotypic characteristics. Most of those studies explain a certain amount of attributable risk for a disease within a population. For the individual the effects are rather small and implementation into healthcare is highly dependent on programmes which would utilize this information in an epidemiological way, i.e. selecting patients for individualized prevention or early detection of a disease. This requires tens if not hundreds of thousands or millions individual decisions in a certain population in order to achieve an effect. This will be another challenge in times of clinical big data application.

One of the problems is that, to achieve this analysis in an empirical approach, huge sample sizes have to be achieved, which is a challenge to achieve a high level of data quality. As mentioned above in the field of molecular epidemiology large consortia and super-consortia have been built including several hundreds of thousands of individuals. As for breast cancer risk factors this effort led to the discovery of around several hundreds of thousands of individuals. As for breast cancer, ovarian cancer, colon cancer, lung cancer and prostate cancer. The studies conducted with this data are called “genome wide association studies (GWAS)”. They examine the correlation between germline gene variations and phenotypic characteristics. Most of those studies explain a certain amount of attributable risk for a disease within a population. For the individual the effects are rather small and implementation into healthcare is highly dependent on programmes which would utilize this information in an epidemiological way, i.e. selecting patients for individualized prevention or early detection of a disease. This requires tens if not hundreds of thousands or millions individual decisions in a certain population in order to achieve an effect. This will be another challenge in times of clinical big data application.

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Combining risk factors and investigating interactions for biological effects or to combine genetic alterations with gene expression or protein function will need even higher sample sizes and approaches, which still have to be developed for the collection of clinical and molecular data. While this in itself is a great challenge there might be even more complex patterns behind the understanding including the plasticity and change of diseases over time. From a molecular standpoint gross molecular pattern can change over time and spatial distribution in the body [122].

The correlation with clinical meaningful data such as treatment response or disease classification is as important as the collection of molecular data of patients and diseases. The alignment of clinical and molecular data in integrative data systems will be one of the next great challenges and improvements using this data for disease understanding and patient treatment.

**G. Digitization Challenges in Precision Medicine**

Recent publications [123], [124] estimate that storage needs for molecular data will exceed by far those of Twitter or YouTube, which is of great concern to researchers and healthcare professionals alike.

This perception is supported by the many large scale population-based initiatives (e.g. the Genomics England 100K project or the NIH precision medicine initiative) that will collect genomic and other biomedical data from individuals the next 5-10 years. A comprehensive and recent overview of these cohort studies from publicly or private funded entities can be found in [50]. The experiences gained from these initiatives will reveal interesting insights and lessons learned about data management of genomic and other ‘omics’ data (e.g. transcriptomics, proteomics, metabolomics, epigenomics), emerging standards, and data privacy topics such as informed consent.

To improve consistently patient outcome and medical value, it will become very important to bridge the gap between all the previously mentioned ‘omics’ data and clinical outcome. Indeed sequencing in the clinics for advanced patient diagnosis is becoming more and more common, but many questions still remain open, e.g. how, where, and what to store from genomic data in the EHR records (see also chapter II)? Here, important consortia such as *emerge* (Electronic Medical Records and Genomics) and *CSER* (Clinical Sequencing Exploratory Research) will hopefully pave the way towards a more integrated view of genomics in the clinic [125]. Structuring, organizing, synchronizing different terminologies across clinical data repositories is the prerequisite to make clinical data meaningful. In that context companies such as Flatiron Health have developed powerful tools and processes to tackle this data integration challenge and offer structured knowledge bases that can yield new insights into the fight against cancer. Therefore data integration concepts such as ontologies will become crucial to organize the clinical data mess.

Aggregating data across many patients for the purpose of learning from their outcome in terms of Clinical Decision Support (CDS) is an active effort. The American Society

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21[http://epi.grants.cancer.gov/ongoarray/]
22[http://datascience.columbia.edu/donate-your-genome-science-learn-more-about-your-ancestry-health]
23[http://www.personalgenomes.org/]
24[https://dna.land/]
25[https://arvados.org/]
26[http://fortune.com/2014/07/24/can-big-data-cure-cancer/]
Among others, Nantworks includes activities on connecting will be a relevant factor in public health. A newly established to implement CancerLinQ \[127]\, \[126]\.

To make CancerLinQ’s vision happen several different data types and technologies have to be orchestrated ranging from longitudinal patient records, cohort analyses, quality metrics to interactive reporting and text analytics \[126]\.

Interoperability between different EHR systems will be another crucial success factor for the CancerLinQ initiative.

Digitization and precision medicine will not only happen in the clinic. With its truly multi-disciplinary character, precision medicine need to serve the patient at any time at any place and will be a relevant factor in public health. A newly established and publicly visible enterprise covering the various dimensions is NantWorks, which consists of several individual companies. Among others, Nantworks includes activities on connecting health data globally (Nanthealth), access to mobile health devices, real-time sequencing, communication infrastructure, secure data and privacy, high speed networks and cloud services. As part of Nantworks strategy many companies have been acquired and have been integrated. Adding another dimension of precision medicine, pharmaceutical R&D will also benefit greatly from digitization in precision medicine. This will include use cases such as smarter clinical trial design, identifying early suitable subpopulations for drug targets (responders vs. non-responders), real time monitoring of patients through mHealth technologies, off-label use for drugs already in clinical use, and ultimately finding new drug targets and biomarkers more efficiently, among others.

Dr. Patrick Soon-Shiong, the driving force behind NantWorks, conveys a vision of healthcare where clinical practice is supported by the newest research results in an interconnected communication network with huge storage capacity and state of the art analytical tools. He was instrumental in forming Cancer MoonShot 2020 coalition with the goal of finding vaccine-based immunotherapies against cancer. The underlying premise is that, “oncologists must learn to be immunologists”.

H. Traditional IT Players are Entering Precision Medicine

The outlined data management and analytics challenges in precision medicine are being addressed by a number of established IT companies. Here are some examples.

SAP has teamed up with American Society of Clinical Oncology (ASCO) to implement CancerLinQ \[127]\, \[126]. SAP’s in memory technology platform SAP HANA will play a crucial role in providing the infrastructure and algorithms to analyze the vast amounts of diverse data to provide clinical decision support.\[27]\.

IBM with its Watson technology \[128]\, \[129] has recently started a collaboration with the New York Genome Center (NYGC) to generate and analyze the exome, complete genome data, and epigenetic data linked to clinical outcomes from participating patients. The partners plan to generate an open knowledge base using the generated data.\[27]\.

Dell is partnering with the Translational Genomics Research Institute (TGen) to tackle pediatric cancer in Europe and in the Middle East. In addition, Dell recently announced that its Cloud Clinical Archive, currently storing over 11 billion medical images and around 159 million clinical studies from multiple healthcare providers, will also support storing and managing genomics data. The long term goal will be to combine medical imaging diagnosis with advanced genomics to impact patient care.

Intel is also looking into the precision medicine space. Saffron, a cognitive computing company that Intel acquired in 2015, is studying how users can gain additional insights from above mentioned Dell’s Cloud Clinical Archive. The company is also offering Natural Language Processing capabilities and the platform can be compared to IBM Watson’s offering. In addition, within the context of Barack Obama’s Precision Medicine Initiative, Intel launched a Precision Medicine Acceleration Program for 2016.\[29]\.

Microsoft also supports the US government’s Precision Medicine Initiative by hosting genomic data sets in Microsoft’s Azure cloud platform by end of 2016 at no additional cost.\[30]\.

Amazon Web Services (AWS) is offering HIPAA-compliant cloud storage and data security offering. Therefore AWS often functions as a backbone of genomics data management platforms and several companies such as Seven Bridges or DNAnexus rely on the AWS technology. As a concrete example the Cancer Genomics Cloud (CGC) which includes the well-known Cancer Genome Atlas (TCGA) is operated by Seven Bridges and runs on the AWS cloud.

Alphabet Inc. is investing heavily in precision medicine. This happens mainly either through the many investments taken by Google Ventures or by own research and development activities from subsidiaries such as Verily or Calico. Investments in companies related to precision medicine from Google Ventures include Flatiron Health, Foundation Medicine, or DNAnexus among others. Selected Google’s initiatives are, e.g., Google Genomics or the Google Baseline Study. Google Genomics is Google’s HIPAA-compliant cloud platform for storing and managing Genomics Data. Besides offering access to publicly available data sets such as The Cancer Genome Atlas (TCGA), customers can load their own genomic data sets and run analyses on the data through the offered API. The Google baseline study aims to collect different types of data such as molecular,
imaging, clinical and data related to patient engagement to understand patterns of healthiness of individuals.

All these efforts illustrate that information technology is moving quickly into personalized healthcare and therefore will be a main enabler to realize the goals of precision medicine. The crucial challenge is to turn these vast amounts of data into knowledge and insights.

I. Outlook

Realizing personalized medicine for every patient globally would result in Big Data challenges of unprecedented scale. Large investments in computing and storage facilities are required and all stakeholders, including patients, doctors, nurses, insurers, lawmakers and the public, need to get involved, educated and trained. Privacy and safety concerns need to be addressed and the general public needs to understand the eventual benefits of a personalized medicine involving Big Data technologies and patient profiling.

Many efforts are underway to strengthen the role of precision medicine. Among them is the President Obama’s “Precision Medicine Initiative” (PMI) [130].

Expectations in powerful joint efforts to fight cancer are great [131].

VIII. Assessments and Conclusions

It is unquestionable that healthcare will experience dramatic changes in the coming years and that digitalization and large-scale data analytics will be among the driving forces. Real-time personalized health care, with enormous potential for a better, more effective, and personalized treatment of cancer and other diseases, will require the acquisition, exchange, storage and analysis of huge amounts of data generated in research and clinical practice. Continuous healthcare (mHealth) will permit the monitoring of patients with chronic problems and will generate data streams to be managed and analyzed in real time. Continuous healthcare has the potential to improve population health and offers new opportunities towards patient health monitoring. Trusted data centers will become an individual’s health memory and support the management of the health of consumers and their families. It enables functionalities such as the initiation of preventive measures, reminders, alarming, and health advice.

The cost explosion in healthcare leaves no choice but to accept these developments: but how exactly and when exactly the impact will be realized is still largely unclear. We are currently still far from generally accepted solutions and data privacy, liability and legal concerns, and viable business models are critical issues. Despite these uncertainties, we currently see a lot of public and private investments.

A challenging question is how an intelligent learning healthcare system should interact with the individual and the caretaker.

Let’s first consider the individual. When and how should such a system interfere with the individual’s life? Should the individual be informed on a likely positive finding? The most discussed example is Huntington’s disease for which genetic tests exist but no cure. Less dramatic but maybe as bothersome are lifestyle issues such as overweight: How often should an individual be reminded that weight loss and exercise would increase longevity? What is just the right level of decision support and interference in an individual’s life? Maybe be an individual does not want to know? Maybe the individual does not want anybody to know?

Similar issues are relevant for the healthcare providers. In addition there is the question of how a learning healthcare system should support treatment decisions. Supplying newest research results on the patient’s problems might obviously be a good idea, but it is largely an open question how decision support can be integrated into the workflow of the caretakers. Can a caretaker accept results from a statistical analysis which uses high dimensional patient information but might not easily be explainable? These issues can make or break the success of digitalization and Big Data!

Most people accept that treating all patients the same is bad, but maybe treating all healthcare providers the same is bad as well. How is it possible to improve the average quality of care without hurting the top performers?

In this paper we have described the state of the healthcare systems and various attempts to improve it via simpler and more effective processes, standardized data formats, data exchange in trusted networks, and improvements in policies and reimbursement rules. It is important that all involved stakeholders, but in particular care takers and patients, personally experience the benefits of the new developments and not just suffer from the additional bureaucratic burden: Trust must be generated and benefits must be apparent since future healthcare only works with support from all groups.

Greatest concerns are clearly associated with data privacy and data security and generally acceptable solutions are not yet available. Here one might want to distinguish between the privacy concerns of patients with a severe health issues, who might see clearer benefits from sharing their data, from individuals without many major health problems, who might not see immediate benefits in data sharing. In general privacy issues are very serious: Imagine a hack which gives access to your complete (in the future more rich and meaningful) health record to un-authorized parties, which would open the door to discrimination and black mail! What if foreign intelligence agencies keep a health profile of each citizen of your country or if your health information is collected by criminal companies to be sold to anybody who can pay the price? Abuse with criminal intend must be severely punished.

Currently business models are still unclear and new reimbursement models must be developed. In particular reimbursement models need to be adapted to personalized medicine which requires huge investments. The legal situation of what is allowed and what is not must be clear and unambiguous, which is not the case in many countries: One cannot build a viable business model on an uncertain legal basis. How should patient consent be dealt with? How long is patient consent valid? What solutions need FDA approval? In Europe there are a number of EU and national regulations which need to be considered and which are mutually inconsistent. These are just a few issues that need to be clarified!
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REFERENCES
[1] S. Biesdorf and F. Niedermann, “Healthcare’s digital future,” McKinsey & Company, 2014.
[2] J. Manyika, M. Chui, B. Brown, J. Bughin, R. Dobbs, C. Roxburgh, and A. H. Byers, “Big data: The next frontier for innovation, competition, and productivity,” McKinsey Global Institute, 2011.
[3] K. Conger, “Data deluge: mastering medicine’s tidal wave, chapter b! g data. what it means for our health and the future of medical research,” 2012.
[4] B. Kayyali, D. Knott, and S. Van Kuiken, “The big-data revolution in us health care: Accelerating value and innovation,” Mc Kinsey & Company, 2013.
[5] Wikipedia, “Health information exchange — Wikipedia, the free encyclopedia,” 2016. [Online]. Available: https://en.wikipedia.org/wiki/Health-information-exchange
[6] National Academies of Sciences, Engineering, and Medicine, “The learning health care system in America,” 2012. [Online]. Available: http://www.nationalacademies.org/hmd/Activities/Quality/LearningHealthCare.aspx
[7] A. Rind, T. D. Wang, W. Aigner, S. Miksch, K. Wongsuphasawat, C. Plaisant, and B. Shneiderman, “Interactive information visualization to explore and query electronic health records,” Foundations and Trends in Human-Computer Interaction, vol. 5, no. 3, pp. 207–298, 2011.
[8] M. A. Musen, B. Middleton, and R. A. Greenes, “Clinical decision-support systems,” in Biomedical informatics. Springer, 2014, pp. 643–674.
[9] T. J. Bright, A. Wong, R. Dhurjati, E. Bristow, L. Bastian, R. R. Coeptiaux, G. Samsa, V. Hasselblad, J. W. Williams, M. D. Musty et al., “Effect of clinical decision-support systems: a systematic review,” Annals of internal medicine, vol. 157, no. 1, pp. 29–43, 2012.
[10] J. Bresnick, “Healthcare big data analytics: From description to prescription,” Healthcare IT Analytics, 2015.
[11] S. Blumenthal and G. Somashekar, “Advancing health with information technology in the 21st century,” Healthy Living, 2015.
[12] SAS, “Applying data to improve patient-centric and personalized medicine,” SAS white paper, 2015.
[13] W. R. Hersh, “Information retrieval for healthcare,” in Healthcare Data Analytics, 2015, pp. 467–505. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-17
[14] R. Rahman and C. K. Reddy, “Electronic health records: A survey,” in Healthcare Data Analytics, 2015, pp. 21–59. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-4
[15] D. Blumenthal, “Launching high tech,” New England Journal of Medicine, vol. 362, no. 5, pp. 382–385, 2010.
[16] D. Charles, M. Gabriel, and M. Furukawa, “Adoption of electronic health record systems among us non-federal acute care hospitals: 2008-2013. 2014,” 2014.
[17] C.-J. Hsiao, E. Hing et al., Use and Characteristics of Electronic Health Record Systems Among Office-Based Physician Practices, United States, 2001-2013. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2014.
[18] J. McCarthy, “Doctors like ehrs even less than they did five years ago,” Healthcare IT News, 2015.
[19] E. Snell, “Top 10 healthcare data breaches of 2015,” 2015. [Online]. Available: http://healthitsecurity.com/news/top-10-healthcare-data-breaches-of-2015
[20] N. Clynch and J. Kellett, “Medical documentation: Part of the solution, or part of the problem? a narrative review of the literature on the time spent on and value of medical documentation,” International journal of medical informatics, vol. 84, no. 4, pp. 221–228, 2015.
[21] M. W. Friedberg, P. G. Chen, F. M. Aunon, K. R. Van Busum, C. Pham, J. P. Caloyeras, S. Mattke, E. Pitchforth, D. D. Quigley, R. H. Brook et al., Factors affecting physician professional satisfaction and their implications for patient care, health systems, and health policy. Rand Corporation, 2013.
[22] C. J. McDonald, F. M. Callaghan, A. Weissman, R. M. Goodwin, M. Mundkur, and T. Kuhn, “Use of internet’s free time by ambulatory care electronic medical record systems,” JAMA internal medicine, vol. 174, no. 11, pp. 1860–1863, 2014.
[23] C. J. McDonald and M. H. McDonald, “Invited commentary — electronic medical records and preserving primary care physicians’ time,” Archives of internal medicine, vol. 172, no. 3, pp. 285–287, 2012.
[24] K. Raja and S. Jonnalagadda, “Natural language processing and data mining for clinical text,” in Healthcare Data Analytics, 2015, pp. 219–249. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-9
[25] D. R. Padfield, P. R. S. Mendonça, and S. Gupta, “Biomedical image analysis,” in Healthcare Data Analytics, 2015, pp. 61–89. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-5
[26] S. Liao, S. Yu, M. Wolf, G. Hermosillo, Z. Yan, Z. Shinagawa, Z. Peng, X. S. Zhou, L. Bogoni, and M. Salganickoff, “Computer-assisted medical image analysis systems,” in Healthcare Data Analytics, 2015, pp. 657–683. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-24
[27] J. Novet, “Deep learning startup enlitic raises $10m from radiology company capitol health,” venturebeat, 2015.
[28] V. Tresp, S. Zillner, M. J. Costa, Y. Huang, A. Cavallaro, P. A. Fasching, A. Reis, M. Sedlmayr, T. Ganslandt, K. Budde et al., “Towards a new science of a clinical data intelligence,” arXiv preprint arXiv:1311.4180, 2013.
[29] C. J. McDonald, J. M. Overhage, P. R. Dexter, L. Blevins, J. Meeks-Johnson, J. G. Suico, M. C. Tucker, and G. Schadow, “Canopy computing: using the web in clinical practice,” Jama, vol. 280, no. 15, pp. 1325–1329, 1998.
[30] J. Bresnick, “How can healthcare big data analytics bust data silos?” Healthcare IT News, 2015.
[31] S. Murphy, G. Weber, M. Mendis, V. Gainer, H. C. Chuell, S. Churchill, and I. Kohane, “Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2),” Journal of the American Medical Informatics Association, vol. 17, no. 2, pp. 124–130, 2010.
[32] B. D. Athey, M. Braxenthaler, M. Haus, and Y. Guo, “transmart: an open source and community-driven informatics and data sharing platform for clinical and translational research,” AMIA Summits on Translational Science Proceedings, vol. 2013, p. 6, 2013.
[33] Y. Park and J. Ghosh, “Privacy-preserving data publishing methods in healthcare,” in Healthcare Data Analytics, 2015, pp. 507–529. [Online]. Available: http://www.crcnetbase.com/doi/abs/10.1201/b18588-18
[34] G. Danenez, J. Domingo-Ferrer, M. Hansen, J.-H. Hoepman, D. L. Metayer, R. Tirtea, and S. Schiffner, “Privacy and data protection by design-from policy to engineering,” arXiv preprint arXiv:1501.03726, 2015.
[35] D. Raths, “Upmc funds pittsburgh health data alliance,” Health Affairs, 2015.
[36] B. Spice, “The future of health care is in the data,” 2015. [Online]. Available: https://www.cs.cmu.edu/news/future-health-care-data
[37] W. Flanagan, “Uiuc and the mayo clinic get $9.3 million to try and solve the biomed big data puzzle,” venturebeat, 2014.
Riley, M. Shukla, B. Chesnick, M. Kadan, E. Papp et al., “Personalized genomic analyses for cancer mutation discovery and interpretation,” *Science translational medicine*, vol. 7, no. 283, pp. 283ra53–283ra53, 2015.

[119] M. A. Morse, A. Chaudhry, E. S. Gabitzsch, A. C. Hobeika, T. Osada, T. M. Clay, A. Amalfitano, B. K. Burnett, G. R. Devi, D. S. Hsu et al., “Novel adenoviral vector induces t-cell responses despite anti-adenoviral neutralizing antibodies in colorectal cancer patients,” *Cancer Immunology, Immunotherapy*, vol. 62, no. 8, pp. 1293–1301, 2013.

[120] J. P. Balint, E. S. Gabitzsch, A. Rice, Y. Latchman, Y. Xu, G. L. Messerschmidt, A. Chaudhry, M. A. Morse, and F. R. Jones, “Extended evaluation of a phase 1/2 trial on dosing, safety, immunogenicity, and overall survival after immunizations with an advanced-generation ad5 [e1-, e2b-]cea (6d) vaccine in late-stage colorectal cancer,” *Cancer Immunology, Immunotherapy*, vol. 64, no. 8, pp. 977–987, 2015.

[121] K. Michailidou, P. Hall, A. Gonzalez-Neira, M. Ghousaini, J. Dennis, R. L. Milne, M. K. Schmidt, J. Chang-Claude, S. E. Bojesen, M. K. Bolla et al., “Large-scale genotyping identifies 41 new loci associated with breast cancer risk,” *Nature genetics*, vol. 45, no. 4, pp. 353–361, 2013.

[122] P. Soon-Shiong, S. Rabizadeh, S. Benz, F. Cecchi, T. Hembrough, E. Mahen, K. Burton, C. Song, F. Senecal, S. Schmechel et al., “Abstract p6-05-08: Integrating whole exome sequencing data with maseq and quantitative proteomics to better inform clinical treatment decisions in patients with metastatic triple negative breast cancer,” *Cancer Research*, vol. 76, no. 4 Supplement, pp. P6–05, 2016.

[123] C. Hayden, “Genome researchers raise alarm over big data,” *Nature News*, 2015.

[124] Z. D. Stephens, S. Y. Lee, F. Faghri, R. H. Campbell, C. Zhai, M. J. Efron, R. Iyer, M. C. Schatz, S. Sinha, and G. E. Robinson, “Big data: Astronomical or genomical?” *PLoS Biol*, vol. 13, no. 7, p. e1002195, 2015.

[125] B. H. Shirts, J. S. Salama, S. J. Aronson, W. K. Chung, S. W. Gray, L. A. Hindorff, G. P. Jarvik, S. E. Plon, E. M. Stoffel, P. Z. Tarczy-Hornoch et al., “Cser and emerge: current and potential state of the display of genetic information in the electronic health record,” *Journal of the American Medical Informatics Association*, p. ocv065, 2015.

[126] A. Shah, A. K. Stewart, A. Kolacevski, D. Michels, and R. Miller, “Building a rapid learning health care system for oncology: Why cancerlinq collects identifiable health information to achieve its vision,” *Journal of Clinical Oncology*, p. JCO650598, 2016.

[127] A. Abernethy, “Asco’s cancerlinq and breast cancer outcomes,” in *European Journal Of Cancer*, vol. 49. Elsevier Sci Ltd The Boulevard, Langford Lane, Kidlington, Oxford Ox5 1Gb, Oxon, England, 2013, pp. S37–S37.

[128] M. Ratner, “Ibm’s watson group signs up genomics partners,” *Nature biotechnology*, vol. 33, no. 1, pp. 10–11, 2015.

[129] T. Savvy, “Watson will see you now: a supercomputer to help clinicians make informed treatment decisions,” 2015.

[130] F. S. Collins and H. Varmus, “A new initiative on precision medicine,” *New England Journal of Medicine*, vol. 372, no. 9, pp. 793–795, 2015.

[131] V. T. DeVita Jr and E. DeVita-Raeburn, *The Death of Cancer: After Fifty Years on the Front Lines of Medicine, a Pioneering Oncologist Reveals why the War on Cancer is Winnable—and how We Can Get There*. Macmillan, 2015.