Translational bioinformatics in the era of real-time biomedical, health care and wellness data streams

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Abstract

Monitoring and modeling biomedical, health care and wellness data from individuals and converging data on a population scale have tremendous potential to improve understanding of the transition to the healthy state of human physiology to disease setting. Wellness monitoring devices and companion software applications capable of generating alerts and sharing data with health care providers or social networks are now available. The accessibility and clinical utility of such

data for disease or wellness research are currently limited. Designing methods for streaming data capture, real-time data aggregation, machine learning, predictive analytics and visualization solutions to integrate wellness or health monitoring data elements with the electronic medical records (EMRs) maintained by health care providers permits better utilization. Integration of population-scale biomedical, health care and wellness data would help to stratify patients for active health management and to understand clinically asymptomatic patients and underlying illness trajectories. In this article, we discuss various health-monitoring devices, their ability to capture the unique state of health represented in a patient and their application in individualized diagnostics, prognosis, clinical or wellness intervention. We also discuss examples of translational bioinformatics approaches to integrating patient-generated data with existing EMRs, personal health records, patient portals and clinical data repositories. Briefly, translational bioinformatics methods, tools and resources are at the center of these advances in implementing real-time biomedical and health care analytics in the clinical setting. Furthermore, these advances are poised to play a significant role in clinical decision-making and implementation of data-driven medicine and wellness care.

Introduction

Precision medicine is defined as the prevention and treatment strategies that take individual variability into account [1]. Implementing precision medicine in a clinical setting requires seamless integration of data from clinical evaluations and biomedical investigations with genomics and other physiological profiling to characterize an individual patient's disease progression. Implementing precision medicine practices in clinical settings requires coordinated efforts to integrate data from both healthy and disease states in individuals. Recently, Li *et al.* [2] showed that converging quantitative data from laboratory measurements, diagnoses and procedure codes from electronic medical records (EMRs), medication data and genomic profiles of Type-2 diabetes patients helped to identify new clusters of patient sub-population that can be targeted using precision therapies. Such examples of precision medicine investigations have illustrated that integrating genomics-based risk profiling and clinical measurements improves our understanding of the onset of disease and variation between individual's illness or wellness phenotypes. Characterizing each person's individual baseline health state instead of resorting to population-based variable distributions could enable earlier identification of true, personalized pathologic changes while preventing unnecessary testing following incidental findings [3–6].

Genome- and phenome-wide studies are effectively using clinical data from EMRs linked to patient samples from clinical repositories or biobanks including studies from eMERGE (electronic MEdical Records and Genomics; http://www.gwas.net) network, Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics (CLIPMERGE PGx) program [7] and Informatics for Integrating Biology and the Bedside (i2b2; https://www.i2b2.org/) [8–15]. Similar initiatives are underway to incorporate diverse data elements including exposome data and assess how patient–environment interactions could impact health [16–21]. Emerging evidence suggests that integrating deep molecular profiling technologies (genomic, transcriptomic, proteomic or metabolomic) collectively defined as multi-omic data with clinical information explains some of the clinical variation between individuals [22–24]. Such cross-platform or multi-technology initiatives are required for the efficient utilization of health monitoring data for prediction, diagnosis and developing smart clinical decision support systems.

Understanding the molecular, physiological, social and environmental basis of healthy states and diversion to complex, common, rare or chronic disease is a challenge for experimental biologists and clinician investigators alike. The patients were characterized earlier in the process of their evolution toward an apparent disease phenotype, and the phenotypic characterizations were often narrow and aimed at eliminating many natural confounders such as comorbidities. Standard clinical research studies collect data routinely after patients have a clinically significant disease phenotype, failing to capture data about the healthy and subclinical state, which limits the discovery of early diagnosis or prophylaxis information. Clinical data repositories maintained by hospitals have limited access to longitudinal health monitoring data captured by personalized health-monitoring devices or vice versa. Better tools and protocols are needed to capture, aggregate, analyze, visualize and use wellness data in the clinical setting. In this article, we provide an overview of biomedical and health care real-time data streams, data types, sources and devices that can generate the data and various scientific and technical aspects for integrating and using such streams to develop data-rich translational bioinformatics resources. Further, we discuss the use of such resources in a clinical setting and how these resources could further enhance the application of translational bioinformatics tools and resources in a clinical setting.

Real-time biomedical, health care and wellness data streams

Translational bioinformatics methods have made progress toward implementation of genomic medicine at the point of care, and seamless integration within EMRs [25–27]. Community-wide efforts improved to the implementation of genomic medicine into the clinic in a short span of time. Similarly, community engagement by patients, providers and payers are critical for integrating wellness science into EMRs and are vital to their use at the point of care [28–33]. Integrating patient-generated health care data with existing health data into the EMR, or personal health records (PHRs) along with other biological and genetic data could provide information to assess patients' progression from health to subclinical disease to a clinically significant pathological state. Further, such efforts may additionally account for heterogeneity among patients. Real-time biomedical and health care data stream refers to the compendium of data aggregated by individuals using health-monitoring devices or data generated and captured in EMR and other health care software systems during ambulatory or inpatient visits that may aid in diagnosis, prognosis, interventions and stratifications. These data types can be

generated using fitness or health-tracking wearable devices (distance walked, steps counted), biosensors (heart rate variability or continuous glucose), by health care providers in the clinical settings (respiration rate) via diagnostic equipment (echocardiography) or clinical monitoring devices (vital signs), and using deep profiling using multiscale biological experiments (whole genome or exome sequencing for profiling mutation landscapes, gene expression analysis or metabolomics experiments to find relevant biomarkers). Further integration of these data with individual-level information including socioeconomic information, variations in weather and location-based environmental quality (pollution) data could provide precise information to develop predictive models capable of identifying and estimating the causal or reactive role of various factors contributing to wellness and illness.

Aggregation of real-time biomedical and health care data

Currently, the biomedical and health care data are captured from clinical research or clinical trials across disparate databases (Table 1). These databases are primarily designed to obtain numerical and categorical data from patients during the incidence of a disease or based on disease prevalence or based eligibility criterion to participate in a clinical trial. On the other hand, integrated application development frameworks like Apple ResearchKit (http://www.apple.com/researchkit/) and Google Fit (https://developers.google.com/fit/?hl=en) offer a convenient option for wellness data gathering. Apple ResearchKit is a comprehensive framework for developing research applications that can interact with various consumer devices and embedded sensors. ResearchKit enables the research community to develop applications that seamlessly integrate data, for example, the accelerometer in iPhone can track walking steps or photoplethysmography-based heart rate sensing can monitor temporal fluctuations in heart rate. Researchers (see AsthmaHealth App: http://apps.icahn.mssm.edu/asthma/) and pharmaceutical companies [34] are now leveraging Apple ResearchKit-based applications for developing applications to recruit directly for clinical trials and gather patient data using mHealth-based applications. Modern health care delivery strategies aim to provide optimal care to individual patients with affordable cost. Application of big data analytics, machine learning and predictive modeling could help in delivering data-driven personalized precision care [35–40].

Publicly available biomedical, health care and wellness data repositories

Public biological data repositories for molecular data are mature and growing, but standards and repositories for wellness and health monitoring data are lacking. Publicly available genomic and phenomic data improve the discovery and translation of research findings from the bench to the bedside [41]. In 2015, the annual database issue of Nucleic Acids Research enlisted 56 new molecular biology databases and reported recent updates to 115 databases. For example, data related to the cancer genome, exome and transcriptome are available for analyses using The Cancer Genome Atlas [42, 43]. Genotype and phenotype data can be retrieved for meta-analyses or replications studies from dbGAP [44, 45]. Gene expression signatures across various disease models were archived at databases as Gene Expression Omnibus [46] or Gene Expression Atlas [47]. Biological pathway data based on community-wide biocuration [48] efforts can be accessed from a variety of databases including BioGPS, KEGG

and WikiPathways [49–51]. Specialized molecular-class-specific databases that catalog a group of proteins related to molecular mechanisms or disease types are also available. For example, proteins associated with 3D domain swapping, a key molecular basis for neurodegenerative diseases, is compiled in the 3DSwap knowledgebase [52]. Such efforts are underway to compile and provide health care data in the public domain. For example, various multi-stream recordings of physiologic data can be obtained from the Massachusetts General Hospital/Marquette Foundation database PhysioNet [53].

While the data on biomolecular genome and phenome data are feature rich and dense, the availability of health monitoring databases in the public domain is scarce. Standard, clinical research studies do not collect data until after patients have a clinically significant disease phenotype, failing to capture data pertaining to the healthy and subclinical state, which limits the discovery of early diagnosis or prophylaxis information. Data on healthy populations and longitudinal health monitoring is rarely captured or archived in a format that enables reuse or deep analyses. With >50% of the population in the United States tracking at least one health-monitoring data type using electronic or paper-based logs, developing data capturing solutions that integrate health data elements with the EMR maintained by heath- and wellness-care providers would deliver better insights. To address this important challenge, collecting health-monitoring data on a population scale and developing scientific and technical resources and methods to correlate it with biomedical, multi-omic data and clinical data from a patient's EMRs are required.

Consumer devices for biomedical, health care and wellness monitoring

Adoption to digital health tools is not surprisingly highest in the subset of population that uses the Internet most (http://rockhealth.com/data/digital-health-consumer-adoption-survey-data/). A recent survey ($n = 4017$) indicates that currently 80% of the Internet-using population leverages one or more digital health tools for gathering information about conditions (71%), reviews about health care services or physicians (50%), health tracking (17%), wearables (12%), genetic information (7%) or telemedicine (7%). Leveraging the wellness and health-monitoring data being generated by patients could help in designing better intervention strategies, but incorporating them in routine clinical research or integration with other data modalities requires better translational bioinformatics resources.

An array of consumer health-monitoring devices is currently available in the market; summaries of features of a sample of some of them are provided (Table 2). The majority of currently available health-monitoring devices (commonly referred as 'wearables' [54–66]) focus on fitness or monitoring of lifestyle-related variables. Common information tracked includes fitness measures such as steps climbed or distance covered in a run or walk, gait and posture analysis, heart rate, calories burned and quality of sleep. Some of the health-monitoring devices also allow users to manually log daily calorie intake and compute calories burned to provide a score. Although such scoring systems often lack extensive validation, the personalized nature of such metrics may motivate individuals to alter maladaptive behaviors over time. A subset of such health-monitoring devices provides the capability to monitor physiological variables including blood pressure, respiration and blood oxygenation levels, as well as other test values that have been routinely measured in a diagnostic laboratory. Scientific investigations on

Table 1. Biomedical and health care data aggregation resources

Data resource	Description	Example	Example URL
Biobank	Biorepository that stores biological samples from volunteers for research use	BioMe BioBank Program	https://icahn.mssm.edu/research/institutes/ipm/programs/biome-biobank
Biorepository	Biological materials repository that collects, processes, stores and distributes biospecimens to support future scientific investigation	Mount Sinai Cancer Institute Biorepository	https://biospecimens.ordr.info.nih.gov/AllRepositories.aspx
Clinical data warehouse	Data aggregation system that collects data from diverse data-capturing system as part of health care delivery and clinical trials	Mount Sinai Data Warehouse	http://icahn.mssm.edu/about-us/services-and-resources/computer-services/resources/research-information-technology/mount-sinai-data-warehouse
Clinical trials database	Disease-, therapy- or intervention-specific database that collects data during a clinical trial	Cardiovascular Health Study	https://clinicaltrials.gov/
Disease registries	Specialized database that contains information about patients diagnosed with a specific type of disease		https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries
Electronic medical record (EMR) or electronic health record (EHR)	Longitudinal record of patient care as documented by care provider and maintained by hospitals	Epic, Cerner	https://www.cms.gov/Medicare/E-Health/EHealthRecords/index.html?redirect=/ehealthrecords/
Health care survey databases	Large-scale health care survey database maintained organizations like center for disease and infection control (CDC), AHRQ, NCI, etc.	Surveillance, Epidemiology and End Results (SEER)	http://www.cdc.gov/nchs/dhcs.htm
Patient Health Record (PHR)	A compendium of health care information maintained by a patient	Microsoft HealthVault	https://www.healthit.gov/providers-professionals/faqs/what-personal-health-record
Patient portal	A web-based data aggregation system to collect demographic data, enable patient-provider interactions and help patients to coordinate health care services	My Mount Sinai chart	https://www.healthit.gov/providers-professionals/faqs/what-patient-portal
Payer databases	Database managed by government or non-government organizations or insurance companies	Database maintained by health insurance companies, state or other federal health agencies. Payer databases are also available as products from data vendors	https://www.health.ny.gov/technology/all_payer_database/

Table 2. Features of consumer health-monitoring devices

Consumer device	Health features monitored	Medical field(s)	Source
Basis B1 wrist band	Heart rate, accelerometer, body temperature, ambient temperature, skin conductance, caloric burn	CV, Endo, Psych	https://www.mybasis.com/
BodyMedia Link Armband	Heat flux, body temperature, motion and skin conductance, activity level, calorie burn and sleep	CV, Endo	http://www.bodymedia.com/
Fitbit Aria	Weight, body fat %, BMI	CV, Endo	https://www.fitbit.com/aria
Fitbit Surge	GPS, altimiter, heart rate, accelerometer, activity, caloric burn and sleep	CV	https://www.fitbit.com/surge
Hexoskin smart shirt	ECG, respiratory rate, tidal volume, acceleromter, position, sleep	CV, Pulm	http://www.hexoskin.com/
iHealth BP5	Blood pressure	CV, Renal	http://www.ihealthlabs.com/
iHealth Glucometer	Blood glucose	Endo	http://www.ihealthlabs.com/
Jawbone UP3	Accelerometer, heart rate, respiratory rate, skin conductance, skin temperature and ambient temperature, activity, sleep and caloric intake	CV, Endo, Pulm, Psych	http://jawbone.com/store/buy/up3
MapMyFitness	Record activity, food intake	CV	http://www.mapmyfitness.com/
Melon Headband	Three-channel EEG, infer concentration, relaxation	Neuro, Psych, Devel	http://www.thinkmelon.com/
Muse headband	Seven-channel EEG, infer concentration, relaxation	Neuro, Psych, Devel	http://www.choosemuse.com/
Nike Fuelband	Activity	CV	http://www.nike.com
Scanadu Scanaflo	Urinalysis	Renal, Endo	https://www.scanadu.com/scanaflo
Scanadu Scout	Temperature, blood pressure, heart rate, blood oxygenation and ECG	CV, Pulm	https://www.scanadu.com/scout
Sensimed Triggerfish	Eye shape and blinking, infer intraocular pressure	Ophtho	http://www.sensimed.ch/
Withings BP Monitor	Blood pressure, heart rate	CV, Renal	http://www.withings.com/
Withings Pulse	Accelerometer, heart rate, blood oxygenation, activity, sleep and caloric burn	CV, Pulm	http://www.withings.com/
Zephyr BioPatch	Heart rate, respiratory rate, accelerometer, ECG, activity	CV, Pulm	http://zephyranywhere.com/

CV, cardiovascular; Devel, development; Pulm, pulmonary medicine; Endo, endocrinology; Neuro, neurology; Ophtho, ophthalmology.

these devices have validated portions of the features they measure [67–69], demonstrated sustained changes in patient behavior [70] and shown benefits to patients with special exercise health considerations [71]. A subset of these devices, such as the Withings blood pressure monitor, have been medically approved in the United States and validated in additional studies that fulfill the European Society of Hypertension International Protocol Revision 2010 requirements [72, 73].

Many sensors or wearable devices have a companion mobile application that uses Bluetooth, Zigbee, infrared waves, ultra band wireless communication or a (universal serial bus) USB-based sync service to update health-monitoring data from the wearable monitor to a connected computer or data aggregation database [74, 75]. As part of the mobile Health initiative (http://www.hhs.gov/open/initiatives/mhealth/), mobile applications have been designed that provide software modules to harness the internal sensors in mobile phones for the capture of health data. A challenge with integrating such data is that most devices are manufactured as a consumer electronic device and are not endorsed by US Food and Drug Administration (FDA) or other regulatory bodies. The data from such health monitors are often isolated in product-specific databases managed by the vendors of the health-monitoring devices. Initiatives and organizations like Human API, Aqua.io, Vivametrica (http://www.vivametrica.com) and 'Here is My Data' (http://www.hereismydata.

com) address unification of data from such diverse resources. While such integration is useful for creating better consumer tools, there remains a relative lack of such efforts that integrate with health care and clinical settings to develop actionable recommendation tools. Meanwhile, the introduction of health monitoring and telemedicine devices approved by the FDA provide real-time and remote health monitoring of patients with chronic conditions for rapid monitoring of blood glucose levels or other variables [76]. While a subset of these data are currently available to the care provider, a systematic way to integrate these data during the 'disease window' of the patient with data from his or her prior healthy state is currently limited.

Vital sign monitoring using wearable devices and biosensors

Several devices are currently in different stages of development including initial marketing, or experimental prototyping to measure physiological variables. Some of the available data streams have a clear and well-established utility for monitoring health and wellness including heart rate, respiratory rate and effort, inhaled/expired CO_2, cardiac output, blood pressure, oxygen consumption and blood oxygenation. More advanced sensors capture additional vital signs such as brain activity with encephalogram (EEG), muscle activity with electromyography

(EMG) and skin monitoring using microfluidics-based sensors. Although these sensors have applicability in managing specific diseases, their utility in terms of general wellness monitoring has yet to be established. Embedded sensors are currently available for glucose monitoring using tears for diabetic patients [77]. Adhesive skin patches or circuits provide opportunities to design a range of wireless physiological monitoring devices capable of passively collecting data for multi-day periods [78]. Medical textiles are being developed that measure vital signs without being obtrusive [79]. Biosensors [80–85] are also being used for various health applications including health monitoring.

Exposome monitoring using wearable devices and biosensors

The 'exposome' is defined as the total of environmental exposure to humans and have shown as an indicator of disease susceptibility (for example, lung cancer among those exposed to cigarette smoke). Additional devices track patients' ambient environmental conditions to assess their local environment for air quality, light [86], climatic variations, ozone [87] and volatile organic compounds [88–90]. Real-time integration of exposome data with health monitoring data and other data elements in EMR or PHR would help to elucidate how environmental factors influence both disease and healthy states of individuals and communities.

Disease-specific monitoring sensors

In addition to consumer devices that monitor health traits that are ubiquitously relevant to health, many consumer devices are being developed that have a particular application setting. Devices to monitor rehabilitation and instrumental activities of daily living have been especially prominent given the essential need to assess how a patient's functionality is changing over time. Gait monitoring has been done through smart insole sensors [91], wearable accelerometers and gyroscopes that can be embedded in smart textiles, goniometers, as well as video recording and floor/environment-based vibration and radio-frequency identification (RFID) sensing. These systems have applications in prosthetic and orthotic design, rehabilitation after an amputation, reconstruction [92] or injury, assistance for patients with neurodegenerative disease [74, 93], identifying movement disorders [94] and detecting/preventing falls [95]. Several brain biofeedback devices are available for consumers that use EEG technology to assess brain activity. Brain activity information can be used for monitoring and/or biofeedback training in patients with neurologic diseases including migraine [96], epilepsy [97] and post-stroke rehabilitation [98, 99]; psychiatric disease including subclinical stress [100], anxiety, depression, addiction and attention deficit/hyperactivity disorder [101]; and developmental disease including autism spectrum disorder [102].

Pharmacological monitoring sensors

Medications are used to treat either existing conditions or symptoms and to prevent prophylactic illness in high-risk individuals. Prescription drugs are used by almost 70% of Americans, and 20% of the population takes five or more; however, only half of the prescribed medications are taken as prescribed, and 20–30% never get filled [103]. Failure to take medications as directed can have devastating consequences, such as organ rejection in transplant recipients; while taking excess medication can increase side effect risks or cause toxicities, such as prolonged nonsteroidal anti-

inflammatory drug (NSAID) use leading to gastric ulceration or excessive anticoagulant use leading to bleeding. Recently, the FDA approved an ingestible sensor that can be co-administered with a medication that wirelessly records patients' pharmacological status and prescription adherence and is highly accurate in multiple clinical contexts (i.e. hypertension, tuberculosis) [104, 105]. This methodology will help to understand how prescription medications might influence health-monitoring traits. Integrating data from a diverse set of vital sign monitoring devices, biosensors or nanobiosensors, environmental exposure and pharmacological profiles into the existing clinical workflows or EMR is a challenge, and there need to be pilot clinical trials and outcome assessment studies of implementation as part of precision medicine workflows.

Real-time monitoring in clinical setting

Mining data streams is an evolving concept in computer science and data mining although is common in finance for risk modeling, financial engineering and stock trading [85, 106–109]. Owing to widespread adoption of EMRs, real-time mining of clinical data is possible in the setting of precision medicine. EMRs are currently used to systematically log a patient's clinical history. In an ambulatory setting, clinical data elements including temperature, blood pressure and other vital signs are measured at the time of appointment and used as a baseline data points for clinical decisions. During an inpatient visit, vital signs are routinely measured with a temporal frequency that depends on the reason for hospitalization as well as the clinical status of the patient. Often, the real-time clinically relevant data monitored during an inpatient stay in the hospitals are not systematically stored in EMR for querying or aggregation for analyses. We propose that initiatives to capture and store real-time data during the duration of hospitalization and correlate it with past and future health monitoring data can improve patient care and reduce costs in both inpatient and outpatient visits including intensive care units. An interest in analyses of real-time data streams and real-time clinical decision support systems has recently been reported, but these implementations had limited access to the historic health monitoring data of the patients during the non-disease states [110–112].

Quality control of real-time data streams for clinical applications

Regardless of the data streams being aggregated, there are several usability issues that clinicians and researchers must evaluate during the selection of a particular device for disease or wellness monitoring. Wireless monitors that are passive, nonintrusive, comfortable and with a long battery life should be ideal. Extensive comparative effectiveness studies are required to understand the choice of device in a disease setting and usability preferences and functionalities in different age and gender groups. Orthogonal validation of data streams generated by a wellness-monitoring device and an equivalent clinical grade monitor is necessary to incorporate data from devices for clinical decision-making and interventions. Hence, device comparison studies that validate the data are also the important factor for considering a wearable for monitoring to improve population health or personalized disease management. The quality of data obtained from the wearables would need multiple levels of quality control and normalization strategies before using for clinical research. A sudden increase in heart rate could be induced by emotional or physical reasons; while the sensors

capture both, the aggregation applications may not be able to differentiate both, and using such data for triggering clinical decisions or actions are not ideal. Annotation of data using various metadata or tags and data cleaning should be part of such integration systems. Real-time biomedical data compiled from various sensors using device-specific data feeds can be aggregated after rigorous quality control using statistical and data normalization techniques into databases and combined with other data elements for analyzes. Visualization tools, shared decision aids and clinical decision systems (CDS) that leverage the real-time health care and wellness care (wellcare) data streams would improve the actionability of such data streams in diagnosis, prognosis, stratification and optimal intervention selection.

Integrating health monitoring data streams into PHRs, EMRs and patient portals

With the advent of large-scale adoption of health-monitoring devices, health care and wellness monitoring data are currently captured in an unprecedented scale. However, the data are captured in a fragmented system, and a user with multiple health-monitoring devices cannot manage or integrate diverse data streams through a single web or mobile application. To use health monitoring data as an important aspect of precision medicine in the clinical setting, efficient protocols and standards for data capture, storage, integration and exchange standards are required. Integration of health monitoring data with clinical data in EMR has great potential to assist both patients and providers in predicting, diagnosing, treating and managing complex or chronic conditions. Providers must realize that health monitoring data can be both reliable and of critical importance. For example, remote monitoring of implanted life-critical devices has been implemented at several institutions

[113, 114], and assessments of these continuous data streams found that they lead to non-inferior patient outcomes [115, 116], cost savings [116, 117] and earlier identification of monitor malfunction [118]. Efforts are underway to connect ResearchKit and HealthKit health data streams into intuitional EMRs or PHRs. Medicare and Medicaid services provide meaningful use (MU; http://www.cms.gov/Regulations-and-Guidance/Legislation/ EHRIncentivePrograms/Meaningful_Use.html) guidelines for health care providers to receive incentive payments. One of the recommendations for the next stage of MU is to engage patients and families in their care by enabling patients to access and transmit patient-generated health information (http://www.healthit. gov/facas/sites/faca/files/MUWG_Stage3_14_Feb_04_v5.pdf).

A systematic approach should be established to consent a potential user, and after completing the consent, the data can be transferred to verified software and database systems at individual hospitals or the health system where the patient seeks care using secured data protocols. Secured data fetching technologies that adhere to privacy and protection of personal health information (PHI) can be used for the data transfer. Further initiative can be taken to streamline the intra-hospital or intra-health system exchange of health monitoring data streams. Existing standards based on Health Level 7 (HL7; https://www.hl7.org/) and health information exchanges (HIE; http://www.healthit.gov/providers-professionals/health-information-exchange/what-hie) could provide a basis for such an integration of a consumer device and clinical data. Unstructured data captured in text format using web forms in wellness or clinical applications can be used as a possible data resource for clinical research using natural language processing (NLP) tools. Historical data on the use of over-the-counter (OTC) medication and diet journaling [119] from health monitoring tools and online journals compiled by patients can be extracted using NLP tools to better understand both health

Table 3. Standards in health and clinical informatics that can leverage integration of health monitoring data to EMRs

Name	Description	URL
CDISC	Clinical Data Interchange Standards Consortium is a standards development collaboration to streamline medical research and health care	http://www.cdisc.org/standards-and-implementations
Health IT at NIST Standards	Provides various information regarding Health IT Standards and details for implementing high-quality health information technology applications and projects	http://healthcare.nist.gov/
HIE	Data interoperability guidelines provided to implement health system, state or national level health information exchanges	https://www.healthit.gov/HIE
HIPAA	The Health Insurance Portability and Accountability Act, a federal act that provides national standards for EHR transactions and identifiers for providers and payors and aid in protecting patient information	http://www.hhs.gov/ocr/privacy/
HITSP	Health care Information Technology Standards designed by public and private partnership to develop health information technology systems that allow better interoperability	http://www.hitsp.org/
HL7	Standards and framework for the exchange, integration, sharing and retrieval of electronic health information that supports clinical practice and the management, delivery and evaluation of health services	http://www.hl7.org/
MU	The Medicare and Medicaid EHR Incentive Programs and associated guidelines provide financial incentives for the 'meaningful use' of certified EHR technology to improve patient care	https://www.healthit.gov/policy-researchers-implementers/meaningful-use-regulations
OMOP	Observational Medical Outcomes Partnership informs the appropriate use of observational health care data sets	http://omop.org/
PHI	Protected health information standard is any patient-related information, including information about the provider or payer and other data that can be linked to an individual. PHI standards and guidelines are designed by institutions to protect patient identify	http://www.hhs.gov/ocr/privacy/

and disease state. Such data streams could help care providers to predict clinical symptoms and suggest therapeutic regimes that may not interact with OTC medications or lead to adverse drug–drug interactions.

Data elements, data capturing technologies, aggregation systems and clinical or health care ontologies for integrating health-monitoring data into EMR were partially defined as the current ecosystem of standards, toolkits and resources (Tables 3 and 4). Integrating health-monitoring data poses several technical challenges to existing data management and analytics of EMR. The high-volume influx of data from health-monitoring devices can be integrated using currently available real-time computational infrastructure platforms (Table 5). To interact with the health monitoring data, Application Programming Interfaces (APIs) can be designed to query, retrieve or integrate required data elements over a period of interest. For example, health-monitoring data-based APIs can be designed to access and compare data from health-monitoring devices before, during and after taking medication—this would help physicians understand the impact of medication on health traits of individual patients. An important part of integration of health monitoring data with EMR would be communicating the temporal trends in health with respect to the onset of disease and other factors using intuitive data visualization tools. Efforts are needed to develop innovative visualization tools to communicate various health trends to both patients and providers. The insight on the individual's longitudinal health and holistic considerations meets the Patient-Centered Outcomes Research Institute (http://www.pcori.org) mission to improve the ability to discern which health care options are best for a particular patient and potentiates informed individualized health decisions. Ontology for home-based care [56] has been proposed, but its integration with existing medical or clinical terminologies are limited; hence, an additional set of ontologies or new terms related to pertinent health monitoring data elements needs to be designed for effective integration of such health monitoring data into the EMR. To facilitate the meaningful interpretation of data, a similar process should be applied to various clinical environments and contexts of health care delivery. Developing ontologies, storage, software and APIs to interoperate health-

Table 4. Resource for extraction, integration, storage or reference of clinically relevant data elements from health care monitoring devices and digital applications to EMRs

Name	Description	Reference
Apache cTAKES	Tools and APIs for unstructured data	http://uima.apache.org/
Apache UIMA	Tools and APIs for unstructured data	http://uima.apache.org/
Aqua.io	Medical vocabulary APIs	http://aqua.io/
CDT	Current dental terminology	http://www.ada.org/en/publications/cdt/
CPT	Current procedural terminology	http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/cpt.page
CVX	HL7 standard code set for vaccines administered	http://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=cvx
FHIR	Fast Health care Interoperability Resources	https://www.hl7.org/fhir/
HCPCS	Health care Common Procedure Coding System	http://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/index.html?redirect=/MedHCPCSGeninfo/
HealthData.gov	Provides diverse health care data sets	http://healthdata.gov/dataset/search
HealthData.gov API	Diverse set of APIs to access HealthData.gov data	http://healthdata.gov/data-api
HealthData.gov Hub	1339 health care data sets (as of May 2014)	http://hub.healthdata.gov/
HumanAPI	An integrated API service	http://humanapi.co/
LOINC	A universal code system for tests, measurements and observations	http://loinc.org/
MedTagger	Text mining tool with options for indexing based on dictionaries, information extraction based on patterns and machine learning-based named entity recognition	http://sourceforge.net/projects /ohnlp/files/MedTagger/
MetaMap	Map biomedical text to the UMLS Metathesaurus or, equivalently, to discover Metathesaurus concepts referred to in text	http://metamap.nlm.nih.gov/#MetaMapJavaApi
OHNLP	Open-source consortium to promote past and current development efforts and to encourage participation in advancing future efforts	http://ohnlp.org/index.php/Main_Page
OpenCDS	Collaborative effort to develop open-source, standards-based CDS tools and resources	http://www.opencds.org/
OpenICE	Open-Source Integrated Clinical Environment is designed as a framework for integrating apps and devices into the Medical Internet of Things	https://www.openice.info/
OpenNLP	Text mining	https://opennlp.apache.org/
PheKB	Knowledgebase for discovering phenotypes from EMRs	http://phekb.org/
RxNORM	Normalized names for clinical drugs and links its names to many of the drug vocabularies commonly used in pharmacy management and drug interaction software	https://www.nlm.nih.gov/research/umls/rxnorm/
SMART	Appstore for health	http://smarthealthit.org/about/
SNOMED CT	Comprehensive, multilingual clinical health care terminology	http://www.ihtsdo.org/snomed-ct/
SPHINX	Web-based tool for exploring drug response implications of genetic variation across the eMERGE PGx project cohort	http://www.emergesphinx.org/

Table 5. Scalable technologies that can be used for computation, integration and analytics of health monitoring data integrated with EMRs

Type	Name	Reference
Distributed computing for batch and streaming data processing	Apache Hadoop	http://hadoop.apache.org/
	Apache Storm	http://storm.incubator.apache.org/
	Apache Spark	https://spark.apache.org/
	Apache Fink	https://flink.apache.org/
	Apache Samza	http://samza.apache.org/
Data storage	Apache Cassandra	http://cassandra.apache.org/
	MongoDb	http://www.mongodb.org/
	Neo4j	http://www.neo4j.org/
	Elastic	https://www.elastic.co/
Data visualization	Gephi	http://gephi.github.io/
	EHDViz	http://ehdviz.dudleylab.org
	Kibana	https://www.elastic.co/products/kibana
Deep learning	Theano	https://pypi.python.org/pypi/Theano
	Tensor Flow	http://www.tensorflow.org/
Graph processing	Pregel	https://kowshik.github.io/JPregel/pregel_paper.pdf
	Apache Giraph	https://giraph.apache.org/
Machine learning	Apache Mahout	http://mahout.apache.org/
	Spark MLlib	https://spark.apache.org/mllib/
	Weka	http://www.cs.waikato.ac.nz/ml/weka/index.html
	Amazon Machine Learning	http://aws.amazon.com/machine-learning/
	Microsoft Azure	http://azure.microsoft.com/
	Ayasdi	http://www.ayasdi.com/

monitoring data with EMRs would also help develop individualized CDS, improve existing CDS and wellness mHealth applications by providing actionable and on-demand feedback to patients.

Data models for health care and wellcare analytics

Currently, biomedical and health care data are captured and analyzed using diverse data models [10, 120–124]. Various data elements like real-time, streaming, structured, unstructured and categorical data can be modeled as unified data model. For example, 'individualome' is defined as a data model that encapsulates data elements that consist of environmental data, social health monitoring data, biomedical data, multi-omic and clinical data elements for an individual (Figure 1). Individualome model captures temporal, categorical and continuous data elements about a patient from various biomedical, health care, wellness, social and environmental data streams. Initiatives to capture and integrate health, biomedical, multi-omic and clinical data, using a unified data model would help us to design precise, data-driven CDS and enable precision medicine as part of routine clinical practice in the near future. Platforms for health outcome research such as the Observational Medical Outcomes Partnership (OMOP; http://omop.org) can already accommodate these additional patient features to improve data utilization in large-scale studies.

Data engineering for real-time biomedical, health care and wellness data streams

The large volume of data coming from all the different health-monitoring devices and constituting the 'individualome' requires large-capacity hardware infrastructures for storage and processing. Such resources can be implemented locally at the data centers associated with hospitals or deployed on secured cloud computing or virtual private server computing environments. In particular, given the sensitivity of the information, only secured

and HIPAA-approved architectures should be considered. To this aim, dedicated cloud-computing platforms, e.g. Amazon cloud, provide a ready-to-use, robust and reliable solution (Table 5) [125]. Local infrastructures are an option as well, but with a higher maintenance cost of system administration. New data is continuously streamed to the system from devices characterized by different formats and protocols. Given the diversity, dynamicity and scale of the data, NoSQL tools (e.g. Apache Cassandra, Elasticsearch) should be preferred to relational databases (e.g. MySQL, PostgreSQL), which would require a predefined and fixed data schema that might be difficult to extend if necessary when new devices are added to the framework.

Every new measurement is independently pushed to the system and related to persons and devices through IDs and medical record numbers. However, to derive person-oriented patterns, data analysis techniques require data to be aggregated and processed by an individual. Consequently, all the data coming from different devices should go through an Extract, Transform and Load (ETL) process before they can be used for automatic analysis [126]. In particular, measurements are first received, pre-processed and normalized or transformed into a person-centered format (e.g. ideally one record per person), which is then loaded into the database to join all the measurements already recorded. The ETL pipeline can be run in real-time (i.e. every time measurements are received) as well as at predefined time intervals (e.g. every night), depending on the requirement of the applications and of the systematic studies. Existing EHR solutions are not designed using data aggregation, normalization or analytics as the primary use case. Thus, an ETL pipeline must be matched with a unified interface to realize the actionable clinical insights obtained by analyzing data from an individual over various time periods.

Continuous streaming data analytics in biomedicine

The availability of large-scale health monitoring data streams introduces endless possibilities to unveil patterns in the EMRs
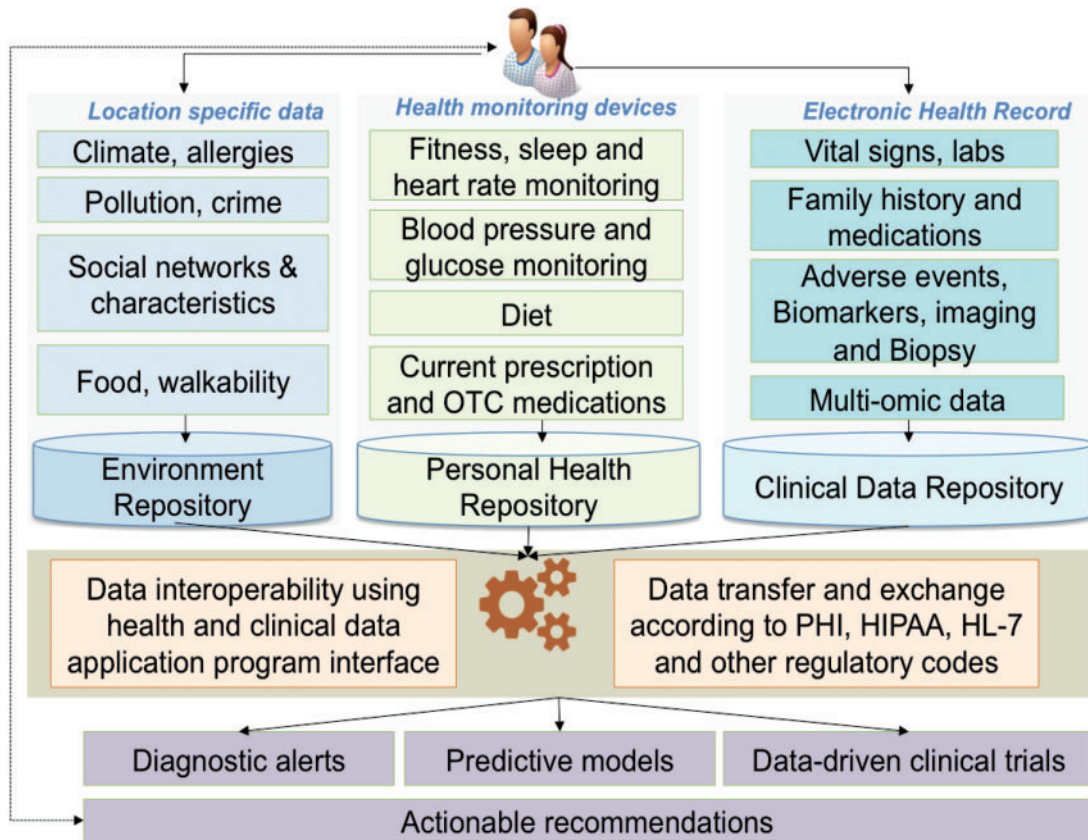
Figure 1. Flowchart of individualome—a health care and wellcare data model for incorporating biomedical, health care and wellness monitoring information with EMRs. Various health data streams can be integrated into a consolidated data model we call individualome. Standards for health care data from Table 2 are indicated at points of implementation. The individualome data can be used for various applications including diagnostics, prognostics and personalized clinical trials. The findings from these applications can be used to generate actionable recommendations, sharing with consumers how to best improve aspects of their health and mitigate personalized disease risks. Current diagnostics and prognostics are based on standard clinical data; by adding multi-omic data and continuous data from environment and personal health repositories, we will be able to build precision models of human health and disease and identify indolent/subclinical stages of disease.

that can be used for clinical support (e.g. disease risk prediction, pharmacogenomics-based drug prescription) [127]. A full review of machine intelligence methods appropriate to these scenarios is beyond the scope of the perspective (also see the recent reviews for a comprehensive overview [128, 129]), but the following points need to be considered in designing informatics solutions for streaming data analytics. First, data should be modeled by defining latent variables that have high predictive value using techniques such as latent Dirichlet allocation, mixture models or Gaussian processes. These techniques define lower dimensionality compact representations of the data that will speed up and improve the training of the prediction models. Both bag-of-words approaches (that do not consider the time sequence of the events) and time series models (such as hidden Markov models, autoregressive models or dynamic time warping) should be considered and might work well depending on the task [130]. Given the continuous streaming nature of new data, incremental learning algorithms should be favored to estimate the different models. In this case, the predictive model is updated each time it sees a new instance of the data. Incremental learning is distinct from batch algorithms where the model is trained using all the data. While this approach can be adapted to stream data by periodic or need-based update or recalibration of predictive models using also the new data, the expected amount of health data streamed by wearable and monitor systems could also influence the scalability of

machine learning and predictive modeling systems. In the literature, there are incremental versions of the most common predictive models, such as support vector machines, neural networks and Bayesian networks. Always for the sake of scalability, unsupervised algorithms mining patterns in the data without requiring any human-based additional information should be favored to supervised approaches that require additional manual work to define training labels. Data quality and false-positive rates are challenging in the implementation of predictive models for real-time, learning health systems [131]. Choice of algorithms, interoperability and end-to-end integration of the algorithm and its actionability will have a direct impact on patient care. Several advanced algorithms are developed and implemented for anomaly detection, intrusion detection or fraud detection in the field of finance [132]. Adopting similar approaches by combining text mining, agglomerative clustering, frequent item set mining, time series modeling, rules engineering that interface with existing EHR systems could aid in developing better solutions.

Patient and physician engagement for real-time data aggregation

Considering patient inputs and patient engagement in designing software systems are essential [133]. Integration of real-time wellness data aggregation system with existing patient portals,

PHRs, health system-wide EMRs or by providing additional measures for patient engagement could lead to better adherence from patient communities. Designing mobile- or web-based applications and visual aids to provide tutorial on how to capture and sync data from various wearable devises. Usability and design of the wearables and the companion software applications are vital for the adherence of wearable and subsequent data aggregation. Designing information pamphlets to educate patient communities about importance of real-time data in clinical research and development of shared decision-making software wizards that offer a walkthrough of risks and benefits associated with data capturing, aggregation, sharing and integration with health informatics software applications.

Physicians have limited time for patient interaction, and introducing additional data burden could affect the physician–patient interaction time [34, 35]. Hence, intuitive user-interface, scalable computing architectures and informatics solutions that seamlessly combine data from wearables, standard clinical care operations and patient profiling experiments are necessary to implement smart, real-time learning health care systems. Such systems could use smart algorithms that distill the data and only alert the physician when there is an actionable task to perform. Ideally, such a solution would not only save physician time but also strengthen his or her ability to quickly address patient concerns. For example, smart algorithms can be designed to auto populate pertinent data for physician review when a patient or provider generates a clinical question.

Ethical, legal and social implications of real-time health monitoring

Integrating real-time health monitoring data would have significant ethical, legal and social implications (ELSI). Hence, the ownership rights of the data and the control of how patients can dynamically opt-in and opt-out of studies are important for building real-time data aggregation systems. Enhancement of existing ELSI and policy guidelines to accommodate incorporation of health monitoring data exchange, integration, sharing
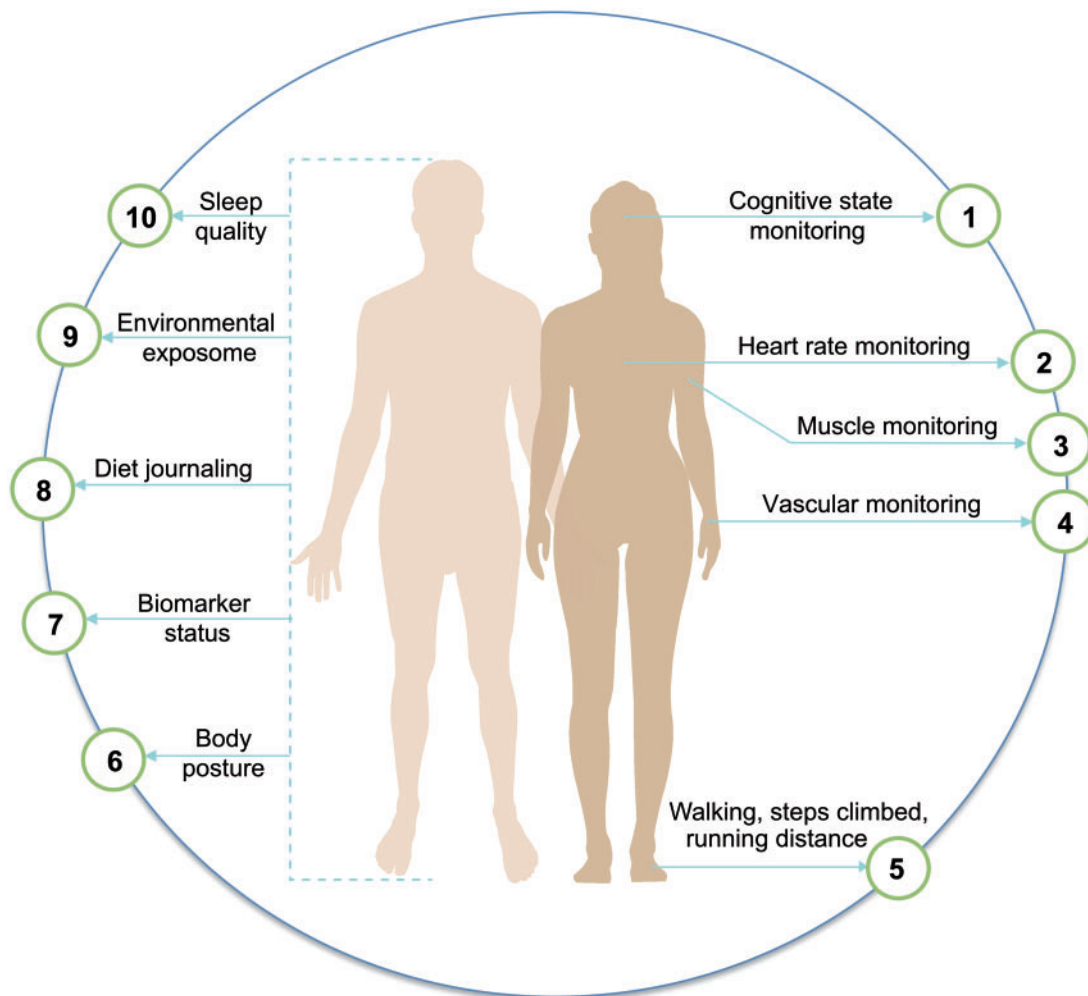
Figure 2. From health monitoring to predictive modeling of diseases: edges are different health monitoring data streams; nodes indicates disease areas where the health monitoring data can be used for prognostic, diagnostic, clinical, therapeutic or wellness interventions. 1: psychiatric and neurological disease, cerebrovascular disease, stress responses/autonomic reactivity, chronic pain; 2: cardiac arrest, myocardial infarction, coronary heart disease, anxiety, aerobic fitness levels; 3: chronic back pain, movement disorders (Parkinsonism), tremors, rehabilitation recovery, agility testing, dystonia, myalgia, chronic fatigue syndrome; 4: hypertension, orthostatic hypotension, chronic kidney disease, peripheral arterial disease, vasculitis (e.g. Lupus, Raynaud's disease); 5: movement disorders, rehabilitation, epilepsy, myalgia; 6: chronic and acute lung diseases, obstructive sleep apnea, sleep disorders, narcolepsy, synucleopathies; 7: insulin level (Type 1 or Type 2 diabetes); 8: diabetes, cardiovascular disease, inflammatory bowel disease, irritable bowel syndrome, gluten sensitivity, eating disorders; 9: chronic and acute lung diseases; 10: hyper/hypothyroidism, female endocrinology, obstructive sleep apnea, narcolepsy, neurologic, psychiatric, chronic fatigue syndrome and developmental disease.

and retrieval will be required to enable such integration. Structured ELSI and policy guidelines would also help patients or healthy volunteers decide on what data should to be integrated into their EMR. Databases that store such high-volume data would need to be secured to ensure a high degree of protection for sensitive patient data [134, 135]. The introduction of the Sensible Oversight For Technology Which Advances Regulatory Efficiency (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf) (SOFTWARE) Act of 2013 provides regulatory guidelines for development and implementation clinical software and health software along with existing regulations recommended by FDA for mobile app [136] and CDS [137]. Twenty-first Century Cures Act (https://www.congress.gov/bill/114th-congress/house-bill/6) further enhances the promise of improving the medical innovation for drug discovery by converging multiple streams of medicine, engineering and science [138]. Data-intensive applications that use wellness data should adhere to these standards for regulatory approval and thus enable reuse and transfer of software applications across multiple hospitals or health systems. Further studies are required to understand the impact of the wellness data sharing from patient perspective and its utility in the clinical setting from physician perspective.

Clinical applications of real-time biomedical and sensor data streams

Real-time biomedical or health monitoring allow for the characterization of intra-individual physiologic variation and the inter-individual impact of circadian fluctuations on physiological measures. Further, such tools allow for clinicians and scientists to examine physiology across a wide range of temporal resolutions that cannot be reproduced using the monitoring methods commonly used in the legacy health care system. Thus, active and passive monitoring and aggregation of individual-level wellness data using wearables and analytics of such data streams in the setting of disease prevalence and comorbidities provides a new way to study human diseases (Figure 2). The factors contributing to wellness state of human physiology are poorly understood, and understanding key cellular and molecular pathways associated with various aspects of wellness including physical-activity-induced health benefits would help to develop new therapies for non-communicable lifestyle diseases like atherosclerosis, heart disease, stroke, obesity and type-2 diabetes [139, 140]. Although this is not a trivial undertaking, such efforts could have a substantial impact on the management of highly prevalent diseases that comprise major sources of health care costs and mortality. Wearables and wearable data have various allied health care and wellness applications including improving recovery, rehabilitation, healthy behavior and mood enhancement [141–144].

Identification of missing variables to understand idiopathic conditions

Prognosis, diagnosis, treatment and management of idiopathic disease are challenging for care providers. Idiopathic conditions require increased hospitalization and affects patients' quality of life, morbidity and mortality [145]. Conditions like idiopathic restrictive cardiomyopathy [146, 147] and idiopathic interstitial pneumonia were associated with significantly higher mortality rates than a comparative disease with known etiology [148]. For example, respiratory diseases classified under interstitial lung disease including idiopathic interstitial pneumonias and its subtypes including idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis-ILD (interstitial lung disease), cryptogenic organizing pneumonia, acute interstitial pneumonia and lymphocytic pneumonia need more extensive investigations than conditions with specific clinical or sub-clinical phenotypes [149–152]. While factors contributing to the clinical phenotypes observed in patients are currently limited, integrating health-monitoring data with clinical data would provide additional features to elucidate subtypes or associations of various idiopathic diseases.

Real-time diagnosis of asymptomatic disease manifestations

Screening and management of patients with asymptomatic cardiovascular diseases including sudden cardiac death [153], asymptomatic incidences of heart attack [154], stroke, peripheral arterial disease and related disease manifestations are associated with significant mortality and morbidity, and the early detection of such pathology is of paramount importance. Emerging evidence suggests that predictive models can be designed to stratify patients at risk for cardiovascular outcomes [155–157]. Capturing continuous vital information for patients as they perform their daily activities of daily living will allow further insight into their state of health than single time-point measurements made in the clinic, translating to improved information for subsequent clinical decision making. Vital signs, like blood pressure, and most measurable physiology demonstrate a circadian pattern with significant fluctuations occurring throughout the day in healthy individuals. Currently, clinical decisions are based on the 'normal' blood pressure of 120/80 mmHg, and patients are considered hypertensive at 140/90 mmHg; however, studies with continuous monitoring of vitals have found that in a single healthy individual, blood pressure can range from ∼100/60 mmHg at night to 480/350 mmHg during heavy weight lifting [158]. For patients who experience episodic symptoms like chest pain on exertion or asthma attacks, continuous health vital sign monitoring provides a way of characterizing acute attacks within the patient's normal daily activities, as opposed to the current practice of using contrived cardiac stress tests or administering provoking drugs as a challenge test to induce acute attacks to make a diagnosis during the clinical visit. Further, such 'everyday monitoring' eliminates the confounding variables associated with the often stressful and anxiety-provoking environment of health care facilities. By capturing continuous vital sign data for populations of patients, we will be able to develop more sophisticated and elegant models for a patient's normal physiology, and enable identification of subtle or activity-specific changes toward pathophysiology early in the course of disease progression [112, 159, 160]. Improved characterization of this healthy-to-disease state transition will open the door to earlier and more effective preventative measures, and may have a substantial impact on developing predictive interventions for highly prevalent and morbid diseases including coronary artery disease and stroke.

Implementing informatics applications using real-time biomedical, health care and wellness data streams

Wearable sensors offer a unique way to gather data not available at the point of care. Integration of data from sensors and developing mHealth, clinical informatics and health informatics

applications to integrate seamlessly with existing infrastructure is essential for the use of diverse sensor data in a clinical setting [142, 161–166]. We are developing several clinical dashboard systems that converge health care and wellness data streams (Figure 3). For example, EHDViz (Figure 3A) is a clinical dashboard development framework to implement dynamic visualization dashboards that leverage a suite of open-source technologies (Manuscript submitted). Developing such clinical informatics or health informatics applications and testing the usability, utility and actionability of such applications are necessary for hospital or health-system wide adherence of such applications.

Role of translational bioinformatics in personalized biomedical, health and wellness monitoring

Data-intensive biological experiments and their translation to effective therapies, diagnostic aids and clinical interventions are common in medicine [167]. The first attempt for the clinical interpretation of whole genome showed that the index patient is at increased risk of cardiovascular disease that were not typically illustrative with existing risk prediction models [168] and the compendium of variants implicated in rare, common or orphan diseases are growing at a rapid pace. Temporal profiling of

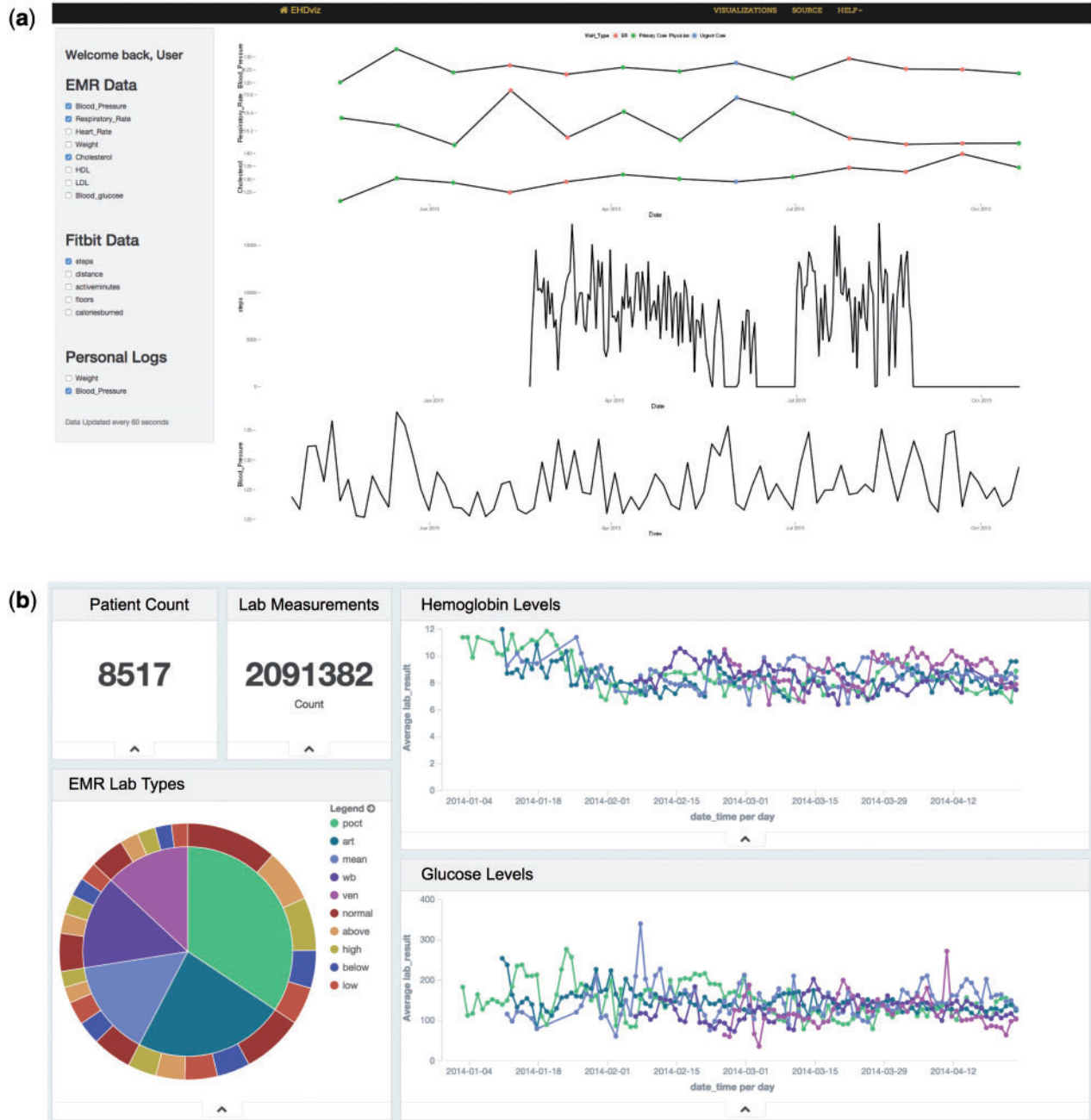
Figure 3. Visualizing biomedical, health care and wellness data streams. (**A**) A screenshot from EHDViz: a clinical data visualization dashboard combining provider generated clinical data with patient generated data. (**B**) Analytics dashboard implemented using Elastic and Kibana to analyze a large cohort of patients ($n = 8517$) with 2.91 million data points of laboratory measurements.

a single patient for 14 days using biological (genomics, proteomics, metabolomics and transcriptomics) and clinical phenotypes have revealed how longitudinal measurements of multiscale biological data showed the dynamics of biological pathways during illness and wellness [169, 170]. ClinicalTrials.gov lists 113 studies that use wearable devices (https://clinicaltrials.gov/ct2/results?term=%22wearable%22). Studies that implement wearables are targeted at patient populations with various conditions including heart failure, osteoarthritis, myocardial infarction, gait imbalance, etc. Wellness or health-monitoring devices are currently used for a variety of clinical studies, but studies that combine genomics or other multiscale biological experiments and wearables are limited [171].

Health monitoring data can complement EMRs for informing clinical decisions in select contexts. Translational bioinformatics approaches will be needed to determine the clinical significance of these new data streams, as there is little prior knowledge to guide the interpretation of results. While these data can provide a greater understanding of an individual's unique state of health and prevent unnecessary testing from incidental clinical findings, individualized risk models must be created that discern harmless deviation from the average population physiology from pathologic changes. In the absence of these models and informed interpretation of their results, innocuous incidental findings in new large data streams can lead to unnecessary follow-up testing and treatment, as previously cautioned against in genomic medicine. Integrating heath monitoring data and correlating it with various multi-omic data types can help elucidate intra-individual variations within a patient, and interaction effects between various clinical traits and disease phenotypes. Such integration would also help to see how the molecular profile of a patient evolves prior, during or after the onset of a disease [172]. Translational bioinformatics applications are required to improve the existing health information technology infrastructure and develop better applications that can integrate multiple biomedical data streams with health care and wellness data streams. Such applications could help in three broad areas: diagnostic alerts, predictive modeling and data-driven clinical trials.

Diagnostic alerts

A recent clinical trial result shows that automated mHealth interventions with tracking and texting would improve physical activity [173]. Wearable devices with EHR integration can be extended to design alert systems that provide continuous feedback to patients and care providers [174]. For example, tracking of the walking trend of a patient using a wearable device and integrating with health care providers during post-operative rehabilitation period and providing regular feedback using a mHealth application and assigning walking tasks could aid in improving the rehabilitation experience.

Predictive modeling

Design, development and implementation of the predictive models using health care, biomedical and wellness data could improve the process of data-driven health care delivery. For example, patients can be assessed for a variety of health risks hospitalization including hospital-acquired conditions like falls or air embolism (HAC, https://www.cms.gov/medicare/medicare-fee-for-service-payment/hospitalacqcond/hospital-acquired_conditions.html) and hospital-acquired infections like sepsis or pneumonia

(HAI; see http://www.cdc.gov/hai/), and necessary stratification measures can be taken. Ambulatory patients can be reviewed for wellness trends and inform them about their compliance or deviation to the wellness guidelines and potential risk of the onset of chronic diseases by integrating genomic risk scores with data from wearable devices. Developing real-time predictive models that aid in HAC, HAI and improving patient-provider feedback will lead to better measures for patient safety and improve the quality of care delivery.

Data-driven clinical trials

A recent FDA guideline for clinical trials and investigations details the importance of the risk-based approach and implementation of monitoring systems as part of clinical trials (See: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf). Patients enrolled in clinical trial require multiple visits to the clinic or clinical trial center for measuring vital signs and compiling data that could contribute to the outcome of the study. For critically ill or bed-ridden patients, this is a challenging task and influences the quality of life. Wearables and real-time data integration using data from wearables or home-based monitoring system with clinical-trial databases would enable such data collection coherent.

Future outlook

Implementing precision medicine in the clinical setting requires careful integration of multiple streams of data. We propose that precision medicine can enhance personalized clinical decisions with the access to health monitoring data of various physiological parameters of a patient before the incidence of disease, during the indolent/subclinical onset of disease and post-treatment. To enable precision medicine, a rapid and rational approach to integrating data from different sources is required. Comparable with the benefit of integrating genomic and other multiscale biological data for clinical decision-making and therapeutic stratification, defining individualized health status as the control of a patient could help to better understand the disease overall and tailor therapies and wellness interventions with better efficiency [175]. Improved big data analytics methods and predictive models that couples environmental data elements like weather and air quality and physiologic health monitoring with the existing EMR or PHR of patient would help to provide a better perspective of complex, chronic or rare human diseases. For example, the individualome data model and its data elements, integrated components and tools built on top of the model could help both health care providers and patient communities to understand, treat and manage diseases in better resolutions. Wellness interventions will also empower patients with timely alerts on health status or prognostic indications. As we continue into the era of individualized medicine, health-monitoring devices capable of monitoring different traits relevant to the disease phenome are integrated into such models, as individualome will play key role in health care. Although a necessary focus of modern data-driven medicine relies on potential methods of meaningfully integrating data from wearable technology and personal physiologic monitors into EMRs, it is important to keep in mind that the PHR may soon emerge as a resource equivalent to that of EMR at a fundamental level. PHRs may slowly comprise greater and greater proportions of EHRs with the relatively low regulatory burden, low financial barriers to entry and the rapid pace at which PHRs and related tools are being developed. PHRs, unlike EMRs, are designed to deliver value to patients, rather than provide an income stream to hospital systems.

The interoperability and portability of many PHR solutions may, over time, drive patients to demand that health care facilities play along. Further, it is this same set of attributes that makes collections of PHRs attractive targets for data collection when conducting health and wellness investigations using personal health monitoring data. Furthermore, a unified effort from industry, academia, health care information technology, regulatory agencies and care providers is required to address this emerging challenge. Initiatives to capture and integrate health care data with multiscale biomolecular and wellness data would help to design precise CDS and provide individualized care models for patients [36, 176].

Conclusions

Currently, clinical data repositories maintained by hospitals have limited access to health monitoring data from personalized health-monitoring devices or vice versa. Transparent, industry-academic-clinical collaborations are required to define health and wellness monitoring data interoperability along with existing initiatives for secure data interoperability that adhere to patient privacy and health care data compliances. New data models and analytic methods are required for effective integration of health monitoring data with EMRs and data types from multiscale biological profiling methods. We envisage that data models like individualome model will emerge as a community standard for wider adoption. As more and more patients and healthy volunteers are using health-monitoring devices, the need to integrate the data from such devices to the EMR and PHR is increasing. In the next 5 years, several open standards, data models and technologies will evolve to integrate health-monitoring data with EMR. Efforts for integration of health monitoring data with clinical, biomedical and multi-omic data types in the EMRs will mature. Advances in nanobiotechnology, microfluidics, material science, integrated circuit design and biosensor technologies will help to create health-monitoring devices with smaller footprints as skin patches or health monitoring tags with the ability to measure unique health traits. Custom designed, individualized devices to capture a particular feature relevant to patients will also be emerging. Practical data integration approaches using wireless protocols would enable seamless integration of health monitoring data and observational data in EMR. One of the use case for the actionability of health monitoring data is in the ability to integrate data from health-monitoring devices with the EMR or PHR of a patient coupled with alerts that patients and providers can receive for clinical, therapeutic or wellness interventions. Such initiatives will also lead to new and better endpoints for patient well-being and disease outcomes and help to define new intervention procedures to improve wellness and avoid or delay the patient transition from wellness to illness.

Key Points

- The ability to combine data from health-monitoring devices with the electronic medical record, personal health record, patient portal or other medically relevant health information data may provide valuable tools to aid in diagnosis, prevention and early interventions.
- New data models, computing infrastructure and integration systems are necessary for effective integration of health monitoring data with electronic medical records, data from pan-omics and multiscale experimental profiling.

- Transparent, industry-academic-clinical collaborations, interoperability guidelines and standardizations are needed to define health-monitoring data interoperability along with existing initiatives for secure data interoperability that adhere to current standards, patient safety and privacy compliances.
- Different features of real-time data capture, aggregation, analytics, visualization and integration of wellness data and its potential scientific, clinical and informatics applications and various challenges associated with scientific wellness are discussed.
- Integrating real-time, streaming biomedical, health care and wellness data with existing translational bioinformatics resources will accelerate the implementation of data-driven medicine in the clinical setting.

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