Translational Bioinformatics to Enable Precision Medicine for All: Elevating Equity across Molecular, Clinical, and Digital Realms

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Summary

Objectives: Over the past few years, challenges from the pandemic have led to an explosion of data sharing and algorithmic development efforts in the areas of molecular measurements, clinical data, and digital health. We aim to characterize and describe recent advanced computational approaches in translational bioinformatics across these domains in the context of issues or progress related to equity and inclusion.

Methods: We conducted a literature assessment of the trends and approaches in translational bioinformatics in the past few years.

Results: We present a review of recent computational approaches across molecular, clinical, and digital realms. We discuss applications of phenotyping, disease subtype characterization, predictive modeling, biomarker discovery, and treatment selection. We consider these methods and applications through the lens of equity and inclusion in biomedicine.

Conclusion: Equity and inclusion should be incorporated at every step of translational bioinformatics projects, including project design, data collection, model creation, and clinical implementation. These considerations, coupled with the exciting breakthroughs in big data and machine learning, are pivotal to reach the goals of precision medicine for all.

Keywords

Bioinformatics, health equity, genomics, precision medicine

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1 Introduction

Translational Bioinformatics is the development and use of computational approaches and tools that can reason over the enormous amounts of life science and clinical data being collected to advance medicine. While bioinformatics methodologies have been used to enable biological discoveries for decades, here the end product has to be translational, or applying to human health and disease [1].

Machine learning, a branch of artificial intelligence that is based upon data-driven model development that can identify patterns and make decisions with minimal human intervention, has become a technique that is increasingly utilized to make sense of health data for translational precision medicine applications. In the past few years, there have been multiple advances in data collection, informatics, and machine learning methodologies for understanding and addressing human diseases, particularly in an era that has been influenced by underlying pressure due to challenges brought on by the COVID-19 pandemic. Not only have there been challenges to control the pandemic due to the changing nature of SARS-CoV-2, the virus that causes COVID-19, but also systemic challenges due to shelter-in-place orders shifting healthcare to increasingly rely on the role of technology to facilitate remote, patient-centric healthcare delivery. Furthermore, the severity of this health crisis has resulted in an explosion of collaborations and data sharing efforts in the realms of molecular omics measurements [2], clinical data, and digital health [3, 4] for the advancement of machine learning approaches in precision medicine in many diseases beyond COVID-19 [5, 6].

These advances provide an incredible opportunity to impact disease therapeutics and diagnostics using data - molecular, clinical, and digital - and to better understand disease in the era of precision medicine [7]. As we explore these realms, it is imperative to evaluate potential inequities across the computational pipeline from data representation, algorithmic bias, healthcare applications, and impact. Scientific advances must be considered within a framework of equity and inclusion in order to prevent bias propagation, to avoid propagating health disparities in translational applications, and ultimately to further the goal of precision medicine to include and benefit diverse populations.

For example, in the past few years, studies leveraging data from the US National Institute of Health "All of Us" research program have explored the prevalence of diseases such as eczema in diverse racialized populations [8] and cardiovascular disease [9] in underrepresented populations, including underrepresented racialized individuals, people over the age of 75, people with disabilities, people who make less income, and people with less formal education. The data have also been used to study disparities

in family health history knowledge and the ability to afford medications for diseases such as glaucoma [10, 11].

In this article, we dive deeper into these domains and address several relevant questions. Can we more precisely and quickly diagnose disease using computational approaches? Can we use data to identify new therapeutics or new uses for existing drugs? How heterogeneous is complex disease? Are there specific groups of patients that might respond to treatment better? How can some of these approaches be implemented in the clinic? We further explore what the potential biases are in these data and approaches - are they really representative of the general population [12]? Finally, we discuss future directions and trends in translational bioinformatics.

2 Methods

For this review, we performed literature searches on PubMed, Google Scholar, and specific journals for publications from 2019 onward. Journals reviewed include Nature, Nature Digital Medicine, Nature Bioengineering, Lancet, The Journal of the American Medical Association, Journal of Medical Internet Research, The New England Journal of Medicine, The Journal of the American Medical Association, Journal of Medical Internet Research, The New England Journal of Medicine, and Bioinformatics.

We also performed keyword searches to identify relevant publications, with keywords chosen by both broad and specific translational informatics topics. Keywords for searches include broad informatics terms (e.g. "precision medicine", "translational bioinformatics", "translational informatics", "bioinformatics", "bias informatics", "machine learning bias", "multi omics", "bioinformatics equity", "diversity informatics", "drug repurposing"), molecularly relevant terms (e.g. "remdesivir covid", "cell free dna", "biomarker discovery", "omics biomarker discovery", "genetic precision medicine"), clinically relevant terms ("ehr", "electronic health record", "emr", "electronic medical record", "clinical trials", "clinical informatics", "all of us research program"), and digital health relevant terms ("digital biomarkers", "digital health", "mobile health"). References were also acquired from citations in papers identified from reviewed journals and keyword searches.

After surveying identified papers, chosen papers were determined by their breadth, novelty, impact, or relevance, with a particular focus on papers that touch upon equity or inclusivity in the informatics fields.

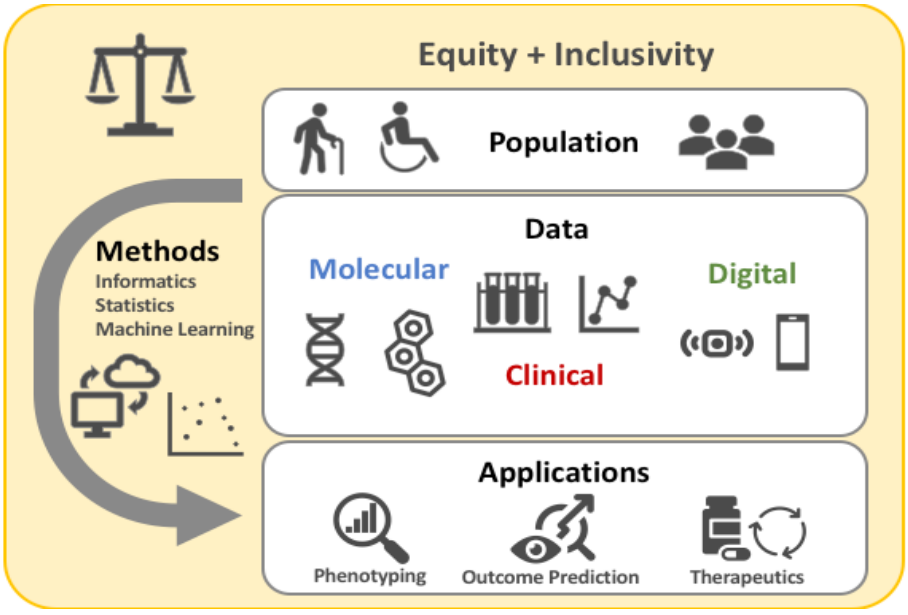

Fig. 1 Translational Bioinformatics in the Era of Precision Medicine. Here we present recent translational bioinformatics approaches that leverage molecular, clinical, and digital data to advance precision medicine. We discuss specific applications such as phenotyping, outcome prediction, and therapeutics, as well as methods including informatics, statistics, and machine learning, all within the context of equity and inclusion.

3 Results

In this review, we cover recent translational bioinformatics approaches for various applications, including disease characterization, predictive modeling, and therapeutics that leverage molecular, clinical, and digital data (Figure 1). In particular, we focus on aspects of equity and inclusion, which should be considered at every step of the process including population identification, data collection, methodology, and applications to achieve precision medicine for all.

3.1 Molecular Informatics

Recently, multiple exciting advances have been made to utilize omics data to gain new insights into heterogeneous diseases, discover new biomarkers, and identify new therapeutics through approaches that include drug repurposing and machine learning. In addition to leveraging diverse molecular measurements including gene expression, proteomics, microbiome, epigenetics, and others, researchers have been able to capture many of these types of measurements on a single cell level. As the technologies become more advanced, there is also an increasing recognition of the need for more equitable representation in omics studies.

Multi-omics studies

The expansion of multi-omics studies has enabled the discovery of potential mechanisms underlying complex diseases and health outcomes. Studies investigating inflammatory bowel disease (IBD) [13] and irritable bowel syndrome (IBS) [14], for instance, integrated the use of host and microbial datasets that included microbial metagenomics and host transcriptomics, among other omics sourc-

es, to investigate the interacting host and microbial factors influencing disease. Such studies can lead to clinically relevant findings, such as targeting purine metabolism for IBS. Crowdsourcing approaches applied to multi-omics data have also been utilized for predicting gestational age and preterm birth using gene expression data and proteomics through an IBM DREAM challenge [15]. These crowdsourcing challenges help to not only bring together multiple skill sets across the medical and computational community, but also help raise awareness of important research questions. Taken together, these studies demonstrate how multi-omics integration and analysis can yield insights into the underlying heterogeneity of a multitude of diseases that could eventually lead to personalized treatment for patients.

Biomarker discoveries

Omics data have been increasingly utilized for biomarker discovery. The Circulating Cell-free Genome Atlas Study (CCGA consortium) used an ensemble machine learning approach to classify patients with cancer, as well as the cancer's tissue of origin, using study participants' (2,482 and 4,207 patients with and without cancer, respectively) methylation patterns derived from cell-free DNA (cfDNA) [16]. This strongly suggests that analyzing methylation patterns from cell-free DNA has the potential to detect cancer at earlier stages when it is usually more treatable. cfDNA approaches to identify infectious disease using metagenomic next generation sequencing have also been studied [17], although full clinical implementation and integration with standard molecular and pathological methods has yet to be achieved.

Drug repurposing

Recent advances in drug repurposing, or identifying new uses for FDA approved drugs, hold promise for identifying potential therapeutics for new and heterogeneous diseases. Recently, our team used a transcriptomics-based drug repurposing pipeline to identify the loop diuretic drug bumetanide as a potential treatment for *APOE4*-associated Alzheimer's disease (AD) [18]. Encouragingly, bumetanide was found to attenuate AD-like phenotypes in mouse models, and patients taking bumetanide were found to have a lower prevalence of AD, demonstrating how this approach may enable personalized treatment for patients based on their individual genetics. Another approach for finding AD treatments utilized machine learning on lists of genes that were differentially expressed in neural cells when exposed to a drug [19]. Logistic regression classifiers to predict early- versus late- stage AD were then trained using these gene-list-specific gene expression data from post-mortem samples, and gene lists with best predictive performances were further probed to identify potential mechanisms underlying AD for therapeutic purposes.

Other studies aim to extend the accessibility of drug-repurposing studies to wet lab scientists. Cancer researchers can now use the Open Cancer TheraApeutic Discovery website (http://octad.org) to compare compound-induced gene expression signatures with gene expression data from cancer patients' tissue samples [20]. We anticipate open-source efforts for drug repurposing to eventually expand to other diseases. The COVID-19 pandemic has also motivated researchers to identify repurposed FDA-approved drugs (e.g., remdesivir [21]) to enable rapid implementation into the clinic for patients with COVID-19. Novel drug repurposing approaches have identified other potential drugs that could treat SARS-CoV-2 infection. Researchers in one study, for instance, leveraged consensus rankings from three AI- and network- based algorithms to identify potential therapeutics [22], resulting in four drugs that could be further evaluated for efficacy against SARS-CoV-2 infection. These drug repurposing methods hold great potential for bringing therapeutic advances to a multitude of diseases in the coming decade.

Equity considerations

Despite many informatics advancements, we must ensure that these advances can benefit everyone equally. The National Human Genome Research Institute's (NHGRI) principles and values for The Forefront of Genomics include recruiting and retaining a diverse genomics workforce as well as the inclusion of individuals from diverse genetic ancestries into genomics studies [23]. The NHGRI anticipates that genomics testing will become part of routine clinical care. Currently, however, genomics testing has the potential to exacerbate existing health disparities, since people of European ancestry are overwhelmingly represented in GWAS studies, accounting for over 80% of participants [24]. Polygenic risk scores derived from such studies can have less predictive power for individuals from ancestries that are not European.

Recent advances and ongoing studies aim to address the underrepresentation of individuals with non-European ancestry. The Population Architecture using Genomics and Epidemiology (PAGE) study recruited nearly 50,000 individuals with non-European ancestry, where researchers found 27 novel loci [25]. These novel loci are associated with a range of phenotypes, including but not limited to lipid (e.g., HDL), lifestyle (e.g., cigarettes smoked on a daily basis), glycemic (e.g., fasting glucose), and anthropometric (e.g., height) traits. Importantly, they also found effect size heterogeneity for variants when individuals were stratified by genetic ancestry. They also discovered new single nucleotide polymorphisms associated with phenotypes in specific genetic ancestries. The PAGE study demonstrates that incorporating diverse populations in studies has the potential to uncover ancestry-specific findings that can ultimately impact clinical care in the era of precision medicine. The All of Us research program [26], which has enrolled nearly 330,000 participants since 2018 [27], aims to ultimately enroll, at a minimum, one million participants that are traditionally underrepresented in research. All of Us collects not only molecular data, but also electronic health record (EHR) data, survey data on sociodemographic factors and other social determinants of health, and digital health data. We anticipate that All of Us studies will continue to derive new insights into human health and disease through the integration and analysis of molecular, clinical, and digital health datasets that are relevant to and beneficial for individuals from diverse genetic ancestries. To ensure that this equitable benefit from precision medicine is realized, it is imperative for

researchers to work with underrepresented communities [28] and to address pressing ethical considerations [29].

3.2 Clinical Informatics

Clinical data is sourced from electronic health records (EHR), clinical trials, imaging, and vital records. In many cases, this data has existed for decades, but has only recently been leveraged in the context of translational bioinformatics research. Researchers can utilize these datasets to connect patients' lab tests, diagnoses, medications, and outcomes. For example, a researcher can trace a diabetes patient's medical history from an abnormal A1C test result to a diabetes diagnosis, then to a metformin prescription, and finally to an improvement in symptoms. These types of clinical analyses can be scaled up to huge cohorts of patients. In one study, researchers explored variation in treatment utilization for 97,231 patients with type 2 diabetes across five major health systems in California [30]. We can also contextualize research questions within economic and social structures. For example, a recent study of patients with pediatric diabetes in the UK found that socioeconomic status and exposure to racism were associated with the type of treatment regimen a patient was on [31].

In the past couple of years, clinical informatics research has yielded exciting breakthroughs in clinical phenotyping, disease prediction, treatment selection, and implementation strategies. It has also raised pressing questions about how to develop and apply clinical algorithms that treat people equitably.

Clinical phenotyping

Clinical phenotyping is the characterization of patients based on their symptoms, diagnoses, demographics, and relevant medical histories. This process is typically carried out quantitatively. It can range from grouping patients by diagnosis counts to performing sophisticated dimensionality reduction algorithms based on thousands of possible clinical features. Unsupervised machine learning algorithms trained on clinical data have identified novel subtypes in many diseases, including type 2 diabetes, Parkinson's disease, Alzheimer's disease, and depression [32–34]. Characterizing disease subtypes can help us better understand their etiologies, how heterogeneous they are, and how to treat them.

Disease prediction

There has been an explosion of research in clinical predictive algorithms [35]. These algorithms are designed to estimate a patient's risk of developing a particular phenotype or requiring a specific type of clinical care. Some recent applications of predictive algorithms include preterm birth [36], mortality of preterm infants [37], cardiovascular events [38], COVID-19 outcomes [39], critical illness [40], impact of environmental disasters [41], acute kidney injury [42], length of hospital stay [42], 30-day hospital readmission [43], retention of care [44], and postoperative in-hospital mortality [45]. Two important considerations described in these studies are interpretability and transportability. Many researchers are moving away from "black box" algorithms and moving towards algorithms whose logic is accessible and aligned with biomedical domain knowledge. Once a model is developed using data from one medical center, it is useful to validate it using data from another medical center. Because there can be huge differences in the patient populations and clinical data systems between institutions, it is important to design algorithms that are resilient to those differences.

Treatment selection

Clinical data research is transforming how we discover and evaluate treatments for diseases. The traditional drug development process can take many years and cost millions, or even billions, of dollars [46]. Meanwhile, many clinical datasets contain decades' worth of patient medication, procedure, and diagnosis histories. In the past few years, scientists have leveraged these datasets to discover candidates for drug repurposing [18, 47, 48], evaluate treatments using in silico clinical trials [49], and characterize treatment utilization across providers [3], institutions [30], and time [51]. Looking ahead, real-world data studies have the potential to complement the existing drug development process and spur new ideas about treating diseases.

Implementation

The final goal for many clinical bioinformatics research is translating them into clinical practice. There have been several success stories, including predicting acute care in patients undergoing radiation therapy [52], identifying adults at risk for in-hospital clinical deterioration [53], guiding ultrasound image capture [54], and managing COVID-19 outbreaks [55]. A key component of successful projects is close collaboration with clinicians and healthcare workers to design a study that would be genuinely useful for them in the clinic [56].

Equity considerations

As bioinformatics and clinical care become increasingly intertwined, it is important to design algorithms that can benefit all patients, particularly those that have been historically excluded or harmed. This starts with the data. Black, Indigenous, Latino, and Asian participants of all genders, in addition to women from all racialized populations, are underrepresented in many clinical trial datasets [57–64]. For LGBTQIA+ patients, EHR datasets often have missing or incorrect information about their gender identities and sexual orientation [65, 66]. In addition to bias from the data, bias can also come from the logic behind the algorithms, either implicitly [12] or explicitly [67]. With careful consideration and minimization of bias, we can work towards building algorithms that can benefit everyone. To this end, it is integral that bioinformatics research teams are formed of people with lived and learned understandings of anti-racism, intersectional feminism, equity, and justice.

3.3 Digital Health Informatics

In the past two years, the COVID-19 pandemic has created many challenges and opportunities in utilizing technology to aid in healthcare when direct face-to-face meetings are less feasible, such as through video

visits (telehealth) and utilization of sensors on mobile phones or through commercially available wearables [68]. This had led to an explosion and maturation of the utilization of digital health, informatics, and machine learning as a way to combat the pandemic from both a public health perspective on prevention and control, as well as with providing individualized healthcare.

Mobile devices and wearables

Mobile phones and wearables help provide a source of data that can be analyzed for health outcomes. Population level information has been utilized to help with contact tracing at the start of the pandemic [69], as well as with modeling infectious spread throughout numerous countries [70, 71]. There have also been efforts to utilize sensor data and machine learning to detect COVID-19 infection [72] via tracking of vital signs, sleep, activity, and even speech [73, 74]. These 'digital biomarkers' provide an alternative proxy to invasive blood tests or molecular biomarkers, and in the past years these portable sensors have also been investigated in their potential for disease diagnostics beyond COVID-19. Some examples of digital biomarker applications include screening for depression [75], diagnosis of mild cognitive impairment [76], prediction of Parkinson's disease severity [77], detection of neurological or psychiatric disorders [78], and evaluating frailty in older people [79]. These applications either provide warnings or recommendations when implemented through consumer applications, or are slowly integrating into medical care as evident in the use of digital biomarkers for onsite patient triage and evaluation.

Translational applications

Given the availability and ease of digital health, there has also been much work from the translational perspective in the past years in applying modeling and analysis approaches to aid in the advancement of medical care. One translational application includes aiding in physician monitoring of disease progression and outcomes to better inform clinical decision-making and management for complex diseases. For example, there are not only efforts to improve inpatient and at-home monitoring of vital signs [80–82], there are also efforts to obtain non-invasive proxies for metrics such as glucose [83] and inflammation status [84]. In the upcoming years, there will likely be more efforts utilizing digital biomarkers for precision medicine applications, such as in cancer and autoimmune diseases [85, 86], in order to identify the most optimal therapeutic approaches that account for disease complexity and heterogeneity. Furthermore, computational approaches are being developed to manage the large data complexity of information acquired to derive scientific or medical insights via phenotyping [87] and application of artificial intelligence for predicting clinical or behavioral states [88, 89].

Some digital health applications explored in the past years include incorporation of interactivity and feedback, such as through patient-facing mobile applications. Mobile applications help aid in patient-centric care via patient education and treatment support, which is of particular importance for healthcare affordability and access to health services and information. There has been an increase in the availability of apps for a variety of diseases, such as for vital sign monitoring, glucose monitoring for diabetes, weight management [90], mental health [91], and even for managing postpartum maternal health [92]. Informatics and artificial intelligence techniques can also be used to guide patients in management of their own care [93], such as in determining optimal drug dosage or timing [94, 95], or in predicting risk and providing recommendations from surveys and inputted data points [96, 97]. In particular, these translational applications have great opportunities for improving equity and inclusion in disease care, such as in aiding health management for those with disabilities [98], complex diseases [99, 100], or in under-resourced locations [101].

Equity considerations

With the impetus that comes from the COVID-19 pandemic, technology and digital health are expected to continually become integrated into clinical care and utilized for scientific and clinical research [68]. This spans a wide range of data types and applications, ranging from public health analysis of phones, networks, the internet, and GPS to individualized applications from both the clinical perspective (EHR, telehealth, medical devices) and from the patient perspective (wearables, mobile applications). There is therefore not a better time than now to talk about opportunities and issues, particularly with consideration of equity. These opportunities include access, affordability, decreased time in the hospital, as well as early detection and prevention for public health [98]. With the maturation of digital health approaches, beyond issues regarding privacy and regulations, considerations will also need to be made for accommodations for different levels of technological literacy [102]; accessibility for culturally diverse populations [103–105], older people [106, 107], and people with disabilities [98, 103]; adaptability to rural environments [108]; simplification for various levels of health literacy [109, 110], and access to fundamental tools and technology [111]. In particular, with modeling and scientific inquiry on digital health data, there will need to be deliberate inclusion of diverse populations in data acquisition [112, 113] and modeling approaches to advance health equity [114]. With these considerations in place, digital health can become an essential way to bring informatics into accessible and equitable translational applications.

4 Discussion

In this review, we discussed the role that molecular, clinical, and digital data paired with advanced computational techniques have played in advancing disease diagnostics and therapeutics. We describe approaches leveraging molecular data, such as multi-omics integration, biomarker discovery, and computational drug repurposing. We also presented sources of clinical data, including electronic health records, clinical trials, imaging, and vital records, and how these resources have been leveraged to carry out predictive modeling and therapeutic discovery for clinical implementation. Finally, we discussed digital health data such as sensors and mobile health, and the types of applications it has been leveraged in for biomedical discovery. In particular, we present

these domains in the context of recent years, including influences from the COVID-19 pandemic and of the importance of equity and inclusion in guiding future translational bioinformatics applications.

Equity is an integral component of precision medicine. In this review, we highlighted several examples of innovative research that explore the process of integrating computational advancements with equity considerations. There is an increasing body of literature that prioritizes equity across the translational bioinformatics pipeline, including in data acquisition, analysis and modeling techniques, and data interpretation and applications. We are hopeful that this will continue and expand in the future.

Bioethicists such as Sandra Soo-Jin Lee have argued that providing biomedical data, including but not limited to omics, EHR, and digital health data, is a 'gift' that carries with it an ethical obligation of responsibility, reciprocity, and respect [29]. Lee proposes that research participation establishes a relationship between researchers and participating individuals and communities that is bound by these relational ethical obligations [29]. If we do not meet these obligations, it has been argued that we could damage trust, which may lead to the reluctance of underrepresented individuals and communities in participating in precision medicine research [28, 29]. We must be mindful of how we can engage with underrepresented individuals and communities in a way that empowers them to make decisions about how their data are being used and accessed, including having underrepresented individuals as part of the 'we'. Keolu Fox, for example, suggests that we can fulfill our obligations of responsibility, reciprocity, and respect by creating new frameworks where individuals and/or communities directly benefit from research findings by receiving proceeds and investments (e.g., through individual- and collective- interest models) [28].

To achieve equity, we must also remedy current inequities in data collection, like the missingness of non-biological data, so that researchers can explore all the factors that can influence a person's health [29]. For instance, systematic inclusion of individuals' racialized identity, gender identity, disabilities, and other demographic factors in EHR data [29, 115] can help researchers better understand potential health disparities that impact individuals with specific identities. Additionally, many health clinics that serve people with fewer economic resources currently do not have EHR systems [29]. Implementing EHR systems more widely can help with gathering data more equitably. Encouragingly, many efforts are underway for equitable data representation, such as through the All of Us research program and deliberate inclusion of diverse populations in research studies, yet this is only the beginning.

Finally, as we have seen, machine learning has become increasingly important in precision medicine research. To achieve equity, ethical considerations must become an essential component of the machine learning pipeline, from defining problems and outcomes to model development and implementation. In particular, we must consider algorithmic fairness, which aims to achieve equal performance for individuals in protected groups. To achieve equity, however, we also need to be mindful of the context in which these models are developed. For example, developers can derive insight into the context of features that they may consider in their models by consulting and collaborating with domain experts (e.g., community experts, health equity researchers, and disease experts) such as in the identification of confounding factors. Mhasawade *et al.*, suggest that we consider and model the complex relationships social determinants have on a person's health, both at an individual level and at a macro level [116]. They also encourage developers to capture these relationships in a way that reflects the flexibility of social determinants; i.e., in a way that captures their intervenability. Additionally, Mhasawade *et al.,* and Lett *et al.*, advocate for the inclusion of variables that race is currently used as a proxy for, such as formal education level and income [116, 117]. Both papers also argue that we must capture intersectionality (e.g., the impact of racism and sexism on an individual) in a meaningful way, for example by utilizing "multi-level analysis of individual heterogeneity and discrimination accuracy", which captures variation between and within groups [116]. Finally, both papers argue that we need models, such as agent-based models, that can capture the complex relationships between an individual and the environments they are embedded in (i.e., the socio-ecological framework). With these considerations, model developersWith these considerations, model developers can build models that benefit diverse individuals and communities. Strategies toward this goal include: evaluating the representativeness of the data analyzed, implementing metrics for model fairness [118] or bias [119], and examining the model through existing frameworks on algorithmic fairness [120, 121]. After model implementation, we can systematically audit these models periodically to ensure that they do not perpetuate bias and remain generalizable [115]. Finally, to leverage machine learning for health equity, Mhasawade *et al.*, emphasize the need for these models to extend beyond clinical decision making in a healthcare context in order to maximize beneficial health outcomes for all.

In this era, there is an ability to acquire limitless data at both population and individual levels that includes but is not limited to genetic data, transcriptomics data, other molecular data, clinical data, laboratory results, sensor data, and digital metrics. These datasets underlie the recent explosion of informatics and machine learning in scientific and translational applications, particularly as demonstrated during the COVID-19 pandemic [22, 122–124]. These techniques have been developed to not only aid in advancing scientific knowledge, but also to identify therapeutic targets and repurpose approved drugs, as well as support medical decision making, precision medicine applications, and patient-centric care delivery. The next decades will allow these applications to continually mature and integrate into various applications in society. With this change, there is a lot of potential for considerations of accessibility, such as integrating diverse datasets and inclusion of those living in remote areas, with disabilities, or with complex diseases [98, 111]. With the internet and patient-centric applications such as interactive user interfaces, there is also a potential for improving health literacy and health education [102, 125, 126].

Nevertheless, there are still many limitations in translational informatics fields. Science and machine learning on diverse populations can only perform as well as the data represented. While there have been recent considerations in acquiring data on diverse populations or accounting for bias,

there is still more work to be done to ensure equitable data collection [29, 113]. Similarly, representation should be considered when reviewing scientific papers or models implemented in clinical practice or in consumer applications. Furthermore, technological literacy is a barrier for both clinicians and patients, which is an important consideration when designing translational tools for clinical support, data acquisition, and the delivery of healthcare. Lastly, basic access to institutions or devices are fundamental to ensure diverse inclusion across the spectrum, from data inclusion to digital healthcare accessibility [127–129]. As such, in the next decade, there is much need to center equity and inclusion when collecting and acquiring data, analyzing data, implementing models, and developing physician- or consumer-facing translational applications.

Given the wealth and availability of genomic, transcriptomic and other types of molecular data together with rich clinical phenotyping and digital health data, computational integrative methods provide a powerful opportunity to improve human health. There are different types of integrative models that can be applied to bring together diverse data to better inform disease diagnostics and therapeutics. More specifically, machine learning has powered a new path to transform data into knowledge through predictive modeling and analytics and has been gaining particular importance in the context of modeling data longitudinally. By integrating data across measurement modalities as well as elevating equity at each step of the research process, we can get a bit closer to achieving precision medicine for all.

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References

1. Butte AJ. Translational bioinformatics: coming of age. J Am Med Inform Assoc 2008 Nov-Dec;15(6):709-14.
2. Nicholls SM, Poplawski R, Bull MJ, Underwood A, Chapman M, Abu-Dahab K, et al; COVID-19 Genomics UK (COG-UK) Consortium. CLIMB-COVID: continuous integration supporting decentralised sequencing for SARS-CoV-2 genomic surveillance. Genome Biol 2021 Jul 1;22(1):196.
3. Bennett TD, Moffitt RA, Hajagos JG, Amor B, Anand A, Bissell MM, et al; National COVID Cohort Collaborative (N3C) Consortium. Clinical Characterization and Prediction of Clinical Severity of SARS-CoV-2 Infection Among US Adults Using Data From the US National COVID Cohort Collaborative. JAMA Netw Open 2021 Jul 1;4(7):e2116901.
4. Gunasekeran DV, Tseng RMWW, Tham YC, Wong TY. Applications of digital health for public health responses to COVID-19: a systematic scoping review of artificial intelligence, telehealth and related technologies. NPJ Digit Med 2021 Feb 26;4(1):40.
5. Maher B, Van Noorden R. How the COVID pandemic is changing global science collaborations. Nature 2021 Jun;594(7863):316-9.
6. Sahoo D, Katkar GD, Khandelwal S, Behroozikhah M, Claire A, Castillo V, et al. AI-guided discovery of the invariant host response to viral pandemics. EBioMedicine 2021 Jun;68:103390.
7. Hartl D, de Luca V, Kostikova A, Laramie J, Kennedy S, Ferrero E, et al. Translational precision medicine: an industry perspective. J Transl Med 2021 Jun 5;19(1):245.
8. Leasure AC, Cohen JM. Prevalence of eczema among adults in the United States: a cross-sectional study in the All of Us research program. Arch Dermatol Res 2022 Feb 11.
9. Acosta JN, Leasure AC, Both CP, Szejko N, Brown S, Torres-Lopez V, et al. Cardiovascular Health Disparities in Racial and Other Underrepresented Groups: Initial Results From the All of Us Research Program. J Am Heart Assoc 2021 Sep 7;10(17):e021724.
10. Hull LE, Natarajan P. Self-rated family health history knowledge among All of Us program participants. Genet Med 2022 Apr;24(4):955-61.
11. Delavar A, Radha Saseendrakumar B, Weinreb RN, Baxter SL. Racial and Ethnic Disparities in Cost-Related Barriers to Medication Adherence Among Patients With Glaucoma Enrolled in the National Institutes of Health All of Us Research Program. JAMA Ophthalmol 2022 Apr 1;140(4):354-61.
12. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science 2019 Oct 25;366(6464):447-53.
13. Lloyd-Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW, et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature 2019 May;569(7758):655-62.
14. Mars RAT, Yang Y, Ward T, Houtti M, Priya S, Lekatz HR, et al. Longitudinal Multi-omics Reveals Subset-Specific Mechanisms Underlying Irritable Bowel Syndrome. Cell 2020 Sep 17;182(6):1460-1473.e17.
15. Tarca AL, Pataki BÁ, Romero R, Sirota M, Guan Y, Kutum R, et al. Crowdsourcing assessment of maternal blood multi-omics for predicting gestational age and preterm birth. Cell Rep Med 2021 Jun 15;2(6):100323.
16. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol 2020 Jun;31(6):745-59.
17. Hogan CA, Yang S, Garner OB, Green DA, Gomez CA, Dien Bard J, et al. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. Clin Infect Dis 2021 Jan 27;72(2):239-45.
18. Taubes A, Nova P, Zalocusky KA, Kosti I, Bicak M, Zilberter MY, et al. Experimental and real-world evidence supporting the computational repurposing of bumetanide for APOE4-related Alzheimer's disease. Nature Aging 2021;1:932–47.
19. Rodriguez S, Hug C, Todorov P, Moret N, Boswell SA, Evans K, et al. Machine learning identifies candidates for drug repurposing in Alzheimer's disease. Nat Commun 2021 Feb 15;12(1):1033.
20. Zeng B, Glicksberg BS, Newbury P, Chekalin E, Xing J, Liu K, et al. OCTAD: an open workspace for virtually screening therapeutics targeting precise cancer patient groups using gene expression features. Nat Protoc 2021 Feb;16(2):728-53.
21. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020 Nov 5;383(19):1813-26.
22. Morselli Gysi D, do Valle Í, Zitnik M, Ameli A, Gan X, Varol O, et al. Network medicine framework for identifying drug-repurposing opportunities for COVID-19. Proc Natl Acad Sci U S A 2021 May 11;118(19):e2025581118.
23. Green ED, Gunter C, Biesecker LG, Di Francesco V, Easter CL, Feingold EA, et al. Strategic vision for improving human health at The Forefront of Genomics. Nature 2020 Oct;586(7831):683-92.
24. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet 2019 Apr;51(4):584-91.
25. Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature 2019 Jun;570(7762):514-8.
26. All of Us Research Program Investigators. The "All of Us" research program. New Engl J Med 2019;381(7):668-76.
27. New Data Release: Filling Out the Pandemic Picture; 2021.
28. Fox K. The Illusion of Inclusion - The "All of Us" Research Program and Indigenous Peoples' DNA. N Engl J Med 2020 Jul 30;383(5):411-3.

29. Lee SS. Obligations of the "Gift": Reciprocity and Responsibility in Precision Medicine. Am J Bioeth 2021 Apr;21(4):57-66.
30. Peterson TA, Fontil V, Koliwad SK, Patel A, Butte AJ. Quantifying Variation in Treatment Utilization for Type 2 Diabetes Across Five Major University of California Health Systems. Diabetes Care 2021 Apr;44(4):908-14.
31. Catherine JP, Russell MV, Peter CH. The impact of race and socioeconomic factors on paediatric diabetes. EClinicalMedicine 2021 Nov 6;42:101186.
32. Landi I, Glicksberg BS, Lee HC, Cherng S, Landi G, Danieletto M, et al. Deep representation learning of electronic health records to unlock patient stratification at scale. NPJ Digit Med 2020 Jul 17;3:96.
33. Alexander N, Alexander DC, Barkhof F, Denaxas S. Identifying and evaluating clinical subtypes of Alzheimer's disease in care electronic health records using unsupervised machine learning. BMC Med Inform Decis Mak 2021 Dec 8;21(1):343.
34. Kung B, Chiang M, Perera G, Pritchard M, Stewart R. Identifying subtypes of depression in clinician-annotated text: a retrospective cohort study. Sci Rep 2021 Nov 17;11(1):22426.
35. Pencina MJ, Goldstein BA, D'Agostino RB. Prediction Models - Development, Evaluation, and Clinical Application. N Engl J Med 2020 Apr 23;382(17):1583-6.
36. Rattsev I, Flaks-Manov N, Jelin AC, Bai J, Taylor CO. Recurrent preterm birth risk assessment for two delivery subtypes: A multivariable analysis. J Am Med Inform Assoc 2022 Jan 12;29(2):306-20.
37. Feng J, Lee J, Vesoulis ZA, Li F. Predicting mortality risk for preterm infants using deep learning models with time-series vital sign data. NPJ Digit Med 2021 Jul 14;4(1):108.
38. Zhao J, Feng Q, Wu P, Lupu RA, Wilke RA, Wells QS, et al. Learning from Longitudinal Data in Electronic Health Record and Genetic Data to Improve Cardiovascular Event Prediction. Sci Rep 2019 Jan 24;9(1):717.
39. Osborne TF, Veigulis ZP, Arreola DM, Röösli E, Curtin CM. Automated EHR score to predict COVID-19 outcomes at US Department of Veterans Affairs. PLoS One 2020 Jul 27;15(7):e0236554.
40. Lauritsen SM, Kristensen M, Olsen MV, Larsen MS, Lauritsen KM, Jørgensen MJ, et al. Explainable artificial intelligence model to predict acute critical illness from electronic health records. Nat Commun 2020 Jul 31;11(1):3852.
41. Boland MR, Davidson LM, Canelón SP, Meeker J, Penning T, Holmes JH, et al. Harnessing electronic health records to study emerging environmental disasters: a proof of concept with perfluoroalkyl substances (PFAS). NPJ Digit Med 2021 Aug 11;4(1):122.
42. Song X, Yu ASL, Kellum JA, Waitman LR, Matheny ME, Simpson SQ, et al. Cross-site transportability of an explainable artificial intelligence model for acute kidney injury prediction. Nat Commun 2020 Nov 9;11(1):5668.
43. Tomašev N, Harris N, Baur S, Mottram A, Glorot X, Rae JW, et al. Use of deep learning to develop continuous-risk models for adverse event prediction from electronic health records. Nat Protoc 2021 Jun;16(6):2765-87.
44. Ramachandran A, Kumar A, Koenig H, De Unanue A, Sung C, Walsh J, et al. Predictive Analytics for Retention in Care in an Urban HIV Clinic. Sci Rep 2020 Apr 14;10(1):6421.
45. Lee CK, Samad M, Hofer I, Cannesson M, Baldi P. Development and validation of an interpretable neural network for prediction of postoperative in-hospital mortality. NPJ Digit Med 2021 Jan 8;4(1):8.
46. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA 2020 Mar 3;323(9):844-53.
47. Zhou M, Zheng C, Xu R. Combining phenome-driven drug-target interaction prediction with patients' electronic health records-based clinical corroboration toward drug discovery. Bioinformatics 2020 Jul 1;36(Suppl_1):i436-i444.
48. Oskotsky T, Maric I, Tang A, Oskotsky B, Wong RJ, Aghaeepour N, et al. Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants. JAMA Netw Open 2021 Nov 1;4(11):e2133090.
49. MacLeod AR, Peckham N, Serrancolí G, Rombach I, Hourigan P, Mandalia VI, et al. Personalised high tibial osteotomy has mechanical safety equivalent to generic device in a case-control in silico clinical trial. Commun Med (Lond) 2021 Jun 30;1:6.
50. Hong JC, Spiegel DY, Havrilesky LJ, Chino JP. High-volume providers and brachytherapy practice: A Medicare provider utilization and payment analysis. Brachytherapy 2018 Nov-Dec;17(6):906-11.
51. Braunlin M, Belani R, Buchanan J, Wheeling T, Kim C. Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011-2019 oncology clinic electronic health record data. Leuk Lymphoma 2021 Feb;62(2):377-86.
52. Hong JC, Eclov NCW, Dalal NH, Thomas SM, Stephens SJ, Malicki M, et al. System for High-Intensity Evaluation During Radiation Therapy (SHIELD-RT): A Prospective Randomized Study of Machine Learning-Directed Clinical Evaluations During Radiation and Chemoradiation. J Clin Oncol 2020 Nov 1;38(31):3652-61.
53. Escobar GJ, Liu VX, Schuler A, Lawson B, Greene JD, Kipnis P. Automated Identification of Adults at Risk for In-Hospital Clinical Deterioration. N Engl J Med 2020 Nov 12;383(20):1951-60.
54. Muse ED, Topol EJ. Guiding ultrasound image capture with artificial intelligence. Lancet 2020 Sep 12;396(10253):749.
55. Reeves JJ, Hollandsworth HM, Torriani FJ, Taplitz R, Abeles S, Tai-Seale M, et al. Rapid response to COVID-19: health informatics support for outbreak management in an academic health system. J Am Med Inform Assoc 2020 Jun 1;27(6):853-9.
56. Adler-Milstein J, Chen JH, Dhaliwal G. Next-Generation Artificial Intelligence for Diagnosis: From Predicting Diagnostic Labels to "Wayfinding". JAMA 2021 Dec 28;326(24):2467-8.
57. Carcel C, Harris K, Peters SAE, Sandset EC, Balicki G, Bushnell CD, et al. Representation of Women in Stroke Clinical Trials: A Review of 281 Trials Involving More Than 500,000 Participants. Neurology 2021 Nov 2;97(18):e1768-e1774.
58. Unger JM, Hershman DL, Osarogiagbon RU, Gothwal A, Anand S, Dasari A, et al. Representativeness of Black Patients in Cancer Clinical Trials Sponsored by the National Cancer Institute Compared With Pharmaceutical Companies. JNCI Cancer Spectr. 2020 Apr 24;4(4):pkaa034.
59. Awad E, Paladugu R, Jones N, Pierce JY, Scalici J, Hamilton CA, et al. Minority participation in phase 1 gynecologic oncology clinical trials: Three decades of inequity. Gynecol Oncol 2020 Jun;157(3):729-32.
60. Trant AA, Walz L, Allen W, DeJesus J, Hatzis C, Silber A. Increasing accrual of minority patients in breast cancer clinical trials. Breast Cancer Res Treat 2020 Nov;184(2):499-505.
61. Andrasik MP, Broder GB, Wallace SE, Chaturvedi R, Michael NL, Bock S, et al. Increasing Black, Indigenous and People of Color participation in clinical trials through community engagement and recruitment goal establishment. PLoS One 2021 Oct 19;16(10):e0258858.
62. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. Circulation 2020 Feb 18;141(7):540-8.
63. Mendis SR, Anand S, Dasari A, Unger JM, Gothwal A, Ellis LM, et al. Female representation in clinical trials leading to FDA cancer drug approvals for gastrointestinal (GI) cancers between 2008 to 2018. J Clin Oncol 2020;38:809-809.
64. Martinkova J, Quevenco FC, Karcher H, Ferrari A, Sandset EC, Szoeke C, et al. Proportion of Women and Reporting of Outcomes by Sex in Clinical Trials for Alzheimer Disease: A Systematic Review and Meta-analysis. JAMA Netw Open 2021 Sep 1;4(9):e2124124.
65. Baker KE, Streed CG Jr, Durso LE. Ensuring That LGBTQI+ People Count - Collecting Data on Sexual Orientation, Gender Identity, and Intersex Status. N Engl J Med 2021 Apr 1;384(13):1184-6.
66. Keuroghlian AS. Electronic health records as an equity tool for LGBTQIA+ people. Nat Med 2021 Dec;27(12):2071-3.
67. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight - Reconsidering the Use of Race Correction in Clinical Algorithms. N Engl J Med 2020 Aug 27;383(9):874-82.
68. Ye J. The Role of Health Technology and Informatics in a Global Public Health Emergency: Practices and Implications From the COVID-19 Pandemic. JMIR Med Inform 2020 Jul 14;8(7):e19866.
69. The Lancet Digital Health. Contact tracing: digital health on the frontline. Lancet Digit Health 2020 Nov;2(11):e561.
70. Jewell S, Futoma J, Hannah L, Miller AC, Foti NJ, Fox EB. It's complicated: characterizing the

time-varying relationship between cell phone mobility and COVID-19 spread in the US. NPJ Digit Med 2021 Oct 27;4(1):152.
71. Badr HS, Du H, Marshall M, Dong E, Squire MM, Gardner LM. Association between mobility patterns and COVID-19 transmission in the USA: a mathematical modelling study. Lancet Infect Dis 2020 Nov;20(11):1247-54.
72. Mishra T, Wang M, Metwally AA, Bogu GK, Brooks AW, Bahmani A, et al. Pre-symptomatic detection of COVID-19 from smartwatch data. Nat Biomed Eng 2020 Dec;4(12):1208-20.
73. Dash TK, Mishra S, Panda G, Satapathy SC. Detection of COVID-19 from speech signal using bio-inspired based cepstral features. Pattern Recognit 2021 Sep;117:107999.
74. Verde L, De Pietro G, Sannino G. Artificial Intelligence Techniques for the Non-invasive Detection of COVID-19 Through the Analysis of Voice Signals. Arab J Sci Eng 2021 Oct 8:1-11.
75. Rykov Y, Thach TQ, Bojic I, Christopoulos G, Car J. Digital Biomarkers for Depression Screening With Wearable Devices: Cross-sectional Study With Machine Learning Modeling. JMIR Mhealth Uhealth 2021 Oct 25;9(10):e24872.
76. Cavedoni S, Chirico A, Pedroli E, Cipresso P, Riva G. Digital Biomarkers for the Early Detection of Mild Cognitive Impairment: Artificial Intelligence Meets Virtual Reality. Front Hum Neurosci 2020 Jul 24;14:245.
77. Sieberts SK, Schaff J, Duda M, Pataki BÁ, Sun M, Snyder P, et al. Crowdsourcing digital health measures to predict Parkinson's disease severity: the Parkinson's Disease Digital Biomarker DREAM Challenge. NPJ Digit Med 2021 Mar 19;4(1):53.
78. Robin J, Harrison JE, Kaufman LD, Rudzicz F, Simpson W, Yancheva M. Evaluation of Speech-Based Digital Biomarkers: Review and Recommendations. Digit Biomark 2020 Oct 19;4(3):99-108.
79. Park C, Mishra R, Golledge J, Najafi B. Digital Biomarkers of Physical Frailty and Frailty Phenotypes Using Sensor-Based Physical Activity and Machine Learning. Sensors (Basel) 2021 Aug 5;21(16):5289.
80. Hamza M, Alsma J, Kellett J, Brabrand M, Christensen EF, Cooksley T, et al. Can vital signs recorded in patients' homes aid decision making in emergency care? A Scoping Review. Resusc Plus 2021 Jun;6:100116.
81. Mohammadzadeh N, Gholamzadeh M, Saeedi S, Rezayi S. The application of wearable smart sensors for monitoring the vital signs of patients in epidemics: a systematic literature review. J Ambient Intell Humaniz Comput 2020 Nov 13:1-15.
82. Leenen JPL, Leerentveld C, van Dijk JD, van Westreenen HL, Schoonhoven L, Patijn GA. Current Evidence for Continuous Vital Signs Monitoring by Wearable Wireless Devices in Hospitalized Adults: Systematic Review. J Med Internet Res 2020 Jun 17;22(6):e18636.
83. Wedlund L, Kvedar J. Innovative new model predicts glucose levels without poking or prodding. NPJ Digit Med 2021 Aug 20;4(1):126.
84. van den Brink W, Bloem R, Ananth A, Kanagasabapathi T, Amelink A, Bouwman J, et al. Digital Resilience Biomarkers for Personalized Health Maintenance and Disease Prevention. Front Digit Health 2021 Jan 22;2:614670.
85. Capobianco E, Meroni PL. Value of digital biomarkers in precision medicine: implications in cancer, autoimmune diseases, and COVID-19. Expert Rev Precis Med Drug Dev 2021;6(4):235-8.
86. Solomon DH, Rudin RS. Digital health technologies: opportunities and challenges in rheumatology. Nat Rev Rheumatol 2020 Sep;16(9):525-35.
87. Onnela JP. Opportunities and challenges in the collection and analysis of digital phenotyping data. Neuropsychopharmacology 2021 Jan;46(1):45-54.
88. Nahavandi D, Alizadehsani R, Khosravi A, Acharya UR. Application of artificial intelligence in wearable devices: Opportunities and challenges. Comput Methods Programs Biomed 2022 Jan;213:106541.
89. Perez-Pozuelo I, Spathis D, Clifton EA, Mascolo C. Wearables, smartphones, and artificial intelligence for digital phenotyping and health. In: Digital Health. Elsevier; 2021. p.33-54.
90. Lim SL, Ong KW, Johal J, Han CY, Yap QV, Chan YH, et al. Effect of a Smartphone App on Weight Change and Metabolic Outcomes in Asian Adults With Type 2 Diabetes: A Randomized Clinical Trial. JAMA Netw Open 2021 Jun 1;4(6):e2112417.
91. Lau N, O'Daffer A, Yi-Frazier JP, Rosenberg AR. Popular Evidence-Based Commercial Mental Health Apps: Analysis of Engagement, Functionality, Aesthetics, and Information Quality. JMIR Mhealth Uhealth 2021 Jul 14;9(7):e29689.
92. Tucker L, Villagomez AC, Krishnamurti T. Comprehensively addressing postpartum maternal health: a content and image review of commercially available mobile health apps. BMC Pregnancy Childbirth 2021 Apr 20;21(1):311.
93. Khoong EC, Olazo K, Rivadeneira NA, Thatipelli S, Barr-Walker J, Fontil V, et al. Mobile health strategies for blood pressure self-management in urban populations with digital barriers: systematic review and meta-analyses. NPJ Digit Med 2021 Jul 22;4(1):114.
94. Sharma R, Singh D, Gaur P, Joshi D. Intelligent automated drug administration and therapy: future of healthcare. Drug Deliv Transl Res 2021 Oct;11(5):1878-902.
95. Eckardt JN, Wendt K, Bornhäuser M, Middeke JM. Reinforcement Learning for Precision Oncology. Cancers (Basel) 2021 Sep 15;13(18):4624.
96. Domin A, Spruijt-Metz D, Theisen D, Ouzzahra Y, Vögele C. Smartphone-Based Interventions for Physical Activity Promotion: Scoping Review of the Evidence Over the Last 10 Years. JMIR Mhealth Uhealth 2021 Jul 21;9(7):e24308.
97. Khan ZF, Alotaibi SR. Applications of Artificial Intelligence and Big Data Analytics in m-Health: A Healthcare System Perspective. J Healthc Eng 2020 Aug 30;2020:8894694.
98. Jones M, DeRuyter F, Morris J. The Digital Health Revolution and People with Disabilities: Perspective from the United States. Int J Environ Res Public Health 2020 Jan 7;17(2):381.
99. Busse M, Latchem-Hastings J, Button K, Poile V, Davies F, O' Halloran R, et al. Web-based physical activity intervention for people with progressive multiple sclerosis: application of consensus-based intervention development guidance. BMJ Open 2021 Mar 16;11(3):e045378.
100. de Batlle J, Massip M, Vargiu E, Nadal N, Fuentes A, Ortega Bravo M, et al; CONNECARE-Lleida Group. Implementing Mobile Health-Enabled Integrated Care for Complex Chronic Patients: Intervention Effectiveness and Cost-Effectiveness Study. JMIR Mhealth Uhealth 2021 Jan 14;9(1):e22135.
101. Menictas M, Rabbi M, Klasnja P, Murphy S. Artificial intelligence decision-making in mobile health. Biochem (Lond) 2019 Oct;41(5):20-24.
102. Smith B, Magnani JW. New technologies, new disparities: The intersection of electronic health and digital health literacy. Int J Cardiol 2019 Oct 1;292:280-2.
103. Noel K, Ellison B. Inclusive innovation in telehealth. NPJ Digit Med 2020 Jun 25;3:89.
104. Brewer LC, Fortuna KL, Jones C, Walker R, Hayes SN, Patten CA, et al. Back to the Future: Achieving Health Equity Through Health Informatics and Digital Health. JMIR Mhealth Uhealth 2020 Jan 14;8(1):e14512.
105. Marwaha JS, Kvedar JC. Cultural adaptation: a framework for addressing an often-overlooked dimension of digital health accessibility. NPJ Digit Med 2021 Oct 1;4(1):143.
106. Yoon H, Jang Y, Vaughan PW, Garcia M. Older Adults' Internet Use for Health Information: Digital Divide by Race/Ethnicity and Socioeconomic Status. J Appl Gerontol 2020 Jan;39(1):105-10.
107. Liu N, Yin J, Tan SS, Ngiam KY, Teo HH. Mobile health applications for older adults: a systematic review of interface and persuasive feature design. J Am Med Inform Assoc 2021 Oct 12;28(11):2483-501.
108. Hilty DM, Gentry MT, McKean AJ, Cowan KE, Lim RF, Lu FG. Telehealth for rural diverse populations: telebehavioral and cultural competencies, clinical outcomes and administrative approaches. Mhealth 2020 Apr 5;6:20.
109. Knitza J, Simon D, Lambrecht A, Raab C, Tascilar K, Hagen M, et al. Mobile Health Usage, Preferences, Barriers, and eHealth Literacy in Rheumatology: Patient Survey Study. JMIR Mhealth Uhealth 2020 Aug 12;8(8):e19661.
110. Crawford A, Serhal E. Digital Health Equity and COVID-19: The Innovation Curve Cannot Reinforce the Social Gradient of Health. J Med Internet Res 2020 Jun 2;22(6):e19361.
111. Hoffman DA. Increasing access to care: telehealth during COVID-19. J Law Biosci 2020 Jun 16;7(1):lsaa043.
112. Yi SS, Đoàn LN, Choi JK, Wong JA, Russo R, Chin M, et al. With No Data, There's No Equity: Addressing the Lack of Data on COVID-19 for Asian American Communities. EClinicalMedicine 2021 Oct 23;41:101165.
113. Bakken S. Replication studies and diversity, equity, and inclusion strategies are critical to advance the impact of biomedical and health informatics. J Am Med Inform Assoc 2021 Aug 13;28(9):1813-4.
114. Sieck CJ, Sheon A, Ancker JS, Castek J, Callahan B, Siefer A. Digital inclusion as a social

determinant of health. NPJ Digit Med 2021 Mar 17;4(1):52.
115. Chen IY, Pierson E, Rose S, Joshi S, Ferryman K, Ghassemi M. Ethical Machine Learning in Healthcare. Annu Rev Biomed Data Sci 2021 Jul;4:123-44.
116. Mhasawade V, Zhao Y, Chunara R. Machine learning and algorithmic fairness in public and population health. Nat Mach Intell 2021; 3(8):659-66.
117. Lett E, Asabor E, Beltrán S, Cannon AM, Arah OA. Conceptualizing, Contextualizing, and Operationalizing Race in Quantitative Health Sciences Research. Ann Fam Med 2022 Mar-Apr;20(2):157-63.
118. Miron M, Tolan S, Gómez E, Castillo C. Addressing multiple metrics of group fairness in data-driven decision making. arXiv preprint 2020; arXiv:2003.04794.
119. Park Y, Hu J, Singh M, Sylla I, Dankwa-Mullan I, Koski E, Das AK. Comparison of Methods to Reduce Bias From Clinical Prediction Models of Postpartum Depression. JAMA Netw Open 2021 Apr 1;4(4):e213909.
120. Wawira Gichoya J, McCoy LG, Celi LA, Ghassemi M. Equity in essence: a call for operationalising fairness in machine learning for healthcare. BMJ Health Care Inform 2021 Apr;28(1):e100289.
121. Leslie D, Mazumder A, Peppin A, Wolters MK, Hagerty A. Does "AI" stand for augmenting inequality in the era of covid-19 healthcare? BMJ 2021 Mar 15;372:n304.
122. Baxter MS, White A, Lahti M, Murto T, Evans J. Machine learning in a time of COVID-19 - Can machine learning support Community Health Workers (CHWs) in low and middle income countries (LMICs) in the new normal? J Glob Health 2021 Jan 16;11:03017.
123. Syeda HB, Syed M, Sexton KW, Syed S, Begum S, Syed F, et al. Role of Machine Learning Techniques to Tackle the COVID-19 Crisis: Systematic Review. JMIR Med Inform 2021 Jan 11;9(1):e23811.
124. Ostaszewski M, Niarakis A, Mazein A, Kuperstein I, Phair R, Orta-Resendiz A, et al; COVID-19 Disease Map Community. COVID19 Disease Map, a computational knowledge repository of virus-host interaction mechanisms. Mol Syst Biol 2021 Oct;17(10):e10387.
125. Dunn P, Hazzard E. Technology approaches to digital health literacy. Int J Cardiol 2019 Oct 15;293:294-6.
126. Kemp E, Trigg J, Beatty L, Christensen C, Dhillon HM, Maeder A, et al. Health literacy, digital health literacy and the implementation of digital health technologies in cancer care: the need for a strategic approach. Health Promot J Austr 2021 Feb;32 Suppl 1:104-14.
127. Kuek A, Hakkennes S. Healthcare staff digital literacy levels and their attitudes towards information systems. Health Informatics J 2020 Mar;26(1):592-612.
128. Zhang X, Hailu B, Tabor DC, Gold R, Sayre MH, Sim I, et al. Role of Health Information Technology in Addressing Health Disparities: Patient, Clinician, and System Perspectives. Med Care 2019 Jun;57 Suppl 6 Suppl 2(Suppl 6 2):S115-S120.
129. Triana AJ, Gusdorf RE, Shah KP, Horst SN. Technology Literacy as a Barrier to Telehealth During COVID-19. Telemed J E Health 2020 Sep;26(9):1118-9.

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