Leading Edge

Commentary

Precision medicine in 2030—seven ways to transform healthcare

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Precision medicine promises improved health by accounting for individual variability in genes, environment, and lifestyle. Precision medicine will continue to transform healthcare in the coming decade as it expands in key areas: huge cohorts, artificial intelligence (AI), routine clinical genomics, phenomics and environment, and returning value across diverse populations.

Ever since the completion of the first human genome sequence in 2003, clinicians have anticipated a data-driven transformation in healthcare. New troves of molecular and phenotypic interrogation would lead to refined diagnoses, more rational treatment, and prevention of disease. In 2011, an *ad hoc* committee at the National Research Council argued for a "new taxonomy of human diseases" based on the emerging field of precision medicine (US National Research Council, 2011).

Today, some of that promise has already been realized. Researchers are routinely using healthcare data for discovery, identifying genomic underpinnings of cancer and many other common and rare diseases, introducing transformative molecularly targeted therapies, and leveraging massive computational capabilities with new machine learning methods. We are beginning to see the fruits of these efforts.

There is perhaps no more poignant example than the response to the COVID-19 pandemic. Genomics and molecular technologies were key in identifying the etiologic agent, developing diagnostics and treatments, and creating vaccine candidates. Rapid case reporting quickly exposed vast health disparities with COVID-19 and highlighted the importance of capturing a more detailed understanding of social determinants of health. Large-scale consortia based on health care data quickly assembled huge data sets for rapid investigations of risk factors and outcomes, demonstrating the power of amalgamated healthcare data. Pooling data from existing research cohorts enabled rapid genomic studies that have identified loci associated with disease susceptibility and patient outcomes. COVID-19 has also called attention to the need for longitudinal cohorts to identify clinical and biologic risk factors and long-term sequelae for acute infectious disease. Many of the elements of the response to COVID-19 are basic capabilities underpinning precision medicine.

At the same time, COVID-19 has highlighted the need for precision medicine to move further and faster. In this paper, we suggest seven opportunities to accelerate an equitable realization of the promise of precision medicine (Figure 1). Their impacts are outlined in Table 1.

Huge, interoperable, longitudinal cohorts

Over the last two decades, national cohorts such as the UK Biobank, the Million Veteran Program, FinnGen, and the *All of Us* Research Program have amassed huge populations with genomic, laboratory, and lifestyle assessments as well as longitudinal follow-up on health outcomes. The depth and breadth of the data are staggering, as are the opportunities for discovery across every area of medicine.

In order to maximize the impact of these resources, an "open science" approach is emerging. For example, the UK Biobank has opened its doors to more than 19,000 "bona fide researchers" from 80 countries, and researchers can start using the *All of Us* Research Program's data cloud in as little as two hours after initial login.

The next step is clear: make it easier for researchers to merge data from multiple cohorts. Currently, this requires painstaking manual phenotype adjudication and building large consortia including experts from each cohort. Fortunately, there are efforts underway to improve this process. Groups such as the Global Alliance for Genomics and Health (GA4GH) are working to develop and to coordinate common data models and file formats to facilitate collaboration and interoperability. In recognition of the need for better collaboration, the International Hundred Thousand Plus Cohort Consortium (IHCC) has brought together more than 100 cohorts in 43 countries comprising more than 50 million participants—nearly two orders of magnitude bigger than the biggest single cohort today (Manolio et al., 2020). It would be hard to overstate the impact this work could have on global research efforts.

Improved diversity and inclusion in science

One of the biggest challenges (and opportunities) before the biomedical enterprise today is the lack of diversity in populations involved in research studies. Less than 3% of the participants in published, genome-wide association studies are of African or Hispanic or Latin American ancestries, and 86% of clinical trial participants are white (Knepper and McLeod, 2018; Mills and Rahal, 2020).

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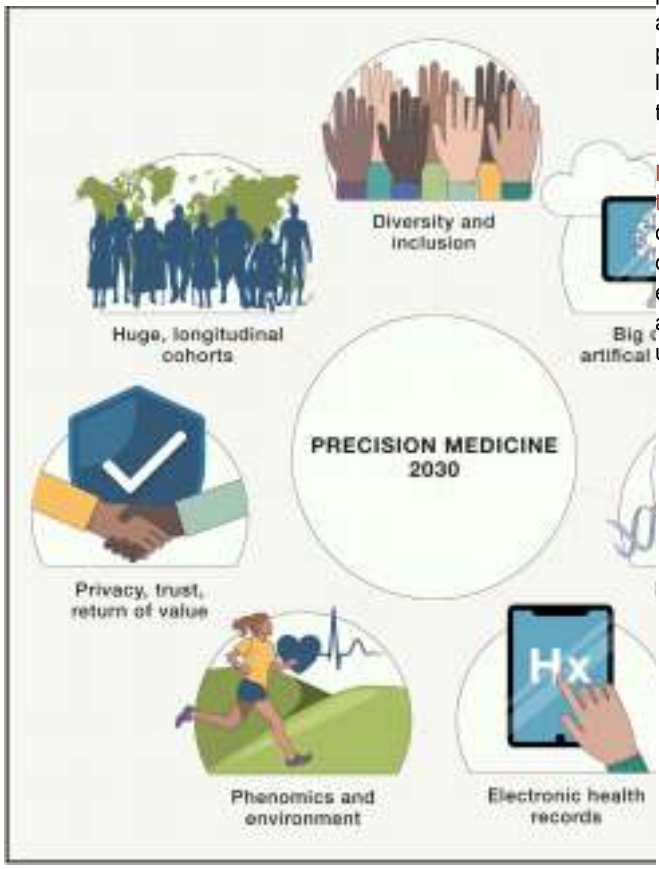

Figure 1. Seven opportunities for precision medicine by 2030

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velocity, come in many varieties, have sig nificant variability, and have intrinsic value. However, AI approaches in medicine have been limited by the (un)availability of large, commonly structured datasets.

Looking forward, biomedical datasets will become increasingly ready for ana lyses. As we discuss in the following sec tions, the growth of clinical data (including image, narrative, and real-time monitoring data), molecular technologies (genomics principal among them), and the availability of devices and wearables to provide high resolution data streams will dramatically expand the availability of detailed pheno type and environmental data not previ ously available at this scale. Applications of machine learning approaches could result in new taxonomies of disease through genomic, phenomic, and envi ronmental predictors.

Routine clinical genomics to guide prevention, diagnosis, and therapy Today, clinical genomic analysis is typi cally performed only when evaluating certain cancers or when a rare genetic disease is suspected, and many commonly ordered tests only evaluate a few genetic loci. Moving forward, whole genome approaches will become a routine, early step in the understanding, prevention, detection, and treatment of

health disparities and also impoverishes biologic discovery that could be appli cable to all populations.

With a growing depth of data, we have an opportunity to replace adjustments for race and ethnicity with more specific measures. In particular, ‘‘race’’ conflates a plethora of social, cultural, political, geographic, and biologic factors together and can perpetuate systemic racism. Routine collection of social determinants of health in both research and clinical care in combination with more precise measures of environmental influences, habits, and genetic ancestry can provide more rational, etiology-based adjust ments and yield better risk stratifications and treatments (Wilkins et al., 2020).

As we work toward increasing the diver sity of populations in studies, we should also increase the diversity of the biomed ical research workforce. A more diverse workforce—in culture, ancestry, beliefs, scientific backgrounds, and methodolog ical approaches—brings increased under standing, innovation, trust, and cultural sensitivity; is more likely to pursue ques tions relevant to different audiences; and ultimately delivers better research (Hofstra et al., 2020).

As international collaborations grow, researchers will also need to consider the ethics of international collaboration and rotate leadership, authorship, and re sources to ensure that research benefits developing countries as well as more advantaged ones. Establishing interna tional infrastructures and science facil ities—not just access to samples and data—will produce long-term benefits that accelerate health and capabilities.

Big data and artificial intelligence Big data and artificial intelligence (AI) are transforming previously intractable prob lems such as search optimization, lan guage translation, image interpretation, and autonomous driving. Many accrued biomedical data sets meet all "5 V's" of big data since they are voluminous, high common and rare diseases.

Rare diseases will increasingly be diag nosed using genomic investigation as a cheaper and more efficient alternative to targeted approaches. Early genome sequencing can solve diagnostic di lemmas and uncover "hidden" Mende lian diseases such as unexplained kidney disease, atypical diabetes, or unex plained development delay (Turro et al., 2020). Some of these Mendelian dis eases point to specific new treatments and screening strategies that could dramatically improve health, such as sul fonylureas for young diabetic patients with *HNF1A* mutations or specific causes of liver or kidney failure.

The last decade has also shown that many common conditions, such as dia betes or hypertension, can be associated with genetic risks at thousands of loci, often found using huge genetic studies aggregating data across hundreds of thousands of participants. While many of these genetic loci may have very small

Table 1. Envisioning how precision medicine will affect clinical medicine and research in the next decade Where we are today Where we will be in 2030

Clinical applications		
Genomics for disease	Primarily limited to rare disease and select cancers.	Genomics is routine. Genetic causes and targeted therapies are discovered for many "common" diseases. Microbiome measures are routinely included. Genome-aware EHRs make PGx easy and automatically update rules from central guidelines. New PGx associations discovered from clinical data.
Pharmacogenomics (PGx)	Common in cancer and within select applications of older medications at select sites.	ACMG59 grows to > 200, variant interpretation improved by huge, diverse sequenced populations. Cell-free DNA becomes a mainstay of cancer screening
Genomics for healthy individuals	In research, whole-genome sequencing and search for mutations in one of the ACMG59 genes, present in about 3% of people. Variant interpretation is hard.	
EHRs	Episodic capture from healthcare without robust genomics support. EHR data is essentially not portable.	Genome- and device- enabled. Data can be easily moved between EHRs and to participant apps.
Environmental influences on health	Patient-reported habits and exposures	Geocode-based exposure linkage Real time monitoring of multiple environmental exposures Precision nutrition
Wearable sensors	Ad hoc use of activity monitors	Continuous monitoring of physical activity, sleep, metabolic parameters
Research applications		
Population demographics	>80% European ancestry	>50% non-European ancestry
Routinely available data	Surveys of health conditions, lifestyle, behavior, and diet. GWAS data, lab assays, structured EHR data, and geocoded exposure linkages.	several million Whole genomes, lab assays, surveys, full EHRs, environmental, genomic and sensor data. Includes imaging, narrative, geocoded, and continuous monitoring approaches to clinical care, activity, precision nutrition, and environment.
Size of cohorts used in analysis	Up to 500K, data downloaded and manually harmonized to sets of	>100M using cloud-based federated analyses facilitated by common standards
	>1M (GWAS)	>50M (GWAS) >2M (WGS)
Largest genomic studies performed on a trait		
Cost of a whole genome	$500	$20*

*Sequencing costs have often fallen faster than Moore's law. Using Moore's law, sequencing costs would be 1/32 of US $500, or $15.63.

genetic effect sizes (with odds ratios < 1.01), they point to pathways involved in disease pathogenesis that may have sig nificant therapeutic implications. Further more, weighted aggregations of genetic variants into polygenic risk scores can achieve similar predictive as rare Mende lian disease variants (Khera et al., 2018). Moreover, use of polygenic risk scores may allow providers to risk-stratify indi viduals who would otherwise be missed by traditional screening approaches, thereby identifying new populations for treatment or screening.

We anticipate that diverse genetic causes and targeted therapies will be un covered for many common diseases, which could lead to more specific treat ment and prevention for the patient and family members. We will likely also discover that many genetic diseases occur on a spectrum of severity, pene trance, and expressivity, guided by the severity of different genetic variants, life style, and environmental interactions. This concept is captured by the scientific agenda of the International Common Dis ease Alliance. Classic examples include different classes of *CFTR* mutations with cystic fibrosis or *SERPINA1* variants with alpha-1 antitrypsin deficiency, both of which can present with different manifes tations and at varying ages given the genetic variant, habits (e.g., smoking),

and exposures (e.g., hepatitis virus co infections).

Routine use of sequencing will produce valuable datasets for secondary research, driving a more comprehensive under standing of disease penetrance, variant pathogenicity, and factors influencing variable expressivity of given genetic var iants. It will also produce more patients for whom incidental pathogenic variants are discovered. The American College of Medical Genetics and Genomics has identified 59 genes for which incidental findings should be considered for patient return (i.e., the "ACMG59") (Kalia et al., 2017). These genes include hereditary cancer syndromes, cardiomyopathies, and potentially fatal arrhythmias, for which actions can be taken to mitigate their risk. Today, about 3% of patients harbor pathogenic variants, the vast ma jority of which were previously unknown to the patient. As genomic knowledge accelerate adop tion. Some countries have substantially reduced drug-induced Stevens Johnson Syndrome using genetic testing (White et al., 2018). Even considering just five drug-genomic interactions, nearly everyone has a pharmacovariant that would affect drug prescribing (Van Driest et al., 2014).

EHRs as a source for phenomic and genomic research

The key to any longitudinal cohort is detailed phenotype, exposure, and health outcome assessment. Many site-based and national research cohorts now use EHRs and other health data to provide up to decades of extant disease and treat ment information that can be repurposed for research, and we only see this use ex panding.

Already EHR-based studies have been instrumental to some of the largest genomic studies of clinically relevant find ings, some of which are exceeding 1 million individuals (Vujkovic et al., 2020). By providing a systematic collection of health-related information, EHRs provide phenotypes and data and enable novel study designs often not available in research collections. For example, one study demonstrated participants had an average of more than 190 clinical notes, 14 radiological studies, and more than 700 lab tests over an average of about 8 years of follow up (Robinson et al., 2018). The power to discover specific en dophenotypes (e.g., cardiac ejection frac tion) or emerging phenotypes (e.g., COVID-19), rare and specific phenotypes (e.g., osteonecrosis of the jaw), or to un derstand specific manifestations of dis ease (e.g., bronchiectasis) often requires access to complete EHR data.

EHR data require cleaning and harmo nization and can reflect clinical and insur ance biases. Unstructured EHR data, such as narrative reports or imaging data, often require advanced methods like natural language processing or ma chine learning to be useful on a population scale. However, all of these tools are increasingly available and applicable, providing access to data on a scale, depth, and detail not feasible with purely research-collected data.

Clinical EHR data can also be combined with participant-provided research data collections to provide a more complete picture of patient outcomes. Research co horts such as the UK Biobank and *All of Us* have integrated both data sources.

Further, as clinical sequencing grows, the number of genotypes derived from clinical care will rapidly grow to dwarf those available from research use cases. Many genomic studies may no longer need separate research biospecimen collection to perform large-scale genetic studies. Collection of research bio specimens could then shift toward measuring other biomarkers, cell-free DNA, exposures, and epigenomics.

Higher variety, higher resolution phenomics and environmental exposure data for both clinical and research use

The next decade will see the continued growth of research and clinical uses for different ways to measure clinical pheno types, exposures, and lifestyle. Data link ages to health claims, national vital statistics, and geospatial resources will become more common as will the use of wearable devices to measure activity, physical measurements, and exposures. Surveys can then be more focused on el ements not covered by other methods, thereby decreasing participant burden. Activity monitors that take a number of clinical measurements such as single lead electrocardiograms and oxygen saturation are becoming inexpensive and can be easily shared with providers. Since the vast majority of a patient's life is spent outside the healthcare system, integration of wearable devices and other patient-provided information would augment the EHR and enable greater tele health capabilities, experienced first at scale during COVID-19. Moreover, inte gration of these tools could produce a shift in which most health-related data is derived outside of the healthcare setting.

Despite clear evidence of the impact of nutrition on health, diet is an environ mental exposure often ignored in much of clinical practice and many research studies. When it is assessed, it is often through episodic and cumbersome sur veys (research) or perfunctory summative questions (in most clinical settings). Re placing dietary assessment

increases, the number of actionable genes and the fraction of the population affected will significantly increase.

Furthermore, pharmacogenomics can improve drug efficacy, reduce adverse events, and reduce cost. In a 2009 inter view, one of the authors of this article (F.S.C.) made the comment, "if every body's DNA sequence is already in their medical record and it is simply a click of the mouse to find out all the information you need, then there is going to be a much lower barrier to beginning to incor porate that information into drug prescrib ing" (Collins, 2009). Over a decade later, we still have a long way to go. While geno mics-guided therapies are becoming the standard of care for some cancers, use of germline pharmacovariants to guide prescribing has been adopted by only a few US medical centers. Implementation has been hindered by a lack of "geno mics-enabled" electronic health records (EHRs), the complexity of the genetics and recommendations, and a lack of clear evidence. Synthesized evidence and rec ommendations from the Clinical Pharma cogenomics Implementation Consortium, ubiquity of EHRs supporting complex de cision support, and common data stan dards offer promise to

with data link ages to grocery stores, digital uploads from restaurants, laboratory and micro biome assessments, or machine learning applied to food imaging would provide more feasible, comprehensive capture of dietary habits. A future of precision nutri tion, as a type of "drug," offers a powerful new modality for treating and preventing disease (Rodgers and Collins, 2020).

Privacy, participant trust, and returning value

The utility of precision medicine is depen dent on broad participation, and broad participation of large populations requires trust, protection of privacy, and a return of value to the participants. We recognize that science has not always been trust worthy or honored all participants equally. Transparency, authentic engagement with communities, and including partici pants within research governance can improve trust, create participant advo cates, and ensure a more thoughtful, culturally sensitive direction. *All of Us* has involved participants in all levels of governance from the beginning and seeks to return value by giving partici pants generated research data wherever possible, such as genomics results or up coming COVID-19 serology results. Participants also need to trust that their data is secure and private. Highly public data breaches, fear of reidentification, and legal concerns about the availability of certain types of information for factors such as insurability can make this chal lenging. Clear and honest communication with participants is essential in building trust. Legal protections for the data and technological approaches to ensure secure information systems (such as dei dentifying and blurring data, controlling access via blockchain, linking data using privacy-preserving hashed identifiers, and analyzing data using homomorphic encryption) also play a role.

Conclusion

The technologies undergirding precision medicine are already transforming care. Transformative molecular treatments have been developed for rare diseases like cystic fibrosis and spinal muscular atrophy. Genomic investigation led to the development of new drugs for hyper lipidemia. In this time of COVID-19, sci ence has been the answer to an existen tial medical threat. Yet we are reminded that many of the benefits of medicine's advancement have not always been available to all. Biomedical approaches, computation algorithms, and the avail ability of high-resolution data will dramat ically increase over the next decade. Implementation of a bold plan to collabo rate internationally, to engage diverse populations of participants and scientists, to deeply measure our populations, to make clinical and research data broadly available, and to implement this knowl edge in clinical practice—in a true learning healthcare system—will allow us to achieve the vision of precision medi cine for all populations.

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