

By Geoffrey S. Ginsburg and Kathryn A. Phillips

DOI: 10.1377/hlthaff.2017.1624  
 HEALTH AFFAIRS 37,  
 NO. 5 (2018): 694–701  
 ©2018 Project HOPE—  
 The People-to-People Health  
 Foundation, Inc.

## OVERVIEW

# Precision Medicine: From Science To Value

**Geoffrey S. Ginsburg**

(geoffrey.ginsburg@duke.edu)  
 is director of the Duke Center  
 for Applied Genomics and  
 Precision Medicine, Duke  
 University, in Durham, North  
 Carolina.

**Kathryn A. Phillips**

is a  
 professor of health economics  
 and health services research  
 at the University of California  
 San Francisco.

**ABSTRACT** Precision medicine is making an impact on patients, health care delivery systems, and research participants in ways that were only imagined fifteen years ago when the human genome was first sequenced. Discovery of disease-causing and drug-response genetic variants has accelerated, while adoption into clinical medicine has lagged. We define *precision medicine* and the stakeholder community required to enable its integration into research and health care. We explore the intersection of data science, analytics, and precision medicine in the formation of health systems that carry out research in the context of clinical care and that optimize the tools and information used to deliver improved patient outcomes. We provide examples of real-world impact and conclude with a policy and economic agenda necessary for the adoption of this new paradigm of health care both in the United States and globally.

**I**n 2011 the National Research Council's *Toward Precision Medicine* adopted the following definition of *precision medicine*: "The tailoring of medical treatment to the individual characteristics of each patient...to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."<sup>1</sup> As this definition suggests, the power of precision medicine lies in its ability to guide health care decisions toward the most effective treatment for a given patient and, thus, improve care quality while reducing the need for unnecessary diagnostic testing and therapies.

## Precision Medicine Is Data-Science Driven

The rise of electronic medical records (EMRs) and robust information technology (IT) systems supporting both research and health care delivery has placed patients and research participants

who agree to provide biospecimens and share their clinical and research data at the epicenter of precision medicine research.<sup>2</sup> The data derived from EMRs and biospecimens generate new findings that are linked to digital phenotypes derived from mobile and wearable devices, family history, and environmental exposures. These can all be captured as part of clinical care. Clinicians can use this growing knowledge base, which is often maintained and curated at clinical laboratories.<sup>3–6</sup> The assembly of genomic, environmental, digital health, and patient-reported data from a variety of sources serves as the foundation for a powerful precision medicine platform that, when coupled to other national and global data and clinical networks, will lead to the dissemination of knowledge that will enable other health care delivery systems to benefit.<sup>7</sup> When such systems are fully developed, clinical practice and research will be able to inform each other, with the goal of improving the efficiency and effectiveness of disease prevention, diagnosis, and treatment.<sup>8</sup>

The precision medicine community must shape the data systems and the data science strat-

egies for how the data are used. Providers require information at the point of decision so they can use it in the context of their clinical workflow, and patients must clearly state their preferences about the use and sharing of their genomic and other information with researchers and others beyond the delivery system in which they receive care. Researchers will identify and adopt best practices for research using EMR-linked genomic information. Health systems will offer providers tools and systems that enable them to make more informed decisions. The health IT community must design secure and interoperable genomics-enabled systems for actionable use in both health care and community settings. Policy makers will address the return of results, privacy, confidentiality, and education while developing regulations and economic incentives that can align the interests of all stakeholders.

### Data Sharing Is A High-Payoff Strategy

Several ongoing efforts in the US public and private sectors are aimed at establishing data repositories for large-scale EMR-linked genomic information.<sup>9,10</sup> Making data standardized, comparable, and consistent facilitates the data's reuse for discovery in multiple contexts beyond their original use. For example, the combination of data in the EMR and gene sequencing information has been a powerful tool for identifying genetic variants associated with disease and for understanding individual responses to therapies.<sup>11</sup> The economics of data sharing might seem obvious: If a health system shares 100 genomes and patient records with ten other systems that agree to do the same, each gains 1,000 genomes and records for the cost of generating 100.<sup>8</sup> The power of genomics-enabled research and health care is proportional to the amount of data that can be accessed and analyzed.

Health care systems supporting cycles that encompass both the analysis of data to produce results and the use of those results to develop changes in clinical practice are systems that will allow optimal learning.<sup>12</sup> Combining information about all people in such systems, genomic data could inform strategies to improve population health and contribute to care management. Including physicians in these systems of clinical decision support, guidelines for clinical action, and more information on the clinical utility of genetic testing would help them make effective use of genomic information and integrate it into their practice as they have done with other medical test information.

### Precision Medicine—Where Are We Today?

A number of applications of precision medicine currently contribute to health care at many points across the lifespan. Genetic screening may be used before conception to predict the risk of passing on genetic disorders to offspring.<sup>13,14</sup> At eight to twelve weeks' gestation, noninvasive prenatal testing may be used to screen for trisomy 13, 18, and 21 in the fetus (all causing developmental abnormalities), and even whole-genome sequencing of the fetus has been performed.<sup>15</sup> At birth, sequencing has been used to rapidly diagnose many critical conditions for which there could be actionable results, leading to reduced morbidity and mortality.<sup>16</sup> Later in life, these approaches can be used to diagnose a variety of diseases, most notably the detection of circulating tumor cell DNA (a process also known as a liquid biopsy) to diagnose cancer.<sup>17,18</sup>

Many genomic markers of efficacy, adverse events, and dosing of therapeutics have been discovered and recommended for clinical use, but their uptake into clinical practice has been variable, even when their actionability has been supported by evidence. In some cases, people who are carriers of the *HLA-B\*5701* or *HLA-B\*1502* genotype, variants of a gene complex that plays a critical role in the immune system, should avoid the HIV drug abacavir and the antiseizure drug carbamazepine, respectively, to avoid serious adverse events. In other cases, such as people with variants in the *TPMT* gene for mercaptopurine, used to treat some cancers and autoimmune diseases) or in *CYP2C9/VKORC1* for warfarin (used to prevent or treat blood clots), adjusting the dose of drug based on genotype can help to avoid toxicity and improve efficacy. However, actionability is not enough to ensure clinical uptake of pharmacogenetic testing. This is demonstrated by the fact that there is no clear consensus among physicians on the use of the antiplatelet drug clopidogrel (also used to treat blood clots), despite its having a Food and Drug Administration (FDA) "black box warning" of varying efficacy among people carrying different *CYP2C19* genetic variants. For established drugs, the use of genetic markers that predict therapeutic efficacy may face a high hurdle, unless there is strong evidence of a test's clinical utility to drive provider acceptance.

### New Research Initiatives In Translational Precision Medicine

To identify and overcome the barriers in translating genome-based discoveries into clinical practice, the National Human Genome Research Institute has funded several initiatives (de-

scribed below) that focus on implementation, evidence generation, and health policy in genomics and precision medicine.

#### **ELECTRONIC MEDICAL RECORDS AND GENOMICS**

Established in 2007, the Electronic Medical Records and Genomics (eMERGE) Network<sup>19</sup> was the first major National Human Genome Research Institute consortium developed to explore the utility of DNA repositories coupled to EMRs for advancing discovery as well as to address the policy issues related to this strategy for precision medicine research. eMERGE created an electronic phenotyping library, the Phenotype KnowledgeBase, and initiated integration of actionable variants into EMRs for use in clinical care. More recently, a series of pilot demonstration projects were initiated to investigate the utility of pharmacogenetics variants to guide treatment using EMR-integrated clinical decision support tools.

#### **CLINICAL SEQUENCING EVIDENCE-GENERATING RESEARCH**

The Clinical Sequencing Evidence-Generating Research (CSER) consortium<sup>20</sup> was formed in 2011 to develop methods for integrating genome sequencing into clinical medicine, improving the discovery and interpretation of genomic variants, and investigating the impact of genome sequencing on health care outcomes. The consortium has defined, generated, and analyzed evidence regarding the clinical utility of genome sequencing; investigated the interactions among patients, family members, health care practitioners, and clinical laboratories that influence implementation of clinical genome sequencing; and identified and addressed real-world barriers to integrating genomic, clinical, and health care utilization data within a health care system to build a shared evidence base for clinical decision making.

CSER has used genome sequencing in diverse care settings and populations for prenatal testing and for the evaluation of newborns, healthy people, and patients with cardiovascular disease; it has also made substantial progress in building the evidence base for clinical sequencing.<sup>21</sup> After the initial studies tested the feasibility of implementing genome sequencing into clinical care, studies are now examining the utility of sequencing information. There is also a focus on recruiting members of diverse racial and ethnic groups and historically underrepresented groups into genomics research,<sup>22</sup> as well as an emphasis on studying diverse clinical health care settings.

**IMPLEMENTING GENOMICS IN PRACTICE** Implementing Genomics in Practice (IGNITE)<sup>23</sup> was formed in 2013 to address the challenges to widespread clinical implementation of genomic medicine, a prerequisite for developing evidence of its real-world utility. IGNITE has investigated

and disseminated genomic medicine practice models that seamlessly integrate genomic data into the EMR and deploy tools for point-of-care decision making. In addition to creating novel educational approaches, the projects include the use of validated genetic markers for disease risk prediction and prevention (for example, the use of the *ApoLI* genetic variant as a marker for kidney disease in African Americans with hypertension to promote control of hypertension), the implementation of electronic family history tools with clinical decision support,<sup>24</sup> and the use of pharmacogenetic data to guide the use of medications (for example, *CYP2C19* variants for clopidogrel and *CYP2D6* variants for pain medication management).

Initial lessons learned from IGNITE include the following: Implementation science requires both a transdisciplinary team with the right expertise and an implementation framework, and implementation frameworks guide intervention deployment, assessment, and analyses. IGNITE adopted and adapted the Consolidated Framework for Implementation Research.<sup>25</sup> Pre-implementation research is often overlooked as a critical element to ensure that researchers understand and take into account the priorities, concerns, and educational needs of the setting and clinical personnel before implementation begins. Genomic medicine research is IT intensive. Broad implementation of genomic medicine requires that IT solutions work with an EMR to either incorporate genomic information into it or extract phenotypic data from it. Thus, IT leadership at the implementing institution needs to prioritize its incorporation.

## **Precision Medicine—A National Research Agenda**

In 2015 President Barack Obama announced a government-funded precision medicine initiative that will enroll over a million people. In what is now called the *All of Us* Research Program,<sup>9</sup> participants are expected to share the data generated or captured over more than ten years by sequencing, EMRs, personally reported information, and digital health technologies. These data will be the subject of analyses intended to drive both a novel scientific agenda to increase understanding of the underlying mechanisms of disease and an agenda for data- and precision-driven health care for individuals and populations. Both agendas should contribute to a novel paradigm of health care expected to affect health and decisions across the lifespan.

Influencing the launch of *All of Us* was a dramatic decline in the cost and increase in throughput of DNA sequencing,<sup>26</sup> the near-ubiquitous

adoption of EMRs across the United States,<sup>27</sup> and the growth of digital health technologies as a source of continuous and rich personal data.<sup>28</sup> Other genome-based technology platforms (for example, RNA assays) are also increasingly being used as diagnostic tests to classify disease states (for example, a blood RNA assay is used to diagnose rejection following a heart transplant without the need for an endomyocardial biopsy)<sup>29</sup> and as prognostic tests to predict future clinical outcomes (for example, an tumor RNA assay is used to predict prognosis and guide treatment strategies in breast cancer).<sup>30</sup> Together, these approaches form the basis for a new molecular taxonomy of disease; provide more precise ways to screen for and detect disease at its earliest molecular manifestations, often preclinically; and allow the selection of certain drugs to be guided by a patient's genetic makeup. In the future, it is likely that periodic molecular and digital profiling will shift the focus of health care strategies from acute intervention and disease management to assessing health and the proactive management of disease risks and prevention.

## Global Efforts To Implement Precision Medicine

Efforts and initiatives are under way worldwide to create national implementation strategies for genomic medicine (exhibit 1).<sup>31</sup> Key barriers that exist to implementing and integrating precision medicine technologies into health care practice include the absence of supporting IT infrastructure, lack of data standards and system interoperability, insufficient decision support technology, and insufficient funding for translational health research. Policies to support progress in these areas will be critical to the adoption and integration of precision medicine technologies into health care worldwide and the collaborative frameworks to support it as a global agenda.

## A Policy Agenda For Precision Medicine

To fully realize the integration of precision medicine into health care, stakeholders must now implement an agenda<sup>32-34</sup> that supports evidence generation, data sharing and its integration into health care, regulation, reimbursement, economic value, and participant engagement.

**EVIDENCE GENERATION** If it is to be widely adopted, precision medicine will require high-quality evidence that it improves patient outcomes. There are currently more than 75,000 unique genetic testing products on the market, and an average of ten new products are added

each day.<sup>35</sup> The market for clinical sequencing—which encompasses the use of sequencing tests for diagnosis, risk prediction, therapy selection and monitoring, and screening—is growing at a compound annual rate of 28 percent.<sup>35</sup> Thus, while the initiatives described above will continue to provide new evidence, the rapid evolution and availability of novel technologies and the growth of multigene panels require innovative strategies to develop evidence.

The challenge is how to obtain the needed evidence when the field is growing and changing so rapidly that the “gold standard” of large randomized clinical trials may be unfeasible. Alternatives have been proposed that offer creative approaches to generating evidence, such as new models of risk sharing and evidence development among technology developers, health care systems, and payers.<sup>36</sup> As an example, the Centers for Medicare and Medicaid Services (CMS) had published twenty two “coverage with evidence development” policies by December 2016.<sup>37</sup> However, there can be no one-size-fits-all approach for evidence generation, since the evidentiary threshold will vary with the risk of the test and the financial impact on the stakeholders.

**DATA SHARING AND INTEGRATION** Precision medicine will require access to large-scale, detailed, and highly integrated patient data. Many initiatives are focused on increasing the interoperability of systems that generate and manage patient data and enhancing those systems for use at the point of care.<sup>38</sup> Although great strides have made in recent years toward achieving a paperless health care system based on EMRs, much more needs to be done to integrate data across systems and to mine data that already exist but remain in silos. The National Institutes of Health (NIH) needs to facilitate cross-site data integration for research, while health systems must do the same for the optimization of patient care.

Many different sectors and activities have to coalesce to promote the implementation and adoption of precision medicine, including the appropriate education, data systems, coverage and reimbursement policies, health system processes, and health policies. These issues are relevant not only to the US but also to other countries and regions that are implementing precision medicine or are likely to do so in the near future (see exhibit 1). Initiatives such as the *All of Us* Research Program in the US and the Genomics England project have been widely publicized, but less attention has been paid to other global initiatives and opportunities. For example, France recently committed \$700 million to fund sequencing centers, and China has committed

## EXHIBIT 1

## Selected programs to implement precision medicine in 13 countries

Country, name of project, and website	Goals of program
<b>AUSTRALIA</b> Australian Genomics Health Alliance, <a href="https://www.australiangenomics.org.au">https://www.australiangenomics.org.au</a>	Develop national framework for translating -omics discoveries into clinical research and practice, incorporating advice on return of results from genomics research and clinical testing.
<b>BELGIUM</b> Belgian Medical Genomics Initiative, <a href="https://biblio.ugent.be/project/120C03412">https://biblio.ugent.be/project/120C03412</a>	Predict clinical outcomes from genomic information and fulfill a pilot role toward concerted integration of genomic information in clinical care in Belgium.
<b>CANADA</b> GenomeCanada, <a href="https://www.genomecanada.ca/">https://www.genomecanada.ca/</a>	Carry out large-scale research projects focused on the application of genomics in the area of precision health. Precision health can be seen as an evidence-based approach to decision making with regard to health care and public health.
<b>ESTONIA</b> Estonian Program for Personal Medicine, <a href="https://www.geenivaramu.ee/en">https://www.geenivaramu.ee/en</a>	Sequence 5,000 people, develop an Estonian genotyping array, pilot of 50,000 Estonian Biobank members, offer to all ages 35–65 (about 500,000 people) and link to EMR.
<b>FRANCE</b> Plan France Médecine Génomique 2025, <a href="https://aviesan.fr/fr/aviesan/accueil/toute-l-actualite/plan-france-medecine-genomique-2025">https://aviesan.fr/fr/aviesan/accueil/toute-l-actualite/plan-france-medecine-genomique-2025</a>	Use the integration of patient care, training, and research to allow access to genomic medicine to all concerned (patients and their families as indicated). By 2020, 235,000 genomes will be sequenced each year.
<b>ISRAEL</b> Bench-to-Bedside Project, <a href="https://www.weizmann.ac.il/WeizmannCompass/sections/features/the-bench-to-bedside-project">https://www.weizmann.ac.il/WeizmannCompass/sections/features/the-bench-to-bedside-project</a>	Sequence 100,000 Israeli genomes from selected patients (this is a project of the Weizmann Institute of Science and Clalit Health Systems).
<b>JAPAN</b> Implementation of Genomic Medicine Project, <a href="http://www.src.riken.jp/english/project/person/">http://www.src.riken.jp/english/project/person/</a>	Use genomics for optimized diagnosis, treatment, and prevention.
<b>KOREA</b> Genome Technology to Business Translation Program, <a href="http://www.cdc.go.kr/NIH/eng/main.jsp">http://www.cdc.go.kr/NIH/eng/main.jsp</a>	Use genomics to develop early diagnosis and treatment approaches for personalized and preventive medicine.
<b>LUXEMBOURG</b> Centre for Systems Biomedicine, <a href="https://wwwfr.uni.lu/recherche/priorites_de_recherche/luxembourg_centre_for_systems_biomedicine_lcsb">https://wwwfr.uni.lu/recherche/priorites_de_recherche/luxembourg_centre_for_systems_biomedicine_lcsb</a>	Focus on early diagnosis and stratification of Parkinson disease.
<b>SINGAPORE</b> Personalized OMIC Lattice for Advanced Research and Improving Stratification, <a href="https://www.a-star.edu.sg/polaris/">https://www.a-star.edu.sg/polaris/</a>	Pilot <i>TGFBI</i> gene testing for disease diagnosis and family risk assessment in stromal corneal dystrophies, then implement a 90-gene panel for gastrointestinal cancers.
<b>THAILAND</b> Pharmacogenomics Network, <a href="http://www.thailandpg.org/">http://www.thailandpg.org/</a>	Implement pharmacogenomics card to identify risk of using top ten drugs associated with SJS/TEN, integrated with nationwide pharmacovigilance program.
<b>UNITED KINGDOM</b> Genomics England, <a href="http://www.genomicsengland.co.uk/">http://www.genomicsengland.co.uk/</a>	Sequence 100,000 whole genomes and link to National Health Service records to treat individual patients and better understand cancer and rare and infectious diseases.
<b>UNITED STATES</b> <i>All of Us</i> Research Program, <a href="https://allofus.nih.gov/">https://allofus.nih.gov/</a>	Recruit one million participants representative of the population and share data from their EMRs, digital health technologies, and genomics to enhance scientific discovery and clinical care.

**SOURCE** Adapted from Manolio TA, et al. Global implementation of genomic medicine (see note 31 in text). **NOTES** EMR is electronic medical record. SJS/TEN is Stevens-Johnson syndrome/toxic epidermal necrosis.

# The democratization of data underpins the scientific advances that enable not only precision medicine but medicine itself.

up to \$10 billion to fund its precision medicine initiative.<sup>39</sup> However, there are few published studies on implementation outside of well-known countries, and thus more research is needed to examine the implementation of precision medicine and to disseminate lessons learned and best practices across countries to enhance their impact on diverse patients and populations.

**REGULATION** A key topic for future discourse will be the evolving regulatory landscape for precision medicine tests. There continues to be uncertainty about how the FDA will regulate molecular and genomic tests. There is also uncertainty about the extent to which the FDA will increase its oversight over laboratory-developed tests, which do not require FDA approval. Most precision medicine tests are currently laboratory developed. A related challenge for the FDA will be to develop its approach to regulating diagnostics that incorporate sequencing technologies, as these tests will require flexible and evolving regulatory approaches.<sup>34</sup> The FDA has recently moved forward on tackling this challenge through the use of parallel review with CMS for sequencing tests.<sup>40</sup> The FDA and CMS will need to develop and refine approaches to regulation and coverage that give precision medicine tests the most effective pathway to the clinic.

**REIMBURSEMENT AND ECONOMICS** As is the case for all new health care interventions, implementation of precision medicine will be stymied if such interventions do not provide demonstrated value or if payers and consumers are unwilling to pay for them. There remain many challenges to determining whether and when precision medicine provides sufficient value relative to its costs, and whether payers should reimburse for testing.

The second author and her colleagues recently analyzed private payers' coverage policies for genetic tests that measure multiple genes (such as panel or whole-exome sequencing tests) and

found that there is limited and variable coverage of such tests,<sup>41</sup> although a more recent unpublished analysis indicates that some tests are increasingly being covered.<sup>42</sup> A study on preemptive pharmacogenetic testing found that one reason why payers hesitate to cover such tests is that they do not fit most payers' "mental models" for coverage decisions.<sup>43</sup> The authors concluded that prospective outcome studies, more precisely defined target populations, and predictive economic models are important considerations for future research.

Demonstrating the economic value and affordability of precision medicine to both patients and organizations is a critical issue that remains in need of further research. For example, an unpublished assessment of the current knowledge base about the economics of precision medicine<sup>42</sup> indicates that the number of economic evaluations of precision medicine is increasing, although evidence of its economic value is still relatively limited, and there are many gaps in the topics covered. Studies have found that precision medicine interventions are generally similar in cost-effectiveness to other types of health care interventions: A majority of interventions have been found to be cost-effective relative to standard practice, but only a minority of studies have found precision medicine to be cost saving.<sup>44</sup> To better assess the economic value of precision medicine, a number of methodological challenges should be addressed, such as identifying relevant studies, dealing with variability across studies, and broadening the focus of studies to other conditions. Thus, to move ahead on a policy agenda for reimbursement and economic value, payers and industry need to work together to develop the necessary evidence base.

**PARTICIPANT ENGAGEMENT** Importantly, patients and consumers must participate in precision medicine for it to achieve its potential. The adoption of precision medicine raises many questions related to patient engagement, and the critical element of trust, including the following: What constitutes truly informed consent? Who owns genetic information and should make decisions about what results are returned to them, and how the results are used? How can privacy be ensured? What outcomes matter most to patients?

A focus of future work should be increasing the emphasis on the ability of precision medicine to affect not only individuals but also populations—what has been termed "precision public health."<sup>45,46</sup> The initial drive toward precision public health is under way, but much more work lies ahead to develop a robust evidentiary foundation for its use.<sup>45</sup> Another area of emphasis should be increased understanding of how

precision medicine could widen or narrow the historical disparities in access to care. Do historically unserved populations have access to precision medicine, and what policies could ensure appropriate access? These questions will need to be addressed within the larger and shifting context of health reform and proposed revisions to Medicaid programs.

### An Action Plan For Precision Medicine

The full realization of precision medicine's disruptive potential will require a multipronged scientific, clinical, and policy agenda. The democratization of data underpins the scientific advances that enable not only precision medicine but medicine itself. Proper incentives for the sharing of data will be required. The precision medicine community—participants, patients, providers, payers, and regulators—will require evidence of value in terms of quality of

life, quality of medical care, and cost efficiency and cost-effectiveness. If precision medicine is successful, more care will occur before disease is apparent, in a shift from disease treatment to disease prevention and early detection. Precision medicine is not uniquely American—it is on the global agenda<sup>31</sup>—and for it to reach its rightful place in health and society will require global leadership and perseverance.

All stakeholders have a role in developing appropriate policies: Researchers need to examine lessons learned on implementation both in the US and globally and to assess the impact on both patients and populations; payers and industry need to work together to develop the necessary evidence base; the NIH needs to facilitate cross-site data integration for research, while health systems must do the same for the optimization of patient care; and the FDA and CMS need to develop and refine approaches to regulation and coverage that give precision medicine tests the most effective pathway to the clinic. ■

Geoffrey Ginsburg received support from the National Institutes of Health (Grant No. U01-HG007282). Kathryn Phillips received support from the National Institutes of Health (Grant Nos. R01-HG007063 and U01-HG009599).

### NOTES

- 1 National Research Council. *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. Washington (DC): National Academies Press; 2011. p. 12.
- 2 Aronson SJ, Rehm HL. Building the foundation for genomics in precision medicine. *Nature*. 2015; 526(7573):336–42.
- 3 Landrum MJ, Lee JM, Benson M, Brown G, Chao C, Chitipiralla S, et al. ClinVar: public archive of interpretations of clinically relevant variants. *Nucleic Acids Res*. 2016; 44(D1):D862–8.
- 4 Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, et al. ClinGen—the Clinical Genome Resource. *N Engl J Med*. 2015;372(23):2235–42.
- 5 Exome Aggregation Consortium. About ExAC [Internet]. Cambridge (MA): ExAC; [cited 2018 Mar 21]. Available from: <http://exac.broadinstitute.org/about>
- 6 Agarwala V, Khozin S, Singal G, O'Connell C, Kuk D, Li G, et al. Real-world evidence in support of precision medicine: clinico-genomic cancer data as a case study. *Health Aff (Millwood)*. 2018;37(5):765–72.
- 7 Institute of Medicine. Genomics-enabled learning health care systems: gathering and using genomic information to improve patient care and research: workshop summary. Washington (DC): National Academies Press; 2015. p. 37–45.
- 8 Ginsburg G. Medical genomics: gather and use genetic data in health care. *Nature*. 2014;508(7497):451–3.
- 9 National Institutes of Health. *All of Us Research Program* [Internet]. Bethesda (MD): NIH; c 2018 [cited 2018 Mar 21]. Available from: <https://allofus.nih.gov/>
- 10 Regeneron. About the Regeneron Genetics Center and Geisinger Health System collaboration [Internet]. Tarrytown (NY): Regeneron; [cited 2018 Mar 21]. Available from: [https://www.regeneron.com/sites/all/themes/regeneron\\_corporate/files/science/RGC\\_FactSheet\\_GHSCollaboration\\_Final.pdf](https://www.regeneron.com/sites/all/themes/regeneron_corporate/files/science/RGC_FactSheet_GHSCollaboration_Final.pdf)
- 11 Rasmussen-Torvik LJ, Stallings SC, Gordon AS, Almoguera B, Basford MA, Bielinski SJ, et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. *Clin Pharmacol Ther*. 2014; 96(4):482–9.
- 12 Williams MS, Buchanan AH, Davis FD, Faucett WA, Hallquist MLG, Leader JB, et al. Patient-centered precision health in a learning health care system: Geisinger's genomic medicine experience. *Health Aff (Millwood)*. 2018;37(5):757–64.
- 13 Kaback MM. Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model. *Eur J Pediatr*. 2000; 159(Suppl 3):S192–5.
- 14 Bell CJ, Dinwiddie DL, Miller NA, Hately SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med*. 2011;3(65):65ra4.
- 15 Kitzman JO, Snyder MW, Ventura M, Lewis AP, Qiu R, Simmons LE, et al. Noninvasive whole-genome sequencing of a human fetus. *Sci Transl Med*. 2012;4(137):137ra76.
- 16 Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, Alnadi NA, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. *Sci Transl Med*. 2012;4(154):154ra135.
- 17 Topol EJ. Individualized medicine from prewomb to tomb. *Cell*. 2014; 157(1):241–53.
- 18 McCarthy JJ, McLeod HL, Ginsburg GS. Genomic medicine: a decade of

- successes, challenges, and opportunities. *Sci Transl Med*. 2013;5(189):189sr4.
- 19 National Human Genome Research Institute. Electronic Medical Records and Genomics (eMERGE) Network [Internet]. Bethesda (MD): National Institutes of Health; [last updated 2017 Nov 3; cited 2018 Mar 21]. Available from: <https://www.genome.gov/27540473/electronic-medical-records-and-genomics-emerge-network/>
  - 20 Clinical Sequencing Evidence-Generating Research Consortium. Clinical Sequencing Evidence-Generating Research [Internet]. Bethesda (MD): CSER; [cited 2018 Mar 21]. Available from: <https://cser-consortium.org/>
  - 21 National Human Genome Research Institute. Integrating genomic sequencing into clinical care: CSER and beyond: workshop report [Internet]. Bethesda (MD): The Institute; 2015 Sep 28 [cited 2018 Mar 21]. Available from: [https://www.genome.gov/Multimedia/Slides/CSER\\_Beyond\\_2015/CSER\\_Beyond\\_WorkshopReport.pdf](https://www.genome.gov/Multimedia/Slides/CSER_Beyond_2015/CSER_Beyond_WorkshopReport.pdf)
  - 22 National Institutes of Health [Internet]. Bethesda (MD): NIH; 2017. News release, NIH accelerates the use of genomics in clinical care: new funding awards focus on diverse and underserved populations; 2017 Aug 8 [cited 2018 Mar 21]. Available from: <https://www.nih.gov/news-events/news-releases/nih-accelerates-use-genomics-clinical-care>
  - 23 Implementing Genomics in Practice. Get started [Internet]. Durham (NC): IGNITE, Duke University; [cited 2018 Mar 21]. Available from: <https://www.ignite-genomics.org>
  - 24 Orlando LA, Wu RR, Myers RA, Buchanan AH, Henrich VC, Hauser ER, et al. Clinical utility of a Web-enabled risk-assessment and clinical decision support program. *Genet Med*. 2016;18(10):1020–8.
  - 25 Consolidated Framework for Implementing Research. Welcome to the CFIR technical assistance website [Internet]. Ann Arbor (MI): CFIR; [cited 2018 Mar 21]. Available from: <http://www.cfirguide.org/>
  - 26 National Human Genome Research Institute. The cost of sequencing a human genome [Internet]. Bethesda (MD): National Institutes of Health; [last updated 2016 Jul 6; cited 2018 Mar 21]. Available from: <https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/>
  - 27 Henry J, Pylpynchuk Y, Searcy T, Patel V. Adoption of electronic health record systems among U.S. non-federal acute care hospitals: 2008–2015 [Internet]. Washington (DC): Department of Health and Human Services, Office of the National Coordinator for Health Information Technology; 2016 May [cited 2018 Mar 21]. (ONC Data Brief No. 35). Available from: [https://www.healthit.gov/sites/default/files/briefs/2015\\_hospital\\_adoption\\_db\\_v17.pdf](https://www.healthit.gov/sites/default/files/briefs/2015_hospital_adoption_db_v17.pdf)
  - 28 Transparency Market Research. Digital health market will reach USD 536.6 billion by 2025 [Internet]. Albany (NY): Transparency Market Research; 2017 Sep 22 [cited 2018 Mar 21]. Available from: <https://globenewswire.com/news-release/2017/09/22/1131466/0/en/Digital-Health-Market-will-Reach-USD-536-6-Billion-by-2025-Transparency-Market-Research.html>
  - 29 Deng MC. The AlloMap™ genomic biomarker story: 10 years after. *Clin Transplant*. 2017;31(3).
  - 30 Kim C, Paik S. Gene-expression-based prognostic assays for breast cancer. *Nat Rev Clin Oncol*. 2010;7(6):340–7.
  - 31 Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, et al. Global implementation of genomic medicine: we are not alone. *Sci Transl Med*. 2015;7(290):290ps13.
  - 32 Pritchard DE, Moeckel F, Villa MS, Housman LT, McCarty CA, McLeod HL. Strategies for integrating personalized medicine into healthcare practice. *Per Med*. 2017;14(2):141–52.
  - 33 Phillips KA, Trosman JR, Kelley RK, Pletcher MJ, Douglas MP, Weldon CB. Genomic sequencing: assessing the health care system, policy, and big-data implications. *Health Aff (Millwood)*. 2014;33(7):1246–53.
  - 34 Personalized Medicine Coalition. The personalized medicine report: 2017 opportunity, challenges, and the future [Internet]. Washington (DC): PMC; [cited 2018 Mar 21]. Available from: [http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The\\_PM\\_Report.pdf](http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The_PM_Report.pdf)
  - 35 Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic test availability and spending: where are we now? Where are we going? *Health Aff (Millwood)*. 2018;37(5):711–17.
  - 36 Ramsey SD, Sullivan SD. A new model for reimbursing genome-based cancer care. *Oncologist*. 2014;19(1):1–4.
  - 37 Carlson JJ, Chen S, Garrison LP Jr. Performance-based risk-sharing arrangements: an updated international review. *Pharmacoeconomics*. 2017;35(10):1063–72.
  - 38 Dzaou VJ, Ginsburg GS. Realizing the full potential of precision medicine in health and health care. *JAMA*. 2016;316(16):1659–60.
  - 39 Bergin J. DNA sequencing: emerging technologies and applications. Wellesley (MA): BCC Research; 2016 May.
  - 40 Foundation Medicine gains FDA Approval, CMS coverage proposal for NGS cancer profiling test. GenomeWeb [serial on the Internet]. 2017 Nov 30 [2018 Mar 21]. Available from: <https://www.genomeweb.com/molecular-diagnostics/foundation-medicine-gains-fda-approval-cms-coverage-proposal-NGS-cancer>
  - 41 Phillips KA, Deverka PA, Trosman JR, Douglas MP, Chambers JD, Weldon CB, et al. Payer coverage policies for multigene tests. *Nat Biotechnol*. 2017;35(7):614–7.
  - 42 Trosman J, Weldon C, Gradishar W, Benson A III, Christofanilli M, Kurian A, et al. Modernizing the framework for insurance coverage policy for contemporary precision medicine—the case of next-generation cancer sequencing. (Unpublished paper, March 2018).
  - 43 Keeling NJ, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. *Genet Med*. 2017 Oct 26. [Epub ahead of print].
  - 44 Berm EJ, Loeff Md, Wilffert B, Boersma C, Annemans L, Vegter S, et al. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. Second update of the literature. *PLoS One*. 2016;11(1):e0146262.
  - 45 Khoury MJ, Galea S. Will precision medicine improve population health? *JAMA*. 2016;316(13):1357–8.
  - 46 Khoury MJ, Iademarco MF, Riley WT. Precision public health for the era of precision medicine. *Am J Prev Med*. 2016;50(3):398–401.