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Stark, Z., Dolman, L., Manolio, T. A., Ozenberger, B., Hill, S. L., Caulfied, M. J., ... North, K. N. (2019). Integrating Genomics into Healthcare: A Global Responsibility. American Journal of Human Genetics, 104(1), 13-20. https://doi.org/10.1016/j.ajhg.2018.11.014

Published in:
American Journal of Human Genetics

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Integrating Genomics into Healthcare: A Global Responsibility

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Genomic sequencing is rapidly transitioning into clinical practice, and implementation into healthcare systems has been supported by substantial government investment, totaling over US$4 billion, in at least 14 countries. These national genomic-medicine initiatives are driving transformative change under real-life conditions while simultaneously addressing barriers to implementation and gathering evidence for wider adoption. We review the diversity of approaches and current progress made by national genomic-medicine initiatives in the UK, France, Australia, and US and provide a roadmap for sharing strategies, standards, and data internationally to accelerate implementation.

Introduction

Five years ago, genomic sequencing was restricted to the research environment. Now, it is increasingly used in clinical practice, and over the next 5 years, genomic data from over 60 million patients is expected to be generated within healthcare.[1] But are our health systems ready for the complexity, volume, and responsibility associated with genomic medicine and the imperative to share clinical, epidemiological, and genomic data on a global scale to optimize the benefits for the individual? Genomic sequencing is a transformative technology, and effective integration in healthcare requires system-wide change.[2] Beyond the technical requirements of establishing sequencing and bioinformatics capacity to process samples, the real barriers to widespread clinical implementation span diverse domains, including data integration and interpretation, workforce capacity and capability, public acceptability and government engagement, paucity of evidence for clinical utility and cost effectiveness, and ethical and legislative issues.[3,4] Frameworks for implementing genomic-medicine programs in single institutions and multi-institution collaboratives are available,[2,5] but information on translating this experience to transform whole healthcare systems is scarce.

This is an international endeavor.[3] Since 2013, the governments of at least 14 countries have invested over US$4 billion in establishing national genomic-medicine initiatives to address implementation barriers and transition testing from centers of excellence to mainstream medical practice (Figure 1 and Table S1). In countries such as the UK, France, Australia, Saudi Arabia, and Turkey, workforce and infrastructure development has been coupled with testing large numbers of patients with rare diseases and cancer, two applications of genomic sequencing expected to have immediate clinical benefits. These "proof-of-principle" programs are driving change and fostering adoption among stakeholders under real-life conditions while simultaneously gathering evidence for wider implementation. Other countries such as the US, Estonia, Denmark, Japan, and Qatar have invested in population-based sequencing projects with return of results to participants, whereas national initiatives in Switzerland, the Netherlands, Brazil, and Finland are primarily focusing on the development of infrastructure, such as common standards and data-sharing policies and platforms. These projects will potentially be dwarfed by the China Precision Medicine Initiative: a 15-year, CN¥60 billion (US$9.2 billion) project aiming to sequence 100,000,000 genomes by 2030.

Here, we illustrate the diversity of approaches and current progress made toward meeting the challenges of integrating genomics into mainstream healthcare at a national level by focusing on the UK, France, Australia, and US, as well as provide a roadmap for sharing tools, strategies, data, and standards internationally to accelerate implementation.

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https://doi.org/10.1016/j.ajhg.2018.11.014.

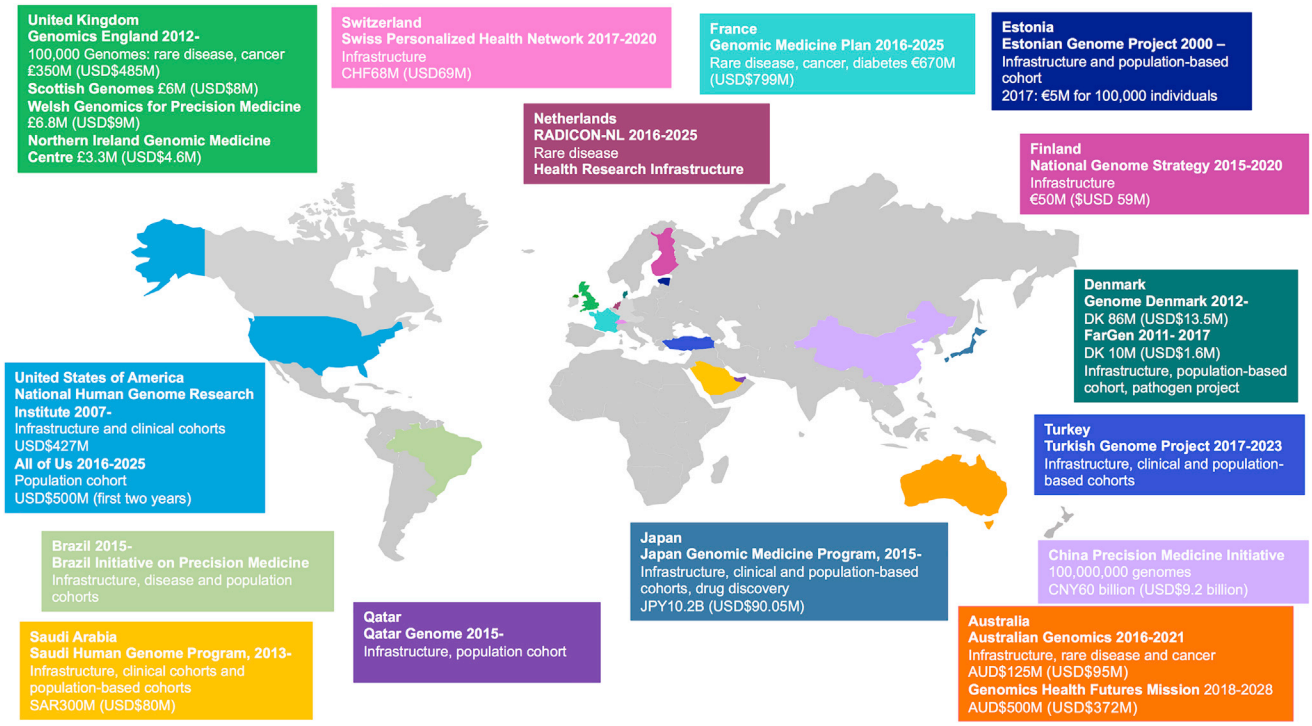

Figure 1. Map of Currently Active Government-Funded National Genomic-Medicine Initiatives

United Kingdom

The UK has a single-payer national healthcare system: the National Health Service (NHS). Genomics England (GEL) was established in 2013 with »300M (US$415M) in government funding and a mandate to sequence 100,000 genomes from patients with over 100 rare diseases and seven common cancers, as well as their family members.[6] This sequencing target was met in December 2018. The majority of rare-disease testing (the exception being that for late-onset adult disease) uses a trio-based approach to optimize large-scale data interpretation. A separate pathogen sequencing project is underway at Public Health England, and Health Education England is delivering 700 person-years of education and training to increase workforce capacity and capability.

GEL has established centralized infrastructure for the delivery of diagnostic whole-genome sequencing (WGS) services, including an NHS Genomic Sequencing Centre in partnership with the Wellcome Trust and Illumina, a standardized bioinformatics and analysis pipeline, a bio-repository, and a data center. NHS England has established 13 Genomic Medicine Centers to identify, acquire consent from, and enroll participants in the project; collect high-quality DNA samples, including the establishment of new pathways for processing fresh and fresh frozen tumor DNA; provide clinical information to facilitate data analysis; and be responsible for the interpretation and clinical actionability of final results. Genomic data are linked to health records in partnership with NHS Digital and are available to researchers and industry through the Genomics England Clinical Interpretation Partnership (GeCIP) and the Discovery Forum. Genomic-medicine initiatives have been funded in Scotland, Wales, and Northern Ireland (»6M [US$8M], »6.8M [US$9M], and »3.3M [US$4.6M], respectively) to establish local clinical and laboratory genomics infrastructure and recruit participants for the 100,000 Genomes Project.

The 2016 annual report of England's Chief Medical Officer ("Generation Genome") called for the transformation of patient care through the systematic use of genomics and made 24 recommendations addressing further changes needed in NHS infrastructure, data sharing, governance, research, and clinician training.[7] The NHS Genomic Medicine Service (GMS) was launched in October 2018 with a mandated test directory linking WGS for defined rare diseases and cancers to reimbursement. A new national network of Genomic Laboratory Hubs is being established, and WGS provision, data, and informatics infrastructure are delivered in partnership with GEL. The recent UK Life Sciences Sector deal, the »65M (US$92.5M) investment by Health Data Research UK in a UK-wide collaborative network to facilitate the integration of health and data science, and the recent government announcement of plans to sequence 5,000,000 genomes in the next 5 years in the clinical and research environments are expected to further strengthen UK's leadership in genomics.

France

France has a healthcare system based on government-funded national health insurance. The French Plan for Genomic Medicine 2025 (Plan

France Médecine Génomique 2025) was commissioned by the prime minister in 2015 and developed by Aviesan (the French National Alliance for Life Sciences and Health) in 2016. It aims to integrate genomic medicine into healthcare and establish a national genomic-medicine industry that promotes innovation and economic growth. Of the €670M (US$822M) invested in the first 5 years, around €230M (US$282M) will come from industry. Genome sequencing will be performed by 12 ultra-high-throughput services, two of which will be launched in 2018. A national data-analysis facility (Collecteur Analyseur de Données) will interpret and store data and interface with other national and international databases. Based at academic centers of excellence, a reference center for innovation, assessment, and transfer (Centre de Référence, d'Innovation, d'Expertise et de Transfert [CRefIX]) will develop procedures, tools, and technologies and will also be responsible for implementation, commissioning, and workforce training. CrefiX is already operational and has launched the first clinical pilot projects in rare disease, cancer, common disease (diabetes), and a population cohort to test technological, clinical, and regulatory barriers to implementation. It is anticipated that 10,000 individuals will be recruited into the initial pilot projects, and France will be capable of sequencing 235,000 genomes per year by 2020, corresponding to 20,000 patients with rare disease and 50,000 patients with metastatic or refractory cancer.

Australia

Australia has a national health system, but clinical and laboratory genetics services are funded by the six state and two territory governments. Thus, the approach to implementing genomic medicine has been based on the "federation" of existing state-based services with the engagement of state and federal governments in the development of a National Health Genomics Policy Framework.[8]

Australian Genomics was established in 2014 as a research partnership of 78 organizations, including diagnostic laboratories, clinical genetics services, and research and academic institutions. It was awarded AU$25M (US$19.2M) by the National Health and Medical Research Council in 2015 to demonstrate the value and practical strategies for implementing genomics into healthcare, and it leverages AU$100M (US$76.8M) from state-based funding for genomics programs.

Australian Genomics comprises four research programs: (1) national diagnostic and research network; (2) national approach to data federation and analysis; (3) evaluation, policy, and ethics; and (4) workforce and education. Currently over 40 rare-disease and cancer flagship projects across 30 clinical sites provide experiential learning while prospectively evaluating diagnostic and clinical utility, cost effectiveness, and new approaches to service delivery and comparing different sequencing modalities, including WGS, whole-exome sequencing (WES), RNA sequencing, and large capture panels. The majority of rare-disease testing uses a singleton approach to optimize resource use. Although sequencing, bioinformatic analysis, data interpretation, reporting, and storage remain the responsibility of diagnostic laboratories, Australian Genomics is developing frameworks for ordering tests, acquiring consent, and capturing phenotypes; developing a federated repository of genomic and phenotypic data compliant with Global Alliance for Genomics and Health (GA4GH) standards; and enabling global data sharing through Beacon,[9] Matchmaker Exchange,[10] and ClinVar.[11] There is active engagement with patient advocacy groups, and a joint committee has been established with the Australian Digital Health Agency to integrate genomic test results into the national electronic health record (MyHealth Record).

Evaluation data are already available from several rare-disease flagship projects, indicating that genomic sequencing not only increases diagnostic yield but also has the potential to reduce diagnostic costs while improving short-term patient management and longer-term patient and family outcomes.[2,12–16] The Australian federal government has recently committed AU$500M (US$372M) over 10 years for a Genomics Health Futures Mission to support new and expanded clinical studies in rare disease, cancer, and complex conditions; early access to clinical trials; and community dialog to understand the privacy, legal, social, and familial affects of genomics. Two initial projects have been announced—a population reproductive-carrier-screening program and a cardiovascular-disease flagship project—and an additional AU$26M (US$18.4M) of funding has been granted to Australian Genomics for these.

United States

The US has a mixed private and public healthcare system and has invested in genomic-medicine implementation since 2011 with the launch of the new strategic plan of the National Human Genome Research Institute (NHGRI).[17] NHGRI's genomic-medicine programs aim to identify barriers to implementation of genomics in clinical care and develop solutions and best practices for widespread dissemination. Many of these landmark projects have recently reported results, establishing evaluation frameworks and providing evidence on the diagnostic, clinical, and economic value of genomic sequencing in specific patient groups, such as healthy and acutely unwell newborns;[18–22] individuals with complex, undiagnosed rare genetic conditions;[23,24] and those in specific healthcare settings, such as primary-care and cardiology clinics.[25–27] NHGRI projects are also addressing specific evidence gaps in the clinical delivery of genomic testing, such as the the return of secondary findings,[28–30] inter-laboratory consistency in variant interpretation,[31,32] integration of genomic resources with electronic records,[33] and sharing implementation and evaluation experience more broadly.[34–37]

Tools for electronic phenotyping (Phenotype KnowledgeBase), clinical decision support (Clinical Decision Support KnowledgeBase), and implementation in resource-limited settings (IGNITE SPARK Toolbox) are openly available, and ClinGen plays a central role internationally in curating and disseminating consensus information on clinically relevant genes and variants.[38–41]

The Precision Medicine Initiative All of Us Research Program, initially funded through a special congressional appropriation of US$500M to the National Institutes of Health in 2016–2017, has now launched throughout the US and has an additional funding commitment of US$1.455B. All of Us is engaging 1,000,000 volunteers of all life stages, health statuses, races and ethnicities, and geographic regions, reflecting the human diversity of the US. Mobilizing rich and constantly evolving data—from electronic health records, biospecimens, and questionnaires to physical evaluations, sensors, and other technologies—the program will support research at the intersection of lifestyle, environment, and genetics to produce new knowledge, leading to the development of innovative prevention strategies and treatments. Both genotyping and WGS are being evaluated as testing modalities initially.

Genomic Medicine in the Private Sector

The increased integration of genomics into public healthcare systems is mirrored by an explosion in the use of genomics in the private sector, particularly in the US. Geisinger Health System's MyCode project, which began as a partnership with Regeneron Pharmaceuticals to perform exome sequencing in 100,000 Geisinger patients and use the results for drug discovery and clinical care,[42] has recently expanded to all consenting Geisinger patients. Foundation Medicine has developed a number of genomics-based tests in the domain of precision cancer medicine while also contributing to public databases, such as the National Cancer Institute's Genomic Data Commons. Direct-to-consumer (DTC) testing companies, such as 23andMe and Ancestry, capture significant health-related genomic information, but public and clinician responses to DTC genomics have been variable.[43–45]

International Collaboration to Accelerate the Implementation of Genomics into Healthcare

The above-mentioned implementation approaches and priorities of genomic-medicine initiatives in high-income countries might not necessarily be applicable to low and middle-income countries.[46] Yet, broad implementation will be crucial in building representative population reference datasets that improve variant interpretation globally[47] and in accelerating the discovery of genes associated with rare disease, particularly in populations where consanguinity is common.[48] Implementation in a range of economic and social contexts will also help address health priority areas with a major contribution to global disease burden, including host-pathogen interactions in infectious diseases; common monogenic disorders, such as sickle cell disease and thalassemias; and complex conditions, including hypertension, dyslipidemia, diabetes, stroke, and kidney disease. The Global Genomic Medicine Collaborative is working to identify and share genomic-medicine implementation activities around the globe, including those in under-resourced areas. National initiatives, even in resource-limited settings, can often move more quickly in response to specific local health needs.[5] The Southeast Asian Pharmacogenomics Research Network, for example, is a multinational collaboration focused on pharmacogenomic risk alleles present at high frequencies in Southeast Asian populations.[49] The Human Heredity and Health in Africa initiative, a large-scale multinational sequencing project that pools infrastructure and human resources, harmonizes data collection, and accelerates capacity development, provides another successful implementation model in low-resource settings.[50]

All of these large-scale initiatives have the opportunity to transform healthcare systems by integrating genomic technologies into clinical care. However, with this comes the responsibility to do so efficiently and effectively and to share knowledge and experience. Concerns about overpromising ("genohype")[51] and the perceived desire to exempt genomic testing from requirements for robust evidence, leading to misallocation of healthcare resources,[52] have been raised. Delays in program evaluation mean that clinical implementation and policy development proceed uninformed by evidence, potentially resulting in inappropriate testing, poor-quality data interpretation, siloed data, and funding arrangements that entrench existing healthcare inequalities. Healthcare systems are already struggling with evidence-based medicine, and the absorptive capacity of frontline clinical teams looms large as a key challenge.[53] Almost all of the initiatives discussed here are subject to time-limited funding, with the danger of creating momentum for genomic medicine, without the guarantee of sustainable healthcare resource allocation.

The scale of the implementation challenge is formidable. Sharing data, tools, experience, and knowledge to create a global "learning health system" is essential if we are to effectively accelerate and sustain the integration of genomics into healthcare. Collaborations across multiple areas are already under way (Box 1), but here we will focus on discussing two key priorities: evidence generation and data sharing.

Building the Evidence Base for Implementation of Genomics in Healthcare

The paucity of evidence for the clinical utility of genomic testing, and the resultant lack of alignment of reimbursement methods to drive transformational change in healthcare, remains a principal barrier to implementation.[3,5] National-level

Box 1. National Genomic-Medicine Initiatives: Collaborative "Cross-Country" Projects Currently Underway

- Align research protocols to enable discovery across larger datasets, as well as compare outcome measures such as diagnostic and clinical utility, cost effectiveness, and patient- and family-reported outcomes (Genomics England, Australian Genomics, NHGRI Newborn Sequencing in Genomic Medicine and Public Health)
- Evaluate new sequencing and computational methods for clinical use (Genomics England and French Genomic Medicine Plan)
- Harmonize collection of clinical and phenotypic data: define the minimum clinical dataset required for interpreting genomic tests and the health informatics infrastructure required for data capture and exchange (Australian Genomics and Genomics England)
- Improve understanding of variant- and gene-disease associations by sharing the curation effort, developing common data models to capture evidence, and contributing to public knowledge repositories (NHGRI ClinGen, Genomics England, and Australian Genomics)
- Develop an evaluation framework for assessing existing educational resources (Australian Genomics and Genomics England); enable broader access, particularly to early adopters in countries with emerging genomic-medicine programs
- Develop strategies and capture experience in engaging culturally and linguistically diverse populations, indigenous populations, the general public, patients, professionals, and funders (Australian Genomics, Genomics England, NHGRI, All of Us, and Japan Agency for Medical Research and Development [AMED])
- Compare national consent procedures: reduce unnecessary heterogeneity, identify common features that represent best practices to allow global data sharing, and explore new models such as dynamic consent platforms (Australian Genomics, Genomics England, Swiss Personalized Medicine Network, and Japan AMED)

initiatives have an important role in presenting a unified voice to governments to inform future policy development and service planning. Outcome evaluation of patient cohorts is a key priority to inform policy decisions but is hampered by a lack of consensus on standard criteria against which the effectiveness of genomic interventions should be evaluated and reported.[54,55] There is a need to develop and share evaluation methodologies specific to different disease groups,[56] funding contexts, and healthcare systems. Although some data are already available on diagnostic yields, short-term clinical utility, and cost effectiveness in small cohorts,[12,13,15,16] more data are needed on longer-term health outcomes following genomic testing, including measures such as the development and progression of disease, quality-adjusted life years gained, patient empowerment, impact on families, and downstream cost effects on healthcare systems[14,25] and society. National genomics initiatives also provide the opportunity to assess the evidence for and against particular approaches for effective, sustainable implementation.[57] The framework developed by NHS England in conjunction with Genomics England to commission WGS for routine care provides an early example of integrating the clinical evidence base with operational and financial considerations.

Genomic Data Sharing

The importance of breaking down data silos to accelerate the development of knowledge databases that directly improve patient outcomes cannot be underestimated.[9] Genomic data generated within healthcare settings are subject to strict national regulatory frameworks that are unlikely to allow large-scale data migration, and innovative solutions are necessary to enable federated data analysis without data movement across geographical borders[58] while maintaining public trust.[59] National genomic-medicine programs have the opportunity to resource and promote best practices in data sharing by structuring data access and consent processes, collecting clinical and genomic data in interoperable formats, committing to global data sharing, and informing public debate and policy development. GA4GH recently launched a 5 year strategic plan—GA4GH Connect—that focuses on the development of standards for responsible sharing of clinical-grade meta-, genomic, and phenotypic data. GA4GH toolkits provide a framework to enable transparent, responsible, and accountable data sharing, as well as practical specifications for genomic data formats and standards for interoperable exchange. Genomics England, Australian Genomics, and All of Us serve as early Driver Projects for GA4GH to inform the iterative development of tools and policies for data sharing, test them under real conditions, and disseminate best practices.

Conclusions

It takes an average of 17 years for research evidence to be implemented in clinical practice.[60] We have a global responsibility to accelerate the implementation of genomic medicine and enable the timely realization of the benefits of genomics for individual patients, families, and healthcare systems. Technical standards and policy guidance are high priorities at this crucial inflection point to enable a shift in the global community toward more responsible and effective

sharing of genomic, epidemiological, and clinical data and facilitate evidence-based implementation. National genomic-medicine initiatives, in partnership with GA4GH and other regional and global alliances, have an important role in strengthening an international collaborative network and creating a global learning healthcare system to enable rapid translation.

Supplemental Data

Supplemental Data include one table and can be found with this article online at https://doi.org/10.1016/j.ajhg.2018.11.014.

Acknowledgments

The Australian Genomics Health Alliance is supported by the Australian National Health and Medical Research Council (GNT1113531). The 100,000 Genomes Project is managed by Genomics England (a wholly owned company of the Department of Health). It is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK, and Medical Research Council have also funded research infrastructure. The 100,000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support. M.L. is funded by Health Data Research UK.

Declaration of interests

E.B. reports consultancies to Oxford Nanopore, GlaxoSmithKline, and Dovetail Genomics; M.L. reports personal fees (unrelated to the current work) from Pfizer.

Web Resources:

All of Us Research Program, https://allofus.nih.gov

Australian Genomics, https://www.australiangenomics.org.au

French Genomic Medicine Plan, http://solidarites-sante.gouv.fr/IMG/pdf/genomic_medicine_france_2025.pdf

Geisinger Health, https://www.geisinger.edu/research

Genomics England, https://www.genomicsengland.co.uk

Global Alliance for Genomics and Health, http://www.ga4gh.org

Global Genomic Medicine Collaborative, https://g2mc.org/

Health Education England, https://www.genomicseducation.hee.nhs.uk

NHGRI Clinical Decision Support KnowledgeBase, https://cdskb.org/

NHGRI Genomic Medicine, https://www.genome.gov/27551170

NHGRI IGNITE Spark Toolbox, https://ignite-genomics.org/spark-toolbox

NHGRI Phenotype KnowledgeBase, https://phekb.org/

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