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VIEWPOINT

Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation

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Author Audio Interview

Supplemental content

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During the past 5 years, next-generation sequencing (NGS) has transitioned from research to clinical use.[1] At least 14 countries have created initiatives to sequence large populations (eg, All of Us, Genomics England), and it is projected that more than 60 million people worldwide will have their genome sequenced by 2025.[1] However, there has not been an assessment of global NGS implementation (defined here as the use of testing in routine clinical care as measured by clinical applications, utilization, and coverage/funding/reimbursement). Implementation is a key pillar in the translational continuum of discovery, utility, implementation, and population health impact.[2] Understanding how NGS is being used and paid for is critical for determining its clinical and economic benefits and addressing current and future challenges to appropriate implementation.

What Is NGS and How Is It Used in Clinical Care?

NGS is a broad term that encompasses several modern sequencing technologies that measure variations in genes that are present at birth or emerge later in life (eg, cancers or viruses). Many NGS tests are available for clinical care and are being used for clinical applications, including risk assessment, diagnosis, prognosis, and therapy selection. The eTable in the Supplement provides examples of tests currently in use in countries that have widespread NGS implementation, as well as several emerging and future tests. Emerging tests (eg, liquid biopsy tests for cancer screening) could influence clinical outcomes and health care budgets. Thus, the identification of emerging and future tests can guide the collection of data needed by clinicians and policy makers to inform appropriate implementation.

This Viewpoint examines use, payment/coverage, and gaps in data availability on implementation of NGS worldwide using 3 common tests[3] as examples of NGS: (1) noninvasive prenatal testing (NIPT), (2) whole-exome sequencing (WES)/whole-genome sequencing (WGS) for suspected genetic disorders, and (3) tumor sequencing (TS).

Use of NGS Around the World

NIPT is widely used and is currently available in at least 90 countries. In the commercially insured population in the US, almost a half-million NIPT tests were reimbursed in 2019, along with 5600 WES tests and 70 300 TS tests.[4] There is increasing, but variable, use of NIPT, WES/WGS, and TS in Canada, Europe, the Middle East, and Asia, and to a more limited extent in Central/South America and Africa. Even some middle-income countries are implementing NGS in clinical care.

Payment and Coverage

Whether tests are covered or funded varies by the type of health care system (private or public). The UK is recognized as a leader in nationally funded coverage for NGS testing, although several other European and Asian countries also have national coverage for some NGS tests.

The US provides an example of how coverage varies depending on the clinical scenario and payer type.[5] Almost all (97%) insured individuals have NIPT coverage, although about half (48%) of this coverage is for women in high-risk categories (eg, advanced maternal age, family history of abnormal pregnancy) only. Most Medicaid enrollees (90%) also have NIPT coverage, but a greater percentage (62%) of this coverage is for women in high-risk categories only. More than half of insured individuals (63%) have WES and/or WGS coverage, although the percentage of Medicaid enrollees with coverage is lower (39%). Most insured individuals (80%) have coverage for TS, although this declines to 56% of Medicaid enrollees having coverage. In contrast, all Medicare enrollees have select TS coverage based on a 2018 National Coverage Determination.

NIPT and small TS panels (<50 genes) have the lowest reimbursement rates (up to approximately $1000), whereas WES/WGS and comprehensive TS have the highest (up to approximately $5000). Patients in the US who self-pay can obtain NIPT for $99 and exome sequencing (trio) for $2500.[5] Despite the high costs of some NGS tests, expenditures for NGS in the US represent a small percentage of health care expenditures (approximately 0.13% of Medicare expenditures).[6]

Gaps in Data Availability on Implementation

There is no central source of information on implementation across countries and clinical applications. Much of the available data are from the US only; in many other countries, little or no data are publicly available. A consistent gap is data on usage, with sparse data available on how many tests are performed even in countries with high implementation, such as the US. Peer-reviewed publications only provide data on select tests and specific health care systems and are based on historical vs current data. As a result of these gaps, data on implementation must be compiled across diverse sources. For example, some data can be found in the gray literature (eg, white papers, health system reports, market analyses, regulatory filings, company websites, news reports, national/international consortia websites) and some data can be obtained from administrative/clinical resources (eg, electronic health records, claims data, fee schedules, industry databases, registries). Much of the needed data are proprietary, costly to obtain, or both, such as lab data and market

analyses. Furthermore, countries define and measure implementation differently; for example, test use may be reported using expenditures rather than the number of tests performed, and whether tests are covered for payment can refer to coverage policies or reimbursement decisions.

Organizations such as the Global Genomic Medicine Collaborative[7] and the World Economic Forum[8] are facilitating global collaborations on the implementation of appropriate genomic testing into clinical practice. The focus has been on governance through consistent coverage and reimbursement policies and infrastructure issues (eg, capacity building; data system interoperability to share data securely and ethically; establishing value frameworks to capture diagnostic, clinical, and personal benefits of genomic testing).[9] These critical steps are fundamental to support appropriate implementation, but they are only a first step.

The next step needs to be greater ability to generate, enable access to, and assess data on implementation. Critical gaps will require innovative approaches to leveraging a range of real-world data sources rather than using data from clinical trials or population initiatives, as well as cooperation across countries and involved parties, such as industry, payers, and government. Data are also needed on the full range of NGS clinical applications and tests. Recent reports have demonstrated that creative approaches to link multiple data sources can provide new information on implementation[4] and that data sharing can be a valuable investment.[9]

Implementation is a key pillar of the translational continuum, but understanding implementation alone is insufficient because it is also essential to assess clinical benefits to patients. Many studies have examined the clinical utility of NGS, but not all NGS tests with demonstrated clinical utility are fully implemented to achieve population health benefit, and conversely, tests without known clinical utility may still be implemented. Without consistent information on clinical utility and how NGS tests are implemented in clinical care, it is not possible to develop an understanding of benefits and harms associated with NGS. It is not always the case that evidence of clinical utility leads to improved outcomes, and evidence about implementation is required to complete the assessment of the effects on population health. Implementation science is intended to support the integration of findings from scientific evidence to uptake in routine clinical care in the ongoing cycle of a learning health care system.[10] Thus, another key next step is to integrate information on both clinical utility and implementation, including studies that examine clinical utility and implementation in the same population as well as across populations, to assess the overall influence of NGS and determine how NGS can benefit patients and populations around the world.

ARTICLE INFORMATION

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REFERENCES

1. Stark Z, Dolman L, Manolio TA, et al. Integrating genomics into healthcare: a global responsibility. *Am J Hum Genet*. 2019;104(1):13-20. doi:10.1016/j.ajhg.2018.11.014

2. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med*. 2007;9(10):665-674. doi:10.1097/GIM.0b013e31815699d0

3. Phillips KA, Douglas MP. The global market for next-generation sequencing tests continues its torrid pace. *J Precis Med*. 2018;4.

4. Babu D, Pritchard D, Wells C, et al. *Understanding Genomic Testing Utilization And Coverage in the US*. Personalized Medicine Coalition; 2020.

5. Illustrative data sources and citations for NGS test coverage, prices, and reimbursement in the US. Accessed September 16, 2020. https://pharm.ucsf.edu/transpers/node/18041

6. *Medicare Laboratory Test Expenditures Increased in 2018, Despite New Rate Reductions*. US Dept of Health and Human Services; 2020.

7. Ginsburg GS. A global collaborative to advance genomic medicine. *Am J Hum Genet*. 2019;104(3):407-409. doi:10.1016/j.ajhg.2019.02.010

8. Precision medicine vision statement: a product of the World Economic Forum Global Precision Medicine Council. World Economic Forum. Published May 28, 2020. Accessed October 19, 2020. https://www.weforum.org/reports/precision-medicine-vision-statement-a-product-of-the-world-economic-forum-global-precision-medicine-council

9. Belsey J, Chaihorsky L, Currie G, Goranitis I, Marshall D. Global data access for solving rare disease: a health economics value framework. World Economic Forum. Published February 2020. Accessed October 19, 2020. http://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf

10. Chambers DA, Feero WG, Khoury MJ. Convergence of implementation science, precision medicine, and the learning health care system. *JAMA*. 2016;315(18):1941-1942. doi:10.1001/jama.2016.3867

Supplemental Online Content

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eTable 1. Next-generation Sequencing (NGS) Test Applications and Examples of Key Current and Emerging/Future Tests

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable. Next-generation Sequencing (NGS) Test Applications and Examples of Key Current and Emerging/Future Tests

Current test	Emerging/future uses
Risk assessment and disease screening	
Germline cancer risk testing (eg, hereditary breast and ovarian cancer, lynch syndrome)	Circulating tumor DNA ("liquid biopsy") for early detection of cancer Healthy patient screening for wide range of disease risks (including monogenic risk or tests based on polygenic risk scores)
Reproductive health decision-making	
NIPT for common trisomy syndromes in fetuses	NIPT for expanded genetic abnormalities in fetuses (eg, rare autosomal aneuploidies, microdeletions, large copy number variants)
Carrier screening for specific recessive genetic disorders (eg, cystic fibrosis)	Expanded carrier screening for a wide range of recessive genetic disorders
Diagnosis of an existing condition	
WES or WGS for diagnosis of specific clinical presentations of suspected genetic diseases (eg, intellectual disability disorders or rare diseases) (multigene panels are also currently used)	WGS as first-line test for diagnosis for suspected genetic diseases broadly
Diagnosis of infectious diseases (eg, SARS-CoV-2, influenza, urinary tract infections)	
Prognosis for a diagnosed disease	
Variation testing for prognosis (eg, FLT-3 in acute myeloid leukemia)	WGS for comprehensive assessment of genomic variations in acute leukemias
Prediction/monitoring of treatment response or adverse events	
Comprehensive tumor sequencing (including circulating tumor DNA liquid biopsy) for therapy selection and monitoring of cancer treatment (multigene panels are also currently used)	WGS for comprehensive assessment of genomic variations across cancer types
Pharmacogenomics panels to target current drug selection	Preemptive pharmacogenomics panels to guide future drug selection

Abbreviations: NIPT, noninvasive prenatal testing; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WES, whole-exome sequencing; WGS, whole-genome sequencing.