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Clinical Integration of Next Generation Sequencing: Coverage and Reimbursement Challenges

Patricia A. Deverka, M.D., M.S., M.Bioethics [Adjunct Associate Professor] and University of North Carolina at Chapel Hill School of Pharmacy where she focuses on issues related to personalized medicine, comparative effectiveness research, evidence standards and stakeholder engagement. She received her B.A. from the University of Virginia, Charlottesville, her M.D. from the University of Pittsburgh School Medicine, her M.S. in Preventive Medicine from the University of Maryland School of Medicine, and her M. Bioethics from the University of Pennsylvania.

Jennifer C. Dreyfus, M.B.A., M.Bioethics [Principal of Dreyfus Consulting] LLC where she focuses on offering practical solutions and insights in the areas of policy and regulatory analysis, as well as reimbursement and risk-sharing expertise. She received her B.A. in Medical Ethics from Tufts University, her M.B.A. from The Wharton School at the University of Pennsylvania, and her M. Bioethics from the School of Medicine at the University of Pennsylvania.

Introduction

Clinical next generation sequencing (NGS) is a term that refers to a variety of technologies that permit rapid sequencing of large numbers of DNA segments, up to and including entire genomes. As an approach that is playing an increasingly important role in obtaining genetic information from patients, it may be viewed by public and private payers either positively, as an enabler of the promised benefits of personalized medicine, or as “the perfect storm” resulting from the confluence of high market demand, an unproven technology, and an unprepared delivery system. A number of recent studies have noted that coverage and reimbursement will be critical for clinical integration of NGS,¹ yet the evidentiary pathway for payer decision-making is unclear. Although there are multiple reasons for this uncertain reimbursement environment, the situation stems in large part from a long-standing lack of alignment between the information needs of regulators and post-regulatory decision-makers such as payers.²

The concept of personalized medicine itself has generally been viewed favorably by health care payers as an opportunity to improve the risk-benefit profile and cost-effectiveness of health care interventions based on a molecular understanding of an individual's disease, prognosis, and likelihood of response to treatment.³ However, the coverage and reimbursement of specific molecular diagnostic tests, which is necessary for real-world adoption of personalized medicine, has been slowed by a lack of evidence of clinical utility.⁴ The term *clinical utility* refers to the assessment of the effects of a broad range of molecular diagnostic (MDx) tests on net patient health outcomes, and is the evidentiary gold standard applied by most payers when evaluating MDx tests for coverage and reimbursement decision-making.⁵ In practice, some payers define clinical utility of a MDx test as evidence that use of the test affects clinical decisions⁶ and may rely on this lower evidentiary

threshold given plausible arguments of hypothesized clinical benefit and other factors such as clinician demand for the test.

The threshold of evidence needed for a molecular diagnostic test to gain regulatory clearance and enter the medical marketplace is considerably lower than that needed for payers to support coverage and determine reimbursement levels. Thus, demand for new MDx tests, including clinical NGS, often precedes evidence of their utility. For example, in a recent report focused on the topic of personalized medicine, United Healthcare found that their expenditures on molecular tests increased 14% annually between 2008 and 2010, a rate significantly higher than that of clinical laboratory services overall.⁷ Another market analyst estimates that molecular diagnostics, including clinical NGS, will increase to \$21 billion by 2020, growing from 11% to 31% of the *in vitro* diagnostic market over 10 years.⁸ United projected that national spending for genetic testing could reach between \$15 and \$25 billion by 2021. In the same report, United Healthcare surveyed 1,254 physicians regarding the use of these tests — over half thought the tests would increase health care costs while only 1 in 5 thought that they were likely to lead to a reduction in health care costs.

While NGS testing is part of a growing molecular diagnostics market, it must be seen in the larger context of payer concerns about managing rising total health care costs.⁹ Increased utilization of new technology is a major contributor to rising health care costs, and genomic innovations are seen as part of this trend. However, new research models that promote increased collaboration between payers and tests developers and flexible study designs will also need to be pursued if we are to increase the number and quality of clinical utility studies available for decision-making.¹⁰ Companies developing NGS tests should expect that payers will seek to sanction only those tests that demonstrate how use of test results lead to improved clinical decisions and actions that result in net health benefits for patients.¹¹

The purpose of this paper is to provide a comprehensive review of the coverage and reimbursement environment that is currently confronting the introduction of clinical NGS, as well as to identify the potentially novel reimbursement challenges that will need to be addressed for this new technology to realize its full clinical potential. The paper first outlines various coverage-related parameters relevant to diagnostic tests broadly, emphasizing factors common to public and private payers in order to provide both a historical perspective and an overview of the current coverage and reimbursement framework. Next, the paper explores coverage and reimbursement initiatives that are unique to MDx tests and where available, clinical NGS coverage policies, covering Medicare, Medicaid, and private insurers. Together the first two sections present an overview of the coverage and reimbursement landscape for NGS tests, assuming that the approach used for MDx tests establishes the critical precedent for how NGS is likely to be assessed by payers.

A more in-depth discussion follows; policy issues which are either unique to clinical NGS or that represent a magnification of current reimbursement policy challenges are then identified. The conclusion is followed by a series of recommendations to help ensure that over time, patients will have access to NGS tests whose benefits outweigh the harms.

Background Common to Public and Private Payers

While the terms “reimbursement” and “coverage” are sometimes used interchangeably, coverage specifically refers to the scope of services a payer will pay for and under what circumstances, while reimbursement refers to the level of payment. Coverage policy has typically focused on approving services within contractually defined categories or for services viewed as “medically necessary,” although the determination of medical necessity has often been controversial, with the trend more recently that larger payers apply evidence-based approaches to coverage decision-making.¹² In addition to explicit definitions of covered services and the concept of medical necessity, payers consider whether they will classify a test as experimental/investigational, a category that is typically excluded from coverage.¹³

There are a series of inquiries made by payers when considering whether to cover and pay for any new diagnostic test, including establishing whether there is sufficient evidence that the test has: (a) analytic validity — how accurately and reliably the test measures the variant(s) of interest; (b) clinical validity — how well the test correlates with a clinical outcome; and (c) clinical utility — whether the information produced by the test leads to improved, measurable clinical outcomes compared to current management without testing.¹⁴

Analytic Validity and Clinical Validity

Governmental and private payers generally require, at a minimum, that a test meets quality standards before agreeing to pay for the technology. Quality standards refer to the test's analytic validity or its ability to accurately measure the phenomenon in question — in this case to accurately determine an individual's genetic sequence. Yet, according to a Report of the Association for Molecular Pathology “...the pace of technology development in NGS is so fast that conventional analytical validation methods may not be feasible or realistic.”¹⁵ Furthermore, there is no proficiency testing available for laboratories conducting clinical NGS in the United States today.¹⁶ This leaves payers with limited ability to determine whether a test has met basic quality standards, despite the fact that such standards play an important role in evaluating whether a test has demonstrated analytic validity as part of coverage determinations. This concern was underscored by United in its interest in strengthening current laboratory accreditation standards.¹⁷

For clinical laboratory tests, the industry requires that each test be either a Laboratory Developed Test (LDT) or a test approved by the U.S. Food and Drug Administration (FDA). An LDT is a test that is developed by a single laboratory that offers testing to the public but not to other laboratories, hospitals, or doctors. As the test is only administered by the laboratory that developed it, that same laboratory is responsible for both developing and validating their particular clinical assays. A technology assessment report prepared by the Agency for Healthcare Research and Quality (AHRQ) for Centers for Medicare & Medicaid Services (CMS) outlined the many challenges and concerns raised in the context of applying this system to MDx testing specifically.¹⁸

LDTs have not been subject to direct FDA review and approval; instead, they are regulated through two avenues. First, FDA has oversight over analyte-specific reagents and, as such,

the reagents require Good Manufacturing Practice compliance. In addition, LDTs used in patient care can only be developed and performed in laboratories that are certified under the Clinical Laboratory Improvement Act (CLIA) as overseen by CMS. Such laboratories must obtain a Certificate of Compliance or a Certificate of Accreditation. CLIA focuses on the analytic validity of the test — using the AHRQ definition “how well does the test measure the properties or characteristic it is intended to measure.”¹⁹ CLIA certification assesses how a laboratory oversees its operations and ensures the quality of test results. There is currently no formal CLIA-approved proficiency testing programs for molecular diagnostics in general, including NGS. Specifically for the Medicare population, CMS has expressed concern about the quality of molecular diagnostics not actively regulated by the FDA and the levels of evidence supporting validation currently being performed on these tests.²⁰

Currently, most clinical NGS tests are performed as LDTs, as there has only been a single FDA approval of an NGS sequencer to date.²¹ To answer some of the questions regarding laboratory standards for analytic validity, the College of American Pathologists (CAP) developed a molecular pathology section of the College's Laboratory Accreditation Program. This includes a checklist establishing the first standards for accrediting next generation sequencing laboratories. These standards were approved by CMS and adopted as of July 2012.²² Similarly, the American College of Medical Genetics and Genomics (ACMG) recently released clinical laboratory standards for NGS, including guidelines for sample preparation, test ordering considerations when developing services, test development and validation, analytics standards, and reporting standards.²³

The Centers for Disease Control and Prevention (CDC) convened a multi-stakeholder work group, the Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT), to define platform-independent approaches for addressing analytic validity and quality control procedures, recognizing that the performance characteristics defined in CLIA and professional guidance documents (even those focused on NGS such as the CAP NGS checklist) do not adequately translate to NGS testing practices.²⁴ This is primarily due to the complexity of the technology and the informatics analyses required for large-scale genome analyses. Although this work group's recommendations originally focused on NGS testing for inherited disorders, they stated that the principles apply equally to testing in the settings of oncology and infectious diseases, where testing may be done for diagnostic, prognostic, and predictive purposes. They acknowledge that there are still important gaps in the ability of laboratories to identify analytical and interpretive errors, and problems in quality control, instrument calibration, and assay design, all which would be addressed by formal proficiency testing programs that currently do not exist.²⁵

Establishing clinical validity is also a critical component allowing for determination of whether the test correlates with health outcomes. With a number of recent successes, clinical NGS has begun to establish itself as contributing clinically valid information.²⁶ For example, specific successes have been found in understanding the genetics of cancer, diagnosing rare Mendelian diseases, targeted drug discovery, and detection of cell-free DNA in maternal blood used for fetal diagnosis.²⁷ It is important to note that clinical validity can vary significantly depending on the genotype and corresponding phenotype; therefore clinical interpretation of NGS test results is often tightly linked with a particular patient's

clinical presentation.²⁸ ACMG concludes that clinical laboratories using NGS disease-targeted gene panels should include only those genes with clear evidence of disease association to maximize the diagnostic yield from the test.²⁹

Clinical Utility and Coverage

Clinical utility was specifically defined by Steven Teutsch et al., as part of the work conducted through the Evidence of Genomic Applications in Prevention and Practice (EGAPP) initiative as

...the evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decisionmaking compared with current management without genetic testing. If a test has utility, it means that the results (positive or negative) provide information that is of value to the person, or sometimes to the individual's family or community, in making decisions about effective treatment or preventive strategies. Clinical utility encompasses effectiveness (evidence of utility in real clinical settings), and the net benefit (the balance of benefits and harms). Frequently, it also involves assessment of efficacy (evidence of utility in controlled settings like a clinical trial).³⁰

Research has demonstrated that the access to evidence of clinical utility drives payers' coverage and reimbursement policies for genetic testing in general.³¹ Clinical utility, as well as information regarding analytic validity and clinical validity and information about the target condition and affected population, provides payers with the evidence base for making an informed coverage determination. In a recent study of the publicly available genetic testing coverage policies of private payers, 50% of respondents specifically referenced the need for evidence of clinical utility; tests that were uniformly covered tended to be those supported by clear evidence and recommended by professional and governmental guidelines.³²

As no regulatory body has specific oversight responsibilities for clinical utility, payers have the *de facto* role of enforcing clinical utility standards, taking seriously their role in supporting improved health outcomes for their membership by purchasing evidence-based health care interventions. To assist in this process, public and private payers seek information from a variety of sources. While EGAPP provides a systematic, evidence-based method to evaluate genomic technology, it is a slow process with only nine recommendations being issued over a seven-year period. As of April 2014, there are two other topics under review, with neither one being an NGS test.

EGAPP recently recommended a number of changes focused on expediting the review process, specifically calling for the following: (a) triaging tests with minimal evidence of clinical validity (considered not currently reviewable); (b) using and updating existing reviews; (c) prioritizing the review of clinical validity before proceeding to review of clinical utility or analytic validity; and (d) using decision modeling to assess potential clinical utility when direct evidence is unavailable.³³ Additionally, the CDC has cross-referenced numerous genetic tests and applications with evidence-based recommendations.³⁴ GAPP Finder is a searchable database of genetic tests that are either in development or available for clinical

use that includes a summary of current evidence of clinical utility (in addition to analytic and clinical validity) if available.³⁵

Private-sector alternatives are also available, including technology evaluations from such services as Hayes³⁶ and ECRI.³⁷ Payers with a large enough membership develop internal capabilities for conducting technology evaluations. For example, the highly respected Blue Cross Blue Shield Technology Evaluation Center (TEC), reviews approximately 20 to 25 new technologies (covering a wide variety of clinical applications) each year.³⁸ TEC utilizes the following criteria:³⁹

- The technology must have final approval from the appropriate governmental bodies
- The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes
- The technology must improve the net health outcome
- The technology must be as beneficial as any established alternatives
- The improvement must be attainable outside the investigational setting

While TEC assessments are silent about whether a new technology should be covered, local BCBS plans, as well as other insurers, use these reports to inform internal coverage decision-making processes. Their process is noteworthy not only because they are using a systematic, evidence-based approach as justification for their assessment of medical necessity, but also to emphasize the disconnection between the levels of evidence to gain marketplace approval for a test versus a favorable coverage decision.

Palmetto, then Medicare's largest Medicare Administrative Contractor (administrative organization paying claims on behalf of Medicare), has had a significant impact on technology evaluations of MDx tests. Palmetto developed the MolDx program to identify a molecular pathology test and conduct a technical assessment in order to determine whether coverage and reimbursement will be provided for that test.⁴⁰ The program began February 2012 and now applies to tests seeking coverage in the state-specific jurisdictions covered by Palmetto (NC, SC, VA, WW) as well as another Medicare Administrative Contractor, Noridian (CA, NV, HI). Palmetto's MolDx program requirements states that "MolDX only provides coverage for MDTs (molecular diagnostic tests) and LDTs that demonstrate analytical validity, clinical validity, and clinical utility."⁴¹

Subject matter experts and/or Palmetto staff assess each test with each being considered investigational (therefore, not covered) until Palmetto determines that the test meets Medicare's reasonable and necessary requirement. Palmetto reviews information from a wide variety of sources, but emphasizes that they prefer published, peer-reviewed, well designed, controlled studies that have adequate sample size to demonstrate clinical significance and have adequate representation from the Medicare population.⁴² Laboratories offering a test and requesting payment apply for program participation in advance of submitting claims. When the test is approved, Palmetto assigns a unique identifier (Z-code, see below) to facilitate claims submission and payment. Currently, there are no approved MolDx codes for

next generation sequencing assays.⁴³ Early in the program, industry raised concerns regarding the MoDx program, including their perception that Palmetto was requesting information beyond what was needed to conduct a reasonable evaluation and there had been little input or no input from laboratories during the course of program development.⁴⁴ Over time, test developers are gaining greater familiarity with Palmetto's evidentiary expectations regarding demonstration of adequate evidence of clinical validity and utility in order to gain coverage; however, there remain some frustrations with the current process as summarized by groups such as the Association for Molecular Pathology (AMP).⁴⁵

Coding

Once a test receives a positive coverage decision, assignment of a corresponding code enables billing and reimbursement for specific services. The American Medical Association (AMA) has developed and holds the copyright for a system of categorizing clinical care activities called Current Procedural Terminology (CPT®) encompassing almost thousands of distinct, widespread, and clinically useful activity and procedure codes. The AMA CPT® system has been adopted as the payment system by virtually all public and private payers. Codes related to genetic services fall into two broad categories: laboratory codes (codes for the test itself) and professional services codes (codes for the professional services associated with patient care, such as counseling or test interpretation). There are currently no MDx codes that describe next generation sequencing technology. It is likely that, once clinical NGS codes are developed and implemented, they will fall under the umbrella of molecular pathology codes.

Traditionally, CPT® codes contain both: (a) a technical component (TC) which is generally the supplies and equipment or, in the case of genetic testing, the automated, mechanized portion of the care; and (b) a professional component (PC) often thought of as requiring the clinical judgment of a qualified individual. In the case of genetic testing, the TC component is generally the assay plus the bioinformatics, while the PC component is the interpretation of the molecular pathogenesis and its potential impact on patient care. The amount of TC and PC may vary from test to test and within tests as individuals with more complex conditions may require additional professional interpretive efforts.

Prior to January 2013, billing for molecular pathology tests was done using combinations of CPT® codes with each CPT® code describing a component of the overall test being performed. This billing method became known as “stacking” since many codes were used to layer on top of each other as they described the individual steps taken to execute a test. There were a variety of problems with this methodology, including many examples where the same molecular pathology test would be billed using different combinations of codes (with variations in both the codes used and the frequency that each was billed per test) or different molecular pathology tests could be billed using the same combination (“stack”) of codes. This lack of transparency to payers about the condition or trait being tested resulted in Molecular Pathology (MoPath) codes being instituted by CMS as part of the Clinical Laboratory Fee Schedule beginning January 2013.⁴⁶

The MoPath codes are organized into two Tiers, with Tier 1 codes applying to commonly performed, simple analyte MDx tests and Tier 2 codes for more complex, less frequently

performed tests. Tier 2 codes include an “unlisted code” that has been used to bill for NGS. Given the original concerns with lack of specificity and transparency in coding, the AMA has committed to developing additional NGS-specific codes, with 2015 as the likely earliest date for their release.

Believing that the newly introduced CMS MoPath codes did not address the complexity of NGS, AMP issued a proposal to address the challenges in coding for genomic sequencing procedures.⁴⁷ In March 2013, AMP called for developing a CPT® strategy that meets the following requirements:

- Transparency — so payers can know what services are provided and make coverage decisions;
- Clinical Utility — as a component in developing and assigning codes with each code clearly noting the clinical question being addressed; and
- Allow for billing for a re-query — using existing genetic sequencing data to ask a different clinical question at a later date or to re-evaluate the same sample as technology advances.

AMP proposes the use of a “code-mate” system that can accommodate separate billing between the sequencing and the interpretive services. In the context of whole exome sequencing (WES) or whole genome sequencing (WGS), this system also recognizes the possibility of re-analysis for an unrelated condition or syndrome and assigns a separate code for this step.⁴⁸

In early 2013, a licensing arrangement for a molecular pathology coding system was announced between AMA and McKesson, a large health care information technology firm with an ongoing relationship supporting Palmetto's MolDx program. Discussions are underway regarding using McKesson's Z-Code Identifiers, originally created for Palmetto's MolDx program as part of the current AMA's CPT® coding structure. These codes will be available for licensing beginning in 2014. Z Codes are expected to track to CPT® codes, but it will not always be a one-to-one match with some Z codes tracking to multiple CPTs® and some not mapping to any CPT® as of yet.⁴⁹ While no Z codes currently apply to NGS tests, it is likely that future NGS codes would fall under the McKesson Z code umbrella. It is noteworthy that, other than Palmetto, few if any public or private insurers currently have the infrastructure to administer Z codes.

Establishing an Appropriate Payment

Public and private payers use a variety of methods to establish appropriate payments for tests. Private payers and Medicaid often look to current Medicare reimbursement practices to assess reasonable starting points for their reimbursement strategy. As Medicare is principally focused on care needed by an aging and disabled population, little guidance is provided regarding prenatal testing or testing focused on individuals from newborn through middle age. Since the implementation of the new molecular pathology codes, Medicare is using a “gap fill” methodology for creating interim payment rates. The gap fill methodology refers to a procedure where for the first year, local Medicare contractors are responsible for setting their own rates, then in the second year, CMS calculates a national payment rate based on

the median of the local fee schedule amounts. However, since there is no standard reimbursement for the unlisted codes currently used to bill NGS testing, each payer, including local Medicare administrative contractors, is free to establish their own reimbursement rate for NGS tests.⁵⁰

Allowing the use of an interim gap filling methodology permitted Medicare Administrative Contractors (MACs) to use additional sources of data to establish payment rates beyond Medicare's own internally generated information. As each MAC may use different data sources, there is variability in payments across MACs compromising the ability of providers to evaluate the resulting rate when it is released. This lack of uniformity in payment and transparency in rate-setting has prompted significant industry reaction, leading to a reevaluation of proposed rates. Almost all Medicare Administrative Contractors have now released their gap fill rates for widely used genetic tests and a number of gap-fill rates are substantially lower than the estimated amounts based on code stacking.⁵¹ Furthermore, an appeal letter signed by nine professional associations raised significant concerns saying, "Medicare contractors are denying molecular pathology claims or significantly reducing payment rates without public justification for those decisions; some contractors are mischaracterizing certain molecular pathology tests as investigational and denying payment."⁵² It is unclear how this issue will ultimately be resolved; however, the current system of denials and lower payments for some tests is perceived as destabilizing for the MDx field by many laboratories and test developers.⁵³ Stability of payment over time is a key element to ensuring adequate investment in new technologies.

Value-Based Payment

Many in the molecular diagnostics industry have been interested in moving MDx as a whole to a new reimbursement paradigm — one based on the value of the test.⁵⁴ NGS would likely be included in any potential shift. UnitedHealthcare's report on Personalized Medicine calls for exploring this issue further. Specifically, it notes that today's fee schedules "...may not reflect the potential value of any improved outcomes or reduced spending resulting from a test."⁵⁵ Lisa Meckley and Peter Neumann link the idea that better reimbursement for genetic testing will arise out of better evidence of clinical utility.⁵⁶ While this is a first step, the Meckley and Neumann proposal is less comprehensive than United's interest in exploring whether test reimbursement should be allowed to fluctuate over time based on the evidence and value of the test in the overall delivery of health care.⁵⁷ As with other MDx test providers, the revenue stream for clinical NGS test providers would be less stable if prices were allowed to fluctuate over time. A more general reimbursement alternative would be to explore United's broad objective of establishing "...a predictable, objective and appropriate third party reimbursement payment structure that will improve patient outcomes, support patient access, and ensure continued investment and innovation."⁵⁸

Altering the premise of reimbursement from cost-based to value-based is likely to have implications for other areas of health care reimbursement. Determining how value would be measured is a topic of much debate and what this might look like in the era of accountable care organizations remains an unknown. Valuing one test over another because of a more favorable clinical utility profile is somewhat implicit within risk-based reimbursement. The

Affordable Care Act and other health care initiatives place providers at increasing risk for resources used in patient care. If NGS can establish a strong linkage to not only clinical utility, but also cost effectiveness — the value paradigm — then the technology may be able to demand premium prices that would be more readily born by those managing patient populations under risk-based arrangements. Absent a demonstration of cost effectiveness or perhaps even cost savings, NGS may be challenged to gain a foothold in an era when providers are assuming responsibility for population-based care. The decline of traditional fee-for-service reimbursement may pose an opportunity for NGS to get somewhat closer to value-based reimbursement — provided these measures of improvements in cost effectiveness can be adequately demonstrated.

Review of Public and Private Payers

Private payers often follow Medicare, using Medicare's fee schedule as a starting point for setting payments and often creating similar coverage policies. Although there are National Coverage Determinations for genetic testing in the area of cytogenetics⁵⁹ and pharmacogenomics,⁶⁰ to date Medicare has not addressed NGS testing specifically. Increasingly, private payers are conducting technology assessments before providing coverage and reimbursement for a new technology. In addition, several payers have singled out genetic testing, and sometimes NGS specifically, as deserving of specific attention. Palmetto's MoDx program is an example of a technology assessment program being developed exclusively for genetic technology. BlueCross BlueShield Association's TEC has conducted many previous evaluations of MDx tests including a companion diagnostics and has recently evaluated whole exome sequencing.⁶¹

Research staff from the Center for Medical Technology Policy and Johns Hopkins Center for Genetics and Public Policy sampled seven payer websites to ascertain how each payer was approaching clinically available NGS tests from a coverage policy perspective. At the time of internet search, these tests included two non-invasive prenatal tests used to identify fetal aneuploidies using maternal blood samples, as well as gene panel-based tests for inherited breast cancer, x-linked intellectual disability and epilepsy. The payers were selected to represent the largest payers in the private payer market place, including one payer primarily focused on Medicaid and another on Medicare. A three-level approach was used. First, a search of each website was done to identify whether a payer had policies for any of the currently available NGS tests. Next, a review was done to generally categorize the approach used by each payer and to determine whether there was evidence that NGS was treated differently than MDx tests. Finally, a general search was done using key words to identify any related activities that might impact NGS. The key words used were genomic testing, massively parallel, next-generation, molecular diagnostic, molecular pathology, genetic testing, whole-exome sequencing, gene panel, non-invasive prenatal testing, and pre-natal diagnosis. Based on this limited experience to date, there was no evidence that NGS is being treated differently than the general category of MDx tests from a coverage determination perspective.

Most private payers had policies covering the non-invasive prenatal tests used determine trisomies 21, 18, and 13. Factors leading to a positive coverage decision included: meeting

TEC criteria (Blue Cross plan) and being supported by recommendations from the American College of Obstetricians and Gynecologists and the National Society of Genetic Counselors. One private payer did not cover the test at the time but has since reversed its decision. The Medicaid plan did not have an explicit coverage policy. Early evidence suggests that the states are not reimbursing for these tests.⁶² In fact, failure of state Medicaid plans to adopt and pay for prenatal NGS services led in part to the downgrading of one vendor's stock.⁶³ None of the payers had policies for the NGS panel-based tests focused on x-linked intellectual disability, epilepsy, or inherited breast cancer.

When this report was first written, it also appeared that no private payers had explicit policies regarding coverage for NGS cancer testing panels, such as FoundationOne™ — a next-generation sequencing test used to look for genomic alterations in 236 cancer-related genes in tumor tissue in patients with complicated or end-stage cancers. The company states that it accepts all types of insurance, although they are not in-network providers with all insurance plans.⁶⁴ Foundation Medicine does offer a patient assistance program based on need. Our interviews indicate that disease-targeted gene panels using NGS are being billed using non-specific codes and the reimbursement is highly variable and often negotiated on a case-by-case basis. Recently, Aetna was the first private payer to publish their decision *not* to cover either the solid tumor or liquid tumor (Heme) panels offered by Foundation Medicine, determining that the peer reviewed medical literature does not support these tests as having sufficient sensitivity or specificity necessary to define their clinical role, and therefore they consider the tests experimental and investigational.⁶⁵

Payers seek persuasive scientific evidence supporting claims of clinical utility and in some cases will use indirect evidence of improved health outcomes. The best example of this is the recent Blue Cross Blue Shield Technology Evaluation Center review of sequencing based tests to determine fetal Down Syndrome from maternal plasma DNA.⁶⁶ The reviewers concluded that while there was good evidence of clinical validity for many of these new tests as compared to traditional screening methods, there was little available evidence of analytic validity but attributed this to nascent stage of NGS testing and lack of standards development under CLIA. Interestingly, their positive conclusions regarding clinical utility were based on decision-analytic models of different test substitution strategies and the modeled outcomes of cases detected, invasive confirmatory procedures required, and miscarriages resulting from invasive procedures.⁶⁷ Currently, prenatal screening for aneuploidy using maternal blood is the only category of NGS tests able to meet these evidence expectations as assessed at payer organizations that make their coverage determinations publicly available.

Unique or Magnified Coverage and Reimbursement Policy Issues

As NGS technology is refined and there is increasing experience with its use in a variety of health care settings, there will be greater clarity about its relative ability to replace Sanger sequencing and the associated total system costs. In addition, while there appears to be widespread acceptance that a reduction in sequencing costs accompanied by an exponential increase in higher quality information will drive technology companies to push NGS into broad clinical use, there are a number of specific clinical problems that the technology is

well-suited to solve. For example, NGS is an attractive alternative in oncology, where there are limitations on the quantity of tissue available for testing and the technology can detect most genomic alterations in all therapeutically relevant cancer genes in a single assay.⁶⁸

From a reimbursement perspective, disease-targeted NGS panels such as those used in oncology settings are highly likely to follow the pathways set by first generation MDx tests, albeit with new NGS-specific codes applied over time. However, for clinical applications outside of disease targeted gene panels, where NGS is used to sequence entire exomes and genomes, many experts have cautioned about the potential social and economic harms that may result without thoughtful application of proactive policies.⁶⁹ These NGS-specific considerations will have implication for payers as well as for patients.

The information-related challenges presented by NGS are not unique per se, but they are different in scope due to genomic data having a high likelihood of incidental findings, findings that are relevant to family members and that require pre-test counseling, and the opportunity for patients to decline testing or certain aspects of test reporting.⁷⁰ Even a small fraction of an individual's whole genome can be highly identifying, necessitating more stringent data security and privacy protections. This also has implications for data sharing because of the much higher likelihood of disclosure of an individual's identity than with other types of health care information.⁷¹ Primary care physicians are not trained to interpret genomic data and have been found to have a high degree of discomfort with interpreting tests results and incidental findings in particular.⁷² The U.S. health care delivery system lacks the infrastructure and support for acquisition and processing of genomic and family history data, making automation of any aspects of NGS test reporting infeasible, assuming that appropriately annotated clinical databases existed for the appropriate interpretation of clinical NGS results.

Currently the field of medical genetics is still debating the controversial ACMG recommendation that clinical laboratories conducting WGS/WES for specific clinical indications also analyze and report any incidental findings from a list of 56 genes containing mutations considered to be clinically actionable.⁷³ Some laboratories are following some or all of the recommendations while others are not and there are justification for both positions.⁷⁴ Clearly, there will be direct costs to payers associated with implementing this recommendation, as well as the potential downstream costs associated with follow-up tests and procedures. A similar situation occurs in the setting of “reanalyses” or the need to conduct data reanalysis and follow-up on variants of unknown significance or those deemed “likely pathogenic” in light of new knowledge that has been published.⁷⁵ However prior to discussing the reimbursement implications of these recommendations, we will discuss the fundamental challenge for clinical NGS, which is to realize the full economic value of the test from payers, given the complexity of test information.

Understanding What Is Being Valued – Reimbursing for Technical and Professional Services

NGS technology moves clinical genetic testing from a simpler approach focused on testing genes associated with a particular disease, to broad-based interrogation of the genome requiring a more complex approach typically involving a team of professionals to analyze

and interpret the results.⁷⁶ Leslie Biesecker called the data generated in clinical genome and exome analysis “stupendously complex.”⁷⁷ Many individual components must now come together to provide the range of services beginning with the assay, through the application of bioinformatics, to the professional interpretation and communication of this information to the patient. Each component in Figure 1 must be adequately valued, requiring a reimbursement structure that recognizes a team approach, compensating various actors for their role in the system.⁷⁸

Next Generation Sequencing Process

Significant decreases in the cost of analyzing many gene sequences in parallel and other performance-related advantages such as greater depth of coverage drive much of the enthusiasm within the pathology community for viewing clinical NGS as a disruptive innovation. One major reason for the disruption is because of the apparent “value proposition” based on the assumption that NGS represents a cost-effective technology platform substitute for a range of molecular, cytogenetic, and histocompatibility testing performed by traditional methods in the laboratory today.⁷⁹ However, as described earlier, only the price of the assay is declining rapidly. Component 2 of clinical NGS testing, including variant calling, visualization, and variance analysis, requires the development of bioinformatics for data collection, analysis, and interpretation.⁸⁰ Interpretation of NGS — Component 3 — includes understanding the origin, uniqueness, and likely clinical significance of variance.⁸¹ At this early stage, the investments required to support both the bioinformatics and professional interpretation components continue to increase unpredictability with respect to their overall clinical development and integration costs.

It is also unclear whether the clinical application of NGS technology will continue to evolve such that all three components of testing will be performed each time a unique clinical question arises. Alternatively, the sequencing may be done once, and then various aspects of the bioinformatics and professional interpretation components would be re-queried and communicated for each clinical event presented by the patient. One noted health economist poses the logical challenge of determining at what point the bioinformatics and interpretation phases become the real “value proposition,”⁸² which requires determining whether Component 2 and/or 3a are uniquely valuable and separable from the assay.

The answer may be shaped less by the science and more by the reimbursement environment. For example, if payment is primarily focused on rewarding NGS test developers for the assay, then assays will likely be repeated regularly, each with a separate application of bioinformatics and professional interpretation. However, assays may be done less frequently if the idea of portable genomic information is embraced. This would create an environment of “genome on a thumb drive” or “genome in the cloud.” In this world, payment may be seen as valuing the bioinformatics of assay interpretation and/or the interpretation of the molecular pathogenesis and its potential impact on patient care. Payment can mold a technology — favoring how an entire industry may evolve. It is important to note that this particular context is primarily applicable to germ line cells and not to sequencing of tumor cells (as reanalyses would be far less likely).

The value placed on the professional interpretation component is also important. There has been much discussion of the insufficient number of genetic counselors available to provide patient services.⁸³ Given this reality, the unresolved question is what types of health care providers will assume the responsibility of counseling patients, and how will they be trained? Assumption of this responsibility implies the ability to be fairly compensated for the service, including having the ability to independently bill for one's services. One estimate is that for each whole genome sequenced, five hours of direct patient contact would be required to communicate the relevant information to the patient.⁸⁴ Considerably more time may be needed depending on a laboratory's approach to incidental findings. At least one author sees clinical scientists as key health care providers in the area of genomics.⁸⁵ Given the discussion about the appropriate role and independence of both genetic counselors and doctoral trained geneticists, a concurrent discussion regarding appropriate compensation is warranted.

There is debate about the adequacy of trained professionals to conduct both the bioinformatics and interpretation components of reimbursement — the components beyond the sequencing itself. As NGS enters health care, these steps are likely to become the bottlenecks as genetic information must be appropriately analyzed and interpreted in light of the clinical status of the patient. Payers may not fully appreciate the complexity of the various stages of the analysis: *base calling* to convert raw data into short sequences of nucleotides; *alignment and variant calling* that maps these short sequences to a reference sequence and then determining the degree of variation from that reference; and *interpretation* which analyzes the variants for their uniqueness and functional impact in the context of a particular patient.⁸⁶ The requisite databases have incomplete and imperfect annotation that makes consistent clinical interpretation of significant variants difficult, despite a growing number of dedicated bioinformatics packages to automate the process.

The problem is exacerbated by a lack of interoperable clinical decision support systems to help clinicians interpret plausibly pathogenic genomic variants, as well as the need to constantly update the supporting clinical databases that classify variants as new discoveries are made. Some experts have called for the creation of a new type of specialist, the “clinical bioinformatician” who would be responsible for interpreting information at the interface between the genomic pathologist and ordering physician on one side and the academic and mathematical bioinformatician on the other.⁸⁷ FDA approval of an NGS sequencing machine does not control for the variability introduced by different software packages used by laboratories or by professional interpretation of the results. These are some of the unique challenges with reimbursement (and other) implications that result from the massively parallel sequencing that is the hallmark of NGS-based approaches to clinical testing.

Communicating Clinically Actionable Information to Providers

Much has been written about the need for physician education in molecular pathology and the need to assist providers in ordering the correct tests at the correct time. In one survey, 75% of physicians saw themselves as “somewhat knowledgeable” about genetics with only 7% indicating that they were “very knowledgeable.”⁸⁸ When UnitedHealthcare asked about specific categories of tests, these numbers fell dramatically with only 28% of physicians

comfortable with oncology test interpretation and 25% with prenatal/newborn tests. Specialists providing care in these areas had higher levels of comfort but only one area (pharmacogenomics) showed a specialist level of comfort greater than 50%.⁸⁹ The National Comprehensive Cancer Network (NCCN) Work Group on Molecular Testing reached its second of two consensus statements around provider education. It noted that "...(i) increased education regarding molecular testing in oncology is needed for patients, clinicians, pathologists, industry, payors and policy-makers to help ensure that these tests are being used safely, effectively, and efficiently in oncology, and that their limitations and the clinical impact of their results is understood."⁹⁰

An additional subset issue is that education on molecular test ordering includes implementing appropriate policies to address situations where providers request a brand name test, limiting the pathologist's ability to select newer, potentially more efficient tests.⁹¹ In addition, payers might implement procedures specifying tests that should be used or preferred laboratories, similar to the mechanisms used now to substitute generic medication.

Specifically, successful integration of NGS into mainstream health care will require education of providers on a variety of issues such as variants of unknown significance, penetrance, and the known and unknown interactions between genes. Overall, clinical NGS is complex with challenges in ensuring that results are well understood by practicing clinicians and tests are used appropriately.⁹² Payers have a vested interest in supporting this effort. While the field of molecular pathology in its entirety shares the challenge of communicating clinical utility to providers, it is particularly problematic for NGS-based tests given the evolving evidence base for variance with plausible, but insufficiently proven clinical significance.

Incidental Findings

The reporting of incidental findings will likely continue to receive considerable attention. ACMG has sparked renewed debate with its recent release of "Recommendation for Reporting Findings in Clinical Exome and Genome Sequencing."⁹³ Most of the controversy has centered on whether the recommendations violate patient autonomy and if the term "incidental" is really a misnomer since the evaluation of the 56 genes called for in the ACMG recommendations are actually a deliberate effort to analyze additional genes above and beyond those that were part of the original test indication. In other words, unless these 56 genes were purposively analyzed, there would be no "findings" to report — that is why the comparison to a medical imaging (e.g., MRI of the chest reveals an incidental finding suspicious for a malignancy that requires follow-up) is felt by some experts to be erroneous.⁹⁴ Moreover, the "opportunistic screening" exercise also violates all tenets of public health screening, since there is no evidence in asymptomatic patients of test performance, procedures for implementing testing in practice, access to education, and counseling and impact on outcomes.⁹⁵

From a coverage and reimbursement perspective, there is concern regarding whether payers are obligated to pay for confirmatory testing related to incidental findings. Claims are paid based on matching a diagnosis with a test, noting that the test is clinically indicated for the particular condition or diagnosis. For confirmatory testing of incidental findings, there is

either no diagnosis or the diagnosis does not appear clinically relevant to the test being done. In either situation, a separate claim for confirmatory testing of incidental findings stands a significant chance of being denied.

To complicate this situation further, incidental findings will likely identify diseases that are presymptomatic. There may be additional follow-up testing and payers often do not cover such testing as it is outside the individual's coverage. As such, it is unclear who would pay for either the initial or confirmatory testing. Of even greater concern is whether coverage would be available for subsequent interventions judged appropriate to evaluate or treat a presymptomatic condition. Payers are also troubled about the possibility of labeling those perceived as “well” as now “at risk.”

With whole genome testing, payers and providers will have access to large amounts of genetic information which may, in the future, allow better risk prediction, early intervention and/or disease prevention. Currently, however, payers and providers have limited ability to both know when to intervene and to identify effective interventions. The appropriate balance of interventions based on genetic knowledge with patient privacy preferences is unclear. It is further compounded by changing societal norms around privacy and major shifts within the health care system regarding the roles of payers and providers in assuming and managing risk, particularly in the context of accountable care organizations.

If potentially successful interventions are available and the risk is identified, which entity will be responsible for interventions? Jeffrey Saffitz describes one possible scenario in which laboratory-based physicians adopt the concept of “primary care pathology” as they assist individuals with proactive disease prediction and prevention.⁹⁶ The locus of responsibility might rest with the individual, with a provider, with the provider group as a whole or even with the payer. The patient and society might perceive each of these differently. In particular, interventions by payers may be viewed less favorably than interventions by providers, although one could imagine a scenario where payers become the vehicle through which lifestyle interventions occur to mitigate an identified risk. At a minimum, the results of NGS testing have the potential to alter the current roles of patients, providers, and payers.

Re-analyses

The AMP has raised concerns about whether there is an obligation to look back at clinical NGS performed previously and formally re-interpret it in the context of new knowledge.⁹⁷ Payer-related concerns include who would be responsible for reimbursing for ongoing data evaluation services? Related questions include: How would the NGS test provider know about health insurance changes, patient geographic movement, etc.? How would the process be started? Where would the results be sent? Is the obligation to look back time limited (e.g., only look back if test was done within five years)? This issue links with data storage considerations discussed later in this section. It also is connected to the earlier discussion of whether the market will value the assay primarily, thereby avoiding extensive data storage and re-query concerns as a new assay will be run each time a specific clinical question is raised. In addition, is it more economically tenable to re-sequence the relevant portion of the

genome rather than store all data for long periods of time and retroactively update the records as needed?⁹⁸

The recently published ACMG guidelines acknowledge that this issue will likely be a problem for laboratories unless they set appropriate expectations and policies with physicians, which may include additional charges for re-analyses.⁹⁹ This same guideline recommends that ordering physicians take responsibility for checking back with the laboratory periodically to see if there have been any updates regarding the status of variants of unknown significance for their patients. While this suggestion seems highly impractical for the reasons stated above, it is clear that resolution of the reimbursement issues will be an important determinant of any final solutions.

Data Storage Challenges

The AMP has raised concerns about how and what portion of clinical NGS results should become part of a patient's clinical record.¹⁰⁰ They note an ongoing debate on whether an electronic health record should store the large, raw data files that were a result of NGS testing. An alternative to storing raw data files would be to retain only the clinical interpretation of the assay. An illustrative comparison that may assist in resolving this challenge is the current practice of storing MRI information separately but with the option of retrieval as needed.¹⁰¹ Reimbursement decisions may drive this as storing vast amounts of data securely is costly, and it is unclear whether there will be adequate levels of compensation for this. Currently, the protocols for obtaining informed consent, return of results and phenotyping algorithms are in development or are being piloted as part of a National Human Genome Research Institute (NHGRI)-funded project to create an electronic medical records genomics network (eMERGE),¹⁰² and are not widely available for use in practice.

The electronic health record is a legal document frequently relied upon by payers to make concurrent and retroactive determinations of coverage. It is theoretically possible that payers, public or private, may be interested in accessing the genomic information generated by NGS testing. While there are current laws preventing use of genetic information to discriminate in insurance or premium pricing, large, raw data files could be used by payers for many other purposes including disease management or lifestyle recommendations as was discussed under Incidental Findings.

In the area of newborn screening, there is concern regarding the large amount of data that might be retained. In addition to long-term newborn screening data storage concerns, retaining vast amounts of newborn genetic data "...may led some parents to view genomic evaluation of newborns as a form of research."¹⁰³

Preconception, Prenatal, and Newborn Screening

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) has advised the Health and Human Services Secretary for many years on newborn screening tests on issues related to "...effectively reducing morbidity and mortality in newborns and children having, or at risk for, heritable disorders."¹⁰⁴ SACHDNC has established a Uniform Screening Panel that includes 31 core disorders and 26 secondary

disorders (those that can be detected in a differential diagnosis of a core disorder). States then adopt all or some of these recommendations, and may add additional ones. Compensation for newborn screening is set at the state level and typically is some combination of public health dollars and requirements that private insurance reimburse for the service.

The focus of newborn screening is one of public health, the principal goal being to diagnose conditions as early as possible in order to avoid severe mental, physical, or developmental harms. Testing is focused on the welfare of the child, and parents have limited ability (if any) to opt out of newborn testing. Concern has been expressed that the advent of NGS technology may expand the focus of newborn screening such that it is no longer primarily a public health strategy of identifying those infants requiring immediate intervention, but one of identifying those newborns who are carriers and/or have a given mutation, which would put them at risk for an adult onset disease. While NHGRI is currently supporting four Clinical Sequencing Exploratory Research centers to evaluate the application of NGS methods to newborn screening,¹⁰⁵ the ACMG does not support its use at this time.

Mendelian disorders account for approximately 20% of infant mortality and about 10% of hospitalizations for pediatric patients.¹⁰⁶ In 2011, a next generation sequencing panel was developed as a preconception carrier screen for 448 severe recessive childhood diseases.¹⁰⁷ The goal was to identify those that were heterozygous for a particular mutation allowing the individual to make informed reproductive decisions. As one author described it, “Current progress in genetic testing technology offers to merge the concepts of carrier testing, pregnancy screening, and prenatal diagnosis for genetic disease into one manageable continuum.”¹⁰⁸ ACMG strongly favors carrier screening over prenatal testing, based on long turnaround times and the complex nature of genomic sequencing.¹⁰⁹ In a May 2012 statement, the ACMG indicated that whole genome sequencing and whole exome sequencing should not be used at this time for prenatal screening.¹¹⁰

This raises a number of policy implications with the reality that many prospective parents consider pregnancy termination when learning about potential health concerns in the fetus. Eugenics concerns are apparent, especially given these actions could be based on carrier status of a recessive gene. As pro-life advocates increasingly target access to abortions based on the reason for the termination, there are numerous issues and implications for termination based on carrier status.¹¹¹ “Mixed messages: the intersection of prenatal genetic testing and abortion” provides an in-depth study of the intersection of prenatal testing and abortion.¹¹² In particular, this article discusses the ways in which the Affordable Care Act will reduce health insurance coverage for pregnancy terminations while providing additional incentives to test and screen. Other examples of regulatory interventions are also explored, particularly given that testing is viewed as a covered benefit while abortion is often considered as an expenditure unrelated to health care.

Moral Hazard

Moral hazard occurs in circumstances where one takes risks or actions expecting another party to bear the burden of that risk. It generally occurs in situations of information asymmetry. If someone at risk for an expensive medical condition buys health insurance that

would not normally be purchased, a situation of moral hazard arises; the purchaser of the insurance has more information than the insurer and is expecting the insurance provider to bear more financial risk than normally would have been anticipated. Moral hazard is one reason why long-term care insurance products are excluded from the Genetic Information Nondiscrimination Act of 2008, as individuals with knowledge of their own genetic predispositions and its related likely ramifications for long-term care needs have significant informational advantage.

A policy of testing and communicating incidental findings to patients has the potential to disrupt the health and life insurance markets, assuming individuals have a choice among insurance products. As a result, it may become increasingly challenging to appropriately price insurance products where genetic knowledge is unequal. This issue may resolve over time as a level of genetic knowledge is assumed within insurance rate structures. However, during the interim years as clinical NGS spreads, it may cause challenges in insurance pricing.

Discussion

Based on a limited number of examples to date, payers are not treating NGS differently than other types of MDx testing when evaluating this technology for coverage and reimbursement decisions. They look for evidence of analytic validity, clinical validity, and clinical utility, although all the evidence required by payers to make an informed decision is not readily available for this emerging technology. However, there is a spectrum of clinical applications for NGS that present an increasingly complex set of challenges for payers, mirroring the volume of sequencing information generated by the approach. Gene panels that use NGS but target known disease-associated genes are more similar to first-generation tests from a reimbursement perspective rather than either WES or WGS; however, the question of demonstrating adequate evidence of clinical utility is still important to resolve. Nevertheless, the unique or magnified reimbursement issues that are related to the volume of sequencing information generated by NGS are seen with many panels and unquestionably in the setting of WES/WGS. These are the issues related to incidental findings, re-analysis and re-interpretation of sequence data in light of new knowledge, data storage and data privacy. While the benefits of this type of testing are potentially great, the discussion of harms has primarily focused on arguments related to autonomy and iatrogenic complications. There also has been an emphasis on the lack of delivery system readiness to appropriately implement NGS from both a human resource and information technology infrastructure perspective, as well as an interest by developers in receiving value-based reimbursement. There has been less attention in the literature to the economic harms of ineffective tests or to the downstream costs of labeling well people as sick or at risk. Nor have there been any attempts to estimate the full costs associated with data interpretation, follow-up, storage, sharing, and privacy protections.

Today, most NGS-based clinical tests are LDTs operating under CLIA certification, raising payers concerns regarding whether there is sufficient regulatory oversight and adequate assurance of the analytic validity for NGS tests. Most payers currently lack the technical sophistication to independently assess the validity of NGS tests, and it is too early to tell

whether the recently released ACMG clinical laboratory standards for NGS testing will be both widely adopted and address possible concerns. The FDA has only recently begun to approve specific applications of NGS technology for clinical use and many unanswered questions remain, particularly in the area of oncology, where there have been no FDA approvals for use of NGS sequencers on tumor samples or as companion diagnostics.¹¹³

Recent successes primarily in the area of prenatal testing have identified specific clinical applications where NGS tests have been assessed by some payers to be medically necessary and able to meet payer's criteria for clinical utility.¹¹⁴ Early examples of covered tests have been limited primarily to the prenatal testing arena where NGS-based tests are substituted for more invasive testing. While payers continue to emphasize that they need evidence of clinical utility to drive coverage and reimbursement decision-making, there are unresolved methodological issues regarding the design of these studies related to the volume and type of information provided. There remain many unanswered questions among governmental and private payers as what constitutes an appropriate level of evidence to demonstrate clinical utility for clinical applications where NGS is likely to be used.¹¹⁵

For example, in oncology there may be a limited number of cases with a particular genomic profile, yet there is interest in running a tumor panel or even profiling the entire tumor in the hopes of targeting treatment based on an understanding of the mutated biological pathways involved in a particular patient's situation. To date, some physicians have been empirically treating patients with a known mutation(s) in a novel cancer based on previously published studies of this biomarker and response to targeted therapies in a different tumor type. However, a recent review by BCBSA Technology Evaluation Center found inconclusive evidence that multiple molecular profiling panels provide valuable in cancer treatment selection based on targeting treatments to the biological pathway identified by the profiling panel.¹¹⁶ The evaluation found only three published studies that reported health outcomes for patients whose treatments were chosen on the basis of their molecular profile as determined by testing multiple molecular markers beyond their established use, typically using more than one assay method. The authors of the report cautioned about the methodological complexities of designing unbiased studies of the clinical utility of these types of tests. Individual institutions or companies may be establishing registries to begin to track patient outcomes, but to date there is only weak evidence of clinical utility and sample sizes are small.

As NGS magnifies the clinical utility challenge as researchers attempt to turn large amounts of sequencing data into clinically actionable information, payers are likely to hesitate to embrace the technology.¹¹⁷ Increasingly, there is exploration of what methodologies would be appropriate beyond a randomized clinical trial, and such an example is the aforementioned methodological standards for designing unbiased clinical utility studies for these types of tests.¹¹⁸ These standards were intended to apply to clinical NGS tests as they were created to be “platform-agnostic.”

A specific type of study that is mentioned with respect to NGS testing is the “N-of-1” trial, referring to a study where an individual patient is the sole unit of observation in a study investigating the efficacy and safety of an intervention. N-of-1 trials have been described as

useful in various areas of medical research, including value for comparative effectiveness and patient-centered outcomes research.¹¹⁹ Molecular diagnostic N-of-1 studies, including those using NGS technology, typically examine an intervention tailored to the molecular profile of the individual. N-of-1 studies are a critical component of the increasing move towards individualized medicine.¹²⁰ Given this scenario, payers and other decision-makers will be increasingly challenged by the rise of N-of-1 clinical trials and how to interpret the ability for such a trial to provide information on clinical utility beyond single patients. It is likely that payers will need to rethink how clinical utility will be evaluated in an N-of-1 situation, including assessing the standards for medical evidence adequacy. Furthermore, it would take significant investments in bioinformatics and interoperability to aggregate data across various clinical NGS platforms in different clinical settings to identify comparable rare genetic mutations. Therefore, aggregating these findings into an N of 20 or 30 for more traditional combined studies or meta-analyses may not be timely or feasible.

It is important to reemphasize that within the three components of clinical NGS-based testing (assay, bioinformatics, and interpretation), currently only the price of the assay is clearly declining and therefore providing the rationale for increased utilization of NGS on the basis of “efficiency” claims. With the increasing complexity represented by both the bioinformatics and interpretation stages, these components will likely increase the costs of delivering test results to the patient in a comprehensive, ethical manner, such that the total costs to the health care system are currently not known. Federally funded research is ongoing to better understand the risk/benefit trade-offs of sequencing;¹²¹ however, much additional work needs to be done to fully understand the economic impact of NGS. From all stakeholder perspectives, each of the three components of testing needs appropriate valuation and reimbursement in order to support their appropriate level of utilization in the real world, recognizing that third-party coverage is essential for most patients to have access to this technology.

As with other medical services, coverage decisions are generally not explicitly based on cost, but it does impact payer decisions to implement programs of precertification, disease management, and pharmacy management.¹²² Payers are not uniform in their process for determining what items should be subject to precertification, with different valuations placed on cost, administrative burden, clinical utility, and other variables.¹²³ Programs such as precertification are designed to create an administrative barrier limiting access to only those uses deemed appropriate. NGS is not unique in this area as payers frequently turn to precertification as a tool to manage utilization.

Coverage of a specific genetic test is not always a simple yes or no question. Payers may vary the level of coverage based on whether NGS testing is done for medical care/treatment of a presenting problem; reproductive decision-making; prenatal decision-making; prognostic testing; or preventive care. Depending on the particular NGS test or reason for ordering the NGS, payers have tools to vary coverage levels by altering such items as copayments, deductibles, and precertification requirements. Payers may choose to implement policies for precertification or disease management if they perceive these cost management tools as effective. The recent announcement that *BRCA* Analysis would be covered as a preventive service under the Affordable Care Act was an interesting

development¹²⁴ in the area of MDx testing; it may portend similar decisions for NGS technologies.

Beyond the difficulties faced by MDx test developers and professional societies regarding educating providers and patients on the appropriate use of the test, NGS-based tests face significant additional challenges given the evolving evidence base for variants with plausible, but insufficiently proven clinical significance, and the obligations of data storage and data sharing with patients and their families. These issues should be further explored by payers, providers, test developers, professional associations, and patients as coding and reimbursement methodologies are developed, incorporating the concerns of data storage economics, technological advantages and disadvantages, privacy and obligations regarding re-analyses and results reporting

Recommendations

NGS testing involves a team of professionals beginning with the assay through the application of bioinformatics, test interpretation and conveying the information to the patient. Each step in the process needs adequate valuation in order to be sustainable from the perspective of integration into clinical practice. If the technology moves towards a model in which the assay is conducted infrequently and bioinformatics are used to query as each additional clinical situation arises, a reimbursement code with appropriate compensation needs to be developed for re-analyses. In addition, payers, both public and private, must determine whether clinical interpretation in light of the patient's phenotype is a valuable component of service. If there is value in this clinical interpretation, the chosen reimbursement methodology should allow for professional interpretation billing. Given the insufficient number of genetic counselors, other health care providers will need to assume the responsibility of counseling patients. Payers, professional associations, and the AMA will need to grapple with what training, support, and reimbursement these individuals will need to accomplish this task.

There is a lack of clinical utility information regarding clinical NGS causing payers to be hesitant to embrace the technology. While this circumstance is a common occurrence for MDx testing generally, it is particularly complicated for WES and WGS in the setting of NGS-based testing where one test generates results that includes data with potential clinical utility as well as ambiguous or unknown clinical significance. Agreement needs to be achieved among payers, test developers, clinicians, and policymakers about what level of evidence is sufficient to establish clinical utility, including how to make meaningful use of N-of-1 trials. The shortage of clinical utility data is exacerbated by the lack of regulatory requirements for clinical utility information, as well as methodological uncertainties regarding how to efficiently design studies to meet the information needs of relevant decision-makers. Multi-stakeholder groups such as the Green-Park Collaborative¹²⁵ — sponsored by the Center for Medical Technology Policy, the Medical Device Innovation Consortium,¹²⁶ and the National Biomarker Development Alliance¹²⁷ — represent pre-competitive, public-private initiatives to address various aspects of the clinical utility problem, but not all groups include the payer perspective. Another mechanism to promote the conduct of clinical utility studies is to encourage the use of reimbursement policy

mechanisms such as coverage with evidence development, where payers provide provisional coverage for a newly developed test under the requirement that patients participate in a study. The goal is to balance the need for additional evidence generation with early access to promising new tests and has been discussed frequently as relevant to the MDx testing arena.¹²⁸

With better information regarding the impact of NGS testing on clinical outcomes, policymakers potentially will be able to address the growing movement within molecular pathology to move reimbursement from a cost-based to a value-based approach. Consideration should be given to the implications on other health care providers, as well as whether value-based reimbursement can be achieved through alternative mechanisms such as moving away from traditional fee-for-service reimbursement to more risk-based arrangements.

A similar multi-stakeholder approach should be adopted when considering how provider organizations and payers would be responsible for addressing the range of ethical and reimbursement-related challenges that are raised by NGS testing across the lifespan. For example, of interest to this broader group would be issues such as whether there is an obligation to look back at NGS performed previously and formally reinterpret it in the context of new knowledge. Practical questions are also important including how the patient will be located, how will the process of doing a re-query be initiated and by whom, who will pay for the re-query and whether there is a limited look back period. Likewise, payers should be part of a multi-stakeholder group that discusses strategies for managing the large, raw data files that accompany each patient's NGS testing. Data retention policies are needed across the industry and should include adequate compensation to ensure that the data is securely stored for the agreed-upon amount of time.

In light of current contracts and benefit plan designs, individual payer organizations are currently evaluating their obligations to pay for pre-symptomatic confirmatory testing related to incidental findings, as well as any subsequent interventions deemed appropriate to evaluate or treat a pre-symptomatic condition in light of current contracts and benefit plan designs. It is not known at this time the degree of variation in coverage policies with respect to incidental findings, but the answer to this empiric question is likely to affect clinical integration of NGS and this trend should be carefully studied.

Consideration should be given to balancing privacy/confidentiality concerns with the ability for public and private payers to access large amounts of genetic information to predict risk, design early interventions, or for purposes of disease prevention. If there is merit in fostering such interventions, a host of public policy considerations are raised and should be explored, including determining whether payers, individual providers, provider groups or patients are responsible for mitigating an identified risk.

There is a disconnect in how insurance coverage often views prenatal genetic testing as a covered benefit, while pregnancy terminations, including terminations occurring based on the results of prenatal genetic testing, are considered an expenditure unrelated to health care. Clinical NGS offers the ability to screen for many severe recessive childhood diseases,

thereby identifying carriers. While carrier screening is preferable over prenatal diagnosis, a rapid expansion of screening for carriers may pose substantial societal and political challenges. Policymakers need to engage a broader audience to explore sensitive concerns of expanding prenatal identification of potential health problems and/or screening for recessive conditions while the options for terminating pregnancy are either increasing in direct cost to the patient (as they are not covered by insurance) or are shrinking due to regulatory restrictions.

Adequate coverage and reimbursement ensures that the appropriate patients have access to needed services. Evidence-based reimbursement policies will promote the adoption of NGS testing that benefits patients while limiting access to testing that does not. Addressing the concerns outlined in this paper will be a critical component of effectively integrating NGS into mainstream health care, ensuring that tests demonstrating clinical utility have appropriate levels of coverage and reimbursement.

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The purpose of this paper is to provide a comprehensive review of the coverage and reimbursement environment that is currently confronting the introduction of clinical NGS, as well as to identify the potentially novel reimbursement challenges that will need to be addressed for this new technology to realize its full clinical potential.

From a reimbursement perspective, disease-targeted NGS panels such as those used in oncology settings are highly likely to follow the pathways set by first generation MDx tests, albeit with new NGS-specific codes applied over time. However, for clinical applications outside of disease targeted gene panels, where NGS is used to sequence entire exomes and genomes, many experts have cautioned about the potential social and economic harms that may result without thoughtful application of proactive policies. These NGS-specific considerations will have implication for payers as well as for patients.

There is debate about the adequacy of trained professionals to conduct both the bioinformatics and interpretation components of reimbursement — the components beyond the sequencing itself. As NGS enters health care, these steps are likely to become the bottlenecks as genetic information must be appropriately analyzed and interpreted in light of the clinical status of the patient.

Today, most NGS-based clinical tests are LDTs operating under CLIA certification, raising payers concerns regarding whether there is sufficient regulatory oversight and adequate assurance of the analytic validity for NGS tests. Most payers currently lack the technical sophistication to independently assess the validity of NGS tests, and it is too early to tell whether the recently released ACMG clinical laboratory standards for NGS testing will be both widely adopted and address possible concerns. The FDA has only recently begun to approve specific applications of NGS technology for clinical use and many unanswered questions remain, particularly in the area of oncology, where there have been no FDA approvals for use of NGS sequencers on tumor samples or as companion diagnostics.

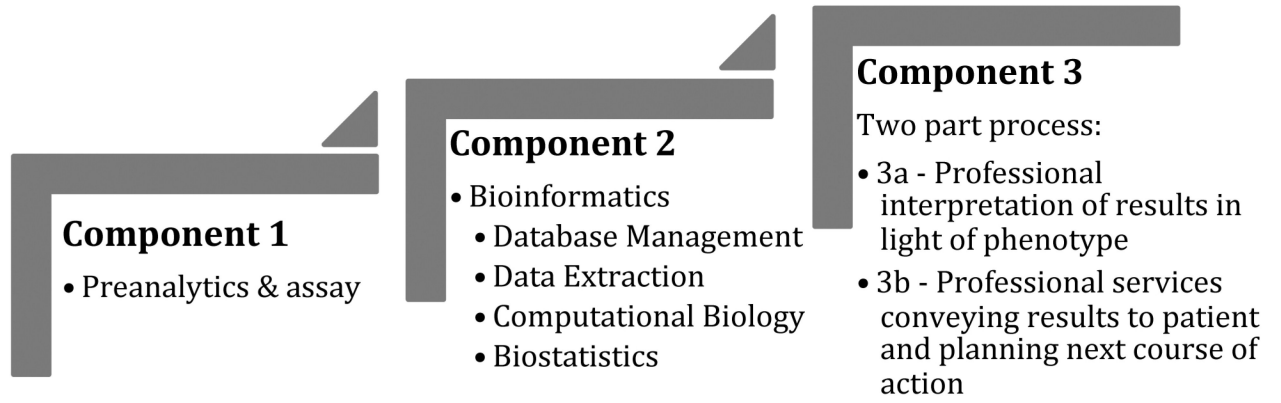


Figure 1.
Next Generation Sequencing Process