Roundtable on Whole Genome Sequencing:
Regulatory and Reimbursement Issues

Workshop White Paper

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This white paper is provided to workshop participants for the purpose of identifying and previewing some of the issues that will be discussed at the April 12 workshop. This white paper first summarizes the development and applications of next generation sequencing (NGS) and whole genome sequencing (WGS), and then focuses on the two central topics that will be the focus of this workshop: (i) regulation and (ii) coverage and reimbursement. For purposes of simplification, we will use the broader term NGS throughout this paper to refer to new sequencing technologies generally.

I. NGS Background

Genomics will play an increasingly prominent role in the delivery of health services over the next two decades, and NGS will play an increasingly dominant role in obtaining genetic information from patients. The first human genome sequence was completed in 2001 as part of the Human Genome Project at a cost estimated at $2.3-3.0 billion dollars. Since that time, the cost and time required to sequence a human genome has dropped precipitously. The cost of sequencing an entire human genome (reagents, labor, amortized cost of equipment) is now below $10,000, and is expected to soon reach the benchmark of $1000 or lower. The NHGRI has been tracking the cost of sequencing, and has demonstrated an exponential decrease in the cost of DNA sequencing (faster than Moore’s law for computer speeds) since 2007.¹ Of course, as the NHGRI and others note, the costs are much higher when the bioinformatics costs and the providers’ time in analyzing and delivering the results are included.

The first generation of DNA sequencing, up until 2007, used the Sanger method, which sequences a known genomic sequence (usually up to 1000 base pairs in length) one base pair at a time using a semi-automated, capillary-based system. Second generation sequencing, also commonly referred to as massively parallel sequencing, involves the simultaneous sequencing of very large numbers of small segments of DNA. These smaller segments of sequenced DNA are then reassembled into longer sequences, which require multiple “reads” of the same sequence to improve fidelity. The number of reads of a given sequence, which has traditionally been about 30 reads per nucleotide in the research context but will likely be higher in the clinical context, is referred to as “depth of coverage.” Third generation sequencing methods, which are now approaching commercial availability, sequence single molecules of DNA even more quickly and cheaply either by incorporating and detecting fluorescently labeled nucleotides or measuring

electric field charges when DNA passes through a nano-pore. These new methods are expected to push the cost of WGS below $1000 and reduce the time required for sequencing an entire genome below one day.

As a result of these technological developments, a variety of sequencing tests are under development. Some of the initial sequencing services available are panels of dozens of different genes relating to a patient’s phenotype that are simultaneously sequenced and analyzed in a single NGS step. For example, the multigene panel may be for X-linked intellectual disability, congenital muscular dystrophy, mitochondrial disorders, or Ashkenazi Jewish carrier screen. Whole exome sequencing (WES) involves sequencing most of the exons in the genome, which is the 1-2 percent of the genome that predominantly encodes proteins. This approach is less costly than sequencing the entire genome, and is likely to detect most of the mutations that result in clinically-recognized phenotypes. However, WES is likely to miss some clinically significant genetic variants, and so although often favored at these early stages of wide-scale human sequencing, is likely to be replaced by whole genome sequencing in the relatively near future as WGS becomes increasingly more affordable. For purposes of simplicity, we refer to all second and third generation sequencing technologies, whether for WGS, WES, or some other subset of the genome, as next generation sequencing or NGS.

While much of the focus on NGS has concentrated on the rapidly improving sequencing technology per se, the bioinformatic processing of the resulting data and the professional interpretation needed to translate and deliver the results to patients are important bottlenecks. Most physicians lack the training and expertise to analyze the massive quantities of genetic data produced by NGS, and there are only 2073 genetic counselors in the entire nation listed by the National Society of Genetic Counselors. This small number of competent NGS interpreters will be overwhelmed by the amount of relevant data produced by each genome sequenced, estimated to include ~150,000 novel SNPs not in the public dbSNP database, including 250-300 disruptive variants in genes, 50-100 human disease gene variants, and ~20 completely inactivated genes. The informed consent process alone is estimated to take several hours per patient. The delivery of the results to the patient has been estimated to take an additional five hours.

While NGS has been undertaken primarily in a research context until recently, it is rapidly moving into clinical applications. Early adopter clinical laboratories and hospitals have begun to offer NGS as a clinical service to selective patients. Influential groups such as the American College of Medical Genetics and Genomics (ACMG), the American Medical Association (AMA), and the Food and Drug Administration (FDA) expect and support the clinical use of NGS in appropriate

2 http://www.nsgc.org/tabid/68/default.aspx
4 Id.
7 American College of Medical Genetics and Genomics (ACMG), Policy Statement: Points to Consider in the Clinical Application of Genomic Sequencing (March 27, 2012) (“there is considerable interest in offering genomic sequencing-based tests on a clinical basis .... There are already instances in which genomic sequencing approaches can and should contribute to clinical care”).
8 American Medical Association, Report 4 of the Council on Science and Public Health (I-12, Clinical Application of Next-Generation Genomic Sequencing, Recommendation 1 (“Our American Medical Association recognizes the utility of next-generation sequencing (NGS)-based technologies as tools to assist in diagnosis, prognosis, and management, and acknowledges their potential to improve health outcomes.”).
circumstances. There are a number of potential applications of NGS in the clinical context, including:

1. Patients with a defined genetic disorder with a high degree of genetic heterogeneity, which can be best understood by simultaneously sequencing multiple (i.e., a panel of) genes;

2. Patients with an idiopathic phenotype that appears to have a genetic etiology but which is not attributable to any known genetic mutation;

3. A fetus with a likely genetic disorder that specific genetic tests available for that phenotype have failed to diagnose;

4. A cancer patient whose tumor cannot be controlled by existing treatments whose tumor genome is compared to his germline genome to look for mutations that could possibly be used to target treatments;

5. Pharmacogenetic testing of patients to detect variants affecting drug metabolism and transport, which are then used to select individualized drug dosing and selection regimes;

6. Population screening for alleles for highly penetrant Mendelian disorders and susceptibility loci (e.g., cystic fibrosis, BRCA)

7. Preconception carrier screening of couples known to be at risk of producing offspring with genetic conditions caused by unknown mutations;

8. Prenatal genetic screening of fetuses not known to be at any particular risk of a genetic condition;


Applications 1, 2, 3, and 4 have been used with anecdotal but often highly publicized successes to date. Various organizations support some but not all of these applications at this time – for example, the ACMG supports applications 1-3 and 7, takes no position on 4-6, but does not support 8 and 9 at this time. Additional types of NGS are also possible, including sequencing of pathogens, epigenetic marker sequencing, and RNA sequencing.

Regulation and coverage/reimbursement of NGS are likely the most important issues affecting the clinical uptake of NGS, and are the primary focus of this workshop. Before focusing in on those key issues, we briefly list a number of other technical, policy and ethical issues raised by the clinical use of NGS, some of which may play at least an indirect role in regulatory and coverage/reimbursement decisions:

- **Standards** – standards and best practices are needed for both providers and laboratories to promote the appropriate clinical use of NGS;

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9 Emily Singer, Making Genome Sequencing Part of Clinical Care, Technology Review Daily Edition (March 8, 2011).
10 ACMG, supra.
• **Reference Sequences** – a set of well-characterized, clinical-grade reference genomes is needed to evaluate the performance of sequencing assays;

• **Informed Consent** – NGS will require new models for informed consent given the massive amount of data and present and future implications that may result from sequencing a patient’s entire genome;

• **Return of Results/Incidental Findings** – what results should be returned to the patient, including incidental findings that will be inevitable whenever a patient’s entire genome is sequenced;

• **Future Findings** – NGS results will be unique in that they will have ongoing new value as new genetic mutations and traits are identified and characterized; what the rights, responsibilities and opportunities for updating clinical assessments of a patient’s previously collected sequencing data is unclear;

• **Data Storage** - NGS runs create an enormous volume of data that must be stored either on-site or in the cloud. A related issue is whether or not the sequence data should be included in or connected to the patient’s electronic health record;

• **Public Data Release** – there would be strong scientific benefits from releasing the results of sequencing in individual patients into publicly available databases, but such release may present privacy risks for patients even if the data are anonymized;

• **Provider Expertise/Training** - The number of health care providers, whether specialists and genetic counselors or physicians generally, who can understand and explain genetic information revealed by NGS will need to increase dramatically.

• **Patenting** – The pending Supreme Court decision this spring could greatly impact the cost and availability of NGS. If the Court upholds patenting of genes, and sequencing is held to violate those patents, then sequencers must either obtain licenses for, or avoid including, patented genes.

### II. Regulation

The advent of NGS comes at a time of enormous change and uncertainty about both the regulation and coverage/reimbursement of molecular diagnostics generally, which compounds the uncertainties for NGS. With respect to regulation, there have historically been two regulatory pathways for molecular diagnostics, both of which will be relevant for NGS.

#### A. CLIA

First, clinical laboratories offering health-related molecular tests and reporting results back to health care providers and/or patients must be certified under the Clinical Laboratory Improvement Amendments (CLIA). A “laboratory” under the statute is defined broadly as one that engages in the “examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the
assessment of the health of human beings.” Most testing laboratories are CLIA certified by the Centers for Medicare and Medicaid Services (CMS), but they can also be certified by approved accreditation agencies or by states with approved programs (New York and Washington).

CLIA certification requires a laboratory to comply with various requirements that are based on the complexity of the tests that are performed, which can be (i) high complexity, (ii) moderate complexity, or (iii) waived (low complexity). Human genetic tests are generally classified as high complexity tests. The CLIA regulations include requirements relating to laboratory personnel qualifications, quality control, and proficiency testing, the latter of which requires the laboratory to demonstrate the accuracy of its testing by performing tests on blinded samples for the testing specialty it provides. There are currently no CLIA proficiency tests specific to genetic testing.

The CLIA regulations permit a certified laboratory to modify an FDA cleared or approved test, or to develop its own test (referred to as a laboratory developed test or LDT), provided that the test system meets performance specifications for “(i) accuracy; (ii) precision; (iii) analytical sensitivity; (iv) analytical specificity to include interfering substances; (v) reportable range of test results for the test system; (vi) reference intervals (normal values); and (vii) any other performance characteristics required for test performance.” The CLIA regulations do not expressly require the laboratory to ensure the clinical validity or clinical utility of the test, but do require that “the test methods selected have the capability of providing the quality of results required for patient care.” However, these requirements generally do not require approval by any governing body.

There are two main sets of issues under CLIA raised by NGS. The first is whether the increased use of sequencing by testing labs will require any modifications to the CLIA oversight. For example, although there is no specialty proficiency testing currently for genetic testing, does the era of widespread genetic sequencing argue for creating such a specialty with its own proficiency testing protocols? The second set of issues relates to the research context, when a non-CLIA research laboratory discovers a genetic mutation in its sequencing that may put the subject at risk of a serious health outcome and which may be actionable if disclosed and acted upon in a timely manner. The recently updated guidelines on reporting genetic research results by a National Heart, Lung, and Blood Institute Working Group was stalemated on the issue of whether all genetic results reported to research subjects must be validated in a CLIA lab. The published report of that Working Group states that “Working Group members disagreed on the interpretation of what constitutes compliance with the CLIA regulations for the return of research results in genetics studies,” and noted that this “is a high-impact issue” in need of “further legal clarification.”

B. FDA

The second regulatory pathway for molecular diagnostics is via the Food and Drug Administration. In vitro diagnostics (IVD) tests must be approved by the FDA’s Center for Devices and Radiological Health (CDRH) as medical devices. The CDRH includes an Office of In Vitro Diagnostics and Radiological Health (OIR) that regulates IVDs. The Federal Food, Drug and Cosmetic Act defines a medical device as “an instrument, apparatus, implement, machine,
contrivance, implant, in vitro reagent, or similar or related article, including a component part, or
accessory which is ... intended for use in the diagnosis of disease or other conditions, or in the cure,
mitigation, treatment, or prevention of disease, in man or other animals.”17 Most health-related
molecular testing products, potentially including NGS systems, are intended for uses related to the
diagnosis, cure, mitigation, treatment or prevention of disease, and thus are potentially subject to
FDA regulation.

FDA has three primary pathways by which it can approve a molecular test. First, the most
stringent regulatory approval pathway is the pre-market approval (PMA) process, which is
required for novel or high-risk (Class III) medical devices such as those used for life-sustaining or
life-supporting applications. Second, if the test is “substantially equivalent” to a product already on
the market (described as the predicate device), the agency may “clear” tests for marketing via the
less burdensome §510(k) clearance pathway. Finally, a low- or medium-risk device that lacks a
predicate device already on the market may be approved via the de novo reclassification pathway.
In approving an IVD under any of these pathways, the FDA reviews the analytical performance of
the test and generally requires clinical evidence to support the intended use of the test and the
test’s ability to identify or predict the health condition or characteristic of interest.18

FDA has long regulated commercially distributed IVD products that often come in kits, but
these have included a relatively small segment of commercial genetic tests. Most genetic tests are
categorized as LDTs, developed and offered by a single laboratory (although numerous different
laboratories often develop and market the same or similar genetic tests). Historically, FDA has not
regulated LDTs, and so most genetic tests have only been regulated under CLIA. FDA has long
asserted that it has regulatory jurisdiction over LDTs but has elected not to regulate such products
under its enforcement discretion, although some stakeholders dispute FDA’s authority to regulate
LDTs.

In recent years, FDA has expressed an increased interest and intention to regulate at least
some molecular and genetic tests categorized as LDTs. For example, in 2005 the FDA determined
that the MammaPrint gene expression testing assay for breast cancer recurrence should be
regulated as a medical device, which ultimately was approved under the de novo reclassification
pathway.19 FDA has also indicated that companion diagnostics, which are tests used in conjunction
with a targeted therapy, should be regulated by the FDA regardless of whether they are IVDs or
LDTs.20 In 2006, FDA issued a draft guidance that was updated in 2007 stating its intention to
regulate LDTs that it classifies as in vitro diagnostic multivariate index assays (IVDMIAs) that use
an algorithm to provide a single patient-specific result or score based on multiple assayed variables
that cannot be independently validated by a health care provider. This guidance received
significant criticism and has not been implemented.

In 2010, FDA announced its intention to develop a more comprehensive approach to the
regulation of LDTs that would likely involve some type of risk-based categorization of LDTs with
differentiated regulatory requirements.21 FDA held an initial public meeting in 2010 to discuss
potential approaches to LDT regulation, but has not yet issued any official proposal. To date, all

18 Personalized Medicine Coalition, Pathways for Oversight of Diagnostics 16 (undated).
19 See Personalized Medicine Coalition, supra, at 10.
20 M. Thomae, Molecular Diagnostics: LDTs Need Approval Too (June 26, 2012), available at
21 FDA, Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments, 75 Fed. Reg. 34463 (June 17,
2010).
NGS tests have been developed as LDTs, and FDA has not yet taken regulatory action on any NGS. If the FDA moves forward with a generic guidance or position on regulation of LDTs generally, that may apply also to NGS.

But FDA is also considering NGS as a separate regulatory domain, as NGS raises a number of unique challenges to FDA for regulation. For example, NGS platforms can be used for a wide variety of applications – from identifying single-nucleotide polymorphisms, to characterizing tumor genomes, to evaluating structural variations. For example, a laboratory may choose to use one NGS assay for many different purposes, perhaps applying an application-specific mask in silico during the interpretation so that only those results known to be relevant to a specific patient’s phenotype will be analyzed. Thus, the same platform will be used for very different patient-specific assays even in in the same laboratory.

Similarly, some laboratories have developed organ-specific NGS assays for different types of cancer, while other labs are developing single assays that are appropriate for multiple cancer types. This multi-analytical diversity both within and between sequencing platforms is very different than most molecular diagnostics that the FDA is tasked with approving, which are intended to measure a single analyte for a specific purpose. This existing regulatory paradigm does not fit NGS, where it is simply not possible to evaluate the clinical validity or utility of each possible current and future application of a given sequencing platform.

Moreover, there will be differences between platforms that will make it difficult if not impossible to compare systems and to establish objective performance metrics. Different sequencing technologies vary in their strengths and weaknesses in detecting duplications and deletions, copy number repeats, homopolymeric regions (long stretches of the same base), GC- or AT-rich regions, and redundant sequences. In addition, sequencing a germline will have different performance specifications than sequencing a tumor, with the latter needing to be more sensitive because of genetic heterogeneity in tumor tissue. Therefore, establishing uniform performance standards will be difficult.

Another challenge is that NGS will produce many different gene results in a single sequencing run that will range from validated biomarkers of risk or prognosis, to suggestive markers, to variants of unknown clinical significance. How should FDA evaluate this range of outcomes? Finally, the rapid pace of change in sequencing technology will challenge FDA to keep pace in the performance standards it imposes, while also ensuring predictability for product developers and market fairness to companies that submit similar products in different timeframes.

The FDA convened a public meeting on June 23, 2011 to explore some of the scientific and technical issues associated with NGS, such as the analytical validity of NGS strategies. The meeting expressly disavowed addressing regulatory issues or developing regulatory recommendations. Since the June 2011 meeting, the FDA has continued to consider how it might oversee human DNA sequencing, but has not yet issued any formal guidance or decisions to date. In

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*22 Association for Molecular Pathology (AMP), Proposal to Address CPT Coding for Genomic Sequencing Procedures (March 2013).
23 AMP, supra.
24 Monica Heger, FDA Mulls Options for Regulating Next-Gen Sequencing Platforms in Clinical Diagnostics, Genomeweb, June 28, 2011.
25 Id.
February 2013, the FDA cleared Life Technologies 3500 Dx Genetic Analyzer, a Sanger sequencing platform, under section 510(k) for diagnostic use.\(^{27}\) Meanwhile, Illumina has recently submitted its MiSeqDx platform to FDA for 510(k) clearance, and has separately submitted two assays that will run on the MiSeqDx platform also for 510(k) clearance.\(^{28}\) This appears to be the first NGS platform submitted to FDA.

**Questions for Discussion**

1. Will NGS be regulated as an LDT or IVD? If treated as an LDT, will/should FDA regulate such tests or is CLIA sufficient?

2. If FDA does not regulate NGS, what modifications, if any, would CLIA require to ensure that NGS results are appropriate for clinical use?

3. If FDA does regulate NGS, should any such regulation be part of a generic approach for all genomic LDTs, or should FDA develop a unique guidance/approach specifically for NGS tests?

4. If FDA regulates NGS tests, should they be regulated via the § 510(k), PMA, or de novo pathways? What factors might influence this determination?

5. Should FDA analyze and approve sequencing platforms separate from the specific uses of that platform that may develop? If the platform is regulated, how can FDA assess its clinical validity and value to patients before it knows how the platform will be used? If the platform is cleared or approved, what regulatory pathway should apply to each subsequent sequencing assay using the platform?

6. How should FDA evaluate the wide variety of genetic variants that will be revealed in a single sequencing run, ranging from validated biomarkers to variants of completely unknown effect and significance? Will the FDA need to evaluate each individual allele or variant? If FDA approves a sequencing technology for only validated markers, will there be a problem with off label uses?

7. What type of data should/will FDA require for clearance/approval of NGS tests? Will it/should it require that the NGS results be confirmed using Sanger sequencing? Will/should clinical trials be required? If not, what types of data will be required?

8. Given the rapid changes in technology expected, how can FDA’s review system be adaptive to changing technologies? And yet at the same time provide some certainty to product developers and market fairness to companies that submit comparable proposals in different time periods?

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\(^{28}\) Monica Heger, *Illumina Growing Clinical and Dx Business with Submission of MiSeqDx, Two CF Assays to FDA*, GenomeWeb, Jan. 9, 2013.
III. Coverage/Reimbursement

CMS and private payers face difficult decisions on whether, when and how to cover and reimburse NGS. As was the case with regulation, the approach for coverage and reimbursement of molecular diagnostics generally is undergoing significant change and uncertainty which is also likely to affect NGS.

A. Coverage

Until this past year, coverage for molecular tests was primarily based on “stacking” the codes for the various methods used in the test procedure. This approach was deemed unsatisfactory because of the lack of transparency to payers about the condition or trait being tested for. On January 1, 2013, the stacking codes were retired for molecular diagnostics and laboratories are now required to use new Current Procedural Terminology (CPT) codes developed by the American Medical Association for coverage of molecular diagnostic tests. These new codes, referred to as Molecular Pathology (MoPath) codes, are specific for the condition or trait (analyte) being tested rather than the methodology used. There are two types of MoPath codes. Type I codes are for commonly performed single-analyte molecular tests. Type 2 codes are for procedures performed less frequently, and are organized into nine ascending levels based on the technical resources and interpretive work performed by the physician or other qualified healthcare professional.

CMS can use one of two methods for setting new CPT codes for molecular diagnostics under Medicare. Under the first method, known as gapfilling, local Medicare contractors are responsible for determining the appropriate fee schedule amounts in the first year, and then CMS calculates a national payment rate in the second year based on the median of the local fee schedule amounts. Each local contractor can use its own methodology to calculate a gapfill payment amount in year one, but is required to take into account the following information when available: (i) charges for the test and routine discounts to charges; (ii) cost of resources required to perform the test; (iii) payment amounts determined by other payers; and (iv) charges, payment amounts, and resources required for other tests that may be comparable.29 The second method CMS can use to set MoPath code rates is crosswalking, in which the agency benchmarks the payment for a new code based on the rate for comparable existing tests or codes. The implementation of these new codes is likely to create uncertainty and delays in the initial period. Commercial payers are also likely to benchmark their rates for many diagnostic tests on these new CMS rates.

The AMA has committed to developing additional CPT codes that will specifically apply to NGS-based diagnostic services.30 There is currently only one multi-gene sequence analysis CPT code: 81280 – Long QT syndrome gene analysis; ... full sequence analysis.31 In March 2013, the Association of Molecular Pathology (AMP) submitted a proposal to the AMA for CPT codes for sequencing-based assays.32 The AMP proposal incorporates two approaches. First, it proposes “a single, methodology agnostic code that includes both technical and interpretive work” for testing for a specific genetic condition or phenotype. Thus, the same code would apply regardless of whether the provider used traditional genetic tests, WES, WGS or any other method to assay the genetic disorder or trait. The second approach, described as the code-mate strategy, would introduce separate codes for technical processes and for interpretive processes.

29 42 C.F.R. § 414.508.
30 AMA, supra.
31 AMP, supra.
32 AMP, supra.
B. Reimbursement

Reimbursement stands as one of the biggest impediments to clinical use of NGS, as many health care providers and institutions point to concerns about payment as a major barrier to their use of NGS.33 Both CMS and private insurers seem reluctant to pay for sequencing without greater demonstration of clinical utility.

Concerns about lack of reimbursement were heightened by an October 2011 statement by Jeffrey Roche, head of the CMS Office of Clinical Standards and Quality Coverage and Analysis, who was quoted as stating that “I hope people realize that whole genome sequencing itself is probably something that CMS would never cover.”34 In a follow-up statement, Roche said he regretted using the word “never,” and clarified: “I should have said that I expected it would be very, very challenging to collect and analyze enough information to convince CMS that whole genome sequencing should be covered by Medicare because of its value in helping physicians make patient care decisions.”35 He continued that Medicare coverage will “depend on evidence that whole-genome sequencing actually makes a difference in patient outcomes.”36

NGS can be cheaper in at least some circumstances than existing care practices, such as when a patient when an unusual phenotype is put through the diagnostic odyssey of multiple and sometimes redundant diagnostic tests.37 A one-time NGS may be both cheaper and more useful for diagnosing the condition.

For example, an unnamed private insurer reportedly agreed to reimburse the whole genome sequencing of a child patient being treated at the Medical College of Wisconsin where the providers were able to demonstrate that whole genome sequencing would be less expensive than the typical string of diagnostic tests that would otherwise be conducted.38 Other providers and sequencing companies have likewise reported anecdotal examples of private insurers paying for whole genome sequencing on a case-by-case basis.39 A 2012 study by DNA Direct found that only three publicly available health plans specifically mentioned whole genome sequencing, but all three specifically state the procedure is experimental and not covered.40

NGS will present some unique challenges to payers in addition to demonstrating clinical utility. The costs of analyzing the DNA will exceed the costs of sequencing the DNA. Typical reimbursement schemes for molecular diagnostics do not provide sufficient coverage for the bioinformatics costs and the cognitive services of the health care provider who must analyze the massive amount of data produced by sequencing. Another issue is that payers generally only pay

33 Monica Heger, Demonstrating Cost Effectiveness of Clinical NGS is Key to Payor Reimbursement, Hospital Uptake, GenomeWeb, Feb. 22, 2012.
36 Id.
37 See, e.g., AMA, supra (“Already WGS and WES have shown remarkable ability to end the diagnostic odyssey for patients with disorders that are resistant to standard diagnostic procedures and targeted genetic testing.”).
38 Singer, supra.
39 Heger, Demonstrating Cost-Effectiveness, supra.
40 Heger, Demonstrating Cost-Effectiveness, supra.
for procedures that have demonstrated clinical utility – yet sequencing is a unique hybrid in that some of the data generated may have clinical utility while most of the data may be of ambiguous or unknown value. This creates dilemmas for payers with respect to what and how much they should reimburse. NGS also presents a unique reimbursement challenge in that the data will require ongoing re-evaluation that will not necessitate any additional technical sequencing work – raising questions about how and whether such “re-querys” will be reimbursed and by whom. 41

Questions for Discussion:

1. What particular applications provide the most promise for NGS to prove that it can provide clinical utility? What is needed for payers to provide coverage and reimbursement for these applications?

2. Should the sequencing and interpretation of the sequence be bundled into a single code and reimbursed together, or should they be separated into two different items (i.e., “code mate” concept discussed by AMP)?

3. How will coverage and reimbursement vary (if at all) for different uses of the same sequencing platform for different patients (i.e., through in silico masking of all results except those known to be relevant to individual patient)? Will the payer be able to identify and differentiate these different uses of the same sequencing platform?

4. Will NGS provide more or less clinical utility and cost-effectiveness in testing for a multi-genic phenotype than a series of single-gene tests for the same condition? How might that change over time? Should coding and reimbursement vary when NGS is used as opposed to multiple individual genetic tests to interrogate the same clinical question (e.g., genetic etiology of a heritable disorder)? Would the Tier 1 and/or Tier 2 codes that would apply if the genes were tested for individually using traditional genetic testing also apply to sequencing that same set of genes in a single NGS assay?

5. Will private insurers and/or CMS pay for NGS sequencing of people who are not ill (e.g., newborns, first-degree relatives of patients with high-risk variants; people who want their DNA sequenced for risk prediction)? What precedent exists for CMS to pay for these types of uses?

6. How serious is the concern that NGS may increase the cost of medicine by patients who require greater medical services in response to information revealed by sequencing, or by doctors who provide more medical services as defensive medicine to protect against liability relating to information revealed or potentially revealed by NGS? How will payers address and try to control these increased costs, if at all?

7. Many physicians will lack the expertise and time to analyze and communicate the results of NGS. If physicians cannot provide these services, who will, and how will they be paid? How do CMS and private payers currently reimburse physicians and genetic counselors for their return of genetic test results?

41 AMP, supra.