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One technology, multiple applications: developing context-specific NGS policy

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To the editor

Clinical next generation sequencing (NGS), which allows for sequencing of entire human genomes, has shown clinical value in oncology and diagnosis of rare diseases, and is expanding to other clinical domains (1). Yet, in the words of the former US Food and Drug Administration (FDA) Commissioner, Margaret Hamburg, and US National Institutes of Health (NIH) Director, Francis Collins, “even the most promising technologies cannot fully realize their potential if the relevant policy, legal, and regulatory issues are not adequately addressed” (2). Currently there is vigorous debate about how to develop effective regulatory and reimbursement policy for NGS-based testing. Ongoing policy movement in these areas introduces challenges, but also creates opportunities for stakeholders to influence the course of further policy development.

Recent events underline the degree to which regulatory policy remains a work in progress. In October 2014, the FDA issued a draft guidance document outlining a proposed framework for regulatory oversight of laboratory-developed tests (LDTs) (3). The proposal, if finalized, would reverse a decades-old policy of enforcement discretion. As the majority of NGS-based tests for specific conditions have been developed as LDTs (only two tests have been submitted for FDA review as in vitro diagnostic test kits), FDA regulation of LDTs could have significant impact on the development of NGS-based testing.

Some commentators have expressed concern about the agency's capacity to address a rapidly evolving technology, as well as the scope of its legal authority (4,5). The FDA and its defenders, arguing that the agency has authority to support the policy shift, point to the increased complexity of newer tests. Specifically, they cite the need for regulatory attention to test characteristics such as clinical validity to complement the regulation of laboratory practice under the Clinical Laboratory Improvement Amendments (CLIA) and the regulation of medical practice under state laws (3). To further support its position, FDA issued a report in November 2015, in advance of a hearing before the House Energy and Commerce Subcommittee on Health, that features twenty case studies on the risks to patients of inaccurate, unregulated tests (6). These include false negatives which may result in a patient not being given access to a helpful therapy, and false positives which may result in harmful or unnecessary procedures. Even regulatory clearance (where legally required) does not necessarily address payers' desire for evidence of clinical utility and cost-effectiveness. In the area of reimbursement, evidentiary standards and coverage policy vary across payers and many existing approaches are inadequate to capture the full value of NGS (7).

Understanding the features of the NGS industry as it develops is essential to adequately address policy issues and to fully realize the potential of clinical NGS. Our previous work showed that companies offering NGS services have disparate business models and offer a range of services, which in turn, has policy implications (8). In this paper we focus on the clinical applications of NGS technology. We map the clinical segmentation of NGS providers, focusing on the multiplicity of clinical applications of sequencing technology. Mapping the clinical segmentation of NGS providers and the distinctive constellation of risks and benefits for each clinical segment is important for developing more targeted and effective policy. To capture the clinical segmentation of NGS providers through a landscape analysis, we built on categories used in reimbursement, scientific, and clinical contexts (1,9). We identified seven relevant categories with distinct regulatory and/or reimbursement implications: (1) preconception carrier screening; (2) prenatal testing, including non-invasive prenatal testing (NIPT) and pre-implantation genetic diagnosis (PGD); (3) newborn screening; (4) whole-genome and whole-exome sequencing for suspected rare disease; (5) oncology and tumor profiling; (6) risk assessment for and diagnosis of other common diseases and conditions; and (7) pharmacogenomics.

We identified forty-three companies and academic laboratories that offer genetic testing services through a CLIA-certified laboratory. (Supplementary Table 1) Figure 1 shows the breakdown of clinical offerings among the forty-three providers. Among the most common clinical offerings, 70% (n=30) of providers offer oncology-related testing, including tumor profiling, followed by 56% (n=24) providing risk assessment and/or diagnosis of other common and chronic diseases and conditions, not including oncology-related tests. One-third of those offering oncology-related testing (n=10) do not offer any other types of testing (Fig. 1 companies shaded in green). The other two-thirds of oncology-related test providers are also offering testing services for common and chronic diseases.

Three companies provide services in all seven clinical segments. Combining preconception, prenatal, and newborn screening, 40% (n=17) of providers are operating in maternal and perinatal NGS services, and approximately half (n=8) are operating only in those clinical

segments (Fig. 1 companies shaded in blue). Of the companies and academic institutions that we identified, none is providing solely pharmacogenomic testing. Similarly, only one company is focused on providing just whole-genome and whole-exome sequencing for suspected rare disease; providers of this type of clinical testing usually also offer testing for oncology and common and/or chronic diseases.

Many commentators support linking oversight of NGS-based testing to risk, and this is largely compatible with current and proposed regulatory frameworks. Under the statute that governs FDA regulation of medical devices, devices are classified based upon the controls necessary to provide reasonable assurance of safety and effectiveness (10). Class III devices, which are subject to the most stringent oversight including premarket approval, are either high stakes or high risk plus there is insufficient information on the adequacy of controls. The two NGS-based cystic fibrosis kits cleared by the FDA as Class II were determined to be substantially equivalent to test kits already on the market and intended for expert use in conjunction with other laboratory and clinical information.

Preconception carrier screening

Of the entities that provide preconception carrier screening, only 9% provide this service exclusively. More than half (69%) also provide prenatal testing, with both clinical applications equally represented among the providers we surveyed (Fig. 1). The primary benefit of preconception carrier screening is to help prospective parents predict the chances of having a child with a Mendelian genetic disorder (Table 1). The American College of Obstetricians and Gynecologists (ACOG) recommends testing for those with a family history of a genetic disorder, or belonging to an ethnic group that has a high rate of carriers of certain genetic disorders (11). NGS-based testing, however, allows screening for a large number of conditions simultaneously, and can provide information on more conditions than the currently recommended screening guidelines. Whereas this may shed light on some new conditions and provide information that guides the health care of future parents, the concern is that expanded panels include conditions that vary in penetrance and presentation, including age of onset. Another concern is that preconception carrier screening may give prospective parents false confidence that leads them to refuse newborn screening (12).

Prenatal testing

Prenatal testing includes an array of technologies. Of the surveyed providers, 30% provide at least one, if not a combination, of these technologies (Fig. 1). PGD, for example, uses *in vitro* fertilization technology to identify embryos with genetic conditions prior to implantation. After implantation, other technologies like chorionic villus sampling (CVS), carried out between ten to twelve weeks of pregnancy, or amniocentesis, conducted after sixteen weeks of pregnancy, can be used to detect chromosomal abnormalities and genetic conditions. These invasive techniques, which carry a small risk of miscarriage, are generally only recommended for women who have an increased risk for genetic and chromosomal problems. A newer technique, NIPT, uses cell-free fetal DNA circulating in maternal blood to allow for earlier detection of genetic diseases and aid in reproductive decision-making and pregnancy management. In this space, a handful of competitive private companies have provided NIPT for trisomies 13, 18, and 21 since 2011. More recently testing has expanded

to include sex chromosome aneuploidies and microdeletion syndromes, for which the European Society of Human Genetics (ESHG), and the American Society of Human Genetics (ASHG) do not recommend using NIPT (13). The American College of Medical Genetics and Genomics (ACMG) believes that the application of genetic technology, particularly in the prenatal setting, should be supported by prospective clinical trials and considered carefully before its incorporation into routine clinical care (14).

NIPT may have the potential benefit of earlier detection without the associated risks of more invasive techniques, but researchers have compared the results from NIPT with cytogenetic results and shown the limitation of NIPT based on the number of false positive cases (15) (Table 1). Specifically, researchers reported the following true-positive rates when comparing cytogenetic results with NIPT results that came back positive: for trisomy 21 – 93%, for trisomy 18 – 64%, for trisomy 13 – 38%, and for sex chromosome aneuploidy – 38% (15). Although NIPT reports high sensitivity and specificity, the positive predictive value is still in question (15). For this reason, researchers as well the ESHG and the ASHG recommend that a positive NIPT result always be confirmed with diagnostic testing via CVS or amniocentesis (13,15).

Newborn screening

The goal of newborn screening is to screen asymptomatic newborns for severe, rare conditions that can be treated early. As the cost of whole genome sequencing declines, some have argued that newborn screening programs could benefit from NGS (16). Newborn screening programs are mandated by all states and usually presume parental consent. If NGS were used to screen the genomes of newborns, potential benefits could include information on conditions not listed in current screening guidelines. This sort of information could lead to more personalized health care, including pharmacogenetic information or carrier status information, which has implications for related family members. An ethical consideration for integrating NGS into newborn screening programs is the consequence of receiving incidental findings and false positive results that require follow-up. The American Academy of Pediatrics (AAP) and ACMG recommend deferring genetic testing for late-onset conditions until adulthood, and generally recommend testing only to help diagnose conditions for which early monitoring and/or intervention are available and effective (17). From a policy point of view, states consider newborn screening programs by assessing the overall public health benefits to the newborn population. Therefore, the use of NGS for state-based programs could potentially require a different level of clinical utility evidence than that for individual testing, because assessment would be made for the clinical benefits to the newborn population as a whole.

Suspected rare disease

Figure 1 shows a small number of market entrants in the rare disease segment compared to oncology. Yet, the literature suggests this is an area where recognition of clinical value is growing (1,18). This is also an area where the impact of the rapid evolution of knowledge is striking (18). The technical challenges associated with NGS-based testing for rare disease are primarily concentrated in the interpretive phase of the NGS clinical pipeline (Table 1). The FDA has already signaled continued enforcement discretion when NGS is used in the

rare disease context (3). Optimally, payers would also adopt a flexible approach for such conditions, recognizing that a traditional approach to demonstrate clinical utility that depends on specific treatment benefit in a population is not well-suited to diseases that affect very few individuals and may have limited treatment options. The outcome may be simply the precise diagnosis of an untreatable condition, which could nonetheless end a tortuous diagnostic odyssey (19). Many companies currently operating in this clinical space have academic affiliations and access to expertise in bioinformatics, medical genetics, and genetic counseling, features that make these institutions good partners to develop alternatives to mitigate risk and establish benefit. Further, since the clinical utility of NGS-based testing for rare disease is intrinsically tied to the availability of large datasets to aid with interpretation of results, the case is especially strong for tying coverage and reimbursement for rare disease testing to the deposition of information in public databases.

Oncology and tumor profiling

NGS technology is rapidly being adopted in oncology, especially for tumor profiling, as demonstrated by the relatively large number of entrants in this space.(Fig. 1) Industry representatives have asserted that the innovation possible via LDTs under the FDA's long-standing policy of enforcement discretion has allowed for correction of problems with existing oncology-related FDA-approved companion diagnostics (20). At the same time, oncology is the area where concerns about risks to patients are heightened because test results can be used to select therapy for life-threatening conditions (3,6). Further, tumor profiling is among the most technically challenging clinical applications of NGS technology (Table 1). In light of such concerns, the rush of providers into NGS-based testing in oncology signals peril— a proliferation of tests that makes assessment more challenging, entry of providers offering low-quality tests, and inflation of claims to garner market share—as well as promise, achieving the anticipated benefits of better matching of patients/tumors with therapy and identifying individuals at heightened risk of cancer faster and at lower cost due to competition. The key policy task is to develop an oversight system tailored to this particular clinical segment, where continuous innovation is beneficial, but where the stakes are high, and test providers may have varying capacities to deliver a high-quality, evidence-based result. Consensus has yet to emerge on the best regulatory approach. However, given the high stakes both in dollars and clinical outcomes, oncology is an area where data sharing is critical, both to facilitate external validation *and to* rapidly and efficiently circulate information about problems. Payers as well as regulators may have a role in creating incentives that are either positive (e.g., accelerated review processes for laboratories that share data, payment to cover sharing data) or negative (e.g., coverage only for tests that can be independently verified with public data sets, certification of laboratories or professionals that requires data sharing, or reimbursement contingent on data sharing). A recent report issued by the Green Park Collaborative, an initiative of the Center for Medical Technology Policy, Baltimore, Maryland, proposes initial medical policy and medical coverage guidelines for NGS-based oncology testing and mentions several positive modes to incentivize data sharing (21).

Risk assessment and diagnosis of common disease

A number of companies and academic institutions are using NGS for the risk assessment or diagnosis of common diseases (Fig. 1). Examples include type II diabetes, coronary artery disease, and hypertension (Table 1). Common, complex disorders, unlike Mendelian diseases, can be influenced by a large number of DNA variants, each of which has a relatively low predictive value. Since most common diseases are not single-gene disorders, researchers have primarily relied on population-based studies, or genome-wide association studies (GWAS) to understand the underlying genetics. Such studies, however, require additional research to determine whether variants with a high statistical correlation are causal. Findings from GWAS typically confer low relative risk and therefore often have lower predictive power with unclear clinical utility (22). Models to combine multiple markers into a cumulative risk score often are flawed and are usually no better than traditional risk factors such as family history and ancestry (22) (Table 1). Whereas common disease testing may have the benefit of earlier screening and identification of disease, it could also lead to interventions without established benefit. Although the overall risk of such testing is relatively low, payers should be cautious in covering such testing that does not have demonstrated clinical value.

Pharmacogenomic testing

Pharmacogenomic testing aims to use genetic variants to better understand and predict the effectiveness of a drug for a particular population. Potential benefits include the avoidance of risks associated with an ineffective therapeutic, and the avoidance of toxicities of therapeutics prescribed at standard doses (Table 1). The anticoagulant warfarin is often held up as a good example, as the genetic variants, CYP2C9 and VKORC1 can be used to determine the optimal starting dose of Warfarin (23). However, chip-based testing for Warfarin dosing and other pharmacogenomics indications has been on the market for over a decade with only weak uptake (24). The introduction of NGS is mainly a technological substitute that might produce the same information at similar or lower cost, but it might also provide information that could identify additional pharmacogenomic diplotypes relevant to the indication. However, this type of test also has inherent risks. Establishing the phenotype of a pharmacogenomic test requires exposure to a drug and the associated risks. On the other hand, pharmacogenomic testing could become folded into testing for other indications, and preferred for the additional drug reaction information provided. Payers might have an incentive for the latter to minimize the cost of ineffective therapeutics.

Although not comprehensive, this discussion shows the importance of attending to the distinctive features of each category within our taxonomy in policy debates related to NGS-based testing. Additionally, it brings to the fore two considerations that we believe merit greater emphasis. The first is the value of transparency in assuring appropriate clinical integration of NGS technology. Both the College of American Pathologists (CAP) and ACMG have been open to FDA premarket review of LDTs that involve methodologies that are not well understood or independently verifiable, where full transparency is not possible, or for products and services developed under non-transparent business models (25,26). Potential alignment with governmental initiatives beyond the FDA are worthy of mention here, such as the Office of the National Coordinator for Health Information Technology's

efforts to encourage use of electronic health records and to facilitate data sharing, and the NIH's investment in resources such as ClinGen and ClinVar which are online platforms to facilitate free access to and sharing of genomic data. The American Society of Clinical Oncology (ASCO) has also updated its policy statement on genetic and genomic testing for oncology and supports an increased role for FDA, and "efforts to catalog and annotate all genomic variants and to create rigorously curated open-access libraries of the variants for use by all laboratories" (27).

Second, policymakers will want to review evidence concerning the full range of outcomes that matter to patients and accommodate ongoing evidence creation. For example, whereas payers often rely on regulators to assess safety and efficacy, they may also seek evidence of clinical utility, or evidence that the test will lead to an improved clinical outcome, before covering an intervention. Scholars have advocated for a broad concept of utility that captures personal utility, meaning the information could help one make non-medical decisions or provide value in other ways (e.g., influence reproductive planning, end a diagnostic odyssey), and utility over time for coverage and reimbursement decisions (7,19). Further, "coverage with evidence development" might establish the feasibility of contingent coverage that does not require all the evidence up front. Payers are experimenting with such policies, with an eye toward identifying situations in which there are viable alternatives to binary choices about coverage.

An FDA discussion paper on NGS points to the broad and "indication-blind" nature of NGS (28). We suggest the ways in which recognizing the different clinical uses of NGS may be helpful in tailoring policies to the clinical context. Some policy issues, such as the appropriate approach to generating and managing secondary findings, will cut across many clinical uses. But the risk/benefit considerations in carrier screening, newborn screening, oncology, pharmacogenomics, and other clinical contexts will differ. Likewise, as professional societies have noted in their recommendations regarding risk-based classification of genetic tests, lack of transparency, especially in the challenging area of variant interpretation, heightens risk. The taxonomy of clinical contexts for NGS can help guide decisions about regulation and reimbursement by helping distinguish risk and benefit from one clinical context to another.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Forty-three companies and academic institutions with CLIA certification were identified as direct providers of human testing services. Each horizontal row represents one provider, categorized in the columns by the types of clinical offerings. Eight blue colored institutions are only providing prenatal or newborn testing services and ten green colored institutions are only providing oncology related testing services.

Table 1

	Preconception Carrier Screening	Prenatal Including PGD & NIPT	Newborn Screening	Suspected Rare Disease	Oncology and Tumor Profiling	Common Disease	Pharmacogenomics
Test Purpose	Risk assessment	Risk assessment and diagnosis	Therapeutic intervention, risk assessment, disease monitoring	Diagnosis, therapeutic intervention	Risk assessment, diagnosis, (individualized) therapeutic intervention	Risk assessment, diagnosis, monitoring, therapeutic intervention	Individualized therapeutic intervention
Example Tests	Panels that include cystic fibrosis, fragile X syndrome, sickle cell disease	Panels that include trisomies 13, 18, 21, and microdeletions	Cystic fibrosis	Whole genome sequencing (WGS) and whole exome sequencing (WES)	Comprehensive genomic profiling in NSCLC	Panel test for cardiovascular disease and diabetes risks	Panel tests for response to abacavir, warfarin, and carbamazepine
Possible Negative Consequences	Increased confusion and unwarranted anxiety (given variable penetrance, VUSs, especially with expanded panels)	Mistaken reliance on NIPT as diagnostic leads to terminations of unaffected fetuses; tests enter clinic without established PPVs	Newborn screening panels rapidly expand beyond AAP and ACMG recommendations; increased anxiety, confusion, and waste of resources	Patients and providers burdened with costs as payers refuse to cover, citing lack of evidence of clinical validity	Poor quality tests and unresolved technical challenges affecting tests lead to patient harm from therapeutic mismatches	Patients seek out interventions without established benefit, possibly with associated risks	Testing is costly but not does not lead to improved outcomes over standard of care
Possible Positive Consequences	Expanded screening lowers disease burden	NIPT as initial screen reduces exposure to risks of CVS and amniocentesis; expanded screening lowers disease burden	Appropriate expansion of newborn screening leads to improved outcomes	Catalyst for coverage policy innovation; leads to more effective therapeutic approaches, or precision medicine	Leads to more effective therapeutic approaches, or precision medicine	Patients are able to access effective interventions earlier, preventing disease or slowing disease progression	Ensures delivery of effective therapeutics and avoidance of toxicities, or precision medicine

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NSCLC: non-small cell lung cancer, VUS: variant of uncertain significance, NIPT: non-invasive prenatal testing, PPV: positive predictive value, AAP: American Academy of Pediatrics, ACMG: American College of Medical Genetics, CVS: chorionic villus sampling