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Payer coverage policies for multigene tests

To the Editor:

New technologies are enabling genetic tests that measure multiple rather than single genes. The availability of ‘multigene tests’ (panels and whole exome/genome sequencing tests) is rapidly growing, which raises critical questions about whether and how payers will cover them. Here, we survey the policies of the five largest US private payers that include multigene tests (including 55 policies that cover 313 multigene tests; **Table 1, Supplementary Methods and Supplementary Table 1**). Our findings reveal that most multigene tests are not covered by payers and that there is a high degree of variability as to how test coverage is assessed. We believe our analysis is the largest systematic review of US coverage policies for multigene tests to date. Efforts to obtain such data and carry out systematic analyses will be essential to increase the transparency and understanding of insurance coverage policies, a fundamental need for informed policy making.

Multigene tests are an integral component of new policy initiatives such as the US National Institutes of Health (NIH) Precision Medicine Initiative and the US National Cancer Institute Cancer Moonshot. For example, experts for the Moonshot Initiative noted that although genome sequencing is rapidly transforming cancer research, only a tiny fraction of cancer patients are having their tumors sequenced. This is because most payers, including Medicare, refuse to pay for the procedure, citing the lack of both clear actionability for the results and evidence that health outcomes are improved as a result of testing¹. These issues are not limited to tumors, but reflect questions about how to best use—and pay for—new genetic tests, which are relatively expensive despite recent decreases in costs. These issues will only intensify as multigene tests are increasingly used and the NIH Precision Medicine Initiative moves forward with the goal of sequencing a large cohort of volunteers.

The rapid expansion in the availability of multigene tests presents challenges regarding how their costs will be covered. As with

other new technologies, a key determinant of whether and how multigene tests will be used is insurance coverage². Many questions remain about these tests’ clinical utility, but many providers are ordering them and thus payers are developing relevant coverage policies. However, currently no systematic registries of payer coverage policies for multigene tests exist that examine coverage across a full range of tests and conditions. Previous studies of coverage for genetic tests predate the specific policy challenges presented by multigene tests^{3,4}. As a result, debates on the topic of multigene test coverage have not been informed by systematic analyses of the current state of insurance coverage of these tests.

With a team of collaborators from multiple institutions (University of California, San Francisco; Tufts Medical Center, Boston; American Institutes for Research, Washington, DC; and the Center for Business Models in Healthcare, Chicago) and funding from the US National Human Genome Research Institute, we have developed an in-house payer coverage policy registry called the University of California San Francisco Center (UCSF) for Translational and Policy Research on Personalized Medicine (TRANSPERS) Payer Coverage Policy Registry. Currently, this registry is not publicly available, but we welcome research collaborations. The registry structure was developed based on a comparative analysis with other registries and input from stakeholders (**Supplementary Methods**). In this context, we define multigene tests as tests that analyze multiple genes by next-generation sequencing or chromosomal microarray analysis, with the resulting test report providing multiple results, not an algorithmic score. The registry includes data on what multigene tests are included in policies, whether multigene tests are covered (“medically necessary”) or not covered (“experimental and/or investigational”), and the evidence cited and rationales for coverage decisions. We report here on coverage across payers and

conditions; other analyses have examined coverage for panels including *BRCA1/2* (ref. 5), coverage of non-invasive prenatal screening tests⁶, and the evidence cited in coverage decisions⁷.

Our initial version (Version 1.0) of the registry includes publicly available national policies from the five largest US private (commercial) payers, representing 112 million enrollees⁸, though these policies do not necessarily reflect regional policies pertaining to particular benefit designs of states, unions, or individual private companies. (To our knowledge, it would be unlikely that such policies would single out multigene tests for separate coverage.) Policies current as of June 2015 were systematically coded by two authors (M.P.D. and P.A.D., with review by a third author K.A.P.) (**Supplementary Methods**). As noted previously⁹, policies are context-specific and thus we classified tests into the following categories: tumor profiling; inherited disease testing for neurologic, cancer, cardiovascular, or biochemical disorders; drug metabolism testing; whole exome or whole genome sequencing; and prenatal testing or carrier testing (**Table 2**). Policies discuss multigene tests using either a general description for the type of panel (e.g., “cancer susceptibility testing”) or a specific brand name (e.g., “BreastNext”). Tests may be included (‘mentioned’) or not included in a policy. When included, tests can be determined to be covered or not covered. Thus, some tests may have unknown coverage because they are not included or mentioned in a policy. Tests were placed into one of three mutually exclusive categories.

1. Covered when mentioned. Test is covered for at least one indication in that policy and not specifically excluded in any other policy. Multigene tests within the same policy that were covered for some clinical indications but not others were coded as “covered.”
2. Not covered when mentioned. Not covered in any policies that specifically mention the test.

Table 1 Multigene test policy coverage by payer

Payer ^a	Number of policies	Number of tests within policies	Percentage of policies covering all included tests	Percentage of policies covering none of included tests	Percentage of policies covering some but not all included tests
Payer no. 1	7	48	43	29	29
Payer no. 2	15	116	13	60	27
Payer no. 3	4	40	25	25	50
Payer no. 4	15	54	13	73	13
Payer no. 5	14	55	29	36	36
Total	55	313	22	51	27

^aWe provide links in **Supplementary Table 3** to the raw data on which the payers' identities can be obtained, but we made the decision for all papers published using the registry ($N = 5$) that we would not name payers directly in tables.

3. Mixed coverage. Explicitly covered in at least one policy but not covered in at least one other policy.

We did not attempt to combine tests by, for example, combining brand name tests with the comparable general test descriptors. Rather, we listed test names as they are listed in the policies. Policies may list the general test name or the brand name or both (**Table 2**). Therefore, because test names listed in policies can be duplicative, we did not calculate the percentage of multigene tests covered.

Fifty-five policies include multigene tests ($n = 313$ tests; **Table 1**). Of these policies, 27% included tests across multiple test categories. The remaining policies focused on specific test categories, with the most common being policies focusing on inherited cancer risk assessment (20%), prenatal testing (13%), and inherited cardiovascular risk assessment (11%) (**Supplementary Fig. 1**). The number of tests included in each policy ranged from 1 to 27.

We found that 51% of policies covered none of the multigene tests specifically noted in the given policy, 22% covered all of the tests in the policy, and 27% covered some but not all of the tests in the policy (**Table 1**). Across policies, most test categories had multigene tests that were covered as well as tests that were not covered (**Table 2** and **Supplementary Table 2**). The exceptions were multigene tests for drug metabolism, whole exome sequencing, and whole genome sequencing, which were not covered in any policies.

Analyses of coverage patterns (**Table 2** and **Supplementary Table 2**) indicate that covered tests are typically those for specific conditions, genes, and populations where there is a base of synthesized evidence supporting genetic testing for that condition (e.g., guidelines), for example, tests for inherited neurological and cardiovascular conditions and prenatal tests are more often covered. For instance, targeted tumor

profiling multigene tests for specific cancer types (myelodysplastic syndromes and non-small cell lung cancer tests with 5–50 genes) are covered by some payers; multigene tests specific to Lynch syndrome, hypertrophic cardiomyopathy, and long QT syndrome are often covered by payers for specific populations. Conversely, tests that are not covered are typically those for broad indications and/or tests that include large or undefined numbers of genes (e.g., multi-syndromic cancer risk testing panels).

We find particularly interesting those tests that are covered in at least one policy but not covered in at least one other policy (**Table 2**, last column). Testing categories that exhibited coverage variation were tumor profiling ($n = 1$ test), inherited disease testing for neurological disorders ($n = 6$ tests), inherited disease testing for cardiovascular disorders ($n = 11$ tests), inherited disease testing for biochemical disorders ($n = 3$ tests), and prenatal testing ($n = 5$ tests). As an example, multigene tests for inherited breast and ovarian cancer risk and tests for hypertrophic cardiomyopathy are covered by some payers but not by others.

Supplementary Table 2 illustrates variation in how similar multigene tests were listed and covered in policies. For example, in one policy a panel to determine whether a thyroid nodule is benign or malignant was covered as a brand name test (ThyGenX), whereas in another policy it was not covered when listed as a general test (“analysis of thyroid nodule fine needle aspiration using multigene tests”), although the brand name test can be assumed to fall into this general test category. Multigene tests for the general category of “hereditary hearing loss” are covered in all policies that mention them, but the more specifically listed tests (“non-syndromic hearing-loss testing multigene tests using multigene NGS [next-generation sequencing] sequencing tests”) are not covered in all policies.

The results in **Supplementary Table 2** also suggest which test characteristics contribute to coverage decisions. One distinguishing characteristic is the number of genes included and the scope of the test (e.g., one payer covers targeted solid organ genomic sequencing multigene tests to test for non-small cell lung cancer when the panel includes 5–50 genes, but not a pan-cancer test that includes 315 genes (FoundationOne)). Another distinguishing characteristic is the population being tested. For example, although a panel, such as MaterniT21 (for non-invasive prenatal screening of pregnant women for fetal aneuploidies) is in the “covered” column, this coverage is for high-risk pregnancies and not necessarily for all indications (e.g., average risk pregnancies).

In summary, whereas some multigene tests are covered by payers, most are not covered, and how tests are addressed in policies varies. Our results are consistent with previous studies showing that genetic tests as a group are often not covered^{3,4}. However, the growing use of multigene tests appears to have prompted an increase in the number of policies covering such tests (e.g., a 2012 review found 41 policies on genetic tests as a whole from ten payers³, whereas we found 55 policies related specifically to multigene tests from only five payers).

The variation in how tests are addressed is unsurprising, given the complexities in multigene testing. Although payers evaluate multigene tests similarly to single-gene tests, using a framework based on analytical and clinical validity and clinical utility, we found in prior work that coverage policies for multigene tests are inherently more challenging for payers than policies for single-gene tests. Multigene tests do not fit the standard testing paradigm where a single (validated) marker provides a single (clinically useful) test result. For example, 80% of payers interviewed stated that the inherent characteristics of tumor sequencing, which provides multiple results and includes novel and often unvalidated markers, challenge the standard definition of ‘medical necessity’ required for coverage¹⁰. Although the intent of our study was exploratory research, and we did not test hypotheses, we found that several test characteristics—the number of genes included, the scope of the test, and the population being tested—appear to be associated with coverage and will thus be examined in future research.

These findings have important policy implications. First, ongoing, systematic analyses of coverage policies are needed

Table 2 Coverage of multigene tests (based on test names as listed in coverage policies; *n* = 55 policies)

Testing category	Tests covered whenever mentioned in policies	Tests not covered when mentioned in policies	Tests covered in at least one policy but not covered in at least one other policy
Tumor profiling	3	19	1
Inherited neurological disease testing (e.g., developmental delays, hearing loss, Parkinson's, X-linked disorders)	11	14	6
Inherited cancer testing	8	20	3
Inherited cardiovascular disease testing	13	16	11
Inherited metabolic/biochemical disease testing	1	11	3
Drug metabolism testing (pharmacogenomics)	0	25	0
Whole exome sequencing	0	9	0
Whole genome sequencing	0	5	0
Prenatal testing	12	4	5
Carrier testing	1	5	0

to provide objective evidence to improve understanding of policies and payer decision-making. Creating a registry, such as USCSF TRANSPERS Payer Coverage Policy Registry, can provide an objective unbiased research tool for organizations (e.g., academics, test developers, payers) to examine coverage policies across conditions or tests, with an ultimate goal of facilitating greater transparency and predictability in payer coverage decision-making as new technologies emerge^{10–13} (see **Supplementary Table 3** for a list of other resources). Given the increase in multigene test use and the importance of coverage for successful adoption of the tests and equitable access, it will be important to continue to systematically review coverage policies as they evolve. Policies often change and our data only reflect policies as of June 2015. Since then, several changes in coverage have already occurred: a payer now covers Foundation Medicine's (Cambridge, MA, USA) tumor profiling panel for patients with metastatic stage IV non-small-cell lung cancer¹⁴, and another payer has issued a policy covering whole exome sequencing when a patient meets all of a detailed list of criteria¹⁵.

A second policy implication is that registries and other types of structured reviews are needed that systematically summarize coverage policies, given that these policies are complex and thus difficult to assess without a structured database. Our findings illustrate how payers present information differently in their policies; for example, payers use general test names

as well as brand names, which make it difficult to determine exactly what tests are covered. Similarly, because payers often add multigene test panels to pre-existing coverage policies, policies often include a range of genetic tests in the same policy. Another complexity is that policies do not always specify the genes or variants included, further complicating the assessment of test coverage. Lastly, the test names listed in policies are not comprehensive, as policies list only a subset of the total number of available multigene tests. A registry can be used to address these complexities by identifying evidence gaps, illuminating variation in payer policies and serving as the baseline (with updating on an annual basis) for future analyses of coverage-related research questions^{10–13}. Of particular interest for future research will be examining the impact of the recent change in CPT (current procedural terminology) coding policies on the use of specific, unique test codes for multigene tests, rather than 'code stacking' (the use of multiple CPT codes for reimbursement of a genetic test, which can result in wide variation in the charge for the same test in different laboratories and often prevents payers from understanding what exactly has been tested).

Our initial analyses have several limitations in terms of the size of our sample, lack of detail in reasons for coverage and on the specifics of individual multigene tests, the inherent limitations of published policies (which do not discuss all of the factors that determine coverage and

which—due to test complexity—require judgment in interpreting the data) and information as to whether tests may be reimbursed even when not formally covered (coverage policies do not dictate payment). Going forward, we intend to add more private payers as well as regional and public payers to our data set; add variables that will enable detailed analyses of reasons for coverage decisions; conduct in-depth analyses of specific multigene tests; and update the results and analyzing policies over time.

In conclusion, coverage and reimbursement of new genetic tests has often been cited as a key requirement for their adoption. Our study provides the first systematic review focusing on coverage of multigene tests to better inform discussions about this issue.

Editor's note: This article has been peer-reviewed.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.3912).

Data availability statement. Data are available from the corresponding author upon reasonable request.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Some of the ethical issues that arise with this technology are common to other technologies as well. This technology can capture sensitive data about users, which is easily shared on social media, for example, or used by employers in health incentive programs. The perceived casualness of the technology may not elicit appropriate concern for data confidentiality and may contribute to problematically low levels of privacy and confidentiality¹.

Poor comprehension of medical consent forms is also a long-standing issue^{2–4} that, if done ineffectively, may be exacerbated by this technology⁵. Specifically, users may not understand that while the primary goal of generating and collecting the data may be clinical, physicians are permitted to share data for research purposes⁶. This raises issues concerning de-identified but linked electronic health records in the context of patient preferences and incidental findings^{7,8}.

As the above issues have already been discussed elsewhere in the literature^{1–5,7,8}, we now turn to three ethical areas in which this technology presents both the most serious concerns and the greatest opportunities.

Consent and engagement

As noted above, consent may be problematic with mobile health technology. However, it also provides new opportunities to transform the process of acquiring consent from a one-way street to an interaction that promises more robust informed consent. Traditionally, information is dumped into a static, difficult-to-digest paper format that largely goes unread. This technology allows more media options (e.g., images and videos) and creates the opportunity for dynamic interaction between researchers and participants, or clinicians and patients. Through quizzes, participants can be tested on their knowledge. Games can be used to convey relevant concepts. Prompts can pop up and be specific to current situations so that participants receive information when they are primed for it. Links can be provided for participants to selectively delve deeper into issues that interest them. Studies suggest that multimedia aids using visual metaphors convey more information regarding consent than text alone⁹ and that users are willing to provide consent in non-traditional ways¹⁰. Further research is needed to determine whether participants consider digital consent forms to carry the same authority as paper ones.

Some research projects are already employing this approach to informed consent through Apple's ResearchKit, such

Consent and engagement, security, and authentic living using wearable and mobile health technology

To the Editor:

Mobile health applications and wearable health technologies are becoming ubiquitous. Although such technology offers great promise for streamlining healthcare and empowering users in their pursuit of health and wellness, it also poses ethical challenges for clinical practice, research, and everyday living. Like any other biomedical technology, accuracy and reliability, informed consent, and privacy and confidentiality must be taken into account when designing and using mobile and wearable health and wellness technologies. But mobile health applications and wearables also pose additional ethical considerations that are important when implementing this technology. These are consent and engagement, security, and authentic living. Here, we identify these issues and provide recommendations for ameliorating any concerns that may arise with this technology. Overall, we argue that for an appropriately informed and engaged user, this technology can provide great benefits, and burdens can be mitigated.

Although wrist-worn activity trackers are probably the best-known kind of wearable technology, such devices are only one part of a larger system of mobile health and wellness technologies that includes smartphones and tablets, as well as ingestibles and even clothing. Defining wearable technology is increasingly difficult; for a broad sample of technologies that we consider to be within the scope, see **Table 1**. Although

some wearable devices (e.g., Fitbit) can be used as stand-alone units, the vast majority is integrated with mobile apps, websites, or computer software that allow users to process and visualize generated data. Moreover, the fact that many individuals always carry their smartphones with them means that smartphones themselves may be used to track behavior and are thus *de facto* wearable devices. Additionally, such platforms as Apple's HealthKit, which can be accessed via one's smartphone, tablet or computer, allow users to combine the data from an array of devices and apps. Given the inextricable relationship between the various elements of these health and wellness technology systems, it is useful, for an initial ethical analysis at least, to group these modalities together. In the interest of brevity, we refer to this class of objects jointly as 'mobile health technology'. In what follows, we map out the ethical promises and challenges of the potential widespread healthcare and wellness uses of these technologies.

There are three salient usage profiles for this technology: consumer-directed clinical, physician-mediated clinical, and research use (**Box 1**). Each of these uses poses different ethical issues. For example, in a clinical setting, inaccurate measurements or unreliable devices may result in useless or harmful medical advice; in the research context, remote usage of the technology may complicate researcher oversight.