Title
EXAMINING EVIDENCE IN U.S. PAYER COVERAGE POLICIES FOR MULTI-GENE PANELS AND SEQUENCING TESTS

Journal
International Journal of Technology Assessment in Health Care, 33(4)

ISSN
0266-4623

Authors
Chambers, James D
Saret, Cayla J
Anderson, Jordan E
et al.

Publication Date
2017

DOI
10.1017/s0266462317000903

Peer reviewed

International Journal of Technology Assessment in Health Care, 33:4 (2017), 534–540.

doi:10.1017/S0266462317000903

EXAMINING EVIDENCE IN U.S. PAYER COVERAGE POLICIES FOR MULTI-GENE PANELS AND SEQUENCING TESTS

James D. Chambers
Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Tufts University School of Medicine
jchambers@tuftsmedicalcenter.org

Cayla J. Saret
Jordan E. Anderson
Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center

Patricia A. Deverka
American Institutes for Research, Department of Research and Evaluation

Michael P. Douglas
University of California at San Francisco, Department of Clinical Pharmacy

Kathryn A. Phillips
University of California at San Francisco, Department of Clinical Pharmacy
UCSF Philip R. Lee Institute for Health Policy and UCSF Helen Diller Family Comprehensive Cancer Center

Objectives: The aim of this study was to examine the evidence payers cited in their coverage policies for multi-gene panels and sequencing tests (panels), and to compare these findings with the evidence payers cited in their coverage policies for other types of medical interventions.
Methods: We used the University of California at San Francisco TRANSPERS Payer Coverage Registry to identify coverage policies for panels issued by five of the largest US private payers. We reviewed each policy and categorized the evidence cited within as: clinical studies, systematic reviews, technology assessments, cost-effectiveness analyses (CEAs), budget impact studies, and clinical guidelines. We compared the evidence cited in these coverage policies for panels with the evidence cited in policies for other intervention types (pharmaceuticals, medical devices, diagnostic tests and imaging, and surgical interventions) as reported in a previous study.
Results: Fifty-five coverage policies for panels were included. On average, payers cited clinical guidelines in 84 percent of their coverage policies (range, 73–100 percent), clinical studies in 69 percent (50–87 percent), technology assessments 47 percent (33–86 percent), systematic reviews or meta-analyses 31 percent (7–71 percent), and CEAs 5 percent (0–7 percent). No payers cited budget impact studies in their policies. Payers less often cited clinical studies, systematic reviews, technology assessments, and CEAs in their coverage policies for panels than in their policies for other intervention types. Payers cited clinical guidelines in a comparable proportion of policies for panels and other technology types.
Conclusions: Payers in our sample less often cited clinical studies and other evidence types in their coverage policies for panels than they did in their coverage policies for other types of medical interventions.

Keywords: Payer coverage policies, Evidence, Multi-gene panels and sequencing tests

Advancements in whole-genome sequencing (determining the complete DNA-sequence of the human genome), whole-exome sequencing (determining the DNA-sequence of the protein coding regions of the genome), and multi-gene panel sequencing (determining the DNA sequence of multiple genes simultaneously) increasingly allow for an individual's health care to be tailored to their unique genetic makeup (see Table 1 for definitions of pertinent terminology). This personalized diagnostic model approach has been heralded as a new dawn in medicine and health care (1;2). In his 2015 State of the Union address, President Obama announced the creation of the Precision Medicine Initiative, which has the goal of improving health and treating disease in part through leveraging advances in genomics (3). In 2016, the National Institutes of Health received $200 million for the Precision Medicine Initiative, and in the same year, Congress enacted the 21st Century Cures Act, which authorized $4.8 billion over 10 years to advance, among other initiatives, the Precision Medicine Initiative (4;5).

Genomic sequencing tests can provide high-speed analysis of a person's genome and generate information to aid clinical diagnosis and prognosis by detecting gene variants in asymptomatic patients and identifying the genetic origins of pre-existing symptoms (6–8). In oncology, genomic sequencing increasingly allows a patient's treatment to be tailored to the genetic characteristics of cancer cells (9).

Payer coverage policies play a key role in the adoption of medical technologies and their diffusion into health care. Studies have found that payer coverage of precision medicine technologies can be inconsistent, with some technologies covered by some payers, but not by others (10;11). To date, payers have most often provided coverage for "single gene/actionable result" testing, for example, cystic fibrosis testing. In contrast, coverage of multi-gene panels, for example, some tests for hereditary breast and ovarian cancers (termed "panels" for brevity), has been largely inconsistent because these panels contain low and moderate risk genes that do not

Table 1. Definitions

Term	Definition
Precision medicine	Using information about an individual's genetic make-up, lifestyle and environment to prevent, diagnose or treat disease.
Multi-gene panel	Tests that analyze multiple genes through next generation sequencing with the resulting test report providing multiple test results.
Single-gene test	Tests that analyze the DNA sequence of a single gene.
Whole-exome sequencing	Determines the genetic sequence of all the protein coding regions of a person's genome (~1% of the genome).
Whole-genome sequencing	Determines the genetic sequence of an individual's entire genome, ~ 3 billion nucleotides.
Clinical utility	Whether use of the test leads to a change in medical management and a change in patient health outcomes.
Clinical validity	How consistently and strongly the genetic variants identified by the test relate to the presence, absence or risk of a specific disease.

Precision medicine: https://ghr.nlm.nih.gov/primer/precisionmedicine/definition
Multi-gene panel: https://www.cancer.gov/publications/dictionaries/genetics-dictionary?cdrid=763019
Single-gene test: https://ghr.nlm.nih.gov/primer/testing/genetictesting
Whole exome-sequencing: http://www.nature.com/jhg/journal/v59/n1/full/jhg2013114a.html
Clinical utility: http://www.cdc.gov/genomics/hugenet/file/print/pub_clincalUtility.pdf
Clinical validity: https://ghr.nlm.nih.gov/primer/testing/validtest

have consensus management guidelines for clinical follow-up (12).

Various reasons for inconsistent coverage have been suggested, including insufficient evidence of clinical validity and utility that prevents payers from judging whether a panel meets payers' standards of medical necessity (6;11;13;14). Furthermore, because genetic panels may include a combination of unvalidated gene sequences, that is, gene sequences that require clinical studies to determine their utility in a clinical setting, and validated genes, that is, gene sequences that can be used to make therapeutic decisions, the payer may determine the entire panel to be "investigational" (15). It has been asserted that the inconsistent way in which these tests are covered has prevented the benefits of panels from being fully realized (1;16). A better understanding of the types of evidence payers review when formulating coverage policies for panels would make patients' access to these tests more predictable.

Our objective in this study was to examine the evidence that payers have cited in their coverage policies for panels. First, we determined whether payers cited specific types of evidence in their coverage policies for panels. Second, we compared the types of evidence payers cited in coverage policies for panels with the types of evidence cited in coverage policies for other intervention types: pharmaceuticals, medical devices, surgeries, and diagnostic tests and imaging.

METHODS

Development of the TRANSPERS Payer Coverage Policy Registry

The starting point for this research was the TRANSPERS Payer Coverage Policy Registry©. The TRANSPERS Payer Coverage Policy Registry© systematically synthesizes payer coverage policies on panels to assess which panels are covered by payers, what factors relevant to coverage decisions are discussed in policies, and how coverage policies vary. The TRANSPERS Payer Coverage Policy Registry© was developed with a team of collaborators from multiple institutions (University of California at San Francisco, Tufts Medical Center, American Institutes for Research, and Center for Business Models in Healthcare), with funding from the National Human Genome Research Institute (R01HG007063) (17). The TRANSPERS Payer Coverage Policy Registry© is a copyrighted product based on proprietary methods; the developers of the Registry do not own copyright on the policies.

The Registry currently includes coverage policies relevant to whole genome sequencing, whole exome sequencing and gene panels. Gene panels in this context are defined 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 panels and testing indications are reviewed, whether panels are covered or not covered, and the evidence and rationale for coverage decisions cited in the policy (20).

The Registry structure was developed based on an extensive review of existing registries. In addition, the Registry was informed by ten semi-structured interviews with a stakeholder advisory group that included private and public payers, genetic laboratory representatives, medical genetics experts, genetic counselors, regulators, consultants, and pathologists (20).

The Registry currently includes policies from the five largest US private (commercial) payers, that is, health insurance companies that offer insurance to groups such as large employers or individuals, based on enrollment (18). These payers represent 112 million enrolled lives. Policies were coded as of

Table 2. Evidence Categories

Evidence category	Description of evidence type	Criteria for determining whether evidence of each type was present in the coverage policy
Clinical studies	Studies that evaluated the clinical validity or utility of the test being considered for coverage.	The coverage policy included at least one clinical study that assessed the clinical validity or utility of a panel test that was featured in the UCSF TRANSPERS Payer Coverage Registry©.
Systematic reviews or meta-analyses	Studies that summarize the results of randomized controlled trials (and often other types of clinical study) to provide a high level of evidence on the effectiveness of an intervention. Meta-analysis is a quantitative procedure to combine data from multiple studies that is often performed as a component of a systematic review.	The coverage policy included at least one systematic review or meta-analysis pertaining to a panel that was featured in the UCSF TRANSPERS Payer Coverage Registry©.
Technology assessments	Multidisciplinary assessments of a technology that may encompass evidence of safety, clinical efficacy, effectiveness, cost, and cost-effectiveness, with the primary purpose of informing regional or national health care decision making.	The coverage policy included at least one technology assessment pertaining to a panel that was featured in the UCSF TRANSPERS Payer Coverage Registry©.
Cost-effectiveness analyses	An analysis of the relative costs and health benefits of competing interventions.	The coverage policy included at least one cost-effectiveness analysis of a panel that was featured in the UCSF TRANSPERS Payer Coverage Registry©.
Budget impact analyses	An assessment of the budgetary implications of introducing an intervention into a health care setting.	The coverage policy included at least one budget impact analysis of a panel that was featured in the UCSF TRANSPERS Payer Coverage Registry©.
Clinical guidelines	Recommendations typically issued by large clinical organizations intended to optimize patient care.	The coverage policy included at least one clinical guideline that provided recommendations on the use of panels in the optimization of patient care. The clinical guideline did not necessarily need to address a panel from the UCSF TRANSPERS Payer Coverage Registry directly©.

UCSF, University of California at San Francisco.

June 2015. Each payer's website was searched using the terms "Genetic Test," "Sequencing," or "Panel" to identify applicable policies. All coverage policies were then obtained from the payers' web sites. Within each policy, information about the policy and each panel found within the policy was coded. The coverage policy was the unit of analysis. Data were coded in Microsoft Excel by two trained coders who independently coded data and convened to resolve any discrepancies. Full details on the development of the TRANSPERS Payer Coverage Policy Registry© can be found elsewhere (17). The database has been used previously to evaluate trends in coverage of multi-gene panels (19–22).

Study Objective 1: To Examine the Evidence Cited in Coverage Policies for Panels

All coverage policies for panels included in the TRANSPERS Payer Coverage Policy Registry© were included in this research. We reviewed all coverage policy documentation present in the registry to determine the types of evidence the payers cited. We categorized the evidence using the following categories: clinical evidence, systematic literature reviews or meta-analyses, technology assessments, cost-effectiveness analyses, budget impact studies, and clinical guidelines (Table 2).

A trained researcher read each coverage policy in full to determine if studies of each evidence type were cited or discussed. When a pertinent citation was identified, the researcher obtained and reviewed it to determine if it met the inclusion criteria presented in Table 2. Each evidence source was considered to determine if it pertained to a panel. When the study title was insufficient to make this judgment, the study abstract (and if necessary the full article) was reviewed. We reported whether at least one of each evidence type pertaining to a panel in the Registry appeared in each coverage policy. Then, we reported the proportion of each payer's coverage policies in which at least one of each evidence type was cited.

Study Objective 2: To Compare the Evidence Cited for Different Types of Interventions

We compared the evidence that the payers cited in their coverage policies for panels with the evidence the payers cited

Table 3. Types of Evidence That Payers Cite in Coverage Policies for Multi-gene Panels and WGS/WES[a] Tests

Payer	Number of policies	Percentage of coverage policies in which one or more of each evidence type was cited					
		Clinical studies	Systematic reviews/ meta-analyses	Technology assessments	Clinical guidelines	Budget impact analyses	Cost-effectiveness analyses
Payer 1	7	71%	71%	86%	86%	0%	0%
Payer 2	15	87%	27%	40%	73%	0%	7%
Payer 3	14	50%	36%	50%	100%	0%	7%
Payer 4	4	75%	50%	50%	75%	0%	0%
Payer 5	15	67%	7%	33%	80%	0%	7%
Average		69%	31%	47%	84%	0%	5%

[a]Whole genome sequencing or whole exome sequencing.

in their coverage policies for other types of intervention using an existing dataset developed for a separate research study conducted at the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center (23). In this separate research study, we reviewed the coverage policies for medical interventions issued by the eighteen largest private payers (18). Also in this research, we reviewed all coverage policies issued by the included payers and identified the six pharmaceuticals, medical devices, diagnostic tests and imaging, and surgical interventions, for which the payers most often issued coverage policies. We included six interventions of each intervention type to ensure that each intervention type was adequately represented across payers.

We reviewed the coverage policies for these interventions and reported whether the payers cited evidence for each intervention using the same method outlined in study objective 1. In other words, we determined whether the payer cited at least one of the evidence types discussed above, that is, clinical evidence (e.g., randomized controlled trials), systematic literature reviews or meta-analyses, technology assessments, cost-effectiveness analyses, budget impact studies, and clinical guidelines, in their coverage policies. The interventions included in study objective 2 are listed in Supplementary File 1. Coverage policies were current as of August 2014.

For the current study, we considered the coverage policies issued by the same payers we considered in study objective 1, that is, the five largest U.S. private (commercial) payers, for the six interventions of each type of intervention. We determined whether the payer cited each type of evidence in each of the considered pharmaceuticals, medical devices, diagnostic tests and imaging, and surgical interventions' coverage policies. We then determined the frequency that each payer cited each type of evidence. Lastly, we compared these frequencies with the frequency that payers cited each type of evidence in their coverage determinations for panels as determined in study objective 1.

RESULTS

Study Objective 1

At the time that this research was performed, the TRANSPERS Payer Coverage Policy Registry© included fifty-five coverage policies. A single coverage policy typically assessed multiple different panel tests. Across the fifty-five included coverage policies the payers judged coverage of 313 panels. We found that different types of evidence were cited in the coverage polices with different frequencies. Clinical guidelines were cited in the largest percentage (84 percent) of coverage polices; the payer that most frequently cited clinical guidelines did so in 100 percent of their policies, the payer that least frequently cited clinical guidelines did so in 73 percent of their policies (Table 3).

Cost-effectiveness analyses and budget impact studies were the study types that were least often cited in the coverage policies; no payer cited budget impact studies in their coverage policies, but three of the five payers cited a cost-effectiveness analysis in a single coverage policy (an average of 5 percent of coverage policies across all five payers; range, 0–7 percent).

On average payers cited clinical studies in 69 percent of their coverage policies (range, 50–87 percent). We found notable variation among the payers in the frequency that technology assessments and systematic reviews and meta-analyses were cited in coverage policies. On average payers cited technology assessments in 47 percent of their coverage policies (range, 33–86 percent), and systematic reviews or meta-analyses in 31 percent of their coverage policies (range, 7–71 percent).

Study Objective 2

Compared with their coverage policies for the other types of interventions (pharmaceuticals, medical devices, diagnostic tests and imaging, and surgical interventions) payers less often cited clinical studies, systematic reviews, technology assessments,

Table 4. Comparison of the Types of Evidence Payers Cited in Coverage Policies for Multi-gene Panels and WGS/WES[a] Tests with Other Technology Types

Intervention type	Number of policies	Percentage of coverage policies in which one or more of each evidence type was cited					
		Clinical studies	Systematic reviews/ meta-analyses	Technology assessments	Clinical guidelines	Budget impact analyses	Cost-effectiveness analyses
Pharmaceuticals	26	92%	46%	42%	77%	0%	19%
Medical devices	25	100%	84%	88%	96%	0%	32%
Diagnostic tests and imaging	22	95%	59%	68%	86%	0%	18%
Surgical Interventions	25	92%	56%	68%	64%	4%	8%
Multi-gene panels and sequencing tests	55	69%	31%	47%	84%	0%	5%

[a]Whole genome sequencing or whole exome sequencing.

and cost-effectiveness analyses in their coverage policies for panels (Table 4). Payers cited clinical guidelines in a similar proportion of their coverage policies (84 percent) for panels as they did in their coverage policies for other technology types. Budget impact studies were only cited in coverage policies for surgical interventions.

DISCUSSION

Rapid advances in panels are transforming our ability to identify and manage various diseases and disorders that result from clinically significant gene variants. It has been argued, however, that advances in sequencing technology have outpaced our ability to integrate the information gleaned from such assays into health care (1;21;24;25). The speed with which sequencing technologies have allowed genetic testing to shift from single gene analysis to multi-gene panels is indicative of this trend.

Payer coverage is fundamental in guiding how medical technologies are used in clinical practice and ultimately what technologies patients have access to (26). To date, coverage of genetic tests has been inconsistent, with some payers covering a particular test but other payers not (10;11). This inconsistency creates confusion for patients and clinicians as to who has access to these tests and how they are used in clinical practice. Researchers have called for greater transparency in payer coverage policies for panels as a means to reduce this confusion (15;26).

We examined the evidence that payers cite in their coverage policies for panels and found that payers did not cite clinical studies in more than one quarter of policies. We also found that the included payers less often cited systematic reviews, technology assessments, and cost-effectiveness studies in coverage policies for panels than they did in their coverage policies for other intervention types. This finding is consistent with the literature describing the lack of available evidence analyzing the clinical validity and utility of panels (13;15;21;27). Furthermore, regulatory approval for panels does not have the same evidentiary requirements as the approval pathways for drugs and, to varying degrees, medical devices (28). We also found that in comparison to other types of interventions payers less often cited systematic reviews, technology assessments, and cost-effectiveness studies. This finding is also expected given that these evidence types are contingent on availability of sufficient contributing clinical evidence.

Notably, we found the category of evidence most often cited in the coverage policies for panels were clinical guidelines. Clinical guidelines are typically formulated through a combination of the available clinical evidence and expert clinical opinion. The frequent citation of clinical guidelines in coverage policies for panels may indicate that in the absence of sufficient supporting clinical evidence, prevailing clinical opinion plays a larger role in payer decision making for these technologies than it does for other intervention types (13). Alternatively, it may be that because guidelines cite the clinical evidence on which they are based, payers that cite the guidelines do not additionally cite the same clinical evidence. Research that evaluates the composition of clinical guidelines cited in coverage policies for panels, and the role of guidelines in decision making, would be valuable.

Study Limitations

This study has several limitations. As we include only five of the largest private payers, it is unclear whether study findings have any generalizability to small- or medium-sized private payers. Furthermore, it is uncertain whether our analysis of U.S. private payers has any generalizability to public payers in the United States, for example, Medicare and Medicaid. Furthermore, the included sample was insufficient for us to perform more rigorous statistical testing of the data and drawing more firm conclusions. In the future, we plan to repeat the analysis with a larger and broader set of interventions.

We assume that the payers comprehensively cite the evidence that they review in their coverage policies. However, it may be that some payers do not disclose all the information that they review. Furthermore, in regard to cost-effectiveness

analyses and budget impact studies, it may be that payers perform their own analyses that they do not report in their coverage policies.

Because we did not assess the prevalence of relevant, high quality clinical evidence for multi-sequence panels, we were unable to determine how comprehensively payers report reviewing the available evidence in their coverage policies. Future research should evaluate how comprehensively payers cite the available relevant evidence for multi-sequence panels and to examine reasons for identified discrepancies, for example, whether payers choose to review only clinical evidence of sufficient quality.

While we determined whether coverage policies included any evidence of each type, we did not account for the frequency that each evidence type was reviewed. We do not account for the fact that payers may weigh different types of evidence differently in decision making, or may base their decisions on a different evidence base.

We report the frequency that the payers report at least one study of each type, rather than the total number of studies of each type that the payers report. This approach prevented us from comparing the volume of evidence that the payers reported reviewing in their coverage policies.

To compare the evidence cited in coverage policies for panels with the evidence cited in coverage policies for other types of interventions we relied on a dataset developed for a separate research study. While the included payers and the used methodologies were consistent between the two datasets, the coverage policies in the second dataset were not as recent as those in the first (August 2014 *vs*. June 2015).

Looking Forward

Genetic testing poses the healthcare system a particular challenge. While offering great promise to improve patient care, health outcomes, and disease prevention, it has been asserted that the lack of evidence demonstrating clinical validity and utility of panels has prevented society from reaping the benefits from the advancing technology (29). Generating evidence of clinical validity and utility for panels has documented difficulties (14). For instance, the long-term clinical data required to confirm that the tests accurately predict disease are typically unavailable to payers making coverage decisions. Also, because many of the genetic variants that sequencing tests are designed to detect are rare, it is challenging to design clinical trials of a sufficient size. Furthermore, improving our understanding of the full range of gene variants identified by panels will be a long-term process and will require widespread use of genomic testing over a period of many years (28;30). While our study addresses only U.S. payer coverage of panels, these highlighted challenges are relevant to payers and other health care decision makers in Europe and elsewhere.

Innovative approaches are required to generate evidence of clinical utility and validity while providing patients reasonable and appropriate access to these technologies. One approach would be to use coverage with evidence development (CED) policies similar to that used by the Centers for Medicare and Medicaid Services, the agency that administers the Medicare program (the federal health insurance program for people who are disabled, have end-stage renal disease and are aged 65 or older), in its national coverage determination for pharmacogenomic testing for warfarin response (31). In CED policies, patients gain access to a technology contingent on their enrollment in an approved registry or clinical study. The intention is that the evidence generated from the registry or clinical study can be used to inform future coverage determinations.

A recent study found that Noninvasive Prenatal Testing associated with good evidence of clinical validity and modeled evidence of clinical utility were rapidly covered by payers (30). However, more research is needed to understand the quality of the current evidence base supporting panels and how rapidly evidence of clinical validity and utility become available once a panel is marketed.

Clarity with respect to the payers' evidence requirements is required. An understanding of what kind of clinical and economic studies payers require would increase the efficiency of evidence generation and the predictability of coverage and patient access. There are several initiatives that are currently facilitating this discussion and are seeking to set evidence standards for panels. For instance, the Molecular Evidence Development Consortium (MED-C) is a U.S.-based nonprofit group that among its goals aims to bring together stakeholders and encourage the collection of high quality evidence and the provision of advanced molecular diagnostics to patients (32). The Green Park Collaborative is a multi-stakeholder collaborative with the goal of creating a consensus on the evidence needed to inform both clinical and payment decisions. One of the Collaborative's aims is to develop methodological guidance and evidence standards for next generation sequencing tests for cancer diagnosis and treatment (33). A goal of the MolDX Program administered by Palmetto GBA, a Medicare administrative contractor, is to establish clinical utility standards for next generation sequencing technologies (34). Among the MolDX Program's functions is to perform technology assessments to determine clinical utility and to establish reimbursement of NGS technologies for the regions under its purview.

CONCLUSIONS

Our findings suggest that the types of evidence payers cite in their coverage policies for panels differ from those they cite in their coverage policies for other types of intervention. We found that payers in our sample less often cited clinical studies and other evidence types in their coverage policies for panels than they did in their coverage policies for other types of medical interventions.

SUPPLEMENTARY MATERIAL

Supplementary File 1:
https://doi.org/10.1017/S0266462317000903

CONFLICTS OF INTEREST

Chambers reports Other from Boehringer Ingelheim, Other from Astellas Pharma, Other from Sanofi-Aventis, and Other from Baxter, outside the submitted work. Saret reports grants from the NIH during the conduct of this study. Authors Anderson, Deverka, Douglas, and Phillips have nothing to disclose.

REFERENCES

1. Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Genet Med*. 2011;13:499-504.
2. Dotson WD, Bowen MS, Kolor K, Khoury MJ. Clinical utility of genetic and genomic services: context matters. *Genet Med*. 2016;18:672-674.
3. President Barack Obama. State of the Union Address. 2015 January 20 [cited 2017 February 28]. https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative (accessed February 28, 2017).
4. Consolidated Appropriations Act, 2016, H.R.2029. Public Law No: 114-113. December 18, 2015. https://www.gpo.gov/fdsys/pkg/CPRT-114HPRT98369/pdf/CPRT-114HPRT98369.pdf (accessed June 5, 2017).
5. House Energy & Commerce Committee. H.R.34 - 21st Century Cures Act. Public Law No: 114–255, December 13, 2016. https://www.congress.gov/bill/114th-congress/house-bill/34 (accessed June 5, 2017).
6. Phillips KA, Trosman JR, Kelley RK, et al. Genomic sequencing: Assessing the health care system, policy, and big-data implications. *Health Aff (Millwood)*. 2014;33:1246-1253.
7. Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A*. 2009;106:19096-19101.
8. Dewey FE, Grove ME, Pan C, et al. Clinical interpretation and implications of whole-genome sequencing. *JAMA*. 2014;311:1035-1045.
9. Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. *Genome Med*. 2015;7:80.
10. Hresko A, Haga SB. Insurance coverage policies for personalized medicine. *J Pers Med*. 2012;2:201-216.
11. Graf MD, Needham DF, Teed N, Brown T. Genetic testing insurance coverage trends: A review of publicly available policies from the largest US payers. *J Pers Med*. 2013;10.
12. Chakradhar S. Insurance companies are slow to cover next-generation sequencing. *Nat Med*. 2015;21:204-205.
13. Khoury MJ, Coates RJ, Evans JP. Evidence-based classification of recommendations on use of genomic tests in clinical practice: Dealing with insufficient evidence. *Genet Med*. 2010;12:680-683.
14. Khoury MJ, Berg A, Coates R, et al. The evidence dilemma in genomic medicine. *Health Aff (Millwood)*. 2008;27:1600-1611.
15. Trosman JR, Weldon CB, Kelley RK, Phillips KA. Challenges of coverage policy development for next-generation tumor sequencing panels: Experts and payers weigh in. *J Natl Compr Canc Netw*. 2015;13:311-318.
16. Deverka PA, Dreyfus JC. Clinical integration of next generation sequencing: coverage and reimbursement challenges. *J Law Med Ethics*. 2014;42(Suppl 1):22-41.
17. University of California San Francisco Department of Clinical Pharmacy. TRANSPERS Center for Translational and Policy Research on Personalized Medicine. March 2, 2016. http://pharm.ucsf.edu/transpers/node/5471 (accessed February 28, 2017).
18. Atlantic Information Services. Atlantic Information Services' Directory of Health Plans 2015. http://aishealth.com/marketplace/aiss-directory-health-plans (accessed February 28, 2017).
19. Trosman J, Weldon C, Douglas M, et al. Payer coverage of hereditary cancer panels: Barriers, opportunities, and implications for the precision medicine initiative. *J Natl Compr Canc Netw*. 2017:15:219-228.
20. Phillips KA, Deverka PA, Trosman JR, et al. Payer coverage policies for multigene tests. *Nat Biotechnol*. 2017;35(7):614–617.
21. Clain E, Trosman JR, Douglas MP, Weldon CB, Phillips KA. Availability and payer coverage of BRCA1/2 tests and gene panels. *Nat Biotechnol*. 2015;33:900-902.
22. Dervan AP, Deverka PA, Trosman JR, et al. Payer decision making for next-generation sequencing-based genetic tests: Insights from cell-free DNA prenatal screening. *Genet Med*. 2017;19:559-567.
23. Chambers JD, Chenoweth MD, Neumann PJ. Mapping US commercial payers' coverage policies for medical interventions. *Am J Manag Care*. 2016;22:e323-e328
24. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol*. 2015;1:943-951.
25. Swisher EM. Usefulness of multigene testing: Catching the train that's left the station. *JAMA Oncol*. 2015;1:951-952.
26. Wang G, Beattie MS, Ponce NA, Phillips KA. Eligibility criteria in private and public coverage policies for BRCA genetic testing and genetic counseling. *Genet Med*. 2011;13:1045-1050.
27. Messner DA, Al Naber J, Koay P, et al. Barriers to clinical adoption of next generation sequencing: Perspectives of a policy Delphi panel. *Appl Transl Genom*. 2016;10:19-24.
28. Evans BJ, Burke W, Jarvik GP. The FDA and genomic tests–getting regulation right. *N Engl J Med*. 2015;372:2258-2264.
29. Deverka PA, Messner DA, McCormack R et al. Generating and evaluating evidence of the clinical utility of molecular diagnostic tests in oncology. *Genet Med*. 2016;18:780-787.
30. Shirts BH, Jacobson A, Jarvik GP, Browning BL. Large numbers of individuals are required to classify and define risk for rare variants in known cancer risk genes. *Genet Med*. 2014;16:529-534.
31. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). August 3, 2009. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&bc=AgAAQAAAAAAA&ncdver=1 (accessed February 28, 2017).
32. Molecular Evidence Development Consortium (MED-C). Molecular Evidence Development Consortium (MED-C). March 2, 2016. https://med-c.org/ (accessed February 28, 2017).
33. Center for Medical Technology Policy. Green Park Collaborative (GPC-USA). March 2, 2016. Available from: http://www.cmtpnet.org/news-room/view/gpc-to-develop-evidence-standards-for-ngs-testing-oncology/ (accessed February 28, 2017).
34. Molecular Diagnostic Program (MolDX®). Palmetto GBA. May 2016. http://palmettogba.com/Palmetto/moldx.Nsf/files/MolDX_Manual.pdf/$File/MolDX_Manual.pdf (accessed February 28, 2017).