Genetics in Medicine (2025) 27, 101329

ELSEVIER

Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

SYSTEMATIC REVIEW

Payer perspectives on genomic testing in the United States: A systematic literature review

Julie Wiedower[1,2,*], Hadley Stevens Smith[3,4], Christopher L. Farrell[1], Veronica Parker[1], Laura Rebek[2], Stephanie Clark Davis[1]

[1]*Clemson University, School of Nursing, Clemson, SC;* [2]*Guardant Health, Redwood City, CA;* [3]*Precision Medicine Translational Research (PROMoTeR) Center, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA;* [4]*Center for Bioethics, Harvard Medical School, Boston, MA*

ARTICLE INFO

Article history:
Received 22 July 2024
Received in revised form
8 November 2024
Accepted 8 November 2024
Available online 15 November 2024

Keywords:
Clinical utility
Coverage decisions
Genomic testing
Payers
Systematic review

ABSTRACT

Purpose: Health care stakeholders' perspectives on the value of genomic testing vary widely and directly affect the access and practice of genomic medicine. To our knowledge, a review of US health care payers' perspectives on genomic testing has not been performed.

Methods: We conducted a systematic literature review of US payers' perspectives on genomic testing in the MEDLINE, PubMed, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Of the 161 nonduplicate records screened, we summarized findings from 20 included records, and using the framework method, common domains were recorded.

Results: Domains included clinical utility, coverage decision frameworks, potential harms, costs, paying for research, demand/pressure, the flexibility of outcomes considered, and personal utility. There was consensus on the definition of clinical utility as improved health outcomes, and the nuances of genomic testing were reported as challenging to fit within existing coverage decision frameworks. Perspectives varied on accepting broader outcomes or uses of genomic testing and whether costs influence coverage decisions. Study methodologies were heterogeneous.

Conclusion: A deeper understanding of how payers approach genomic testing may allow comparison with other stakeholders' perspectives and may identify challenges, opportunities, and solutions to align a conceptual and evidentiary framework better to demonstrate the value of genomic testing.

Introduction

The advancement of genomic testing technologies has led to a broad expansion and integration of genomic tests into clinical care within the US health system. As utilization has increased, the costs and complexities of genomic testing have prioritized this area for US health care payers. However, the approaches to coverage and reimbursement decisions have been inconsistent

*Correspondence and requests for materials should be addressed to Julie Wiedower, 24 Deerberry Forest Circle, Little Rock, AR 72211. *Email address:* jkaylor@guardanthealth.com

doi: https://doi.org/10.1016/j.gim.2024.101329

among plans and compared with the guidelines.[1,2] Payers manage health care service utilization through coverage policies. However, other forms exist, such as prior authorization, provider gold-carding (removing steps or barriers for providers from a particular specialty or practice group), and claims integrity audits. Private payers provide health insurance coverage for two-thirds of Americans and now administrate Medicare Advantage plans, albeit using Medicare coverage policies.[3] The coverage of genomic tests and services by payers has been a critical facilitator or barrier to patient access and provider utilization.[4,5] The coverage decisions and evidence cited within genomic coverage policies also vary, suggesting that payers use different methods of evidence assessment and criteria.[6]

A fundamental limitation to the uptake of genomic testing is the challenge of collecting evidence demonstrating value to health care stakeholders, such as payers.[7] Porter describes value in health care as health outcomes achieved relative to costs.[8] There are nuances among stakeholders regarding what constitutes an "outcome" of genomic testing.[7,9] The value of genomic testing has been traditionally challenging to assess, leading to initiatives such as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group to create frameworks. In the EGAPP initiative, the task force members noted stakeholders' differing language and priorities in assessing the analytical validity, clinical validity, clinical utility, and ethical/legal/societal implications of genomic tests.[10] Although assessment frameworks are challenging to apply broadly in other areas of medicine, outcomes and interventions are more directly related.[11] Understanding payer perspectives on decision-making for genomic tests is essential to clarify what evidence may be needed to secure coverage. Although individual studies have investigated payer perspectives on genomic testing for specific clinical scenarios, a comprehensive review and synthesis of insights has not been performed. An analysis of what is known and areas of alignment or disagreement among US payers may guide industry, providers, and patient advocacy groups seeking to address payer concerns. This study aims to evaluate existing studies that examine payer perspectives on genomic testing and identify common domains.

Materials and Methods

We conducted a systematic review of the peer-reviewed academic literature. Our goal with this review was to evaluate the evidence base describing US private payer perspectives regarding genetic testing. The review was not prospectively registered, but the protocol is available at https://osf.io/y4rt7/?view_only=2d86a199b5f0476da76980862cf6b96c.

We systematically searched for publications addressing or capturing direct perspectives of the US private payer population. After initial iterations, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 systematic review guidelines were used to inform this study's development, conduct, and reporting. The primary research question informing the review is "What are US payer perspectives regarding genomic testing?" with secondary research questions being "How do payer perspectives on genomic testing differ depending on the type of genomic testing?" and "What methods have been used to study US payer perspectives on genomic testing?" Search terms and strategies were created under the supervision of a research librarian through Clemson University. Based on the population, intervention/phenomenon of interest, context, and outcome (PICO) measures framework, we developed a search strategy that included key terms from essential papers.[12,13] Inclusion and exclusion criteria were developed and refined using the PICO framework (Supplemental Table 1). Articles were included if they (1) reported perspectives, thoughts, opinions, or decision-making attributable to US payers as individual respondents or in aggregate or were authored by US payer representatives or experts in US payer policy, (2) centered on genomic testing technologies, (3) based on US health care environment, or (4) published in an English language peer-reviewed journal between January 1, 2000, and June 30, 2024. Articles were excluded if they (1) reported perspectives not attributable to US payers, (2) reported perspectives not relating to genetic testing technologies (such as reports on genetic counseling services or genetic insurance discrimination without broader context), or (3) were based outside of US health care system or (4) were reviews of coverage policies, (5) were conference proceedings, letters to the editor, abstracts, case studies, or protocols, or (6) were published before 2000 given the Human Genome Project impact on commercially accessible genomic technologies.

Searches were conducted across 2 databases (PubMed and Cumulative Index to Nursing and Allied Health Literature [CINAHL]) for articles published from 1 January 2000 to June 30, 2024, the last search date. The PubMed, MEDLINE, and CINAHL databases were searched using key terms (Supplemental Table 1). Search results were exported to a spreadsheet. One author (J.W.) independently selected records that appeared to fulfill inclusion criteria based on a review of abstracts and titles. Articles were retained for full-text review when they seemed to meet inclusion criteria or when there was insufficient evidence to exclude them (Figure 1).

Data collected included title, authors, year, objectives, study design, population studied, instrumentation used, and type of genomic testing. A framework analysis approach was used to categorize and organize data across studies thematically.[14] One reviewer (J.W.) examined the complete set of included articles to create an analytical framework centered on each of the primary foci of this review: perspectives of US payers on genomic testing. Major domains were identified and data iteratively analyzed and integrated into the framework for all included records. A second reviewer (L.R.) reviewed the included records and independently validated the analytical framework and thematic

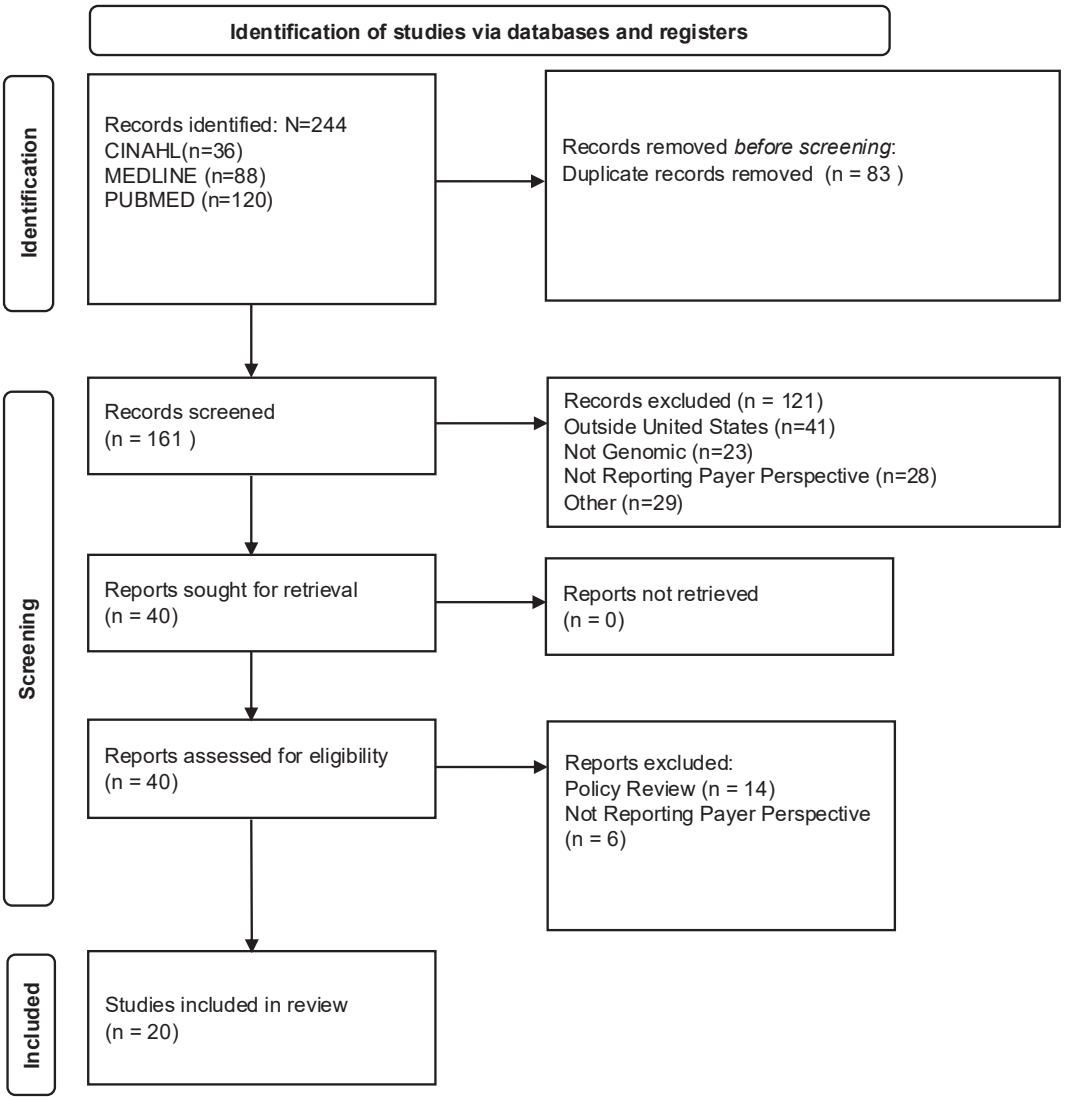

Figure 1 Study selection process per preferred reporting items for systematic reviews and meta-analyses guidelines.

identification and analysis. Any disagreements regarding the analytic framework or thematic characterization were resolved by discussion between reviewers. A narrative synthesis of results was performed, and no additional analysis, such as subgroup analysis or meta-regression, was planned or undertaken. The literature search was concluded on June 30, 2024.

Critical appraisal of the included articles was not performed because the domains of interest for this review were often not the study's primary endpoints or were not assessed in a methodological approach. Undetected biases may exist in the records described here.

Results

The study selection process (outlined in Figure 1) resulted in 20 studies undergoing full review, inclusion, and data abstraction, which are presented in detail in Table 1.[2,7,12,13,15-29] Publication dates ranged from 2009 to 2022. Interviews, surveys, and discussions account for most studies reflecting payer perspectives. The study designs include 9 semistructured interviews or discussion groups, 2 Delphi studies, 2 reviews, 3 commentaries/presentation summaries, 2 consensus group reports, 1 discrete choice experiment, and 1 original clinical study with a payer author (Table 1).[2,7,12,13,15-29]

Our analysis framework identified 7 major domains relating to payer perspectives of genomic testing (Table 2). Although methodologies and populations varied considerably among the reviewed studies, some common domains emerged, as seen in Table 2 and discussed below.

Clinical utility

Clinical utility traditionally considers the ability of an intervention to improve health outcomes; however, definitions vary slightly by payer respondents and testing type or

Table 1 Studies evaluating payer perspectives identified through literature review

Author, Year	Study Objective	Study Design	Population Studied	Type of Genomic Testing
Deverka et al,[15] 2020	Describe the current landscape of whether and how payers use real-world evidence (RWE) as part of their coverage decision making	Scoping review	Scientific and gray literature ranging from January 2013 to November 2019 pertinent to RWE	Next-generation sequencing
Dhanda et al,[17] 2020	Define attributes of genomic testing important to payers and elicit payer preferences using a discrete choice experiment	Discrete choice experiment	150 Payer respondents in public and private sector	Precision medicine
Doble and Lorgelly,[16] 2015	Provide expert insights into stakeholder perspectives with recommendations in oncology	Expert editorial	Health and value economists with global payer insights	Tumor NGS
Epstein et al,[18] 2009	Study payer perspectives of pharmacogenomic test and drug development	Semi-structured interview/focus group	Payers included health plans, employers and government payers	Pharmacogenomics ranging from allergy to cancer
Faulkner et al,[19] 2012	Present an overview of key issues with PGx applications from the payer and manufacturer perspective	Consensus report supported by literature and expert comment	ISPOR Precision Medicine Working Group with payer representation	Pharmacogenomics
Frueh,[20] 2013	Study of perspective and review of regulation and reimbursement evidence and future directions	Review	No systematic design referenced	Pharmacogenomics
Guzauskas et al,[30] 2013	Study opinions of genomic services stakeholders on the potential usefulness of decision-analytic modeling to inform their reimbursement decision making	Survey, discussion	Nineteen state public health genomics leaders, professional family advocates who are employed in advocacy organizations, and state Medicaid executive leadership	All
Keeling et al,[21] 2019	Study of awareness, knowledge and perspectives on germline preemptive pharmacogenomic testing	Semistructured interviews	Fourteen Pharmacy and medical directors for commercial and government payers and ancillary entities such as benefit managers	Germline preemptive pharmacogenomic testing
Kogan et al,[22] 2018	Provide payer commentary regarding precision medicine value	Expert commentary	Health Value, Precision Medicine, and Insurance Plan personnel for integrated health plan/system	All
Latchaw et al,[23] 2010	Describe insurance coverage policy and approaches in the state of Illinois	Semi-structured interview and survey	Three senior medical directors from 3 private insurance plans in Illinois	All

(continued)

Table 1 Continued

Author, Year	Study Objective	Study Design	Population Studied	Type of Genomic Testing
Messner et al,[2] 2016	Obtain expert insights defining barriers of clinical adoption and policy solutions	Delphi panel approach with 2 rounds	Panel of experts with significant knowledge of the field of genomics, government, health policy, patient advocacy, or law-Included 3 payers of 48 participants	NGS
Newcomer,[24] 2016	Provide payer commentary regarding precision oncology quality	Expert commentary	Medical director of national health plan	Precision oncology
Pearson et al,[25] 2013	Describe what core elements inform payers' coverage considerations for Alzheimer disease biomarker testing	Consensus report supported by literature and expert comment	Members of an independent policy development group for the Institute of Clinical and Economic Review including representatives from one commercial payer and 2 integrated health plan/systems	Alzheimer disease
Phillips et al,[12] 2012	Assess payers' considerations for coverage of GS vs coverage of ES and requirements payers have for coverage of GS	Semistructured interviews via group and individual settings when necessary	12 representatives of private payers including 6 large national plans and 3 regional plans along with 2 experts	ES, GS
Reitsma et al,[26] 2019	Review outcomes following health plan coverage of comprehensive genomic profiling in advanced cancer patients	Retrospective review of medical records and health plan data	Advanced cancer patients at a single cancer center; and a single health plan	Tumor NGS
Scheuner et al,[7] 2019	Define stakeholder's views of clinical genomic intervention outcomes	Delphi panel approach to surveys in 2 rounds with discussion	Administrators, Clinicians, policy makers/payers, patients, researchers, patients or family experienced in precision medicine	All
Trosman et al,[13] 2010	Examine the overarching issue of what strategies private payers use to develop policy for personalized medicine	Semistructured interviews and literature review	Private payers including 7 representatives from 6 plans	gene expression classifier
Trosman et al,[27] 2015	Identify payers' challenges to establishing formal coverage for next-generation tumor sequencing panels	Semistructured interviews	Senior executives at 7 of the top 10 largest US health plans and at 4 regional plans in the payer cohort	Precision oncology

(continued)

Table 1 Continued

Author, Year	Study Objective	Study Design	Population Studied	Type of Genomic Testing
Trosman et al,[28] 2017	Study of private payers' perspectives on barriers and opportunities for insurance coverage of hereditary cancer panels	Qualitative semistructured interviews	Eleven payers, including senior executives with coverage decision-making responsibilities from the 8 largest US private payers and 3 regional payers	Hereditary cancer panels
Trosman et al,[29] 2020	Study payers' views and perspectives on pediatric and prenatal ES decision making	Semistructured interviews	Senior Executives at 14 US payer entities including national, regional, Medicaid, and benefit manager	ES for pediatric and prenatal applications

ES, exome sequencing; *GS*, genome sequencing; *ISPOR*, International Society for Pharmacoeconomics and Outcomes Research; *NGS*, next-generation sequencing; *PGx*, pharmacogenomics.

application. Clinical utility was the most referenced domain across studies.[2,7,12,13,17,19-25,27-29] One medical director and a consensus report described it as the "most important factor."[12,13] There was general agreement on the primary definition of clinical utility, and there was broad consensus across studies that clinical utility is most traditionally met when there is evidence that a test result was used to guide care, resulting in improved health outcomes in a real-world setting.[2,7,12,13,16,17,20,23,25,27-29] As stated by one payer, "You have to establish an outcome."[21] The specific health outcomes may depend on the testing type and clinical scenarios in which the testing is used. Some payers reported flexibility in the application of clinical utility in coverage decisions. Payers and stakeholders have cited the inconsistencies in the payer definition of clinical utility as barriers to coverage for genomic testing.[2,19] The discrete choice experiment showed that payers felt that improved quality of life (defined as improved health and function) was the most important, followed by increased life expectancy.[17] Clinical utility was also thought to be demonstrated best through prospective clinical studies, including health outcomes, such as clinical trials. Clinical trial outcomes were noted as often lacking the myriad factors impacting how an intervention may impact actual patients, and it was also noted that clinical trial data may be infeasible in genomic disorders.[20,22,24,27] Some adoptions of clinical utility affected medical decision-making and medical management.[12,13,24] Half of the payers felt that ending the diagnostic odyssey was an element of clinical utility[29]in one exome sequencing study. A common sentiment within the discussion of clinical utility and flexibility of outcomes that might result in coverage was noted in several studies.[12,13,21,22,25,28,29] For exome sequencing and oncology gene expression classifiers, some payers characterized the evidence of clinical utility as insufficient but issued coverage based on other factors, such as perceived standard of care or ending the diagnostic odyssey.[13,29] Some payers noted intermediate endpoints as acceptable when the prolonged progression of some disorders or scarcity of clinical cohorts for trials make traditional health outcomes infeasible.[12,18] Some payers also pointed out that the ability to affect clinical decision-making and management might be considered in coverage, particularly regarding how patients are managed and what interventions follow.[21,25,29] The type of evidence to demonstrate improved health outcomes was also flexible. Some payers noted that observational studies, registries, and pooled analyses would be informative for coverage decisions if they are large and adequately powered for these findings.[28] One study showed that payers may be open to new technologies that effectively substitute those addressed by the existing expert recommendations.[12] In one study, payers varied on whether it was sufficient for clinical utility even when reviewing the same evidence simultaneously.[13]

Cost

The cost was a consideration among studies with variable import or assessment approaches.[12,13,17-22,24,25,27,29] Compared with alternatives or interventions, the cost of the test itself was broadly reported as influential in coverage assessments.[16-18,20,21,25,27] The costs of downstream services incurred or avoided are relevant, and economic modeling cost-effectiveness analyses or similar studies impact payers.[12,16,18,19,25,30] Costs associated with testing would ideally be offset by clinical value, and coverage of panel testing would be considered if the portions outside of policy or without clinical utility were not submitted for reimbursement.[24] Interestingly, the cost was noted to be precluded from payer perspectives or decision-making in at least 3 studies, 1 unanimously among participants, and the

Table 2 Common domains among literature reporting payer perspectives on genomic testing

Domain	Prevalence in Literature	Key Concepts
Clinical utility is important, but definitions varied	16 studies	Commonly considered to be improved health outcomes in real-world setting beyond standard of care May also include changes in medical decision making/management/treatment which are proven or likely to be effective May include ending diagnostic odyssey Intermediate outcomes or endpoints may be considered for coverage decisions Varied definitions by stakeholders makes a uniform approach difficult
Cost	13 studies	Cost of testing and downstream costs are often considered, but not always Cost of testing or related intervention may impact management of test Some say they explicitly exclude cost from coverage decisions, yet some of those same studies mentioned cost factors Cost, when considered, weighed in relation to benefit gained
Potential harms	10 studies	Unable to keep pace with advancing genomic tests Frameworks cannot reckon with blend of clinically actionable and less studied elements of genomic tests Types of evidence traditional to frameworks may not account for all the nuances of genomic testingConflict with regulatory frameworks Conflict with regulatory frameworks
Potential harms	10 studies	Includes patient anxiety, lack of consent, education Includes overutilization leading to unnecessary testing and/or interventions Types of evidence traditional to frameworks may not account for all the nuances of genomic testingConflict with regulatory frameworks
Paying for research	6 studies	Payers have contractual obligations to members and employers not to spend resources on research/unproven services If the only interventions following a test are through research, this is a concern Clinical trial enrollment/participation may be seen as a benefit, particularly in cancer care, but this view was not consistent
Demand pressure	5 studies	Demand or Pressure from multiple sources (patients, customers/employer groups, professional societies, popular media) was mentioned but not universally influential among payers Provider/patient adoption which is widespread may indicate standard of care Pressure from demand/increased utilization may escalate review of a policy or in some rare cases drive coverage decisions Case-level reviews may escalate review of a policy Influence of notable societies or guidelines such as National Comprehensive Cancer Network, Clinical Pharmacogenetics Implementation Consortium, Food and Drug Administration, Centers for Medicare and Medicaid Services or United States Preventive Services Task Force
Personal utility	4 studies	Personal utility outcomes seen as a benefit or element of clinical utility but not sufficient as a standalone criterion Information or "knowing" not seen as factor in coverage decisions

others with payers divided or conflicting messages.[12,13,25] Regarding genome sequencing, some payers "do not directly consider reimbursement in coverage decisions," whereas cost was a concern for other payers.[12] When evaluating a gene expression assay, all payers "stated explicitly that cost-effectiveness analyses do not influence coverage decisions."[13] A discrete choice experiment crystallized this dichotomy, with cost ranking fifth of 6 influential attributes of genomic testing. Yet, an increase in the plan's cost decreased the payer's utility for reimbursement.[17]

Coverage decision frameworks

Coverage decision frameworks are used to evaluate services informing coverage policies and case-level decisions. They were most frequently described as hinging on analytical validity, clinical validity, and clinical utility as supported by

clinical evidence.[2,17,19-22,24,25,27,28,30] Existing frameworks are not easily applied to genomic tests.[2,15,27,28,30] One multistakeholder study agreed that current coverage frameworks were inadequate to keep pace with advancing genomic testing.[2] Current frameworks used in other areas of medicine in which more straightforward lines exist between what is diagnostic, prognostic, risk, or therapy selecting may not be as apparent in genomic testing, and this conflict was most frequently described in the discussion of genomic panel testing.[16,27,28] By existing frameworks, some payers would consider an entire test "experimental" or "investigational" if any component were unproven.[2,27,28] Some payers could not cover a panel for which some of the included genes do not have clinical utility for the patient tested or the indication for testing. Payers agreed that frameworks do not account for the nuanced features and benefits of certain types of genomic testing.[28] Decision-analytic modeling studies were considered valuable and influential in coverage decisions.[30] Although regulatory frameworks focus on safety and efficacy, payer frameworks often consider cost-effectiveness and real-world clinical outcomes at a population level, meaning that regulatory approval does not confer coverage.[15,20,25] Only a minority of payers felt that frameworks should be modified to align with the nuance of genomic tests.[28] One multistakeholder group identified the current approaches as 2-fold, incorporating the framework for an assessment and coverage decision-making criteria and the kind of evidence required for the evaluation.[19] The lack of evidence-based guidelines by professional societies for genomics was noted in one study as a barrier.[21] Payers reported considering professional society guidelines as a sign of "standard of care," which tips toward coverage. However, they reviewed the clinical evidence independently of the guidelines in a study of an oncology assay.[13]

Potential harms or risks

Potential harms or risks of genomic testing gave payers pause in consideration of coverage.[2,12,18,19,22,24,25,27,29] The ability of genomic tests to give surplus information—beyond what may lead to effective treatment—was highlighted in several studies, whether referring to incidental and secondary findings, variants of uncertain significance (VUS), or leading to off-label therapies. The impact of VUS to guide inappropriate treatment or overburden the health care system was of concern to several payers across studies.[12,29] Some payers were less concerned about the impact of VUS because of existing coverage policies and protocols, which they felt adequately addressed the risks. There was concern that VUS would lead to downstream testing, care, and costs. Other payers were concerned about test accuracy potentially leading to incorrect diagnosis and treatment.[18,19] In addition to clinical impact and utilization, payers concerned with test performance noted that coverage of poorly validated tests may jeopardize their place in the market.[18,25] Some payers expressed concerns or harms centered on the patient experience, such as the potential to cause anxiety and the challenges of patient engagement.[2,28]

Paying for research

Paying for research concerns more than 1 payer.[2,12,24,27-29] Payers felt that many genomic tests evaluated had some research application rather than being entirely for clinical application. Most payers in one study of hereditary cancer panels shared the common concern of paying for research. The availability of a test without prospective outcomes evidence or a test for which the only interventions available are through a research setting falls into this category.[29] Additionally, the composition of that test, including genes without clinical utility evidence, represents a research application and conflicts with payer statutes or responsibilities.[12] Some payers would categorically deem any test with a mix of genes that have evidence and those without as investigational. In contrast, others accepted a test as having clinical utility if most genes did.[2,27] Payers cited good reasons for such concerns because they have a mandate or edict to cover only nonexperimental technologies. Coverage of research activities may cause employer objections or confer legal implications depending on the type of agreements in place.[2,12,28] Solutions were proposed to overcome this limitation, such as multistakeholder projects, patient registries in which evidence may be developed, and coverage with evidence development agreements,[26,28] as noted in one study. Additionally, one payer thought that the costs of generating data for clinical trials may be acceptable if the clinical benefit offsets them.[24]

Demand or pressure

Demand or pressure was reported to be a factor influencing some payers.[18,21,23,27,29] Payers reported prioritizing policies or reviews with increased costs, political or press attention, utilization, provider, and patient demand. The presence of provider/patient demand was reported to drive interest in genomic testing or escalate a review of an existing policy.[13,18,29] The impact of such pressure varies among payer stakeholders and by testing type. Payers reported that demand or press pressure would be insufficient to factor into pharmacogenomic coverage for allergies. However, cancer care is already challenging, controversial, and more sensitive to external pressure or risk.[18] Broad adoption by physicians or medical societies via guidelines developed and published by medical societies indicates that a test represents the standard of care.[13] Some payers considered pressure and demand as a factor in coverage decisions when evidence was insufficient for a gene expression assay. Still, about half of payers reported this as an unimportant factor.[13]

Personal utility

Personal utility is a well-studied and variable set of behavioral, affective, cognitive, and social outcomes from

genomic testing, although it is sometimes described as the personal or familial value of nonactionable information or the nonhealth-related uses of information.[31-33] Yet, payers are challenged to value these outcomes in traditional decision frameworks or definitions of clinical utility, as reported in several studies.[7,23,25,29] A discrete choice experiment showed that payers found less utility in screening/preventative tests compared with testing that resulted in treatment changes, deprioritizing nonhealth-related uses.[17] One study noted that outcomes such as patient/family planning, reassurance, and quality of life may provide advantages but are not routinely judged as a health benefit by insurers.[25] Notably, none of the studies reviewed presented a holistic set of personal utility outcomes for payer perspectives. Payers felt that information and support resources were elements of, but insufficient to demonstrate clinical utility without more traditional clinical outcomes.[29] Some payers saw reproductive planning as an element of, but not adequate to demonstrate clinical utility.[29] In another study, payers felt reproductive decision-making had value as an outcome and that testing for this purpose should be reimbursed.[7] A similar trend was noted for family member education and information. Payers in one study saw the benefit to family members as an element of clinical utility, blurring the definitions; however, it was insufficient to constitute clinical utility. In contrast, payers in another study saw the value and need for reimbursement for tests that provide information and risk refinement for family members.[7,29] Payers from the state of Illinois stated that personal utility was insufficient to cover a genomic test without more traditional clinical utility. They did not see the benefit to a patient of "just knowing" their genomic status or see value to "satisfy curiosity."[23]

In the studies with multiple stakeholders represented, payers did not significantly differ from other stakeholders in most assessments; however, perspectives were not easily attributable to payer participants in all studies. There was consensus, for example, that evidence is often insufficient to make informed coverage decisions for new tests and that the potential of a test to benefit a single patient does not necessitate coverage for all patients.[30] Payers and clinicians had strikingly similar assessments of value for genomic intervention outcomes. They had similar assessments of uncertainty surrounding genomic testing and less uncertainty than patients in the same study.[7]

Insights and perspectives of payers regarding different testing types were gleaned mainly from studies centered around specific testing scenarios or indications. For example, in an exome and genome sequencing study, payers reported merit for the testing approaches in pediatric populations but not for prenatal indications, citing a lack of clinical interventions.[29] In one Delphi study, respondents felt strongly that payers should cover next-generation sequencing tumor testing (77%) but felt less strongly about coverage for newborn screening (49%) or disease risk prediction (29%).[2] For risk prediction of Alzheimer disease, the cost of therapies was felt to affect comparative value, and this sentiment was also noted in a commentary regarding precision medicine, in which the ability to direct toward or away from high-cost specialty drugs was a consideration in the value proposition.[24,25] In addition to test-specific insights, some records included a discussion of solutions proposed by payers, mostly centering on providers, researchers, and professional societies. Practice-related solutions included requiring a genetics professional involvement to address concerns of misuse and centers of excellence to advance coverage.[12,28] Payers also suggest broader solutions for the systemic delivery of genomic testing, such as end-to-end delivery infrastructure, including laboratory data collection, electronic medical record integration and collection of results, and development of referral and care processes, including recontacting patients with relevant results.[24,27]

Solutions or recommendations were made regarding research and evidence generation, such as conducting head-to-head comparative analyses for new technologies vs standard of care, vast clinical trials, randomized controlled trials, real-world observational studies, and claims data research to strengthen the evidence base.[21,22,24,25] Some made suggestions for professional societies, suggesting Clinical Pharmacogenetics Implementation Consortium (CPIC) should go further and define testing criteria and patient recommendations, citing National Comprehensive Cancer Network (NCCN) guidelines as an example.[21] Another proposed improved standards for genetic testing.[24] Interestingly, only 1 study mentioned improvements in health technology assessments or payer processes.[19]

Discussion

This systematic review identified 7 distinct domains considered by US payers regarding their approach to genomic testing coverage and utilization: clinical utility, cost, coverage decision frameworks, potential harms, paying for research, demand/pressure, and personal utility. Common perspectives and an enhanced understanding of payer priorities highlight opportunities for evidence development and advocacy, which affect coverage. Payer perspectives varied greatly, even within the 7 domains. The heterogeneous nature of studies regarding payer perspectives and the omission of some intuitive concepts indicate that further study of this population is needed.

Some domains were evident even in the limited range of research performed on payer perspectives. Clinical utility was prevalent in records and was universally considered to be defined by an improvement in health outcomes. Health outcomes are also unanimously considered in definitions of clinical utility for genomic testing set forth by various entities, including the American College of Medical Genetics and Genomics, the Centers for Disease Control, the Association of Molecular Pathology, and the National Institutes

of Health National Cancer Institute.[34-39] Still, some payers remained open to expanded definitions or other elements of utility that may influence decision-making, such as psychological well-being. These responses indicate a progressive contingent among payer decision-makers. Together with more progressive payers, clinical researchers and laboratories may collaborate on pilot programs of conditional coverage using broader sets of outcomes that may generate data supporting coverage expansion by more conservative payers.

Similarly, consensus group definitions of clinical utility include outcomes encompassing treatment decisions, quality-of-life outcomes, and other impacts to patient or family.[34,38,39] Payers in the identified studies struggled to apply or develop frameworks to assess elements of personal utility, including behavioral, affective, cognitive, and social outcomes arising from genomic testing.[31-33,40] Definitions of personal utility have only recently been more formalized, and assessment tools have been proposed.[32,33] This may have affected the inconsistent inquiry of all personal utility elements in the identified studies. Future research may use standardized definitions and aspects of personal utility and explore language or elements studied in other areas of medicine, such as quality-of-life and patient-reported outcomes.[41-43] Although some payers reported considering such outcomes, some were dismissive of aspects of personal utility, such as just knowing.[23] This conflicts with the American College of Medical Genetics and Genomics work surrounding clinical utility, in which arriving at a diagnosis is an outcome.[38] Patients and families have also reported benefits from diagnostic genomic testing in areas not captured by quality of life or psychological well-being outcomes and thus the need for a conceptual personal utility.[31] The consensus acceptance of improved health outcomes might guide genomic researchers to push personal utility assessment further by associating outcomes with health metrics more readily accepted by US payers. For example, health care utilization patterns have been shown to differ among pediatric patients for whom a diagnosis is certain vs uncertain.[44]

Applying coverage decision and evidence assessment frameworks to genomic testing is a challenge to payers, especially for panel testing in which all parts of a test must be medically necessary. This aligns with sentiments that a health plan is contractually obligated to avoid payment for services not proven to improve health outcomes. Although no specific frameworks were regularly referenced, analytical validity, clinical validity, and clinical utility were nearly universal in framework discussions; however, payers varied based on sufficient evidence. Frameworks have been proposed for the evaluation of health care services, such as the PICO and EGAPP working group's Analytic Validity, Clinical Validity, Clinical Utility, and Ethical/Legal/Social Implications model.[35,45] Ethical, legal, social, and psychosocial outcomes were not referenced in the discussion of frameworks; yet, these were referenced when alluding to potential harms and personal utility. This suggests that, although evidence of benefit in these areas is not routinely considered, evidence of harm in these areas is sufficient to cause concern.

Reviews of coverage policies have found that medical necessity determinations and evidence bases vary greatly across payers, indicating a lack of a standardized approach to evidence review and coverage determinations via frameworks.[6] Evidence hierarchies distinguish between professional society/expert consensus opinion statements and evidence-based guidelines founded on systematic literature reviews.[46,47] Guidelines were discussed by payers in the reviewed studies within the domains of coverage decision frameworks and demand/pressure. Evidence-based guidelines may affect coverage decisions through critical appraisal of evidence, consistent with evidence hierarchies and fitting easily into most frameworks. However, consensus opinions and statements may affect coverage decisions by signifying demand and adoption. The specific role of guidelines and consensus statements was not richly discussed in the reviewed studies, a key limitation given the known challenges for guideline development and implementation in genomics. A 2022 study examining multigene panel testing for tumor profiling in advanced cancer patients with nonsmall cell lung cancer, breast, cutaneous melanoma, and prostate cancer found that, although NCCN guidelines are cited in ~90% of policies, 71% are more restrictive than NCCN guidelines.[1] Even when guidelines exist which are "based on critical review of the best available evidence," there is still inconsistent acceptance by payers.[48] In rare diseases for which high-level evidence may be limited, the lack of evidence-based guidelines may be a barrier to coverage given the current frameworks. The varying coverage landscape presents significant challenges to providers, laboratories, and patients, and some state legislation has recently been enacted to mandate coverage of certain types of testing, including genomic tests.[49] The legislative language often defines clinical utility as demonstrated by any of the following: Food and Drug Administration approval of a companion diagnostic test, Medicare inclusion through national coverage determination or local coverage determination, nationally recognized clinical guidelines, evidence-based clinical practice guidelines, consensus statements, and in some states, peer-reviewed clinical evidence.

Interestingly, some payers categorically excluded cost from decision-making; yet, it was an essential assessment element for others, deemed somewhat price insensitive by authors.[17] The common domain of payer concern of paying for research also includes considering the cost of the entire health plan membership for unclear or narrow benefits. Recent studies have aimed to demonstrate the economic benefit of clinical trial participation in addressing this concern.[50-52] The complexity of costs and cost-effectiveness research in genomics remains challenging in explaining the budgetary impact for a commercial payer population.[53] The impact of appeals or grievances was not specifically commented upon, but these processes affect cost, and demand/pressure. The effect of cost upon assessment may warrant further study, and the discussion of economic studies in genomics may be helpful to include in inquiries with payers.

The potential harms of genomic testing were often discussed regarding test performance or accuracy, patient anxiety, and inappropriate services in response to genomic results. Concerns of payers are mirrored in literature discussing genomic testing used in manners deemed inappropriate by genomics professionals, leading to psychological or physical harm, driving therapeutic anarchy, or that providers are ill-equipped to translate results to effective clinical action.[54-57] However, recent studies have begun to address payer concerns of harm, such as the psychological benefit of genomic testing and the lack of off-label therapy use after testing.[58] In the reviewed studies, the evaluation of harms was not as richly discussed as the evidence needed for other outcomes, suggesting that payers may accept the potential of harm but require proof of benefit. This could be an opportunity for clinical researchers.

Patient advocacy groups and clinical providers in a payer network may generate demand or pressure for coverage of specific types of genomic testing, presenting an opportunity for influence outside of evidence generation. Other areas of demand are important, such as competition from other payers and legal pressure arising from overturned denials.[59] Other sources of pressure may come from heightened scrutiny of genomics in popular media, in which potential harms and disproportionate spending have been noted.[60,61]

Other related domains may seem intuitive or are discussed in nongenomic payer studies but were absent from the included studies and represent opportunities for researchers. These include the impact of genomic testing on insurance purchasing behavior, the impact of appeal and grievance processes, legal implications of coverage, guideline language, genomic discrimination as a consideration in policy, and asymmetry of risk information or antiselection affecting insurance actuaries.[62,63]

Despite a broadly scoped literature review, there is a dearth of studies directly investigating payer perspectives. The studies identified through this review mainly consisted of semi-structured interviews using instrumentation developed with expert consultation. The myriad approaches to interviews and instrumentation leave researchers with little generalizability for reported findings; however, such studies provide an essential base upon which to build. A consolidation or consensus of best practices or standardized instrumentation would allow harmonization and reproducibility of reported results and direct comparison with other health care stakeholders. Instruments for eliciting feedback in the identified studies were primarily guided by expert input and existing research during development. Although such development adds utility and credibility to the studies and results, the instruments and guides often present incomplete, complex concept representations. Notably, there was a lack of inquiry surrounding quality-of-life outcomes in most studies despite a wealth of evidence showing that these outcomes may be necessary to payers.[41] Future studies may also benefit from updated and expanded definitions of clinical utility, personal utility, and value. In the identified research, responses were sometimes not attributable to a payer participant; therefore, the perspective was not readily apparent.

Limitations

This review has limitations that may affect the interpretation and application of results. First, it is possible that vital data were missed, although the literature review search methodology was structured and performed with a research librarian trained in health sciences. To reduce the risk of reviewer bias, both reviewers (J.W. and L.R.) have professional experience with health plan genomic testing benefit management and policy. The literature reviewed was highly heterogeneous in terms of methodologies and temporality. This significantly affects the ability to draw conclusions regarding specific areas of genomics or trends over time. The insights may overrepresent challenges inherent to emerging areas of testing—because many studies evaluated testing recently available at the time of the study. Some important stakeholders affect payer coverage, such as laboratory benefit managers, evidence assessment entities, and policy clearinghouses, which were not assessed in reviewed studies. The variable quality of the reporting in the included studies may result in reporting bias. The exclusion of gray literature and policy reviews may also have led to the omission of insights. Future studies may benefit from the triangulation of reviewers or methodologies to ensure the validity and reproducibility of common domains and critical findings.

Clinical and research implications

Payers are among the most influential stakeholders in US health care; yet, there has been little research to understand how they make decisions regarding genomic testing. From the available literature, there are insights into critical domains, such as a common definition of clinical utility, the willingness of some payers to expand beyond that definition, the importance and challenges considering costs, and variability among perspectives and approaches. These insights may serve as a base to inform practices that enhance payer coverage, develop more research, and expand upon or discover new areas of influence within payer decision-making. Standardization among payer perspectives and processes is a priority for research and implementation, which may be investigated by payers, industry groups, and health policy stakeholders. Practitioners may consider clinical documentation processes to capture all outcomes from testing and pre- and posttest counseling to ensure the appropriate use of genomic testing. Clinical researchers may study a genomic test's utilization and diagnostic yield, the impact on medical management, and the downstream effects on health outcomes. Laboratorians may develop clinical implementation evidence and invest in research demonstrating the benefit of testing and a lack of harm. Professional societies may develop guidelines and recommendations using methods that are more readily considered by payers and reflect the desired standard of care. Further research may also investigate themes that were not well explored in existing literature, such as the role of

appeals processes, legislation, and guideline language on coverage decisions.

Data Availability

Abstraction data beyond that reported in supplementary materials are available upon individual request.

Funding

A grant award was provided by the National Society of Genetic Counselors Laboratory and Industry Special Interest Group for support of J.W. and L.R. review and framework creation.

Author Contributions

Conceptualization: J.W., S.C.D., H.S.S.; Investigation: J.W., L.R. Formal Analysis: J.W., L.R., S.C.D., H.S.S.; Writing-original draft: J.W.; Writing-review and editing: J.W., S.C.D., H.S.S., C.L.F.; Supervision: S.C.D., V.P.

Ethics Declaration

Because of the nature of the study, an ethical review from an Institutional Review Board or Research Ethics Committee was not required.

Conflict of Interest

Julie Wiedower and Laura Rebek are employees of and hold stock in Guardant Health, a molecular diagnostics laboratory. Hadley Stevens Smith has received consulting income from Illumina, Inc that is unrelated to this work.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2024.101329) contains supplemental material, which is available to authorized users.

References

1. Wong WB, Anina D, Lin CW, Adams DV. Alignment of health plan coverage policies for somatic multigene panel testing with clinical guidelines in select solid tumors. *Per Med*. 2022;19(3):171-180. http://doi.org/10.2217/pme-2021-0174
2. 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. http://doi.org/10.1016/j.atg.2016.05.004
3. Health insurance coverage in the United States. Census.gov. Accessed April 29, 2024. https://www.census.gov/library/publications/2023/demo/p60-281.html
4. Lin GA, Trosman JR, Douglas MP, et al. Influence of payer coverage and out-of-pocket costs on ordering of NGS panel tests for hereditary cancer in diverse settings. *J Genet Couns*. 2022;31(1):130-139. http://doi.org/10.1002/jgc4.1459
5. Sheinson DM, Wong WB, Meyer CS, et al. Trends in use of next-generation sequencing in patients with solid tumors by race and ethnicity after implementation of the Medicare national coverage determination. *JAMA Netw Open*. 2021;4(12):e2138219. http://doi.org/10.1001/jamanetworkopen.2021.38219
6. Chambers JD, Saret CJ, Anderson JE, Deverka PA, Douglas MP, Phillips KA. Examining evidence IN U.S. payer coverage policies for multi-gene panels and sequencing tests. *Int J Technol Assess Health Care*. 2017;33(4):534-540. http://doi.org/10.1017/S0266462317000903
7. Scheuner MT, Russell MM, Chanfreau-Coffinier C, et al. Stakeholders' views on the value of outcomes from clinical genetic and genomic interventions. *Genet Med*. 2019;21(6):1371-1380. http://doi.org/10.1038/s41436-018-0344-6
8. Porter ME. What is value in health care? *N Engl J Med*. 2010;363(26):2477-2481. http://doi.org/10.1056/NEJMp1011024
9. Botkin JR, Teutsch SM, Kaye CI, et al. Outcomes of interest in evidence-based evaluations of genetic tests. *Genet Med*. 2010;12(4):228-235. http://doi.org/10.1097/GIM.0b013e3181cdde04
10. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. The EGAPP initiative: lessons learned. *Genet Med*. 2014;16(3):217-224. http://doi.org/10.1038/gim.2013.110
11. Payer perspectives on improving usability of effective health care products: bridging the gap between information needs and evidence translation. Effective health care (EHC) Program. Accessed November 1, 2022. https://effectivehealthcare.ahrq.gov/products/payer-usability/white-paper
12. Phillips KA, Trosman JR, Douglas MP, et al. US private payers' perspectives on insurance coverage for genome sequencing versus exome sequencing: a study by the Clinical Sequencing Evidence-Generating Research Consortium (CSER). *Genet Med*. 2022;24(1):238-244. http://doi.org/10.1016/j.gim.2021.08.009
13. Trosman JR, Van Bebber SL, Phillips KA. Coverage policy development for personalized medicine: private payer perspectives on developing policy for the 21-gene assay. *J Oncol Pract*. 2010;6(5):238-242. http://doi.org/10.1200/JOP.000075
14. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol*. 2013;13(1):117. http://doi.org/10.1186/1471-2288-13-117
15. Deverka PA, Douglas MP, Phillips KA. Use of real-world evidence in US payer coverage decision-making for next-generation sequencing–based tests: challenges, opportunities, and potential solutions. *Value Health*. 2020;23(5):540-550. http://doi.org/10.1016/j.jval.2020.02.001
16. Doble B, Lorgelly P. Clinical players and healthcare payers: aligning perspectives on the cost-effectiveness of next-generation sequencing in oncology. *Per Med*. 2015;12(1):9-12. http://doi.org/10.2217/pme.14.81
17. Dhanda DS, Veenstra DL, Regier DA, Basu A, Carlson JJ. Payer preferences and willingness to pay for genomic precision medicine: a discrete choice experiment. *J Manag Care Spec Pharm*. 2020;26(4):529-537. http://doi.org/10.18553/jmcp.2020.26.4.529

18. Epstein RS, Frueh FW, Geren D, et al. Payer perspectives on pharmacogenomics testing and drug development. *Pharmacogenomics*. 2009;10(1):149-151. http://doi.org/10.2217/14622416.10.1.149
19. Faulkner E, Annemans L, Garrison L, et al. Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group. *Value Health*. 2012;15(8):1162-1171. http://doi.org/10.1016/j.jval.2012.05.006
20. Frueh FW. Regulation, reimbursement, and the long road of implementation of personalized medicine—a perspective from the United States. *Value Health*. 2013;16(6):S27-S31. http://doi.org/10.1016/j.jval.2013.06.009
21. Keeling NJ, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. *Genet Med*. 2019;21(5):1224-1232. http://doi.org/10.1038/gim.2017.181
22. Kogan JN, Empey P, Kanter J, Keyser DJ, Shrank WH. Delivering on the value proposition of precision medicine: the view from healthcare payers. *Am J Manag Care*. 2018;24(4):177-179.
23. Latchaw M, Ormond K, Smith M, Richardson J, Wicklund C. Health insurance coverage of genetic services in Illinois. *Genet Med*. 2010;12(8):525-531. http://doi.org/10.1097/GIM.0b013e3181e3916d
24. Newcomer LN. Payer view: how do we assess quality in the age of precision medicine? *J Oncol Pract*. 2016;12(10):845-846. http://doi.org/10.1200/JOP.2016.014167
25. Pearson SD, Ollendorf DA, Colby JA, ICER Alzheimer's Diagnostics Policy Development Group. Biomarker tests for the diagnosis of Alzheimer's disease: generating evidence to inform insurance coverage determinations. *Alzheimers Dement*. 2013;9(6):745-752. http://doi.org/10.1016/j.jalz.2013.06.002
26. Reitsma M, Fox J, Borre PV, et al. Effect of a collaboration between a health plan, oncology practice, and comprehensive genomic profiling company from the payer perspective. *J Manag Care Spec Pharm*. 2019;25(5):601-611. http://doi.org/10.18553/jmcp.2019.18309
27. 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(3):311-318. http://doi.org/10.6004/jnccn.2015.0043
28. Trosman JR, Weldon CB, Douglas MP, et al. Payer coverage for hereditary cancer panels: barriers, opportunities, and implications for the precision medicine initiative. *J Natl Compr Canc Netw*. 2017;15(2):219-228. http://doi.org/10.6004/jnccn.2017.0022
29. Trosman JR, Weldon CB, Slavotinek A, Norton ME, Douglas MP, Phillips KA. Perspectives of US private Payers on Insurance Coverage for Pediatric and prenatal exome sequencing: results of a study from the Program in prenatal and Pediatric Genomic Sequencing (P3EGS). *Genet Med*. 2020;22(2):283-291. http://doi.org/10.1038/s41436-019-0650-7
30. Guzauskas GF, Garrison LP, Stock J, Au S, Doyle DL, Veenstra DL. Stakeholder perspectives on decision-analytic modeling frameworks to assess genetic services policy. *Genet Med*. 2013;15(1):84-87. http://doi.org/10.1038/gim.2012.92
31. Kohler JN, Turbitt E, Biesecker BB. Personal utility in genomic testing: a systematic literature review. *Eur J Hum Genet*. 2017;25(6):662-668. http://doi.org/10.1038/ejhg.2017.10
32. Kohler JN, Turbitt E, Lewis KL, et al. Defining personal utility in genomics: a Delphi study. *Clin Genet*. 2017;92(3):290-297. http://doi.org/10.1111/cge.12998
33. Turbitt E, Kohler JN, Angelo F, et al. The PrU: development and validation of a measure to assess personal utility of genomic results. *Genet Med*. 2023;25(3):100356. http://doi.org/10.1016/j.gim.2022.12.003
34. Evaluating genomic tests. Centers for Disease Control and Prevention. Accessed October 4, 2021. https://www.cdc.gov/genomics/gtesting/index.htm
35. ACCE model process for evaluating genetic tests. Centers for Disease Control and Prevention. Accessed October 2, 2021. https://www.cdc.gov/genomics/gtesting/acce/index.htm
36. Definition of clinical utility – NCI Dictionary of Genetics Terms. National Cancer Institute. Accessed July 23, 2023. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/clinical-utility
37. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genet Med*. 2006;8(7):448-450. http://doi.org/10.1097/01.gim.0000227935.26763.c6
38. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2015;17(6):505-507. http://doi.org/10.1038/gim.2015.41
39. Joseph L, Cankovic M, Caughron S, et al. The spectrum of clinical utilities in molecular pathology testing procedures for inherited conditions and cancer: a report of the association for molecular pathology. *J Mol Diagn*. 2016;18(5):605-619. http://doi.org/10.1016/j.jmoldx.2016.05.007
40. Bunnik EM, Janssens ACJW, Schermer MHN. Personal utility in genomic testing: is there such a thing? *J Med Ethics*. 2015;41(4):322-326. http://doi.org/10.1136/medethics-2013-101887
41. Wu WK, Sause RB, Zacker C. Use of health-related quality of life information in managed care formulary decision-making. *Res Social Adm Pharm*. 2005;1(4):579-598. http://doi.org/10.1016/j.sapharm.2005.09.004
42. Weldring T, Smith SMS. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights*. 2013;6:61-68. http://doi.org/10.4137/HSI.S11093
43. Kim A, Chung KC, Keir C, Patrick DL. Patient-reported outcomes associated with cancer screening: a systematic review. *BMC Cancer*. 2022;22(1):223. http://doi.org/10.1186/s12885-022-09261-5
44. Marshall TL, Hagedorn PA, Sump C, et al. Diagnosis code and health care utilization patterns associated with diagnostic uncertainty. *Hosp Pediatr*. 2022;12(12):1066-1072. http://doi.org/10.1542/hpeds.2022-006593
45. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc*. 2006;2006:359-363.
46. Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and their role in evidence-based medicine. *Plast Reconstr Surg*. 2011;128(1):305-310. http://doi.org/10.1097/PRS.0b013e318219c171
47. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. http://doi.org/10.1136/bmj.39489.470347. AD.
48. Development and update of guidelines. National Comprehensive Cancer Network. Accessed September 13, 2024. https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines
49. Access to biomarker testing. American Cancer Society Cancer Action Network. Accessed June 23, 2024. https://www.fightcancer.org/what-we-do/access-biomarker-testing
50. Merkhofer C, Chennupati S, Sun Q, et al. Effect of clinical trial participation on costs to payers in metastatic non-small-cell lung cancer. *JCO Oncol Pract*. 2021;17(8):e1225-e1234. http://doi.org/10.1200/OP.20.01092
51. Merkhofer CM, Eaton KD, Martins RG, Ramsey SD, Goulart BHL. Impact of clinical trial participation on survival of patients with metastatic non-small cell lung cancer. *Clin Lung Cancer*. 2021;22(6):523-530. http://doi.org/10.1016/j.cllc.2021.04.003
52. Wiedower JA, Forbes SP, Tsai LJ, Liao J, Raez LE. Real-world clinical and economic outcomes for patients with advanced non-small cell lung cancer enrolled in a clinical trial following comprehensive genomic profiling via liquid biopsy. *J Manag Care Spec Pharm*. 2024;30(7):660-671. http://doi.org/10.18553/jmcp.2024.30.7.660

53. Phillips KA, Deverka PA, Marshall DA, et al. Methodological issues in assessing the economic value of next-generation sequencing tests: many challenges and not enough solutions. *Value Health*. 2018;21(9):1033-1042. http://doi.org/10.1016/j.jval.2018.06.017
54. Bajguz D, Danylchuk NR, Czarniecki M, Selig JP, Sutphen R, Kaylor J. Utilization of genetic testing: analysis of 4,499 prior authorization requests for molecular genetic tests at four US regional health plans. *J Genet Couns*. 2022;31(3):771-780. http://doi.org/10.1002/jgc4.1543
55. Dickerson JA, Cole B, Conta JH, et al. Improving the value of costly genetic reference laboratory testing with active utilization management. *Arch Pathol Lab Med*. 2014;138(1):110-113. http://doi.org/10.5858/arpa.2012-0726-OA
56. Oliveri S, Ferrari F, Manfrinati A, Pravettoni G. A systematic review of the psychological implications of genetic testing: a comparative analysis among cardiovascular, neurodegenerative and cancer diseases. *Front Genet*. 2018;9:624. http://doi.org/10.3389/fgene.2018.00624
57. Moscow JA, Fojo T, Schilsky RL. The evidence framework for precision cancer medicine. *Nat Rev Clin Oncol*. 2018;15(3):183-192. http://doi.org/10.1038/nrclinonc.2017.186
58. Wiedower J, Zhang N, Nagy R, Lang K, Saha J. Off-label use of precision oncology therapeutics in advanced solid cancers following identification of associated variants via multicancer next-generation sequencing panel: a real-world evidence pilot study. *J Clin Pathw*. 2023;9(5):36-42. http://doi.org/10.25270/jcp.2023.09.02
59. Steiner CA, Powe NR, Anderson GF, Das A. Technology coverage decisions by health care plans and considerations by medical directors. *Med Care*. 1997;35(5):472-489. http://doi.org/10.1097/00005650-199705000-00005
60. Genomic malpractice: what healthcare providers need to know to reduce the risk. Precision Medicine Advisors. Accessed July 1, 2021. https://www.precisionmedicineadvisors.com/precisionmedicine-blog/2019/6/10/why-fear-of-genomic-malpractice-might-make-healthcare-providers-more-likely-to-use-genetic-tests
61. Medicare part B spending on lab tests increased in 2021, driven by higher volume of COVID-19 tests, genetic tests, and chemistry tests. HHS Office of Inspector General. Accessed July 23, 2023. https://oig.hhs.gov/oei/reports/OEI-09-22-00400.asp
62. Golinghorst D, de Paor A, Joly Y, et al. Anti-selection & genetic testing in insurance: an interdisciplinary perspective. *J Law Med Ethics*. 2022;50(1):139-154. http://doi.org/10.1017/jme.2022.18
63. Peters WP, Rogers MC. Variation in approval by insurance companies of coverage for autologous bone marrow transplantation for breast cancer. *N Engl J Med*. 1994;330(7):473-477. http://doi.org/10.1056/NEJM199402173300707