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## Challenges of Coverage Policy Development for Next-Generation Tumor Sequencing Panels: Experts and Payers Weigh In

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### Abstract

**Background**—Next-generation tumor sequencing (NGTS) panels, which include multiple established and novel targets across cancers, are emerging in oncology practice, but lack formal positive coverage by US payers. Lack of coverage may impact access and adoption. This study identified challenges of NGTS coverage by private payers.

**Methods**—We conducted semi-structured interviews with 14 NGTS experts on potential NGTS benefits, and with 10 major payers, representing more than 125,000,000 enrollees, on NGTS coverage considerations. We used the framework approach of qualitative research for study design and thematic analyses and simple frequencies to further describe findings.

**Results**—All interviewed payers see potential NGTS benefits, but all noted challenges to formal coverage: 80% state that inherent features of NGTS do not fit the medical necessity definition required for coverage, 70% view NGTS as a bundle of targets versus comprehensive tumor characterization and may evaluate each target individually, and 70% express skepticism regarding new evidence methods proposed for NGTS. Fifty percent of payers expressed sufficient concerns about NGTS adoption and implementation that will preclude their ability to issue positive coverage policies.

**Conclusions**—Payers perceive that NGTS holds significant promise but, in its current form, poses disruptive challenges to coverage policy frameworks. Proactive multidisciplinary efforts to

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define the direction for NGTS development, evidence generation, and incorporation into coverage policy are necessary to realize its promise and provide patient access. This study contributes to current literature, as possibly the first study to directly interview US payers on NGTS coverage and reimbursement.

## Background

Precision oncology, the use of genomic and molecular markers to tailor treatment for individual patients, has achieved landmark advances illustrating the potential to transform cancer care and improve patient outcomes.<sup>1-4</sup> One of the most important technological advances enabling precision oncology is next-generation tumor sequencing (NGTS), the use of massively parallel technologies to simultaneously examine large numbers of genetic tumor alterations.<sup>5-10</sup> NGTS offers a host of advantages, including unprecedented accuracy and speed.<sup>11-14</sup> Although early in its evolution, it has crossed over to clinical practice,<sup>13,15-18</sup> enabled by the recent sharp decline in costs<sup>19-22</sup> and the increasingly rapid return of results.<sup>13,14,16</sup> The arrival of NGTS in clinical care is also signaled by its inclusion in some oncology guidelines,<sup>23,24</sup> the emergence of commercial offerings,<sup>25-27</sup> and its heightened visibility to the general public.<sup>28-31</sup>

With the emergence of NGTS in clinical practice, insurance coverage and reimbursement for NGTS are becoming forefront issues: most US payers have not issued formal positive coverage policies, and some recently issued noncoverage decisions.<sup>32-35</sup> Although it is possible to receive reimbursement for NGTS,<sup>36,37</sup> the lack of formal coverage causes payment uncertainty and variability, and limits patient access.<sup>38-41</sup>

Our exploratory study identified payers' challenges to establishing formal coverage for NGTS. We focused on private payers, who represent important stakeholders in US reimbursement, covering more than two-thirds of the US insured population.<sup>42</sup> Understanding insurance coverage considerations for NGTS is vital for all oncology stakeholders, including oncologists, pathologists, laboratories, patients, and researchers.

Our study contributes to current literature, representing possibly the first study to directly interview US payers on NGTS reimbursement. We interviewed senior executives at 7 of the top 10 largest US health plans and at 4 regional plans, with a combined membership representing more than 125,000,000 enrollees. This builds on our previous studies involving private payers on coverage and reimbursement of precision oncology, using similar methods.<sup>43-47</sup>

## Methods

This interview study was conducted with approval from the University of California, San Francisco's (UCSF's) Institutional Review Board (IRB). We used the framework approach of qualitative research<sup>48</sup> to guide design and data analyses. These methods are effective in exploratory studies on novel topics,<sup>49,50</sup> and we and others have previously used these methods for examining coverage and adoption challenges of precision medicine.<sup>43-47,51-56</sup>

Study participants were identified using purposive sampling<sup>50</sup> and recruited through the UCSF's Center For Translational and Policy Research on Personalized Medicine (TRANSPERS) Advisory Board. We developed 2 cohorts for this study: the expert cohort (individuals who are experts in clinical and research topics related to NGTS) and the payer cohort (senior executives from large national plans and regional plans, responsible for coverage decisions and evidence evaluation).

The semi-structured interviews were conducted from April through August 2013. We first conducted expert interviews to identify salient NGTS features and potential benefits. We then interviewed payers to examine how these features and potential benefits are considered for coverage decisions (a summary of the interview questions is provided in Table 1, available online, in this article, at [JNCCN.org](http://JNCCN.org)). All interviews were conducted by telephone, lasted 30 to 45 minutes, and were recorded and transcribed. The interview questions were sent to participants before the interview. Two investigators independently analyzed the interviews, resolving disagreement through discussion and consensus. We used simple frequencies to further describe the coded data where relevant.

We focused the interviews on NGTS panels, sequencing assays interrogating tens to hundreds of tumor genetic and molecular targets of varying clinical significance. The topics of germline genetic testing, sequencing technical and platform issues, and comparison of specific NGTS products were excluded. We described conventional molecular diagnostics as “single test/single result” assays, because they return a single biomarker result or a single value, such as cancer recurrence scores. Examples of NGTS panels and conventional tests were provided, but specific tests were not discussed.

## Results

### Participant Characteristics

The expert cohort included 14 individuals—7 pathologists and 7 oncologists from 6 NCI-designated cancer centers—with firsthand knowledge and experience of NGTS technology, research applications, and/or clinical use. The payer cohort included 10 senior executives responsible for coverage policy from 7 of the 10 largest national plans and 4 regional plans. The experts represent leading US cancer institutions, and the payers cover more than 125,000,000 enrollees combined. Participants and organizations are not named here to protect anonymity. Our cohorts are representative because within each we achieved theme saturation (repetition of input).<sup>57</sup>

### Experts' Perspectives on NGTS Panels

**How NGTS Panels May Be Used**—To illustrate potential NGTS uses, experts described 4 categories of targets included in an NGTS panel (Table 2). Three categories group individual targets based on the degree of proven significance in a specific cancer (“established” or “novel”) or across cancers (“pan-cancer”). The fourth, integrative category incorporates multiple targets into one integrated set, enhancing the multifaceted understanding of a patient's tumor. Each category may serve multiple purposes. Experts uniformly described some purposes as clinical or research, whereas their designation of

other uses (eg, pan-cancer applications) varied: some considered it research activity and others considered it clinical practice.

Similarly, experts' reports varied regarding the settings in which their institutions use NGTS. Some use it in research settings only. Others describe a “patient care setting,” which is a hybrid environment that has elements of both clinical (use of a Clinical Laboratory Improvement Amendments laboratory; routine tumor sequencing for specific cancers; funded by internal, institutional budgets, billed to payers for reimbursement, or billed to the patient) and research practices (conducted under an IRB approval; results are used for both standard-of-care and research purposes, including clinical trial enrollment).

**Unique Features of NGTS Panels**—Expert participants described distinguishing NGTS features and potential benefits that may transform oncology research and practice (Table 3, available online, in this article, at [JNCCN.org](http://JNCCN.org)). Because NGTS simultaneously interrogates large numbers of established and novel targets, it enables concurrent clinical and research activities with unprecedented efficiency because of optimized use of tumor tissue and returning results in a clinically relevant time frame. Conversely, current one-target-at-a-time testing may take up to 6 weeks or exhaust precious biopsy specimen on the first test. This limits patients' therapeutic choices—standard of care or experimental—or imposes risks, delays, and costs of a repeat biopsy. Experts remarked that NGTS potentiates the integration of standard of care and research for one patient in a truly patient-centric fashion, conferring current benefit from identifying established biomarkers, along with potential future benefit through identifying novel targets that may guide future treatments, as evidence expands.

Experts commented that NGTS benefits must yet be proven, but conventional clinical research methods used for single target/single drug trials are infeasible and may be obsolete in the era of NGTS. There was consensus that the ability to comprehensively categorize tumor genotypes allows for novel enrichment designs in clinical trials and may also enable in silico models simulating a tumor's reaction to therapy. The expert cohort believed that NGTS necessitates development of new clinical research methods, such as N-of-One, basket multicancer and/or multitarget/agent studies, and “big data” approaches.

### **Payers' Perspectives on NGTS Panels**

Of the interviewed payers, 80% agreed that NGTS has substantial potential to benefit patients and transform cancer care. However, all payers reported one or more challenges to issuing a positive coverage policy for NGTS, with key challenges categorized as follows and in Table 4.

**Not Fitting Definitions of “Medically Necessary” and “Experimental/Investigational”**—Payers must determine that a technology is “medically necessary” and not “experimental/investigational” to grant coverage; 80% of payers stated one or more reasons why NGTS does not fit these concepts. Additionally, 70% commented that although NGTS panels include medically necessary targets, inclusion of any novel targets deems the entire panel experimental/investigational. They explained that coverage may signal endorsement of novel targets and related off-label therapy use. However, 30% noted that inclusion of novel targets may not preclude NGTS coverage if they are labeled unvalidated

and associated treatments are not submitted for reimbursement. They also may be willing to support NGTS for cancer research, a new direction for their organizations.

Although payers regarded NGTS pan-cancer application a “reasonable hypothesis,” 60% considered it investigational. They will not cover it without outcomes evidence in each cancer, concerned that NGTS will dramatically increase off-label drug use. However, 40% considered the pan-cancer NGTS application beneficial, because it provides rationale for selected off-label drug use, which is already common in oncology. Payers may not formally cover pan-cancer therapies, but could continue payment on exception bases. However, they also expressed concern that NGTS will drive higher exception volume, and called for establishing consistent criteria for pan-cancer uses.

Although payers agreed with several other NGTS advantages, such as efficiency of testing and future benefit from sequencing, these lack precedent for coverage and do not fall under a benefit that could be determined medically necessary. Payers expressed difficulty with evaluating how these will directly benefit patients and improve outcomes.

**Misalignment With Single Test/Single Result Approach to Coverage**—Seventy percent of payers will evaluate each target included in an NGTS panel individually, using single test/single result approaches. Although acknowledging this daunting, they will not evaluate NGTS as one package, because they do not perceive the integrated benefit of NGTS, such as comprehensive tumor characterization. The other 30% would consider NGTS as one test for coverage, but noted the lack of methodology and few or no precedents for evaluating integrative NGTS benefits.

Payers also stated absent precedent for evaluating the bioinformatics component of NGTS. Sixty percent recognized the importance of this component, and acknowledged it may warrant higher reimbursement for NGTS or a separate payment. Consequently, payers considered it necessary to evaluate bioinformatics for accuracy (eg, sensitivity and specificity) similarly to diagnostic tests. Yet, payers have no methodologies for evaluating bioinformatics and whether and how to establish related coverage policies.

**Evidence Methods Proposed for NGTS Do Not Fit Payers' Evidentiary Standards**—When evaluating a diagnostic, 100% of payers require evidence of analytic validity, clinical validity, and clinical utility (including outcomes from treatments guided by the diagnostic), and all of them will apply these requirements to NGTS coverage. Regarding health outcomes, 70% realize that phase III randomized control trials are not feasible for the many-to-many target-drug combinations, and may accept lower levels of evidence, especially for pan-cancer applications already approved in one cancer. The other 30% will require the same phase III evidence as for the initially approved indication. Separately, 30% acknowledged that integrative features of NGTS, such as tumor pathway characterization, require novel study methods. Illustratively, one payer noted, “Sequencing is far beyond conventional tests, and we may need to get out of the box.” However, 70% were skeptical about new study models but expressed interest in better understanding them.

**Adoption and Care Delivery Concerns**—Eighty percent of payers believed that implementing NGTS in practice will face difficulties, and expressed concerns that these difficulties will preclude the promised advantages. Fifty percent expressed sufficient concerns about NGTS adoption and implementation that will preclude their ability to issue positive coverage. Although appreciating the potential benefit of increased personalization facilitated by NGTS, 50% were concerned that this will drive departure from the current trend toward standardization and the use of consistent treatment pathways. They noted that NGTS will lead oncologists back to the art of decision-making, increasing variability of care and outcomes.

Before coverage, 30% of payers want to see an indication that laboratories and cancer centers offering NGTS develop the necessary infrastructure for end-to-end delivery, beyond buying a sequencer or ordering a panel. This may include capturing NGTS results in electronic medical records, preparing physicians to use results in care, and establishing care processes, such as future recontacting of patients. Of specific concern was the establishment of the NGTS infrastructure and care delivery processes in community oncology, to avoid overwhelming community oncologists with this new technology, while ensuring patient access beyond academic centers. Forty percent of payers want to establish more transparency in this field, including providers' transparency to payers and patients on how NGTS is implemented, validated, used, and explained, not oversold, to patients.

## Discussion

Our study identified private payers' considerations and challenges for coverage of NGTS panels. To our knowledge, this is the first study to directly interview US payers on this topic. We discovered that although payers consider NGTS benefits a compelling hypothesis, NGTS conflicts with the concept of medical necessity, does not fit the current single test/single result coverage framework, and presents adoption concerns that must be addressed before coverage. Payers generally do not consider new clinical evidence methods proposed for NGTS acceptable for coverage.

Our findings indicate that some challenges are common between NGTS and other novel diagnostic tests, and could potentially be addressed within the existing coverage and evidence framework. However, other challenges are unique to NGTS and may be disruptive to the current coverage and evidence framework. Both types of challenges are discussed and an approach for addressing the challenges unique to NGTS is suggested.

Evidentiary challenges to coverage are not unique to NGTS and include absent evidence standards and a dearth of clinical utility proof.<sup>12,47,58–61</sup> However, NGTS may exacerbate these challenges,<sup>8,62</sup> partly, as we found, because no methodology exists for evaluating its unique features (eg, integrative features) within current evidence assessment frameworks created for single test/single result assays. To our knowledge, to date, only one evidence evaluation group undertook an assessment that included an NGTS unique feature—pathway characterization—commenting on difficulty of assessing this feature and related evidence.<sup>63</sup> Although evidence evaluation groups call for new research methods for diagnostics (eg, observational studies, big data approaches),<sup>62,64–66</sup> they have not included methods

potentially suited for NGTS evidence (eg, N-of-One, basket pan-cancer studies). Some evidence evaluation groups deem these methods immature,<sup>63</sup> echoing payers in our study.

Evidentiary challenges, although substantial, could be conceivably addressed within the existing evidence and coverage framework through agreeing on novel research methods and developing corresponding evidence. However, other NGTS challenges are inherently disruptive to the existing coverage and evidence approach. Currently, for single test/single result assays, a linear trajectory to a “yes/no” medical necessity and coverage decision exists. Despite evidentiary challenges, arguably any such assay, if worthwhile, can follow this trajectory as its evidence base is developed, until determined sufficient and related benefit medically necessary. The assay is covered thereafter. All currently covered tests underwent this path. However, NGTS does not fit this trajectory. As indicated by our findings, because important NGTS benefits are predicated on inclusion of novel (along with established) targets, the panels will be deemed experimental/investigational and not medically necessary. The inclusion of novel targets is not a temporary, but a permanent, NGTS feature: as evidence is developed for novel targets and they become established, other novel targets will emerge and be included. Therefore, no new evidence may deem the entire panel medically necessary.

Our findings indicate another disruptive aspect of NGTS: it facilitates the transformation of oncology toward a model that is highly personalized and integrates research and standard care. Although this model holds substantial promise, it may run contrary to current coverage/reimbursement and clinical practice trends. Two examples illustrate this disruptive challenge.

First, NGTS supports integration of all care for one patient, both standard and experimental, facilitating choice of existing treatments and determination of trial eligibility in a clinically relevant time frame. This may substantially increase patient therapeutic options, and advance patient-centric oncology. However, it counters the current model of financing patient care, which requires fragmentation of standard-of-care versus experimental activities for reimbursement purposes. Experimental activities are further fragmented, because pharmaceutical trial sponsors require single-marker testing and may not finance NGTS as a shared utility. To address this issue, MD Anderson developed a sophisticated sequential multistep tumor sequencing process, which separates reimbursable and investigational sequencing.<sup>4</sup> However, this experience of the world's largest cancer center may not be easily repeated in other centers, and the impact on costs and result turnaround time must be assessed.

Second, the increased personalization of patient care facilitated by NGTS, although being the premise of precision oncology, may counter the existing trends toward care decision standardization and treatment pathway adoption. Integrative, multitarget NGTS features, such as comprehensive tumor characterization, are not yet conducive to being incorporated into a treatment pathway or a decision algorithm, potentially causing increased variation in decisions and treatments. Practice variation is considered a culprit in the current health care environment striving for standardization.

Our findings raise a critical question for oncology stakeholders: do we redefine NGTS to fit the coverage and evidence framework, or do we redefine the coverage and evidence framework to fit NGTS? The former option would require limiting NGTS disruptive features, such as inclusion of novel targets or pan-cancer applications. Although it may diminish the potential for transformative benefits, it will have important merits, such as reducing the risk and health care costs, which is highly compelling in the current oncology environment. The latter option is undoubtedly more uncertain and complex, but provides a potential for realizing arguably unprecedented benefits. This option requires a 3-pronged collaborative approach across stakeholders: (1) explicitly define disruptive features of NGTS, (2) adjust the evidentiary framework, including methods of evidence research and approaches to evidence evaluation, and (3) adjust the coverage and reimbursement framework to align with the evidentiary framework and allow incorporation of NGTS advantages.

Addressing NGTS-related challenges may require that payers, clinicians, clinical researchers, and laboratory-based scientists acknowledge and adapt to the dynamic and rapidly evolving interface between the clinical and research realms in oncology, facilitated by NGTS—an interface that must not be a barrier but rather a new arena of long-awaited, immense promise.

This study had several limitations. We used a small payer cohort that did not allow statistical power and did not include public payers, which are important coverage decision-makers. This was mitigated by the fact that the included payers cover a third of the US population, and 7 are the top-10 largest plans whose policies influence other private and public payers. As an exploratory effort, our study identified key issues but did not provide an exhaustive account of challenges that must be addressed, nor did it examine specific issues in detail. Future studies should conduct deeper examination of these challenges with broader and larger sets of stakeholders to allow the crafting of possible solutions.

## Conclusions

Payers perceive that NGTS panels hold significant promise but, in their current form, pose disruptive challenges to coverage policy framework. Proactive multidisciplinary efforts to define the direction for NGTS development, evidence generation, and incorporation into coverage policy are necessary to realize its promise and provide patient access.

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**Table 2**  
**Clinical Expert Perspectives: Categories of Sequencing Targets Included in Next-Generation Tumor Sequencing Panels and Corresponding Uses**

Target Category <sup>a</sup>	Description	How It May Be Used	Type of Use
Established targets	Standard-of-care alterations: proven validity and utility for specific cancers acknowledged by guidelines and/or covered by payers	Guide the use of a targeted therapy approved for specific cancer (predictive targets)	Clinical
		Inform prognostication (prognostic targets)	Clinical
		Match a patient to a biomarker-driven clinical trial of a novel drug for an established target	Research
Novel targets	Alterations with known or suspected, but less proven validity and/or utility, or new alterations for known tumor suppressor genes with existing targeted therapies	Guide the use of targeted therapy if available for established variant of same gene	Clinical or research
		Match patients to biomarker-driven clinical trials, if available	Research
		Inform genomic and drug discovery	Research
Pan-cancer targets	Alterations with established validity and utility in another cancer	Guide the use of an approved targeted therapy based on the target/drug model from another cancer	Clinical or research
All of the above	Enhanced understanding of a patient's tumor	Assess tumor heterogeneity	Clinical or research
		Determine tumor pathways (eg, resistance to therapies)	Clinical or research
		Assess temporal tumor behavior and evolution during treatment (via repeat monitoring)	Clinical or research

<sup>a</sup>Tumor genetic or molecular alterations and biomarkers interrogated by next-generation sequencing panels.

**Table 4**  
**Payer Perspectives: Current Challenges to Developing Coverage Policy for NGTS Panels**

Challenge Category	% of Payers Noting at Least One Challenge (n=10)	Description of Specific Challenges	% of Payers Noting a Specific Challenge (n=10)
NGTS does not fit the definition of “medically necessary” and “experimental/investigational”	80%	Novel targets and research activities informed by NGTS deem the entire panel “experimental/investigation”	70%
		Pan-cancer applications are really just the use of off-label approaches and are experimental/investigational	60%
		Efficiency of testing does not quality as medically necessary	40%
		Future utility and benefit cannot be determined as medically necessary	50%
Misalignment with “single test/single result” approach to coverage	70%	Considering NGTS a bundle of targets	70%
		No precedent to evaluate integrative benefits of NGTS	50%
		Bioinformatics must be considered as its own diagnostic, with validity and accuracy; no precedent to pay for it separately	60%
Evidence methods proposed for NGTS do not fit payers' evidentiary standards	70%	Large correlative studies are still required	70%
		Skepticism and lack of experience with new study methodologies (eg, N-of-One, basket studies, in silico modeling, data pooling)	70%
		Pan-cancer evidence must be as extensive as initial indications	30%
Concerns about adoption and implementation of NGTS in oncology care	50%	Departure from standard care protocols because of increased personalization; increases care variability and reduces decision reproducibility	50%
		Lacking infrastructure for implementation and care delivery	30%
		Lack of transparency on how NGTS is implemented and used	40%

Abbreviation: NGTS, next-generation tumor sequencing