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## Themed Section: Assessing the Value of Next-Generation Sequencing

# From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing



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### ABSTRACT

Next-generation sequencing promises major advancements in precision medicine but faces considerable challenges with insurance coverage. These challenges are especially important to address in oncology in which next-generation tumor sequencing (NGTS) holds a particular promise, guiding the use of life-saving or life-prolonging therapies. Payers' coverage decision making on NGTS is challenging because this revolutionary technology pushes the very boundaries of the underlying framework used in coverage decisions. Some experts have called for the adaptation of the coverage framework to make it better equipped for assessing NGTS. Medicare's recent decision to cover NGTS makes this topic particularly urgent to examine. In this article, we discussed the previously proposed approaches for adaptation of the NGTS coverage framework, highlighted their innovations, and outlined remaining gaps in their ability to assess the

features of NGTS. We then compared the three approaches with Medicare's national coverage determination for NGTS and discussed its implications for US private payers as well as for other technologies and clinical areas. We focused on US payers because analyses of coverage approaches and policies in the large and complex US health care system may inform similar efforts in other countries. We concluded that further adaptation of the coverage framework will facilitate a better suited assessment of NGTS and future genomics innovations.

**Keywords:** insurance coverage, next-generation sequencing, precision medicine, precision oncology, reimbursement, tumor sequencing.

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### Introduction

Precision medicine—the use of genomics to guide health care decisions—is permeating many areas of health care [1]. The advent of massively parallel next-generation sequencing to simultaneously identify large numbers of genetic mutations promises even more significant advancements of precision medicine [2,3]. Nevertheless, this revolutionary technology has been faced with challenges in insurance coverage [4–7]. Although next-generation sequencing is increasingly used in clinical practice [8–10] and may be reimbursed by US payers [11], the lack of explicit insurance coverage from payers causes payment uncertainty and variable access [12–14], and thus should be understood and addressed.

One of the challenges of insurance coverage for next-generation sequencing is that it pushes the very boundaries of the underlined framework used by insurers in coverage decisions [15–17]. For example, to receive insurance coverage, a medical technology must

be determined “medically necessary” and not “experimental/investigational.” Next-generation sequencing blurs the boundaries between these two concepts, making coverage decisions difficult [16–18]. Hence, a number of experts have called for adaptation of coverage framework for next-generation sequencing [6,16,17,19].

In oncology, with more than 8,200,000 annual cancer deaths worldwide and more than 609,000 annual US cancer deaths [20,21], next-generation sequencing holds a particular promise that interrogating multiple genes in one's tumor (or next-generation tumor sequencing [NGTS]) will lead to identification of genetic targets for life-saving or life-prolonging treatments and optimization of an overall therapeutic strategy. Although a growing number of US cancer centers offer NGTS in clinical settings, public and many private payers have not been formally covering it—a position congruent with that of some experts who consider clinical adoption of NGTS premature [20,21]. The recent announcement by the Centers for Medicare & Medicaid Services (CMS) of a new national

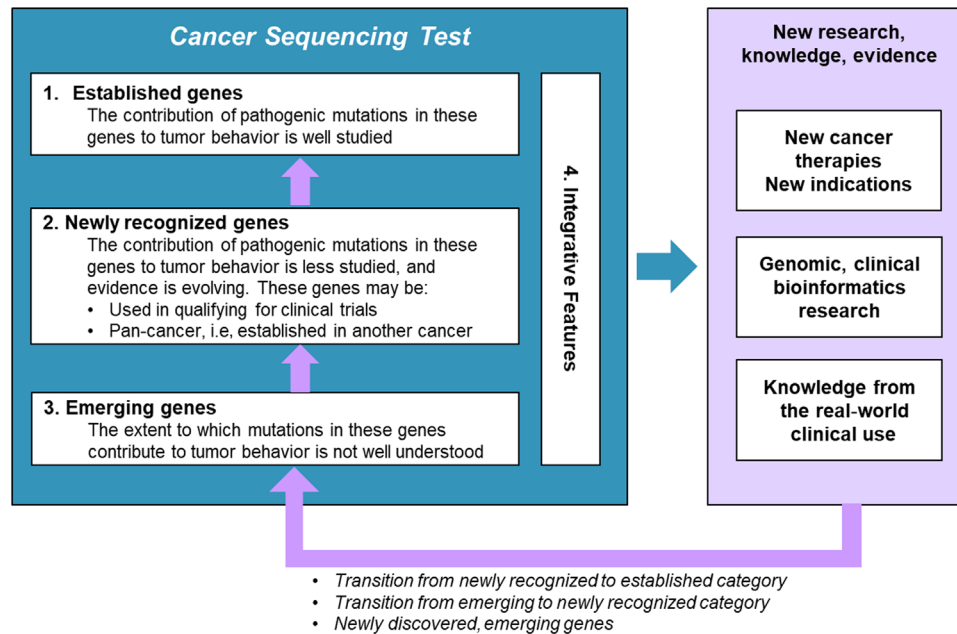
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**Fig. 1 – Inherent evolutionary nature of cancer sequencing. Source: Authors' analysis.**

coverage policy for NGTS in advanced solid cancers [22] made the topic of NGTS coverage even more controversial and urgent, as evidenced by immediate debate [23–26] and 315 public comments on the previous draft policy of CMS [27].

Our objective is to describe the previous proposals to adapt the insurance coverage framework for NGTS and discuss the new CMS coverage policy in the context of these proposals. We reviewed literature to identify the adaptation approaches relevant to coverage for NGTS and assessed these approaches on the basis of a specific illustrative proposal for each. We then assessed the CMS policy against the previously proposed adaptation approaches and identified areas of alignment and misalignment, as well as opportunities for further development of the coverage framework. We focused on US payers because analyses of insurance coverage approaches and policies in the large and complex US health care system may inform similar efforts in other countries.

Importantly, we did not advocate for or against clinical adoption or insurance coverage of NGTS. Instead, we aimed to highlight the challenges of evaluating it for insurance coverage and to discuss potential opportunities for addressing these challenges.

## NGTS Explained

NGTS refers to simultaneously interrogating multiple genes in one's tumor using next-generation sequencing technology. Knowing tumor genetic mutations can inform the understanding of one's cancer (e.g., prognosis) and guide selection of therapy either targeting an alteration (targeted therapy) or mobilizing one's immune system to fight cancer (immunotherapy). In the past, single-gene tests were used to identify relevant mutations one at a time, often requiring numerous tests, multiple invasive biopsies, prolonged time, and significant cost [28,29]. NGTS produces the needed information in one test, potentially resolving these issues, and possibly offering other benefits not feasible in the single-gene test era. These benefits result from profiling not only established (well-studied) genes, but also newly recognized (less studied) and emerging (not well-understood) genes concurrently in one test (Fig. 1). Table 1 presents the unique

features of NGTS, compared with single-gene testing, and we describe several key aspects herein.

By including all three categories of genes (established, newly recognized, and emerging), NGTS can provide information that supports both clinical and research purposes, such as qualifying patients for a clinical trial of targeted therapy or immunotherapy and collecting data for further genetic research. Testing the same set of genes across different cancers (pan-cancer testing) allows identification of targeted therapy effective in one cancer and using it for a patient with a different cancer, but with the same mutation. This use of therapies across cancers based on a common cancer genetic mutation may potentially extend survival for patients with advanced cancer with no other therapeutic options.

Another unique feature of NGTS is its integrative utility—cumulative analysis of interrogated genes—informing anticipation of tumor behavior, such as resistance to therapy, as well as the calculation of a tumor mutational burden that may predict response to immunotherapy, the newest class of cancer drugs [30]. Tumors, especially in advanced stages, often mutate, developing resistance to therapy and requiring repeat sequencing to identify genetic targets for other therapies. This serial sequencing pathway allows tailoring one's treatment strategy to tumor development and creates a full picture of temporal tumor behavior.

## Rationale for Adapting the Insurance Coverage Framework for Evaluating NGTS

US payers typically cover a medical technology if they determine it medically necessary and not experimental/investigational. The concepts of “medically necessary” and “experimental/investigational” are the cornerstone of insurance coverage framework and are typically considered mutually exclusive (Table 2). Accordingly, payers do not cover technologies that are under research. Payers have been applying this framework to coverage decisions on conventional genetic tests, which typically generate a single result (e.g., a cancer recurrence score, or whether a tumor is HER2/neu-positive or -negative). For genetic tests that guide treatment decisions, payers have based determination of medical necessity on how well the test predicts benefit from the related

**Table 1 – Features of NGTS conflicting with the current insurance coverage framework.**

NGTS feature	Conflict with the current insurance coverage framework
1. Dual utility: clinical and research	Applies to both “medically necessary” and “experimental/investigational” categories [15,16]
2. Informing enrollment in clinical trials	Clinical trial is a guideline-recommended setting for cancer treatment, and is therefore both “medically necessary” and “experimental/investigational” [13,32]
3. Comparative cost of NGTS, relative to single-gene testing	Cost is not a formal factor of coverage framework [19,39]
4. “Sequencing pathway” utility—serial use over time	Typically focused on one technology and one point in disease trajectory [6,19]
5. Inherent evolutionary nature of evidence for tumor sequencing tests	Conflicts with the linear trajectory of evidence development and binary coverage decision [16,19]
6. Informing pan-cancer use of drugs	Conflicts with medical necessity definition for a specific indication [6,16,19,39]
7. “Many-genes-to-many-drugs” utility	Conflicts with the one-marker-one-drug evaluation of medical necessity [6,19,39]
8. Integrative utility based on compound analysis of mutations	Sequencing is considered a “bundle” of individual gene tests [15,16]

NGTS, next-generation tumor sequencing.

treatment. For such tests, the treatment should be already approved by the US Food and Drug Administration (FDA) for the specific clinical indication under consideration for coverage. Payers' decision making on genomic tests is based on clinical evidence, but may also include additional considerations, such as patients' demand, clinicians' acceptance, logistical feasibility of testing, and other health care factors [31–33]. Nevertheless, US payers in the past have not included cost—an important health care factor—in their coverage decisions: public payers are prohibited from including costs in coverage decisions, and private payers often follow suit [32,33].

This traditional coverage framework is challenging for making decisions on NGTS because the NGTS features conflict with several aspects of the coverage framework. Table 1 presents the key features of NGTS and indicates how they conflict with the coverage framework. Herein we describe several of these conflicts in more detail.

Unlike conventional genetic tests, NGTS includes well-established and newly recognized genes in one test and thus supports both clinical and research purposes. This puts it in both medically necessary and experimental/investigational categories simultaneously [16,18], conflicting with traditional delineation [34].

**Table 2 – Description of concepts: “medically necessary” and “experimental/investigational” (based on an Institute of Medicine report [34]).**

<p>Concept of “experimental/investigational” technology or service</p> <ul style="list-style-type: none"> <li>• A technology is experimental/investigational if the evidence of its efficacy and safety is insufficient to determine whether it is medically necessary</li> </ul> <p>Concept of “medically necessary” technology or service</p> <ul style="list-style-type: none"> <li>• Definitions vary across payers</li> <li>• The Institute of Medicine Committee did not develop a single definition, but recommended criteria for medical necessity, consistent with best practices and supported by legal precedent. Medically necessary services/technologies are</li> </ul> <ol style="list-style-type: none"> <li>1. Clinically appropriate for the individual patient</li> <li>2. Based on the best scientific evidence, taking into account the available hierarchy of medical evidence</li> <li>3. Likely to produce incremental health benefits relative to the next best alternative that justify any added cost</li> </ol>
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The use of NGTS to qualify patients for clinical trials is considered experimental/investigational because the therapies informed by NGTS results are experimental and not yet approved. Clinical trials are, however, often the best or only therapeutic option for patients with advanced cancer, and cancer clinical guidelines encourage a clinical trial as the “best management for any cancer patient” [35]. Therefore, NGTS may in fact be considered medically necessary for these patients. Accordingly, it has been proposed to recognize tests informing enrollment in oncology trials, such as NGTS, as part of “direct clinical management of the patient” and thus medically necessary [36].

Likewise, the pan-cancer use of NGTS and therapy guided by its results is considered experimental/investigational because the therapy may be FDA-approved for a specific cancer but considered “off-label” for other cancers. Yet, the off-label use of this therapy may be the only option available to some patients [15], and therefore medically necessary for them. An example of a pan-cancer therapy is pembrolizumab, immunotherapy recently approved by the FDA on the basis of a pan-cancer genomic feature rather than an anatomic location of the tumor [37]. This is the first pan-cancer FDA approval, but numerous other pan-cancer uses of genomic analysis and therapies remain experimental.

Within the current coverage framework, researchers generate clinical evidence for a test until deemed sufficient by a payer, after which coverage is granted. If NGTS had a static composition of genes, it could follow this trajectory of evidence generation until all newly recognized and emerging genes are well studied. Nevertheless, a unique feature, and arguable advantage, of NGTS is the dynamic gene composition (Fig. 1): in a cyclical process, as new evidence is generated, the less studied genes become more established and newly discovered genes are added. Thus, the inclusion of less studied genes is a permanent feature of NGTS, allowing ongoing updates to NGTS tests on the basis of new discoveries. Continued evidence collection and analyses are needed [15,38]. Under the current coverage framework, this dynamic, evolutionary feature will always deem NGTS experimental and not medically necessary [16].

Another feature of NGTS is its arguable cost advantage compared with stepwise single-gene testing. NGTS may also contribute to reducing costs by ruling out ineffective, toxic treatments. Nevertheless, because cost is not a factor in the current coverage framework, NGTS' cost impact (whether advantage or disadvantage) does not influence coverage decisions.

Although the medically necessary concept will remain a cornerstone of the coverage framework, this describes why an adaptation of the coverage framework is necessary to allow multifaceted assessment of NGTS in coverage decisions [6,16,19,39,40].

#### *Approaches and Illustrative Proposals to Adapt Insurance Coverage Framework for NGTS*

We identified three types of approaches for adapting the coverage framework relevant to NGTS: 1) real-world performance-based risk-sharing arrangements (PBRsAs), 2) a technology-specific coverage framework, and 3) coverage with evidence development (CED). Within each approach, we identified an illustrative example relevant to NGTS.

We now describe and compare the three approaches, followed by a discussion of the CMS policy in the context of these approaches. It is important to note that the CMS policy is not the “fourth framework,” but rather a product of a “framework” that the CMS uses. Because the exact framework that the CMS used to generate this policy is unknown, we compared the policy with the three frameworks proposed for NGTS evaluation and discussed whether the policy followed any aspects of the proposals.

#### *Real-world PBRSA (illustrated by “PBRSA for Genome-Based Cancer Care,” proposed by Ramsey and Sullivan [39])*

Real-world PBRSA is a contract between a payer and a health product/service provider, in which reimbursement for the product/service is contingent on its future real-world performance [41]. The goal is to provide early, limited access to promising, but unproven technologies while reducing risk for the payer [39,41,42]. Real-world PBRsAs have received strong and growing interest from payers and product manufacturers internationally; they have been implemented mostly in Europe for therapeutics and medical devices in various diseases, including cancer [41,43]. An illustration of real-world PBRSA for NGTS is the cancer-related proposal by Ramsey and Sullivan [39]. It entails establishing an agreement (performance-based risk-sharing agreement for cancer genomics [PBRSA-C]) between a payer and a cancer center, under which physicians and patients may use NGTS to inform a choice between the standard of care and an off-label pan-cancer therapy that showed early promise in the patient’s cancer (e.g., on the basis of published cases or small studies). The payer would reimburse the costs of NGTS and the therapy, subject to meeting predefined patient-specific therapeutic success measures, for example, survival, tumor response to treatment, and/or toxicity. If the measures are not met, the cancer center becomes responsible for the cost of NGTS, the drugs, and the associated care. Risk sharing would include provisions to err on the side of the cancer center given complexities of data analyses and requirements for “reasonably sophisticated” information systems to track the necessary data.

#### *Technology-specific coverage framework (illustrated by the proposal from the Center for Medical Technology Policy [19])*

This approach entails developing a coverage framework focused on a specific technology [6]. An example of this approach is the proposal by the Center for Medical Technology Policy (CMTP’s) Green Park Collaborative. The proposal is a detailed template of a coverage policy for NGTS and therapies guided by its results. Different coverage criteria are recommended for NGTS on the basis of the number of genes. For the tests with 50 genes or fewer, at least 5 must be “established,” and the cost of NGTS may not exceed the total cost of single-gene tests. Coverage for tests with more than 50 genes is proposed for six specific clinical

indications, such as new diagnosis of stage IV adenocarcinoma of the lung. For these conditions, in addition to standard-of-care drugs, the off-label pan-cancer therapies may also be covered if supported by peer-reviewed publications. The drug manufacturer pays for the first 3 months of this therapy, and the payer reimbursement starts thereafter if positive or stable results are observed. The CMTP describes this as “patient-specific medical necessity.”

#### *Coverage with evidence development (illustrated by the MoIDX program [44])*

Under CED, a promising but unproven medical technology is granted provisional insurance coverage contingent on concurrent generation of evidence sufficient for definitive coverage. If evidence is not generated according to CED conditions, a negative coverage decision follows [45]. CED has received considerable attention in the United States and internationally [41–43,45,46]. More than 20 documented US CED initiatives by public and private payers have been reported as of 2017 [43]. An example of CED relevant to NGTS is the MoIDX program for evaluating molecular diagnostics, implemented by Palmetto GBA, a Medicare contractor, in 2011, and adopted by several other Medicare contractors. The program is applicable to NGTS, but considers any molecular diagnostic test. A test may receive full coverage, limited coverage (for strictly limited indications), coverage with data development (based on a study protocol and data-generation plan), or noncoverage. Palmetto GBA described MoIDX as a new reimbursement paradigm: in addition to medically necessary and experimental/investigational categories, it uses a third, transitional category contingent on data development [15]. A “transitional” status is temporary until the test developer provides or fails to provide sufficient evidence, resulting in full coverage or noncoverage, respectively.

#### *Assessment of the Three Frameworks—Advantages and Gaps*

Overall, we considered PBRSA-C as the most promising among the three frameworks in terms of addressing important features of NGTS. PBRSA-C’s advantage is placing the decision into the patient-physician interface, but with predefined accountability, allowing them flexibility in the choice of NGTS tests and therapies. A major concern with PBRSA-C is the complexity of implementation because of the need for real-time information systems, the intricacy of risk-sharing contractual arrangements, the need to establish agreements between individual payers and multiple cancer centers, variability in terms across contracts, and potential lack of acceptance of risk sharing by cancer centers.

From the implementation feasibility perspective, MoIDX had an obvious edge, because it had been operational for a number of years. Nevertheless, MoIDX is also the least accommodative of the NGTS features, because it leaves many of them unaddressed (Table 3).

The sharp focus of the CMTP proposal on NGTS may be viewed as an advantage. This framework is more concrete, detailed, and more easily adoptable than PBRSA-C. Nevertheless, the coverage tied to the number of genes is a limitation, appearing arbitrary and not medically or economically justified. Nevertheless, using a concrete criterion, even if arbitrary, is a step forward, allowing coverage for some NGTS tests, versus denial of all.

Consideration of medical necessity at the patient level by PBRSA-C and the CMTP is an innovation. Nevertheless, unlike PBRSA-C, the CMTP applies this concept to pan-cancer (off-label) therapies only, and not to NGTS, leaving the conflict between NGTS and medical necessity unresolved. The MoIDX’s transitional category of tests is a general advancement, but not applicable to NGTS: the transitional status is a temporary

**Table 3 – Illustrative proposals for a coverage framework relevant to NGTS.**

Framework aspect	PBRSA-C*	CMTP†	MolDX‡
	<i>General framework aspects</i>		
Framework type	Risk-based reimbursement/contract	Technology-oriented insurance coverage	Evaluation-oriented insurance coverage
Framework focus	Specific to NGTS and related therapies	Specific to NGTS and related therapies	Focus on molecular diagnostics, including NGTS
Key criteria for coverage/payment	Effectiveness of therapy informed by sequencing in specific patients (e.g., 5-mo survival for a stage IV patient)	Based on the number of established and total genes; for tests with larger number of genes: cover for specific clinical indications	Impact of the test on clinical outcomes, not just on clinical decisions
How medical necessity was innovated	For pan-cancer therapies—introducing patient-level medical necessity For sequencing—made less relevant, in the context of payment agreements for both sequencing and therapy	For pan-cancer therapies—introducing patient-level medical necessity For sequencing—based on the number of established and total genes	Introducing a “transitional” category, between medically necessary and experimental
	<i>How features of NGTS are addressed or evaluated</i>		
Dual utility: clinical and research	Does not require addressing under the combined payment for test and therapy	Addressed by allowing novel genes in sequencing tests	Not addressed
Informing enrollment in clinical trials	Not addressed	Not addressed	Not addressed
Comparative cost of NGTS, relative to single-gene testing	Cost of sequencing is included in the contract payment, but is not an explicit factor	Evaluated explicitly: cost of sequencing should not exceed cost of single-gene testing	Not evaluated
“Sequencing pathway” utility—serial use over time	Not addressed	Not addressed	Not addressed
How the evolutionary nature of evidence is addressed	Does not require addressing under the combined payment for test and therapy	Not addressed	Not addressed
Informing pan-cancer use of drugs	Subject to individual patient response to therapy at a cancer center	For pan-cancer drugs: payment subject to patient’s response after first 3 mo of use The use of sequencing in pan-cancer context: not addressed	Not addressed
“Many-genes-to-many-drugs” utility	Does not require addressing under the combined payment for test and therapy	Not addressed	Not addressed
Integrative utility based on compound analysis of mutations	Does not require addressing under the combined payment for test and therapy	Not addressed	Not addressed

Source: Authors’ analysis.

CMTP, Center for Medical Technology Policy; NGTS, next-generation tumor sequencing; PBRSA-C, performance-based risk-sharing agreement for cancer genomics

\* Proposed by Ramsey and Sullivan [39].

† The proposal by CMTP’s Green Park Collaborative.

‡ MolDX is the program by Palmetto GBA.

designation for a test while evidence is being produced. Nevertheless, because the transitional nature of NGTS is permanent, it may be “stuck” in this category indefinitely. In contrast to MoIDX, the CMTF noted that coverage with data development is not a suitable approach for evaluating NGTS.

A shortcoming of all three frameworks is that two key aspects of NGTS are not addressed: the use of NGTS to qualify patients for trials and the “sequencing pathway” feature, that is, serial use of NGTS over time to assess tumor molecular development and emergence of mutations associated with resistance to treatment.

### CMS' National Coverage Determination for NGTS: Addressing Some Challenges and Creating New Ones

On March 16, 2018, the CMS announced a national coverage determination for NGTS, as an outcome of an innovative parallel FDA/CMS review process [22]. The coverage announcement was surprising to both opponents and proponents of NGTS adoption, was followed by immediate commentaries [23–26], and fueled 315 public comments during the previous comment period [27]. The policy provides coverage for NGTS for advanced solid cancers if 1) the patient has not been tested with the same test for the same diagnosis, 2) the patient seeks further treatment, 3) the test is FDA-approved or cleared as a companion diagnostic for the indication in that patient's cancer and the report template specifies treatment options. In cases in which conditions 1 and 2 are met, but 3 is not, test coverage is up to the decision by local Medicare administrative contractors (MACs).

The CMS NGTS policy has broad and far-reaching implications for oncology clinical practice, research, and health policy [25,26] and will likely be extensively studied over time. Here we focused on the question “How does this policy compare with the traditional and proposed coverage frameworks, and what are the implications for coverage frameworks going forward?”

In two important aspects, the CMS policy goes beyond the current and proposed frameworks. First, its approach to medical necessity will cover an NGTS test even if it includes newer genes [22]. This is contrary to the approach of the current frameworks, which require that all genes in a test be established, or the approach by the CMTF, which is based on the number of established and total genes. Second, the CMS policy may be a step toward addressing pan-cancer use of drugs informed by NGTS. Although the policy does not discuss the use of therapeutics, it does not prohibit such drug use, and states that prohibiting such use would increase burden and decrease flexibility for innovative developments.

The CMS policy, however, leaves several gaps unaddressed. It does not allow repeat NGTS that may be required for patients with treatment-resistant cancers [22]. It appears to prohibit coverage of an NGTS assay when the number of included novel genes is expanded, until the updated assay is approved/cleared by the FDA. The CMS policy does not address the use of NGTS for enrollment in clinical trials—a gap in the three proposed frameworks we reviewed earlier. Notably, this gap was addressed in the draft policy, which included a CED requirement for clinical trials and other NGTS uses considered investigational. Nevertheless, the CED component was removed in the final version, leaving potential CED considerations to MACs. It remains to be seen if/how the MACs will apply CED to coverage decisions for NGTS in their respective jurisdictions. In addition, unlike PBRSA-C and the CMTF, the CMS policy does not address the cost impact of NGTS. Although the CMS cannot by law include cost in its coverage decision, this is a serious limitation to its decision making in the era of cost containment.

Private payers will likely consider the CMS policy in their coverage decision making, but it is uncertain whether/how they will follow suit. They may consider certain innovative aspects of

the CMS policy (e.g., its framing of medical necessity), as well as address the gaps that the CMS policy left, notably, consideration of cost impact. Unlike the CMS, private payers are not precluded by law from considering costs and have the ability to incorporate them in coverage decisions.

In considering the implications of the CMS policy for overall coverage decision making on NGTS and other genomics, it is essential to note that it is just that—a single policy, not a framework. It is unclear whether the features of this policy pertain only to NGTS for advanced solid cancers or signal a new approach by the CMS to other multigene sequencing panels and other clinical areas. Thus, uncertainty remains about CMS' overall framework for coverage decisions on genomics, as well as the future of CMS' coverage for other tests, such as liquid biopsy sequencing assays (which test blood instead of tumor tissue), hereditary cancer panels, interrogated inherited cancer risk, or multigene panels in cardiovascular or other diseases, where genomic sequencing began to emerge. Significant attention will be paid to how future policies of private payers, MACs, and state Medicaid agencies frame coverage of NGTS and whether they address the gaps we described here.

### Conclusions

We reviewed three approaches to adapting the insurance coverage framework for NGTS, focusing on US payer decision making. We discussed the recent CMS' national coverage determination for NGTS in the context of these proposals and the overall need to align coverage frameworks with the features of NGTS. Taken together, the proposed adaptations and the new CMS policy form a potential foundation for future work on coverage policy framework for genomics. Further adaptation of the coverage framework for NGTS and other genomic tests may help to facilitate a better suited assessment of future genomics innovations.

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