Green Park Collaborative

A partnership for innovation and effectiveness

Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology

Report and Recommendations

The Green Park Collaborative is a major initiative of the Center for Medical Technology Policy

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Sean Tunis, MD, MSc, President and Chief Executive Officer, CMTP, provided strong leadership, vision, insight, and support throughout this effort.

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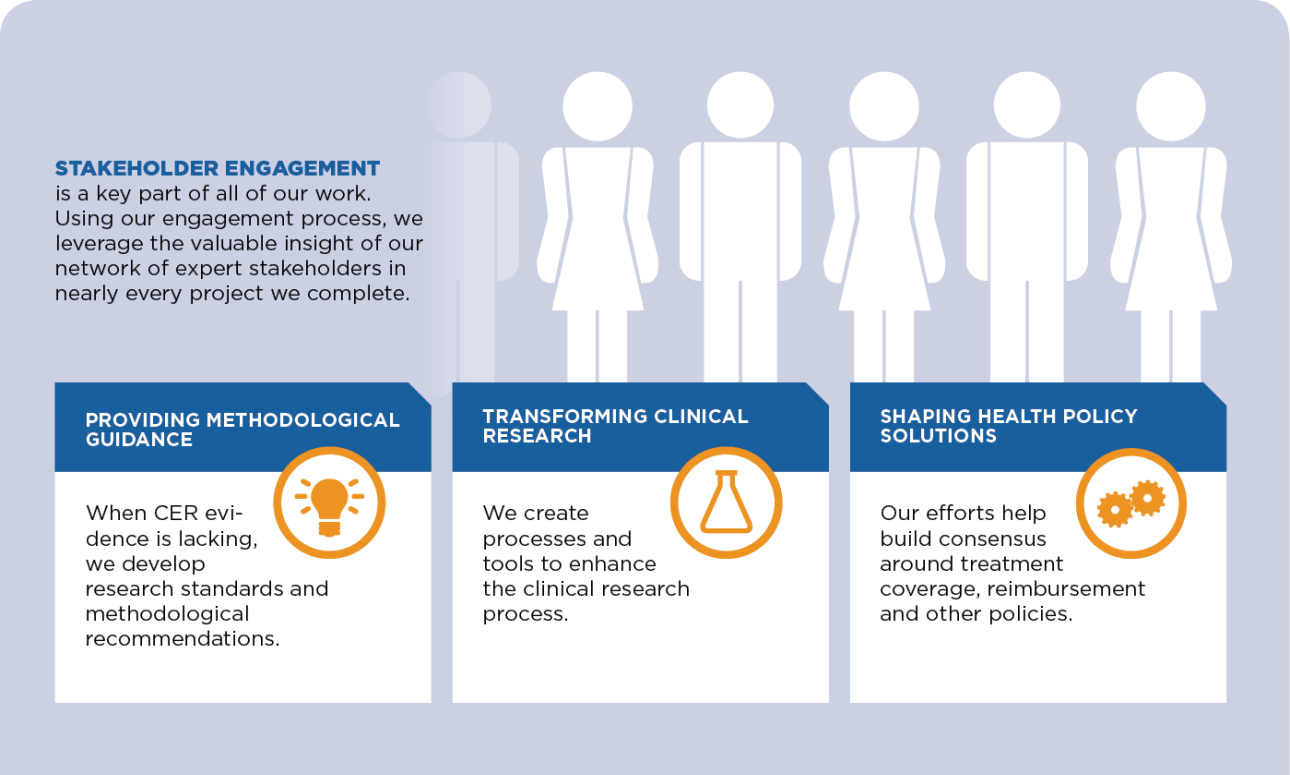
ABOUT CMTP

The Center for Medical Technology Policy (CMTP) is an independent, non-profit dedicated to developing a health care system where patients, clinicians, health care policymakers, and payers have the evidence they need to make informed health decisions. We convene and collaborate with a national and international network of thought leaders, patients, patient advocates, clinicians, policymakers, and payers. Together, we support the next generation of clinical research. We do this by providing methodological guidance, shaping health policy solutions, and transforming clinical research.



GREEN PARK COLLABORATIVE – USA

The Center for Medical Technology Policy hosts the Green Park Collaborative – USA (GPC-USA), a multi-stakeholder forum that develops condition and technology-specific study design recommendations to guide the generation of evidence needed to inform both clinical and payment decisions in the United States. GPC-USA includes a diverse mix of payers, life sciences companies, patients, clinicians, researchers, regulators, and other stakeholders.

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I. EXECUTIVE SUMMARY

Through its Green Park Collaborative, the Center for Medical Technology Policy has hosted a series of meetings and conference calls with a diverse group of stakeholders to discuss standards for clinical utility and model coverage guidelines for diagnostic testing using next generation sequencing (NGS) in oncology. The purpose of this project is to meaningfully engage all key stakeholders to overcome barriers to more rapid clinical evaluation, clinical uptake, and coverage of efficacious DNA sequencing for the benefit of patients with cancer. While this effort is focused on cancer, many aspects of this work on evidence generation and clinical use of sequencing data will apply across many clinical areas besides oncology.

The effort entailed two in-person workshops held in Baltimore on July 7, 2014[1] and April 4, 2015, as well as a series of teleconferences which ran between October 20, 2014 and June 22, 2015. The initial focus of the first meeting and early teleconferences was on the evidence needed to demonstrate clinical utility for NGS-based testing. However, as described in detail below, the project discussions gradually evolved from a narrow focus on evidence standards to consideration of larger coverage policy issues. The goal was to develop a framework for NGS coverage incorporating rigorous yet flexible standards of evidence for clinical utility, provisions for assurance of analytic and clinical validity, applicability to panels and other types of genomic sequencing, and promotion of systematic data collection, among other features.

In February and March, 2015, multiple stakeholders, representing diverse and often conflicting interests, were consulted in the creation of a "straw man" policy framework for discussion. Deliberations of this framework took place in the April 4, 2015 in-person meeting. The framework was then revised for review and continued discussion in teleconferences on June 4 and June 22, 2015.

This framework was thus developed through a process designed to balance to the greatest extent possible the needs and interests of all stakeholders. Our hope and intent is that medical policy committees, health system leaders, and others responsible for decisions on patient access to NGS testing will use these recommendations as the framework for their own medical policy documents.

The draft model policy document addressed the following key topics:

1) assurance of analytic and clinical validity of NGS testing for payers
2) coverage of panels
3) coverage of whole exome and whole genome sequencing
4) coverage of off-label drugs and biologics
5) policy levers to incentivize systematic data-collection and clinical research on the use of genomics in oncology

This report sets out conclusions drawn from the deliberations of the draft document, including policy recommendations and steps for future action. The work was motivated by the view that having a clearly defined clinical policy framework for this class of testing technologies offers the best chance of promoting the rapid uptake and use of testing that improves patient outcomes while reducing spending on useless or harmful testing.

The framework was developed through an interactive, multi-stakeholder dialogue and aims to reflect the perspectives of payers, diagnostics companies, clinicians, patients and other key stakeholders. To the extent possible, CMTP has built recommendations around discussion points where a reasonable

level of consensus has been achieved. However, no assumption should be made that all participating stakeholders have agreed on all points.

Framework conclusions for each addressed topic are as follow.

Analytic and Clinical Validity
Payers should require laboratory accreditation through the College of American Pathology (CAP), including successful compliance with CAP's new laboratory accreditation checklist requirements and proficiency testing program for NGS analytic wet bench process and bioinformatics analysis processes.

Payers are expected to add requirements for FDA review when more clarity is available on the FDA role in regulating NGS and laboratory-developed tests (LDTs). Additional discussion is needed on how to achieve transparency for payers when laboratories are out-of-compliance.

Coverage of Panels
A key point of consensus in our discussions was that when multiplex panels of up to 50 genes analyze for a subset of 5 or more genes considered to be standard-of-care for use with a given diagnosis, then those panels should be covered. The covered panels must fit the American Medical Association's Current Procedural Terminology (CPT®) codes for panels comprised of 5 to 50 genes for solid organ neoplasms (CPT® 81445) or hematolymphoid neoplasms or disorders (CPT® 81450). (Criteria are specified in the framework below.)

Payer-stakeholders in our discussions did not favor routine coverage of panels comprising more than 50 genes. Further discussion is merited to determine if a consensus position can be achieved on future conditions, or current exceptional circumstances, that might apply to larger panels. A proposal is provided in the framework for further consideration.

Coverage of Whole Exome and Whole Genome Sequencing
Currently, comprehensive sequencing of cancer tumor genomes is considered to add little benefit to targeted analysis of known genes; panels targeting known genes are preferred for cancer care.[2] For this reason, whole exome and whole genome sequencing are still considered investigational and not covered.

Coverage of Off-label Drugs and Biologics
In general payers do not cover variant-directed drugs or biologics when the gene-drug combination is not listed in a US Food and Drug Administration (FDA) label. However, it might be practicable for payers to cover off-label variant-directed drugs or biologics for individual patients who have already demonstrated a benefit after 3 months of treatment with the off-label agent. Under these circumstances, it may also be reasonable to ask the drug-maker to provide the agent free-of-charge to the patient for the initial 3 months of use. In this manner, patients would not be financially responsible for the cost of expensive targeted cancer therapies during this period. While many stakeholders found these proposals attractive, substantive additional discussion is needed to achieve a framework acceptable to patients, payers and drug-makers.

Policy Levers to Incentivize Systematic Data-collection and Research
When panels composed of 5 to 50 genes are covered as described above, it is crucial that the full scope of data produced (including any data above and beyond what is indicated for patient care) is

systematically gathered along with patient information and outcomes. In this way, systematic learning and hypothesis generation can be advanced from real-world practice.

In general, there was consensus that this type of data-gathering is needed, and that coverage and reimbursement policy levers can be used to promote more rapid learning on the use of genomics in clinical oncology. Further discussion is needed to elaborate a specific set of policies that are practicable for payers, oncologists and patients, including whether cancer patients need to be enrolled in a registry or whether a specific entity should be tasked with coordinating the data gathering effort. Proposals for further consideration are included in the framework below.

II. BACKGROUND: PROJECT EVOLUTION

The initial focus of the first meeting and early teleconferences was on the evidence needed to demonstrate clinical utility for NGS-based testing. CMTP has previously prepared an Effectiveness Guidance Document on generating evidence of clinical utility for molecular diagnostic tests in adult oncology,[3] which broadly applies to all molecular diagnostics, including sequencing-based testing. However, stakeholders indicated that it would be helpful to engage with payers and discuss specific methods and policy challenges raised by next-generation sequencing, including the specific studies payers will require to cover NGS-based sequencing in clinical care, potentially including whole exome and whole genome analyses.

A number of challenges presented themselves in the course of discussions with stakeholders.

1) Some payers signaled concern that we were discussing standards for clinical utility when questions persist over the analytic and clinical validity of NGS testing. Most commercial payers do not see it as their role or within their technical expertise to create standards for assessing analytic and clinical validity, yet continuing discomfort in our discussions pointed to a need for a transparent process payers could rely on to assure the quality and consistency of covered testing.
2) Discussions of standards for clinical utility tended to focus on evidence for individual variants or gene mutations for use in a specific clinical context, but did not directly address the larger question of how to evaluate the clinical benefits and risks of panels or other NGS-based testing approaches that analyze for many different genes and variants at one time. Yet this key aspect of NGS testing has been an important barrier to securing affirmative coverage decisions and must be addressed if a viable coverage policy for NGS testing is to be established.
3) The current lack of evidence of clinical utility (and corresponding lack of coverage) even for older methods of doing genetic and genomic testing points to a fundamental failure in evidence-generation that cannot be addressed solely through the articulation of standards. At issue is a growing flood of new genomic variants in need of study and a lack of economic and commercial incentives for testing companies and laboratories to perform the kinds of studies payers and health technology assessment groups generally expect to see. A more comprehensive framework is needed to promote high-quality evidence generation by many methods, greater acceptance by payers of multiple evaluation methods, and the use of novel partnerships and policies to accomplish these goals.

In addition, individual coverage decisions are made by each payer organization on a case-by-case basis, taking into consideration the preponderance of available evidence and the medical necessity of the underlying test, which entails consideration the medical need of patients and the availability of other effective clinical tools in a specific clinical setting. These assessments can include consideration of published clinical guidelines and other sources of evidence, including expert recommendations based on varying bodies of evidence, to weigh the aggregate evidence of potential benefits or harms for individual patients. The balance of acceptable risks, benefits, and evidence for each situation therefore cannot be seen as a bright line. Discretion is ultimately needed for each coverage determination. Consequently, although the payers engaged in this project have substantively discussed their preferences for evidence-based coverage decision-making, a clear-cut set of consistently applied rules for "how much utility evidence is enough" for coverage in each individual circumstance is unlikely to be practicable.

Accordingly, as the project discussions matured and evolved, the team moved from a narrow focus on evidence standards to consideration of larger coverage policy recommendations for NGS that would incorporate standards of evidence amenable to flexible application, provisions for assurance of analytic and clinical validity, applicability to panels and other types of genomic sequencing, and promotion of valid and systematic data collection, among other features.

III. DISCUSSIONS OF GUIDELINES: KEY POINTS

ASSURING ANALYTIC AND CLINICAL VALIDITY OF NGS TESTING

Next generation sequencing (NGS) platforms represent a significant challenge for coverage decision-making due to the complexity and variability of procedures across the entire test cycle (sample preparation, assay, library preparation and bioinformatics, and interpretation). Between-laboratory differences in technology, quality metrics, and procedures can result in substantive differences in the information patients and clinicians receive for decision-making.[4,5] However to cover NGS testing routinely, payers need assurance that the results and quality of analysis are reasonably consistent across platforms. Standards for analysis set individually by health plans would be onerous for the laboratories to follow and also for payers to administer and track. A preferable solution would be for an independent standard-setting body to establish standards and an accreditation process to which payers can refer to assure between-laboratory consistency and quality.

For this reason, an early version of the guidelines recommended that the College of American Pathologists (CAP) set payer-acceptable standards for sample preparation, analytic parameters, and interpretation of results to be used for clinical NGS analyses; that CAP expand its laboratory accreditation program to include proficiency testing of these payer-acceptable performance standards; and that health plans recognize the CAP NGS accreditation program by specifying that all covered NGS testing is limited to laboratories participating in the CAP NGS accreditation program.

Generally speaking stakeholders were supportive of the aims of these proposals, but many expressed concerns that a new overlay of requirements would be added to clinical laboratories, which are already relatively highly regulated. Participants made it clear that any attempt to create a new set of standards or accreditation process should be coordinated with all standard-setting bodies (including CMS and CAP, the State of New York, the FDA, and others). In addition, while supporting the effort, representatives of

CAP expressed concern that the recommendations, as written, would exceed CAP's remit under the authority of CLIA. Representatives of CAP suggested that the College's new and emerging programs for proficiency testing of both germline and somatic variants should serve to assure payers of the quality of CAP-accredited laboratories.

Even so, the CAP program under CLIA is still focused on analytic validity (which is the accurate and reliable ability to detect certain variants when they are present), rather than clinical validity (which is the reliable association of a variant with the presence or absence of a particular phenotype). In addition, as the FDA has noted in recent proposed guidance, CLIA does not provide for a premarket review process to assure test quality and relevance before routine clinical use begins.[6] Representatives from the FDA suggested that the Agency's proposed plans for regulating laboratory developed tests, including NGS, will fill these gaps. The Medicare contractor Palmetto, as part of its MolDx program for evidence evaluation, registration, and coverage of diagnostic tests, has developed a detailed set of standards for analytic and clinical validity applicable to NGS testing which could conceivably also be adopted by commercial payers.[7] However, health plan representatives participating in our discussions expressed the view that Palmetto's approach, while rigorous, is too granular for many of them to implement. Another possible avenue to assurance of consistent analytic performance standards across laboratories is in development through Tapestry Network's SPOT/Dx Working Group, which is working towards consensus standards for the use of laboratory developed test (LDT) versions of FDA-approved companion diagnostics.[8]

Based on these discussions, we have concluded that the standards represented by the CAP program for NGS represent a reasonable basis for payers to use for assurance of NGS analytical performance. Additional requirements can be added as new oversight programs (such as FDA requirements for clinical validity) are developed. Some payers have commented that identities of deficient laboratories (i.e., those that have failed two out of three consecutive proficiency testing "events" in the CAP accreditation program), are reported to CMS (as CMS has statutory authority for quality assessment of clinical laboratories under CLIA), but not to other payers. For proficiency testing to be an effective tool to guide payer assessments of laboratory quality, all payers must be aware of performance deficiencies. Mechanisms should therefore be developed for CMS to share updated deficiency information with other payer organizations. This is a topic in need of further discussion.

NGS PANELS AND ASSOCIATED COVERAGE CHALLENGES

In our discussions of covering NGS-based testing, payers expressed the concern that few of the genes on panels are really needed to guide decisions for an individual patient's care. This concern has been a barrier to coverage of most NGS-based testing.

In an effort to overcome this barrier, the policy model draft document divided genetic variants into three broad categories: 1) Established variants are those which have been adopted into the standard of care for molecular biomarker-directed diagnosis, prognosis, or therapy in clinical oncology; 2) Emerging variants are those for which varying degrees of evidence suggests clinical utility in oncology, with recognition that some additional information may be desirable to inform clinical use optimally; 3) Unknown variants are those for which clinical significance is unknown or speculative (e.g., based on an unproven biologic rationale). This latter group are often called variants of unknown significance (VUS). Definitional criteria were proposed for each category which implicitly included varying levels of evidence for clinical utility.

The original draft framework envisioned that payers would be willing to cover mixed (containing all types of variants) NGS gene panels if they could only pay for the clinically indicated genes on the panel; i.e., pay only for the established variants, regardless of other variants concurrently analyzed or detected, and require that only these provider-ordered variants be reported out. It also set out suggestions for designing disease-specific panels on the assumption that payers would find this design more compatible with current coverage policies. In discussions with our payer-stakeholders, however, a consensus formed that although it was theoretically possible for them to sort out which variants met the criteria for payment, for most of them, doing so represented an undesirable level of granularity and complexity in coverage and reimbursement policy. In addition, no stakeholders favored placing limitations on reporting of emerging and unknown variants. Participating payers largely agreed they would prefer to provide coverage through the use of the American Medical Association's Current Procedural Terminology (CPT®) code for panels comprised of 5 to 50 genes for solid organ neoplasms (CPT® 81445) or hematolymphoid neoplasms or disorders (CPT® 81450) whenever medically necessary genes are part of the analysis. The recommendations below (see Section III) therefore suggest that, so long as the cost of the panel is comparable to the cost of sequencing individual genes by other methods, coverage for NGS panels should be provided when any genes on a CPT® 81450 or 81455 panel are deemed medically necessary for the care of the patient.

COMPREHENSIVE PANELS

In group discussions, payers generally expressed the opinion that panels containing more than 50 genes (CPT® code 81455) (as well as whole exome and whole genome sequencing, for which there are also CPT® codes) are largely investigational in nature and should therefore generally be excluded from coverage. Some proponents of using more expansive "comprehensive" panels argue that it is potentially more beneficial and cost effective to do comprehensive profiling up-front, upon first diagnosis of disease, rather than to do initial targeted panel testing followed later by re-biopsy and re-testing after the standard options have been exhausted. Others reply that it need not be assumed that standard options will be exhausted, and, in any event, tumor genetics are fluid; after some period of guideline-directed treatment, the molecular biology of the tumor may have changed, indicating the potential need for repeat testing to guide further therapy.

Nevertheless, the current trend is towards the creation of larger panels as increasing numbers of genes and gene variants are implicated in cancer genetics, prognosis, and treatment. Moreover, although some of the recently added genes may be considered more speculative, evidence for utility ultimately must be considered along a continuum. The three-category framework of variants ("established," "emerging," and "unknown") described above is a convenient and common-sense shorthand to consider the level of uncertainty associated with specific clinical uses of variants that might be detected on panels. But this categorization has the disadvantage of masking the true complexity of decision criteria for clinical genomics; it creates categories with sharp boundaries when the reality is a spectrum of uncertainty. Identifying where the line should be drawn between "emerging" and "established" is a matter of judgment that takes into account the underlying medical need of the clinical situation, weighing potential benefits and harms against available evidence, as described above. In this view, a patient with high medical needs (e.g., a metastatic cancer patient who has exhausted standard treatment regimens), may tend to shift the balance in favor of somewhat greater uncertainty in defining medically necessary variants.

It may therefore be reasonable for payers to consider comprehensive oncology panels medically justifiable under limited circumstances of high medical need. One possible concern raised in our deliberations is that this type of policy might invite lawsuits from patients having non-covered conditions. Yet one regional health plan has recently published a policy for covering comprehensive panels under these types of circumstances.[9] Hence, the ability to adopt this type of policy may vary according to differing state laws, patient populations served, business models, and other variables. Not all of our payer-stakeholders expressed positions on this issue, possibly due to a lack of clarity on the full implications for their organizations. We therefore have included for further discussion a proposal for covering comprehensive panels comprised of more than 50 genes under certain circumstances.

WHOLE EXOME AND WHOLE GENOME SEQUENCING

Currently, comprehensive sequencing of cancer tumor genomes is considered to add little benefit to targeted analysis of known genes; panels targeting known genes are preferred.[2] For this reason, whole genome and whole exome sequencing is not recommended to be covered at this time. Nevertheless, sequencing of ever larger quantities of DNA may become increasingly informative as new developments in bioinformatics, new discoveries in medical genomics, and supporting clinical evidence accrue. As comprehensive panels grow larger, perceived distinctions between "large" panels and whole exome or genome sequencing will become increasingly difficult to sustain. Additional discussion is therefore merited on circumstances under which large-scale sequencing may be clinically relevant in oncology in the future, and the types of evidence appropriate to demonstrate its clinical utility.

POLICIES FOR OFF-LABEL DRUG USE

An operating premise of the model policy guidelines is that NGS-directed use of off-label drugs and biologics should not be expected to be covered when evidence of patient benefit is lacking. This is to say that generally speaking, if the decision to prescribe a therapy is directed by gene variants not listed in an FDA label for the underlying agent and indication, then therapy with that agent is deemed investigational. There may be good evidence for a biologic rationale and other scientific support to suggest the proposed use may be beneficial. However, whether favorable patient outcomes are achieved from the proposed use is a hypothesis in need of testing, since the drug company's FDA registration trials did not evaluate the use of the variant with the drug for the proposed indication.

Nevertheless, some stakeholders have suggested that if a patient with an unfavorable prognosis is prescribed an NGS-directed off-label therapy and experiences benefit in the first three months of treatment, then the off-label therapy has demonstrated value for that patient. Under these circumstances, the continued use of the agent may be deemed as medically necessary. In other words, after three months of demonstrated patient benefit, the off-label therapy may be seen as meeting coverage criteria for that patient only; if so, coverage could begin in the fourth month of therapy.

Since the first three months of the off-label use of the drug in this situation effectively constitutes investigational use in a single case, our deliberations also featured the suggestion that pharmaceutical manufacturers should accept requests from providers to supply therapeutics free of charge during the first three months of off-label treatment. This new potential off-label drug coverage policy will only be feasible if pharmaceutical companies agree to this provision since the large majority of cancer patients would not be able to afford the first three months of targeted therapies, which can often cost in the range of $10,000 a month.

While not a point of consensus, many stakeholders found these suggestions appealing and reasonable. Given the complexities of this novel approach, we believe further discussion is merited during Phase 2 of this project on a possible process or novel coverage program, as it would be an especially important program for supplying expensive new specialty products to patients in whom it is reasonable to believe a benefit might be achieved, but coverage is not initially available because population-based evidence is still lacking. It may also be possible to structure a registry for these patients that allows pharmaceutical manufacturers to prospectively collect data to support new indications for previously approved therapies.

PROMOTING BETTER EVIDENCE THROUGH POLICY

Another basic premise of the policy model framework and discussion is that the translation of new genomic discoveries into clinically useful tools is hampered by a persistent lack of evidence supporting the clinical utility of variants believed to have a role in cancer. Test developers often remark that payer standards for coverage are obscure and need to be clarified, or that between-payer differences in requirements hinder clinical development plans. However, even if there were transparent, consistently applied evidence rules, there would still be a persistent deficit of the clinical utility evidence needed by payers for new variants associated with cancer due to a lack of incentives for laboratories and diagnostics companies to produce this evidence, and slowness of the drug industry to test approved drugs for new variant-directed indications. When DNA is not patentable subject matter and newly discovered genes and variants flow into a marketplace in which anyone can use them and anyone can test for them, who will bear the cost of doing the studies? This challenge is made more acute by the high cost of conducting high-quality studies and a limited research infrastructure that leads to insufficient research.

The answer is not for health plans to lower expectations for evidence, nor for them to broaden their definition of medical necessity (e.g., to include non-medical benefits to patients). Rather, if patients are to benefit medically from new genomic discoveries, innovative partnerships between the drug industry, health plans, laboratories, and public agencies must be fostered and incentives must be created to produce the needed evidence. For this to be successful, all of these stakeholders and medical professionals must collaborate effectively, putting the benefit of patients at the forefront.

In our discussions of the role of payers to promote evidence development, stakeholders representing the commercial health plans strongly made the point that the “coverage with evidence development” program Medicare has developed is not readily transferrable to most private payer organizations and should not be included in the framework. Although some large, self-insured employers do see value in this approach [ref], provisions for covering patients on condition that they enroll in clinical trials have been omitted from these recommendations.

The model policy framework does recommend that payers develop programs to promote appropriate, high-quality evidence generation. These could include:

- Payment incentives to clinicians who refer patients to appropriate, high-quality clinical studies
- Payment incentives to laboratories for data-sharing

- Payer participation in collaborative initiatives for enrolling patients into high-quality registries and clinical trials for molecular biomarkers evaluation, such as ASCO TAPUR and the Medical Evidence Consortium (MED-C).

Participation in initiatives such as TAPUR or MED-C need not involve direct coverage of testing for patients enrolled in studies, but could entail payment incentives, data-sharing agreements, charitable foundation support, or other mechanisms for promoting high-quality studies of molecularly guided care. We believe that we achieved broad consensus that payers can have an important role in supporting evidence development, even as different payers may prefer to take different roles according to their own organizational priorities and strategies. However, more exploration is needed to shed light on the best ways for health plans to be supportive of this work. Accordingly, we also plan to focus deeper attention on possible partnerships and mechanisms for payer promotion of high-quality evidence generation in Phase 2 of our work.

IV. MODEL COVERAGE POLICY FRAMEWORK

1. ASSURANCE OF ANALYTIC VALIDITY

Payers should require laboratory accreditation through the College of American Pathologists (CAP), including successful compliance with CAP's new laboratory accreditation checklist requirements and proficiency testing program for NGS analytic wet bench process and bioinformatics analysis processes.

2. RECOMMENDED CRITERIA FOR COVERAGE OF PANELS COMPRISED OF FROM 5 TO 50 GENES.

Panels containing from 5 to 50 genes should be covered when the following criteria are met:

a. A subset of at least 5 constituent genes or variants is cited in the label of an FDA-approved companion diagnostic indicated for the treatment of the patient; OR
b. A subset of at least 5 constituent genes or variants is recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines, such as those of the National Cancer Comprehensive Network (NCCN), or the American Society of Clinical Oncology (ASCO) or other guidelines that meet the IOM criteria for clinical guidelines;[10] OR
c. A subset of at least 5 constituent genes are designated as standard of care for the underlying condition by the molecular testing committees of at least 3 NCCN member institutions; OR
d. The provider has submitted two peer-reviewed journal articles of studies designed to demonstrate the safety and effectiveness of using the genomic information in question for clinical management of the patient's diagnosis and support the conclusion that use of the information is reasonably likely to provide a health benefit for the patient.

   AND, in all cases:

e. The cost of analysis by NGS does not exceed the cost of individual sequencing of the target genes by other methods, AND
f. The laboratory conducting the analysis is CLIA-certified and accredited by CAP for NGS testing.

3. PROPOSED CRITERIA FOR COVERAGE OF PANELS COMPRISED OF GREATER THAN 50 GENES

Payers should consider covering panels containing greater than 50 genes when providers have sought prior authorization based on documentation showing the patient:

a. Is newly diagnosed with Stage IV adenocarcinoma of the lung;[11] OR
b. Is newly diagnosed with carcinoma of unknown primary site;[12] OR
c. Is newly diagnosed with Stage IV rare or uncommon solid tumors for whom no systemic treatment exists in clinical care guidelines and/or pathways; OR
d. Is newly diagnosed with Stage IV solid tumors where the median overall survival is less than two years (e.g., pancreatic cancer); OR
e. Has stage IV solid tumors and has exhausted established guideline-driven systemic therapy options and requisite molecular testing and maintains functional status (ECOG score 0-2); OR
f. Has newly diagnosed hematologic malignancies with limited treatment options in defined clinical care guidelines.

4. COVERAGE OF WHOLE EXOME AND WHOLE GENOME SEQUENCING

Whole exome and whole genome sequencing are considered investigational when used in oncology and are not recommended for coverage at this time.

5. PROPOSED CRITERIA FOR NGS-DIRECTED DRUG AND BIOLOGIC THERAPIES

A. Drugs and biologics prescribed on the basis of NGS results will be covered when:

i. The usage for the patient is an FDA-approved indication, OR
ii. The drug is listed in one of the following compendium: The American Hospital Formulary Service Drug Information; Thomson Micromedex DrugDex or DrugPoints; The National Comprehensive Cancer Network (NCCN) Guidelines; Clinical Pharmacology

B. Proposal: Drugs and biologics prescribed on the basis of NGS results which do not meet conditions under Section 5A are not covered unless:

i. The patient meets the medical necessity criteria listed in 3a – f above, AND
ii. The provider submits peer-reviewed journal article(s) having the primary purpose of evaluating the use of the drug for the off-label use intended, and supporting a decision by the health plan that the off-label use of the drug is reasonably likely to provide a net health benefit to the patient. The provider may submit either:
    a. One peer-reviewed journal article describing a randomized controlled trial, OR
    b. Two peer-reviewed journal articles describing observational studies, OR
    c. For rare diseases, at least 4 peer-reviewed, published cases

C. Drugs and biologics prescribed on the basis of NGS results which do not meet the conditions of 4A or 4B are not covered for the first three months of therapy.

D. Proposal: <u>After the first three months of therapy,</u> ongoing off-label NGS-directed therapy may be covered on the fourth month of treatment if:

i. the patient maintains performance status (EGOC score 0-2), AND

ii. the patient experiences either a clinically significant reduction in a relevant tumor biomarker during the first three months of treatment OR at least partial tumor regression by RECIST criteria or by Immune-Related Response Criteria; OR experiences stable disease during this time

iii. the pharmaceutical manufacturer agrees to a special access program for providers to request the drug or biologic free-of-charge for patients for the first three (investigational) months of treatment under these circumstances

6. PROPOSED POLICIES FOR PROMOTING DATA GENERATION

Health plans should craft policies to promote high-quality data collection. Possible policies include:

A. Compensating providers for supplying information and assistance to patients to enroll in appropriate clinical trials or registries
B. Compensating providers for gathering and submitting patient outcome data to high-quality databases
C. Compensating laboratories for submitting new variant data to well-curated, public access databases of somatic mutations
D. Actively supporting public-private partnerships and collaborative initiatives for clinical studies such as ASCO TAPUR and MED-C

V. NEXT STEPS

Significant progress has been made in finding areas of consensus between stakeholders in the past year of deliberations through the Green Park Collaborative. In the upcoming year CMTP will delve more deeply through GPC to explore key questions raised by this past year of work on policy and standards for NGS and other advanced genomic testing in clinical oncology.

These activities include:

- Meetings with CAP, CMS, Palmetto, major payers, and other stakeholders to discuss ways to make the CAP NGS accreditation program results optimally useful to payers, and to further dialog on programs such as those under development by the US Food and Drug Administration (FDA) or the Tapestry Network SPOT/Dx Working Group to further assure the clinical validity of NGS testing.
- Meetings with major payers, CMS, and pharmaceutical companies to discuss potential policy options for covering off-label drugs
- Discussion of policy levers to incentivize data-sharing, enhanced clinical trial participation of patients, and real-world systematic data collection to capitalize on supplemental variant information found when analyzing panels
- Discussion of future conditions under which comprehensive cancer panels may be covered, and the type of evidence needed to support the clinical utility of large scale genomic sequencing approaches, such as whole exome and whole genome sequencing, in oncology

In addition, broader public consultation will be needed to gain the perspectives and support of key stakeholder groups that have not been as deeply engaged in Phase 1. We are reaching out to a broader assortment of patient groups, academic laboratories, and community cancer centers. We would also seek to engage a larger universe of public and private payers to review and consider adoption of the framework and participate in the refinement process.

Throughout these meetings, we will continue to engage all stakeholders in open and transparent discussions to look for common ground, dispensing with recommendations that are shown to have no support from key groups and embracing those for which further discussion is merited. In so doing, we hope to overcome barriers to more rapid clinical evaluation, clinical uptake, and coverage of DNA sequencing that is efficacious for patients with cancer.

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APPENDIX

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