

Decision Memo for NEXT GENERATION SEQUENCING (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

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Decision Summary

A. Coverage

The Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
 - a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
 - b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
 - c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
2. The diagnostic laboratory test using NGS must have:
 - a. FDA approval or clearance as a companion in vitro diagnostic; and
 - b. an FDA approved or cleared indication for use in that patient's cancer; and
 - c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

B. Other

Medicare Administrative Contractors (MACs) may determine coverage of other Next Generation Sequencing (NGS) as a diagnostic laboratory test for patients with cancer only when the test is performed in a CLIA-certified laboratory, ordered by a treating physician and the patient has:

- a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and

- b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
- c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

See Appendix D for the NCD manual language.

[Back to Top](#)

Decision Memo

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Subject: Decision Memorandum on Diagnostic Laboratory Tests using Next Generation Sequencing (NGS) for Medicare Beneficiaries

Date: March 16, 2018

After considering the public comments and additional evidence, we are revising our proposed decision.

I. Decision

A. Coverage

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II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented. Please find here a list of these acronyms and corresponding full terminology.

ACCE – Analytical validity, clinical validity, clinical utility, ethical, legal and social implications of genetic testing
ACS – The American Cancer Society
AD – Lung adenocarcinoma
ADSQ – Adenosquamous carcinoma
AHRQ – Agency for Healthcare Research and Quality
AKT – Protein kinase B

ALK – Anaplastic lymphoma receptor tyrosine kinase
AMVAC – Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin
ANOVA – Analysis of Variance
ARID1A – AT-Rich Interaction Domain 1A
ASCO – American Society of Clinical Oncology
ATC – Anaplastic thyroid carcinoma
ATM – Ataxia telangiectasia, mutated
BRAF – B-Raf, proto-oncogene B-Raf, v-Raf murine sarcoma viral oncogene homolog B
BRCA1 – Breast CAncer gene 1
BRCA2 – Breast CAncer gene 2
BSC – Best supportive care
BTC – Biliary tract cancer
CAP – College of American Pathologists
CCND1 – Cyclin D1
CD8 – Cluster of differentiation 8
CDKN2A – Cyclin-dependent kinase inhibitor 2A
CED – Coverage with Evidence Development
cfDNA – cell free DNA
CFR – Code of Federal Regulations
CGH - Comparative Genomic Hybridization
CGP – Comprehensive Genomic Profile
CHEK2 – Checkpoint Kinase 2
CI - Confidence Interval
CLIA – Clinical Laboratory Improvement Amendments
CMS - Centers for Medicare & Medicaid Services
CNA – Copy Number Alteration
COSMIC - Catalogue Of Somatic Mutations In Cancer, database
CR – Complete Response
CRC – Colorectal cancer
CRGAs – Clinically relevant genomic alterations
CS – Current smoker
cSCC – Cutaneous squamous cell carcinoma
CTCAE – Common Terminology Criteria for Adverse Events
ctDNA – circulating tumor DNA
CTEP – NIH-NCI Cancer Therapy Evaluation Program
CTNNB1 – Catenin Beta 1
c-kit – proto-oncogene c-Kit
DAB - Departmental Appeals Board
DFS – Disease-free survival
DNA - Deoxyribonucleic acid
DOT – Duration of treatment
EC – Endometrial cancer
EGFR – Epidermal growth factor receptor
EHCCA – Extrahepatic cholangiocarcinoma
ER – Estrogen receptor
ERBB2 – Receptor Tyrosine-Protein Kinase Erb-B2
ES – Ex-smoker
F1CDx - FoundationOne CDx™
FANCC – Fanconi Anemia Complementation Group C
FBXW7 – F-Box And WD Repeat Domain Containing 7
FDA - Food and Drug Administration
FFPE – formalin-fixed paraffin embedded
FGFR – Fibroblast growth factor receptor
FISH – Fluorescence in-situ hybridization
FLT3 – Fms-like tyrosine kinase 3
FR – Federal Register
GA – Genomic Alteration
GTB - Genomic Tumor Board
GTR – NIH Genetic Testing Registry
HHS - U.S. Department of Health and Human Services
HR – Hazard Ratio
IOM - Institute of Medicine
IQR – Interquartile range
LADC - lung adenocarcinoma
LDT – laboratory developed test
MAC - Medicare Administrative Contractor
MRD - minimal residual disease
MSI – microsatellite instability
MTB - Molecular Tumor Board

NCA - National Coverage Analysis
NCD - National Coverage Determination
NCI – National Cancer Institute
NGS - Next Generation Sequencing
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
ORR – Objective Response Rate
OS – Overall Survival
PD – Progressive Disease
PFS – Progression Free Survival
PR – Partial Response
QOL - Quality of Life
RECIST - Response Evaluation Criteria in Solid Tumors
RR – Response Rate
RRR – Relative Response Ratio
S.D. - Standard Deviation
SD – Stable Disease
SEER - Surveillance, Epidemiology, and End Results Program
SWOG – NCI supported organization conducting clinical trials in adult cancers
TCGA – The Cancer Genome Atlas
TKI – tyrosine kinase inhibitor
TMB – tumor mutational burden
TTF – Time to Treatment Failure
U.S. - United States
WES - Whole Exome Sequencing

A. What is cancer?

Cancer is a collection of related diseases during which normal cells behave abnormally to grow and divide without control, which can lead to invasion and spread into surrounding tissues. Malignant cancer cells can form solid masses distinct from benign tumors and are likely less developed than nearby mature healthy cells. These malignant tumors may influence the surrounding microenvironment to further growth and development of the tumor or evade normal immune-mediated responses. The spread of cancer cells from the place formed to another part of the body is called metastasis. In metastasis, cancer cells break away from the original primary tumor, travel through the blood or lymph system, and form a new tumor in other organs or tissues of the body. This additional metastatic tumor is the same type of cancer as the primary tumor. Cancer that has been treated can also return, usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the primary tumor or to another place in the body and is known as recurrent cancer.

There are other collections of related diseases in which normal cells proliferate or behave abnormally but are not cancer. Hyperplasia is an increase in the number of normal cells in an organ or tissue. Dysplasia is the presence of abnormal cells in an otherwise normal organ or tissue. Carcinoma in situ is an increase in the number of abnormal cells in an otherwise normal organ or tissue. Carcinoma in situ is distinct from cancer as these abnormal cells have not spread into normal tissue.

Cancer is the result of genetic changes to deoxyribonucleic acid (DNA) that can be inherited or acquired during the lifetime. While each cancer may have unique genetic changes that could vary among cells of the same tumor type, there are certain mutations that commonly cause cancer, including mutations to tumor suppressor genes, DNA repair genes, or proto-oncogenes. Moreover, metastatic cancer cells and cells of the original cancer usually

have some molecular features in common, such as the presence of changes to specific chromosomes containing DNA.

B. What is the incidence and prevalence of cancer?

The American Cancer Society (ACS) Cancer Facts & Figures – 2017 estimated 1,688,780 new cases of cancer and 600,920 deaths based on 1999-2013 incidence rates reported by the North American Association of Central Cancer Registries and 2000-2014 US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention respectively. The Surveillance, Epidemiology, and End Results Program (SEER) Cancer Statistics Review calculates that the median age of cancer patient at diagnosis is 66 years old when all races, genders and sites of cancer are considered together.

To estimate the prevalence of cancer, on January 1, 2014 the SEER reviewed the population diagnosed in the previous 22 years by age at prevalence. This review was based on US 2014 cancer prevalence counts and US population estimates from the US Bureau of the Census. Prevalence was calculated using the first invasive tumor for each cancer site diagnosed during the previous 39 years (1975-2013). Statistics based on SEER estimate the prevalence at 9.8334% by age 60-69, 17.1858% by age 70-79, and 20.0608% by age 80+ when considering both sexes and all races.

Chronic Conditions among Medicare Beneficiaries is a chartbook prepared by CMS to provide an overview of chronic conditions that correspond with the conditions used in the Department of Health and Human Services (HHS) Strategic Framework on Multiple Chronic Conditions. Chronic conditions were examined for over 31 million Medicare beneficiaries who were continuously enrolled in the Medicare fee-for-service program in 2010 and limited cancer focus to breast, colorectal, lung, and prostate cancers.

Approximately 8% of Medicare fee-for-service beneficiaries indicated at least one of the measured cancer chronic conditions and such an indication was more common for non-dual eligible, men, over 65 years old. Co-morbidity among chronic conditions for Medicare fee-for-service beneficiaries is common, with over 90% of those with cancer having other chronic conditions.

In order to provide data on health disparities in the Medicare population, the CMS Office of Minority Health provides a Mapping Medicare Disparities Tool to identify areas of disparities between sub-populations in health outcomes, service utilization, and health-related data geographically, which may be used to target populations for potential interventions. Measuring the prevalence in a limited focus to breast, colorectal, lung, and prostate cancers identified disparities in the prevalence of these cancers in 36 states for Black and in 40 states for Hispanic relative to White males over 85 years old.

C. Diagnosis of Cancer

In most cases, examination of malignant tumors includes sampling the abnormal cells with a biopsy procedure, which may be performed with a needle, endoscope or during surgery. Clinical laboratory services involve the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the diagnosis, prevention, or treatment of a disease or assessment of a medical condition. Pathologic examination of the biopsy can provide information such as gross and microscopic descriptions of abnormal and normal cells, diagnosis of cancer, and distinction of cancer type or grade of cancer. To provide genetic information about the normal or abnormal cells sampled, including genetic alterations (GAs), additional diagnostic tests using specialized techniques may also be performed. This includes the following types of tests:

- Southern blot hybridization
- Polymerase chain reaction
- Sequencing
- In situ hybridization
- Northern blot hybridization
- Immunohistochemistry
- Western blot hybridization
- Next generation sequencing (NGS)

More recently, sequencing technology such as NGS to read the order of nucleotide molecules on DNA has improved to more effectively provide detailed information on multiple types of GAs simultaneously. The NGS oncology panel tests also provide patients and their providers a more comprehensive genetic profile of cancer and information relevant to potential cancer treatments. NGS oncology panel tests hold potential for patients and providers in optimizing (personalizing) therapies that target specific characteristics of individual patient cancers. However, it is important that these tests produce valid results that are useful in guiding therapies to improve outcomes for patients with advanced cancer.

Parallel Review

Since 2010, the FDA-CMS Parallel Review program has been a collaborative effort intended to reduce the time between FDA marketing approval or clearance and a CMS national coverage determination. This pathway is distinct because it meets manufacturers before FDA approval. Typically, CMS does not engage with manufacturers until after FDA approval or clearance. By the manufacturer engaging FDA and CMS together while under FDA review, a stronger evidentiary base could be developed in a more efficient manner, accelerating patient access to innovative medical devices.

In past national coverage determinations on diagnostic tests using imaging, we consider the evidence to support utility of the diagnostic in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process (see Appendix B) for Evaluating Genetic Tests (Haddow et al., 2003). Tests are evaluated for the components of the disorder and setting, analytical validity, clinical validity, clinical utility, and related ethical/legal/social issues. This evaluation model is consistent with recommendations of the HHS Secretary's Advisory Committee on Genetic Testing (65 FR Printed on 5/2/2018. Page 7 of 151

76643). Analytical validity includes the ability of the test to accurately and reliably detect the mutation and/or variant, while clinical validity includes the ability of the test to accurately and reliably detect the disease of interest in the defined population. Test validity is typically assessed by the FDA during the approval or clearance processes. Additionally, the FDA has recently announced third party reviewers such as the New York State Department of Health (NYSDOH) for *in vitro* diagnostics including NGS oncology panels "to reduce the burden on test developers and streamline the regulatory assessment of these types of innovative products." (<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm>). Therefore, FDA evaluates analytical and clinical validity, while CMS evaluates improvements in health outcomes (i.e., clinical utility). CMS is most focused on assessing clinical utility to include whether use of the test to guide patient management and treatment improves health outcomes.

We note that our approach to this FDA-CMS parallel review project is consistent in approach with the first parallel review project (2014). As noted in the tracking sheet and national coverage analysis, the first review was opened on the class of stool DNA tests used for screening for colorectal cancer (entitled National Coverage Analysis (NCA) Tracking Sheet for Screening for Colorectal Cancer - Stool DNA Testing (CAG-00440N)). A difference is the commercial availability of tests: there was one stool DNA test at the time of review and final decision (there is still one test in this class) compared to several NGS tests with FDA approval or clearance. Another difference is that our first review was based on the Secretary's authority under 1861(pp) of the Social Security Act (the Act) to add new colorectal cancer screening tests, which is not applicable to this decision.

CMS initiated this national coverage determination (NCD) to consider coverage under the Medicare Program for a diagnostic laboratory test using NGS. For this NCD analysis, we proposed coverage for any next generation sequencing diagnostic testing with the scope of this review limited to patients with advanced cancer. We do note this decision is not applicable to all diagnostic laboratory tests using NGS, but rather to a unique diagnostic laboratory test that uses NGS for patients with cancer to manage the patient's cancer by identifying either targeted therapies with known efficacy or in some cases, eligibility for a cancer clinical trial.

Foundation Medicine's FoundationOne CDx™ (F1CDx) companion diagnostic was accepted into Parallel Review in 2016. F1CDx is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB), using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The Foundation Medicine F1CDx is intended to be used in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc. intended to be used as a companion diagnostic to identify patients that may benefit from treatment following detection of specific genetic changes.

Since acceptance of the Foundation Medicine F1CDx test into the Parallel Review Program, there have been three other companion *in vitro* diagnostic laboratory tests using NGS for advanced cancers approved by the FDA.

D. Interventions

When we have made national coverage determinations for other diagnostic tests, we have considered the evidence to support utility of the diagnostic in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes (importantly overall survival), in this case, patients with advanced cancer.

A list of FDA cleared or approved companion diagnostic in vitro devices using NGS is currently available at <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>.

III. History of Medicare Coverage

CMS does not currently have an NCD on NGS.

A. Current Request

Foundation Medicine, Inc. is participating in the FDA – CMS Parallel Review Program. On November 17, 2017, CMS received a formal request from Foundation Medicine, Inc. to initiate a national coverage analysis (NCA) for comprehensive genomic profile testing with F1CDx, a next generation sequencing comprehensive genomic profile (CGP) for solid tumors. The formal request letter can be viewed via the tracking sheet for this NCA on the CMS website at <https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=290>.

CMS opened this NCA to thoroughly review the evidence to determine whether or not a diagnostic laboratory test using NGS may be covered nationally under the Medicare program for cancer patients. The scope of the final decision is more narrow than the proposed.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For NGS, the following statute is applicable to coverage:

Under §1861(s)(2)(C) diagnostic services

Under §1861(s)(3) diagnostic laboratory tests, and other diagnostic tests

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
November 30, 2017	CMS initiates this national coverage analysis for NGS for advanced cancer and posts the proposed decision memorandum. A 30-day public comment period begins.
January 17, 2018	Public comment period ends. CMS receives 315 comments.

V. Food and Drug Administration (FDA) Status

The Food and Drug Administration (FDA) first obtained comprehensive authority to regulate all *in vitro* diagnostics as medical devices in 1976. *In vitro* diagnostics for the purposes of this decision memorandum are limited to tests that can further describe diseases or conditions, used in laboratory or other health professional settings, and market authorized by the FDA. A companion diagnostic for the scope of this decision memorandum, is an *in vitro* diagnostic that is essential for the safe and effective use of a corresponding therapeutic product.

Currently FDA approved companion diagnostic tests using NGS and indications for use include the following:

FoundationFocus™ CDxBRCA (Foundation Medicine, Inc.) is a next generation sequencing based *in vitro* diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in FFPE ovarian tumor tissue. The test detects sequence alterations in BRCA1 and BRCA2 (BRCA1/2) genes. Results are used as an aid in identifying ovarian cancer patients for whom treatment with Rubraca™ (rucaparib) is being considered. If a patient is positive for any of the deleterious alterations specified in the BRCA1/2 classification, the patient may be eligible for treatment with Rubraca™. This is a single-site assay performed at Foundation Medicine, Inc.

F1CDx (Foundation Medicine, Inc.) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and

select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB), using DNA isolated from FFPE tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from certain treatments with targeted therapies. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by physicians for patient management according to professional guidelines in oncology for cancer patients with any solid tumor. It is a single-site assay performed at Foundation Medicine, Inc.

Oncomine™ Dx Target Test (Thermo Fisher Scientific, Inc.) is a qualitative *in vitro* diagnostic test that uses targeted NGS technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from FFPE tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System. The test is indicated to aid in selecting NSCLC patients for treatment with select targeted therapies.

Praxis™ Extended RAS Panel (Illumina, Inc.) is a qualitative *in vitro* diagnostic laboratory test using targeted NGS for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from FFPE colorectal cancer (CRC) tissue samples. The test is indicated to aid in the identification of patients with CRC for treatment with Vectibix® (panitumumab) based on a no mutation detected test result. The test is intended to be used on the Illumina MiSeqDx® instrument.

In addition, the FDA granted marketing authorization to another NGS-based tumor profiling test for use in patients diagnosed with cancer, which include the following:

MSK-IMPACT™ (Memorial Sloan Kettering Cancer Center's (MSK) IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)) is an *in vitro* diagnostic test that uses next-generation sequencing (NGS) to rapidly identify the presence of mutations in 468 unique genes, as well as other molecular changes in the genomic makeup of a person's tumor. MSK-IMPACT™ is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. It is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within one or more benefit categories is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The critical appraisal of the evidence during a national coverage analysis enables us to determine to what degree we are confident that: 1) the specific assessment of a clinical question relevant to the coverage request can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be redacted or, in some cases, will not be made available to the public. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final decision memorandum.

VII. Evidence

A. Introduction

This section provides a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, as well as those found by a CMS literature review.

Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies evaluating diagnostic interventions using NGS for advanced cancers. There was particular emphasis on the FDA-approved list of companion diagnostics, but other applications of NGS including testing performed during the conduct of research was considered for their serial and sometimes overlapping roles in patient management. The emphasis focused less on specific techniques and more on

outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies.

Systematic reviews were used to help locate some of the most primary literature.

Keywords and logic used in the search included next generation sequencing, EGFR, ALK, BRAF, ERBB2, KRAS, BRCA1, BRCA2, non-small cell lung cancer, melanoma, breast cancer, colorectal cancer, ovarian cancer, gastric cancer AND (Clinical Trial[ptyp] AND full text[sb] AND ("2010/01/01"[PDat] : "2017/07/20"[PDat]) AND Humans[Mesh] AND English[lang]). Publications that included outcomes such as overall survival and progression free survival were given priority over other publications that resulted from the same search.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than smaller, cohort studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important.

Included studies were limited to those with adult subjects. Review and discussion of high-throughput but not next generation sequencing techniques are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. Abstracts such as presentations from conference proceedings and non-English publications were excluded.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS included trial statuses recruiting patients.

As part of Parallel Review, Foundation Medicine submitted published evidence (see Appendix C), and we have incorporated additional studies here and into our review as appropriate.

Heilmann et al. Comprehensive genomic profiling of clinically advanced medullary thyroid carcinoma. Oncology, 2016.

The aim of this study was to determine the genomic alterations (GAs) of advanced medullary thyroid carcinoma (MTC). This study used data from 34 consecutively submitted samples with MTC. Study demographics included median age 53 years (range 21-85 years), 71% male and 97% with stage IV disease, while the characteristics of the index patient included age 42 years, male, with sporadic MTC after failing standard of care therapy. The analysis method included CGP performed in a CLIA-certified, CAP- accredited, NYSDOH reviewed reference laboratory (Foundation Medicine, Inc.) and a computational method was used to predict somatic versus germline RET variant status without a matched normal control. Index patient was consented on trial NCT01582191 at The University of Texas MD Anderson Cancer Center (supported by CA016672), while tumor response was measured about every 6-8 weeks using RECIST v1.1. This study found that all cases harbored at least one GA (range 1-11). While RET was the most frequently altered gene, other clinically relevant alterations occurred in CCND1, CDKN2A, FGF19, KRAS, and VHL. The index patient specimen harbored RET M918T mutation and ATM truncations L804fs*4 and S978fs*12. After 2 cycles of therapy, the patient had designated stable disease for at least 8 months. The investigators concluded that CGP of MTC has the potential to inform optimal management of patient by identifying potential markers of response to approved targeted therapies.

Ikeda et al. Metastatic basal cell carcinoma with amplification of PD-L1: exceptional response to anti-PD1 therapy. NPJ Genom Med., 2016.

The aim of this case report was to present GAs and response to anti-PD1 antibody as a single agent for metastatic basal cell carcinoma. The incidence of metastatic basal cell carcinoma was reported to be between 0.0028 and 0.55%. This study used data from a male aged 58 years old diagnosed with metastatic basal cell carcinoma managed in accordance with the University of California San Diego guidelines (supported by CA016672). The analysis included NGS performed by Foundation Medicine, Inc. This study found ten GAs including PTCH1 Q1366*, W197*, and CDKN2A P81L. NGS was also performed on cfDNA from plasma and a liver biopsy specimen, and revealed copy number alterations (CNAs) amplification of PD-L1, PD-L2, and JAK2, respectively. In association with a multidisciplinary Molecular Tumor Board, anti-PD1 therapy was discussed. After four months of treatment, complete resolution of hepatic lesions was reported. The investigators concluded the need to explore biomarker-driven therapy for metastatic basal cell carcinoma.

Kato et al. Rare Tumor Clinic: The University of California San Diego Moores Cancer Center Experience with a Precision Therapy Approach. The Oncologist, 2017a.

The aim of this study was to further an in-depth understanding of the biology of rare tumors. This study used data from 40 patients consecutively presenting at a rare tumor clinic consistent with The University of California San Diego guidelines for the Profile Related Evidence Determining Individualized Cancer Therapy (PREDICT) protocol (NCT 02478931). The study reported that rare tumors account for approximately 25% of cancers. Study demographics included median age 58 years (31-78 years), 70% women with the most common diagnoses were sarcoma and Erdheim-Chester disease. The analysis method included NGS of tissue (32 of 33 patients) and circulating tumor DNA (ctDNA) for 15 of 33 patients performed by one of three sites (Foundation Medicine, Inc., Cambridge MA; Washington University St. Louis, MO; and NantOmics, Culver City, CA). Response to therapy was evaluated using the RECIST v.1.1. This study found that 37 of 40 patients (92.5%) had a GA actionable by either an FDA-approved or investigational agent directed by NGS, ctDNA, IHC, or similar test. The most common GAs

were in TP53, CDKN2A/B, FRS2, MDM2, RB1, and KRAS. The median number of GAs per patient was 3 (range 0-24). Among 21 patients receiving matched therapies, 3 attained stable disease (SD) for 6 months or longer, 6 attained partial response (PR) and 2 attained complete response (CR). Median PFS with matched therapy was 19.6 months (range 0.99 to 26.1 months). The investigators concluded that identification of GAs was feasible in rare/ultrarare tumors.

Lipkin et al. Therapeutic approach guided by genetic alteration: use of MTOR inhibitor in renal medullary carcinoma with loss of PTEN expression. Cancer Biol Ther., 2015.

The aim of this case report was to present a molecular analysis of a renal medullary carcinoma (RMC) to direct maintenance therapy. This study used surgical specimen from an age 27 year-old African-American male with staged pT3a pN1 Mx RMC. The analysis method included NGS and molecular profiling (Caris Life Sciences). This study found that the tumor biomarker profile indicated potential benefit of gemcitabine, nabpaclitaxel, and doxorubicin, while the molecular analysis demonstrated potential targets, including PTEN loss, for MTOR inhibition. Results from the maintenance therapy led to months of CR and extension of life 14 months past diagnosis. The investigators concluded that while NGS is not feasible or necessary for every patient with a malignant tumor, additional knowledge about driver mutations may help in guiding therapy to improve survival in patients with RMC.

Tabone et al. Multigene profiling to identify alternative treatment options for glioblastoma: a pilot study. J Clin Pathol., 2014.

The aim of this study was to identify mutations that could inform future treatment options for patients with glioblastoma (GBM). The investigators reported that the 5-year relative survival from disease is less than 5%. This study screened DNA from 44 GBM specimens for somatic mutations in 50 oncogenes. Study demographics included specimens of the Australian Genomics and Clinical Outcome of Glioma Biospecimen Resource with primary GBM, and IDH1 wild type at position 132. The median age at diagnosis was 63.3 years (range 24 to 85 years) with males:females 30:14 and the majority of patients had total tumor resection at first surgery. The analysis method included somatic mutation profiling using the AmpliSeq Cancer Hotspot Panel v2. This study found that 9 cases had no significant mutations, while the remaining identified mutations per tumor averaged 1.5 (range 0 to 4) for 35 of 44 patients. The most frequent GAs were in TP53, PTEN, EGFR, and PIK3CA. The investigators concluded that while identifying mutations to inform treatment is feasible, future large-scale trials will be required to validate and determine the true clinical utility of this approach for implementation into clinical practice.

We also received additional evidence in public comment and feedback on the proposed decision (see Appendix E). The following summary includes evidence that cited outcome measures of overall survival, progression free survival, partial response, complete response, stable disease, time to tumor progression, overall response rate, or time to treatment failure.

Blakely et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. Nature Genetics, 2017.

The aim of this study was to link clinical outcomes to genetic co-alterations in a cohort of advanced-stage *EGFR* mutant lung cancer patients profiled by multiplex sequencing. Source of data was from a previous study performed at UCSF (no. 16-19636). Study population included patients with advanced-stage *EGFR*-mutant lung cancer (no further detail on demographics was provided). Specimen samples were shipped to a CLIA-certified, CAP-accredited laboratory (Guardant Health) for genetic analysis. The researchers identified 1,122 *EGFR*-mutant lung cancer cell-free DNA samples and conducted whole exome analysis of seven longitudinally collected tumor samples from a patient with *EGFR*-mutant lung cancer. They identified critical co-occurring oncogenic events in most advanced-stage *EGFR*-mutant lung cancers. They also defined new pathways limiting *EGFR*-inhibitor response, including *WNT/β-catenin* alterations and cell-cycle-gene (*CDK4* and *CDK6*) mutations. They concluded that the concept of the prevailing single-gene driver-oncogene perspective and the concept of the linkage of clinical outcomes to co-occurring genetic alterations in patients with advanced-stage *EGFR*-mutant lung cancer needs to be revisited.

Bryce et al. Experience with precision genomics and tumor board, indicates frequent target identification, but barriers to delivery. Oncotarget, 2017.

The aim of the study was to determine whether or not the use of a Genomic Tumor Board (GTB) was helpful in the exchange of knowledge regarding genomic testing results of advanced cancers, as well as to investigate the utility of genomic testing in clinical practice. The source of the data were medical records of patients who were managed at Mayo Clinic Center for Individualized Medicine. Patients ranged in age from 18 months to 86 years with a median of 53 years. Cases were divided between solid tumors (58%) and hematological malignancies (42%). The most common solid tumors were gynecologic and gastrointestinal in nature, while acute leukemia and lymphoma were the most common hematological malignancies. Clinical genetic testing of tumors, including next-generation sequencing panels, array comparative genomic hybridization (CGH) and whole exome sequencing (WES), was conducted in CLIA certified laboratories. These laboratories included: Foundation Medicine, Baylor College of Medicine, Caris Life Sciences, Genoptix, and Mayo Clinic. The authors found actionable mutations in 92/141 patients (65%) for whom testing was ordered. Of this number 28% (39/141) of tumors tested possess at least 1 actionable mutation. Another 8% (11/141) had informative mutations only. A quarter of patients tested (25%) had no actionable or informative targets identified by the GTB. The authors concluded that treatment decisions driven by tumor genomic analysis can lead to significant clinical benefit in patients.

Dawson et al. Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer. N Engl J Med, 2013.

The aims of the study were to provide a direct comparison between circulating cfDNA carrying tumor-specific alterations and the current standard of care for the noninvasive monitoring of metastatic breast cancer patients receiving systemic therapy. The analysis methods included measuring ctDNA in serially collected specimens by conducting a microfluidic digital polymerase-chain-reaction (PCR) assay using the Fluidigm BioMark system or direct plasma sequencing by means of tagged amplicon deep sequencing using the Fluidigm Access Array and sequencing on the Illumina HiSeq2500 instrument. ctDNA was successfully detected in 29 of the 30 women (97%) in whom somatic genomic alterations were identified; CA 15-3 and circulating tumor cells were detected in 21 of 27 women (78%) and 26 of 30 women (87%), respectively. ctDNA levels showed a greater dynamic range, and greater correlation with changes in tumor burden, than did CA 15-3 or circulating tumor cells. Among the

measures tested, ctDNA provided the earliest measure of treatment response in 10 of 19 women (53%). They found that increasing levels of ctDNA were associated with inferior overall survival (p-value<0.001). Increasing numbers of circulating tumor cells and increasing levels of circulating tumor DNA indicated that absolute levels of each is informative in guiding prognosis. The authors concluded that their proof-of-concept analysis showed that in the detection of metastatic breast cancer, circulating tumor DNA shows superior sensitivity to that of other circulating biomarkers, has a greater dynamic range that correlates with changes in tumor burden, and often provides the earliest measure of treatment response.

Gutierrez et al. Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. Clin Lung Cancer, 2017.

The purpose of this study was to determine the genomic testing patterns for patients with advanced NSCLC diagnosed in a large multisite community-based US oncology practice and to examine the potential barriers to adherence with published biomarker guidelines. The source of the data was medical record review of patients treated within the Regional Cancer Care Associates network that consists of 15 community oncology sites throughout New Jersey and Maryland from January 1, 2013 and December 31, 2015. Participants included 814 patients with Stage IIIB and IV nonsquamous NSCLC. The median age of the patient population was 67 years, with 57% > 65 years old and 28% > 75 years old; 53% of the patients were women and 72% were white. Extensive and comprehensive NGS was used. Cell-free DNA analysis was also performed. The study revealed that of the 814 patients (89% with stage IV; 11% with stage IIIB) identified in the study, 479 (59%) met the guideline recommendations for EGFR and ALK biomarker testing; 63 (8%) underwent comprehensive genomic profiling for all four major types of alterations (point mutations, indels, fusions, and copy number amplifications). Gender, age, race, site of care, and practice size did not influence comprehensive genomic profiling frequency. The authors noted that among those not tested for EGFR and ALK, 52% received chemotherapy without documented reasons for no testing, 32% did not receive antineoplastic therapy, and 13% had insufficient tissue for genotyping. The authors concluded that genomic testing presents multiple logistical challenges, but opportunities exist for improvement in guideline adherence, possibly through new technologies such as "liquid biopsies," which the authors believed obviates the need for tissue biopsy samples in select settings.

Harada et al. Implementation and utilization of the molecular tumor board to guide precision medicine. Oncotarget. 2017.

The purpose of this study was to report the experience of the molecular tumor board (MTB), and its importance in implementation in personalized medicine. The study was conducted at the University of Alabama in Birmingham. The researchers wanted to determine if the use of a molecular tumor board was helpful before extensive molecular testing was performed. In the study, patients were reviewed by the MTB for appropriateness of comprehensive next generation sequencing (NGS) cancer gene set testing based on set criteria that was in place. The source of the data were medical records of patients treated at the institution. The vast majority of molecular testing was performed at Genomics and Pathology Services at Washington University for Comprehensive Cancer, though testing at other commercial vendors was also performed (Foundation One and Caris Life Sciences). A total of 191 cases were submitted to the MTB (50 male, 141 female; median age 57 years) and 132 cases were approved and tested. Of those tested, 46 cases (34.8%) had driver mutations that were associated with an active targeted therapeutic agent, including *BRAF*, *PIK3CA*, *IDH1*, *KRAS*, and *BRCA1*. 15 cases were considered for targeted therapy, 13 of which received targeted therapy. One patient experienced a near complete response. Seven of 13 had stable disease or a partial response. The authors concluded that the MTB reviews led to detection of actionable mutations and that their findings of actionable mutations may be higher because of their approach.

Herzog et al. Impact of molecular profiling on overall survival of patients with advanced ovarian cancer. Oncotarget, 2016.

The aim of the study was to determine the value of biomarker profiling in patients with recurrent epithelial ovarian cancer. The data source used was the Caris observational Registry (NCT02678754). Direct sequence analysis was performed on genomic DNA isolated from FFPE tumor samples using the Illumina MiSeq platform. The study involved 224 patients with advanced ovarian cancer divided into two cohorts: matched (n=121) to receive both one treatment associated with potential benefit and no treatments associated with lack-of-benefit, and unmatched (n=103) to receive at least one treatment associated with potential lack-of-benefit. Results of the study showed that matched patients experienced a significantly greater improvement in overall survival from the time of molecular profiling (36 months) when compared to unmatched patients (27 months) (HR 0.62, 95% CI 0.41-0.96; p-value < 0.03). Also, patients who received more than one drug in the lack-of-benefit category trended towards worse overall survival than patients who received only a single drug in this category. The median overall survival from the time of diagnosis for matched patients was 80 months compared to 56 months for unmatched patients (HR 0.65, 95% CI 0.43-0.99; p-value=0.045). The authors concluded that the study demonstrated the usefulness of multi-platform molecular profile testing.

Kato et al. Utility of genomic analysis in circulating tumor DNA from patients with carcinoma of unknown primary. Cancer Res, 2017b.

The aim of the study was to investigate the association between hypermutated blood-derived ctDNA and checkpoint inhibitor response. The data source was medical records maintained by the University of California San Diego Moores Cancer Center, La Jolla, California. Sequencing was performed by a CLIA certified and CAP-accredited clinical laboratory (Guardant Health, Inc.). Of the 1,262 patients who had NGS performed on cell-free, ctDNA derived from liquid (blood) biopsies, 69 patients with diverse malignancies who received checkpoint inhibitor-based immunotherapy and blood-derived ctDNA NGS testing were included in the study. Median patient age was 56 years (range, 22–85 years) and 43 patients (62.3%) were men. The most common tumor types were melanoma, lung cancer, and head and neck cancer. The most common type of immunotherapy used was anti-PD-1 or PD-L1 monotherapy, which was administered to 54 patients (79.7%). Results of the study revealed that 63 patients (91%) had at least one ctDNA alteration. Of the 69 patients, 20 (29%) had >3 VUSs in their circulating tumor DNA (ctDNA) versus 71% with ≤3 VUS ctDNA alterations. Twenty-three patients (33.3%) had <6 total ctDNA alterations and 66.7% had ≤6 total ctDNA alterations. The results showed improvement in PFS was associated with high alteration number in variants of unknown significance (VUS, >3 alterations) and SD >6 months/PR/CR. Improvement in OS was also associated with high VUS alteration status. Responders had a median PFS of 23 versus 2.3 months for non-responders. The authors concluded that because of the association of alteration number on liquid biopsy and checkpoint inhibitor-based immunotherapy outcomes, further investigation of hypermutated ctDNA as a predictive biomarker is warranted.

Khagi et al. Hypermutated Circulating Tumor DNA: Correlation with Response to Checkpoint Inhibitor-Based Immunotherapy. Clin Cancer Res, 2017.

The aim of this study was to examine how sequencing results from cfDNA and FFPE samples can be used to guide decisions in referring patients with metastatic colorectal cancer (mCRC) to matched biomarker-related clinical trials. Data from a survey on 128 patients provided by the University of Texas- MD Anderson Cancer Center
Printed on 5/2/2018. Page 18 of 151

comparing the use of cfDNA and FFPE tissue collections for patients with mCRC was used. The Assessment of Targeted Therapies against Colorectal Cancer protocol, designed to molecularly profile tumors of patients with refractory mCRC was used (NCT01196130). The median age of participants was 53 years, an equal number of males and females were included, and 76% of participants were white. Results of the study showed that using cfDNA sequencing, 78% (100/128) of samples had a detectable somatic genomic alteration. It also showed that 50% of cfDNA cases had potentially actionable alterations, and 60% of these could be genomically matched to at least one clinical trial with 50% (15/30) of patients enrolled onto trial. The authors concluded that cfDNA testing improved the quality of care they could provide in 73% of the cases, and that 89% of patients reported greater satisfaction with the efforts to personalize experimental therapeutic agents.

Landgren et al. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplant, 2016.

The aim of this meta-analysis was to better define the role of minimal residual disease (MRD) negativity in relation to clinical outcomes. In the study a systematic search for clinical trials of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes was conducted using MEDLINE, EMBASE, and Cochrane's Central Register of Controlled Trials. Of the 390 potential studies found, only four were included in the study. None of the four studies used NGS to assess genomic variants, but instead used multiparameter flow cytometry or allele-specific quantitative polymerase chain reaction. Four studies with information on MRD status and hazards ratios for progression-free survival were included in the final analysis and three of these had information on overall survival. Some studies had no deaths during the original follow-up window (up to 30 months) and only two studies provided hazards ratios for overall survival. Based on the two studies that provide hazard ratios, the analysis showed that remaining MRD positive was associated with a higher risk of death (HR=2.08; 95% CI 1.44–3.01; p-value<0.001). The authors concluded that MRD negativity is associated with better progression-free survival and overall survival in newly diagnosed multiple myeloma.

Long et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017.

The aim of the study was to assess whether adjuvant treatment would improve outcomes in patients with melanoma with BRAF V600 mutations. The study used data from a double-blind, placebo-controlled, phase 3 trial that randomly assigned patients with completely resected, stage III melanoma with BRAF V600E or V600K mutations to receive oral dabrafenib plus trametinib or two matched placebo tablets. Patients were enrolled at 169 sites in 26 countries. The analysis methods included BRAF V600 mutation status confirmed by a central reference laboratory at each study site. The study demographics included 870 under randomization, with 438 patients assigned to receive combination therapy and 432 patients to receive matched placebo tablets for 12 months, with median age for each group 50 years (range 18-89 years) and 51 years (range 20-85 years), respectively. Women comprised 55% of either group. The results showed investigator-assessed 3-year relapse-free survival was significantly longer in the combination therapy group than in the placebo group, representing a 53% lower risk of relapse (HR, relapse or death, 0.47; 95% CI 0.39 to 0.58; p-value<0.001). The higher rate of relapse-free survival was consistent across patient subgroups, including those aged 65 years old or more (HR, death, 0.38; 95% CI, 0.24 to 0.60). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group (HR, death, 0.57; 95% CI, 0.42 to 0.79; p-value=0.0006), but the level of improvement did not cross the prespecified interim analysis boundary of p-value=0.000019. Rates of distant metastasis-free survival and freedom from relapse were also higher in the combination-therapy group than in the placebo group. The authors concluded that the adjuvant therapy resulted in a significantly lower rate of recurrence than the adjuvant use of placebo in patients with stage III melanoma with BRAF V600E or V600K mutations.

Maia et al. Association of Circulating Tumor DNA (ctDNA) Detection in Metastatic Renal Cell Carcinoma (mRCC) with Tumor Burden. Kidney Cancer, 2017.

The aim of this study was to examine the correlation between ctDNA detection and clinicopathologic characteristics in patients with mRCC treated at a single institution. ctDNA was assessed through a CLIA-certified, CAP-accredited laboratory comprehensive plasma assay analyzed using the HiSeq2500 Sequencing System (Illumina). Tumor burden was equated to the sum of longest diameter of all measurable lesions. In this study, 34 patients with mRCC had ctDNA assessed with majority male ($n = 18$) and median age of 62 years (range 34–84 years). Results showed 18 patients (53%) had ctDNA detected, with a median of 2 genomic alterations (GAs) per patient. The study noted that patients with detectable ctDNA had a longer lesions compared to patients with no detectable ctDNA (8.81 vs 4.49 cm; p -value= 0.04) with the number of GAs correlated with sum of longest diameter (p -value=0.01). The authors concluded that this surrogate for tumor burden is higher in mRCC patients with detectable ctDNA.

Mateos et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med, 2017.

The purpose of this study was to report the interim analysis of the ALCYONE randomized, phase 3 trial (NCT02195479) of patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation. The trial consisted of 706 patients who were ineligible for high-dose chemotherapy with stem-cell transplantation, due either to coexisting conditions or an age of 65 years or older. The median age in both the intervention and control group was 71 years. Minimal residual disease was assessed by Adaptive Biotechnologies clonoSEQ NGS assay. The results showed that the 18-month progression-free survival rate was 71.6% in the daratumumab group and 50.2% in the control group (HR, disease progression or death, 0.50; 95% CI, 0.38 to 0.65; p -value<0.001). The overall response rate was 90.9% in the daratumumab group and 73.9% in the control group (p -value<0.001), and the rate of complete response was 42.6% and 24.4% respectively (p -value<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease as compared with 6.2% of those in the control group (p -value<0.001). The authors concluded that among patients with newly diagnosed multiple myeloma who were ineligible for stem cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab.

Maxwell et al. Comparative clinical utility of tumor genomic testing and cell-free DNA in metastatic breast cancer. Breast Cancer Res Treat, 2017.

The aims of this study were to determine the concordance of genomic alterations in shared genes on different clinical tumor and cfDNA panels, to identify reasons for discordance that impacts clinical interpretation by treating oncologists, and to identify potential genomic alterations that could be useful in predicting treatment response in breast cancer management. The study used data from patients undergoing tumor testing and concurrent cfDNA testing at the time of clinically indicated metastatic confirmatory tumor biopsy, as part of METAMORPH (Metastatic Markers of Recurrent Tumor Phenotype) Study. The analysis methods included tumor DNA analyzed on Illumina miSeq platform and whole blood sent to Guardant Health Inc. for the Guardant360 cfDNA test. The study demographics of 70 patients enrolled with 53 (80%) tested, including 35 with cfDNA testing had an overall median age of 56 years (range 31–79 years) with whites comprising 81% of the tumor cohort. The results

showed the proportion of patients with at least one genomic alteration was lower in tumor than in blood tested with the cfDNA assay (69% vs. 91%, p-value=0.06). After restricting analysis to alterations covered by both assays, 83% of tumor alterations were detected in blood, while 90% of blood alterations were detected in tumor and only 29 of 100 variants (29%) were concordantly identified. A substantial fraction (53 of 71, 75%) of discordant results occurred due to technical issues such as differences in test coverage of genes, variant reporting practices of the clinical laboratory, and variant classification. Time to progression on subsequent treatment was significantly shorter for patients whose metastatic breast cancer (MBC) tumors had high panel-specific mutational load compared to those with a low mutational load (HR 0.31, 95% CI 0.12–0.78, p-value=0.0112) or the presence of a TP53 mutation in either the tumor or cfDNA (HR 0.35, 95% CI 0.20–0.79, p = 0.00374), after adjusting for stage at presentation, hormone receptor status, prior treatment type, and number of lines of metastatic treatment. The authors concluded that oncologists must distinguish platform differences from true biological heterogeneity when comparing tumor and cfDNA genomic testing results in order to avoid erroneous conclusions about potential therapeutic targets.

Mok et al. Osimertinib or Platinum–Pemetrexed in EGFR T790M–Positive Lung Cancer. N Engl J Med, 2017.

The aim of the study was to report the results from AURA3 trial (NCT02151981), which was conducted to compare osimertinib with platinum therapy plus pemetrexed as standard of care for patients with centrally confirmed T790M-positive locally advanced or metastatic NSCLC after first-line EGFR-TKI therapy. The study randomized patients 2:1 to receive either oral osimertinib or intravenous pemetrexed plus either carboplatin or cisplatin. The analysis methods included documented presence of an EGFR mutation and central confirmation of the T790M variant on the cobas EGFR Mutation Test (Roche Molecular Systems). All patients were required to provide a blood sample at screening to test for T790M in plasma circulating tumor DNA (ctDNA) on the cobas EGFR Mutation Test, version 2. The study demographics were that a total of 419 patients underwent randomization, 279 to the osimertinib group and 140 to the platinum–pemetrexed group. The median age of the osimertinib and the platinum-pemetrexed groups was 62 years (range: 25 to 85 years) and 63 years (range: 20 to 90 years), respectively; women comprised 62 percent and 69 percent of the groups, respectively; and Asians comprised 65 percent and 66 percent of the groups, respectively. Results showed median duration PFS was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; HR 0.30; 95% CI, 0.23 to 0.41; p-value<0.001) with ORR significantly higher with osimertinib (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; p-value<0.001). The authors concluded that osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non–small-cell lung cancer in whom disease had progressed during first-line EGFR-TKI therapy.

Newman et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nat Med, 2014.

The aims of the study were to examine technical performance and clinical utility of Cancer Personalized Profiling by deep Sequencing (CAPP-Seq) in patients with early and advanced NSCLC. The study used data from patients undergoing treatment for newly diagnosed or recurrent NSCLC enrolled in a study at Stanford University. DNA was profiled in 90 samples, including two NSCLC cell lines, 17 primary tumor samples with matched peripheral blood leukocytes, and 40 plasma samples from 18 human subjects, including five healthy adults and 13 patients with NSCLC. The analysis methods included multiplexed libraries sequenced on an Illumina HiSeq 2000. CAPP-Seq was used to quantify ctDNA. The study demographics included age range 35-90 years and 59% women. The results showed ctDNA detected with 100% sensitivity in stage II–IV and 50% in stage I NSCLC, with 96% specificity for mutant allele fractions down to ~0.02%. Levels of ctDNA significantly correlated with tumor volume. The study reported CAPP-Seq correctly classified 100% of patient plasma samples with ctDNA above fractional abundances of 0.4% with a false positive rate of 0%. The authors concluded that CAPP-Seq could be

routinely applied clinically to detect and monitor diverse malignancies, thus facilitating personalized cancer therapy and monitoring of cancer.

Ramalingam et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol, 2017.

The aim of the AURA study (NCT01802632) was to examine the clinical activity and safety of osimertinib as first-line treatment of EGFR-mutated advanced NSCLC. The study used data from two cohorts of treatment-naïve patients and the methods included ctDNA extracted from baseline plasma samples analyzed using BEAMing digital PCR. Plasma samples collected at or after progression were analyzed using both an NGS 56-gene panel and a 73-gene panel. The study demographics at data cutoff include median age 63.5 years (range 38-91 years), 75% female and 72% Asian in which 25 of 60 patients (42%) were still receiving study treatment. The results showed ORR was 77% (95% CI 64% to 87%) across all treatment groups with median PFS time 20.5 months (95% CI, 15.0-26.1 months). At 18 months, 56% (95% CI, 42%-68%) of patients were alive and progression free. Of 38 patients with post-progression plasma samples, 50% had no detectable circulating tumor DNA and there was no evidence of acquired EGFR T790M mutation in post-progression plasma samples. The authors concluded that osimertinib in this first-line study showed durable clinical activity and manageable tolerability in treatment-naïve patients with advanced EGFR- tyrosine kinase inhibitor (TKI)-sensitizing mutation NSCLC.

Remon et al. Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. Ann Oncol, 2017.

The aim of the study was to assess the efficacy of osimertinib when T790M status is determined in ctDNA from blood samples in progressing advanced EGFR-mutant NSCLC patients. Data for the study was obtained from medical records of patients treated at Gustave Roussy Medical Facility (Villejuif, France) between April 2015 and April 2016 with EGFR-mutation in the initial biopsy (Del19, L858R), clinical or radiological progression to at least one first- or second-generation EGFR TKI, and ineligibility for a new tissue biopsy (due to lack of available tissue, localization and/or patient's refusal) for testing T790M status at the time of progression. Liquid biopsies were used to identify T790M mutations in ctDNA with DNA extracted and analyzed by the InVision assay, using enhanced Tagged Amplicon-Sequencing; eTAmSeq.™ In the study, 48 patients with advanced EGFR-mutant NSCLC had a median age of 65 years (range 37-83) and 36 patients (75%) were women and 58% were never-smoker. EGFR mutation status was Del19 in 33 (69%) and L858R in 15 (31%) NSCLC patients. Results showed the ctDNA T790M mutation was detected in 50% of NSCLC patients, and among assessable patients osimertinib gave a PR rate of 62.5% and a SD rate of 37.5%. After a median follow up of 8 months, median PFS by RECIST criteria was not achieved (95% CI, 4-NA), with 6- and 12-months PFS of 66.7% and 52%, respectively. The authors concluded that ctDNA could be used as a surrogate marker for T790M in tumor tissue.

Sarfaty et al. RET Fusion Lung Carcinoma: Response to Therapy and Clinical Features in a Case Series of 14 Patients. Clin Lung Cancer, 2017.

The aim of the study was to describe the natural history of RET fusions in lung cancer. The study used data from a retrospective case series of patients with RET-rearranged LADC. The analysis methods included RET fusions identified from tissue or blood using NGS with the FoundationOne (12 cases) or Guardant360 (2 cases) assay, respectively. The study demographics of 14 consecutive patients included median age 61 years (range 28-72 years), 8 women (57%) and stage IV disease in 11 patients (78.6%), locally advanced disease in 2 (14.3%), and early-stage disease in 1 patient (7.1%). The results showed 3 of 10 patients achieved a CR 15-17 months, and 5 achieved a PR 2-9 months. Platinum- and pemetrexed-based chemotherapy induced ORR of 80%, with a median PFS of 7 months (range 0-17 months). Seven patients were treated with cabozantinib, 2 were not evaluable resulting in an ORR of 60%, and median PFS 2.5 months (range 1-8 months). Two patients treated with cabozantinib experienced a PR and two patients' tumors showed programmed cell death ligand 1-positive staining but did not respond to pembrolizumab. The authors concluded that RET-rearranged LADC tended to occur as bilateral disease with early visceral involvement, especially with KIF5B fusion and treatment with cabozantinib achieved responses, including one complete response.

Schwaederle et al. Use of Liquid Biopsies in Clinical Oncology: Pilot Experience in 168 Patients. Clin Cancer Res, 2016c.

The aim of the study was to report on the clinical experience with the ctDNA testing in patients with diverse cancers followed at UC San Diego, Moores Cancer Center. The study used data from a retrospective review of patients with diverse solid cancers as part of UCSD-PREDICT (Profile Related Evidence Determining Individualized Cancer Therapy) study (NCT02478931). The analysis methods included patients having NGS Digital Sequencing™ performed by Guardant Health, Inc. on their plasma and 101 patients also had NGS performed on their tissue by Foundation Medicine using FoundationOne™. The study demographics included median age at diagnosis 54.5 years (95% CI 51-59 years), majority Caucasian (67%), followed by Asian (15.5%) and other (8.9%) with slightly more women than men (58%). The results showed 58% of patients (98/168) had ≥1 ctDNA alteration(s) with 71.4% having ≥ 1 alteration potentially actionable by an FDA-approved drug. A limited percentage of patients (12%) had alterations potentially actionable by a drug approved by the FDA for their disease (on-label use). Overall concordance for tissue and ctDNA were 70.3% for TP53 and EGFR, 88.1% for PIK3CA, and 93.1% for ERBB2 alterations. Twenty-two of 63 patients (35%) had ≥1 alteration in common between the tissue and ctDNA. There was a significant correlation between the cases with ≥ 1 alteration with ctDNA ≥ 5% and shorter survival (median overall survival 4.03 months versus not reached at median follow up 6.1 months; p-value=0.0001 in multivariable analysis). Five of the twelve evaluable patients (42%) matched to a treatment targeting an alteration(s) detected in their ctDNA and achieved stable disease ≥ 6 months/partial remission compared to two of 28 unmatched patients (7.1%) (p-value=0.02). The authors concluded that their initial study demonstrates that ctDNA tests provide information complementary to that in tissue biopsies and may be useful in determining prognosis and treatment.

Tafe et al. Implementation of a Molecular Tumor Board: The Impact on Treatment Decisions for 35 Patients Evaluated at Dartmouth-Hitchcock Medical Center. The Oncologist, 2015.

The aims of this study were to describe the Molecular Tumor Board (MTB) established by Dartmouth-Hitchcock Medical Center, and show interpretation of individual patients' tumor genetic profiles to provide treatment recommendations. The source of data was medical records of patients followed at the Dartmouth-Hitchcock Medical Center. DNA from tumor specimens was sequenced in a CLIA-certified laboratory to identify coding mutations with a 50-gene panel (n = 34) or a 255-gene panel (n = 1). Cases were then evaluated by a multidisciplinary MTB team. In the study, libraries sequenced specimens using the Ion Torrent Personal Genome Machine System and Ion 318 Chips (Life Technologies), though one tumor specimen was sent to Foundation Medicine for genetic profiling using FoundationOne. Tumor specimens included colorectal and lung cancer (23% each), breast cancer (14%), brain cancer (9%), sarcoma (6%), skin cancer (11%), and other (14%). No further

information about patient demographics was provided. Among the 35 cases evaluated, 3 patients had early stage disease and had not yet started treatment, 4 patients had recurrent or metastatic disease and had not yet been treated in the advanced/metastatic setting, and 28 patients had previous treatment for advanced/metastatic disease. Results showed that of the 35 cases evaluated by the MTB, 32 presented for recommendations on targeted therapies, and 3 were referred for potential germline mutations. In 56.3% of cases, MTB recommended treatment with a targeted agent based on evaluation of tumor genetic profile and treatment history. Four patients (12.5%) were subsequently treated with a MTB-recommended targeted therapy; 3 of the 4 patients remained on therapy, 2 of whom experienced clinical benefit lasting more than 10 months. The authors concluded that for the majority of cases evaluated, the MTB was able to provide treatment recommendations based on targetable genetic alterations.

Verri et al. Mutational profile from targeted NGS predicts survival in LDCT screening-detected lung cancers. J Thoracic Oncology, 2017.

The aims of the study were to gain insight into the association of low-dose computed tomography (LDCT)-detected lung tumors and specific clinicopathologic characteristics and a plasma miRNA signature classifier. The study used data from LDCT-detected lung cancers from a consecutive series of subjects participating in three LDCT screening trials in Milan, Italy since 2000. The analysis methods included microRNA (miRNA) expression (Thermo Fisher Scientific) on plasma samples. Targeted NGS analysis used the Ion AmpliSeq Cancer Hotspot Panel v.2 on tumor samples. The study demographics of 94 patients included median age 64 years and 70% male. The results showed TP53 was the most frequently altered gene (44 cases [47%]) and the mutational spectrum and frequency observed in the screening series was similar to that reported in public data sets of The Cancer Genome Atlas (TCGA), although a larger number of tumors without mutations in driver genes was detected in this study. The 5-year OS rates of patients with and without mutations in the tumors were 66% (n = 74) and 100% (n = 20), respectively (log-rank, p-value=0.015). Combining the mutational status with the microRNA signature stratified patients into three groups with 5-year OS rates ranging from 42% to 97% (p-value < 0.0001) and the prognostic value was significant after controlling for stage (p-value=0.02). The authors concluded that the use of tissue based mutation profile along with a miRNA-based signature can provide additional information in planning clinical follow-up in lung cancer LDCT screening programs.

Villaflor et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. Oncotarget. 2016.

The aims of this study were to evaluate a targeted ctDNA NGS gene panel in a prospective series of consented NSCLC cases from a single institution, to determine the frequency and distribution of genomic alterations across cases as compared to tissue NGS results, and to characterize cases in which ctDNA was undetectable in a clinical practice setting. The study used data from subjects with a diagnosis of NSCLC who had at least one ctDNA test at a single commercial ctDNA laboratory and were seen at the University of Chicago. The analysis methods included cfDNA sequencing and analysis performed at Guardant Health Inc. using a single ctDNA assay, Guardant360™. Samples were sequenced on an Illumina Hi-Seq 2500. Genomic alterations in cfDNA were identified from Illumina sequencing data by Guardant Health's proprietary bioinformatics algorithms. The study demographics included average age at diagnosis 64 years (range 16–91 years) with 36 African-American subjects (53%) 29 Caucasian subjects (43%) with 65% female. The results showed 83% of subjects (56 of 68) had at least one non-synonymous ctDNA genomic alteration detected in plasma. The most commonly mutated genes were TP53, KRAS and EGFR. Approximately 82% of patients had a matched clinical trial based on their diagnosis and/or genomic alteration and another 39% had a genomic alteration with an FDA-approved therapeutic target in a different indication. Subjects with no detectable ctDNA were more likely to have small volume disease, lepidic growth pattern, mucinous tumors, or isolated leptomeningeal disease. Over 80% of patients had detectable ctDNA, with median PFS in 6 patients of 11.5 months (range 7.5–29 months; 95% CI 5.7–28.7). The authors concluded that

this clinic-based series of NSCLC patients assessed outcomes of targeted therapies using a commercially available ctDNA assay outside of the investigational setting.

Villaruz et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. Cancer, 2015.

The aim of the study was to delineate the clinicopathologic features and prognosis of *BRAF* mutant lung cancers compared with other genomic subsets identified through the Lung Cancer Mutation Consortium, a 14-institution collaborative effort established in 2009 to assess lung adenocarcinomas for driver genomic alterations in 10 genes (*EGFR*, *KRAS*, *HER2*, *AKT1*, *BRAF*, *MEK1*, *NRAS*, *PIK3CA*, *ALK* translocations, and *MET* amplification) to study and treat patients by their molecular subtype. The study involved 1007 patients with adenocarcinomas including patients with stage IV or recurrent adenocarcinomas of the lung and SWOG performance status 0, 1, or 2. The article made no reference to type of platform used for sequencing. Results showed 951 patient tumors were tested for *BRAF* mutations, in whom 21 (2.2%: 95% CI 1.4 to 3.4%) *BRAF* mutations were identified (17 *BRAFV600E* and 4 non-*BRAFV600E* mutations). There were 733 cases that tested positive for all 10 genes and patients whose tumors harbored *BRAF* mutations were older than patients with *ALK* rearrangements (median ages 65 and 54 years old; p -value=0.002). Significant differences were seen in gender between patients with *BRAF* mutations and patients with sensitizing *EGFR* mutations (50% patients with *BRAF* mutations were female, compared with 76% patients with sensitizing *EGFR* mutations, mid- P =0.02). *BRAF* mutations were more likely to occur in current or former smokers and patients with *BRAF* mutant tumors had the longest median OS (56 months), whereas patients with doubletons had the shortest estimated median OS (24 months). The authors concluded comprehensive genomic profiling is important in assessing patients with advanced lung adenocarcinomas.

Wang et al. Noninvasive genotyping and monitoring of anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer by capture-based next-generation sequencing. Oncotarget, 2016.

The aim of the study was to assess the feasibility and performance of targeted deep sequencing to plasma cfDNA to detect and quantify *ALK* rearrangements and other somatic driver mutations. The study used data from 364 patients with advanced NSCLC screened for *ALK* rearrangements at Department of Respiratory and Critical Care Medicine, West China hospital affiliated with Sichuan University in China. The analysis methods included targeted ultra-deep sequencing on 73 plasma cfDNA samples obtained from 40 patients. DNA was profiled using a commercially available capture-based targeted sequencing panel by Burning Rock Biotech Ltd, and 30 samples were sequenced on a NextSeq 500 by Illumina, Inc. The study demographics included mean age 48.1 years (range 30-66 years) with 58% female. Results showed *ALK* rearrangements were successfully detected in 19 of 24 patients at baseline with 79.2% sensitivity (95% CI 57.9%, 92.9%) and 100% specificity (36/36) when compared to FISH. The authors concluded that capture-based targeted deep sequencing of plasma cfDNA from NSCLC patients can detect and quantify *ALK* rearrangements and other somatic mutations.

Yates et al. Genomic Evolution of Breast Cancer Metastasis and Relapse. Cancer Cell, 2017.

The purpose of this study was to determine whether or not newly emerging driver mutations in patients with metastatic breast cancer might offer opportunities for personalized therapy. The source of the data was from tissue samples submitted from the different institutions that participated in the study. Breast tissue samples were taken from patients with locally relapsed or metastatic breast cancer. Illumina HiSeq platform was used to sequence whole genome or a panel of 365 genes on 299 samples from 170 patients. Study results indicate that at the time of initial diagnosis, the genome of the primary would have been a good proxy for that of the cells that ultimately seeded the relapse. The researchers also found that clones seeding metastasis or relapse, disseminate late from primary tumors, but continue to acquire mutations, mostly accessing the same mutational processes active in the primary tumor. Most distant metastases acquired driver mutations not seen in the primary tumor, including a number of clinically actionable alterations and mutations inactivating SWI-SNF and JAK2-STAT3 pathways. The authors conclude that their work showed potential clinical impact, provided insights into patterns of clonal evolution, and pathways that could represent new therapeutic targets.

C. Discussion of Evidence

1. Evidence Question

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" CMS is interested in answering the following question:

Is the evidence sufficient to conclude that next generation sequencing when used as a diagnostic test for patients with advanced cancer meaningfully improves health outcomes?

The evidence reviewed is directed towards answering this question.

2. Internal Technology Assessment

In this NCA, articles will be arranged in the following order: systematic reviews, meta-analysis, randomized controlled trials, prospective observational studies, retrospective observational studies, case series, and other studies.

Jardim et al. Impact of a Biomarker-Based Strategy on Oncology Drug Development: A Meta-Analysis of Clinical Trials Leading to FDA Approval. J Natl Cancer Inst., 2015.

Jardim and associates used a meta-analysis to compare efficacy outcomes between approved treatments that employed a personalized therapy strategy vs those which did not. Only agents approved for the treatment of adults with advanced solid and hematologic malignancies were included in the analysis. Sources of information included MEDLINE, and the ASCO meetings website. Valid biomarker results were used in the analysis. Hazard Ratios (HR), and relative response rate ratio (RRR) for personalized trials vs non-personalized were also reported with definitions consistent with RECIST.

The authors found 57 randomized (18 [32%] personalized) and 55 nonrandomized trials (26 [47%] personalized; n=38,104) trials. Trials that adopted a personalized strategy more often included targeted agents (100% vs 65%, p-value<0.001) and were associated with higher RRRs compared with their corresponding control arms (RRRs = 3.82, 95% confidence interval [CI] = 2.51 to 5.82, vs RRRs = 2.08, 95% CI = 1.76 to 2.47, adjusted p-value=0.03), longer PFS (HR=0.41, 95% CI = 0.33 to 0.51, vs HR = 0.59, 95% CI = 0.53 to 0.65, adjusted p-value<0.001), but a non-statistically significantly longer OS (HR = 0.71, 95% CI = 0.61 to 0.83, vs HR = 0.81, 95% CI = 0.77 to 0.85, adjusted p-value=0.07) compared with non-personalized trials. Similar findings were found in the experimental arm, though OS was found to be statistically significant. In all 112 registration trials (randomized and nonrandomized), they demonstrated that personalized therapy was associated with higher response rate (48%, 95% CI = 42% to 55%, vs 23%, 95% CI = 20% to 27%, p-value<0.001) and longer PFS (median = 8.3, interquartile range [IQR] = 5 vs 5.5 months, IQR = 5, adjusted p-value=0.002) and OS (median = 19.3, IQR = 17 vs 13.5 months, IQR = 8, Adjusted p-value=0.04). The authors found that personalized strategy was an independent predictor of better RR, PFS, and OS, but treatment-related mortality rate was similar for personalized and non-personalized trials.

The authors concluded that personalized therapy is associated with increased clinical benefit across tumor types and markers, as demonstrated by substantially higher response rates, longer time to disease progression, and longer overall survival.

Schwaederle et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. J Clin Oncol., 2015.

The aim of this study was to compare the main outcome end points between trials that adopted a personalized therapy strategy versus those that used an unselected population. The endpoints chosen for this study included RR, PFS, and OS. This study used data that were stratified by multiple factors such as personalized or non-personalized approach, study design, patient experience with chemotherapy, impact factor of journal for the published studies, and number of patients per arm.

The authors found that the personalized approach, compared with a non-personalized approach, correlated with higher median RR (31% v 10.5%, respectively; p-value<0.001) and prolonged median PFS (5.9 v 2.7 months, respectively; p-value<0.001) and OS (13.7 v 8.9 months, respectively; p-value<0.001). Personalized arms using a genomic biomarker had higher median RR and prolonged median PFS and OS (all p-value≤0.05) compared with personalized arms using a protein biomarker. A personalized strategy was associated with a lower treatment-related death rate than a non-personalized strategy (median, 1.5% v 2.3%, respectively; p-value<0.001).

The authors concluded that across malignancies, a personalized strategy was an independent predictor of better outcomes and fewer toxic deaths.

Schwaederle et al. Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis. JAMA Oncol., 2016a.

The aim of this study was to analyze the impact of a biomarker-based personalized cancer treatment strategy in the setting of phase 1 clinical trials by comparing patient outcomes between studies that used a personalized approach with those that did not. To be included, the study had to be published between January 1, 2011, and December 31, 2013 and report adequate efficacy end points, including at least response rate (RR). Personalized therapy was defined as a treatment that met one of the following criteria: (1) test for a cognate biomarker used for treatment selection or (2) no cognate biomarker used, but at least 50% of patients are known to harbor the cognate biomarker. For the meta-analysis, the authors used a random effects model and performed a multivariable pooled analysis of the data using the weighted least squares method.

The search identified 1854 results and 351 arms comprising 13,203 patients among the phase 1 trials. Fifty-eight arms were personalized and accrued a total of 2655 patients compared with 293 arms for trials using a non-personalized strategy (10,548 patients). Multivariable analysis (meta-regression and weighted multiple regression models) demonstrated that the personalized approach independently correlated with a significantly higher median RR (30.6% versus 4.9%; p-value<0.001) and a longer median PFS (5.7 months [95% CI 2.6-13.8] versus 2.95 months [95% CI, 2.3-3.7 months; p-value<0.001). Targeted therapy arms that used a biomarker-based selection strategy (n = 57 trials) were associated with statistically improved RR compared with targeted therapy arms (n = 177 arms) that did not (31.1% versus 5.1%; p-value<0.001). Survival was not analyzed owing to insufficient data (data were provided in only 27 of 346 studies [n = 4 were personalized studies]). The median treatment-related mortality was not statistically different for arms that used a personalized strategy versus those that did not (1.89% versus 2.27%; p-value=0.31).

The authors concluded that use of a biomarker-based approach was associated with significantly improved outcomes for RR and PFS.

Le Tourneau et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol., 2015.

The aim of this study assessed whether the histology-agnostic use of marketed molecularly targeted agents outside their indications based on tumor molecular profiling could improve outcomes for patients with any kind of cancer for whom the standard of care had failed. This study involved use of molecularly targeted agents and tumor molecular profiling in patients with refractory cancer. This study used data from eight academic sites in France. The study demographics (n=741) included patients 18 years and older with any kind of recurrent or metastatic solid tumor for whom standard of care therapy had failed. Of those initially screened, 293 (40%) had at least one molecular alteration, and 195 (26%) patients had been randomly assigned, with 99 in the experimental group and 96 in the control group. The average age of molecularly targeted agent group was 61 years (range 54-69), while the average for patients treated at physician's choice was 63 years (54-69).

The analysis included molecular profiling performed on tumor samples by targeted next generation sequencing (AmpliSeq cancer panel on an Ion Torrent/PGM system); gene copy number alterations by Cytoscan HD, and expression of estrogen, progesterone, and androgen receptors by immunohistochemistry. The molecularly targeted agents that were given to the experimental group were drugs that were approved for clinical use in France, but outside their indications. Therapeutic agents were selected in accordance with a predefined treatment algorithm. In both the experimental and control groups, treatments were given according to the approved product information, and were continued until evidence of disease progression. If tumors had several molecular alterations, prioritization was discussed by the Molecular Biology Board. Tumor assessments were done before patients started the study treatment (baseline), then every 8 weeks. Primary endpoint included progression-free survival, according to RECIST, and secondary endpoints included safety and proportion of patients with an objective response to treatment as assessed by RECIST.

This study found that 41 (21%) patients had at least two molecular alterations that would potentially lead to different choices of molecularly targeted agents. 82 patients had a molecular alteration affecting the hormone receptor pathway, 89 patients had alterations in the PI3K/AKT/ mTOR pathway and 24 had alterations in the RAF/MEK pathway. Median follow-up was 11.3 months in the experimental group and 11.3 months in the control group. Median PFS was 2.3 months (95% CI 1.7–3.8) in the experimental group versus 2.0 months (1.8–2.1) in the control group (HR 0.88, 95% CI 0.65–1.19, p-value=0.41). PFS at 6 months was 13% (95% CI 7–20) in the control group and 11% (6–19) in the experimental group. Objective responses were noted in four of 98 assessable patients in the experimental group and three of 89 assessable patients in the control group (p-value=0.19). For statistical purposes, there was no interaction between the altered molecular pathway and treatment effect (p-value=0.49).

Grade 3–4 adverse events were noted for 43 (43%) of the 100 patients who received a molecularly targeted agent including 99 patients from the experimental group, and 32 (35%) of the 91 patients who received cytotoxic chemotherapy (p-value=0.30). No deaths related to study drugs occurred during the trial.

The authors concluded that using molecularly targeted agents outside their indications did not improve progression-free survival compared with treatment at physician's choice in heavily pretreated patients with cancer. They also discouraged off-label use of molecularly targeted agents, but suggested that enrollment in clinical trials should be done to assess predictive efficacy.

Le Tourneau et al. Randomised proof-of-concept phase II trial comparing targeted therapy based on tumour molecular profiling vs conventional therapy in patients with refractory cancer: results of the feasibility part of the SHIVA trial Br J Cancer. 2014.

Le Tourneau and associates initiated a trial that compared molecularly targeted therapy based on tumor molecular profiling vs conventional, but not standard of care chemotherapy. If no molecular abnormality for which an approved matched molecularly targeted agent was identified, then patients were not eligible for the randomization and entered into a prospective observational cohort.

The first one hundred patients screened were included in the study. An overall number of 58 out of the 95 patients (61%) who had a complete molecular profile. Median timeframe from tumor biopsy/resection to Molecular Biology Board presentation was 26 days (range: 14–42). Thirty-eight patients had molecular abnormalities for which a molecularly targeted agent was available in the frame of the trial. These were related to the hormone receptor pathway, the PI3K/AKT/mTOR pathway, and the MAPK pathway was found in 23 (61%), 13 (34%), and 2 (5%) patients, respectively. Also the discovery of mutations, gene copy number alterations, and IHC analyses was found in 63 (66%), 65 (68%), and 87 (92%) patients, respectively. The authors concluded that a comprehensive tumor molecular profile was safe, feasible, and compatible with clinical practice in refractory cancer patients.

Papaxoinis et al. Significance of PIK3CA mutations in patients with early breast cancer treated with adjuvant chemotherapy: A Hellenic Cooperative Oncology Group (HeCOG) Study. PLoS ONE 2015.

The aim of the study was to examine the role of different types of PIK3CA mutations in combination with molecular biomarkers related to PI3K-AKT signaling in patients with early breast cancer. The study included data from 1008 early breast cancer patients from two randomized adjuvant chemotherapy trials, HE10/97 and HE10/00. Tissue blocks were collected retrospectively in the first trial (HE10/97) and prospectively in the second (HE10/00). 610 tumor DNA samples were examined with next-generation sequencing (NGS).

This study found that PIK3CA mutations were detected in 235/1008 tumor samples (23%) with Sanger/qPCR and in 149/610 tumor samples (24%) with NGS. The investigators noted that concordance between test methods was good with a Kappa coefficient of 0.76 (95% CI 0.69–0.82). Across three PIK3CA mutations, the percentage of patients > 50 years were 59 percent, 61 percent, and 64 percent. Median disease-free and OS did not significantly differ with respect to PIK3CA mutation presence and type. Comparing 90 percent 4-year OS for those with PIK3CA mutation to 89.1 percent 4-year OS for those with PIK3CA wild-type, the p-value is 0.89. The authors concluded that their study did not show any prognostic significance of specific PIK3CA mutations in a

large group of predominantly lymph-node positive breast cancer women treated with adjuvant chemotherapy.

Peeters et al. Massively parallel tumor multigene sequencing to evaluate response to Panitumumab in a randomized phase III study of metastatic colorectal cancer. Clin Cancer Res., 2013.

The aim of this study was to investigate whether EGF receptor (EGFR) pathway mutations predicted response to monotherapy with panitumumab among metastatic colorectal cancer (mCRC) patients. The study used data from 320 samples collected from 463 patients with metastatic colorectal adenocarcinoma enrolled in the randomized multicenter phase III study (NCT00113763). The patients enrolled were randomly assigned 1:1 to receive panitumumab plus best supportive care (BSC) or BSC alone. Endpoints included PFS, objective response rate (ORR) per modified RECIST version 1.0 and OS. The analysis methods included mutation analysis carried out using the 454 Amplicon Variant Analysis software version 2.0 (Roche 454 Life Sciences).

The study demographics for the 463 participants included a median age of 62 years with a range from 27 years to 83 years. Men comprised 63 percent of the group and 99 percent of patients were White. For the gene mutation analysis, 320 archival tumor samples were available from the 463 patients in the original phase III study, 288 (288 of 320; 90%) of which provided information for multiple genes. Mutation rates included KRAS (codons 12, 13, and 61) (45%), NRAS (5%), BRAF (7%), and EGFR (1%).

Among patients with wild-type KRAS (codons 12/13/61), treatment compared to BSC was associated with improved PFS (HR, 0.39; p-value<0.001). In patients with wild-type KRAS (codons 12/13/61) and mutant NRAS (n = 11), treatment was not associated with longer PFS (HR, 1.94; p-value=0.38). No significant difference in OS was observed between the treatment arms in the original randomized study (HR, 1.00; 95% CI, 0.82–1.22; p-value=0.81) and KRAS status was not predictive for OS.

The authors concluded that although only KRAS mutational status predicted response to treatment with panitumumab, among patients with wild-type KRAS, objective responses did not occur in patients with mutations in NRAS or BRAF.

Prospective Observational Studies

Kim et al. The NEXt-1 (Next generation pErsonalized tX with mulTi-omics and preclinical model) trial: prospective molecular screening trial of metastatic solid cancer patients, a feasibility analysis. Oncotarget, 2015.

The aim of this study was to survey the feasibility of genomic profiling in oncology patients and to compare response rates in matched treatment group versus non-matched conventional treatment group. The study used data from 428 metastatic solid tumors in patients from the NEXT-1 trial (NCT02141152) and the LUNG PERSEQ trial (NCT02299622) depending on the cancer types at Samsung Medical Center in Korea. At the time of genomic analysis, patients were informed of 1) available genome-matched trials, 2) genome matched treatments in practice, and 3) clinical trials or cytotoxic chemotherapies regardless of available genomic data. The analysis methods included the Ion Torrent AmpliSeq Cancer Hotspot Panel v2 used to survey 2,855 somatic mutations in 50 commonly mutated oncogenes and tumor-suppressor genes.

Patients enrolled in this series had a median age of 56 years (range: 18 – 82 years). Men comprised 59 percent of the study population. All patients were Korean. The most frequent cancer types included gastric cancer (GC; n = 133, 31.1%), non-small cell lung cancer (NSCLC; n = 94, 22%), colorectal cancer (CRC; n = 60, 14%), and melanoma (n = 12, 2.8%). The mutational profiles were obtained for 407 (95.1%) patients, and 342 (84.0%) patients had one or more aberrations detected. The most frequently detected amplifications were MET (2.1%) EGFR (1.8%), HER2 (1.8%), KRAS (1.8%), and FGFR2 (1.4%). The RR was significantly higher in the genome-matched treated group for gastrointestinal/hepatobiliary/rare tumors (matched versus non-matched treatment, 42.6% versus 24.3%, p-value=0.009) and lung cancer cohort (matched versus non-matched treatment, 61.2% vs 28.6%, p-value<0.001) when compared with the non-matched group. The authors concluded that genome-matched treatment based on molecular profiling resulted in better treatment outcome.

Sohal et al. Prospective Clinical Study of Precision Oncology in Solid Tumors. J Natl Cancer Inst., 2016.

The aim of this study was to evaluate the feasibility of routine next-generation sequencing of solid tumors at a large academic medical center, and determine the impact of testing on enrollment in clinical trials and therapeutic decision-making. The study demographics (N=242 patients) included patients with histopathologic diagnosis of select solid tumor malignancies, metastatic disease without a curative therapeutic option, age 18 years or older, and measurable disease. The most common cancers included colorectal (25%), breast (18%), lung (13%), and pancreatobiliary (13%). The median age of participants was 60 (range 24–94). Sequencing of tissue specimens was performed using the FoundationOne next generation sequencing test. Using seven days as a median number of days from consent, the process was feasible in 82.2% (95% confidence interval [CI] = 77% to 87%) of case patients. Nineteen patients (8%) had insufficient tissue for analysis. 214 patients (96%) had at least one alteration, with a median of four (0–20) alterations per specimen.

The study found that a genomics tumor board reviewed all 223 samples within a median of six (3–45) days of result, and a therapeutic recommendation was noted in 200 (90%) reports. An actionable alteration was seen in 109 (49%) case patients. The most common actionable targets were *KRAS* (n = 22), *CDKN2A/B* (n = 16), *PIK3CA/PIK3R* (n = 15), *FGFR* (n = 13), *PTEN/AKT* (n = 12), and *HER2* (n = 8). Non-actionable targets (eg, *TP53*, n = 59) and non-availability of trials targeting potentially actionable alterations (eg, *NRAS*, n = 32) were also discussed. The study also identified 134 treatment recommendations (1–2 per patient), including 102 (77%) clinical trials, 22 (17%) off-label uses, eight (6%) on-label uses, and two uses of epidermal growth factor receptor (EGFR) antibodies in colorectal cancer with previously unknown *RAS* alterations. Of 109 patients with a treatment recommendation, 24 received genomic-driven therapy including 12 clinical trials, nine off-label uses, and three on-label. There were 83 patients who did not have their treatment influenced by tumor genomic profiling because of clinical deterioration, death, use of other therapies or other causes. Of the 22 patients who received other therapies, the most common reason (n = 17) was non-availability of recommended clinical trial. The authors concluded that the study demonstrated the feasibility of next-generation sequencing of solid tumors and that such testing increases enrollment in clinical trials and therapeutic decision-making.

Subbiah et al. Next generation sequencing analysis of platinum refractory advanced germ cell tumor sensitive to Sunitinib (Sutent®) a VEGFR2/PDGFR β /c-kit/ FLT3/RET/CSF1R inhibitor in a phase II trial. J Hematol Oncol., 2014.

This study was designed to determine if Sunitinib (Sutent) possessed important clinical activity in metastatic germ cell tumors (GCTs) that are refractory to first line chemotherapy treatment. The primary endpoint in this study was 12 week PFS. This study used data from patients with progressive metastatic GCTs in males after failure of first line therapy and at least one salvage regimen, and the patients had evaluable disease by clinical or radiological studies. Response evaluations were performed consistent with RECIST. The study used genomic profiling from the HiSeq 2000 (Illumina).

The patient demographics (N=5) of in the study ranged from 17 to 52 years old. The study found that one patient was free of disease progression for more than 12 weeks (17 weeks). An examination of this tumor revealed several genetic alterations found to have reported information in treated tumors or cells, including RET amplification, PTEN loss, EGFR amplification and KRAS amplification. A review of the medical literature was performed by the investigators to determine the level of evidence of clinically relevant genes. The investigators concluded that the RET amplification, EGFR amplification and KRAS amplification were validated.

Takeda et al. Clinical application of amplicon-based next-generation sequencing to therapeutic decision making in lung cancer. Ann Oncol., 2015.

The purpose of this study was to determine feasibility of detecting actionable mutations to influence treatment recommendations for patients with lung cancer. The study used data from the Ion AmpliSeq Colon and Lung Cancer Panel and Ion AmpliSeq RNA Fusion Lung Cancer Research Panel to assess mutational hotspots in 22 genes as well as 72 major variants of ALK, RET, ROS1, and NTRK1 fusion transcripts, respectively. The patient demographics (N=110) included those with a histologically confirmed diagnosis of lung cancer without restrictions on tumor histology, disease stage, subsequent or previous treatment, or performance status.

Thirty-seven (34%) patients were female, and 39 (35%) were never or light smokers, with the median age of all patients being 70 years (range, 39–87). Seventy-eight (71%) patients had adenocarcinoma, and 60 (55%) had stage IV disease. Seventy (64%) specimens were derived from tissue obtained at the time of the tumor biopsy, and 40 (36%) were from surgically resected tissue.

The two primary end points for the study included (i) the percentage of patients with additional therapy options uncovered by detection of potentially actionable genetic alterations, and (ii) the percentage of patients who actually received genotype-directed therapy based on their genetic test results. A secondary end point was the success rate of genetic testing, which was defined as the percentage of successful sequencing of DNA and RNA simultaneously extracted from the formalin-fixed paraffin embedded (FFPE) sample. The study found adequate

amount of material for DNA sequencing and mutational profiling for 104 of the 110 samples (95%), while adequate amounts of material for RNA analysis were available for 101 of the 110 patient samples. Actionable genetic alterations were identified in 44 (40%) of the 110 study patients and included mutations in AKT1, BRAF, EGFR, KRAS, NRAS, PIK3CA, and STK11 as well as ALK, RET, and ROS1 fusions. Thirty-nine (50%) of the 78 patients with adenocarcinoma harbored an actionable alteration, whereas only 3 (14%) of the 22 patients with squamous cell carcinoma, and none of those with small-cell lung cancer had actionable alterations. The decision to recommend a targeted therapy to a patient with a tumor harboring an actionable genetic change was left to the treating physician. Thirty-seven patients with advanced or recurrent lung cancer harbored actionable mutations, and 23 patients (62%) received targeted therapy. Eighteen (95%) of the 19 patients harbored EGFR mutations and 18 patients (95%) received targeted therapy. Three patients harboring a gene fusion received targeted therapy. 8 patients harbored KRAS mutations and 2 (25%) received targeted therapy. Three patients harbored PIK3CA mutations however none received targeted therapy. The study found that the OS of patients with advanced or recurrent cancer who also had an actionable mutation and received targeted therapy was significantly longer compared to patients with no mutation (18.1 months, p-value= 0.041) and significantly longer compared to patients with a mutation but not treated (6.1 months, p-value= 0.0027).

Wheler et al. TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics. Mol Cancer Ther., 2016a.

The aim of this study was to evaluate the usefulness of comprehensive genomic profiling (CGP) using a 236 gene next-generation sequencing (NGS) panel in patients whose diverse tumors harbored the TP53-mutation, and to determine if they had improved outcomes when treated with VEGF or VEGF receptor antagonist. The study used data from tumors that had the TP53 mutations to determine whether the presence of such mutation(s) associated with a better outcome when antiangiogenic agents were administered. The study included 500 patients with 17 different tumor types. Gastrointestinal malignancies were the most common tumor (affected 18% of patients). The study test method included NGS from Foundation Medicine in a CLIA-certified lab. Outcomes of interest included SD >6 months, PR, CR, time-to-treatment failure (TTF) and OS.

The study found that 188 patients (37.6%)—55% were 60 years old or younger and 65% were women—had at least one molecular alteration. The median number of molecular alterations was five per person (range, 1–14). One hundred and six patients (56% of 188) had tumors that harbored TP53 mutations. One hundred and eighty-two treated patients (97%) were evaluable for assessment of SD > 6 months/PR/CR, and all 188 were evaluable for TTF and OS. The most frequent reasons for the inability to evaluate a patient for treatment were insufficient tissue, progressive cancer or succumbing to disease. The study found that the median OS for all 188 patients was 8.0 months (range, 0.3–23.6 months). There was a trend for participants with TP53 wild-type tumors to survive longer than the TP53-mutant tumor-bearing patients, but this did not reach statistical significance (9.2 vs. 7.6 months; p-value<0.132).

VEGF/VEGF receptor inhibitor therapy was independently associated with improvement in all outcome parameters for the patients harboring TP53-mutant cancers, but improvement was not seen in any of these parameters for patients with TP53 wild-type neoplasms.

The authors concluded that TP53 mutations helps predict sensitivity to VEGF/ VEGF receptor inhibitors, and that TP53 alterations could be a useful biomarker for treatment with antiangiogenic agents.

Retrospective Observational Studies

Ali et al. Comprehensive Genomic Profiling of Advanced Penile Carcinoma Suggests a High Frequency of Clinically Relevant Genomic Alterations. Oncologist, 2016.

The aim of this study was to look at the results of CGP in a cohort with advanced squamous penile cancer. This study used data from CGP based on targeted NGS in a CLIA-certified laboratory (Foundation Medicine). Study demographic information (N=20) revealed a median age of 60 years (range 46–87 years), 17 patients (85%) with stage IV disease, and 3 patients (15%) with stage III disease. The study found that CGP revealed 109 GAs, with an average of 5.45 GAs per patient with 44 GAs (40%) having clinical relevance occurring at a mean frequency of 2.2 GAs per case. At least one GA with clinical relevance was detected in 19 out of the 20 patients, including *CDKN2A* (8 patients [40%]), *NOTCH1* (5 patients [25%]), *PIK3CA* (5 patients [25%]), *CCND1* (4 patients [20%]), *EGFR* (4 patients [20%]), *BRCA2* (2 patients [10%]), *RICTOR* (2 patients [10%]) and *FBXW7* (2 patients [10%]). The authors concluded that CGP offers the hope of guiding rational use of targeted therapy in patients with advanced penile carcinoma.

Bailey et al. Progression-free survival decreases with each subsequent therapy in patients presenting for phase I clinical trials. J Cancer., 2012.

The aim of this study was to examine PFS between systemic therapies of commercially available agents prior to presenting a phase I clinical trial evaluation for diverse tumor types. The study demographics (N=165) included adult participants—77 men and 65 women—with a median age at diagnosis of 55.3 years (range 9.4–81.6). The most common advanced cancers included colorectal cancer (n=20 [13.9%]), other gastrointestinal cancer (n=17 [11.8%]), non-small cell lung cancer (n=13 [9.0%]), breast cancer (n=12 [8.3%]), and ovarian cancer (n=11 [7.6%]). Patients had a median of three systemic chemotherapy or hormonal treatments received prior to phase I evaluation. This study found a significant decrease in PFS in systemic therapy for advanced disease from treatment 1 to treatment 2 to treatment 3 (p-value=0.002) as well as from treatment 1 through treatment 5 (p-value< 0.001). The authors concluded that in an advanced cancer population of diverse tumor types, the data showed a statistically significant decrease in PFS with each successive standard therapy.

Haslem et al. A retrospective analysis of precision medicine outcomes in patients with advanced cancer reveals improved progression-free survival without increased health care costs. J Oncol Pract., 2017.

The aim of this study was to compare the clinical outcomes in patients with advanced cancer who received precision cancer medicine targeted therapies with a historical control cohort treated with a non-targeted approach. The study demographics included 72 patients with advanced, refractory metastatic cancer being referred to the precision medicine clinic where they received genomic testing, an in-depth interpretation of the

genomic results from a multi-institutional molecular tumor board (MTB), and a list of treatment options for implementation at the discretion of the treating oncologist. The mean age at time of treatment was 67.8 years for the precision medicine group and 67.0 years for the historical control group (p-value=0.748). Both groups were 61 percent male (n=44) and 100 percent (n=36) were non-Hispanic White in the precision medicine group while 83.3 percent (n=30) non-Hispanic White in the control arm. Both groups were comprised of patients with diverse solid tumor types encompassing 10 different histologically distinct cancers, with non-small cell lung cancer (NSCLC) as the largest subtype (n=11; 31%) followed by colon cancer (n=8; 22.2%) then breast cancer (n=5; 13.9%). The primary end point was PFS measured every 8 weeks consistent with RECIST v1.1. The analysis methods included patient samples analyzed in a CLIA-certified laboratory with NGS performed on a MiSeq platform. Some samples were initially tested by an external laboratory (Caris Biosciences, Foundation Medicine, or TOMA Biosciences).

The study used data from 61 patients with an actionable mutation who had received precision medicine, and outcomes of 36 patients who received genomic testing and targeted therapy compared with 36 matched historical control patients who received standard chemotherapy (n=29) or best supportive care (n=7). The study found that the primary end point of average PFS was significantly prolonged in the precision medicine group compared with the historical control group (mean PFS 22.9 versus 12.0 weeks, respectively; p-value=0.002). The authors concluded that the results suggest a survival benefit for patients who received precision cancer medicine treatment compared with patients who received standard therapy.

Ho et al. Correlation Between Molecular Subclassifications of Clear Cell Renal Cell Carcinoma and Targeted Therapy Response. Eur Urol Focus, 2016.

The aim of the study was to determine if an association exists between genomic alterations (GAs) detected by comprehensive genomic profiling (CGP) in the course of clinical care and the response to anti-VEGF receptor (VEGFR) and anti-mTOR pathway targeted therapies. Study demographics (n=31) included patients with metastatic clear cell renal cell carcinoma (mccRCC) who received directed therapies at one of two institutions. With this study design, it was not possible to accurately characterize RECIST-defined response and associated PFS. The analysis methods included DNA extraction and CGP based on targeted NGS of established cancer-related genes performed on hybridization-captured libraries in a CLIA-certified laboratory (Foundation Medicine).

The study found that 27 patients (87%) had received VEGF-directed therapy and a smaller proportion of patients (39%) had received mTOR-directed therapy. Patients receiving VEGF-directed therapy were male (81%) and White (85%), with a median age of 61 years. The most common GAs detected in this series were in VHL (70%), PBRM1 (48%), and SETD2 (32%). Exceptional responses (duration of treatment [DOT] >21 mo) were more. The study reported frequent responses among patients with GAs associated with VEGF-directed therapy, and less frequent responses among patients with GAs associated with mTOR-directed therapy. The investigators concluded that their study highlighted the feasibility of CGP ordered to identify molecular sub classifications of mccRCC patients while accumulating knowledge that improves the future treatment of such patients.

Hortobagyi et al. Correlative analysis of genetic alterations and Everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from BOLERO-2. J Clin Oncol., 2015.

The aim of this study was to explore the genetic landscape of tumors from patients enrolled on BOLERO-2 and identify potential correlations between genetic alterations and efficacy of Everolimus treatment. The study demographics for BOLERO-2 included 724 patients with advanced breast cancer who were randomly assigned in a ratio of 2:1 to Everolimus plus Exemestane or placebo plus Exemestane. The analysis methods included archival tumor samples from 302 patients that underwent NGS using the Illumina HiSeq2000 by Foundation Medicine.

The study found that the samples represented 42% of the BOLERO-2 population with the NGS subgroup comprising 209 (43.1%) of 485 patients from the treatment arm and 93 (38.9%) of 239 patients from the placebo arm. The median age for the treatment subgroup within the NGS group was 62 years (range 56–70 years) and 73% White. This study also found that for PFS with treatment in the NGS subgroup HR was 0.44 (95% CI 0.33 to 0.59). The genes most frequently altered were PIK3CA (47.6%), TP53 (23.3%), and FGFR1 (18.1%). The authors concluded that PFS benefit was maintained regardless of alteration status of PIK3CA and FGFR1 or the pathways of which they are components.

Javle et al. Biliary Cancer: Utility of Next-Generation Sequencing for Clinical Management. Cancer, 2016.

The aim of this study was to report on the prognostic relevance of genomic variants detected by examining their association with OS after accounting for clinical variables. The study used data linked to clinical and targeted therapy response data retrieved from the institutional databases of 3 major cancer centers. The analysis method included CGP performed with NGS at a CLIA-certified, NYSDOH- and CAP-accredited laboratory (Foundation Medicine).

From a larger database of 554 cases, this study found that a total of 321 biliary tract cancer (BTC) met the clinical correlation criteria for inclusion. Of these 321 cases, 224 were intrahepatic cholangiocarcinoma (IHCCA), 42 were extrahepatic cholangiocarcinoma (EHCCA), and 55 had gallbladder carcinoma GBCA. The study demographics included age ranging from 56 to 62 years, 72.6% White, and majority female in the IHCCA (55.8%) and GBCA (70.9%) groups, but majority male in the EHCCA group (71.4%).

The study found that the most frequently altered genes in IHCCA were TP53 (27%), CDKN2A/B (27%), and KRAS (22%). For EHCCA, the most frequently altered genes were KRAS (42%), TP53 (40%), and CDKN2A/B (17%). For GBCA, the most frequently altered genes were TP53 (59%), CDKN2A/B (19%), and ERBB2 (16%). BRAF base substitutions were uncommon in all 3 tumors with frequency from 1% to 5%. The study also found TP53 (p-value= 0.001) and KRAS (p-value=0.049) mutations in IHCCA were associated significantly with poor OS. In the multivariate analysis, TP53 (HR 1.68, p-value=0.015) and FGFR (HR 0.478, p-value=0.03) pathways contained clinically relevant genetic aberrations. Patients with FGFR GAs had longer OS with FGFR-targeted therapy versus standard regimens (p-value=0.006). The authors concluded that the current study indicates that BTC is enriched with actionable mutations and indicates the potential of CGP for improving outcomes in the management of BTC patients.

The aim of this study was to determine whether the number or type of mutations identified using NGS was correlated with response to anti-PD-1 in melanoma. This study used data from patient samples (n=65) retrospectively selected with metastatic melanoma and started on anti-PD-1 or anti-PD-L1. Imaging, baseline, treatment response, PFS, and OS were obtained through medical record and tumor imaging review. Patients were classified as responders or non-responders by RECIST v1.1. Sequencing was performed using NGS from Foundation Medicine.

The researchers found that the mutation load in anti-PD-1/PD-L1 responders was significantly greater than in non-responders (median, 45.6 vs. 3.9 mutations/MB; p-value<0.003), and similar findings were observed in the validation cohort (median, 37.1 vs. 12.8 mutations/MB, p-value< 0.002). Results were similar between samples obtained within 12 months of starting treatment compared with all other samples. The results also showed that when dividing patients into high (>23.1 mutations/MB), intermediate (3.3–23.1 mutations/MB), and low (<3.3 mutations/MB) mutation load groups that higher ORR were noted in the high mutational load group, followed by intermediate and low groups (82% vs. 36% vs. 10% p-value=0.003). Patients who responded to anti-PD-1/PD-L1 had higher mutational loads in an initial cohort (median, 45.6 vs. 3.9 mutations/MB; p-value< 0.003) and a validation cohort (37.1 vs. 12.8 mutations/MB; p-value< 0.002) compared with non-responders. This study also found longer PFS (high vs. low HR, 0.14, p-value<0.001) and OS (high vs. low HR, 0.09, p-value<0.001) was longer in the high mutation load group.

The authors concluded that because mutation number detected by NGS strongly correlated with benefit from anti-PD-1/PD-L1, and the relationship between anti-PD-1 responses and mutation load in melanoma that stratifying patients into high, intermediate, and low mutation load cohorts provided a clinically feasible marker of response to anti-PD-1/PD-L1 in advanced melanoma.

Johnson et al. Enabling a Genetically Informed Approach to Cancer Medicine: A Retrospective Evaluation of the Impact of Comprehensive Tumor Profiling Using a Targeted Next-Generation Sequencing Panel. Oncologist, 2014.

The aim of this study was to determine if NGS could be helpful in identifying actionable or potentially actionable genetic alterations that might influence treatment selection, and assess the spectrum of potentially actionable alterations identified across malignancies and the demographics of patients tested. Actionable alterations were classified into one of four groups: gene variant predicts sensitivity to approved therapy in a particular malignancy (Group 1); gene variant predicts sensitivity for an approved therapy in any malignancy, but data for efficacy is lacking in that tumor Type (Group 2); gene variant is an eligibility criterion for a clinical trial, or there is published evidence of clinical efficacy with an investigational agent (Group 3), and gene variant with only preclinical support for use of an investigational therapy (Group 4).

(VICC) of 103 samples (101 solid tumors and 2 hematologic malignancies) in either stage IV malignancy (85%) or stage III disease (unresectable or resected at high risk of recurrence). The most common tumor evaluated was breast adenocarcinoma, followed by tumors arising in the head and neck (squamous cell carcinomas, salivary gland tumors, and thyroid carcinomas), melanomas, sarcomas, and lung carcinomas. The analysis method included NGS from Foundation Medicine. Two co-primary endpoints of the study were to assess the percentage of patients with additional therapy options uncovered by detecting potentially actionable genetic alterations, and to evaluate the percentage of patients who actually received genotype-directed therapy.

The researchers found that at least one genetic alteration was identified in 97 tumor samples (94%) with a median of three alterations detected per tumor. Potentially actionable mutations were identified in 86 patients (83%) with a median number of two actionable mutations per patient. Three or greater potentially actionable genetic alterations were detected in 34 biopsied tumor specimens.

Actionable alterations were identified throughout tumor types, including in 100% of breast carcinomas and melanomas as well as gastrointestinal and hematologic malignancies. Renal carcinomas were the least likely to harbor actionable mutations (33%). Six tumors (two adenoid cystic carcinomas, salivary gland adenocarcinoma, lung large cell neuroendocrine tumor, soft tissue granular cell tumor, and Merkel cell carcinoma) harbored no identified mutations. Cell cycle-associated genes, mutations in TP53, MAPK, and PI3-AKT pathways were identified in a large proportion of samples. Eighty-six (83%) patients were found to have potentially actionable GAs in their tumors and 22 patients (26%) had alterations that predicted sensitivity to targeted agents already approved for the tumor type assessed. Eighteen patients received genotype-directed therapy—7 received clinically available agents, and 11 were enrolled in clinical trials. Of note, one patient with refractory T-cell prolymphocytic leukemia with disease progression through five different lines of standard therapy was found to harbor a JAK1 mutation and was treated with a JAK1/2 inhibitor as a result of CGP from NGS.

The authors concluded that targeted use of NGS in patients with advanced cancer could help identify potentially targetable genetic alterations in the majority of patients across tumor types.

Joshi et al. Relationship of smoking status to genomic profile, chemotherapy response and clinical outcome in patients with advanced urothelial carcinoma. Oncotarget, 2016.

The aim of this study was to determine how smoking history impacts genomic profile and chemotherapy response. The study included clinicopathologic data collected for patients (n=83) with metastatic UC (mUC) across 3 academic medical centers with median age 62 years (range, 44–84 years). The analysis of CGP based on targeted NGS of established cancer-related genes was performed in a CLIA-certified lab (Foundation Medicine). Unsupervised hierarchical clustering based on smoking status was used to visualize GA frequencies among different smoking cohorts and to categorize the frequency of GAs among current smokers (CS), ex-smokers (ES) and non-smokers (NS). Across the three smoking status groups, Caucasians comprised 83.3 percent to 89.5 percent of the groups. Seventy-nine patients (95%) had stage IV disease. A total of 47 patients received platinum-based chemotherapy in the first-line setting. The study found that CS had more frequent alterations in DNA repair genes and other targetable signal transduction mediators, while ES exhibited more frequent alterations in selected epigenetic and DNA repair moieties. The ORR, combining CR and PR, was 37.5% (6/16), 47% (16/34) and 19% (3/16) in CS, ES, and NS, respectively (p-value=0.149). The median OS of CS was lower as compared to a combined cohort comprised of ES and NS (15.6 vs 51.6 months; p-value=0.04). The authors concluded that the data from the present study suggest that current smoking status portends worse overall

survival in patients with advanced UC.

Meric-Bernstam et al. Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials. J Clin Oncol., 2015.

The aim of this study was to describe the frequency of actionable alterations across tumor types, subsequent enrollment onto clinical trials and the challenges for trial enrollment at the Molecular Testing for the MD Anderson Cancer Center Personalized Cancer Therapy Program (NCT01772771). The study demographics (N=2000 patients) with median age 55 years and a majority of patients had metastatic, inoperable locally advanced or locally recurrent disease. Patients were mainly accrued in disease centers with genomically relevant trials; also enrolled were patients with diseases for which there were no disease-specific trials but the treating physicians expressed interest in referring patients for phase I trial enrollment. The analysis method included standardized hotspot mutation analysis and NGS performed in a CLIA –certified laboratory.

The study found that the most frequently mutated genes were TP53, KRAS, and BRAF. 789 patients (39%) had at least one mutation in a potentially actionable gene. Actionable alterations were most frequently found in pancreatic cancer (79%), melanoma (77%), colorectal cancer (67%), lung cancer (53%), and breast cancer (33%). Among the 789 patients with potentially actionable alterations, 83 (11%) went on genotype-matched trials after genomic testing. The study also found that 230 patients with PIK3CA/AKT1/PTEN/BRAF mutations returned to receive a new treatment at MD Anderson Cancer Center. As a result, 40 patients (17%) were treated on genotype-selected trials, 16 patients (7%) were treated on genotype-relevant trials targeting a genomic alteration without biomarker selection, 35 patients (15%) were treated on other trials, and 40 patients (17%) received a genotype-relevant drug off trial after testing. The authors concluded that challenges to trial accrual included patient preference of non-investigational treatment or local treatment, lack of trials, and lack of reimbursement. A major obstacle was the paucity of genomically matched trials, especially for less common tumor types and for the less commonly mutated genes. The author stated that broad implementation of multiplex hotspot testing is feasible; however, only a small portion of patients with actionable alterations were actually enrolled onto genotype-matched trials.

Moynahan et al. Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR+, HER2-advanced breast cancer: results from BOLERO-2. Br J Cancer, 2017.

The aim of this study was to evaluate the impact of PIK3CA mutations on Everolimus efficacy. This study used data from BOLERO-2 participants (N=724). Sample analysis included plasma collection, cell free DNA (cfDNA) extraction, and quantification and analysis of PIK3CA mutations. Median PFS was the outcome of interest. The study found PIK3CA mutations in 238 patients (43.3%); the most prevalent was H1047R (25.1%), followed by E545K (11.1%) and E542K (7.1%). Plasma-derived cfDNA samples were available in 247 of the 302 patients who underwent mutation analysis on archival tumor samples (198 primary; 49 metastatic) by NGS. The overall concordance in PIK3CA mutation status between archival tumor and cfDNA sample pairs was 70.4%, with a higher concordance (81.6%) for metastatic lesions. The median PFS in treatment vs placebo arms was similar in patients with tumors that had wild-type or mutant PIK3CA (hazard ratio (HR), 0.43 and 0.37, respectively). The investigators concluded that mutation analysis suggests that PFS benefit was maintained irrespective of PIK3CA genotypes, consistent with the previous analysis of archival tumor DNA by NGS.

Padovan-Merhar et al. Enrichment of Targetable Mutations in the Relapsed Neuroblastoma Genome. PLoS Genet., 2016.

The study aim was to retrospectively determine the frequency by which a therapeutically relevant lesion was discovered either at diagnosis, in the midst of therapy, or at disease relapse, and to infer if NGS could provide the potential for patient benefit. The study demographics (n=138 patients) included 44 samples obtained at diagnosis, 42 samples at second look surgery or biopsy for stable disease after chemotherapy, and 59 samples at relapse. Nine patients had multiple tumor biopsies. The age range for the 138 individuals was 0 to 67 years with all but one patient diagnosed before age 25. The analysis method included molecular profiling by Foundation Medicine.

The study found that ALK was the most commonly mutated gene, with a higher frequency of suspected oncogenic ALK mutations in relapsed disease than at diagnosis. On average, samples taken at relapse had a higher number of potentially actionable variants (0.57 at diagnosis vs. 0.95 at relapse; p-value=0.048). The authors concluded that the prevalence of 'potentially actionable' mutations increased at relapse.

Perez et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol., 2014.

The aim of this study was to perform a joint analysis of two large adjuvant randomized trials evaluating patients with breast cancer treatment by OS and disease-free survival (DFS). Data from this study included 4,046 patients with HER2-positive breast cancer from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and the North Central Cancer Treatment Group (NCCTG) N9831 (sponsored by the National Cancer Institute). Study demographics included women age 18 years or older with primary, operable, and histologically confirmed node-positive or high-risk node-negative invasive breast cancer with no evidence of distant metastases. To participate on study the patients' tumors had to be strongly HER2-positive (either HER2 gene amplified or expressed) and confirmed by an approved reference laboratory (B-31) or central or reference laboratory (N9831).

This study found that adding trastuzumab to chemotherapy led to a 37% relative improvement in OS (HR 0.63; 95% CI 0.54 to 0.73; p-value<0.001) and an increase in 10-year OS rate from 75.2% to 84%. Women randomly assigned to the trastuzumab-containing arm had a significantly increased OS relative to those in the control arm when adjusted for age, tumor size, and extent of surgery (adjusted HR, 0.61; 95% CI, 0.52 to 0.71; p-value<0.001). There was an improvement in DFS of 40% (HR, 0.60; 95% CI, 0.53 to 0.68; p-value<0.001). The authors concluded that the addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early-stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence.

Plimack et al. Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in

The aim of this study was to discover and validate genomic biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy for muscle-invasive bladder cancer (MIBC). This study used data from discovery and validation sets that consisted of prospectively collected pretreatment archival tumor samples identically collected from all MIBC patients treated during two previously reported but separate trials (NCT01031420 and NCT01611662). Study demographics included median age 64 years (range 44-83 years) in the discovery set (n = 34) and 68 years (range 55-82) in the validation set (n = 24). Males comprised 68% of the discovery set and 71% of the validation set. Whites comprised 91% of the discovery set and 96% of the validation set. DNA sequencing was performed using the HiSeq (Illumina) in a CLIA-certified laboratory.

The study found that within the discovery set, 728 alterations in 212 genes were detected while for the validation set, 434 alterations were detected among 170 genes. Patients with a pathologic CR had more alterations than those with residual tumor in both the discovery (p-value=0.024) and validation (p-value=0.018) sets. In the discovery set, alterations in ATM, RB1, or FANCC was correlated with pathologic response (p-value< 0.001), PFS (p-value=0.0085), and OS (p-value=0.007). The study also found in the validation set that ATM/RB1/FANCC signature was confirmed to be predictive for pathologic response (p-value=0.033) with a trend towards increased OS (p-value=0.0545).

The authors concluded that genomic alterations in ATM, RB1, and FANCC predicted response and clinical benefit after cisplatin- based chemotherapy for MIBC.

Radovich et al. Clinical benefit of a precision medicine based approach for guiding treatment of refractory cancers. Oncotarget, 2016.

The aim of this study was to determine the clinical benefit of a precision medicine approach in patients treated with genomically- guided therapy vs. non-genomically guided therapy. This study used data from 168 patients with metastatic solid refractory or rare tumors who had progressed on at least one line of standard of care therapy. Progression was measured by RECIST on at least one prior regimen for advanced disease. Study demographics included a majority of patients with a diagnosis of soft tissue sarcoma, breast cancer, pancreatic cancer, or colorectal cancer. The mean age in the genomic directed group (n = 44) was 55.5 years while the mean age in the non-genomically directed group (n = 57) was 58.4 years (p = 0.22). Females comprised 52.3 percent of the genomic directed group while they comprised 54.4 percent of the non-genomic directed group (p-value=0.83). Patients were evaluated by the Indiana University Health Precision Genomics Program on a referral basis for which the patient served as own control. The analysis included treatment recommendations based on NGS (Paradigm Diagnostics) from a multidisciplinary advisory board. This study calculated the PFS ratio, by dividing the PFS of the new therapy by the PFS for the patient during their most recent regimen on which the patient had experienced progression. NGS was performed on an Ion Torrent Personal Genome Machine and using NGS from Foundation Medicine in CLIA-certified laboratories.

The study found that 43.2% (19 of 44) of patients treated according to genomic recommendations were found to have a PFS ratio > 1.3 compared to 5.3% (3 of 57) of patients who did not receive treatment guided by genomic recommendations (p-value < 0.0001). Overall, patients who received genomically directed therapy had higher PFS ratios compared to non-genomically guided therapy (mean PFS ratio: 1.34 vs 0.8, p = 0.05). Patients treated with genomically guided therapy had a median PFS of 86 days compared to those treated with non-genomically guided therapy with a median PFS of 49 days (p-value=0.005, HR=0.55). The authors concluded that patients with refractory metastatic cancer who receive genomically guided therapy have improved PFS ratios and longer median PFS compared to patients who do not receive genomically guided therapy.

Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. Int. J. Cancer, 2016a.

The purpose of this study was to perform genomic profiling on malignancies identified as having BRAF gene fusions, determine histologic subtypes, and provide examples of response to therapies targeting activated BRAF fusions. This study used data from a database of 20,573 consecutive clinical samples from patients with primarily relapsed and refractory solid tumors and hematologic malignancies. NGS (Foundation Medicine) was used to identify clinically relevant alterations that could be targeted using anticancer therapies or alterations required for entry in a mechanism-driven registered clinical trial.

The authors noted BRAF fusions in 55 (0.3%) samples. The primary tumor was sequenced in 33 (60%) of the cases and a metastatic biopsy was sequenced in 22 (40%) cases. The study found that BRAF fusions were distributed across 12 (3%) tumors including melanoma, glioma, thyroid cancers, pancreatic carcinoma, non-small cell lung cancer, colorectal cancers, breast carcinomas and unknown primary carcinomas. Fusions between KIAA1549 and BRAF were the most frequent BRAF fusions identified in the study and involved 14 (25%) of the 55 BRAF fusion positive tumors. A total of 20 novel fusion partners not previously reported in public databases (COSMIC, TCGA) or the published literature (PubMed) were identified across 20 samples (36%). Clinically relevant alterations affecting, MET, PDGFRA, RET and TSC2 were found in three tumors. Clinical outcomes were available for two patients—a spitzoid melanoma from a 46-year-old Caucasian woman that harbored a ZKSCAN1BRAF fusion and a malignant spindle cell tumor of the chest wall treated as a soft tissue sarcoma with KIAA1549BRAF fusion.

Ross et al. Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations. Cancer, 2016b.

The aim of this study was to conduct a CGP-based report of recurrent and metastatic UC and to detect clinically relevant GAs. The study used data (n=295) from a database of 20,573 consecutive clinical samples of recurrent and refractory metastatic solid tumors. The study demographics included 221 men (75%) and 74 women (25%) with a median age of 66 years and advanced stages of disease (stage III [20%] and stage IV [80%]). The analysis methods included CGP (Foundation Medicine) performed at a CLIA- certified, NYSDOH - and College of American Pathologists (CAP)-accredited laboratory.

The study found that the most frequent GAs were TP53 (55.6%), CDKN2A (34.2%), and ARID1A (25.8%) and 275 cases (93%) featured at least one clinically relevant GA with a mean of 2.6 clinically relevant GAs. The most common clinically relevant GAs included CDKN2A (34%), FGFR3, (21%), and ERBB2 (17%). More specifically, 29 of ERBB2-altered cases were ERBB2 amplifications and 29 were other ERBB2 alterations (28 base substitutions and 1 short insertion). The authors concluded that using a CGP capable of detecting all classes of GAs simultaneously would provide a higher frequency of GAs with clinical relevance.

Schwaederle et al. Precision Oncology: The UC San Diego Moores Cancer Center PREDICT Experience. Mol Cancer Ther., 2016b.

The aim of this study was a retrospective review to collect the clinical, pathologic, and outcomes data of patients with advanced solid malignancies seen at the UC San Diego Moores Cancer Center. The study used data from 340 consecutive patients. The study demographics noted that the most common primary tumor sites were gastrointestinal (27.1%), followed by breast (23.7%), and brain (10.4%) and the majority of patients were females (59%). NGS was performed using testing from Foundation Medicine. The outcomes of study included SD, PR, CR, PFS, and OS.

This study found that the median number of alterations per patient was 4.0 (range, 0–16), 87 patients (25%) were treated with a matched therapy following molecular profile results, and 93 patients received an unmatched therapy (26.8%). The remaining patients were not evaluable, mainly due to death or lost to follow-up before treatment. The study also found that more patients in the matched group achieved SD greater than 6 months relative to PR or CR, 34.5% vs. 16.1%, (p-value < 0.020). Matched patients also had a longer median PFS (4.0 vs. 3.0 months, p-value < 0.039). Finally, patients with a matching-score greater than 0.2 had a median OS of 15.7 months compared with 10.6 months when the matching-score was 0.2 (p-value < 0.040). The investigators concluded that matched patients achieved better outcomes than unmatched patients on multiple outcome parameters.

Singhi et al. Identification of Targetable ALK Rearrangements in Pancreatic Ductal Adenocarcinoma. J Natl Compr Canc Netw., 2017.

The aim of this study was to describe ALK translocations in pancreatic ductal adenocarcinoma (PDAC). Study demographics (N=3170 cases) included locally advanced and metastatic PDACs with 1,724 (54%) men and 1,446 (46%) women and median age 63 years (range 19 to 88 years). The analysis method included CGP using NGS performed in a CLIA-certified and CAP-accredited laboratory (Foundation Medicine).

The study found that 5 PDACs (0.16%) harbored an ALK rearrangement. Four patients were treated with ALK inhibitors and three of these patients demonstrated SD. The study also found OS of 5, 10, 20, and 52 months. The authors concluded that PDACs with ALK translocations are characterized by young patient age at presentation, an absence of KRAS mutations, and a clinical response to ALK inhibitors.

Suh et al. Comprehensive Genomic Profiling Facilitates Implementation of the National Comprehensive Cancer Network Guidelines for Lung Cancer Biomarker Testing and Identifies Patients Who May Benefit From Enrollment in Mechanism-Driven Clinical Trials. The Oncologist, 2016.

The aim of this study was to describe a data series of all NSCLC cases over a 33-month period to demonstrate clinical utility of CGP. This study used data from 6,832 NSCLC samples. The study demographics included median age 64 years (range 13-88 years) and 53% female. 5,380 cases (79%) were lung adenocarcinoma (AD), 1,345 (20%) were non-small cell carcinoma, not otherwise specified (NSCLC-NOS), 72 (1%) were adenosquamous carcinoma (ADSQ), and 35 (0.5%) were large cell carcinoma (LCC). The analysis included CGP performed in a CLIA-certified, CAP-accredited laboratory (Foundation Medicine).

The study found genomic alterations involving EGFR, ALK, BRAF, ERBB2, MET, ROS1, RET, or KRAS in 4,876 cases (71%). Of this number 1,342 cases (20%) harbored EGFR alterations, 280 (4.1%) harbored ALK alterations, 388 (5.7%) harbored BRAF alterations, 408 (6.0%) harbored ERBB2 alterations, 383 (5.6%) harbored MET alterations, 100 (1.5%) harbored ROS1 alterations, 166 (2.4%) harbored RET alterations, and 2,178 (32%) harbored KRAS alterations. In the cohort of lung AD without these known drivers, 273 cancer-related genes were altered in at least 0.1% of cases, many of which are associated with potential benefit from targeted therapies or allow enrollment in mechanism-driven clinical trials, including STK11 (21%), MYC (9.8%), RICTOR (6.4%), CDK4 (4.3%), CCND1 (4.0%), BRCA2 (2.5%), BRCA1 (1.7%), NTRK1 (0.7%), and NTRK3 (0.2%). The authors concluded that CGP facilitates implementation of the National Comprehensive Cancer Network guidelines for lung cancer biomarker testing by enabling simultaneous detection of genomic alterations for driver oncogenes (EGFR, ALK, BRAF, ERBB2, MET, ROS1, and RET).

Swisher et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol., 2017.

The aim of this study was to identify molecular predictors of rucaparib sensitivity in patients with platinum-sensitive recurrent high-grade ovarian carcinoma. The study demographics included patients with a history of high-grade serous or endometrioid ovarian, fallopian, high-grade serous or endometrioid ovarian, fallopian or primary peritoneal carcinoma and had received at least one previous platinum therapy, be at least 18 years old, and not previously treated with a PARP inhibitor. The study subgroups included *BRCA* wild-type and loss of heterozygosity (LOH) high, *BRCA* wild-type and LOH low, and *BRCA* wild-type and LOH unclassified. Additional mutations were also identified by NGS (Foundation Medicine). Of these, 192 treated patients were classified as *BRCA* mutant (n=40), LOH high (n=82), or LOH low (n=70) Tumor response was assessed using RECIST, and the primary endpoint used in the study was PFS, while a secondary endpoint included the proportion of patients achieving an OR.

The study found that the median duration of treatment for the 204 treated patients was 5.7 months (IQR 2.8–10.1). Twenty-four patients in the *BRCA* mutant subgroup, 56 patients in the LOH high subgroup, and 59 patients in the LOH low subgroup had disease progression or died. Median PFS was 12.8 months (95% CI 9.0–14.7) in the *BRCA* mutant subgroup, 5.7 months (CI 5.3–7.6) in the LOH high subgroup, and 5.2 months (CI 3.6–5.5) in the LOH low subgroup. PFS was significantly longer in the *BRCA* mutant subgroup (HR 0.27, 95% CI 0.16–0.44, p-value<0.0001) and LOH high subgroup (HR 0.62, 95% CI 0.42–.90, p-value<0.011) than in the

Printed on 5/2/2018. Page 45 of 151

LOH low subgroup. The authors concluded that assessment of tumor LOH could be used to identify patients with *BRCA* wild-type platinum-sensitive ovarian cancers who might benefit from rucaparib.

Vanden Borre et al. Pediatric, Adolescent, and Young Adult Thyroid Carcinoma Harbors Frequent and Diverse Targetable Genomic Alterations, Including Kinase Fusions. Oncologist, 2017.

The aim of this study was to identify clinically relevant genomic alterations (CRGAs) in papillary thyroid carcinoma (PTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC) that could suggest benefit from targeted therapy. This study used data from 512 patients with thyroid carcinoma, and included 303 cases of papillary thyroid carcinoma (PTC), 132 cases of anaplastic thyroid carcinoma (ATC), and 77 cases of medullary thyroid carcinoma (MTC). The study demographics included 51% (262/512) female patients and a median age of 60 years (range 7 to 96 years). CGP was performed from NGS of over 236 cancer-related genes in a CLIA-certified, CAP-accredited, NYSDOH-regulated laboratory (Foundation Medicine).

This study found that CGP identified at least one GA in 99% (505/512) of cases. The mean number of GAs was 2.5 (PTC), 4.5 (ATC), and 1.8 (MTC). A 34-year-old man, with novel RET alterations experienced clinical benefit from kinase inhibitors. The investigators concluded that patients with advanced thyroid carcinoma can benefit from CGP and rationally matched targeted therapy.

Wheler et al. Anastrozole and everolimus in advanced gynecologic and breast malignancies: activity and molecular alterations in the PI3K/AKT/mTOR pathway. Oncotarget. 2014.

The aim of this study was to investigate the use of anastrozole in combination with everolimus in patients with estrogen receptor (ER) or progesterone receptor (PR)-positive breast and gynecologic tumors, including ovarian and endometrial cancer. The study included 55 women with advanced or metastatic breast, ovarian, endometrial or cervical cancer. The study demographics included 23 patients with previous exposure to aromatase inhibitors. Outcomes of study included progressive disease (PD), SD, PR and CR, OS and TTF. NGS (Foundation Medicine) was performed to determine biomarker mutations.

This study found that 12 patients (24%) achieved SD > 6 months including 5 patients (10%) with a PR or CR. Five of the 23 patients (22%) who had been previously treated in the metastatic setting with an aromatase inhibitor achieved SD ≥ 6 months, including 3 patients (13%) with complete or partial response. The authors concluded that combination anastrozole and everolimus is active in heavily-pretreated patients with ER+ and/or PR+ breast, ovarian and endometrial cancers.

Wheler et al. Thymoma patients treated in a phase I clinic at MD Anderson Cancer Center: Responses to mTOR inhibitors and molecular analyses. Oncotarget, 2013.

The aim of this study was to describe the clinical and molecular characteristics and outcomes of patients with advanced or metastatic thymoma or thymic carcinoma referred to the Clinical Center for Targeted Therapy at The University of Texas MD Anderson Cancer Center. The study demographics (n=21) included median age 52 years (range, 26-73 years) and ten patients (48%) were women. The most common metastatic sites were lung, pleura, and lymph nodes. The analysis method included NGS performed by Foundation Medicine in seven patients with available tissue. Responses were categorized per RECIST v1.0.

The study found actionable mutations in PIK3CA (1; 8%); EGFR (1; 8%); RET (1; 14%); and AKT1 (1; 14%). Twenty patients were treated in 13 different phase I clinical trials. Six of 10 patients (60%) treated with mTOR inhibitor combination regimens achieved SD \geq 12 months or a PR. TTF of \geq 12 months was achieved by six of 10 patients on an mTOR inhibitor-containing regimen versus one of 10 patients treated with other agents (p-value=0.057). The median TTF was significantly longer in nine patients treated on mTOR inhibitor combinations (11.6 months) compared to median TTF on the last standard therapy prior to referral (2.3 months; p-value=0.024). The median OS from the time of diagnosis of advanced/metastatic thymoma or thymic carcinoma to death or last follow up was 85.7 months. The authors concluded that patients with advanced or metastatic thymoma or thymic carcinoma demonstrated prolonged TTF on mTOR inhibitor-based therapy as compared to prior conventional treatment.

Case Series

Ali et al. Comprehensive genomic profiling of different subtypes of nasopharyngeal carcinoma reveals similarities and differences to guide targeted therapy. Cancer. 2017.

The aim of this study was to understand clinically relevant GAs in nasopharyngeal cancer (NPC) patients. This study included data from 20 patients with nasopharyngeal adenocarcinoma (NPAC), 62 patients with nasopharyngeal squamous cell carcinoma (NPSCC), and 108 patients with nasopharyngeal undifferentiated carcinoma (NPUC).

The analysis method included NGS and measurement of tumor mutation burden (TMB) performed in a CLIA-certified laboratory. This study identified 723 GAs including 320 clinically relevant GAs. The study found that GAs were similarly distributed among the 3 subtypes with 74 GAs in NPAC cases (3.7 GAs per sample), 257 GAs in NPSCC cases (4.1 GAs per sample), and 395 GAs in NPUC cases (3.7 GAs per sample). *IDH2* was found to be the most significantly altered gene across the 3 NPC subtypes (15.7% in NPUC and 0% in NPAC and NPSCC). The study also found an association of TMB with NPC subtypes, with the frequency of NPCs harboring more than 10 mutations/Mb as 15% for NPSCC, 10% for NPAC, and 5% for NPUC. The authors concluded that the different NPC subtypes harbor different CRGAs. They also note that tumor mutation burden is associated with NPC subtypes.

Ali et al. Prospective Comprehensive Genomic Profiling of Advanced Gastric Carcinoma Cases Reveals Frequent Clinically Relevant Genomic Alterations and New Routes for Targeted Therapies. Oncologist, 2015.

The aim of this study was to identify GAs associated with a potential response to FDA approved targeted therapies or clinical trials. The study included 116 locally advanced, relapsed or metastatic gastric cancer (GC) cases with median age 62 years (range 26–87 years) and 65 (56%) male patients. CGP using NGS was performed in a CLIA-certified, CAP-accredited laboratory (Foundation Medicine).

The study found 501 GAs of which the investigators determined 210 (42%) were clinically relevant. Moreover, 78% of GC cases harbored at least one clinically relevant GA. Clinical relevance was measured by the association with FDA approved targeted therapies or mechanism-based clinical trials. The most common clinically relevant GAs included KRAS, ERBB2, and MDM2. The most frequent GAs included TP53 (50%), KRAS (16%), and ERBB2 (8.5%). Alterations in receptor tyrosine kinases (RTKs) were harbored by 24 cases (20.6%). One patient with MET-amplified GC received a tyrosine kinase inhibitor antineoplastic agent and achieved disease control for 5 months. The investigators concluded that identifying clinically relevant alterations by CGP in the course of clinical care of GC may drive clinical decision-making, which in turn will generate preliminary data on the efficacy of targeted therapies and care of future patients through systematic investigation such as clinical trials.

Al-Rohil et al. Evaluation of 122 advanced-stage cutaneous squamous cell carcinomas by comprehensive genomic profiling opens the door for new routes to targeted therapies. Cancer. 2016.

The aim of this study was to assess potential genomic therapy targets that could help identify potential strategies for the use of targeted therapies in recurrent and refractory advanced-stage cutaneous squamous cell carcinoma (cSCC). The analysis of GAs was performed by NGS in a CLIA-certified laboratory. Actionable GAs were defined as those whose effect is targetable using FDA approved anticancer drugs or registered clinical trials.

The study included 21 women (17%) and 101 men (83%) with cSCC. The primary cSCC site was used for sequencing in 77 cases (63%), while metastatic lesions were sequenced in 45 cases (37%). The study found 1120 total genomic with a median 9 alterations per case. All 122 cSCC cases harbored at least 1 GA. One hundred and seven cases of cSCC (88%) harbored at least 1 clinically relevant GA. The most frequent clinically relevant GAs were *NOTCH1* (43%); *PTCH1* (11%); *BRCA2* (10%); *HRAS* (8%); *ATM* (7%); *ERBB4* (7%); *NF1* (7%); *ERBB2* (6%); *PIK3CA* (6%); *CCND1* (6%); *EGFR* (5%); and *FBXW7* (5%). The authors concluded that patients with cSCC harbor clinically relevant GAs that have the potential to guide treatment.

Frampton et al. Activation of MET via Diverse Exon 14 Splicing Alterations Occurs in Multiple Tumor Types and Confers Clinical Sensitivity to MET Inhibitors. Cancer Discov., 2015.

The aim of this study was to demonstrate the oncogenic potential of MET exon 14 alterations, and to report on the durable response of MET-targeted therapy in patient tumors that harbored MET alterations. This study used data from 38,028 tumor specimens from patients with advanced cancers. The analysis included CGP using NGS performed in a CLIA-certified laboratory (Foundation Medicine). The study found a total of 224 distinct *MET*ex14 alterations in 221 specimens. The results were distributed among lung adenocarcinoma (3%), other lung neoplasms (2.3%), brain glioma (0.4%) tumors of unknown primary origin (0.4%), and other tumor types (<0.1%). Such alterations were not found in tumors of the female reproductive system (n=7,436), colon and rectum (n=3,714), pancreas (n=1,424). The study also found other receptor tyrosine kinase mutations in the 4,402 lung adenocarcinoma specimens, including activating mutations in *KRAS*, *EGFR*, *ERBB2*, *BRAF*, and *MET* as well as gene fusions involving *ALK*, *RET*, and *ROS1*. Tumors with *MET* exon 14 alterations rarely harbored other known drivers of lung adenocarcinoma. When looking at clinical outcomes in patients that harbor *MET* exon 14 alterations, the researchers also found a small number of patients treated with targeted therapies. Notably, patients with *MET* exon 14 alterations who were treated with MET inhibitors tended to have favorable responses. The authors concluded that patients whose tumors harbored MET alterations could achieve meaningful clinical benefit from MET inhibitors.

Hirshfield et al. Clinical Actionability of Comprehensive Genomic Profiling for Management of Rare or Refractory Cancers. The Oncologist, 2016.

The aim of this study was to assess utility, feasibility, and limitations of CGP for guided therapy in the setting of a MTB. This study included data from 100 patients with rare or refractory tumors evaluated at the Rutgers Cancer Institute of New Jersey. The analysis method included NGS performed in a CLIA-certified laboratory (Foundation Medicine).

The study found that of 92 patients tested, 88 (96%) had at least one GA (average 3.6, range 0–10) and 87 had clinically relevant GAs with urothelial and endometrial cancers displaying the highest mutational burden. The most commonly altered genes included TP53 (41%), KRAS (16%), PIK3CA (15%), and BRAF (7%). There were also GAs in tyrosine kinase genes and tumor suppressor genes. The study also found that approximately 31% of study patients received genomically guided therapy. The authors concluded that use of targeted NGS with a MTB is feasible and has clinical actionability.

Hyman et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med., 2015.

The aim of this study was to identify promising signals of activity in individual tumor types that could be explored. This study used data from a histology-independent phase 2 'basket' study of 122 patients with BRAF V600 mutation-positive multiple nonmelanoma cancers. The study demographics included age range from 18 to 83 years and 33-80% males. BRAF V600 mutations were identified by means of mutational analysis assays routinely performed at each participating site. The pre-specified cancers included non-small cell lung, ovarian, colorectal, cholangiocarcinoma, breast, multiple myeloma, and an-others cohort to enroll patients with any other BRAF V600 mutation-positive cancer. This cohort included cervical cancer, brain tumors, head and neck cancer, esophageal and gastric cancers, pancreatic cancer, sarcoma, and carcinoma of unknown primary type. The ovarian, breast, and multiple myeloma cohorts did not have sufficient sample sizes to undergo formal analysis as distinct groups.

The study found response rate 42% and median PFS 7.3 months for 19 patients with non-small-cell lung cancer. One response were observed for the 37 patients with colorectal cancer, and the median PFS and OS were 0.5 months and 9.3 months, respectively.

There was an anecdotal response noted by the authors for one ovarian cancer patient. The authors concluded that the histology- independent, biomarker-selected, early phase 2 basket study showed modest antitumor activity in cancers, and that histologic context is an important determinant of response in BRAF V600-mutated cancers.

Ko et al. A Multicenter, Open-Label Phase II Clinical Trial of Combined MEK Plus EGFR Inhibition for Chemotherapy-Refractory Advanced Pancreatic Adenocarcinoma. Clin Cancer Res., 2016.

The aim of this study was to perform a phase II clinical trial using a non-random single arm to assess the safety and efficacy of combined MEK and EGFR inhibition in patients with advanced pancreatic adenocarcinoma (PDAC) who had progressed on first-line chemotherapy. This study also examined potential predictive biomarkers and explored the feasibility of monitoring molecular events in the tumor through sequencing analysis of cell-free DNA (cfDNA) in plasma. Outcomes of interest included OS and PFS. This study included data from 46 patients enrolled in the study.

Thirty-six patients (78.2%) experienced at least one grade 3 or higher adverse event. Point mutations in *KRAS* were identified in 24 of 26 (92%) tumor samples. The majority of mutations (66%) identified in pre-treatment plasma samples were also present in on- treatment samples. This study found no significant association between circulating tumor cell concentration and treatment effect. The most frequently mutated genes in pre-therapeutic plasma samples, in which circulating tumor fraction is > 0.4%, was *KRAS* (85%), followed by *TP53* (60%), *ATM* (30%), and *CDKN2A* (15%).

This study found that no ORs were observed, 19 patients (41%) showed evidence of SD for ≥ 6 weeks and the median PFS was 1.9 months (95% CI, 1.4-3.3 months), with a median OS of 7.3 months (95% CI, 5.2-8.0 months). Objective radiographic responses measured by RECIST v1.0. The investigators concluded that patients with tumors exhibiting an epithelial phenotype were more likely to be sensitive to treatment, and tumor-derived DNA was detectable in plasma from the majority of patients.

Mateo et al. DNA-repair defects and Olaparib in metastatic prostate cancer. N Engl J Med., 2015.

The aim of the study was to test the hypothesis that prostate cancers with DNA-repair defects would respond to PARP inhibition. Study demographics included 50 patients with median age of 67.5 years (range 40.8-79.4 years) who had histologically confirmed, metastatic, castration-resistant prostate cancer with progression after one or two regimens of chemotherapy. The study used data from TOPARP-A which was an open-label, single-group, two stage, phase II, multi-site study. The analysis included CGP using NGS.

The study found 16 patients responded to PARP inhibition (33%; 95% CI, 20-48). NGS also identified deleterious mutations in BRCA1, BRCA2, ATM, Fanconi's anemia genes, and CHEK2. Of these 16 patients, all 7 patients with BRCA2 loss responded. Median PFS was significantly longer in the DNA-repair defect-positive group compared to the -negative group (9.8 vs. 2.7 months; p-value<0.001) and median OS increased in the DNA-repair defect-positive group (13.8 months) compared to 7.5 months in the -negative group (p-value=0.05). The hazard ratio for OS in the DNA-repair defect-positive group as compared with the -negative group was 0.47 (95% CI, 0.22 to 1.02; p-value=0.05). The authors concluded that treatment with PARP inhibitors in patients whose prostate cancers were no longer responding to standard treatments and who had defects in DNA repair genes led to a high response rate. However, the study authors could not determine whether PARP inhibition improves overall survival among patients with metastatic, castration-resistant prostate cancer and DNA-repair defects.

Middleton, et al. The National Lung Matrix Trial: translating the biology of stratification in advanced non-small cell lung cancer. Ann Oncol., 2015.

The aim of this study was to determine whether there is sufficient signal of activity in any drug-biomarker combination. The National Lung Matrix Trial (NLMT)—a UK-wide study exploring the activity of rationally selected biomarker and targeted therapy combinations for non-small cell lung cancer (NSCLC)—includes patients allocated to the appropriate targeted therapy according to the molecular genotype of their cancer. The umbrella trial design allows for new arms to be entered via substantial amendment. At study initiation, there are eight drugs being used to target 18 molecular cohorts. The trial includes a common set of outcome measures for all molecularly defined cohorts with flexibility to select a cohort-specific primary end point with response rate as the primary outcome.

The Cancer Research UK (CRUK) Stratified Medicine Programme 2 (SMP2) is undertaking the large volume national molecular pre- screening which integrates with the NLMT.

The screening of patients' tumor biopsies through the SMP2 is performed with NGS carried out in one of three dedicated genotyping centers. At present, 28 genes are interrogated but the platform is adaptable to allow new genomic biomarkers to be added. The authors report that the results from SMP2 can demonstrate the incorporation of Bayesian adaptive designs, creation of molecular exclusion rules and provision of large scale genetic screening to inform entry into the NLMT.

Myers et al. Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG

The purpose of this study was to identify molecular markers that predict benefit in patients with endometrial cancer (EC). This study used data (N=73 patients) from a previous randomized phase II study (GOG 248) that compared Temezirolimus alone with Temezirolimus and alternating Megestrol acetate and Tamoxifen in patients with advanced EC. Data was prospectively collected in order to explore the association of genetic biomarkers with clinical response. NGS was performed (n=55 samples) with a panel of 504 genes with relevance in cancer at the Dana Farber Cancer Institute. Response Rate (RR) and PFS were the outcomes evaluated.

The study found that the RR was 20% and median PFS was 4.9 months. The study also identified samples with GAs in PTEN (45%), PIK3CA (29%), PIK3R1 (24%), K-RAS (16%), CTNNB1 (18%). GAs were least common in AKT1 (4%), TSC1 (2%), TSC2 (2%), NF1 (9%) and FBXW7 (4%). Associations between RR and PFS were independently evaluated with each candidate gene. The study found that AKT1 was associated with increased PFS (HR 0.16; 95% CI 0.01–0.78) and RR. CTNNB1 was associated with an increase in PFS (HR 0.46; 95% CI 0.20–0.97) but not RR. The authors concluded that CTNNB1 mutations were associated with longer patient PFS, and that mutations in AKT1, TSC1 and TSC2 may predict clinical benefit.

Patel et al. Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib. Blood. 2015.

The aim of this study was to identify genes that may predict response to chemotherapy. The study demographics included a cohort of 95 patients with myelofibrosis (MF) with mean age 66 years (range 40-84 years) and 44% females who were treated with ruxolitinib in a previous phase 1/2 study. The analysis included NGS using Illumina MiSeq and a customized TruSeq Amplicon Cancer Panel to screen for mutations in cancer-related genes in the investigators' CLIA-certified laboratory.

The study found that 93 patients (97.9%) had a mutation in more than one gene with 79 patients (82.1%) having a JAK2 V617F mutation, 3 patients (3.1%) having MPL mutations. Mutations in NRAS, KRAS, PTPN11, GATA2, and TP53 were found in <5% of patients. Spleen response ($\geq 50\%$ reduction in palpable spleen size) was inversely correlated with the number of mutations.

Specifically, patients with ≤ 2 mutations had nine-fold higher odds of a spleen response than those with ≥ 3 mutations (odds ratio=9.37; 95% CI, 1.86-47.2). Patients with ≥ 3 mutations also had a shorter time to treatment discontinuation (TTD) and shorter OS than those with fewer mutations (HR=5.97; 95% CI, 2.81-12.65; p-value<0.001). The authors concluded that patients with ≥ 3 mutations had the worst outcomes and may represent more aggressive disease that is less amenable to treatment with chemotherapy.

Plimack et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol., 2014.

The aim of this study was to determine whether or not three cycles of accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) in the neoadjuvant setting would be safe and efficient, and yield similar pathologic response rates compared with historical controls, to shorten the time to cystectomy. The researchers also wanted to analyze GAs to identify biomarkers predictive of response. This prospective phase II multicenter study involved 44 patients with muscle-invasive bladder cancer (MIBC). NGS was analyzed for all classes of genomic alterations, including base substitutions, indels, copy number alterations, and selected rearrangements, however the findings reported relate only to p53. The study demographics (n=44) included median age 64 years (range 44-83 years), with 32% > 70 years, 68% males, and 91% White. Sixty percent of patients had clinical stage III or IV disease at baseline.

The study found that 15 patients (38%) had no residual cancer found in their surgical specimens at the time of cystectomy, meeting the primary end point of the study. The study also found that 65% (95% CI, 50% to 80%) of evaluable patients were down-staged to a lower pathologic stage at cystectomy. Chi-square tests were used to evaluate the relationship between p53 mutation status and pathologic CR, however p53 mutation did not predict response to chemotherapy or toxicity. The investigators concluded that AMVAC is safe, well tolerated, and should be considered for MIBC in the neoadjuvant setting.

Rosenberg et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single arm, phase 2 trial. Lancet, 2016.

The aim of this study was to evaluate the efficacy and safety of immunotherapy and to explore the association between PD-L1 expression profiling, and tumor mutation load. This study included data from 315 patients with a median age of 66 years undergoing treatment at multiple centers between May and November 2014. The study demographics included 74% with bladder cancer and 21% with an upper tract primary tumor. Cisplatin based chemotherapy was previously administered in 73% of patients, and carboplatin based chemotherapy was used in 26%. The co-primary endpoints of the study was ORR by RECIST v1.1 and immune modified RECIST, which compared response rates between the treatment arm and historical control. Secondary endpoints included: duration of response, PFS, OS, 12-month OS, and safety. This study analysis included mutation detection and mutation load assessment by targeted CGP using NGS (Foundation Medicine). A total of 486 patients were screened and 310 patients were evaluated after treatment. The study found that treatment significantly improved objective response rate for each pre-specified IC group [IC2/3, 27% (95% CI 19 to 37), p-value<0.0001; IC1/2/3, 18% (95% CI 13 to 24), p-value=0.0004; and all patients, 15% (95% CI, 11 to 20), p-value=0.0058] compared to a historical control (ORR 10%). The study also found 11% of patients achieved a CR. With a median follow-up of 11.7 months, ongoing responses were observed in 84% of responders with median OS 11.4 months for the IC2/3 group, 8.8 months in the IC1/2/3 group, and 7.9 months for the entire cohort. The 12-month OS rate was 36% in the intent to treat population. Grade 3-4 adverse events occurred in 16% and grade 3-4 immune-mediated adverse events occurred in 5% of patients.

Gene expression analysis (n=195) was used to classify patients into luminal (n=73) and basal (n=122) subtypes. Responses occurred in all subtypes but was significantly higher in the luminal cluster II subtype than others, which demonstrated an ORR of 34% (p-value=0.0017). The median mutation load was significantly increased in

responders (12.4/Mb) compared to non-responders (6.4/Mb) (p -value <0.0001). The study concluded that the study demonstrated that PD-L1 IC status, and mutation load were clearly associated with response.

Schrock et al. Pulmonary Sarcomatoid Carcinomas Commonly Harbor Either Potentially Targetable Genomic Alterations or High Tumor Mutational Burden as Observed by Comprehensive Genomic Profiling. J Thorac Oncol., 2017.

The aim of this study was to develop targeted therapeutic strategies for pulmonary sarcomatoid carcinoma (PSC), a high-grade NSCLC. The study used data from a series of 15,867 NSCLCs collected prospectively. The study demographics included 125 PSCs (0.8% of all NSCLC cases) with median age 67 years (range 32–87 years), and 58% males. Clinical disease stage was available for a subset of cases, and 78% (64 of 82) of patients were stage IV, 11% (nine of 82) were stage III, 9% (seven of 82) were stage II, and 2% (two of 82) were stage IB. The analysis included CGP using NGS (Foundation Medicine). Tumor mutational burden (TMB) was calculated using an algorithm based on the number of somatic base substitution or indel alterations per megabase (Mb).

The study found a median of five GAs per tumor, and at least one GA was identified in all but one case (99%). The most frequent GAs were in TP53 (73.6%), CDKN2A (37.6%), KRAS (34.4%), and CDKN2B (23.2%). A proportion of PSC cases (30%) harbored GAs in genes recommended for testing in the NSCLC National Comprehensive Cancer Network (NCCN) guidelines, including MET (17 of 125 [13.6%]), EGFR (11 of 125 [8.8%]), and BRAF (nine of 125 [7.3%]). The median TMB in this series of PSCs was 8.1 mut/Mb (mean 13.6 mut/Mb, range 0–165.2). The fraction of PSC with a high TMB (>20 mut/Mb) was higher than in non-PSC NSCLC (20% versus 14%, p -value=0.056). The investigators concluded that CGP in clinical care may provide important treatment options for PSC.

Shaw et al. Crizotinib in ROS1-Rearranged Non-Small-Cell Lung Cancer. N Engl J Med., 2014.

Given that ALK and ROS1 rearrangements rarely occur in the same tumor, and each GA describes a different molecular subgroup of NSCLC, the aim of this study was to determine if ROS1 may represent another therapeutic target of the ALK inhibitor in patients with advanced, ROS1-rearranged NSCLC. This study used data from 49 patients identified using break-apart fluorescence in situ hybridization (FISH), and one patient identified using a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. The study was later amended to include an expansion cohort of patients screened for ALK rearrangement and MET amplification using FISH. The study demographics included median age 53 years (range 25–77 years) 44% males and 54% were White. Seventy-eight percent of patients had never smoked and 98% had histologic features of adenocarcinoma. Most patients (86%) had received at least one previous line of standard therapy for advanced NSCLC. To further analyze ROS1 rearrangement, targeted NGS was performed (Zheng et al. 2014).

The study found an ORR of 72% (95% CI 58 to 84), with 3 CRs and 33 PRs. The median duration of response was 17.6 months, and the median PFS was 19.2 months, with 25 patients (50%) still in follow-up for progression. There was no correlation between the type of ROS1 rearrangement and the clinical response to ALK inhibitor. The

safety profile was similar to that seen in patients with ALK-rearranged NSCLC. The authors concluded that ALK inhibition also has potent antitumor activity in patients who had advanced NSCLC with a ROS1 rearrangement.

Tsimberidou et al. Personalized Medicine in a Phase I Clinical Trials Program: The MD Anderson Cancer Center Initiative. Clin Cancer Res., 2012.

The aim of this study was to initiate a personalized medicine program in the context of early phase I clinical trials, using targeted agents matched with tumor molecular aberrations. The study included patients with advanced or metastatic cancer that was refractory to standard therapy, had relapsed after standard therapy, or had a tumor for which there was no standard therapy available. Patients whose tumors had a molecular aberration were preferably treated on a clinical trial with a matched targeted agent, when available.

The study demographics included 2,350 patients seen in the single clinic during this time period and enrolled on a protocol, and 1,144 patients with adequate tissue available for molecular analysis. The analysis included molecular profiling performed as a screening procedure in the CLIA-certified Molecular Diagnostics Laboratory at MD Anderson. Physicians prioritized matched therapy on the basis of (i) having an actionable molecular aberration; (ii) matched targeted therapy available; (iii) eligibility criteria; (iv) insurance coverage and (v) patients agreement to comply with study requirements. Patients were treated with a variety of regimens that included agents targeting PIK3CA, mTOR, BRAF, MEK, EGFR, and RET. Outcomes of interest included TTF, OS, CR, PR, or prolonged SD. The best phase I therapy based on longest TTF was considered for analysis.

The study found that 460 patients had one or more molecular aberrations. The most common aberrations were TP53 (44); KRAS (136); PTEN (76); BRAF (123); PIK3CA (82); and RET mutation (18). The cancers most commonly found to harbor mutations were melanoma (73% of patients), thyroid (56%), and colorectal cancer. More than 30% of patients with endometrial, lung, pancreatic, and breast cancers also had discernible aberrations.

In patients with at least one molecular aberration, the study found matched therapy (n = 175) compared with treatment without matching (n = 116) was associated with a higher overall RR (27% vs. 5%; p-value<0.0001), longer median TTF (5.2 vs. 2.2 months; p-value<0.0001), and longer median survival (13.4 vs. 9.0 months; p-value=0.017). Matched targeted therapy resulted in longer TTF compared with the own patients' prior systemic therapy (5.2 vs. 3.1 months, p-value<0.0001). There was no correlation between response and number of prior therapies in the matched therapy (p-value=0.73) or non-matched therapy groups (p-value=0.99). The authors concluded that identifying specific molecular abnormalities and choosing therapy based on these abnormalities is relevant in phase I clinical trials.

Wheler et al. Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. Cancer Res., 2016b.

The aim of the study was to prospectively investigate the clinical utility of NGS in the phase I oncology ecosystem, including the feasibility CGP on routine biopsy specimens. Study demographics included patients with diverse advanced malignancies (N=500) with median age of 59 years (range 19–82 years) and 35% male. The most common cancers were ovarian (18%), breast (16%), bone and soft tissue (13%), and renal (7%). The study was designed as a navigation trial, as the physician could use the CGP diagnostic to choose a therapy, such as a clinical trial within the phase I program. The analysis included CGP using NGS performed in a CLIA- certified laboratory (Foundation Medicine). A matching score was developed and calculated by dividing the number derived from the direct and indirect matches in each patient (numerator) by the number of aberrations (denominator).

This study found a median number of 5 molecular alterations per patient (range 1–14). Of the 339 patients with CGP, 317 (93.5%) had ≥ 1 potentially actionable alteration. Matched versus unmatched therapy was independently associated with longer TTF, but showed only a trend toward higher rates of SD and there was no association with OS. In contrast, a high matching score was independently associated with higher proportion of SD ≥ 6 months [22% (high scores) vs. 9% (low scores), p-value=0.024], longer TTF [HR=0.52; p-value=0.0003], and increased OS (HR=0.65; p-value=0.05). The authors concluded that this study offered a clinical proof of concept for using CGP to assign therapy to patients with refractory malignancies.

Other Study Designs

Rodriguez-Rodriguez. Use of comprehensive genomic profiling to direct point-of-care management of patients with gynecologic cancers. Gynecol Oncol., 2016.

The aim of this study was to determine the feasibility and clinical utility of CGP to identify clinically relevant GAs for patients with rare or refractory gynecologic cancers. This study used data from 100 participants and the results of the first 67 patients were included in the analysis. The study demographics included ovarian (n=41) or uterine (n=25) cancers that were rare or refractory to prior therapy, and advanced vaginal (n=2) or cervical cancers (n=1). CGP was performed in a CLIA-approved laboratory (Foundation Medicine). All classes of genomic alterations were assessed. The time from acquisition of the tumor specimen and date of consent for study enrollment was less than 90 days for approximately half of the overall study population and the average turnaround time from testing laboratory report to generation of formal recommendations was approximately three weeks. Clinical endpoints included PFS, and response rate using RECIST as CR, PR, SD, or PD.

This study identified outcomes available for 64 patients, all who were found to have at least one detectable GA (mean=4.97; median=4; range 1–26) and 81% of patients (n=52) had recurrent or progressive disease at the time of CGP. The study found that 39% of patients implemented one or more recommendations of targeted therapy by the treating physician, and 64% of patients receiving targeted therapy based on a CGP result experienced radiologic response or showed evidence of clinical benefit or stable disease. The authors concluded that CGP of gynecologic tumors can provide results that can be implemented at the point of care setting.

The aim of this study was to develop a model to predict response to therapy. The study used data from a cohort of 46 patients with advanced melanoma treated in a phase I clinical trial with pembrolizumab. The study demographics included 22 responders and 24 non-responders. Baseline biopsies from a comparison group of 15 additional patients with advanced melanoma were used as a validation cohort. The predictive model used qualitative and quantitative analysis, including NGS of T-cell receptors. A logistic regression model was constructed using pre-treatment CD8+ (cells/mm²) versus the outcome of clinical response (PR+SD vs PD) using the study cohort. This fixed effects model was then applied to the CD8+ density measurements in the validation cohort to compute predicted probabilities of response.

The study analysis found that responding patients with proliferation of intratumoral CD8+ T-cells directly correlated with radiographic reduction in tumor size. Pre-treatment samples obtained from responding patients showed a more clonal T-cell receptor population. In serially sampled tumors from responders, pSTAT1 expression was also found to be significantly higher during treatment when compared to baseline (p-value=0.007). The analysis failed to reveal a significant association between previous treatment with ipilimumab and expression levels of CD8, PD-1, PD-L1, CD4 expression, and clonality markers in terms of treatment outcome.

The investigators concluded that the predictive model was able to demonstrate and confirm that tumor regression following therapeutic PD-1 blockade requires pre-existing CD8+ T cells that are negatively regulated by PD-1/PD-L1 mediated adaptive immune resistance.

3. External Technology Assessments

- a. CMS did not request an external technology assessment (TA) on this issue.

- b. There was one AHRQ review assessed on a related topic.

Technology Assessment of Molecular Pathology Testing for the Estimation of Prognosis for Common Cancers.
Meleth S. et al., 2014.

Search strategy was similar to that of the Internal Technology Assessment, however sources were only searched through November 2013. Referenced methodology included dideoxy sequencing, pyrosequencing and next generation sequencing. The following two articles using next generation sequencing were excluded from assessment: Timmermann et al was excluded as a result of the intervention used and Tuononen, Maki-Nevala, Sarhadi, et al. was excluded as a result of the outcomes assessment.

c. Blue Cross/Blue Shield Health Technology Assessments

Blue Cross Blue Shield Association (BCBSA) currently uses a proprietary, subscription-based web platform, Evidence Street™, to collect and analyze available peer-reviewed evidence on devices, diagnostics and pharmaceuticals.

d. The COCHRANE database was last accessed on 15 October 2017, and in particular the Health Technology Assessment Database contained four assessments of next generation sequencing. Three assessments were eliminated for the original text was not in the English language.

Next generation DNA sequencing: a review of the cost effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 06 February 2014. Published by John Wiley & Sons, Ltd.

Authors concluded that limited evidence was found to establish the cost-effectiveness of these approaches. In the scope of this investigation no established standardized guidelines were identified. The guidelines described are the results of evidence based review and expert opinion, and provide recommendations on implementation of next generation sequencing programs. No recommendations regarding specific clinical applications of the technology were identified.

e. National Institute for Health and Care Excellence (NICE).

King's Technology Evaluation Centre. Medtech innovation briefing [MIB120]: Caris Molecular Intelligence for guiding cancer treatment. Published date: September 2017. ISBN: 978-1-4731-2632-9

The main points from the evidence summarized in this briefing are from five observational studies including a total of 1,572 adults in secondary and tertiary care centers. Most evidence shows that test guiding treatment is associated with better progression-free survival than clinician decisions alone. There is also some evidence that this test may lead to improved overall survival. Key uncertainties around the evidence are that there are currently no randomized controlled studies comparing this test-guided treatment with treatment unguided by this specific test, either for site-specific cancers or for metastatic cancer of unknown primary origin. The authors note the intended place for this test in therapy would be as a tool to help guide treatment decisions for locally advanced or metastatic cancer in people who are fit for further treatment but have exhausted standard evidence-based treatment options and for whom no further guidance on therapy exists.

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

A MEDCAC meeting was not convened on this issue.

5. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

The National Comprehensive Cancer Network® (NCCN®) is "a not-for-profit alliance of 27 leading cancer centers devoted to patient care, research, and education" and "is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives." The NCCN Clinical Practice Guidelines in Oncology "document evidence-based, consensus-driven management to ensure that all patients receive preventive, diagnostic, treatment, and supportive services that are most likely to lead to optimal outcomes."

NCCN guidelines uses the following grading system: "NCCN Categories of Evidence and Consensus

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted."

Clinical Trials: "NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged."

Breast Cancer

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer NCCN Evidence Blocks™. Version 2.2017. April 26, 2017. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others): "Along with ER and PR, the determination of HER2 tumor status is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible. The NCCN Breast Cancer Panel endorses the College of American Pathologists (CAP) accreditation for anatomic pathology laboratories performing HER2 testing.

HER2 status can be assessed by measuring the number of HER2 gene copies using in situ hybridization (ISH) techniques, or by a complementary method in which the quantity of HER2 cell surface receptors is assessed by IHC. Assignment of HER2 status based on mRNA assays or multigene arrays is not recommended. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive as well as false-negative HER2 test results are common." (Discussion Update in Progress)

BRCA is discussed in familial risk assessment (Daly et al. 2017) which is outside the scope of this decision.

Colon Cancer

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer NCCN EvidenceBlocks™. Version 2.2017. March 13, 2017. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among other recommendations):

1. "Routine EGFR testing is not recommended, and no patient should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results."
2. The panel "strongly recommends KRAS/NRAS genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer.
3. The panel "strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer for RAS (KRAS exon 2 and non-exon 2; NRAS) and BRAF at diagnosis of stage IV disease. The recommendation for KRAS/NRAS testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of KRAS/NRAS status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner and the patient and provider can discuss the implications of a KRAS/NRAS mutation, if present, while other treatment options still exist."
4. "Fresh biopsies should not be obtained solely for the purpose of KRAS/NRAS genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that KRAS, NRAS, and BRAF gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing. No specific testing methodology is recommended."
5. "Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing. Universal MMR or MSI testing is recommended in all patients with a personal history of colon or rectal cancer."

Melanoma

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Melanoma NCCN Evidence Blocks™. Version 1.2017. November 16, 2016. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others): "For stage IV patients, the clinician is responsible for reporting the number and sites of metastatic disease. In addition to histologic confirmation of metastatic disease whenever possible, pathologists are now strongly encouraged to test for and report the presence or absence of gene mutations (BRAF, KIT) that may impact treatment options in patients with metastatic melanoma. Because these inhibitors of BRAF or KIT are recommended only for patients with advanced disease, BRAF and c-KIT mutational analyses are clinically useful only for patients with advanced disease considering these molecular targeted therapies. In the absence of metastatic disease, testing of the primary cutaneous melanoma for BRAF mutation is not recommended." (Discussion Update in Progress)

Non-Small Cell Lung Cancer (NSCLC)

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer NCCN Evidence Blocks™. Version 6.2017. June 7, 2017. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others):

1. "Testing for ALK gene rearrangements and EGFR mutations is recommended (category 1 for both) in the NSCLC algorithm for patients with non-squamous NSCLC or NSCLC not otherwise specified (NOS) so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as erlotinib, gefitinib, afatinib, and crizotinib."
2. "Testing for ROS1 rearrangements is also recommended in the NCCN Guidelines."
3. "Broad molecular profiling systems, such as next-generation sequencing (NGS) (also known as massively parallel sequencing), can detect panels of mutations and gene rearrangements if the NGS platforms have been designed and validated to detect these genetic alterations. It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is primer dependent, the panel of genes and abnormalities detected with NGS will vary depending on the design of the NGS platform."
4. The NCCN Panel "strongly advises broader molecular profiling (also known as precision medicine) to identify rare driver mutations to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents."

Occult Primary - Cancer of Unknown Primary (CUP)

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Occult Primary (Cancer of Unknown Primary [CUP]). Version 2.2017. October 17, 2016. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others): "More recently, another active area of investigation has been next generation sequencing (NGS) to characterize the genome of occult primary tumors. NGS has the potential to identify actionable biomarkers outside of tissue-specific markers, but this approach remains experimental. Data from ongoing studies evaluating effectiveness of novel targets against specific mutations will help define the role of this approach."

Ovarian Cancer

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer NCCN Evidence Blocks™. Version 1.2017. May 16, 2017. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others): "A recent trial assessed olaparib in women with recurrent advanced ovarian cancer; the overall response rate was 34% (complete response, 2%; and partial response, 32%). The NCCN Panel recommends single-agent olaparib as recurrence therapy for patients with advanced ovarian cancer who have received 3 or more lines of chemotherapy and who have a germline BRCA mutation (detected using an FDA-approved test or other validated test performed in a CLIA-approved facility) based on this trial and the FDA approval." (Discussion Update in Progress)

Prostate Cancer

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer NCCN Evidence Blocks™. Version 1.2017. May 16, 2017. At: https://www.nccn.org/professionals/physician_gls/default.aspx#occult

The NCCN reported (among others):

1. "Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or radiotherapy, and likelihood of developing metastasis after operation or salvage radiotherapy. No randomized controlled trials have studied the utility of these tests."
2. "Table 1[see guideline, page MS-46] lists these tests in alphabetical order and provides an overview of each test, populations where each test independently predicts outcome, and supporting references. These molecular biomarker tests listed have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time. Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer."

a. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. March 2017.

Additional considerations should include specimen processing (including microdissection or macrodissection, histologic processing, and fixation times) and reagent stability and storage. Proper controls should be introduced and used to assess as many of the potential mutations detected by the assay and to verify the limit of detection identified in the validation. With high-throughput (NGS) sequencing, assessing all possible mutations through control material and specimens is impossible, and continuing validation may need to occur. If NGS is used, bioinformatics pipelines should be properly validated using multiple types of mutations (single- nucleotide variants and insertions/deletions). Finally, reporting should be carefully considered during the validation process.

Resources to assist laboratories with solid tumor molecular testing have also been made available through the Clinical and Laboratory Standards Institute.

b. Guidelines for Validation of Next-Generation Sequencing Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists. May 2017.

These recommendations are limited to analytical validation and emphasize using an error-based approach that allows the laboratory director to identify potential sources of errors that may occur throughout the analytical process and addressing these potential errors through test design, method validation, or quality controls so that no harm comes to the patient. The recommendations on sample preparation, library preparation, sequencing, and data analysis intend to assist clinical laboratories with the validation and ongoing monitoring of NGS testing for detection of somatic variants and to ensure high quality of sequencing results.

c. The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer: A Report of the Association for Molecular Pathology. September 2016.

The Association for Molecular Pathology recommends a definition of clinical utility for molecular diagnostic procedures on the basis of a modified analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications (ACCE) framework (see Appendix B) as follows: clinical utility for molecular diagnostics is the ability of a test result to provide information to the patient, physician, and payer related to the care of the patient and his/her family members to diagnose, monitor, prognosticate, or predict disease progression, and to inform treatment and reproductive decisions. Additional recommendations include alternatives to Randomized Controlled Trials to promote patient-centered definitions of clinical utility, utilizing a modified ACCE model, recognize the critical role of the molecular professional in disease management, increase engagement between professional associations and other stakeholders, and encourage incorporation of comparative effectiveness research and health economics consideration into professional practice guidelines.

d. Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine Committee Opinion. December 2016.

While not explicit on applications in advanced cancers, this committee opinion recognized a few limitations of current applications of next generation sequencing, including the long turnaround time associated with more comprehensive sequencing. The second major limitation noted was the high number of variants of uncertain significance that may create anxiety and be challenging for patients and obstetrician-gynecologists and other health care providers. Finally, the current cost and limited insurance coverage were cited as areas of review needed before ordering the procedure.

e. The evaluation of clinical validity and clinical utility of genetic tests. PHG Foundation. National Genetics Reference Laboratory, Manchester UK. September 2007.

The summary acknowledged various national approaches to genetic test evaluation and noted that each had strengths and weaknesses, which were country and health system specific. They also noted how the different approaches included health technology assessment, government advisory groups, collaborative laboratory networks, public/government agencies and academic and government partnerships and that the outputs of the evaluations could include reports, guidelines, healthcare policy and direct provision of tests following approval.

"It was agreed that one of the main barriers to performing genetic test evaluations was the lack of evidence and data for clinical validity and clinical utility. In particular, there was limited information on clinical outcomes of testing. One approach to improve this would be to establish robust systems for the collection of post-implementation data. It was agreed that infrastructure development and the creation of national and international networks to share data that could be used in genetic test evaluation are of high priority."

f. Consultation with Outside Experts

Consistent with our authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of diagnostic laboratory tests using NGS for Medicare beneficiaries with advanced cancer.

6. Other Reviews

a. Institute of Medicine (IOM)

IOM (Institute of Medicine). 2012. Evolution of Translational Omics: Lessons Learned and the Path Forward. Washington, DC: The National Academies Press.

Patients who look to the scientific and clinical communities to innovative omics-based tests expect that such tests will detect disease or predict response to specific drugs with academic rigor. However, transforming these new technologies into clinical laboratory tests that can help patients directly has happened more slowly than anticipated. Challenges to transformation converged during a recent case involving premature use of omics-based tests in clinical trials. Flawed gene-expression tests developed by cancer researchers were used in three lung and breast clinical trials aimed at determining which chemotherapy treatment patients would receive. The IOM committee report identifies best practices to enhance development, evaluation, and translation of omics-based tests and specific steps to be taken to ensure that these tests are appropriately assessed for scientific validity before they are used to guide patient treatment in clinical trials. If decisions about patient care will be guided by omics-based test findings in a clinical trial, the committee affirms that consultation with FDA is a legal requirement. A clinical test should be fully defined, validated, and locked down before crossing the bright line to enter the stage in which the test undergoes evaluation for its intended clinical use. These guidelines, if adopted, can ensure that progress in omics-based test development is grounded in sound scientific practice, which the committee believes will result in improved health care.

b. National Institutes of Health (NIH)

McShane et al. Criteria for the use of omics-based predictors in clinical trials: explanation and elaboration. *BMC Medicine* 2013, 11:220.

Following the IOM report, the authors of the National Cancer Institute (NCI) present a checklist of criteria to consider when evaluating the body of evidence supporting the clinical use of a predictor to guide patient therapy. Included are issues pertaining to specimen and assay requirements, the soundness of the process for developing predictor models, expectations regarding clinical study design and conduct, and attention to regulatory, ethical, and legal issues. The authors believe that the proposed checklist should serve as a useful guide to investigators preparing proposals for studies involving the use of omics-based tests. The NCI refers to these guidelines for review of proposals for studies involving omics tests, and it was hoped at the time of publication that other sponsors will adopt the checklist as well.

c. The New York State Department of Health (NYSDOH), Wadsworth Center

The Clinical Laboratory Evaluation Program (CLEP) adopted Clinical Laboratory Standards of Practice, which includes standards for reports of Molecular and Cellular Tumor Markers, which shall: i. indicate the testing methodology used; ii. indicate the limits of sensitivity (both analytic and diagnostic) of the method used; iii. include an interpretation of findings; and iv. contain the signature of the qualified person who reviewed, approved, and interpreted the test results. A qualified person is an individual holding a valid New York State certificate of qualification in the Oncology – Cellular Tumor Markers subcategory.

7. Pending Clinical Trials

ClinicalTrials.gov

Using the terms and synonyms searched in our internal technology assessment identified the following Interventional studies currently recruiting patients aged 65 years or older in the United States:

NCT Number	Study Title	Sponsor/Collaborators	Outcome Measures
03178552	A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)	Hoffmann-La Roche	Objective Response, based on RECIST v1.1
02795156	Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations	SCRI Development Innovations, LLC Foundation Medicine Boehringer Ingelheim Bayer	Overall response rate

NCT Number	Study Title	Sponsor/Collaborators	Outcome Measures
01946100	Treatment of Multifocal Lung Adenocarcinoma	Mayo Clinic	Overall survival, progression free survival

In addition, a search for Interventional studies using NGS currently recruiting patients aged 65 years or older in the United States identified the following additional studies relevant to patients with any cancer:

NCT Number	Study Title	Sponsor/Collaborators	Outcome Measures
02899793	Pembrolizumab in Ultramutated and Hypermutated Endometrial Cancer	Yale University Merck Sharp & Dohme Corp	Objective Response, based on RECIST v1.1, adverse events as assessed by CTCAE v4, progression free survival, overall survival
02132845	Next Generation Sequence Target-Directed Therapy in Treating Patients With Cancer	Fox Chase Cancer Center, National Cancer Institute (NCI)	Overall response rate, progression free survival, mutation rate
01506973	A Phase I/II/Pharmacodynamic Study of Hydroxychloroquine in Combination With Gemcitabine/Abraxane to Inhibit Autophagy in Pancreatic Cancer	Abramson Cancer Center of the University of Pennsylvania	Overall survival
02551718	High Throughput Drug Sensitivity Assay and Genomics-Guided Treatment of Patients With Relapsed or Refractory Acute Leukemia	University of Washington, National Cancer Institute	Percentage of patients who test and initiate treatment in 21 days, rate of complete remission, survival
02580981	Acute Lymphoblastic Leukemia Therapies Informed by Genomic Analyses	New Mexico Cancer Care Alliance	ALL characterization
02927106	Beat AML Core Study	University of Florida, Oregon Health and Science University, Cellworks Group Inc., The Leukemia and Lymphoma Society	the genomic abnormality spectrum, rug sensitivity
02688517	Targeted Genomic Analysis of Blood and Tissue Samples From Patients With Cancer	Rutgers, The State University of New Jersey, National Cancer Institute, Rutgers Cancer Institute of New Jersey	Frequencies of individual specific mutations and combinations of mutations of related pathway genes, Rate of actionable mutations in rare and/or poor prognosis cancers

NCT Number	Study Title	Sponsor/Collaborators	Outcome Measures
03072238	Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients With Metastatic Castrate-Resistant Prostate Cancer	Hoffmann-La Roche	Radiographic Progression-Free Survival (rPFS), Time to Pain Progression, Time to Initiation of Cytotoxic Chemotherapy
02969837	Study of Initial Treatment With Elotuzumab, Carfilzomib, Lenalidomide and Dexamethasone in Multiple Myeloma	University of Chicago, Bristol-Myers Squibb, Amgen, Multiple Myeloma Research Foundation	Rate of Complete Response, rate of negative minimal residual disease, adverse events

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS' experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS responds in detail to the public comments on a proposed decision and uses the public comments to inform the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: <https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=290>.

CMS received 315 public comments on this proposed decision. Twelve comments are not publicly posted because they contain excessive personal health information (PHI) that could not be appropriately redacted. Of the 315 public comments, 97 comments were from academic medical centers, 40 comments were from patients and patient-advocates, 39 comments were from hospitals, 36 comments were from laboratories, 27 comments were from professional organizations, and 76 did not self-identify. Ninety-three support this proposed decision but requested some modifications as described below. One hundred twenty-nine commenters did not support this proposed decision. An additional 93 comments requested modifications to this proposed decision. Below is a summary of the comments CMS received.

Proposed NCD non-coverage of diagnostic laboratory tests using NGS

Comment: Commenters stated that the proposed coverage criteria in section (C) of the proposed NCD that non-covered certain diagnostic lab tests using NGS is too broad and may be construed to include diagnostic laboratory test using NGS for conditions other than oncology. Commenters recommended clarifying the proposed non-

coverage of NGS as a diagnostic laboratory test for patients with advanced cancers or when the test does not meet the above-noted criteria.

Response: After reviewing the public comments, the final NCD nationally covers any FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS only for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). All other diagnostic lab tests are at contractor discretion only if the patient criteria are met. Contractor discretion means that Medicare Administrative Contractors will act on behalf of CMS to make reasonable and necessary determinations under section 1862(a)(1)(A) of the Act, so long as specific limitations are satisfied. The patient criteria specific to this NCD are explained further in comment and response.

National Coverage under Section 1862(a)(1)(A) of the Social Security Act

Comment: Many commenters commend CMS on the proposed expansion of coverage, noting that coverage for these items and services is uncertain or gapped because of different local coverage policies. Some commenters were uncertain which specific lab diagnostic tests using NGS would be considered covered and would not require coverage with evidence development.

Response: The final NCD will nationally cover FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) will be made by Medicare Administrative Contractors.

Comment: Some commenters stated the proposed coverage for diagnostic tests would be provided only for a limited number of cancers, while others believe that the proposed coverage is provided to a limited number of laboratories rather than specific lab tests.

Response: The final NCD does not limit the number or specific type of cancers eligible for coverage or laboratories including academic medical centers and community hospitals that are able to meet the coverage criteria in section A of the final coverage decision. The final NCD will nationally cover FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) will be made by Medicare Administrative Contractors.

Comment: A few commenters requested that the proposed national decision be revised to expand coverage of a diagnostic laboratory test using NGS beyond the proposal of coverage of diagnostic laboratory test using NGS
Printed on 5/2/2018. Page 69 of 151

that is FDA approved as a companion diagnostic.

Response: In the final coverage decision, we expanded full coverage to both FDA-approved and FDA-cleared diagnostic laboratory tests using NGS as a companion diagnostic. In the proposed decision, we only covered FDA-approved tests as reasonable and necessary under 1862(a)(1)(A) of the Social Security Act. With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) will be made by the Medicare Administrative Contractors.

Comment: Some commenters requested that new tumor types without a companion diagnostic available also should be nationally covered when medical evidence or oncology guidelines indicate sequencing greater than five genes in such tumor types provides clinical benefit in guiding therapeutic decision making.

Response: Under this final NCD, we considered medical evidence and oncology guidelines on tumor types without a companion diagnostic. We disagree that coverage should be limited to tumor types indicated by oncology guidelines to sequence five or more genes in that tumor type. Our final decision will cover any tumor type indicated by an FDA-approved or -cleared companion in vitro diagnostic. Other diagnostic laboratory tests using NGS for cancer patients meeting these coverage criteria are at the discretion of Medicare Administrative Contractors.

Scope of NCD

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address the scope of the NCD. Commenters provided professional experience in molecular testing to support reasons for expanding or narrowing the proposed NCD by clinical conditions, clinical scenarios, and test methodologies in support of their views.

Response: We appreciate all of the comments regarding the scope of the NCD. The final NCD scope provides national coverage for any diagnostic laboratory test using NGS when all other criteria are also met.

Comment: Many commenters stated the NCD should really address a single test (e.g. F1CDx™) and nothing else. A few commenters disagreed with the single test recommendation, and admired the aspiration to issue a broad coverage determination that provides similar coverage for similar tests nationwide rather than a narrower decision limited to coverage of a single test. One commenter responded that the reason to disagree with a narrower decision was that there are several competitor assays that will be able to meet coverage criteria set forth in the proposed NCD, and both clinicians and Medicare beneficiaries deserve to choose from a variety of NGS assays that meet these high standards. The commenter suggested that limiting the NCD to a single test

would effectually eliminate all existing NGS competitive assays from the marketplace and halt the innovation and growth of smaller laboratories working to improve cancer care through NGS assay development, noting that even the CED criteria are an important part of the NCD.

Response: We understand and appreciate the comments. As noted in the decision memo, CMS initiated this national coverage determination to consider coverage under the Medicare Program for a diagnostic laboratory test using NGS. This is to ensure that similar claims for these tests will be covered in the same manner under Medicare. This decision is in line with the vast majority of NCDs (see <https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>). Most NCDs are decisions about a type of device and not a specific manufacturers' technology. We believe this will create equitable national coverage for diagnostic laboratory tests using NGS regardless of manufacturer and create predictable coverage for NGS testing. Our research identified a number of other diagnostic laboratory tests using NGS for comparable clinical purpose (i.e., diagnosing BRAF V600E mutation in cancer). We reviewed all of the evidence in this technology space and are making a favorable NCD that expands coverage for those tests that meet the necessary requirements that we have identified based on this evidence. After reviewing all the public comments, we are revising the final decision on NGS as a class of services rather than a single manufacturers' NGS diagnostic test. We believe this will create equitable national coverage for all NGS testing regardless of manufacturer and create predictable coverage for a diagnostic laboratory test using NGS. We also want to be responsive to commenters stating that limiting coverage to a single manufacturer's test could result in a lack of national access and predictable coverage to other diagnostic laboratory tests using NGS. We believe there is more than one test that will meet these coverage criteria in this final decision and would not want to limit access to additional diagnostic laboratory tests using NGS as they become FDA-approved or -cleared companion diagnostics. Based on the comments and the evidence reviewed we finalized an NCD on diagnostic laboratory tests using NGS rather than a single test. With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) may be made by Medicare Administrative Contractors.

Comment: CMS had several comments that requested we include liquid biopsies under the NCD. One commenter observed that at present there are no FDA-cleared or approved liquid-based multi-gene sequencing panel tests for oncology that use an NGS platform.

Response: The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis four studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met.

Comment: A few commenters highlighted inconsistencies between proposed coverage and current coding structures. One commenter observed that two laboratories may bill under the same genomic sequencing CPT code to measure the same 12 genetic loci, with one laboratory assessing the genetic loci using NGS-based methodology and one laboratory using another technology. Although one commenter noted that coding and payment are not germane to this coverage policy the issues logically follow after coverage. Another commenter noted that the Protecting Access to Medicare Act of 2014 (PAMA) took effect January 1, 2018 and provides for the assignment of a unique HCPCS code for an advanced diagnostic laboratory test (ADLT). To this end, a few commenters urged CMS to take steps to clarify how it will operationalize coverage for these tests through coding and payment.

Response: We appreciate these comments about how we will operationalize coverage for these tests through coding and payment. We expect to provide operating instructions to contractors to use HCPCS codes only when CPT codes are unavailable or do not meet our coding needs. In the event that we will need to assign a new HCPCS code to test, we will make such assignments on a quarterly basis, consistent with our current process for updating HCPCS codes. Any temporary HCPCS code will be considered for replacement by a permanent CPT code when it is made available by the AMA, and if it satisfies our coding and payment needs, as part as the annual laboratory public meeting process. We will keep these comments in mind as we implement this NCD.

Comment: Several commenters stated that coverage must be aligned with evidence-based best clinical practices and cost-efficient patient care. To achieve this alignment, a few commenters recommended differential reimbursement based on the evidence available for the diagnostic laboratory test using NGS.

Response: The process of establishing payment rates for diagnostic laboratory tests are described in the Code of Federal Regulations, Title 42, Part 414, Subpart G: Payment for Clinical Diagnostic Laboratory Tests. An NCD does not include a determination of what code, if any, is assigned to a service or a determination with respect to the amount of payment to be made for the service.

Patient Criteria

Comment: Many commenters support the proposed changes in Medicare coverage specifically to provide coverage for diagnostic laboratory testing using NGS for beneficiaries with advanced cancer. These commenters stated this proposed decision puts patients first by recognizing the power of precision medicine for cancer patients.

Response: Thank you for the comment. We note that the final NCD is narrower in scope. The final NCD outlines coverage criteria for diagnostic lab tests using NGS that will be nationally covered for patients with recurrent, relapsed, refractory, metastatic, and advanced stages III or IV cancer. Coverage determinations for any other diagnostic lab test using NGS for these same patients would be made by Medicare contractors. Therefore, all NGS tests for the patients that meet the patient criteria are left to contractor discretion. Any diagnostic lab test using NGS that is FDA approved or cleared as a companion diagnostic for any patient that meet the patient criteria recurrent, relapsed, refractory, metastatic, and advanced stages III or IV cancer will be covered nationally under this NCD.

Comment: Many commenters requested that CMS reconsider and expand the patient indication aspect of coverage criteria. Some commenters requested that we note whether a patient must have all or any of the listed disease states of recurrent, metastatic, or advanced stage IV cancer. A few commenters reminded CMS that the proposed coverage decision evidence of patients with stage III cancer (Plimack et.al., and analysis by Schrock et. al.) while other commenters believed that the proposed NCD overlooked stage III cancers and non-resectable cancers. As a result, a few of these commenters requesting additional coverage provided additional publications (Long et al., 2017, Gormally et al., 2006, and Verri et al., 2017) to support the recommendation that

coverage should be available for a Medicare beneficiary with advanced stage III cancer, when consistent with the FDA approved or cleared test. One commenter recommended that we delete the word "advanced" and add the words "relapsed" and "refractory," suggesting these changes would be more consistent with the interpretation that CMS intended to include hematological malignancies.

Response: We appreciate the comments. Therefore, this final decision has been expanded to include recurrent, relapsed, refractory, metastatic, and advanced stages III or IV cancer as part of the patient eligibility for any diagnostic laboratory test using NGS, including those at the discretion of Medicare Administrative Contractors.

Comment: Many commenters noted that the patient coverage criteria of the proposed NCD were not specific enough and requested that CMS address each covered malignancy as opposed to the proposed patient characteristics of recurrent, metastatic, and stage IV cancer. Commenters recommended that CMS issue NCDs on each cancer type. To support the concept of doing specific NCDs for each cancer, a few commenters cited evidence related to the clinical management of cancers or, provided their experience such as the diagnosis and management of breast cancer.

Response: By not limiting to a specific cancer, we believe this decision is patient-centered. This will allow the patient and his/her oncologist to have an informed discussion of whether a lab diagnostic test using NGS is appropriate. Further, based on the totality of the evidence, we believe we should not limit national coverage to only a few cancers, but that patients with any advanced cancer diagnosis should have access to evidence-based diagnostic laboratory tests using NGS if reasonable and necessary. We also believe that specifying coverage criteria for each cancer diagnosis will not provide the flexibility for innovative approaches to diagnostic laboratory tests using NGS.

Comment: We received public comments expressing a variety of opinions on which patient populations should be eligible for diagnostic laboratory tests using NGS, including screening and diagnosing earlier stages of cancer (e.g., Stage I or II cancers). Many of these same commenters asked that the earlier stages of cancer be left to contractor discretion.

Response: We appreciate the requests and supporting evidence to expand the patient criteria to earlier cancers or screening. After reviewing the evidence, including evidence submitted by public commenters, the evidence does not support national coverage under 1862(a)(1)(A) for earlier stages of cancers. However, based on the evidence submitted we did expand the patient criteria to include stage III cancers. The patient coverage characteristics now include patients with either recurrent, metastatic, relapsed, refractory or stages III or IV advanced cancer. CMS will watch the evidence base on earlier stages of cancers closely and when additional evidence is published, a reconsideration may be requested as described on our website (please see: <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/howtorequestanNCD.html>).

With regard to screening, a Medicare beneficiary who has no signs or symptoms of illness or disease and has not been diagnosed with cancer, but has a family history of cancer, is outside the scope of this policy because such

testing would be considered screening rather than a diagnostic test. For "additional preventive services" to be covered, the statute requires that the service identify medical conditions or risk factors that the Secretary determines are reasonable and necessary for the prevention or early detection of an illness or disability, recommended with a grade of A or B by the United States Preventive Services Task Force, and appropriate for individuals entitled to benefits under part A or enrolled under part B. See 1861(ddd)(1) of the Social Security Act.

Comment: A few commenters stated that less advanced cancer is easier to treat and therefore earlier stages of cancer should not be included in this policy.

Response: We agree. Based on the evidence earlier stage cancers should not be covered at this time.

Comment: A few commenters asked for clarification on whether specific clinical scenarios are nationally covered including advanced pediatric and adult solid tumors that are unresectable or metastatic where measurement of the microsatellite instability (MSI) and utilization of checkpoint inhibitors, such as Keytruda® (pembrolizumab), are being considered.

Response: We appreciate the comment. We have revised the final NCD language. All coverage criteria in the final NCD must be met. The NCD has been significantly modified but, without more detail, it is not possible to specifically answer the clinical scenarios described in the comment. However, in general if a patient is diagnosed with metastatic or unresectable stage III or IV cancer, then the diagnostic laboratory test using NGS for that patient is coverable under this coverage policy. Depending on the diagnostic test using NGS is ordered, it is either covered nationally because the diagnostic laboratory test using NGS is FDA approved or cleared as a companion diagnostic for the patient's specific cancer or the coverage determination will be made by Medicare Administrative Contractors.

Comment: Some commenters noted that a diagnostic laboratory test for MSI does not require using NGS and identified multiple other technologies being used today (e.g., Sanger sequencing, ddPCR, MLPA, IHC, FISH, CISH, etc.). These commenters also provided evidence supporting their comments that compared the benefits and challenges of these different technology platforms (Möhrmann et al., 2018).

Response: We appreciate the comment but any diagnostic lab test not using NGS is outside the scope of this NCD. Coverage decisions for all of the tests mentioned by the commenter continue to be made by Medicare Administrative Contractors.

Comment: Some commenters questioned if other unspecified coverage criteria, such as an age requirement, were indirectly included as part of the patient criteria in the proposed coverage determination. A few commenters
Printed on 5/2/2018. Page 74 of 151

asked that CMS provide coverage when the Medicare beneficiary is younger than 65 years old. Some commenters stated that current cancer panels are built for adult tumors and are not intended nor appropriate for pediatric tumors.

Response: We appreciate these comments acknowledging that the Medicare population has a diverse composition, including beneficiaries under age 65 years. This decision applies to all eligible Medicare beneficiaries, and some of those beneficiaries are younger than 65 years old. There were no unspecified coverage criteria in our proposed decision, and no unspecified coverage criteria in this final decision.

Comment: A few commenters disagreed with the patient coverage criteria, stating this proposed decision would not allow coverage for NGS-based tests with indications unrelated to cancer.

Response: This decision is only about diagnostic lab tests using NGS for Medicare patients with advanced cancer as described in this final decision. Coverage of NGS testing for other conditions or indications that are not cancer are outside the scope of this NCD. In the absence of an NCD, it is left to the Medicare Administrative Contractors to make a coverage decision of these tests.

Comment: Commenters requested that CMS provide coverage in cases when a test is used off-label. One commenter asked CMS to provide coverage of a laboratory developed test when the laboratory cannot provide an FDA-approved or cleared test because the FDA-approved or cleared test has specific indications for use that cannot be met by the laboratory.

Response: Under this NCD, the uses mentioned by the commenter are outside the scope of this NCD. Medicare Administrative Contractors would make the 1862(a)(1)(A) determination if a claim was submitted under such circumstances described by the commenter.

Frequency of Testing

Comment: Commenters requested that the final NCD not limit coverage to a single diagnostic laboratory test using NGS in a patient's lifetime. One commenter noted that some clinical trials now require sequencing of a tumor at many different points in time.

Response: We have revised our final decision to clarify that beneficiaries are not limited to a single NGS diagnostic test in a patient's lifetime. We agree that a diagnostic laboratory test using NGS should be available for any new cancer. The final NCD has been revised to include that repeat testing using the same diagnostic laboratory test using NGS in the same patient is covered only when a new primary diagnosis of cancer is made by the treating physician.

Comment: Many commenters recommended that the test should be covered for each cancer recurrence (comes back) where evidence shows that the genetic make-up of the type of cancer changes over time (Puig et al., 2016, Wang et al., 2016, Mok et al., 2017), with one commenter stating that some patients may have three to four tests during the course of treatment.

Response: Based on our review and analysis of all the evidence reviewed for the proposed coverage decision as well as the evidence submitted during the public comment period, we do not believe there is evidence to support coverage of the same diagnostic lab test using NGS should be performed on the same patient for the same diagnosis of cancer. The patient has already had the same test for the same cancer. However, based on comments, the final decision allows for the same or a different lab diagnostic test using NGS (i.e., repeat testing) for the same patient when the patient has a new cancer diagnosis. Additionally, the final decision does not limit additional test methodologies, such as immunohistochemistry, *in situ* hybridization, and polymerase chain reaction, to generate a complete genetic profile of the patient's cancer.

Comment: A few commenters provided evidence in the form of personal or professional experience that in general tumor cells continue to change and evolve in order to survive, grow, and metastasize. Other commenters noted that intra-tumoral diversity and clonal evolution in cancer is accompanied by change (acquisition and loss) in genetic alterations over the course of disease (Dagogo-Jack et al., 2017; Yates et al., 2017). These commenters suggested that an NGS panel at the time of progression helps identify mechanisms of resistance or tumor heterogeneity after treatment with a targeted agent, often independent of the original driver mutation detected at the time of diagnosis.

Response: While we appreciate the comments, we acknowledge that currently only companion *in vitro* diagnostic laboratory tests using NGS have clinical utility for national coverage under this NCD, and we did not identify evidence supporting repeating the same diagnostic laboratory test using NGS in the same patient for the same cancer. Therefore, repeat testing using the same NGS test in the same patient is covered only when a new cancer diagnosis is made by the treating physician.

Comment: Commenters recognized specific clinical scenarios they believe necessitate repeat testing, including individuals who develop more than one type of cancer in their lifetime and those who present with two or more tumors. These commenters believe that including more flexibility regarding test frequency for individual considerations would help to prevent the NCD from becoming an obstacle to rapid advancement in the fight against cancer.

Response: Repeat testing is allowed under certain circumstances. If a patient has been diagnosed with a cancer diagnosis, any lab diagnostic test using NGS is coverable. Any lab diagnostic tests using NGS that are FDA approved/cleared as a companion diagnostic are nationally covered (i.e., no contractor discretion) under this NCD, and coverage determinations for the rest of the diagnostic lab tests using NGS will be made by Medicare Administrative Contractors. If the patient has not been diagnosed with a new cancer, diagnostic lab testing using NGS is coverable but only if when a different diagnostic lab test is furnished from what was furnished previously.

Comment: A few commenters requesting coverage for each recurrence recommended that a repeat test should only be performed on a second distinct sample to inform targeted therapy selection or discontinuation. A few commenters stated that those who have multiple simultaneous tumors might need more than one tissue sample tested with the same diagnostic laboratory test using NGS.

Response: We agree with the commenters' suggestion to obtain a sample of the patient's cancer to perform the diagnostic laboratory test. This final decision does not require a specific method of sampling. This decision is only about the diagnostic test using NGS. The decision would cover repeat testing that meets the specified criteria in this coverage decision.

Comment: A few commenters with an opposing opinion cited ASCO clinical practice guidelines that stated repeat testing is not required for most patients.

Response: We thank the commenters for the additional evidence submitted. The proposed decision did limit the same diagnostic laboratory test using NGS to once in a lifetime. However, we agree that more frequent testing should be available for any new cancer. Therefore, the final NCD has been revised to include that repeat testing using the same diagnostic laboratory test using NGS in the same patient is covered only when a new cancer diagnosis is made by the treating physician.

Treating Physician

Comment: We received comment on the proposed decision to cover a diagnostic laboratory test using NGS when ordered by a treating physician. Some commenters supported this proposal, noting that the treating oncologist, not the laboratory professional, engages with the patient over the full course of their disease and recovery. A few commenters suggested a greater role for a treating physician, suggesting that a treating physician would know the stage, type of cancer, and appropriate treatment based on the test results and therefore, clinical decision making including ordering diagnostic tests should be left to the treating physician.

Response: We appreciate the support of these commenters and recognize the important role of the treating physician. The national coverage determination is based on published evidence to assess whether an item or service is reasonable and necessary and has set certain patient and disease characteristics. Within these parameters, physician and patient decision making remains important in determining when to order the test in a patient's course, the choice of covered tests, and subsequent treatment selection.

Comment: Other commenters disagreed with the role of the treating physician as proposed in the NCD. These commenters wanted the definition of treating physician to include other practitioners, such as a pathologist. The commenters provided several examples to support the statement. For example, a commenter noted exceptions in CMS publication 100-02, Chapter 15, Section 80.6.5 for surgical and cytopathology when pathologists order additional testing to provide a complete and accurate diagnosis to the treating provider to utilize such results in the treatment decisions. Another commenter noted that analysis of NGS data require a significant level of expertise to properly integrate into a series of previous test results obtained for the patient's cancer.

Response: This exception cited by the commenter applies to an independent laboratory's pathologist or a hospital pathologist who furnishes a pathology service to a beneficiary who is not a hospital inpatient or outpatient, and where the treating physician does not specifically request additional tests the pathologist may need to perform. This exception is not applicable to this coverage determination because the treating physician is engaged in decision making with the patient as to whether to order a diagnostic laboratory test using NGS to identify targeted treatment options or enroll in a cancer clinical trial. We believe that results from this test must be used by the treating physician in the management of the patient. Therefore, we have clarified language in our final decision to reiterate that a diagnostic laboratory test using NGS must be ordered by the treating physician.

Comment: One commenter cited guidance for laboratories performing molecular pathology (Cree et al., 2014) to support the role of the pathologist and medical multidisciplinary team in ordering diagnostic tests. A few commenters recommended the proposed decision be revised to replace the term "treating physician" with "treatment team" or "physicians on the treatment team."

Response: We appreciate the additional evidence submitted by the commenters. We agree that, consistent with Cree et al., 2014 good communication is required between the laboratory, the oncologists, surgeons, and the treating physician to ensure that appropriate tests are requested at the appropriate time. The treating physician can therefore best coordinate a treatment team of physicians to integrate results from different diagnostic laboratory tests for their patient's cancer. We believe that because results from this test must be used by the treating physician in the management of the patient, then this diagnostic laboratory test must be ordered by the treating physician. Therefore, we have clarified language in our final decision to reiterate that any NGS diagnostic lab test must be ordered by the treating physician.

Requiring FDA Approval

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address

approval by FDA and the New York State Department of Health (NYSDOH). Commenters provided professional laboratory experience to explain the time it takes to compile data demonstrating analytical and clinical validity to submit to the FDA or the NYSDOH, and the variables that affect the duration of this time.

Response: While we continue to believe that FDA approval or clearance demonstrates analytical and clinical validity, we are finalizing this NCD to nationally cover FDA approved or cleared lab diagnostic test using NGS as a companion diagnostic for patients with advanced cancer that meet certain clinical criteria. For all other tests using NGS for patients with advanced cancer that meet those requirements, we are leaving up to local contractor discretion.

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address other possible approaches alternative to that of the FDA to analytically and clinically validate a diagnostic laboratory test. A few commenters provided their observations when an assay developed within their department has outperformed and provided better patient care than an FDA approved assay. Other commenters remarked that laboratory-developed tests can be as sensitive and specific as FDA-approved testing (Kaul et al., 2017; Kim et al., 2017; Nagarajan et al., 2017).

Response: While we continue to believe that FDA approval or clearance demonstrates analytical and clinical validity, we are finalizing this NCD to nationally cover FDA approved or cleared lab diagnostic test using NGS as a companion diagnostic for patients with advanced cancer that meet certain clinical criteria. For all other tests using NGS for patients with advanced cancer for patients meeting those requirements, we are leaving up to local contractor discretion.

Companion Diagnostics

Comment: We received several comments on the proposed coverage criteria for companion *in vitro* diagnostics. A few commenters stated their recognition of a critical public health role for companion diagnostic tests in supporting safe and effective use of therapeutic products and supported access to these important tests that play an integral role in personalized medicine.

Response: We thank the commenters for their statements. The new NCD does provide national coverage. The final NCD will nationally cover FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) will be made by Medicare Administrative Contractors.

Comment: Commenters requested expansion of coverage beyond companion *in vitro* diagnostics, stating that the marketplace of FDA-approved companion diagnostics is extremely limited. For example, a few commenters recommended deleting the word "companion" in the phrase "companion *in vitro* diagnostics," to permit coverage of other types of FDA-cleared or approved NGS *in vitro* diagnostic tests such as tumor profiling tests.

Response: The final NCD will nationally cover FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) will be made by Medicare Administrative Contractors.

Comment: Another commenter recommended including FDA-approved or cleared tests that have been shown to reliably identify genetic mutations for which there are specific FDA-approved therapies, independent of individual companion diagnostic approvals because FDA clearance is not conclusive or prescriptive for labeled use of any specific therapeutic product.

Response: We agree that coverage should be expanded to accommodate promising diagnostic laboratory tests using NGS. Based on these comments we recognize that more than one pathway may be available to identify such devices. We have updated the coverage criteria to expand coverage to test is an FDA-approved or cleared companion *in vitro* diagnostic that has an FDA-approved or cleared companion diagnostic indication for that patient's cancer and provides an FDA-approved or cleared report of test results to the treating physician that specifies FDA-indicated treatments. In addition, any test that is not FDA-approved or cleared as a companion diagnostic is coverable from the Medicare Administrative Contractors.

Comment: A few commenters asked that the proposed coverage criteria recognize the contributions of complementary diagnostic tests using NGS in clinical practice.

Response: We appreciate the comments. The final NCD permits Medicare contractors to make the coverage determination for complementary diagnostics if the patient meets the criteria outlined in the NCD.

Comment: A few commenters asked that we consider a modification to expand coverage for diagnostic devices that FDA has determined meet the statutory standards for classification as Class II devices (i.e., FDA-cleared). Alternatively, another commenter disagreed and suggested that the 510(k) pathway for Class II devices is not stringent enough to be included as coverage criteria.

Response: We agree with the comments to expand coverage and updated the NCD coverage criteria to include FDA-approved and FDA-cleared companion diagnostics so if FDA re-classifies these devices coverage will remain

Printed on 5/2/2018. Page 80 of 151

the same.

Comment: A few commenters observed the recent *de novo* classification by FDA. Specifically, the FDA has recently announced the marketing authorization of three tumor profiling NGS tests, Thermo Fisher Scientific's Oncomine Dx Target Test, MSK-IMPACT and Foundation Medicine's F1CDx™, which are important advancements in the real-world application of precision oncology.

Response: We appreciate the observation by the commenters. We also note that the classifications of medical devices by the FDA into Class I, Class II, and Class III is separate and distinct from the classification of items and services by CMS into benefit categories.

Comment: A few commenters expressed confusion over whether a test or a malignancy is given a companion diagnostic indication.

Response: A test and not a cancer is assigned a companion diagnostic indication by FDA, therefore we have clarified this final decision that the test must have an FDA-approved or cleared companion diagnostic indication for that patient's cancer to be covered (see section I for full decision).

Comment: A few commenters observed that targeted therapies often do not work absent the required genetic signature, making the accurate diagnosis of mutations within a tumor absolutely critical. For example, a commenter provided the case of a diagnostic laboratory test using NGS approved for the detection of the EML4-ALK fusion gene in lung cancer would be covered for that indication only and not for detection of other genes not in the initial FDA approval. Similarly, a commenter requested that the proposed NCD be revised to clarify that the FDA-approved companion *in vitro* diagnostic is only covered to the extent that the test is used in a cancer for which that specific test has an FDA-approved companion diagnostic indication.

Response: We have updated the final NCD to reflect that the FDA-approved or cleared companion *in vitro* diagnostic is only covered to the extent that the test is used in a cancer for which that specific test has an FDA-approved or cleared companion diagnostic indication. All other indications, assuming other coverage criteria (e.g., patient criteria, CLIA-lab certified, ordered by the treating physician) are met as set out in Section I of this NCA, are left to contractor discretion.

Comment: Many commenters identified specific situations where an FDA-approved test could be modified and asked whether the modified test would continue to be covered.

Response: We disagree that the only way to perform testing to identify additional mutations is with a diagnostic laboratory test using NGS that is not FDA-approved or -cleared. We note several public comments named several additional test methods to identify additional mutations. We acknowledge that some providers or practitioners may use an FDA-approved or -cleared *in vitro* diagnostic inconsistent with the applicable market authorization as part of the practice of medicine. However, the final NCD will nationally cover FDA approved or cleared *in vitro* companion diagnostic laboratory tests using NGS for certain patients (at this time there are 4 specific FDA approved companion diagnostic tests using NGS). With respect to other NGS tests for cancer patients meeting criteria, coverage determinations under 1862(a)(1)(A) are at the discretion of Medicare Administrative Contractors.

Report of test results

Comment: We received several comments on the proposed coverage criteria that requires the inclusion of a report of test results to the treating physician. One commenter expressed uncertainty, stating that a "report" or "result" is not clearly defined. A few commenters believed that the criteria would likely lead to an increase in off-compensated use of drugs, a practice that one commenter believed requires CED to ascertain where there is and where there is not efficacy. Another commenter urged revision of the criteria to specify that NGS results do not constitute a basis for coverage of a drug or combinations of drugs that would not be supported by the drug(s) FDA label or statutorily approved compendia. One commenter requested that we consider additional requirements for the report of test results, including a policy on lab reporting of possible germline mutation findings.

Response: We disagree with the request to include additional requirements on the report of test results provided to the treating physician. We believe this will increase burden and decrease flexibility for innovative developments in testing. We acknowledge that while a companion diagnostic is indicated for use of a companion therapeutic product, this NCD covers NGS diagnostic lab testing for advanced cancer and does not discuss or make any coverage determination on the therapeutic interventions. However, we believe that a report of test results provides a more complete picture of genetic information on the patient's cancer to the treating physician, and therefore require that the diagnostic laboratory test using NGS have results provided using a report template to the treating physician that specifies treatments to the treating physician.

Comment: One commenter questioned the proposed coverage criteria regarding the requirement of the report to include FDA-indicated treatment options. The commenter interprets this requirement to mean that the test results must be provided in an FDA-approved format and not that coverage is dependent upon the biomarker status as only a particular biomarker status would lead to the ability or inability of the report to contain indicated treatment options. The commenter believes this test result requirement as interpreted by the commenter to be an appropriate component of the NCD.

Response: It was our intention to indicate that the test results must be provided with interpretation of results in a format. To this end, we have clarified the coverage criteria to state the diagnostic laboratory test using NGS have results provided using a report template to the treating physician that specifies treatment(s). We believe this requirement is necessary for the treating physician to use the results in the management of the beneficiary's specific medical problem.

Comment: A few commenters suggested that a clarification or discussion of testing and reporting of germline and somatic changes be explicit as a requirement for the report of test results in the final NCD.

Response: The final decision allows laboratories and diagnostic laboratory test developers to determine what is included in the test report. Further, the final decision is unchanged from the proposed decision in that it does not exclude coverage for testing of somatic mutations, provided the other coverage criteria are met. We note germline testing in the absence of signs or symptoms is designated a screening test and not a diagnostic laboratory test, which remains outside the scope of this NCD.

Comment: Other commenters cited the most recent FDA Standards Guidance document is specifically geared towards questions of using the NGS platform for testing somatic mutations.

Response: We thank the commenter for this information.

Innovation and the NCD

Comment: Many commenters support the proposed NCD because they believe it provides for the ability to innovate. Commenters stated that they will begin to order these diagnostic laboratory tests using NGS proposed as covered under the proposed NCD and not constantly worry about the administrative process and potential lack of insurance coverage, which they expressed is a significant step forward.

Response: We appreciate the comment.

Comment: Several commenters questioned the currently available evidence for the majority of genetic mutations identified by some diagnostic laboratory tests using NGS as they remain under investigation either because information on genetic variants provide unclear clinical significance for a given disease, or the disease does not have a targeted treatment available. Additionally, a few commenters stated that institutions across the country have continued to perform this testing despite the gaps in coverage and reimbursement.

Response: We appreciate the comment.

Comment: Commenters note that simply performing a comprehensive genomic profiling assay on all stage IV cancers would lead to increased healthcare spending, particularly given that many clinical questions can routinely be addressed with single analyte gene testing or genomic sequencing of 50 genes or less. Some commenters also stated that identification of variants for which the clinical management is uncertain may lead to unnecessary follow-up testing, treatments, and procedures, all of which have their own inherent risks and costs to patients. A few commenters recommended that CMS perform a study on cost-effectiveness. The commenters recommended that the impact of test results related to non-indicated mutations and variants of uncertain significance must first be well-defined and account for the possibility that the information may cause harms such as anxiety, radiation exposure from imaging, or complications by leading to additional unnecessary interventions that would not otherwise be considered based on the patient's clinical presentation.

Response: CMS does not consider cost or do a cost-effectiveness analysis when making coverage determinations. We appreciate the recommendation from commenters to consider additional social and emotional implications of information gained from a diagnostic laboratory test using NGS. However, we did not study these outcomes in our Internal Technology Assessment but rather focused on the overall survival, progression free survival, objective response rate, and patient reported outcomes when available.

Comment: Commenters stated that many trials are ongoing to see if diagnostic laboratory test using NGS in oncology is useful in treatment with targeted therapy (NCI-MATCH and ASCO TAPUR) and encouraged awaiting the trial results before further pursuing any decisions.

Several commenters disagreed, stating that the proposed NCD limits innovation by preventing laboratories from being able to quickly respond as new molecular alterations become clinically actionable and molecular technology improves.

Response: We agree that Medicare patients should have appropriate access to proven innovation and recognize the importance targeted cancer therapies. We strongly encourage additional evidence generation around these important scientific and clinical questions will assist patients and their physicians in making informed treatment decisions.

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address how laboratories address clinical utility. To provide context, commenters acknowledged that their interpretation of clinical utility is far wider ranging than how it is described in this decision memo, which is to guide targeted therapy or work as companion diagnostic. Commenters suggested that clinical utility includes (1) recognizing a mutation associated with intolerance of chemotherapy, (2) indicating that a bone marrow transplant should be performed earlier rather than later, (3) determining whether a patient with EGFR mutated non-small cell lung cancer may have a high risk of that cancer transforming into small cell lung cancer, (4) determining a diagnosis that informs the best course of therapy, (5) determining a prognosis in certain cancers to provide therapeutic and

life-planning activities, and (6) tracking diseases longitudinally. Additionally, a few commenters believe that the appropriate standard to evaluate a clinical laboratory test cannot always be tied to patient outcomes.

Response: We appreciate this context from commenters. The scope of the final NCD has been narrowed to provide national coverage to FDA approved or cleared lab diagnostic test using NGS as a companion diagnostic for patients with advanced cancer that meet certain clinical criteria. All other tests using NGS for patients with advanced cancer and meeting specific requirements remain at local contractor discretion.

Comment: To directly respond to the question posed by CMS to address other possible approaches to determine clinical utility for a diagnostic laboratory test, commenters provided varied alternative recommendations.

Response: We thank the commenters for providing their perspectives on assessment of clinical utility as applied to diagnostic laboratory tests using NGS. We agree that high quality evidence on improvements in patient outcomes is important and remains the key to national coverage determinations. We also agree that all appropriate types of published evidence should be considered in determining clinical utility. While there is an important role for professional society guidelines in the coverage determination process, it is but one part of the detailed efforts of clinicians and scientific experts to synthesize available evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary (see Appendix A). At this time we are finalizing this NCD to nationally cover FDA approved or cleared lab diagnostic test using NGS as a companion diagnostic for patients with advanced cancer that meet certain clinical criteria. For all other tests using NGS for patients with advanced cancer and who meet specific requirements, we are leaving up to local contractor discretion.

Comment: A few commenters cited innovative payment models to provide other possible approaches to determining clinical utility of a laboratory diagnostic test using NGS.

Response: We appreciate the comment on collaboration and additional efforts of innovative payment models to inform coverage criteria.

Local Coverage Determinations

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address examples of circumstances in which the commenters believe coverage would be adequately addressed by a local Medicare Administrative Contractor (MAC).

Response: Through this NCD, we are providing consistent national coverage for FDA approved or cleared diagnostic lab tests using NGS as a companion diagnostic for patients with advanced cancer meeting certain criteria. Coverage determinations for all other NGS tests for these same patients are left to Medicare contractors.

Clinical Laboratory Improvement Amendments (CLIA)

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as another possible alternative approach to that of the FDA to analytically and clinically validate a diagnostic laboratory test. Commenters appreciate the opportunities to pursue both FDA and non-FDA test development pathways, however, some commenters observed that some financially driven laboratories have exploited the longstanding CLIA approach to LDTs for monetary gain.

A few commenters expressed that allowing development of non-FDA-approved tests is reasonable given that laboratories need only to complete a rigorous validation study to implement new biomarkers.

Other commenters disagreed, citing that according to the CLIA regulations (Subpart K, Sec 493.1253: Standard: Establishment and verification of performance standards (b)(2)), in-house developed tests should require analytical validity assessments, not independent clinical outcome data. A few other commenters stated that CLIA generally does not assess clinical validity, however, some of these commenters believe that analytical assay equivalence should be the only requirement if there is already one FDA-approved panel for the same gene targets. One commenter recommended that the coverage criteria should refocus efforts to ensure that laboratory staff and directors, the individuals performing and interpreting test results are qualified to do so, in order to work towards preventing patient harm.

Response: The Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective. CLIA provides for a laboratory to establish certain performance characteristics relating to analytical validity for the use of a test system in the laboratory's own environment. This analytical validation is limited, however, to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are not meaningful outside of the laboratory that did the analysis. Furthermore, the laboratory's analytical validation is reviewed during its routine biennial survey – after the laboratory has already started testing. In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and therefore, prior to the use of the test system on patient specimens in the clinical diagnosis-treatment context. Moreover, the FDA's premarket clearance and approval processes assess the analytical validity of a test system in greater depth and scope as well as clinical validity, which is the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient, as part of the review that is focused on the safety and effectiveness of a test system. Unlike the FDA regulatory scheme, CMS' CLIA program does not address the clinical validity of any test system. Thus, the two agencies' regulatory schemes are different in focus, scope and purpose, and are intended to be complementary. Therefore, we disagree with comments proposing

Printed on 5/2/2018. Page 86 of 151

CLIA as an alternative approach to that of the FDA to analytically and clinically validate a diagnostic laboratory test.

MEDCAC and Technical Assessments

Comment: A few commenters questioned why we did not convene a MEDCAC or commission an external Technical Assessment (TA) when developing the proposed NCD. Additionally, one commenter urged us to consult the Clinical Laboratory Improvement Advisory Committee (CLIAC) as clinical experts.

Response: CMS recognizes the important role of the MEDCAC and external technical assessments. Similar to most NCDs, CMS did not commission a TA or hold a MEDCAC. This was part of parallel review. CMS consulted extensively with the FDA experts and NIH experts throughout the NCD process. We also reviewed all of the public comments and supporting evidence submitted by commenters. In addition, CMS met with every stakeholder that requested a meeting to discuss the coverage criteria of the NCD. While we appreciate the suggestions to include CLIAC the advice and guidance CLIAC provides to HHS pertains to general issues related to improvement in clinical laboratory quality and on specific questions related to possible revision of the CLIA standards rather than evidence for a specific type of lab test.

Coverage with Evidence Development

Comment: We received many comments regarding coverage with evidence development (CED). These comments included requests to remove CED, support CED, or make revisions to CED.

Response: We appreciated all of the comments on CED. CMS implemented CED under §1862(a)(1)(E) of the Social Security Act to provide access to Medicare beneficiaries while evidence is continuing to be developed on important health outcomes for Medicare patients. CED supports innovation and provides earlier access for an item or service when it may not be reasonable and necessary under §1862(a)(1)(A) of the Social Security Act while developing evidence to demonstrate improvement in health outcomes.

For this specific coverage determination, commenters noted that CED is not necessary because they are already developing the evidence or have developed the evidence to demonstrate these diagnostic laboratory tests using NGS improve health outcomes. These same commenters stated that the diagnostic laboratory test developers are equipped to conduct their own studies to generate any needed evidence to demonstrate improved health outcomes. We strongly encourage continuing these studies and publishing the results of these studies especially on the endpoints of overall survival, progression free survival, objective response, and patient reported outcomes relevant to the quality of life for Medicare beneficiaries. This is not only important to ensuring that patients,

caregivers and their providers can make informed evidenced-based decisions, but it also is important to continue to develop and publish results, which form the basis for the dissemination of new technologies into the healthcare system. In addition to our interest in evidence-based medicine, we note the important work of the National Institutes of Health's National Clinical Trials Network (NCTN), such as the NCI-MATCH trial. After reviewing all the public comments we have removed coverage with evidence development in this final NCD.

CED Questions

Comment: Some commenters commented on the CED questions CMS proposed.

Response: We appreciate the comment. In general, CED questions are developed to provide evidence to answer the NCD questions that provide evidence to determine whether use of the item or service improves health outcomes for Medicare patients. After reviewing all the public comments we have removed coverage with evidence development in this final NCD.

NIH Genetic Testing Registry (GTR)

Comment: One commenter noted that the NIH-NLM genetic testing registry (GTR) serves a critical role in research and efforts to improve patient health. This commenter believed that an additional reporting requirement for such submissions may create additional burden without added scientific value. Another commenter questioned whether data on analytical and clinical validity as well as clinical utility available in the GTR were reviewed or curated.

Response: We appreciate these comments. We note that the technological advances and accelerated discoveries about complex genetic tests also brings challenges to accessing accurate and detailed information about these tests. One specific challenge that could result is that health care providers cannot make informed clinical decisions about the use of genetic tests for patient care. To this end the GTR arose from the 2008 recommendation by the Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) that called for a publicly available web-based registry to enhance the transparency of genetic testing (<https://www.genome.gov/pages/about/nachgr/may2008agendadocuments/genoversightreccs.pdf>). Other policy and advocacy groups also called for a registry to enable informed decision-making regarding genetic testing. To enhance access to test information, the NIH developed the GTR (www.ncbi.nlm.nih.gov/gtr/), which serves as a free online resource of comprehensive information about genetic tests, submitted by test providers. We believe that by promoting access of this information to patients and their providers we will collaboratively improve communication of complex test information for better evidence-based informed decision making. We note that the GTR was a proposed requirement of coverage with evidence development and after reviewing all the public comments we have removed coverage with evidence development in this final NCD.

CED Requirement in NCTN

Comment: A few commenters noted support for coverage of NIH-NCI National Clinical Trial Network (NCTN) clinical trials, citing NCCN guidelines that they believe suggest clinical trials may often offer the best treatment option in first- and subsequent-line settings. Several commenters requested broader allowance for trials outside of the NIH-NCI NCTN, including investigator-initiated and industry sponsored trials, the ASCO TAPUR study and studies of the Worldwide Innovative Networking (WIN) Consortium, and Prostate Cancer Clinical Trials Consortium (PCCTC). A few commenters expressed confusion, stating that Diagnostic laboratory tests using NGSs are rarely provided as part of a clinical trial, that only around 4% of cancer patients eligible to partake in clinical trials actually participate.

Response: We appreciate these comments. As noted above, we removed the requirement of CED. We acknowledge that while overall trial participation may be below 10% that such trials are still clinically and scientifically rigorous and we continue to encourage continuing to develop good evidence through these and other rigorous trials. However, after reviewing all the public comments we have removed coverage with evidence development in this final NCD.

Qualified Clinical Data Registry (QCDR)

Comment: Commenters observed that there are no additional CED criteria in the proposed NCD to differentiate a registry from a CMS qualified clinical data registry (QCDR) under the Merit-based Incentive Payment System (MIPS). To this end a few commenters requested adoption of existing Clinical Document Architecture (CDA) standards and to address the provision of a governance framework to support interoperability as part of other data sharing requirements and aligned with existing standards defined by HHS, ONC and FHIT. A few commenters also recommended the requirement for laboratories to participate in Quality Improvement Registries (QIR), suggesting that the differences between a traditional registry and a QIR can be thought of as how data are collected and what questions can be answered with the data (Gliklich et al., 2014).

Response: We appreciate the commenters' remarks, but after reviewing all the public comments we have removed coverage with evidence development in this final NCD.

Communication of NCD

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address communication of the information discussed in this NCD. A few commenters questioned the ability of pathologists to integrate information in the electronic medical record. Additionally, commenters observed that oncologists are

confused by the reports of test results coming out from diagnostic laboratory tests using NGS as some reports are long, with more information than most people can practically digest, and the information is not personalized to each patient clinical scenario. Therefore, a few commenters noted that the professional interpretation of the test results needs standardized, not the tests themselves.

Response: We recognize that test result reports may contain much information and agree that clear presentation is needed to guide the patient-physician discussion and decision making. We do not believe that additional requirements in this NCD will standardize the professional interpretation of test results, but look forward to continued research in this area.

Comment: Commenters urged convening public meetings to more thoroughly ascertain the impact on patient access to clinical testing of the other proposed provisions of the NCD. These commenters suggest that CMS and FDA engage stakeholders in a public process to ensure that physicians and their patients realize all the benefits of precision medicine. In addition, commenters recommended development of consensus through such meetings on solutions to major issues with the proposed CED requirements. Many commenters welcomed the opportunity to bring expertise to the table in what we anticipate would be collaborative ongoing discussions with CMS and other stakeholders.

Response: We appreciate the interest by commenters to convene additional discussions and bring expertise to bear on further conversations of this final decision. CMS is open to meeting with all stakeholders and attend various public meetings throughout the year.

Comment: Commenters directly responded to specific questions posed by CMS in the proposed NCD to address how the information in this proposed NCD can be clearly communicated to health care practitioners, patients, and their care-givers. A few commenters suggested communicating this information through the College of American Pathologists since the majority of molecular pathology labs are CAP members. Other commenters recommended annual Medicare notices, targeting of senior citizen organizations, foundations, institutes, associations, annual conferences, academic centers, community hospitals, and oncology offices to provide information regarding the availability of NGS coverage. One commenter stated that personalizing NGS information with patient's stories should be included in periodic press releases. Another commenter noted that all forms of social media will need to be utilized to inform the public about any changes in NGS coverage.

Response: We appreciate these remarks from commenters and note that we have published this final decision on our website. We will take these considerations into account as we implement this final decision.

Comment: Commenters also recommended coordination with MACs to develop a more thorough communications process than usual for disseminating this information to practitioners through provider organizations, particularly those focused on treatment of cancer, those that might have existing cancer registries that could potentially be eligible for CED, and those that work with academic medical centers and clinical trial providers. Commenters also encourage establishment of a standardized process to quickly inform local Medicare contractors of new FDA-

approved diagnostic laboratory tests using NGS, including working with FDA to ensure prompt coverage and patient access.

Response: As part of our standard practice, we coordinate with our contractors. After reviewing all the public comments we have removed coverage with evidence development in this final NCD.

Comment: Commenters requested coordination with CMS and Medicare Advantage plans to actively inform their provider networks of the NCD (e.g., provide language for inclusion in provider newsletters, facilitate the adoption of NCD coverage directly into plan medical policies by offering appropriately formatted documents, etc.). To this end, commenters recommended the development and maintenance of a website that lists tests covered under the NCD (and the covered indications for each such tests).

Response: We understand the importance of communication in dissemination of complex NCDs and have several options to inform stakeholders in written and oral communications.

Additional NCD Requests

Comment: A few commenters made additional requests for specific NCDs.

Response: There is a formal process to request an NCD that is described in the August 7, 2013 *Federal Register Notice*. We encourage those wishing to request an NCD to read and refer to this notice for additional information on what constitutes a complete, formal request. Additionally, this notice contains information about initiating informal contact with CMS prior to the submission of a complete, formal request. Requests for NCDs may be submitted electronically to NCDRequest@cms.hhs.gov.

Miscellaneous Comments

Comment: One commenter stated that the proposed NCD will deny provider choice to Medicare patients.

Response: We disagree. Several FDA approved tests are available nationally. This NCD creates coverage for tests that demonstrate clinical utility (improved health outcomes Medicare patients). All other diagnostic lab tests using NGS for patient's that meet certain criteria are left to contractor discretion.

Comment: One commenter suggested that issuing an NCD was inconsistent with the policies supporting Executive Order 12866, that regulations only be issued when there is a "compelling public need."

Response: We disagree with the commenter that an NCD is the promulgation of a significant rule. National coverage determinations are not regulations, but establish controlling policies for Medicare contractors and adjudicators that ensure similar claims will be covered and paid in a consistent manner across the nation. The Supreme Court has recognized that "[t]he Secretary's decision as to whether a particular medical service is 'reasonable and necessary' and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions." Heckler v. Ringer, 466 U.S. 602, 617 (1984). We believe that the final NCD will be useful for Medicare beneficiaries by providing nationwide coverage for certain NGS tests.

Comment: A few commenters stated that NGS is not a diagnostic test for which an NCD can reasonably be promulgated.

Response: We disagree with the commenter for several reasons. We believe that a diagnostic laboratory test using NGS is a diagnostic test that falls within an appropriate Medicare benefit category under Part B. Moreover, an NCD is a decision regarding whether to cover a particular item or service nationally under title XVIII of the Social Security Act. In most cases, Medicare coverage is limited to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury (and within the scope of a Medicare benefit category). NCDs are made through an evidence-based process, with opportunities for public participation. Specifically, this NCD is not on NGS broadly, but on diagnostic laboratory tests using NGS for cancer only when certain coverage criteria are met. All other diagnostic laboratory tests using NGS for certain patients remain at local Medicare Administrative Contractor discretion.

Comment: Some commenters believed that CMS should include additional opportunities for public comment. A few commenters stated that to finalize an NCD with significant changes within a short period of only 90 days is unprecedented.

Response: The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (see section 1862(I) of the Social Security Act) amended several portions of the NCD development process with an effective date of January 1, 2004. Specifically, this required that the public comment period on a proposed decision shall last 30 days, and comments will be reviewed and a final decision issued not later than 60 days after the conclusion of the comment period. Additional information is available in our Federal Register notice, (78 FR 48164-69), updating the process used for opening, deciding or reconsidering NCDs under the Social Security Act. During this NCD

process, we have reviewed many comments and publications submitted by commenters and have focused this final NCD on specific indications for cancer and test specific criteria.

Comment: One commenter stated that this NCA is based on an assessment from a different government agency, FDA, which violates statute preventing the regulation of medical practice.

Response: We disagree. This NCD was based on our evaluation of relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for Medicare patients. Like all technologies we review, we take into account, among many other factors, FDA approval (see Appendix A of this decision).

Comment: A few commenters cited a Special Fraud Alert issued by the Office of Inspector General (OIG) in June 2014 which addresses payments made to physicians for submitting patient data to a registry or database, answering patient questions about a registry, or reviewing registry reports. The commenters suggest that CMS coordinate with OIG to relax those criteria and ensure registry accessibility in the CED pathway.

Response: We are aware of this report, however CMS does not influence what OIG investigates or does not investigate. CMS does not pay providers to submit data to registries. The question of whether a registry pays a physician to report data or answer questions is outside the scope of this specific NCD on whether a diagnostic laboratory test using NGS for Medicare beneficiaries with advanced cancer is reasonable and necessary.

Comment: Commenters questioned the adherence of the NCA to the NCD process. Specifically, the commenters are not aware that CMS consulted with appropriate outside clinical experts, which is required under statute when CMS does not consult with MEDCAC.

Response: We disagree. CMS consulted with physicians, molecular diagnostic experts, researchers, patient advocates and professional societies as part of the NCD process. We direct the commenters to sub-section 4. Professional Society Recommendations / Consensus Statements / Other Expert Opinion.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage.

Moreover, with limited exceptions, the expenses incurred for items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." (§1862(a)(1)(A) of the Act).

As noted earlier, our analysis sought the answer to the following question:

Is the evidence sufficient to conclude that next generation sequencing when used as a diagnostic test for patients with advanced cancer meaningfully improves health outcomes?

For this NCD, we analyzed over 200 articles submitted by Foundation Medicine and based on the inclusion and exclusion criteria cited in the Evidence section we reviewed an additional 55 articles through our internal technology assessment that included case series, retrospective studies and prospective case-control trials. Twenty-seven studies from our evidence review applied a Foundation Medicine test. In addition, there have been three other next generation sequencing tests for advanced cancers approved or cleared by the FDA (Illumina Inc., Praxis™; Life Technologies, Oncomine™; MSK-IMPACT™ (Memorial Sloan Kettering Cancer Center), and Foundation Medicine, FoundationFocus™) and reviewed by CMS.

During the public comment period, commenters submitted 379 references. CMS created general categories to classify these references: there were 21 references on analytical validity; 54 references on clinical validity; 79 references on clinical utility; 59 reviews; 31 guidelines; 10 primary studies; 6 references on molecular tumor boards; 119 were outside the scope of this NCD for example references to ephemera such as press releases. Consistent with the search criteria of this determination, the primary studies and articles on clinical utility were evaluated in accordance with the evidence review criteria used for the initial evidence review for the proposed NCD. Twenty-five studies were added to the evidence and considered in the analysis for the final determination. See Appendix E for references.

Because Foundation Medicine was the requestor of CMS-FDA parallel review, we considered evaluating only Foundation Medicine's NGS companion diagnostic test, F1CDx™, for coverage as a universal companion diagnostic for Medicare beneficiaries. However, after reviewing all of the evidence, including national guidelines, it became clear that the evidence evaluates when a diagnostic test is clinically useful for an advanced cancer indication, rather than the utility of a single manufacturer's test. To this end, we identified relevant professional society guidelines in oncology for the patient population with cancer. These guidelines describe clinical scenarios that required further review and further diagnostic laboratory or other testing before treatment decisions are made. The guidelines do not focus on manufacturer specific NGS tests but rather types of cancers that would benefit from molecular diagnostic testing which includes NGS. For instance, the NCCN Lung Cancer guidelines (2017), based on evidence, suggests that further determination of specific genetic or genomic alterations is critical for patients with metastatic non-small cell lung cancer (NSCLC). In contrast, the NCCN guideline also suggests that current standards of care available for earlier stages of lung cancer do not justify routine molecular diagnostic testing. Therefore, we believe that because these guidelines describe the molecular markers that contribute to diagnostic decision making, rather than the type of diagnostic laboratory test using NGS, the scope of this NCD is supported by the evidence reviewed.

Since our evidence question and analytic framework apply to molecular diagnostic tests for advanced cancer we are considering the type of technology so that claims for similar tests will be covered in a similar manner nationwide under title XVIII. In addition, NGS oncology panels typically target many of the same genetic or genomic alterations creating considerable overlap in the evidence base between available existing oncology panels. However, this evidence review has identified many publications that do not explicitly identify what diagnostic laboratory test using NGS was administered in the publication of clinical study results. This has led to further evidentiary questions about the clinical utility of diagnostic tests without direct evidence applicable or generalizable to the Medicare population. Lastly and most importantly, reviewing diagnostic laboratory tests using NGS for patients with cancer (see Evidence section) for coverage allows predictable access to high quality technologies for patients and their treating physicians. This enables patients and physicians to make an informed decision from multiple matched therapies, or if no targeted therapies are available, it may direct the patient to a relevant clinical trial.

Evidence base for diagnostic laboratory tests using NGS: We recognize there are a number of key factors that make comparisons between test methods distinct for our national coverage analysis. First, the different test methods described in the Background section (including polymerase chain reaction, *in situ* hybridization, and immunohistochemistry) can apply different sample materials, including DNA, RNA, or protein. Different test methods also apply varying levels of experience by the test developer and those performing and/or interpreting test results. Additionally, it is important to consider the test methods relative to the needs of different patients with advanced cancers. For example, the NCCN guidelines (2017) note the importance of molecular testing in patients diagnosed with non-small cell lung cancer because of the evidence supporting the available treatments after identifying relevant biomarkers EGFR, ROS1, and PD-L1. Because of these biomarkers, one or more diagnostic test methods could apply to their identification. As mentioned in the response to comments, we acknowledge that the scope of this final decision could be applicable to several test methods, however we have limited the scope of this final decision to diagnostic laboratory tests using NGS for the reasons noted above. Several studies and guidelines describe cancers that express multiple clinically relevant genetic alterations, and suggests that some advanced cancers may benefit from more comprehensive molecular testing using one or more methods (Johnson et al. 2014, Ali et al. 2016, Ho et al. 2016, Ross et al. 2016, Suh et al. 2016, Wheler et al. 2016). However, it is difficult to directly compare a comprehensive molecular profiling diagnostic laboratory test using NGS testing to a molecular diagnostic test that examines a single or a few biomarkers. Such comparisons may not provide meaningful information for patients and their treating physicians to choose the right test at the right time. Thus, this national coverage analysis focuses on diagnostic laboratory tests using NGS for advanced cancer patients.

When making national coverage determinations, it is important to consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully review the demographic characteristics and comorbidities of study participants as well as the practitioner training and experience. This section of the decision memorandum provides an analysis of the evidence we analyzed during our review. The evidence includes the published medical literature and guidelines pertaining to diagnostic laboratory tests using NGS. In this analysis, we address the following question:

Is the evidence sufficient to conclude that next generation sequencing when use as a diagnostic test for patients with advanced cancer meaningfully improves health outcomes?

The expectation that a diagnostic test informs physician management is well established. It is also consistent with

federal regulations at 42 C.F.R. §410.32(a), which requires that:

". . . diagnostic tests must be ordered by the physician who. . . treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem."

We recognize that the medical literature often describes test characteristics and has not consistently considered the impact of testing on physician decision making and patient health outcomes, such as mortality, morbidity or reduction of invasive testing. However, we believe that evidence of improved health outcomes is more persuasive than descriptions of test characteristics. (Please see Appendix A: General Methodological Principles of Study Design).

There are a number of structured methods for evaluating diagnostic tests. In past decisions on diagnostic imaging, we considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. We believe that assessing Level 5 using evidence of improved patient health outcomes is more persuasive than using evidence of test characteristics.

To analyze evidence in this framework for an *in vitro* laboratory diagnostic test, we utilized the ACCE Model Process (see Appendix B) for Evaluating Genetic Tests (Haddow et al., 2003). Tests are evaluated for the components of the disorder and setting, analytical validity, clinical validity, clinical utility, and related ethical, legal, and social issues. Analytical validity includes the ability of the test to accurately and reliably detect the mutation and/or variant with sensitivity and specificity, while clinical validity includes the ability of the test to accurately and reliably detect the disease of interest in the defined population. Test validity is typically assessed by the FDA during the approval or clearance processes, therefore, FDA evaluates analytical and clinical validity, while CMS evaluates clinical utility. CMS is focused on assessing clinical utility to include whether use of the test to guide patient management and treatment improves health outcomes.

This assessment of clinical utility includes consideration for diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients. The ACCE Model Process utilizes criteria acknowledged by the PHG Foundation for the evaluation of clinical utility of genetic tests (2007) and is consistent with recommendations from The Association for Molecular Pathology (2016) as described in the evidence reviewed. We note that this differs from The American College of Medical Genetics and Genomics (ACMG) position statement on clinical utility (2015) in that it does not also take into account effects on economic impact on health-care systems, nor the value a diagnosis can bring to families or societies in general. However, we believe that the application of the ACCE Model Process best allows us to understand how a diagnostic laboratory test using NGS can produce changes in the treating physician's diagnostic thinking, the patient management plan, and patient outcomes to most closely focus on the specific needs of the individual patient's advanced cancer.

FDA-approved or cleared companion *in vitro* diagnostic laboratory tests using NGS demonstrate clinical utility

CMS proposed under §1862(a)(1)(A) to cover NGS as a diagnostic laboratory test when the test is used as an FDA-approved companion *in vitro* diagnostic, and provides results to the treating physician that includes specified treatment options to patients with metastatic, recurrent, or advanced stage IV cancer for FDA-labeled indications. Based on the evidence reviewed, diagnostic laboratory tests using NGS are most clinically useful for patients when the test reliably gives results that allow the patient and physician to make informed treatment decisions based on evidence-based interventions that improve health outcomes and therefore such uses of these tests require no further study to support clinical utility.

The clinical validity and clinical utility of individual diagnostic tests are condition-specific as well as test-specific. Review of the analytical and clinical validity of individual components of the complete diagnostic laboratory test using NGS from the sample preparation to the report of test results provides information to CMS that answer specific questions in the ACCE Model Process. Without this information it is unclear whether the genetic mutation(s) tested demonstrate clear clinical significance, which could not lead to evidence demonstrating changes in patient management. Therefore, this final NCD provides national coverage for a diagnostic laboratory test using NGS when the test has FDA approval or clearance as a companion *in vitro* diagnostic for certain patients.

Patient covered indications: Based on the evidence reviewed, patient characteristics most likely to benefit from molecular diagnostic tests are patients having recurrent, metastatic, or advanced stage IV cancer (see Takeda et al 2015, Johnson et al 2014, and Ross et al 2016 including 55%, 85%, and 80% patients with stage IV disease, respectively). However, not every cancer is described clinically consistently by stages in the publications reviewed. For example, Ali-Rohil et al 2016 described patients with squamous cell carcinoma as having advanced cancer, and studies that include patients with liver cancers such as Kim et al 2015 could use a liver cancer specific staging system, such as the Barcelona Clinic Liver Cancer (BCLC) system, or the Cancer of the Liver Italian Program (CLIP) system, or the Okuda system, or chosen to include a liver function classification such as the Child-Pugh score for cirrhosis, or simply described such cancer by the extent to which the tumor could be removed surgically. The American Joint Committee on Cancer (AJCC) established an evidence-based anatomic staging, which can be used to communicate cancer through standardized terms found in their Cancer Staging Manual for the tumor node metastasis (TNM) staging system. In contrast, the SEER program uses summary stages of in situ, localized, regional, distant, and unknown to focus on categorizing how far a cancer has spread from a point of origin. There can be limitations also to the ability to clinically use or report staging. For examples, cancers which are not typically treated surgically, or cancers that are treated surgically after treatment with anti-cancer agents, could under-estimate tumor stage. In addition to staging of cancers, the evidence demonstrates that recurrent cancers could also benefit from additional diagnostic laboratory testing using NGS (Meric-Bernstam et al 2015, Swisher et al 2017). Therefore, based on the evidence review we proposed that a diagnostic laboratory test using NGS be covered for patients with recurrent, metastatic, or advanced stage IV cancer.

Of the 25 studies added to the evidence and analysis, one tissue based study (Yates et al., 2017) provided evidence supporting the proposed determination on clinical validity of diagnostic laboratory tests using next generation sequencing for metastatic breast cancer and additionally relapsed breast cancer, supporting expansion of the patient criteria included for coverage. An additional randomized trial (Long et al., 2017) provided stronger evidence supporting the proposed determination on clinical utility (higher overall survival and relapse free survival) of BRAF V600 mutations treated with adjuvant dabrafenib plus trametinib in stage III melanoma and supporting inclusion of stage III cancers in this final decision.

The proposed NCD included evidence from advanced stage III and stage IV cancers (Johnson et al, 2014; Plamack et al., 2014; Ali et al., 2016; Ross et al., 2016b; Schrock et al., 2017) to support the proposed decision for advanced recurrent, metastatic, or stage IV cancer. Additionally, we reviewed further evidence submitted in public comment (Newman et al., 2014; Gutierrez et al., 2017; Long et al., 2017) that included multiple studies of earlier stage III cancer. Evidence that was reviewed on earlier stages of cancer did not report patient health outcomes (Newman et al., 2014, Schrock et al., 2017). Therefore, after reviewing the additional evidence and public comments, we have expanded our decision to include earlier stage III cancers. To further clarify our intention to include patients with cancer that has returned, we have updated the final decision to also include relapsed and refractory patients, to reflect the variety of scenarios encountered in clinical practice (e.g. Wang et al., 2016). These criteria apply to nationally covered tests as well as diagnostic laboratory tests using NGS that remain at local Medicare Administrative Contractor discretion.

Frequency of testing: We also reviewed the evidence to support the frequency of performing a diagnostic laboratory test using NGS. The publications reviewed did not show that patients received multiple diagnostic laboratory tests using NGS. Rather studies such as Papaxoinis et al 2015 showed a subset of patients receiving diagnostic laboratory tests using NGS and additional studies showed use of complementary and/or confirmatory testing for research using multiple methods (Le Tourneau et al. 2014, Ko et al. 2016). Our analysis did not identify benefits of further diagnostic laboratory testing using NGS beyond identification of genetic alterations of the patient's advanced cancer, which would lead the patient to select from companion therapeutic products, FDA approved anti-cancer agents, or enrollment into cancer clinical trials.

Research is ongoing to identify the extent of acquired mutations due to treatment with chemotherapy or radiation. Indeed researchers are continuing to identify the molecular markers involved in invasion (Friedl and Alexander 2011) and metastasis (Roubaud et al. 2017) to further develop tests that may predict a higher risk of a more aggressive cancer or the likelihood of response to one or more treatments. However, this research has not yet demonstrated the improvements of patients with advanced cancer and their health outcomes after performing multiple diagnostic laboratory tests using NGS. Therefore, we proposed to cover NGS as a diagnostic laboratory test if the patient has not previously received the same diagnostic laboratory test using NGS.

Furthermore, a patient who is no longer seeking treatment for his or her advanced cancer could not benefit from further diagnostic laboratory testing as such results would not be used to select from available treatments for the patient's cancer. The FDA-label indicates that diagnostic laboratory tests using NGS are intended to be used to identify patients who may benefit from treatment following detection of specific genetic alterations. Therefore, we proposed that a diagnostic laboratory test using NGS be covered for a patient who decided to seek further cancer treatment (e.g., therapeutic chemotherapy) and remains a candidate for further therapy.

During the comment period, commenters provided focused evidence (Mok et al., 2017; Remon et al., 2017) for patients with locally advanced or metastatic NSCLC after first-line EGFR-TKI therapy and the benefits of detection of an EGFR T790M mutation. To this end, we summarized the evidence and note the use of an FDA-approved companion *in vitro* diagnostic (cobas® EGFR Mutation Test v2) that does not use NGS but is available to identify patients with NSCLC whose tumors have defined EGFR mutations and for whom safety and efficacy of osimertinib has been established. As a result, we have not eliminated this requirement, but rather clarified in this decision that repeat testing using the same NGS test in the same patient is covered only when a new primary cancer diagnosis is made by the treating physician.

Additional clarifications in this final decision include acknowledgement that both FDA-approved and FDA-cleared tests could be indicated as companion *in vitro* diagnostics and that a companion diagnostic indication is a type of test indication and not an indication for a type of cancer.

Companion Diagnostic with Analytical and Clinical Validity: A companion diagnostic provides information that is essential for the safe and effective use of a corresponding drug or biological product. These types of tests help the treating physician select a particular therapeutic product for their patient based on the test results. The indications for use of a companion diagnostic approved or cleared by the FDA therefore includes the analytical and clinical validity, as well as the clinical utility to support covering companion diagnostic laboratory tests and for this coverage determination we have outlined specific coverage requirements in section I. We acknowledge that clinical utility includes demonstration that the patients have improvements in health outcomes from clinical studies using a companion diagnostic test that has been analytically and clinically validated. In order to provide evidence demonstrating improvements in health outcomes, we expect that the test will serve to directly manage the patient's cancer in two specific ways. First, when the validated test is essential for the use of one or more therapeutic interventions and second, when the validated test identifies patients in the same population who have been previously studied to benefit from such therapeutic interventions. To this end, FDA approval ensures that the device has been analytically and clinically validated in the population previously studied to support CMS to identify the patient health outcomes associated with the benefit of a specific therapeutic intervention as described on the FDA label.

Health outcomes of interest: We believe based on the evidence review that the health outcomes of interest were best summarized by Jardim et al. (2015). Specifically, the investigators performed a meta-analysis of 57 randomized and 55 non-randomized trials representing a total of 38,104 patients to compare efficacy outcomes between approved treatments. The analysis of the study identified that personalized therapy is associated with increased clinical benefit across tumor types and markers as demonstrated substantially higher response rates, longer time to disease progression, and longer overall survival. Systematic evidence reviews and meta-analysis that are well designed and include a number of comparable trials representing a large pool of patients such as the analysis by Jardim et al. provide a strong level of evidence. In addition, 5 observational studies reported improvements in progression free survival for patients studied, including Haslem et al. 2017, Hortbogyi et al. 2016, Johnson et al. 2016, Radovich et al. 2016, and Swisher et al. 2017. Improvements in overall survival were reported in observational studies including Hortobogyi et al. 2016, Javle et al. 2016, Schwaederle et al. 2016b, Singhi et al. 2017, and Wheler et al. 2013. While observational studies in general represent a lower level of evidence, the studies do provide consistent supportive evidence across a broad number of patients with cancer.

Several publications in the evidence review identify diagnostic laboratory tests performed by Foundation Medicine using NGS to identify patients who may benefit from selecting an FDA-approved treatment consistent with the FDA-approved indications for use. Specifically, the Foundation Medicine F1CDx™ companion diagnostic is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB), using DNA isolated from FFPE tumor tissue specimens. According to the analytic framework used in this national coverage analysis, clinical trials on targeted therapies that were used to demonstrate improvements in health outcomes such as overall survival also provide important evidence to establish clinical utility for some diagnostic laboratory tests. These trials are presented and analyzed in the summaries of safety and effectiveness as part of the proven targeted therapies but will not be re-reviewed in the evidence or analysis.

The Pre-Market Approval Application approved by the FDA includes a summary of safety and effectiveness data (SSED) of the Foundation Medicine F1CDx™ demonstrating the analytical and clinical validity. This includes data supporting the following indications noted in the table here:

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso® (osimertinib)
	<i>ALK</i> rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast cancer	<i>ERBB2</i> (HER2) amplification	Herceptin® (trastuzumab), Kadcyca® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix® (cetuximab)
	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3, and 4) and <i>NRAS</i> wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)

Indication	Biomarker	Therapy
Ovarian cancer	BRCA1/2 alterations	Rubraca® (rucaparib)

In addition to the Foundation Medicine F1CDx™, there are three next generation sequencing *in vitro* companion diagnostic tests approved by the FDA with SSEDs available for each PMA. This includes data supporting the following indications that:

- The FoundationFocus™ CDxBRCA for patients with BRCA1 and BRCA2 alterations may indicate efficacy with rucaparib in ovarian cancer.
- The Oncomine™ Dx Target Test for patients with single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 may indicate efficacy for select targeted therapies listed in the table here in accordance with the approved therapeutic product labeling in non-small cell lung cancer:

Gene	Variant	Targeted Therapy
BRAF	BRAF V600E	TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)
ROS1	ROS1 fusions	XALKORI® (crizotinib)
EGFR	L858R, Exon 19 deletions	IRESSA® (gefitinib)

- The Praxis™ Extended RAS Panel for patients without specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] may indicate efficacy with panitumumab in colorectal cancer.

Observational studies in the evidence section that did not include such health outcomes were able to demonstrate that the laboratory test using NGS could identify patients who could be matched to a more personalized therapy. For example, Johnson et al. (2014) noted 26% of patients observed had genetic alterations that predicted sensitivity to targeted agents already approved for the tumor type assessed. This identification of genetic alterations from results of the diagnostic laboratory test using NGS can lead patients to the available therapies with known evidence for improvement of the patient’s health outcomes. Additionally, Le Tourneau et al. 2015 concluded that using molecularly targeted agents outside their indications did not improve PFS compared with treatment at physician’s choice in heavily pretreated patients—those previously exposed to multiple anticancer regimens—but the authors suggested enrollment of such patients in cancer clinical trials.

A review of the evidence and these FDA PMA results support our proposal that an FDA-approved *in vitro* diagnostic test used as companion diagnostic to provide FDA-approved test results to the treating physician would guide treatment for a patient with recurrent, refractory, or relapsed, metastatic or locally invasive stage III or stage IV cancers to improve the patient’s health outcomes because the patient would be making a more

informed decision on selecting treatments with demonstrated evidence of efficacy. Since the proposed decision was posted, the FDA has cleared a companion diagnostic as a class II medical device. Specifically, on December 22, 2017, the FDA cleared the MolecularMD Corporation's MRDx BCR-ABL Test (K173492) intended to be used in the identification of CML patients in the chronic phase being treated with nilotinib who may be candidates for treatment discontinuation and for monitoring of treatment-free remission. While not a diagnostic laboratory test using NGS, the availability of a companion *in vitro* diagnostic for patients with cancer as a result of the FDA 510(k) clearance process indicates that such tests can be developed with evidence. Therefore, after reviewing the public comments and further evidence, we have expanded the final NCD to include FDA-approved as well as FDA-cleared companion diagnostic laboratory tests using NGS.

To answer the question, *Is the evidence sufficient to conclude that some next generation sequencing when used as a diagnostic test for patients with advanced cancer meaningfully improves health outcomes?*

Yes. Based on the evidence reviewed we believe that FDA-approved and FDA-cleared laboratory *in vitro* diagnostic tests using NGS as a companion diagnostic is sufficient for patients with recurrent, relapsed, refractory, metastatic, or advanced stage III, or stage IV cancer to expect meaningful improvement in their health outcomes, such as PFS. These FDA-approved or cleared companion diagnostics using NGS have demonstrated improvements in patient health outcomes when used by the treating physician and the patient to guide selection of proven treatments. Therefore, we are covering such a test under section 1862(a)(1)(A) of the Social Security Act (see section I for full coverage decision).

Next generation sequencing as an in vitro diagnostic test without proven clinical utility included in additional clinical studies

We believe it is important for clinical studies for patients with advanced cancer, who cannot identify a companion diagnostic available for their specific clinical scenario to continue in this field, such as in the case of a patient seeking to participate in a cancer clinical trial. In general, CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies with the collection of additional clinical data. In making coverage decisions involving CED, CMS decides after a formal review of the medical literature to cover an item or service only in a clinical study. Participation in a clinical study should enroll enough patients to examine the clinical utility of the diagnostic laboratory test using NGS when results of the test can only identify patients as candidates for an investigational trial. The results of such clinical studies moves health care further toward an evidence-based practice and development of standard of care practices to manage the patient's advanced cancer. This evidence-based practice is critical when the standard care plan, with known clinical utility, is unavailable.

CMS implemented CED under §1862(a)(1)(E) of the Social Security Act to provide access to Medicare beneficiaries while evidence is continuing to be developed on important health outcomes for Medicare patients. CED supports innovation and provides earlier access for an item or service when it may not be reasonable and necessary under §1862(a)(1)(A) of the Social Security Act while developing evidence to demonstrate improvement in health outcomes.

For this specific coverage determination, commenters noted that CED is not necessary because they are already developing the evidence or have developed the evidence to demonstrate these diagnostic laboratory tests using NGS improve health outcomes. These same commenters stated that the diagnostic laboratory test developers are equipped to conduct their own studies to generate any needed evidence to demonstrate improved health outcomes. After reviewing all the public comments we have removed coverage with evidence development in this final NCD. We strongly encourage continuing the studies and publishing the results of these important studies especially on the endpoints of overall survival, progression free survival, objective response, and patient reported outcomes relevant to the quality of life for Medicare beneficiaries. This is not only important to ensuring that patients, caregivers and their providers can make informed evidence-based decisions, but it also is important to continue to develop and publish results, which form the basis for the dissemination of new technologies into the healthcare system.

In addition to use of the test to guide treatment selection, we also recognize that the results from an FDA approved or cleared *in vitro* diagnostic test using NGS could identify an absence of genetic alterations and for which no targeted treatment is available. Indeed, in our Evidence section we identify publications that show patients proceeding to participate in cancer clinical trials as a result of the use of NGS as a diagnostic laboratory test. The majority of studies reviewed, including four randomized trials and multiple observational studies, did not provide evidence of clinical utility but demonstrated some clinical significance of a diagnostic laboratory test using NGS for such patients. Specifically, we reviewed four publications on data from randomized clinical trials. Two trial results (Papaxoinis et al., 2015; Peeters et al., 2013) reported no significant improvement in overall survival but reported positively the ability to detect genetic alterations and direct patient management. Two additional publications (Le Tourneau et al., 2015; Le Tourneau et al., 2014) of a single trial reported promising results and suggested the benefit to further study of patients enrolling in cancer clinical trials. However, many observational studies also reported mixed results. Fourteen observational studies reported the ability to detect genetic alterations, which could lead to changes in the direct management of the patients' cancers, including Ali et al. 2016, Ho et al. 2016, Johnson et al. 2016, Meric-Bernstam et al. 2015, Padovan et al. 2016, Plimack et al. 2015, Radovich et al. 2016, Ross et al. 2016, Sohal et al. 2016, Suh et al. 2016, Takeda et al. 2015, Vanden Borre et al. 2017. We also note two observational studies (Joshi et al., 2016, Kim et al., 2015) that reported improvements in response rate for patients receiving targeted therapies. Due to these mixed results, there are outstanding evidentiary questions of clinical utility when the test is used as part of a clinical trial and as a result such use of a diagnostic laboratory test using NGS is not reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act.

Future clinical study outcomes that support clinical utility: To determine the relevant patient-centered health outcomes for clinical studies that support clinical utility of diagnostic laboratory tests using NGS for cancer patients, we extensively searched for primary studies evaluating diagnostic interventions using NGS for cancers. As a reminder, for the purpose of this NCD analysis, we defined advanced cancer to include stage III or stage IV, metastatic, and relapsed, refractory, or recurring disease. Studies we reviewed include those with health outcomes meaningful to patients and generalizable to our population. The outcomes of interest include the ability to measure the patient's overall survival, progression free survival, time to treatment failure and objective response rate. While we continue to believe that curing cancer and improving the patient's overall survival are the most desirable goals of treatment, we also recognize those are not the only patient-centered outcomes that are important.

We proposed to include measuring the patient's objective response consistent with the Response Evaluation Criteria In Solid Tumours (RECIST) to measure the response of tumors to treatment or intervention. The use of an objective response as an endpoint for evidence of effect is important and supported by evidence suggesting that early clinical studies of interventions that decrease tumor prominence in a proportion of patients also may subsequently demonstrate improvement in overall survival or other time to event measures in later phases of clinical studies (Buyse et al. 2000). However, an objective response to an intervention is only useful when based on standardized criteria that consider the anatomical tumor burden. The first published standard response criteria to introduce the concept of overall assessment of tumor burden in 1981 was from the World Health Organization (WHO) for use in trials where tumor response was the primary endpoint (Miller et al. 1981). Since then, an International Working Party formed in the mid-1990s from cooperative groups and pharmaceutical companies

that used modified WHO criteria harmonized additional standards and as a result RECIST 1.0 were published in 2000 (Therasse et al. 2000) and updated as RECIST 1.1 in 2009 (Eisenhauer et al. 2009). It is from this evolution of the evidence that we recognize the importance of standardization in objectively measuring response to better understand the impact on patient's health outcomes.

While RECIST are objective criteria, and we strongly encourage the application of an objective measurement of objective response, we also want to recognize the study of patient-centered health outcomes. For example, the Patient-Centered Outcomes Research Institute (PCORI) funds research that offers patients and caregivers the information they need to make important healthcare decisions. Under their research infrastructure program, they are creating a national network to foster a wide range of observational studies known as PCORnet, the National Patient-Centered Clinical Research Network, to find a faster, less expensive, more powerful way to improve the nation's health and health care.

Next generation sequencing diagnostic tests without proven validity as a diagnostic test

As discussed in the proposed NCD, tests that cannot demonstrate evidence of analytical and clinical validity cannot be assessed for clinical utility to determine whether use of the test to guide management and treatment improves health outcomes for Medicare beneficiaries. Tests that are not validated risk discrepancies in consistency and accuracy of test results. This is concerning because patients and physicians rely on these tests to help with cancer treatment decisions. For example, flawed gene-expression tests developed by cancer researchers were used in three lung and breast clinical trials aimed at determining which chemotherapy treatment patients would receive. As a result, the Institute of Medicine (IOM now the National Academy of Medicine) issued a 2012 committee report. The report identifies best practices to enhance development, evaluation and translation of comprehensive tests. The report further provides specific steps to ensure these tests are appropriately assessed for scientific validity before they are used to guide patient treatment in clinical trials. We agree with the IOM and believe that consultation with FDA through approval or clearance processes fully validates the diagnostic test before crossing into clinical use. This provides some uniformity in evidence thresholds and transparency on the criteria a diagnostic laboratory test using NGS must meet for approval, as well as confidence that benefits will likely outweigh harms for patients. Further, it provides assurance to treating physicians and patients that the test is scientifically valid before they rely on the results for selection of cancer treatment. Despite these concerns, many public commenters were generally opposed to the national non-coverage aspect of our proposed decision memorandum. These commenters reported that they are already developing the evidence or have developed the evidence to demonstrate these diagnostic laboratory tests using NGS improve health outcomes for Medicare beneficiaries with cancer. These same commenters stated that laboratories developing diagnostic laboratory tests using NGS for Medicare patients with cancer are equipped to conduct their own studies to generate needed evidence that use of the test improves health outcomes for the Medicare population. In this final decision, Medicare Administrative Contractors will examine this specific information in making coverage determinations for particular diagnostic laboratory tests using NGS that will not already be covered under our national coverage determination.

CMS implemented CED under §1862(a)(1)(E) of the Social Security Act to provide access to Medicare beneficiaries while evidence is continuing to be developed on important health outcomes for Medicare patients. CED supports innovation and provides earlier access for an item or service when it may not be reasonable and necessary under §1862(a)(1)(A) of the Social Security Act while developing evidence to demonstrate improvement in health outcomes.

For this specific coverage determination, commenters noted that CED is not necessary because they are already developing the evidence or have developed the evidence to demonstrate these diagnostic laboratory tests using NGS improve health outcomes. These same commenters stated that CED is not necessary and that the diagnostic laboratory test developers are equipped to conduct their own studies to generate any needed evidence to demonstrate improved health outcomes. After reviewing all the public comments we have removed coverage with evidence development in this final NCD. While we have removed the CED requirement, we note that evidence gaps remain. Stakeholders have recommended randomized controlled trials and evidence development (Prasad, 2018; Eisenberg and Varmus, 2017). As noted in the proposed, we believe there are strong research study designs in the NIH NCTN. We also note the importance of data standards and harmonization and encourage researchers, manufacturers and laboratories to continue to enhance these components. We strongly encourage continuing the studies and publishing the results of these important studies especially on the endpoints of overall survival, progression free survival, objective response, and patient reported outcomes relevant to the quality of life for Medicare beneficiaries. This is not only important to ensuring that patients, caregivers and their providers can make informed evidence-based decisions but it also is important to continue to develop and publish results, which form the basis for the dissemination of new technologies into the healthcare system. This final NCD identifies the national coverage criteria for diagnostic laboratory tests using NGS for patients with cancer and provides predictable national coverage for tests that meet the specified criteria in Section I of this final NCD.

Health Disparities

The background information on the incidence and prevalence of cancer identified areas of health disparities among those with specific cancers between different races/ethnicities. This information may be used to target populations for potential interventions. However, the evidence presented here includes several publications in which the study population was greater than 75% White (Peeters et al. 2013, Plimack et al 2014 and 2015, Ho et al. 2016, Joshi et al. 2016, Haslem et al. 2017), which suggests that those with identified health disparities also comprise a minority of study participants in the area of applying NGS as a diagnostic laboratory test for advanced cancer. To better understand the barriers to accessing genetic testing, Suther and Kiros (2009) assessed the knowledge and concerns of genetic testing, and suggested that additional education and communication is needed among different ethnic and racial groups. Further research to identify the barriers that are unique to accessing and increasing the inclusion of a diverse population of patients in cancer clinical trials is warranted.

IX. Decision

A. Coverage

The Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
 - a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
 - b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
 - c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).
2. The diagnostic laboratory test using NGS must have:

- a. FDA approval or clearance as a companion in vitro diagnostic; and
- b. an FDA approved or cleared indication for use in that patient's cancer; and
- c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

B. Other

Medicare Administrative Contractors (MACs) may determine coverage of other Next Generation Sequencing (NGS) as a diagnostic laboratory test for patients with cancer only when the test is performed in a CLIA-certified laboratory, ordered by a treating physician and the patient has:

- a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
- b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
- c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

See Appendix D for the NCD manual language.

X. Appendices

A. Appendix A—General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique

methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials

- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention’s potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study’s selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention’s benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology’s benefits and risk of harm to Medicare beneficiaries.

B. Appendix B — ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing

Element	Component	Specific Question
<i>Disorder / Setting</i>		What is the specific clinical disorder to be studied?
		What are the clinical findings defining this disorder?

Element	Component	Specific Question
		<p>What is the clinical setting in which the test is to be performed?</p> <p>What DNA test(s) are associated with this disorder?</p> <p>Are preliminary screening questions employed?</p> <p>Is it a stand-alone test or is it one of a series of tests?</p> <p>If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results</p>
<i>Analytic Validity</i>		Is the test qualitative or quantitative?
	Sensitivity	How often is the test positive when a mutation is present?
	Specificity	How often is the test negative when a mutation is not present?
		Is an internal QC program defined and externally monitored?
		Have repeated measurements been made on specimens?
		What is the within- and between-laboratory precision?
		If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?
		What range of patient specimens have been tested?
		<p>How often does the test fail to give a useable result?</p> <p>How similar are results obtained in multiple laboratories using the same, or different technology?</p>
<i>Clinical Validity</i>	Sensitivity	How often is the test positive when the disorder is present?
		How often is the test negative when a disorder is not present?
	Specificity	Are there methods to resolve clinical false positive results in a timely manner?
	Prevalence	What is the prevalence of the disorder in this setting?
		Has the test been adequately validated on all populations to which it may be offered?
		What are the positive and negative predictive values?
		What are the genotype/phenotype relationships?
		What are the genetic, environmental or other modifiers?

Element	Component	Specific Question
<i>Clinical Utility</i>	Intervention	What is the natural history of the disorder?
		What is the impact of a positive (or negative) test on patient care?
		If applicable, are diagnostic tests available?
		Is there an effective remedy, acceptable action, or other measurable benefit?
		Is there general access to that remedy or action?
		Is the test being offered to a socially vulnerable population?
	Quality Assurance	What quality assurance measures are in place?
	Pilot Trials	What are the results of pilot trials?
	Health Risks	What health risks can be identified for follow-up testing and/or intervention?
		What are the financial costs associated with testing?
	Economic	What are the economic benefits associated with actions resulting from testing?
	Facilities	What facilities/personnel are available or easily put in place?
	Education	What educational materials have been developed and validated and which of these are available?
		Are there informed consent requirements?
	Monitoring	What methods exist for long term monitoring?
	What guidelines have been developed for evaluating program performance?	
<i>Ethical, Legal, Social Implications</i>	Impediments	What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues?
		Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?
	Safeguards	What safeguards have been described and are these safeguards in place and effective?

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C. Appendix C— Articles Submitted by the Requestor

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APPENDIX D
Medicare National Coverage Determinations Manual

Draft

This material represents a preliminary draft of Medicare's national coverage determination (NCD). The information is subject to formal revision and formatting changes prior to the release of the final NCD contractor instructions and publication in the Medicare National Coverage Determinations Manual.

Table of Contents
(Rev.)

[XXX.X]

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, *in vitro* companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. . Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory diagnostic test, such as when used as a companion *in vitro* diagnostic test.

Patients with advanced cancer can have recurrent, metastatic, and/or stage IV disease. From results of clinical studies it has been shown that genetic variations in a patient's cancer can, in concert with clinical factors, predict how each individual responds to specific treatments.

In application, a report of results of a diagnostic laboratory test using NGS (i.e., information on the cancer's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad, or none at all. Applications of NGS to predict a patient's response to treatment occurs ideally prior to initiation of the drug.

B. Nationally Covered Indications

Effective for services performed on or after [Month/XX] [Day/XX], [20XX] The Centers for Medicare & Medicaid Services (CMS) has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally, when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
 - a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
 - b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
 - c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:
 - a. FDA approval or clearance as a companion in vitro diagnostic; and
 - b. an FDA approved or cleared indication for use in that patient's cancer; and
 - c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

C. Other

Medicare Administrative Contractors (MACs) may determine coverage of other Next Generation Sequencing (NGS) as a diagnostic laboratory test for patients with cancer only when the test is performed in a CLIA-certified laboratory, ordered by a treating physician and the patient has:

- a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
- b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
- c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

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[Back to Top](#)

[Bibliography](#)

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