ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
9650 Rockville Pike, Suite 205. Bethesda, Maryland 20814
Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

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Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Proposed Decision Memorandum on Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG #00450N)

Dear Ms. Jensen,

The Association for Molecular Pathology (AMP) is pleased to offer comments on the proposed decision memorandum entitled, "Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer." This National Coverage Analysis (NCA) was issued in conjunction with the Food and Drug Administration (FDA)'s approval of the FoundationOne CDx (F1CDx), an NGS-based test as an in vitro diagnostic (IVD). The test was reviewed as part of FDA and the Center for Medicare & Medicaid Services' (CMS) Parallel Review Program, where the FDA approval process and the CMS evaluation for coverage occur concurrently. We thank CMS for granting an extension to the comment period to allow additional time to address this proposed policy.

AMP is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the, academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

AMP has been very supportive of streamlining the approval and coverage processes and applauds CMS for their recognition of the value of precision oncology diagnostics in the care of cancer patients as evidenced by the positive elements of the proposed National Coverage Analysis (NCA). However, the policy as written is deeply flawed. The requirements for coverage are unduly narrow in scope. In many clinical scenarios gene mutation analysis for cancer is standard of care. That is why over a hundred laboratories today offer NGS-based testing that is used in the care of literally thousands of patients every year. The proposed policy would render most of the tests offered by those laboratories as not covered with widespread negative ramifications.

AMP recommends CMS refocus this policy so that is applies <u>ONLY</u> to FDA-approved NGS-based tests (such as the F1CDx assay) and does not apply to any other NGS-based test. Coverage for other clinically- and analytically- validated NGS-based tests should continue to be covered as determined by existing local coverage determinations (LCDs) administered by local Medicare Administrative Contractors (MACs). This approach will be much less disruptive, allowing ongoing coverage evaluation and clinical scientific progress to continue and for coverage policies to respond more quickly to changes in the science.

Today most academic centers, leading cancer institutions, and essential community cancer centers have Clinical Laboratories Improvement Amendment (CLIA) certified laboratories providing validated laboratory developed gene panels using NGS technology. This policy, if finalized would supersede existing local coverage policies for most of those tests and create barriers for Medicare beneficiaries' access to clinically useful testing. The policy imposes two very narrow restrictions that threaten the viability and accessibility of those tests to Medicare beneficiaries. First, it effectively concentrates all NGS-based cancer testing to a limited number of commercial entities. It eliminates coverage or imposes severely restrictive coverage with evidence (CED) requirements for all other laboratory tests utilizing NGS for cancer. These tests are currently recognized as the standard of care in oncology diagnostics and are being used to deliver high-quality, advanced cancer care across the country. These tests meet or exceed CLIA standards, and/or other federal, state, professional practice standards, and provide clinically significant information for patients with advanced cancer. Many have demonstrated to be of highest quality by peer review through the College of American Pathology (CAP) laboratory inspection processes. This policy, by denying coverage to those tests, eliminates coverage for tests at leading academic center and cancer care programs in every jurisdiction, with the end result of a decrease in the quality of care being delivered to the sickest and most vulnerable Medicare patients being treated for cancer.

The policy is also flawed by recognizing coverage only for cancers with an FDA-approved companion diagnostic indication, *i.e.,* lung, melanoma, breast, ovarian and colon cancers. There is clear scientific evidence, some provided below, that the value of NGS-based testing in cancer extends far beyond these first diseases for which coverage is granted. The existence of an FDA-approved companion diagnostic indication should not be an evidentiary standard required for coverage. Rather, the science and data should determine what care patients receive and what tests are reimbursed.

CMS should clarify that local MACs may continue to evaluate NGS-based tests to determine the scope of coverage within their individual jurisdictions for tests other than FDA-approved NGS-based IVDs. AMP offers the following detailed comments with supporting evidence to bolster our recommendation to refocus the scope of the final policy and highlight significant inconsistencies with current coverage and coding structures for molecular pathology procedures utilizing NGS-based platforms. Our aim remains to ensure that high-quality clinically-proven testing continues to be available broadly when appropriate. We welcome the opportunity to discuss the current state of molecular diagnostic testing, including NGS technology, with CMS to inform this and other future coverage policies.

Background on Next Generation Sequencing as a Laboratory Methodology

Molecular diagnostics is a field dominated by NGS-based approaches and laboratories continue to migrate testing protocols to NGS-based platforms. For this reason, NGS has become the most frequently utilized laboratory method for standard-of-care for genomic tumor profiling. While individual gene mutations tests can provide essential information regarding genomic aberrations, NGS technology can provide cost efficient interrogation of a large set of genes simultaneously (Kulkarni, S *et al*). This testing strategy is critical for small specimens such as fine needle aspirates, which is the specimen most often obtained for characterizing lung tumors. Use of the technology can be found at more than 120 CLIA-certified clinical diagnostic laboratories that provide professional services for cancer diagnosis and treatment (Nagarajan, R *et al*).

NGS is not in itself a diagnostic test. Laboratory testing using NGS technology has applications in the management and treatment of patients with a variety of conditions including inherited diseases, infectious diseases, and cancer. While most samples are derived from solid tissue, NGS can be performed on liquid specimens, as well, and the benefits of non-invasive specimen collection will accelerate the development of non-solid tissue NGS applications.

By drafting a coverage policy based on broad applications of a specific methodology or technology platform, NGS in this case, rather than a specific diagnostic test, CMS sets policy incongruous with existing local and national coverage policies. CMS coverage decisions for precision medicine are based on the clinical utility (medical usefulness) of a proven effective biomarker/cancer subtype combination, independent of test methodology and whether a test has undergone FDA review. Some examples of local policies that address diagnostic testing for oncology include National Government Services coverage policy "Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (L36926)" and Palmetto MolDX's "NSCLC, Comprehensive Genomic Profile Testing (L36143)" that covers both NGS-based and non-NGS based technologies that meet the stated criteria.

Specifically, AMP has significant concerns about applying the non-coverage portion of this policy to all NGS-based testing. The language within the non-coverage section of the policy (Section C) is very broad and can be construed to include NGS tests for conditions other than oncology. On page 75 of the NCA, CMS states that "Conditions other than oncology are outside the scope of this decision, therefore, we propose that only indications of cancer, other than those advanced cancers noted explicitly in our decision are non-covered." We wish to point out that any attempt to expand the scope of this policy beyond oncology contradicts the wording in the NCA included above.

The NCA Conflicts with Current CPT Coding Structure for Molecular Pathology Procedures

The approach CMS has taken with this NCA runs counter to how the American Medical Association (AMA) Current Procedural Terminology (CPT) coding for molecular pathology procedures was established and structured. The updated CPT codes for molecular pathology procedures (including genomic sequencing procedures (GSPs)) are method-agnostic; NGS is one of several methods that can be used to simultaneously analyze multiple genetic regions (CPT Professional Spiral 2018). For example, two laboratories may bill under the same genomic sequencing procedure 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. However, under the proposed NCD, the NGS-based assay would be non-covered under this NCD, despite the same CPT code used to bill for both procedures.

Use of NGS as a methodology is not limited to multi-gene panels. Assay of single analytes (*e.g.*, *IDH1*, *IDH2*, *EGFR*, *BRAF*, *KRAS*, or *NRAS*) can be performed utilizing a variety of techniques, including, but not limited to PCR, Sanger Sequencing, and NGS. NGS-based testing is, therefore, also being utilized by laboratories when assessing for single analytes, genomic aberrations in 1-4 genes, and when larger panels are performed. Thus, the proposed NCA is incompatible with current coding structure and will likely create significant uncertainly for local coverage policies and laboratory billing across the country.

Effect on Local Coverage Determinations and the Cancer Team

If finalized, the NCA will disrupt coverage for targeted cancer mutation panels established by existing local coverage policies. The scope of this NCA extends beyond coverage for the F1CDx test, which was the sole NGS-based test to have gone through the dual FDA-CMS review track. There is no precedent or justification for producing an overly broad, universal, and method-specific NCA in response to a voluntary proposal by a single company for a single test. By broadening the scope, CMS imposes restrictive criteria on other tests using a similar, but not identical, methodology that will, if finalized, supersede local coverage policy for NGS-based tests for solid tumor testing. By doing so, the proposed policy will eliminate coverage for other tests in active clinical use that utilize NGS platforms for advanced cancer patients enrolled in Medicare. These tests are currently

recognized as the standard of care and are being used to deliver high-quality, advanced cancer care across the country. While some NGS based testing is restricted to clinical trials, there is extensive utilization of NGS-based testing in the clinical realm as evidenced by laboratories across the spectrum, including community medical centers, academic medical centers, and separate molecular pathology laboratories offering services.

Precision oncology is a medical practice that occurs at the local level, at the patient's bedside, and in interactions between local healthcare professionals including molecular pathologists. The flexibility to triage urgent patient samples, to discuss in depth the findings at local tumor boards with a multidisciplinary team, provide medical education and training, and to participate in quality improvement initiatives specific to institutions will all be lost if testing is effectively centralized to one national laboratory as proposed by this NCA (Harada S, *et al*) (Bryce, AH *et al*) (Knepper, TC *et al*) (Tafe, LJ *et al*) (Erdmann J) (Schwaederle, M *et al*). To date, coverage of this technology has been determined by MACs, which provides opportunity for a coverage policy better suited to local needs and changes in the standard of care.

AMP believes the broadly restrictive nature of the preliminary NCA could potentially stifle innovation, a hallmark and highlight of the American healthcare system. Particularly in these in areas where the science is advancing rapidly, coverage policy must remain nimble to adapt to advances in understanding in the science and application to good patient care.

The difficulty and infrequency of modifications to national coverage determinations raises additional concerns. We are confident the rapidly-changing state of the science in this area will require frequent, multiple revisions of this policy if finalized as proposed. For these reasons, coverage of NGS-based testing is better suited at the local level through the ongoing LCD process.

Coverage Policy Should Align with Existing Clinical Practice Guidelines

As per long-standing policy, CMS should allow the MACs to continue to provide coverage for NGS-based tests that are used in CLIA accredited laboratories with appropriate analytical and clinical validation and that adhere to evidence-based guidelines. Numerous evidence-based guidelines written by professional medical societies have been published recently to ensure the delivery of high quality NGS-based testing services, bioinformatics driven technical and clinical interpretation, and clinical report generation, with additional evidence based guidelines also currently in development (Jennings, L *et al*) (Li, M *et al*) (Roy, S *et al*).

In all of these guidelines, clinical utility of a biomarker test is assessed independently of the test methodology. They address clinically significant information that can guide disease diagnosis, prognosis, monitoring, and/or therapy for patients (Joseph L, Cankovic M, Caughron S, Chandra P *et al*). When guidelines support the utility of a test, CMS should cover the test.

Evidence-based guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), Association of Molecular Pathology (AMP), CAP, and World Health Organization (WHO) support the clinical utility of molecular alterations in various diseases (Appendix A). Such alterations can also be detected by other non-NGS technologies, and as such, coverage policy should not be restricted to a specific method, but to the genetic alteration(s), cancer type, and targeted therapy combination that together defines clinical relevance. Coverage policies for laboratory developed testing procedures (LDPs), including those that utilize NGS technology, must be aligned with these evidence-based best clinical practices and cost-efficient patient care.

It is critical that Medicare cover tests that direct patient care and are deemed clinically relevant and useful by the team of treating physicians. Often, treating clinicians request laboratory testing for an indication not included in the label of the FDA-approved diagnostic and the off-label use of these tests, by definition, is the practice of medicine. Well-established clinical guidelines support the utilization of many NGS-based tests, including F1CDx, to guide patient care. The results from these tests are used in conjunction with other laboratory tests to inform clinical decisions, such as diagnosis, prognosis, disease monitoring, and often targeted therapy. AMP has included references for 42 articles that confirm the utility of these tests in clinical cancer care in Appendix B.

CMS coverage policy for Medicare beneficiaries should not exclude entire *categories* of testing, *i.e.*, those that use NGS technology, when such testing is performed in CLIA-certified laboratories and adheres to evidence-based guidelines developed by leading scientists and subject matter experts and endorsed by medicine's preeminent professional societies, including AMP, CAP, ASCO, ASH, WHO, and NCCN.

Coverage Policy Should Not Distinguish Regulatory Review Pathways

The NCA presents differing proposals for coverage based on whether a test has been FDA-approved or cleared. While FDA reviews a PMA application as a novel device, as part of a 510(k) submission, the test developer must demonstrate that the test is comparable to an already cleared predicate test, which has been demonstrated to be safe and effective. Thus, both FDA-approved and -cleared tests have successfully demonstrated that they are safe and effective as the term is applied by FDA. It is unclear why CMS has decided to withhold coverage for FDA-cleared tests unless additional evidence development requirements are met.

Worse, the preliminary NCA also disregards another responsibility of CMS: overseeing laboratories and LDPs. Clear legal guidelines for CMS' oversight of LDPs exist currently and allow laboratories to pursue both FDA and non-FDA test development pathways. Inexplicably, CMS is proposing an overly broad, method-specific, universal non-coverage policy in this NCA based on an assessment from a different government agency, FDA, which violates statute preventing the regulation of medical practice, including laboratory physicians. Such a decision would represent a grave inconsistency that serve to harm providers and patients alike.

Every laboratory performing clinical testing is CLIA-certified by federal mandate. These requirements continuously assure laboratory performance standards and the tests' accuracy and reliability over the entire lifetime of a test. As part of this certification, CLIA requires laboratory inspections, and additionally, those performing high-complexity tests must, under CLIA, undergo regular proficiency testing. Many laboratories obtain CLIA certification through accreditation by CMS-approved accrediting agencies, such as CAP or the Joint Committee on Hospital Accreditation. The standards of these accreditation programs must meet or exceed those of the CLIA regulations. The programs often go well beyond CLIA including more stringent requirements for proficiency testing, as well as documentation of clinical validity.

In summary, the NCA fails to acknowledge that there are other proven, time-tested federal government oversight entities responsible for verifying the accuracy and reliability of LDPs. Requiring FDA approval or clearance as a condition for coverage is inconsistent with the FDA's position on enforcement discretion for LDPs including its 2016 announcement that it does not intend to finalize the draft guidance establishing a framework to regulate them. In fact, FDA officials have stated on numerous occasions that it would like Congress to legislate how the LDP pathway would be modernized. AMP supports modernizing the oversight framework for high complexity clinical laboratory developed testing services and procedures primarily through reform of the Clinical Laboratory Improvement Amendments (CLIA).

There are serious repercussions associated with exclusively accepting FDA as the only entity that can verify analytical and clinical validity. FDA review mandates that once a test is approved or cleared, no modifications can be made without submitting an application for additional review. This freezes a test in time and does not allow laboratories to modify their tests in light of new scientific understanding. The need to update a test is exceedingly common, as new information is constantly being identified which impacts the scope and technical specifications of individual testing. A recent comparison of LDPs and FDA approved assays for *BRAF, EGFR, KRAS* tests found 6,897 blinded proficiency testing responses that LDPs and FDA-approved companion diagnostics both performed well, with both test types exceeding 97% accuracy for all three cancer mutations (Kim, A *et al*). This study also found that more than 60% of participants using an FDA-approved companion diagnostic reportedly modified the assay to allow for a greater breadth of sample types, minimum tumor content, and instrumentation (Kim, A *et al*). This comprehensive study confirms that often times, the most current test offered is not the FDA-approved or -cleared test. As a result, this NCA may be promoting coverage of a test that does not fully meet patient care needs. An unintended consequence of this proposal would be to incentivize laboratories to shift away from NGS-based testing, despite its wide deployment nation-wide, and move backwards to single gene testing, which is not in the best interest of patients.

CED Requirements Present an Insurmountable Barrier

The coverage with evidence development (CED) requirements is not a reasonable pathway to coverage.

While the proposed NCD appears to allow for CED of certain LDPs using NGS technology that are provided to patients as diagnostic tests within the NIH-NCI National Clinical Trial Network clinical trials and that are registered in the NIH Genetic Testing Registry, this provision is unnecessarily restrictive. For example, laboratories cannot enroll patients in a prospective registry that tracks overall survival and patient reported outcomes. It is the treating oncologist, not the laboratory professional, who engages with the patient over the full course of their disease and recovery. Often when a sample is submitted to a laboratory, information regarding the registry status of the patient likely would not even be included. In addition, requiring that patients be enrolled in an NIH-NCI National Clinical Trial Network clinical trial would exclude patients who are enrolled in other relevant clinical trials or are obtaining testing in a clinical setting and not as part of a trial.

Thank you again for the opportunity to review and comment on this proposed policy. AMP urges you not to finalize this policy as proposed and instead, refocus this policy so that is applies ONLY to FDA-approved NGS-based tests, including the F1CDx assay, and not to any other NGS-based test, thereby preserving coverage for the NGS-based tests currently utilized by local laboratories and covered under local coverage policies. We welcome the opportunity to work with you to ensure CMS coverage policy supports this evolving field of medicine. Please direct your correspondence to Tara Burke, AMP Director of Public Policy and Advocacy, at tburke@amp.org.

Sincerely,

Kojo S.J. Elenitoba-Johnson, MD
President, Association for Molecular Pathology

References:

Jennings, L et al. Guidelines for Validation of Next-Generation Sequencing–Based Oncology Panels. May 2017.

CPT Professional Spiral 2018. American Medical Association. 2017

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

Bryce AH, Egan JB, Borad MJ, et al. Experience with precision genomics and tumor board, indicates frequent target identification, but barriers to delivery. *Oncotarget*. 2017 Apr 18.

Knepper TC, Bell GC, Hicks JK, et al. Key Lessons Learned from Moffitt's Molecular Tumor Board: The Clinical Genomics Action Committee Experience. *Oncologist*. 2017 Feb.

Tafe LJ, Gorlov IP, de Abreu FB, et al. Implementation of a Molecular Tumor Board: The Impact on Treatment Decisions for 35 Patients Evaluated at Dartmouth-Hitchcock Medical Center. *Oncologist*. 2015 Sep.

Erdmann J. All aboard: Will molecular tumor boards help cancer patients? *Nat Med*. 2015 Jul.

Schwaederle M, Parker BA, Schwab RB, et al. Molecular tumor board: the University of California-San Diego Moores Cancer Center experience. *Oncologist*. June 2014.

Kaul, K et al. The Case for Laboratory Developed Procedures. *Academic Pathology.* July 2017.

Kim, A et al. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for *BRAF, EGFR,* and *KRAS* Testing. *JAMA Oncol.* December 14 2017.

Kulkarni, S et al. Clinical Genomics 1st Edition. October 1 2014.

Li, M et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer. *J Mol Diagn.* January 2017.

Nagarajan, R et al. A Window into Clinical Next-Generation Sequencing–Based Oncology Testing Practices. *Arch Pathol Lab Med*. December 2017.

Roy, S et al. Standards and Guidelines for Validating Next-Generation Sequencing Bioinformatics Pipelines. *J Mol Diagn.* January 2018.

Joseph L, Cankovic M, Caughron S, Chandra P et al. The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer. A Report of the Association for Molecular Pathology. *J Mol Diagn.* September 2016.

Appendix A

Clinical Practice Guidelines

NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2017. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2018. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

NCCN Clinical Practice Guidelines in Oncology. Myelodysplastic syndromes. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf

NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative Neoplasms. Version 2.2018. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf

NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.217. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

Arber Daniel A., Borowitz Michael J., Cessna Melissa et al. Initial Diagnostic Workup of Acute Leukemia: Guideline from the College of American Pathologists and the American Society of Hematology. Archives of Pathology & Laboratory Medicine. 2017 October.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. 2017.

Sepulveda AR, Hamilton SR, Allegra CJ et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline from the American Society for Clinical Pathology. J Clin Oncol. 2017 May 1.

Appendix B

Evidence to support the utility of NGS in clinical cancer care:

Pai SG, Carneiro BA, Chae YK, Costa RL, Kalyan A, Shah HA, Helenowski I, Rademaker AW, Mahalingam D, Giles FJ. Correlation of tumor mutational burden and treatment outcomes in patients with colorectal cancer. *J Gastrointest Oncol.* 2017 Oct

Pezo RC, Chen TW, Berman HK, Mulligan AM, Razak AA, Siu LL, Cescon DW, Amir E, Elser C, Warr DG, Sridhar SS, Yu C, Wang L, Stockley TL, Kamel-Reid S, Bedard PL. Impact of multi-gene mutational profiling on clinical trial outcomes in metastatic breast cancer. *Breast Cancer Res Treat.* 2017 Nov 24.

Furtado LV, Samowitz WS. Colorectal cancer molecular profiling: from IHC to NGS in search of optimal algorithm. *Virchows Arch.* 2017 May 27

Griewank KG, Schilling B. Next-Generation Sequencing to Guide Treatment of Advanced Melanoma. Am *J Clin Dermatol.* 2017 Jun.

Hamblin A, Wordsworth S, Fermont JM et al. Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. *PLoS Med.* 2017 Feb 14.

Kyrochristos ID, Glantzounis GK, Ziogas DE, Gizas I, Schizas D, Lykoudis EG, Felekouras E, Machairas A, Katsios C, Liakakos T, Cho WC, Roukos DH. From Clinical Standards to Translating Next-Generation Sequencing Research into Patient Care Improvement for Hepatobiliary and Pancreatic Cancers. *Int J Mol Sci.* 2017 Jan 18.

Hynes SO, Pang B, James JA, Maxwell P, Salto-Tellez M. Tissue-based next generation sequencing: application in a universal healthcare system. *Br J Cancer.* 2017 Feb 28.

Surrey LF, Luo M, Chang F, Li MM. The Genomic Era of Clinical Oncology: Integrated Genomic Analysis for Precision Cancer Care. *Cytogenet Genome Res.* 2016.

Rozenblum AB, Ilouze M, Dudnik E, Dvir A, Soussan-Gutman L, Geva S, Peled N. Clinical Impact of Hybrid Capture-Based Next-Generation Sequencing on Changes in Treatment Decisions in Lung Cancer. J Thorac Oncol. 2017 Feb.

Blumenthal DT, Dvir A, Lossos A, Tzuk-Shina T, Lior T, Limon D, Yust-Katz S, Lokiec A, Ram Z, Ross JS, Ali SM, Yair R, Soussan-Gutman L, Bokstein F. Clinical utility and treatment outcome of comprehensive genomic profiling in high grade glioma patients. *J Neurooncol.* 2016 Oct.

Fox AJ, Hiemenz MC, Lieberman DB, Sukhadia S, Li B, Grubb J, Candrea P, Ganapathy K, Zhao J, Roth D, Alley E, Loren A, Morrissette JJ. Next Generation Sequencing for the Detection of Actionable Mutations in Solid and Liquid Tumors. *J Vis Exp.* 2016 Sep 20.

Deans ZC, Costa JL, Cree I, Dequeker E et al. Integration of next-generation sequencing in clinical diagnostic molecular pathology laboratories for analysis of solid tumours; an expert opinion on behalf of IQN Path ASBL. IQN Path ASBL. *Virchows Arch*. 2017 Jan.

Grenader T, Tauber R, Shavit L. Next-generation sequencing in patients with advanced cancer: are we ready for widespread clinical use? A single institute's experience. *Anticancer Drugs.* 2016 Oct.

Søreide K, Watson MM, Lea D, Nordgård O, Søreide JA, Hagland HR. Assessment of clinically related outcomes and biomarker analysis for translational integration in colorectal cancer (ACROBATICC): study protocol for a population-based, consecutive cohort of surgically treated colorectal cancers and resected colorectal liver metastasis. *J Transl Med.* 2016 Jun 29.

Joseph L. The clinical utility of molecular genetic cancer profiling. *Expert Rev Mol Diagn*. 2016 Aug.

Szalat R, Munshi NC. Next-Generation Sequencing Informing Therapeutic Decisions and Personalized Approaches. Am Soc Clin Oncol Educ Book. 2016.

Kotelnikova EA, Pyatnitskiy M, Paleeva A, Kremenetskaya O, Vinogradov D. Practical aspects of NGS-based pathways analysis for personalized cancer science and medicine. *Oncotarget.* 2016 Aug 9.

Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. *Cancer Biol Med.* 2016 Mar.

Mantripragada KC, Olszewski AJ, Schumacher A, Perez K, Birnbaum A, Reagan JL, Mega A, Khurshid H, Bartley C, Lombardo A, Rossiter R, Papa A, Bakalarski P, Safran H. Clinical Trial Accrual Targeting Genomic Alterations After Next-Generation Sequencing at a Non-National Cancer Institute-Designated Cancer Program. *J Oncol Pract.* 2016 Apr.

Schwaederle M, Parker BA, Schwab RB, Daniels GA, Piccioni DE, Kesari S, Helsten TL, Bazhenova LA, Romero J, Fanta PT, Lippman SM, Kurzrock R. Precision Oncology: The UC San Diego Moores Cancer Center PREDICT Experience. *Mol Cancer Ther.* 2016 Apr.

de Abreu FB, Peterson JD, Amos CI, Wells WA, Tsongalis GJ. Effective quality management practices in routine clinical next-generation sequencing. *Clin Chem Lab Med.* 2016 May.

Chau NG, Li YY, Jo VY, Rabinowits G et al. Incorporation of Next-Generation Sequencing into Routine Clinical Care to Direct Treatment of Head and Neck Squamous Cell Carcinoma. *Clin Cancer Res.* 2016 Jun 15

Kurzrock R, Colevas AD, Olszanski A et al. NCCN Oncology Research Program's Investigator Steering Committee and NCCN Best Practices Committee Molecular Profiling Surveys. *J Natl Compr Canc Netw.* 2015 Nov.

Pongor L, Kormos M, Hatzis C, Pusztai L, Szabó A, Győrffy B. A genome-wide approach to link genotype to clinical outcome by utilizing next generation sequencing and gene chip data of 6,697 breast cancer patients. *Genome Med.* 2015 Oct 16.

Siu LL, Conley BA, Boerner S, LoRusso PM. Next-Generation Sequencing to Guide Clinical Trials. Clin *Cancer Res.* 2015 Oct 15.

Paweletz CP, Sacher AG, Raymond CK, Alden RS, O'Connell A, Mach SL, Kuang Y, Gandhi L, Kirschmeier P, English JM, Lim LP, Jänne PA, Oxnard GR. Bias-Corrected Targeted Next-Generation Sequencing for Rapid, Multiplexed Detection of Actionable Alterations in Cell-Free DNA from Advanced Lung Cancer Patients. *Clin Cancer Res.* 2016 Feb 15.

LeBlanc VG, Marra MA. Next-Generation Sequencing Approaches in Cancer: Where Have They Brought Us and Where Will They Take Us? *Cancers (Basel).* 2015 Sep 23.

Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, Gooding WE, LeBeau SO, Ohori NP, Seethala RR, Tublin ME, Yip L, Nikiforova MN. Impact of the Multi-Gene ThyroSeq Next-Generation Sequencing Assay on

Cancer Diagnosis in Thyroid Nodules with Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance Cytology. *Thyroid.* 2015 Nov.

Le Tourneau C, Delord JP, Gonçalves A 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 Oct.

Gagan J, Van Allen EM. Next-generation sequencing to guide cancer therapy. *Genome Med.* 2015 Jul 29.

Damodaran S, Berger MF, Roychowdhury S. Clinical tumor sequencing: opportunities and challenges for precision cancer medicine. *Am Soc Clin Oncol Educ Book.* 2015.

Gallego CJ, Shirts BH, Bennette CS, Guzauskas G, Amendola LM, Horike-Pyne M, Hisama FM, Pritchard CC, Grady WM, Burke W, Jarvik GP, Veenstra DL. Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis. *J Clin Oncol.* 2015 Jun 20.

Cheng DT, Mitchell TN, Zehir A et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. *J Mol Diagn.* 2015 May.

Hagemann IS, Devarakonda S, Lockwood CM et al. Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer.* 2015 Feb 15.

Saba NF, Wilson M, Doho G, DaSilva J, Benjamin Isett R, Newman S, Chen ZG, Magliocca K, Rossi MR. Mutation and Transcriptional Profiling of Formalin-Fixed Paraffin Embedded Specimens as Companion Methods to Immunohistochemistry for Determining Therapeutic Targets in Oropharyngeal Squamous Cell Carcinoma (OPSCC): A Pilot of Proof of Principle. *Head Neck Pathol.* 2015 Jun.

Sehn JK, Hagemann IS, Pfeifer JD, Cottrell CE, Lockwood CM. Diagnostic utility of targeted next-generation sequencing in problematic cases. Am J Surg Pathol. 2014 Apr.

Chang F, Li MM. Clinical application of amplicon-based next-generation sequencing in cancer. *Cancer Genet.* 2013 Dec.

Bombard Y, Bach PB, Offit K. Translating genomics in cancer care. *J Natl Compr Canc Netw.* 2013 Nov.

Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. *JAMA Intern Med.* 2014 Feb 1.

Cottrell CE, Al-Kateb H, Bredemeyer AJ et al. Validation of a next-generation sequencing assay for clinical molecular oncology. *J Mol Diagn.* 2014 Jan.

Mauer CB, Pirzadeh-Miller SM, Robinson LD, Euhus DM. The integration of next-generation sequencing panels in the clinical cancer genetics practice: an institutional experience. *Genet Med.* 2014 May.

McCourt CM, McArt DG, Mills K, Catherwood MA, Maxwell P, Waugh DJ, Hamilton P, O'Sullivan JM, Salto-Tellez M. Validation of next generation sequencing technologies in comparison to current diagnostic gold standards for BRAF, EGFR and KRAS mutational analysis. *PLoS One.* 2013 Jul 26.