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Re: Genetic Testing for Oncology – DL39367 (First Coast) and DL39365 (Novitas)

Dear Medical Directors:

On behalf of the Association for Molecular Pathology (AMP), thank you for the opportunity to review and comment on First Coast and Novitas' proposed coverage policy for Genetic Testing for Oncology (DL39367 and DL39365).

AMP is an international medical and professional association representing approximately 2,600 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

We appreciate that First Coast and Novitas are aiming to develop coverage policies for genetic testing for cancer that are able to evolve along with the science. However, we have significant concerns about the way this policy is currently drafted that will unintentionally lead to coverage gaps and prevent the policy from being forward-thinking. We have outlined our concerns below, which include specific procedural concerns at the end of the letter. AMP welcomes the opportunity to work as a partner to ensure that this policy does not impede patient access to care and contribute to overly burdensome requirements for providers.

General Concerns

AMP appreciates First Coast and Novitas' interest in developing a comprehensive coverage policy for genetic testing for oncology, which is a significant clinical area for genetic testing. However, we are concerned that the policy as written could be preemptively limiting, and impact coverage of certain tests already covered.

It is our understanding that this draft policy will replace the longstanding policy, entitled "Biomarkers in Oncology" (L35396). We are concerned that this replacement will result in gaps in coverage, and commonly used and currently covered biomarkers and tests will lose coverage under this policy shift. The draft policy as written does not address any tests that are protein-based and retiring this policy will result in a gap in coverage for these tests. It is unclear why tests for protein-based biomarkers will be non-covered going forward, as the draft policy does not include a review of specific evidence that led to the non-covered decision as required by the 21st Century Cures Act ("the Act").

Further, this draft policy conflates somatic and germline testing, referring to everything as "molecular testing." **AMP strongly recommends that First Coast and Novitas clearly delineate the requirements for each type of testing.** As an example of delineating these two types of testing, we encourage the Medicare Administrative Contractors (MACs) to consider how the Next Generation Sequencing National Coverage Determination 90.2 (NGS NCD) is formatted and categorized, which has clear recommendations that distinguish between somatic and germline, and we encourage the recommendations in this draft policy to be organized by somatic and germline testing in a similar manner.

Covered Indications

The draft policy identifies coverage indications for when genetic testing for oncology will be considered medically reasonable and necessary.

Comment #1

The draft policy limits coverage to tests that meet the criteria established by at least one of the following three evidence-based databases and/or knowledge bases: National Comprehensive Cancer Network (NCCN), National Institute of Health funded Clinical Genome Resource (ClinGen), and Memorial Sloan Kettering Cancer Center Oncology Knowledge Base (OncoKB). These three knowledge bases have been identified as valid and reliable sources, yet none are designed to assess clinical utility and analytical validity. Further, none of these databases are designed to be test technology validators. **AMP requests justification as to why these three databases were chosen.**

Moreover, AMP is concerned that these three databases do not meet the evidentiary requirements established in the Program Integrity Manual (PIM) for LCDs. Specifically, PIM §13.5.3 outlines the required evidentiary content stating:

In every proposed and final LCD, the MAC must summarize the evidence that supports coverage, limited coverage, maintenance of existing coverage in cases of LCD reconsideration or noncoverage. At a minimum, the summary should include the following:

- *a complete description of the item or service under review;*
- *a narrative that describes the scientific evidence supporting the clinical indications for the item or service;*
- *the target Medicare population; and*
- *whether the item or service is intended for use by health care providers or beneficiaries.*

While the draft LCD includes a summary and analysis of evidence, it does not meet the specific standards outlined in the PIM as the narrative regarding the three databases does not address all of the required elements.

PIM §13.5.3: goes on to state:

In conducting a review, MACs shall use the available evidence of general acceptance by the medical community, such as published original research in peer-reviewed medical journals, systematic reviews and meta-analyses, evidence-based consensus statements and clinical guidelines.[1]

It is important to note that data often takes a long time to be included in databases like these. AMP believes it is reasonable for the inclusion of a biomarker in one of these databases to be used as inclusion criteria for coverage. However, it is not reasonable to use lack of inclusion in a database as exclusion criteria for coverage due to the lag in updating evidence. **Therefore, we ask that First Coast and Novitas recognize alternative**

evidence-based guidelines, such as professional society guidelines, as acceptable sources for coverage inclusion.

Comment #2
Coverage indication #1 states:

> *The provider has either established a diagnosis of cancer or found significant evidence to create suspicion for cancer in their patient via a clinical evaluation and abnormal results (cancer or suspicious for cancer) from histologic and/or cytologic examination. If then, as a next step in the clinical management of the patient, genetic testing would directly impact the management of the patient's condition, the testing would be indicated.*

AMP believes this coverage indication is too narrow and restrictive. Specifically, the language, "clinical evaluation and abnormal results (cancer or suspicion for cancer) from histologic and/or cytologic examination" is too restrictive and would exclude many patients from getting tests that are currently established as required tests for the diagnostic evaluation of cancer or suspected cancer. While the policy specifies that a histologic and/or cytologic examination is required to establish the diagnosis of cancer or suspicion for cancer, other diagnostic testing methods, such as flow cytometry,[2,3] cytogenetics, including karyotyping and fluorescence in situ hybridization,[4] and antigen receptor gene rearrangement assays for B- and T-lymphoid cells[5,6] are well-established as routinely used tests for the diagnostic evaluation of hematologic and lymphoid malignancies in addition to radiological imaging, which is commonly used to establish the diagnosis of cancer. Some lesions are not amenable to direct histologic and/or cytologic examination because of their location. Additionally, the organ-specific RADS system is an additional method for addressing criteria for establishing reasonable suspicion for cancer.[7,8]

Furthermore, this language seems to imply that a tissue biopsy is required in order for a molecular test to be indicated. This is not ideal because some patients may present with extensive cancer and be too sick for an invasive procedure required for a tissue biopsy, and must be treated based on a clinical diagnosis alone in conjunction with blood-based tests. Other patients may present with cancer in anatomic sites that are not easily accessible for a biopsy. Such patients may be diagnosed with cancer by only a blood-based assay, such as flow cytometry to detect cancer cells in hematologic malignancies. Requiring a tissue biopsy may also limit access, especially for patients who live in rural settings where access to an image guided biopsy is limited.

Finally, in certain circumstances cell-free, circulating tumor deoxyribonucleic acid (ctDNA) testing from a liquid biopsy[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23] may be a reasonable and non-invasive modality to identify actionable biomarkers for patients who are unable to undergo a repeat tissue biopsy. Currently, studies are being performed to evaluate ctDNA testing in the management of patients with hematologic and non-hematologic cancers, including for minimal residual disease (MRD) testing by ctDNA analysis in hematologic and lymphoid malignancies. As this policy is designed to be forward-facing, it is important to recognize that additional diagnostic modalities may become available in the future that do not require histologic and/or cytologic examination.

Therefore, AMP recommends the following change to reflect current standard of clinical care and increase the durability of the draft LCD:

> *The provider has either established a diagnosis of cancer or found significant evidence to create suspicion for cancer in their patient via a clinical evaluation and abnormal results (cancer or suspicious for cancer) ~~from histologic and/or cytologic examination~~. If then, as a next step in the clinical management of the*

patient, genetic testing would directly impact the management of the patient's condition, the testing would be indicated.

Coverage Limitations

Outlined below are the coverage limitations in the draft policy:

The following are considered not medically reasonable and necessary:

1. *A genetic test where either analytical validity, clinical validity, or clinical utility has not been established.*
2. *Interventions with levels of evidence not identified by either ClinGen, NCCN, or OncoKB as demonstrating actionability in clinical decision making as noted in Covered Indications.*
3. *Genetic testing in patients who do not have either an established diagnosis of cancer or substantiated suspicion of cancer as determined by a clinical evaluation and abnormal results (cancer or suspicious for cancer) from histologic and/or cytologic examination.*
4. *Genetic testing of asymptomatic patients for the purposes of screening the patient or their relatives.*
5. *Repetitions of the same genetic test on the same genetic material.*

Comment #1

AMP requests that coverage limitation #1 be removed. Specifically, we are concerned about how analytical validity is expected to be assessed for laboratory developed tests and the potential to unintentionally restrict coverage due to lack of clarity in the requirements. Regulatory requirements stipulated in the Clinical Laboratory Improvement Amendments (CLIA) already provide strict validation requirements that must be followed before an assay can be offered to patients. CLIA also requires quality assurance and proficiency testing by federally approved programs for these assays. These tests meet or exceed CLIA standards, and/or other federal, state (e.g., NYSDOH clinical laboratory evaluation program), and professional practice standards, as well as provide clinically significant information to patients. Many have been demonstrated to be of highest quality by peer review through the CAP laboratory inspection and proficiency testing processes.

Additionally, AMP has concerns around perceived clinical utility of panels that include multiple biomarkers. While a portion of the biomarker content may have shown utility in specific cancer types under the three databases mentioned in this policy, panel content may include genes that are relevant in other tumor types. Limiting clinical utility to biomarkers included in the database, but not exceeding in content, would lead to reduced coverage for innovative assays that are becoming standard of care in guiding cancer treatment selection.

Comment #2

As explained in detail in the Covered Indications comments, AMP has concerns regarding the requirement that only histologic and/or cytologic examination be used to establish diagnosis of cancer or substantiated suspicion of cancer. AMP recommends that "*from histologic and/or cytologic examination*" be struck from coverage limitation #3:

3. *Genetic testing in patients who do not have either an established diagnosis of cancer or substantiated suspicion of cancer as determined by a clinical evaluation and abnormal results (cancer or suspicious for cancer)* ~~*from histologic and/or cytologic examination*~~*.*

Comment #3
Regarding coverage limitation #4, asymptomatic testing may be necessary for some patients in need of genetic testing to determine whether they need enhanced surveillance and reproductive counseling. Further, this is necessary if the patient is considered high risk given family history, symptoms, age, etc.

Comment #4
Coverage limitation #5 states that repetition of the same genetic test on the same genetic material is not medically reasonable and necessary. AMP believes this will negatively impact patients as there are clinical indications for repeat genetic testing at several stages during the monitoring of a patient who is being treated for cancer. For example, minimal residual disease (MRD) testing involves repetition of the same genetic test on the same genetic material. MRD testing has two very important uses—to diagnose cancer recurrence before clinical or radiological evidence, and to monitor response to therapy. Monitoring response to therapy automatically involves testing more than once during the lifetime of a patient as it is repeated over the duration of the treatment. It is important to note that an initial diagnostic test may or may not be the same assay that is utilized to follow a patient over time, depending on the design of the test panel. If you are using the same NGS-based test for diagnosis and monitoring, there will be more than one of these tests performed during the patient's lifetime. MRD testing is being adopted more broadly and the importance of MRD testing in a number of Hematopoietic Malignancies is specifically mentioned in the NCCN guidelines. As the NCCN recommendation conflicts with the coverage limitation, it is unclear how this type of testing would be covered under the draft policy. **As the coverage limitation goes against current medical practice, AMP recommends removing coverage limitation #5.**

Comment #5
The coverage limitations also state the following:

> *Genetic tests for hereditary cancer syndromes, which are considered germline testing, may only be performed once per beneficiary's lifecycle.*

AMP believes that the decision to retest a patient should be undertaken by treating providers who can best assess the incremental benefit of repeat testing for additional mutations. For example, Mosaic hereditary cancer syndromes are more common than previously thought and these situations can require several tests to establish the diagnosis and can have the same implications for the patient and their family as non-mosaic hereditary cancer syndromes (e.g. enhanced screening, germline testing for family members).[24]

Additionally, patients should be able to benefit from advances in technology, improved tests, and the vastly expanded list of known variants and their implications for a patient's health. For example, BRCA testing is much better now than it was in the year 2000 and this may warrant repeat testing for some patients. As such, AMP is concerned that this policy may be preemptively limiting as the field of molecular pathology and scientific knowledge are rapidly evolving over time, with increasing clinical applicability for improvements in patient care.

Restricting testing to "once per lifetime" will prevent providers and patients from having access to future, state of the art testing, which may improve quality and cost effectiveness of care. **Therefore, AMP recommends removing coverage limitation #4 to allow for repeat testing as science advances and additional tests become available that help contribute to the management of patient care.**

<u>Provider Qualifications</u>
The draft policy includes the following qualifications for providers:

The ordering provider of a genetic test for a patient with an established diagnosis of cancer or substantiated suspicion of cancer:

- *Must be the treating clinician who is responsible for the management of the patient's cancer; and,*
- *Understands how the test result will impact the patient's condition; and,*
- *Has presented this information to the patient eliciting patient understanding.*

These qualifications do not reflect current clinical practice and the recommended procedures for ordering molecular tests for cancer. In many instances, the ordering provider at an institution is the treating physician for that point in their care such as the surgeon or interventional radiologist (IR) who obtained the tissue sample for testing as a part of standard of care, but may not be the oncologist who will treat the patient following testing. Working as a comprehensive cancer care team, this person indicates that the tissue should undergo appropriate genetic testing as laid out in a predefined pathway once an appropriate diagnosis is established. A number of AMP members report that they utilize a standardized reflex pathway to ensure that appropriate molecular testing is initiated as soon as a corresponding pathology diagnosis is rendered. Many times, the treating oncologist may not be assigned to the patient at this point in time; therefore, it would be impossible for the ordering provider to be the treating clinician in this circumstance and would result in costly delays for patients if they must wait to see an oncologist prior to ordering standard testing. AMP believes that multi-disciplinary teams are the gold-standard in oncology care, thus coverage policies should align with the workflows that support this model.[25]

In addition, it is very difficult, if not impossible, for the laboratory to know if the information has been presented to the patient and that they gave their understanding. Additionally, it is important to note that pathologists do not have conversations with patients, and often do not have access to patients' medical records and samples are often deidentified. For these reasons, this requirement would be impossible for most laboratories to implement, particularly for small laboratories.

AMP believes these requirements, if finalized, will greatly impact workflow, and we strongly recommend that they be removed from this draft policy.

Procedural Concerns

Besides our concerns regarding the coverage criteria outlined above, AMP has overarching procedural concerns regarding the summary of evidence that was considered by the contractor during the development of the coverage determination and the list of the sources of such evidence. Additionally, we are concerned that basing coverage and non-coverage determinations by third-party databases is inconsistent with the PIM §13.2.3 and §13.5.3 discussed above and may also be inconsistent with the evidentiary standard articulated in the Act. Therefore, **in light of the concerns raised in this letter and our larger procedural concerns, AMP requests that you do not finalize this policy and reconsider the full range of evidence that meets the requirements of both the Act and the PIM.**

Billing and Coding

In accordance with the recommendations above and to ensure that appropriate coverage is maintained for tests included in the Biomarkers for Oncology LCD, AMP requests that the following CPT codes and ICD-10 diagnosis codes be added to the draft policy. Please note that these lists are not intended to be comprehensive.

CPT Codes

We recommend the inclusion of additional CPT codes, including, but not limited to, those listed below:

CPT Code	Long Code Descriptor
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/ retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/ retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed, paraffin-embedded tissue, algorithm reported as a recurrence score
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed, paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype
0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis

ICD-10 Codes
Due to the expansive nature of the policy as written, an exhaustive list of ICD-10 codes is required for appropriate coverage and access. Please find in the attached **Appendix** a non-comprehensive list of ICD-10 codes that we request be added to the local coverage articles DA59123 and DA59125.

Thank you again for the opportunity to review and comment on this proposed policy. We invite the opportunity to have a conversation regarding our procedural concerns about this draft policy and to determine how this draft policy can be changed to reflect the current standard of care, be more forward facing, and ensure that it will keep up with technology developments. We again urge you to not finalize this policy and instead gather sufficient stakeholder feedback before proceeding. Should you have additional questions or require our expertise, please direct your correspondence to Sarah Thibault-Sennett, AMP's Director, Public Policy & Advocacy at sthibaultsennett@amp.org.

Sincerely,

Samuel K. Caughron, MD
Chair, Economic Affairs Committee
Association for Molecular Pathology

[1] https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/pim83c13.pdf

[2] Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. Blood. 2008 Apr 15;111(8):3941-67. doi: 10.1182/blood-2007-11-120535. Epub 2008 Jan 15. PMID: 18198345

[3] McKinnon KM. Flow Cytometry: An Overview. Curr Protoc Immunol. 2018 Feb 21;120:5.1.1-5.1.11. doi: 10.1002/cpim.40. PMID: 29512141

[4] Cancer Cytogenetics: Chromosomal and Molecular Genetic Aberrations of Tumor Cells. 4th edition. Eds. Heim S. and Mitelman F. Wiley-Blackwell; 2015.

[5] Langerak AW, Groenen PJ, Brüggemann M, Beldjord K, Bellan C, Bonello L, Boone E, Carter GI, Catherwood M, Davi F, Delfau-Larue MH, Diss T, Evans PA, Gameiro P, Garcia Sanz R, Gonzalez D, Grand D, Håkansson A, Hummel M, Liu H, Lombardia L, Macintyre EA, Milner BJ, Montes-Moreno S, Schuuring E, Spaargaren M, Hodges E, van Dongen JJ. EuroClonality/BIOMED-2 guidelines for interpretation and reporting of Ig/TCR clonality testing in suspected lymphoproliferations. Leukemia. 2012 Oct;26(10):2159-71. doi: 10.1038/leu.2012.246. Epub 2012 Aug 24. PMID: 22918122

[6] van den Brand M, Rijntjes J, Möbs M, Steinhilber J, van der Klift MY, Heezen KC, Kroeze LI, Reigl T, Porc J, Darzentas N, Luijks JACW, Scheijen B, Davi F, ElDaly H, Liu H, Anagnostopoulos I, Hummel M, Fend F, Langerak AW, Groenen PJTA; EuroClonality-NGS Working Group. Next-Generation Sequencing-Based Clonality Assessment of Ig Gene Rearrangements: A Multicenter Validation Study by EuroClonality-NGS. J Mol Diagn. 2021 Sep;23(9):1105-1115. doi: 10.1016/j.jmoldx.2021.06.005. Epub 2021 Jun 26. PMID: 34186174

[7] https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf

[8] https://www.acr.org/-/media/ACR/Files/RADS/TI-RADS/TI-RADS-chart.pdf?la=en

[9] Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, Dimopoulos M, Kulakova M, Lam A, Hashim M, He J, Heeg B, Ukropec J, Vermeulen J, Cote S, Bahlis N. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020 Dec 8;4(23):5988-5999. doi: 10.1182/bloodadvances.2020002827. PMID: 33284948

[10] Deshpande S, Tytarenko RG, Wang Y, Boyle EM, Ashby C, Schinke CD, Thanendrarajan S, Zangari M, Zhan F, Davies FE, Morgan GJ, van Rhee F, Walker BA. Monitoring treatment response and disease progression in myeloma with circulating cell-free DNA. Eur J Haematol. 2021 Feb;106(2):230-240. doi: 10.1111/ejh.13541. Epub 2020 Nov 10. PMID: 33107092

[11] Mithraprabhu S, Hocking J, Ramachandran M, Choi K, Klarica D, Khong T, Reynolds J, Spencer A. DNA-Repair Gene Mutations Are Highly Prevalent in Circulating Tumour DNA from Multiple Myeloma Patients. Cancers (Basel). 2019 Jun 29;11(7):917. doi: 10.3390/cancers11070917. PMID: 31261969

[12] Mithraprabhu S, Morley R, Khong T, Kalff A, Bergin K, Hocking J, Savvidou I, Bowen KM, Ramachandran M, Choi K, Wong BKL, Reynolds J, Spencer A. Monitoring tumour burden and therapeutic response through analysis of circulating tumour DNA and extracellular RNA in multiple myeloma patients. Leukemia. 2019 Aug;33(8):2022-2033. doi: 10.1038/s41375-019-0469-x. Epub 2019 Apr 16. PMID: 30992504

[13] Mack EKM, Hartmann S, Ross P, Wollmer E, Mann C, Neubauer A, Brendel C, Hoffmann J. Monitoring multiple myeloma in the peripheral blood based on cell-free DNA and circulating plasma cells. Ann Hematol. 2022 Apr;101(4):811-824. doi: 10.1007/s00277-022-04771-5. Epub 2022 Feb 1. PMID: 35106639

[14] Charalampous C, Kourelis T. Minimal Residual Disease Assessment in Multiple Myeloma Patients: Minimal Disease With Maximal Implications. Front Oncol. 2022 Jan 26;11:801851. doi: 10.3389/fonc.2021.801851. eCollection 2021. PMID: 35155198

[15] Colmenares R, Álvarez N, Barrio S, Martínez-López J, Ayala R. The Minimal Residual Disease Using Liquid Biopsies in Hematological Malignancies. Cancers (Basel). 2022 Mar 3;14(5):1310. doi: 10.3390/cancers14051310. PMID: 35267616

[16] Lauer EM, Mutter J, Scherer F. Circulating tumor DNA in B-cell lymphoma: technical advances, clinical applications, and perspectives for translational research. Leukemia. 2022 Jun 14. doi: 10.1038/s41375-022-01618-w. Online ahead of print. PMID: 35701522

[17] Choucair K, Mattar BI, Van Truong Q, Koeneke T, Van Truong P, Dakhil C, Cannon MW, Page SJ, Deutsch JM, Carlson E, Moore DF, Nabbout NH, Kallail KJ, Dakhil SR, Reddy PS. Liquid Biopsy-based Precision Therapy in Patients with Advanced Solid Tumors: A Real-world Experience from a Community-based Oncology Practice. Oncologist. 2022 Mar 11;27(3):183-190. doi: 10.1093/oncolo/oyac007. PMID: 35274713

[18] Tie J, Cohen JD, Lahouel K, Lo SN, Wang Y, Kosmider S, Wong R, Shapiro J, Lee M, Harris S, Khattak A, Burge M, Harris M, Lynam J, Nott L, Day F, Hayes T, McLachlan SA, Lee B, Ptak J, Silliman N, Dobbyn L, Popoli M, Hruban R, Lennon AM, Papadopoulos N, Kinzler KW, Vogelstein B, Tomasetti C, Gibbs P; DYNAMIC Investigators. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. N Engl J Med. 2022 Jun 16;386(24):2261-2272. doi: 10.1056/NEJMoa2200075. Epub 2022 Jun 4. PMID: 35657320 Clinical Trial.

[19] Nassiri F, Chakravarthy A, Feng S, Shen SY, Nejad R, Zuccato JA, Voisin MR, Patil V, Horbinski C, Aldape K, Zadeh G, De Carvalho DD. Detection and discrimination of intracranial tumors using plasma cell-free DNA methylomes. Nat Med. 2020 Jul;26(7):1044-1047. doi: 10.1038/s41591-020-0932-2. Epub 2020 Jun 22. PMID: 32572265

[20] Nuzzo PV, Berchuck JE, Korthauer K, Spisak S, Nassar AH, Abou Alaiwi S, Chakravarthy A, Shen SY, Bakouny Z, Boccardo F, Steinharter J, Bouchard G, Curran CR, Pan W, Baca SC, Seo JH, Lee GM, Michaelson MD, Chang SL, Waikar SS, Sonpavde G, Irizarry RA, Pomerantz M, De Carvalho DD, Choueiri TK, Freedman ML. Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. Nat Med. 2020 Jul;26(7):1041-1043. doi: 10.1038/s41591-020-0933-1. Epub 2020 Jun 22. PMID: 32572266

[21] Lu H, Liu Y, Wang J, Fu S, Wang L, Huang C, Li J, Xie L, Wang D, Li D, Zhou H, Rao Q. Detection of ovarian cancer using plasma cell-free DNA methylomes. Clin Epigenetics. 2022 Jun 9;14(1):74. doi: 10.1186/s13148-022-01285-9. PMID: 35681212

[22] Vandekerkhove G, Lavoie JM, Annala M, Murtha AJ, Sundahl N, Walz S, Sano T, Taavitsainen S, Ritch E, Fazli L, Hurtado-Coll A, Wang G, Nykter M, Black PC, Todenhöfer T, Ost P, Gibb EA, Chi KN, Eigl BJ, Wyatt AW. Plasma ctDNA is a tumor tissue surrogate and enables clinical-genomic stratification of metastatic bladder cancer. Nat Commun. 2021 Jan 8;12(1):184. doi: 10.1038/s41467-020-20493-6. PMID: 33420073

[23] Waldeck S, Mitschke J, Wiesemann S, Rassner M, Andrieux G, Deuter M, Mutter J, Lüchtenborg AM, Kottmann D, Titze L, Zeisel C, Jolic M, Philipp U, Lassmann S, Bronsert P, Greil C, Rawluk J, Becker H, Isbell L, Müller A, Doostkam S, Passlick B, Börries M, Duyster J, Wehrle J, Scherer F, von Bubnoff N. Early assessment of circulating

tumor DNA after curative-intent resection predicts tumor recurrence in early-stage and locally advanced non-small-cell lung cancer. Mol Oncol. 2022 Jan;16(2):527-537. doi: 10.1002/1878-0261.13116. Epub 2021 Oct 31. PMID: 34653314

[24] Steinke-Lange V, de Putter R, Holinski-Feder E, BM. Claes K. Somatic mosaics in hereditary tumor predisposition syndromes. European Journal of Medical Genetics. 2021; 64(12). Doi: https://doi.org/10.1016/j.ejmg.2021.104360.

[25] https://www.emjreviews.com/oncology/article/multidisciplinary-team-approach-in-cancer-care-a-review-of-the-latest-advancements-s130921/