August 10, 2015

Arthur Lurvey, MD, FACP, FACE
Noridian, LLC
900 42nd Street S
PO Box 6704
Fargo, ND 58108-6781
Arthur.Lurvey@Noridian.com
policyb.drafts@noridian.com

RE: MolDX: NSCLC, Comprehensive Genomic Profile Testing (DL36194, DL36198)

Dear Dr. Lurvey:

Thank you for the opportunity to comment on DL36194 and DL36198. AMP (Association for Molecular Pathology) 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 government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

The College of American Pathologists (CAP) is a national medical specialty society representing more than 17,000 physicians who practice anatomic and/or clinical pathology. College members practice their specialty in clinical laboratories, academic medical centers, research laboratories, community hospitals and federal and state health facilities.

Both AMP and CAP members are experts in molecular pathology and the implementation of this coverage policy will directly impact their practices as well as deny testing for Medicare beneficiaries. We will address our primary concerns in this summary coverage letter and expand upon them in the attached. We are submitting joint comments because at this time both of our respective organizations share the same concerns regarding this draft LCD, and we request that Noridian consider the recommendations outlined in this letter.

1. Proposed Coverage for Multiplex/NGS Testing

AMP and CAP applaud Noridian for proposing to provide coverage for multiplex/NGS testing. However, we believe that this proposal is unreasonably restrictive and we would like to work with you to devise a more reasonable strategy for coverage and reimbursement of these tests. Cost effectiveness studies increasingly are demonstrating the value of multiplex tumor testing.[i]

2. Multiplex/NGS Testing Is No Longer Experimental

There is significant scientific literature demonstrating that multiplex/NGS testing is no longer experimental, specifically in patients with non-small cell lung cancer.

3. Sequential Testing Should Not Be Required

Noridian proposes a policy under which an initial first round of single-gene EGFR/ALK tests must be pursued prior to multiplex/NGS testing. We strongly disagree with this approach as this sequential testing algorithm may harm patients by both delaying therapy and exhausting tissue samples, and potentially increasing costs by requiring additional invasive procedures for additional tissue acquisition. Furthermore, there are other common actionable alterations that can be identified in addition to EGFR and ALK.

4. Laboratory Verification by MolDx

AMP and CAP strongly disagree with the laboratory verification requirements imposed under MolDx and continue to assert that the Centers for Medicare and Medicaid Services (CMS) is the only entity with the authority to regulate analytical validity pursuant to the Clinical Laboratory Improvement Amendments (CLIA).

5. Limitation of CGP to Non-Smokers and Former Light Smokers

Noridian's proposal limits multiplex/NGS testing to non-smokers and former light smokers. We summarize the scientific literature that demonstrates that actionable drivers that may be identified by multiplex/NGS testing are common in smokers. Therefore, this testing should not exclude smokers.

6. Clinical Outcomes Reporting Requirements

While we are generally supportive of gathering outcomes data, the proposal outlined by Noridian is not scientifically, financially or ethically feasible for laboratories.

We respectfully ask that you consider these comments which were prepared by a consortium of providers in the Noridian jurisdiction as well as other members of the Association for Molecular Pathology, laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by Noridian. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this draft LCD. Please direct your correspondence to Mary Steele Williams, AMP Executive Director, at mwilliams@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@amp.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

1. Proposed Coverage for Multiplex/NGS Testing

AMP and CAP applaud Noridian for taking this first step to cover multiplex/NGS testing. However, this initial attempt appears to be unreasonably restrictive for the reasons outlined in this letter. We are happy to work with you to devise a more feasible reimbursement strategy that is mutually beneficial to all stakeholders, particularly patients who are adversely impacted by this LCD.

AMP has developed a publicly available, comprehensive health economic model that it has distributed to its members to allow them to accurately access the total costs incurred by laboratories to provide this type of testing. AMP believes that this information will inform both the Centers for Medicare and Medicaid Service (CMS) and Noridian and the other Medicare Administrative Contractors (MACs) as you engage in gap filling and/or other reimbursement methods for these important tests. AMP would be happy to meet and share this tool to discuss both the health and economic implications of the various NGS testing algorithms.

2. Multiplex/NGS Testing Is No Longer Experimental

Multiplex/NGS testing is no longer experimental. There is significant literature that validates use of this important testing approach in patients with NSCLC. The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial is the first completed prospective, adaptively randomized study in heavily pretreated NSCLC patients that mandated tumor profiling with "real-time" biopsies, taking a substantial step towards personalized lung cancer therapy.[ii] In another study, tumors from 1007 patients were tested for mutations in at least 1 gene, and 733 patients were tested for mutations in 10 genes. An oncogenic driver was found in 466 of these 733 patients (64%). Among these 733 tumors, 182 tumors (25%) had the *KRAS* driver; sensitizing *EGFR*, 122 (17%); *ALK* rearrangements, 57 (8%); other *EGFR*, 29 (4%); 2 or more genes, 24 (3%); *ERBB2* (formerly *HER2*), 19 (3%); *BRAF*, 16 (2%); *PIK3CA*, 6 (<1%); *MET* amplification, 5 (<1%); *NRAS*, 5 (<1%); *MEK1*, 1 (<1%); *AKT1*, 0. Results were used to select a targeted therapy or trial in 275 of 1007 patients (28%). The median survival was 3.5 years for the 260 patients with an oncogenic driver and genotype-directed therapy compared with 2.4 years for the 318 patients with any oncogenic driver(s) who did not receive genotype-directed therapy.[iii]

In this draft LCD, Noridian cites the study by Drilon AE, et al, entitled, "Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alternations in "driver-negative" lung adenocarcinomas". This study itself demonstrates the effectiveness of multiplex/NGS testing. In particular, Drilon et al conclude that NGS testing identified actionable genomic alterations in 65 percent of the patients tested. The authors concluded that their findings support first-line (not second-line) profiling of lung adenocarcinomas using this approach, calling it more efficient compared with non-NGS testing.[iv] Furthermore, the fact that this particular landmark study utilized a biased cohort of patient samples enriched for never-smokers and in which sequential testing was employed should not be the basis of coverage policy (additional data provided below).

3. Sequential Testing Should Not Be Required

The draft LCD recommends performing sequential testing for *EGFR* mutations and *ALK* rearrangements at the outset, and only if these first-line tests are negative would subsequent second-tier multiplex/NGS testing be

reimbursed. The draft states the following as a pre-requisite for coverage of a genomic test: *Patient previously tested negative for EGFR and/or ALK translocations through non-CGP methods.* AMP and CAP strongly disagree with this requirement to perform sequential testing for the following reasons:

NCCN Guidelines Recommend Multiplex/NGS Testing from the Outset

The National Comprehensive Cancer Network (NCCN) guidelines recommend that multiplex/NGS testing be performed at the outset for patients with non-small cell lung cancer.[v] Sequential testing as required by this policy has significant risks for the patient. The time that elapses when performing sequential testing will delay the patient's access to targeted therapy; in these cases with critically ill patients, the delay can significantly impact their health and the outcome of the treatment.

Sequential Testing Delays Therapy and Exhausts Tissue Samples

Importantly, Noridian's proposed 2-step testing approach would necessarily consume a substantial portion of the available tissue for the up-front ALK/EGFR testing, often leaving no available material for subsequent multiplex/NGS testing. This would then force these direly sick patients to undergo additional biopsy procedures to procure more tissue, often using invasive approaches with potential morbidities. The Drilon et al study that appears to be Noridian's model for the 2-tier testing approach encountered this inevitable tissue exhaustion problem quite often. In particular, Drilon et al report that, of 47 patients with lung adenocarcinomas with no evidence of a genomic alteration through non-NGS testing, tissue exhaustion preventing subsequent NGS testing occurred in 34 percent of cases, and a repeat biopsy was either not feasible or declined by the patient.[vi]

As patients with Stage IV non-small cell lung cancer are, by definition, not candidates for resection, available biopsy specimens are nearly always quantitatively extremely limited. Thus, requiring EGFR and ALK testing before consideration of genomic testing will result in delays and a commonplace finding of no residual tissue for the second-tier multiplex/NGS testing. The majority of such patients will test negative for EGFR and ALK alterations and ultimately will require multiplex/NGS testing, thus resulting in minimal cost savings by implementing this approach. Noridian should save Medicare financial resources, and importantly, reduce delays (and unnecessary repeat invasive procedures) to achieving a multiplex/genomic result and forego the requirement for sequential testing.

Because targeted therapies exist for patients who test positive for EGFR and ALK alterations, we agree that knowing whether a patient is positive or negative for either of these markers is important, but opting to use a multiplex/NGS panel (or equivalent) at the outset will still provide this information. First-line testing of ALK/ EGFR prior to use of a multiplex/NGS panel is redundant. For those NGS/multiplex assays that do not detect ALK rearrangements (which, if not directly evaluated by NGS will be covered by a concomitant FISH approach), a single-plex methodology for ALK rearrangement (usually by FISH) could be implemented as a second-line test.

It is clear that the literature supports the use of multiplex/NGS testing, but we recommend that NORIDIAN also reimburse laboratories that choose to utilize assays that are not NGS panels as long as they provide the same information at the same or lesser cost. For instance, the FDA approved Vysis ALK FISH Break-Apart assay will provide the required information on actionable ALK rearrangements and can be effectively utilized in combination with (often small) targeted multiplex/NGS panels to achieve a similar testing outcome compared to large multiplex/NGS testing.

Actionable Driver Mutations for NSCLC Beyond EGFR and ALK Are Common

Another benefit of multiplex/NGS panels is that they include other driver mutations or cooperating mutations that may impact the patient's course of therapy and outcome even for those who are EGFR and ALK positive.[vii] Evidence shows that genotyping lung cancer is linked to better survival, most likely because it allows for the delivery of targeted anti-tumor drugs to the right patients.[viii] These targeted therapies have improved a patient's rate of survival. In a study by Kris et al, they found the following:

"The 260 patients with an oncogenic driver [identified through multiplex testing] and treatment with a targeted agent had a median survival of 3.5 years; the 318 patients with a driver and no targeted therapy, 2.4 years; and the 360 patients with no driver identified, 2.1 years."[ix]

Multiplex/NGS testing is an accepted and validated form of testing for patients with NSCLC. It limits the risk to the patient by minimizing the probability of the need for re-biopsy, and provides more up-front information about the patient's genomic profile that will influence the course of therapy. Attached to these comments, in Appendix A, we have attached a spreadsheet that lists mutations that provide actionable information in the *treatment* of NSCLC. The level of evidence cited for each study referenced is based on the process outlined in the article entitled, *Current Methods of the U.S. Preventive Services Task Force.*[x] As discussed above, this testing is not considered experimental and can provide significant benefit to the patient by eliminating the need for repeat biopsies and reduce the time it takes for a patient to begin life-extending targeted treatment.

As detailed below, there are additional actionable alterations which can be identified using a multiplex/NGS approach which can impact clinical decision-making

REQUEST:

Noridian should carefully review the evidence presented in Appendix A and cover up-front multiplex/NGS panels for patients with NSCLC given the scientific evidence demonstrating that there will be significant benefits to patients.

4. <u>Laboratory Verification by MolDx</u>

Another requirement imposed by Noridian before multiplex/NGS testing can be performed states that *"Testing is performed by a lab that satisfies the MolDX Contractor's published AV criteria."*

CMS is the only entity with the authority to regulate analytical validity as authorized by the Clinical Laboratory Improvement Amendments (CLIA). We are not aware that Noridian has been delegated this authority by CMS.

REQUEST:

AMP and CAP continue to believe that Noridian and the other Medicare administrative contractors do not have the authority to evaluate analytical validity under the MolDX program. Please see the letter dated December 14, 2014, sent to Palmetto in response to DL33599 Molecular Diagnostic Tests that outlines our concerns about this requirement in detail. It can also be found online at http://amp.org/publications_resources/position_statements_letters/documents/CAP-AMP-lettertoPalmetto-LCD.pdf**.**

5. Limitation of CGP to Non-Smokers and Former Light Smokers

Besides requiring sequential testing, Noridian also requires the following before multiplex/NGS testing can be employed: *Patient is a lifetime non-smoker or former light smoker with = 15 pack a year history.* We believe that this requirement unnecessarily limits testing and ultimately denies smokers with NSCLC the life-extending availability of targeted therapies. While EGFR and ALK mutations are indeed more common in non-smokers and former light smokers, consensus guidelines based on systematic review have already specifically determined that smoking status is not an appropriate criteria for determining NGS/multiplex testing eligibility. A recent paper published in *Science* confirms there are improved treatment responses in NSCLC patients with higher mutation burdens that can be identified by broad-based multiplex/NGS testing; these enhanced treatment outcomes were even more pronounced in smokers.[xi]

The authors of the Drilon study upon which Noridian modeled this draft LCD also recognized that clinically actionable lung cancer drivers are found in smokers, as well as non-smokers. These authors state:

"However, while many clinically actionable lung cancer drivers are more commonly found in tumors of never smokers, these drivers have been identified in tumors from smokers as well, and patients treated with the associated therapy appear to fare as well as the never or light former smoker population.(26, 27) In addition, other actionable drivers such as some BRAF (13, 28) and KRAS mutations(29, 30) are enriched in tumors from patients with a significant history of smoking. No clinical characteristics can be used to select NSCLC patients whose tumors should be tested, and current guidelines recommend routine ALK and EGFR testing of tumors from all patients (preferably as part of a multiplex panel) with adenocarcinomas, large cell carcinomas, NSCLC NOS (not otherwise specified), and squamous lung cancers from never smokers and small diagnostic biopsies.(31)"[xii]

The CAP, the International Association for the Study of Lung Cancer (IASLC), and AMP developed an evidence-based guideline, "Molecular Testing Guideline for the Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors," that establishes standards for EGFR and ALK testing, helping to guide targeted therapies.[xiii] These guidelines do not link EGFR and ALK testing to a patient's smoking history, and explicitly dictate that the utilization of such a smoking characteristic for determination of testing is inappropriate, as some patients not fitting these criteria are identified with EGFR and ALK alterations.[xiv] This recommendation was based on the finding that although EGFR and ALK alterations are more commonly seen in those with no or light smoking history, they are not exclusively seen in this patient cohort. Patients not falling under this description are found with these alterations and do benefit from therapy. As multiplex/NGS testing aims to evaluate alterations in addition to EGFR and ALK, extension of this observation is inevitable, and is backed by extensive data demonstrating that no alterations observed in NSCLC are entirely restricted to never and light smokers. There is no evidence that smokers cannot benefit from NGS testing and the targeted therapy it can identify, allowing the physician to tailor therapy to all actionable targets. Many smokers have EGFR, ALK and other alterations and do respond to tailored treatment.

Other Actionable Mutations Found in Smokers

Noridian should also consider the evidence related to a BRAF mutation, as there is convincing data demonstrating the efficacy of targeted therapies in these patients. The most clinically advanced data on BRAF mutated NSCLC is on V600E. Of 36 patients with V600E mutated lung cancer, only 8 percent were never smokers. Preliminary data shows a 56 percent disease control rate in these patients.[xv]

While mutational alternations in ERBB2 (HER2), which would be detected by multiplex/NGS assays, are more commonly associated with non- and light smokers, they are also seen in smokers, who as a population are far more widely affected by NSCLC. In a study including 65 cases with a HER2 mutation, 11 patients were former smokers and 12 patients were current smokers; the combined frequency of HER2 mutations in those classified as current and former smokers was 35.4 percent.[xvi] In a recent study, 7 patients out of 920 had an HER2 mutation and a smoking history.[xvii] While this number may seem low, based on 200,000 new cases of NSCLC in former and current smokers each year, there could be as many of 1400 patients in this category who have a HER2 mutation, making the smoker versus non-smoker distinction inappropriate. The detection of HER2 somatic mutations is proving to be a substantial predictive marker, as evidenced in multiple ongoing clinical trials and published experiences.[xviii xix xx]

As the LCD is currently written, Noridian limits multiplex/NGS testing to approximately 10 percent or less of lung cancer patients based on smoking status alone, before consideration of other restrictions placed on testing in this LCD. Given the lethal nature of advanced lung cancer, restricting testing and opportunities for targeted therapy to this patient population is a substantial detriment to the treatment and outcomes for these patients.

Furthermore, imposition of this pre-testing requirement creates logistical and ethical barriers in the implementation of laboratory medicine. When a patient's treating physician orders testing, they are doing so in consideration of the entire clinical context. It is uncommon for the submitting physician to provide detailed smoking history with such requests, thus placing a burden on the laboratory if it is to spend what can amount to a substantial effort to identify this information. It is unreasonable to place the burden of obtaining such information on testing laboratories (particularly referral labs), which do not routinely receive this information. Furthermore, imposition of such a policy could have the potentially negative unintended consequence of dissemination of this requirement in the patient community, thus resulting in patients understating their smoking history in order to gain access to testing.

REQUEST:

Multiplex/NGS testing should not be limited to non-smokers and former light smokers. All NSCLC patients, regardless of their smoking history, can benefit from multiplex/NGS testing and should have access to it. AMP and CAP request that Noridian eliminate this requirement.

6. <u>Clinical Outcomes Reporting Requirements</u>

We have serious concerns about the reporting requirements of clinical outcomes data as proposed in this LCD. This level of clinical outcomes reporting is not practical (or feasible) for labs without additional resources. Furthermore, collection of such information by a payor is tantamount to a clinical trial, and imposition of such requirements by Noridian raises substantial ethical concerns with regards to the role of a payor in the design, implementation and analysis of any generated outcomes data.

Noridian proposed the following reporting requirements every six months:

- *Number of patients tested;*
- *Total number of patients with no EGFR/ALK translocations by CGP;*
- *Number of patients with EGFR/ALK translocations by CGP whose mutations were not identified by non-CGP methods. Report on whether the mutation(s) occurred outside the defined analytic framework of*

the genes identified by the respective CDx and whether the mutations are attributed to insertions or deletions (indels), duplications (dups), or translocations.

- *For each identified EGFR/ALK translocation by CGP, the response status and duration of response.*
- *At the discretion of a lab, other mutations that are identified.*

We agree that gathering this outcomes data is important for determining outcomes, and, that with additional resources and appropriate IRB approval, it could potentially be feasible for some research-motivated labs to report some of this data. However, without additional resources, it would be unreasonably burdensome for labs to report data with regard to patient responses to therapy. To find and report this complex outcomes data, which is not provided to the lab as part of its routine clinical service, labs would have to arrange permission (and potentially pay) for medical record reviews. Unless Noridian is planning to routinely reimburse labs for these medical record reviews, this expense is not a reasonable one for labs, particularly in an era of shrinking reimbursements.

The medical record review process required for obtaining such outcomes data would also likely require local Institutional Review Board (IRB) approval, which, in addition to the ethical ramifications, adds yet another substantial lab cost. The LCD also suggests sharing of response/outcome data in a manner that likely preserves patient identity with a party outside the individual medical center, which is generally explicitly prohibited without initiation of a clinical trial and patient consent. As Noridian is the MAC covering such patients, they can use internal data extraction methodologies, and perform such studies based on submitted claims for each patient as an internal evaluation, rather than requiring individual sites to participate in what amounts to an unfunded clinical trial.

Laboratories not immediately connected with a medical center (i.e. labs serving in a reference capacity) have no direct access to such outcomes information. Even if they were allocated resources to pursue examination of medical records, they would have no legal authority to do so. Before laboratories can collect this information, the following must occur:

- Data extraction must evolve sufficiently to make acquisition of this information trivial in terms of time and effort
- Local requirements for data release must be sufficiently evaluated and addressed; and
- Issues related to patient consent must be considered.

In the absence of the above concerns being addressed, very substantial concerns regarding the legal and ethical implications of this requirement remain.

To appropriately evaluate outcomes, a well-structured clinical study is required. This cannot and will not be accomplished by asking laboratories to submit detailed data that will not control for co-morbidities or other factors that must be considered in well-designed scientific studies.

For the outcomes-based clinical trial that is proposed in this LCD, it would be essential, from a scientific perspective, that Noridian provide further information on the likely statistical power of this LCD-based clinical trial for its probability of successfully answering the scientific questions being hypothesized? Will these laudable scientific goals be reasonably achievable by the proposed study? Individual labs, in comparison, are being required by Noridian as proposed to provide an analogous degree of clinical validity/utility statistical data as part

of their MolDx-based applications for other reimbursable molecular diagnostic tests. Holding Noridian to a similar degree of scientific/statistical scrutiny as they are requesting from individual labs would certainly be a minimal expectation.

In the event that such scientific, fiscal, and ethical concerns are addressed, AMP and CAP would also recommend that clinical outcomes information be collected once annually, not twice, as proposed. Reporting once annually would be more consistent with the compliance, reporting, and review requirements already imposed on labs. Besides being more feasible for labs and their staff, reporting once annually would also be more consistent with examining patient outcomes. The 6-month reporting would not provide a complete picture of the results from targeted therapies.

Additionally, a retrospective evaluation of over 30,000 patients demonstrated that "a personalized strategy was independently associated with higher response rates, longer median progression free survival and overall survival as well as fewer toxic deaths."[xxi] Though this study was not conducted on lung cancer patients, it supports the position that patients who receive a treatment matched to a tumor molecular profile likely have a longer progression free survival.

REQUEST:

- **AMP and CAP share and applaud Noridian's goal of attempting to generate outcomes data for NGS-tested patients, but collecting and reporting outcomes data has considerable unfunded costs and implicates potentially substantial breaches in legal and medical-ethical requirements.**

- **In the event that these scientific, fiscal, legal, and ethical concerns are addressed, we nevertheless view this proposed requirement as an unfunded mandate until either Noridian subsidizes this data collection, or the cost of acquiring this data decreases significantly. We recommend removing this reporting requirement until the cost to labs is much lower, or until Noridian provides a reimbursement structure to compensate laboratories for the effort involved in generating this information.**

- **If these requirements are to be implemented as above, the reporting frequency should be changed from twice annually to once annually. This will harmonize reporting with other requirements already placed on labs, and provide a more accurate picture of patient outcomes.**

---

[i] Li Y, Bare LA, Bender RA, Sninsky JJ, Wilson LS, Devlin JJ, Waldman FM. Cost Effectiveness of Sequencing 34 Cancer-Associated Genes as an Aid for Treatment Selection in Patients with Metastatic Melanoma. Mol Diagn Ther. 2015 Apr 30. [Epub ahead of print]

[ii] Kim, ES, et al. (2011) The BATTLE Trial: Personalized Therapy for Lung Cancer. *Cancer Discovery*; 1(1); 44-53.

[iii] Kris, MG et al (2014), Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA, 311*(19). doi: doi:10.1001/jama.2014.3741.

[iv] Drilon, AE, et al. (2015) Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in "driver-negative" lung adenocarcinomas, pii: clincanres.2683.2014. [Epub ahead of print]

[v] National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 4.2015). https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 23, 2015.

[vi] Drilon, AE, et al. (2015) Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in "driver-negative" lung adenocarcinomas, pii: clincanres.2683.2014. [Epub ahead of print]
[vii] Kris, MG et al (2014), Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA, 311*(19). doi: doi:10.1001/jama.2014.3741.
[viii]Phend, Crystal. (2013 Nov 6) *Genotyping Lung Cancer Linked to Better Survival.* Retrieved from http://www.medpagetoday.com/HematologyOncology/LungCancer/42731.
[ix] Kris, MG et al (2014), Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA, 311*(19). doi: doi:10.1001/jama.2014.3741.
[x]Harris R.P. et al (2001) Current Methods of the U.S. Preventive Services Task Force. *American Journal of Preventive Medicine, 20* (3S), 21-35.
[xi] Rizvi, NA, et al, Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer *Science* DOI: 10.1126/science.aaa134
[xii] Drilon, AE, et al. (2015) Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in "driver-negative" lung adenocarcinomas, pii: clincanres.2683.2014. [Epub ahead of print]
[xiii] Lindeman NI et al (2013), Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors. *Journal of Molecular Diagnostics, 15*(4), 415-53: DOI: http://dx.doi.org/10.1016/j.jmoldx.2013.03.001.
[xii] *Id.*
[xiii]Planchard D, Kim TM, Mazieres J et al., Dabrafanib in Patients with BRAF V600E-Mutant Advanced Non-Small Cell Lung Cancer: A Multicenter Open-Label Phase II Trial (BRF113928) Annals of Oncology (2014) 25 (suppl 4): doi: 10.1093.annonc/mdu438.46.
[xiv] Mazieres, J, et al. (2013) Lung cancer that harbors a HER2 mutation: Epidemiologic characteristics and therapeutic perspectives. *Journal of Clinical Oncology (31)*16, 1997-2003.
[xv] J Clin Oncol 33, 2015 (suppl; abstr 8006)

[xiv] J Clin Oncol 33, 2015 (suppl; abstr 8006)
[xv]Besse B, Soria J-C, Yao B et al (2014), Neratinib (N) with or Temsirolimus (TEM) in Patients with Non-Small Cell Lung Cancer Carrying HER2 Somatic Mutations: An International Randomized Phase II Study. *Annals of Oncology, 25* (Supp 4): doi:10.1093/annonc/mdu438.47.
[xix] Tomizawa, et al (2011). Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung cancer (Amsterdam, Netherlands), 74(1), 139–44.
[xx] De Grève, J, et al. (2012). Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu.Lung cancer (Amsterdam, Netherlands), 76(1), 123–7.
[xxi] Von Hoff et al JCO 2010;28 4877-4883, Tsimberridou et al., Clin Cancer Res 2014;20 4827-4836, Schwaederle et al (Abstract 11097 - http://meetinglibrary.asco.org/content/111346?format=posterImg&poster=1)