



ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
9650 Rockville Pike. Bethesda, Maryland 20814

Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

December 13, 2015

Facts FDA Ignored: An analysis of the FDA report, “The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies”

Introduction:

On November 16, 2015, the U.S. Food and Drug Administration (FDA) released a report entitled “The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies.”¹ In this report, FDA outlines 20 laboratory developed tests (LDTs) that the Agency claims may have caused or have caused actual harm to patients in the “absence of compliance with FDA requirements.”² A report produced by FDA officials that is used to support FDA regulation of LDTs, which we prefer to call laboratory developed testing procedures (LDPs), should be based on complete and sound scientific evidence. Unfortunately, rather than referencing peer reviewed studies published in scientific journals, FDA in this report makes dubious claims, fails to provide significant context for the information provided, and relies on articles from the lay news media to assert its scientific positions. It is irresponsible for the Agency to release a document that could cause unwarranted stress to patients, needlessly scare the American public, and lead patients to unduly question the quality of the care provided to them by their physicians. Below, we correct inaccurate information in the report, and provide the relevant context that FDA omitted.

After reviewing the case studies, The Association for Molecular Pathology (AMP) concluded that only a few of the 20 tests identified by the FDA could cause patient harms that FDA oversight might have prevented. The Centers for Medicare & Medicaid Services (CMS) has the statutory authority to evaluate these tests through the CLIA program utilizing a robust network of third party network of medical and scientific experts, and had that authority been fully exercised, would arguably have been more successful than FDA at addressing problems with the LDPs. The remaining examples summarized in the report were either highly speculative; reflected a problem with treating physicians using treatments outside accepted medical practice; analytical errors, which both FDA and CMS acknowledge are best addressed by CLIA; or failure of treating physicians to follow up a screening test with a diagnostic confirmation test. Further, the report also fails to acknowledge that decisions about clinical care are rarely based on the information provided by a single test. A competent physician always considers laboratory test results in the context of a clinical exam, additional relevant diagnostic procedures and other medical information.

Most important, the report fails to acknowledge that even if all of the case studies presented had concerns that might have been addressed by FDA oversight (although, this is clearly not the case), these tests are a miniscule fraction of the thousands of LDPs that are designed, developed, validated, and interpreted by appropriately trained and qualified health care professionals. Absent from FDA’s report is a discussion of the enormous benefits of the hundreds of thousands of LDPs that have helped patients since the implementation of the CLIA regulations in 1992. FDA’s examples, even had they been fairly and accurately depicted, could never justify the

¹ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf> Accessed December 10, 2015

² <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm472773.htm> Accessed December 10, 2015

imposition of an additional regulatory system that would eliminate thousands of critical tests that are performed in academic medical centers, hospitals and health systems, major cancer centers and independent laboratories, and are essential for appropriate patient care.

The development and use of LDPs is an area of medical practice that requires specialized expertise. Specialized physicians (pathologists), geneticists, and scientists with many years of education, clinical training, and board exam certification are legally responsible for the accuracy and reliability of the LDPs they develop and perform. FDA's proposal will interfere with the practice of medicine in violation of statutory constraints on the agency³, and will encroach on an area traditionally regulated by the states. We believe that the Clinical Laboratory Improvement Amendments (CLIA) of 1988 provide sufficient legal authority for CMS to address any significant public health issues related to laboratory testing through the CLIA program, including those relating to LDPs, and in fact, mandate that CMS do so.⁴ The most reasonable and effective path is for Congress to insist that the CLIA program modernize, expand its current network of third party medical experts, and utilize scientific expertise from FDA and the Centers for Disease Control and Prevention (CDC) rather than relinquishing its duties regarding the accuracy and reliability of LDPs. We urge the Department of Health and Human Services and the Office of Management and Budget to perform a thorough, scientifically unbiased analysis of potential harms and benefits of FDA regulation of LDPs prior to embarking on a massive new regulatory program that would be enormously disruptive to health care and would likely have profound adverse consequences for patients across the country.

³ 21 U.S.C. § 374(a)(2)(B) 21 U.S.C. § 360(g)(2)

⁴ Selected portion of CLIA regulations:

(f) Standards

(1) In general

The Secretary shall issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations and other procedures. Such standards shall require each laboratory issued a certificate under this section—

(A) to maintain a quality assurance and quality control program adequate and appropriate for the validity and reliability of the laboratory examinations and other procedures of the laboratory and to meet requirements relating to the proper collection, transportation, and storage of specimens and the reporting of results,

(B) to maintain records, equipment, and facilities necessary for the proper and effective operation of the laboratory,

(C) in performing and carrying out its laboratory examinations and other procedures, to use only personnel meeting such qualifications as the Secretary may establish for the direction, supervision, and performance of examinations and procedures within the laboratory, which qualifications shall take into consideration competency, training, experience, job performance, and education and which qualifications shall, as appropriate,

be different on the basis of the type of examinations and procedures being performed by the laboratory and the risks and consequences of erroneous results associated with such examinations and procedures,

(D) to qualify under a proficiency testing program meeting the standards established by the Secretary under paragraph (3), and

(E) to meet such other requirements as the Secretary determines to assure consistent performance by such laboratories of accurate and reliable laboratory examinations and procedures.

Lyme Disease Diagnostic Tests

FDA Analysis: Large numbers of patients with positive results do not have Lyme disease; FDA believes its oversight would ensure the test meets minimum performance standards. In addition, FDA complains of a laboratory contamination issue.

Facts that FDA ignored:

1. FDA cleared tests for Lyme disease have high false positive rates, *i.e.*, large numbers of patients with positive results do not have Lyme disease. Both FDA and LDP tests for Lyme disease commonly experience false positive results. It is of huge clinical importance to identify Lyme disease early because it can be treated with the best chance of full recovery and with the least chance of treatment side effects. The consequences of missing a patient with Lyme disease are dire and can lead to patients being physically and neurologically debilitated. For this reason, both FDA cleared tests and LDPs for Lyme disease are intentionally designed to have a higher sensitivity, at the concomitant cost of a lower specificity, to catch as many patients as possible, which can result in a higher false positive rate.

The FDA report indicates eight (8) instances of false positive results among 50,000-70,000 tests performed. This means that only 0.016% were falsely positive. If FDA's "minimum standards" seek to reduce this proportion of false positive tests further, patients with early stage disease, who are most effectively treated, will be missed.

2. The FDA report describes contamination that occurred during a novel culture enhanced testing method. Assay contamination is a laboratory operations issue for which inspection under the CLIA program is responsible and would not be fixed by an FDA review of clinical validity. Additionally, a review of the literature reveals that the FDA wrongly characterized the publications it cited. For instance, an article by Johnson et al. of the Centers for Disease Control and Prevention (CDC)⁵ discloses errors of fact and misrepresentations in the Agency's critique of the work of Sapi et al.⁶ Specifically, statements by Johnson et al. that living borreliae from strains B023, Fuji P1, and 297 contaminated 41 of the Sapi et al. blood culture isolates are unproven assertions. Further CDC misrepresentations to *Journal of Clinical Microbiology* readers include wording that *garii*-type *Borrelia* human infections vectored by ticks in the Western Hemisphere have never been described. These statements are in conflict with current published literature.⁷

Lyme disease can be difficult to diagnose, particularly for physicians not used to dealing with Lyme, so the involvement of an experienced specialist who can assess laboratory results in the context of clinical findings is essential. Lyme disease tests (both IVDs and LDPs) cannot compensate for poor clinical judgment. This is the main reason why Lyme disease testing is *supportive* of the clinical diagnosis (which includes symptoms, signs, and known risk factor/exposure). Lyme disease testing works well when used in the right patient population (high risk) and poorly when used in the wrong patient population (general

⁵ Johnson BJ, Pilgard MA, Russell TM. Assessment of new culture method for detection of *Borrelia* species from serum of Lyme disease patients. *Journal of Clinical Microbiology* 2014;52:721-4.

⁶ Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Improved culture conditions for the growth and detection of borrelia from human serum. *Int. J. Med. Sci.* 2013;10:362-376.

⁷ MacDonald AB. No evidence for contamination of *Borrelia* blood cultures: a review of facts. *Journal of Clinical Microbiology* 2014;52:1803.

population). FDA's example actually reflects a medical practice error by providers who used a test inappropriately.

Conclusion: FDA regulatory review could negatively impact a physician's ability to treat patients as soon as possible. FDA approved tests for Lyme disease have a high false positive rate, as do LDPs, as they are designed to have a sensitivity that would identify as many affected patients as possible. Contamination is a laboratory operation issue and would not be solved by FDA oversight, but by CLIA. A diagnosis of Lyme disease and the interpretation of a test result should be based on the totality of the clinical information at hand. This activity is within the practice of medicine.

Ovacheck Ovarian Screen and Detection Test:

FDA analysis: FDA observes a lack of validation that the test predicts or detects ovarian cancer and therefore the laboratory inflated accuracy claims. FDA asserts that its oversight would assure the test meets minimum performance standards, assures consistent manufacturing practices and standardized instrument calibration, and evaluate the claims made by the laboratory.

Facts that FDA ignored: This test was never offered in the United States. Following publication of the research that would have formed the basis for the test, other scientists reanalyzed the data and found significant flaws in the original investigators' work.^{8,9} Thus, the ordinary process of peer-reviewed publication functioned as it should to ferret out scientific mistakes in research publications. FDA should not claim credit for uncovering this error, as the Agency weighed in after this information was in the public domain and had been widely publicized.

Conclusion: FDA premarket review was unnecessary because data transparency and third party review by experts halted the offering of this test.

OvaSure Ovarian Cancer Screening Test:

FDA analysis: FDA states that this test contained no validation that the test predicts or detects ovarian cancer and that the laboratory inflated positive predictive values, resulting in false positive results.

Conclusion: This test lacks validity. Modernized CLIA oversight, such as that proposed by AMP¹⁰, would have prevented this test from being offered to patients. It is important to note, however, that screening tests are not diagnostic. All screening tests should be considered in conjunction with other clinical information and professional practice guidelines should determine their appropriate use. This falls within the practice of medicine and FDA oversight would not address physicians who inappropriately follow up on screening tests.

⁸ Sorace J. M. & Zhan, M. 2003. BMC Bioinformatics 4, 24

⁹ Baggerly, K. A., Morris, J. S. & Coombes, K. R. 2004. Bioinformatics 20, 777-785

¹⁰ Association for Molecular Pathology (AMP) Proposal for Modernization of CLIA Regulations for Laboratory Developed Testing Procedures (LDPs). Online at <http://www.amp.org/advocacy/CLIAModernization.cfm>

PreOvar KRAS-Variant Ovarian Cancer Screening Test:

FDA analysis: FDA claims that the test lacks validation that this KRAS-variant correlates with cancer risk. FDA believes that its oversight would assure the test meets minimum performance standards. FDA asserts that it would evaluate manufacturer claims and the company's data analysis.

Facts that FDA ignored: The PreOvar test looks for a change or variant in the KRAS gene which was reported in one study to increase risk for ovarian cancer, especially when there is also a family history of ovarian cancer. These data are in dispute and appear not to have been confirmed in a larger study. Ovarian cancer is deadly, largely because the disease typically presents at later stages when it is incurable. There is a strong need for identifying markers for early detection of ovarian cancer.

Irrespective of whether the PreOvar test in fact suggests a predisposition to ovarian cancer, it should be clear that if there is a predictive effect of the marker it would not be direct and that the individual odds of actually developing the disease would remain low. This should be obvious to practicing physicians, and is why the Society of Gynecologic Oncology recommended against its use.

Even if the marker is valid, as a screening test, its use should solely be to support risk adjusted screening for ovarian cancer. The test would obviously not appropriately serve as the basis for a surgical procedure. Therefore, any possible harms resulting from this test are likely well-circumscribed.

Conclusion: This test is a screening test, not a diagnostic test. All screening tests should be considered in conjunction with other clinical information. Practice guidelines should determine the appropriate use of screening tests. Third party experts operating under the CLIA program are capable of evaluating and making determinations about tests of this kind.

Whooping Cough (Pertussis) Diagnostic PCR Test:

FDA Analysis: FDA claims that false positive results caused physicians to declare a pseudo-outbreak.

Facts that FDA ignored: FDA mischaracterized this issue to be a problem with the LDP, when in fact, the actual problem was that the clinician incorrectly interpreted the results of the test and made an incorrect clinical decision. At the time, the laboratory performing the test underwent an intensive investigation by both the CDC and the College of American Pathologists (CAP) and collaborated with other laboratories. CAP reviewed all of the Dartmouth validation data and results and concluded that the Dartmouth LDP assay was sound, properly clinically validated, and suitable for clinical use under the CLIA regulations as well as CAP's guidelines for test validation. CDC claimed that the Dartmouth LDP was too sensitive, based on its own LDP. Yet, the adjudicating LDP for pertussis the CDC developed has been questioned. No patients were harmed.

Conclusion: The issue was the result of incorrect interpretation of the test by treating physicians. Clinical information should be used to assist in the interpretation of all tests. Oversight of LDPs by FDA will not control how clinicians choose to act on test results. FDA has no authority under the Food, Drug, and Cosmetics Act to regulate the practice of medicine.¹¹

¹¹ 21 U.S.C. § 374(a)(2)(B) 21 U.S.C. § 360(g)(2)

Oncotype DX HER2 Breast Cancer RT-PCR test:

FDA analysis: FDA report states that this test has poor sensitivity, *i.e.*, the test may report normal HER2 levels when samples actually have high HER2 levels. FDA believes its oversight would assure the test meets minimum performance standards.

Facts that FDA ignored: There *is no* distinct LDP called “Oncotype DX HER2 RT-PCR.” The Oncotype DX Breast Cancer Test is a standard of care test that predicts risk of breast cancer recurrence in patients with early stage disease. This information is extremely useful to oncologists in eliminating overtreatment of low risk patients. Although HER2 is among the markers in the test, it is not intended to be independently used for therapy decisions. Thus, as misleadingly implied by FDA, neither the Oncotype DX Recurrence Score nor its underlying markers are intended to guide the decision to use trastuzumab. Rather, independent HER2 testing is generally performed for this purpose in advance of ordering Oncotype DX. The specific HER2 data provides more detailed information that can be useful to physicians in interpreting the Oncotype DX Breast Cancer results. Although treating physicians requested the individual information for HER2 as a comparator for the commonly used HER2 tests, which occasionally yield ambiguous results, the HER2 information provided as part of the Oncotype DX Recurrence Score must be assessed by physicians in the context of the other clinical and laboratory data in their evaluation of the patient. It is important to note that less than 1% of Oncotype DX tests are performed on HER2 positive tumor tissue as the test is explicitly intended for estrogen receptor positive and *HER2 negative* disease. Extensive data have supported use of the Oncotype DX test to help guide chemotherapy treatment decisions in more than 500,000 breast cancer patients to date, including prospective outcomes in the NCI-sponsored TAILORx study, one of the largest-ever adjuvant breast cancer clinical trials. (For relevant references, see footnotes ^{12,13}.)

Conclusion: FDA seems to presume an intended use that does not exist. Oncotype Dx Breast Cancer Test is used to predict risk of breast cancer recurrence in patients with early stage disease, not to guide decisions about the use of trastuzumab. The test is valid for its intended purpose and FDA review would not have revealed any issues with analytical and clinical validity.

Human Papillomavirus Test using SurePath Collection Medium:

FDA Analysis: Tests used with the SurePath collection medium have unknown sensitivity.

Facts that FDA ignored: This is a case where CLIA and/or its surrogates did not properly assure that its statutory requirements for proper validation were performed by laboratories performing HPV testing with FDA approved HPV tests and using alternative sample types. CLIA requires that any deviation from an FDA cleared/approved test be shown through validation that its performance is not adversely affected by those changes in the laboratory’s patient population. This includes not only analytical validation, but also validation of any other parameters of importance, including sample stability.

FDA has demonstrated in their case study for the use of Surepath for HPV testing that they lack fundamental understanding of not only the science of cervical cancer screening, but also the practice of medicine involved in cervical cancer screening. FDA approval of a test for use with a specific transport medium does not assure adequate clinical performance of a test. FDA referenced a newspaper article that relied on anecdotes and no

¹² Sparano, J.A. et. al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015; 373: 2005-2014.

¹³ <https://clinicaltrials.gov/show/NCT00310180> Accessed December 10, 2015

bibliographic citations for any peer-reviewed scientific journal articles to support its suppositions. In addition, the author of the newspaper article extrapolated that an unconfirmed number of cervical cancers were missed based on a small study. Studies have shown issues with false negative results with FDA approved tests using FDA approved transport medium.^{14,15}

The June 2012 technical bulletin cited by the FDA stating that the use of cervical samples in the SurePath collection medium for HPV testing “may, under certain conditions, provide false-negative results” actually references a study performed by the manufacturer of Surepath medium and looked at only one of the six FDA approved HPV tests. That study did not use clinical specimens but instead used simulated samples in which cultured cell lines were spiked into negative Surepath medium. The results demonstrated that false negatives occurred only after 5 weeks of sample storage, a time period beyond which virtually all clinical cervical cancer screening samples are routinely tested as part of cervical cancer screening.¹⁶ Therefore, the risk of false-negatives due to the use of Surepath medium is virtually negligible.

FDA has also selectively cherry-picked a portion of the latest professional society guidelines for cervical cancer screening to support its position by stating those guidelines state that LDPs should not be used for HPV testing (with FDA claiming that the use of an FDA approved HPV test with Surepath is an LDP). Those same guidelines¹⁷ also state that other HPV tests that have been clinically validated so that the sensitivity of HPV testing for CIN3+ and CIN2+ should be greater than or equal to 90%, and the percentage of women in the general population who test (screen) positive, as a measure of false positive results, should be less than or equal to established thresholds from well-validated HPV DNA tests^{18,19,20}. All of the FDA approved HPV tests have met those criteria using Surepath samples with studies published in the peer-reviewed literature. This includes the ARTISTIC Study, used by the United Kingdom to approve HPV testing from Surepath samples as part of the NHS cervical cancer screening program. The study found that most of the FDA approved HPV tests met the requirements stated above when using Surepath as the sample type.²¹

Conclusion: FDA approval of HPV tests is not based on higher level of evidence than what is used by health care professionals to validate LDPs. Concerns about false negatives have to do with samples stored beyond five weeks, which is something that can and should be addressed by CLIA.

Non-invasive Prenatal Testing (A.K.A. Cell-free DNA testing)-

FDA Analysis: FDA claims that non-invasive prenatal testing (NIPT) lacks clinical validation to properly detect and predict fetal abnormalities at an appropriate rate, and may lead to false negatives and positives. FDA believes its oversight would ensure the test meets minimum performance standards and proper evaluation of manufacturer claims.

¹⁴ Castle PE, Fetterman B, Thomas Cox J, Shaber R, Poitras N, Lorey T, Kinney W. 2010. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. *Obstet Gynecol* 116:76-84.

¹⁵ *J Lower Genital Tract Disease* 2010; 14: 247A, 255A

¹⁶ 980-08364-00 Rev 1. Summary Document BD SurePath™ Sample Stability

¹⁷ (*Am J Clin Pathol.* 2012;137(4):516-42)

¹⁸ Meijer CJ, et al. 2009. *Int J Cancer.* 124:516-520.

¹⁹ Stoler MH, et al. 2007. *Am J Clin Pathol.* 127:335-337.

²⁰ Kinney W, et al. 2010. *Am J Clin Pathol.* 134:193-199.

²¹ Moss SM, et al. 2014. Comparison of the performance of HPV tests in women with abnormal cytology: results of a study within the NHS cervical screening programme. *Cytopathology* 25(5): DOI: 10.1111/cyt.12210.

Facts that FDA ignored:

1. NIPT tests for the presence of an abnormal number of chromosomes are available from several laboratories. Studies have demonstrated clinical validity with improved sensitivity and specificity over the traditional maternal serum screening (MSS). Analytical studies have shown high accuracy and reproducibility.

FDA oversight requirements most likely would impede this innovative test from being offered, resulting in countless unnecessary invasive procedures. LDPs adhering to rigorous CLIA validation have benefitted thousands of women. FDA has not provided evidence that problems exist with NIPT screening, or that FDA review would have prevented false results, or impacted a woman's decision to terminate without confirmation with a diagnostic test. Finally, FDA provided no analysis of the public health impact of preventing unnecessary invasive procedures. Such an analysis by Benn et al. demonstrated that NIPT screening reduced invasive procedures by 60%, and procedure-related loss of normal fetuses by 73.5%.²²

2. NIPT is a screening test, not a diagnostic test, and therefore confirmatory testing such as chorionic villus sampling (CVS) or amniocentesis is necessary. Both the American College of Obstetrics and Gynecology (ACOG) and the American College of Genetics and Genomics (ACMG) recommend confirmatory testing. An updated opinion from the ACOG in 2015 states that "any woman may choose to have NIPT DNA screening," and notes that the clinician should explain the benefits and limitations of screening.²³ This committee opinion also stressed in their recommendations that the clinician should recommend a diagnostic test when a patient has a positive NIPT result. Management decisions such as termination of pregnancy should never be based on the screening test alone. Furthermore, guidelines from ACMG recommend that NIPT aneuploidy screening should not replace a first-trimester ultrasound. ACMG also reiterates the need for confirmatory testing, stating that "NIPS is not diagnostic; therefore, confirmatory testing (chorionic villus sampling or amniocentesis) is recommended, and the risks of those procedures should be reviewed." FDA review of the LDPs would not have prevented terminations in women who were not offered, or who were offered and declined, confirmatory testing.
3. The rarity of fetuses with trisomy 18 and trisomy 13 reduces the positive predictive value for these aneuploidies, regardless of whether the test is FDA approved or not. Prenatal screening tests are important to avoid the risks of miscarriage and other dangers inherent with invasive procedures such as amniocentesis and CVS. Studies have shown NIPT to have a false positive rate of 0.08%.²⁴ The non-invasive test that FDA recommends as an alternative ("quad testing of multiple substances combined with ultrasound imaging") has a detection rate of 75-80% and a false positive rate of 5-6% (trisomy 21), and a detection rate of approximately 80% with a false positive rate of <0.5% (trisomy 18)²⁵, generating many more false positive and false negative results than the NIPT screen. Of note, the often used "quad

²² Benn, P et al. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. PLOS One 2015 10(7): e0132313. doi:10.1371/journal.pone.0132313

²³ Cell-free DNA screening for fetal aneuploidy. Committee Opinion No. 640. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e31-7.

²⁴ Dar P, Curnow KJ, Gross SJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. American J Obstet Gynecol. 2014;211(5):527.e1-17.

²⁵ <http://ltd.aruplab.com/Tests/Pdf/311> Accessed December 9, 2015

test” is not FDA cleared for trisomies; neither is the diagnostic (confirmatory) chromosome analysis. These tests are offered only as LDPs. (For other relevant references, see footnotes ^{26,27}.)^{28,29}

Conclusion: NIPT is a screening test with higher sensitivity than currently available (non-FDA cleared) maternal serum screening for trisomies. A treating physician should confirm any screening test result with diagnostic testing prior to performing a pregnancy termination. This falls within the practice of medicine and FDA oversight would not address physicians who inappropriately follow up on screening tests. This is best addressed through practice guidelines, which have already been finalized by ACOG and ACMG.

Fibromyalgia FM/a Diagnostic Test:

FDA Analysis: FDA maintains the biomarker has not been shown to be associated with fibromyalgia.

Conclusion: Modernized CLIA oversight that utilizes third party medical experts, such as that proposed by AMP, would appropriately assess LDPs for clinical validity.

KIF6 Genotyping Test to Predict Heart Disease Risk and Statin Therapy Response:

FDA Analysis: FDA maintains that the marker has not been adequately validated.

Conclusion: Modernized CLIA oversight that utilizes third party medical experts, such as that proposed by AMP, would appropriately assess LDPs for clinical validity.

Target Now Cancer Biomarker Test:

FDA Analysis: The panel used by Target Now to suggest chemotherapy has not been shown to have an impact for a patient's particular cancer.

Facts that FDA ignored: To our knowledge, Target Now was used most often in patients who had rare tumors without established treatment protocols or in cancer patients who had exhausted all other therapeutic options. The test extrapolated potential effects of therapies that appeared for one or more active tumors with specific genetic markers to other tumor types with those same markers. The test therein provided a potential scientific rationale to treat end-stage or otherwise untreatable cancer patients. Although ultimately therapy is a joint decision between the patient and her or his oncologist, and insurance companies are reluctant to pay for expensive therapies administered on the basis of limited clinical evidence, it is quite possible that some or many

²⁶ Grody, W.W., et al. 2013. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med*; 15: 482-3

²⁷ Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M. 2015. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. *PLOS One* | DOI:10.1371/journal.pone.0132313

²⁸ Palomaki GE et al., DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study *Genet Med* 2011;13:913-20

²⁹ Bianchi DW et al., Integration of noninvasive DNA testing or aneuploidy into prenatal care: What has happened since the rubber met the road? *ClinChem*2014;60:78-87

patients have been helped by the Target Now test. However, given the clinical state of these dying cancer patients, it seems unlikely that significant harms resulted from its use, and whatever harms, if any, that resulted from its use clearly outweighed the possible benefits arising from use of the test. Finally, we believe the CLIA regulations should be administered to more thoroughly scrutinize tests of this nature to help resolve these important questions.

Conclusion: The test was likely administered to terminal cancer patients with limited options. Tests developed based on scientific evidence used in the context of a patient's clinical condition should be available especially in cases of compassionate care use.

Prolaris Prostate Cancer Biomarker Test:

FDA Analysis: FDA believes the test was not evaluated for its ability to meaningfully improve clinical outcomes as claimed by the laboratory.

Facts that FDA ignored: Prostate cancer is the most common malignancy in elderly men with autopsy studies suggesting that over 25% of men may have the disease. In the vast majority of cases, prostate cancer is an indolent disease that will not progress in a significant manner during patients' lifetimes. However, in a minority of patients, prostate cancer can be a very aggressive disease causing substantial morbidity and death. A major current medical challenge is identifying the small number of patients in whom prostate cancer will progress in order to provide more aggressive therapies so as to cure or minimize the impact of the cancer. The test at issue is one potential solution to this key clinical problem, and is used to predict recurrence following prostatectomy. Although FDA criticizes the absence of prospective studies that establish the effectiveness of the test, the test's use is supported by peer-reviewed retrospective studies.³⁰ Prospective studies are time consuming and expensive, and could delay introduction of a potentially important advance for years. The decision to use this test based on currently available data is a decision for the patient, his physician, and potentially his health insurance company. Of note, Medicare covers this test, and we are unaware of any evidence of harm resulting from its use.

Importantly, the FDA-approved prostate specific antigen test (PSA) fails to meaningfully improve clinical outcome in U.S. patients when used for screening, and the US Preventive services Task Force recommends against its use.³¹ There is abundant clinical evidence that suggests that the FDA approved PSA screening may do more harm than good. Indeed, it seems likely that the original FDA approval of PSA screening led to vast overuse, many unnecessary prostate biopsies, and diagnosis of cancer in men who would not have died of disease. (For another relevant reference, see footnote ³²)

Conclusion: Use of this test is supported by peer reviewed scientific journal articles. FDA review would delay patient access to useful tests that are interpreted in the context of other clinical information and possibly, more informative than FDA approved tests.

³⁰ Cuzick, J, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet* 2011: 245-255

³¹ <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening> Accessed December 12, 2015

³² Validation of a Cell-cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort. Cooperberg MR, Simko JP, Cowan JE, et al. *J Clin Oncol.* 2013;31:1428–1434

Chronic Fatigue Syndrome XMRV Test:

FDA Analysis: FDA observed that an initial assertion that XMRV was linked to chronic fatigue syndrome was disproven.

Facts that FDA ignored: The observation that XMRV was not, in fact, associated with chronic fatigue syndrome probably had little medical significance. The diagnosis of chronic fatigue syndrome is made on the basis of clinical characteristics, including the exclusion of other disease conditions, and there is no indication that there was any significant clinical reliance upon XMRV testing to make the diagnosis. All evidence suggests that every lab that ran this test accurately determined the presence or absence of XMRV. Clinical investigation rapidly determined that original case reports linking XMRV to chronic fatigue syndrome were based on the presence of a contaminant. Specimen contamination is the type of issue that CLIA can identify, and that is not generally amenable to identification in the FDA review process. False association between a potential organism and a disease is routinely found in the scientific process.

Conclusion: Issues with the test were a result of laboratory operations that are under the jurisdiction of CLIA. Modernized CLIA oversight that utilizes third party medical and scientific experts, such as that proposed by AMP, would have appropriately assessed this LDPs for clinical validity.

CARE Clinics Autism Biomarker Test:

FDA Analysis: FDA asserts there is no evidence that the biomarkers identified by the test correlate with autism leading children to undergo unnecessary treatment.

Facts ignored by FDA: There is no evidence that testing was performed in a CLIA accredited laboratory. More important, the CARE clinics were operating entirely outside the spectrum of acceptable medical practice. The use of chelation therapy, hyperbaric oxygen, and intravenous vitamin therapy are inappropriate medical practice for children with autism spectrum disorders, and are far outside the scope of laboratory medicine. The CARE autism clinics case represents an example of improper conduct that extends far beyond any of the putative 'laboratory tests' used to perpetuate this apparent scheme. There are other more appropriate vehicles for addressing the apparently fraudulent behavior FDA illustrated in this case. The CARE autism clinics were willing to use hyperbaric oxygen therapy off-label despite clear evidence that FDA takes enforcement action against this off-label use. Therefore, it is unclear why FDA believes additional authority to regulate LDPs would have enabled more effective or timely action against the Center for Autism Spectrum Disorders.

Conclusion: There is no evidence that the test was performed by a CLIA accredited laboratory. Modernized CLIA oversight that utilizes third party medical experts, such as that proposed by AMP, would appropriately assess this LDP for clinical validity. Additionally, these clinics were providing treatments not accepted as appropriate medical practice. State medical practice boards have the authority to deal with substandard medical practice.

Heavy Metal Chelation Challenge Test:

FDA analysis: FDA claims that in clinical use, patients with positive urine chelation challenge tests may not have heavy metal toxicity and the laboratory claims are unsupported by evidence.

Facts that FDA ignored: The practices described in the FDA analysis have little, if anything, to do with the use of LDPs. Administration of toxic heavy metals to children and the use of chelation therapy are not within the standard of care for medical practice. The willingness to use unacceptable medical therapies is not predicated upon the existence of any laboratory test, but rather a willingness to ignore medical evidence. State medical practice boards have adequate authority to deal with substandard medical practice. Laboratories that perform the standard tests per clinicians' request will not know if chelation therapy was or was not performed. LDPs to detect heavy metals, used appropriately, can identify individuals with high levels and at risk for associated toxicities. Of note, an LDP was developed to detect high levels of cobalt and chromium to address a failure by the FDA to identify a risk from metal-on-metal implants.³³

Conclusion: The problem is not the accuracy of the test, but the use of therapies not within the standard of care for medical practice. FDA review of the LDP would not address the problem of substandard medical practice.

OMAPRO Companion Diagnostic to New Leukemia Medication:

FDA Analysis: FDA claims that lack of standardized LDPs led to unreliable selection of patients for clinical trial enrollment; drug sponsor used two different, non-comparable LDPs to enroll patients in a clinical trial; researchers did not obtain the proper investigational device exemption needed to carry out a research study.

Facts that FDA ignored: FDA describes an issue of detection of a molecular genetic marker, the T315I resistance mutation in chronic myelogenous leukemia (CML), the presence of which is associated with response to a novel therapy targeted to that marker. Although assays can vary in their sensitivity at detecting the genetic marker, response to the drug is generally accepted to be based on the presence or absence of the marker, and therefore the method by which it is tested is irrelevant. The trial sponsor utilized two different methods to assess for the presence of the marker. It was FDA's decision to invalidate the results of the trial and to delay introduction of the drug with a general disregard of this fundamental principle. Although we do not have access to the underlying trial data, we suspect that the decision not to accept the trial data was probably an overly conservative choice by the Agency.

While it is reasonable to expect the clinical trial design to use a single test, the performance of the LDPs themselves was not at fault. Many laboratories currently offer LDPs to detect the T315I mutation in CML, which is found in approximately 20% of patients with resistance to older therapies for CML (e.g. imatinib). In delaying introduction of the drug, apparently based on its own bias, FDA injured the many patients who had no effective and available drug therapy to treat their leukemia.

Interestingly, in analyzing this important drug for CML patients, FDA deviated from prior precedent as the Agency previously approved Herceptin® for treatment of breast cancer on the basis of a clinical trial that used two different immunohistochemical LDPs for subject selection.³⁴ (For relevant references, also see footnotes ^{35,36}.)

³³ Towers SS. 2010. Arthroprosthetic Cobaltism: Neurological and Cardiac Manifestations in Two Patients with Metal-on-Metal Arthroplasty. *The Journal of Bone & Joint Surgery*. 92-A(17):2847-2851.

³⁴ FDA Premarket Approval P980018, original submission.

³⁵ Omacetaxine: The FDA Decision. Ellin Berman, MD Attending Physician Leukemia Service Division of Hematologic Oncology Memorial Sloan-Kettering Cancer Center New York, New York.

³⁶ Advances in LLM. Current Developments in the Management of Leukemia, Lymphoma, and Myeloma. Section Editor: Susan O'Brian, MD.

Conclusion: FDA has approved other drugs based on clinical trials using two different LDPs, thus offering support for this practice and the agency has failed to be consistent in its requirements. Enhanced transparency about the sensitivity of the test would allow for expert comparison of LDPs, which can be accomplished through CLIA.

Duke University Chemotherapy Assessment Test:

FDA Analysis: Errors in data management and analysis; lack of clinical validation.

Facts that FDA ignored: This test was never offered to patients in a clinical setting. Further, the controversies surrounding the clinical trials in question resulted from investigator misconduct and data falsification involving this NIH-supported research and was not due to the performance of an LDP. In 2009, three clinical trials involving the NIH-funded research came under scrutiny after peer review and an independent analysis of published literature. The trials were initially suspended and then permanently stopped in 2010. Interestingly, FDA reviewed one of the studies in 2009, several years after its initiation, and concluded that the study would require an Investigational New Drug application, which had not been submitted. An FDA audit in 2011 further showed that an Investigational Device Exemption application had not been filed, but otherwise found no significant deficiencies in Duke's Institutional Review Board conduct. FDA oversight of LDPs is unlikely to have solved problems of research data falsification and investigator misconduct. (For relevant reference, also see footnote ³⁷.)

Conclusion: This test was not offered in a clinical setting and did not cause patient harm. FDA review of an LDP would not uncover scientific misconduct and data falsification within a broader research study.

Vitamin D Deficiency Test:

FDA Analysis: FDA suggests that the test in question gave incorrect results due to faulty calibration of the test and lack of standardization.

Facts that FDA ignored: The laboratory company at issue found that a small percentage of its tests may possibly have provided inaccurate results because some of its laboratories did not follow proper procedures, and some calibration materials may have been faulty. Failure of laboratory personnel to follow established procedures is a CLIA issue, and problems with calibrators can occur with FDA-cleared tests as well. In fact, rather than requiring FDA intervention, the Company upon discovery of possibly erroneous results was diligent and extremely inclusive in notifying providers despite the likelihood that most of the reported results were indeed correct.

FDA failed to present evidence of significant patient harms that resulted from possible inaccuracies in this vitamin D testing and actually failed to present any evidence of harms at all. It is noteworthy that the Institute of Medicine in a 2011 report³⁸ demonstrated skepticism about the clinical utility of the FDA-cleared vitamin D tests in common use, noting that:

- The lack of clarity concerning the validity of the serum 25OHD measure as a biomarker of effect;

³⁷ Evolution of Translational Omics: Lessons Learned and the Path Forward. IOM Report 2012. ISBN 978-0-309-22418-5 | DOI 10.17226/13297

³⁸ <http://www.nap.edu/read/13050/chapter/2#12> Accessed December 12, 2015

- The variability surrounding measures of serum 25OHD concentrations owing to different methodologies used;

Based on the IOM analysis, it is difficult to support the FDA contention that the LDP in question would be more likely to result in clinical harm than the FDA-cleared comparison device. Finally, CLIA inspection is better suited to identify the types of analytical errors ultimately identified in association with this testing than is FDA pre-introduction review.

Conclusion: Failure of laboratory personnel to follow established procedures is a CLIA issue and problems with calibrators can occur with FDA-cleared tests as well. FDA review would not have solved this issue. CLIA inspection is better suited to identify the types of analytical errors ultimately identified in association with this testing than is FDA pre-introduction review.

OncoVue Genetic Breast Cancer Risk Test:

FDA Analysis: FDA suggests that OncoVue lacked validation of test performance in clinical use and the specificity of the LDP was not assessed. FDA believes its oversight would assure the LDP meets minimum performance standards and would evaluate laboratory claims.

Facts that FDA ignored:

1. Irrespective of the relative merits of this test in combination with current risk assessment parameters for breast cancer versus use of contemporary risk assessment parameters alone, this test, merely provides information additional to those screening tests for increased breast cancer risk. It is not a test for diagnosis of breast cancer. As stated on the Company's website:

OncoVue® is not intended as a stand-alone test for the determination of breast cancer risk in women. OncoVue® results are intended for use by physicians as a predictive tool only in conjunction with other breast cancer risk assessment tools such as the Gail Model, family history, lifestyle factors, breast density and other clinical factors which may contribute to breast cancer risk.³⁹

2. Therefore, despite questions about the quality of the underlying data supporting improvements to existing risk assessments and the extent of any such improvements, these data would be incorporated and their significance weighted by patients' treating physicians. Moreover, given that this test is used in conjunction with existing, commonly used risk factors for breast cancer to improve patient risk assessment, potential harms from its use seem likely to be limited. Finally, we believe the CLIA should be administered to more thoroughly scrutinize tests of this nature to help resolve these important questions. (For other relevant references, see footnotes ^{40,41}.)

³⁹ <http://www.gentesttx.com/physicians-oncovue-and-practice.html>. Accessed December 12, 2015

⁴⁰ Cancer Res 2013;73(24 Suppl): Abstract nr P2-14-05.

⁴¹ Jupe E, Pugh T, Knowlton N et al. Accurate Identification of Women at High Risk of Breast Cancer Using OncoVue. 2010 San Antonio Breast Cancer Symposium; Poster P6-09-04.

Conclusion: This test is not intended for the diagnosis of breast cancer and appropriate follow up should occur to confirm a diagnosis. Third party expert review of the test through the CLIA program should be used to scrutinize the test.

BRAF V600E Genetic Mutation Test to Guide Melanoma Treatment:

FDA analysis: FDA suggests that there is a lack of evidence to support laboratory claims that LDPs performs better. FDA believes its oversight would ensure the test meets minimum performance standards and proper evaluation of laboratory claims.

Facts that FDA ignored:

1. The FDA approved test reliably detects only a single codon 600 mutation, V600E. Therefore, use of the FDA approved test would deny patients with other V600 mutations such as V600K, the benefit of potentially effective treatment with BRAF targeted therapies.
2. BRAF testing has been effectively performed as an LDP for over 10 years, most commonly for patients with colon cancer and thyroid cancer. Therefore, it is disingenuous and misleading for FDA to imply that the manufacturer it cited discovered the BRAF marker or invented BRAF testing.
3. The logical conclusion to which FDA's reasoning leads, is that laboratories would need to order the particular FDA approved test for each drug that is directed toward any given molecular marker. This impractical and unnecessary reasoning means that FDA would force laboratories to maintain multiple tests for the identical marker, with the use of each test solely dependent on the specific drug the physician would want to give.
4. The deficiencies in FDA's position are well-illustrated by the FDA approved test for KRAS-mutation testing in metastatic colorectal cancer. KRAS testing is used in this setting to identify patients who will not benefit from antibody therapies directed toward the epidermal growth factor receptor. The FDA approved KRAS test only assesses for a limited number of KRAS mutations, those in codons 12 and 13 in exon 2. By contrast, medical guidelines such as those promulgated by the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO) both recommend extended KRAS testing including additional mutations in exons 3 and 4. Thus, the FDA approved KRAS test has rapidly become obsolete. All extended KRAS testing is performed using laboratory developed procedures. Forced use of the FDA approved KRAS test would overtly conflict with recommended medical practice and would severely compromise patient care.

(For an additional relevant reference, see footnote ⁴².)

Conclusion: BRAF LDPs provide superior patient care over the FDA approved test and better identify patients that could respond to targeted therapy. The FDA approved KRAS test has rapidly become obsolete and is an excellent example of how FDA review could slow innovation.

⁴² Puzanov I, Amaravadi RK, McArthur GA, Flaherty KT, Chapman PB, Sosman JA, Ribas A, Shackleton M, Hwu P, Chmielowski B, Nolop KB, Lin PS, Kim KB. Long-term outcome in BRAF(V600E) melanoma patients treated with vemurafenib: Patterns of disease progression and clinical management of limited progression. *Eur J Cancer*. 2015;51:1435-43.