Comment and Response Document for our DRAFT Molecular Diagnostic Testing Policy

Comment: The: Draft language: General Coverage Rules: "*No additional "personalized medicine" or "therapy-directing" testing will be included under the coverage purview of this LCD."* It is not clear how this statement should be interpreted and what it means in terms of coverage of tests that might be interpreted to be included as 'personalized medicine' or 'therapy-directed' testing.

Response: The intent was to indicate we are only addressing the specific tests we have outlined in the LCD. We agree, that is a bit confusing and have removed it from the document.

Comment: The Draft language specifically the General Coverage Rules and Documentation identified in Appendix A. *"Instead, providers are reminded that we will allow payment for such tests, either those currently available or those to be brought into use in the future, based on applicable FDA approval and labeling (if such exists) and appropriate Medicare regulations and its standards of medical reasonableness and necessity*"

You may already be aware, many molecular pathology tests have not been FDA cleared or approved. In fact, FDA approval is not required for laboratory developed tests which are validated under the authority of CLIA and other laboratory certifying agencies. Their safety and effectiveness has been established with studies that demonstrate analytic validity, clinical validity and clinical utility under CLIA, CAP, ACMG etc. guidance.

Response: the inclusion of "*if such exists"* was meant to indicate FDA labeling may not be available. We have reworded this sentence to: Providers are reminded that we will allow payment for such tests, either those currently available or those to be brought into use in the future, based on applicable approval such as FDA labeling, if such exists, CLIA and appropriate Medicare regulations and its standards of medical reasonableness and necessity.

Comment: As we review the narrative, it is our understanding that this Draft LCD separates the molecular pathology tests into 3 groups. One group is for those tests that are covered for specific conditions (Indications I-VII, ICD-9 Codes that Support Medical Necessity) and another group is for those tests that are not covered and the rest of the codes there is no policy.

It is our understanding that claims submitted for the tests in the 3rd group will be paid with the assumption **t**hat they meet the criteria provided: they are FDA cleared (e.g. 510K) or approved (PMA) tests, if they meet standards of medical reasonableness and necessity and the 4 criteria listed and the lab criteria listed. We understand that the indications for the test need to be documented and that documentation provided upon request. If it is not the intent of the narratives, we request the language be modified to clarify the intent. We would also recommend including tests that have been cleared by the FDA (e.g. 510K) or other Medicare regulations which include CLIA as its designates.

Response- Yes, the LCD addresses specific tests that will be covered under certain conditions and we have a second list of procedures that we have reviewed and determined to be not covered. Tests that are not listed in this LCD are subject to medical reasonable and necessary requirements. We have included CLIA. See our response above.

Comment: We received a few comments on the 4th criteria of our Lab requirements-
4. Credentialing of laboratory directors and staff by the American Board of Medical Genetics (ABMG).
Requiring lab directors to be ABMG – certified in order to bill Medicare for otherwise – appropriate Molecular Diagnostic Testing is arbitrary and unnecessary under CLIA. The CLIA guidelines at 42 CFR 493.1433 generally require lab directors to be licensed as such by the state; be a board – certified doctor of medicine or osteopathy,

and; have either direct training or experience in A) conducting the relevant kinds of testing, and/or B)supervising lab technicians in conducting the relevant kinds of testing.

"It is the Centers for Medicare & Medicaid Services (CMS) that regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). The objective of the CLIA program is to ensure quality laboratory testing. All clinical laboratories must be properly certified to receive Medicare or Medicaid payments. (CMS/CLIA)

Response: We have changed # 4 to laboratory director must hold an earned doctoral degree in a chemical, physical, biological or clinical laboratory science from an accredited institution and be certified and continue to be certified by a board approved by HHS. Currently, there are 10 boards listed on CMS website- http://www.cms.gov/Regulations-and-uidance/Legislation/CLIA/Certification_Boards_Laboratory_Directors.html

Comment: As noted in the draft policy, there are other cancers associated with Lynch Syndrome: "Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel". We request that testing be covered when any of these are present consistent with the Revised Bethesda Guidelines, used by the CDC2, EGAPP3, and NCCN4 in making their recommendations for testing:

In molecular testing for Lynch Syndrome, genetic testing is usually not the first step. The algorithms for testing recommend starting with testing for microsatellite instability (MSI), Mis-Match Repair deficiency by immunohisto-chemistry (IHC) and methylation status by *BRAF* V600E mutation determination and/or hMLH1 promoter methylation analysis.

We recommend adding CPT codes for these tests to the list of covered procedures for HNPCC.
• Microsatellite instability - CPT Code 81301
• *BRAF* V600E Variant – CPT 81210

Comment:
Primary colorectal carcinoma (CRC) is a solid tumor that occurs commonly in US adults, with approximately 142,000 new cases in 2011. Loss-of-function defects in DNA mismatch repair (MMR), which manifest as microsatellite instability (MSI), occur in approximately 15% of CRC. Most MMR-deficient CRC is sporadic, but 15-20% is due to an inherited predisposition known as Lynch Syndrome. There is a high penetrance of CRC in germline MMR gene mutation carriers. Cancers of other organs also are associated with Lynch Syndrome. In addition to identification of specific mutations in hMLH1, hMSH2, hMSH6 and PMS2 noted in Part II, many laboratories, including SBMF, perform MSI by PCR and/or MMR by immunohistochemistry (IHC) on CRC tumor tissue. We believe coverage should be extended for these tests. Recent NCCN Guidelines v2.2013 for Lynch Syndrome indicate that CRC should be tested for Lynch Syndrome by IHC and/or MSI when the patient is younger than 50; there are synchronous or metachronous CRC or other LS-related tumors, regardless of age; the CRC has histologic features associated with MSI-H in a patient who is younger than 60 years of age; CRC is diagnosed in a patient with one or more first-degree relatives with an LS-related cancer, with one of the cancers diagnosed under age 50; and when CRC is diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancers, regardless of age. Additionally, the IHC MMR test, when positive, may be helpful in directing the more expensive sequencing assay to the specific implicated gene.

Response:
We have added CPT codes 81301 and 81210 and 88342 to our policy. We agree the list of colorectal cancer and endometrial cancer at the end of this section is confusing. They have been removed. We have modified the policy to include the Revised Bethesda and Amsterdam criteria II.

Comment: CPT code 81403, a Tier 2 molecular pathology code, as the BCR/ABL test which is may be covered under a particular set of diagnosis codes. This is the incorrect code to use for BCR/ABL testing. While CPT code 81403, representing Tier 2 Level 4 molecular pathology procedures, does contain a test for the ABL1 gene, this test is rarely performed. The common and more clinically accepted testing practice involves CPT codes 81206 (BCR/ABL1 translocation analysis; major breakpoint, qualitative or quantitative) and 81207 (minor breakpoint, qualitative or quantitative), and these are the BRL/ABL CPT codes which should be covered for the set of diagnosis codes listed in the Draft LCD. The diagnosis codes that meet coverage criteria for testing for the BCR/ABL fusion gene should include several additional diagnosis codes:
201.x, Hodgkin's diseases
245.2, Chronic lymphocytic thyroiditis
288.50, Leukocytopenia, unspecified
288.61, Lymphocytosis, symptomatic
288.62, Leukemoid reaction

Response:
We have added CPT codes 81206 and 81207. No literature was given to support the additional diagnosis codes.

Comment: The Draft LCD states, "APC and MYH gene testing for Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP), or MYH associated polyposis (MAP) is covered for the following individuals: (1) A beneficiary with ≥ 20 cumulative colorectal adenomas over a lifetime…" This statement presents numerous potential problems for clinical laboratories providing this testing. As a threshold matter, logically, a beneficiary's lifetime is not complete at the time of testing; it is possible that WPS means "≥ 20 cumulative colorectal adenomas prior to the time of testing." Even if this were WPS's intention, clinical laboratories still may have difficulty complying with this policy. A beneficiary likely has seen numerous physicians throughout his or her lifetime, so it may be difficult or impossible for a clinical laboratory to discern the number of colorectal adenomas to date. While a physician ordering an APC or MYH test may have access to a more complete version of a beneficiary's medical record, a clinical laboratory – whose payment depends on meeting this criteria – most likely does not. (A physician also may have difficulty determining whether this criterion has been met, since even in the midst of widespread transition to electronic health records, most beneficiaries' complete medical records are not in one place.)

Additionally, this standard of "≥ 20 cumulative colorectal adenomas prior to the time of testing" is twice as stringent as current NCCN guidelines, which advise APC and MYG for patients with a personal history of ≥ 10 adenomas. ACLA believes that WPS should bring any such metric in its coverage policy more in line with professional society guidelines which are grounded in peer-reviewed clinical data.

Response: We reviewed the NCCN Colon Cancer Screening Guidelines (v2.2013) and have changed the policy to ≥ 10 adenomas.

Comment: Will CPT 81225 CYP2C19 gene, to determine a patient's ability to metabolize Plavix, will the provider be given an opportunity to demonstrate that the procedure is medically reasonable and necessary, or does the draft LCD state that such procedures will not be reimbursed under any circumstances?

Response: CPT codes 81227 (CYP2C9) and 81355 (VKORC1) will be covered in accordance with NCD 90.1 and should be reported with HCPCS code G9143 warfarin responsiveness testing and 1 unit of service. Information on Pharmacogenomic Testing for Warfarin Response can be found in the Internet Only Manual (IOM) Pub 100-03 National Coverage Determinations, section 90.1 and Pub 100-04 Medicare Claims Processing, Chapter 32, sections 250.1-250.3.
This information has been added to our Billing and Coding Guidelines that is associated with this LCD.

Comment: EGFR mutation analysis and ALK1 assessment for Non-Small Cell Lung Carcinoma (NSCLC), particularly adenocarcinoma: The Draft document does not mention genetic testing for NSCLC. We believe coverage should be extended for these tests. According to a recent practice guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (Arch Pathol Lab Med loi: 10.5858/arpa.2012-0720-OA), testing for EGFR mutations and ALK fusions should be used to guide patient selection for therapy with an epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitor, respectively, in all patients with advanced-stage adenocarcinoma of the lung, regardless of sex, race, smoking history, or other clinical risk factors.

Response: We have added CPT 81235 and the following information to our LCD:
Epidermal growth factor receptor (EGFR) mutation testing is indicated for patients with NSCLC who are being considered for first-line therapy with an EGFR tyrosine kinase inhibitor (TKI), i.e., for patients who have not previously received chemotherapy or an EGFR TKI, should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy. This will be covered for diagnosis codes 162.0-162.9 malignant neoplasm of trachea - malignant neoplasm of bronchus and lung unspecified and 163.0-163.9 malignant neoplasm of parietal pleura - malignant neoplasm of pleura unspecified

Comment: BRAF mutation analysis in melanoma treatment: Skin cancer is by far the most common of all cancers. While malignant melanoma accounts for less than 5% of skin cancers, it causes a large majority of deaths due to skin cancer. The rate of melanoma is increasing in the United States, and it is estimated that about 76,690 new cases will be diagnosed in 2013 (American Cancer Society). About half of all melanomas have mutations in the BRAF gene. Analysis for BRAF V600E, V600K, and possibly other BRAF mutations is currently recommended to select patients with metastatic melanoma who will more likely benefit from vemurafenib, dabrafenib, or trametinib therapy. We believe coverage should be extended for this test.

Response: Literature was not submitted to support adding this to our policy.

Comment- We received several requests to expand our covered diagnosis code list. Below is a list of requested diagnosis codes and our responses:

Request for colorectal cancer (HHPN) diagnosis codes:
151.0 - 151.6 Malignant neoplasm of cardia - malignant neoplasm of greater curvature of stomach unspecified
151.8 Malignant neoplasm of other specified sites of stomach
151.9 Malignant neoplasm of stomach unspecified site
(152) Malignant neoplasm of small intestine, including duodenum (152.0-152.3, 152.8, 152.9)
155.0 - 155.2 Malignant neoplasm of liver primary - malignant neoplasm of liver not specified as primary or secondary
155.1 Bile ducts Adenocarcinoma Low, but increased
151.0-151.9 Stomach Adenocarcinoma
156.1 Malignant neoplasm of extrahepatic bile ducts
156.9 Malignant neoplasm of biliary tract part unspecified site
157.0-157.9 Pancreas Adenocarcinoma
189.0 - 189.2 Malignant neoplasm of kidney except pelvis - malignant neoplasm of ureter
189.8 Malignant neoplasm of other specified sites of urinary organs
(191) Malignant neoplasm of brain
211.3 Benign neoplasm of colon
706.8 Other specified diseases of sebaceous glands
V10.00 Personal history of malignant neoplasm of unspecified site in gastrointestinal tract
V10.43 Personal history of malignant neoplasm of ovary
V10.53 Personal history of malignant neoplasm of renal pelvis

V10.59 Personal history of malignant neoplasm of other urinary organs
V10.85 Personal history of malignant neoplasm of brain
193.0 Thyroid Papillary thyroid carcinoma
(173) Other malignant neoplasm of skin
(188) Malignant neoplasm of bladder

Response: All were added to our coverage of HNPCC with the exception of Thyroid (193.0), other neoplasm of the skin (173) and malignant neoplasm of the bladder (188). We did not receive any information to support there inclusion in the policy.

Request for additional diagnosis codes for JAK2 TESTING
238.4 Polycythemia Vera
238.7 Essential Thrombocythemia
238.75 Myelodysplastic Syndrome
238.79 Other lymphatic and hematopoietic tissues

Response: We have added the requested diagnosis codes.

DIAGNOSES FOR HLA-B*5701
Recommend adding the following diagnoses:
995.3 Allergy
995.27 Other drug allergy
V58.69, Encounter for long-term (current) use of other medications
780.79, Other malaise and fatigue

Response: These diagnosis codes are not specific enough to be added to the policy. No additional literature was sent in to support these diagnosis codes.

DIAGNOSES FOR BRCA1 AND BRCA2 GENE MUTATIONS TESTING
Recommend that "familial HBOC with prostate cancer" be included.

Response: No specific code or literature was submitted to support adding it.

Comment:
The indications of the different tests were not consistently and extensively covered. The following points should be made: 1) "Autosomal dominant" does not mean that half of the family members are affected. Rather, it means that there is a 50% chance of inheriting disease-causing mutation from an affected parent (3rd paragraph, last sentence); 2) BRCA1/2 mutation-positive males are at increased risk for prostate cancer;

Response: We have changed the policy to: autosomal dominant inheritance to (50% chance of inheriting the disease-causing mutation from an affected parent). The policy does cover BRCA mutation testing for men with breast cancer.

Comment:
Screening using a molecular genetic test should not be equated to screening of a condition, i.e. endocrine/metabolic/biochemical, where a specific biomarker is readily available from which a diagnosis can be made. A genetic condition, though usually involves a family, may be sporadic/de novo/spontaneous and without a biomarker that can be easily tested. Only nucleic acid-based tests may be available in most instances. Though it is clear that genetic tests for therapeutic, diagnostic, and prognostic purposes are covered, the presymptomatic and predictive are not. Each condition should be treated separately based on the known genotypic and phenotypic facts about the condition - onset, penetrance, clinical heterogeneity, variable expressivity, pleitropy, allelic

heterogeneity, etc to refine the indications and weigh the benefits of genetic testing. There should be deemed users for sets of genetic tests to avoid misuse, and this way, presymptomatic and predictive genetic tests will be appropriately utilized.

Response: Pre-symptomatic testing is not a covered benefit unless explicitly outlined in the regulations.

Comment: Literature supports coverage of NRAS mutation testing (81404) in patients with skin, thyroid or large intestine cancers for whom treatment with an EGFR therapy is contemplated. The evidence for thyroid cancer is based on an experimental agent that is currently in clinical trials; however, data such as this emphasize the growing interest in NRAS as a potential target for cancer therapy.

Response: This LCD has been written to address specific tests and conditions. We realize there are numerous codes that are not addressed. Codes not mentioned in the policy are not necessarily non-covered.

Comment: "Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Syndrome is currently referred to as Lynch Syndrome.

Response: We have replaced "Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Syndrome" with "Lynch Syndrome" wherever appropriate in the LCD.

Comment:
Under the Documentation section of the LCD it states that the laboratory or billing provider must have on file the physician who provides the diagnosis or condition (ICD-9-CM code) that warrants the test. The documentation must be made available from the billing provider (i.e., the laboratory) upon request by the contractor. It is unclear who is expected to provide any supporting information contained in the patient's medical record. Much of this information is not accessible by or in possession of the laboratory, and should be requested from the ordering physician.

Response:
Documentation must be adequate to verify that coverage guidelines have been met. The documentation, which must be made available upon request from the laboratory or billing provider, must include personal and family history information consistent with this policy.

The laboratory or billing provider must have on file the physician requisition which sets forth the diagnosis or condition (ICD-9-CM code) that warrants the test. The documentation must be made available from the billing provider (i.e. the laboratory) upon request by the contractor.

We have added the following excerpts from the Internet Only Manual (IOM) 100-08 to our LCD to help clarify the requirements:

Third-party Additional Documentation Request (IOM 100-08, 3.2.3.3)-
We will request information from the billing provider/supplier. The treating physician, another clinician, provider, or supplier should submit the requested documentation. However, because the provider selected for review is the one whose payment is at risk, it is this provider who is ultimately responsible for submitting, within the established timelines, the documentation requested.

Special Provisions for Lab Additional Documentation Requests (IOM 100-08, 3.2.3.7)
The following documentation shall be requested from the billing lab:

• The order for the service billed (including sufficient information to allow the reviewer to identify and contact the ordering provider);
• Verification of accurate processing of the order and submission of the claim; and
• Diagnostic or other medical information supplied to the lab by the ordering provider, including any ICD-9 codes or narratives.

The contractor shall deny the claim if a benefit category, statutory exclusion, or coding issue is in question, or send an ADR to the ordering provider in order to determine medical necessity. The contractor shall review information from the lab and find it insufficient before the ordering provider is contacted. The contractor shall send an ADR to the ordering provider that shall include sufficient information to identify the claim in question.

If the documentation received does not demonstrate that the service was reasonable and necessary, the contractor shall deny the claim. Beneficiaries cannot be held liable for these denials unless they have received proper liability notification before services were rendered.

Comment: We have reviewed the draft, the list of codes and the clinical conditions associated with the tests and the role of the test in patient care. This section does not indicate what the reason for the non-coverage is. It is important we have a statement of the type of non-coverage for each test/code.

The reason for a denial is an important distinction for the patient to understand and their financial liability for the service/test. It also impacts providers because we have a responsibility to notify the patient about coverage of a test and obtain ABN only when indicated. There are 3 reasons for Medicare to deny an item or service: there is no benefit category (e.g. eye glasses), the law does not allow coverage (statutory exclusion) or it does not meet the medically "reasonable and necessary" criteria.

Response: We have created a Billing and Coding Guideline for this LCD that includes a list of CPT codes that are not covered since they are considered to be screening tests and are statutorily excluded from coverage.

Comment: We believe that testing for the UGT1A (81350) should be covered, based on these requirements. Irinotecan, a topoisomerase I inhibitor, has been added to numerous chemotherapeutic combination treatment regimens in multiple cancer types, including colorectal pancreatic, gastric, and Ewing's sarcoma. However, UGT1A1 genotype can significantly affect metabolism of irinotecan, leading to risk of increased hematologic toxicity in patients homozygous for the UGT1A1*28 allele.

Response: There is insufficient evidence to support the clinical utility for this test. It is not considered medically reasonable and necessary.

Comment: Claims processing for CPT Codes 81401-82408 when ICD-9s have been identified for coverage. The structure of these codes raises some practical considerations for claims submission and processing. The molecular pathology codes have a number of subparts, identified by specific genes. This means there could be a number of genes reported with the same CPT code. Each of those genes could have related ICD-9 codes. It would require reporting of the specific gene to be able to link the code with a diagnosis.
In this draft coverage policy, 4 of the codes [81401, 81403, 81405, and 81406] have been associated with testing for Lynch Syndrome and would be covered for specific diagnosis codes. However, there are many genes under those same codes and other conditions that would be covered, e.g. lymphoma, leukemia which are covered conditions (NCD §190.3).

Will claims for other gene testing reported under the same codes be denied because they do not have the ICD-9 for Lynch Syndrome? How are we to report testing for other genes and conditions reported under the same CPT code, so that they are not all inappropriately denied?

Response: These CPT codes are not gene specific and can be used for multiple tests. The higher level CPT codes are noted in the LCD to let providers know they are covered for the conditions listed in the policy. All other conditions are subject to the test being reasonable and medically necessary. We will request additional documentation for conditions or diseases that are not listed in the LCD for 81401, 81403, 81405 and 81406.

Comment RetnaGene is an active and effective testing being used in our practice today. This testing allows patients who have a family history along with early symptoms of age-related macular degeneration to understand how the disease can advance over time. This testing can be used for two different categories of patients; patients who have already lost vision in one eye from the disease, or patients with binocular vision with early disease. RetnaGene aids us in the follow-up of these patients and the future care. When high risk patients are identified, follow-up will be more frequent compared to low risk patients. Identifying high risk patients also allows us to do preventative care to maintain vision. This includes life style changes such as quitting smoking, dieting, exercise and control of blood pressure and cholesterol. Early detection and prevention leads to decreased medical costs to the patient. It also allows the patient to live independently for more years.

Response: CPT 81401 CFH/ARMS2 test stratifies individuals into one of five macula risk (MR) categories, with MR3 through MR5 representing an increased risk of AMD. This is a screening test and is not a covered benefit under the Medicare program.

Comment: FXTAS Fragile X Tremor Ataxia Syndrome (FXTAS) FXTAS is a late-onset neurodegenerative disorder whose onset is typically in the 6th-7th decade. FMR1 testing is indicated to confirm or rule out a diagnosis of Fragile X-associated Tremor Ataxia Syndrome (FXTAS) in males and females older than age 50 years. There are a variety of treatments that can slow the progression of FXTAS so diagnosis is important.

Testing should be considered as part of the diagnostic evaluation of ataxia along with other acquired, non-genetic causes of ataxia, such as multiple sclerosis, alcoholism, vitamin deficiencies, vascular disease, primary or metastatic tumors, or paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung

Comment: SNRPN/UBE3A (81331) testing is indicated in patients presenting with mild cognitive impairment and features that may include hypothalamic hypogonadism, adrenal insufficiency and hypothyroidism, and excessive eating (hyperphagia: obsession with food) to confirm or rule out Prader Willi Syndrome (PWS). Though this syndrome is rare, dual eligible Medicare beneficiaries may be affected and require testing. Each year new diagnoses of PWS are made in patients aged in their 20s and 30s. Many people in this group seem to have previously been given an alternative diagnosis, 20 commonly general intellectual disabilities, Asperger syndrome, autism spectrum disorder or even some other chromosomal abnormality such as a subtype of Fragile X syndrome.

Proper diagnosis of these patients is critical for preventing obesity-related problems as these patients are at high risk for all obesity-related medical problems and these should be addressed appropriately. Controlling eating is essential. In addition to the risk of obesity, overeating can lead to overextension and even rupture of the stomach. Addressing obesity through strict limitation of food intake is the cornerstone of effective management of PWS.

Treatment with recombinant human Growth Hormone is a consideration for children and adults with confirmed Prader-Willi Syndrome.

Response: This test is considered to be a screening test and is therefore not covered under Medicare regulations.

Comment: Genetic testing for Long QT Syndrome (CPT Codes 81280-81282) According to the Guidelines developed in 2011 by the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) and endorsed by the American Heart Association, "comprehensive and targeted LQTS genetic testing is recommended". They also state that Long QT genetic testing has diagnostic, prognostic and therapeutic implications in the treatment of Long QT Syndrome.

LQTS is usually inherited by autosomal dominant transmission. This means that it affects boys and girls equally, and that each child of an affected parent has a 50% chance of inheriting the gene. Once a family member is identified with LQTS, it is extremely important that other family members be tested for the syndrome. It is especially important to know which parent and grandparent has the abnormality, since brothers and sisters, aunts, uncles, nephews, nieces, and cousins on the affected side are potentially at risk. This prospective screening is extremely important so that all affected family members are identified and treated early in order to prevent the tragic and unnecessary sudden deaths that may occur.

These patients mutation could have been identified through genetic testing and they could have received an inexpensive beta blocker medication that could have saved their life. Unfortunately these are not isolated incidents and continue to be a problem when someone's ECGs are borderline and not within a diagnostic range

Response: Tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute.

Comment:
It is absolutely right that genetic tests (constitutional) may only be performed once in a lifetime. However, the definition of unaffected patients may change depending on the particular condition and gene(s) involved. In a familial condition that clearly demonstrates clinical variability; a seemingly unaffected member may carry the disease-causing variant that may become clinically apparent with time.

Response: Testing performed solely based on familial history is considered screening.

Comment: We believe that coverage for genetic testing in some pre-symptomatic patients or for some predictive purposes is appropriate as the generated data 1) will be utilized in management of the patient and 2) is currently standard of care that is recommended by a number of practice guidelines

Response: The Medicare benefit requires the beneficiary to have signs and symptoms of disease. Coverage of molecular testing for carrier status or family studies is considered screening and is statutorily excluded from coverage.

The following comments are related to our draft policy that included a list of non-covered tests:

Comment: Cystic fibrosis (81221, 81223, 81224): Cystic fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. It is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, and gastrointestinal systems and leads to early death (medial survival is approximately 37 years). Current Indiana State Law recognizes the usefulness of CF screening tests and requires that all newborns born in the state, symptomatic or not, to be screened for cystic fibrosis and a number of other genetic conditions.

81200: ASPA GENE
The definitive diagnosis test is molecular analysis by sequencing (>50 different mutations identified) for proper management and to avoid cost from other unnecessary tests / procedures. Identifying at risk 1st degree relatives for carrier status and to adopt proper preventive measures

81205: BCKDHB
Although not deleterious, molecular genetic test is the only definite diagnostic assay necessary for proper neonatal to adulthood management of the patient, and in case of female – her pregnancy management, and to identify 1st degree relatives to adopt proper preventive measures

81209: BLM GENE
Bloom syndrome patients have a high mutation rate and therefore are at high risk of developing malignancies. Early and accurate diagnosis results in them being entered into appropriate cancer screening protocols.

81220-81222, 81224: CFTR
Molecular genetic analysis of the gene is the only means of identifying mutations (over 1600 different types of mutations are detected). Type of the mutation and configuration of the mutation in affected individuals has implications on the severity of the disease and management. This is the most cost effective method to manage these patients. ACMG and ACOG recommended a panel of mutations that are more prevalent and this is the standard panel that should be used for screening.

81228: CYTOGENETICS MICROARRAY TEST
Cytogenomic microarray analysis (CMA) is a high resolution chromosomal analysis. This whole genome scan offers a much higher level of resolution (20-140 kilobases) when compared with other cytogenetic technologies: conventional cytogenetic analysis (karyotyping, 3-4 megabases) and the targeted technique of fluorescence in situ hybridization (FISH, 300-400 kilobases). It is in wide clinical use in the postnatal population for patients with congenital anomalies. In addition, for patients with mental retardation and developmental delay, this technology greatly improves the diagnostic yield of classical conventional cytogenetic analysis and allows for the simultaneous evaluation of hundreds of loci for the detection of many microdeletion and microduplication disorders. The increased detection rate of chromosome abnormalities with this higher resolution technology not only improves patient care but is cost effective. Once the patient receives a definitive genetic diagnosis no additional testing is necessitated, and key family members also at risk can be identified and evaluated with the established genetic aberration also obviating the need for additional costly genetic testing. This test is not a screening test. It is also not performed in the absence of clinical signs and symptoms of a disease or without a diagnosis-specific indication.

81242: FANCC
Fanconi anemia can result in bone marrow failure and hematopoietic malignancy. Early genetic diagnosis allows for screening bone marrow biopsies to guide treatment and for genetic counseling of this autosomal recessive inherited condition. Molecular genetic tests for the three genes listed above covers at least 90% of mutations associated with FA. This provides definitive diagnosis which is essential for developing proper management and early screening for the development of cancer.

81243: FMR1 GENE
Molecular testing for this gene has existed for more than 30 years and it is well established that this is the only test that can reliably identify affected patients and carrier females. Definitive diagnosis is essential to manage the patients and to adopt preventive measures.

81250: G6PC GENE
About 80% of patients with this disorder had mutations in this gene. This is the most reliable diagnostic test for definitive diagnosis. This is necessary for proper clinical management and to adopt preventive measures.

81251: GBA GENE
Glucocerebrosidase - certain mutations are associated with Gaucher's disease and others are associated with Parkinsonism. Gaucher's disease can be treated with gene therapy, and Parkinson's patients with GBA mutations

respond differently to treatment. Since Gaucher's disease in an autosomal recessive condition, knowledge of exact mutations can be used for genetic counseling.

81304: MECP2 GENE DUP/DELET VARIANT
Clinical necessity for molecular tests: PML/RARALPHA 1 BREAKPOINT testing is used to assess the risk of hematological relapse (HR) in patients in clinical remission after the completion of consolidation therapy for promyelocytic leukemia to identify patients at high risk of HR as a basis for initiating salvage therapy on the premise that this will provide a more favorable outcome while persistent or recurrent disease is still sub-clinical according to NCCN guidelines.

Comment:
Molecular genetic tests will help the patient by instituting proper management of the current condition, early detection of predisposed diseases, identifying high risk individuals in the family and instituting early screening programs. Since several of these diseases are incurable or have crippling life conditions prevention is an important aspect of management. These results will help prospective parents in implementing preventive measures (fetal screening, in vitro fertilization etc). Therefore, providing coverage for these tests is highly cost saving in the long run (for current patients and by preventing in future). This is the era of genomic medicine, and it is growing rapidly.

Comment: Huntington's disease (HD) testing. HD is an autosomal dominant, progressive neurodegenerative disorder with a typical onset of symptoms between at age 30-50, and is uniformly fatal. There is an inverse relationship between the size of the gene mutation for HD (a CAG repeat expansion), and the age of symptom onset, with larger expansions associated with earlier disease. Patients may or may not have symptoms of disease at the time genetic testing is requested, often in the context of a medical genetics evaluation of suggestive family history. A recent publication from the Huntington's Disease Society of America, A Physician's Guide to the Management of Huntington's Disease, 3rd edition, M. Nance et al 2011, indicates that, "the clinical diagnosis of HD is typically made on the basis of family history and the presence of an otherwise unexplained characteristic movement disorder, and may be confirmed by a gene test. The gene test is particularly useful when there is an unknown or negative family history (as occurs in cases of early parental death, adoption, misdiagnosis, or non-paternity), or when the family history is positive, but the symptoms are atypical." We believe coverage should be extended for HD testing in these circumstances.

Response: Testing that is performed in the absence of signs, symptoms, complaints, or personal histories of disease or injury are considered screening. Medicare does not cover screening tests unless explicitly outlined in the statutes.