



July 15, 2013

[Olatokunbo Awodele](#), MD

WPS Medicare
3333 Farnam Street
Omaha, NE. 68131

RE: Draft Local Coverage Determination: **Molecular Diagnostic Testing (PATH-037) CMS ID #DL33219**

Dear Dr. Awodele:

Thank you for the opportunity to comment on Draft Local Coverage Determination: Molecular Diagnostic Testing. It is imperative in working with patients to be able to explain the coverage status of testing to allow them informed decision-making and we request that WPS reconsider several issues and provide greater explanation regarding language in the DLCD. We will address our main concerns in the cover letter and have included additional information regarding diagnosis codes for the different tests, other details and references in Appendix A-Detailed Comments and Appendix B-CPT Codes and NCD §190.3.

The primary issues we will address are the following:

1. Coverage status for tests not specifically addressed in the DLCD
2. Laboratory requirements for providing genetic testing
3. Covered Testing and Conditions: Cytogenetics
4. Covered conditions and CPT Codes: additional tests and codes to consider
5. CPT/HCPCS Codes Group 2 Paragraph: Not covered, Group 2 Codes, starting with 81200 through 81350. General Issues
6. Coding: CPT/HCPCS Codes. Group 2 Paragraph: Not Covered: Group 2 Codes. Specific Codes
7. Tests we believe meet the “reasonable and necessary” criteria for coverage
8. Claims processing for CPT Codes 81401-82408 when ICD-9s have been identified for coverage.

1. Coverage status for tests not specifically addressed in the DLCD

- a) 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.
- b) 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"

We have 2 questions about this statement regarding FDA approval and Coverage status

i) FDA approval for tests

As 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.

ii) Coverage status

As we review the narrative of the DLCD, it is our understanding that this DLCD separates the molecular pathology tests into 3 groups:

- those covered for specific conditions (Indications I-VII, ICD-9 Codes that Support Medical Necessity: Group 1 Paragraph and Codes through Group 6 Paragraph and Codes);
- those not covered (Group 2 Paragraph: Not Covered: Group 2 Codes); and
- the rest of the codes for which there is no specific policy.

From this DLCD, it is our understanding that claims submitted for the tests in the 3rd group will be paid with the assumption that 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.

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.

2. Laboratory requirements for providing genetic testing

Draft LCD Language specifically under the General Coverage Rules;

"Genetic analysis must be provided through a laboratory which meets the American Society of Clinical Oncology (ASCO) recommended requirements:

- 1. The lab must meet appropriate Clinical Laboratory Improvement Amendment (CLIA) 1988 regulations;*
- 2. Successful participation in the American College of Medical Genetics (ACMG)/College of American Pathologists (CAP) inspection and survey program;*
- 3. Appropriate state licensing; and*
- 4. Credentialing of laboratory directors and staff by the American Board of Medical Genetics (ABMG).*

The referenced recommendations by ASCO, though merit worthy, do not consider the role of CLIA in setting standards for and certification of laboratories as well as CLIA acceptable mechanisms for

laboratory inspection established by CMS, e.g. JCAHO and others and the ability of laboratory directors to be credentialed by other valid professional and laboratory organizations such as the American Board of Pathology, among others.

“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). In total, CLIA covers approximately 225,000 laboratory entities. The Division of Laboratory Services, within the Survey and Certification Group, under the Office of Clinical Standards and Quality (OCSQ) has the responsibility for implementing the CLIA Program. CMS has identified 6 accrediting bodies. (<http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/AOList.pdf>).

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](#))

Item #3 is not supported by the CLIA requirements. CLIA requires that laboratories participate in proficiency testing (PT) programs. The College of American Pathologists (CAP) offers one such PT program, in conjunction with ACMG for certain analytes, but this is not the only PT program available to laboratories.

With respect to #4, CLIA requirements include standards for the qualifications of the laboratory director and the director of a quality management system unique to molecular testing. The ABMG has no standing in credentialing laboratory directors and staff. We have provided an excerpt from the molecular checklist regarding director and technologist qualifications from the CAP Laboratory Accreditation Program, one of the entities with deemed status for accreditation under CLIA:

CAP GUIDELINES – Molecular Checklist (part of the laboratory accreditation program)

MOL.49650 Director Qualifications Phase II

The director of the molecular pathology laboratory is a pathologist, board-certified physician in a specialty other than pathology, or doctoral scientist in a chemical, physical, or biologic science, with specialized training and/or appropriate experience in molecular pathology.

MOL.49655 Personnel – Bench Testing Phase II

The person in charge of bench testing of the molecular pathology laboratory is qualified as one of the following.

1. Person who qualifies as a director
2. MB(ASCP), BS, BA, or MLS(ASCP)/MT(ASCP) with at least 4 years of experience (at least 1 of which is in molecular pathology methods) under a qualified director

MOL.49660 Technologist Qualifications Phase II

Persons performing the technical aspects of molecular pathology qualify as one of the following.

1. Experienced in the field under the direct supervision of a qualified director or supervisor, and,

- | |
|---|
| 2. for laboratories subject to US regulations, qualified to perform high complexity testing
MT(ASCP) certified or equivalent |
|---|

REQUEST: We believe the CLIA regulations by CMS establish sufficient credentialing requirements for all lab tests and personnel, including molecular pathology. The 4th criterion creates a requirement that is not consistent with the function of ABMG. In short, we request that the laboratory requirements for providing genetic testing language be removed.

3. Covered Testing and Conditions: Cytogenetics

Medicare has a national coverage position on testing for genetic disorders (NCD §190.3).

“Medicare covers these tests when they are reasonable and necessary for the diagnosis or treatment of the following conditions:

- | |
|---|
| <ul style="list-style-type: none">• Genetic disorders (e.g., mongolism) in a fetus (See the Medicare Benefit Policy Manual, Chapter 15, “Covered Medical and Other Health Services,” §20.1• Failure of sexual development; or• Chronic myelogenous leukemia.• Acute leukemias lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or• Myelodysplasia.” |
|---|

Broadly speaking, cytogenetics is the study of chromosome and gene mutations. It has evolved over time from conventional microscopic karyotyping to molecular cytogenetics. This NCD statement references the earlier methods used to study genes, conventional cytogenetic analysis, such as karyotyping, the accepted cytogenetic test of the day. Karyotyping is an undirected diagnostic and it considers the entire genome, but at a fraction of the resolution offered by molecular cytogenetic methods, like cytogenomic arrays and other tests described by the molecular pathology codes. Many of the conventional studies performed for genetic analysis 10-15 years ago have been replaced by newer, more accurate procedures, which are reported under the molecular pathology code set.

We have reviewed both the CPT procedure codes and the ICD-9 codes in light of this NCD. Based on that review we have 2 sets of recommendations.

A. Coverage of tests performed *in utero*.

There are specific tests in Tier 1 and Tier 2 of the molecular pathology codes that are performed *in utero*. To facilitate the implementation of this NCD, we have provided a list of the codes and genes for your consideration, see Appendix B.

B. Coverage of tests for CML, ALL, AML and unclassified, myelodysplasia and delayed sexual development

We have reviewed the test codes and diagnoses, as well. To facilitate the implementation of this NCD, we have provided a list of the codes and genes for your consideration, see Appendix B.

REQUEST: We request that the coverage status of codes be modified to reflect coverage of tests consistent with NCD §190.3, see Appendix B.

4. Covered conditions and CPT Codes: additional tests and codes to consider

Lynch Syndrome: II. Hereditary Colorectal and Endometrial Cancer Syndromes and Conditions Group 2 Paragraph and Group 2 Codes.

- a) 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”.

REQUEST: We request that testing be covered when any of these are present consistent with the Revised Bethesda Guidelines, used by the CDC, EGAPP, and NCCN in making their recommendations for testing, see Appendix A for details.

- b) Algorithms recommend starting with testing for mis-matched repair (MMR) deficiency using microsatellite instability PCR and immunohistochemistry (IHC) methods to initially identify a patient who may have Lynch Syndrome. If either of these tests is positive then the next step is to perform testing for methylation status using *BRAF* V600E mutation and *MLH1* promoter hypermethylation. If the results of these tests are compatible with Lynch syndrome, sequencing of the appropriate genes can be performed to identify the possible causative mutations as outlined in this policy. Variations in the algorithm may occur depending on the institution and access to particular testing.

RECOMMENDATION: We recommend adding these CPT codes for Lynch Syndrome testing to the list of covered procedures for HNPCC as referred to in Appendix A.

- ▶ Microsatellite instability - CPT Code 81301
- ▶ *BRAF* V600E Variant – CPT Code 81210

5. CPT/HCPCS Codes Group 2 Paragraph: Not covered, Group 2 Codes, starting with 81200 through 81350. General Issues

A. Need for specific reason for not covering each test/CPT code

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 noncoverage 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. (CMS-ABN)

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. The hierarchy of reasons for denying a claim are outlined in PIM 100-08. Chapter 3 §3.6.2.5-Denial Types. A. Distinguishing Between Benefit Category, Statutory Exclusion and Reasonable and Necessary Denials.

Statutory Exclusion:

If there is a benefit category, then the next reason to consider is whether the service/item “Is statutorily excluded by other than §1862(a)(1) of the Act;” (PIM, §3.6.2.5) The informational brochure for providers on ABN includes a list of the program exclusions. The ABN does not apply to these items/services.

Not Medically Necessary denial:

A service/item can be denied because it is not considered to meet the “reasonable and necessary” condition as defined under §1862(a) (1) of the Act. These types of services would require an ABN. (ABN Brochure) (PIM, §3.6.2.5)

The ABN brochure states:

Medicare defines medical necessity as services that are:

- *Reasonable and necessary,*
- *For the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member, and*
- *Not excluded under another provision of the Medicare Program.*

As per the PIM instructions Chapter 13, (13.5.1 - Reasonable and Necessary Provisions in LCDs) provides additional elements to consider: some of which are that it is

- safe and effective;
- meets but does not exceed the patient’s medical need; and
- “at least as beneficial as an existing and available medically appropriate alternative”.

‘Diagnosis’ as a valid reason for testing

In addition to its use in treatment selection and management, we are pleased to see the DLCD includes ‘diagnosis’ as a reason for testing. We have entered a new era in medicine with the addition of molecular pathology, a valuable diagnostic tool akin to the addition of CT, MRI, and PET scans over the past 30 years. Like other radiologic and lab testing, it allows the physician to confirm what has only been a clinical diagnosis in the past. Like EKGs, cardiac enzymes, BNP, glucose and A1c and other tests, it can confirm a diagnosis.

The act of confirming a clinical diagnosis based on symptoms and clinical criteria is a valuable step in medical care, one supported by the law. It is a common practice: ordering an x-ray to confirm a simple fracture, ordering a chest x-ray to confirm the clinical diagnosis of pneumonia even in the uncomplicated patient, blood glucose to confirm diabetes in the presence of hyperglycemic symptoms, CT or MRI in the presence of clear symptoms/signs of a stroke. It confirms the clinical diagnosis, provides the reason for the patient’s symptoms. If the condition has known treatment, the importance of testing is obvious. However, even if there is no known treatment for a condition at the time it’s diagnosed, obtaining a diagnosis for a patient’s symptoms/illness is still important and directly impacts the care of the patient in a number of ways.

It has major direct impact on the patient. Obtaining a definitive diagnosis is the reason a person seeks medical attention – to get a diagnosis so they know what is causing symptoms, whether it can be cured, what will help the symptoms, whether the prognosis is, how the disease/symptoms will progress. Making sure one is not missing a curable condition is major for the patient and the

physician. Knowing the diagnosis can mean that the long, often costly search for a cause can be over, that no further testing is required to explain the symptoms. It can confirm the fact that there is a medical reason for the patient's symptoms, that it is not 'all in their head'. Having a diagnosis helps the patient with decision-making about life issues affected by the condition, its prognosis, its natural history. It can also provide guidance with respect to treatment options. By confirming the diagnosis, it can explain why a current treatment course be appropriate for the presumed diagnosis is not as effective as expected. This would influence the physician recommendations and the patient's decision about whether to continue said therapy. It can also prevent the patient pursuing treatment for presumed (incorrect) diagnoses, treatment that carries its own risks and may be less effective or not effective at all for the accurate diagnosis. It helps the patient evaluate other approaches they have been pursuing to cure or help their illness, eg vitamins or supplements, massage, acupuncture. If there is no known treatment to cure the condition, it can shift attention to symptomatic care and discussion of long-term implications and decision-making. It can also open the door to resources about the condition and support from others with the condition. From a patient's perspective, these are all direct result of having a definitive diagnosis even when there is no cure or treatment. Someday, there may be a clinical trial or a new drug that will work for symptoms related to their condition.

Coverage Status – Applicable to all Medicare beneficiaries

We would also like to address the audience to whom the DLCD apply. While the majority of beneficiaries covered by Medicare are over 65, Medicare also covers people who are disabled and have chronic kidney disease. In 2012, there were a total of 50,829,000 beneficiaries of which 8,624,000 were disabled or 17%. There were 3,000 under the age of 19. In FFS, which is most impacted by LCDs, the disabled make up 23% of the Medicare beneficiaries (6,874,000 out of 37,214,000 beneficiaries in FFS).(CMS-Statistical Supplement) The LCDs need to be appropriate for all Medicare beneficiaries, regardless of age. The beneficiaries under 65 should receive the care that is medically necessary and appropriate for them just as those over 65.

Many of the conditions diagnosed by genetic testing do present in early childhood/infancy and testing would be conducted at the time of diagnosis. Some of them could potentially be one of the 3000 Medicare beneficiaries under 19. However, testing and appropriate diagnosis may not occur in childhood, before a person becomes a Medicare beneficiary. There are a number of reasons testing in adults may be appropriate: 1) the patient was never tested and appropriately diagnosed and diagnosis is relevant, 2) testing has evolved with more sensitive/specific now and the patient tested negative at the time of initial presentation or tested positive but it was a false positive and prognosis/treatment decisions require accurate diagnosis; 3) the phenotypic presentation can vary significantly and the diagnosis was not apparent or considered.

“at least as beneficial as an existing and available medically appropriate alternative

Molecular pathology testing should be held to the same standard, and not more rigorous or limited, as other tests covered when used to confirm suspected medical diagnoses– like chest x-rays, CT, MRIs, PET scans, EKG, and other blood tests.

REQUEST: That decisions about coverage and determinations of medical necessity be appropriate for all Medicare beneficiaries, whether eligible by age or disability status.

- B. **CLAIMS PROCESSING IMPLICATIONS:** We have reviewed the tests included in Group 2 Paragraph: Not covered. We have provided our perspective on tests which we believe meet the medical necessity requirements in Appendix A.

The challenge is that most tests have 2 uses: 1) to diagnose a condition in a person with signs/symptoms, which would meet the language of the law and 2) a second use to identify carrier status, including reproductive risk, which would not be medically necessary because the person is asymptomatic. There is a benefit category: medical care, diagnostic testing. Most tests should be covered for diagnosis of beneficiaries with symptoms consistent with the diagnostic criteria. Based on the language of the law, tests being used to only assess carrier status or to address reproductive risk in the asymptomatic person would not be considered “reasonable and necessary” because they are not being used ‘*for the diagnosis or treatment of an illness or injury*’.

Possible solution:

In 2002, Medicare created modifiers just for this purpose. Per Medicare instructions, CPM104 Chapter 23. §20.9.1.1.E. Coding for Noncovered Services and Services Not Reasonable and Necessary

GA - Waiver of liability statement on file. (The physician expects Medicare deny a service as not reasonable and necessary and they do have an ABN signed by the beneficiary)

GZ - Item or service expected to be denied as not reasonable and necessary. (The physician expects Medicare deny a service as not reasonable and necessary and they do NOT have an ABN signed by the beneficiary)

If the test is being used in the asymptomatic person to define carrier status or reproductive risk, it would not meet the “reasonable and necessary” condition as defined under §1862(a) (1) of the Act. This is the definition for the GA or GZ modifier, depending on whether there is an ABN on file. When the test is used to diagnose an illness, symptoms, it is consistent with the language of the law defining Medicare, it would not have the modifier and should be covered.

RECOMMENDATION: We suggest that all tests performed in the asymptomatic person for purposes of screening for carrier status or to address reproductive risk have either the GA or GZ modifier attached, depending on whether there is a signed ABN on file.

6. **Coding: CPT/HCPCS Codes. Group 2 Paragraph: Not Covered: Group 2 Codes.**
Specific Codes

- A. There are a number of tests we believe **should be covered**. We have addressed them in detail in the Appendix A including patient selection and references.
- 1) All tests performed *in utero* when the mother is a beneficiary are covered under Medicare and tests for conditions identified in NCD §190.3.

2) FMR1 (CPT codes 81243 and 81244)

FMR1 testing is indicated to confirm or rule out a diagnosis of Fragile X Tremor Ataxia Syndrome (FXTAS) in males and females older than age 50 years. FXTAS is a late-onset neurodegenerative disorder whose onset is typically in the 6th-7th decade. It presents with progressive cerebellar ataxia with or without intentional tremor. See Appendix B for additional details.

3) SNRPN/UBE3A (CPT Code 81331)

This test diagnoses Prader-Willi Syndrome, which is often diagnosed in the very young. However, there are 3 types of PWS, each with different clinical implications. It also has a heterogeneous phenotypic presentation so that not all those with the condition are tested during their youth. This is one example where the testing has evolved and earlier testing was not as accurate.

4) Long- QT Syndrome (CPT Codes 81280-81282)

It is a common cardiac arrhythmia and a major cause of morbidity and mortality because of long-term medication use, stroke, and congestive heart failure. Prevention of primary manifestations includes prophylactic use of beta blockers in asymptomatic children and adults dependent on genotype and age to prevent syncope, cardiac arrest, and sudden death and possible ICD for those with beta-blocker-resistant symptoms, inability to take beta blockers, and/or history of cardiac arrest.

5) Cytogenomic constitutional microarray analysis (CPT Codes 81228-81229)

Cytogenomic or genome-wide microarrays are recommended as first-tier tests for the evaluation of patients with clinical manifestations suggestive of these conditions. Children and young adults who present with signs of developmental delay (DD), intellectual disability (ID), previously referred to as mental retardation, autism spectrum disorder (ASD) and/or multiple congenital abnormalities present a challenge to clinicians and to parents.

Medicare beneficiaries who present with manifestations suggestive of these conditions, who have not had appropriate genetic testing to obtain a specific diagnosis so that appropriate treatment, including monitoring for associated complications and comorbidities, can be accomplished.

B. Tests not on the list that are **not covered by national policy.**

We are assuming that this policy is intended to provide a comprehensive position on coverage for molecular pathology by WPS according to its jurisdiction. We note the codes that apply to NCD §19, pharmacologic testing for warfarin, CYP2C9 (81227) or VKORC1 (81350), are not in the ‘not covered’ list. We have not been able to identify other information, e.g. an article or other instruction on the status of this NCD and how claims with testing consistent with the NCD should be submitted.

7. Tests we believe meet the medically “reasonable and necessary” criteria for coverage.

In your Draft LCD DL33219 you indicated that you were aware that there remained “numerous potentially medically reasonable and necessary therapy directing genetic tests either currently available or in the development pipeline” and indicated that you would “allow payment for such tests” based on “appropriate Medicare regulations and its standard of medical reasonableness and necessity.” Many of these tests exist and were identified in the Tier 2 group of Molecular Pathology Procedures. We request that these Molecular Pathology CPT codes (81400-81408) be covered based on the following information.

CPT Codes 81400 through 81408 represent Molecular Pathology Procedures that were established for valid clinical testing for procedures with small volumes of tests performed nationally. These codes describe nine levels of complexity ranging from the least to the most complex, 81400 through 81408, and correlate with the level of technical resources required to perform the service. These nine codes met the strict criteria for Category 1 placement that was established by the AMA CPT Editorial Panel. Additionally, all of the listed analytes have been scrutinized by the AMA CPT editorial panel for acceptance to the appropriate level of code.

We understand that many of the MACs have deemed that many of these services are experimental or investigational. We believe that this is a misinterpretation since the intent of these codes was to provide payers with the ability to understand what testing was performed. We request that all of these codes be covered with payment determinations. We have listed examples of analytes and disease entities for which Medicare beneficiaries may require testing. We also request that if limitations are placed on these codes that an appropriate amount of time is provided to allow adequate response in demonstrating their significance, as required by the LCD process defined by CMS when a contractor is placing a restriction on coverage for a service or item. Additional information and references are provided in Appendix A.

1) CPT Code 41402 – KIT

Diagnosis: Systemic Mastocytosis.

Chemotherapy is indicated for rapid debulking and selection of Imatinib therapy is indicated in the presence for KIT D816-unmutated patients.

2) CPT Code 81403 – IDH1

Diagnosis: Glioma

IDH1 mutations vary by brain tumor subtype. Analyses of IDH1 status is of significant utility for diagnosis. They are more frequent in oligodendrogliomas (53.2%) than in astrocytic tumors (22.8%) and are more often found in sGBMs (84.2%) than in pGBMs (1.8%).

NCCN-2013 Guideline for CNS Cancers highlights the value of IDH1 and IDH 2 testing and the presence or absence of deletions on 1p and 19q molecular aberration because of their prognostic value. The presence or absence of mutations has implications for prognosis, which has clinical value to the patient for decision-making. Determination of IDH1 mutation

status (in hotspot R132) could help guide treatment decisions related to TMZ and PCV treatment – both of which are in the NCCN compendium for brain tumors.

3) CPT Code 81404: KIT

KIT testing is indicated for Gastrointestinal Stromal Tumor (GIST) diagnosis and treatment and Melanoma.

GIST: Testing is appropriate when imatinib treatment and resistance is a consideration.

MELANOMA: Mutation profiling has value in melanoma. The NCCN Guidelines for Melanoma address treatment selection (imatinib) based on C-KIT status. Activation of the KIT receptor tyrosine kinase may be rare in melanoma (20-40%), but many activating mutations have been shown to be highly sensitive to imatinib.

4) CPT Code 81404: PDGFRA

Diagnosis: GIST

Most GISTs are KIT- or PDGFRA-driven neoplasms, as evidenced by the fact that more than 95% of GISTs express KIT, and more than 80% carry gain of function mutations of KIT or PDGFRA.

The diagnostic importance of PDGFRA sequence analysis is underscored by the NCCN biomarker compendium that states that “several ancillary techniques are useful in support of GIST diagnosis, including ... molecular genetic testing for mutations in KIT or PDGFRA”.

The value of PDGFRA profiling rests not only with the differentiation of WT from mutated, but with the exact determination of the underlying mutation. An excellent example is imatinib, a selective inhibitor of KIT and PDGFRA, which leads to initial disease control for most patients with metastatic disease. However, resistance to imatinib appears inevitable. The PDGFRA-D842V mutation– found in approximately 5% of GISTs - has been shown to be highly imatinib- and sunitinib-resistant.

5) CPT Code 81404: RET

Diagnosis: MEN2, Familial Medullary Thyroid Carcinoma

As part of the workup when a diagnosis of medullary thyroid carcinoma has been found on FNA, testing for the RET proto-oncogene mutations is indicated. The results of the testing determine which type of MEN is present, its level of aggressiveness and that guides treatment decisions including the extensiveness of surgery required (e.g. thyroidectomy, central neck dissection) and treatment. For some, the testing will be required annually to monitor for the presence of pheochromocytoma.

Selection of chemotherapeutic agents is influenced by the RET status, e.g. RET inhibitory therapeutic agents like vandetanib and cabozantinig.

8. 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, 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).

QUESTIONS:

- i. Will claims for other gene testing reported under the same codes be denied because they do not have the ICD-9 for Lynch Syndrome?
- ii. 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?

We respectfully ask that you consider our comments which were prepared by a consortium of members of the Association for Molecular Pathology, the American College of Medical Genetics, and Laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by WPS Health Insurance. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this DLCD. Please direct your correspondence to Aaron Bossler, MD, PhD, Director of the Molecular Pathology Laboratory, University of Iowa Hospitals and Clinics and AMP Economic Affairs Committee Co-Chair.

Sincerely,



Jennifer L. Hunt, MD, MEd
President

Aaron D. Bossler, MD, PhD
Director of the Molecular Pathology Laboratory
University of Iowa Hospitals and Clinics
200 Hawkins Dr, C606GH
Iowa City, IA 52242
319-384-9566

Elizabeth Berry-Kravis MD PhD
Professor of Pediatrics, Neurological Sciences,
Biochemistry
Rush University Medical Center
1725 West Harrison Street
Chicago, IL 60612
312-942-4036
FAX 312-942-4168

Randi J. Hagerman, M.D.
Medical Director of the M.I.N.D. Institute
Endowed Chair in Fragile X Research
UC Davis Health System
2825 50th Street
Sacramento, CA 95817
randi.hagerman@ucdmc.ucdavis.edu
(916) 703-0247
Fax (916) 703-0240

Qing Li, Ph.D.
Director of New Technology and Test Development
South Bend Medical Foundation
530 N. Lafayette Blvd.
South Bend, IN 46601
574-234-4176 ext. 1584
qli@sbfm.org

Christina Lockwood, PhD, DABCC
Assistant Professor, Pathology & Immunology,
Washington University School of Medicine
Co-Medical Director, Molecular Diagnostics Lab, Barnes-
Jewish Hospital
(314) 747-0521
clockwood@path.wustl.edu

Mark A. Micale, Ph.D. FACMG
Medical Director, Clinical Cytogenomics Laboratory,
Beaumont Health System
Department of pathology and Laboratory Medicine
Beaumont Hospital, Royal Oak
248.898.9063
mmicale@beaumont.edu

Jan A. Nowak, PhD,MD
Department of Pathology and Laboratory Medicine
Evanston Hospital
NorthShore University HealthSystem
2650 Ridge Avenue
Evanston, IL 60201
(847)570-2876

Michael S. Watson, MS, PhD, FACMG
Executive Director
American College of Medical Genetics and Genomics
7220 Wisconsin Ave.,
Suite 300
Bethesda, MD 20814
Tel: 301-718-9603
Fax: 301-718-9604
mwatson@acmg.net

ATTACHMENT: Appendix A-Detailed Comments and Appendix B-CPT Codes and NCD §190.3

REFERENCES:

CMS-ABN CMS MLN Advance Beneficiary Notice of Noncoverage (ABN): Part A and Part B Information for Medicare FFS Providers. http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/abn_booklet_icn006266.pdf

CMS Statistical Supplement - <http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareMedicaidStatSupp/2013.html> Accessed 07.09.2013

PIM 100-08. Chapter 3 §3.6.2.5-Denial Types. A. Distinguishing Between Benefit Category, Statutory Exclusion and Reasonable and Necessary Denials. <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/pim83c03.pdf>

PIM – Publication #100,8 PIM Chapter 13 Local Coverage Determination. <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/pim83c13.pdf> Accessed from <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019033.html?DLPage=1&DLSort=0&DLSortDir=ascending> 07.08.2013

APPENDIX A: Detailed Comments

4. Covered Conditions and CPT Codes; Additional tests and codes to consider

We are pleased to see the coverage for hereditary colorectal cancer. We would like to suggest additional diagnoses for the testing for malignancies within Lynch Syndrome.

Code(s)	81201, 81202, 81203, 81275, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, 81401, 81403, 81405, 81406 and 88363
Rationale	<p>II. Hereditary Colorectal and Endometrial Cancer Syndromes and Group 2 Paragraph and Group 2 Codes.</p> <p>FROM DRAFT POLICY: "...hereditary colorectal cancer (HNPCC) including endometrial and/or ovarian cancer when the latter two are reasonably considered as part of the Lynch syndrome, Familial Adenomatous Polyposis (FAP) testing as well as for KRAS testing, when such testing is used to determine suitability of the use of either erbitux or panitumumab within the limitations noted above:"</p> <p>1. 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".^{1,2}</p> <p>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:</p> <div style="border: 1px solid black; background-color: #e6f2e6; padding: 10px; margin: 10px 0;"> <p>EXCERPT FROM CDC:</p> <p>Amsterdam II Criteria: Gastroenterology 1999;116:1453–1456</p> <ol style="list-style-type: none"> 1. There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis) 2. One should be a first-degree relative of the other two 3. At least two successive generations should be affected 4. At least one should be diagnosed before age 50 5. Familial adenomatous polyposis should be excluded in the CRC case(s), if any 6. Tumors should be verified by pathological examination <p>Revised Bethesda Guidelines: J Natl Cancer Inst 2004;96:261– 8; J. Med. Genet. 2007;44;353-362</p> <p>Tumors from individuals should be tested for MSI in the following situations:</p> <ol style="list-style-type: none"> 1. CRC diagnosed in a patient who is less than 50 years of age. 2. Presence of synchronous, metachronous colorectal, or other HNPCC associated tumors,* regardless of age. </div>

3. CRC with the MSI-H[†] histology[‡] diagnosed in a patient who is less than 60 years of age.
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age < 50 years.
5. Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumor, regardless of age.

*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.

[†]MSI-H = microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute–recommended panels of microsatellite markers.

[‡]Presence of tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

2. 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.⁵

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

¹ Kohlmann W, Gruber SB. Lynch Syndrome. 2004 Feb 5 [Updated 2012 Sep 20]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1211/>

² CDC Public Health Genomics Genetic Testing Health Professionals: More About Genetic Testing for Lynch Syndrome. http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/lynch_more.htm#considerations Last accessed 07/01/2013

³ Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med* 2009. 11 (1): 35-41. <http://www.egappreviews.org/docs/EGAPPWG-LynchRec.pdf> Last accessed 07/01/2013.

⁴ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Colorectal Cancer Screening. Version 2.2013 Accessed 07/02/2013.

⁵ CDC Genomics, Gene Testing for Health Professionals - Lynch Syndrome http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf

References

- Microstatellite instability - CPT Code 81301
- *BRAF* V600E Variant – CPT 81210

Suggested

CURRENT DIAGNOSES IN WPS DRAFT POLICY:

**ICD-9
Diagnoses**

153.0 MALIGNANT NEOPLASM OF HEPATIC FLEXURE
153.1 MALIGNANT NEOPLASM OF TRANSVERSE COLON
153.2 MALIGNANT NEOPLASM OF DESCENDING COLON
153.3 MALIGNANT NEOPLASM OF SIGMOID COLON
153.4 MALIGNANT NEOPLASM OF CECUM
153.5 MALIGNANT NEOPLASM OF APPENDIX VERMIFORMIS
153.6 MALIGNANT NEOPLASM OF ASCENDING COLON
153.7 MALIGNANT NEOPLASM OF SPLENIC FLEXURE
153.8 MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF LARGE INTESTINE
153.9 MALIGNANT NEOPLASM OF COLON UNSPECIFIED SITE
154.0 MALIGNANT NEOPLASM OF RECTOSIGMOID JUNCTION
154.1 MALIGNANT NEOPLASM OF RECTUM
154.2 MALIGNANT NEOPLASM OF ANAL CANAL
154.3 MALIGNANT NEOPLASM OF ANUS UNSPECIFIED SITE
154.8 MALIGNANT NEOPLASM OF OTHER SITES OF RECTUM RECTOSIGMOID JUNCTION AND ANUS
179 MALIGNANT NEOPLASM OF UTERUS-PART UNS
182.8 MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES OF BODY OF UTERUS
183.0 MALIGNANT NEOPLASM OF OVARY
183.2 MALIGNANT NEOPLASM OF FALLOPIAN TUBE
197.5 SECONDARY MALIGNANT NEOPLASM OF LARGE INTESTINE AND RECTUM
V10.05 PERSONAL HISTORY OF MALIGNANT NEOPLASM OF LARGE INTESTINE
V10.06 PERSONAL HISTORY OF MALIGNANT NEOPLASM OF RECTUM
RECTOSIGMOID JUNCTION AND ANUS
V10.42 PERSONAL HISTORY OF MALIGNANT NEOPLASM OF OTHER PARTS OF UTERUS
V12.72 PERSONAL HISTORY OF COLONIC POLYPS

WE REQUEST THAT GROUP 2 CODES COVERAGE BE EXPANDED TO INCLUDE THE FOLLOWING CANCER TYPES

- 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
- 155.0 - 155.2 Malignant neoplasm of liver primary - malignant neoplasm of liver not specified as primary or secondary
- 156.1 Malignant neoplasm of extrahepatic bile ducts
- 156.9 Malignant neoplasm of biliary tract part unspecified site
- (157) Malignant neoplasm of pancreas
- (173) Other malignant neoplasm of skin
- (188) Malignant neoplasm of bladder
- 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

- | | |
|--|--|
| | <ul style="list-style-type: none">• 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 |
|--|--|

5. Coding: CPT/HCPCS Codes. Group 2 Paragraph: Not Covered: Group 2 Codes.

We request that the following codes be covered based on the information provided:

Code(s)	81243 and 81244 – FMR1
Rationale	<p>Rationale to support coverage</p> <p>FMR1 testing is indicated to confirm or rule out a diagnosis of Fragile X disorders (premutation or full mutation disorders) in a number of situations.</p> <p>There are 5 indications for testing for Fragile X.</p> <ol style="list-style-type: none"> 1. Any male or female with intellectual disabilities, developmental delay, speech and language delay, autism or learning disabilities of unknown cause. 2. Any female with infertility, elevated FSH levels, premature ovarian failure, primary ovarian insufficiency or irregular menses. 3. Any adult over 50 with features of FXTAS, including intention tremors, ataxia, memory loss, cognitive decline, personality change, especially in combination with a positive family history of Fragile X. 4. Any preconception or pregnant woman who expresses interest in or requests Fragile X carrier testing. 5. Any adult with a family history of fragile X syndrome, FXTAS, intellectual or learning disabilities or autism of unknown cause, or infertility <p>As a diagnostic test used to evaluate signs of an illness or medical condition, the first 4 would be covered for Medicare beneficiaries. The 5th involves an asymptomatic person and would be considered screening for carrier status; it is not covered as defined by the Medicare law.</p> <p><u>Testing beneficiaries – Indication #1-2</u></p> <p>Although many will have been evaluated earlier in their life, possibly before they were eligible for Medicare, this is not always the case. There are medical reasons to document the presence of Fragile X; in addition to counseling about the life history of the condition, there are also associated conditions that should be monitored and treated as early as necessary, such as sleep apnea, hypothyroidism and hypertension which are associated with the premutation.</p> <p><u>FXTAS</u></p> <p>Fragile X Tremor Ataxia Syndrome (FXTAS) in males and females older than age 50 years. 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.</p> <p>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</p>

Code(s)	81243 and 81244 – FMR1		
	<p>Signs consistent with classic FXTAS include action tremor, cerebellar gait ataxia, parkinsonism, and cognitive decline, especially executive function deficits. Additional features that are often associated with, or may be the presenting features of FXTAS, include peripheral neuropathy, autonomic dysfunction, dementia, a family history of ataxia, autism spectrum disorder or intellectual disability and a family or personal history of primary ovarian failure (POF). Males are more commonly affected than females. Other frequent findings are parkinsonism, peripheral neuropathy, psychiatric symptoms (depression, anxiety, agitation), and autonomic dysfunction.^{1,2,3,4}</p> <p><i>Testing guidelines for fragile X-associated tremor/ataxia syndrome¹</i></p> <p>Clinician should test for <i>FMR1</i> mutation if the patient has any of the following:</p> <ul style="list-style-type: none"> • Onset of cerebellar ataxia of unknown cause in an individual over 50 yr • Onset of action tremor of unknown cause in individual over 50 yr with parkinsonism or cognitive decline • Prior diagnosis of multiple system atrophy, cerebellar subtype • Middle Cerebral Peduncle (MCP) sign on T2/FLAIR images of MRI in a patient with signs consistent with FXTAS • Positive family history of <i>FMR1</i> mutation in an individual who could be a carrier based on position in pedigree if signs consistent with FXTAS are present • Family or patient history of infertility/premature menopause in a patient with signs consistent with FXTAS <p>Fragile X testing would also be appropriate¹</p> <ul style="list-style-type: none"> • The presence of an MCP sign (increased T2 signal intensity in the middle cerebellar peduncles), • A family history of <i>FMR1</i> mutation and possible carrier status, and • A patient history of POF (premature ovarian failure), even without clinical signs of FXTAS would be appropriate criteria testing for an <i>FMR1</i> mutation. • Or persons presenting with a constellation of neurologic symptoms associated with FXTAS such as memory and executive function deficits, balance problems, neuropathy and autonomic dysfunction⁵. <p>RATIONALE FOR TESTING:</p> <ul style="list-style-type: none"> • Obtain a correct diagnosis in those who have symptoms diagnosed and treated as Parkinson 's disease who have not been responsive to medication. Patients with FXTAS may not be as responsive to the PD medications. • Alert the clinician and guide a workup for associated conditions, e.g. hypothyroidism, sleep apnea, hypertension, and immune dysfunction. • Guide therapy, e.g. Exercise recommendations, antioxidant therapy, SSRIs if needed • New drug therapy has been indentified which may impact the progression of FXTAS i.e. allopregnanolone⁶ and others will be found. • Initiate genetic counseling for extended family members who will be identified with a premutation or a full mutation through cascade testing⁷. <p>Diagnostic Criteria^{1,3,5,8}</p> <table border="1" data-bbox="388 1458 1497 1487"> <tr> <td data-bbox="388 1458 533 1487">Molecular</td> <td data-bbox="533 1458 1497 1487">55 to 200 CGG repeats (permutation)</td> </tr> </table>	Molecular	55 to 200 CGG repeats (permutation)
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Code(s)	81243 and 81244 – FMR1																													
		<table border="1" data-bbox="384 154 1497 483"> <tr> <td colspan="2" data-bbox="384 154 537 191">Clinical</td> </tr> <tr> <td data-bbox="384 191 537 224">• Major</td> <td data-bbox="537 191 1497 224">Intention tremor</td> </tr> <tr> <td colspan="2" data-bbox="384 224 537 256">Cerebellar gait ataxia</td> </tr> <tr> <td data-bbox="384 256 537 289">• Minor</td> <td data-bbox="537 256 1497 289">Parkinsonism</td> </tr> <tr> <td colspan="2" data-bbox="384 289 537 321">Moderate to severe working memory deficit</td> </tr> <tr> <td colspan="2" data-bbox="384 321 537 354">Executive function deficit</td> </tr> <tr> <td colspan="2" data-bbox="384 354 537 386">Radiologic</td> </tr> <tr> <td data-bbox="384 386 537 418">• Major</td> <td data-bbox="537 386 1497 418">MRI white matter lesions involving middle cerebellar peduncles</td> </tr> <tr> <td data-bbox="384 418 537 451">• Minor</td> <td data-bbox="537 418 1497 451">MRI lesions involving cerebral white matter</td> </tr> <tr> <td colspan="2" data-bbox="384 451 537 483">Moderate to severe generalized brain atrophy</td> </tr> </table> <p data-bbox="384 500 703 537">Diagnostic categories^{1,3,5,8}</p> <table border="1" data-bbox="384 537 1497 727"> <tr> <td colspan="2" data-bbox="384 537 1497 570">Presence of expanded CGG repeat (molecular) and</td> </tr> <tr> <td data-bbox="384 570 537 634">Definite</td> <td data-bbox="537 570 1497 634">Presence of one major radiological sign and (i) one major clinical symptom or (ii) the presence of FXTAS inclusions</td> </tr> <tr> <td data-bbox="384 634 537 699">Probable</td> <td data-bbox="537 634 1497 699">Presence of two major clinical symptom or one minor clinical symptom and one major radiological sign</td> </tr> <tr> <td data-bbox="384 699 537 727">Possible</td> <td data-bbox="537 699 1497 727">Presence of one major clinical symptoms and one minor radiological sign</td> </tr> </table>	Clinical		• Major	Intention tremor	Cerebellar gait ataxia		• Minor	Parkinsonism	Moderate to severe working memory deficit		Executive function deficit		Radiologic		• Major	MRI white matter lesions involving middle cerebellar peduncles	• Minor	MRI lesions involving cerebral white matter	Moderate to severe generalized brain atrophy		Presence of expanded CGG repeat (molecular) and		Definite	Presence of one major radiological sign and (i) one major clinical symptom or (ii) the presence of FXTAS inclusions	Probable	Presence of two major clinical symptom or one minor clinical symptom and one major radiological sign	Possible	Presence of one major clinical symptoms and one minor radiological sign
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References	<ol data-bbox="346 784 2003 1336" style="list-style-type: none"> <li data-bbox="346 784 2003 849">1. Berry-Kravis E, et al. Fragile X-Associated Tremor/Ataxia Syndrome: Clinical Features, Genetics, and Testing Guidelines Movement Disorders 2007;22(14):2018-2030 <li data-bbox="346 849 2003 914">2. Hall D, O’Keefe JA. Fragile X-Tremor Ataxia Syndrome: The expanding clinical picture, pathophysiology, epidemiology, and update on treatment. Tremor and other Hyperkinetic Movements 2012; 2: http://tremorjournal.org/article/view/56 <li data-bbox="346 914 2003 979">3. Hall DA, Berry-Kravis E, Jacquemont S, et al. Initial diagnosis of the fragile X associated tremor/ataxia syndrome (FXTAS). Neurology 2005;65(2):299-301. <li data-bbox="346 979 2003 1044">4. Hall DA, Howard K, Hagerman R, Leehey MA. Parkinsonism in FMR1 premutation carriers may be indistinguishable from Parkinson disease. Parkinsonism Relat Disord 2009;15(2):156-9 <li data-bbox="346 1044 2003 1109">5. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the <i>FMR1</i>premutation and fragile X-associated tremor/ataxia syndrome Lancet Neurology. In press. Publication anticipated July 2013 <li data-bbox="346 1109 2003 1174">6. Cao Z, Hulsizer S, Tassone F et al. Clustered burst firing in FMR1 premutation hippocampal neurons: amelioration with allopregnanolone Human Molecular Genetics, 2012, Vol. 21, No. 13 2923–2935, <li data-bbox="346 1174 2003 1239">7. Sorensen PL, Gane LW, Yarborough M, Hagerman RJ, Tassone F. 2012. Newborn screening and cascade testing for FMR1 mutations. Am J Med Genet Part A 9999:1–9. <li data-bbox="346 1239 2003 1336">8. Jacquemont et al. Fragile X permutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. Am J Hum Genet 2003;72:869-878. Accessed from http://ac.els-cdn.com/S0002929707606090/1-s2.0-S0002929707606090-main.pdf?_tid=c5e33d04-e9ba-11e2-91ba-00000aab0f01&acdnat=1373500096_2ad2d5917bca9701b68799c13b2a7f3d 																													
Suggested ICD-9 Diagnoses	<p data-bbox="296 1336 1241 1369">WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING NEUROLOGICAL SYMPTOMS:</p> <ul data-bbox="296 1369 915 1469" style="list-style-type: none"> <li data-bbox="296 1369 915 1401">• 331.82 Dementia with lewy bodies <li data-bbox="296 1401 915 1433">• 333.1 Essential and other specified forms of tremor <li data-bbox="296 1433 915 1469">• 334.3 Cerebellar ataxia NOS 																													

Code(s)	81243 and 81244 – FMR1
	<ul style="list-style-type: none"> • 356 Hereditary and idiopathic peripheral neuropathy • 781 Abnormal involuntary movements

Code(s)	81228 and 81229 Cytogenomic Microarrays
Rationale	<p>Children and young adults who present with signs of developmental delay (DD), intellectual disability (ID), previously referred to as mental retardation, autism spectrum disorder (ASD) and/or multiple congenital abnormalities present a challenge to clinicians and to parents. A large proportion of cases of developmental delay, intellectual disability, and autism are associated with any of a very large number of genetic abnormalities. Hence, current guidelines for these patients recommend cytogenomic evaluation to identify genetic abnormalities that may be clinically significant.</p> <p>Cytogenomic or genome-wide microarrays are recommended as first-tier tests for the evaluation of patients with clinical manifestations suggestive of these conditions. The goal of traditional cytogenetic analysis is to identify a specific genetic cause for the patient’s symptoms by examining the genome in as much detail as possible. Cytogenomic or genome-wide microarrays are now recommended as first-tier tests for the evaluation of patients with clinical manifestations suggestive of these conditions.</p> <p>Genomic microarrays are used to assess DNA copy number and detect chromosomal imbalances (copy number variations (CNVs)) at a much higher resolution than conventional cytogenetic analysis, such as karyotyping. CNVs are deletions and duplications of large segments of genomic material. The resolution and yields of CMA are materially higher than that of other cytogenetic technology, such as karyotyping.</p> <p>We ask you to consider that NCD has established that cytogenetic testing (which includes cytogenomic arrays) is a covered Medicare service when it is used to diagnose and treat genetic disorders in children.</p> <p>RECOMMENDATION: Those Medicare beneficiaries primarily those with disability eligibility, who have not been evaluated for the genetic basis of their condition, should be covered.</p>
References	<ul style="list-style-type: none"> • Manning, M, and Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. <i>Genetics in medicine: official journal of the American College of Medical Genetics</i> 12, no. 11: 742–745. • Vermeesch, JR, Fiegler H, de Leeuw N, et al. Guidelines for Molecular Karyotyping in Constitutional Genetic Diagnosis. <i>European Journal of Human Genetics: EJHG</i> 15, no. 11: 1105–1114. • Saam J, Gudgeon J, Aston E, Brothman AR. 2008. How physicians use array comparative genomic hybridization results to guide patient management in children with developmental delay. <i>Genet. Med.</i> 10:181–186. • Michelson, D J, M I Shevell, E H Sherr, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. <i>Neurology</i> 77, no. 17: 1629–1635. • Moeschler JB, Shevell M. 2006. Clinical genetic evaluation of the child with mental retardation or developmental delays. <i>Pediatrics.</i> 117:2304–2316.

<p>Suggested ICD-9 Diagnoses</p>	<p>WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING ICD-9 DIAGNOSES:</p> <p><u>ICD-9 Diagnostic Codes:</u></p> <p>299.00 - 299.01 Autistic Disorder 315.00 - 315.9 Specific delays in development code range 317 - 319 Mental retardation code range 759.7, 759.89, 759.9 - multiple congenital anomalies</p> <p>HCPCS S3870 Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation</p>

Code(s)	81331
Rationale	<ul style="list-style-type: none"> • SNRPN/UBE3A 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). The phenotypic presentation can vary. In addition, all those currently diagnosed as PWS may not in fact have PWS; the phenotypic presentation may be due to other genetic conditions. In addition, because of the improvement in testing, many who tested positive for PWS in the past do not in fact have PWS under the current, more accurate testing. In one study 10 out of 56 with the diagnosis of PWS did not have a genotype consistent with the diagnosis. • 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. • The physiologic characteristics of PWS and clinical conditions associated with it make accurate diagnosis important as it should influence the management of persons with PWS. For example those with PWS have a high pain threshold and difficulty localizing pain, have a dysfunction in thermoregulation, and generally do not vomit. Awareness of these factors is critical to primary care and emergency room physicians assessing new symptoms. There must be a high degree of awareness and attention to what seem to minor fractures or injuries. What is described as minor pain after a fall but continues to have swelling or bruising may in fact reflect significant injury, e.g. fracture. Serious infections may exist without fever. Thermodyregulation can be associated with hyperthermia or hypothermia due to cold temperatures, after swimming. In the absence of vomiting response, emetics are generally ineffective and other active intervention in the ED is required to manage food poisoning, ingestion of non-food items or other overdoses of potentially toxic substances. Because of the hyperphagia, the lack of interest in food or eating represents a sign of a potentially serious illness. Water intoxication associated with hyponatremia is an extension of the hyperphagia and needs to be addressed as a serious issue when it present to the ED or primary care physician. Finally, those with PWS are sensitive to drugs and anesthesia and may have unusual responses to standard dosages. • Treatment with recombinant human Growth Hormone is a consideration for children and adults with confirmed Prader-Willi Syndrome. (Deal et al).
References	<ul style="list-style-type: none"> • Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2012 Oct 11]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1330/ • Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HM, Boer H, Curfs LM, Schrande-Stumpel CT. The use of medical care

	<p>and the prevalence of serious illness in an adult Prader-Willi syndrome cohort. Eur J Med Genet. 2013 Jun 20. doi:pii: S1769-7212(13)00130-4. 10.1016/j.ejmg.2013.05.011. [Epub ahead of print] PubMed PMID: 23792791.</p> <ul style="list-style-type: none"> • Scheermeyer E. Prader-Willi syndrome - care of adults in general practice. Aust Fam Physician. 2013 Jan-Feb;42(1-2):51-4. PubMed PMID: 23529462. • Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS; 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants; EVIDEM Collaboration. Growth hormone research society workshop summary: consensus guidelines for recombinant human growth hormone therapy i
<p>Suggested ICD-9 Diagnoses</p>	<p>WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING ICD-9 DIAGNOSES:</p> <p>278.00- obesity 299.00 - 299.01 Autistic Disorder 315.00 - 315.9 Specific delays in development code range 317 - 319 Mental retardation code range</p>

Code(s)	81280, 81281, 81282 Long QT Syndrome
Rationale	<ul style="list-style-type: none"> • Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. This condition is a major cause of morbidity and mortality because of long-term medication use, stroke, and congestive heart failure. Risk factors for AF include advanced age, hypertension, structural heart disease, and congestive heart failure. Familial AF has been linked to mutations in genes that cause Long QT syndrome (LQTS). • LQTS is a disorder of the heart's electrical activity and can cause sudden, uncontrollable, dangerous arrhythmias in response to exercise or stress. Not everyone who has LQTS has dangerous heart rhythms, but when they do occur, they can be fatal. Patients are usually identified due to a syncopal spell. Presymptomatic diagnosis and treatment is important to prevent sudden cardiac death. • The majority of patients with LQTS are identified as young adults but infants to middle aged individuals have been identified. • LQTS can arise from mutation of one of several genes. These mutations tend to prolong the duration of the ventricular action potential (APD), thus lengthening the QT interval. LQTS can be inherited in an autosomal dominant or an autosomal recessive fashion. The autosomal recessive forms of LQTS tend to have a more severe phenotype, • Diagnosis/testing. is established by prolongation of the QTc interval in the absence of specific conditions known to lengthen it (for example, QT-prolonging drugs) and <u>molecular genetic testing</u> of the genes known to be associated of which <i>KCNQ1</i> (<u>locus name</u> LQT1), <i>KCNH2</i> (locus name LQT2) and <i>SCN5A</i> (locus name LQT3) are the most common. Other, less frequently involved genes are <i>KCNE1</i> (locus name LQT5), <i>KCNE2</i> (locus name LQT6), <i>CAV3</i> (locus name LQT9), <i>SCN4B</i> (locus name LQT10), <i>AKAP9</i> (locus name LQT11), <i>SNTA1</i> (locus name LQT12) and <i>KCNJ5</i> (locus name LQT13). Though this list is not complete as approximately 25% of families meeting clinical diagnostic criteria for RWS do not have detectable mutations in one of the above genes. • More than half of the people who have untreated, inherited types of LQTS die within 10 years. However, lifestyle changes and medicines can help people who have LQTS prevent complications and live longer. Some of these lifestyle changes and treatments include: Avoiding strenuous physical activity or startling noises. Beta-blocker medication is the primary treatment for the autosomal dominant RWS; possible use of a pacemaker in those individuals with LQT1 and LQT2 phenotypes with symptomatic bradycardia associated with beta-blocker therapy; possible implantable cardioverter-defibrillator (ICD) for symptomatic individuals with the LQT3 <u>phenotype</u>. • <i>Prevention of primary manifestations:</i> Prophylactic use of beta blockers in asymptomatic children and adults dependent on <u>genotype</u> and age to prevent syncope, cardiac arrest, and sudden death; possible ICD for those with beta-blocker-resistant symptoms, inability to take beta blockers, and/or history of cardiac arrest. • <i>Surveillance:</i> Regular assessment of beta-blocker dose for efficacy and adverse effects in all individuals and; regular periodic

	<p>evaluations of ICDs for inappropriate shocks and pocket or lead complications.</p> <ul style="list-style-type: none"> • <i>Agents/circumstances to avoid:</i> Drugs that cause further prolongation of the QT interval or provoke <i>torsade de pointes</i>; competitive sports/activities associated with intense physical activity and/or emotional stress.
References	<ul style="list-style-type: none"> • Alders M, Mannens MMAM. Romano-Ward Syndrome. 2003 Feb 20 [Updated 2012 May 31]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1129/ • Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL, Jr, Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. <i>Circulation</i>. 2008;117:1927–1935. doi: 10.1161/CIRCULATIONAHA.107.757955.
Suggested ICD-9 Diagnoses	

5. Tests we believe meet the reasonable and necessity criteria for coverage.

We request that these Molecular Pathology CPT codes (81400-81408) be covered based on the following information: CPT Codes 81400 through 81408 represent Molecular Pathology Procedures that were established for valid clinical testing for procedures with small volumes of tests performed nationally. These codes describe nine levels of complexity ranging from the least to the most complex, 81400 through 81408, and correlate with the level of technical resources required to perform the service. These nine codes met the strict criteria for Category 1 placement that was established by the AMA CPT Editorial Panel. Additionally, all of the listed analytes have been scrutinized by the AMA CPT editorial panel for acceptance to the appropriate level of code.

We understand that many of the MACs have deemed that many of these services are experimental or investigational. We believe that this is a misinterpretation since the intent of these codes was to provide payers with the ability to understand what testing was performed. We request that all of these codes be covered with payment determinations. We have listed examples of analytes and disease entities for which Medicare beneficiaries may require testing.

Code	81401	
	HTT (huntingtin) (eg, Huntington disease), evaluation to detect abnormal (eg, expanded) alleles	<ul style="list-style-type: none"> • 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. • 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
		<p>References Huntington’s Disease Society of America, A Physician’s Guide to the Management of Huntington’s Disease, 3rd edition, M. Nance et al 2011</p>
		<p><u>ICD-9 Diagnosis Codes</u> Chorea Huntington disease</p>
	FIP1L1/PDGFR (del[4q12]) (eg, imatinib-sensitive chronic eosinophilic leukemia), qualitative, and quantitative, if performed	<p>Chronic eosinophilic leukemia</p> <p><u>ICD-9 Diagnosis Codes</u> Chronic eosinophilic leukemia</p>

Code	81401	

Code	81402	
	<p>KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), common variants (eg, D816V, D816Y, D816F)</p>	<ul style="list-style-type: none"> • Systemic mastocytosis (SM) results from a clonal proliferation of abnormal mast cells (MC) in one or more extra-cutaneous organs. Patients present with constitutional symptoms with fatigue and weight loss, skin manifestations including urticaria and pruritus, musculoskeletal complaints or mediator-related systemic events such as flushing, syncope tachycardia or diaphoresis. • DIAGNOSIS: morphologically abnormal mast cells in the bone marrow and elevated serum tryptase level, abnormal mast cell expression of CD25 and/or CD2, and presence of the activating point mutation in the KIT gene (KIT D816 mutation). • MANAGEMENT: Treatment options vary depending on the type of mastocytosis that is diagnosed. Options include palliative care, symptom-directed therapy, and cytoreductive therapy for those patients with refractory symptoms. Chemotherapy is indicated for rapid debulking and selection of Imatinib therapy is indicated in the presence for KIT D816-unmutated patients.
		<p>References Pardanani A. Systemic mastocytosis in adults: 2012 Update on diagnosis, risk stratification, and management. Am J Hematol. 2012 Apr;87(4):401-11. doi: 10.1002/ajh.23134. Review. PubMed PMID: 22410759.</p>
		<p><u>ICD-9 Diagnosis Codes</u> Mastocytosis</p>

Code	81403	
	<p>IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common exon 4 variants (eg, R132H, R132C) and IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common exon 4 variants (eg, R140W, R172M)</p>	<ul style="list-style-type: none"> • IDH1 mutations appear to vary by brain tumor subtype – and are more frequent in oligodendrogliomas (53.2%) than in astrocytic tumors (22.8%) and are more often found in sGBMs (84.2%) than in pGBMs (1.8%). Analyses of IDH1 status is thus of significant utility for diagnosis. • NCCN-2013 CNS Cancers highlights the value of IDH1 and IDH 2 testing and the presence or absence of deletions on 1p and 19q molecular aberration because of their prognostic value. The presence or absence of mutations has implications for prognosis, which has clinical value to the patient for decision-making. • With gliomas, the histopathological diagnosis often lacks the precision that is needed for tailored treatments. Determination of IDH1 mutation status (in hotspot R132) could help guide treatment decisions related to TMZ and PCV treatment – both of which are on NCCN compendium for brain tumors. <p>References</p> <ul style="list-style-type: none"> • Erdem-Eraslan, L., Gravendeel, L. A., De Rooi, J., Eilers, P. H. C., Idbaih, A., Spliet, W. G. M., Den Dunnen, W. F. A., et al. (2013). Intrinsic molecular subtypes of glioma are prognostic and predict benefit from adjuvant procarbazine, lomustine, and vincristine chemotherapy in combination with other prognostic factors in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. <i>Journal of Clinical Oncology</i>, 31(3), 328–36. doi:10.1200/JCO.2012.44.1444 • Wick, W., Hartmann, C., Engel, C., Stoffels, M., Felsberg, J., Stockhammer, F., Sabel, M. C., et al. (2009). NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. <i>Journal of Clinical Oncology</i>, 27(35), 5874–80. doi:10.1200/JCO.2009.23.6497 • Houillier, C., Wang, X., Kaloshi, G., Mokhtari, K., Guillevin, R., Laffaire, J., Paris, S., et al. (2010). IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. <i>Neurology</i>, 75(17), 1560–6. doi:10.1212/WNL.0b013e3181f96282 • Weller, M., Felsberg, J., Hartmann, C., Berger, H., Steinbach, J. P., Schramm, J., Westphal, M., et al. (2009). Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. <i>Journal of Clinical Oncology</i>, 27(34), 5743–50. doi:10.1200/JCO.2009.23.0805 • Bujko, M., Kober, P., Matyja, E., Nauman, P., Dyttus-Cebulok, K., Czeremszyńska, B., Bonicki, W., et al. (2010). Prognostic value of IDH1 mutations identified with PCR-RFLP assay in glioblastoma patients. <i>Molecular diagnosis & therapy</i>, 14(3), 163–9. doi:10.2165/11537170-000000000-00000 <p>ICD-9 Diagnosis Codes Gliomas</p>

Code	81404	
	<p>KIT (C-kit) (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, GIST, acute myeloid leukemia, melanoma), targeted gene analysis (eg, exons 8, 11, 13, 17, 18) Gastrointestinal Stromal Tumor Acute Myeloid Leukemia Melanoma</p>	<ul style="list-style-type: none"> • KIT mutations are found in soft tissue tumors including gastrointestinal stromal tumors (GISTS), genital tract, hematopoetic/lymphoid tissue including acute myeloid leukemia as well as large intestine. • AML: Currently, the NCCN Biomarker Compendium recognizes KIT as a gene to determine treatment decisions in patients with Acute myeloid leukemia (AML). • GIST: KIT profiling has been clinical impactful for in GIST for several years, there is ample evidence to support tumor testing and the selection of tyrosine kinase inhibitor therapy using Gleevec in particular. • MELANOMA: Mutation profiling has value in melanoma. The NCCN Guidelines for Melanoma address treatment selection (imatinib) based on C-KIT status. Activation of the KIT receptor tyrosine kinase may be rare in melanoma (20-40%), but many activating mutations have been shown to be highly sensitive to imatinib. <p>References</p> <ul style="list-style-type: none"> • NCCN Guidelines Melanoma http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf • Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) (2010). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. <i>Journal of Clinical Oncology</i>, 28(7), 1247–53. • Chen, P. (2010). Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: A meta-analysis. <i>World Journal of Gastroenterology</i>, 16(33), 4227. • Heinrich, M. C., Maki, R. G., Corless, C. L., Antonescu, C. R., Harlow, A., Griffith, D., Town, A., et al. (2008). Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. <i>Journal of Clinical Oncology</i>, 26(33), 5352–9. • Antonescu, C. R., Besmer, P., Guo, T., Arkun, K., Hom, G., Koryotowski, B., Leversha, M. a, et al. (2005). Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. <i>Clinical Cancer Research</i>, 11(11), 4182–90. • Carvajal, R. D., Antonescu, C. R., Wolchok, J. D., Chapman, P. B., Roman, R.-A., Teitcher, J., Panageas, K. S., et al. (2011). KIT as a therapeutic target in metastatic melanoma. <i>JAMA</i>, 305(22), 2327–34. • Antonescu, C. R., Busam, K. J., Francone, T. D., Wong, G. C., Guo, T., Agaram, N. P., Besmer, P., et al. (2007). L576P KIT mutation in anal melanomas correlates with KIT protein expression and is sensitive to specific kinase inhibition. <i>International journal of cancer</i>. 121(2), 257–64. • Handolias, D., Hamilton, A. L., Salemi, R., Tan, A., Moodie, K., Kerr, L., Dobrovic, A., et al. (2010). Clinical responses observed with imatinib or sorafenib in melanoma patients expressing mutations in KIT. <i>British journal of cancer</i>, 102(8), 1219–23.
		<p>ICD-9 Diagnosis Codes Gastrointestinal Stromal Tumor Acute Myeloid Leukemia Melanoma</p>

<p>NRAS</p>	<p>Literature supports coverage for NRAS mutation testing in patients with skin, thyroid or large intestine cancers for whom treatment with an EGFR targeted therapy (e.g. cetuximab, erlotinib) is contemplated as being appropriate. A publication list of studies, which demonstrate the clinical utility of NRAS mutation testing is provided in the appendix.</p> <p>NRAS testing results include:</p> <ul style="list-style-type: none"> • Identifying genomic abnormalities in tumors of patients with NRAS driver mutations • Providing information specific to recommendations for therapy • Identification of clinical trials for patients who have failed first line therapies <p>Overview of Clinical Practice for the use of NRAS mutations:</p> <p>Good correlative evidence has been found for colorectal cancer and EGFR-targeted antibody therapies cetuximab and panitumumab with the presence of NRAS mutations indicating a lack of clinical utility for EGFR targeted therapies. NRAS testing thus helps rule out extremely expensive monoclonal antibody therapy for these patients and suggests that other types of therapy would be more likely to achieve clinical benefit for these patients. In addition, there are several melanoma-related studies that suggest that therapeutic benefit may be impacted by NRAS mutational status. In addition, profiling for NRAS could help triage patients into clinical trials.</p>
	<p>References</p> <ul style="list-style-type: none"> • Peeters, M., Oliner, K. S., Parker, A., Siena, S., Van Cutsem, E., Huang, J., Humblet, Y., et al. (2013). Massively Parallel Tumor Multigene Sequencing to Evaluate Response to Panitumumab in a Randomized Phase III Study of Metastatic Colorectal Cancer. <i>Clinical Cancer Research</i>, 19(7), 1902–12. doi:10.1158/1078-0432.CCR-12-1913 • De Roock, W., Claes, B., Bernasconi, D., De Schutter, J., Biesmans, B., Fountzilias, G., Kalogeras, K. T., et al. (2010). Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. <i>The lancet oncology</i>, 11(8), 753–62. • André, T., Blons, H., Mabro, M., Chibaudel, B., Bachet, J.-B., Tournigand, C., Bennamoun, M., et al. (2012). Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. <i>Annals of Oncology</i>, 1–8. • Joseph, R. W., Sullivan, R. J., Harrell, R., Stemke-Hale, K., Panka, D., Manoukian, G., Percy, A., et al. (2012). Correlation of NRAS mutations with clinical response to high-dose IL-2 in patients with advanced melanoma. <i>Journal of immunotherapy (Hagerstown, Md. : 1997)</i>, 35(1), 66–72. doi:10.1097/CJI.0b013e3182372636 • Trunzer, K., Pavlick, A. C., Schuchter, L., Gonzalez, R., McArthur, G. a., Hutson, T. E., Moschos, S. J., et al. (2013). Pharmacodynamic effects and mechanisms of resistance to vemurafenib in patients with metastatic melanoma. <i>Journal of clinical Clinical Oncology</i>, 31(14), 1767–74. doi:10.1200/JCO.2012.44.7888 • Ho, A. L., Grewal, R. K., Leboeuf, R., Sherman, E. J., Pfister, D. G., Deandreis, D., Pentlow, K. S., et al. (2013). Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer. <i>New England Journal of Medicine</i>, 368(7), 623–632. doi:10.1056/NEJMoa1209288
	<p>ICD-9 Diagnostic Codes</p> <p>Colorectal carcinoma</p> <p>Melanoma</p>

	PDGFRA	<ul style="list-style-type: none"> • Most GISTs are KIT- or PDGFRA-driven neoplasms, as evidenced by the fact that more than 95% of GISTs express KIT and more than 80% carry gain of function mutations of KIT or PDGFRA. • The diagnostic importance of PDGFRA sequence analysis is underscored by the NCCN biomarker compendium that states that “several ancillary techniques are useful in support of GIST diagnosis, including ... molecular genetic testing for mutations in KIT or PDGFRA”. • The value of PDGFRA profiling rests not only with the differentiation of WT from mutated, but with the exact determination of the underlying mutation as they may confer resistance or sensitivity to imatinib (Gleevec), a selective tyrosine kinase inhibitor of KIT and PDGFRA, which leads to initial disease control for most patients with metastatic disease. It has been well-established that for the PDGFRA-D842V mutation, found in approximately 5% of GISTs to be highly imatinib- and sunitinib-resistant. <p>References</p> <ul style="list-style-type: none"> • Heinrich, M. C., Owzar, K., Corless, C. L., Hollis, D., Borden, E. C., Fletcher, C. D. M., Ryan, C. W., et al. (2008). Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Gr. <i>Journal of Clinical Oncology</i>, 26(33), 5360–7. doi:10.1200/JCO.2008.17.4284 • Lasota, J., & Miettinen, M. (2008). Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. <i>Histopathology</i>, 53(3), 245–66. • Corless, C. L., Schroeder, A., Griffith, D., Town, A., McGreevey, L., Harrell, P., Shiraga, S., et al. (2005). PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. <i>Journal of Clinical Oncology</i>, 23(23), 5357–64. • Cassier, P., Fumagalli, E., Rutkowski, P., Schoffski, P., Van Glabbeke, M., Debiec-Rychter, M., Emile, J.-F., et al. (2012). Outcome of patients with Platelet Derived Growth Factor Receptor Alpha-mutated GIST in the tyrosine kinase inhibitor era. <i>Clinical Cancer Research</i>. doi:10.1158/1078-0432.CCR-11-3025 <p>ICD-9 Diagnosis Codes GIST</p>
	RET	<p>As part of the workup when a diagnosis of medullary thyroid carcinoma has been found on FNA, testing for the RET proto-oncogene mutations is indicated. The results of the testing determine which type of MEN is present, its level of aggressiveness and that guides treatment decisions including the extensiveness of surgery required e.g. (thyroidectomy, central neck dissection) and treatment. For some, the testing will be required annually to monitor for the presence of pheochromocytoma.</p> <p>Selection of chemotherapeutic agents is influenced by the RET status, e.g. RET inhibitory therapeutic agents like vandetanib and cabozantinig.</p> <p>References: NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf</p> <p>Diagnosis MEN2 Familial Medullary Thyroid Carcinoma</p>

Code	81406	
	Cytogenomic microarray analysis (CMA) for Neoplasia	<ul style="list-style-type: none"> • Neoplastic processes are a complex group of disorders that develop as a result of the accumulation of genetic alterations including gene mutations, chromosomal rearrangements, gain and loss of genetic material, epigenetic changes, loss of heterozygosity (LOH), and various other genetic changes. Defining the genetic alterations of specific neoplastic disorders influences the diagnoses, prognoses, and therapeutic choices for patients with malignant neoplasms. • Conventional cytogenetic analysis has been valuable in identifying diagnostic and prognostic information, but the success rate of chromosomal analysis has been hampered by the lack of growth of tumor cells in cell cultures and the presence of subtle chromosomal (often clonal) abnormalities that are missed by this technique. Fluorescent in situ hybridization (FISH) panels have dramatically improved the detection rate of clonal abnormalities particularly in hematological malignancies but only a few loci may be examined at a time. Neither conventional karyotyping nor FISH can detect copy neutral loss of chromosomal material that can be associated with hematological malignancies often due to mutations and subsequent selection of tumor suppressor genes and oncogenes • Chronic lymphocytic lymphoma (CLL) is one such example that is a clinically heterogeneous B-cell lymphoid neoplasm with variable clinical course. Prognosis includes identification of chromosomal copy number changes. CMA for neoplasia allows for genome wide analysis for the myriad of variations with greater sensitivity. <p>References</p> <ul style="list-style-type: none"> • Byrd JC, Mrózek K, Dodge RK, et al.; Cancer and Leukemia Group B (CALGB 8461). Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). <i>Blood</i> 2002;100:4325–4336. • Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. <i>N Engl J Med</i> 2000;343:1910–1916. • Heim S, Mitelman F. <i>Cancer Cytogenetics, Chromosomal and Molecular Genetic Aberrations of Tumor Cells</i>, 3rd edn. Wiley: Hoboken, New Jersey, 2009. • Moorman AV, Harrison CJ, Buck GA, et al.; Adult Leukaemia Working Party, Medical Research Council/National Cancer Research Institute. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. <i>Blood</i> 2007;109:3189–3197. • Armengol G, Canellas A, Alvarez Y, et al. Genetic changes including gene copy number alterations and their relation to prognosis in childhood acute myeloid leukemia. <i>Leuk Lymphoma</i> 2010;51:114–124. • Gunnarsson R, Staaf J, Jansson M, et al. Screening for copy-number alterations and loss of heterozygosity in chronic lymphocytic leukemia—a comparative study of four differently designed, high resolution microarray platforms. <i>Genes Chromosomes Cancer</i> 2008;47:697–711. • Okamoto R, Ogawa S, Nowak D, et al. Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism

		<p>oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica 2010;95:1481–1488.</p> <ul style="list-style-type: none"> • Slovak ML, Bedell V, Hsu YH, et al. Genomic alterations in Hodgkin and Reed/Sternberg (HRS) cells at disease onset reveals distinct signatures for chemo-sensitive and primary refractory Hodgkin lymphoma. Clin Cancer Res 2011;17:3443–3454. • Walter MJ, Payton JE, Ries RE, et al. Acquired copy number alterations in adult acute myeloid leukemia genomes. Proc Natl Acad Sci USA 2009;106:12950–12955. • Yu L, Slovak ML, Mannoer K, et al. Microarray detection of multiple recurring submicroscopic chromosomal aberrations in pediatric T-cell acute lymphoblastic leukemia. Leukemia 2011;25:1042–1046. <p><u>ICD-9 Diagnosis Codes</u> Chronic lymphocytic leukemia Acute lymphoblastic leukemia Acute myeloid leukemia</p>
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