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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,

for laboratories subject to US regulations, qualified to perform high complexity testing
2. 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:
>
> - 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.

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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 6^{th}-7^{th} 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 abnormities 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,

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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	**II. Hereditary Colorectal and Endometrial Cancer Syndromes** and Group 2 Paragraph and Group 2 Codes. 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:" 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] We request that testing be covered when any of these are present consistent with the Revised Bethesda Guidelines, used by the CDC[2], EGAPP[3], and NCCN[4] in making their recommendations for testing: EXCERPT FROM CDC: **Amsterdam II Criteria:** Gastroenterology 1999;116:1453–1456 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 **Revised Bethesda Guidelines:** J Natl Cancer Inst 2004;96:261– 8; J. Med. Genet. 2007;44;353-362 Tumors from individuals should be tested for MSI in the following situations: 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.

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.

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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

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[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

	• 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	**Rationale to support coverage** 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. There are 5 indications for testing for Fragile X. 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 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. <u>Testing beneficiaries – Indication #1-2</u> 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. **<u>FXTAS</u>** 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. 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

Code(s)	81243 and 81244 – FMR1

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]

Testing guidelines for fragile X-associated tremor/ataxia syndrome[1]

Clinician should test for *FMR1* mutation if the patient has any of the following:

- 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 *FMR1* 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

Fragile X testing would also be appropriate[1]

- The presence of an MCP sign (increased T2 signal intensity in the middle cerebellar peduncles),
- A family history of *FMR1* 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 *FMR1* 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 dysfunction[5].

RATIONALE FOR TESTING:

- 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. allopregnanolone[6] 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 testing[7].

Diagnostic Criteria[1,3,5,8]

Molecular	55 to 200 CGG repeats (permutation)

Code(s)	81243 and 81244 – FMR1

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

Diagnostic categories[1,3,5,8]

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

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
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
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.
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
5. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the *FMR1*premutation and fragile X-associated tremor/ataxia syndrome Lancet Neurology. In press. Publication anticipated July 2013
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,
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.
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

WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING NEUROLOGICAL SYMPTOMS:

- 331.82 Dementia with lewy bodies
- 333.1 Essential and other specified forms of tremor
- 334.3 Cerebellar ataxia NOS

Code(s)	**81243 and 81244 – FMR1**
	• 356 Hereditary and idiopathic peripheral neuropathy • 781 Abnormal involuntary movements

Code(s)	81228 and 81229 Cytogenomic Microarrays
Rationale	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 abnormities 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. 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. 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. 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. RECOMMENDATION: Those Medicare beneficiaries primarily those with disability eligibility, who have not been evaluated for the genetic basis of their condition, should be covered.
References	• Manning, M, and Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genetics in medicine: official journal of the American College of Medical Genetics 12, no. 11: 742–745. • Vermeesch, JR, Fiegler H, de Leeuw N, et al. Guidelines for Molecular Karyotyping in Constitutional Genetic Diagnosis. European Journal of Human Genetics: EJHG 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. Genet. Med. 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. Neurology 77, no. 17: 1629–1635. • Moeschler JB, Shevell M. 2006. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics. 117:2304–2316.

Suggested ICD-9 Diagnoses	WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING ICD-9 DIAGNOSES: **ICD-9 Diagnostic Codes:** 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 HCPCS S3870 Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or mental retardation

Code(s)	81331
Rationale	• 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. Thermodysregulation 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	• 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, Schrander-Stumpel CT. The use of medical care

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Suggested ICD-9 Diagnoses	WE REQUEST THAT COVERAGE INCLUDE THE FOLLOWING ICD-9 DIAGNOSES: 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

Code(s)	81280, 81281, 81282 Long QT Syndrome
Rationale	• 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 molecular genetic testing of the genes known to be associated of which *KCNQ1* (locus name LQT1), *KCNH2* (locus name LQT2) and *SCN5A* (locus name LQT3) are the most common. Other, less frequently involved genes are *KCNE1* (locus name LQT5), *KCNE2* (locus name LQT6), *CAV3* (locus name LQT9), *SCN4B* (locus name LQT10), *AKAP9* (locus name LQT11), *SNTA1* (locus name LQT12) and *KCNJ5* (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 phenotype. • *Prevention of primary manifestations:* Prophylactic use of beta blockers in asymptomatic children and adults dependent on genotype 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. • *Surveillance:* Regular assessment of beta-blocker dose for efficacy and adverse effects in all individuals and; regular periodic

	evaluations of ICDs for inappropriate shocks and pocket or lead complications. • *Agents/circumstances to avoid:* Drugs that cause further prolongation of the QT interval or provoke *torsade de pointes*; competitive sports/activities associated with intense physical activity and/or emotional stress.
References	• 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. Circulation. 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	• 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
		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
		ICD-9 Diagnosis Codes Chorea Huntington disease
	FIP1L1/PDGFRA (del[4q12]) (eg, imatinib-sensitive chronic eosinophilic leukemia), qualitative, and quantitative, if performed	Chronic eosinophilic leukemia
		ICD-9 Diagnosis Codes Chronic eosinophilic leukemia

Code	81401	

Code	81402	
	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), common variants (eg, D816V, D816Y, D816F)	• 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.
		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.
		ICD-9 Diagnosis Codes Mastocytosis

Code	**81403**	
	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)	• 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.
		References • 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. Journal of Clinical Oncology, 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. Journal of Clinical Oncology, 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. Neurology, 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. Journal of Clinical Oncology, 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. Molecular diagnosis & therapy, 14(3), 163–9. doi:10.2165/11537170-000000000-00000
		ICD-9 Diagnosis Codes Gliomas

Code	81404	
	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	• 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.
		References • 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. Journal of Clinical Oncology, 28(7), 1247–53. • Chen, P. (2010). Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: A meta-analysis. World Journal of Gastroenterology, 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. Journal of Clinical Oncology, 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. Clinical Cancer Research, 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. JAMA, 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. International journal of cancer. 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. British journal of cancer, 102(8), 1219–23.
		ICD-9 Diagnosis Codes Gastrointestinal Stromal Tumor Acute Myeloid Leukemia Melanoma

	NRAS	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 in provided in the appendix. NRAS testing results include: • 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 Overview of Clinical Practice for the use of NRAS mutations: Good correlative evidence has been found for colorectal cancer and EGFR-targeted antibody therapies cetuximab and panitummumab 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.
		References • 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. Clinical Cancer Research, 19(7), 1902–12. doi:10.1158/1078-0432.CCR-12-1913 • De Roock, W., Claes, B., Bernasconi, D., De Schutter, J., Biesmans, B., Fountzilas, 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. The lancet oncology, 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. Annals of Oncology, 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. Journal of immunotherapy (Hagerstown, Md. : 1997), 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. Journal of clinical Clinical Oncology, 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. New England Journal of Medicine, 368(7), 623–632. doi:10.1056/NEJMoa1209288
		ICD-9 Diagnostic Codes Colorectal carcinoma Melanoma

	PDGFRA	• 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.
		References • 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. Journal of Clinical Oncology, 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. Histopathology, 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. Journal of Clinical Oncology, 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. Clinical Cancer Research. doi:10.1158/1078-0432.CCR-11-3025
		ICD-9 Diagnosis Codes GIST
	RET	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.
		References: NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
		Diagnosis MEN2 Familial Medullary Thyroid Carcinoma

Code	81406	
	Cytogenomic microarray analsys (CMA) for Neoplasia	• 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.
		References • 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). Blood 2002;100:4325–4336. • Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910–1916. • Heim S, Mitelman F. Cancer Cytogenetics, Chromosomal and Molecular Genetic Aberrations of Tumor Cells, 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. Blood 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. Leuk Lymphoma 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. Genes Chromosomes Cancer 2008;47:697–711. • Okamoto R, Ogawa S, Nowak D, et al. Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism

		oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica 2010;95:1481–1488. • 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, Mannoor K, et al. Microarray detection of multiple recurring submicroscopic chromosomal aberrations in pediatric T-cell acute lymphoblastic leukemia. Leukemia 2011;25:1042–1046.
		ICD-9 Diagnosis Codes Chronic lymphocytic leukemia Acute lymphoblastic leukemia Acute myeloid leukemia

Appendix B: Molecular Pathology Tests/CPT Codes **July 15, 2013**

Status in WPS DL33219 and National Coverage Decisions

NDC column – test is done *in utero or* is consistent with other listed conditions

NC= Not covered CPT list

CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81161			*In utero*		**DMD** (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed
81200			*In utero*	**NC**	**ASPA** (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81201				**Group 2: HNPCC, FAP** **Group 2. Medical Necessity Asterisk** **V12.72 should be used to denote any of the polyposis conditions	**APC** (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202				**Group 2: HNPCC, FAP**	known familial variants
81203				**Group 2: HNPCC, FAP**	duplication/deletion variants
81205			*In utero*	**NC**	**BCKDHB** (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81206			**YES**	**Group 5 codes: 204-206, 208**	**BCR/ABL1** (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207			YES		minor breakpoint, qualitative or quantitative
81208			YES		other breakpoint, qualitative or quantitative
81209			*In utero*	**NC**	**BLM** (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81210				**Melanoma?**	**BRAF** (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81211				**Group 1 – Cover for breast/ovarian cancer**	**BRCA1, BRCA2** (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

Appendix B: Molecular Pathology Tests/CPT Codes **July 15, 2013**
Status in WPS DL33219 and National Coverage Decisions
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CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81212				**Group 1**	185delAG, 5385insC, 6174delT variants
81213				**Group 1**	uncommon duplication/deletion variants
81214				**Group 1**	**BRCA1** (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215				**Group 1**	known familial variant
81216				**Group 1**	**BRCA2** (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217				**Group 1**	known familial variant
81220			*In utero*		**CFTR** (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221			*In utero*	NC	known familial variants
81222			*In utero*	NC	duplication/deletion variants
81223			*In utero*	NC	full gene sequence
81224			*In utero*	NC	intron 8 poly-T analysis (eg, male infertility)
81225					**CYP2C19** (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226					**CYP2D6** (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227			**NDC – not covered****		**CYP2C9** (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228			***In utero***	**NC**	**Cytogenomic constitutional (genome-wide) microarray analysis**; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

Appendix B: Molecular Pathology Tests/CPT Codes **July 15, 2013**
Status in WPS DL33219 and National Coverage Decisions
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CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81229			***In utero***	NC	interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81235					**EGFR** (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81240					**F2** (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241					**F5** (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242			***In utero***	**NC**	**FANCC** (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243			*In utero*	**NC**	**FMR1** (Fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244			*In utero*	NC	characterization of alleles (eg, expanded size and methylation status)
81245		**AML**	**YES**		**FLT3** (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81250			*In utero*	**NC**	**G6PC** (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251			*In utero*	**NC**	**GBA** (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252			*In utero*	**NC**	**GJB2** (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253			*In utero*	NC	known familial variants
81254			*Iin utero*	**NC**	**GJB6** (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255			*in utero*	**NC**	**HEXA** (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg,

CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
					1278insTATC, 1421+1G>C, G269S)
81256					**HFE** (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257					**HBA1/HBA2** (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81260			*in utero*	**NC**	**IKBKAP** (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81261					**IGH@** (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81262					direct probe methodology (eg, Southern blot)
81263					**IGH@** (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264					**IGK@** (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81265					**Comparative analysis using Short Tandem Repeat (STR) markers**; patient and comparative specimen (eg, pretransplant recipient and donor germline testing, posttransplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
81266					each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

Appendix B: Molecular Pathology Tests/CPT Codes **July 15, 2013**
Status in WPS DL33219 and National Coverage Decisions
NDC column – test is done *in utero or* is consistent with other listed conditions
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CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81267					**Chimerism** (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268					with cell selection (eg, CD3, CD33), each cell type
81270		**Myeloproliferative disorder, ALL, CLL**	**YES**	**Group 3 codes Covered for these ICD-9 groups: 204: ALL, CLL; 288.51, 288.61, 288.8, 453.0**	**JAK2** (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81275				**Group 2: HNPCC, FAP**	**KRAS** (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
81280			*in utero*	**NC**	**Long QT syndrome** gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2) ; full sequence analysis
81281			*in utero*	NC	known familial sequence variant
81282			*in utero*	NC	duplication/deletion variants
81290			*in utero*	**NC**	**MCOLN1** (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291					**MTHFR** (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292				**Group 2: HNPCC, FAP**	**MLH1** (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293				**Group 2: HNPCC, FAP**	known familial variants
81294				**Group 2: HNPCC, FAP**	duplication/deletion variants
81295				**Group 2: HNPCC, FAP**	**MSH2** (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296				**Group 2: HNPCC, FAP**	known familial variants

Appendix B: Molecular Pathology Tests/CPT Codes **July 15, 2013**
Status in WPS DL33219 and National Coverage Decisions
NDC column – test is done *in utero or* is consistent with other listed conditions
NC= Not covered CPT list

CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81297				**Group 2: HNPCC, FAP**	duplication/deletion variants
81298				**Group 2: HNPCC, FAP**	**MSH6** (mutS homolog 6 [E. coli]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299				**Group 2: HNPCC, FAP**	known familial variants
81300				**Group 2: HNPCC, FAP**	duplication/deletion variants
81301				**CDC - Lynch**	**Microsatellite instability** analysis (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81302			*in utero*	**NC**	**MECP2** (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303			*in utero*	NC	known familial variant
81304			*in utero*	NC	duplication/deletion variants
81310		**AML**	**YES**		**NPM1** (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants **Print Publication Date: January 1, 2012**
81315		**Promyelocytic leukemia**	**YES**		**PML/RARalpha**, (t(15;17)), (promyelocytic leukemia/ retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316		**Promyelocytic leukemia**	**YES**		single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81317				**Group 2:HNPCC, FAP**	**PMS2** (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318				**Group 2:HNPCC, FAP**	known familial variants
81319				**Group 2:HNPCC, FAP**	duplication/deletion variants
81321					**PTEN** (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

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81322					known familial variant
81323					duplication/deletion variant
81324					**PMP22** (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325					full sequence analysis
81326					known familial variant
81330			*in utero*	**NC**	**SMPD1**(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331			*in utero*	**NC**	**SNRPN/UBE3A** (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332					**SERPINA1** (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81340					**TRB@** (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341					using direct probe methodology (eg, Southern blot)
81342					**TRG@** (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81350			***In utero***	**NC**	**UGT1A1** (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355			**NDC-not covered****		**VKORC1** (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
81370					**HLA Class I and II typing**, **low resolution** (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1

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CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81371					**HLA-A, -B, and -DRB1/3/4/5** (eg, verification typing)
81372					**HLA Class I typing, low resolution** (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
81373					one locus (eg, HLA-A, -B, or -C), each
81374					one antigen equivalent (eg, B*27), each
81375					**HLA Class II typing, low resolution** (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376					one locus (eg, *HLA-DRB1 /3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1*), each
81377					one antigen equivalent, each
81378					HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379					**HLA Class I typing, high resolution** (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380					one locus (eg, HLA-A, -B, or -C), each
81381				C - HIV-prior to initiating abacavir	one allele or allele group (eg, B*57:01P), each
81382					**HLA Class II** typing, high resolution (ie, alleles or allele groups); one locus (eg, *HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1*), each
81383					one allele or allele group (eg, HLA-DQB1*06:02P), each
81479					Unlisted molecular pathology procedure
81400					**Molecular pathology procedure, Level 1** (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	ACADM	**Medium chain acyl dehydrogenase deficiency**	*In utero*		
	FGFR3	**Muenke syndrome**	*In utero*		
	SHOC2	**Noonan-like syndrome with loose anagen hair**	*In utero*		

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CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81401				**Group 2:HNPCC, FAP**	**Molecular pathology procedure, Level 2** (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	AR	**Spinal and bulbar muscular atrophy muscular atrophy, Kennedy disease, X chromosome inactivation**	*In utero*		
	CBFB/MHY 11	**AML**	YES		
	DMPK	**Myotonic dystrophy**	*In utero*		
	E2A/PBX1 (t(1;19)) (eg, acute lymphocytic leukemia	**ALL**	**YES**		
	ETV6/RUNX1 (t(12;21))	**ALL**	**YES**		
	FIP1L1/PDGRFA	**imatinib-sensitive chronic eosinophilic leukemia**	**YES**		
	FXN	**Friedreich ataxia 1**	*In utero*		
	HBB		***In utero***		
	MLL/AFF1	**ALL**	**YES**		
	MLL/MLLT3	**ALL**	**YES**		
	RUNX1/RUNX1T1	**AML**	**YES**		
	Septin9 methylated DNA				

CPT Code	Gene	Condition	NDC 190.3	WPS DL33219	Code Descriptor
81402					**Molecular pathology procedure, Level 3** (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	MEFV	**Familial Mediterranean Fever**	*In utero*		
	MPL	**Myeloproliferative leukemia**	**YES**		
81403				**Group 2:HNPCC, FAP**	**Molecular pathology procedure, Level 4** (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	BCR/ABL fusion gene	**ALL, CLL**	**YES**	**Group 5 Codes: for ALL, CCL, myeloid leukemia (ICD-9: 204-206, 208, 288.69, 288.8**	
	CEBPA	**AML**	**YES**		
	DNMT3A	**AML**	**YES**		
	F8	**Hemophilia A**	*In utero*		
	FGFR3	**Isolated craniosynostosis**	*In utero*		
	HBB	**Beta thalassemia**	*In utero*		
	MPL	**myeloproliferative leukemia**	**YES**		
	JAK2	**ALL, CLL, myeloproliferative disorder**	**YES**	**Group 3 codes 204: ALL, CLL; 288.51, 288.61, 288.8, 453.0**	
81404					**Molecular pathology procedure, Level 5** (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic

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					mutation disorder/triplet repeat by Southern blot analysis)
	ACADS	**Short chain acyl-CoA dehydrogenase deficiency**	*In utero*		
	FKRP	**Congenital muscular dystrophy type 1C**	*In utero*		
	HBA1/HBA 2	**Alpha thalassemia**	*In utero*		
	HBB		***In utero***		
	KIT	**GIST, AML, Melanoma**	**YES**		
	STK11			**Shld cover-lynch syndrome**	(serine/threonine kinase 11) (eg, Peutz-Jeghers syndrome), duplication/deletion analysis
	TP53				
81405					**Molecular pathology procedure, Level 6** (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	ABCD1	**Adrenoleukodystrophy**	*In utero*		
	GLA	**Fabry disease**	*In utero*		
	SPRED1	**Legius Syndrome**	*In utero*		
	STK11			**Group 2:HNPCC, FAP**	
	TP53				
81406				**Group 2:HNPCC, FAP**	**Molecular pathology procedure, Level 7** (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for

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					neoplasia)
	ACADVL	**Very long chain acyl-coenzyme A dehydrogenase deficiency**	*In utero*		
	CDKL5	**Early infantile epileptic encephalopathy**	*In utero*		
	POMGNT1	**Muscle-Eye-Brain Disease**	*In utero*		
81407					**Molecular pathology procedure, Level 8** (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	CHD7	**CHARGE syndrome**	*In utero*		
	JAG1	**Alagille syndrome**	*In utero*		
81408					**Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)**
	COL1A1	**Osteogenesis imperfecta**	*In utero*		
	NF1	**Neurofibromatosis**	*In utero*		
88363				**Group 2:HNPCC, FAP**	EXAMINATION AND SELECTION OF RETRIEVED ARCHIVAL (IE, PREVIOUSLY DIAGNOSED) TISSUE(S) FOR MOLECULAR ANALYSIS (EG, KRAS MUTATIONAL ANALYSIS)