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RE: Draft Local Coverage Determination: **Biomarkers Overview** (#DL33640 and DL33638)

Dear Ms. Mandella:

Thank you for the opportunity to comment on Draft Local Coverage Determination: Biomarkers Overview. 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 Novitas 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 the attachment.

The primary issues we will address are the following:

1. **Use of testing in diagnosis and management**
2. **Reasons for not covering tests in individuals**
3. **Coverage for all Medicare beneficiaries regardless of eligibility by age or disability**
4. **Covered Testing and Conditions: Cytogenetics**
5. **Coverage for tests based on medical condition: Upper Age Limits**
6. **Specific tests which meet 'reasonable and necessary' criteria**
7. **Coverage for tests performed under a CED**

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1. Use of testing in diagnosis and management

The Draft Policy Language states:

> "Second, there must be a recognized decision impact of such biomarkers by the clinical community. In other words, there must be acceptance/uptake of specific testing into patient management." (Fundamental principles for predicting local Medicare coverage of biomarkers)
>
> "Medicare considers genetic testing medically necessary to establish a molecular

diagnosis of an inheritable disease when all of the following criteria are met:

- The beneficiary displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic); and
- The result of the test will directly impact the treatment being delivered to the beneficiary; and
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, such testing can be coverable. (from Germline (Hereditary) Mutations)

While we agree in principle with these statements that it is the interpretation and their application to services and care provided that is critical, Medicare recognizes that diagnosis and treatment are covered medical services, specifically including diagnostic testing. In the MLN ABN brochure it 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*.

Also, the PIM instructions, Chapter 13, Local Coverage Determinations §13.5.1 - Reasonable and Necessary Provisions in LCDs, provide additional elements the contractor is to consider in deciding if a service or treatment meets these criteria. Some of additional points to be considered are whether 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".

We understand that use of testing must be medically necessary and appropriate for the patient and condition. However, we would like to emphasize that molecular pathology testing should be held to the same standard, and not a more rigorous or limited one, than other diagnostic tests covered like chest x-rays, CT, MRIs, PET scans, EKG, or other blood tests when used to confirm suspected medical diagnoses. Along these lines there are two further points we would like to emphasize (a. and b. below).

a. The result of the test will directly impact the treatment being delivered to the beneficiary

We want to be sure we are defining this in the same way so that it reflects the full practice of medicine. Many times, this is interpreted to mean that the test has to be directly linked to selecting a drug for cure or a surgical intervention for cure or to reduce symptoms. The type of impact, a direct impact on treatment, depends on the purpose of the test, whether it is a diagnostic or pharmacogenomic test. We will address the general diagnostic testing first.

FOR DIAGNOSTIC TESTING

We think of it in terms of "care of the patient ", the "plan of care" or the "treatment plan". As in other areas where they are used by Medicare, e.g. SNF, Home Care, Hospice, the treatment plan includes everything related to the care of the patient. It is more than just how the physician uses the information and how it influences recommendations. It includes how the information is used

by the patient with respect to the condition, their life, and the future. That is an important part of a "treatment plan".

We will expand on some of the following examples of the direct impact of a test

- Confirming the diagnosis
- Directing other tests to obtain a diagnosis – ruling out some causes, redirecting to others
- Options for curative intervention: drug choices/response; Surgical or invasive interventions
- Options for symptomatic management – physical and mental/emotional
- Identification of associated comorbidities to be assessed and/or monitored.
- Decision-making about life issues, including management of comorbid conditions

- Confirming the diagnosis
  This has a major impact on the "plan of care". It confirms the clinical diagnosis. 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, what 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. Having a confirmed diagnosis can mean that the long, often costly search for a cause can be over, and 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 and that it is not 'all in their head', an important outcome for patient, family, friends and physician!

- Identifying options for treatment
  There are conditions for which the treatment options and timing of treatment is affected by the genetic results, especially the subtype. An example is Long QT Syndrome. There are others for which there is no treatment or cure. The diagnosis still impacts the treatment. By confirming a different diagnosis, it can explain why a current treatment course which was 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, e.g. 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.

- Options for symptomatic management
  Knowing the conditions and its natural history can help guide recommendations for symptom management and prevention (or delay of) secondary complications. Referrals and treatment planning by PT, OT, and SLP may be involved. Emotional support and treatment may be appropriate as the patient adjusts to the diagnosis with its implications for the present and future. They may need to learn new coping skills and create a network of support, which has been found to improve morbidity and mortality. Having a specific diagnosis can 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.

- Impact on decision-making
  Having a diagnosis helps the patient with decision-making about life issues affected by the condition, its prognosis, its natural history.

- Identification of associated comorbidities to be assessed and/or monitored.
  Many of the genetic conditions are complicated medically, not only because of the primary presenting condition but also because of other conditions that are associated with the primary condition and/or because of how the condition presents and affects the patient.
  Examples:
  - Fragile X – permutations of the FMR1 may not present as Fragile X (developmental delay, autism, etc.). They may present later in life displaying the neurodegenerative effect: ataxia, tremor, memory loss, and peripheral neuropathy. They also have an increased association with sleep apnea, hypothyroidism, autonomic dysfunction, depression/anxiety/agitation, and hypertension.
  - Prader-Willi Syndrome – patients may not demonstrate the full phenotypic features and be may not be properly diagnosed in their youth. Having an accurate diagnosis is relevant to the primary care physician. Features of PWS that are relevant to the physician providing daily care or evaluating the patient in the ED: very high threshold for pain and inability to localize pain, thermal dysregulation and failure to develop fevers, lack of vomit response in light of ingestion of toxic substances or pathogens, hyperphagia for food and water to the point of rupture/water intoxication, and sensitivity to anesthesia.

FOR THE IMPACT OF PHARMACOGENOMIC TESTING:

If the test is performed for pharmacogenomic reasons, then the impact should be considered from that perspective. The key questions are whether the test will be able to guide choice of drug, dosing, side effects, or testing, or duration of treatment. The criteria provided by Medicare become more relevant in this case: specifically providing care that does not exceed the patient's need and is "at least as beneficial as an existing and available medically appropriate alternative".

We provide the example of warfarin testing because it is relevant to the decision about whether a test will meet "reasonable and necessary" criteria and be covered. In 2009, Medicare initiated a National Coverage Analysis (NCA). They reviewed the literature, developed a draft position, reviewed public comments and issued their recommendations (NCD 90.1). In their analysis and final decision they considered whether pharmocogenomic testing improved the outcome. "improving outcome" would be in comparison with the current standard of care: does it do as well as the current standard, does it do better? Can it replace the current approach or is it done in addition to the current approach?

For warfarin, the question was whether the test results affected the decision to use warfarin, the initial dose, the dosing amount or interval, the need for testing, and/or the number of adverse events because of increased bleeding risk from high PT/INR. From Medicare's perspective,

- If the test did "as well as" the standard, it could potentially be covered depending on how it relates to the current standard approach.
- Does the evidence indicate that the test in question is sufficient and could be an alternative to or substitute for the standard approach or would modify the standard approach significantly if both were used (e.g. frequency of PT/INR testing)?
- If it cannot replace the current recommended testing, then would it be provided 'in addition' to the standard? If it is done 'in addition', the critical question is whether it results in any real changes in the management of the patient.
- If it would be done in addition to the standard approach and it didn't improve the results, then it would 'exceed the patient's need' and not be medically needed. It would not be considered to be an important part of their care and the decisions for care.

There are a number of conditions and drugs for which the evidence and guidelines demonstrate the importance of gene testing in the choice and/or dose of drugs for treatment with respect to directing or limiting treatment options all should follow the same criteria as listed above.

b. Coverage based on the level of clinician's uncertainty in making the diagnosis

Diagnostic testing is used for a number of recognized purposes in the practice of medicine:

- To confirm a suspected diagnosis
- To provide additional information about the physiologic/structural conditions associated with the signs/symptoms and provide additional guidance on the cause

Standards of practice have been developed for diagnosing many conditions and include genetic testing requirements and recommendations.

i. Cases in which the diagnosis is made on the basis of phenotype, presentation, and other lab tests (genetic testing is not needed).

ii. In most cases, even if the clinical presentation is consistent with a diagnosis of a genetically-based condition, the definitive diagnosis cannot be made until the genetic testing confirms it. This is similar to the use of diagnostics to confirm a presumptive diagnosis made on the basis of history, symptoms, and examination, such as glucose testing to confirm the suspected diagnosis of diabetes or an x-ray to confirm the suspected diagnosis of fracture of a bone.

It would be medically inappropriate to give the diagnosis of a genetically-based condition without performing the testing that would confirm the genetic evidence, especially if they are part of the clinical guidelines for that condition. This is especially true when it is a hereditary mutation that would have implications for reproduction and family member risk.

2. Reasons for not covering tests in individuals

"Key limitation: Genetic testing of tissue samples from other family members (e.g. possible/probably carriers) is not statutorily covered by Medicare." (From 1. Germline (Hereditary Mutations))

This raises a very important issue for patients and providers alike which needs clarity. It is not clear from this statement whether the family members are also Medicare beneficiaries. If they are not, the test would not be covered because the family members are not covered under Medicare. If they are Medicare beneficiaries, we would disagree with the reason given for not covering the test in family members.
The reason for denial has implications for beneficiary financial liability. It has technical implications for providers because we have a responsibility to notify the patient about coverage of a test and obtain ABN only when indicated. (CMS-ABN) We need to have instructions from the MAC about how we are to appropriately bill these services.

Reason for not covering the test
Medicare has defined a hierarchy of reasons for denying a claim as outlined in PIM 100-08. §3.6.2.5. There are 3 main 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.

> Benefit Category: in this case, the benefit category would be medical and other health services: physician services and diagnostic services.
>
> 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 100-8, §3.6.2.5) Statutory exclusions from Medicare benefits are addressed in §1862(b). The informational brochure for providers on ABN includes a list of the program exclusions listed in §1862(b), e.g. personal comfort items, cosmetic surgery, dental care, eye exams for eye glasses or contacts, hearing aids, routine dental services, and services resulting from acts of war. The requirement for an ABN does not apply to these items/services.
>
> Not Medically Necessary denial:
> A service/item can be denied because it is "not reasonable and necessary as defined under §1862(a) (1) of the Act" (PIM 100.8, §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 instructions (PIM 100-8, §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".

Molecular pathology is a subset of pathology, which is a subset of physician services, a Medicare benefit category. Pathology testing is not excluded by the statute. However, like any service or item, individual tests within the pathology subset can fail to meet the "reasonable and necessary" criteria of the law depending on the individual situation. The decision about whether Medicare would cover the test depends on a) the individual's status - whether they have symptoms or not) and b) the purpose of testing. The reason for not covering the test when it is dependent on the situation would be addressed by the "reasonable and necessary" criteria.

Individual uses which do not meet the 'reasonable and necessary' criteria:

a) Individual's status: a Medicare beneficiary is asymptomatic but genetic testing is recommended to assess carrier status for any number of reasons. For example, because a family member is positive for a mutation, testing of the beneficiary is recommended to assess the risk of developing the condition and need for active intervention, for future healthcare decisions such as assessing reproductive risk, or for genetic counseling for family members.
b) Purpose of test: as a national policy, Medicare has determined that pharmacogenomic testing of warfarin does not meet the 'medical necessity' criteria for general use but it can be covered when it is performed within the context of a clinical trial.

CLAIMS PROCESSING IMPLICATIONS:

Given that testing for germline mutations can be done for different reasons: 1) to diagnose a condition in a person with signs/symptoms, which would be covered and 2) a second use to identify carrier status, including reproductive risk, which would not be covered because the person is asymptomatic, physicians need to have a mechanism to tell Novitas which use is being billed for so that they can get the appropriate denial, specifically for the second use.

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 will 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, or in response to 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 Novitas instruct physicians 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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3. Coverage for all Medicare beneficiaries regardless of eligibility by age or disability

We would also like to address the beneficiaries 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 million beneficiaries of which 8.624 million 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 (6.87 million out of 37.214 million beneficiaries in FFS). (CMS-Statistical Supplement) The LCDs need to be appropriate for all Medicare beneficiaries, regardless of age. The beneficiaries under 65 should the same coverage for 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 or 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 while the diagnosis is relevant; 2) testing has evolved to be more sensitive/specific now; 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.

REQUEST: We would request that decisions about coverage and determinations of medical necessity be appropriate for all Medicare beneficiaries, for those eligible by age (>65) and disability status. Tests which are used to diagnose a condition should be covered in those who are eligible by disability status, assuming other criteria for medical necessity are met. The beneficiary and their providers should not have to appeal an inappropriate denial.

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4. Coverage for tests based on medical condition: Upper Age Limits

In the table on tests for Germline Mutations, there are a number of tests where an upper age limit for coverage is indicated. The value and use of genetic testing depends on the condition and the patient and how the test will be used. The clinical guidelines describe the algorithm for diagnosis and

treatment. The treating physician would adjust the algorithm based on the individual patient characteristics. Applying a global limitation for genetic testing based on age should be applied in two situations: 1) when the condition never occurs at or above a set age, or 2) when the medical literature and standard of practice is in agreement that diagnosis and/or treatment linked to genetic tests is not appropriate for ANY patient over a specified age. We are not aware of evidence which supports either type of global exclusion of patients based on age.

Age Limits in Oncology:
We would point out that there are two uses for test results. The first is diagnostic, to define the genetic line and related syndromes. This is important to management of the index cancer as well as screening for other cancers associated with the genetic line. In the past, germline screening was limited by age but additional clinical studies demonstrated this was inappropriate given the clinical experience. Since then, age limits for germline identification have been removed (NCCN Clinical Practice Guidelines in Oncology: Breast Cancer: NCCN Clinical Practice Guidelines in Oncology: Colon Cancer; NCCN Clinical Practice Guidelines in Oncology: Senior Adult Oncology, and Recommendations from the EGAPP Working Group).

In a review of the diagnosis and treatment guidelines, e.g. NCCN guidelines, the recommendations do not place a limit on germline testing based on absolute age. NCCN has reviewed their position and convened specialists to address the applicability of oncology management to those over 65. They have provided a guideline for clinicians to assess the individual patient's factors and comorbidities to determine how to proceed with cancer treatment (NCCN Senior Adult Oncology). It recommends that the clinician approach each individual and assess risk factors, the patient's ability to tolerate treatment, life expectancy and other comorbidities. When genetic testing is part of the treatment algorithm, the genetic testing would be appropriate based on the clinical assessment of the patient and the choices for treatment.

They have presented the following disease-specific issues related to age.

Breast Cancer :
"Older adults (65 years or older) with breast cancer enrolled in cooperative group trials of adjuvant chemotherapy derive similar benefits (disease-free and overall survival) compared to younger patients. However, older patients have an increased risk of side effects and treatment-related mortality." (NCCN Senior Adult Oncology)

Colon Cancer:
In their recommendations with respect to adjuvant therapy and metastatic disease, they note that "older adults derive similar benefit as younger patients (In terms of disease-free and overall survival) .. Older adults are at increased risk for hematologic toxicities." They summarize the research for different drugs and make recommendations, primarily individual assessment.

Age Limits on Gene Testing for Other Conditions
Alpha-1-Antitrypsin Deficiency (CPT Code 81332 – SERPINA1)
Not all patients with A1AT present early in life. Milder forms in particular can present later in life. Emphysema/COPD in a person who has never smoked should prompt evaluation for A1AT, regardless of age. For more information, see the Appendix: Detailed Comments

REQUEST: We are not aware of evidence which supports either type of global exclusion of patients based on age and therefore request that these be removed from the policy.

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5. 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:
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> - 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 leukemia lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or
> - Myelodysplasia."

Broadly speaking, cytogenetic is the study of genes and their structure. 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. There are specific tests 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. The tests and their CPT codes which are performed in utero that are not listed as covered in the table are: 81161, 81200, 81205, 81209, 81220-81224, 81330-81331, and 81302-81304

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

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6. Specific tests which meet 'reasonable and necessary' criteria

There are a number of tests we believe **should be covered**. We have addressed them in detail including references in the Appendix .

a. CFTR (CPT codes 81220-81224) Cystic Fibrosis

Atypical CF often presents as unusual pneumonia in Medicare-age population. Identifying the patient as atypical CF helps to manage potential future episodes of pneumonia and can also be associated with some of the malabsorption issues though typically milder.

b. 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.

c. 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 heterogenous 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.

d. 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.

e. 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.

RECOMMENDATION: 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.

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7. Coverage for tests performed under a CED

We appreciate the information about coverage for testing associated with a CED. From a claims processing perspective, we need clarification and a mechanism to report a test that has been performed consistent with the CED requirement.

a. CED criteria cited

We have been unable to identify the authority and parameters for a contractor to develop local coverage policies for experimental or investigational services or items. We are aware that Medicare has the authority and uses the CED process in conjunction with the National Coverage Determination process. The contractors implement the CED coverage at the operational level as part of the NCD, as instructed in PIM 100-8 and described in the Draft CED guidance.

It is clear the contractors 1) are expected to make medical necessity decisions about claims for services and items but the instructions specify that the service/item must not be investigational or experimental and 2) have the authority to develop Local Coverage Determinations for care, but the PIM 100-8 specifically states that the service addressed in the LCD is:

> *"Not experimental or investigational (exception: routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary)" §13.5.1;*

We have not been able to identify language or instructions from CMS that extend the authority of the contractors to develop LCDs using their own CED process to cover investigational or experimental services/items within their jurisdiction. If that authority does indeed exist, if the contractor is to exercise independent authority to approve coverage under the auspices of a CED, then we would expect that the criteria and requirements be consistent with and not exceed the requirements defined by CMS for coverage of services/items within the context of a national policy (NCD).

Specifically, the DLCD makes requirements that are in conflict with the NCD-CED and Draft Guidance as demonstrated below.

Issue	Novitas DL22638/33640	NCD-CED Issued July 12, 2006	Draft Guidance - 2012
Who does the study	"conducted by individuals "capable of executing the proposed studies successfully"	"sponsored by a credible organization or individual capable of executing the proposed trial successfully"	"The study is sponsored by an organization or individual capable of completing it successfully"
Making results public	"results must be made public within 12 months of the end of data collection"	"within 24 months of the end of data collection"	"If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
Publication	"Subsequent articles must be accepted by a journal for publication within 30 months of the finalization of this LCD"	"no later than 36 months after the end of data collection".	"CMS expects that results of all CED approved studies will be analyzed and published in peer reviewed clinical journals."

Reports	Submit progress reports to Novitas every 6 months	Not required	Not required

b. Pharmacogenomic Testing for Warfarin Response.
In the MLN Matters article on the subject (MLN-MM6715) CMS has indicated that the NCD does not determine coverage to identify CYP2C9 (CPT Codes 81227) or VKORC1 (CPT Codes 81355) alleles for other purposes, nor does it determine national coverage to identify other alleles to predict warfarin responsiveness. The CMS Transmittal 1889 contains instructions for billing for warfarin testing. MLN Matters article on the subject contains the following information:

> Institutional clinical trial claims for pharmacogenomic testing for warfarin response are identified through the presence of all of the following elements:
> • ICD-9 diagnosis code V70.7*:
> • Condition code 30: 8-digit clinical trial number(when present on the claim) (per MM5790);
> • HCPCS modifier Q0 for outpatient claims only; and,
> • HCPCS code G9143 (to be carrier priced for claims with dates of service on or after August 3, 2009, that are processed prior to the January 2011 CLFS update).
>
> Practitioner clinical trial claims would be identified with the following:
> • ICD-9 diagnosis code V70.7*;
> • 8-digit clinical trial number (when present on the claim);
> • HCPCS modifier Q0; and,
> • HCPCS code G9143 (to be carrier-priced for claims with dates of service on and after August 3, 2009, processed prior to the January 2011 CLFS update).

* V70.7 Examination of a participant in a clinical trial

REQUEST: We would request that Novitas clarify whether we to bill for these claims as per the MLM instructions?

c. Cytochrome P450 CYP2C19 (CPT Code 81225) and CYP2D6 (CPT Code 81226) allele testing for pharmacogenomics

We do not know the status of these CPT codes for purposes of claims processing and beneficiary notification.

1) Will all claims be denied as not medically necessary, as per this draft policy?
2) Will all claims submissions for pharmacogenomics be approved when a CED is in place? Will a clinical trial number be required? Should we bill using the ICD-9 diagnosis code V70.7*?

d. Other non-oncologic biomarkers.
Draft Language: "Other non-oncologic biomarkers may arise, and find a possible niche with a CED-based approach, which is specified". It is not clear what this statement means and leaves us with the following questions:

1) Does it only apply to biomarkers created in the future? How does it apply to existing biomarkers?
2) If a biomarker is in a clinical study, this statement suggests Novitas could potentially cover it under as a CED, as defined by Novitas.

- When CMS invokes the CED process, it is done in conjunction with a National Coverage Decision which defines the clinical questions and condition. As an NCD, the topic goes through the national coverage process, is reviewed by their medical advisory group and goes out for public comment.
- If Novitas is using the CED process on the basis of its authority to develop Local Coverage Determinations, will the topics for coverage under CED go through the LCD process?

2) Biomarker not in clinical study and is in use, it may or may not have a specific CPT code.

- There are many existing tests that are not addressed in this draft policy, outside those related to oncology. It is not clear what their status is. Should it be assumed that the test is covered until there is a decision to the contrary? ORIs it the intention of this statement to have ALL NEW biomarkers go through the CED process?

In our opinion we have not been able to find evidence that Novitas has the authority to create a draft policy for CED and would request that they remove this requirement from the DLCB. If Novitas can demonstrate that they have authority we would request that they revise the language in the DLCB to match that of the national CED-NCD and Draft Guidance.

We hope that there will be an article accompanying this LCD with instructions on billing and other relevant information.

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 Novitas 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 Vivianna Van Deerlin, MD, PhD, Director of the Molecular Pathology Laboratory, Hospital of the University of Pennsylvania or Dara Aisner, MD PhD, Co-Director, Colorado Molecular Correlates Laboratory, University of Colorado Denver.

Sincerely,

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ATTACHMENTS:
Appendix- Detailed comments

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
- NCD With Data Collection as condition of Coverage: Coverage with Evidence Development. July 12, 2006. NCD-CED Issued July 12, 2006 accessed 07.16.2013Draft Guidance for the public, Industry, and CMS Staff Coverage with Evidence Development in the context of coverage decisions. http://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=23 Accessed 07.18.2013

CLINICAL REFERENCES (additional references in the Detailed Section)

- ATS/ERS Standards for the diagnosis and management of Individuals with Alpha-1Antitrypsin Deficiency http://alpha-1foundation.org/wordpress/wp-content/uploads/2012/03/ATS-ERS-Standards.pdf Accessed 07.16.2013
- NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. Accessed 07.2013. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
- NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, Version 3.2013. Accessed 07.17.2013. http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
- NCCN Clinical Practice Guidelines in Oncology: Senior Adult Oncology, Version 2.2013. Accessed 07.17.2013. http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf
- **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;11:35-41.**
- **Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11:42-65.**

Specific Tests identified in the Germline Mutation table for which an upper age limit is not consistent with the clinical experience, guidelines and medical evidence

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

CPT codes	**81332 Alpha-1 antiproteinase, antitrypsin deficiency**
Rationale	This is not a condition of childhood in general. The age at onset can be quite variable but it rarely presents before the age of 25. The Alpha-1 Research Registry and AlphaNet collectively follow close to 6,000 patients with AATD. Their average age at diagnosis is nearly 60 years old. Many of those followed are in the 70s and 80s and a few are in their 90s. In addition, the liver disease associated with AATD most often presents either as a newborn or after the age of 65 years. (Per Dr. Sandhous data, Alpha-1 Foundation.) The current guidelines for the diagnosis and management of AATD (see reference 1) give a category A recommendation that all individuals with the diagnosis of chronic obstructive lung disease (COPD) be tested for AATD. Obtaining an accurate diagnosis is important for 2 reasons. The first is that there is specific treatment that can be offered to the patient. The augmentation therapy has been shown to slow or halt the progression of the lung disease. There is no upper age limit for patient selection for treatment. It is often started in the older patients as well. Lung transplantation (LT) has become an option for many patients with end-stage lung disease. Approximately 12% of all LTs are performed for emphysema secondary to AATdeficiency. The second reason for the definitive diagnosis is that A1AT deficiency is a multisystem condition. It is usually the lung that is first symptomatic and brings the patient in for diagnosis. However, the genetic mutation is also associated with other conditions, e.g. liver disease and skin disorders. With an accurate diagnosis, other symptoms and conditions of the patient can be reevaluated in light of the genetic finding. As noted in the ATS guideline, " the most impressive finding in more recent studies is the predominant role of cirrhosis-related mortality, especially in elderly never-smokers". While the presentation, risks and
References	American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. Am J Respir Crit Care Med, Vol 168. pp 818–900, 2003

Specific Tests identified in the Germline Mutation table which meet 'reasonable and necessary' criteria for coverage

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

CPT codes	**81220-81224 Cystic Fibrosis**
Rationale	While CF is more often identified in the infant/early childhood, new diagnoses are made at later ages. The Cystic Foundation registry indicates that, from 2005 to 2012, about 1000 new cases were identified each year after age 12. For example atypical CF can presents as atypical pneumonia. For those beneficiaries who present with symptoms for which testing is appropriate, the diagnostic testing should be available. It has definite and direct impact on treatment decision related to pulmonary conditions as well as other associated conditions. Identifying the patient as having the CF genetic mutation helps to manage potential future episodes of pneumonia. It is relevant because the diagnosis dictates rigorous management routines outlined in the CF guidelines. Because it is a multisystem condition, other associated conditions include pancreas involvement and diabetes, liver disease, disorders related to nutritional factors like osteoporosis and fat soluble vitamin insufficiency.
References	Mogayzel PJ Jr et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013; 187(7):680-689. PMID:23540878 For additional information, please feel free to contact Dr. Bruce Marshall, CF Foundation, VP of Clinical Affairs at the CF Foundation, 301-951-4422.

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 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

Code(s)	81243 and 81244 – FMR1

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)
Clinical	
• Major	Intention tremor
	Cerebellar gait ataxia
• Minor	Parkinsonism

Code(s) **81243 and 81244 – FMR1**

	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

.

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 allopregnanoloneHuman 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

Code(s)	81331 Prader-Willi Syndrome and/or Angelman Syndrome
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 disability, 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 are 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 extention 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 and

Code(s)	81331 Prader-Willi Syndrome and/or Angelman Syndrome
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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.

Code(s)	**81280, 81281, 81282 Long QT Syndrome**
	• *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.