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RE: Genetic Testing for Cardiovascular Disease DL39084 (First Coast) and DL39082 (Novitas)

Dear Medical Directors:

Thank you for the opportunity to review and comment on your proposed coverage policy for Genetic Testing for Cardiovascular Disease LCD, DL39084 (First Coast) and DL39082 (Novitas).

The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,500 physicians, doctoral scientists, and medical technologists who perform, or are involved with, laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

The College of American Pathologists (CAP) is the world's largest organization of board-certified pathologists and the leading provider of laboratory accreditation and proficiency testing programs. The CAP serves patients, pathologists, and the public by fostering and advocating for excellence in the practice of pathology and laboratory medicine worldwide.

Together, AMP and the CAP would like to thank First Coast and Novitas for their thoughtful consideration of the clinical evidence regarding genetic testing for cardiovascular disease, which is a significant clinical area for genetic testing. However, we have identified two overarching concerns regarding this proposed policy.

First, it is unclear whether the policy is intended to apply only to broad, panel-based testing (i.e., genomic sequencing procedures), or whether it will apply to all genetic testing (e.g., Tier 1 and Tier 2 molecular pathology CPT codes). This ambiguity will make it difficult for healthcare providers to know what is covered or denied and how to comply with the policy. Further, AMP and CAP believe that this coverage uncertainty will adversely affect access to critical testing for Medicare beneficiaries. **We recommend that the final policy clearly state at the beginning of the LCD which types of tests or genes are included in the policy.**

Second, although LCD policies are useful to providers for determining the conditions under which a test will qualify for reimbursement, this policy offers principles of coverage and coverage criteria, but then states that no genetic testing for cardiovascular disorders or conditions is eligible for reimbursement. Specifically, the Billing and Coding Article DA58797 (First Coast) and DA58795 (Novitas) states, "No genes currently meet criteria for coverage as outlined in the LCD." To our knowledge, this is the first such policy to establish acceptability criteria for reimbursement and simultaneously pre-emptively deny coverage for all testing. We respectfully disagree with pre-emptive denial of coverage for all testing, and we request that First Coast and Novitas consider the following recommendations outlined in this letter.

I. Covered Indications

A. The draft policy states, *"Genetic testing for hereditary cardiovascular disease will be considered medically*

reasonable and necessary if:
The evidence for the gene-disease association is evaluated by the evidence-based, transparent, peer-reviewed process of the National Institutes of Health (NIH) sponsored Clinical Genome Resource (ClinGen) and is determined to demonstrate actionability in clinical decision making, meeting all bulleted metrics:

- *Disease severity of sudden death, possible death or major morbidity, modest morbidity*
- *Substantial or moderate evidence of a >40% likelihood of disease*
- *Substantial or moderate evidence of a highly effective or moderately effective intervention*
- *The nature of intervention is either low risk/medically acceptable/low intensity intervention or moderately acceptable/risk/intensive interventions"*

It is well established in the literature and in clinical practice that genetic testing is informative and useful for the clinical management of various inherited cardiovascular diseases such as cardiomyopathies, arrhythmic disorders, thoracic aortic aneurysms and dissections, and familial hypercholesterolemia (FH).[6]

Several diseases/conditions are often not clearly diagnosable based on clinical criterial alone and therefore genetic testing is needed to enable therapeutic intervention. All of the disorders that are included in the LCD have high clinical overlap so, in short, the rationale presented in the LCD is fundamentally flawed as it does not recognize this. For example, in Fabry disease enzyme replacement therapy the responsible gene is GLA which is part of all hypertrophic cardiomyopathy (HCM)gene panels, as Fabry disease can manifest with isolated hypertrophy (i.e., without the other syndromic features that would enable a clear clinical diagnosis), therefore masquerading as HCM. Because it is often not possible to distinguish Fabry from HCM, it is necessary to order a full gene panel or single HCM test. In this case, it follows that all HCM needs a molecular test because it could be Fabry. Testing for HCM is an integral part of the assessment and management of patients with cardiomyopathies and their families. The results of which influence the approach to treatment interventions, such as an implantable cardioverter defibrillator. Additionally, testing for dilated cardiomyopathy (DCM) and other arrhythmogenic disorders.[6]

The low-density lipoprotein receptor (LDLR) gene is another appropriate example. If a patient has high cholesterol and no family history, the physician may not put a patient on a statin, but if that patient does have the familial LDLR mutation and is at the threshold for LDL, then the physician would put the patient on a statin.

Other examples of causative genes that can affect risk assessment and recommended treatment/therapeutic decisions are the Long-QT syndrome,[1,2,8] restrictive cardiomyopathy (e.g., transthyretin amyloidosis),[3,4] and Familial hypercholesterolemia (FH) where a confirmed diagnosis can affect use and choice of lipid lowering therapies (e.g., improved patient adherence to therapy, earlier initiation of therapy, more aggressive therapy or lower LDL-C targets).

Table 1 below lists several diseases/conditions and related genes for which published literature and clinical practice support genetic testing as informative and useful for the clinical management of various inherited cardiovascular diseases. AMP and CAP believe these diseases/conditions meet the coverage criteria within the LCD and therefore, are appropriate for coverage under this policy.

Table 1

Disease/Condition	Role in Patient Management	Corresponding Gene(s)
Arhythmic Disorders		
Long-QT syndrome[1,4]	Causative gene can affect recommended treatment/ therapeutic decisions and risk assessment; aids with identification of family members at risk for the condition	KCNQ1, KCNH2, SCN5A
Short-QT syndrome[6]	To confirm diagnosis, clarify risks, or inform management.	KCNH2, KCNJ2, KCNQ1
Cardiomyopathies		
Hypertrophic cardiomyopathy (HCM), definitive syndromic genes for which isolated left	influences approach to treatment interventions including, but not limited to ICD therapy	PLN, CACNA1C, DES, FHL1, FLNC, GLA, LAMP2, PRKAG2, PTPN11, RAF1, RIT1, TTR

ventricular hypertrophy can be seen[6]		
Restrictive cardiomyopathy[6]	Causative gene can guide choice of therapy (e.g., transthyretin amyloidosis).	TTR; consider HCM or DCM panel
Lipid Disorders		
Familial hypercholesterolemia (FH)[9]	Confirmed diagnosis can affect use and choice of lipid lowering therapies (e.g., improved patient adherence to therapy, earlier initiation of therapy, more aggressive therapy or lower LDL-C targets).	LDLR, APOB, PCSK9

Recommendation: We recommend that the third bullet point mentioned above be amended to include "substantial or moderate evidence of change in patient management such as increased patient monitoring and/or, intervention" and that the diseases and genes in the above table be covered and included in the LCD. Further, advances in this field continue to develop and other CV diseases which have a genetic component, such as Duchenne/Becker muscular dystrophy, that have experimental treatment as a component, should be included in the LCD when further data is made available that supports patient management.

II. Limitations

AMP and CAP believe that the limitations outlined in this draft policy are restrictive to coverage for genetic testing for cardiovascular disease and do not align with current clinical practices.

The draft policy states, *"The following are considered not medically reasonable and necessary:*

1) *A genetic test where either analytical validity, clinical validity, or clinical utility has not been established.*
2) *Genetic testing in patients who do not demonstrate the disease-appropriate phenotype of the gene-disease association.*
3) *Genetic testing of asymptomatic patients.*
4) *Genetic testing solely for purposes of proband identification.*
5) *Genetic testing with family history as the only indication.*

Gene tests for cardiovascular disease are considered germline testing, and therefore only permitted once per beneficiary's lifecycle."

A. It is important to note that a large proportion of genetic testing for cardiovascular disease is performed for family testing—after the genetic diagnosis of the disease is established in the affected person(s), unaffected family members are routinely tested for predictive purposes and early intervention. Examples of cardiovascular condition for which early intervention or monitoring in those with a genetic diagnosis has been demonstrated to improve outcomes include, but are not limited to, Familial Hypercholesterolemia and Brugada syndrome. Access to cascade testing for the familial variant(s) is important for risk stratification.

Recommendation: We recommend that policy points 2, 3, and 5 be clarified to permit cascade genetic testing for the familial variant(s) in family members at 25% or greater risk of the condition.

B. The limitations statement, *"Gene tests for cardiovascular disease are considered germline testing, and therefore only permitted once per beneficiary's lifecycle."* This limitation is listed as a subtext below Limitation #5, and we believe this is a typographical error, and it was your intent to list this as Limitation #6. Notwithstanding, current knowledge of genetic causes of cardiovascular conditions is incomplete, and as new gene-disease associations are demonstrated, additional testing is expected to increase clinical sensitivity. The AMP and CAP believe that the decision to retest a patient should be undertaken by treating providers who can best assess the incremental benefit of repeat testing for additional mutations. Restricting testing to "once per lifetime" will prevent providers and patients from having access to future, state of the art testing, which may improve quality and cost-effectiveness of care.

Recommendation: AMP and CAP recommend revising this language to allow for repeat testing as science advances and additional tests become available that help contribute to the management of

patient care.

III. Summary of Evidence

The fourth paragraph under the Analysis of Evidence section contains the following two statements which appear to be confusing:

> "*The decision to perform genetic testing should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high risk from a previously identified pathogenic variant in their family."*
>
> *"However, Medicare does not cover genetic screening for cardiovascular disease, in which case family history alone would be insufficient for coverage*."

AMP and CAP find this statement to be inconsistent with each other and also with the language in points 2,3 and 5 under the "Limitations" section discussed above.

Recommendation: Consistent with our first recommendation under the "Limitations" section, we recommend **that First Coast and Novitas clarify that genetic testing will be covered for beneficiaries at risk of genetic cardiovascular disease in kinships with previously identified familial variance.**

IV. Billing and Coding

In accordance with the recommendations above, we request that the following CPT codes and ICD-10 diagnosis be added to the LCD. These lists are not intended to be comprehensive.

CPT Codes

Condition	Gene	CPT Code and Descriptor
Long QT Syndrome		
	Multiple	81413 Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	Multiple	81414 Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
	KCNQ1	81406 KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (e.g., short QT syndrome, long QT syndrome), full gene sequence
	KCNH2	81406 KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2) (e.g., short QT syndrome, long QT syndrome), full gene sequence
	SCN5A	81407 SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (e.g., familial dilated cardiomyopathy), full gene sequence
Short QT Syndrome		
	Multiple	81413 Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic

		ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	Multiple	81414 Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
	KCNH2	81406 KCNH2 (potassium voltage-gated channel, subfamily H [eag-related], member 2) (e.g., short QT syndrome, long QT syndrome), full gene sequence
	KCNJ2	81403 KCNJ2 (potassium inwardly rectifying channel, subfamily J, member 2) (e.g., Andersen-Tawil syndrome), full gene sequence
	KCNQ1	81406 KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) (e.g., short QT syndrome, long QT syndrome), full gene sequence
Hypertrophic Cardiomyopathy/Dilated Cardiomyopathy		
	Multiple	81439 Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)
Familial Hypercholesterolemia		
	APOB	81401 APOB (apolipoprotein B) (e.g., familial hypercholesterolemia type B), common variants (e.g., R3500Q, R3500W)
	APOB	81407 APOB (apolipoprotein B) (e.g., familial hypercholesterolemia type B) full gene sequence
	LDLR	81406 LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), full gene sequence
	LDLR	81405 LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), duplication/deletion analysis
	PCSK9	81406 PCSK9 (proprotein convertase subtilisin/kexin type 9) (e.g., familial hypercholesterolemia), full gene sequence

ICD-10 codes

E75.21	Fabry disease
I45-81	Long-QT syndrome
I49.8	Short-QT syndrome
I42	Cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.1	Cardiomyopathy hypertrophic
I42.2	Cardiomyopathy obstructive

I42.5	Restrictive cardiomyopathy
E78.01	Familial Hypercholesterolemia

Thank you again for the opportunity to provide comments on this draft policy. Should you have any questions or require additional information, please direct your correspondence to Tara Burke, Senior Director of Public Policy and Advocacy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

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