ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

March 30, 2021

The Honorable Scott Peters
US House of Representatives
1201 Longworth House Office building
Washington, DC 20515

The Honorable Eric Swalwell
US House of Representatives
174 Cannon House Office building
Washington, DC 20515

Dear Representatives Peters and Swalwell:

On behalf of the American College of Medical Genetics and Genomics (ACMG), we want to thank you for your interest in ensuring that pediatric patients on Medicaid have access to DNA sequencing services. We also wanted to take this opportunity to provide information from the perspective of genetic healthcare providers for you to consider as you prepare legislation for introduction in the 117th Congress.

ACMG is the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics, and the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization. ACMG is the largest membership organization specifically for medical geneticists, providing education, resources and a voice for more than 2,400 clinical and laboratory geneticists, genetic counselors, and other healthcare professionals, nearly 80% of whom are board-certified in the medical genetics specialties. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education, and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health.

Access to appropriate testing is critical for establishing a diagnosis and plan for medical management and treatment of affected individuals. For heritable conditions, understanding the genetic causes of disease is important for family planning as well as medical management of the condition. When applying the concepts of precision medicine, diagnosis means selecting the right test for the right patient at the right time in order to choose the right treatment.

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Selecting the right test

There are various types of genetic tests, including DNA sequencing-based tests which detect variations in genetic material that require extensive interpretation to determine if the genetic variants are the cause of the observed condition. Not all genetic tests detect the same variations. As such, it is critical that patients suspected of having a disease caused by a change in their genome have access to appropriate genetic testing as recommended by a physician knowledgeable about the different types of genetic tests.

- **Genome sequencing** – Genome sequencing (GS) is the unbiased sequencing of DNA. This approach includes sequencing of both coding and noncoding regions of the genome. Current clinical GS methods face limitations for detection of certain structural variants, such as larger deletions, duplications, or inversions. This may improve as long-read sequencing technology is developed, but such technology is currently considered investigational and has not yet been adapted for clinical applications. The depth of sequencing, meaning the number of times each nucleotide of DNA is read, affects how accurately and reliably variants are detected. The sequencing depth varies among laboratories and among different GS services that a single laboratory may offer. The ability to read the nucleotides is also not uniform across the entire genome. These challenging sections of the genome may result in gaps in GS data, especially at lower sequencing depths. Higher sequencing depths result in better coverage and fewer errors, but it also increases the cost of sequencing. Complex bioinformatics are required to interpret GS data. Bioinformatics can vary widely between different laboratories and significantly impact the type of clinically relevant information that can pulled from the raw GS data. Because our understanding of variants' association with disease is constantly changing, reanalysis of previously generated GS data may also reveal clinically relevant information not previously identified. At this time, GS is generally not covered by Medicaid programs in the US.

    - Rapid genome sequencing – Rapid genome sequencing (rGS) sacrifices the depth of sequencing for lower cost and a faster turn-around-time. This may be of benefit for critically ill individuals who cannot wait weeks for test results, such as an infant in the Neonatal Intensive Care Unit (NICU) with intractable seizures and for whom a rapid diagnosis is crucial for appropriate treatment. However, the resulting data may have more coverage gaps and more errors. An increasing number of studies have demonstrated that rGS is effective in the setting of a critically ill patient with suspected genetic disease with a diagnostic yield that approaches that of traditional testing approaches such as exome sequencing. While rGS can miss diagnoses in some patients, studies that have followed rGS with more traditional methods have found this number to be small. Given the critical nature of the illnesses the rapid turnaround outweighs the risk of missing a diagnosis, particularly given that in most settings rGS is followed by more traditional methods.

- **Exome sequencing** (ES; may also be referred to as whole exome sequencing although this is a misnomer, as the nature of exome sequencing is that it will not capture 5-10% of the exome) – Exons are the sections of DNA that provide instructions for making proteins, and the term exome refers to all exons in the genome. The majority of known disease-causing variations occur in the exome. Compared to GS, ES offers higher sequencing depth for a lower cost since less genetic material is being sequenced. It also results in a more manageable dataset for interpretation. The parameters of exome sequencing, such as the sequencing depth and how much genetic material flanking each exon is sequenced, can vary between laboratories. As with GS, the bioinformatics pipeline used by the laboratory also can impact the resulting clinical data. Additionally, periodic reanalysis of previously generated ES raw data may reveal clinically relevant information not identified from initial testing, either because our understanding of a variant's association with disease has changed or because the bioinformatic approach has improved. There is evidence that ES/GS for patients with congenital anomalies, developmental delay, or intellectual disability informs clinical and reproductive decision-making, which could lead to improved outcomes for patients and their family members (Malinowski, et al, *Genetics in Medicine*, 22, 986–1004 (2020)). Many Medicaid plans do not currently cover ES or only cover them in very limited situations. Plans that do cover some ES often require prior authorization processes that result in significant delays in access to testing, high residual cost to patients, or denial of coverage.

- **Gene panel tests** – Gene panels look for variations in multiple different genes associated with diseases with similar symptoms. For example, a gene panel for epilepsy may include several hundred genes. Since there are multiple genetic conditions that can cause epilepsy, panel testing can be a more efficient, reliable, and cost-efficient way of identifying the underlying cause. The genes included on a panel may vary between laboratories, meaning that a patient receiving one panel could have a diagnostic finding in a gene that another laboratory would not detect because they chose not to include the gene on their panel. Alternatively, including genes for which there is dubious evidence for causing disease could lead to the return of information to physicians and patients that could interfere with appropriate management of the condition. The number of genes appropriate for testing will likely change over time as more clinical data become available. At present, there is no standardized way to assess evidence to inform the construction of panels. While many Medicaid plans cover some gene panels, that coverage often only applies to select gene panels used when narrow criteria are met. Also, prior authorizations are often required, resulting in significant delays in access to testing, high residual cost to patients, and repeated denial of coverage.

- **Single gene tests** – Single gene tests look for variations within a single gene. A physician may recommend a single gene test when clinical signs and symptoms indicate a specific genetic condition. Single gene tests in general have better coverage by Medicaid programs, but there are still many variations and limitations depending on which specific gene is being tested. Future policies must ensure that single gene tests will still be

covered even if a more comprehensive genetic test was performed first. A single gene test may be needed to confirm findings of previous testing or provide additional details regarding a specific test result.

- **Chromosomal microarrays** – Chromosomal microarrays (CMAs) detect larger variations in genetic material that may be missed by genome and exome sequencing. They detect regions of the genome that contain too many (duplications) or too few (deletions) copies of genetic material, referred to as a copy number variation (CNV). Coverage of CMA by Medicaid programs is generally better than that for GS, ES, or gene panels, at least when it is ordered as a first-tier test. However, coverage policies also must allow for coverage of CMA as a second-tier test, as the diagnostic yield of CMA is significantly less than that of ES (10% to 30%), but ES does not detect the CNVs that can be detected by CMA. These tests should be viewed as being complementary in nature, as they test for different types of variation in the genome.

For the genetic tests described above, it is important to note that variations between laboratories are expected. Test parameters, design, and coverage will vary among laboratories as will the bioinformatics used to analyze sequencing data. For this reason, it is important that a physician knowledgeable about genetic and genomic tests be involved in identifying the most appropriate genetic test for a patient. It is also important to note that the bullets above represent some common genetic tests, but the list is in no way comprehensive. Further, many important genetic tests are not sequencing-based tests.

<u>The right patient at the right time</u>

In order to be effective, a diagnosis must be made in time for the patient to benefit from targeted treatment. While some critically ill children referred to intensive care may benefit from genetic testing, waiting until a patient's symptoms are so severe that they require referral to intensive care may be too late for a genetic diagnosis to impact the course of the disease. The age range of patients intended to benefit from genetic testing must also be considered. For example, it may be more common to refer neonates to the NICU following signs of any abnormalities. However older children, teens, and young adults may not be referred to intensive care until symptoms become severe or life-threatening. Therefore, different eligibility criteria may need to be considered for neonatal versus older pediatric patients.

While there are many patients, including adults, who may benefit from advanced genetic testing, we understand that your proposed legislation is intended to focus on critically ill children likely to benefit from better access to genetic testing. Generally, eligibility criteria should be based on recommendations from a knowledgeable physician regardless of whether there is a referral to intensive care. However, if there is a need to narrow the focus of the bill, one pediatric population that may be more likely to benefit, and that may be identified prior to requiring referral to an intensive care unit, are undiagnosed children with medically complex conditions. These children are often characterized as having significant chronic health issues resulting in functional limitations and high healthcare needs or utilization. Their complex health management

often requires coordinated care among multiple healthcare providers. Title XIX, Sec. 1945A of the Social Security Act currently defines a child with medically complex conditions as a child that has at least:

> (I) one or more chronic conditions that cumulatively affect three or more organ systems and severely reduces cognitive or physical functioning (such as the ability to eat, drink, or breathe independently) and that also requires the use of medication, durable medical equipment, therapy, surgery, or other treatments; or
> (II) one life-limiting illness or rare pediatric disease (as defined in section 529(a)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360ff(a)(3))).

For both critically ill neonates and undiagnosed children with medical complexity, additional criteria may need to be met such as 1) a physician suspects that the chronic condition has a genetic etiology, and 2) a physician knowledgeable about appropriate testing options has recommended genetic testing. By providing timely access to such tests, a diagnosis may be made in time to result in improved medical interventions and treatment and, thereby, to prevent or slow disease progression and possibly obviate the need for costly referrals to intensive care.

The right treatment

Establishing a genetic diagnosis facilitates decision-making and increasingly offers the opportunity to qualify for therapies that target specific diseases based on the genetic changes identified through testing. Decision-making is generally a function of the stage in life at which the diagnosis is made. This holds true for nearly all medical conditions. Unique to the use of genomic technologies in establishing a diagnosis is that these technologies can help to categorize disease severity and treatment responsiveness, based on the genetic changes or variants identified. Examples include targeting cancer using specific drug therapies, treating cystic fibrosis – a genetic disease of the lungs and digestive system - with medication that is effective only when specific genetic variants are present, and treating spinal muscular atrophy – a progressive early age of onset lethal neurologic condition- with lifesaving molecular therapies which were recently developed and are now marketed.

Additional information

In genetic medicine, testing of the affected individual's biological parents increases the diagnostic yield of the test, is required to identify whether the condition was inherited which allows assessment of potential impact to other family members and/or future children, and leads to better understanding of which symptoms are likely attributed to the observed genetic variation. In such cases, testing must be performed on both biological parents in order to obtain the necessary information for comparison. Therefore, it is important that testing of both biological parents be covered when recommended by a knowledgeable physician.

In summary, appropriate genetic testing options, including those that are not sequencing-based, should be made available to ill individuals when a physician suspects a genetic cause for the condition. Test coverage should include all appropriate genetic testing options, both first- and second-tier testing, not currently and uniformly covered by Medicaid. A physician

knowledgeable in the benefits and limitations of different genetic tests should be responsible for identifying the most appropriate test following medical evaluation and review of the patient's medical and family history. Coverage of the test should include analysis, interpretation, reanalysis of previous data, and any follow-up testing necessary to confirm a diagnosis. Testing of both biological parents should be covered when necessary to interpret the significance of a genetic variation in the affected individual. Finally, it is critical to avoid unnecessary prior authorization requirements or processes that result in delays in access or denial of coverage of genetic testing. All of this is critical to achieving the ultimate goal of being able to identify the right treatment options that lead to an improved quality of life for the patient.

We appreciate your attention to this topic and hope that we can be of assistance to you as you consider legislation for the 117th Congress. For questions or additional information, please contact Dr. Michelle McClure at mmcclure@acmg.net.

Sincerely,

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