

# Access to Genetic Testing for Rare Diseases

**Prepared for the North Carolina Advisory Council on Rare Diseases**

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## Executive Summary

There are more than 7,000 rare diseases, with about 80 percent being genetic, affecting nearly one in 10 Americans<sup>1</sup>. Genetic testing is a rapidly evolving clinical diagnostic tool for identifying genetic causes of rare diseases. Trying to find an underlying diagnosis for many rare diseases can be a very long and frustrating experience for patients and health care providers. With some rare diseases, a “diagnostic odyssey” can take years before the diagnosis is confirmed, often by a genetic test.

The experience across the genetics providers in North Carolina is that this burden is high and the first step in mitigating the effects of these genetic disorders would be to provide better patient access to genetic testing services. Children are disproportionately affected by rare disorders and a rough estimate illustrates the magnitude of the problem regarding access to genetic testing.

There are approximately 2.3 million children in North Carolina (2017 census data) and approximately 50% of North Carolina’s 120,000 live births per year are Medicaid eligible. Assuming a conservative prevalence of rare diseases of 5% would result in an estimate that about 6,000 newborn children per year could be affected with rare diseases. The current North Carolina Medicaid policy covers some genetic testing and assuming that 20% of the Medicaid-eligible children obtain a diagnosis with the covered testing (including chromosomal microarray) then several thousand newborns per year could have few resources for obtaining an accurate diagnosis and treatment. Thus, the magnitude of the problem is of public health importance. Furthermore, lack of coverage of genetic tests for these children would prevent more non-specific diagnostic testing, such as brain MRIs, as well as repeated specialist clinical consultations in attempts to find the underlying cause. These expenses, currently covered by Medicaid, would be preventable with the coverage of genetic testing.

Whole exome sequencing (WES) is becoming the standard of care for patients with difficult to diagnose rare diseases. For rare diseases, trio testing (patient and both parents) is preferred as there is a higher diagnostic yield with a single charge to cover the cost. As the cost of WES and whole genome sequencing (WGS) continue to come down, the cost of genetic testing should no longer be a barrier. Instead, the availability of clinical geneticists and the ability to interpret the genetic information may become a more significant barrier. North Carolina, like most states, has a shortage of clinical geneticists and genetic counselors and wait times for an appointment can be long.

The cost of genetic tests and the insurance coverage and reimbursement are significant factors in a patient’s decision to undergo genetic testing. Reimbursement for genetic testing varies widely depending upon the type of genetic test performed and whether the insurance payer is private insurance, Medicare, or Medicaid. Single gene tests cost about \$200 whereas multi-gene panels range from a few hundred to several thousand dollars. Most private health insurance plans will cover all or part of the cost of genetic testing, including WES, when recommended by a physician. CLIA approved testing laboratories negotiate a reimbursement price for WES testing with each private insurance payer that is typically between \$2,500 and \$5,000. Some labs charge the same for a WES singleton, duo or trio. The rationale for insurance coverage for WES is supported by several publications that have shown that

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<sup>1</sup> Global Genes Rare Disease Facts and Figures. <https://globalgenes.org/raredaily/rare-disease-facts-and-figures/>

the early utilization of WES can significantly reduce the diagnostic cost and time, especially for patients with rare diseases.

While clinical WGS is less prevalent, it is likely to become more widely available as costs continue to come down. For example, the Rady Children's Institute for Genomic Medicine charges \$8,500 for a singleton-rapid WGS and \$12,000 for a trio-rapid WGS.

Genetic tests used to diagnose or determine treatment in the presence of signs and symptoms of disease can be covered by Medicare. A common use of genetic tests in the Medicare population is to assist in determining cancer treatment. Some state Medicaid programs (for example, Georgia, Louisiana, and Florida) will reimburse for WES on a case-by-case review basis with the typical reimbursement of \$2,200. However, North Carolina Medicaid does not reimburse for any genetic testing except for 4 CPT billing codes associated with chromosomal microarray, cystic fibrosis, fragile-X syndrome, and Duchene muscular dystrophy. The proper use and interpretation of genetic testing is optimized by the involvement of a clinical geneticist and/or genetic counselor. For this reason, some private insurance companies require that a patient see a genetic counselor prior to authorization of genetic testing.

There is a national and North Carolina shortage in the number of clinical geneticists (physicians specializing in medical genetics) and genetic counselors (masters-level degrees in human genetics). The UNC-Chapel Hill and Duke University Schools of Medicine are the only places in North Carolina that are training clinical geneticists. There are approximately 20 practicing medical clinical geneticists in North Carolina located at UNC Hospital (10 geneticists), Duke University Medical Center (5), Wake Forest Baptist Hospital (1), Levine Children's Hospital of Atrium Health in Charlotte (1), Mission Fullerton Genetics in Asheville (2), and East Carolina University Brody School of Medicine (1). Several of these medical institutions have open positions and are actively recruiting new clinical geneticists.

Wait times for appointments with North Carolina clinical geneticists can be long. At UNC Hospital it may take patients 4-6 months to schedule a routine genetic evaluation. At Duke University Medical Center new patient appointments to see a clinical geneticist were taking about 6 months. Duke University Medical Center decided to only take Duke Hospital referrals to the Division of Medical Genetics. The genetics program at the Levine Children's Hospital is not accepting patients outside of the Atrium Health system. An appointment to see the sole clinical geneticist at Wake Forest Baptist Hospital may take more than 12 months. Mission Fullerton Genetics Center has 2 full time clinical geneticists and the best wait times, approximately 1 month for general genetics evaluations.

The University of North Carolina at Greensboro Program in Genetic Counseling graduates 8 genetic counselors per year. The program could accept more students but is limited by the number of clinical rotation opportunities available at the hospitals in North Carolina.

Despite the benefits of genetic counseling, reimbursement remains limited. This is primarily because genetic counselors are not recognized as independent non-physician providers by Medicare and can only bill directly for their services using CPT code 96040 – Medical Genetics and Genetic Counseling Services. Licensure is thought to be an approach to convincing insurers to allow genetic counselors to bill for fee for service. North Carolina does not currently offer state licensing for genetic counselors, but some groups are currently exploring this as a future possibility.

Rural communities in North Carolina are underserved. Wake Forest Baptist, Mission Health, and UNC Hospital used to receive state grants to see patients needing genetic services in rural areas. However, the state funding has not been renewed. The North Carolina Department of Health and Human Services program used to support a network of 6 genetic counselors each in a different region of the state. Today, there is only one genetic counselor located in Wilmington, NC, who covers the state.

Physicians see many patients in a day and do not always recognize a patient with a potential rare disease and recommend the patient for genetic testing. The increase in the availability of genetic testing, including direct-to-consumer genetic testing, has exceeded the ability of many practicing physicians who do not have a strong background in genetics to order tests and interpret their results. More than 12 million people have used direct-to-consumer genetic testing to get information on their disease risk, ancestry or genealogy, kinship, and lifestyle. There is currently no requirement for practicing physicians to have any specific knowledge or competency in genomics leaving the physician workforce unprepared for any large-scale application of genomic medicine. Non-genetic physicians feel unprepared to order genomic tests and interpret and explain test results, incorporate test results into clinical decision making, or refer patients to a clinical geneticist. A significant percentage of providers have never ordered genetic testing for a patient.

Some people who receive genetic testing may be concerned about the privacy of their test results and whether insurance companies could use a genetic diagnosis to deny medical coverage or determine health insurance premiums. Instead, they may choose to pay for the testing themselves. The Genetic Information Nondiscrimination Act (GINA) of 2008 (P.L. 110-233) protects most individuals against discrimination based on their genetic information in health coverage and in employment. However, GINA does not provide individuals protection from using their genetic information by insurers for long term care insurance, life insurance, or disability insurance. Housing, mortgage lending, education and public accommodations are also not covered by GINA. Some state consumer genetic privacy laws expand the GINA protections to cover these areas. North Carolina General Statute § 58-3-215 - Genetic information in health insurance - requires compliance with GINA. North Carolina General Statute § 95-28.1A - Discrimination against persons based on genetic testing or genetic information prohibited – does not require compliance with GINA.

Recently, a funding opportunity for the National Institutes of Health *All of Us* Research Program Genetic Counseling Resource (OT2), OT-PM-19-001, was announced with an application due date of February 1, 2019. The *All of Us* Research Program Genetic Counseling Resource will be responsible for: 1) developing the capacity to provide genetic counseling call center services for program participants (ultimately numbering > 1 million) and their health care providers, 2) delivering to participants clinical reports of findings of medically-actionable monogenic disease variants and providing initial genetic counseling and hand-off to medical care, 3) contributing to the development of genetic/genomic educational resources for the program, 4) contributing to protocol development, for Institutional Review Board and/or for regulatory agency review, 5) developing innovative technologies and approaches for population-scale genetic counseling services, 6) establishing strong collaborative relationships with other awardees contributing to the *All of Us* genomics platform, and 7) contributing to strategic planning for the program as a member of the *All of Us* consortium.

In 2003, the North Carolina State Plan for Genomics and Public Health was published. Now 15 years old, the North Carolina Division of Public Health, Children and Youth Branch, Genetics and Newborn

Screening Unit is facilitating an effort to revise and update the State Plan by June 2019 with actionable goals at 1 year, 3 years and 5 years. The 3 primary focus areas are communication and education, genetic testing and services, and epidemiology and surveillance.

## Examples of Genetic Testing

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disease.<sup>2</sup> Some of the better-known genetic testing laboratory companies are Invitae, GeneDx, Illumina, and Baylor Miraca Genetics.

Several methods can be used for genetic testing:

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder. Conventional molecular testing of patients with genetic disorders relies primarily on single gene or panel testing or microarrays.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a metabolic disorder.

The choice of a genetic testing method or specific test depends on the clinical scenario. A molecular genetic test targeted to a specific gene might be indicated if the patient's presentation is highly suggestive of a disorder known to be caused by mutations in a known disease gene. Single-gene testing compares the patient's DNA sequence of a specific gene to a reference sequence in order to identify a genetic variant or mutation. This type of test is often appropriate when the patient's phenotype suggests that a diagnosis is known to be caused by variants in a specific gene. For example, a single-gene test of the *CFTR* gene can confirm cystic fibrosis or the *BRCA1* gene for breast cancer.

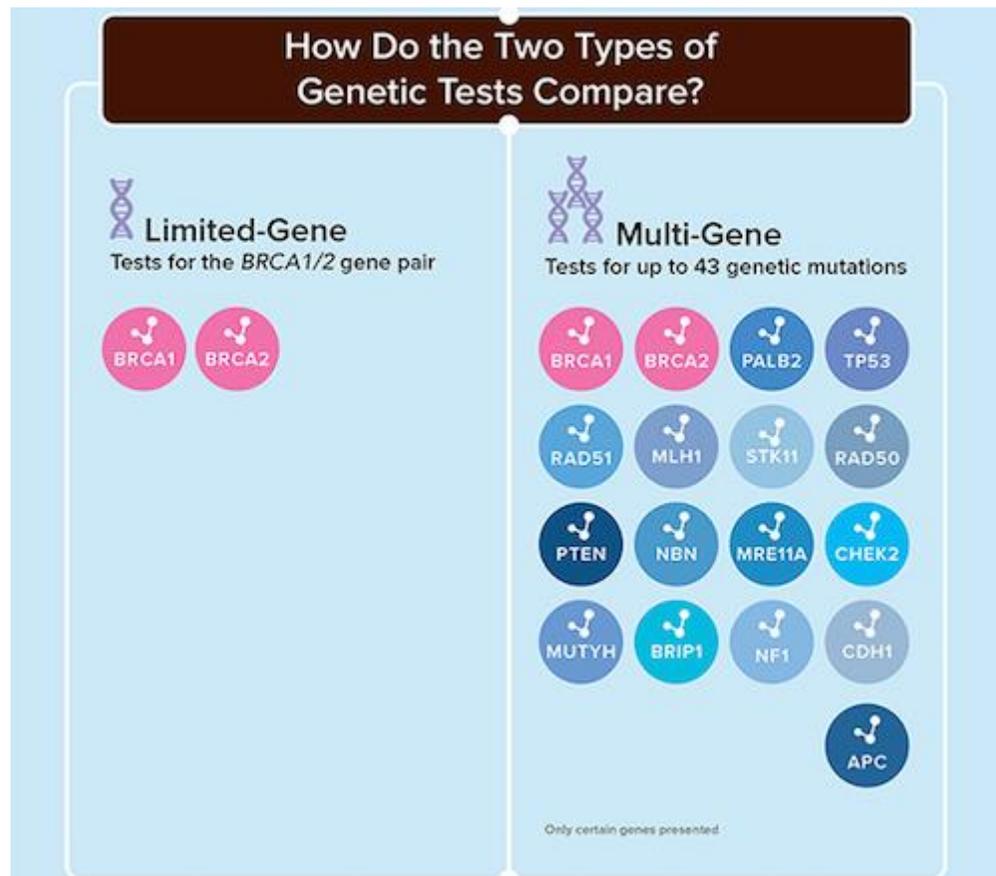
Multi-gene panels allow testing of many genes in a single procedure, and they are particularly appropriate for disorders that are known to have a specific phenotype. Gene panels provide "depth of coverage" by analyzing many genes that may be associated with a specific genetic disease. The functional segments of the genes of interest are isolated and then sequenced, typically with next generation sequencing (NGS) methods. The patient's sequence is compared with a reference sequence to detect genetic changes. This method is faster and usually less expensive than testing for each gene known to be responsible for the phenotype in question.

Gene panels using NGS are currently available in the areas of cancer, cardiovascular disease, neurologic disease, psychiatric disorders, pediatric conditions, and for reproductive testing. Testing laboratories offer gene panels that will analyze several hundred genes at one time. Design and composition of genetic panel tests have not been standardized. Panel tests vary by laboratory, and different commercial products for the same condition may test different sets of genes. In addition, the composition of any

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<sup>2</sup> U.S. National Library of Medicine, "What is Genetic Testing?", <https://ghr.nlm.nih.gov/primer/testing/genetic-testing>  
Accessed July 9, 2018.

individual panel is likely to change over time, as new genes are discovered and added to the existing panels.<sup>3</sup>



Reference: <http://www.breastlink.com/blog/nimmi-s-kapoor-md-gene-tests-asbs/> accessed July 27, 2018.

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<sup>3</sup> Regence Medicare Advantage Policy Manual M-GT64, "Genetic and Molecular Diagnostics – Next Generation Sequencing and Genetic Panel Testing", July 1, 2018  
<http://blue.regence.com/medicare/gt/m-gt64.pdf>  
Accessed July 9, 2018.

## Case Study – Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is an inherited autosomal recessive condition affecting around 1 in 15,000 people. In people with PCD, microscopic motile cilia found in the lining of the trachea do not move normally, resulting in impaired clearance of mucus and debris leading to repeated sinopulmonary infection. If diagnosis is delayed, then permanent bronchiectasis and deterioration of lung function occurs. Cystic fibrosis (CF) shares a number of features with PCD including progressive bronchiectatic disease and decline in lung function.<sup>4</sup>

There are currently 37 known genes associated with PCD, which counts for an estimated 75% of patients who have this disease. This means that genetic mutations on any of these genes can potentially result in PCD. In comparison, cystic fibrosis is caused by mutations on a single gene called *CFTR*. On that one gene, there are close to 2,000 individual mutations that cause cystic fibrosis. Some result in more severe disease, some in less severe. And this is on only one gene. PCD has 37 genes and an unknown number of mutations per gene that can lead to PCD.<sup>5</sup>

The feasibility of testing a multi-gene panel of PCD genes at a reasonable cost is becoming a reality, as several Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories and companies have recently begun to offer such services. For example, the University of North Carolina Hospital Medical Genetics Laboratory will perform a gene panel test using the Invitae Primary Ciliary Dyskinesia Panel that analyzes up to 36 genes that are associated with PCD with an average turn-around time of 14 to 28 days.<sup>6</sup> It is estimated that ~65-70% of patients with PCD can be identified by genetic testing as having two mutations in one of these genes.<sup>7</sup> Dr. Michael Knowles, professor of pulmonary and critical care medicine at University of North Carolina School of Medicine, reports that the cost of the multi-gene panel can be less than \$1,000. Invitae's panels are normally \$1,500 max but the patient pay price for a panel is \$250.

In other scenarios where a specific disease is not suspected and more exploratory genetic testing is warranted genetic testing that sequences the whole exome (a WES) or the whole genome (a WGS) might be more appropriate.<sup>8</sup> WES presents an attractive genetic testing method when the genetic cause of a rare disease is unknown or difficult to diagnose. WES is becoming the standard of care for undiagnosed rare diseases. Exons, which make up approximately 1.5 percent of a person's genome, are responsible for providing the instructions for making proteins and contain 85 percent of all known disease-causing mutations. Together, all the exons in a genome are known as the exome, and the method of sequencing them is known as WES. This method allows variations in the protein-coding

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<sup>4</sup> Collins SA, Walker WT, Lucas JS. Genetic Testing in the Diagnosis of Primary Ciliary Dyskinesia: State-of-the-Art and Future Perspectives. *Journal of Clinical Medicine*. 2014;3(2):491-503. doi:10.3390/jcm3020491.

<sup>5</sup> PCD Foundation, <https://pcdfoundation.org/pcd-terminology/> accessed July 25, 2018.

<sup>6</sup> Invitae Primary Ciliary Dyskinesia Panel

[https://www.invitae.com/en/physician/tests/04101/?utm\\_source=pcd&utm\\_medium=print&utm\\_campaign=pcd\\_card&utm\\_content=pcd\\_panel](https://www.invitae.com/en/physician/tests/04101/?utm_source=pcd&utm_medium=print&utm_campaign=pcd_card&utm_content=pcd_panel)

<sup>7</sup> Knowles M, Zariwala M, Leigh M. Primary Ciliary Dyskinesia. *Clinics in chest medicine*. 2016;37(3):449-461. doi:10.1016/j.ccm.2016.04.008.

<sup>8</sup> National Academies Press, An Evidence Framework for Genetic Testing, Chapter 2, Page 24, March 27, 2017.

<https://www.nap.edu/read/24632/chapter/4#24>

Accessed July 9, 2018.

region of any gene to be identified, rather than in only a select few genes. Because most known mutations that cause disease occur in exons, WES is thought to be an efficient method to identify possible disease-causing mutations. However, researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders or variations that WES would miss.<sup>9</sup> Results from WES are typically not available for several weeks or months due to the large amount of data the test yields. Diagnostic yield for a singleton-WES genetic test is about 25 to 30%. WES testing may or may not be covered by private insurance companies.

GeneDx has a great deal of experience with clinical WES testing. They have sequenced more than 120,000 whole exomes and they are performing about 5,000 WES tests per month. GeneDx charges the same price for a WES singleton, duo (patient and one parent), or trio (patient and both parents) test. They have found that WES trio testing increases the diagnostic accuracy and other genetic testing labs would agree with this conclusion. GeneDx does offer to perform whole genome sequencing but none of the major private insurance companies will reimburse for this genetic testing.<sup>10</sup>

Whole genome sequencing (WGS) analyzes essentially the entire DNA sequence, which would include areas between the exons and between the genes. Most of the genome is made up of highly repetitive sequences that have little or no recognized function (about 45%), introns (about 35%), and a large number of functional non-protein-coding elements. It is not clear how these non-exon portions of the genome contribute to genetic diseases. However, it has been previously shown that WGS, while an expensive test, may actually decrease overall cost (particularly downstream cost) of diagnostic evaluations of medically complex children.<sup>11</sup>

Recently the Rady Children's Institute for Genomic Medicine began to offer a paid service for Rapid WGS (rWGS) for U.S. newborns with undiagnosed genetic diseases admitted to neonatal intensive care units (NICU) in children's hospitals across the country. In a 2017 study, Rady reported that rWGS provides a faster diagnosis (24-48 hours), enabling precision medicine interventions in time to decrease the morbidity and mortality of infants with genetic diseases.<sup>12</sup> rWGS diagnosed 19 genetic diseases in 18 of 42 infants (43%). Specific changes in medical or surgical treatment occurred as a result of molecular diagnoses (clinical utility) in 13 (31%) of 42 infants receiving rWGS. Four infants (22% of diagnosed) avoided major morbidity. Mortality through median day of life 430 was two (11%) of 18 diagnosed by rWGS compared with seven (29%) of 24 infants who did not receive diagnoses. The total cost of rWGS in 42 families was \$674,645. Overall for all 42 infants, inpatient cost was estimated to be reduced by \$128,555. The UNC Medical Center is expected to join the Rady network in a multisite research study. Rady's industry partner Illumina has a budget to pilot rWGS in other states.

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<sup>9</sup> U.S. National Library of Medicine, "What are Whole Exome Sequencing and Whole Genome Sequencing?" <https://ghr.nlm.nih.gov/primer/testing/sequencing> Accessed July 9, 2018.

<sup>10</sup> Personal communications with David Keane (GeneDx) On August 20, 2018.

<sup>11</sup> Hays, R. Z. et al. Care and cost consequences of pediatric whole genome sequencing compared to chromosome microarray. *Eur. J. Hum. Genet.* 25, 1303–1312 (2017).

<sup>12</sup> Farnaes, L. et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med.* 2018 Apr 4;3:10. doi: 10.1038/s41525-018-0049-4. <https://www.nature.com/articles/s41525-018-0049-4>

## Reimbursement for Genetic Testing

The cost of genetic tests and the insurance coverage and reimbursement are significant factors in a patient's decision to undergo genetic testing. Reimbursement for genetic testing varies widely depending upon the type of genetic test performed and whether the insurance payer is private insurance, Medicare, or Medicaid. Single gene tests cost about \$200 whereas multi-gene panels are available for \$600. Most private health insurance plans will cover all or part of the cost of genetic testing, including WES, when recommended by a physician. However, all coverage and reimbursement are subject to Medicare, Medicaid, and third-party payer benefit plans which may have different policies about which genetic tests are covered.

For example, Cigna-administered plans require patients to have genetic counseling from an independent genetics professional on Cigna's list of participating genetic counselors prior to undergoing certain genetic tests in order for precertification to be approved.<sup>13</sup> Cigna genetic counselors are located in Asheville (6 counselors), Cary (4), Chapel Hill (19), Charlotte (10), Durham (6), Greensboro (2), Raleigh (13), Winston-Salem (12) and a few other locations in North Carolina (8).

CLIA approved testing laboratories negotiate a reimbursement price for WES testing with each private insurance payer that is typically between \$2,500 and \$5,000. Some labs charge the same for a WES singleton, duo or trio. The rationale for insurance coverage for WES is supported by several publications that have shown that the early utilization of WES can significantly reduce the diagnostic cost and time, especially for patients with rare diseases.<sup>14</sup>

While clinical WGS is less prevalent, it is likely to become more widely available as costs continue to come down. For example, the Rady Children's Institute for Genomic Medicine charges \$8,500 for a singleton-rapid WGS and \$12,000 for a trio-rapid WGS.

Medicare does not pay for preventive screening tests except for those specifically authorized by statute (e.g., prostate-specific antigen test). Since the Centers for Medicare & Medicaid Services (CMS) considers predictive tests to be screening tests, genetic tests for this purpose are not covered by Medicare. However, genetic tests used to diagnose or determine treatment in the presence of signs and symptoms of disease can be covered by Medicare. A common use of genetic tests in the Medicare population is to assist in determining cancer treatment.<sup>15</sup> Medicare coverage for genetic counseling is also limited by the program's screening exclusion.

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<sup>13</sup> Cigna Genetic Testing and Counselor Resources, <https://www.cigna.com/health-care-providers/resources/genetic-testing-and-counseling-program> Accessed July 9, 2018.

<sup>14</sup> Tan TY, et.al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children with Suspected Monogenic Conditions. *JAMA Pediatr.* 2017 Sep 1;171(9):855-862. doi: 10.1001/jamapediatrics.2017.1755.

Shashi V, et.al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med.* 2014 Feb;16(2):176-82. doi: 10.1038/gim.2013.99. Epub 2013 Aug 29.

<sup>15</sup> U.S. Department of Health and Human Services, Office of Inspector General, Memorandum Report: Coverage and Payment for Genetic Laboratory Tests, OEI-07-11-00011, June 12, 2012. <https://oig.hhs.gov/oei/reports/oei-07-11-00011.pdf>

Medicare uses a combination of national and local coverage determinations for making coverage decisions for genetic tests. National coverage determinations (NCD) are made at the Federal level and apply to all Medicare beneficiaries and the eight Medicare administrative contractors (MAC). For example, on March 18, 2018, CMS finalized a National Coverage Determination that covers FDA approved diagnostic laboratory tests using Next Generation Sequencing (NGS) for patients with advanced cancer (i.e., recurrent, metastatic, relapsed, refractory, or stages III or IV cancer).<sup>16</sup>

Most genetic tests for rare diseases get lumped into 10 CPT billing codes. There is a miscellaneous CPT code that covers a list of genes that if testing is done then one can use that code. The new International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) still does not cover very many rare diseases.

Medicaid is a joint Federal and State health insurance program. Most State Medicaid programs will not reimburse for genetic testing, with some exceptions. The North Carolina Medical Assistance Clinical Coverage Policy 1S-4 (amended January 1, 2016)<sup>17</sup> describes the eligibility and coverage for genetic testing for Medicaid patients. North Carolina Medicaid follows the CMS Clinical Laboratory Fee Schedule (see Appendix C) and does not reimburse for genetic testing except for 4 CPT billing codes associated with chromosomal microarray, cystic fibrosis, fragile-X syndrome, and Duchene muscular dystrophy. This means that other single gene tests, gene panels, and WES are not covered unless the testing meets all of the Specific Criteria Covered in section 3.2 of Policy 1S-4, severely limiting the ability of clinicians to make diagnoses and management decisions for almost anyone who presents with symptoms and signs that are consistent with an underlying genetic disorder. Due to this restrictive policy of covering genetic testing, most genetic disorders are not diagnosable in patients who are on North Carolina Medicaid.

Clinical geneticists across the state often have to tell their Medicaid eligible patients that they may be billed for the genetic testing. This results in most individuals not undergoing the test, since the costs are prohibitive for them. Duke University Medical Center and UNC Hospital often absorb the cost for the genetic testing not covered by Medicaid. Other major hospitals in North Carolina will not offer any genetic testing to Medicaid patients except for the 4 billing codes noted above. Patients that are part of the Duke Undiagnosed Disease Network can get genetic testing including WES and WGS paid for under that program. However, this is not a sustainable model since the number of patients that can be enrolled in the network is very limited because it is a research study with specific inclusion criteria.

North Carolina uses the NTRACKS<sup>18</sup> portal to allow North Carolina physicians to request prior authorization for genetic testing. Unfortunately, NTRACKS only permits registered in-state providers and not testing laboratories to access the portal. Other states will permit testing laboratories, whether in-state or out-of-state, to enter data for prior authorization.<sup>19</sup>

In order for patients to have full access to the benefits of genetic testing, payers such as insurance companies and Medicare need systematic ways of evaluating genetic tests for reimbursement. One challenge insurers face is the difficulty of deciding when to reimburse for genetic tests that health care providers have offered their patients. Payers typically base coverage decisions for genomic tests on an

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<sup>16</sup> <https://www.cms.gov/newsroom/press-releases/cms-finalizes-coverage-next-generation-sequencing-tests-ensuring-enhanced-access-cancer-patients>

<sup>17</sup> [https://files.nc.gov/ncdma/documents/files/1S4\\_1.pdf](https://files.nc.gov/ncdma/documents/files/1S4_1.pdf)

<sup>18</sup> <https://www.nctracks.nc.gov/content/public?version=portal-jwap-trunk-10065-15243-production-VJ&why=Root>

<sup>19</sup> Personal communication with David Keane (GeneDx) on August 20, 2018.

evaluation of the clinical validity of the test (accuracy with which a test can predict the presence or absence of a phenotype), as well as evidence of clinical utility (the effects of testing on net patient health outcomes).<sup>20</sup>

Furthermore, payers may not be able to easily evaluate what type of genetic test was performed. Phillips<sup>21</sup> recently reported that there are approximately 75,000 genetic tests on the market, representing approximately 10,000 unique test types. Eighty-six percent of the genetic tests were single-gene tests. The remaining tests were panel tests, including 9,311 multi-analyte assays with algorithmic analyses, 85 noninvasive prenatal tests, 122 whole exome sequencing tests, and 873 whole genome analysis tests (which included whole genome sequencing tests). Insurance payers are having trouble keeping up with the volume of new genetic and next-generation sequencing tests that are coming onto the market. This makes it even more difficult to evaluate which tests should be covered and under what circumstances they should be covered.<sup>22</sup>

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<sup>20</sup> Deverka PA, Kaufman, D, McGuire AL. Overcoming the Reimbursement Barriers for Clinical Sequencing. JAMA. 2014 November 12; 312(18): 1857-1858. Doi:10.1001/jama.2014.14915.

<sup>21</sup> Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic Test Availability and Spending: Where Are We Now? Where Are We Going? *Health affairs (Project Hope)*. 2018;37(5):710-716. doi:10.1377/hlthaff.2017.1427.

<sup>22</sup> National Human Genome Research Institute, "Coverage and Reimbursement of Genetic Tests, <https://www.genome.gov/19016729/>  
Accessed July 9, 2018

## Availability of Clinical Geneticists and Genetic Counselors

There is a national and North Carolina shortage in the number of clinical geneticists and genetic counselors. In the United States there are approximately 1,583 MD clinical geneticists.<sup>23</sup>

### NUMBER OF ABMGG CERTIFIED SPECIALISTS IN MEDICAL GENETICS AND GENOMICS

	EXAMINATION YEAR						TOTAL
	1982-2007	2009	2011	2013	2015	2017	
<b>TOTAL NUMBER OF NEW DIPLOMATES</b>	<b>2100</b>	<b>135</b>	<b>159</b>	<b>188</b>	<b>175</b>	<b>180</b>	<b>2937</b>
<b>MEDICAL GENETICS SPECIALTIES - EXAM</b>	<b>1982-2005</b>	<b>2009</b>	<b>2011</b>	<b>2013</b>	<b>2015</b>	<b>2017</b>	<b>TOTAL</b>
MD Clinical Genetics and Genomics	1178	73	79	90	85	78	1583
PhD Medical Genetics	155						155
Clinical Biochemical Genetics	236	15	19	20	18	15	323
Clinical Cytogenetics and Genomics	584	37	32	47	36	39	775
Clinical Molecular Genetics and Genomics	388	41	65	60	89	100	743
Clinical Biochemical/Molecular Genetics (c)	49						49
<b>Subspecialty Certificates</b>	<b>2001-2005</b>	<b>2009</b>	<b>2011</b>	<b>2013</b>	<b>2015</b>	<b>2017</b>	<b>TOTAL</b>
Medical Biochemical Genetics		14	16	17	16	14	63
Molecular Genetic Pathology	8	0	0	0	0	0	9
Joint subspecialty certificates issued by ABPath							

(a) last examination offered in 2007

(b) Only offered 1990/1993

(c) Certificate name changes effective 2015: Clinical Genetics to **Clinical Genetics and Genomics**, Clinical Cytogenetics to **Clinical Cytogenetics and Genomics**, and Clinical Molecular Genetics to **Clinical Molecular Genetics and Genomics**

2011 clinical certification numbers updated Jan-2018

Document Updated Jan-2018

The UNC and Duke University Schools of Medicine are the only programs in North Carolina that train clinical geneticists. Recognizing that there may be a problem with the genetic workforce, the Department of Defense and Labor, Health and Human Services, and Education Appropriations Act, 2019 (P.L. 115-245) requests the U.S. Government Accountability Office (GAO) to perform a nationwide analysis of the medical genetics workforce that includes all medical genetics professionals.<sup>24</sup>

The American Board of Medical Genetics and Genomics (ABMGG)<sup>25</sup> lists genetics specialists broken down into categories with clinical biochemical geneticists, clinical geneticists, and medical biochemical geneticists the three main categories. These 3 categories include both physicians board-certified in genetics who see patients and laboratory geneticists. There are more pediatric medical geneticists than adult medical geneticists. According to the ABMGG, there are 51 genetic specialists in North Carolina.

<sup>23</sup> American Board of Medical Genetics and Genomics, Number of Certified Specialists in Genetics, By Specialty. <http://www.abmgg.org/pdf/Statistics%20for%20Webpage.pdf>

<sup>24</sup> ACMG Applauds Increase in Funding for Newborn Screening and Medical Genetics Workforce Study in FY 2019 LHHs Appropriations. October 15, 2018.

[https://www.acmg.net/PDFLibrary/Statement\\_%20FY2019%20LHHS%20Appropriations\\_10.10\\_Final.pdf](https://www.acmg.net/PDFLibrary/Statement_%20FY2019%20LHHS%20Appropriations_10.10_Final.pdf)

<sup>25</sup> American Board of Medical Genetics and Genomics, Number of Certified Specialists in Genetics, By State. <http://www.abmgg.org/pdf/SpecialistsByState%20February%202018.pdf>

There are approximately 20 practicing medical clinical geneticists in North Carolina located at UNC Hospital (10 geneticists), Duke University Medical Center (5), Wake Forest Baptist Hospital (1), Levine Children's Hospital of Atrium Health in Charlotte (1), Mission Fullerton Genetics in Asheville (2), and East Carolina University Brody School of Medicine (1).<sup>26</sup> Several of these medical institutions have open positions and are actively recruiting new clinical geneticists.

Wait times for appointments with North Carolina clinical geneticists can be long. At UNC Hospital it may take patients 4-6 months to schedule a routine genetic evaluation. At Duke University Medical Center new patient appointments to see a clinical geneticist were taking about 6 months. Duke University Medical Center decided to only take Duke Hospital referrals to the Division of Medical Genetics. The genetics program at the Levine Children's Hospital is not accepting patients outside of the Atrium Health system. An appointment to see the sole clinical geneticist at Wake Forest Baptist Hospital may take more than 12 months. Mission Fullerton Genetics Center has 2 full time clinical geneticists and the shortest wait times, approximately 1 month for general genetics evaluations.<sup>27</sup>

Genetic counseling is still a relatively small field. The American Board of Genetic Counseling (ABGC) sets standards for genetic counseling and certifies individuals without medical degrees as genetic counselors. There are approximately 4,000 certified genetic counselors in the U.S. and about 80 genetic counselors in North Carolina. There are currently 39 programs in the U.S. and 43 additional worldwide. Most genetic counselors are employed at clinical sites at university or private hospital centers. The average salary in North Carolina is about \$70,000 per year.<sup>28</sup>

Rural communities in North Carolina are underserved. Wake Forest Baptist, Mission Health and UNC Hospital used to receive state grants to see patients needing genetic services in rural areas. However, the state funding has not been renewed.<sup>29</sup> The North Carolina Department of Health and Human Services program used to support a network of 6 genetic counselors each in a different region of the state. Today, there is only one genetic counselor located in Wilmington, NC who covers the state.

The University of North Carolina at Greensboro Program in Genetic Counseling graduates 8 genetic counselors per year. The program could accept more students but is limited by the number of clinical rotation opportunities available at the hospitals in North Carolina.

Despite the benefits of genetic counseling, reimbursement remains limited. This is primarily because genetic counselors are not recognized as independent non-physician providers by Medicare and can only bill directly for their services using CPT code 96040 – Medical Genetics and Genetic Counseling Services. Unfortunately, reimbursement for this code is low because Medicare will not separately pay for genetic counseling at hospitals and genetic centers. Under the 2016 Outpatient Prospective Payment System (OPPS) and the Physician Fee Schedule (PFS), it is not a separately reimbursable service. Private payers vary in their coverage. According to one study by the Cleveland Clinic, only 62% of genetic counseling encounters billed to private payers using code 96040 received some reimbursement. Due to these reimbursement limitations, cancer programs often adopt a variety of billing approaches to

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<sup>26</sup> Personal communication with Dr. Cynthia Powell (UNC Hospital) on September 6, 2018.

<sup>27</sup> Personal communications with Dr. Cynthia Powell (UNC Hospital), Dr. Vanda Shashi (Duke University Medical Center), and Dr. Chad Haldeman-Englert (Mission Fullerton Genetic Center).

<sup>28</sup> <https://www1.salary.com/NC/Genetics-Counselor-salary.html>

<sup>29</sup> Personal communication with Dr. Chad Haldeman-Englert (Mission Health) on August 2, 2018.



## Medical Education and Training in Genetics for Practicing Physicians

The increase in the availability of genetic testing, including direct-to-consumer genetic testing, has exceeded the ability of many practicing physicians who do not have a strong background in genetics to order tests and interpret their results. There is currently no requirement for practicing physicians to have any specific knowledge or competency in genomics, leaving the physician workforce unprepared for any large-scale application of genomic medicine.

In fact, there is ample research suggesting that physicians are largely unprepared to use genetic and genomic data. For instance, physicians feel unprepared to order genomic tests, explain test results, incorporate results into clinical practice, or refer a patient to a clinical geneticist. Meanwhile, the volume and nature of big data more generally in the clinical encounter is anticipated to grow beyond the interpretative capacity of physicians.<sup>32</sup>

Physicians see many patients in a day and do not always recognize a patient with a potential rare disease and recommend the patient for a genetic evaluation or genetic testing. A significant percentage of providers have never ordered testing for a patient. In surveys of physicians about their awareness of genetic and genomic testing options they generally admit that they do not have a working understanding of the testing menu available or the specific indications for the tests. For instance, there seems to be general confusion amongst clinicians around the distinction between genomic sequencing and array-based genotyping.<sup>33</sup>

Alternatively, some doctors order a genetic test, or the wrong genetic test, when it is not necessary. Further straining the physician-patient relationship is the inability of some physicians to interpret clinical or direct-to-consumer genetic test results. Sometimes the test result will discover a “variant of unknown significance” and the physician will tell the patient that he/she has a genetic disease instead of referring the patient to a clinical geneticist or genetic counselor who are better able to interpret the genetic test results.

Time is the enemy for most practicing physicians who need to know about genomic medicine. In 2013, the Inter-Society Coordinating Committee for Physician Education in Genomics (ISCC)<sup>34</sup> formed in an effort to improve physician education in genomics by resources that could fit the needs of various professional organizations and medical specialties. Genomic medicine continuing education initiatives have also embraced electronic- and web-based methods. The North Carolina Area Health Education Centers (AHEC) and the North Carolina Pediatric Society may be able to provide better education outreach/seminars for genetic testing. The Charlotte AHEC has developed a Medical Genomics 101 web based professional development course that costs \$199 and issues the physician CME credits.<sup>35</sup>

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<sup>32</sup> Rubanovich, CK et.al. Physician preparedness for big genomic data: a review of genomic medicine education initiatives in the United States. 10 May 2018. *Human Molecular Genetics*, Volume 27, Issue R2, 1 August 2018, Pages R250–R258, <https://doi.org/10.1093/hmg/ddy170>

<sup>33</sup> Murray, MF. Educating physicians in the era of genomic medicine. *Genome Med.* 2014;6(6):45. Published 2014 Jun 27. doi:10.1186/gm564

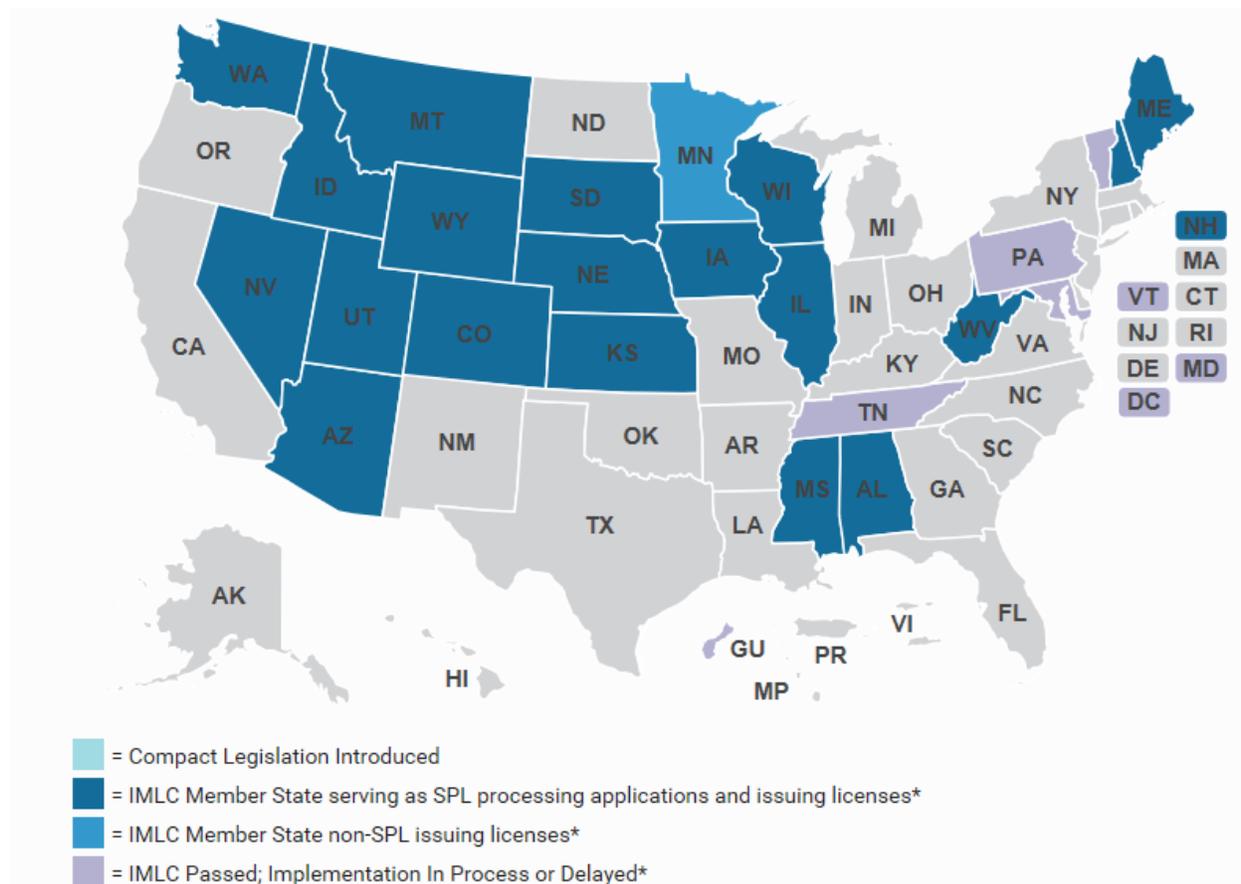
<sup>34</sup> <https://www.genome.gov/27554614/intersociety-coordinating-committee-for-practitioner-education-in-genomics-iscc/>

<sup>35</sup> <https://www.charlotteahec.org/continuing-professional-development/event.cfm?eventid=56237>

To help meet the growing demand for genetics services amid a national shortage of genetic providers, some health systems have turned to telemedicine. Presently, it is difficult for a physician to practice telemedicine across state lines because the physician would have to be licensed in both states. Mission Health in Asheville has recently started a telemedicine program to provide genetic services to the Franklin, NC area. UNC Hospital, Duke University Medical Center, Novant Health, and Atrium Health provide cancer genetic counseling via telemedicine. Some southeastern states such as Florida, Georgia, and South Carolina have telemedicine programs within their states.

The Southeast Regional Genetics Network through Emory University has a grant to continue development of new telemedicine programs, as well as optimization of existing telegenetics programs.<sup>36</sup> Genome Medical is a San Francisco-based startup that has created an independent network of clinical genomic experts to offer genetic consultation services to patients and providers via telehealth. Genome Medical has certified clinical geneticists and genetic counselors in North Carolina.

The Interstate Medical Licensure Compact<sup>37</sup> offers a new, voluntary expedited pathway to licensure for qualified physicians who wish to practice in multiple states. Although not limited to telemedicine nor genomic medicine, the IMLC could make it easier for clinical geneticists to practice in multiple states.



<sup>36</sup> <https://southeastgenetics.org/about.php>

<sup>37</sup> <https://imlcc.org/>

## Examples of State and Federal Efforts to Provide Access to Genetic Testing and Services

The National Institutes of Health (NIH) *All of Us* Research Program, a key element of the Precision Medicine Initiative (PMI), is a historic effort to gather data, including genetic information, over many years from one million or more people living in the United States, with the ultimate goal of accelerating research and improving health. Unlike research studies that are focused on a specific disease or population, *All of Us* will serve as a national research resource to inform thousands of studies, covering a wide variety of health conditions.

Recently, a funding opportunity for the *All of Us* Research Program Genetic Counseling Resource (OT2)<sup>38</sup>, OT-PM-19-001, was announced with an application due date of February 1, 2019. The *All of Us* Research Program Genetic Counseling Resource will be responsible for: 1) developing the capacity to provide genetic counseling call center services for program participants (ultimately numbering > 1 million) and their health care providers, 2) delivering to participants clinical reports of findings of medically-actionable monogenic disease variants and providing initial genetic counseling and hand-off to medical care, 3) contributing to the development of genetic/genomic educational resources for the program, 4) contributing to protocol development, for Institutional Review Board and/or for regulatory agency review, 5) developing innovative technologies and approaches for population-scale genetic counseling services, 6) establishing strong collaborative relationships with other awardees contributing to the *All of Us* genomics platform, and 7) contributing to strategic planning for the program as a member of the *All of Us* consortium.

In 2003, the North Carolina State Plan for Genomics and Public Health was published. Now 15 years old, the North Carolina Division of Public Health, Children and Youth Branch, Genetics and Newborn Screening Unit is facilitating an effort to revise and update the State Plan by June 2019 with actionable goals at 1 year, 3 years and 5 years. The 3 primary focus areas are communication and education, genetic testing and services, and epidemiology and surveillance.

The purpose of the NIH funded **Newborn Sequencing In Genomic medicine and public Health (NSIGHT)** program is to explore the implications, challenges and opportunities associated with the possible use of genomic sequence information for newborn genetic disorders. Dr. Cynthia Powell and Dr. Jonathan Berg at UNC-Chapel Hill are Principal Investigators for **NC NEXUS, North Carolina Newborn Exome Sequencing for Universal Screening**, one of four projects funded through this program.

The Undiagnosed Diseases Network (UDN) is a national NIH funded network that facilitates diagnostic workups including the use of whole exome and whole genome sequencing to diagnose individuals that present with symptoms and signs that are consistent with rare diseases and to pursue further research into these. Dr. Shashi at Duke is one of the Principal Investigators of the Duke clinical site of the UDN. In addition, Dr. Shashi runs the Genome Sequencing Clinic at Duke (supported by Duke Health) wherein children with rare diseases undergo whole exome sequencing for diagnosis, at no cost to the patients or families. Fifty patients are seen annually at this clinic and receive all services, including the clinical

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<sup>38</sup> <https://allofus.nih.gov/funding/current-funding-opportunities>

evaluations and the results communication and genetic counselors' services. This is an important service to the community of individuals with rare diseases.

The North Carolina Clinical Genomic Evaluation by Next-generation Exome Sequencing 2 (NCGENES 2) study will generate evidence regarding the clinical utility of genomic sequencing as a first-line diagnostic test using a prospective randomized controlled trial that compares usual care plus exome sequencing to usual care. Dr. Jonathan Berg and Dr. Bradford Powell are the Principal Investigators at UNC-CH for this research project.

The North Carolina Biotechnology Center has established a Precision Health Collaborative (NCPHC)<sup>39</sup> to stimulate growth in the precision health sector within the State. Some of the North Carolina state resources participating in the NCPHC include:

- RTI Precision Medicine: The RTI team leverages its collective expertise in genomics, proteomics, metabolomics, the microbiome, and biomarker discovery to better understand disease states and inform individualized approaches to treatment and prevention.
- Duke's Applied Genomics & Precision Medicine: The Duke Center for Applied Genomics & Precision Medicine was created to focus on developing interdisciplinary science and pragmatic implementation strategies and capabilities to enhance our ability to diagnose and predict patient outcomes across the continuum from health to disease.
- UNC School of Medicine: The Department of Genetics and the Lineberger Comprehensive Cancer Center are actively engaged in precision medicine. The Department of Genetics focuses on providing basic and applied genetic/genomic research, education and training, while the Lineberger Center is leading an emerging scientific approach to cancer treatment that is building on advances in genetic sequencing.
- The Personalized Medicine (PM) Clinic at Mission Health: This clinic was developed to help clinicians and patients better manage medications and help predict future medication therapy responses.

South Carolina has an interesting model for a centralized genetic testing laboratory around the Greenwood Genetic Center (GGC). Headquartered in Greenwood, SC, GGC joined with the Medical University of South Carolina and the University of South Carolina School of Medicine in 1979 to form the South Carolina Consortium of Regional Genetic Centers. Through the Consortium, the Centers share clinical and laboratory expertise, provide educational programs, and plan for the delivery of genetic services in South Carolina. GGC extends its reach as a resource to all residents of South Carolina with satellite offices in Charleston, Columbia, Florence and Greenville.

In June 2018, California Governor Jerry Brown signed the state budget that includes \$2 million in funding for an initiative that will investigate the use of whole-genome sequencing within the California Medical Assistance program (Medi-Cal). The pilot project, dubbed "Project Baby Bear," will use the funding for the Rady Children's Institute for Genomic Medicine to perform rWGS on at least 100 neonatal and

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<sup>39</sup> North Carolina Biotechnology Center, Precision Health, <https://www.ncbiotech.org/transforming-life-science/sectors-of-attention/precision-health>  
Accessed August 14, 2018

pediatric patients at various Medi-Cal sites, with the goal of determining the potential clinical and financial benefits of sequencing to the state's public healthcare coverage program.<sup>40</sup>

In 2017, University of Alabama at Birmingham (UAB) School of Medicine, in partnership with the HudsonAlpha Institute for Biotechnology, launched the Alabama Genomic Health Initiative (AGHI) to better meet health needs across the state. AGHI, funded by an initial \$2 million appropriation from the Alabama Legislature to UAB, supports one of the nation's first statewide efforts to harness the power of genomic analysis to identify individuals with a high risk of genetic disease. Over a five-year period, the AGHI will provide genomic testing, interpretation, and counseling free of charge to 10,000 residents in each of Alabama's 67 counties.<sup>41</sup> Also in 2017, HudsonAlpha in collaboration with the UAB School of Medicine and the University of Mississippi Medical Center, was awarded a four-year, \$10 million grant from the National Institutes of Health to investigate how whole genome sequencing can help with the diagnosis and care of newborn babies in neonatal nurseries with birth defects and genetic disorders. The project, "Clinical Sequencing Across Communities in the Deep South," is part of a network of nationwide sites called the Clinical Sequencing Evidence-Generating Research Consortium, or CSER2.<sup>42</sup>

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<sup>40</sup> <https://www.rchsd.org/about-us/newsroom/press-releases/rady-childrens-launchesproject-baby-bear/>

<sup>41</sup> <https://www.uabmedicine.org/aghi>

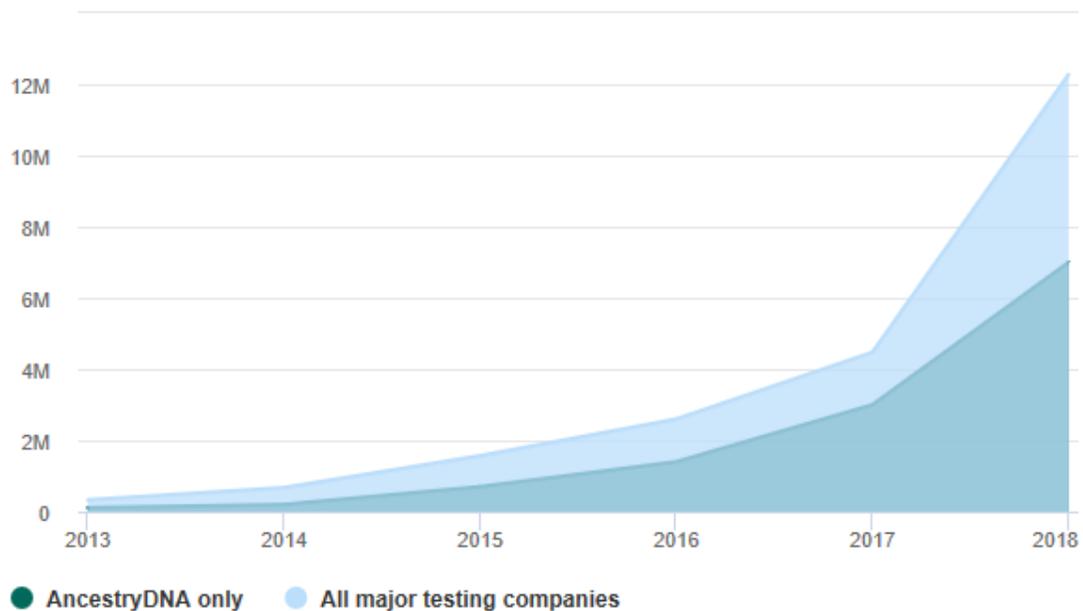
<sup>42</sup> HudsonAlpha and UAB awarded \$10 million for newborn whole genome sequencing project. August 8, 2017. <https://www.uab.edu/news/research/item/8549-hudsonalpha-and-uab-awarded-10-million-for-newborn-whole-genome-sequencing-project>

## Direct-to-Consumer Genetic Testing

The most popular direct-to-consumer genetic testing companies are 23andMe and Ancestry.com. These companies test genetic variations to make predictions regarding an individual's disease risk, ancestry or genealogy, kinship, and lifestyle. More than 12 million people have used direct-to-consumer genetic testing.

### Up, up, and away

Total number of people tested by consumer genetics companies, in millions.



ISOGG, Leah Larkin, company reports

Source: MIT Technology Review. Accessed October 24, 2018.

<https://www.technologyreview.com/s/610233/2017-was-the-year-consumer-dna-testing-blew-up/>

Direct-to-consumer genetic testing provides people access to their genetic information without necessarily involving a healthcare provider or health insurance company in the process. These genetic tests are marketed directly to customers via television, print advertisements, or the Internet, and the tests can be bought online or in stores. Customers send the company a saliva sample and receive their results directly from a secure website or in a written report. The number of companies providing direct-to-consumer genetic testing is growing, along with the range of health conditions and traits covered by these tests. Because there is currently little regulation of direct-to-consumer genetic testing services, it is important to assess the quality of available services before pursuing any testing.<sup>43</sup>

<sup>43</sup> What is direct-to-consumer genetic testing? U.S. National Library of Medicine.

<https://ghr.nlm.nih.gov/primer/dtcgenetic-testing/directtoconsumer>

Accessed October 24, 2018.

Rather than providing a comprehensive genetic risk assessment, these direct-to-consumer genetic tests analyze a limited set of variants, which are not necessarily causal of conditions. The tests interpret single-nucleotide polymorphisms (SNPs), and while SNPs can indicate a gene is associated with a disease, many are benign and have no impact on health. While this may be clear to those with a background in genetics, the lack of public awareness around genetic science combined with the limited genetic knowledge healthcare professionals possess, provides a perfect storm of risk for patients. In 2017 the FDA<sup>44</sup> approved marketing for the first direct-to-consumer genetic test for 23andMe's Personal Genome Service Genetic Health Risk (GHR) tests for 10 diseases or conditions. However, the approval came with a caveat preventing test results being used to ascertain a consumers' overall risk for developing a condition. Still, everyday members of the public order these tests, receive the results and visit their doctors who may not be up-to-date on genetics to decipher the information, despite the disclaimers and warnings.<sup>45</sup>

There are concerns regarding maintaining privacy of direct-to-consumer genetic test results. The Genetic Information Nondiscrimination Act of 2008 (GINA, P.L. 110-233) prohibits health insurance companies and most employers from using an individual's genetic information from making decisions regarding health insurance premiums and employment. There are also HIPAA privacy protections. However, GINA does not provide federal protection from using genetic information in setting premiums for life, long-term care, and disability insurance. Furthermore, since direct-to-consumer genetic testing is not performed under the supervision of a physician, HIPAA privacy protections may not apply.

In 2018, GlaxoSmithKline (GSK) made a \$300 million investment in 23andMe which allows GSK to use 23andMe's genetic data on 5 million individuals for the purpose of drug discovery. Although 23andMe's customer consent form states that a customer's "de-identified data may be used to identify potential areas or targets for therapeutics development and to conduct or support the development of drugs, diagnostics or devices and may be done so in collaboration with third parties"<sup>46</sup>, it is reasonable to assume that most customers did not expect 23andMe would sell their genetic data for profit to a large pharmaceutical company.

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<sup>44</sup> FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions. April 6, 2017. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm>

<sup>45</sup> The dark side of direct-to-consumer genetic tests. PmLive. October 1, 2018. [http://www.pmlive.com/pmhub/healthcare\\_digital\\_communications/blue\\_latitude/white\\_papers\\_and\\_resources/the\\_dark\\_side\\_of\\_direct-to-consumer\\_genetic\\_tests](http://www.pmlive.com/pmhub/healthcare_digital_communications/blue_latitude/white_papers_and_resources/the_dark_side_of_direct-to-consumer_genetic_tests)

<sup>46</sup> A Major Drug Company Now Has Access to 23andMe's Genetic Data. Should You Be Concerned? Time. July 26, 2018. <http://time.com/5349896/23andme-glaxo-smith-kline/>

## Genetic Information Privacy Laws

Some people who receive genetic testing may be concerned about the privacy of their test results and whether insurance companies could use a genetic diagnosis to deny medical coverage or determine health insurance premiums. Instead, they may choose to pay for the testing themselves.

The Genetic Information Nondiscrimination Act (GINA) of 2008 (P.L. 110-233)<sup>47</sup> protects most individuals against discrimination based on their genetic information in health coverage and in employment. It is against the law for health insurance companies to request, require, or use genetic information to make decisions about a patient's eligibility for health insurance or a patient's health insurance premiums, contribution amounts, or terms of coverage. However, the health insurance protections of GINA do not apply to members of the U.S. military who receive their health insurance through Tricare, veterans who receive their health care through the Veterans Administration, the Indian Health Service, and Federal employees enrolled in the Federal Employee Health Benefits Plan. North Carolina is the home to many of these groups and there are policies in place to provide health insurance protections similar to, but not the same as, GINA.

It is also against the GINA law for employers to use genetic information to make employment decisions about hiring, firing, promotion or pay or otherwise discriminate against an employee based up genetic information. GINA's employment protections do not apply to members of the U.S. military and Federal employees. However, an Executive Order protects federal employees from genetic discrimination in employment, and the military has its own policies. Also, GINA does not apply to employers with fewer than 15 employees.<sup>48</sup>

With the passage of the Affordable Care Act (ACA), beginning in 2014, health insurance plans cannot refuse medical coverage to an individual nor charge more for coverage because of an individual's pre-existing health condition even if the condition was diagnosed by genetic test. Further, once an individual has medical insurance coverage, the insurer cannot refuse to cover treatment due to a pre-existing condition. This is true even if a patient has been turned down or refused medical coverage in the past.<sup>49</sup> Despite current protections, fear of future changes or elimination of the ACA impacts patient decisions about pursuing clinical genetic testing or participating in research studies that may lead to results being placed in the medical record.<sup>50</sup>

GINA does not provide individuals protection from using their genetic information by insurers for long term care insurance, life insurance, or disability insurance. California and Alaska have the strongest consumer genetic privacy protections. California's law, CalGINA, expands the protections list to include housing, mortgage lending, education and public accommodations. The law also allows victims of genetic discrimination to seek unlimited monetary damages. As of May 2018, 17 states have laws that

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<sup>47</sup> Public Law 110 - 233 - Genetic Information Nondiscrimination Act of 2008. <https://www.gpo.gov/fdsys/pkg/PLAW-110publ233/content-detail.html>

<sup>48</sup> GINA and You. [http://www.ginahelp.org/GINA\\_you.pdf](http://www.ginahelp.org/GINA_you.pdf)

<sup>49</sup> American Society of Clinical Oncology, "Genetic Testing Coverage & Reimbursement", <https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/integrating-clinical-cancer-genetics-2>  
Accessed July 9, 2018.

<sup>50</sup> Personal communication with Dr. Cynthia Powell

go beyond GINA, to restrict the use of genetic information for determining life, disability or long-term care insurance.<sup>51</sup>

North Carolina General Statute § 58-3-215 - Genetic information in health insurance<sup>52</sup> – prohibits a health insurer from:

- (1) Raising the premium or contribution rates paid by a group for a group health benefit plan on the basis of genetic information obtained about an individual member of the group.
- (2) Refusing to issue or deliver a health benefit plan because of genetic information obtained about any person to be insured by the health benefit plan.
- (3) Charging a higher premium rate or charge for a health benefit plan because of genetic information obtained about any person to be insured by the health benefit plan.

General Statute § 58-3-215 also requires compliance with GINA.

North Carolina General Statute § 95-28.1A - Discrimination against persons based on genetic testing or genetic information prohibited<sup>53</sup> - prohibits an employer from denying or refusing employment to any person or discharging any person on account of the person's having requested genetic testing or counseling services, or on the basis of genetic information obtained concerning the person or a member of the person's family.

General Statute § 95-28.1A does not explicitly require compliance with GINA.

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<sup>51</sup> Privacy and consumer genetic testing don't always mix. Science News. June 5, 2018.

<https://www.sciencenews.org/blog/science-public/privacy-and-consumer-genetic-testing-dont-always-mix>

<sup>52</sup> [https://www.ncleg.net/enactedlegislation/statutes/pdf/bysection/chapter\\_58/gs\\_58-3-215.pdf](https://www.ncleg.net/enactedlegislation/statutes/pdf/bysection/chapter_58/gs_58-3-215.pdf)

<sup>53</sup> [https://www.ncleg.net/enactedlegislation/statutes/pdf/bysection/chapter\\_95/gs\\_95-28.1a.pdf](https://www.ncleg.net/enactedlegislation/statutes/pdf/bysection/chapter_95/gs_95-28.1a.pdf)

## Appendix A – Genetic Testing Terms

The **Clinical Laboratory Improvement Amendments (CLIA)** regulate laboratory testing and require clinical laboratories to be certificated by their state as well as the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.

**Current Procedural Terminology (CPT)** is a medical code set that is used to report medical, surgical, and diagnostic procedures and services to entities such as physicians, health insurance companies and accreditation organizations.

**Gene Panel.** Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called multigene test and multiple-gene test.

**Next Generation Sequencing.** A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel. Also called massively parallel sequencing and NGS.

A **variant of uncertain (or unknown) significance (VUS)** is an allele, or variant form of a gene, which has been identified through genetic testing, but whose significance with disease risk is not known. The term "variant" is favored over "mutation" because it can be used to describe an allele more precisely. When the variant has no impact on health it is called a "benign variant". When it is associated with a disease it is called a "pathogenic variant".

**Whole Exome Sequencing.** A laboratory process that is used to determine the nucleotide sequence primarily of the exonic (or protein-coding) regions of an individual's genome and related sequences, representing approximately 1% of the complete DNA sequence.

**Whole Genome Sequencing.** A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence of 20,000 genes, including non-coding sequence.

## Appendix B - Experts Interviewed

Dr. Cynthia Powell – UNC School of Medicine

Dr. Michael Knowles and Dr. Maimoona Zariwala – UNC School of Medicine

Lauren Doyle - Program Director, UNCG Program in Genetic Counseling

Dr. Chad Haldeman-Englert - Mission Fullerton Genetics Center

Dr. Stephen Kingsmore - President and CEO, Rady Children’s Institute for Genomic Medicine

Dr. Gillian Hooker - Concert Genetics

Dr. Patricia Deverka – American Institutes for Research

Dr. Vandana Shashi - Duke University Medical Center

Dr. Sara Imhof - North Carolina Biotechnology Center

David Keane – GeneDx

Dr. Nancy Henley – Medical Director, NC Medicaid

Dr. Geoffrey Ginsburg – Director, Duke Center for Applied Genomics & Precision Medicine

## Appendix C – CMS Laboratory Fee Schedule

CPT Code	Procedure description	2018 CMS Clinical Diagnostic Fee Schedule (\$)
81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, <u>must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK</u>	0
81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); <u>duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1</u>	0
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1	0
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	0
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, <u>each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)</u>	0
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); <u>re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)</u>	0
81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21	0
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	0
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, <u>each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)</u>	0
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); <u>re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)</u>	0
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); <u>genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1</u>	0
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); <u>duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes</u>	0
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); <u>genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53</u>	0
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); <u>duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</u>	0
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A	0

81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); <u>genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11</u>	\$796.75
81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); <u>duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11</u>	\$796.75
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL	0
81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL	0
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP	0
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1	0
81445	Targeted genomic sequence analysis panel, <u>solid organ neoplasm</u> , DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	\$597.91
81450	Targeted genomic sequence analysis panel, <u>hematolymphoid neoplasm or disorder</u> , DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed	\$648.40
81455	Targeted genomic sequence analysis panel, <u>solid organ or hematolymphoid neoplasm</u> , DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed	0
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), <u>genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection</u>	0
81465	Whole mitochondrial genome <u>large deletion analysis panel</u> (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed	0
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); <u>genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</u>	0
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); <u>duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2</u>	0