Whole Genome and Whole Exome Sequencing AHS – M2032

Definitions
Whole genome sequencing (WGS) is the strategy of using next-generation technology to sequence the entire genome. Whole Exome Sequencing (WES) refers to sequencing of the exome, or coding, regions of a genome. Next generation sequencing involves sequencing of multiple small fragments of DNA in parallel, producing fast, accurate sequencing results (Hulick, 2019).

Related Policies
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will provide coverage for whole exome sequencing when it is determined the medical criteria or reimbursement guidelines below are met.

Whole Genome Sequencing is considered investigational for all indications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Whole Genome and Whole Exome Sequencing is covered
Whole exome sequencing and comparator analysis (e.g. parents/siblings) whole exome sequencing is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorder in children when all the following criteria are met:

a. The patient has been evaluated by a board-certified clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing
b. WES results will directly impact patient management and clinical outcome for the individual being tested
c. A genetic etiology is the most likely explanation for the phenotype
d. No other causative circumstances (e.g. environmental exposures, injury, infection) can explain the symptoms
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e. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing (e.g., comparative genomic hybridization/chromosomal microarray analysis) is available
f. The differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following:
   i. WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis
   ii. WES results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing

When Whole Genome and Whole Exome Sequencing is not covered

If WES has been previously performed, further genetic tests involving only exome analyses is considered investigational.

WES is considered investigational for all other indications, including but not limited to, tumor sequencing.

Whole genome sequencing is considered investigational for all indications.

Policy Guidelines

Background
DNA sequencing is a critical tool for the evaluation of many medical conditions. The two primary methods of DNA sequencing in the clinical setting are Sanger sequencing and next-generation sequencing or NGS. NGS is a recently developed technique that allows for the rapid sequencing of multiple strands of DNA. It is not limited to one specific type of test; rather it encompasses numerous technologies that produce swift and high-volume sequencing. NGS can be used to sequence larger sequences, such as the exome or the entire genome. This is opposed to the traditional Sanger sequencing which is more useful for sequencing a specific gene. (ACMG, 2012a; Hulick, 2019).

The NGS procedure typically includes the following steps: first the patient’s DNA is prepared to serve as a template, then DNA fragments are isolated (on solid surfaces such as small beads) where sequence data is generated. Then these results are compared against a reference genome. Any DNA sample may be used if the quality and quantity of that sample are sufficient, but the methods of library generation and data analysis often vary from panel to panel. Evaluating the results of a gene panel typically requires expertise in bioinformatics. Since NGS reports data on any variants found, great care must be taken to evaluate these gene variants, especially variants of unknown significance (VUS) and secondary findings (Hulick, 2019; Rehm et al., 2013).

Exome and genome sequencing are usually performed with NGS. The exome represents all the protein-encoding genes, and at least 85% of pathogenic mutations are found in the exome. The exome only represents approximately 1.5%-2% of the genome, thereby making it more cost effective than whole genome sequencing. The entire exome includes approximately 30 megabases compared to the genome’s 3.3 gigabases. However, sequencing an entire genome may be useful as a pathogenic mutation may be in a noncoding region of the genome, such as gene regulation dysfunction. Most clinical NGS testing uses targeted panels or whole exome sequencing, and whole genome sequencing is only used in select cases. For instance, conditions such as nonsyndromic hearing loss (possible pathogenic variants in over 60 genes) may benefit from WES evaluation (Hulick, 2019). Many proprietary technologies for WES and WGS are available.

Clinical Validity and Utility

Yang et al conducted a single-center observational study of 2000 patients with clinical whole-exome sequencing performed for a suspected genetic disorder. A molecular diagnosis was reported for 504
patients (25.2%) with 58% of the diagnostic mutations not previously reported. The investigators concluded that “the yield of whole-exome sequencing may offer advantages over traditional molecular diagnostic approaches in certain patients (Yang et al., 2014).” Best et al reviewed thirty-one different WES studies and noted that the diagnostic rates varied between 6.2% and 80%; however, they note that the “differences in inclusion criteria and trio versus singleton approaches to sequencing largely account for the wide range of diagnostic rates (Best et al., 2018).”

Tammimies et al (2015) evaluated the molecular diagnostic yield of chromosomal microarray analysis (CMA) and whole-exome sequencing (WES) in children with autism spectrum disorder (ASD). The patient cohort included 258 consecutively enrolled unrelated children with ASD, stratified into three groups based on the presence of major congenital abnormalities and minor physical anomalies. All probands underwent CMA, with WES performed for 95 proband-parent trios. The molecular diagnostic yields of CMA and WES were comparable. Among the 95 patients undergoing WES, 8 children (8.4%) received an ASD-related molecular diagnosis. Among the children who underwent both CMA and WES testing, the estimated proportion with an identifiable genetic etiology was 15.8%. The investigators concluded that “if replicated in additional populations, these findings may inform appropriate selection of molecular diagnostic testing for children affected by ASD (Tammies et al., 2015).

Taylor et al performed whole genome sequencing in 217 individuals across a broad spectrum of genetic disorders in whom previous screening had identified no pathogenic variants. Disease-causing variants were identified in 21% of cases, with the proportion increasing to 34% (23/68) for mendelian disorders and 57% (8/14) in family trios. The investigators concluded that the results “demonstrate the value of genome sequencing for routine clinical diagnosis but also highlight many outstanding challenges (Taylor et al., 2015).”

Miller et al performed exome/whole genome sequencing to identify the genetic cause in patients with craniosynostosis, in whom prior clinically driven genetic testing had been negative. Out of the 40 patients’ tests, associated mutations were identified in 15 patients (37.5%), involving 14 different genes. In 5 of the 15 positive cases, the molecular diagnosis had immediate, actionable consequences in patient management. The investigators concluded that the study results show “the benefits of exome/whole genome sequencing to identify causal mutations in craniosynostosis cases for which routine clinical testing has yielded negative results (Miller et al., 2017).”

Shrivastava et al conducted a retrospective cohort study on 78 children with neurodevelopmental disabilities and unrevealing workup prior to WES. The overall presumptive diagnostic testing rate was 41% (32/78 patients). Results of WES affected patient management in all cases, most often related to reproductive planning (27/78). The investigators concluded that the high diagnostic yield of WES could lead to earlier diagnosis, impacting medical management, prognostication, and family planning (Srivastava et al., 2014).

**Parent-child trio testing**

Lee et al reported on the initial clinical indications for clinical exome sequencing (CES) referrals and molecular diagnostic rates for different indications and for different test types. CES was performed on 814 patients with undiagnosed, suspected genetic conditions who underwent WES. CES was conducted using a trio-CES technique which involves both parents and their affected child sequenced simultaneously. Overall, a molecular diagnosis with a causative variant in a well-established clinical gene was provided for 213/814 (26%) cases. The trio-CES was associated with higher molecular diagnostic yield (31%; 127/410 cases) than proband-CES or traditional molecular diagnostic methods. The investigators concluded that “additional studies designed to validate these findings and to explore the effect of this approach on clinical and economic outcomes are warranted (Lee et al., 2014).”

Soden et al performed diagnostic WGS and/or WES in parent-child trios for 100 families with 119 children with neurodevelopmental disorders (NDD). 45% of the families received molecular
diagnoses of an established genetic disorder (53/119 affected children). An accelerated sequencing modality, rapid WGS, yielded diagnoses in 73% of families with acutely ill children (11/15). In this study, WES proved to be less costly than continued conventional diagnostic testing of children with NDD in whom initial testing failed to yield a diagnosis. The investigators concluded that “initial diagnostic evaluation of children with NDD should include trio WGS or WES, with extension of accelerated sequencing modalities to high-acuity patients (Soden et al., 2014).”

Another study compared fetal WES versus trio analysis WES on fetuses with sonographic abnormalities. The researchers found that trio analysis yielded a positive/definitive diagnosis in 30% (3/10) of the cases as compared to only 14.3% (2/14) of the singleton cases. They conclude, “In order to expedite interpretation of results, trio sequencing should be employed, but interpretation can still be compromised by incomplete coverage of relevant genes (Drury et al., 2015).” Similarly, these data are supported by another study of trio analysis of thirty different cases. 10% of the cases were positive for a pathogenic finding, and 17% were de novo, inherited recessive, or X-linked variants. The authors conclude, “This study outlines the way for a substantial improvement in the diagnostic yield of prenatal genetic abnormalities through the application of next-generation sequencing (Carss et al., 2014).”

Yates et al performed WES, including trio analysis, using samples obtained from deceased fetuses with ultrasound anomalies. They note that 20% of cases were positive overall with a definitive diagnosis with another 45% positive for possible pathogenic candidate variants. Comparing trio analysis to singleton analysis, 24% (n=11) of trio analysis resulted in a definitive diagnostic finding versus 14% (n=3) for singleton testing (Yates et al., 2017).

Guidelines and Recommendations

American College of Medical Genetics (ACMG)

In 2012, the ACMG released a policy statement outlining points to consider in the clinical application of genomic sequencing to the detection of germline mutations. The ACMG recommended that WGS/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

- “The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.”
- “A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.”
- “A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.”
- “A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.”

ACMG stated that “WGS/WES may be considered in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny,” ACMG further stated that WGS and WES should not be used at this time as an approach to prenatal screening or as a first-tier approach for newborn screening (ACMG, 2012b).

ACMG released a guideline on informed consent for genome/exome sequencingIn that guideline, they noted that WGS/WES was not recommended “before the legal age of majority” unless for “phenotype-driven clinical diagnostic uses or circumstances in which early monitoring or interventions are available and effective” (ACMG, 2013).
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In 2014 the ACMG published guidelines (Alford et al., 2014) for the clinical evaluation and etiologic diagnosis of hearing loss which state: “Pretest genetic counseling should be provided, and, with patient’s informed consent, genetic testing, if available, should be ordered to confirm the diagnosis—this testing may include single-gene tests, hearing loss sequencing panels, whole-exome sequencing (WES), whole-genome sequencing (WGS), chromosome analysis, or microarray-based copy-number analysis, depending on clinical findings”.

The ACMG has released a list of genes for which secondary findings should be disclosed. Secondary findings refer to incidental findings unrelated to why a genetic test was originally ordered but are of significant clinical value to the patient. The portion of the table containing the conditions, the associated genes, and which variants should be reported is listed below (Kalia et al., 2016):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene(s)</th>
<th>Variants to Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast/ovarian cancer</td>
<td>BRCA1, BRCA2</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>BMPR1A, SMAD4</td>
<td>KP, EP</td>
</tr>
<tr>
<td>PTEN hamartoma syndrome</td>
<td>PTEN</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2,</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>KP, EP</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td>MUTYH</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Von Hippel Lindau syndrome</td>
<td>VHL</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1, TSC2</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>WT1</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia 1 or 2</td>
<td>MEN1 (1), RET (2)</td>
<td>KP</td>
</tr>
<tr>
<td>Familial medullary thyroid cancer</td>
<td>RET</td>
<td>KP</td>
</tr>
<tr>
<td>Hereditary paraganglioma-pheochromocytoma syndrome</td>
<td>SDHD, SDHAF2, SDHC, SDHB</td>
<td>KP, EP for all but SDHAF2 (KP only)</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Hypertrophic or dilated cardiomyopathy</td>
<td>MYBPC3, MYH7, TNNT2, TNN13, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</td>
<td>KP, EP for LMNA, GLA, MYBPC3, TNNT2, KP only for MYH7, TNN13, MYL2</td>
</tr>
<tr>
<td>Catacholamenergic polymorphic ventricular tachycardia</td>
<td>RYR2</td>
<td>KP</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>PKP2, DSP, DSC2, TMEM43, DSG2</td>
<td>KP, EP for all but DSP (KP only)</td>
</tr>
<tr>
<td>Romano-Ward Long QT syndromes, Brugada syndrome</td>
<td>KCNQ1, KCNH2, SCN5A</td>
<td>KP, EP for all</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDLR, APOB, PCSK9</td>
<td>KP, EP for LDLR, KP only for APOB and PCSK9</td>
</tr>
<tr>
<td>Ehlers Danlos syndrome</td>
<td>COL3A1</td>
<td>KP, EP</td>
</tr>
<tr>
<td>Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysms and dissections</td>
<td>FBN1, TGFB1, TGFB2, SMAD3, ACTA2, MYH11</td>
<td>KP, EP for all</td>
</tr>
<tr>
<td>Malignant hyperthermia sensitivity</td>
<td>RYR1, CACNA1S</td>
<td>KP only</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Wilson disease (copper metabolism)</th>
<th>ATP7B</th>
<th>KP, EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ornithine transcarbamylase deficiency (urea cycle)</td>
<td>OTC</td>
<td>KP, EP</td>
</tr>
</tbody>
</table>

**American College of Obstetricians and Gynecologists (ACOG)**

The ACOG (2016) published a committee opinion on Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology which states: “the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer reviewed data and validation studies are published.” This committee opinion was reaffirmed in 2019 (ACOG, 2019).

However, ACOG notes that WES may be considered when “specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to determine a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder”. ACOG further clarifies that “in select circumstances (recurrent or lethal fetal anomalies in which other approaches have been noninformative), WES may be considered as a diagnostic tool, but only after appropriate testing has been noninformative and after extensive counseling by an OB-GYN or other health care provider with genetics expertise who is familiar with these new technologies and their limitations (ACOG, 2016).”

**Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) (2018)**

Per the guideline, the word “sequencing” is used to refer to “whole exome sequencing, targeted analysis using clinical panels, and whole genome sequencing”.

“The use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis (CMA), has already been performed and is uninformative or is offered concurrently according to accepted practice guidelines, or for whom expert genetic opinion determines that standard genetic testing is less optimal than sequencing for the presenting fetal phenotype.”

Routine use of prenatal sequencing as a diagnostic test cannot be supported due to “insufficient” validation and data about benefits and pitfalls.

Within the section on recommendations for all diagnostic applications of genome-wide sequencing, concerning trio analysis, they state, “Diagnostic sequencing for fetal indications is best done as a trio analysis, where fetal and both parental samples are sequenced and analyzed together. The trio approach currently benefits timeliness of result interpretation and aids assignment of pathogenicity for detected sequence variants. If proband-only sequencing is performed, validation of diagnostic or potentially diagnostic findings best includes a determination of inheritance through targeted testing of samples from biological parents.” However, the guideline could not recommend one sequencing method over another, nor was the guideline certain on the best way to interpret variants found in genome-wide sequencing.

The guideline provides three scenarios in which fetal sequencing may be “beneficial”:

“A current pregnancy with a fetus with a single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic etiology, but no genetic diagnosis was found after CMA; or in select situations with no CMA result, following a multidisciplinary review and consensus, in which there is a fetus with a multiple anomaly ‘pattern’ that strongly suggests a single gene disorder.”
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“A personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single anomaly or multiple anomalies suggestive of a genetic etiology, and a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA. In addition, when such parents present for preconception counseling and no sample is available from the affected proband, or if a fetal sample cannot be obtained in an ongoing pregnancy, it is considered appropriate to offer sequencing for both biological parents to look for shared carrier status for autosomal recessive mutations that might explain the fetal phenotype. However, where possible, obtaining tissue from a previous abnormal fetus or child for exome sequencing is preferable.”

“In families with a history of recurrent stillbirths of unknown etiology after karyotype and/or CMA, where the fetus in the current pregnancy has a recurrent pattern of anomalies” (ISPD, SMFM, & PQF, 2018).

American Academy of Neurology (AAN)/American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

The AAN/AANEM published guidelines (Kang et al., 2015) on the evaluation, diagnosis, and management of congenital muscular dystrophy (CMD) which state: “In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).”

The AAN/AANEM published guidelines (Narayanaswami et al., 2014) on the diagnosis and treatment of limb-girdle and distal dystrophies which state: “In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C).”

Applicable Federal Regulations

Genotyping is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81415, 81416, 81417, 81425, 81426, 81427, 0010U, 0012U, 0013U, 0014U, 0036U, 0094U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources
Whole Genome and Whole Exome Sequencing AHS – M2032

For the policy titled: Whole Genome Whole Exome Sequencing


American College of Medical Genetics and Genomics (2012). Points to consider in the clinical application of genomic sequencing. Genetics in Medicine, 14:759-761.


For the policy titled: Whole Genome and Whole Exome Sequencing
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doi:10.1038/gim.2013.94


https://www.nature.com/articles/gim2016190#supplementary-information


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Policy Implementation/Update Information

For the policy titled: Whole Genome Whole Exome Sequencing

1/1/2019   BCBSNC will provide coverage for whole exome sequencing when it is considered to be medically necessary because criteria and guidelines are met. Whole genome sequencing is considered investigational for all indications. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For policy titled: Whole Genome and Whole Exome Sequencing

9/10/2019   Reviewed by Avalon 2nd Quarter 2019 CAB with title change. Added Related Policies to Description section. The following statement was added to the When Covered section: “and comparator analysis (e.g. parents/siblings) whole exome sequencing”; Minor revision to When Not Covered with replacement of “whole exome sequencing” with “WES”. Policy guidelines and references updated. Added the following codes to the Billing/Coding section: 0010U, 0012U, 0013U, 0014U, 0036U, and 0094U, and removed code table. Medical Director reviewed 8/2019. (jd)

10/29/19   Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.