BAYLOR GENETICS

Provider FAQs

Whole Genome Sequencing & Whole Exome Sequencing

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FAQs

This resource is intended to support providers by addressing common questions related to test interpretation, reanalysis, billing, and patient support. It also outlines how Baylor Genetics safeguards patient privacy, enables access to genetic counseling, and supports shared decision-making.

Clinical & Technical Specifications

Whole Genome Sequencing

What is Whole Genome Sequencing (WGS)? WGS is the most comprehensive genetic test available at Baylor Genetics, analyzing up to 98% of the human genome. This includes both nuclear DNA (protein-coding and non-coding regions) and the mitochondrial genome.

How does WGS differ from other genetic tests? Less comprehensive genetic tests like panels and Whole Exome Sequencing focus either on specific genes or the exons (protein-coding regions) of the genome. WGS, by contrast, analyzes the entire genome and can detect a broader range of variant types.

The broader scope of WGS can increase the chances of detecting genetic variants that may be missed by other methods, making it a valuable first-line test in cases with unclear presentations or where other tests have been negative.

Note: Whole Exome Sequencing cannot detect short tandem repeat expansions due to limited coverage of intronic and repetitive regions.

What types of variants does WGS detect? WGS can detect most single nucleotide variants (SNVs), small insertions and deletions (indels), copy number variants (CNVs), complex structural variants (SVs), short tandem repeat expansions (STRs), and variants in the mitochondrial genome in a single test. WGS can additionally detect methylation of the *FMR1* gene. This total genomic approach enables detection of variants that may be missed by more targeted genetic testing.

What is diagnostic yield? Diagnostic yield is the percentage of cases where genetic testing has identified a pathogenic or likely pathogenic variant. In other words, diagnostic yield reflects how often the test provides a genetic diagnosis. This yield can vary by test type, patient indication, prior testing history, and the availability of additional closely related family member samples for analysis.

What is the diagnostic yield for WGS? Diagnostic yield varies by indication but typically ranges from 27-41% of all cases.[1-4] Using closely related relatives (such as biological parents or siblings) as part of duo, trio, and quad testing has been shown to increase the diagnostic yield of WGS over proband-only analysis, as comparators can allow for better understanding of inheritance of variants, variant phasing, and other information.

Detailed clinical information, including the patient's phenotype, previous test results, and family history information, is crucial to improving overall diagnostic yield for WGS.

When are additional analyses performed as part of WGS? In select cases, additional analyses such as short tandem repeats (STRs) evaluation, methylation testing, complex SV analysis, or confirmatory testing using orthogonal methods may be performed when clinically indicated. These analyses are integrated with WGS and are not ordered as stand-alone tests. Additional specimens may be requested as needed.

Which STRs can WGS at Baylor Genetics detect? STRs are DNA sequences that are repeated multiple times. When these repeats expand beyond normal ranges, they can cause serious genetic disorders, including Friedreich ataxia, Fragile X syndrome, and various forms of spinocerebellar ataxia.

Pathogenic events of short tandem repeats can be detected within the genomic regions of the following genes: *ABCD3, AFF2, AFF3, AR, ARX, ATN1, ATXN1, ATXN10, ATXN2, ATXN3, ATXN7, ATXN8OS/ATXN8, BEAN1, C9orf72, CACNA1A, CBL, CNBP, COMP, CSTB, DAB1, DIP2B, DMPK, EIF4A3, FGF14, FMR1, FOXL2, FXN, GIPC1, GLS, HOXA13, HOXD13, HTT, JPH3, LRP12, MARCHF6, NOP56, NOTCH2NLC, NUTM2B-AS1, PABPN1, PHOX2B, PPP2R2B, PRDM12, PRNP, RFC1, RILPL1, RUNX2, SAMD12, SOX3, STARD7, TBP, TCF4, THAP11, VWA1, XYLT1, YEATS2, ZFHX3, ZIC2, ZIC3*.

How long does WGS at Baylor Genetics take to complete? Our standard WGS turnaround time (TAT) is 21 calendar days after specimen receipt with completed documentation, including the date of collection (DOC). The DOC is required for all samples to meet lab regulations and billing requirements.

For Rapid WGS (rWGS), our goal is to deliver a complete written rWGS report within 5 calendar days of specimen receipt with completed documentation. If your case needs to be escalated to rapid testing after a sample has already been received, you should complete a Test Revision Authorization Form (TRAF).

TAT may vary depending on factors such as specimen quality and quantity, date of collection, completeness of clinical information provided, and receipt of all required family member samples. Please keep in mind that samples requiring tissue culture can add an additional 2 weeks to the test's TAT.

In some cases, additional analyses may be performed when clinically indicated, including evaluation for short tandem repeat (STR) expansions, *FMR1* methylation analysis, or complex structural variant analysis using Optical Genome Mapping (OGM). These analyses are not ordered as stand-alone tests and are performed only when a suspected finding is identified.

WGS TAT

Test / Analysis	Typical TAT	How Results Are Reported
WGS	21 calendar days	Final report
rWGS	5 calendar days	Final report
STR Expansion Analysis	Reported within the standard WGS TAT when possible. If additional time is required, results are reported once analysis is complete	Included in the final report or issued as an addended report when applicable
FMR1 Methylation Analysis	Reported within the standard WGS TAT when possible. If additional time is required, results are reported once analysis is complete	Included in the final report or issued as an addended report when applicable
Complex Structural Variant Analysis (OGM)	Results reported up to approximately 28 days after the initial WGS report or after receipt of a new specimen when required	Addended report

STR and *FMR1* methylation results are incorporated into the final WGS report within the standard TAT when possible. If additional analysis time is required or a new specimen is needed, results may be issued once testing is complete.

Complex structural variant analysis using OGM is performed on blood samples only and is reported as an addended report, typically within 28 days after the initial WGS final report or after receipt of a new specimen if applicable.

Is WGS available to order in New York State? Some additional analyses (complex SV analysis with OGM as well as STR and methylation analysis of *FMR1* using long-read sequencing) are not currently available to order in New York State. If these analyses cannot be performed due to state regulations, the ordering provider will be contacted.

Whole Exome Sequencing

What is Whole Exome Sequencing (WES)? WES analyzes the protein-coding regions of the genome, known as exons, which make up about 1-2% of the genome but contain approximately 85% of known disease-causing variants. It is more targeted than WGS and may be appropriate in cases with strong phenotypic clues or when insurance or other limitations are a factor.

What types of variants does WES detect? WES is primarily designed to detect single nucleotide variants (SNVs) and small insertions or deletions (indels) within coding regions. It may also detect some copy number variants (CNVs), but structural and non-coding variants are generally not detected.

Mitochondrial (mtDNA) analysis and short tandem repeat (STR) expansions are **not** included in standard WES.

What is the diagnostic yield for WES? WES has a diagnostic yield typically ranging from 20-30%, depending on the indication.[5,6] It remains a widely accepted first-tier test, particularly in cases with a strong phenotype-genotype correlation or when insurance policies are limited in coverage for genome sequencing. Using closely related relatives (such as parents or siblings) as part of duo, trio, and quad testing has shown to increase the diagnostic yield of WES over proband-only analysis as comparators can allow for better understanding of inheritance of variants, variant phasing, and other information.

Detailed clinical information, including the patient's phenotype, previous test results, and family history information, is crucial to improving overall diagnostic yield for WES.

How long does WES take to complete? Standard WES turnaround time (TAT) is 21 calendar days **after** specimen receipt with completed documentation, including the date of collection (DOC). The DOC is required for all samples to meet lab regulations and billing requirements. For Rapid WES (rWES), our goal is to deliver a complete written rWES report within 5 calendar days of specimen receipt with completed documentation.

If your case needs to be escalated to rapid testing after a sample has already been received, providers should complete a Test Revision Authorization Form (TRAF).

TAT may vary depending on factors such as specimen quality and quantity, DOC, completeness of clinical information provided, and receipt of all required family member samples. Samples requiring tissue culture may add an additional 2 weeks to the test's TAT.

WES TAT

Test / Analysis	Typical TAT	How Results Are Reported
WES	21 calendar days	Final report
rWES	5 calendar days	Final report

Ordering Questions

When should I consider ordering WGS or WES v. other genetic tests? WGS can be valuable for diagnosing complex or atypical presentations where the phenotype does not clearly point to a specific gene or disorder. WES may be suitable when there is a well-defined phenotype, budgetary constraints, or insurance requirements that limit access to WGS. Although WGS may provide more comprehensive insight in some cases, both tests can be useful in evaluating:

- Autism Spectrum Disorder
- Cerebral Palsy
- Congenital Anomalies (such as cardiac, skeletal, and genitourinary anomalies)
- Developmental Delays
- Epilepsy
- Extensive Differential Diagnosis
- Failure to Thrive
- Hypotonia
- Intellectual Disability
- Immunodeficiencies
- Metabolic Disturbances
- Neurodevelopmental Disorders
- Neuromuscular Disorders
- Previous Genetic Testing Uninformative
- Prolonged and/or Recurrent Hospital Stays
- Vision and Hearing Loss

Recent guidelines from the American College of Medical Genetics and Genomics (ACMG) and the American Academy of Pediatrics (AAP) recommend consideration of exome or genome sequencing (ES / GS) in patients with congenital anomalies, developmental delay, or unexplained pediatric disorders.[7,8]

The National Society of Genetic Counselors (NSGC) and the American Epilepsy Society (AES) strongly recommend ES or GS for all individuals with unexplained epilepsy as a first-tier test.[9]

When should I consider ordering rWGS or rWES? rWGS or rWES is recommended when timely genetic results are critical for guiding acute clinical management, particularly with hospitalized or critically ill patients. Rapid testing can help shorten the diagnostic process, inform treatment decisions, and reduce unnecessary interventions. Common indications include:

- Cardiac Arrest
- Congenital Anomalies (e.g., cardiac, skeletal, & genitourinary anomalies)
- Developmental Delays
- Epilepsy
- Extensive Differential Diagnosis
- Failure to Thrive
- Hypotonia
- Intellectual Disability
- Immunodeficiencies
- Metabolic Disturbances
- Neurodevelopmental Disorders
- Neuromuscular Disorders
- Previous Genetic Testing Uninformative
- Prolonged and/or Recurrent Hospital Stays
- Respiratory Insufficiency at Term

Can genetic testing rule out all genetic conditions? No. While highly accurate, genetic testing cannot detect all types of genetic variants and cannot exclude all genetic conditions. Results may not always predict disease progression or change clinical management.

What options for reporting are available with WGS and WES?
For WGS and WES, providers may select from several reporting options:

- ACMG Secondary Findings: Each tested family member may choose to opt in to receive these results.
- Other Incidental Findings: Unrelated to the proband's phenotype, available as an opt-in for the proband only.
- Candidate Gene Findings: When both parents are tested, providers may opt in to receive findings in genes with no currently known clinical association. As with incidental findings, these genes will be reported for the proband only.

For additional details, see the Clinical Interpretation & Reporting section.

Do you report findings in genes associated with adult-onset neurodegenerative conditions? By default, these variants will not be reported unless they are related to your patient's phenotype. However, variants in specific genes can be requested to be reviewed prior to reporting. Each gene needed should be specified in the *Genes of Interest* section of the order or requisition.

Can WGS and WES be ordered as a duo (proband + one biological parent), trio (proband + both biological parents), or quad (proband + parents + closely related family members)? Yes, duo, trio, or quad testing is strongly recommended as it can improve diagnostic yield over proband-only testing, particularly for de novo variants* and compound heterozygous findings.[5]

** De novo variants are new genetic changes not inherited from either parent*

Why do you request samples from family members? Including samples from closely related, biological family members (called comparators) provides critical context for interpreting the patient's (proband) results. Comparator data helps determine whether a variant is inherited from an affected or unaffected parent, which can assist in determining pathogenicity. This additional information can increase diagnostic yield and reduce uncertainty in interpretation.

What should family members consider when participating in testing for WGS or WES? While testing focuses on the proband, closely related family members who provide samples as comparators may receive results that could impact their health or future care. Each family member should understand the information outlined in the WGS/WES consent before sample collection. Providers should ensure that family members are aware of the potential for incidental or secondary findings.

Will separate reports be issued for family members? For proband-only analyses, only a report for the proband will be issued, including any variants that were identified related to the patient's phenotype and secondary findings (if opted in).

For duo, trio, and quad analyses, a separate report for each of the tested family members will be issued to the ordering provider, specifying whether secondary finding results were declined or requested, and if so, any secondary findings that were detected.

Some advanced analyses performed after sequencing, including *FMR1* methylation analysis, STR expansion evaluation, and complex structural variant analysis using OGM, are performed on the proband only. Results from these analyses are not issued for comparators.

Is there a separate charge for family member testing as part of a duo, trio, or quad testing? No. When the ordering provider determines that family member testing is clinically necessary and orders it at the same time as the proband's test, the cost is included in the cost of the proband's test.

What clinical information should I provide with the test order? Detailed phenotypic information can significantly improve result interpretation and test accuracy. Please include primary clinical features, age of onset, family history, and previous genetic testing results. Where possible, we also recommend providing Human Phenotype Ontology (HPO) terms with each order as these terms precisely define each part of a patient's phenotype.

What specimen types are accepted for WGS and WES? For the patient and comparators, we accept whole blood (3-5mL in EDTA tube), saliva, buccal swab, cord blood, cultured skin fibroblast,* and extracted DNA (minimum 20µg at 50ng/µ L concentration; A260/A280 of ~1.7).

Important: Each submitted specimen must indicate the relevant date of collection to avoid processing delay.

** If direct skin biopsy is received, please note that the lab will need to culture the sample prior to testing. This process typically takes 2 weeks to complete.*

Is genetic counseling required before ordering WGS or WES? While not mandatory, pre-test genetic counseling is strongly recommended given the comprehensive nature of this testing and the possibility of additional or unexpected findings.

What if I need help interpreting my patient's results or addressing patient questions? Baylor Genetics' genetic counselors are available to discuss results and support providers. You can contact our team directly at 1800-411-4363 or help@baylorgenetics.com. You can help your patient find a local genetic counselor through the NSGC directory

[https://findageneticcounselor.nsgc.org/] for additional support.

Billing & Insurance

What are the CPT codes for WGS and WES? The primary CPT code for WGS is 81425. Additional codes may apply for duo, trio, and quad analyses (81426) or specific variant confirmation.

The CPT code for WES is 81415 for proband-only, and 81415 + 81416 for duo, trio, and quad analyses. Both WES and WGS may include additional codes depending on testing components.

What documentation is required for insurance prior authorization? Most insurers require detailed clinical history, previous genetic testing results (if any), family history, and medical necessity documentation. You can find templated letters of medical necessity for WGS and WES here that you can modify as appropriate for your specific circumstance.

We provide prior authorization support and can assist with appeals when necessary. Please complete our Verification of Benefits form for more information.

How long does prior authorization typically take? Standard prior authorization takes around 5 business days but can take up to 3 weeks. We recommend initiating authorization early in the clinical decision-making process.

What insurance plans do you accept? We partner with a wide range of commercial and government insurance providers. However, in-network status may vary by plan type, location, and insurance product. We recommend that patients and providers confirm network participation with the health plan before ordering.

For an up-to-date list of our insurance partners, visit our Insurance Plans page.

Do you accept Medicaid / Medicare? Yes, we accept many Medicaid plans, and we are a certified Medicare provider. Visit our Insurance Plans page for a detailed list of state Medicaid plans we partner with.

What is the patient's financial responsibility if insurance denies coverage? We offer patient financial assistance programs and payment plans. Our maximum patient responsibility program caps out-of-pocket costs for qualifying patients. Visit our Financial Assistance page for detailed information and contact our Billing team at vob@baylorgenetics.com to discuss payment options.

Clinical Interpretation & Reporting

What types of results can I expect? Our testing is designed to detect genetic variants, which are changes in someone's DNA that differ from what is typically expected.

A result may be any of the following:

1. **Positive:** A pathogenic or likely pathogenic variant or combination of variants was identified and determined to be clinically relevant to the patient's phenotype.
2. **Indeterminate / Variant of Uncertain Significance (VUS):** Genomic variants possibly related to the patient's phenotype were detected. However, the clinical significance is unclear at this time.
3. **Negative:** No reportable variants were identified that are related to the patient's phenotype.

It is important to note that the classification of variants may change over time. Our clinical team is available to discuss results from testing and answer questions that you may have.

Will I receive more than one report? In some cases, additional analyses performed after initial sequencing may be issued as an addended report once testing is complete.

What is the reporting policy for ACMG secondary findings? Secondary findings include pathogenic and likely pathogenic variants in a series of genes as recommended by the American College of Medical Genetics and Genomics (ACMG). The list of genes is selected based on the availability of proactive screening or intervention to prevent morbidity and mortality from genetic disorders unrelated to the patient's phenotype, such as underlying susceptibility to cancer or cardiac conditions.

Baylor Genetics allows for each family member to individually opt in to receiving ACMG secondary findings:

- For proband-only analyses, only a report for the proband will be issued, including any variants that were identified related to the patient's phenotype and secondary findings (if opted in).
- For duo, trio, and quad analyses, a separate report for each of the tested family members will be issued to the ordering provider, specifying whether secondary finding results were declined or requested, and if so, any secondary findings that were detected.

Does Baylor Genetics report other secondary / incidental findings? Yes, we report other secondary and incidental findings beyond those recommended by ACMG, if separately indicated on the test order. These findings include variants in genes associated with early-onset, highly penetrant conditions that are unrelated to the patient's current phenotype but may have implications for medical management. These are reviewed and reported on a case-by-case basis.

Testing may find a variant in a gene that is not known to cause disease. This may be helpful to learn more about these genes in the future. These results do not currently impact medical management or indicate a diagnosis.

Can I request a reanalysis in the future? Yes, reanalysis can be ordered for WGS (test code 1897) [https://catalog.baylorgenetics.com/details/1897] and WES (test code 1900) [https://catalog.baylorgenetics.com/details/1900] as new clinical or scientific evidence becomes available.

We offer one complimentary (no cost) reanalysis for patients who have undergone WES or WGS performed at Baylor Genetics. Please note that we are unable to provide reanalysis for testing conducted by other laboratories.

If an additional reanalysis is requested beyond the initial no-cost analysis, insurance may be billed using the appropriate CPT codes (e.g., 81425 for WGS, 81417 for WES, or 81479 for targeted analysis). Please note that reimbursement is subject to payer medical policy and may require documentation of medical necessity.

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