

# CONCERT GENETICS GENETIC TESTING: EXOME AND GENOME SEQUENCING FOR THE DIAGNOSIS OF GENETIC DISORDERS

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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

## OVERVIEW

[Exome sequencing \(ES\)](#) (also known as ‘whole exome sequencing (WES)’) involves sequencing and copy number variant (CNV) analysis of the portion of the genome that contains protein-coding DNA, which are termed exons. Together, all of the exons in a genome are known as the exome, which constitutes approximately 1% of the genome and is currently estimated to contain about 85% of heritable disease-causing variants.

[Genome sequencing \(GS\)](#) (also known as ‘whole genome sequencing (WGS)’) is a comprehensive method that sequences both coding and noncoding regions of the genome. GS has typically been limited to use in the research setting, but is emerging in the clinical setting and has a greater ability to detect large deletions or duplications in protein-coding regions compared with ES. GS requires greater data analysis but less DNA preparation prior to sequencing.

ES and GS have been proposed for use in patients presenting with disorders and anomalies not immediately explained by standard clinical workup. Potential candidates for ES and GS include patients who present with a broad spectrum of suspected genetic conditions. GS has been shown to have a higher diagnostic yield compared to ES when used as a first line test. ES reanalysis is often performed approximately 18 months to 2 years following initial, uninformative ES. Studies have

shown that the diagnostic yield of ES reanalysis is comparable to performing GS after an uninformative ES.

Rapid exome sequencing (rES) and rapid genome (rGS) sequencing involves sequencing of the exome or genome, respectively, in an accelerated time frame. Preliminary results can typically be returned in less than 7 days, and a final report in less than two weeks. Studies suggest that the use of rES or rGS in acutely-ill infants, presenting with complex phenotypes that are likely rare genetic conditions, can identify a genetic diagnosis more quickly, allowing clinicians and family members to change acute medical or surgical management options and end the diagnostic odyssey.

## POLICY REFERENCE TABLE

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT<sup>®</sup>). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

<a href="#">Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<a href="#">Standard Exome Sequencing</a>	Genomic Unity Exome Plus Analysis - Proband (Variantyx)	0214U	F70-F79, F80.0-F89, Q00.0-Q99.9	1, 3, 5, 7, 8, 11, 12, 13
	Genomic Unity Exome Plus Analysis - Comparator (Duo or Trio) (Variantyx Inc.)	0215U		

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	XomeDx - Proband (GeneDx)	81415		
	Exome - Proband Only (Invitae)			
	XomeDx - Duo (GeneDx)	81415, 81416		
	XomeDX - Trio (GeneDx)			
	Exome - Duo (Invitae)			
	Exome - Trio (Invitae)			
<a href="#">Reanalysis of Exome or Genome Sequencing Data</a>	Exome Reanalysis (Ambry)	81417	F70-F79, F80-F89, Q00.0-Q99.9	4, 9, 10, 12
	Whole Genome Reanalysis (ARUP)	81427		
<a href="#">Rapid Exome Sequencing</a>	XomeDxXpress (GeneDx)	81415, 81416	F70-F79, F80-F89, Q00.0-Q99.9	1, 3, 5, 6, 7, 8, 11, 12, 13
	ExomeNext-Rapid (Ambry)			
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)			
	STAT Whole Exome Sequencing (PerkinElmer Genomics)			
<a href="#">Standard Genome Sequencing</a>	Genomic Unity Whole Genome Analysis - Proband (Variantyx Inc.)	0212U	F70-F79, F80-F89, Q00.0-Q99.9	1, 3, 5, 7, 8, 11, 12, 13
	Genomic Unity® Whole Genome Analysis - Comparator (Variantyx Inc.)	0213U		
	GenomeSeqDx (GeneDx)	81425, 81426		
	TruGenome Trio (Illumina)			
	Whole Genome Sequencing (PerkinElmer Genomics)			
	MNGenome (MNG Laboratories)			
	0265U			

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	Praxis Whole Genome Sequencing (Praxis Genomics LLC)			
<a href="#">Rapid Genome Sequencing</a>	Rapid Whole Genome Sequencing (Rady Children’s Institute for Genomic Medicine)	0094U	F70-F79, F80-F89, Q00.0-Q99.9	2, 3, 6, 8, 11
	Rapid Whole Genome Sequencing, Comparator Genome (Rady Children’s Institute for Genomic Medicine)	0425U		
	Ultra-Rapid Whole Genome Sequencing (Rady Children’s Institute for Genomic Medicine)	0426U		
	STAT Whole Genome Sequencing (PerkinElmer Genomics)	81425, 81426		
	MNGenome STAT (Labcorp/MNG Laboratories)			

## OTHER RELATED POLICIES

This policy document provides criteria for exome and genome sequencing for the diagnosis of genetic disorders in patients with suspected genetic disorders and for population-based screening. Please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic genetic testing performed after a child has been born.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to prenatal carrier screening, preimplantation genetic testing, or preconception carrier screening.

- **Genetic Testing: Prenatal Diagnosis (via Amniocentesis, CVS, or PUBS) and Pregnancy Loss** for coverage related to prenatal exome sequencing.
- **Genetic Testing: General Approach to Genetic and Molecular Testing** for criteria related to exome and genome sequencing that is not specifically discussed in this or another non-general policy.

## CRITERIA

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

### STANDARD EXOME SEQUENCING

- I. Standard exome sequencing (81415, 81416, 0214U, 0215U), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member/enrollee has not previously had genome sequencing, **AND**
  - B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - D. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
  - E. The member/enrollee meets at least one of the following clinical findings:
    1. The member/enrollee has unexplained epilepsy diagnosed at any age, **OR**
    2. The member/enrollee has [global developmental delay](#) or [intellectual disability](#) with onset prior to age 18 years, **OR**

3. The member/enrollee was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
4. The member/enrollee has at least **TWO** of the following:
  - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
  - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**
  - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
  - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
  - e) Autism, **OR**
  - f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
  - g) Period of unexplained developmental regression (unrelated to epilepsy or autism).
- II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational**.
- III. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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## **REANALYSIS OF EXOME OR GENOME SEQUENCING DATA**

- I. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **medically necessary** when\*:

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- A. The member/enrollee had exome or genome sequencing at least 18 months ago, **OR**
  - B. The member/enrollee's phenotype has expanded to include clinical findings\*\* that were not present at the time of the initial exome or genome sequencing analysis, **AND**
    - 1. Results of prior exome or genome sequencing do not explain these new clinical findings.
- II. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **investigational** for all other indications.

\*If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

\*\*See [Standard Exome Sequencing](#) or [Standard Genome Sequencing](#) criteria for qualifying clinical findings.

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## **RAPID EXOME SEQUENCING**

- I. Rapid exome sequencing (81415, 81416), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member/enrollee is an acutely-ill infant (12 months of age or younger), **AND**
  - B. The member/enrollee has not previously had genome sequencing, **AND**
  - C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - D. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - E. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**

- F. The member/enrollee meets at least one of the following clinical findings:
1. The member/enrollee has unexplained epilepsy , **OR**
  2. The member/enrollee has [global developmental delay](#), **OR**
  3. The member/enrollee was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
  4. The member/enrollee has at least **TWO** of the following:
    - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
    - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy), **OR**
    - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
    - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
    - e) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
    - f) Period of unexplained developmental regression (unrelated to epilepsy or autism).
- II. Rapid exome sequencing (81415, 81416) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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## STANDARD GENOME SEQUENCING

- I. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **medically necessary** when:



- A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
- B. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
- C. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
- D. The member/enrollee meets at least one of the following clinical findings:
  - 1. The member/enrollee previously had uninformative exome sequencing (ES), **AND**
    - a) [ES reanalysis is not possible](#), **OR**
  - 2. The member/enrollee has unexplained epilepsy diagnosed at any age, **OR**
  - 3. The member/enrollee has [global developmental delay](#) or [intellectual disability](#) with onset prior to age 18 years, **OR**
  - 4. The member/enrollee was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
  - 5. The member/enrollee has at least **TWO** of the following:
    - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
    - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**
    - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
    - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
    - e) Autism, **OR**

- f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
  - g) Period of unexplained developmental regression (unrelated to epilepsy or autism).
- II. Repeat standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational**.
- III. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

**Note:** When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

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## **RAPID GENOME SEQUENCING**

- I. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member/enrollee is an acutely-ill infant (12 months of age or younger), **AND**
  - B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - D. The member/enrollee's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
  - E. The member/enrollee meets at least one of the following clinical findings:

1. The member/enrollee has multiple [congenital abnormalities](#) (functional and/or structural) affecting unrelated organ systems, **OR**
  2. The member/enrollee has epileptic encephalopathy, **OR**
  3. The member/enrollee has at least **TWO** of the following:
    - a) Abnormality affecting at least one organ system, **OR**
    - b) Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global [developmental delay](#), [intellectual disability](#)), **OR**
    - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
    - d) Laboratory findings suggestive of an inborn error of metabolism, **OR**
    - e) Abnormal response to standard therapy.
- II. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

**Note:** When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

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## DEFINITIONS

1. **Exome Sequencing (ES):** A genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
2. **Genome Sequencing (GS):** A genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

3. **Trio Testing:** Testing of the child and both biological/genetic parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.
4. **Comparator Exome Sequencing:** Used only for comparison with the proband (individual undergoing exome sequencing) and is used to inform the pathogenicity of variants. A comparator exome is typically one or both biological/genetic parents to the proband.
5. **Congenital anomalies:** According to ACMG, congenital anomalies are multiple anomalies not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.
6. **Global Developmental delay:** An individual that is slow-to-meet or not reaching milestones in the expected way for a child's age in at least two of the areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills)  
**Intellectual disability (ID):** Defined by the DSM-V as:
  - a. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
  - b. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.
  - c. Onset of intellectual and adaptive deficits during the developmental period.
7. **Exome sequencing (ES) reanalysis** may not be possible in some situations. Sequencing platforms may have changed substantially enough that the performing lab can no longer use the data from the original ES in their pipeline. Specifically, ES reanalysis may not be possible if there have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or there is new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing.

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## CLINICAL CONSIDERATIONS

Trio testing is preferred whenever possible. Testing of one available parent is a valid alternative if both are not immediately available and one or both parents can be done later if needed. Exome sequencing or genome sequencing can reveal incidental findings or secondary findings. These findings are defined as results that are not related to the indication for undergoing the sequencing, but may be of medical value or utility. Disclosure of these findings has been a topic of intense debate within the medical genetics community. In 2013, ACMG published recommendations for reporting secondary findings that included a list of conditions to be included. The list currently includes 59 genes that confer highly-penetrant and medically actionable conditions.

Pre-test and post-test genetic counseling that facilitates informed decision-making, the possibility to identify secondary finding with the option to ‘opt out’ of receiving these results, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs is strongly advised.

If a genetic diagnosis is not found by ES or GS, periodic reanalysis of the previously obtained genomic sequence is recommended. Reevaluation can occur on the variant-level or case-level. Any variants identified and reported prior to the current ACMG variant classification standards should be reevaluated using the current ACMG standards.

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## BACKGROUND AND RATIONALE

### Standard Exome Sequencing

*American College of Medical Genetics and Genomics (ACMG)*

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (Manickam, 2021), which included the following:

- ACMG recommends using exome or genome sequencing as a first- or second-tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or for patients with intellectual disability/developmental delay before the age of 18. (p. 2031)
- ACMG recommends exome or genome sequencing for active and long-term clinical management of the proband, as well as for implications on family-focused and reproductive outcomes. (p. 2032)

Of note, ACMG states that “Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing.” (p. 2034)

ACMG also released a systematic evidence-based review (Malinowski, 2020) of 167 published studies examining the clinical impact of exome sequencing (ES) and genome sequencing (GS) in individuals with congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID). This systematic review “provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family members, noting that a “change in clinical management” resulted in over half of the patients examined as a result of their ES/GS results. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

#### *National Society for Genetic Counselors*

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

“The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs”

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

*Patient-Centered Laboratory Utilization Guidance Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR
  - b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
  - c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
  - d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
  - e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)

- iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
  - v. Family history strongly suggestive of a genetic etiology, including consanguinity
  - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
  - vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
  3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.” (p. 7)

*Rehm et al (2023)*

Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

*Belanger, et al*

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

**Reanalysis of Exome or Genome Sequencing Data***Tan, et al*



A study from 2020 examined data from 58 unsolved cases referred for any indication to evaluate the systematic reanalysis of singleton exome sequencing (ES). The authors performed a reanalysis at multiple timepoints following initial testing, and ultimately suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis. (p. 1)

*Alfares, et al.*

This study from 2018 compared the detection rates of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in a clinical setting. The study included 108 patients with negative array CGH and negative or inconclusive WES results. WGS was performed on all patients, and the results of the study showed that 30% of the positive cases identified by WGS could be identified by reanalyzing WES raw data, and WGS achieved an only 7% higher detection rate. (p. 1328) The paper concluded that, although WGS is a more powerful tool than WES, in this study, “we showed that WGS has additional, but limited, clinical utility compared with reanalyzing WES data, and until the cost of WGS approximates that of WES, reanalyzing WES raw data is recommended before performing WGS.” (p. 1333)

*American College of Medical Genetics*

A statement from ACMG (Deignan, 2019) included considerations for case-level exome re-analysis, which include the following:

- Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering processes)
- Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing. (p. 1269)

*Patient-Centered Laboratory Utilization Guidance Services*

The PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease” state the following regarding reanalysis of exome or genome sequencing data: “Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months. The authors suggest

that an interval of greater than 18 months from the original report may be optimal for reanalysis.” (p. 3)

The guidelines also state: “Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis...” (p. 8)

### **Rapid Exome Sequencing**

*American College of Medical Genetics and Genomics (ACMG)*

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (Manickam, 2021), which included the following:

- ACMG recommends using exome or genome sequencing as a first- or second-tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or for patients with intellectual disability/developmental delay before the age of 18. (p. 2031)
- ACMG recommends exome or genome sequencing for active and long-term clinical management of the proband, as well as for implications on family-focused and reproductive outcomes. (p. 2032)

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In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

#### *National Society for Genetic Counselors*

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

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- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

#### *Patient-Centered Laboratory Utilization Guidance Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR

- b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
  - c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
  - d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
  - e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
    - iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
    - v. Family history strongly suggestive of a genetic etiology, including consanguinity
    - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
    - vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.” (p. 7)

*Rehm et al (2023)*

Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing

tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

*Kingsmore SF, Cakici JA, Clark MM et al. 2019*

This report is from the NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, primarily from the NICU, PICU, and CVICU at Rady Children's Hospital, San Diego (RCHSD) to compare the effectiveness and outcomes between rWGS and rWES, with analysis as singleton probands and familial trios. The inclusion criteria for the 1,248 ill infants defined the maximum age at the time of admission as four months. They found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results. (p. 725)

*Belanger, et al*

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

## **Standard Genome Sequencing**

*American College of Medical Genetics and Genomics (ACMG)*

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (Manickam, 2021), which included the following:

- ACMG recommends using exome or genome sequencing as a first- or second-tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or for patients with intellectual disability/developmental delay before the age of 18. (p. 2031)
- ACMG recommends exome or genome sequencing for active and long-term clinical management of the proband, as well as for implications on family-focused and reproductive outcomes. (p. 2032)

Of note, ACMG states that “Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing.” (p. 2034)

ACMG also released a systematic evidence-based review (Malinowski, 2020) of 167 published studies examining the clinical impact of exome sequencing (ES) and genome sequencing (GS) in individuals with congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID). This systematic review “provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family members, noting that a “change in clinical management” resulted in over half of the patients examined as a result of their ES/GS results. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

#### *National Society for Genetic Counselors*

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

“The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.”

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended.

*Patient-Centered Laboratory Utilization Guidance Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR
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  - e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)

- iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
  - v. Family history strongly suggestive of a genetic etiology, including consanguinity
  - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
  - vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
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**Rapid Genome Sequencing***Patient-Centered Laboratory Utilization Guidance Services*



In the PLUGS June 2022 guidelines entitled “Rapid Genome Sequencing,” the following clinical criteria are recommended for coverage for “acutely-ill individuals” who meet “ALL of the following criteria”:

“1. The etiology of the patient’s features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on one of the following

a) Multiple congenital abnormalities affecting unrelated organ systems, OR

b) Epileptic encephalopathy, OR

c) TWO of the following criteria are met:

- abnormality affecting at minimum a single organ system
- symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability)
- family history strongly suggestive of a genetic etiology, including consanguinity
- laboratory findings suggestive of an inborn error of metabolism
- abnormal response to standard therapy

2. Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND

3. rGS is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity)...” (p. 3 and 4)

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The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

“The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.”

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Diagnosis of Genetic Disorders  
V2.2024  
Date of Last Revision: 04/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
<p>Semi-annual review. Updated title to reflect V1.2024 version. Throughout policy: replaced “coverage criteria” with “criteria. Overview, coding, reference-table, background and references updated. For Overview: added “GS has been shown to have...”. For Other Related Policies: added “and Molecular”. For Standard Exome Sequencing: under I.A.1. added “diagnosed”; under I.A.2. removed “etiology of the member/enrollee’s features...” and replaced with “member/enrollee has developmental delay...”; under I.A.3. added “The member/enrollee was diagnosed...”; added I.A.4. added “The etiology of the member/enrollee’s features...”; under I.A.4.b. removed “criteria are met” and added “Abnormality of at least one”; under I.B. added “The member/enrollee has not previously...”; under I.F. removed “during the hospitalization”; under I.G. replaced “Board Certified...” with “Medical Geneticist” and added “(APGN)”; under I.H. removed “Board Certified...” and added “Genetic Counselor”; under II. removed “for the above indications...” and added “is considered not medically necessary”; removed II.A. “Significant new symptoms...”; removed II.B. “The member/enrollee has been re-evaluated...”; removed II.C. “There have been improvements...”; removed III. “Repeat standard exome...” and added “Standard exome sequencing...”; added “Reanalysis of Whole Exome Sequencing Data...”. For Rapid Exome Sequencing: under I.B. removed “Board Certified...” and replaced with “Medical Geneticist...”; under I.B. added “AND”; under I.C. added “Non-genetic etiologies...”; under I.D.2. removed “criteria are met”; under I.2.a. removed “significantly” and “minimum a single” and added “least one”; under I.D.2.d. removed “Dysmorphic features, OR”; for I.D. removed “Alternate etiologies...”; under I.F. removed “standard” and added “and other standard laboratory...”; under I.H. removed “Board Certified” and added “(APGN)”. For Standard Genome Sequencing Panel: removed “0209U...” and added “0212U...”; under I.A. added “The member/enrollee previously had...” under I.A.1. added “WES reanalysis...”; under I.B. added “The member/enrollee meets...” under I.B.1. added “The member/enrollee has unexplained...”; under I.B.2. added “The member/enrollee has developmental...”; under I.B.3. added “The member/enrollee was diagnosed...”; under I.B.4. added “The etiology of the member/enrollee’s...”; under I.B.4.a. added “Multiple congenital abnormalities...”; under I.B.4.b. added “TWO of the following...”; under I.B.4.b.1. added “Abnormality...” under I.B.4.b.2. added “Dysmorphic features...”; under I.B.4.b.3. added “Encephalopathy...”; under I.B.4.b.4. added “Symptoms of a complex...”; under I.B.4.b.5. added “Family history strongly...”; under I.B.4.b.6. added “Clinical or laboratory...”; under I.B.5. added “Alternate etiologies...”; under I.B.6. added “Clinical presentation...”; under I.B.7. added “There is a predicted...”; under I.B.8. added “Pre-and post-test...”; under I.C. added “Standard genome sequencing...”.</p>	10/23	10/23

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
<p>For Rapid Genome Sequencing Panel: under I.B. removed “Board -Certified...” and added “Genetic Counselor”; under I.C.2. removed “criteria are met:”; under I.C.2.a. removed “significantly” and “minimum a single” and added “least one”; under I.I. removed “Board Certified” and added “(APGN); under I.J. replaced “scutely ill infant” with “member/enrollee” and removed “diagnoses:”. For Clinical Considerations: removed “While trio sequencing...”; removed “When appropriate, retesting...”; removed “Variant-level reanalysis...”; removed “Case-level reanalysis...”. For Background and Rationale: added “which included the following:”; added “for patients”; added “Of note, ACMG...”; removed “In regards to repeat exome sequencing...”; removed “UpToDate...”; removed “Rapid Genome Sequencing...”; added “Traditional genetic testing...”; added “Reanalysis of Whole Exome Sequencing Data...”; added “Rapid Exome Sequencing...”; for Standard Genome Sequencing: added “A 2021 revision...”; removed “Sequencing may be performed...”; removed “(section E.6); added “Abul-Husn, et al...”; added “Chung, et al...”; added “Patient-centered Laboratory...”; added “National Society of Genetic Counselors...”; added “Rehm et al (2023)...”. For Rapid Genome Sequencing: removed “(p.3)”; added “Rehm et al (2023)...”.</p>		
<p>Added CPT codes 0425U, 0426U to the policy reference table and criteria for Rapid Genome Sequencing.</p>	11/23	
<p>Semi-annual review. Updated title to reflect V2.2024 version. In Reanalysis of Exome or Genome Sequencing Data criteria, expanded to allow a path to approval for patient to get reanalysis prior to 18 months if they have new qualifying findings (supported by PLUGS). In Standard Exome Sequencing criteria, minor expansion in coverage in response to client feedback to remove burdensome criteria and better align with guidelines (e.g., bilateral sensorineural hearing loss of unknown etiology plus one other eligible clinical finding is now covered under the policy). In Standard Exome Sequencing criteria, minor restriction - changed developmental delay definition to “global developmental delay” based on medical director feedback and to be consistent with guidelines. In Rapid Exome Sequencing criteria, minor expansion in coverage in response to client feedback to remove burdensome criteria and better align with guidelines (e.g., bilateral sensorineural hearing loss of unknown etiology plus one other eligible clinical finding is now covered under the policy). In Rapid Exome Sequencing criteria, removed “diagnosed at any age” from unexplained epilepsy criteria statement, since rapid exome sequencing is only appropriate for individuals 12 months of age or younger. Removed “intellectual disability” and “autism” from criteria set, since rapid exome sequencing is only appropriate for individuals 12 months of age or younger and these cannot be diagnosed until an older age Minor restriction - changed developmental delay</p>	04/24	04/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
<p>definition to “global developmental delay” based on medical director feedback and to be consistent with guidelines. In Standard Genome Sequencing criteria, minor expansion in coverage in response to client feedback to remove burdensome criteria and better align with guidelines (e.g., bilateral sensorineural hearing loss of unknown etiology plus one other eligible clinical finding is now covered under the policy). In Standard Genome Sequencing, minor restriction - changed developmental delay definition to “global developmental delay” based on medical director feedback and to be consistent with guidelines. In Rapid Genome Sequencing criteria, minor expansion in coverage in response to client feedback to remove burdensome criteria and better align with guidelines (e.g., Epileptic encephalopathy is now an eligible clinical finding covered under the policy). In Reanalysis of Exome or Genome Sequencing Data criteria, criteria set name changed (formerly “Reanalysis of Whole Exome Sequencing Data”). Minor rewording for clarity throughout. Coding, reference-table, background and references updated.</p>		

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and

accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

**Note: For Medicaid member/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare member/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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