Today’s Attendance URL and QR code:

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Reminder: Questions

- Type your questions into the “Q&A” box
- Monitored by committee members
  - Will verbally answer as many as time allows (at the end)
  - May receive a typed answer through the Q&A box from a committee member
  - Unanswered questions will be saved for consideration during the March 12 Q&A webinar

CNV Interpretation and Reporting

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ACMG TECHNICAL STANDARDS

Genetics in Medicine

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Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen)

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Erin Rooney Riggs, MS, CGC[1], Erica F. Andersen, PhD[2,3], Athena M. Cherry, PhD[4], Sibel Kantarci, PhD[5], Hutton Kearney, PhD[6], Ankita Patel, PhD[7], Gordana Raca, MD, PhD[8], Deborah I. Ritter, PhD[9], Sarah T. South, PhD[10], Erik C. Thorland, PhD[6], Daniel Pineda-Alvarez, MD[11], Swaroop Aradhya, PhD[4,11] and Christa Lese Martin, PhD[1]

Postnatal – first-tier approach for the evaluation of individuals with intellectual disability, developmental delay, autism spectrum disorder, and/or multiple congenital anomalies

Prenatal – evaluation of fetuses with structural anomalies observed by ultrasound

Genome-wide Interpretation of CNVs

- Many recurrent CNVs have been well-characterized
- But… most CNVs are unique
- Accurate clinical interpretation and appropriate use in clinical care requires *consistent methods* of evaluating the genomic content of a CNV region and correlating clinical findings with those reported in the medical literature – DEL & DUP SCORING METRICS
- GOAL – to produce consistent, evidence-based clinical classification and reporting *across* laboratories

Genome-wide Interpretation of CNVs

- Scoring metrics help guide which pieces of evidence to evaluate and how to weigh them towards classifying a CNV:
    - Genomic content
    - Dosage sensitivity
    - Predicted functional effect
    - Clinical overlap with patients in the medical literature
    - Case/control data
    - Inheritance patterns

Why is standardization important?

- Inconsistency among laboratories can create confusion for clinicians and patients, leaving them unable to confidently use genetic information to manage health care decisions

- Using consistent terminology in clinical reporting facilitates unambiguous communication of clinical significance throughout the medical community

Why is standardization important? EXAMPLE

17q12 deletion:

- if classified as VUS instead of pathogenic, just because a patient doesn't have a diagnosis of autism, one of the common phenotypes observed with this deletion, the opportunity is missed to check for renal issues and MODY, other clinical conditions caused by this deletion

- a laboratory should not take the standpoint of "reporting the finding as pathogenic if the CNV matches a given phenotype, but not reporting it as pathogenic if the phenotype doesn't match" – *there is still evidence that the 17q12 deletion is a pathogenic variant*

The 5 CNV Classification Categories

- Pathogenic
- Likely Pathogenic
- Variant of Uncertain Significance (VUS)
- Likely Benign
- Benign

The 5 CNV Classification Categories

- Pathogenic
- Likely Pathogenic
- Variant of Uncertain Significance (VUS)
- Likely Benign
- Benign

These are the standardized classification categories that <u>should</u> be used. Using other terms only causes confusion for clinicians and families – additional information can be provided in the text to further explain the result.

Example text from actual clinical report:

RESULT:
Only includes ISCN nomenclature – no variant classification

Section 1:
Neither of these individual's parents carries the variant in ##### previously reported to be of unknown clinical significance. Presuming the parents are asymptomatic, this variant is likely to be a disease-associated aberration responsible for this individual's symptoms. *IS THIS LIKELY PATHOGENIC OR PATHOGENIC?*

Section 2:
CMA of this individual revealed a loss on chromosome #####. The size of the deletion is approximately 1.6 Mb and includes 2 genes. The significance of this variant is unknown. A list of genes located within this region is on page 2. *OR VUS?*

CNV Reporting Criteria

- Cytogenetic location (chromosome number and band designation)
- CNV size and genomic coordinates (minimum coordinates – maximal may also be provided; specify genome build)
- Copy number state with mechanism specified, if known
- Intragenic CNVs may be described using ISCN (if detected via CMA) or HGVS nomenclature (if detected via NGS)

CNV Reporting Criteria – Additional Information

- Description of criteria used for inclusion of CNV in report
  - CNV size
  - classification type (e.g., may not report benign or only report LP/P for prenatal)
- Classification of CNV
  - encourage inclusion of the evidence that led to the final classification for each CNV

CNV Reporting Criteria – Additional Information

EXAMPLE – Inclusion of Evidence on Report

Duplication of 22q11.21:

- includes triplosensitive region with dosage sensitivity score of 3
- can specifically list on report:
  Evidence for Classification: Category 2A, 1.0 points = Pathogenic
- *Anyone reading the clinical report should be able to follow the logic that was used in evaluating and scoring the evidence to come up with the final clinical classification*

CNV Reporting Criteria – Prenatal Testing

- The CNV (del and dup) metrics and evaluation process should be used in the same manner for prenatal and postnatal testing.
- Laboratories offering prenatal CNV testing should clearly outline which CNVs they will report, for example:
    - Only likely pathogenic or pathogenic variants
    - Only variants larger than a specific size threshold

Secondary or Incidental Findings

- During the course of clinical testing, a CNV may be identified that is unrelated to the patient's reason for referral, but is medically relevant
  - **Secondary Finding**: CNV includes a gene listed on the ACMG SF list Curated by ClinGen Dosage Sensitivity Curation Working Group: https://dciw.clinicalgenome.org/acmg.shtml
  - **Incidental Finding** : gene/region not included on the ACMG SF list, and is unrelated to the patient's reason for referral, but has clear medical relevance for the patient's care.

- Recommendation that any LP/P CNVs be reported in these genes – *be sure to consider the mechanism for pathogenicity*

Uncoupling CNV Classification from Clinical Presentation

- CNV classification should be performed *independent* from determining how it contributes to the diagnosis of the individual in whom it is discovered
- Uncoupling CNV classification from the clinical features reported in the proband is key to objective and consistent interpretation of genomic variants
- While the phenotype of the proband should be taken into account when assessing evidence supporting the pathogenicity of a CNV, classification should not be solely driven by the presentation of the patient under investigation (without consideration of other available evidence)

Uncoupling CNV Classification from Clinical Presentation - EXAMPLE

- Compelling evidence exists in the literature that deletion of Gene X results in Disease X
- Laboratory evaluating a deletion of this gene is able to reach 0.99 points using the scoring metric = Pathogenic classification
- BUT – the patient does NOT currently have features of disease X
- The laboratory should NOT disregard all previously collected evidence and classify the variant as “uncertain” solely because the patient did not display features of Disease X

Uncoupling CNV Interpretation – Prenatal Testing

- For prenatal CNV interpretation, the same principles as postnatal classification should be followed.
- It is important to remember – we are evaluating the classification of the variant uncoupled from the clinical features reported in the prenatal case
- All phenotypes are not able to be ascertained prenatally (e.g., autism) – however, just because of this limitation, the variant should not be called a VUS; if the evidence for the VARIANT is pathogenic, then the classification for a prenatal case should be pathogenic

Uncoupling: X-linked Disorders

- Gene on the X chromosome has substantial evidence for being disease-causing via a loss of function mechanism
- Therefore, deletions involving this gene should receive a classification of Pathogenic - whether observed in hemizygous male or heterozygous female
- Within the report, the laboratory should classify such a variant as Pathogenic, and then explain the potential consequences of such a deletion for the patient under study:

  Male proband – variant could be diagnostic finding

  Female proband – variant could represent carrier status (reproductive risk); could also be affected female – need clinical correlation

Uncoupling: X-linked Disorders

- A study by Riggs et al. (Hum Mut 2018) that examined discrepancies in CNV classifications in ClinVar revealed:
  - Variants involving the X chromosome represented almost 20% of conflicts flagged that overlapped known dosage sensitive genes
  - Of these, 85% were due to inconsistencies in the way variants observed in female patients were classified (from benign to pathogenic)

Uncoupling: Autosomal Recessive Disorders

- Detection of some CNVs, particularly deletions, will indicate carrier status for recessive disorders
- These variants should be reported as Pathogenic – based on the consequences of the variant itself
- A further description of the clinical impact of the variant in the proband being tested can then be provided in the report to explain that *two* Pathogenic variants are needed to cause this *recessive* disorder
- If the proband has clinical features consistent with the recessive disorder, the laboratory should recommend further molecular testing for the disorder in an effort to identify the second disease-causing variant.

Dividing the Clinical Report into Sections

- To make laboratory reports easier to read for users of the laboratory and alert them to follow up is needed, it is recommended that reports be divided into sections:
  - Describe primary variants considered relevant to the stated reason for referral first – and separately from other findings
  - Describe other variants that represent secondary findings, incidental findings, or carrier status
  - Laboratories can decide if other subcategories are needed

Recommendation for appropriate clinical follow-up

- The laboratory should include recommendations for:
  - any necessary further cytogenetic characterization of the CNV
  - genetic counseling
  - evaluation of relevant family members
  - continued surveillance of the medical literature and variant databases if the CNV was reported as a variant of uncertain significance

Example Reports

Case 1

Single CNV as diagnosis

Reason For Referral (RFR): Jane Doe is 9 year old female referred for autism spectrum disorder.

Report Summary: A PATHOGENIC 1.4 Mb deletion of 3q11.2 involving 10 protein-coding genes, including Gene X, was identified. Heterozygous loss of function (LOF) variants in Gene X have been identified in individuals with neurodevelopmental disorders, such as developmental delay, intellectual disability, and autism (see discussion of Gene X below for more detailed information). THIS FINDING IS BELIEVED TO BE CAUSATIVE OF THIS INDIVIDUAL'S CLINICAL FINDINGS. Genetic counseling is recommended.

Copy Number Variation (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:

This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	***Disease***	***Mode of Inheritance***	***Relevance Category***	***Notes***
Gene X	Neurodevelopmental Disorder (NDD)	AD	Related to RFR	This finding is thought to be causative for the reported RFR. Genetic counseling is recommended.

Gene X

Include a more detailed description of Gene X and its relationship to Neurodevelopmental Disorder 1, including any appropriate references. Describe the evidence supporting Gene X that led the CNV to classified as Pathogenic.

Case 2

Incidental Finding Only

Reason For Referral (RFR): Jane Doe is 9 year old female referred for developmental delay and autism spectrum disorder.

Report Summary: This test did not identify any variants that can explain the patient's reported clinical features at this time. However, a PATHOGENIC 1.4 Mb deletion of 3q11.2 involving 10 protein-coding genes, including Gene Y, was identified. Heterozygous loss of function (LOF) variants in Gene Y have been identified in individuals with autosomal dominant progressive sensorineural hearing loss (see discussion of Gene Y below). Jane Doe was not reported to have hearing loss; this may represent an incidental finding, or a cause for a phenotype that was not reported or that may be observed in the future. Clinical correlation and genetic counseling are recommended.

Copy Number Variant (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:

This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Gene Y	Progressive sensorineural hearing loss (SNHL)	AD	Incidental Finding	Though Jane Doe was not reported to have hearing loss, she is thought to be at risk to develop hearing loss given this finding. Clinical correlation and genetic counseling are recommended.

Gene Y

Include a more detailed description of Gene Y, its relationship to progressive sensorineural hearing loss, and the evidence leading to the classification, including any appropriate references.

Other genes included in this deletion are: Gene A, Gene B, Gene C, Gene D, Gene E, Gene F, Gene G, Gene H, and Gene X. [*Optional. If the gene list is extensive, the laboratory may not wish to note them all. May include any other relevant information, links, etc. regarding the other genes in the interval.*]

Case 3

Carrier Status Only

Reason For Referral (RFR): Jane Doe is 9 year old female referred for developmental delay and autism spectrum disorder.

Report Summary: This test did not identify any variants that can explain the patient's reported clinical features at this time. However, a PATHOGENIC 1.4 Mb deletion of 3q11.2 was identified involving GeneZ, a gene associated with an autosomal recessive condition, Disease 1. This finding indicates that Jane Doe is at least a CARRIER for Disease 1. Note that this variant alone is insufficient to cause autosomal recessive Disease 1. Clinical correlation is recommended; if warranted, consider additional testing to determine a genetic etiology for the stated reason for referral and/or to identify a second variant in Gene Z. Genetic counseling is also recommended.

Copy Number Variant (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:

This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Gene Z	Disease 1	AR	Carrier status	This variant alone is *insufficient* to cause disease; a second pathogenic variant on the opposite allele (*in trans*) is required. This finding alone DOES NOT explain the patient's reported phenotype. Clinical correlation is required to determine if additional testing is warranted.

Gene Z

Include a more detailed description of Gene Z, its relationship to Disease 1, and the evidence leading to the classification, including any appropriate references.

Other genes included in this deletion are: Gene A, Gene B, Gene C, Gene D, Gene E, Gene F, Gene G, Gene H, and Gene X. [*Optional. If the gene list is extensive, the laboratory may not wish to note them all. May include any other relevant information, links, etc. regarding the other genes in the interval.*]

Case 4

CNV with multiple genes:
Single gene as diagnosis, with two additional genes with pathogenic findings unrelated to referral

Reason For Referral (RFR): Jane Doe is 9 year old female referred for autism spectrum disorder.

Report Summary: A PATHOGENIC 1.4 Mb deletion of 3q11.2 involving 10 protein-coding genes, including Gene X, was identified. Heterozygous loss of function (LOF) variants in Gene X have been identified in individuals with neurodevelopmental disorders, such as developmental delay, intellectual disability, and autism (see discussion of Gene X below for more detailed information). THIS FINDING IS BELIEVED TO BE CAUSATIVE OF THIS INDIVIDUAL'S CLINICAL FINDINGS. Genetic counseling is recommended.

This deletion also includes Gene Y. Heterozygous loss of function variants in Gene Y have been identified in individuals with autosomal dominant progressive sensorineural hearing loss (see discussion of Gene Y below for more detailed information). Jane Doe was not reported to have hearing loss; this may represent an incidental finding, or provide a cause for a phenotype that was either not reported or may be observed in the future. Clinical correlation is recommended.

This deletion also includes Gene Z. Biallelic loss of function variants in Gene Z have been identified in individuals with Disease 1, an autosomal recessive condition. This finding indicates that Jane Doe is at least a carrier for Disease 1. Note that this variant alone is insufficient to cause Disease 1 (see discussion of Gene Z below for more detailed information). Clinical correlation is recommended to determine if additional testing to identify a second pathogenic variant in Gene Z is warranted.

Copy Number Variation (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Gene X	Neurodevelopmental Disorder (NDD)	AD	Related to RFR	This finding is thought to be causative for the reported RFR. Genetic counseling is recommended.
Gene Y	Progressive sensorineural hearing loss (SNHL)	AD	Incidental Finding	Though Jane Doe was not reported to have hearing loss, she is thought to be at risk to develop hearing loss given this finding. Clinical correlation is recommended.
Gene Z	Disease 1	AR	Carrier Status	This variant alone is insufficient to cause Disease 1. A second pathogenic variant on the opposite allele (*in trans*) is necessary to cause disease. Clinical correlation is required to determine if additional testing is warranted.

Gene X
Include a more detailed description of Gene X and its relationship to Neurodevelopmental Disorder 1, including any appropriate references. Describe the evidence supporting Gene X that led the CNV to classified as Pathogenic.

Gene Y
Include a more detailed description of Gene Y and its relationship to progressive sensorineural hearing loss, including any appropriate references.

Gene Z
Include a more detailed description of Gene Z and its relationship to Disease 1, including any appropriate references.

Other genes included in this deletion are: Gene A, Gene B, Gene C, Gene D, Gene E, Gene F, and Gene G. [*Optional. If the gene list is extensive, the laboratory may not wish to note them all. May include any other relevant information, links, etc. regarding the other genes in the interval.*]

Case 5

CNV with multiple genes:
Single gene pathogenic – incidental finding, additional gene with unclear relationship to reason for referral

Reason For Referral (RFR): Jane Doe is 9 year old female referred for autism spectrum disorder.

Report Summary: **This test did not identify any variants that can explain the patient's reported clinical features at this time.** However, a PATHOGENIC 1.4 Mb deletion of 3q11.2 involving 10 protein-coding genes, including *Gene X*, was identified. Heterozygous loss of function (LOF) variants in *Gene X* have been identified in individuals with hereditary breast and ovarian cancer (see discussion of *Gene X* below for more detailed information). Jane Doe was not reported to have cancer; this may represent an incidental finding, or a cause for a phenotype that was not reported or that may be observed in the future. Clinical correlation and genetic counseling are recommended.

This deletion also includes Gene Y. At this time, heterozygous loss of function variants in Gene Y have been identified in 2 individuals with intellectual disability; it is questionable whether these variants are truly causative of their phenotypes (see discussion of Gene Y below for more detailed information). At this time, there is insufficient evidence to say with certainty that loss of this gene is a cause for Jane Doe's autism spectrum disorder. Clinical correlation is recommended to determine if additional testing is warranted to further investigate genetic etiologies for her autism spectrum disorder.

Copy Number Variation (CNV): 1.4 Mb 3q11.2 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 3q11.2 (XXXXXXX-XXXXXXX) x 1	Deletion	1.4 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes 10 protein-coding genes, including the following, which are relevant to this report:

Gene	***Disease***	***Mode of Inheritance***	***Relevance Category***	***Notes***
Gene X	Hereditary Breast and Ovarian Cancer	AD	Incidental Finding	Though Jane Doe was not reported to have cancer, she is thought to be at risk to develop cancer given this finding. Clinical correlation is recommended.
Gene Y	Reports of variants in individuals with intellectual disability; insufficient evidence to confirm gene-disease relationship	Possible AD; Insufficient Evidence to confirm mode of inheritance	Related to RFR	There is insufficient evidence to confirm a relationship between loss of Gene Y and neurodevelopmental disorders. At this time, this finding is not believed to be causative of Jane Doe's RFR; consider additional testing to investigate other genetic etiologies. See discussion of Gene Y below for detailed information.

More detailed gene information

Gene X
Include a more detailed description of Gene X and the evidence supporting its relationship to Hereditary Breast and Ovarian Cancer, including any appropriate references. Describe the evidence supporting Gene X that led the CNV to classified as Pathogenic.

Gene Y
Heterozygous loss of function (LOF) variants in Gene Y have been reported in two unrelated individuals with intellectual disability (Reference 1). Both variants were identified following targeted Sanger sequencing of Gene Y in a cohort of individuals with intellectual disability. Variant 1 was identified in Proband 1; the authors do not specify if any other testing was performed on the proband to rule out other potential causes of intellectual disability, and no inheritance information was provided. Variant 1 is not present in gnomAD. Variant 2 was identified in Proband 2; the authors report that this individual had previously had negative Fragile X repeat analysis. The variant was said to be de novo, but is present in 6/123456 alleles from the European non-Finnish population in gnomAD. No other variants in this gene have been reported in the literature. Based on this information alone, there is insufficient evidence to suggest that loss of Gene Y is associated with neurodevelopmental disorders. This assessment may change over time as additional information becomes available.

Other genes included in this deletion are: Gene A, Gene B, Gene C, Gene D, Gene E, Gene F, and Gene G. [*Optional. If the gene list is extensive, the laboratory may not wish to note them all. May include any other relevant information, links, etc. regarding the other genes in the interval.]*

Include any other relevant report information, such as methods, quality metrics, disclaimers, resources, etc.

Case 6

Pathogenic CNV with low penetrance/variable expressivity *related* to reason for referral

Reason For Referral (RFR): Jane Doe is 9 year old female referred for developmental delay and autism spectrum disorder.

Report Summary: A PATHOGENIC duplication of 22q11.21 was identified. This duplication is approximately 2.5 Mb in size and corresponds to the recurrent 22q11.2 proximal region involving breakpoints A-D. Duplications of this region are associated with LOW PENETRANCE AND VARIABLE EXPRESSIVITY; these duplications have been observed in individuals with neurodevelopmental disorders (references) as well as in apparently normal individuals, even within the same family (see below for additional information). This duplication is likely contributing to Jane Doe's reported phenotype. Clinical correlation is recommended to determine if additional testing is warranted.

Copy Number Variant (CNV): 2.5 Mb 22q11.21 Duplication

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 22q11.21 (18912231_21465672) x3	Duplication	2.5 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes a known recurrent genomic region relevant to this report:

Genomic Region	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Recurrent 22q11.2 proximal region, breakpoints A-D	Neurodevelopmental disorders	AD	Related to RFR; Low penetrance and variable expressivity	Variant known to be associated with neurodevelopmental disorders, but with LOW PENETRANCE and VARIABLE EXPRESSIVITY. Clinical correlation is recommended to determine if additional testing is warranted.

Duplication 22q11.21, proximal regions, breakpoints A-D
Include a more detailed description of duplications of the 22q11.21 proximal region (breakpoints A-D), the evidence supporting this classification, and the spectrum of associated clinical observations, including any appropriate references.

Reason For Referral (RFR): Jane Doe is 9 year old female referred for developmental delay and autism spectrum disorder.

Report Summary: A PATHOGENIC duplication of 22q11.21 was identified. This duplication is approximately 2.5 Mb in size and corresponds to the recurrent 22q11.2 proximal region involving breakpoints A-D. Duplications of this region are associated with LOW PENETRANCE AND VARIABLE EXPRESSIVITY; these duplications have been observed in individuals with neurodevelopmental disorders (references) as well as in apparently normal individuals, even within the same family (see below for additional information). This duplication is likely contributing to Jane Doe's reported phenotype. Clinical correlation is recommended to determine if additional testing is warranted.

ClinGen has established a Low Penetrance Working Group that is working on defining additional "descriptors," such as "low penetrance," that can be added with the 5 primary classification categories

Recurrent 22q11.2 proximal region, breakpoints A-D	Neurodevelopmental disorders	AD	Related to RFR; Low penetrance and variable expressivity	Variant known to be associated with neurodevelopmental disorders, but with LOW PENETRANCE and VARIABLE EXPRESSIVITY. Clinical correlation is recommended to determine if additional testing is warranted.

Duplication 22q11.21, proximal regions, breakpoints A-D
Include a more detailed description of duplications of the 22q11.21 proximal region (breakpoints A-D), the evidence supporting this classification, and the spectrum of associated clinical observations, including any appropriate references.

Case 7

Pathogenic CNV with low penetrance/variable expressivity *unrelated* to reason for referral

Reason For Referral (RFR): Jane Doe is 9 year old female referred for hearing loss.

Report Summary: **This test did not identify any variants that can explain the patient's reported clinical features at this time.** However, a PATHOGENIC duplication of 22q11.21 was identified. This duplication is approximately 2.5 Mb in size and corresponds to the recurrent 22q11.2 proximal region involving breakpoints A-D. Duplications of this region are associated with LOW PENETRANCE AND VARIABLE EXPRESSIVITY; these duplications have been observed in individuals with neurodevelopmental disorders (references) as well as in apparently normal individuals, even within the same family (see below for additional information).

Jane Doe was not reported to have features of a neurodevelopmental disorder; this may represent an incidental finding, or a cause for a phenotype that was not reported. This finding alone DOES NOT diagnose Jane Doe with a specific neurodevelopmental disorder, such as autism; such diagnoses are made based on clinical presentation. Genetic counseling and clinical correlation are recommended to determine the significance of this finding for Jane Doe and her family. Clinical correlation is also recommended to determine if additional testing is warranted to further investigate genetic etiologies for her hearing loss.

Copy Number Variant (CNV): 2.5 Mb 22q11.21 Duplication

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 22q11.21 (18912231_21465672) x3	Duplication	2.5 Mb	*De Novo*	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes a known recurrent genomic region relevant to this report:

Genomic Region	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
Recurrent 22q11.2 proximal region, breakpoints A-D	Neurodevelopmental disorders	AD	Not related to RFR; Low penetrance and variable expressivity	Variant known to be associated with neurodevelopmental disorders, but with LOW PENETRANCE and VARIABLE EXPRESSIVITY. Clinical correlation is recommended to determine if additional testing is warranted.

Duplication 22q11.21, proximal regions, breakpoints A-D
Include a more detailed description of duplications of the 22q11.21 proximal region (breakpoints A-D), the evidence supporting this classification, and the spectrum of associated clinical observations, including any appropriate references.

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