Supplemental Material 4: Example Reports

The following example reports are meant to illustrate how certain concepts might be conveyed on a clinical report, such as:

- A single CNV that represents a cause for the reason for referral, an incidental finding, and is indicative of carrier status (Example Report 1)
- Incidental findings (Example Report 2)
- Carrier status (Example Report 3)
- Variants associated with low penetrance/variable expressivity…
    - …that are seemingly related to the reason for referral (Example Report 4.1)
    - …that are seemingly unrelated to the reason for referral (Example Report 4.2)
- Multiple CNVs observed in a single proband (Example Report 5)
- X-linked findings in a female (Example Report 6)
- A variant classified as "uncertain" that is unlikely to be of clinical relevance (Example Report 7)

Note that several of the examples are populated with generic information ("Gene X," "Disease Y," etc.). In general, this is to keep the focus on the reporting concepts, rather than the underlying data. In other examples, actual well-known genes and genomic regions are used in the hopes that familiarity with the underlying data would help solidify the reporting concept.

These examples are not meant to represent complete reports. For brevity, many important aspects are omitted, such as dates, sample information, test limitations, detailed follow-up recommendations, etc. The wording choices presented here represent suggestions; the clinical laboratory is ultimately responsible for deciding how information is presented on their clinical reports.

Example Report 1: Single CNV involving multiple genes, related to reason for referral, incidental finding, and carrier status

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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.]*

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

Example Report 2: CNV involving multiple genes, unrelated to reason for referral (incidental finding)

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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.]*

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

Example Report 3: CNV involving genes conferring carrier status ONLY

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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.]*

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

Example Report 4.1: CNV associated with low penetrance, matching phenotype

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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.

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

Example Report 4.2: CNV associated with low penetrance, non-matching phenotype

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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	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.

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

Example Report 5: Multiple CNVs

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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

Report Summary: A PATHOGENIC 1.4 Mb deletion at 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.

The 3q11.2 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). Jane Doe was not reported to have hearing loss; this may represent an incidental finding, a cause for a phenotype not reported, or a phenotype not yet observed. Clinical correlation is recommended.

A second copy number variant (CNV), a 350 kb duplication at 5q13.1 was also identified. This CNV is a VARIANT OF UNCERTAIN SIGNIFICANCE; it is unclear at this time what effect (if any) this variant may have on Jane Doe's current or future health. See below for additional information. Genetic counseling is recommended.

Copy Number Variant (CNV) #1: 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

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

Gene Y
Include a more detailed description of Gene Y and its relationship to progressive sensorineural hearing loss, 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, and Gene H. [*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.]*

Copy Number Variant (CNV) #2: 350 kb 5q13.1 Duplication

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 5q13.1 (XXXXXXX-XXXXXXX) x 3	Duplication	350 kb	*De Novo*	Heterozygous	Uncertain Significance

This duplication includes 2 protein-coding genes:

Gene I
Describe any available information about Gene I, the evidence (or lack thereof) leading to the classification, including any appropriate references.

Gene K
Describe any available information about Gene K, the evidence (or lack thereof) leading to the classification, including any appropriate references.

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

Example Report 6: X-linked finding in a female

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

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 maternally inherited, PATHOGENIC 124 kb deletion of Xq21.1 (involving the *ATP7A* gene) was identified. Hemizygous loss of function variants in this gene have been associated with Menkes disease in MALES; as Jane Doe is a FEMALE, this finding likely represents CARRIER STATUS for Menkes disease. Female carriers of pathogenic *ATP7A* variants are typically asymptomatic, though unfavorably skewed X-inactivation could result in clinical findings related to this disorder. Genetic counseling and clinical correlation are recommended to discuss the potential reproductive implications of this finding and to determine if additional testing is warranted to identify a genetic etiology for Jane Doe's hearing loss.

Copy Number Variant (CNV): 124 kb Xq21.1 Deletion

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] Xq21.1 (77226076-77350000) x 1	Deletion	124 kb	Maternal	Heterozygous	Pathogenic

Relevant Genomic Content:
This deletion includes a single gene relevant to this report:

Gene	*Disease*	*Mode of Inheritance*	*Relevance Category*	*Notes*
ATP7A	Menkes disease	X-linked	Carrier Status	Female heterozygous carriers of pathogenic variants in *ATP7A* TYPICALLY DO NOT display overt clinical features of Menkes syndrome, an X-linked condition affecting predominantly males. This finding DOES NOT explain the patient's reported clinical features. Clinical correlation is recommended to determine if additional testing is warranted.

ATP7A
Include a more detailed description of ATP7A, Menkes disease, and the evidence supporting this classification, including any appropriate references.

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

Example Report 7: 17q21.31 dup

Patient Name: Jane Doe
DOB: 01/01/2010
Laboratory ID: 1234567
Test ordered: Chromosomal Microarray

Include any other important header information, such as: relevant dates, additional patient demographics, ordering provider information, sample information, etc.

Reason For Referral (RFR): Jane Doe is 9 year old female. No reason for referral was reported.

Report Summary: This test did not identify any variants of predicted clinical relevance at this time. However, an UNCERTAIN 654 kb duplication at 17q21.31 was identified. This duplication includes 23 protein-coding genes, but, at this time, none of them are known to cause human disease as the result of the presence of an extra copy (triplosensitivity). Please note that the classification of this variant could change over time as additional evidence emerges. Further, because no clinical indication for testing was provided, full clinical correlation could not be performed by the laboratory. Clinical correlation is recommended to determine if additional testing is necessary to identify a genetic etiology for Jane Doe's clinical features.

Copy Number Variant (CNV): 654 kb 17q21.31 Duplication

ISCN	Type	Size	Inheritance	Zygosity	Classification
arr [GRCh37] 17q21.31 (41784108-42438203) x 3	Duplication	654 kb	Unknown; parental testing not performed	Heterozygous	Uncertain

This deletion includes 23 protein-coding genes. At this time, none of the genes in the region have been reported to cause disease when present as an extra copy.

The classification of this CNV is UNCERTAIN at this time per the 2019 ClinGen/ACMG constitutional copy number variant interpretation standards (reference). While this duplication does include protein-coding elements (Category 1A, 0 points), it does not overlap any known dosage sensitive genes/genomic regions (Section 2, all categories, 0 points). Twenty-three protein-coding genes are duplicated (Category 3A, 0 points), but, per literature evaluation, triplosensitivity is not a known mechanism for disease for any of these genes(Categories 4A-K, 0 points). There is no significant case-control or population variant overlap with this duplication (Category 4L-O, 0 points). Finally, no information was provided about the patient's phenotype, her family history, or the inheritance of the observed CNV (Category 5 F, 0 points). The final tallied score is 0 points, which corresponds to a variant classification of UNCERTAIN (0 total points).

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