Children's Hospital of Philadelphia
Division of Genomic Diagnostics

CHOP Genomic Tests: Clinician Information Sheet

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CHOP Medical Exome: Background Information

What is the CHOP Medical Exome?

- The CHOP Medical Exome version 4 (v4) is a next generation sequencing test designed to identify underlying alterations associated with an individual's clinical indication for exome sequencing as indicated by the ordering provider.
- The CHOP Medical Exome focuses on identifying and *reporting potentially diagnostic sequence and copy number variants* that are *highly likely* to underlie the patient's reason for study based on our current understanding of Mendelian genetic disorders. The test does not target variants contributing to disorders with multifactorial inheritance.
- The analysis prioritizes variants that primarily affect exons identified by genomic sequencing based on a combination of molecular characteristics (*e.g.* presence in controls/variant databases, inheritance, variant impact, etc.), zygosity, and clinical information. For information about prior versions of the CHOP Medical Exome, please see Appendix 2.

When should I order the CHOP Medical Exome?

The CHOP Medical Exome is an appropriate clinical test for patients with a complex presentation or those who do not have a clear clinical diagnosis, as well as for patients with phenotypes that could be caused by one of several different genes. It is also a useful diagnostic test for disorders in which a gene or genes have been implicated but for which no targeted clinical diagnostic test is available.

What types of results will be reported on the CHOP Medical Exome?

The results report may include:

- Sequence variants (in the exons and intron/exon borders) or copy number variants involving *known disease genes* that may be associated with the patient's clinical indication for testing. In addition, noncoding disease genes and potential disease-causing variants (as reported in HGMD and ClinVar) in regulatory and deep intronic regions might also be analyzed and reported,
- Sequence or copy number variants involving *candidate genes* that do not yet have a well-established role in genetic disease but are suspected to be potential disease genes based on animal models, functional studies, and/or other evidence,
- Previously reported variants that were detected on a prior CHOP test or a test at an outside laboratory *if* they are prioritized in the bioinformatics pipeline and meet at least one of the following criteria:
  - Overlaps with the patient's current clinical indication for exome
  - Is a clinician-requested *Gene of Interest* in the exome order
- *Optional*: Pathogenic and/or likely pathogenic variants involving genes/conditions on the ACMG secondary findings list, *if* the patient/family member indicates that they want this information on the consent form. See CHOP Medical Exome Secondary and Incidental Findings below for more information about the laboratory's approach to these findings.
- Rarely, incidental findings that are unrelated to the patient's clinical indication and are not on the ACMG secondary findings list, if they are clearly disease-causing and meet the lab's reporting criteria. See CHOP Medical Exome Secondary and Incidental Findings below for more information about the laboratory's approach to these findings.

CHOP Medical Exome: Copy Number Variant Analysis

Does the CHOP Medical Exome include Copy Number Variant (CNV) analysis?

Yes, copy number variant (CNV) analysis was incorporated into the CHOP Medical Exome analysis pipeline in May 2021. The CHOP Medical Exome v4 CNV workflow uses the DRAGEN copy-number variant caller and an in-house pipeline for filtering, annotating, and prioritization.

There are several important things to know about this analysis:

- It is dependent on data quality.
- This analysis excludes CNVs involving regions of the genome that are difficult to sequence and mosaic CNVs. If the CNV is associated with a rearrangement (e.g. unbalanced translocation or marker chromosome), follow-up studies will still be needed to identify or confirm their presence.
- The reporting of CNVs on the exome is based on the likelihood it is contributing to the patient's reason for study.

CNV analysis is attempted on all exome cases analyzed with the exome v4 pipeline, and reportable CNVs will be included in the results report, once they are confirmed with another molecular methodology (if necessary). If CNV analysis cannot be performed, it will be noted in the overall summary of the report.

How does copy number variant analysis and reporting differ between the CHOP Medical Exome and other CHOP tests?

As with sequence variants detected on exome, CNVs will only be reported if they involve a *disease or candidate gene* that o*verlaps with the patient's clinical indication* or if they meet incidental findings criteria. Thus, reporting may differ from other tests. Unlike on the CHOP chromosomal SNP microarray, CNVs will not be reported based on size criteria; certain findings that would be reported on SNP microarray will not be reported on exome, including:

- Recurrent CNVs associated with phenotypes with low penetrance and variable expressivity, unless they have strong overlap with patient phenotype
- CNVs that do not involve known disease or candidate genes, even if relatively large (*e.g.*, >200 kb)
- Pathogenic findings that do not overlap phenotype or meet incidental findings criteria
- Heterozygous variants involving genes associated with autosomal recessive disease, unless there is clear overlap with the patient's reason for study.

For a more detailed comparison of differences in reporting between the CHOP chromosomal SNP microarray, targeted panels, and exome, see the table in Appendix 1 below.

My patient had a copy number variant of uncertain significance (VOUS) detected on chromosomal SNP microarray, and parental testing was recommended. Can the parental testing for the CNV be performed as a part of the exome analysis?

When follow up parental testing of a copy number VOUS is recommended on the SNP microarray report, this testing should typically be performed via the SNP microarray, rather than exome. This approach helps ensure similar data quality, coverage, analysis, and reporting. In addition, unlike the CHOP chromosomal SNP microarray, exome analysis is not validated to detect mosaicism, which could be relevant for

recurrence risk assessment. Note: If CHOP SNP microarray analysis was performed more than 6 months ago, please contact the laboratory to confirm that parental testing is still needed for variant interpretation prior to submitting parental samples.

Are there circumstances in which copy number analysis will not be performed?

Occasionally, copy number variants may not be analyzed due to data quality issues. If typical CNV analysis is unable to be completed, it will be noted in the report. For cases with suboptimal data quality, abbreviated analysis can often exclude the presence of larger multigenic CNVs, such as those that would be detectable on chromosomal SNP microarray, but it cannot rule out the presence of smaller CNVs. Please contact the laboratory to discuss questions or recommendations for additional copy number analysis for your patient.

What are the limitations of copy number variant analysis on the CHOP Medical Exome?

Certain types of copy number variants and chromosomal abnormalities may not be detected in Next Generation Sequencing (NGS) data, including:

- Specific sex chromosome abnormalities
- Small copy number changes (especially those <1kb in size, and/or involving the first coding exon or only part of an exon)
- Copy number changes involving genes with pseudogenes or high homology to other regions of the genome, such as *STRC* and *CYP21A2*
- Mosaicism
- Balanced structural rearrangements, or structural rearrangements associated with a CNV

Will copy number variant analysis include analysis of the genes/conditions on the ACMG's secondary finding list?

Yes, the laboratory will look for and report copy number variants involving the genes/conditions on the ACMG's secondary finding list if the patient/family *opts in* to this analysis. In rare cases, a copy number variant involving a gene on the secondary findings list may be reported in a patient who completely *opted out* of this analysis if the CNV also involves a gene that is related to the patient's clinical indication. See the section on CHOP Medical Exome Secondary and Incidental Findings below for more information about the laboratory's approach to these findings.

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DGD-GDL Next Generation Sequencing Test Options and CPT Codes

The Division of Genomic Diagnostics' Genomic Diagnostic Laboratory (DGD-GDL) offers multiple next generation sequencing tests that vary in their scope, requirements for written consent, analysis/reporting practices, and options for secondary findings analysis.

What is the difference between the various CHOP genomic tests?

1. CHOP Medical Exome v4 (https://www.testmenu.com/chop/Tests/785130)
   - Scope: Genomic sequencing with analysis of exons (protein-coding portions) and intron/exon boundaries of nuclear genes. In addition, noncoding disease genes and potential disease-causing variants (HGMD and ClinVar) in regulatory and deep intronic regions might also be analyzed and reported
   - Written consent: Required for proband & family members
   - Analysis/Reporting:
     - Sequencing variants and copy number variants will be reported on the CHOP Medical Exome v4
     - Variant filtration/reporting based on pathogenicity predictions and overlap with patient phenotype
     - Secondary findings analysis (*optional*)
     - It is encouraged to submit family members (preferred: father and mother) as part of a 'Trio' exome analysis for an improved diagnostic yield.
   - For information about prior versions of the CHOP Medical Exome, please see Appendix 2.

2. CHOP Medical Exome v4 + MitoGenome Combined Test (https://www.testmenu.com/chop/Tests/947051)
   - Scope: Genomic sequencing with analysis of exons and intron/exon boundaries of nuclear genes. In addition, noncoding disease genes and potential disease-causing variants (as reported in HGMD and ClinVar) in regulatory and deep intronic regions might also be analyzed and reported. MitoGenome includes full sequencing and deletion analysis of the mitochondrial genome (mtDNA) with heteroplasmy calculation.
   - Written consent: Required for proband & family members (CHOP Medical Exome v4 portion only)
   - Analysis/Reporting (Test results reported separately)
     - CHOP Medical Exome v4 (see above)
       - Secondary findings analysis (*optional*)
     - MitoGenome
       - All variants classified as variants of uncertain significance or higher are reported, including heteroplasmy.
       - Submission of a maternal family member sample (via the Maternal Relative Exome + MitoGenome Combined Test Epic order) can be used to assess pathogenicity of potentially reportable variants identified in the mitochondrial genome.

3. CHOP Medical Exome Reanalysis (https://www.testmenu.com/chop/Tests/912524)
   - Scope: Genomic sequencing and copy number analysis of exons and intron/exon boundaries of nuclear genes. In addition, noncoding disease genes and potential disease-causing variants (as reported in HGMD and ClinVar) in regulatory and deep intronic regions might also be analyzed and reported. Reanalysis uses either the Exome v3 or Exome v4 bioinformatic pipeline to reanalyze

CHOP exome data that was previously obtained on the original proband. See below for more details.

- Ordering:
  - CHOP Medical Exome Reanalysis should be considered for individuals who have had the CHOP Medical Exome signed out more than one year prior to ordering the reanalysis and/or has a significantly different indication for study compared to the initial exome analysis (e.g. a newly emerging phenotype)
  - Exome reanalysis for exomes ordered before February 8, 2023 (v1, v2, and v3) will utilize the Exome v3 bioinformatic pipeline
  - Exome reanalysis for exomes ordered after February 8, 2023 (v4) will utilize the Exome v4 pipeline
  - Exome reanalysis for exomes ordered before February 8, 2023 (v1, v2, and v3) will not be available on the Exome v4 bioinformatic pipeline. If exome analysis on a v1, v2, or v3 exome is desired using the Exome v4 bioinformatic pipeline, the CHOP Medical Exome v4 will need to be authorized and ordered.
- Written consent:
  - Required for probands
  - Required for family members who originally consented before 12/8/2020 or who want secondary findings (regardless of date of initial consent). ***Please contact the lab if a family member that was part of the original analysis (performed prior to 12/8/20) is no longer available to provide consent.***
- Analysis/Reporting
  - Analysis and reporting will follow the CHOP Medical Exome v4 outline (see above) or the v3 analysis and reporting structure. For prior CHOP Medical Exome versions, see Appendix 2.
  - Secondary findings analysis (*optional*)
  - Family members who were not sequenced as part of the proband's original CHOP Medical Exome can be submitted for Sanger confirmation as part of the reanalysis but will not undergo full sequencing.

4. Disease/Phenotype Slice Panels

- Scope: Genomic sequencing with analysis of exons and intron/exon boundaries of nuclear genes with targeted analysis and reporting of sequence and copy number variants of specific genes known to cause the disease/phenotype of interest
  - Some panels have additional test components.
  - Family member analysis is not available for any Disease/Phenotype Slice Panel.
- Ordering: Please see test menu for specific panel information including CPT codes, genes, and turnaround time.
- Written consent: Not required for proband
- Analysis/Reporting: Secondary findings analysis NOT available

5. CHOP Medical Exome v4 from Disease/Phenotype Slice Panel

(https://www.testmenu.com/chop/Tests/1025370)

- Scope: Sequence and copy number analysis of the exons and intron/exon boundaries of nuclear genes in the existing genomic data from the previously performed slice panel(s) performed after February 8, 2023 (without needing to re-sequence the patient's DNA).

- Limitation: Next generation sequencing panels performed prior to February 8, 2023 cannot have a CHOP Medical Exome v4 run without re-sequencing the patient's DNA. Contact the lab for more information.
- Written consent: Required for proband & family members
- Analysis/Reporting:
  - CHOP Medical Exome v4 (see above)
  - Secondary findings analysis (*optional*)
  - It is encouraged to submit family members (preferred: father and mother) as part of a 'Trio' exome analysis for an improved diagnostic yield.
    - Family members can only be included in the full exome analysis if the original exome-based panel was ordered after February 8, 2023.

What CPT code(s) should I authorize? CPT codes for the most frequently ordered tests are below. For CPT codes for our disease/phenotype slice panels please reference the test menu. Please contact the lab if you need additional information.

Test and family structure		Order Name	CPT Code(s) for Proband
Exome Analysis	Proband Only	- CHOP Medical Exome v4	81415x1
	Trio (Proband & 2 parents)	- CHOP Medical Exome v4 - Exome v4, Family Member *(in both parents' charts)*	81415x1; 81416x2
Exome & MitoGenome	Proband Only	- CHOP Medical Exome v4 + MitoGenome Combined Test	81415x1, 81460x1, 81465x1
	Trio (Proband & 2 parents)	- CHOP Medical Exome v4 + MitoGenome Combined Test (in the proband's chart) - Exome v4, Family Member *(in the father's chart)* - Maternal Relative Exome v4 + MitoGenome Combined Test *(in the mother's chart)*	81415x1, 81460x1, 81465x1, 81416x2
Exome Reanalysis	Proband Only	- CHOP Medical Exome v4 Reanalysis	81417x1
	Trio (Proband & 2 parents)*	- CHOP Medical Exome Reanalysis (in the proband's chart) - Exome Reanalysis, Family Member *(in both parents' charts)*	81417x1 (No separate charge for reanalysis of family member)
Exome Analysis from Panel	Proband Only	- CHOP Medical Exome v4 from Panel	81415x1
	Trio (Proband & 2 parents)*	- CHOP Medical Exome v4 from Panel (in the proband's chart) - Exome v4, Family Member *(in both parents' charts)*	81415x1; 81416x2

*New family members (who did not undergo exome sequencing with the original exome order) can only be submitted for Sanger sequencing (via the DNA Extraction order). Please contact DGDGeneticCounselor@chop.edu to discuss the options for testing additional family members.

CHOP Medical Exome: Ordering Considerations and Background

Who can I contact for more information about CHOP next generation sequencing tests or help with obtaining insurance approval and/or informed consent?

- The Division of Genomic Diagnostics-Genomic Diagnostic Laboratory (**DGD-GDL) Genetic Counseling Core** (DGDGeneticCounselor@chop.edu or 267-426-1447) can help address general test-related questions, including turn-around-time, test benefits/limitations, and reporting practices.
- The **Roberts Individualized Medical Genetics Center (RIMGC)** of the CHOP Division of Human Genetics sees and evaluates patients to facilitate access to complex genetic testing at CHOP, including assisting with insurance authorization, test selection/ordering, providing pre- and post-test genetic counseling, detailed phenotyping, obtaining informed consent, and return of results. The RIMGC can be reached at 267-426-7418 (or CHOP pager: 14642). For more information, visit: https://www.chop.edu/centers-programs/individualized-medical-genetics-center-imgc

What if my patient is in the clinic, but I don't have insurance authorization approval, or they are not prepared to complete the consent process?

Please place an order in Epic for **'DNA Extraction'** for the proband and any family members also present who will be included in the analysis. This will allow the patient/family members to have blood drawn and DNA extracted at no charge. Once the authorization is approved and the patient/family has signed consent, please place the order for the exome test (see below).

If I placed 'DNA Extraction' and have now obtained authorization and consent, what do I do next?

Please place the order in Epic, choose "Specimen in Lab" as the order class, match the specimen type and source with the DNA Extraction order, AND email DGDGeneticCounselor@chop.edu to let us know to initiate the analysis.

What if my patient is critically ill and the parents are not available/able to consent for the CHOP Medical Exome?

If the patient is critically ill and the parents are not available/able to consent at the time that the genomic testing needs to be ordered, please submit the order in Epic and select the consent attestation option indicating that the patient is critically ill. Contact the lab (267-426-1447; DGDGeneticCounselor@chop.edu) to alert us that there is a case that will need to be triaged. We will work with you to determine the appropriate course of action for testing. We will contact clinicians at ~14 days to notify them of any missing samples/consents. If consent for the proband is not obtained within 30 days of ordering, the test will be cancelled.

What will happen to the proband testing if all expected family members are not received?

Ideally, all samples for a genomic test should be submitted at the time of the proband order. If a family member's sample is being collected separately (*e.g.* a saliva sample is being sent to the lab), proband testing will only be held for **30 days**. We will contact clinicians at ~14 days to notify them of any missing samples. After 30 days, testing will proceed with the samples in the lab and additional family members cannot be added to the analysis structure. If parental samples are received while the analysis is in progress, they may be used for Sanger confirmation.

What sample types are accepted?

Preferred: 2-3mL whole blood in EDTA (purple-top) tube, minimum amount 1mL
Also accepted: saliva*, DNA extracted by a CLIA-certified lab (3µg at concentration 5µg/µL)

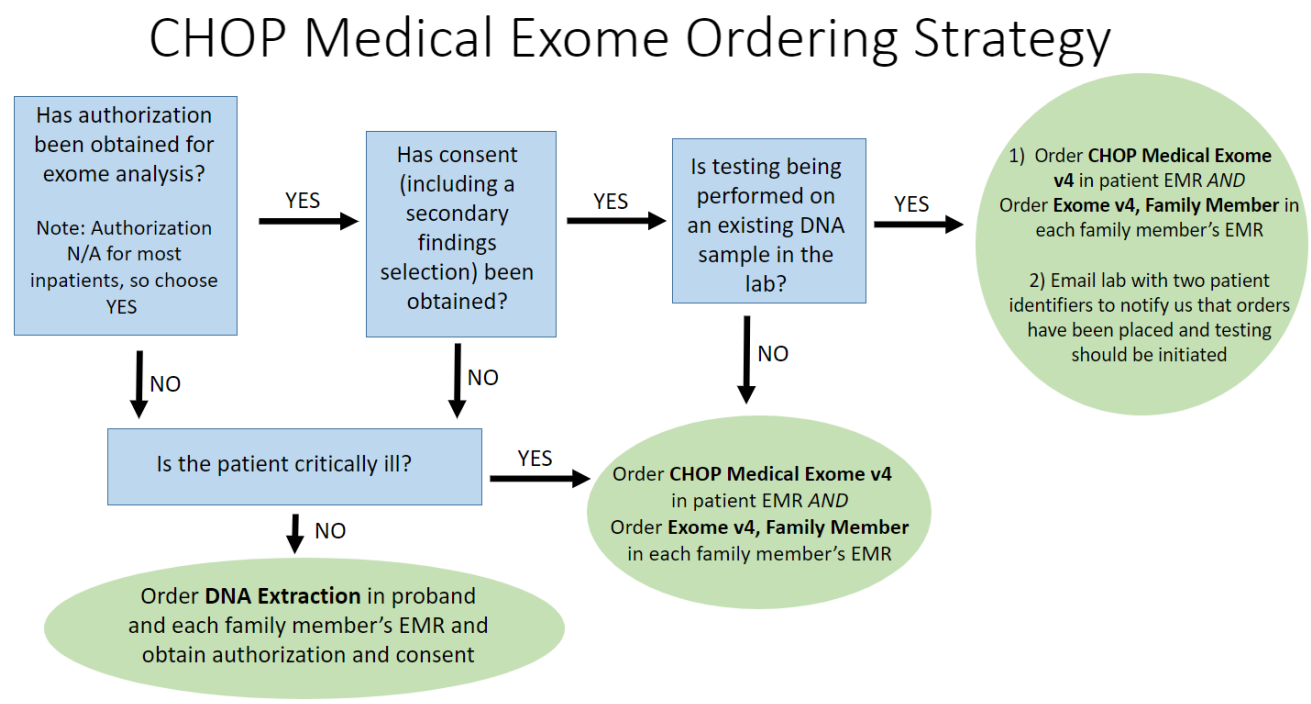
* To request saliva collection kits for CHOP patients/family members, please place an Epic order for DGD Mail Specimen Collection Kit to Patient (Status: Specimen in Lab; Specimen Type: Saliva).
To request saliva collection kits for non-CHOP patients/family members (client cases), please contact DGDGeneticCounselor@chop.edu.

NOTE: Due to the increased potential for quality/quantity issues of DNA extracted from saliva, **blood is still the preferred sample type** when feasible, particularly for urgent testing.

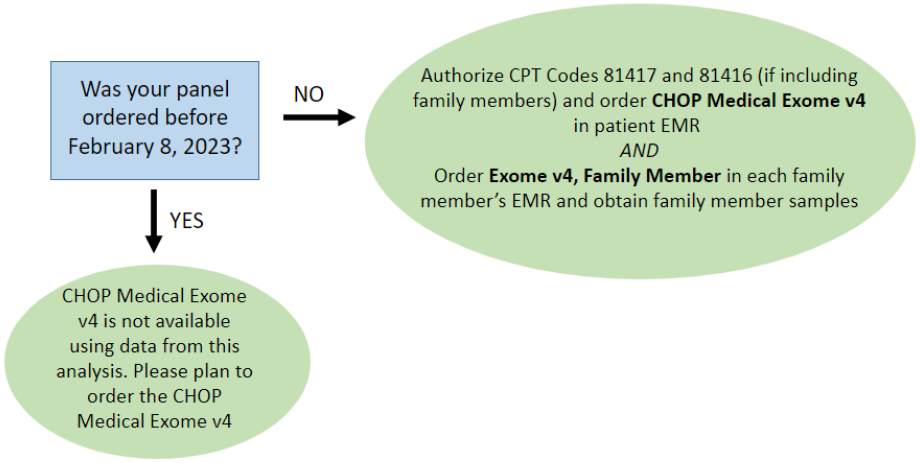
How do I inform the lab about the reason for testing and the key phenotypes/genes that should be considered during the analysis?
The lab uses the clinician-provided *clinical indication* and the *genes of interest* (both of which are fields in the Epic order) to target the analysis for the given patient's phenotype and differential diagnosis.

Decision Trees to Support Next Generation Sequencing Test Ordering

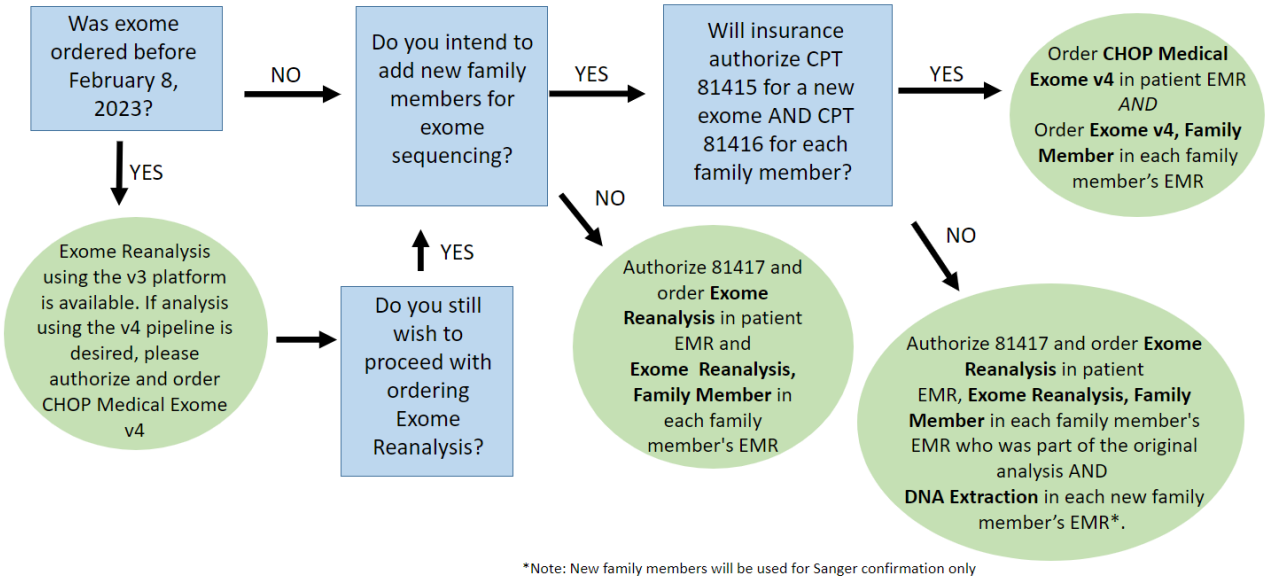
What tools are available to help guide me through the decision process for ordering next generation sequencing tests? Please see the appropriate decision tree below. Please note: Genetic counseling should be provided, and appropriate consent obtained prior to placing the order. Benefits investigation is required prior to sample submission for all exome-based tests ordered during an outpatient encounter, as well as certain types of inpatient admissions.



Medical Exome From Slice Panel Testing Strategy



CHOP Exome Reanalysis Testing Strategy



*Note: New family members will be used for Sanger confirmation only

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CHOP Medical Exome Ordering Logistics & Consent Requirements

How should I place the exome order(s) in Epic?

- Complete the consent process with the patient/family member (required for attestation in the order).
  - The proband and family member consent forms are available at https://www.chop.edu/centers-programs/division-genomic-diagnostics/requisition-forms.
  - Completed consent forms should be uploaded into the electronic medical record.
- Enter the order in the patient's Epic chart.
  - The *clinical indication* determines the phenotype to target for analysis and reporting. Please be certain to include all key clinical features that should be used for the analysis.
  - Genes of interest (≤10) may also be entered in the Epic order to guide the lab's analysis.
  - The order includes a clinician's attestation that consent has been obtained.
  - The Epic orders cannot be signed until a secondary findings decision is selected. (Please see "What if my patient is in the clinic, but I don't have authorization approved or they are not prepared to complete the consent?" for more information.)
- If family members will be submitted as part of the analysis, please place order(s) in the family member(s) Epic chart(s) for **'Exome, Family Member'**.

How are the clinician-provided genes of interest used in the analysis?

You may specify up to 10 genes of interest in the proband's Epic exome order. All variants in the genes of interest that make it through the bioinformatics filter will be reviewed by an exome analyst, even if they are not prioritized by the bioinformatics pipeline.

How should I choose genes of interest for my patient?

Please select genes that are:

1. Not otherwise captured by the patient's clinical indication
2. Associated with an expanding phenotype spectrum
3. Newly described in association with disease
4. Known to have reduced penetrance
5. Previously reported variant/gene that is still of interest

How do I inform the lab if the patient/family member wants to change their decision regarding secondary findings?

If a patient/family wants to change their selection for ACMG secondary findings, the DGD-GDL will need to receive an updated consent form within 7 days of the testing being submitted to the lab. A revised copy of the consent form (with the new secondary findings selection documented) should be emailed to the laboratory in a communication indicating that the secondary finding selection has changed AND the clinician should upload a copy to Epic. Please be sure to confirm that the laboratory has received this communication.

What are the consent requirements for the CHOP Medical Exome?

A completed written consent form is required for both probands and family members undergoing the CHOP Medical Exome. The consent forms are available at: https://www.chop.edu/centers-programs/division-genomic-diagnostics/requisition-forms. Please contact the laboratory if there are

extenuating circumstances that make it difficult to obtain written consent in a timely manner. (Note: There is a different version of the proband requisition and consent form for non-CHOP clients.)

What are the consent requirements for CHOP Medical Exome Reanalysis?

A new completed proband exome consent form is required in order to perform exome reanalysis. Family member consent form requirements vary:

- Family members of patients who had their original CHOP Medical Exome ordered *before 12/8/20* require a written consent form in order to be included in the reanalysis of the patient's data, unless an exception is approved after the GDL reviews the specific case with the CHOP General Counsel.
- Family members of patients who had their original CHOP Medical Exome ordered *on or after 12/8/20* do not require a written consent form in order to be included in the reanalysis, unless they wish to be informed if they carry secondary and/or incidental finding(s) detected in the proband.

CHOP Medical Exome Secondary and Incidental Findings

What are patients' options for receiving ACMG secondary findings?

As of December 8, 2020, the CHOP Medical Exome offers patients three options for secondary findings analysis and reporting of the genes/conditions listed on the ACMG secondary findings list [Miller 2021, PMID: 34012069]. The list will change periodically based on ACMG recommendations (see Appendix 2 for additional details), and the Current CHOP Secondary Findings List being analyzed on the CHOP Medical Exome can be accessed on our website: https://www.chop.edu/centers-programs/division-genomic-diagnostics/requisition-forms.

The three options for secondary findings analysis and reporting include:

- Option 1 – The lab will ***look for and report ALL*** detected disease-causing variants in genes/conditions on the ACMG Secondary Findings List.
- Option 2 - The lab will ***NOT look for or report any*** ACMG secondary findings.
- Option 3 – The lab will ***not purposefully look for*** ACMG secondary findings but ***will report them if they are identified by chance and are immediately medically actionable*** in the patient.

Proband Secondary Findings Options in the Proband Exome Consent Form (Version 12/8/20):

Secondary Findings Options				
Initial in the Box Next to Your Choice	**Option**	**Lab Looks for Secondary Findings**	**Lab Reports Secondary Findings**	**Details**
	Option 1	Yes	Yes	I want the lab to look for and report ALL detected disease causing variants on the Secondary Findings List. NOTE: It is possible that this test will not detect all secondary findings. In addition, this test will not look for all causes of the conditions on the Secondary Findings List.
	Option 2	No	No	I DO NOT want the lab to look for or report *any* secondary findings. I understand that some of these findings may be *immediately medically actionable* in the patient. I am aware that I will not have access to these results later. NOTE: If you choose this option, findings that are possibly related to the patient's reason for testing and also involved a gene/ condition on the Secondary Findings List will still be reported.
	Option 3	No	Yes, if found by chance and immediately medically actionable	I DO NOT want the lab to purposefully look for secondary findings. I want the lab to report secondary findings identified by *chance* if they are *immediately medically actionable* in the patient.

Family Members Options:
In addition, family members who undergo exome sequencing can choose whether or not they want the laboratory to *look for and report* incidental and/or secondary finding(s) in them, if these findings are identified and reported in the proband.

Family Member Secondary and Incidental Findings Options in the Family Member Exome Consent Form:

- Option 1: If secondary or incidental findings (unrelated to the patient's reason for testing) are identified and reported in the patient (proband), I choose to have the laboratory look for and report these findings in me.
- Option 2: If secondary or incidental findings (unrelated to the patient's reason for testing) are identified and reported in the patient (proband), I DO NOT want the laboratory to look for or report these findings in me. I am aware that I will not have direct access to these results later, although I may be able to pursue separate testing if desired.

It is important to note that the absence of reported secondary or incidental findings does not rule out these conditions, as this test will not detect all variants in these genes.

When does a family need to make a decision about ACMG secondary findings?

- A decision regarding secondary findings is required at the time the test is ordered. This decision cannot be deferred.
- In order to accommodate families who are undecided about secondary findings analysis, clinicians can place an Epic order for "DNA Extraction" at no additional charge to ensure that a sample is obtained. Exome testing would then be ordered when the consent documentation is complete.
- In extenuating circumstances, a secondary findings decision may be changed after the test order is placed if:
  1) the analysis has not yet started (7-day limit)
  and
  2) a revised copy of the consent form (with the new secondary findings selection documented) is emailed to the lab in a communication indicating that the selection has changed AND a copy is uploaded to Epic. Please be sure to confirm that the laboratory has received this communication.

What is an incidental finding and what types of incidental findings may be reported?

Incidental findings are results that are unrelated to the patient's reason for exome testing. Unlike the *purposeful* analysis of genes/conditions on the ACMG secondary findings list, incidental findings are identified *by chance or incidentally* while performing the test. We expect the identification of reportable incidental findings to be rare.

- The lab will report *medically actionable* incidental findings that are likely to cause serious health problems and have a well-established change in management or treatment. These include childhood onset conditions or conditions with a recommended change in medical care that could take place within about ten or twenty years (*e.g.,* biallelic pathogenic *CFTR* alterations known to cause cystic fibrosis).
  *Note: If a patient *opts out* of secondary findings analysis, variants associated with the genes/conditions on the ACMG secondary findings list will NOT be reported, even if they are identified incidentally during the analysis, unless they overlap with the patient's phenotype.
- ♦ There are rare exceptions when we may report incidental findings that are *not* medically actionable. Examples include but are not limited to:
  1) if they explain some of the patient's symptoms that are not included in the clinical indication for testing,
  2) if they are associated with another finding (such as a large deletion or missing region of genetic material) that is believed to be associated with the patient's clinical indication for testing, or
  3) if they are associated with an untreatable, serious, childhood onset disorder that is highly likely to cause symptoms (as reporting these findings could help to avoid additional testing and future delays in diagnosis). For example, Rett syndrome.

Sample/Data Requests

How do I request a patient's left-over samples or raw genetic data?

Once your patient's test is resulted, you may wish to obtain the left-over samples or raw data used for the analysis. Samples and/or data can typically be released for research purposes with a completed HIPAA authorization or research consent form. If data or samples are being requested for a large number of patients, an attestation form documenting that Institutional Review Board (IRB) consent has been obtained for each patient can be completed in lieu of providing separate consent forms for each individual. Please contact the laboratory at DGDGeneticCounselor@chop.edu for more details and the specific forms required.

Questions

Please contact the Genetic Counseling Core of the DGDGeneticCounselor@chop.edu or 267-426-1447 with any questions.

Appendix 1

The table below compares the scope of copy number variant (CNV) analysis and reporting on the CHOP constitutional Chromosomal SNP Microarray, CHOP Exome-based Panels, and the CHOP Medical Exome:

TABLE: Types of CNVs Typically Reported on the CHOP Chromosomal SNP microarray, Panels, and Exome				
		SNP Array	**CNV from Panels**	**CNV from Exome**
General Reporting Principles of Test:		Must meet size criteria or overlap phenotype (for smaller CNVs)	Must involve gene from panel	Must overlap phenotype or meet incidental findings (IF) criteria
Type of Copy Number Variant (CNV)		**SNP Array**	**CNV from Panels**	**CNV from Exome**
Pathogenic CNV (any size, related to phenotype)		Yes	Yes (If involves gene from panel)	Yes
Non-diagnostic CNVs	**Het for AR disease**	Yes (if meets size criteria or overlaps phenotype)	Yes (if involves gene from panel)	Yes (if overlaps phenotype)
	VOUS with known disease genes	Yes (if meets size criteria or overlaps phenotype)	Yes (if involves gene from panel)	Yes (if overlaps phenotype)
	VOUS without known disease genes	Yes (if meets size criteria)	No	No
	Recurrent CNV with low penetrance and variable expressivity	Yes (if meets size criteria)	Yes (if involves gene from panel)	No (unless significant phenotype overlap)
	Pathogenic without phenotype overlap	Yes (if meets size criteria)	Yes (if involves gene from panel)	Maybe (if meets incidental findings criteria)
Aneuploidy	**Non-sex chromosomal abnormality**	Yes	Yes (If involves gene from panel)	Yes (non-mosaic)
	Sex chromosome abnormality	Yes	No*	No*
Exonic deletion/duplication	**Multiple exons (≥3)**	Yes (if overlaps phenotype)	Yes (if involves gene from panel)	Yes (if overlaps phenotype or meets IF criteria)
	1-2 exons (not exon 1 or non-coding exons)	Maybe (depends on probe coverage)	Maybe (if involves gene from panel; depends on mappability)	Maybe (depends on mappability; if overlaps phenotype or meets IF criteria)
	1-2 exons (exon 1 or non-coding exons)	Maybe (depends on probe coverage)	Maybe (if involves gene from panel; depends on mappability)	Unlikely*
Mosaicism		Yes	No*	No*
Balanced structural rearrangement		No	No	No
Uniparental disomy (UPD) or Regions of homozygosity (ROH)		Yes (isoUPD and ROH)	No	No*
Reflex to cytogenetics if needed		Yes (if green top received)	No	No

Key: VOUS - Variant of uncertain significance; * - Unlikely to be detected by current CNV NGS analysis pipeline

Children's Hospital of Philadelphia
Division of Genomic Diagnostics

Appendix 2
Updates to the CHOP Medical Exome Over Time

Versions of the CHOP Medical Exome

- Exome v1: Launched in 2014, the CHOP Medical Exome version 1 (v1) was largely phenotype-driven and thus focused on identifying findings of interest that overlapped with the patient's clinical indication.
- Exome v2: Launched in February of 2020, the CHOP Medical Exome version 2 (v2) incorporated an analysis that prioritizes variants for analysis based on their molecular characteristics and frequency (e.g. *de novo* status, loss-of-function, and absence from control databases), while reporting is still primarily based on overlap with the patient's phenotype.
- Exome v3: Launched on 5/12/2021, the CHOP Medical Exome version 3 (v3) incorporated copy number variant analysis.
- ♦ Exome v4: Launched on 2/8/2023, the CHOP Medical Exome version 4 (v4) introduced genomic sequencing with analysis of sequence variants in the exons and intron/exon borders or copy number variants involving *known disease genes* that may be associated with the patient's clinical indication for testing. In addition, noncoding disease genes and potential disease-causing variants (as reported in HGMD and ClinVar) in regulatory and deep intronic regions might also be analyzed and reported.

ACMG Secondary Findings:

- As of 12/8/2020, the laboratory started offering three options for secondary findings analysis and reporting, instead of the prior two options. For further details, see the section above on CHOP Medical Exome Secondary and Incidental Findings.
- The Current CHOP Secondary Findings List being analyzed on the CHOP Medical Exome can be accessed on our website: https://www.chop.edu/centers-programs/division-genomic-diagnostics/requisition-forms.