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Refining the Structure and Content of Clinical Genomic Reports

MICHAEL O. DORSCHNER*, LAURA M. AMENDOLA, BRIAN H. SHIRTS, LESLI KIEDROWSKI, JOSEPH SALAMA, ADAM S. GORDON, STEPHANIE M. FULLERTON, PETER TARCZY-HORNOCH, PETER H. BYERS, and GAIL P. JARVIK

Abstract

To effectively articulate the results of exome and genome sequencing we refined the structure and content of molecular test reports. To communicate results of a randomized control trial aimed at the evaluation of exome sequencing for clinical medicine, we developed a structured narrative report. With feedback from genetics and non-genetics professionals, we developed separate indication-specific and incidental findings reports. Standard test report elements were supplemented with research study-specific language, which highlighted the limitations of exome sequencing and provided detailed, structured results, and interpretations. The report format we developed to communicate research results can easily be transformed for clinical use by removal of research-specific statements and disclaimers. The development of clinical reports for exome sequencing has shown that accurate and open communication between the clinician and laboratory is ideally an ongoing process to address the increasing complexity of molecular genetic testing.

Keywords

exome sequencing; Clinical Laboratory Improvement Amendments (CLIA); College of American Pathologists (CAP); incidental findings; laboratory report

INTRODUCTION

Molecular genetic testing is rapidly expanding, largely fueled by technological advances in next generation sequencing (NGS) and, in parallel, the accelerated discovery of the genetic basis of human diseases. Over the past several years, NGS and associated technologies have enabled clinical laboratories to convert cumbersome Sanger-based assays to streamlined and less costly, comprehensive targeted gene panels. The use of whole exome sequencing (WES) and genome sequencing (GS) allows molecular diagnosticians to examine the known genes responsible for target phenotype(s) and to identify previously unrecognized causes for the heritable disorder for which the test was indicated. Such testing also identifies incidental findings (IFs), or off-target sequence alterations unrelated to the reason for testing, that could affect the participant's health now or in the future. As test complexity increases with

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*Correspondence to: Michael O. Dorschner, 1959 NE Pacific Street Box 356560 Seattle, WA 98195-6560. mod@uw.edu.

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SUPPORTING INFORMATION

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exome and genome sequencing, it becomes challenging to provide clinicians, geneticists, and non-geneticists, with readily interpretable test reports. In addition, new “meaningful use” components of Medicare and Medicaid EHR (Electronic Health Record) Incentive Programs [Centers for Medicare and Medicaid Services, 2013] permit patients to directly access results from all clinical laboratory tests, which create a new audience that may struggle to interpret complex genomic reports. With any rapidly evolving technology comes growing pains and caveats. Clinical laboratories that report results from exome or genome sequence data must be able to communicate the outcomes of those efforts effectively. As a first step in developing an effective report for exome sequencing, the purpose of this study was to define the ideal content and format of a report according to experienced users of molecular genetic test reports and in keeping with the requirement and recommendations of the Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP).

METHODS

Study Background

The National Human Genome Research Institute (NHGRI), partnering with the National Cancer Institute (NCI), recently launched the Clinical Sequencing Exploratory Research (CSER) consortium to bring together multidisciplinary teams of clinicians, laboratory scientists, bioinformaticists, ethicists, and others to identify challenges in the implementation of genomic medicine, including the creation of comprehensive reports of exome or genome sequence data that derive from the clinic and to develop effective reports that can be read and understood by clinicians and lay people. As one of the academic sites in this consortium, we are conducting a randomized controlled trial of usual care versus the addition of exome analysis for patients who are referred for clinical genetic testing for susceptibility to colorectal cancer/polypsis (CRCP), called the NEXT (New Exome Technology) Medicine study. To accomplish this, we established a CLIA-certified laboratory to generate exome data and an exome summary test report for the patient’s medical record which includes all results returned by the study. To place these results in the medical record, we developed structured narrative text reports, consistent with CLIA/ CAP regulations, supplemented with additional information to aid clinicians with the presentation and interpretation of exome data.

The UW NEXT Medicine study focuses on the examination of approximately 25 CRCP-related genes (similar to a “panel”) but, in contrast to the usual “panel”, also examines 96 non-CRCP genes that may contain actionable incidental findings (IFs) in adults as well as nine pharmacogenetic genes. Identification of pathogenic variants in the IF genes could impact the participant’s health and had potential preventive, screening, or treatment implications; the pharmacogenetic genes relevance depended on the potential for exposure to the relevant drug. The ACMG recently recommended that IFs in a minimum list of 56 genes be reported to all patients receiving exome and genome sequencing [Green et al., 2013]. While the ACMG list was built with knowledge of our list and all adult-relevant ACMG genes are included in our list, our NEXT RORC (Return Of Results Committee)

achieved consensus for return of additional genes [Berg et al., 2013]. In addition to these actionable IFs, well-established pharmacogenetic variants are returned in the IF report.

Study Participants

A RORC was assembled to provide expert guidance on the return of research results to NEXT Medicine study participants. As part of that activity, the RORC reviewed the WES report template and provided input for improvement. This committee was composed of 24 members: 14 clinical geneticists, 3 genetic counselors, 3 non-geneticist physicians, 2 genomicists, 3 bioethicists, and 4 molecular genetic laboratory directors. Some individuals have more than one area of expertise. The clinicians and genetic counselors on this committee possessed an average of 20 years of experience in the field of clinical genetics. A smaller, partially overlapping, Variant Subcommittee (VS), consisting of four molecular genetic laboratory directors, four clinical geneticists, one non-geneticist physician, three genomicists, two statistical geneticists, two genetic counselors, and a research coordinator was charged with developing reports for communicating exome sequence results and classification of sequence variants. The VS obtained and researched information regarding regulatory compliance, example reports, and drafted and revised the WES report template. Members of the RORC and VS committees were principal investigators, co-investigators, and clinical or research personnel associated with the NEXT Medicine project. An expert panel of non-geneticist physicians was assembled to reflect other medical specialties likely to order genetic tests. This panel of six non-geneticists consisted of a gynecological oncologist, a cardiologist, a primary care physician, a neurologist, a hematologist, and an endocrinologist. These individuals participated in informal interviews to solicit information about draft WES reports.

The NEXT Medicine study had IRB approval (UW IRB #41829) for all of its activities, including the formation of an expert panel to advise on various aspects of the return of genomic results, including the development of the electronic health record genomic test report.

Process Overview

Development of a final report template consisted of three phases: (1) creation of a draft report based on the structure of multi-gene panel examples and review of regulatory requirements. This work was an iterative process undertaken by the VS over the course of several discussions. An initial draft report can be found in the Supplemental Materials (Fig. S1). (2) presentation of the draft report template to the larger RORC for input (Supplemental Materials). Members of the RORC committee were asked to review the template and make suggestions for modification. Discussion amongst the entire committee was prompted as members made suggestions. These suggestions were recorded so the VS could make changes to the report template; and (3) solicit input from six non-genetics physicians via three informal dyadic interviews where the proposed incidental finding report format was reviewed and discussed. An outline for conducting these interviews (Fig. S2) and draft reports (Figs. S3 and S4) is contained in the Supplemental Materials (see Supporting Information Online).

Data Sources

Publications available from several regulatory and professional societies, including CLIA, CAP, Centers for Disease Control (CDC), and the American College of Medical Genetics (ACMG) were reviewed to identify the key elements required and recommended for reporting molecular genetic testing results [Gulley et al., 2007; Chen et al., 2009]. De-identified hard copy example reports from multiple laboratories were provided and reviewed to draft an initial report template. Test reports were provided by the University of Washington Collagen Diagnostics Laboratory (Recessive OI (osteogenesis imperfecta) Panel and Vascular Aneurysm Panel), the Laboratory for Molecular Medicine, Partners Healthcare Center for Personalized Genetic Medicine (cardiomyopathy panels), the University of Washington, Department of Laboratory Medicine, Genetics and Solid Tumors Laboratory (ColoSeq™) and the Baylor College of Medicine Whole Genome Laboratory (focused and expanded WES tests). The proceedings from all meetings, discussions and interviews were recorded for analysis by the VS.

Data Analysis

Minutes from several VS meetings (over 3 months) were compiled and reviewed along with content from publications pertaining to regulatory compliance and professional guidelines to synthesize a draft WES report. Notes from a presentation of the draft report template to the RORC were reviewed and input integrated by the VS into subsequent report versions. Responses recorded during interviews with non-geneticist physician were compared to identify themes to questions regarding format and content of draft reports. Modifications to reports were made in response to comments provided by the interviewees.

RESULTS

Our investigation commenced with a review of the current regulations and recommendations made by government agencies and professional societies for reporting test results. The content of clinical molecular genetic test reports must comply with CLIA report requirements (42 CFR §493.1291). Briefly, clinical test reports for genetic testing should include, (1) patient name and identification number or unique identifier, (2) laboratory name and address, (3) specimen source (when appropriate), (4) test performed, (5) test results and (if applicable) units of measurement or interpretation, (6) information regarding the condition and disposition of specimens that did not meet laboratory criteria for acceptability, and (7) test report date. The College of American Pathologists (CAP) [Gulley et al., 2007], American College of Medical Genetics and Genomics (ACMG) and Centers for Disease Control (CDC) [Chen et al., 2009] have provided recommendations to supplement the CLIA general report format for molecular testing. These organizations recommend including, (1) indication for testing, (2) interpretation of results, including clinical implications, follow-up test recommendations, and referral for genetic counseling, (3) ethnicity/race (where appropriate), and (4) references with evidence supporting the interpretation.

Initially, we devised a single WES structured narrative report that included the CRCP, non-CRCP actionable IF and pharmacogenetic genes. When it became clear this could be lengthy as well as confusing for clinicians to navigate and extract relevant information, we divided

the information into two reports; one focused on CRCP susceptibility genes; and a separate report for IFs and pharmacogenetic variants. Notably, in order to allow sufficient time to return and explain the CRCP results, we return the pharmacogenetic results and IFs to the subjects at a separate, later clinic visit. This is facilitated by the generation of two separate reports.

Examination of WES Structured Narrative Report by Genetics and Non-Genetics Professionals

The Variant Subcommittee developed a proposed WES report format and the NEXT RORC was asked to review it and give input for modification. This group agreed with the VS that WES results should be separated into two reports, CRCP and IFs, and made several additional suggestions. The major proposed changes from the RORC focused on the order in which elements were reported. As a consequence the results and interpretation sections were placed at the beginning of the report, and the test methods were moved to the end. Other areas of discussion included how best to present variant information, such as the inclusion of HGVS (Human Genome Variation Society) nomenclature, as well as appropriate terminology for describing a pathogenic finding, for example, use of the term “disease-causing variant” versus “mutation.”

We next brought the revised IF report format to a small group of non-geneticist, senior physicians, who represented potential report users, for their feedback. Views were solicited in three informal (typically dyadic, i.e., between two clinicians and two members of the study team) conversations in which two hypothetical reports, one with only pharmacogenetic IFs and one with both pharmacogenetic and disease-related IFs, were provided for immediate review and discussion. When these non-geneticist physicians were asked about their impressions of the WES reports, the majority asked for less information or to have the most clinically salient information clearly highlighted near the beginning of the report. Most non-geneticist physicians simply wanted the punch line: Patient X has variant Y, which is consistent with the diagnosis of disorder Z, followed by a clear and concise recommendation. Given that the recommendations for a specific genetic finding may be a “moving target,” a general statement, such as “refer to medical genetics,” was also suggested. It was emphasized that the report should include enough information to explain the necessity of following the recommendation and convey a sense of urgency, where appropriate.

Conversely, the non-geneticist physicians with an interest or experience in genetics were interested in more detailed genomic data and interpretations. For example, there was mixed feedback regarding the need to include the penetrance of a condition and frequency of a variant. This raised the need to include both basic and higher level information in the report. Non-geneticist physicians all expressed a desire for a more basic description of the study context up front, with definitions of technical terms when necessary, and the transition of legal text with disclaimers about test and study limitations to the end of the report. Finally, the ability to imbed links to resources, such as databases, and references related to each genetic finding was raised as a suggestion independently in each dyadic discussion.

Modifications to the Standard Single Gene or Gene Panel Report Structure

In response to these comments, we made several modifications to the structured report format and added project-specific language in multiple sections. Standard clinical reports are more abbreviated and do not require language to indicate that the data are derived from a research project. To keep the format as close to a clinical report format as possible while indicating research-related caveats, we chose to make the following modifications:

1. **Report title and description:** To make sure that clinicians viewing this report in the medical record understand that the WES results, in this instance, derive from a research study, we added a short paragraph to describe the study. An advisory statement was included to warn clinicians about rapidly changing sequencing technology and the evolving interpretation of sequence variants. Because the study does not include a comprehensive analysis of the entire exome, we advised clinicians who believe their patient has a genetic condition to seek evaluation by a genetic specialist as additional testing may be required.
2. **Focused molecular test results:** Ideally, clinical test reports are limited to a single page; however, it was not possible to limit exome and genome sequencing to one page and still provide a comprehensive report. Because clinicians are busy and do not have time to read volumes of text, we chose to include a brief table on the first page of the report that described the results including the gene name, variant, clinical significance, and recommendation. The list of CRCP associated genes analyzed was listed with this table on the CRCP report to indicate which genes were examined for potential disease-causing variants. As more genes are shown to be causative and added to the CRCP gene list, the report will be revised to reflect these additions. We chose not to include a gene list for the IF report for two reasons: (1) the IF gene list is frequently updated and therefore constantly changing and (2) we wanted to reinforce the fact that this part of the test, as we perform and analyze it for this project, is not comprehensive (e.g., only variants currently known to be pathogenic and actionable are returned).
3. **Interpretation:** On the second page of the report each variant was listed in the interpretation section including a table with detailed genomic location information and text that described the current state of knowledge about its pathogenicity. The table includes the gene and chromosome name, with Genbank reference file ID, the hg19 variant position, nucleotide variant name (with zygosity), and protein variant name. The text includes all evidence compiled to classify the variant including the frequency of the variant, in silico predictions, functional evidence, and a summary of the literature that describes the variant's association with disease.
4. **Procedure, including limitations:** We included a description of the WES laboratory process and data analysis. Exome and genome sequencing still present significant limitations to their ability to provide comprehensive (all variant types) testing. Some of these limitations are the results of the sequencing technology itself—and others are due to limitations of analytical tools. It is very important to describe what the test does NOT perform well; for example, tools for identifying copy number variants from WES data are not highly sensitive or specific.

5. Coverage statistics: On the CRCP report only we included coverage information for the genes related to the primary test indication. Coverage information was not included on the IF report based on the decision not to include the list of the genes tested in these reports. To accurately call variants within the desired gene regions, at a high sensitivity and specificity, a minimum read coverage must be obtained. Laboratories should establish a minimum coverage sufficient to identify variants, and report any regions that fall below this minimum coverage. Some laboratories supplement low coverage regions with Sanger-or NGS-based amplicon sequencing; others provide a list of regions that fall below the laboratory's minimum coverage threshold.

The proposed WES/GS report content is outlined in Table I. The proposed outline is adapted from the descriptions recommended by multiple groups for the format of molecular genetic reports [Lubin et al., 2009; Scheuner et al., 2012, 2013]. Final indication-specific and IF sample reports are provided in the Supplemental Materials (Figs. S5 and S6).

Considerations for Writing an Effective Report: Variant Annotation, Text Language and Available Clinical Information

During the course of committee discussions regarding report structure, several other topics were decided to be highly relevant to the content of WES/ GS reports. Standardization of variant annotation and nomenclature, as well as the language used to communicate results and information supplied to laboratories were deemed critical elements to successful report writing.

In our study, annotated variants are provided in two separate files, those that affect our selected CRCP panel genes, and those that alter the actionable IF genes and pharmacogenetic loci. Each variant is presented with over 25 pieces of information, including read depth, genotype, quality metrics, genomic coordinate (hg19 reference), reference sequence ID, HGVS nucleotide and protein names, exome variant server allele frequency, and presence or absence in the Human Genetic Mutation Database (HGMD). Variants for which there is uncertainty about the clinical significance are brought to a board of expert geneticists and genetics professionals to weigh the evidence for pathogenicity.

Many clinical laboratories employ the variant interpretation guidelines put forth by the ACMG [Richards et al., 2008]. New guidelines are due to be published in 2014. We have developed a rigorous, evidence-based classification scheme described in detail in Dorschner et al. [2013]. For CRCP-associated loci, we report pathogenic, likely pathogenic and variants of unknown significance. Similar to the recommendation recently published by the ACMG for incidental findings, for IF genes we report only known pathogenic variants, classes of variants expected to cause disease (e.g., nonsense, splice, frameshift in appropriate genes), or well-established, actionable pharmacogenetic variants in IF genes.

The use of terms to describe results, such as normal/abnormal, positive/negative, must be qualified when reporting exome or genome sequencing results. To perform WES, and report to a patient or participant that the exome is negative for disease-causing variants related to an indication would be inappropriate. Laboratories must qualify these statements by

reinforcing the limitations of their test. Even though the report may have a section where it lists the limitations of the test, providers and patients may not make the appropriate association. For example, many genes that cause neurodegenerative phenotypes, particularly the genes that contain trinucleotide repeats and the cause of the phenotype is expansion of the repeat size, cannot be assessed by WES and currently require a separate test. Also, stating that the test is negative for genes known to cause the given phenotype, and not providing the list of genes is inadequate. The list of known genes for a phenotype can change rapidly. Our preference is to use the terms “mutation (or causative variant) detected” or “no mutation (or causative variant) detected,” followed by a brief explanation. Use of the wrong terminology and/or not qualifying the results and interpretation could inadvertently lead patients and providers down the wrong path.

DISCUSSION

To communicate the results of WES to participants of our randomly controlled use trial, we developed a clinical genomic report modeled after those employed for targeted gene panels. We expanded sections already part of the report and added sections to specifically address research-related specifications and caveats. Several issues related to the technical limitations of WES, such as target coverage, ability to detect specific mutation types (such as large deletions and duplications) are highlighted. An example of our report is included in the Supplemental Materials.

Feedback from geneticists and non-geneticists was crucial to the development of our report. Geneticists recommended basic structural changes, such as the separation of indication-specific and incidental findings into separate reports, re-ordering of the report sections and the use of specific terminology to more clearly communicate results. Non-geneticists, who are less comfortable communicating results of genetic testing, unanimously asked for clarity. Getting to the punch line early in the report and providing more guidance with respect to recommendations were among their requests. These findings were similar to those described by previous investigations focused on development of templates for reporting single-gene molecular test results [Lubin, 2009; Sheuner, 2012], in which experts recommended presentation of the results and interpretation/recommendations at the beginning of the test report, with test methodologies, limitations, disclaimers, and references later in the report. Many clinicians are ill equipped to understand the limitations of complex WES/GS testing and it is incumbent on the laboratory to provide guidance with respect to the completeness of testing. Clarity is essential as physicians are using these results for clinical decision-making. In certain circumstances it may be important for a clinician to order a comprehensive single-gene analysis, especially when therapeutic choice or changes in disease surveillance would be impacted if a mutation were left undetected.

While this paper proposes modifications and refinement to the content of test reports, the ability of clinical laboratories to provide the best interpretation relies on completeness of the test requisition. Many times requisition forms are incomplete so that important elements of clinical description, racial or ethnic background, and family history are left blank and these data are crucial for variant interpretation. For example, a variant is unlikely to be pathogenic when the sequence alteration is common in the patient’s ethnic group [Dorschner et al.,

2013] but not found or very rare in others. Providers, and professionals, such as medical assistants, nurses, and clerks, may not always understand why these elements are important. The more information the lab has, the more complete and accurate an interpretation can be made.

In addition, a detailed description of the test indication is essential for appropriate WES interpretation and reporting. Determining which findings are categorized as diagnostic findings and which are categorized as incidental findings depends on knowledge of the test indication. In clinical WES testing there may be multiple indications. For example, a hypertrophic cardiomyopathy or breast cancer associated mutation may be considered incidental in a patient being tested for colon cancer, but would be diagnostic if the clinician notes this as a primary or secondary indication of testing because of observed family history.

The reports produced by our lab are currently transferred to our electronic health record (EHR) as a structured narrative document in portable document format (PDF) which is human readable but is not readily computable as discrete data elements for clinical decision support. This is the common approach employed across the initial six CSER sites [Tarczy-Hornoch et al., 2013]. We are thus in parallel implementing methods to enter the relevant report information as discrete computable data into the EHR to enable greater visibility of genomic results as well piloting and evaluating the use of active decision support rules in the production EHR. To do this we are leveraging pathways currently used for single gene genetic tests that return discrete results to implement the return of the actionable findings from WES. For genomic medicine to become a fully integrated into medical care, we must determine how genomic reports can be more readily and usefully adapted for entry into the EHR and how reports can be automatically updated as our understanding of variant pathogenicity changes.

The refined report format developed for our research project can easily be transformed for clinical deployment by removal of research-related statements and disclaimers in the test description section. Clinical genomic reports will continue to evolve as test complexity increases. Our process for the development of WES clinical reports has shown that accurate and open communication between the clinician and laboratory is ideally an ongoing process, both for individual reports and for general report formatting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Michael Dorschner is Research Assistant Professor of Psychiatry & Behavioral Sciences and Pathology at the University of Washington. He is a clinical molecular geneticist with interests in the application of genomics to molecular diagnosis and the genetic basis of neurodegenerative disorders.

Laura Amendola is a genetic counselor at the University of Washington Medical Center. She provides genetic counseling to patients referred to the adult Genetic Medicine clinic for a variety of conditions, and coordinates research on the incorporation of whole exome sequencing into clinical genetics.

Brian Shirts is Assistant Professor of Laboratory Medicine at the University of Washington. His research focuses on the informatics involved in communicating complex genetic information to clinicians and patients.

Lesli Kiedrowski is a clinical genetic counselor. Her research interests include the application of genomic technologies to clinical cancer and hereditary cancer gene discovery.

Joseph Salama is a research coordinator with an interest in health service research, particularly focused on how clinicians access and utilize electronic health records in patient care.

Adam Gordon is a graduate student in Genome Sciences at the University of Washington. His research focuses on developing high-throughput sequencing tools for clinical pharmacogenetic implementation and discovery.

Stephanie M. Fullerton is Associate Professor of Bioethics & Humanities at the UW School of Medicine. Her research focuses on the ethical and social implications of genetic and genomic testing, including clinician, researcher and patient/participant perspectives on informed consent, result return, and data sharing.

Peter Tarczy-Hornoch is Chair and Professor of the Department of Biomedical Informatics and Medical Education at the University of Washington. He is a neonatologist with research interests focused on foundational and applied research in the context of biomedical informatics support for translational and clinical research.

Peter H. Byers is Professor of Pathology and Medicine at the University of Washington. He is an internist and clinical medical geneticist with research interests aimed at understanding the molecular pathogenesis of inherited connective tissue disorders.

Gail Jarvik is the Arno G. Motulsky Chair and Head of the UW Medicine Division of Medical Genetics. She is an internist and clinical medical geneticist whose research interests include the genetic basis of common diseases and genomic medicine implementation.

TABLE I

Recommended Exome/Genome Report Content

Laboratory/patient/sample identifiers
Name address of reporting laboratory (optional: phone, FAX, e-mail, web site)
Patient's name (first and last with middle initial or middle name)
ID No. (medical record number) and/or date of birth
Date of specimen collection
Date of receipt or accession in laboratory, with accession number
Specimen source and how tissue was received (fresh, frozen, paraffin-embedded, etc.)
Ordering physician
Indication
Reason for referral with pertinent clinical history
Results
For each identified variant, list the variant-containing standardized gene name (HUGO gene name), variant ID (HGVS convention) with zygosity, clinical significance, and recommendation (if applicable)
List genes examined associated with indication for testing
Interpretation
Interpretation involves synthesizing analytic and clinical information to describe what the result means for the patient. Results should be interpreted in a clinically relevant manner and explain how technical limitations might affect the use of test results. When appropriate, test results may be explained with reference to family members and whether they possess the identified variant
Should include gene and chromosome names, variant position (with respect to genome reference used) and nucleotide and protein variant designations according to HGVS nomenclature. The interpretation also includes text describing the current state of knowledge regarding the detected sequence variant and its disease-causing classification according to current recommendations for sequence interpretation
Comments/recommendations
Significance of the result in general or in relation to this patient
Correlate with prior results (if applicable)
Recommend additional measures (additional testing, genetic counseling, etc.)
Condition of specimen that may limit accuracy of testing (e.g., partially degraded DNA)
Pertinent assay performance characteristics or interfering substances
Residual risk of disease (or carrier status) by Bayesian analysis
Document interdepartmental consultation
Incorporate information specifically requested on the requisition (e.g., ethnicity)
Answer specific questions posed by the requesting clinician (e.g., rule out)
Reason specimen rejected or not processed to completion
Disposition of residual sample (e.g., sample repository)
Chain of custody documentation, if needed
If the report is amended or addendum report, describe the changes or updates
Describe discrepancies between preliminary and final reports
Name of testing laboratory, if transmitting or summarizing a referral laboratory's results
References
Cite medical literature supporting interpretation
Procedure
Type of procedure (e.g., exome sequencing, genome sequencing, etc.)
Defined target (e.g., exome reference)

Pertinent details of procedure, for example, analyte-specific reagent or kit version and manufacturer, instrument type

Disclaimer on non-FDA approved test

Limitations of assay (e.g., does not detect large deletions and duplications)

Signature of laboratory director or designee when interpretation is performed (reports may be signed electronically)

Date of report

Demographic information

Accession number, and specimen number from referring laboratory

Genetic counselor, when appropriate

Clinic/inpatient location; or name/address/phone of outside facility

Research statement

If data were produced for a research project requiring return of results to the study participant, a brief statement describing the assay's use and limitations should be provided prior to the indication section