

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

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Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other health-care providers to help them provide quality medical genetic services. Adherence to these recommendations does not necessarily ensure a successful medical outcome. These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, geneticists and other clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these recommendations.

In clinical exome and genome sequencing, there is a potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing but of medical value for patient care. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement on clinical sequencing that emphasized the importance of alerting the patient to the possibility of such results in pretest patient discussions, clinical testing, and reporting of results. The ACMG appointed a Working Group on Incidental Findings in Clinical Exome and Genome Sequencing to make recommendations about responsible management of incidental findings when patients undergo exome or genome sequencing. This Working Group conducted a year-long consensus process, including an open forum at the 2012 Annual Meeting and review by outside experts, and produced recommendations that have been approved by the ACMG Board. Specific and detailed recommendations, and the background and rationale for these recommen-

ations, are described herein. The ACMG recommends that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the "normal" of tumor-normal subtractive analyses in all subjects, irrespective of age but excluding fetal samples. We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected.

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Exome and genome sequencing (collectively referred to in this report as clinical sequencing) are rapidly being integrated into the practice of medicine.^{1,2} The falling price of sequencing, coupled with advanced bioinformatics capabilities, is creating opportunities to use sequencing in multiple medical situations, including the molecular characterization of rare diseases, the individualization of treatment (particularly in cancer),

pharmacogenomics, preconception/prenatal screening, and population screening for disease risk.^{3,4} In all of these applications, there is a potential for the recognition and reporting of incidental (or secondary) findings, which are results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient. Considerable literature discusses

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the utility and ethics of reporting incidental findings discovered in the course of research,⁵⁻⁹ but relatively little has been written about doing so in the clinical context.¹⁰⁻¹⁴ Last year, the American College of Medical Genetics and Genomics (ACMG) published a policy statement related to clinical sequencing¹⁵ that emphasized the importance of secondary or incidental results in pretest patient discussions, clinical testing, and reporting of results. Here, we provide the recommendations of the ACMG Working Group on Incidental Findings in Clinical Exome and Genome Sequencing (hereafter referred to as the Working Group). These recommendations have been approved by the Board of the ACMG.

PROCESS

The chairs of the Working Group were appointed in November 2011, and a written charge to the Working Group was approved by the ACMG Board of Directors in January 2012. The Board charged this Working Group with evaluating the need for and principles that would govern recommendations for analyzing and reporting incidental findings from sequencing in the clinical context. The Working Group was then asked to generate an initial list of genes and categories of variants to be reported as incidental findings. Working group members were appointed and approved by the ACMG Board in January 2012 and met weekly by teleconference between January and September 2012 and by e-mail throughout the development of this article. The Working Group began by establishing general processes for accomplishing its charge. We decided to consider both broad categories of disorders as well as specific genes. The initial list of genes considered by the Working Group was derived from the genes evaluated in a survey of genetics experts by Green et al.¹⁰ and supplemented by a provisional list of genes¹³ being evaluated at the University of Washington for return of results.

The Working Group presented its principles and plans and solicited feedback at an open forum at the ACMG Annual Meeting in March 2012. These principles and plans were further developed based on feedback from ACMG members and were provisionally reviewed by the ACMG Board in May 2012 and again in November 2012. Twenty additional experts were nominated by the Working Group members in May 2012. Fifteen agreed to serve as external reviewers, and feedback from these additional reviewers was solicited in conference calls in June 2012 and by e-mail in January 2013. The recommendations and this article were revised based on this feedback. Final approval by the ACMG Board occurred on 19 March 2013.

The Working Group used the ACMG policy statement titled "Points to Consider in the Clinical Application of Genomic Sequencing"¹⁵ as a starting point for its deliberations. That document includes a definition of clinical sequencing, describes the indications for such testing, and provides guidance on pretest considerations, reporting of results, genetic screening issues, and posttest considerations. Those issues were not revisited by this Working Group except to the extent that such considerations may be specifically affected by incidental findings.

DEFINITIONS

Clinician

This term refers to the individual practitioner who has direct contact with the patient and family or a clinical team that is responsible for direct contact with the patient and family. The clinician should be properly trained and prepared in genetics and genomics with an understanding of genetic counseling, pedigree analysis, and risk assessment to provide pretest and posttest patient care associated with clinical sequencing.¹⁵

Laboratory

This term refers to the entity that takes responsibility for analysis, interpretation, and report generation of sequencing performed for clinical purposes. The Working Group recognizes that in some cases, one entity may generate the raw sequencing data and another may further evaluate and interpret the sequence, consider additional or confirmatory testing, and issue a clinical report. The latter is the focus of these recommendations.

Patient

This term is used to describe adults who undergo clinical sequencing and are competent to make their own health-care decisions. The term, as used here, also refers to parents of minor children or guardians of decisionally impaired adults who may undergo this testing. In cases in which young children or decisionally impaired adults undergo sequencing, pre- and posttest counseling and consent of parents or guardians on behalf of the minor or decisionally impaired adult should occur, but teenagers and mildly decisionally impaired adults should not be excluded from these discussions, and assent should be sought in appropriate cases.

Primary finding

This term is used to describe pathogenic alterations in a gene or genes that are relevant to the diagnostic indication for which the sequencing was ordered (e.g., a mutation in *MECP2* in a girl with loss of developmental milestones).

Incidental finding

This term has been used in a variety of clinical and research contexts to indicate unexpected positive findings. Other terms have been used to describe these findings, particularly when they are actively sought (rather than being unexpectedly discovered). These terms include "serendipitous and iatrogenic" findings,¹⁶ "non-incidental secondary findings,"¹⁷ "unanticipated findings,"¹⁸ and "off-target results."¹ We use "incidental findings" in this article to indicate the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered.

WORKING GROUP CONSIDERATIONS

The clinical utility of incidental findings

Some have argued that incidental findings should not be reported at all in clinical sequencing until there is strong

evidence of benefit, whereas others have advocated that variations in any and all disease-associated genes could be medically useful and should be reported.¹⁹ The Working Group acknowledged that there was insufficient evidence about benefits, risks, and costs of disclosing incidental findings to make evidence-based recommendations. Nonetheless, based on available evidence and clinical consensus among its members, the Working Group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing. In reaching this consensus, we recognized that our clinical experience has been derived largely from patients with disease symptoms or positive family histories. As additional evidence accrues on the penetrance of these variants among persons without symptoms or family history, these recommendations are expected to evolve.

The Working Group elected to present recommendations in the form of a “minimum list” of incidental findings to report from clinical sequencing. Although all the disorders are rare, most of these genes and variant categories were selected because they are associated with the more common of the monogenic disorders, and because the Working Group reached a consensus that they met criteria described below. The Working Group specified a set of disorders, the relevant genes that are associated with the disorders, and certain categories of variants that should be reported, based on a consensus-driven assessment of clinical validity and utility. In cases in which evidence was lacking, the Working Group drew upon the clinical judgment of its members. The Working Group acknowledged that its membership (and the ad hoc reviewers listed in the Acknowledgments) were not always in complete agreement, could not fully represent the opinions of others in the field, and did not have detailed knowledge of all the conditions that were considered.

The Working Group tried to include conditions on the list for which confirmatory approaches for medical diagnosis would be available, although we recognized that this standard could not be met for all the conditions listed. The Working Group prioritized disorders for which preventive measures and/or treatments were available and disorders in which individuals with pathogenic mutations might be asymptomatic for long periods of time. In most cases, the Working Group recommended restricting the variants to be reported as incidental findings to those fitting two descriptive categories: “Sequence variation is previously reported and is a recognized cause of the disorder” or “Sequence variation is previously unreported and is of the type which is expected to cause the disorder”.²⁰ For the purposes of these recommendations, variants fitting these descriptions were labeled as Known Pathogenic (KP) and Expected Pathogenic (EP), respectively. These categories were chosen because we recognized the challenge of attempting to report and interpret variants of unknown significance as incidental findings. Given the low prior probability that an individual has a monogenic disorder that could be identified incidentally through exome or genome sequencing, we recommended that only variants with a higher likelihood of causing disease be reported as incidental

findings, although we recognize that there are limited data available in many cases to make this assessment.

Although some definitions of incidental findings allude to findings that are discovered without actually searching for results, this was not the basis for our recommendations. The Working Group recommended that the laboratory actively search for the specified types of mutations in the genes listed in these recommendations.

In making these recommendations, the Working Group addressed only the circumstance in which the report of incidental findings would be delivered to the clinician who ordered the clinical sequencing. It was expected that this clinician would contextualize any incidental findings for the patient in light of personal and family history, physical examination, and other relevant findings. This places responsibility for managing incidental findings with the ordering clinician, because we believe that the clinician–patient interaction is the appropriate place for such information to be explained and discussed.^{21,22}

Limitations and interpretation of incidental findings

The Working Group recognized that when a laboratory evaluates genes for the specified categories of variants recommended here as incidental findings, the analysis may not be technically equivalent to examining these genes as a primary finding. For example, clinical sequencing could have areas of diminished or absent coverage in the genes examined for incidental findings that would be filled in by Sanger sequencing or other supplementary approaches if the gene were being evaluated for a primary indication. In addition, although genome sequencing can provide increasingly reliable information on copy-number variation and translocations, exome sequencing is currently less reliable, and neither technology can be used to measure tandem repeat size accurately. For these reasons, we did not include some disorders for which structural variants (e.g., translocations and inversions), repeat expansions, or copy-number variations are the primary cause and have not recommended that laboratories utilize orthogonal techniques to search for these variants in the genes named in the minimum list. Therefore, the Working Group recommended that laboratories evaluate these genes for the specified categories of variants to the extent that the available data from the genome or exome sequence allow. We did not recommend that laboratories ensure a depth of coverage for these genes equivalent to molecular testing for a primary indication. Given these recommendations, the Working Group was concerned that a negative incidental findings report could be misconstrued by clinicians or patients as an assurance of the absence of a pathogenic variant, which is not always the case. To address this, we recommended that the report of incidental findings issued by the laboratory include distinct language differentiating the quality of the incidental findings report from the quality of molecular testing that would be conducted for a primary indication.

On the other hand, when there is a positive incidental finding, the Working Group recommended that laboratories review available literature and databases at the time of the sequence interpretation to ensure there is sufficient support for

pathogenicity before reporting a variant. The Working Group recognized that there is no single database currently available that represents an accurately curated compendium of known pathogenic variants, nor is there an automated algorithm to identify all novel variants meeting criteria for pathogenicity. Therefore, evaluation and reporting of positive findings in these genes may require significant manual curation.

Patient preferences and incidental findings

Standards for molecular testing in clinical genetics have largely evolved around testing an affected individual or suspected carrier for a mutation or testing an unaffected relative of a patient with a known mutation. In these situations, extensive pretest counseling can ascertain with confidence the preference of the individual to be tested in terms of choosing whether or not to obtain a particular genetic test for a specific hereditary condition. By contrast, after clinical genome or exome sequencing for a specific indication, the patient has already undergone an assay of all other disease-associated genes. To respect preferences in the same manner as with targeted testing, the patient whose exome or genome is sequenced would have to undergo an extensive, and possibly overwhelming, amount of genetic counseling for numerous conditions unrelated to the primary indication for sequencing. This will become impractical as clinical sequencing becomes more common, and both its lack of standardization and its application to patients of all circumstances might result in deeply varying levels of truly informed preference setting.

Even if preferences about receiving a limited set of incidental findings were accurately explained, carefully noted, and clearly communicated to the laboratory, the laboratory would have to mask the informatics analysis of specific genes or ignore findings of potential medical importance in order to honor those preferences. All of this may be feasible in an environment where the laboratory is an interactive partner in the clinical assessment of a patient by clinicians skilled in genetics and genetic counseling but will become increasingly unwieldy as clinical sequencing becomes more common and more commonly ordered by clinicians with varying levels of ability and experience in genetic counseling. On the basis of these considerations, the Working Group did not favor offering the patient a preference as to whether or not their clinician should receive a positive finding from the minimum list of incidental findings described in these recommendations. We recognize that this may be seen to violate existing ethical norms regarding the patient's autonomy and "right not to know" genetic risk information. However, in selecting a minimal list that is weighted toward conditions for which penetrance may be high and intervention may be possible, we felt that clinicians and laboratory personnel have a fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy, just as it does in the reporting of incidental findings elsewhere in medical practice. The Working Group therefore recommended that whenever clinical sequencing is ordered, the ordering clinician should discuss with the patient the possibility of incidental findings and

that laboratories should seek and report findings from the list described in [Table 1](#) without reference to patient preferences. Autonomy is preserved since patients have the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing.

Incidental findings in children

The standards for predictive genetic testing in clinical genetics recognize a distinction between the scenario where a clinician provides results to adults versus children and adolescents, with consistent recommendations that predictive testing for adult-onset diseases not be performed on children.²³⁻²⁵ However, these recommendations can be inconsistent with the general practice of respecting parental decision making about their children's health, and questions have been raised about the sustainability of these standards in an era of comprehensive genomic testing.²⁶ One of these recent policy statements noted "results from genetic testing of a child may have implications for the parents and other family members. Health-care providers have an obligation to inform parents and the child, when appropriate, about these potential implications."²⁴ This statement suggests an important consideration in the era of genomic medicine because after sequencing a child for a primary indication it becomes relatively easy for a laboratory to report a limited number of variants for conditions that could be medically important to that child's future or to the rest of the family.

The Working Group recognized that this is a transitional moment in the adoption of genomic medicine where the parents of children undergoing sequencing do not have easy access to inexpensive, readily interpretable exome or genome sequencing in order to obtain personal risk information for the conditions on our minimum list. In the future, when parents might all have such access, the identification of adult-onset disease variants in their children could be restricted. But at this moment in the evolution of clinical sequencing, an incidental finding relevant to adult disease that is discovered and reported to the clinician through clinical sequencing of a child may be the only way in which that variant will come to light for the parent. As with the argument against preferences, the Working Group felt that masking or tailoring the reporting of such information according to the age of the patient could place an unrealistic burden on the laboratories facing increasing volumes of clinical sequencing. The Working Group also felt that the ethical concerns about providing the clinicians of children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding for which intervention might be possible. Therefore, the Working Group recommended that recommendations for seeking and reporting incidental finding to ordering clinicians not be limited by the age of the person being sequenced.

Circumstances not addressed in these recommendations

The Working Group elected not to address a number of issues related to incidental findings in clinical sequencing. Conditions that were part of routine newborn screening were excluded

because they have their own assessment criteria and are applied in a specific public health framework. Similarly, these recommendations address incidental findings sought and reported during clinical sequencing for a specific clinical indication but do not address preconception sequencing, prenatal sequencing, newborn sequencing, or sequencing of healthy children and adults. In particular, the issues associated with genomic sequencing in healthy individuals of any age will become increasingly salient as costs decline and informatics interpretation algorithms improve, but the value of population screening for prevention and health promotion raises complex questions of potential benefits as well as downstream risks and costs that will need considerably more data to resolve.^{27–30} We acknowledged but did not address the possibility that clinical sequencing may be ordered by specialists who may not feel comfortable discussing incidental findings pertaining to another organ system, thus generating additional consultations and medical costs. We elected not to consider questions of data ownership or the legal ramifications of returning or withholding raw sequencing results from families that request these. We also did not address issues of patents in making these recommendations or any of the issues associated with duty to re-contact ordering clinicians and update the interpretation of their clinical sequences.³¹ We have not addressed the implications of including incidental findings in laboratory reports that will become part of the patient's health record and the potential for discrimination that could arise from this circumstance. We recognize that laboratories that adopt these recommendations may add significant costs to at least some of their sequencing reports with primer design and Sanger confirmation of positive findings, evidence review, report generation, and sign-out. We do not know the implications that this may have on reimbursement for clinical sequencing.

There is an active debate about the return of incidental findings in genomic research, and recommendations for this setting are evolving. Although we hope that investigators find our process and these recommendations useful in their attempts to design thresholds and lists for the return of genomic findings to research participants, we did not design this list for that purpose. The Working Group has designed these recommendations for the situation in which a clinician orders exome or genome sequencing for a specific clinical indication. In this circumstance, a laboratory report will be returned to that clinician, who will ideally be in a position to integrate such findings with the medical and family history and the physical examination, taking into account the psychological state of the patient and the patient's family. Although we recognize that this ideal may not always be realized, this is nonetheless a very different scenario from the disclosure of sequence information outside of the medical care system. The return of incidental findings discovered in the course of a clinical laboratory investigation is consistent with such practices in other disciplines of medicine.

RECOMMENDATIONS

1. Constitutional mutations found in the genes on the minimum list (**Table 1**) should be reported by the laboratory

to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered.

- Additional genes may be analyzed for incidental variants, as deemed appropriate by the laboratory.
 - Incidental variants should be reported regardless of the age of the patient.
 - Incidental variants should be reported for any clinical sequencing conducted on a constitutional (but not tumor) tissue. This includes the normal sample of a tumor-normal sequenced dyad and unaffected members of a family trio.
2. The Working Group recommends that laboratories seek and report only the types of variants within these genes that we have delineated (**Table 1**).
 - For most genes, only variants that have been previously reported and are a recognized cause of the disorder or variants that are previously unreported but are of the type that is expected to cause the disorder, as defined by prior ACMG guidelines,²⁰ should be reported.
 - For some genes, predicted loss-of-function variants are not relevant (e.g., *COL3A1* and most hypertrophic cardiomyopathy genes).
 - For some genes (e.g., *APOB*), laboratories should only report variants for certain associated conditions.
 3. It is the responsibility of the ordering clinician/team to provide comprehensive pre- and posttest counseling to the patient.
 - Clinicians should be familiar with the basic attributes and limitations of clinical sequencing.
 - Clinicians should alert patients to the possibility that clinical sequencing may generate incidental findings that could require further evaluation.
 - Given the complexity of genomic information, the clinical geneticist should be consulted at the appropriate time, which may include ordering, interpreting, and communicating genomic testing.
 4. These recommendations reflect limitations of current technology and are therefore focused on disorders that are caused by point mutations and small insertions and deletions, not those primarily caused by structural variants, repeat expansions, or copy-number variations.
 5. The Working Group recommends that the ACMG, together with content experts and other professional organizations, refine and update this list at least annually.

DISCUSSION

The ACMG recommends that for any evaluation of clinical sequencing results, all of the genes and types of variants in **Table 1** should be examined and the results reported to the ordering clinician. The conditions listed in **Table 1** are those that the Working Group and external reviewers considered most likely to be verifiable by other diagnostic methods and amenable to medical intervention based on current evidence and the clinical consensus of the Working Group members. Reporting these incidental findings to the ordering clinician

Table 1 Conditions, genes, and variants recommended for return of incidental findings in clinical sequencing

Phenotype	MIM-disorder	PMID-Gene Reviews entry	Typical age of onset	Gene	MIM-gene	Inheritance ^a	Variants to report ^b		
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	<i>BRCA1</i>	113705	AD	KP and EP		
				<i>BRCA2</i>	600185				
Li–Fraumeni syndrome	151623	20301488	Child/adult	<i>TP53</i>	191170	AD	KP and EP		
Peutz–Jeghers syndrome	175200	20301443	Child/adult	<i>STK11</i>	602216	AD	KP and EP		
Lynch syndrome	120435	20301390	Adult	<i>MLH1</i>	120436	AD	KP and EP		
				<i>MSH2</i>	609309				
				<i>MSH6</i>	600678				
				<i>PMS2</i>	600259				
Familial adenomatous polyposis	175100	20301519	Child/adult	<i>APC</i>	611731	AD	KP and EP		
<i>MYH</i> -associated polyposis; adenomas, multiple colorectal, <i>FAP</i> type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	<i>MUTYH</i>	604933	AR ^c	KP and EP		
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	<i>VHL</i>	608537	AD	KP and EP		
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	<i>MEN1</i>	613733	AD	KP and EP		
Multiple endocrine neoplasia type 2	171400	20301434	Child/adult	<i>RET</i>	164761	AD	KP		
	162300								
Familial medullary thyroid cancer ^d	1552401	20301434	Child/adult	<i>RET</i>	164761	AD	KP		
<i>PTEN</i> hamartoma tumor syndrome	153480	20301661	Child/adult	<i>PTEN</i>	601728	AD	KP and EP		
Retinoblastoma	180200	20301625	Child	<i>RB1</i>	614041	AD	KP and EP		
Hereditary paraganglioma–pheochromocytoma syndrome	168000 (PGL1)	20301715	Child/adult		<i>SDHD</i>	AD	KP and EP		
	601650 (PGL2)				<i>SDHAF2</i>			613019	KP
	605373 (PGL3)				<i>SDHC</i>			602413	KP and EP
	115310 (PGL4)				<i>SDHB</i>			185470	
Tuberous sclerosis complex	191100	20301399	Child	<i>TSC1</i>	605284	AD	KP and EP		
	613254			<i>TSC2</i>	191092				
<i>WT1</i> -related Wilms tumor	194070	20301471	Child	<i>WT1</i>	607102	AD	KP and EP		
Neurofibromatosis type 2	101100	20301380	Child/adult	<i>NF2</i>	607379	AD	KP and EP		
Ehlers–Danlos syndrome, vascular type	130050	20301667	Child/adult	<i>COL3A1</i>	120180	AD	KP and EP		
Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700	20301510	Child/adult	<i>FBN1</i>	134797	AD	KP and EP		
	609192	20301312		<i>TGFBR1</i>	190181				
	608967	20301299		<i>TGFBR2</i>	190182				
	610168			<i>SMAD3</i>	603109				
	610380			<i>ACTA2</i>	102620				
	613795			<i>MYLK</i>	600922				
	611788			<i>MYH11</i>	160745				

^aSome conditions that may demonstrate semidominant inheritance (SD) have been indicated as autosomal dominant (AD) for the sake of simplicity. Others have been labeled as X-linked (XL); ^bKP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list. ^cAlthough carriers may have modestly increased risk, we recommend searching only for individuals with biallelic mutations; ^dOn the basis of evidence presented to the Working Group after the online posting of these Recommendations, the decision was made to remove one gene, *NTRK1*, from the recommended list.

Table 1 Continued on next page

Table 1 Continued

Phenotype	MIM-disorder	PMID-Gene Reviews entry	Typical age of onset	Gene	MIM-gene	Inheritance ^a	Variants to report ^b	
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197	20301725	Child/adult	<i>MYBPC3</i>	600958	AD	KP and EP	
	192600			<i>MYH7</i>	160760		KP	
	601494			<i>TNNT2</i>	191045		KP and EP	
	613690			<i>TNNI3</i>	191044		KP	
	115196			<i>TPM1</i>	191010			
	608751			<i>MYL3</i>	160790			
	612098			<i>ACTC1</i>	102540			
	600858			<i>PRKAG2</i>	602743			
	301500			<i>GLA</i>	300644		XL	KP and EP (hemi, het, hom)
	608758			<i>MYL2</i>	160781		AD	KP
115200	<i>LMNA</i>	150330		KP and EP				
Catecholaminergic polymorphic ventricular tachycardia	604772			<i>RYR2</i>	180902	AD	KP	
Arrhythmogenic right-ventricular cardiomyopathy	609040	20301310	Child/adult	<i>PKP2</i>	602861	AD	KP and EP	
	604400			<i>DSP</i>	125647			
	610476			<i>DSC2</i>	125645			
	607450			<i>TMEM43</i>	612048			KP
	610193			<i>DSG2</i>	125671			KP and EP
Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome	192500	20301308	Child/adult	<i>KCNQ1</i>	607542	AD	KP and EP	
	613688			<i>KCNH2</i>	152427			
	603830			<i>SCN5A</i>	600163			
	601144							
Familial hypercholesterolemia	143890	No GeneReviews entry	Child/adult	<i>LDLR</i>	606945	SD	KP and EP	
	603776			<i>APOB</i>	107730	SD	KP	
				<i>PCSK9</i>	607786	AD		
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	<i>RYR1</i>	180901	AD	KP	
				<i>CACNA1S</i>	114208			

^aSome conditions that may demonstrate semidominant inheritance (SD) have been indicated as autosomal dominant (AD) for the sake of simplicity. Others have been labeled as X-linked (XL); ^bKP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list. ^cAlthough carriers may have modestly increased risk, we recommend searching only for individuals with biallelic mutations; ^dOn the basis of evidence presented to the Working Group after the online posting of these Recommendations, the decision was made to remove one gene, *NTRK1*, from the recommended list.

will offer the clinician, or an appropriate consulting clinician, the opportunity to re-evaluate the patient's personal and family history and consider appropriate surveillance or intervention for patients and their family members who are deemed to be at increased risk for these conditions. These recommendations should be understood to represent a minimum list that is a starting point for the selection and reporting of incidental findings, fully acknowledging that as additional evidence and expertise are applied, these recommendations will require ongoing modification. The ACMG recognizes that laboratories may need to take some time to implement these recommendations.

For most of the recommended genes, only variants that have been previously reported and are a recognized cause of the disorder, or variants that are previously unreported and are of the

type expected to cause the disorder, have been recommended for analysis and reporting. An argument could be made for the examination and reporting of a broader range of novel variation predicted informatically to be of possible significance. However, because informatics tools are still unreliable predictors of variant impact, particularly for missense variants, and because incidental findings are, by definition, identified in persons outside of the clinical indication for testing, these patients are at a low prior probability of being affected by the conditions in **Table 1**. The conditions and variant thresholds we selected for reporting incidental findings have therefore been set to try to maximize the benefits (increasing the likelihood of true-positive results) and minimize the harms (decreasing the likelihood of false-positive results).

There is a concern that incidental variant reporting could be misinterpreted as an exhaustive evaluation of all variation within the genes on this list. These recommendations should not be construed as an expectation that the laboratory comprehensively assess these genes for all variants but rather that the laboratory evaluate the sequence data on these genes that are generated in the course of routine clinical sequencing. There is potential for confusion and even harm to patients if the clinician misunderstands these limitations of the incidental findings report. For example, if incidental findings are returned without identification of mutations for any of the cancer susceptibility syndromes, and it later comes to light that the patient has a family history suggestive of a Mendelian cancer susceptibility syndrome, the patient or other family members might incorrectly consider themselves to have been “tested” and found to be “negative.” In fact, a novel missense mutation could be segregating with affected family members and may (appropriately) not have been included in the report of incidental findings. An analogous situation has been noted with false-negative findings in newborn screening.³² To ensure that these considerations are properly presented to the clinicians, we recommend that laboratories develop an appropriate reporting metric that will make clear the extent of the evaluation that has been conducted. This will allow clinicians to consider the sensitivity of the analysis when making clinical assessments and will help avoid overinterpretation of a negative incidental variant analysis.

All of these considerations should be incorporated into an incidental or secondary results report that provides clinicians with a clear summary of the analysis that was performed, the depth of coverage and other quality metrics, and any findings. We estimate from a limited amount of published data³³ that ~1% of sequencing reports will include an incidental variant from **Table 1**. As recommended in the ACMG policy statement on clinical sequencing,¹⁵ the clinician ordering these tests is responsible for providing or ensuring the provision of pretest counseling so that the patient is aware of not only the implications and limitations of the primary testing but also the analysis that is being performed for incidental findings. The clinician should also provide posttest counseling and medical follow-up as described in the prior ACMG policy statement on Clinical Application of Genomic Sequencing. The informed consent process for clinical sequencing should follow the forthcoming guideline from the ACMG.

The return of incidental findings to clinicians who have ordered clinical sequencing on minor children presents difficult issues. The Working Group felt it best not to place arbitrary age restrictions or limitations on the return of incidental variants because such variants would likely have implications for others in the family. For example, the sequencing of a child and the discovery of incidental findings that increase the risk of adult-onset cancer predisposition may be medically important to one of the parents of that child. In this scenario, the result has been generated and is fully available. To mask or withhold the incidental finding from the clinician is to state that the child’s right

not to know supersedes the parent’s opportunity to discover a life-threatening risk factor. We recognize that this recommendation differs from those developed around candidate gene testing. There are legitimate concerns about whether pediatricians should be asked to receive and manage results pertaining to adult-onset conditions and about the psychological impact of such information on the family. We further acknowledge that there are groups proposing to avoid this issue when sequencing children by sophisticated masking of off-target genes, making them unavailable for evaluation.³⁴ Nonetheless, we believe that sequencing creates a different calculus than that which was envisioned with predictive testing for a familial condition. In the absence of clarifying data about the actual harms of learning about adult-onset conditions in children, or the actual benefits to parents who might learn previously unsuspected risk information through sequencing of their child, we have recommended disclosure of the conditions, genes, and variants listed in **Table 1** in reports sent to the clinicians of both adults and children who undergo clinical sequencing.

The Working Group recognizes that there is a wide range of opinions about what constitutes incidental findings in clinical sequencing and how they should be managed. On one side are genetic libertarians who feel that patients have the right to full and complete accounting of all possible risks conveyed by both established and novel variants, or even variants of unknown significance in disease genes. On the other side are genetic empiricists who believe that there is insufficient evidence about the penetrance of most pathogenic variants in the general population to warrant the sharing of any incidental findings, and that it is irresponsible to create the psychological burdens of being a “patient in waiting”³⁵ or to expose patients to iatrogenic harm of possibly unnecessary surveillance or diagnostic testing. An argument is sometimes made that if the search for incidental findings were warranted, then it would follow that broad-based population screening should be advocated. In reality, seeking and reporting of incidental findings represents a form of “opportunistic screening”³⁶ that has a long history in clinical medicine. When patients complain of symptoms in the digestive system, the well-trained physician examines cardiac and respiratory systems as well, both for clues to a multisystem disease and to incidentally discover any unrelated signs. When radiographs are read for a particular anatomical focus, the radiologist scans the entire radiograph and also reports on abnormal findings in regions not indicated as the primary reason for the study. In these situations, unlike population screening with its requirement of extensive cost and infrastructure, the patient has already presented to the medical care system, has been evaluated, and is under the care of a clinician. Moreover, much of the cost of the study and any associated risk has already been sustained for the primary indication, lowering the cost/risk-to-benefit ratio for the discovery of incidental findings.

The Working Group recognizes that many of the concerns, debates, and widely varying opinions described here are the consequences of a lack of empiric data. We recognize this critical limitation but nonetheless agreed that an initial set

of recommendations was appropriate at this time. To address the lack of data, the Working Group encourages prospective research on incidental or secondary findings and the development of a voluntary national patient registry to longitudinally follow individuals and their families who receive information about incidental or secondary findings from their clinicians as part of clinical sequencing and document the benefits, harms, and costs that may result.

In summary, the ACMG that when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician, who can place them into the context of that patient's medical and family history, physical examination, and other laboratory testing. We have recommended that these findings be reported without seeking preferences from the patient and family and without considering the limitations associated with patient's age. In this, we attempt to strike a balance between the positions of genetic libertarians and the genetic empiricists, guided by the currently available scientific literature, clinical experience, the consensus of our Working Group members, and the traditions of clinical medicine. This list should, and will, evolve as further empirical data are collected on the actual penetrance of these variants and on the health benefits and costs that might follow from their disclosure as incidental findings.

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