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Discussion paper of the IARC Ethics Committee on the management of incidental findings in genomic research studies

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Disclaimer

The International Agency for Research on Cancer (IARC) Ethics Committee (IEC) analysed articles, guidelines, and position papers on the management of incidental findings in genomic studies, published up to December 2015. This discussion paper does not claim to reflect a systematic or exhaustive review of the literature, but represents the views of the IEC based on different ethical, scientific, and practical considerations. This paper does not represent the position or policy of IARC or of the World Health Organization (WHO) on this matter, and it should be regarded simply as a starting point for engaging in discussions.

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Abstract

There is a growing body of literature on incidental findings (IFs) in genomic research, which provides substantial discussion of the ethical issues, but limited useful guidance exists and there is no consensus about how to manage IFs in the context of genomic studies.

Overall, support seems to be emerging in favour of a conditional return of information to research participants for clinically relevant and “actionable” IFs. However, there is at present no list, developed from systematic evidence-based reviews, of genomic IFs that satisfy these conditions and that should be returned to participants in research studies. In addition, there are no internationally agreed standards or guidelines about the process for managing the return of information on IFs, particularly in a research context without intended clinical application. The International Agency for Research on Cancer (IARC) Ethics Committee (IEC) considers that the conditions for implementing the return of information on IFs in genomic research studies have currently not been fulfilled. Therefore, the current proposal is not to require IARC studies conducted in a research setting to return information on IFs to study participants.

Because this field is developing, in this paper we (i) address the ethical and practical issues associated with the management of IFs, guided by the logic and constraints of medical screening and medical responsibility, and (ii) develop a draft proposal for dealing with studies where IFs may occur, in order to engage in discussion with scientists and ethicists on the possible implementation of the return of information on IFs.

1. Introduction

Among the emerging ethical challenges associated with the development of new technologies in the areas of molecular biology, genetics, and bioinformatics applied to human research, one of the most difficult is the management of incidental findings (IFs) in genomic studies [1, 2]. Various terms have been proposed for these findings, such as “unrelated findings”, “unanticipated findings”, or “individual genomic results”, but “incidental findings” seems to be the most widely used term. In this context, IFs are mutations or genetic variants that are associated with increased risk of certain conditions but that are unrelated to the question under investigation (for which the related results are the primary findings) and are discovered during the analysis of whole-genome or whole-exome sequencing data (as secondary, unintentional findings) [3].

The problem of IFs is neither new nor unique to genomic research. The growing body of literature on this subject provides substantial discussion of the associated ethical issues, and in some cases suggests the *conditional return* of information to research participants only for clinically relevant and “actionable” IFs, i.e. those that potentially lead to improved prognosis or quality of life. However, limited useful guidance exists, and no international consensus, developed from systematic evidence-based reviews, is available about which specific IFs could or should be returned to study participants.

Box 1 lists some of the key questions raised by the management of IFs in genomic studies. In broad terms, these fall into three main categories: the validation of the IFs, the clinical relevance and actionability of the IFs, and the process for disclosure of the IFs. These issues are briefly discussed below.

Sequencing performed in a research setting is not intended to serve for diagnostic purposes, and the duty of care of researchers is usually restricted to the context of the study. Whole-genome and whole-exome sequencing platforms used for genomic research without intended clinical application are less stringent than conventional genetic testing. The bioinformatic analysis pipelines used to analyse the sequencing data have been calibrated to detect variants in a research context, with sensitivity and specificity not suited for clinical application. Also, research laboratory workflows do not have the validation protocols to enable confirmation of genetic variants at standards expected in clinical genetic testing. Therefore, a significant proportion of IFs detected in genomic research studies are likely to be false-positives, which are not suitable as a basis for clinical decision-making without prior confirmation through properly validated clinical genetic tests.

In addition, the frequency at which clinically relevant IFs may be identified from each whole-genome sequence remains unclear. It has been estimated that each person carries an average of 50–100 germline heterozygous variants classified by the Human Gene Mutation Database as causing inherited disorders [4], although many of these associations may be due to errors in asserting the pathogenicity of the variants or in curation of the data [5].

In contrast, the sequencing requested by a geneticist in a clinical setting anticipates a higher probability of encountering a real, clinically significant finding, and the return of the information takes place in the context of the clinical encounter. Information on genomic findings, including IFs, in a research context should also be returned only by a clinical practitioner, such as a genetic counsellor, who is able to interpret the findings and advise

about their relevance and about the options available for the prevention or treatment of the condition concerned, and to provide access to psychosocial support.

Box 1. Key questions raised by incidental findings (IFs) in genomic studies

- Are the findings "real" (i.e. are the research results reliable enough)?
- Is the prediction based on these findings reliable enough (e.g. does the variant have high penetrance)?
- How should a decision be made about what specific findings to return to the research participants (i.e. those that are clinically relevant and actionable)?
- Does an "established" intervention to prevent or treat the condition exist (i.e. an intervention that is efficacious and reasonably safe as proven by carefully reviewed available evidence)?
- Does the individual have access to the intervention to prevent or treat the condition in the context of local health care, and who is responsible for providing it?
- Who will provide the information to the participant, and are there structures in place to provide this information in context (e.g. clinical genetic counselling)?
- What impact would the communication of positive findings (i.e. associated with increased risk of certain conditions) have for the individual research participant (i.e. how to weigh the adverse effects of the prediction on the individual, in cases of both correct and erroneous predictions, or its potential benefits)?
- What impact would the communication of IFs have for the family members of the individual research participant, considering that they have not consented to participate in a research study?
- What are the conditions to be fulfilled in the application of the "right not to know" of individual research participants and their family members? Are there trade-offs to be foreseen between autonomy and beneficence (i.e. the individual's right not to know and the benefits as suggested by scientific and clinical research)?
- What impact would the communication of negative findings (i.e. not associated with increased risk of certain conditions) have for the individual research participant (i.e. how to communicate the degree of uncertainty of the results and the limited set of variants tested)?
- How will additional costs associated with managing IFs, both the validation of IFs and the process for their disclosure, be funded?
- What kinds of systems and processes need to be put in place to ensure that emerging evidence about the utility of findings may inform changing practice on the return of IFs?

The criterion of actionability presupposes that the research participant has access to health-care interventions required to prevent or treat the condition concerned. Therefore, the appropriate conditions for the return of information on IFs are directly dependent on the health-care infrastructure in which the research is conducted. Moreover, disclosing IFs to research participants requires that this complex issue is appropriately explained in consent forms, so that study participants can make a truly informed choice about the return of information on IFs.

Finally, the issue of incremental costs associated with managing IFs in genomic research studies – both the validation of the IFs and the process for their disclosure – raises policy questions and requires additional resources both from the research institution and from the health-care system. Notably in low- and middle-income countries, the time and resources required for disclosure of IFs may compete with those needed for more relevant interventions for patient care. Although data on the real costs of managing IFs in large-scale studies are lacking, a recent study [6] suggested that actionable IFs may be found in only a small percentage of research participants. However, this percentage may increase with new evidence on the pathogenicity of more genetic variants.

In this discussion paper, we summarize the available guidance on the management of IFs in genomic studies and propose the adoption of a pragmatic approach based on the ethical principles of autonomy, justice, beneficence, and non-maleficence, guided by the logic and constraints of medical screening and medical responsibility [7]. Once the required standards and guidelines have been developed, new studies should offer participants the *choice* about whether to be informed of clinically relevant and actionable IFs, and the information should be returned only by a clinical practitioner, such as a genetic counsellor.

2. Available guidance

Most of the published guidance summarized below relates to the management of IFs discovered in clinical settings.

To tackle the challenges facing the deployment of whole-genome sequencing in clinical practice and public health, in 2011 Berg et al. [8] proposed a useful framework for classifying individual variants into categories of clinical significance and actionability. The authors developed a standardized, evidence-based process to define those genetic variants that should or could be reported in the context of clinical genomic tests (Fig. 1) [4, 8].

In 2012, a working group of the United States National Human Genome Research Institute (NHGRI) [9] provided some useful insights, particularly in deciding whether a specific IF should or should not be returned. They suggested that information on IFs should be returned only when all of the following conditions are met:

- the findings are scientifically valid and clinically confirmed;
- the findings have significant implications for the health of the study participant or the health of their offspring;
- the findings are actionable, i.e. a course of action to prevent, ameliorate, or treat the condition is readily available, and there is a strong net benefit for the participant; and
- the study participant has agreed to receive the information.

The NHGRI expert group did not discuss the criteria for clinical confirmation of the observed findings, for deciding which specific IFs satisfy the condition of having significant implications for the health of the participant or their offspring, or for assessing the availability of the course of action to prevent or treat the condition in different socioeconomic and health-care settings.

In 2013, in a different initiative, a working group of the American College of Medical Genetics and Genomics (ACMG) published a “minimum list” of IFs to report in clinical exome and genome sequencing (see Table 1) [10, 11], developed based on the variant’s likelihood of causing serious disease and the availability of preventive measures and/or treatment.

Initially, the ACMG recommended that laboratories should actively search for the specified mutations in all clinical genomics tests and report the findings to the clinician, who would then communicate them to the patients. This recommendation was the subject of much debate, and the authors subsequently mitigated their position, presenting their list more as an educational resource for medical geneticists and other health-care providers rather than as a recommendation of adherence [12].

The ACMG expert group estimated that, based on published data, approximately 1% of sequencing test reports will include an incidental variant from the list. Although these recommendations were made for sequencing data obtained in the clinical setting, this minimum list is a useful starting reference for further recommendations, for example for IFs in a research setting. Since then, several articles have reported estimates of the expected proportion of IFs; these have shown substantial variability, probably largely due to the lack of standardization in assessing the pathogenicity of a variant in the absence of a uniform, well-defined set of criteria for classification of variants [13–18].

In 2013, Goddard et al. [4] extended the framework proposed by Berg et al. [8] by developing a standardized process to categorize genetic variants as reportable IFs according to three criteria: actionability, penetrance, and severity/burden of the condition. They proposed a three-stage process, which they considered feasible [19] for genome-wide analysis of known variants (Fig. 1) [4, 8].

The report of Goddard et al. [4] was the first to propose a standardized, efficient, evidence-informed process to determine which genetic variants belong in the category of reportable IFs, and was a significant step towards identifying a list of reportable IFs on a genome-wide scale. However, no list of variants was explicitly published, and the approach was presented as a pilot. In 2016, Berg et al. [20] developed a semiquantitative scoring metric to assess the clinical actionability of genetic variants, in an effort to further guide the definition and listing of genetic variants to be considered for return to individuals.

With regard to research settings, the Foundation for Genomics and Population Health published a thoughtful review in the context of the United Kingdom's 100 000 Genomes Project [21]. Although the recommendations in that review were broadly similar to those of the NHGRI expert group, described above, the specific context of research compared with the clinical setting was emphasized. However, in practice, the 100 000 Genomes Project has taken a different route from this advice, and participants can request access to all data generated from their samples [22].

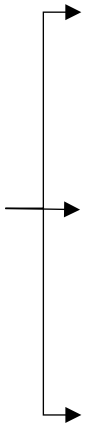
3. Proposals for the management of IFs in genomic research studies

The recent reports described above highlight the fact that there is significant activity in this area, which may lead in the near future to the definition of agreed guidelines for the management of IFs in genomic studies. The emerging trend from the literature suggests that the best practice for new studies should be the conditional return of information on IFs, provided that the findings are reliable and actionable, not only in theory but also in practice, according to the context and resources available where the research is conducted, including the availability of evidence-based clinical guidelines and relevant local expertise.

Fig. 1. Management of incidental findings in genomic research studies.

The figure summarizes the proposals by Goddard et al. [4] and Berg et al. [8] for managing the return of genomic findings.

Evaluation of the genetic variant	
Stage I	Preliminary evaluation to rule out reporting below a threshold of evidence
Stage II	Data gathering to document criteria using a standardized approach
Stage III	Evaluation of the evidence gathered in Stage II by an expert panel to consistently recommend whether results should be reported



Evaluation of return of the genetic variant		
Evaluation criteria of clinical utility and validity		**Recommended action**
Bin 1	Reliably associated with clinical outcomes and clinically actionable	Reportable
Bin 2	Reliably associated with clinical outcomes but of little benefit Reliably associated with clinical outcomes but of low penetrance Reliably associated with clinical outcomes but not actionable	Reportable only if elected by the patient
Bin 3	Not reliably associated with clinical outcomes	Not reportable

The IARC Ethics Committee (IEC) considers that the conditions for returning information on IFs in genomic research studies have not yet been fulfilled, and its position at present is not to require genomic research studies to return information on IFs to study participants. Although the possibility of IFs should be acknowledged, it is difficult to envisage in practice which IFs should be reported, and how, until specific guidance has been developed.

Once the required standards and guidelines have been developed, new studies should offer participants the choice about whether to be informed of clinically relevant and actionable IFs, where possible and feasible, according to the principles of autonomy. The return of information should be proposed within the constraints and the logic of medical screening and medical responsibility, i.e. information should be returned only if it is useful, potentially leading to improved prognosis and quality of life. A simple approach of returning all information regardless of its utility based on the "right to know" is considered inadequate. The requirement to provide individual feedback in all new studies would be unrealistic and, in some circumstances, undesirable.

Specifically, the right of access to individual results can be implemented through "active" approaches (the participant needs to actively ask for the results) or "passive" approaches (the investigators communicate the results to the participant or to the participant's physician). In principle, we recommend returning information on IFs based on an "active" scheme for access.

Ethics committees should require the principal investigators of all relevant studies to file an annual report on the occurrence of IFs and, for those studies that offer to return the information, on the process of returning it to study participants. Furthermore, ethics committees should require monitoring of the occurrence and the procedures put in place to deal with the return of information on IFs.

However, some specific situations may make it impossible in practice to return information on IFs or to return this information under appropriate conditions. For example, this applies for studies conducted in regions where no adequate local expertise or facilities exist to deal effectively with the return of information (e.g. the absence of genetic counsellors and/or the lack of health-care infrastructure to provide the needed clinical intervention), or in the case of new studies that use stored samples collected for a previous study, where the return of information is specifically excluded in the original informed consent or where it would be practically unfeasible to trace the participants.

Therefore, these situations may constitute valid exceptions to the general principle of offering the option of return of information on IFs, but the rationale for conducting the study in those particular settings (rather than in other settings with the adequate infrastructure) and/or with those specific samples must be fully justified by the study investigators in the submission for clearance by an ethics committee. This applies also to the rare occasions when samples have been fully anonymized per protocol, i.e. when the key linking the participants and the samples does not exist. In these studies, the participants should be informed in the consent form that no information on IFs will be returned to them, and that their participation in the study indicates their acceptance of these conditions.

Because this field is developing, we intend to engage in future consultation with scientists and ethicists on the possible implementation of the return of information on IFs. In this

context, we propose below an approach for dealing with IFs in different research scenarios, related to studies that collect new samples and studies that are conducted on existing biorepositories. Although the boundary between clinical and research settings can be difficult to maintain in practice, the current proposals apply only to genomic sequencing as performed for non-clinical purposes.

3.1 Studies that collect new samples

In studies that seek consent for genetic analyses, the possibility of returning information on IFs should be explicitly addressed. The consent form should emphasize the fact that the information produced by the study is valid only for research purposes. The possibility of false-positive and false-negative results should be explained to the research participants. The information on IFs should not be given directly to the study participant but should be provided to someone who can interpret it and provide advice on whether to take further action to clinically validate the findings, such as a genetic counsellor or, if one is not available, the participant's personal physician.

In studies that actively look for identified actionable variants, it should be made clear to the participant that only a limited list of variants will be considered: those for which an evidence-based assessment of clinical significance and actionability exists, based on the state of knowledge at the time (Table 1) [10, 11]. The results returned to the participant should include the full list of variants tested, stating clearly that any findings should be confirmed in a clinical setting because false-positive findings may be frequent in the research setting, and conversely, that the absence of IFs should not be interpreted as the absence of clinically significant genetic variants, due to the possibility of false-negative results and to the limited set of variants tested. Finally, the consent form should also make it clear that the involvement of the study ends when the information is passed on to the person in charge of discussing the results with the participant, and that from that time onward, the continuing care of the patient would not be the responsibility of the study.

In summary, the consent form should explain (please see Box 2):

- that the possibility of IFs exists;
- the types of IFs that may be encountered, with specific examples;
- that research results are not validated to a clinical standard, and therefore there may be errors in the genome sequencing data that result in false-positives or false-negatives;
- under which circumstances this information would be returned (i.e. clinically significant and actionable findings), and to whom;
- the advantages and potential disadvantages of learning this information;
- that the participant can choose whether or not to receive the information on IFs, meaning that the participant has the "right not to know";
- that if the participant chooses to access this information, they would have to actively request it (and instructions on how to make this request should be provided); and
- that the continuing care of the patient would not be the responsibility of the study.

In studies where the possibility of IFs exists but the study investigators feel that the return of this information to participants would not be possible or appropriate, the rationale for this decision must be thoroughly justified in the submission for ethical clearance, including a justification of why the study needs to be carried out in those particular settings. It is then up to an ethics committee to make a judgement about whether it is acceptable for the study to be allowed to proceed, and to approve a waiver of return of IFs.

Box 2. Examples of questions and answers that can be included in a consent form or information sheet on the issue of potential incidental findings (IFs)

1. Studies that offer the return of information on IFs

What will my samples be used for?

The biological samples obtained will be used for research purposes only. Any material that is not used immediately will be stored for future research to help scientists learn more about the environment, genetic changes, and health. The research results are not suitable for use as clinical tests for your medical care.

Your samples may possibly be used in future studies that examine the genetic material (DNA and RNA), and may undergo a procedure called whole-genome sequencing. These studies could determine many or all of the features of your DNA, but we are interested only in results that are relevant to health research studies.

Could any of the results be relevant and useful for my health?

It is possible that during the analyses of your samples we may find, by chance, genetic sequence results that suggest that you may have a higher risk of a genetically determined illness. However, unlike clinical investigations of genetic conditions, the information produced by the study does not provide a reliable basis for making medical decisions; it is valid only for research purposes.

If you wish to access potential results that may be of clinical relevance, you will have to contact [*name of the local coordinator*]. Before doing so, it is important that you understand the following.

- Your samples may not be among those that will undergo whole-genome sequencing, in which case no such findings can be retrieved.
- We are not in a position to indicate when and whether your samples will undergo sequencing.
- Knowledge about genetic susceptibilities is constantly progressing. We will only be able to search for genetic variants that are known at the time of the study. We will rely on variants listed by expert groups and will provide the list of variants tested.
- The results will be passed on to [*name of the local coordinator*], who will evaluate them and decide whether this information could be useful for your health care, for example in cases where the condition is potentially serious, where there is a reasonable probability that you or your relatives will be affected, and where the condition can be prevented or treated.
- The results of research tests are not as reliable as those of clinical tests, and therefore research tests can give positive (and negative) results that are not correct. This means that positive research results, which may lead you to experience anxiety, may be inaccurate. In addition, negative research results should not be interpreted as indicating the absence of clinically significant genetic conditions.
- Any positive test results would need to be re-investigated in the clinical setting. This will need to be coordinated by [*name of the local coordinator*] and your personal physician.
- You have the right not to know the information about these genetic sequence results.
- It is important to realize that genetic information of this type only suggests a possibility that you may develop a certain condition. For these reasons, if you choose to be given this information, you may undergo treatment for a condition that you would never actually develop.
- You should also understand that the involvement of the study ends at the point when the information is passed on to [*name of the local coordinator*]; your continuing care for any condition that is discovered is not the responsibility of the study.

2. Alternative for studies that do not offer the return of information on IFs

Could any of the results be relevant and useful for my health?

It is possible that during the analyses of your samples, we may find, by chance, genetic sequence results that suggest that you may have a higher risk of a genetically determined illness. However, unlike clinical investigations of genetic conditions, the information produced by the study does not provide a reliable basis for making medical decisions; it is valid only for research purposes. For this reason, we will not provide any personal genetic results to the study participants.

3.2 Studies conducted on existing biorepositories

Although some of the literature provides useful recommendations on dealing with IFs in the context of new prospective studies, few reports or reviews, if any, offer guidance on how to deal with IFs in the context of studies that use stored biological samples.

As mentioned above, in most of these studies it would not be possible to return information on IFs based on the original consent, because the return of research results is usually explicitly excluded. The only option would be to contact the participants and re-consent their participation in the new study, giving them the option to opt in to the return of IFs. However, it may prove technically unfeasible to trace individual participants to re-consent; in addition, re-contacting individual research participants or their families is likely to cause distress, raising additional ethical concerns.

For these reasons, for studies using stored samples, we consider that the investigators should not return information on IFs if the following criteria are justified:

- the study needs to be conducted with these particular samples;
- the use of the samples will serve a scientific objective that is coherent with the primary objectives as stated when the samples were collected, and the original consent made clear that the samples would be used for genetic tests;
- the local infrastructure cannot appropriately deal with the return of information on IFs; and
- re-consenting the study participants is materially unfeasible (this would be an extension of Guideline 11 of the International Ethical Guidelines of the Council for International Organizations of Medical Sciences [23]), or re-contacting the individual research participants or their families is likely to cause distress and raises ethical concerns.

4. Conclusions

We consider that the conditions for returning information on IFs in genomic research studies have not yet been fulfilled. Although the possibility of IFs should be acknowledged, it is difficult to envisage in practice which IFs should be reported, and how, until specific guidance has been developed. Our position will be continually reviewed and may evolve as new evidence becomes available, and the use of the term “incidental findings” should be revisited if the option to specifically search through known variants is put in place. Once the required standards and guidelines have been developed, new studies should offer participants the choice about whether to be informed of IFs, where possible and feasible, according to the principles of autonomy. The return of information should be proposed within the constraints and the logic of medical screening and medical responsibility, i.e. information should be returned only if it is useful, potentially leading to improved prognosis and quality of life. Ethics committees should require monitoring of the occurrence of IFs and the process of returning the findings to study participants.

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Table 1. Minimum list of identified actionable variants to be reported in clinical exome and genome sequencing

Adapted with permission from the American College of Medical Genetics and Genomics (ACMG) expert group recommendations [11].

Disease name and associated MIM number[a]	Genetics information	Genetic test information	Clinical significance
Adenomatous polyposis coli (MIM 175100)	MedGen	APC (MIM 611731)	ClinVar
Aortic aneurysm, familial thoracic 4 (MIM 132900)	MedGen	MYH11 (MIM 160745)	ClinVar
Aortic aneurysm, familial thoracic 6 (MIM 611788)	MedGen	ACTA2 (MIM 102620)	ClinVar
Aortic aneurysm, familial thoracic 7 (MIM 613780)	MedGen	MYLK (MIM 600922)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604400)	MedGen	TMEM43 (MIM 612048)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 8 (MIM 607450)	MedGen	DSP (MIM 125647)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 9 (MIM 609040)	MedGen	PKP2 (MIM 602861)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 10 (MIM 610193)	MedGen	DSG2 (MIM 125671)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 11 (MIM 610476)	MedGen	DSC2 (MIM 125645)	ClinVar
Breast-ovarian cancer, familial 1 (MIM 604370)	MedGen	BRCA1 (MIM 113705)	ClinVar
Breast-ovarian cancer, familial 2 (MIM 612555)	MedGen	BRCA2 (MIM 600185)	ClinVar
Brugada syndrome 1 (MIM 601144)	MedGen	SCN5A (MIM 600163)	ClinVar
Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)	MedGen	RYR2 (MIM 180902)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	LMNA (MIM 150330)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	MYBPC3 (MIM 600958)	ClinVar
Ehlers-Danlos syndrome, type 4 (MIM 130050)	MedGen	COL3A1 (MIM 120180)	ClinVar
Fabry's disease (MIM 301500)	MedGen	GLA (MIM 300644)	ClinVar
Familial hypercholesterolemia (MIM 143890)	MedGen	APOB (MIM 107730)	ClinVar
		LDLR (MIM 606945)	ClinVar
Familial hypertrophic cardiomyopathy 1 (MIM 192600)	MedGen	MYH7 (MIM 160760)	ClinVar
Familial hypertrophic cardiomyopathy 3 (MIM 115196)	MedGen	TPM1 (MIM 191010)	ClinVar
Familial hypertrophic cardiomyopathy 4 (MIM 115197)	MedGen	MYBPC3 (MIM 600958)	ClinVar
Familial hypertrophic cardiomyopathy 6 (MIM 600858)	MedGen	PRKAG2 (MIM 602743)	ClinVar
Familial hypertrophic cardiomyopathy 7 (MIM 613690)	MedGen	TNNI3 (MIM 191044)	ClinVar
Familial hypertrophic cardiomyopathy 8 (MIM 608751)	MedGen	MYL3 (MIM 160790)	ClinVar
Familial hypertrophic cardiomyopathy 10 (MIM 608758)	MedGen	MYL2 (MIM 160781)	ClinVar
Familial hypertrophic cardiomyopathy 11 (MIM 612098)	MedGen	ACTC1 (MIM 102540)	ClinVar
Familial medullary thyroid carcinoma (MIM 155240)	MedGen	RET (MIM 164761)	ClinVar
Hypercholesterolemia, autosomal dominant, 3 (MIM 603776)	MedGen	PCSK9 (MIM 607786)	ClinVar
Left ventricular noncompaction 6 (MIM 601494)	MedGen	TNNT2 (MIM 191045)	ClinVar
Li-Fraumeni syndrome 1 (MIM 151623)	MedGen	TP53 (MIM 191170)	ClinVar
Loeys-Dietz syndrome type 1A (MIM 609192)	MedGen	TGFBR1 (MIM 190181)	ClinVar
Loeys-Dietz syndrome type 1B (MIM 610168)	MedGen	TGFBR2 (MIM 190182)	ClinVar
Loeys-Dietz syndrome type 2A (MIM 608967)	MedGen	TGFBR1 (MIM 190181)	ClinVar
Loeys-Dietz syndrome type 2B (MIM 610380)	MedGen	TGFBR2 (MIM 190182)	ClinVar
Loeys-Dietz syndrome type 3 (MIM 613795)	MedGen	SMAD3 (MIM 603109)	ClinVar
Long QT syndrome 1 (MIM 192500)	MedGen	KCNQ1 (MIM 607542)	ClinVar
Long QT syndrome 2 (MIM 613688)	MedGen	KCNH2 (MIM 152427)	ClinVar
Long QT syndrome 3 (MIM 603830)	MedGen	SCN5A (MIM 600163)	ClinVar
Lynch syndrome (MIM 120435)	MedGen	MLH1 (MIM 120436)	ClinVar
	MedGen	MSH2 (MIM 609309)	ClinVar
	MedGen	MSH6 (MIM 600678)	ClinVar
	MedGen	PMS2 (MIM 600259)	ClinVar

Disease name and associated MIM number[a]	Genetics information	Genetic test information	Clinical significance
Malignant hyperthermia (MIM 145600)	MedGen	RYR1 (MIM 180901)	ClinVar
	MedGen	CACNA1S (MIM 114208)	ClinVar
Marfan's syndrome (MIM 154700)	MedGen	FBN1 (MIM 134797)	ClinVar
Marfan's syndrome (MIM 154700)	MedGen	TGFBR1 (MIM 190181)	ClinVar
Multiple endocrine neoplasia, type 1 (MIM 131100)	MedGen	MEN1 (MIM 613733)	ClinVar
Multiple endocrine neoplasia, type 2a (MIM 171400)	MedGen	RET (MIM 164761)	ClinVar
Multiple endocrine neoplasia, type 2b (MIM 162300)	MedGen		
MYH-associated polyposis (MIM 608456)	MedGen	MUTYH (MIM 604933)	ClinVar
Neurofibromatosis, type 2 (MIM 101000)	MedGen	NF2 (MIM 607379)	ClinVar
Paragangliomas 1 (MIM 168000)	MedGen	SDHD (MIM 602690)	ClinVar
Paragangliomas 2 (MIM 601650)	MedGen	SDHAF2 (MIM 613019)	ClinVar
Paragangliomas 3 (MIM 605373)	MedGen	SDHC (MIM 602413)	ClinVar
Paragangliomas 4 (MIM 115310)	MedGen	SDHB (MIM 185470)	ClinVar
Peutz-Jeghers syndrome (MIM 175200)	MedGen	STK11 (MIM 602216)	ClinVar
Pilomatrixoma (MIM 132600)	MedGen	MUTYH (MIM 604933)	ClinVar
PTEN hamartoma tumour syndrome (MIM 153480)	MedGen	PTEN (MIM 601728)	ClinVar
Retinoblastoma (MIM 180200)	MedGen	RB1 (MIM 614041)	ClinVar
Tuberous sclerosis 1 (MIM 191100)	MedGen	TSC1 (MIM 605284)	ClinVar
Tuberous sclerosis 2 (MIM 613254)	MedGen	TSC2 (MIM 191092)	ClinVar
Von Hippel-Lindau syndrome (MIM 193300)	MedGen	VHL (MIM 608537)	ClinVar
Wilms' tumour (MIM 194070)	MedGen	WT1 (MIM 607102)	ClinVar

[a] MIM, Mendelian Inheritance in Man.

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