

Secondary findings in the era of genomic medicine

Zuzana Kubiritová

Institute for Clinical and Translational Research, Biomedical Research Center, Slovak Academy of Sciences, Bratislava

By the using of whole exome and whole genome analyses in the field of genomic medicine, an amount of data generated is increasing widening thus also the spectrum of results from genetic analyses. Secondary findings (SF) represent the results of genetic analysis that are not directly related to the primary aim of the analysis. These are positive findings in genes known to cause rare genetic diseases for which there is currently some form of therapy or prevention. The association of *American College of Medical Genetics and Genomics (ACMG)* recommends to investigate these genes in parallel with the every primary analysis ordered and encourage laboratories/clinicians to disclose these results to patients. However, besides that such SF have potential medical benefit, they also represent additional work for the laboratories/clinicians, and certain psychological burden for patients and their relatives. Therefore, there are different views on ACMG recommendations and the question is widely debated.

Keywords: secondary findings; incidental findings; genetic testing and screening; massively parallel sequencing

Sekundárne zistenia v ére genomickej medicíny

Pri používaní celoexómových a celogenómových analýz v genomickej medicíne narastá množstvo generovaných dát, teda aj spektrum výsledkov genetických analýz. Sekundárne zistenia predstavujú výsledky genetickej analýzy, ktoré sa netýkajú priamo primárnej analýzy. Sú to pozitívne nálezy v génoch, o ktorých je známe, že zapríčiňujú zriedkavé genetické ochorenia, pre ktoré v súčasnosti existuje nejaká forma terapie či prevencie. Spoločnosť Amerického kolégia lekárskej genetiky a genomiky (ACMG) odporúča vyšetrovať takéto gény popri primárnej analýze, pričom odporúča tiež, aby laboratóriá/lekári reportovali tieto výsledky pacientom. Hoci sekundárne zistenia majú potenciálny medicínsky benefit, predstavujú prácu navyše pre laboratóriá a lekárov, ako aj psychickú záťaž pre pacienta a jeho príbuzných. Preto na odporúčania ACMG existujú rôzne názory.

Kľúčové slová: sekundárne zistenia; náhodné zistenia; genetické testovanie a skrining; masívne paralelné sekvenovanie

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Introduction

Due to technological advances and decreasing cost of DNA sequencing, especially the massively parallel (MPS) versions of it, this method became accessible for many indications and for many health care providers⁽¹⁾. Applications of MPS expand to many other fields. They are useful for identification of *de novo* variants, diagnostics of monogenic and complex diseases and also for prognostic, reproductive and prenatal diagnostics and in choosing of appropriate therapy^(2,3). Fast implementation of MPS into clinical practice in a relatively short time brought many challenges and barriers, which must be overcome for effective use of benefits and opportunities offered by MPS in the context of improving healthcare. At present, there are available plenty of molecular-diagnostics tests, ranging from analysis of single gene or gene panels to sequencing analysis of whole exomes (WES) or even whole genomes (WGS). Secondary findings represent one of many benefits offered by MPS. This article provides an overview of main aspects and problems regarded of managing of secondary findings, which are currently the most discussed topic in the field of genomic medicine. Practical application of secondary findings analysis represent another important part of this topic, however they are not subject of this article.

Incidental and secondary findings

As DNA sequencing getting scaled up to exome and genome levels, it increases the probability of identification of potential abnormalities that are not directly related to the reasons, for which testing was primarily ordered. These findings are named by a well-known term „incidental findings“ (IF)⁽⁴⁾. It is estimated that during WES the probability of identification of such type of finding in adult population is 1,2%-5% and is rising if the analyzed region is increasing⁽⁵⁾. The primary findings are always results of active investigation of primary genomic targets for which the test was designed. However, IF do not describe always the same and for example for patient undergoing testing due to suspected diagnosis, IF could mean something different as for clinician who can expect such findings (known as anticipatable findings). On the other hand, for healthy individuals undergoing genetic testing from various reasons virtually all findings are incidental^(4,6). In 2013, the association of *American College of Medical Genetics and Genomics (ACMG)* created the minimum list of genes and recommended to investigate these genes in addition with any ordered primary genomic analysis. From the findings in these genes they recommended to report well known pathogenic and likely pathogenic variants to patient as IF. The list included 56 genes that are associated with rare

monogenic diseases for which there is an effective therapy or prevention available (so called preventable clinical conditions). These are mainly cardiologic conditions and specific types of cancers⁽⁷⁾. The ACMG also elaborated a process for including/excluding genes for the minimum list and established the Working Group for overseeing of updating the list. In line with this, in 2016 they published the updated ACMG recommendations with 59 genes on the list (**Table 1**) and several updates on recommendations. The ACMG recognized the need for detailed informed consent in which patient can choose if want to know the results of such analysis. Second change was that the term „secondary finding“ (SF) replaced the original term of „incidental findings“, because „IF“ is not suitable name for process in which genes from the list are intensively investigated, i.e. they are not truly incidental⁽⁸⁾. The term „incidental findings“ was reserved to those which are to be found in the region of the primary analysis but are not related to the primary diagnosis. It was reported that approximately 2% of all samples sequenced had such a finding⁽⁹⁾, while similar frequency of positive SF was also confirmed in a recent study in which 1%-1,5% out of 5000 participants have a SF in genes from the ACMG list⁽¹⁰⁾.

Attitudes to the analysis of secondary findings

Genomic testing has tended to move from research to clinical practice, however it is important to emphasize that

the research and the clinical field are two fundamentally different activities. While the main objective of research is progress in science, in clinical field it is a responsibility for patient. Participants of research studies are usually patients recommended by clinician, so it is necessarily to set up conditions in accordance with ethic principles which are common in clinical field. It means that a component of research should be the ethic protocol, which is a generally adhered in clinical care, although in research normally does not exist⁽¹¹⁾. Because of this it is difficult to decide how to approach of processing SF and so various views exist on the ACMG recommendations. Also, other organizations have published the recommendations regarding SF in genomic sequencing. Unlike ACMG recommendations these differ mainly in attitude to opportunistic screening also in the case of life threatening clinically relevant findings. As an example, the recommendations of the Canadian College of Medical Genetics (CCMG)⁽¹²⁾ and the recommendations of the European Society for Human Genetics (ESHG)⁽¹³⁾, these prefer cautious approach in analysis of SF regarding to lack of empiric knowledge about clinical significance of some variants. Both recommendations prefer targeted approach for analysis of genomic results and with the use of selective filtering process they limit the analysis only to narrow choice of genes related to primary request of testing. By this approach they avoid of detection of SF (**Table 2**). Recently, The French Society of Predictive

Table 1. The list of genes recommended by ACMG for analysis of secondary findings. In the table there are 29 phenotypes of rare diseases and 59 genes associated with them. Next to the gene it is indicated a mode of inheritance.

Phenotype	Gene and inheritance
Hereditary breast and ovarian cancer	<i>BRCA1</i> ^{AD} , <i>BRCA2</i> ^{AD}
Li-Fraumeni syndrome	<i>TP53</i> ^{AD}
Peutz-Jeghers syndrome	<i>STK11</i> ^{AD}
Lynch syndrome	<i>MLH1</i> ^{AD} , <i>MSH2</i> ^{AD} , <i>MSH6</i> ^{AD} , <i>PMS2</i> ^{AD}
Familial adenomatous polyposis	<i>APC</i> ^{AD}
<i>MYH</i> -associated polyposis; adenomas, multiple colorectal, <i>FAP</i> type 2	<i>MUTYH</i> ^{AR}
Juvenile polyposis	<i>BMPR1A</i> ^{AD} , <i>SMAD4</i> ^{AD}
Von Hippel-Lindau syndrome	<i>VHL</i> ^{AD}
Multiple endocrine neoplasia type 1	<i>MEN1</i> ^{AD}
Multiple endocrine neoplasia type 2	<i>RET</i> ^{AD}
Familial medullary thyroid cancer	<i>RET</i> ^{AD}
<i>PTEN</i> hamartoma tumor syndrome	<i>PTEN</i> ^{AD}
Retinoblastoma	<i>RB1</i> ^{AD}
Hereditary paraganglioma-pheochromocytoma syndrome	<i>SDHD</i> ^{AD} , <i>SDHAF2</i> ^{AD} , <i>SDHC</i> ^{AD} , <i>SDHB</i> ^{AD}
Tuberous sclerosis complex	<i>TSC1</i> ^{AD} , <i>TSC2</i> ^{AD}
WT1-related Wilms tumor	<i>WT1</i> ^{AD}
Neurofibromatosis type 2	<i>NF2</i> ^{AD}
Ehlers-Danlos syndrome, vascular typer	<i>COL3A1</i> ^{AD}
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aneurysms and dissections	<i>FBN1</i> ^{AD} , <i>TGFBR1</i> ^{AD} , <i>TGFBR2</i> ^{AD} , <i>SMAD3</i> ^{AD} , <i>ACTA2</i> ^{AD} , <i>MYH11</i> ^{AD}
Hypertrophic cardiomyopathy, dilated cardiomyopathy	<i>MYBPC3</i> ^{AD} , <i>MYH7</i> ^{AD} , <i>TNNT2</i> ^{AD} , <i>TNNI3</i> ^{AD} , <i>TPM1</i> ^{AD} , <i>MYL3</i> ^{AD} , <i>ACTC1</i> ^{AD} , <i>PRKAG2</i> ^{AD} , <i>GLA</i> ^{XL} , <i>MYL2</i> ^{AD} , <i>LMNA</i> ^{AD}
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i> ^{AD}
Arrhythmogenic right ventricular cardiomyopathy	<i>PKP2</i> ^{AD} , <i>DSP</i> ^{AD} , <i>DSC2</i> ^{AD} , <i>TMEM43</i> ^{AD} , <i>DSG2</i> ^{AD}
Romano-Ward long -QT syndrome types 1, 2, 3, Burgada syndrome	<i>KCNQ1</i> ^{AD} , <i>KCNH2</i> ^{AD} , <i>SCN5A</i> ^{AD}
Familial hypercholesterolemia	<i>LDLR</i> ^{SD} , <i>APOB</i> ^{SD} , <i>PCSK9</i> ^{AD}
Wilson disease	<i>ATP7B</i> ^{AR}
Ornithine transcarbamylase deficiency	<i>OTC</i> ^{XL}
Malignant hyperthermia susceptibility	<i>RYR1</i> ^{AD} , <i>CACNA1S</i> ^{AD}

AD – autosomal dominant; **SD** – semidominant; **AR** – autosomal recessive; **XL** – X-linked⁽⁸⁾

and Personalized Medicine (SFMP) published similar recommendations as ACMG. These are related to the management of SF in cancer-related genes in adults. They created the list of 60 hereditary cancer-related genes (of which 22 are on the ACMG list). Genes were divided into 3 classes according to the evaluation the risk, actionability and level of evidence from the literature. Based on these criteria SFMP recommends informing clinician and patients of SF in actionable predisposition genes related to hereditary cancers (class 1), but the informed consent must be given. The SFMP emphasize the need for double consent, i.e. after a period of time, patients can go back to their decision and can express their opinion again⁽¹⁴⁾.

How to proceed in the management of secondary findings?

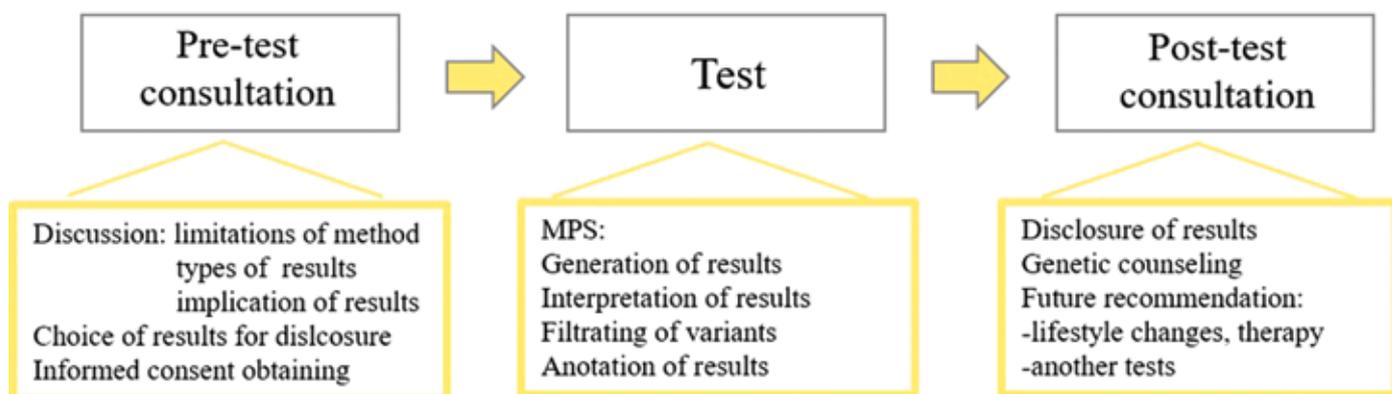
Controversy recommendations of ACMG met a lot of criticism. They are subject of many debates, on which the ethic aspects of genomic testing and views on reporting of results in the field of research and clinical diagnostics are discussed. Based on recent studies, arguments for non-disclosing of results are various. The most often argument is the possibility of psychologic harm, stress, anxiety or behavioral changes due to disclosing of sensitive information, from which not all could be solved. Beside this, all clinical data could cause discrimination and stigmatization in private life but also from the part of employers or insurance companies^(15,18). These negative implications of knowledge of results affect patient and his relatives. Arguments for non-disclosing of results re-

gard also the need of verification such findings and it represents increasing cost of laboratories for validation tests and beside this, there is the need for qualified specialists who should mediate managing of SF. The most significant concern is that after detecting of SF a therapy is needed, and this could be itself harmful and expensive and it may not be covered by insurance company⁽¹⁵⁻¹⁷⁾. Arguments for disclosing of results are not so various, they focus on patient's health due to that medically relevant findings could initiate an early treatment and prevent development of disease. Not only patient but also his relatives could profit from such findings⁽¹⁸⁾. In other studies, experts and also general public express their opinion on managing SF, why and in what case SF should be investigated, which results should be disclosed, who is authorized to make a decision regarding of disclosing results and who should report these results^(15,19,20). Many studies discuss the motivations and worries of patients from genetic testing and if the patients are willing to pay for such analysis. Patients preferences regarding types of disclosed results are also discussed⁽²¹⁻²³⁾. It follows from recent studies that, the view of most of the responders is that for the better healthcare the SF should be investigated, but it is appropriate to know the patient's preferences. The most of patients or participants want to know results also in the case that not all results are actionability findings, but there are also patients who want to know only the results of the primary analysis. Before testing, patients should get relevant information regarding of analysis, types of results, their implications and the possibilities of therapy or prevention in the

Table 2. Attitude of selected organizations to analysis of secondary findings. In the table there are 3 organizations dealing with human genetics and their views on analysis of SF summarized in 4 key points^(edited from 32)

Key points	ACMG (7,8)	CCMG (12)	ESHG (13)
Informed consent	Possibility of SF, and which might be returned, must be discussed during informed consent		
Opportunistic screening	Laboratories should screen list of genes known to be associated with medically important conditions for pathogenic variants	Laboratories should take a targeted approach, limiting their search to genes relevant to the primary indication where possible	Laboratories should take a targeted approach, limiting their search to genes relevant to the primary indication
Opt out	Participants can opt out of the screening of the list of additional variants	Where an additional list of genes is screened, participants can opt out of their screening	
Children	Should be screened for adult-onset disorders as they are clinically useful to parents	Should not be screened for adult-onset disorders as standard practice	Guidelines need to be established as to which information should be returned in children

Figure 1. Scheme of secondary findings analysis. The picture illustrates how should be manage secondary findings analysis. The analysis should consist of 3 main steps which should be perform step by step as indicated by arrows. The text under each step express what should be included in this step. MPS-massively parallel sequencing.



case of identifying of positive findings. Based on these information, patients could decide if they want to know these results and if yes which one. After testing the disclosing of result should be managed by the genetic specialist during the counseling (**Figure 1**).

Secondary findings in minors

Issues related to reporting of clinically significant findings from genetic testing of children and minors represent a special category of discussions to SF. While genetic testing and screening of newborn are common, genetic testing of pediatric patients are not so common and should be indicated only in the case of suspected diagnosis or selecting or setting up a dose of pharmacologic drugs. Positive family history of genetic disease should be known in the case of predictive testing of pediatric patient and an early intervention should positively affect the morbidity and mortality⁽²⁴⁾. In many countries information from genetic testing of child not related to his health condition are not generated. Also, late onset diseases are not investigated. For the maintaining of children autonomy testing of carrier status and reporting of results are postponed until the time when a child will be able to decide and actively present during pre- and post- test consultation⁽²⁵⁾. Views on reporting these findings are different among organizations^(8,12,13). Although this information could have radical mental and emotional impact due to the child is „predestinated“ that a disease will develop in him in a few years⁽²⁶⁾, they represent a medical benefit and only single way how to detect pathogenic variants in parents or in other relatives. Because of that ACMG recommends to screen genes with known clinical significance and report results of IF and SF without limitation of age of patient⁽⁷⁾.

Informed consent in genetic testing

Informed consent serves as protection of patient's or participant's autonomy based on ethical principles of respect of human rights⁽²⁷⁾. Although genomic analyses have benefits they have some risks also and this all should be discussed during informed consent obtaining process. Informed consent would not meet its purpose in the case of not adequately explained aspects related to: technical and interpretational limitations; probability of detecting clinically significant findings (IF or SF); or the risk of loss of privacy or private information⁽²⁸⁾. Informed consent should include describing of method, process of testing and their limitations. Determining of patient's preferences related to types of results for disclosing should be also included in informed consent. Important part of informed consent is related to process of disclosing results in the case that patient dies prior to disclosing results. And another important part of informed consent is related to data re-analysis or storing the results in medi-

cal records of patient⁽²⁹⁾. It is essential to discuss these issues clearly and understandable for patient and this is related to the process of genetic counseling and to the need of specialized genetic counselor⁽³⁰⁾. Currently, it is not clear who is authorized to obtain informed consent from patient, however the recommendations of ACMG state that the clinician who ordered a testing is responsible for obtaining informed consent and, he should provide pre- and post- consultations for patient⁽⁷⁾. During the consultation patients should get important information based on which they can decide what they prefer to know. On the other hand, during the consultations in addition to results, the recommendations how to follow in the case of detecting a positive finding would be provided for patient^(18,31).

Conclusion

Secondary findings have potential to reveal severe rare diseases in a patient but also in his relatives and so allow to prevent disease development or to initiate an early treatment. The main objective of ACMG recommendations is to prevent morbidity and mortality related to rare diseases, for which there is available some form of therapy and ultimately, to improve healthcare. Among laboratories providing genetic testing, however, there are different views on managing SF. Some of them consider the minimum list of genes as a starting point or as an indicative list of genes to which add other genes based on their years of practice. Instead of adoption of ACMG recommendations, they create their own rules which they follow in their routine procedures. To make it possible to effectively use the potential medical benefits of such analyses in routine clinical care it is desirable to create a uniform approach together with a standard informed consent protocol for managing SF.

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Mgr. Zuzana Kubiritová

Institute for Clinical and Translational Research
Biomedical Research Center
Slovak Academy of Sciences
Dúbravská cesta 9, 845 05 Bratislava
e-mail: kubiritova.zuzka@gmail.com