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ORIGINAL ARTICLE

Opt-in for secondary findings as part of diagnostic whole-exome sequencing: Real-life experience from an international diagnostic laboratory

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Abstract

Background: Discussion about the risks and benefits of offering secondary findings as part of genome-wide diagnostics lacks real-life data. We studied the opt-in decisions of patients/families referred to whole exome study (WES) in Blueprint Genetics (BpG), a genetic testing company with customers in over 70 countries to receive secondary findings. Based on the American College of Medical Genetics (ACMG) recommendations for reporting secondary findings, BpG offered testing of specific actionable genes without additional charge for specimens submitted to WES diagnostics.

Methods: Individuals could opt-in for a secondary findings analysis by using a separate electronic consent form. Data from BpG database of electronic consent forms was used for the analysis.

Results: During the selected study period there were 3263 WES referrals, from which 2012 were index patients. About half of the individuals (50.4%) opted in to receiving secondary findings. Of patients who opted in, a secondary finding was detected for 2.7%, similar to other studies. We detected huge differences relating to opt-in between individuals from different countries; for instance, 90% of the 41 patients and their family members in Romania opted to receive secondary findings, while none of the 98 patients in Luxembourg chose that option.

Conclusion: Differences between sexes or between children and adults were small. This data offers one view to the interest of patients and family members to opt in to receiving secondary findings. Research is needed to understand the influence of factors like age, education etc. and possible participation in pre-test counseling to receiving/not receiving secondary findings.

KEYWORDS

clinical diagnostics laboratory, genetic testing, secondary findings

1 | INTRODUCTION

The animated discussion around so-called secondary genetic findings (also called incidental or unsolicited findings, or opportunistic screening) has provided both strong support and a more restricted view about reporting them with clinical diagnostic testing (Green et al., 2013). The term "secondary findings" is preferred, when referring to disease-causing variants that are intentionally being analyzed alongside clinical genetic testing, as opposed to genetic variants found accidentally or incidentally (de Wert et al., 2021).

The American College of Medical Genetics and Genomics (ACMG) Working Group on incidental findings in clinical exome and genome sequencing published in 2013 a list of 56 genes with variants that can cause serious consequences, which however could with certain means be avoided (e.g., medication or regular follow-up for early detection). The ACMG working group recommended that pathogenic (and some likely pathogenic) variants in these genes should be reported to both adults and children who undergo clinical exome and genome sequencing (Green et al., 2013). Subsequently, the ACMG established the Secondary Findings Maintenance Working Group to develop a process for curating and updating the list over time. The ACMG guidelines were updated in 2016 and 2021 (Kalia et al., 2017; Miller et al., 2021) and the most recent update from 2022 lists 78 genes. The Group has recently announced that it will update the list annually (Miller et al., 2022).

The European Society of Human Genetics (ESHG), in its Recommendations on whole genome sequencing in 2013 took a more cautious position towards secondary findings, especially relating to children (de Wert et al., 2021). In a recent communication in 2021, ESHG continues to recommend a cautious approach and underlines the importance of informed consent and offer of counseling. ESHG also recommends gathering evidence by pilots of opportunistic screening in a research setting (de Wert et al., 2021). In addition to ACMG, some other professional genetics societies and networks, such as eMERGE Network and the French Society of Predictive and Personalized Medicine, have also stated that "actionable" secondary genetic findings should or at least could be reported (French Agency of Biomedicine, n.d.; Gordon et al., 2020). The initiative by ACMG also led to vivid discussion focusing beyond diagnostic testing and secondary findings to returning, in addition to the ACMG list, also other possibly "actionable" genetic data to biobank donors and research participants as well as weighing the economic value of reporting such variants (De Clercq et al., 2017; Douglas et al., 2016; Kochan et al., 2020). In addition, liability issues relating to failure to analyze and communicate genomic secondary findings or miscommunication of them have been discussed (Marchant et al., 2020). In the field of direct-to-consumer testing, there appears to be growing interest in offering testing of actionable variants for the clients (Horton et al., 2019; Schaper & Schicktanz, 2018).

While the discussion about pros and cons of such testing is still ongoing, very little data is available about patients' views on secondary findings, especially factors that may lead to different views, such as age, sex, or country of origin of the patients. However, a few studies have addressed participant related issues, for instance, Rini et al. (2018), assessed participants' sociodemographic characteristics (Rini et al., 2018). O'Daniel et al. published in 2017 a survey on practices for genomic sequencing test interpretation and reporting processes in 21 US laboratories. They reported that all surveyed laboratories offered reporting of secondary findings according to the ACMG recommendations. Only four of the 21 clinical laboratories in this study required opt-in for secondary findings, which would reflect deliberate patient choice (O'Daniel et al., 2017). In the present study, we assessed what proportion of patients opted in to receive secondary findings using the data from an international diagnostic laboratory; we also examined the data by taking into consideration the age, sex, and country of origin of the patients. We believe that this data reflects the attitudes of patients and families, guided by the clinicians (often clinical geneticists), towards receiving genetic results not related to the initial clinical question, which will add new data to the ongoing discussion.

2 | MATERIALS AND METHODS

Blueprint Genetics (BpG, a Quest Diagnostics Company) is a genetic testing company focused on inherited diseases with a world-wide customer base. Most of the customers use one of the over 220 gene panels but whole exome testing (WES) is also increasingly requested. Along with WES, BpG offers at no additional cost testing of actionable genes according to the developing ACMG Recommendations for Reporting Secondary Findings in Clinical Exome and Genome Sequencing; during the study period the 2016 version was used (Kalia et al., 2017) and base the classification of variants on the joint consensus recommendation of ACMG and Association for Molecular Pathology (Richards et al., 2015).

To receive the report of the secondary findings, a separate consent form must be signed. Data for opting/not opting in to receive secondary findings has been saved in electronic form since March 2020. Thus, we analyzed data about consents during a certain period starting in March 2020, except relating to health care providers, countries or

projects that had opted out from this possibility. BpG database provided additional data, including sex, adult/child (under 18 years), and the country from which the referral had been sent.

For children or people with intellectual disability or impairment, informed consent could be given by a parent or legal guardian. The report was sent to the ordering healthcare provider. If parents or other family members participated in the WES analysis, they also had the option to opt in for analysis and reporting of secondary findings, independent of the decision relating to the index patient. The index patient got his/her secondary findings report as part of the report of the diagnostic testing (an example of a Secondary findings report in Appendix S1). Secondary findings for additional family members were reported in separate clinical reports.

We observed all index patients' and their family members' choices to give or not to give consent to report secondary findings, and the results were presented by country. We separated the referrals of index patients per country by adult/child and expressed giving or not giving consent to the secondary findings as a percentage. We also reported the percentages of the consents to report secondary findings for children, divided by sex and the consents of adults, divided by sex.

3 | RESULTS

From the 3263 studied participants, 50.4% ($n = 1643$) opted in to receive the secondary findings. Of those who opted in, 45 (2.7%) had secondary findings reported, from which 25 were index patients and 20 were family members. Altogether, of the 3257 referrals, 2010 were index patients and 1247 were family members. The demographic data was not complete for 25 individuals, and these were excluded.

In this paper we present data separately from each country (Table 1, Figures 1–4). In case of very small number of referrals from a country, there might have been risk of identifying an individual referring clinician or even a patient/family. Therefore, we chose to combine data from the three European countries (Italy, Hungary and Poland) with fewer than 40 referrals under the label Other European countries (total 83 referrals). The only non-European country with fewer than 40 referrals was omitted (6 referrals) was omitted from the data presented in the Table and the Figures. The proportion of individuals who opted in to receive secondary findings varied widely by country, as high as 90% in Romania down to 0% in Luxembourg (Figure 1). Similar striking differences were not observed relating to ages (adults vs. children) or gender (Figures 2–4).

TABLE 1 Referrals for WES per country ($n = 3257$).

Country	*N* all
Australia	303
Canada	1607
Finland	538
Latvia	97
Luxembourg	98
New Zealand	237
Other European countries	83
Romania	41
Saudi Arabia	84
United States	169
Together	3257

4 | DISCUSSION

About half of the individuals (50.4%) opted in to receiving secondary findings. A secondary finding was detected in 2.7% of the cases. The frequency was very similar with other studies, for instance the recent publication from the eMERGE study reported that secondary findings were detected in 2.54% of 21,915 participants in the 59 genes listed in ACMG recommendation (Gordon et al., 2020).

Differences were observed in the opt-in decisions to receive results of secondary findings between patients/families from different countries (Figure 1). As two extremes, 90% of patients and family members from Romania opted for the alternative to know their secondary findings while those from Luxemburg never chose that option. One explanation to the high interest of Romanian patients to receive secondary findings might be that in their health care system, patients themselves (or maybe private insurance companies) paid for the test. This might have created a societal bias absent in other European countries.

Also, we do not know how much our results reflect the opinions of the patients/families and how big influence the referring clinicians, often clinical geneticists, possibly had. In Finland we know that the experience in some laboratories of the University Hospitals is very different from our data relating to Finnish patients/families referred to BpG: approximately 80%–90% of patients referred to exome studies at some Finnish University Hospitals consent to receiving secondary findings (Anttonen A-K, personal communication). We do not know the reason for this difference, but we have noticed that the Finnish clinicians referring samples to BpG are often non-geneticist physicians who might not have felt that they have the knowledge and skills to inform the patients of the concept of actionable secondary findings. According to a recent Australian study (Nisselle et al., 2021), medical specialists

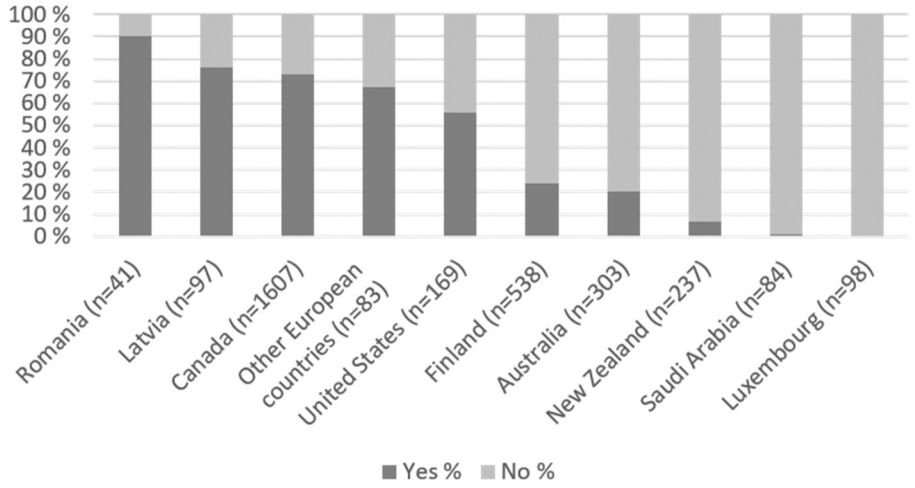

FIGURE 1 Referrals of index patients and their family members per country ($n = 3257$). Yes = consent to inform secondary findings, No = no consent to report secondary findings.

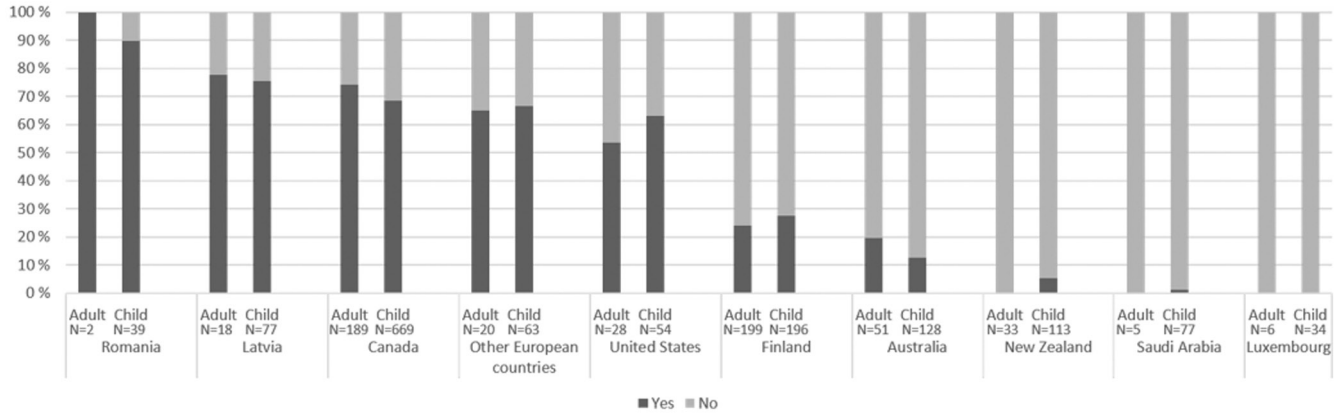

FIGURE 2 Referrals of index patients per country by adult/child ($n = 2001$). Yes = consent to inform secondary findings, No = no consent to report secondary findings.

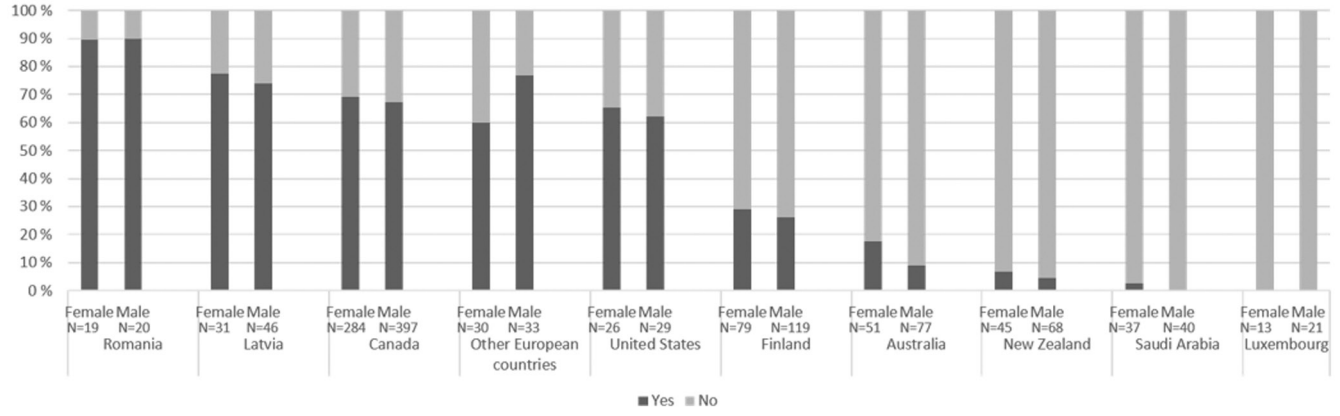

FIGURE 3 Referrals for children per country by gender ($n = 1465$). Yes = consent to inform secondary findings, No = no consent to report secondary findings.

feel that there is need for more education about genomic medicine, particularly on genomic technologies and clinical utility of testing.

The tradition of supporting non-directive genetic counseling is strong in Western countries, and striving for non-directiveness is especially important when

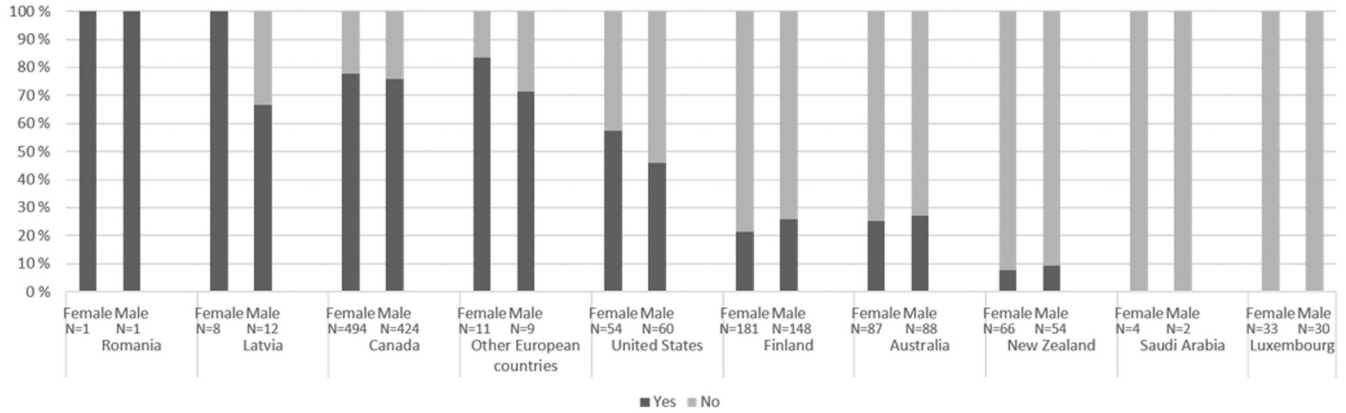

FIGURE 4 Referrals of adults per country by gender ($n = 1767$). Yes = consent to inform secondary findings, No = no consent to report secondary findings.

addressing tests predicting non-actionable diseases like Huntington's, as discussed by Clarke and Wallgren-Pettersson (2019). They, however, admit that the situation is clearly different for actionable diseases where family members can be counseled to have a test for the disease in the family. For secondary findings, there is no "case in the family" or at least it is not the primary indication for testing. Thus, comprehending the possible benefit of knowing the risk may be difficult. Only 2.7% ($n = 45$) of patients in our study were found to have a secondary finding. We do not know if they had affected individuals in their families nor how they reacted to the results. According to the data from the report of Clinical Sequencing Exploratory Research (CSER) Consortium report (Green et al., 2016) 32% of those with a detected secondary finding had positive family history. Recently, Leitsalu et al. (Leitsalu et al., n.d.) reported high satisfaction among biobank donors at receiving results on the genes listed in the ACMG recommendation. We do not know what proportion of the patients participated in pre-test genetic counseling nor how well the tradition of non-directive genetic counseling is respected in the countries included in this study.

In their recent paper, Rego et al. notified that medical informed consent assumes decision-making capacity, voluntariness, comprehension, and adequate information (Rego et al., 2020). In real clinical situations, the patient's capacity and the clinic's resources to provide adequate information may not be optimal. In a recent study focusing on counseling process in the UK 100,000 genomes project, Sanderson et al. noticed big differences between professionals involved in the counseling process related to time used (11 to 52 min) and expressing positive or negative attitudes towards health-related secondary findings (Sanderson et al., 2019).

As many of the actionable diseases associated with the genes listed in the ACMG recommendation have their onset in adulthood, one might expect that adults, most of whom were referred for whole exome family testing (trio), would choose the option of receiving secondary findings more often for themselves than for their children. According to our data, this was observed in some but not all countries and the differences were overall rather small (Figure 2).

Only a very small propotion of population is referred for WES, so this approach of offering secondary findings has a great individual but small population health effect. However, there is growing interest to offer genomic results to large parts of the population as part of biobank studies (Genomics England, n.d.; Vrijenhoek et al., 2021) and to develop tools for communicating such results (O'Daniel et al., 2017). Most European Biobanks describe that according to their national legislation they are allowed to contact participants to inform about results concerning their health (Brunfeldt et al., 2018).

In line with our results, if in coming years approximately 50% of the individuals undergoing genomic tests choose to know their risks for actionable diseases and approximately 2%–3% of them are found to carry variants in 78 genes included in the present ACMG recommendations, the national health care systems have to be prepared to provide appropriate treatments, genetic counseling and cascade screening required to optimally deal with such situations.

5 | LIMITATIONS

The referrals came from different countries, different specialties and for patients of different ages and for very different indications. For these reasons, we did not perform statistical analysis. Thus comparisons between groups in the results were not based on statistical tests.

The option of receiving secondary findings was introduced to patients and families at a time when they may have been overwhelmed with other worries as the diagnostic process was under way. In addition, we did not know how

much time the patients/family members had for asking questions when filling in the consent form and how much background information they had received. In addition, we did not know the specialties of the referring clinicians. Of note, this data was collected from a time period during simultaneous Covid-19 pandemic which means that many of the contacts between the clinicians and the patients/families maybe happened via remote access. For these reasons, the situations were maybe not optimal to make decisions. In the consent, only the opt in decision was recorded, rather than whether it was an informed decision.

We had no information on how the clinicians in our study communicated the results to the patients/families and whether cascade screening in the families was organized.

Here we present our results separately for each country or group of countries, but we do not know how well our figures represent the opt-in decisions to receive secondary findings in each country in general as our figures only represent the situation in those clinics from which samples were sent to BpG.

6 | CONCLUSION

Our data offers one view to the opt-in decisions of patients and their family members to receive information about possible genetic risks for actionable diseases. The opt-in decisions varied greatly between the referrals coming from different countries. This data only reflects the situation over a certain time period in a limited set of countries. Nevertheless, we believe that this data shed some light on receptiveness to secondary findings in a clinical setting. However, factors such as age, education, etc., and possible participation in pre-test counseling, that we were not able to analyze, may greatly affect the receptiveness. More research is clearly needed to fully understand the attitudes of patients towards receiving secondary findings as part of diagnostic genetic testing.

AUTHOR CONTRIBUTIONS

M. Brunfeldt analyzed the data, participated in designing of the study and writing the manuscript. H. Kääriäinen, M. Kaare, I. Saarinen and J. Koskenvuo participated in designing of the study and writing the manuscript.

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CONFLICT OF INTEREST STATEMENT

MB participates in the FinnGen research collaboration. MK and IS are employees at Blueprint Genetics. JK is Executive Director and Medical & Lab Director at Blueprint Genetics. HK is Consultant Geneticist in Blueprint Genetics.

ETHICS STATEMENT

In the study, according to the approval by BpG legal department, we used registry level data from BpG customer register (country of referral, male/female, child/adult, consent yes/no). No personal information was shared with researchers outside BpG and the customers/patients could not be identified from the data. Therefore ethical committee approval was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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