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ORIGINAL ARTICLE

Attitudes of geneticists and patients toward incidental findings in Saudi Arabia

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ABSTRACT

Background: In Middle East countries, including Saudi Arabia, 60%–70% of all marriages occur between first cousins, leading to uniquely common genetic disorders compared to Western countries. The primary objective of this study is to investigate differences between the attitudes of genetics professionals and patients toward incidental findings identified through whole-genome sequencing (WGS)/whole exome sequencing (WES).

Methodology: A mixed qualitative and quantitative cross-sectional study was done to assess the ethical dilemmas and challenges faced in providing genetic information to Saudi patients attending a genetics clinic. A web-based survey was used to interview the participants. A total of 50 subjects were enrolled in this cross-sectional study, including 20 genetics professionals (MG: medical geneticists and GC: genetic counselors) and 30 patients who were interviewed before and after Next-Generation Sequencing tests.

Results: Among the total, 55% of genetic professionals disagreed on patients being provided with their genetic results and raw data, and they preferred focusing on actionable results that yield benefits such as medical treatment and disease prevention. However, the majority of patients (73.3%) were interested in receiving all the raw genomic data for themselves and their children, while 26.7% felt opposite.

Conclusion: This study identified differences in the attitudes of genetics professionals and patients toward the reporting of incidental findings from WES/WGS. Overall, the results suggested that GCand MGshould be aware of variations in individual preferences and should respect the beliefs and preferences of their patients.

Keywords: WES, WGS, incidental findings, attitudes, genetics professionals, patients.

Introduction

In Middle East countries including Saudi Arabia, 60%–70% of all marriages occur between first cousins, leading to uniquely common genetic disorders compared to Western countries. Many genetic disorders have been first described/mapped in the Saudi Arabian population (1, 2). The advancement in technologies that could inexpensively sequence entire genomes means has enabled researchers and clinicians to access vast stores of genomic data across the globe freely available in public databases. Some of these data could be of great use to research participants or patients, but most of them remain uncertain, or of no use for medical diagnosis (3). In clinical exome and genome sequencing, there is a potential for the recognition and reporting incidental or secondary findings, which may be of clinical importance to the ordering physician and the patient (4). Incidental findings that reveal a high risk for cancer or other specific serious circumstances could be lifesaving. However, incidental findings are mostly difficult to interpret or may cause excessive concern to patients. In 2013, the American College of Medical Genetics and Genomics (ACMG) released recommendations for how genome-sequencing laboratories should report incidental findings after a physician orders full or partial genome sequencing. It defines a minimal list of about 56 genes that should be reported to the physician as part of each patient's care, irrespective of the patient's choice. However, the guidelines stop short of recommending that all risk factors should be passed to the physicians and patients (5). The ACMG added four new genes to the list and removed one gene in 2016. Also, it standardized the process of evaluating genes for inclusion in the list by including a semiquantitative metric for determining actionability and outlined its plan to consider genetic variants important from a pharmacogenomics perspective (6). Many of the problematic aspects of these recommendations were

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acknowledged by the ACMG Working Group, including the potential harm of reporting false positives to unwary patients and their relatives due to errors in the medical literature (7). Also, they acknowledged that patients cannot decline unwanted information. The only choice patients have is to decline to sequence altogether, even if it is medically instructed. The ACMG imposes these testing and reporting requirements for all patients, including children who have no medical need for such results during their childhood. It is necessary to obtain informed consent because patients are entitled to have access to the information needed to make medical decisions in keeping with their values. Autonomy protects the patient's right to make a different decision from that of the clinician, and even reject information and treatment that could maximize life expectancy. Although most physicians and many patients might want to be provided with such information, it should not necessarily be forced on all physicians and patients (8). The primary objective of this study was to investigate differences between the attitudes of genetics professionals and patients towards incidental findings identified through whole-genome sequencing (WGS)/whole exome sequencing (WES). Secondary objectives included: (1) to study the attitudes of genetics professionals and patients regarding incidental findings; (2) to compare the attitudes of the genetics professionals with those of patients; and to (3) explore perceptions of genetics professionals and patients regarding the minimal list of reportable findings from the ACMG.

Subjects and Methods

A mixed qualitative and quantitative research design was followed to study the ethical dilemmas and challenges faced in the provision of genetic information to Saudi families. Also, the study examined how patients respond when they receive incidental findings from their test results. Furthermore, this study also assessed the role of healthcare professionals in imparting information and test procedures to the patients. These investigations were performed by exploring the attitudes, beliefs, principles, values, and experiences of the study participants. A web-based survey was used to interview the participants (Supplementary Material 1). A total of 50 subjects enrolled in this cross-sectional study, who included 20 genetics professionals (MG: medical geneticists and GC: genetic counselors) and 30 patients who were interviewed before and after Next-Generation Sequencing (NGS) tests. Both groups were either affiliated with of King Faisal Specialist Hospital and Research Center in Riyadh, Saudi Arabia. The response rate was 83%. The respondents varied in their age, educational level, and background. The interview guide was developed from the clinical experience and based on Yu et al. (9) and Elli et al. (10). Each member of the genetic professional cohort was anonymously assigned an identification number by combining letters from the profession (GC and MG) and a serial number for tracking quotes. This study was approved by the Alfaisal institutional review board (IRB-37-17).

Results

Genetics professionals

The survey of genetic professionals (sociodemographic characteristics shown in Table 1) was divided into: (i) receiving and (ii) delivering genetic results and raw data, and (iii) the challenges of reporting incidental findings. The surveys of both cohorts are provided in Supplementary material 2. Among the total, many genetic professionals (55%) disagreed that patients should be able to receive all their genetic results and raw data. In addition, around 60% of the respondents indicated that they would not give all the WES/WGS results to patients, but will give results related to the patient's clinical presentation and actionable data. Furthermore, 12 genetics professionals (60%) thought that it is the responsibility of healthcare professionals to decide which of the incidental findings included in the ACMG's minimal list should be reported to a patient since healthcare providers could effectively determine whether a reported incidental finding contributes to an individual's health or not. The remaining (40%) felt that patients should have the right to choose which genes to receive since the consent was taken from the patient. With regard to reporting incidental findings to young patients, 60% of the genetic professionals responded that they would not report incidental findings on the ACMG's minimal list to young patients, mainly because they do not want to stress the patient and make them worried for their entire life. Meanwhile, 40% highlighted the importance of reporting incidental findings to young patients in different cases including predisposition to childhood cancer, to investigate the carrier status of parents, or to preserve the autonomy of the patient requesting such

Table 1. *Characteristics of the genetics professionals.*

Gender	
Male	*n* = 11, 55%
Female	*n* = 9, 45%
Age	
25–34	*n* = 7, 35%
35–44	*n* = 9, 45%
45–54	*n* = 4, 20%
Education	
Bachelor's degree	15%
Master's degree	35%
Ph.D.	10%
Professional degree	30%
Other	10%
Current work	
Medical geneticists	60%
Genetic counselors	40%

findings. A hypothetical situation, whereby the patient declines to receive all incidental findings, was created to examine the genetic professional's attitudes. Among them, 75% of the genetic professionals reported that the patient management plan (which precedes the NGS test) would be unaffected by the patient's refusal of receiving incidental findings. Almost two-thirds (65%) of the participants stated that the laboratory has no right to select which genes from ACMG should be included in the report. Moreover, 85% of the cohort demanded that laboratories should include all genes reported in the minimal list. When asked about what benefits the patient gains from receiving incidental findings from clinical WES/WGS following ACMG recommendations, responses included prevention of disease complications, counseling, and early introduction of treatment when disease occurs. Nevertheless, genetics professionals indicated that challenges of reporting incidental findings include inadequate pretest counseling, psychological burden, especially in cases of the unmanageable disease, patients believing that "the future is in god's hands," and the process of sharing information with other family members. Genetic professionals declared that sharing information should be considered case by case, unless in cases of minor patients whereby parent should be involved in this process. Among the genetic professionals, 80% felt that they usually provide sufficient information to the patient before genetic testing to enable them to provide informed consent. Meanwhile, 20% felt that pretest counseling sessions could be improved by adding more tests and result-related information. Most of the genetic counselors and geneticists (90%) asserted that patients should have the freedom to decide whether to undergo NGS testing. However, almost half (45%) of the cohort were not comfortable with using NGS technology to test themselves.

Table 2. *Characteristics of the patients.*

Gender	
Male	*n* = 8, 26.7%
Female	*n* = 22, 73.3%
Age	
18–24	*n* = 8, 26.7%
25–34	*n* = 11, 36.7%
35–44	*n* = 6, 20%
45–54	*n* = 3, 10%
55–64	*n* = 2, 6.7%
Education	
Less than high school	16.7%
High school graduate	23.3%
Bachelor's degree	46.7%
Master's degree	13.3%
Current work	
Life, Physical, and Social Science	3.3%
Healthcare Support	13.4%
Business and Financial Operations	6.2%
Healthcare Practitioners and Technical	16.7%
Sales and Related	3.3%
Management	3.3%
Education, Training, and Library	10%
Housewife	20%
Unemployed	10%
Other	13%

Patients

The cohort survey of 30 enrolled patients (sociodemographic characteristics shown in Table 2) was divided into: (i) the interest toward genetic raw data, (ii) the type of genetic conditions, and (iii) mode of delivering incidental findings. The majority of patients (73.3%) were interested in receiving all the raw genomic data for themselves and their children, while 26.7% felt the opposite. Regarding the type of conditions that they prefer to receive information about, almost all patients preferred to know about life-threatening and preventable conditions (Figure 1). The main reason for this was because patients wanted to be prepared for and aware of any unusual symptoms they might face in the future due to such conditions. Regarding non-life threatening and unpreventable conditions, the patients wanted to know about such conditions because they wanted to practice their rights, and to know the reasons behind the cause of his/her symptoms so they would not attribute the condition to "the evil eye," and to be proactive in awareness about the genetic condition in their family. Among the patients, 83.3% felt that being informed of incidental findings from clinical WES/WGS following the ACMG's recommendations may cause anxiety and depression. Furthermore, 76.7% of the patients thought that the risk percentage of the incidental findings could affect their decision-making. Similarly, most patients wanted to be informed of the incidental findings if the risk of inheritance was above 50%. The patients also indicated that support by healthcare providers was important for explaining the results and associated risks. The most challenging aspects for patients in receiving the information of incidental findings were the acceptance of positive results and the lifelong psychological impact of carrying such information. Most patients clearly stated that the responsibility for telling other family members about the results of WES/WGS belonged to a patient, rather than the healthcare professionals. In addition, most patients (70%) agreed that their healthcare provider should provide enough information before testing to enable them to retain consent. Most respondents (73.3%) also felt that they should have the freedom to decide whether they want to know about incidental findings or not.

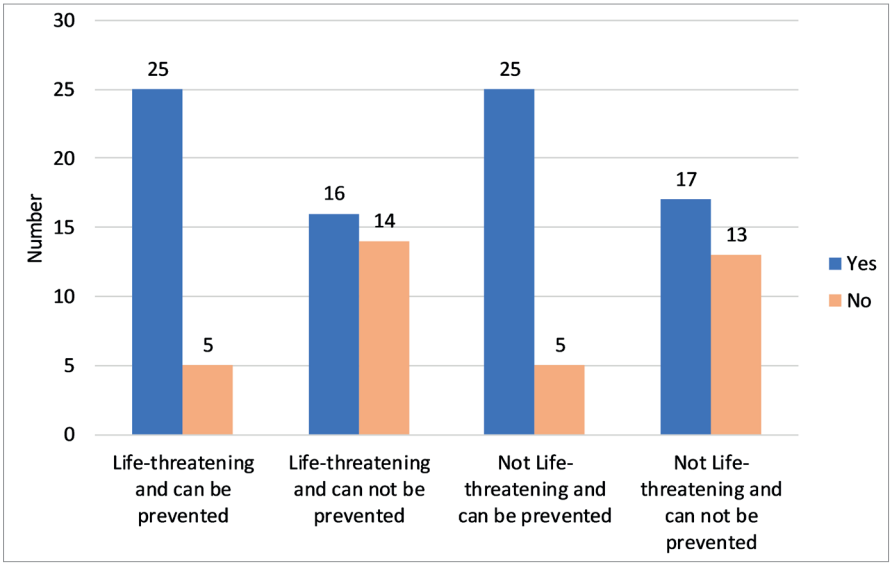

Figure 1. *The kind of conditions the patients wanted to know.*

Discussion

Genetic disorders impose a remarkable health burden on the national economy and a heavy psychological burden on individuals and families. In the last few years, especially after the completion of the Human Genome Project, there has been an increase in the frequency of requests for WES/WGS in genetics clinics. In addition, many questions have arisen regarding the ethical considerations surrounding the reporting of incidental findings from WES/WGS. In this study, we gathered attitudes from genetic professionals and patients toward incidental findings. The main finding of this study was the difference between the attitudes of genetic professionals and patients regarding incidental findings. We found that most genetics professionals would not share all WES/WGS results with their patients, but rather the results yield benefits like medical treatment and disease prevention. However, most patients desired to receive all genetic results for themselves and their children. In addition, the patients preferred to know about preventable conditions, rather than receiving uncertain information. This could be because the patient did not want to feel overwhelmed, which could impact their social life and ability to think rationally. The survey results differed with similar studies that investigated the attitudes of genetic professionals. These previous studies report that genetic professionals agreed on providing the incidental results to patients (9,10). In the most recent version of ACMG recommendations (ACMG SF v2.0), the updated minimal list of reportable incidental findings includes 59 medically actionable genes for which variants are recommended to be reported from clinical genomic sequencing. The goal of the subsequent clinical management of patients with such variants should be to identify and manage risks for the selected highly penetrating genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality (6). Both genetic professionals and patients agreed that the healthcare professional should be responsible for deciding which of the incidental findings in the ACMG minimum list should be reported to a patient/family. The genetics professionals reported that they are less likely to perform WES/WGS and inform the patient about incidental findings on the ACMG minimum list if a patient/family declined to receive all the incidental findings. Most of the genetics professionals also reported that they would not report incidental findings to young patients. However, some highlighted exceptions included cases of childhood cancer or if there is a medical necessity. The genetics professionals mentioned that the main benefit for patients in knowing about the incidental findings is centered on the potential for preventing the development of future possible conditions. In addition, they highlighted various challenges in disclosing incidental findings to a family; for example, the difficulty of breaking bad news and uncertainty about the psychological state of the individual or their emotional reaction. For patients, the main challenges included difficulties of accepting and dealing with such information. For that reason, the patients wanted healthcare providers to support them at the time of disclosing the results by explaining all results and risks, answering their questions in a simple and soft language, and discussing the available choices. Both genetic professionals and patients agreed that patients should have the right to know the results and not share it with other family members. Moreover, both groups agreed that, before commencing with genetic testing, the healthcare providers should provide enough information to enable the patients to retain consent, and that patients should have the freedom to decide whether they are informed about incidental findings. When we asked the genetic professionals, who had extensive experience in the field of clinical genetics, whether they

would undertake WES or WGS for themselves if, given the opportunity, some stated that they would refuse to undertake such tests and only those with a genetic family history wanted to do so. The limitations of this study include a small survey, and that, most patients were pre-WES/WGS patients responding to hypothetical questions, whereby their behavior might differ in real cases. Based on previous studies, it has been assumed that patients would refuse to be informed about any incidental findings. We originally hypothesized that genetics professionals would prefer to provide all the incidental findings to the patients. However, we found that many genetics professionals would not provide incidental findings, while patients preferred to know all the incidental findings. The difference between this study and previous studies may originate from differences in cultural and religious views, and the complexity in concerns of both patients and genetic professionals. Thus, the acceptability of providing incidental findings should always be established on an individual basis.

Conclusion

This study identified differences in the attitudes of genetics professionals and patients (pre- or post-WES/WGS) towards the reporting of incidental findings from WES/WGS to patients. Overall, the results suggested that genetic counselors and medical geneticists should be aware of variations in individual preferences and should respect the beliefs and preferences of their patients. The present study encourages researchers to conduct further studies nationally or globally about this relatively new and sensitive issue.

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Declaration of conflicting interests
None.

Ethical approval
This study was approved by the Alfaisal University Institutional Review Board via letter number (IRB-37-17).

Consent for publication
Informed consent was obtained from the parents.

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Supplementary Data

Genetics Professionals:

1. Do you think that the patient should be able to receive all of his/her genomic results? (Yes, No)
2. Would you give all results from clinical WES/WGS? If no what kind of result do you give? (Yes, No)
3. Do you think it is the responsibility of the health care professional to decide which incidental findings found on the minimum list be reported to a patient / family? And Why? (Yes, No)
4. Would you give the incidental findings on the minimum list regardless of the age of the patient? And why? (Yes, No)
5. If a patient / family declines to receive all the incidental findings on the minimum list, would you perform WES/WGS and inform the patient about the incidental findings on the minimum list? And why? (Yes, No)
6. If a patient / family declines to receive all the incidental findings on the minimum list, would you perform WES/WGS and not inform the patient about the incidental findings? (Yes, No)
7. If you don't give the incidental findings will you be still documenting in the patients' chart? (Yes, No)
8. Do you think the laboratory have the right to choose the type of incidental findings that they have to write it on the report? (Yes, No)
9. Do you think that all laboratory has to follow the ACMG recommendations and include all genes on the minimum list on the report? (Yes, No)
10. What is the benefit for the patient to receive the incidental findings from clinical WES/WGS following the ACMG recommendations?
11. With whom would you share this information within the family? Is that expected to include parents? Why?
12. What are the greatest challenges in disclosing the incidental findings to family?
13. Do you think that you usually give enough information to the patient before genetic testing to enable them to providing a consent?
14. Do you think they have a free choice to decide?
15. If you have a chance to do WES or WGS for yourself will you do it? And why? (Yes or NO)

Patient:

1. Do you want to be able to receive all of your genomic results? (Yes, No)
2. If your child went undergo WES/WGS, do you want to be able to receive all of your child genomic results? (Yes, No)
3. If you had the choice to receive information about conditions that are life-threatening and can be prevented, would you want to know? (Yes, No)
4. If you had the choice to receive information about conditions that are life-threatening and cannot be prevented, would you want to know? If yes, why? ____ (Yes, No)
5. If you had the choice to receive information about conditions that are not life-threatening and can be prevented, would you want to know? (Yes, No)
6. If you had the choice to receive information about conditions that are not life-threatening and cannot be prevented, would you want to know? If yes, why? ____ (Yes, No)
7. Do you think the return of incidental findings from clinical WES/WGS following the ACMG recommendations may cause anxiety to an individual, and could lead to experience depression? (Yes, No)
8. Do you think it's responsibility of the health care professional to return the incidental findings on the minimum list even if you decline to receive all the incidental findings on the minimum list? (Yes, No)
9. Do you think the risk percentage of the incidental findings will affect your decision? (Yes, No)
10. From your opinion what is the risk percentage that can affect your decision?
11. How would you want health care provider to support you at the time of receiving your genetic testing results?
12. Who would you want the health care provider to share this information within the family? Why?
13. What are the greatest challenges in receiving the information of incidental findings?
14. Did the health care provider give you enough information before the testing to enable you to retain consent? (Yes, No)
15. Did you feel you had a free choice to decide? (Yes, No)

Please list any questions and/or comments you may have:

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