GeneFocus

Exome Sequencing: Knowledge, Attitude, and Perspectives of Non-geneticist Clinicians in India

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Abstract

In India, due to the large population, high prevalence of consanguinity and decreasing trend for infectious and nutritional diseases, genetic diseases account for significant mortality and morbidity. However, trained genetic professionals are very few, hence, non-geneticist clinicians i.e. clinicians without formal training in medical genetics, are often involved in the diagnosis and management of genetic diseases. In recent years, exome sequencing (ES) has become more accessible in clinics due to lower costs and is being promoted for diagnostic and screening purposes. We designed this questionnaire-based study to know about the knowledge and perspectives of non-geneticist clinicians towards exome sequencing. In March 2018, a questionnaire containing 25 questions about prior knowledge, usage of exome sequencing in various settings like diagnostic, predisposition, preconceptional, etc. was filled by one hundred clinicians who did not have prior training in medical genetics. Only half (53%) of these doctors had ever heard of exome sequencing. Though 84% of participants felt that exome sequencing is a useful technique, only 31% felt that they were ready to order the test. This study shows that knowledge about exome sequencing is less and needs to be imparted to doctors, the majority of whom are eager to learn and consider exome sequencing a significant diagnostic technique in their clinical practice.

Introduction

Exome sequencing (ES) has an established role in the diagnosis of various monogenic diseases with a yield of 20-50% in different clinical settings (Meng et al., 2017; Yang et al., 2013). It is also being increasingly utilized in preconceptional expanded carrier screening, prenatal diagnosis, pharmacogenomics and predisposition testing. The use of ES in newborn screening is also an area of increasing interest. With increasing availability, decreasing costs of ES and heterogeneity of health care providers, there is a peculiar situation arising in the developing countries, especially India, where in certain areas, ES is being rapidly pushed into the clinics for diagnostics and screening purposes. This is of concern because, due to a dearth of trained genetic professionals, the burden of diagnosis and management of genetic diseases often lies with the non-geneticist clinicians (Verma, 2015; WHO, 2006). Although they are the ones to first suspect genetic disorders, most non-geneticist clinicians lack the required knowledge as there is not much thrust on medical genetics and the latest developments in the field are not included in the medical education curriculum of undergraduate and specialist medical courses in India.

Various studies have evaluated the diverse perspectives of the general public and genetic professionals towards ES in various situations like prenatal screening, newborn screening and issues regarding secondary findings (Yu et al., 2014; Sapp et al., 2014; Kalynchuk et al., 2015). We designed this study as a cross-sectional questionnaire-based survey to assess the knowledge of ES among the Indian clinicians who did not have a formal genetic training.

Methods

We included specialists and superspecialist doctors in the study. Initially, 136 doctors were contacted. This included 40 superspecialists and 96 specialists. All the participants were either contacted in-person by a phone call (n=50; 40 superspecialists, 10

specialists, all working in the same institute as the authors) or via email (n=86; all specialists, mostly friends and colleagues of authors, working in different tertiary care institutes). All the participants were asked to submit the filled questionnaire within two weeks. The questionnaire was designed in the English language and contained 25 questions which aimed to analyse the pre-existing knowledge of ES among the participants and their views regarding the use of ES for diagnostic and screening purposes in patients and self, in different clinical scenarios. Before filling the questionnaire, all the participants were required to read the attached information sheet containing an introduction to ES, briefly explaining the technique, uses, strengths, limitations, ethical dilemmas, cost, and emerging applications. This information sheet was designed by the authors taking a standard genetics textbook as reference (Nussbaum et al., 2016). The questionnaire and information sheet are attached as supplementary material.

Results

The response time taken by participants to answer the questionnaire ranged from one day to two weeks and the average time taken was 8 days. Responses within two weeks were obtained from 100 doctors (30 superspecialists and 70 specialists), making the response rate of these two groups, 75%, and 73% respectively with an overall response rate of 74%. The response rates were higher when participants were contacted in person (80%, 40/50) versus when contacted via email (70%, 60/86). Out of 100 participants, 69 were males and 31 were females. The age of participants ranged from 25 to 35 years. Table 1 gives the clinical specialty-wise distribution of the participants. Participants' responses to survey questions were summarised as percentages and graphical representation. A more formal statistical analysis and comparison between the specialist and superspecialist doctors' groups could not be attempted due to the smaller sample size and heterogeneity of the two groups.

The study results show that only half (53%) of the participants had ever heard of ES. But, if we analyse data in groups, 93% (28/30) of superspecialist doctors had heard about ES as compared to 36% (25/70) of the specialist doctors. Only 30% of participants were previously aware of the information and issues related to exome sequencing. None of the specialist doctors had ordered ES but 16% (5/30) superspecialist doctors had previously ordered ES and 80% (4/5) of them had found it to be useful in their patient management. Most of the clinicians (87%) agreed that ES is a useful diagnostic technique and 84% of participants opted for more information on exome sequencing. Thirty-one percent of the participants felt that they would be prepared to deal with the issues related to exome sequencing when a patient brings a report of exome sequencing.

Table 1 Clinical specialty wise distribution of the participants.

Superspecialists	**30**
Nephrology	3
Gastro-medicine	4
Cardiology	6
Clinical Immunology	3
Critical care Medicine	2
Endocrinology	1
Paediatric Gastroenterology	1
Urology	4
Neurosurgery	1
Neurology	5
Specialists	**70**
Pediatrics	19
Obstetrics and Gynaecology	21
Ophthalmology	2
Radiotherapy and oncology	8
General Medicine	10
Orthopedics	5
Psychiatry	2
General Surgery	3

Besides the established use of ES in the diagnosis of single gene defects, 30% participants said the use of ES for preconceptional carrier screen appealed most to them, around 29% said ES for prenatal testing of fetus appealed to them and 15% participants said none of the other uses appealed to them (Figure 1). The use of ES for newborn screening is a matter of active research and in pilot phases of research (Berg et al., 2017). On being asked if the clinicians would consider exome sequencing for newborn screening, 20% of participants said yes, 11% were not sure and the rest 69% were not in favor of ES for newborn screening. Most participants felt that if they

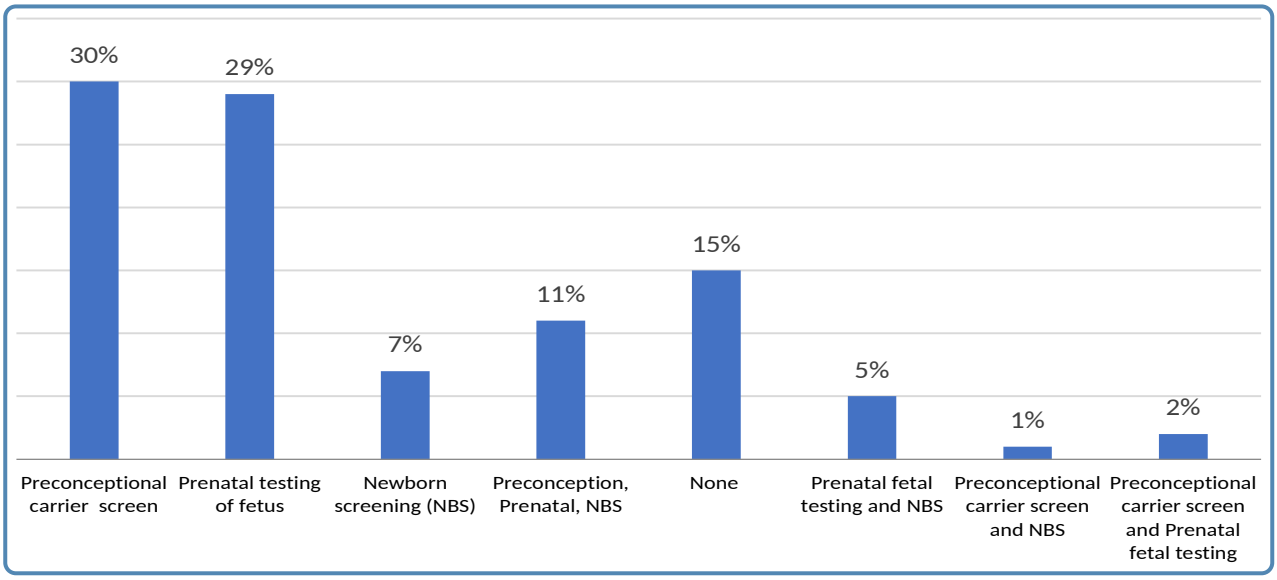

Figure 1 Responses to the most appealing form of testing by ES, besides the established role in monogenic diseases (*n* = 100 participants).

did exome sequencing of a newborn, as a part of newborn screening, they would like to know the treatable genetic conditions and the carrier status for recessive diseases which can have only reproductive implications (Table 2).

Table 2 Findings that the participants expressed they would like to know from Exome Sequencing done as a part of newborn screening (*n* = 100).

Disease condition	Yes	No	Not sure
Treatable genetic disease	96	–	4
Untreatable genetic conditions	37	53	10
Late onset genetic conditions	49	40	11
Carrier status of recessive diseases for reproductive implications	56	36	8

In response to the option of getting their exomes sequenced, 33% of participants said they would like to go ahead. The reasons cited for opting for ES were to know their risk for multifactorial diseases and take preventive actions (61%), general curiosity (15%), carrier status for reproductive planning (12%) and pharmacogenomic testing (6%) (Figure 2).

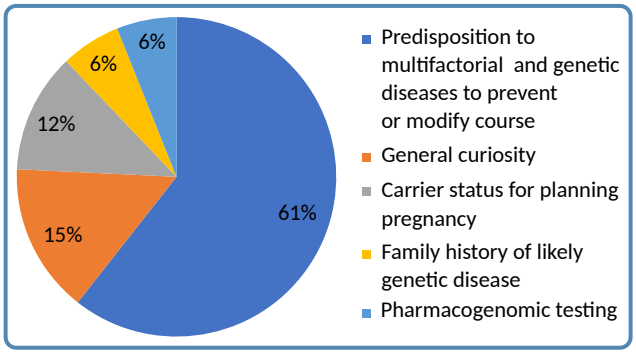

Figure 2 Reasons given by participants for getting Exome Sequencing done for self (*n* = 33).

We asked participants which authority should decide regarding the inclusion of incidental findings (IF) in ES reports. Around 36% of participants said the in-charge doctor should decide; another 36% said that the patient themselves should decide;13% were of an opinion that a central body should decide, and 2% of participants thought that the testing laboratory should decide (Figure 3). When asked which incidental findings should be shared in the ES report of the patient, 40% of participants considered incidental findings of diseases where early diagnosis can lead to treatment should be shared and 23% of participants said incidental findings should be shared according to patient's own choice. Around 17% percent said

all disease mutations should be shared in ES, 14% said pharmacogenetic and treatable conditions should be shared and 2% said no IF should be shared (Figure 4).

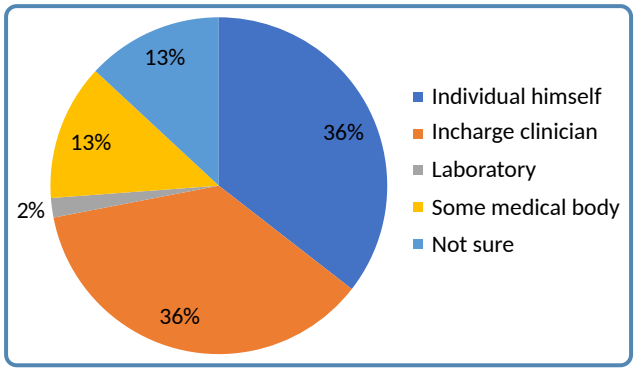

Figure 3 Participants' opinion regarding which authority should decide if incidental findings should be shared in the Exome Sequencing report.

Discussion

Patients with monogenic disorders are first seen by physicians who are specialists but not medical geneticists. Some of the specialists and super-specialists have started ordering ES though the numbers may be small. As the number of medical geneticists in India is small, a greater number of non-geneticists will be taking care of patients and families with genetic disorders. For appropriate ordering and interpretation of ES, physicians need to be aware of the principle of the NGS, interpretation of sequence variations and related issues. The results of this small study try to get an idea at present of the Indian scenario. About half of the participants knew of ES and most of them felt that this is a useful diagnostic technique and opted for more information on exome sequencing. In our study, 33% of participants said that they would like to get their exome sequenced which is lesser than similar studies in developed nations (including genetic and non-genetic professionals) where 49-77% of participants expressed their desire to get their ES. This probably reflects the fact that our participants are not as informed and familiar with ES. The secondary/incidental findings detected in ES have always been an area of major debate and the ACMG periodically releases its statement to address this issue (Kalia et al., 2017). In a study of genetics professionals to learn about their attitudes towards the return of incidental results from ES, 50% thought that offered results should not be limited to those deemed clinically actionable and the vast majority (81%) thought that individual preferences should guide return of the results (Yu et al., 2014). In another study by Lemke et al. most genetic professionals said that most importantly, two types of findings i.e. adult-onset clinically actionable disease, and a childhood-onset non-clinically actionable disease should be disclosed to patients. In another study, non-genetic professionals laid impetus on actionable findings but expressed that even 'not clinically actionable' findings should also be made available (Strong et al, 2014). A study of non-genetic professionals from Greece reported that clinically valid and actionable IFs should be returned, but always with caution and taking into consideration the patients' wishes, although several experts reported returning IFs according to their clinical discretion (Gourna et al, 2014). When compared to previous studies, the non-geneticist clinicians in our study also held the same views favoring sharing of actionable incidental findings but also many expressed views ranging from providing all disease-causing mutations in ES report to those advocating that it should be based solely on the patients' choice.

Thirty-one percent of participants felt that they would be prepared for ordering ES. This was their personal opinion and this study did not judge the capabilities. In the questions and comments section, the participants asked about the availability of ES, cost, turnaround time, limitations and commented that basic genetic training should be included in the medical curriculum, as presently no medical genetics training is provided at any level of education in the medical curriculum. This reinforces the participants' interest in ES and their desire to use it for patient management.

One of the main causes of bias in our study could be related to questionnaire design. No pilot testing of the study questionnaire was done. The questions drafted were hypothetical and sometimes complex. While answering many questions, the participants could have been confused about whether to answer the question for self or the patient. It is possible that inclusion of the information sheet aimed at providing a minimum level of genetics education, itself introduced an unintended bias. Other causes of bias would be a small study sample size, many participants being friends of the authors and belonging to nearby

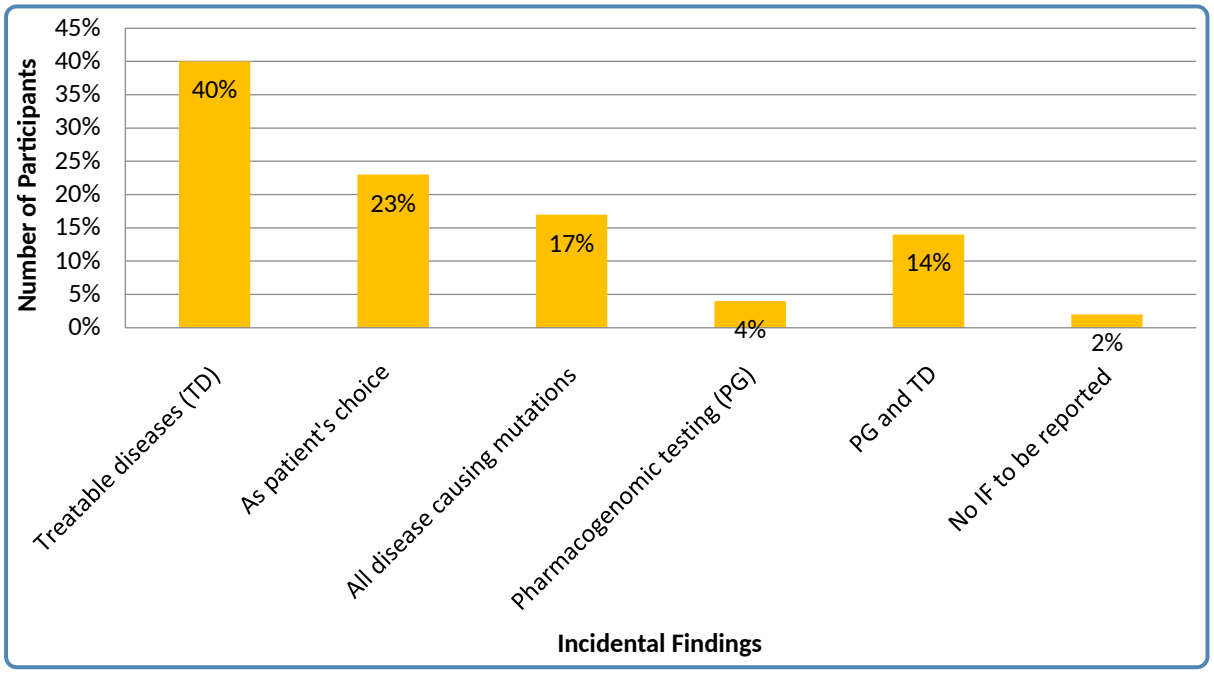

Figure 4 Participants' opinions on which incidental findings (IF) from Exome Sequencing should be shared with the patient.

institutes, this study does not represent the views of non-geneticist clinicians across India.

As more private laboratories keep pushing ES for diagnostic and screening purposes into clinics and more clinicians order ES, they might require more support from genetic health professionals to understand and interpret genomic laboratory reports and help with genetic counseling. Also, in the field of medical genetics, knowledge and scientific understanding are constantly developing. In developing countries like India, the genetic health professional support mechanisms are limited. This lacuna might lead to the decreased utility of ES, where we might miss guiding patients for timely health care intervention to ameliorate disease effects, facilitate carrier testing, prenatal diagnosis and genetic counseling. Realizing this unaddressed need, in recent years, a nation-wide framework of collaborative research initiatives catering to the rare disease community and provision of training in medical genetics have emerged (GUaRDIAN Consortium, 2019) (Aggarwal & Phadke, 2015).

Conclusion

In a large and heterogeneous country like India it is vital that training and awareness in medical genetics be inculcated at the level of undergraduate medical school and residency and through continuing medical education programs. As the medical genetics community in the world is trying to deal with waves of ethical and psychological dilemmas arising from the powerful technique of ES, we are trying to get an idea about awareness of ES amongst clinicians without formal training in medical genetics, to take up the challenge of large scale meaningful use of ES and other next-generation sequencing-based diagnostics.

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Dr. Meenakshi Lallar and Dr. Shubha Phadke declare that they have no conflict of interest.

The questionnaire and information sheet used for the study are provided as Supplementary material with the online version of the journal.

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