GeNeViSTA

Secondary Findings in Genomic Testing

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Introduction

Next generation sequencing (NGS) has changed the landscape of genetic diagnoses with shorter time to diagnosis, discovery of novel disease-causing variants/genes and newer insights into molecular mechanisms of disease. But one of the challenges with this powerful technology is the discovery of secondary findings in addition to primary results (which are pathogenic variants relevant to the disease, for which the test is ordered). Secondary findings (SF) (previously termed 'incidental findings') are defined as findings, which are unrelated to the primary purpose of testing, but can be of clinical significance to an individual (Green et al., 2013). These findings are proposed to have a significant effect on an individual's health outcomes, but its disclosure can pose challenges to the healthcare professionals, patients and their families. This review briefly discusses the current debate on SF in the era of next generation sequencing and explores the benefits and challenges associated with SF. We also discuss the recommendations from professional bodies around the world regarding disclosure of SF.

Proposed benefits of reporting secondary findings

SF are proposed as 'opportunistic screening' for patients seeking medical attention for some other ailment (Green et al., 2013). The reporting of SF with confirmed clinical utility is expected to aid patients to seek detailed clinical evaluation, appropriate specialty referrals and regular follow-up to monitor for early signs of disease. This may also help in early intervention in certain medical conditions and thus improve the clinical outcome. At-risk individuals can take steps for disease prevention along with regular screening. Screening can also be offered to family members who are at risk of developing the disease.

From a clinical perspective, for a profession that has always aimed to do good to the patients, it may be incorrect to discard the valuable information generated by NGS, which may have potential lifesaving benefits (Mackley et al., 2017).

Pitfalls of reporting SF

The main argument against return of SF is the inadequate evidence about clinical utility of secondary findings. Diseases with variable penetrance can give rise to unnecessary anxiety and psychological stress for a disease that may never occur. Revealing a diagnosis for which the patient has no symptoms can lead to information overload. It can also lead to stigmatization (Mackley et al., 2017).

The American College of Medical Genetics and Genomics (ACMG) recommends disclosure of SF for everyone who undergoes broad spectrum testing, irrespective of his or her age (Kalia et al., 2016). Although, reporting of SF in children is expected to help family members, disclosure of information regarding adult-onset diseases may create conflict between the beneficence of the parents and autonomy of the child.

In many instances, the coverage of the genes in which secondary findings are found, is questionable and the variants are not usually confirmed by an alternative method. Further, exome sequencing does not detect large deletions, duplications, chromosomal rearrangements and nucleotide repeat variants. Disease-causing variants other than point variations would never be looked into, giving the patient false assurance of not being at-risk of developing the listed diseases. On the other hand, identification of a positive finding further

demands validation of the variant, causing delay in turnaround time of the test and adding to the cost of the investigation (Mackley et al., 2017). Return of SF may be a burden on resources, research infrastructure, lab personnel, counselors and clinical geneticists. In a publicly funded healthcare setting, this could pose a huge economic burden.

Guidelines and recommendations from professional bodies

The ACMG study group recommends an active search, routine evaluation and reporting of 59 medically actionable genes with every exome or genome sequencing (Kalia et al., 2016). Most of these are cancer predisposition genes and genes predisposing to cardiac arrhythmias. Only previously reported variants identified in these genes are eligible to be reported as SF and novel variants predicted to be disease-causing should not be considered for reporting. ACMG also recommends appropriate follow up evaluation of individuals for these conditions. ACMG suggests that these findings should be reported in both adults and children. ACMG labels this as a minimum list and says it is flexible to modifications with availability of evidence in the future. The list is just a recommendation and individual laboratories are free to devise their own policies for reporting of these SF.

The European Society of Human Genetics (ESHG) recommends targeted analysis of genome whenever possible to avoid generation of secondary findings. However, in scenarios where genome wide sequencing is indicated, variants causing serious health issues that may be benefited with treatment or prevention are recommended to be reported after informed consent from the patient (van El et al., 2013).

The Canadian College of Medical Geneticists does not recommend the intentional clinical analysis of disease-associated genes other than those linked to the primary indication until evidence of benefits are established (Boycott et al., 2015).

Conclusion

Secondary findings have stemmed out of the overwhelming genetic data generated by next generation sequencing techniques. The access to this information would tempt physicians to reveal it to patients. But there are many limitations and ethical issues, which need to be addressed. When there is enough evidence for benefit, return of SF can be considered for reporting, after informed consent.

References

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