

Adopting genetic screening for Familial Hypercholesterolaemia



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Since the mapping of the human genome was completed a decade ago, our knowledge of genetic drivers of disease continues to evolve at an ever-quickening pace. Consequently, today we stand on the threshold of the 'Genomic Era', where the rise of genetic testing and pharmacogenomics within the healthcare system have generated the knowledge that has empowered us to both understand and influence our lifelong health through pre-emptive intervention.

The degree of progress made to date in genomics and its impact on healthcare is understated; from genotyping patients to predict drug response, to stratifying patients according to the risk of a disease, molecular testing is having a very positive impact on many patient treatment pathways.

An area of molecular medicine that has received much public attention involves understanding causative drivers of inherited genetic conditions. A recent paper by Dr Raphael and colleagues reported the increase in demand for genetic services following a much-publicised announcement where a Hollywood actress, having discovered she carried the BRCA1/2 mutation, underwent prophylactic mastectomy. One Canadian clinic received double the volume of genetic testing requests in the ensuing six months.

Undoubtedly, we are now more aware and in control of our health than ever before. It is no surprise then that the molecular diagnostic market has become the fastest growing segment of the IVD industry with assays serving the gamut of disease areas and breaking new boundaries in personalised healthcare.

Despite the public appetite and availability of powerful molecular diagnostic assays that can unequivocally diagnose genetic disorders, their use is far from routine. Many traditional diagnostic tests continue to under-diagnose, leading to missed opportunities for early and appropriate therapy intervention of potentially life-threatening diseases. One prime example where a molecular diagnostic approach can improve health is testing for familial hypercholesterolaemia (FH).

FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

FH is an inherited genetic disorder, affecting the body's ability to clear LDL-cholesterol (LDL-C) which, if untreated, can lead typically to atherosclerosis and premature onset of cardiovascular disease in men in their 40s and women in their 50s.

The main gene responsible for the genetic defects associated with FH is the low-density lipoprotein receptor (LDLR) gene, with at least one in 500 of the general population harbouring mutations in this gene.

However, certain mutations within this gene are seen more frequently in specific populations, for example 'the Arabic allele', a rare mutation in the LDLR gene that has been observed specifically in the Arabic population. In another study, the 'Lebanese allele' was detected in almost 30% of the study cohort, which consisted of Brazilian families with Arab ancestry. This has been linked as a causative factor of FH in Brazil, North American and Western European countries with a large Arab population due to migration.

Whilst FH can be diagnosed clinically or genetically, the UK, US and international guidelines recommend that probable or possible FH patients undergo a DNA test to confirm the diagnosis of FH. Recommendations also advocate that once an activating mutation has been found in one family member (the index case), cascade screening of that mutation in first degree relatives of the index case should proceed.

Cascade screening using a molecular assay can thus identify index family members who may otherwise be asymptomatic, particularly children or adolescents. FH is treatable, with earlier detection and intervention bringing greatest benefit. Early and aggressive treatment of FH in young carriers can reduce their lifetime risk of CHD to levels not dissimilar to a non-FH population, so there is compelling justification for cascade screening and early intervention. New confirmed cases from the relatives are treated as new index cases and their first-degree relatives can also be screened where appropriate.

However, only a handful of countries currently have national genetic screening programmes for FH despite evidence demonstrating that implementing such a program is highly cost-effective. Since FH is an autosomal dominant disorder, the children of a carrier have a 50% chance of inheriting the mutation, thus screening demonstrating the cost-effectiveness of implementing such a programme.

Worldwide, FH has a high prevalence of one in 500 in most countries; however, recent landmark research using direct screening in a Northern European population has now placed prevalence around one in 200, putting FH alongside hereditary haemochromatosis. Remarkably, despite these estimated figures, only 15-20% of individuals with FH have been diagnosed, with the remainder of the FH population unaware of their condition and therefore not receiving the appropriate interventional treatment to prevent early onset cardiovascular disease.

With an eight-fold increase in risk of coronary heart disease compared to unaffected relatives (RR 8.54; 95% CI 5.29 to 13.8), accurate and early diagnosis of specific mutations in FH carriers is crucial in ensuring better overall outcome for patients through the prescribing of tailored treatments, such as statin drug therapy, to reduce morbidity and mortality from premature cardiovascular disease. Diagnosis of FH through lipid profiling (LDL, HDL and total cholesterol, for example) is not sufficient to distinguish FH from other hyperlipidaemias and will not guide appropriate treatment. FH requires a much more aggressive treatment regime, with higher levels of statins or combined therapies to effectively reduce the risk of CHD and stroke, so definitive mutation analysis is a more accurate option.

Further, FH management can be dictated by the type of mutation harboured by the patient, such as the poorer response to lipid-lowering therapy observed with specific LDLR mutations. Consequently, accurately identifying the gene mutation involved can potentially aid the clinician to decide on how aggressive the treatment strategy should be.

DETERMINING MUTATIONAL STATUS

To date, more than 1,200 different LDLR mutations have been reported, with prevalence varying amongst different populations. The abundance of different FH mutations can make genetic testing labour-intensive and costly, with many laboratories defaulting to performing expensive and lengthy NGS tests in an effort to ensure a comprehensive mutational screen.

However, as our understanding of the genetic drivers of FH, as well as common population-specific mutations, increases, new novel assays and techniques are being developed to meet the needs facing clinical genetics laboratories, including cost and time to result.

Multiplex assays that have been specifically designed to detect the most common mutations, provide a cost-effective and clinically relevant alternative to NGS testing. Rather than screening the whole genome, targeting the most likely mutations in that population enables diagnosis within hours rather than months. Where a mutation is identified in an index patient, cascade testing of family members only requires the mutation in question to be targeted; therefore negating the use of broad profiling approaches such as NGS in this setting.

CONCLUSION

FH is a common yet underdiagnosed condition that poses a significant risk to Public Health worldwide. In 2008, cardiovascular diseases were the leading cause of non-communicable deaths worldwide, with an estimated mortality rate of 17 million people. Raised cholesterol was attributed to 2.6 million deaths. Understanding a person's genetic predisposition to cardiovascular disease through genetic testing will allow patients to receive appropriate therapeutic and interventional treatment to reduce morbidity and mortality associated with cardiovascular disease.

Adopting national genetic screening programmes to further identify cases of FH is recommended to ensure that cases are unequivocally diagnosed early for optimal patient outcomes.

Utilising pioneering multiplex diagnostic assays, tailored to incorporate the relevant FH-causing mutations, provides a promising future for both the routine genetic laboratories; where a rapid, cost effective approach to determine mutational status in cases of suspected FH is enabled; and ultimately the patient, whose treatment and care pathway is managed effectively.

REFERENCES

References available on request (magazine@informa.com)