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Next Generation Diagnostics

Improving genetic diagnosis of Familial Hypercholesterolaemia

NewGene recently played a pivotal role in an ambitious project to improve diagnosis of the common inherited condition Familial Hypercholesteraemia, utilising their expertise in genotyping using the Agena Bioscience MassARRAY® platform to bring significant and ongoing benefits to patients and regional healthcare providers.

This exemplar project demonstrates NewGene's ability to develop and deliver innovative new clinical assays, integrated within complex clinical research activities that cross a wide variety of disciplines. A new diagnostic service which brings meaningful benefits to patient care was developed and delivered in a cost-effective manner, with sustained uptake after an initial period of grant funding. 220 patient samples were assayed, realizing a 17% cost saving compared to previous practice.

Successfully carrying out the FH project required co-ordination of activities along the entire care pathway, from community nurses, through consultant lipidologists to diagnostic laboratory staff. The benefits of this coherent approach are now apparent – taking a holistic view of the care pathway has enabled the project to achieve the planned outcomes on time and on budget, with adoption of the assay service into routine care.

Future projects which require a similar cross-disciplinary approach will benefit greatly from this experience, enhancing outcomes for both partners and patient groups.

Project background

FH is an autosomal, dominant genetic disorder that leads to an abnormally elevated Low Density Lipoprotein Cholesterol (LDL-C) plasma concentration and consequently a dramatically increased risk of atherosclerosis. It is one of the most common inherited conditions, with an estimated prevalence of between 1 in 250 and 1 in 500 people[1], although it is thought that only around 12% of patients are diagnosed[2]. Untreated, people with FH are at risk of major cardiovascular events early in life. Key to improving outcomes is early identification of affected individuals and initiation of high intensity statin treatment, effectively eliminating FH associated excess cardiovascular disease risk[3].

'Cascade' testing of the relatives of patients with genetically confirmed FH is the most effective strategy for early identification of undiagnosed individuals and the National Institute for Health and Care Excellence (NICE) published Clinical Guideline CG071 in 2008, updated in 2016, recommending that patients with FH should be offered genetic testing to confirm the cause of their disease and identify affected relatives[4]. Improved rates of diagnosis are expected to lead to significant benefits to patients and healthcare providers, with optimal treatment of FH greatly reducing the risk of a patient suffering from cardiovascular disease[3], saving the NHS an estimated £1.7m per year in associated treatment costs[5].

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Development of a new genetic testing service

In order to establish a cost-effective and clinically-relevant cascade testing service for FH in the North East and Cumbria region, a consortium consisting of NewGene, Newcastle upon Tyne Hospitals NHS Foundation Trust, the NIHR Diagnostic Evidence Co-operative Newcastle, the Northern Clinical Network and Senate, the Northern Clinical Commissioning Groups forum and AstraZeneca was formed in 2013, with additional financial contribution made by the North East and North Cumbria Academic Health Science Network.

Work began in 2014 and concluded in 2015, with establishment of a clinical service fully supported by local CCGs.

As a specialist provider of high-complexity genetic diagnostic services, NewGene's role within this project was to develop appropriate assays and carry out analysis of patient samples.

FH can be caused by a variety of genetic abnormalities; some are relatively common, whereas others are rare.

To create a rapid and cost-effective service, an innovative sequential approach to testing was developed, utilising the Agena MassARRAY® system to first perform rapid and low-cost genotyping on all samples, identifying those with commonly occurring mutations. Samples from patients with a strong clinical phenotype of monogenic FH but none of the common mutations are then analysed by more expensive and time-consuming targeted gene sequencing using the Illumina MiSeq® platform. As the only Agena certified service provider in the UK, NewGene are uniquely positioned to perform sequential testing in this manner.

Over the 12 month project duration, 220 samples were processed; of these 37% were diagnosed with a FH mutation. 58% of FH mutations were detected by MassARRAY® genotyping, with 7 common mutations making up 75% of all those detected using this system. Mean cost-to-diagnose each FH patient was 17% less than workflows based entirely upon sequencing, a saving which will increase as assay volume increases.

Project impact

Prior to this project commencing, genetic diagnostic services for families affected by FH were not widely available, leading to many patients remaining undiagnosed and untreated.

This is expected to have resulted in many of them suffering from cardiovascular disease with consequential mortality and morbidity; treatment of these patients will have incurred substantial excess costs for healthcare providers.

Following completion of the AHSN-funded project the FH diagnostic service has now been added to NewGene's assay portfolio, with funding for patient testing made available by regional CCGs.

Introduction of the new service has greatly increased the number of FH patients diagnosed correctly within the North East and Cumbria region with consequential benefits to their health and savings to regional healthcare providers.

References

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