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Message from the editor

Reading through this edition of "pathology@viapath", it struck me that each of the articles relied on some form of collaboration, either between laboratories within Viapath or with the wider scientific community, and all focus on improving patient care. For example, the Haematological Malignancy Diagnostic Centre provides an integrated approach for the diagnosis of haematological cancers, the Nutrastasis Unit reviewed the folate status of patients and have made recommendations for testing regimes, and the Genetics Laboratories have worked together to produce a webinar on Next Generation Sequencing tools.

The Advancing Healthcare Awards also promotes collaboration and recognises healthcare professionals who lead innovation resulting in a difference being made to patients' lives. There is still time to enter for the Award so if you or your colleagues have a project that is making a vital difference to healthcare delivery, please submit an entry.

Novel human NFKB2 protein mutation in two unrelated patients with common variable immunodeficiency

What is common variable immunodeficiency?

Common variable immunodeficiency (CVID) is one of the most common, clinically significant primary immunodeficiencies[1]. It is caused due to genetic defects that result in impaired B-cell differentiation leading to defective antibody production. Mutations in approximately 23 different genes have been linked to CVID, many of which are involved in B-cell differentiation and antibody production[2]. Most patients have sporadic disease, but 10–25% of them have familial inheritance. Genetic testing is therefore a key aspect of CVID diagnosis. Respiratory tract infections are the most common among patients due to the absence of protective antibodies[3]. Nevertheless, there are also patient subgroups that present with a range of other complications including malignancy, immune dysregulation and autoimmune conditions[4].

What is the link between CVID and nuclear factor kappa-B subunit 2?

Evidence from published cases indicates that approximately 5% of the CVID population has mutations in the nuclear factor kappa-B subunit 2 (NFKB2) gene that encodes the p100 subunit of the transcription factor complex NFKB and is a key player in the non-canonical NFκB signalling pathway[2].

Figure 1 is a diagrammatic representation of the domains of NFKB2 (p100) showing the rel homology domain (RHD), ankyrin repeat domain (ARD) and death domain (DD). Multiple alignments of indicated sequences are shown, with two highlighted conserved serine residues (S866/S870). When the non-canonical NFκB pathway is activated, these serines are phosphorylated which marks the p100 protein for partial cleavage into functional p52 that then translocates to the nucleus of the cell to initiate transcriptional regulation of downstream target genes[5].

Clinical Implications

Lack of antibodies, recurrent infections, adrenocorticotropic hormone (ACTH) deficiency and autoimmune hair loss are features in patients that have been associated with mutations in the NFKB2 gene[2,6]. We therefore postulated a causative NFKB2 gene defect in two unrelated cases from Epsom & St. Helier University Hospitals, with these clinical features. To verify this, we sequenced the NFKB2 gene in these patients, measured the expression of protein p100, evaluated B- and T-cell subsets and performed quantitative functional assessment of the non-canonical NFκB signalling pathway.

Sequencing identified novel heterozygous genetic variants at position 2604 in the NFKB2 gene in both patients, causing the same amino acid change i.e tyrosine to termination at position 868 in the encoded protein p100. This resulted in a truncated form of p100, p100Δ33, which is 33 amino acids shorter than the normal form of the protein. Interestingly, this mutation in the two unrelated patients is identical to that of the known Nfkb2$^{Lym1/+}$ mice[7]. Loss of serine870 disrupts the phosphorylation essential for processing of p100 to p52. Immunoblotting showed accumulated unprocessed mutant p100Δ33 and reduced p52. DNA binding by functional p52 was quantitatively abrogated. Circulating B and T cells (including T follicular helpers) were significantly reduced.

Thus, patients presenting with lack of antibodies, recurrent infections, ACTH deficiency and autoimmune hair loss should be tested for mutations in the NFKB2 gene. Further research using samples from these unrelated patients and the Nfkb2$^{Lym1/+}$ mice will help us better understand the molecular pathogenesis of CVID.

This study was undertaken by

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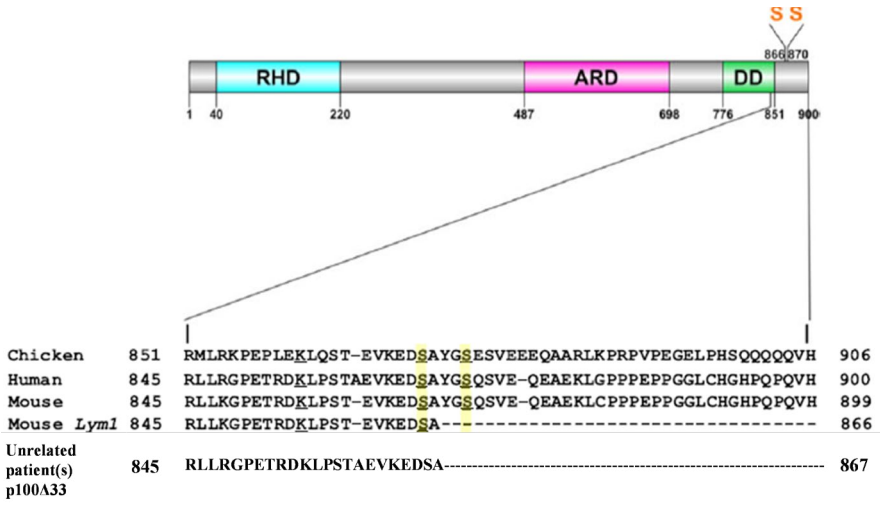

Figure 1 - Diagrammatic representation of the domains of protein p100 showing rel homology domain (RHD), ankyrin repeat domain (ARD) and death domain (DD). Multiple alignments of indicated sequences are shown, with two highlighted conserved serine residues (S866/S870). Their phosphorylation is essential for NIK/IKK α-mediated p100 processing. The mutation Y868 in both patients is identical to that of the known Nfkb2$^{Lym1/+}$ mice (7). It creates a premature stop codon and results in the removal of S870, thus resulting in impaired p100 processing and reduced p52 production.*

Dihydropyrimidine dehydrogenase and fluoropyrimidine toxicity: testing times ahead

Pharmacogenetics of purine and pyrimidine drug analogues

The classic example of pharmacogenetics in clinical practice is the association between thiopurine methyltransferase deficiency and life-threatening toxicity to the immunosuppressant thiopurine drugs azathioprine and mercaptopurine. Less well known is the association between dihydropyrimidine dehydrogenase (DPD) deficiency and severe, sometimes fatal, toxicity to the fluoropyrimidine drugs 5-fluoruracil (5FU) and capecitabine, both widely used in the treatment of solid tumours including colorectal and metastatic breast cancers. The first report of severe toxicity due to DPD deficiency in a patient treated with 5FU was reported by Tuchman et al in 1985, thirty years after 5FU was developed. Whilst there is now a considerable body of peer reviewed scientific literature supporting the association between DPD deficiency and fluoropyrimidine toxicity (Lunenburg et al 2016), it has taken a further thirty years for this information to reach the popular press under the headline "How hundreds are being killed by chemo meant to save them" (Daily Mail Online. 6th October 2018).

Testing for DPD and its use in determining dosage

Approximately 80 to 90% of 5FU is degraded through the normal pyrimidine degradation pathway with the first step catalysed by the enzyme DPD. As 5FU has a narrow therapeutic window, impaired DPD activity leads to overdosing and toxicity. We have previously reported that four DPYD genetic variants with significant frequencies in the UK populations predict severe (grade 3 to 4) fluoropyrimidine toxicity (Loganayagam et al 2013). These four variants formed the basis of the 5FU pharmacogenetics testing panel we introduced. We subsequently included the DPYD variant c.1236G>A/HapB3 which tags the deep intronic variant c.1129-5923C>G (Meulendijks et al 2015). This variant creates a splice site leading to miss-splicing of an intronic sequence into the DPYD mRNA. All five variants in our current panel have a high penetrance, meaning that the majority of patients carrying these variants in a heterozygous genotype will experience toxicity. These DPYD variants do not however all have the same effect on DPD enzyme activity. Two variants, the splice junction variant c.1905+1G>A and the exonic variant c.1679T>G (p.A560S) result in a non-functional DPD enzyme. In a heterozygous genotype, DPD activity is 50% of normal and consequently, the fluoropyrimidine dose should also be reduced to 50% of the normal dose (Table 1). By contrast, the other three variants shown in Table 1 are associated with significant residual activity. In heterozygous genotypes, DPD activity is estimated to be 75-80% of normal and the dose given should be a corresponding 75-80% of the normal dose. Although heterozygous genotypes are most commonly seen, compound heterozygous or homozygous genotypes are found and these patients experience extreme toxicity at normal fluoropyrimidine doses. The effect of these alleles on dose reduction is additive, for example a patient homozygous for the c.1905+1G>A variant will have completely deficient DPD activity and should not be given fluoropyrimidines. The compound heterozygous genotype c.2846T/c.1236A is associated with 50% DPD activity and would require a 50% dose reduction.

In a large Dutch study (Deenen et al 2016), testing for the variant DPYD*2A (c.1905+1G>A) only has been shown to have a marginal cost benefit. We have reported that patients experiencing severe toxicity who also carry a DPYD variant account for a disproportionate number of hospital bed days compared to DPYD wildtype patients experiencing toxicity (Loganayagam et al 2013). There is also anecdotal evidence that DPD–related toxicity is associated with prolonged hospital stays (De Sousa et al, 2015). More importantly, the Deenen study estimated death due to fluoropyrimidine toxicity in patients heterozygous for the c.1905+1G>A variant treated with a normal fluoropyrimidine dose to be approximately 10%. For some colorectal cancer patients the Daily Mail headline could equally have read "Cured by surgery, killed by chemo".

Changing Clinical Practice

In conclusion, there is a considerable body of evidence supporting testing for DPYD variants prior to the start of fluoropyrimidine therapy to avoid severe, sometimes fatal toxicity.

Variant	% of normal dose for a heterozygous genotype
DPYD*2A IVS14+1G>A, c.1905+1G>A, rs3918290	50%
c.1679T>G, p.A560S rs55886062	50%
c.2846A>T, p.D949V rs67376798	75%
c.1236G>A/HapB3 tags c.1129-5923C>G deep intronic variant rs75017182	75%
c. 1601G>A, pS534N rs1801158	80%. Dose increment to normal dose if tolerant after first cycle

Table 1 - Fluoropyrimidine dose reduction associated with heterozygous variant DPYD genotypes

Patients carrying a DPYD variant should be treated with reduced dose therapy or an alternate therapy. Although there is increasing awareness of testing among patients, clinical practice has been slow to change.

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Haematological cancers: an integrated approach to detecting Acute Myeloid Leukaemia (AML)

The Haematological Malignancy Diagnostic Centre (KHMDC) based at King's College Hospital provides specialist diagnostic services for diagnosing haematological cancers. The department has an Immunophenotyping laboratory which processes approximately10,000 samples per year by flow cytometry, and a Cytogenetics laboratory which analyses samples by G-banded chromosome analysis and fluorescence in-situ hybridisation (FISH). Morphology, Histopathology and Molecular Genetics laboratories complete the department to assist diagnosis of haematological cancers.

Case Study of Patient A

This case study follows a sample taken from Patient A aged 61, through the different laboratories in the KHMDC. Patient A's blood results showed that the white blood cell count (WBC) was within the normal range, a pancytopenia with haemoglobin, neutrophil and platelet count below normal levels. Pancytopenia can be caused by various diseases, including severe vitamin deficiencies, myelodysplasia, leukaemia, aplastic anaemia, viral infections and hypersplenism amongst others. Due to the clinical picture and an abnormal blood film, Patient A was suspected to have Acute Myeloid Leukaemia (AML) which can also be a cause of pancytopenia.

AML is a haematological malignancy where the bone marrow produces abnormal myeloblasts, an immature cell precursor. Because of a high number of leukemic cells in the bone marrow, normal blood cell production is replaced/suppressed resulting in , bone marrow failure. As a result, patients are often very anaemic, prone to infections and have a low platelet count.

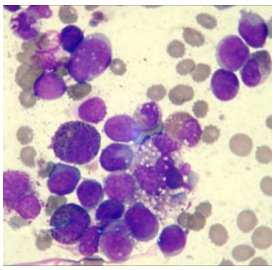

Figure 1 - Patient A

Morphology

To collect bone marrow samples, a needle is inserted through skin and into the posterior iliac crest of the pelvic bone, under local anaesthetic. The liquid bone marrow aspirate withdrawn into a syringe and samples separated

for testing in the different laboratories. . A solid sample (core) of bone marrow tissue is also taken with a larger trephine needle. A small sample of Patient A's bone marrow aspirate was examined under a microscope to study the appearance of the cells and detect any abnormal morphology. It was confirmed that Patient A had increased numbers of early immature myeloblasts, which are shown in figures 1 & 2. This can be a sign of AML.

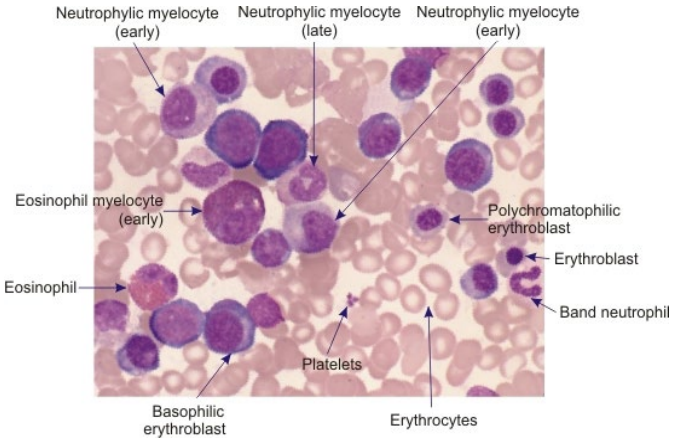

Figure 2 - Leukaemia morphology

Immunophenotyping

Flow cytometry was used to examine Patient A's sample and immunophenotyping showed an expanded population of CD34+ and CD34- myeloid progenitors along with an increase in promonocytes and eosinophils.

This abnormal excess of blasts and promonocytes in the bone marrow aspirate sample accounts for 25% of TNC's. This is suggestive of AML as having at least 20% blasts in the marrow is consistent with acute leukaemia, with a FAB-subtype of AML-M4 with eosinophilia

Histopathology

Patient A's bone marrow trephine was investigated in histopathology. The results from this solid biopsy showed an increase in the number of immature granulocytes.
Due to this, erythropoiesis was markedly reduced to absent by morphology. Megakaryocytes were similarly reduced, but appear morphologically normal where present. Immunostaining with CD34, CD117 and CD123 was positive in 10-20%, ~20% and ~20% of TNC's respectively with features consistent with AML.

Molecular Genetic Testing

The presence or absence of certain mutations can affect the prognosis in AML patients. Molecular genetic testing is therefore carried out in all patients with suspicion of AML. In the case of Patient A, polymerase chain reaction (PCR) was used to test for Nucleophosmin 1 (NPM1) insertion and FMS-like Kinase 3 internal tandem duplication (FLT3-ITD). Patient A's molecular testing was negative for both the NPM1 and FLT3-ITD mutations, which is associated with an intermediate prognosis risk group.

Cytogenetic Testing

A G-banded karyotype was performed and showed an inversion of material in one chromosome 16 homologue. This is a recurrent finding in AML, resulting in fusion of the CBFB gene located at 16q22 to MYH11 at 16p13, and is consistent with the suspicion of AML-M4with increased eosinophils suggested by morphology. FISH studies confirmed this inversion of chromosome 16 using a fluorescent probe to visualise the gene fusion.

Conclusion

From the testing carried out by the various laboratories, Patient A was diagnosed as having AML with inv(16)(p13.1q22); CBFB-MYH11, which has a favourable prognosis.

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How to assess folate (vitamin B9) status

Folate is essential for the prevention of a wide spectrum of health issues, most notably megaloblastic anaemia and neural tube defects. Chronic suboptimal folate states may increase the risk of cognitive decline, depression, neuropathy and some cancers. However, this is often overlooked. The folate status of patients following cessation of treatment for previously identified deficient states is rarely monitored. There is also a poor awareness of the utility of functional markers of folate status and of the possible negative consequences of excessive folic acid intake. Viapath's Nutristasis Unit makes recommendations for the diagnosis of folate deficiency in the clinical setting.

Folate deficiency and excess

Poor dietary intake is the most common cause of folate deficiency. However increased folate turnover (i.e. in pregnancy, breastfeeding, skin disease, gastrointestinal malabsorption and haematological disorders) can also lead to folate deficiency. Furthermore, folate deficiency is the most common cause of elevated plasma concentrations of total homocysteine (tHcy), a risk factor for cardiovascular diseases and dementia.

The synthetic form of folate, folic acid, is added to foods and supplements. The intakes of folic acid, that exceeded the upper tolerable limit of 1 mg/day, increased in populations and unmetabolised folic acid is also increasingly detected in serum, especially in countries where a mandatory folic acid supplementation has been implemented. The excessive folic acid intake has been associated with adverse biochemical profiles and health effects. Most notably,

the adverse effects were observed in the combination of high (defined as 20µg/L) folate with poor vitamin B_{12} status. Moreover, some researchers suggest that the daily upper tolerable limit for folic acid of 1 mg/day is set too high as adverse neurological effects have been observed from long-term exposure to folic acid at doses of 0.5-1 mg in the presence of B_{12} deficiency. The combination of high folate and low vitamin B_{12} in mothers may also contribute to insulin resistance in the offspring and a higher risk of small for gestational age infants.

Diagnosing folate deficiency and excess

We propose three lines of folate status assessment (Figure 1). As a first line assessment, serum folate should be determined. Since serum folate concentrations rise for up to 2 hrs in response to folic acid/folate ingestion and then decline rapidly, a fasting sample is preferable for this measurement.

As a second line testing, total plasma homocysteine (tHcy) and red cell folate (RCF) can be utilised. tHcy is a sensitive marker of folate status and correlates well with serum folate and RCF. However, its specificity is compromised in patients with deficiencies in vitamins B_2, B_6 or B_{12}, as well as in the cases of inborn errors/polymorphisms in genes related to homocysteine metabolism i.e. MTHFR, MS and CBS.

The concentration of folate in red cells is a strong indicator of folate status, because it is not influenced by transient changes in dietary intake, and it is set at the time of cell production. Low values strongly suggest folate deficiency.

As a third line testing, if clinically and analytically indicated, we suggest individual folate forms in serum, red cells or cerebrospinal fluid (CSF), folic acid and genetic testing e.g. polymorphisms in MTHFR gene. For example, individuals with the MTHFR 677TT genotype have lower 5-methyltetrahydrofolate (5-MTHF; the main form of folate) and higher homocysteine as a consequence of a diminished capacity to convert 5,10-methylenetetrahydrofolate to 5-MTHF.

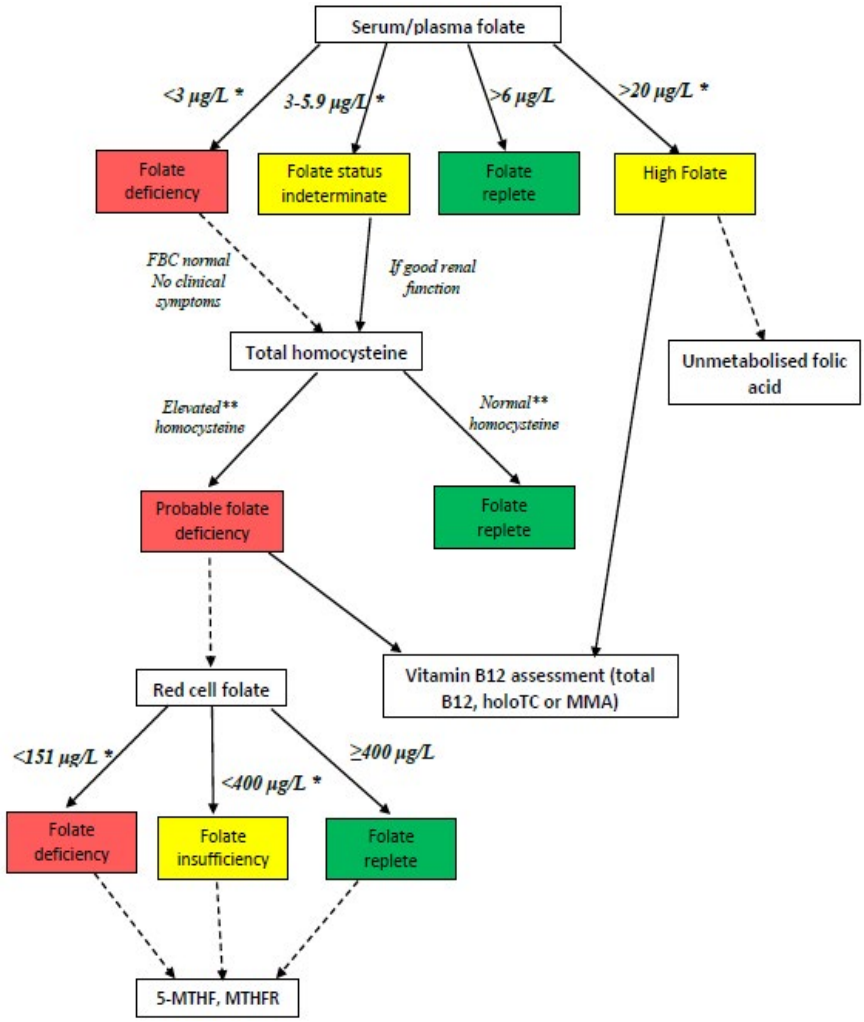

*Figure 1 An algorithm to assess the folate status. FBC (full blood count), 5-MTHF (5-methyltetrahydrofolate), holoTC (holotranscobalamin), MMA (methylmalonic acid), MTHFR (methylene tetrahydrofolate reductase). *WHO recommended.6 **Age, sex and pregnancy related i.e. <10 µmol/L for children <15 years and pregnant women,5 <13 µmol/L for females and <15 µmol/L for males aged 19-64 yrs1 and <20 µmol/L for elderly >65 years. Dashed arrows indicate optional testing.*

The analysis of folic acid has gained additional interest after reports about the unmetabolised folic acid in people consuming fortified foods and folic acid supplements, and reported correlations with adverse health effects.[2,3] The concentration is typically < 2 nmol/L but values as high as 278 nmol/L have been reported in healthy individuals consuming 5 mg of folic acid daily for 90 days.[4]

5-MTHF measurement in CSF has been utilised for the diagnosis and monitoring of cerebral folate deficiency (CFD), a neurological condition associated with low concentrations of 5-MTHF in the CSF and normal concentrations of serum folate/5-MTHF.

Conclusion

Low serum/plasma folate in the presence of clinical symptoms strongly suggests folate deficiency. Suboptimal folate status should be treated, especially if accompanied by elevated tHcy. Monitoring of folate status following cessation of folic acid supplementation is required to ensure adequate folate status. RCF testing may be helpful, providing that the appropriate cut-offs is used. High folate status should be reviewed and the adequacy of B_{12} confirmed.

Further information including folate absorption, metabolism, sample requirements, stability data and the interpretation of markers of folate status can be found at https://www.ncbi.nlm.nih.gov/pubmed/30228213 or contact:

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Scaling end-to-end Next Generation Sequencing solutions for clinical diagnostics in the cloud

Next Generation Sequencing (NGS) has become an essential tool in clinical diagnostic laboratories, however this technology introduces many well described challenges around data processing, storage and analysis. In order to overcome these, Viapath's Genetics Laboratories have implemented an automated, scalable and cost-effective bioinformatics pipeline utilising the power of cloud computing.

The DNAnexus Platform is used to run bioinformatics workflows specific to diagnostic test types such as exomes for paediatric developmental disorders and an amplicon panel for assessing epidermal growth factor receptor (EGFR) in lung cancer, all of which are ISO15189-accredited. These automated and scalable workflows perform secondary bioinformatics analysis and then pass results directly into QIAGEN Ingenuity Variant Analysis (IVA) for tertiary analysis. IVA takes advantage of the Qiagen clinical knowledge base to enable systematic filtering, prioritisation and analysis of variants, including automated ACMG classification.

The DNAnexus Platform is also used to manage data which is archived for long term storage using Amazon Glacier; this provides a low-cost and resilient solution.

For further details on these innovative developments, please watch our webinar which discusses:

- Advantages of DNAnexus and IVA platforms
- The development process for building DNAnexus apps and workflows
- How pipelines can be automated from sequencer to analysis
- How these tools have helped ViaPath scale with changing service requirements
- Interpretation of exome variants using IVA
- The dual strategy of clinically-defined gene panels and phenotype-driven (gene-agnostic) variant prioritisation
- Clinical case studies

The webinar is available to watch on demand at:

https://www.labroots.com/webinar/scaling-end-to-end-ngs-solutions-clinical-diagnostics-cloud

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The Advancing Healthcare Awards is now in its 13th year and aims to recognise and reward projects and professionals that lead innovative healthcare practice and make a real difference to patients' lives.

The awards are open to healthcare scientists, allied health professionals and those who work alongside them in support roles. The awards are unique in that they are UK-wide and cover all these professional and specialists groups whose achievements so often go unnoticed.

There are 14 award categories in total with an overall winner chosen from the category winners. The deadline for entries is Monday 14th January 2019. At least one team member in any entry should be a healthcare scientist working in the UK. To find out more about the award categories and the Advancing Healthcare Awards 2018 visit https://www.ahpandhsawards.co.uk and you can download the guide to writing a winning entry at https://www.ahpandhsawards.co.uk/wp-content/uploads/2018/09/AA6496-AHA-Awards-2019-how-to-write-a-winning-entry_V3.pdf

Viapath is sponsoring The Viapath award for innovation in healthcare science and is about recognising and rewarding the vital contribution of science to healthcare delivery. We are looking for innovation that is sustainable, transferable and plays a demonstrable part in delivering service transformation. The judges will be looking for scientific initiatives for delivering care that have improved the integration of services, speeded up diagnosis and treatment and given patients greater control of their own care.

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