pathology@viapath

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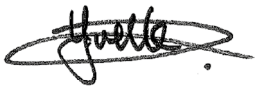
pioneers in pathology

Message from the editor

It feels like it has been a longer winter than usual and, even as I write, there has just been another deluge of snow here in London. But spring has officially arrived, the days are lengthening and hopefully the sun will make an appearance soon. However, before you rush to sit out in the garden or jump onto a sunbed, do take a look at the article on the damaging effects of sunlight. It is quite thought-provoking.

As well as changes in the weather, there are changes in our laboratories which demonstrate Viapath's continued commitment to innovating pathology. Artificial intelligence is breathing new life into molecular diagnostics by automating the analysis and reporting of results and a new, more sensitive, method has altered how 5-hydroxyindole acetic acid is measured.

On March 8th, Viapath celebrated International Women's Day by focusing on the wealth of experience and diversity of its female employees. I was also interested to learn that the majority of Viapath's workforce are women.



Measurement of Direct Oral Anticoagulants

History of anticoagulation

For more than 50 years, the vitamin antagonists have been the anti-coagulants of choice for treatment and prevention of venous thromboembolism (VTE). The main advantages were the mode of intake and reversibility. The high bioavailability and high-water solubility made them desirable too. Although these agents have served the patients well over the years, their use is not without challenges.

Disadvantages of the vitamin K antagonists

The vitamin K antagonists have been associated with increased risk of bleeding particularly intracranial haemorrhage. The main disadvantage of these anticoagulants is the interactions with foods and other drugs; medicinal and recreational. The interindividual variability and unpredictable pharmacokinetics and pharmacodynamics, makes monitoring a must, and this comes with extra costs. The vitamin K antagonists have also been associated with embryopathy and foetopathy. Direct oral anticoagulants were therefore developed as an improvement.

What is a good oral anticoagulant

A good anticoagulant is one that can be taken orally. It should be quick acting and should not interact with food or other medicines. A predictable pharmacokinetic (PK) and pharmacodynamics (PD) would remove the need for individual

dose adjustments.

An ideal anticoagulant should also have a specific target and be reversible in case of an accidental or intentional overdose.

Direct Oral anticoagulants (DOACS)

Many of the old anticoagulants were a product of serendipitous discoveries. The arrival of the synthetic direct oral anticoagulants will help in some of the issues identified with the old generation anticoagulants. The main DOACs can be divided into 2 groups, the direct thrombin inhibitors, dabigatran and the factor Xa direct inhibitors; Rivaroxaban, Apixaban and Edoxaban. The advantages with this group of anticoagulants is that they are taken orally, have specific targets and are said to have a predictable PK and PD, having minimal interactions with other medicines and not require monitoring or dose adjustments.

Our Experience at Viapath and King's College Hospital (KCH)

Being early adopters of the DOACs, we have first hand experience of patients on these drugs and listed below are articles that have culminated from collaborative work between the Haemostasis laboratory staff and clinical team at KCH, a convergence of expertise. Although it was argued that the dosing strategy adopted was based on data from large clinical trials, it is well recognised that clinical trial populations do not necessarily represent real-world populations, particularly older and/ or frail adults in whom significant use of these agents is likely. There are therefore situations when it will be helpful to measure the drug level. Examples under which measuring may be useful include:

- Haemorrhage
- Suspected overdose
- Presence of interacting drug
- Renal impairment
- Extreme body weight
- Emergency surgery pre-assesment
- To monitor efficacy in patients presenting with a thrombosis while anticoagulated
- Assess compliance/ adherence
- During bridging

Post intestinal surgery were absorption rates may be affected

Trough levels to assess potential accumulation in very elderly patients

Testing of DOACS at KCH

The British Committee on Standards in Haematology guidelines on monitoring non-coumarin anticoagulants recommend that laboratories determine the sensitivity of their routine assays to the DOACS. They have also published target trough and peak levels for prescribers to aim for.

The Viapath laboratory at KCH introduced testing for drug levels under specific conditions including total drug measurement using turbulent flow liquid chromatography with high resolution mass spectrometry and activity tests for the agents.

Direct Thrombin inhibitor: Dabigatran

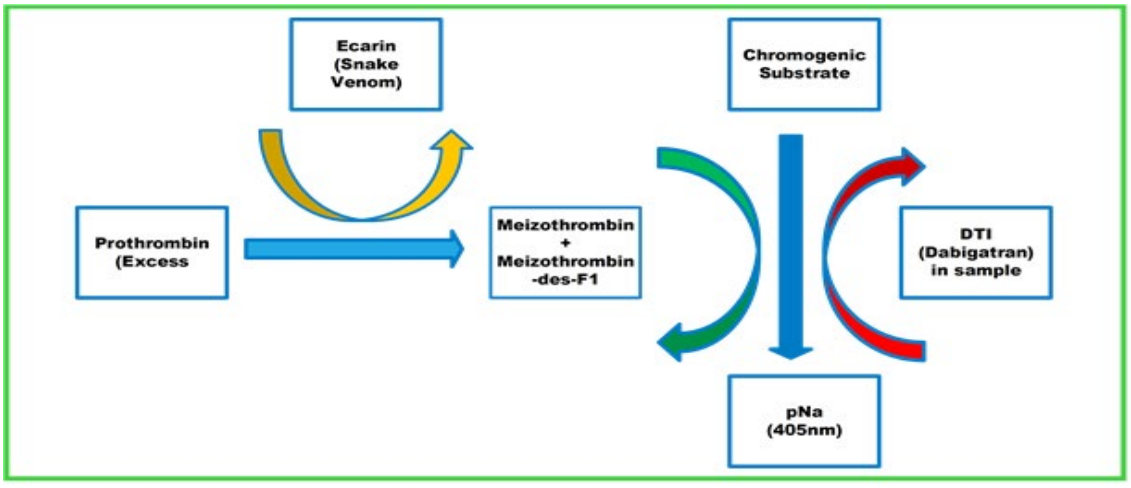
Viapath's laboratory uses a chromogenic Ecarin assay to measure activity of the drug and utilises this to determine the level of drug in the sample. In this assay snake venom is used to activate prothrombin to meizothrombin. Meizothrombin acts on the chromogenic substrate to generate colour. This reaction is inhibited by dabigatran; therefore, the intensity of the colour change is inversely proportional to the amount of the drug in the sample. Routine tests like thrombin time and activated partial thromboplastin time (APTT) are sensitive to this drug.

The laboratory, in conjunction with the KCH thrombosis team, developed a haemorrhage protocol to be employed in the emergency department should an anticoagulated patient present with a massive haemorrhage. As the APTT using the laboratory reagent is positively related to dabigatran drug levels, a normal APTT suggests that the bleed is unlikely to be due to dabigatran overdose. Thrombin time is also very sensitive to dabigatran, therefore a normal result suggest the bleed is not due to an overdose.

Anti- Xa inhibitors: Rivaroxaban, Apixaban and Edoxaban

These factor Xa inhibitors are measured using a chromogenic Xa assay, but drug specific calibrators and controls are employed to determine the specific drug level. In this assay, excess amount of Xa is added into the reaction before a chromogenic substrate is introduced to the mixture. The Xa that has not been inhibited by the drug in the sample is responsible for cleaving the substrate resulting in a colour change. The intensity of the colour is inversely proportional to the amount of drug in the original sample.

Rivaroxaban and edoxaban have a positive relationship with the laboratory thromboplastin time and therefore a normal



prothrombin time (PT) suggests the patient is not overdosed. The KCH thrombosis team guidelines recommend using PT as initial screen for patients presenting with a haemorrhage in the emergency department.

For further information, please contact Blood Sciences Department, King's College Hospital

Relevant Publications

1. Patel, J. P., Chitongo, P. B., Dighe, P., Roberts, L. N., Vadher, B., Patel, R. K. and Arya, R. (2018), Prothrombin times in the presence of edoxaban – *in-vivo* experience from King's College hospital. Br J Haematol. doi:10.1111/bjh.15101

2. Patel, J. P., Roberts, L. N., Chitongo, P. B., Patel, R. K. and Arya, R. (2013), More on normal prothrombin times in the presence of therapeutic levels of rivaroxaban – early experience from King's College Hospital. Br J Haematol, 162: 717–718. doi:10.1111/bjh.12423

3. Patel, J. P., Couchman, L., Chitongo, P. B., Flanagan, R. J. and Arya, R. (2015), New oral anticoagulants: dosing and monitoring. BMJ 2015 May 19;350:h2655. Epub 2015 May 19

4. Gous T, Couchman L, Patel JP, Paradzai C, Arya R, Flanagan RJ. Measurement of the direct oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in human plasma using turbulent flow liquid chromatography with high resolution mass spectrometry. Therapeutic Drug Monitoring 2014; 36: 597-605

Automating Molecular Diagnostics

Viapath has begun working with diagnostics.ai to implement artificial intelligence into its laboratory's molecular assays. The technology automates the analysis and reporting of results, with built-in quality control, ensuring accuracy and standardisation.

The innovative system removes the manual steps associated with analysing the data, delivering a digitised and paperless system (tying into the NHS Five Year Forward View - Paperless 2020), as well as enabling faster turnaround times, reduced risk and improved laboratory capacity.

The initial laboratory implementation will be in Viapath's South London Specialist Virology Centre at King's College Hospital. The first systems to be automated will be the high-volume real-time PCR testing, used for a wide range of sample types and tests including respiratory, STD and gastrointestinal assays through the use of diagnostics.ai's cloud-based service, pcr.ai. The implementation began in February 2018, demonstrating Viapath's continued commitment to setting the standard for the future of pathology.

To illustrate the complexities of manually analysing real time PCR assay data, figure 1 shows a typical set of amplification curves. The instrument's software plots the

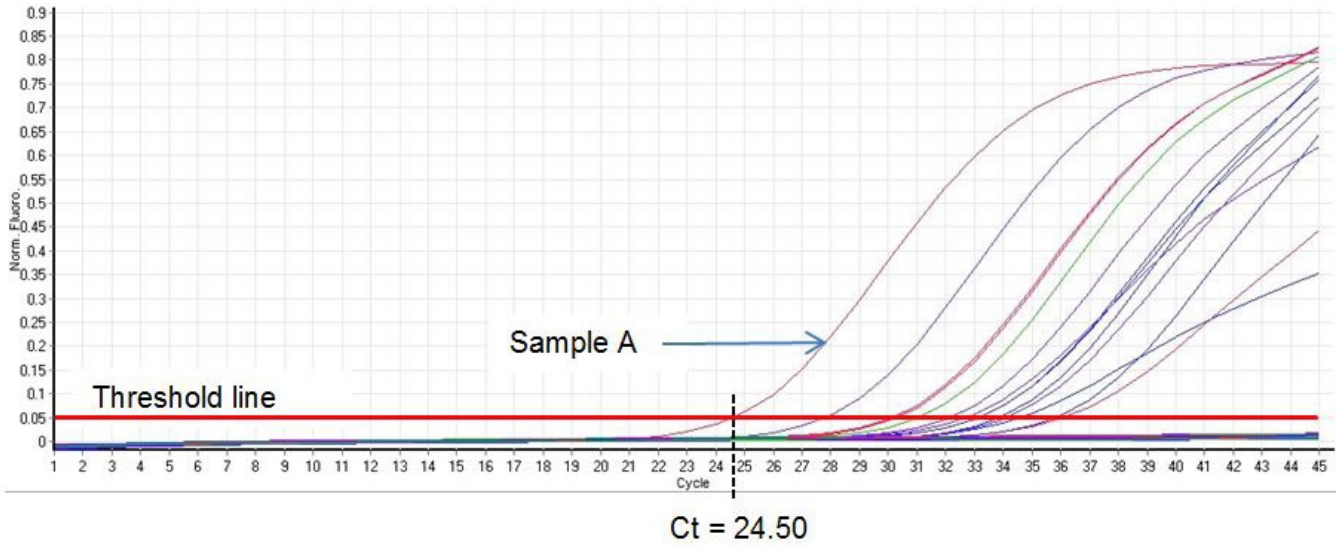


Figure 1: A typical real-time PCR assay amplification plot for a single virus in a four target multiplex (three pathogens and an extraction control). Positive samples are shown as S-shaped curves; negative samples are shown as flat lines below the red threshold line.

amplification of viral nucleic acid during the reaction based on the increase in signal from fluorescent probes, specific to the viral target. During the amplification reaction more and more copies of the target are made, allowing more probes to bind resulting in an increase in the fluorescent signal. A sample is positive if an S-shaped curve is produced that crosses the red threshold line. This results in a Ct value (the cycle number on the X-axis). In figure 1 sample A is positive with a Ct value of approximately 24.5.

The example above comes from a multiplex assay that detects three viruses together with an extraction control. This means that there are four separate amplification plots that need to be checked manually for each run. This can be a time consuming process, particularly if there are any difficult to interpret amplification traces. This will require further, time-consuming analyses which can involve re-setting reaction parameters such as baseline and threshold values, or noise-band ranges to determine which samples are positive and which are negative.

Furthermore, quality assurance data has to be entered for the standards for each target together with values for the extraction control, which is used to monitor each sample for reaction inhibition. This is to ensure that if a sample is negative, it is a true negative and not because the reaction has failed due to an inhibitor carried over during the extraction process. Setting reaction parameters and visual interpretation of results is by definition subjective and requires considerable time, expertise and quality control procedures. In contrast, a patented machine learning algorithm that automatically interprets both quantitative and qualitative real-time PCR tests and digitises the results without manipulating the raw data has been developed by diagnostics.ai. This means that there is no need for manual interpretation, or to look at the amplification traces to analyse the results, although the software allows the user to call up each trace if required. The end result is a fully automated process from assay interpretation to reporting, with full and continuous QA data logging.

'diagnostics.ai has developed a patented machine learning algorithm that automatically interprets both quantitative and qualitative real-time PCR tests and digitises the results without manipulating the raw data.'

The company has successfully collaborated with a number of laboratories both here and abroad, including the Department of Laboratory Medicine at the University of Washington, where over 4,000 cytomegalovirus samples were analysed. Diagnostics.ai software was found to be highly accurate and efficient at quantifying CMV viral loads and that the automatic data analysis reduced errors and required less hands-on analysis time.

Another study was carried out with the West of Scotland Specialist Virology Centre at the Gartnavel General Hospital in Glasgow. This showed that results from different assays analysed and run on different types of thermal cyclers were in complete agreement with manual methods. However, interpretation was significantly faster using the new software, with the additional benefits of reducing turn-around times and staff costs.

A summary of some of the benefits of diagnostics.ai technology are shown in table 1.

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1	Time (and cost) savings and higher throughput benefiting clinicians and patients as turn-around time will be reduced.
2	BMS time in reporting & assay data manipulation will be reduced allowing staff to focus on other areas of the laboratory.
3	Continuous, standardised monitoring of inter and intra-assay variation will allow prospective determination of assay efficiencies, maintaining quality and adherence to clinical governance standards. The automated system will save considerable time in continuously producing and maintaining QA records in real-time, allowing full document control and simplifying data production for internal audits.
4	The system permits universal usage – it has been designed to import files from all of the major equipment manufacturers (such as Thermofisher, Roche, Qiagen) and can also import text-based files. This flexibility means the system can be deployed across all Viapath laboratories to gain maximum benefits

Table 1: Highlighting some of the benefits of implementing diagnostics.ai technology

'Dying for a tan' - Evidence for photocarcinogenesis

The incidence of skin cancer is rising. It is the most common type of cancer in the U.S. In fact, the *Skin Cancer Foundation estimates (http://www.skincancer.org/skin-cancer-information/skin-cancer-facts)* that one in five Americans will develop some form of the disease in their lifetime. According to the Foundation's web site, "nearly 800,000 Americans are living with a history of malignant melanoma (MM) and 13 million are living with a history of non-melanoma skin cancer, typically diagnosed as basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)". In the UK, around 102,000 cases of non-melanoma skin cancer are diagnosed each year. Cancer Research UK figures (2014) state that there were around 15,400 new cases of melanoma skin cancer in the UK. That's 42 cases diagnosed every day. Melanoma skin cancer is the fifth most common cancer in the UK (2014) and it accounts for 4% of all new cases. In the case of non-melanoma skin cancer the stated figures are, in reality, a considerable under-estimate, as a percentage of BCC's never get recorded as many people do not seek medical treatment for them.

The most significant risk factor for the development of both melanoma and non-melanoma skin cancer is exposure to the sun's rays. It is within the spectrum of ultra violet light, most significantly UVB (wavelength 280-315nm) and to a lesser extent UVA (wavelength 315-400nm), that is commonly associated with photo induced sun damage to our skin.

Figure 1: Celtic redhead / auburn haired individual equivalent to skin type 1

Figure 2: All six skin types from around the world

Broadly speaking there are 6 skin types (I-VI) in the world. Each skin type has differing tanning ability and also varying degrees of resistance to the development of skin cancer. Skin type I (the northern European or Celtic skin type) is the most susceptible to the development of skin cancer and correspondingly this skin type also has the least tanning ability. Conversely skin type VI (the Afro-Caribbean population) is the least susceptible to the development of skin cancer and has the highest tanning ability (Figures 1 and 2).

As we age there is a chronological deterioration in the healthy functioning of our skin. Significantly the more exposure we have to sunlight during our life time, the more rapid these degenerative changes are likely to be. The harmful effects of exposure to UVA and UVB include:

- Acute inflammation (sunburn/erythema)
- DNA and oxidative damage
- Mutation (e.g. p53)
- Immunosuppression
- Skin cancer
- Photoageing
- Photodermatoses (premalignant skin lesions such as solar keratosis and actinic keratosis)

A recently published large cohort study of 109 thousand women in the US, from the years 1989-2009, looked at the incidence of BCC, SCC and MM[1]. The study revealed that for MM, participants with 5 or more blistering sunburns between ages of 15-20 years old resulted in an 80% increase in the chances of developing MM, similarly there was also a 68% increase in the chances of developing BCC or SCC. Such data shows a close correlation with sunburn episodes and the likelihood of developing skin cancer later in life. Studies evaluating the significance of sunburn episodes in young life (before the age of 10) show a frighteningly similar, if not more elevated, trend analysis. In addition to the growing data on the risks associated with natural sunlight exposure, there is also a worrying trend with the associated risk related to the exposure to artificial sunlight in the form of sun bed usage. Across USA and Europe, 40-50% of teenagers between the ages of 15-18 years old, have used indoor tanning devices with the highest incidence recorded in Scandinavia and Minnesota[2]. Epidemiological studies have shown that exposure to sunbeds increases the risk of both melanoma and non-melanoma skin cancers. There is also an increased risk with long term usage (cumulative exposure). The associated risk of sunbed use in MM patients younger than 30 years old may be as high as 43-76% depending on which studies you read. The fundamental premise is that sun bed usage

in adolescents should be strongly discouraged.

In terms of photobiology, the key sequences that result in carcinogenesis involve signal transduction pathways, oncogene and tumour suppressor gene interactions, DNA damage and repair processes, immunological surveillance and the significance of chemo-preventive and/or therapeutic agents. What is becoming increasingly apparent is the fact that cumulative 'sun burn episodes' do a great deal of harm to our skin over our life time and these effects are often non reversible. Thus studying the effects of 'sun burn episodes' has formed the basis of unravelling the long term effects of sun damaged skin changes. (Figure 3)

Histological evaluations of trials based on assessments of minimal erythemal dose (MED) sun burn episodes on skin, provide us with an insight into what cellular changes can be seen immediately following a sun burn episode and, then subsequently, how our skin undertakes repair processes that enable the skin to return back to a normal state. It also provides data on the consequences of repeated sun burn episodes. Evaluation of antibody panels to assess cellular changes in this manner include markers for cellular proliferation such as Ki67, Thymine Dimer markers for DNA damage, p53 for oncogene expression, CD1a for monitoring immune surveillance of Langerhan cells within the epidermal compartment and also apoptosis regulator makers such as Bcl2. These studies, if done in parallel with the same individuals whilst also examining sunscreen protected skin, can act as a good control to study the cause and effect of photodamage and photocarcinogenesis analysis. A fairly consistent observation in studies of this type reveals that p53 expression is depleted in sun screen protected sites and Langerhan cells actively migrate away from the epidermal compartment even when mild erythema (sun burn) is present. In conclusion the use of daily sunscreens can prevent the epidermal effects of repeated daily-erythemal solar simulating radiation (SSR) exposure.

The evidence indicates that sun tans are in fact contributing to the damage caused by the sun to skin in a long term manner.

Acknowledgment

This article reflects studies performed in collaboration with Professor Antony Young at St. John's Photobiology Research Unit, St. John's Institute of Dermatology, Kings College London.

For further information, please contact:

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Email: guy.orchard@viapath.co.uk

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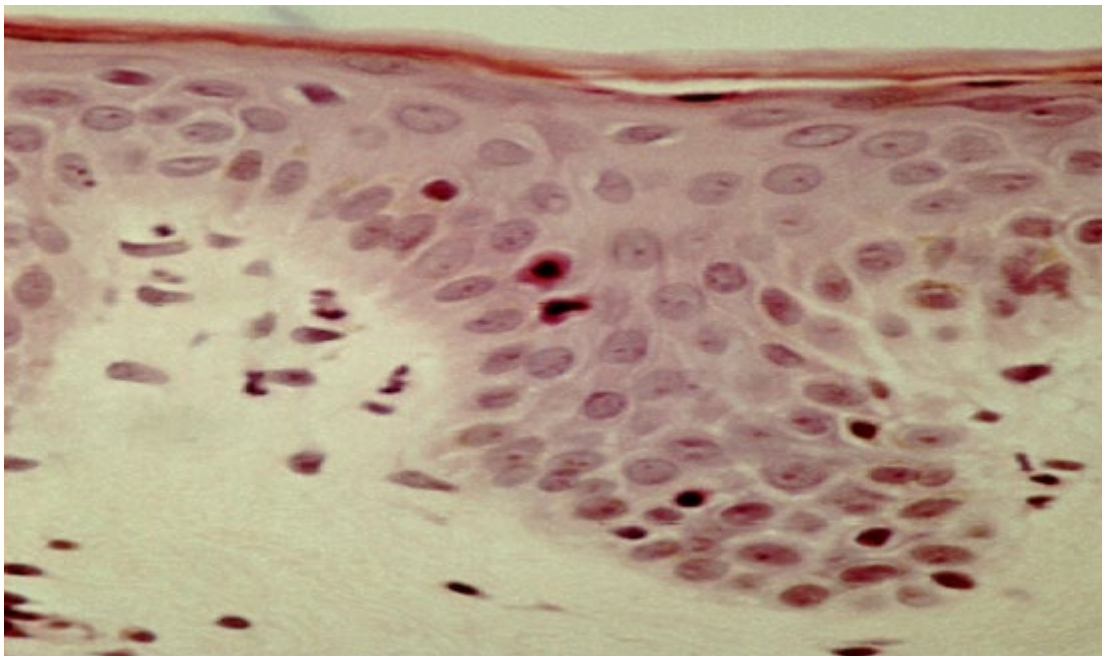


Figure 3: Haematoxylin and eosin stain of sun damaged skin, demonstrating the presence of apoptopic sunburnt cells within the epidermal compartment just above the basal layer (basement membrane).

Urine 5-hydroxyindole acetic acid: Methodology change

Why test for 5-hydroxyindoleacetic acid?

The urine 5-hydroxyindoleacetic acid (5HIAA) test is used to aid in the diagnosis of carcinoid tumours of the gastro urinary (GI) tract.

5-HIAA is the metabolite of serotonin (5-hydroxytryptamine). Serotonin is produced by the argentaffin cells of the GI tract where it is used to regulate intestinal movement. In the carcinoid tumours of the GI tract, serotonin is over-produced, thus 5-HIAA is invariably increased in classical carcinoid tumours, although some tumours may be non-secretory. 5-HIAA is also increased with high dietary serotonin intake or other GI tract disease e.g. coeliac disease.

Methodology change

Viapath's Reference Biochemistry Department at King's College Hospital is moving from a kit based HPLC method with electrochemical detection to a fully validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. This is primarily a service improvement, as the mass spectrometry methodology provides greater sensitivity for the quantitative measurement of 5HIAA in urine.

Reference ranges will remain unchanged (< 42 umol/24h or <4.0 umol/mmol creatine) and results generated using LC-MS/MS will be indicated on the report issued.

For further information, please visit:

http://www.viapath.co.uk/our-tests/5-hiaa

or

http://www.acb.org.uk/docs/default-source/committees/scientific/amalc/5-hydroxyindoleacetic-acid.pdf

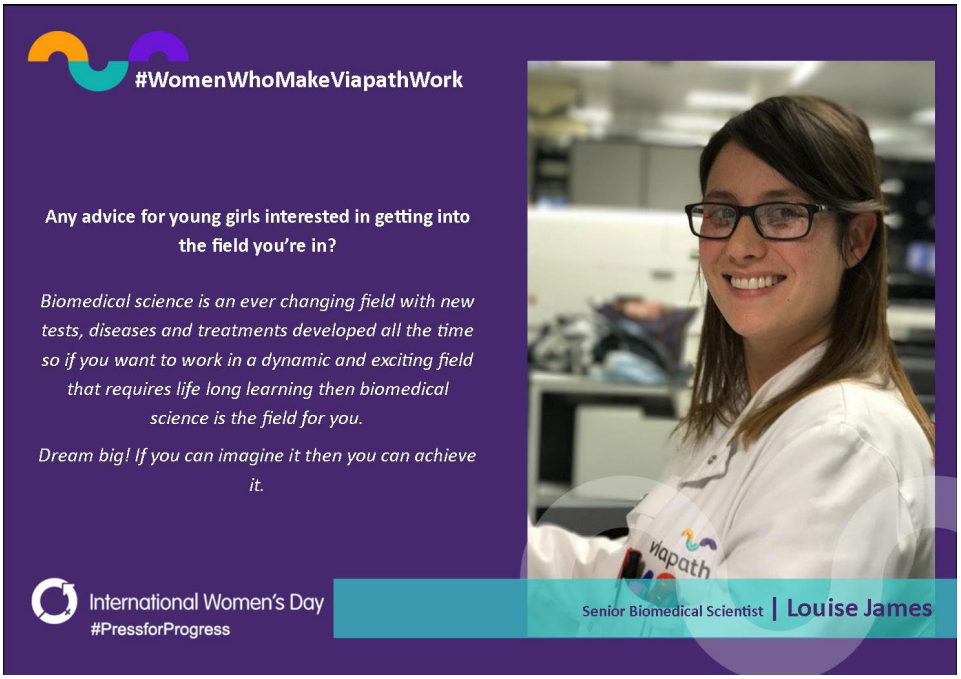
International Womens Day 2018 - The women who make Viapath work

Thursday March 8th marked International Women's day, a global day celebrating the social, economic, cultural and political achievements of women with a different theme each year. The theme of this year was #PressforProgress. Viapath joined in the celebrations by championing the many women who are employed at Viapath, from female scientists who work in various Viapath laboratories, to corporate female staff in department's including Finance, Human Resources, Quality and many more.

The female staff took over Viapath's Twitter account to share their stories using the hash tag, #TheWomenWhoMakeViapath.

The women featured hoped to inspire the next generation of women in persuing their goals.

To see the full coverage, and hear more of the women of Viapath's stories, head over to @ViapathUK twitter page.



Ferritin and vitamin B_{12} reference intervals: a modified Hoffmann's approach

Establishing defined reference intervals in the laboratory can prove difficult. Here, Agata Sobczyńska-Malefora, Nadia Munim, Martin Crook, Dominic Harrington and Alexander Katayev provide some guidance.

Age and/or gender-specific population-based reference intervals (RIs) are rarely available or are difficult to establish in clinical laboratories. With an increased focus on the between-method standardisation and harmonisation of test results, the development of universal RIs for standardised and harmonised assays may help laboratories to improve patient care.

Both serum ferritin and serum vitamin B_{12} concentrations vary with age and gender, yet unified RIs are often applied. Both lower and upper limits for these markers are clinically important, as low values suggest deficiency leading to anaemia, and high values may reflect iron overloading/acute phase (ferritin) or abnormalities in vitamin B_{12} binding proteins (eg as seen in some cancers [B_{12}]). Therefore, accurate and subgroup-specific RIs should be applied.

The aim of the present study is to establish RIs for ferritin and B_{12} using a modified Hoffmann's approach.[1]

Modified Hoffmann's method

In 1963, Hoffmann described a simple, indirect method of calculating RIs using existing patient data from a laboratory database, named the 'probability paper method'.[2] Later, the first computerised software based on Hoffmann's approach was developed.[3]

In brief, Chauvenet's criteria were used for the detection of outliers (Figure 1a). Following the removal of outliers (Figures 1b and 2), the cumulative frequency of each test result was determined. Values from the linear portion of the cumulative frequency graph were used for computing the best fitting linear regression equation, $\gamma i=\alpha*\chi+\beta+\varepsilon i$ (Figure 3). The RIs were then determined from the linear regression equation following extrapolation of the preceding curve, and calculated (for x=2.5% and 97.5%): RImin= $\alpha*2.5+\beta$, RImax= $\alpha*97.5+\beta$.

When the source data distribution is significantly skewed, a Box-Cox transformation may be applied (Figure 2), with back transformation after the linear portion is calculated from the transformed data. In this work, a fully computerised and validated method, with new functions and algorithms added, was used.

Methodology

All ferritin results processed between August 2014 and July 2015, and B_{12} results processed between January and June 2013 on the i2000SR (Abbott Diagnostics) from a population served by Guy's and St. Thomas' hospitals in London, UK, were used to calculate RIs. Data were partitioned in accordance with literature-based knowledge about gender/age-related differences in these markers.

Results

The RIs with percentage of values below and above the cut-offs are shown in Table 1. Owing to low sample numbers, separate RIs for the 0–12 months age group for ferritin and for the 0–5 years age group for B_{12} were not calculated (Table 2). A combined RI for B_{12} for the 0–19 years age group was calculated (inclusive of 96 patients aged 0–5 years).

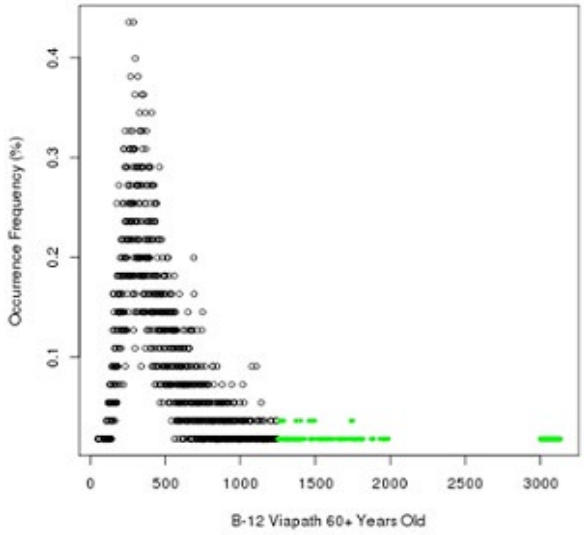


Figure 1. An example of a dot-plot showing 'good' data (black dots) and outliers (green dots). Data for total B_{12}, age group 60+ yrs.

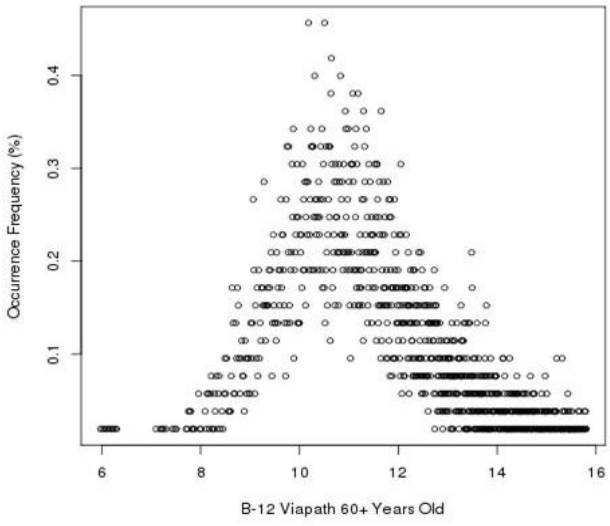


Figure 2. An example of a dot-plot (no outliers) after Box-Cox transformation (total B_{12}, age group 60+ yrs)

Size of data:	5514
Number of outliers:	258
Maximum Error Threshold:	0.465
Maximum Error:	0.464
% of data in linear range:	90.487
Start cut point:	2.707
End cut point:	93.189
RI:	[9.059, 13.91]
Regression	y = (0.051)x + (8.932)
Boxcox	c=0, ?=0.2
Inversed RI:	[175.789, 773.72]
CI:	[153.958, 200.028], [701.429, 851.851]
% of data in calculated RI:	83.079
% of data above the upper limit of calculated RI:	12.786
% of data below the lower limit of calculated RI:	4.135
Mean of all data:	521.011
Median of all data	390
SD of all data:	482.695
Mean (linear region):	339.597
Median (linear region):	370
SD (linear region):	156.253

Table 1. An example of a representative, selected report (total B_{12}, age group 60+ yrs)

Discussion

The RIs for serum ferritin and B_{12}, calculated using a modified Hoffmann's approach are consistent with RIs established using harmonized methods and may serve as universal RIs for other laboratories using the same methodology. They incorporate variations related to age, gender, method and the population being tested. The variations in upper limits for ferritin are of particular interest in view of iron overloading and deserve further investigations. Application of these RIs can assist with a better assessment of iron and vitamin B_{12} status.

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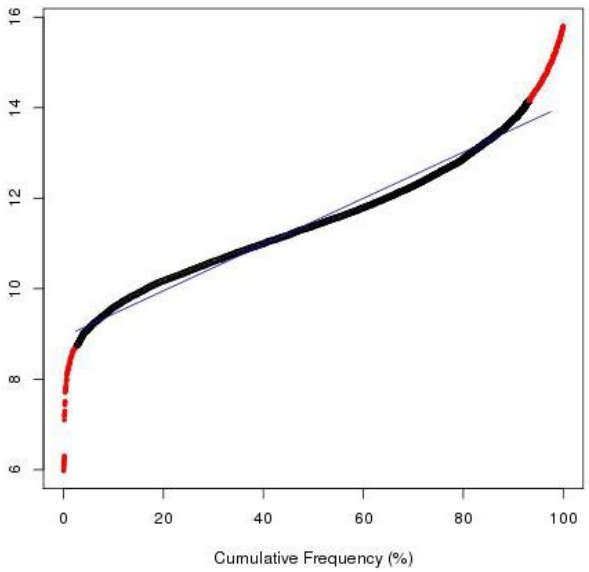

Figure 3. An example of cumulative frequencies (dots) and regression line (total B_{12}, age group 60+ yrs)

Ferritin					Total B_{12}				
Partition group; gender/age	Data size	RIs (ng/mL)	% below lower limit	% above upper limit	Partition group by age	Data size	RIs (ng/L)	% below lower limit	% above upper limit
M/1-5 yrs	845	**9 - 70**	5.2	30.0	0-19 yrs	720	**224 - 1001**	5.7	10.8
F/1-5 yrs	488	**10 - 73**	3.3	32.2	6-19 yrs	624	**218 - 878**	5.6	10.6
M/6-11 yrs	899	**14 - 85**	3.1	28.5	20-59 yrs	11641	**194 - 829**	4.8	10.1
F/6-11 yrs	802	**13 - 74**	3.5	38.6	60+ yrs	5514	**176 - 774**	4.1	12.8
M/12-19 yrs	1122	**17 - 143**	3.5	31.7					
F/12-19 yrs	1760	**7 - 75**	3.7	22.9					
M/20-55 yrs	9767	**34 - 314**	6.8	15.4					
F/20-55 yrs	25823	**9 - 102**	5.7	13.9					
M/56+ yrs	9360	**25 - 503**	7.6	12.0					
F/56+ yrs	11575	**19 - 262**	6.8	15.3					

Table 2. Age and/or sex related RIs for serum ferritin and total B12

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