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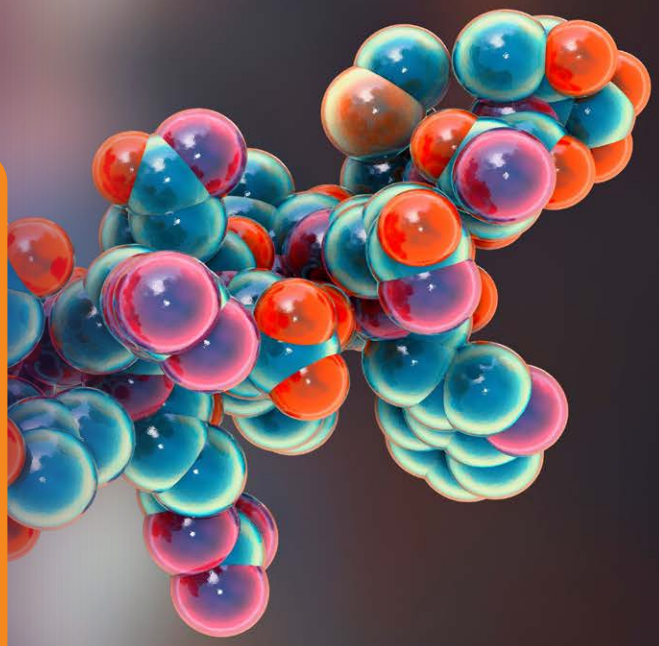

Featured articles:

New diabetes diagnosed post COVID-19

By Dr David Deam

Pre-existing diabetes and COVID-19

COVID-19 and diabetes can interact at multiple levels. We know that in patients with existing diabetes the risk of developing COVID-19 is higher, as is the risk of a more severe illness. Also, similar to other viral infections, diabetes may be more difficult to control and require medication changes during an acute COVID-19 infection.

Developing type 2 diabetes following COVID-19 infection

Several recent studies have also shown that some people can also develop type 2 diabetes after COVID-19 infection.

Study One

One such study is from Germany and was published in 2022.[1]

The subjects were from a primary care setting who mostly had mild COVID-19 disease. The incidence of new diabetes was compared with a control group who had non-COVID-19 acute upper respiratory tract infections. The two groups were matched on a range of factors including sex, age, health insurance coverage, month of disease and comorbidity factors including obesity, hypertension, hyperlipidaemia, myocardial infarction and stroke. Patients with a prior history of diabetes or steroid use were excluded. Each group had a total of almost 36,000 participants.

The COVID-19 group had a 28% higher rate of developing type 2 diabetes compared with the control group. (15.8 vs 12.3 per 1000 person-years). There was no increased rate for other forms of diabetes.

Study Two

A second paper[2] is from the USA and utilised the databases of the US Department of Veterans Affairs for patient data.

They also compared post-acute phase COVID-19 patients (181,000) with a control group who had not contracted SARS-CoV-2 (4,100,000), as well as a historical control group (4,300,000) from a pre-pandemic era. All members of these groups were free of diabetes prior to the study and were followed up for a median of 352 days.

Measures of incident diabetes and anti-hyperglycaemic use, and a composite of the two outcomes were used to assess the development of diabetes post COVID-19. They reported the results as a hazard ratio and burden per 1000 people at 12 months.

People with COVID-19 exhibited an increased risk (40% higher) than the control group and excess burden (13·46 per 1000 people) of incident diabetes. This was also seen in antihyperglycaemic use with an increased risk (85% higher) than the control group and excess burden (12·35 per 1000 people). The composite endpoint gave an increased risk (46% higher) than the control group and an excess burden of 18·03 per 1000 people at 12 months.

The hazard ratios and burdens increased according to the severity of the acute phase of COVID-19 (whether patients were non-hospitalised, hospitalised or admitted to intensive care). All the results were consistent in analyses using the historical control as well as the reference category.

These are just two of several studies that have shown the link between diabetes and COVID-19.

Most of the studies associate COVID-19 with type 2 diabetes and a Scottish study found no increase in type 1 diabetes post COVID-19.[3]

Why can diabetes present after COVID-19?

There are several possible mechanisms by which COVID-19 could increase the incidence of type 2 diabetes.

One is by altering the metabolic and hormonal status of post COVID-19 patients which results in higher blood glucose levels and diabetes, especially in people who are predisposed to the condition.

It is also possible that the virus may affect the beta cells of the pancreatic islets and cause disruption of normal insulin production and release. The virus could also result in cross-reacting antibodies which could affect the beta cells.

Other factors which also should be considered include any drugs, such as steroids, that may have been used by COVID-19 infected patients, as well as the diet, weight and exercise level of people post COVID-19.

We also should not discount the effect of post COVID-19 patients having more medical contact which may increase the pick-up rate of diabetes.

Clinical Labs anecdotes

Anecdotally, we have seen several patients who have had new diagnoses of diabetes with elevated HbA1c levels both during acute COVID-19 and post COVID-19 infections.

Some have been patients with pre-diabetes who have moved into the diabetic ranges in their test results.

Examples we have seen include:

- a 74-year-old man who had shortness of breath post COVID-19 and was found to have an elevated HbA1c
- a 48-year-old man with foot swelling post COVID-19 and had an HbA1c in the diabetic range
- a 66-year-old woman with pre-diabetes, who complained of tiredness post COVID-19 and was also found to have an HbA1c which was now in the diabetic range

"... it may be wise to have a high index of suspicion and check for diabetes if there are any features suggestive of diabetes in post COVID-19 patients, especially if they already have risk factors or pre-diabetes."

Discussion

As the COVID-19 patients in the above studies were only followed for a relatively short time, further follow-up is needed to determine if the diabetes is just temporary and may resolve or whether it becomes a chronic condition.

Although type 2 diabetes is not likely to be a problem for the vast majority of people who have mild COVID-19 and there are no specific guidelines yet to screen post COVID-19 patients for diabetes, it may be wise to have a high index of suspicion and check for diabetes if there are any features suggestive of diabetes in post COVID-19 patients, especially if they already have risk factors or pre-diabetes.

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Primary aldosteronism: A collaborative approach for diagnosis in hypertensive patients

By Dr Tony Mak

Primary aldosteronism (PA), also known as Conn's syndrome, is autonomous secretion of aldosterone by a tumour or hyperplasia of the adrenal glands resulting in hypertension. This condition is remarkably underdiagnosed. We advocate for a collaborative approach to enhance its recognition.

Why screen for primary aldosteronism

PA is the most common secondary hypertension. Among the hypertensive patients in primary care, 5-10% have the condition.[1] It has been demonstrated that PA gives rise to more severe end organ damage in comparison to primary hypertension: stroke, myocardial infarction, atrial fibrillation and death from cardiovascular causes.[2] Once diagnosed, specific surgical intervention or medical treatment can lessen the damage and may even cure the hypertension.[2] It is therefore beneficial to diagnose and control the condition as early as possible.

> ***"Once diagnosed, specific surgical intervention or medical treatment can lessen the damage and may even cure the hypertension."***

Whom to screen[1]

Patients with hypertension which is difficult to control or associated with one or more of the following conditions should be screened for PA:

- Hypokalaemia
- Adrenal incidentaloma
- Sleep apnoea
- Family history of hypertension or cerebrovascular accident occurring at a young age
- First-degree relatives with PA

How to diagnose

After appropriate preparations, an early morning blood specimen taken after at least two hours in the ambulatory position is measured for renin and aldosterone to derive an Aldosterone/Renin Ratio (ARR). A high ARR signifies a positive screening result.[1,3,4]

Why the screening test is underutilised

Given the high prevalence, the more severe consequences and the potentially curable nature of the condition, it is unsatisfactory that only an extremely low proportion of hypertensive patients in general practice are screened for PA.[1] This gap signifies that there are some obstacles in the process. Awareness of the condition is one. Fortunately, within our community, numerous excellent efforts have been made to raise awareness.[1,3,4] Secondly, the apparently "simple" screening test can be difficult. Laboratories use different renin and aldosterone assays, and the numerical cut-off ARR values are not the same and can be confusing.

> ***"Given the high prevalence, the more severe consequences and the potentially curable nature of the condition, it is unsatisfactory that only an extremely low proportion of hypertensive patients in general practice are screened for PA."***

Most importantly, it is widely known that the commonly used antihypertensive drugs interfere with the diagnostic tests in different directions and magnitudes. Whilst sustained-release verapamil, prazosin, moxonidine and hydralazine have minimal effects on the screening test, how to modify antihypertensive drug treatment to prepare a patient for the screening test can be daunting.

Some researchers have tried to simplify this step by minimising or even eliminating drug changes.[2,3,5] Interpretation of the results, of course, need to take into account the possible effects of the remaining drugs in use.

Practitioner and pathologist collaboration for testing

A collaborative approach can overcome PA screening hurdles. The primary and most important role of a general practitioner in this process is to identify patients indicated for the screening test. Once identified, a pathologist can be engaged to recommend steps to optimise patient preparations. The pathologist can advise on correction of potassium status, other patient preparations for specimen collection, modification of antihypertensive treatment if required and interpretation of the screening test result.

For patients with a positive screening result, referral to an endocrinologist or a hypertension specialist should be made to confirm the diagnosis and determine the subtype. With this collaborative approach, more hypertensive patients can benefit from an earlier detection of the condition.

Special note: This short article is meant to be a concise summary of PA. For comprehensive reviews, several excellent local publications are available.[1,2,4]

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How to order

1. Identify hypertensive patient as meeting the recommendations for screening, as listed above.
2. Engage with your local Clinical Labs chemical pathologist to discuss patient preparations for an optimised screening result. Please call 1300 134 111 to speak to your local pathologist today.
3. Provide patient with referral form for Aldosterone/Renin Ratio testing with Clinical Labs.
4. Contact your local Clinical Labs chemical pathologist to discuss how to interpret patient results for diagnosis of PA.

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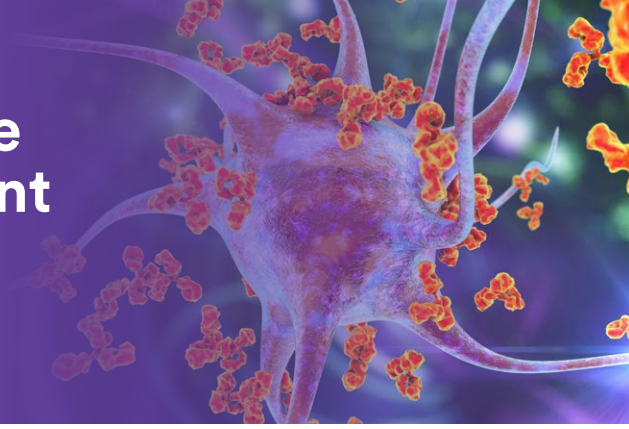
Is DFS70 a negative predictive indicator of a SARD in a patient with positive ANA?

By Associate Professor Louise Smyth



History

The description of the LE cell by Hargraves, in 1948 [1], and the subsequent demonstration of induction of the phenomenon by plasma from patients with Systemic Lupus Erythematosus [2], opened the door to the demonstration of the autoantibodies that together comprise Antinuclear Antibody (ANA) as we understand it, almost three quarters of a century later.

Very early, it was recognised that a very large number of macromolecules were contained within the human nucleus and induced different autoantibodies in lupus patients, with differing sensitivity, specificity, PPV, NPV and disease profile associations. The low Positive Predictive Value but very high Negative Predictive Value of ANAs for lupus was recognised very early, resulting in the need to identify the "sub-specificities" that could/would provide high quality information for both diagnostics and management, including disease monitoring, in the autoimmune diseases.

In 1957, two European groups – in France and Italy [3] [4] – demonstrated that a substance reacting with native DNA was present in the blood of patients with lupus. In the early 1960s a rush of articles appeared describing different patterns of fluorescence seen when ANAs were detected by Indirect Immunofluorescence (IIF), including PJ Lachman's and Henry Kunkel's correlation of specific antibodies and nuclear patterns. By 1967, a review in *Arthritis and Rheumatism* [5] described three types of ANAs with different significance:

- Antinucleoprotein (anti-DNP) producing the LE cell phenomenon
- Anti-DNA reacting with native DNA, not complexed with nuclear proteins
- Antibodies reacting with nuclear antigens that could be extracted in isotonic buffer solution (Extractable Nuclear Antigens or ENA).

Furthermore, some, such as anticentromere antibody, show very specific patterns.

Over time, many more antibodies with specific antigen binding with or without disease specificity have been described, including at least 180 in lupus alone (Yaniv & al., 2015). Among the more recently defined ANA patterns is DFS (Dense Fine Speckled or Fine Dense Speckled). As with many ANA patterns, the DFS pattern may be associated with several nuclear antigens, but it is mainly due to antibody directed against the DFS70/LEDGF chromosome-associated protein. Frustratingly, the clinical significance of this antibody has continued to throw up challenges.

> ***"...there is a consensus view that monospecific anti-DFS70 antibody does not indicate the presence of a Systemic Autoimmune Rheumatic Disorder (SARD)..."***

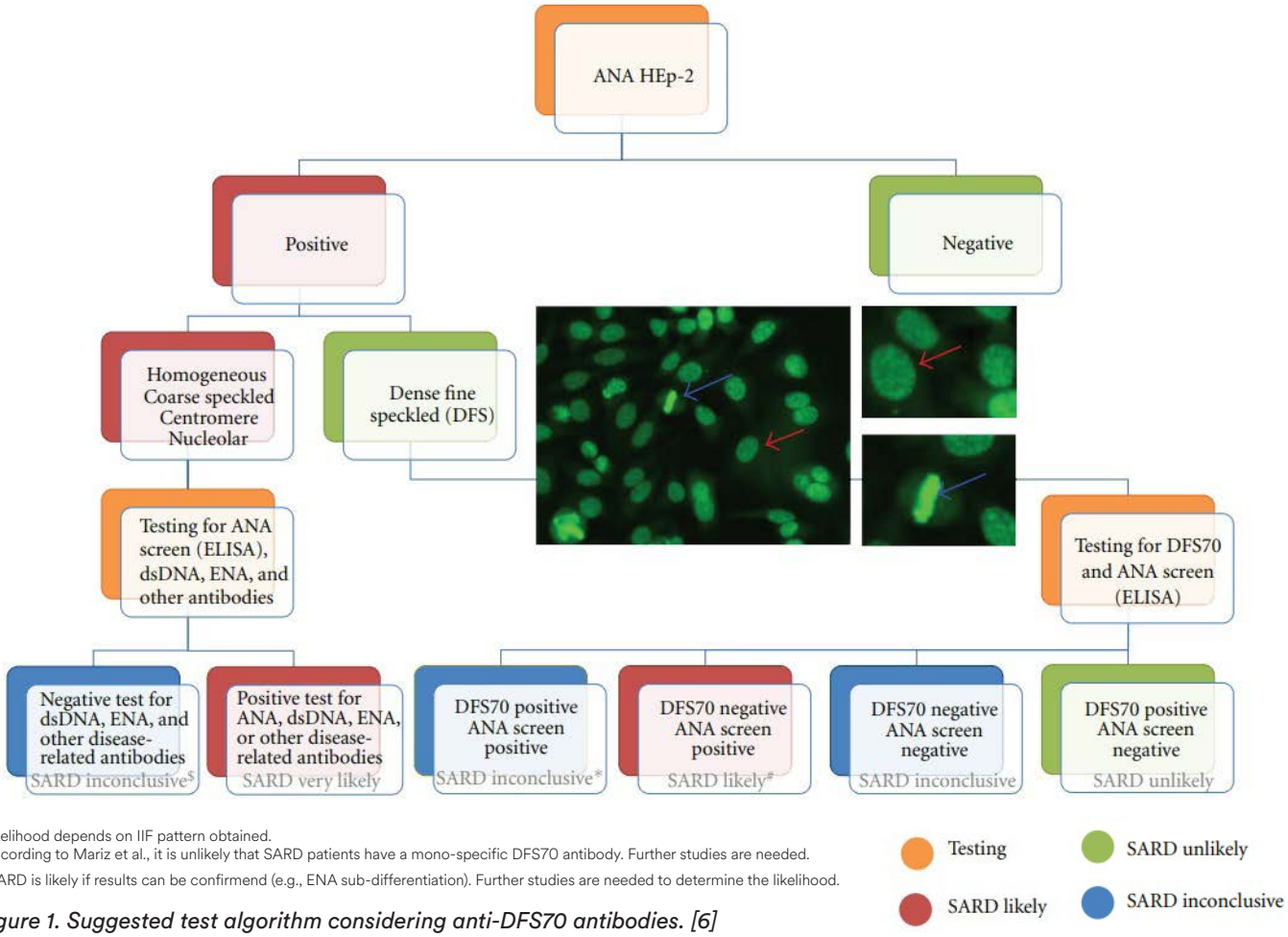
Nevertheless, there is a consensus view that monospecific anti-DFS70 antibody does not indicate the presence of a Systemic Autoimmune Rheumatic Disorder (SARD) since this antibody occurs more frequently in individuals who do not carry such a diagnosis than in those who do. Mahler and Fritzler reported this IIF pattern in up to 33% of healthy individuals with a positive ANA, which occur in low concentration in up to 20% of ANA tests [6], with higher frequency in females. Their observations led to the recommendation for a testing algorithm (see Figure 1).

Extractable nuclear antigens

The earliest described ENAs and their associations (or predominant associations) were anti-Smith (Sm) vs an acidic nuclear protein – lupus, anti-U1-ribonucleoprotein (RNP) – Mixed Connective Tissue Disease and SSA/Ro60 and SSB/La – Sjögren syndrome. Anti-SSA is also a marker for lupus and creates a risk for foetal heart block. These antibodies were reliably detected at clinically significant concentrations by the double immunodiffusion method of Örjan Ouchterlony which, like immunofluorescence microscopy, had been introduced before the discovery of LE cells, for use in infectious diseases.

DFS70 was not characterised by routine immunodiffusion techniques. Modern immunopathology laboratories have been offering antigen-specific methods for detection of both anti-dsDNA and ENA antibodies, with an increasing number of clinically useful antibodies distinguishable in routinely available, economic and reliable assays. These newer tests can confirm specific antibody to DFS70/LEDGF when the DFS pattern is detected by IIF. Furthermore, they crucially distinguish between monospecific antibody and cases in which anti-DFS70 occurs with another, SARDs related, antibody.

Recently, several publications have noted that the presence of this autoantibody may have a broader significance such as a possible role as a biomarker of inflammation or, perhaps, disease profile/severity [7] [8] [9]. Such studies must be noted as preliminary. An increased understanding of the antigen for the ENA-defined antibody is contributing to better clinical interpretation of its significance [10]. It is even proposed that, in blocking stress-related pathways of survival, it may have a protective function in autoimmunity, infection and neoplasia [11].



$Likelihood depends on IIF pattern obtained.
*According to Mariz et al., it is unlikely that SARD patients have a mono-specific DFS70 antibody. Further studies are needed.
#SARD is likely if results can be confirmend (e.g., ENA sub-differentiation). Further studies are needed to determine the likelihood.

Figure 1. Suggested test algorithm considering anti-DFS70 antibodies. [6]

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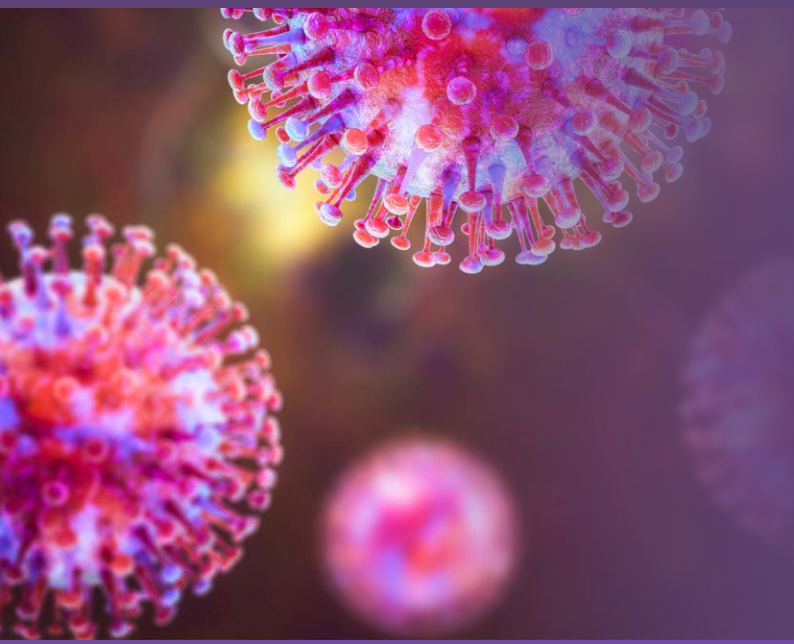

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Going paperless: The world has changed

By Associate Professor Chris Barnes

GO *Paperless*

Now that some time has passed since the pandemic started, perspective has shown us that in many ways it was a 'before and after' event. One of the ways we are clearly seeing this is the shift towards remote ways of working, and by extension, the large uptake in digital technologies to support the new paradigm. Conversely, it shines a harsh spotlight on the old paper-based forms that are now looking even more out of date than they were prior to the pandemic.

As the world makes progress, so must the medical sector and, consequently, the way we approach patient care.

One of the big areas of focus that Clinical Labs is striving towards is encouraging all of our referring clinicians to Go Paperless. We acknowledge the role our contribution can play in helping to address global sustainability challenges and have considered our Environmental, Social and Governance (ESG) position accordingly. Our teams are busy designing new, completely digital solutions that are more sympathetic to remote ways of providing patient care, as well as more sustainable, paper-free workflows that we feel all purposeful organisations should aim for.

From a patient-based perspective we feel it is a no-brainer. The minority of doctors who still opt to receive their patient results by snail-mail will have noticed the longer AusPost delivery times since the pandemic. With a quick registration to Clinical Labs eResults or eDownloads, you can have your patient's results as soon as they appear from the lab, with the ability to access them 24/7 from your mobile device, or directly from your PMS. Recently, our eHealth team has even added a new eResults feature so you can get notified by email for certain urgent or abnormal results.

Similarly, by using our eOrders platform, you can order a test at a telehealth consultation, with the pathology referral being emailed directly and automatically to the patient – with no paper being used whatsoever.

I strongly encourage you to give your Clinical Labs representative a call today so they can work with you to get rid of that fax machine, digitise your pathology experience and Go Paperless – and we'll be sure to keep you 'e-posted' as we roll out some exciting, new paperless initiatives.

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GP Connect DFS70: Significance in testing for SARDs

GP Connect is designed to share our pathologists' responses to commonly asked questions about specific pathology tests with the wider GP community. We hope you find the answers to the following questions useful in your practice.

A/Prof Louise Smyth
(Pathologist)

BA MBBS GCUT DipHPE FRCPA

Associate Professor Louise Smyth is an immunopathologist at Australian Clinical Labs. Louise also works at the School of Medicine at the University of Notre Dame Australia, Fremantle. Assoc. Prof. Smyth's main interest is autoimmunity and her other interests include transplantation, immune deficiency and allergy.

Dr Greg Caddy
(General Practitioner)

MBBS DipRANZCOG

Dr Greg Caddy is an experienced general practitioner who practised for a decade in Kalgoorlie/Boulder, Western Australia before returning to a solo outer metropolitan practice. Now in group practice, he has special interests in obstetrics, paediatrics, palliative care and rheumatology.

Dr Greg Caddy (General Practitioner)
When I have requested an ANA as an investigation for a suspicion of a systemic autoimmune rheumatic disorder (SARD), some laboratories have commented on DFS70. Can you explain the significance of this, particularly with respect to the ANA result?

A/Prof Louise Smyth (Pathologist)
The importance of identifying, and commenting on, the presence of anti-DFS70 antibodies is tied to the status of IIF as an ANA screening method. In a recent participation study by Mahler et al., the difficulty of accurate inference of the antibody specificity, by IIF varied from <10% for mixed patterns to >95% for the classical pattern, anticentromere antibody. This is important because the clinical implications, referred to above, apply to monospecific anti-DFS70, rather than more broadly to the IIF pattern, and certainly not to mixed antibodies. Since the NPV of monospecific anti-DFS70 for any SARD is so high as to discourage further testing, it is critical to be certain that it is the truth, the whole truth and nothing but the (clinically relevant) truth – as far as we can be certain.

Dr Greg Caddy (General Practitioner)
Patients have requested information on this antibody which has been found by other practitioners (medical and alternative). Could you suggest what information should be given to patients?

A/Prof Louise Smyth (Pathologist)
Depending, of course on your clinical assessment, patients with monospecific anti-DFS70 can receive reassurance that any SARD is less likely after receiving that result than it was pre-test. The possibility that it behaves as another inflammatory biomarker would seem to roughly align it with ESR or CRP, in the appropriate clinical space.

Dr Greg Caddy (General Practitioner)
Just to clarify, if ANA and DFS70 are both positive, is there any need for any further related antibody testing?

A/Prof Louise Smyth (Pathologist)
As always, your clinical assessment drives investigation. However, the confirmatory assay used at Clinical Labs is an ENA Characterisation assay. By using this assay to confirm the antigen producing the DFS pattern we also exclude almost all of the potential confounders at the first episode and can reassure both doctor and patient. In the few cases where another unidentified autoantibody that requires more extensive testing may still be present, our review of the clinical history and other results (inflammatory markers, FBP, CK, U&Es, LFTs, etc.) before releasing the report will generate an indicative comment. These will be a very small group.

Dr Greg Caddy (General Practitioner)
Could you comment on the clinical relevance of actually knowing the level of this antibody and does having this knowledge alter management?

A/Prof Louise Smyth (Pathologist)
That is a very good question. Despite the recent publications concerning various roles beyond the SARDs, none refer specifically to the concentration of antibody. At a practical level though, it is generally present in high concentration which, in the IIF, makes it more likely to obscure other more clinically relevant antibodies. The presence of the antibody, at any concentration, shouldn't influence management, except to dissuade any unnecessary further investigation or referral.

Dr Greg Caddy (General Practitioner)
Is the cost of the test justifiable in terms of patient outcome?

A/Prof Louise Smyth (Pathologist)
Yes, since it is imperative to specify the antibody and to exclude concomitant antibodies (including anti-dsDNA) that are disease markers, or even pathogenic antibodies. If the suggested protocol is followed, unnecessary further testing and referrals have been shown to be very cost-effective, as well as helping clinicians to assuage patient anxiety. A recent Spanish study of its cost effectiveness showed that following a 10-year follow-up of 181 patients with only anti-DFS70 (confirmed), the reduction in costs associated with further autoantibody testing and outpatient referrals (down 70%) was >€60,000 [1]. That equates to around $AU500 per patient.

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