NHS Greater Glasgow & Clyde Immunology and Neuroimmunology		
MP_14	Immunology And Neuroimmunology Laboratory Handbook	Version: 3
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9713

Immunology and Neuroimmunology Laboratory

Queen Elizabeth University Hospital, Glasgow

User Handbook

INTRODUCTION

The Immunology and Neuroimmunology Department provides a quality diagnostic service for the patients of NHS Greater Glasgow and Clyde, NHS Scotland and external users from further afield. The service offers a range of Immunological and Neuroimmunological tests covering areas of autoimmunity, autoimmune neuropathies, immunodeficiency, allergy and aspects of lymphoproliferative disorders.
The department aims to provide a comprehensive, appropriate and clinically relevant service with robust analytical and advisory components and is accredited by the United Kingdom Accreditation Service (UKAS). UKAS Medical accreditation number 9713 (Accredited to ISO 15189:2012). Our accreditation is limited to those activities described on our UKAS schedule of accreditation found here:
UKAS Schedule of Accreditation 9713

Additionally, the Immunology department comprises both Clinical and Laboratory Services. During routine hours a member of the medical staff is available for consultation and provision of clinical advice. We are happy to answer enquiries about the use & interpretation of test results. A limited out of hours service is provided on weekend mornings to support the cardiac transplant service.

The Neuroimmunology service is available to clinicians throughout the UK and overseas. Tests are all supported by medically qualified personnel that offer an excellent clinical support and advice service during core hours.

http://www.nhsggc.org.uk/immunologyneuroimmunology.

Core Laboratory Working Hours

09:00 to 17:00 Monday to Friday
Limited out of hours service is provided on weekend mornings to support the cardiac transplant service.

COSTS

Contact the laboratory for current assay charges.
Billing is by quarterly invoice in arrears to the hospital or institutional finance department or, if preferred, to a named individual within the requesting department.

CLINICAL IMMUNOLOGY SERVICES

Immunodeficiency Clinics

A comprehensive service is provided for the investigation and management of adults with suspected or confirmed primary immunodeficiency (including hereditary angioedema/ C1 inhibitor deficiency). Outpatient clinics are held at West Glasgow Ambulatory Care Hospital, Dalnair Street, G3 8SJ. Day ward facilities are available at Gartnavel General Hospital for patients requiring regular immunoglobulin replacement therapy and a home therapy training programme is taken place. Paediatric Immunodeficiency services are based at the Royal Hospital for Children

Allergy Clinics

Allergy clinics are not provided directly by the Immunology department, although Consultant Immunologists contribute to the service. Adults with allergic problems may be referred either to the appropriate organ-based specialty or to the Anaphylaxis Service at the West Glasgow Ambulatory Care Hospital. Paediatric Allergy services are based at the Royal Hospital for Children.

INFORMATION FOR PATIENTS

Your sample has been referred to the Immunology and Neuroimmunology Laboratory for a diagnostic screening test. The medical specialist in charge of your case has requested a particular test from the list that we offer (Test Repertoire on website). The results will be reported back to your specialist who will offer an interpretation in conjunction with knowledge about your clinical problem.

The requirements for preserving data integrity and patient and staff confidentiality are laid down in the Data Protection (1998) Act supported by the NHSGG&C IT policies. The department follows guidelines detailed in the GGC Confidentiality & Data Protection Policy. NHS GG&C Confidentiality and Data Protection Policy

FEEDBACK

Suggestions about our service may be raised by email, letter, phone call or by calling personally at the laboratory.
All complaints are dealt with in accordance with the NHSGG&C Complaints Policy and the departmental complaints and feedback policy.
The laboratory manager will investigate the complaint and issue a response (within twenty days of receipt of the complaint), if a satisfactory outcome cannot be achieved the complaint will be passed to the Clinical Services Manager.

CONTACT DETAILS

CLINICAL STAFF

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Postal Address and Laboratory Enquiries

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Quality, Training and H&S Manager
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SAMPLES / REQUESTS/ RESULTS

Please use electronic test requesting where available. Where this facility is not available, please complete a laboratory request form, available from our websites (link above)

We cannot process samples unless we can be sure about the patient's identity, the test(s) required and where to send the result. Samples accompanied by incomplete forms will not be processed. A CHI number is essential for results to appear on SCI store and Clinical Portal.

For external organisations ordering tests from us: please note that, by sending us a sample and completed request form, you will be entering into an agreement with us.

Sample Identification Requirements

SAMPLES MUST HAVE

- Patient's full name (or proper coded identifier)
- Date of birth and/or hospital or CHI number
- Date and time of sample (Essential for anaesthetic reactions and other serial samples).

REQUEST FORMS MUST HAVE

- Patient's full name (or proper coded identifier)
- Date of birth and CHI number (if CHI unavailable, hospital number or patient's address)
- Destination for report
- Name of patient's consultant or GP
- Tests required
- Date and time of sample (for anaesthetic reactions, cellular and complement tests)

DESIRABLE

- Relevant clinical information
- Name and contact/pager number of requesting clinician
- Pre-printed adhesive labels (addressograph labels) may be used if available.

Where the information on request form and sample do not match, samples will not be tested.

Urgent Immunology or Neuroimmunology Requests

There is a limited out-of-hours immunology service on weekend mornings for cardiac transplant samples. No other out-of-hours service is provided. **Please contact the laboratory to discuss all urgent requests** – writing 'urgent' on request forms is insufficient.

High Risk Samples

These include samples from patients known or thought likely to have infectious diseases e.g. Hepatitis B or C, HIV infection, Creutzfeldt-Jacob disease. Please contact laboratory to discuss patients with suspected viral haemorrhagic fever prior to sending any samples.
The nature of the hazard should be indicated and both the form and specimen(s) must be marked with the yellow 'Danger of Infection' labels.

Sample Dispatch

Local Users:

Local users from within the hospital can send whole blood and CSF samples via the porters or pod system. Users within GG&C can send whole blood, serum and CSF samples via the hospital transport systems.

External Users (Outwith GG&C):

Unless otherwise stated in the test repertoire, serum and CSF samples are not required to be sent frozen. Samples should be refrigerated and arrive within 2 days.

Users wishing to send frozen samples should do so by dispatching by courier on dry ice.

Samples from within the UK should be sent by first class mail and outwith the UK by courier.

The Laboratory also uses the DX System: DX 6490401 Cardonald 90G. We share the box with several other laboratories so please ensure the address is clearly stated on the box.

The following tests should be sent directly to Biochemistry:

1. Bence-Jones Protein / Urinary Free Light chains

Sample: 20mL urine in plain preservative free container

2. Immunoglobulins & electrophoresis

Sample: 5 mL clotted, gel activated, blood (Gold top)

3. Cryoglobulin

Sample: specific arrangement & flask is required - contact biochemistry before taking samples

The following tests should be sent directly to Haematology at Glasgow Royal Infirmary:

1. Cardiolipin Antibodies and Phospholipid Antibodies

Sample: 5 mL clotted, gel activated, blood (Gold top)

Packaging

Packaging must meet the requirements of relevant UN3373 and postal regulations.

Place all specimen tubes into a secondary leak proof container; include absorbent material to absorb any spillage.

Place the leak proof container and a completed request form into an external package strong enough to withstand postal transit.

Avoid placing paperwork on the outside of the package as it may be discarded with packaging.

Reports and Results

We aim to report 90% of results within stated target turnaround times; samples requiring additional work such as titrations or repeat testing may take longer. Further details are provided in the Test repertoire below. Electronic reports are available on the Clinical Portal and Greater Glasgow & Clyde SCI store where this facility exits. Additionally results are sent out by internal or royal mail with the exception of sites which have opted for a paperless/electronic report only service. Please note that the laboratory computer system cannot generate extra 'copy to' reports.
Reference ranges and/or interpretative comments are available; on printed reports and electronic reports. Please contact the laboratory for advice where required.
Uncertainty of measurement, in crude terms, relates the result the laboratory provides to the range of values that result could represent. Information regarding uncertainty of measurement of specific analytes can be provided to users of the laboratory on request – please contact the duty Immunologist to discuss.

Repeat Requests / Additional Test Requests

The laboratory uses request intervention software to minimise unnecessary repeat testing. The time interval is recorded under the individual tests in the test repertoire below. All requests for repeat tests are checked by a member of staff and those with a valid reason for repeat testing are re-instated. Therefore if you require a repeat test, please ensure that the reason that the test needs to be repeated within this time interval is clearly stated on the request form or phone laboratory to discuss. Rejected tests are reported out through the normal channels.

Samples sent for testing to Neuroimmunology are stored at -80^{o}C for up to five years. Add on requests may be made within this time-frame, where appropriate.

TEST REPERTOIRE

We are currently verifying different analyser platforms for some tests (Marked *). Results produced may not be UKAS accredited during implementation period. Please contact the laboratory for further information if required.

Referred Tests

Arrangements with referral laboratories are reviewed and evaluated periodically to ensure that ISO 15189 standards are met (ISO 15189 4.5.1)
For more than 2 referred tests, additional serum is required.

Neuroimmunology

Acetylcholine Receptor Antibodies (ACH, AchR,ACR)	
SAMPLE	1ml Serum (5ml Gold Gel tube)
METHOD	Radioimmunoassay (RIA)
TURN AROUND TIME	16 days
NORMAL RESULT	<0.5nmoll/L is Negative
REPEAT TESTING INTERVAL	60 days
UKAS ACCREDITED	Yes
DESCRIPTION	Antibodies to the acetylcholine receptor (anti-AChR) are present in a very high proportion of patients with the neuromuscular transmission disorder, myasthenia gravis (MG).

Oligoclonal Bands in CSF and Serum

SAMPLE	1 ml CSF **and** 1ml Serum (5ml Gold Gel tube)
METHOD	Isoelectric Focusing (IEF)
TURN AROUND TIME	14 days
REPEAT TESTING INTERVAL	NA
NORMAL RESULT	No Bands in Serum or CSF
UKAS ACCREDITED	Yes
DESCRIPTION	The clinical diagnosis of multiple sclerosis can be supported by analysis of cerebrospinal fluid (CSF). In a very high proportion of patients with multiple sclerosis (>90%) the CSF contains oligoclonal bands that are not present in the serum.
REFERENCES	1. Anderson, M., Alvarez-Cermeno, J., Bernardi, G., Cogato, I., Fredman, P., Fredrikson, S., et al. (1994). Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J Neurol Neurosurg Psychiatry* , 897-902. 2. Keir, G., Luxton, R. W., & Thompson, E. J. (1990). Isoelectric Focusing of Cerebrospinal Fluid Immunoglobulin G: An Annotated Update. *Annuls of Clinical Biochemistry* , 436-443. 3. Thompson, E. J., & Keir, G. (1990). Laboratory Investigation of Cerebrospinal Fluid Proteins. *Annuls of Clinical Biochemistry* , 425-435.

Myelin Associated Glycoprotein antibodies (Anti-MAG IgM)

SAMPLE	1ml Serum (5ml Gold Gel tube)
METHOD	ELISA
TURN AROUND TIME	21 days
REPEAT TESTING INTERVAL	90 days
NORMAL RESULT	<1000 BTU
UKAS ACCREDITED	Yes
DESCRIPTION	A clinically important form of IgM paraproteinaemic neuropathy is associated with antibodies to myelin associated glycoprotein (MAG).

Ganglioside Antibodies (IgG and IgM)

GM1,GM2,GD1a,GD1b,GQ1b

SAMPLE	1 ml Serum (5ml Gold Gel tube)
METHOD	In House ELISA
TURN AROUND TIME	10 days
REPEAT TESTING INTERVAL	11 days
NORMAL RESULT	< 1/500
UKAS ACCREDITED	Yes
DESCRIPTION	Glycolipid antibodies are found in a significant proportion of patients with a variety of autoimmune peripheral neuropathies.
REFERENCES	1. Willison, H. J. (1994). Antiglycolipid antibodies in peripheral neuropathy : fact or fiction. *Journal Neurology Neurosurgery Psychology* , 57:1303-1307. 2. Willison, H. J. (1996). Ganglioside Autoantibodies. In *Autoantibodies* (pp. 277-284). Elsevier. 3. Willison, H.J. (1999). Inter-Laboratory validation of an ELISA for determination of serum anti-ganglioside antibodies. European Journal of Neurology 1999, 6:71-77

Paraneoplastic Antibodies (Neuronal)

SAMPLE	1 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence Assay (IFA)
CONFIRMATION	Western Blot
TURN AROUND TIME	16 days
REPEAT TESTING INTERVAL	30 days
NORMAL RESULT	Negative
UKAS ACCREDITED	Yes *
DESCRIPTION	Neuronal antibodies are present in the serum of patients with paraneoplastic disorders affecting the nervous system. These disorders have a very wide range of clinical presentations and often enter the differential diagnosis of complex neurological problems.

Glutamate Receptor (Type NMDA) Antibodies

SAMPLE	1 ml Serum (5ml Gold Gel tube) **or** 1 ml CSF
METHOD	Indirect Immunofluorescence Test (IIFT)
TURN AROUND TIME	16 days
REPEAT TESTING INTERVAL	30 days
NORMAL RESULT	Negative
UKAS ACCREDITED	YES*
DESCRIPTION	Anti-NMDA receptor encephalitis manifests along a spectrum of psychosis, altered behaviour, movement disorder, seizures, autonomic dysfunction and decreased consciousness. Antibodies against the NMDA receptor have a very high positive and negative predictive value.
REFERENCES	1. Waldinger, K. P., Saschenbrecker, S., Stoecker, W., & Dalmau, J. (2011). Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. *Journal Neuroimmunology* , 86-91.

Voltage Gated Potassium Channel Associated Proteins (LGI1 and CASPR2)Antibodies

SAMPLE	1 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence Test (IIFT)
TURN AROUND TIME	16 days
REPEAT TESTING INTERVAL	30 days
NORMAL RESULT	Negative
UKAS ACCREDITED	YES*
DESCRIPTION	Antibodies against the VGKC associated proteins LGI1 and Caspr2 are associated with a number of neurological syndromes.
REFERENCES	1. Reid, J., Willison, H., & Foley, P. (2009). 3.Voltage-gated potassium channel-associated limbic encephalitis in the West of Scotland: case reports and literature review. Scottish Medical Journal , 27-31. 2. Vincent, A., Buckley, C., Schott, J., Baker, I., Dewar, B., Detert, N., et al. (2004). Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic. Brain: A journal of Neurology , 701-12.

Glutamic Acid Decarboxylase Antibodies (GAD) (Stiff person)

SAMPLE	1 ml Serum (5ml Gold Gel tube)
METHOD	ELISA
TURN AROUND TIME	28 days
REPEAT TESTING INTERVAL	90 days
NORMAL RESULT	<5 U/ml
UKAS ACCREDITED	Yes
DESCRIPTION	Antibodies against GAD are associated with Stiff-Person Syndrome.
REFERENCES	1. Solimena M, Folli F, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy and type I diabetes mellitus. NEJM 1988 April 21 318:101220 2. McKeon A, Tracy J. GAD65 neurological autoimmunity. Muscle Nerve 2017 56:15-27

Voltage Gated Potassium Channel (VGKC)Antibodies
Voltage Gated Calcium Channel (VGCC) Antibodies
Muscle Specific Kinase (MuSK) Antibodies
Striated muscle Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube) Additional serum if more than 2 tests requested
TURN AROUND TIME	THESE ARE REFERRED TESTS: Department of Immunology Churchill Hospital Old Road, Heddington Oxford OX3 7JL
UKAS ACCREDITED	9782

Aquaporin, Neuromyelitis Optica (AQUAP4, NMO)Antibodies Glycine Receptor Antibodies Ganglionic AchR Antibodies Glutamate Receptor (AMPA 1&2 and GABA) Antibodies Myelin Oligodendrocyte Glycoprotein (MOG) Antibodies NMDA-R (Live) Antibodies	
SAMPLE	2 ml Serum (5ml Gold Gel tube) Additional serum if more than 2 tests requested
TURN AROUND TIME	THESE ARE REFERRED TESTS: Department of Immunology Churchill Hospital Old Road, Heddington Oxford OX3 7JL
UKAS ACCREDITED	No (9782)

Basal Ganglia Antibodies Beta Interferon (neutralising antibody) VEGF	
SAMPLE	2 ml Serum (5ml Gold Gel tube) Additional serum if more than 2 tests requested
TURN AROUND TIME	THESE ARE REFERRED TESTS: Neuroimmunology Laboratory UCLH Institute of Neurology Queens Square London WC1N 3BS
UKAS ACCREDITED	8045

Gliadin Antibodies	
SAMPLE	2 ml Serum (5ml Gold Gel tube)
TURN AROUND TIME	THESE ARE REFERRED TESTS: The Immunology Laboratory Northern General Hospital Herries Road Sheffield S5 7AU
UKAS ACCREDITED	8494

Tysabri (Natalizumab) – For local users only	
SAMPLE	2 ml Serum (5ml Gold Gel tube) **Samples to be brought to the laboratory within 60 minutes of collection.**
TURN AROUND TIME	THESE ARE REFERRED TESTS: Barts and The London Immunology Department Pathology and Pharmacy Building 2nd Floor, 80 Newark Street Whitechapel London E1 2ES
UKAS ACCREDITED	8285

Allergy / Hypersensitivity Tests

Total IgE		
SAMPLE	2 ml Serum (5ml Gold Gel tube)	
METHOD	Fluorescence Enzyme Immunoassay (FEIA)	
TURN AROUND TIME	21 days	
NORMAL RESULT	Age related normal ranges (kU/L)	
	0-12 weeks	0-11
	12 weeks – 1 year	0-29
	1 year – 5 years	0-52
	5 years – 10 years	0-63
	10 years – 15 years	0-75
	15 years and over	0-81
REPEAT TESTING INTERVAL	30 days	
UKAS ACCREDITED	Yes	
DESCRIPTION	IgE binds to the high affinity receptors (FcεRI) on mast cells, basophils, and eosinophil[1]. Allergen binding and cross-linking of these receptors may lead to degranulation and mediator release [2, 3]. Serum concentration of IgE may be elevated in patients suffering from allergic asthma, allergic rhinitis or atopic eczema. The increase during childhood is slow, adult values are not reached until 15-20 years of age [1]. Raised total IgE levels can also be seen in patients with parasitic disease, Wiskott-Aldrich syndrome and Hyper-IgE syndrome. A normal IgE level does not exclude significant allergic disease. Monoclonal increase in IgE – see under paraproteins	
REFERENCES	1. Gounni AS, Lamkhioued B, Ochiai K, et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature. 1994;367(6459):183-6. 2. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007. 3. Prussin C and Metcalf D. IgE, mast cells, basophils and eosinophils. J Allergy Clin Immunol. 2006. 117(2):S450-S456.	

Allergen Component Specific IgE

SAMPLE	2 ml Serum (5ml Gold Gel tube) sufficient for 6-7 allergens
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	21 days
NORMAL RESULT	< 0.35 kU/L
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	Yes
DESCRIPTION	In conventional measurement of allergen specific IgE, the target allergen usually contains a mixture of allergenic proteins and peptides. In allergen component specific IgE testing the target allergens consist of single purified peptides. This can aid risk assessment of clinical allergy and can also help determine if sensitisation is primary or secondary to cross-reactive allergens. A limited range of component specific IgE tests is available following formal assessment by an allergist or immunologist

Allergen Specific IgE
Previously Known as 'RAST'

SAMPLE	2 ml Serum (5ml Gold Gel tube)sufficient for 6-7 allergens
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	21 days
NORMAL RESULT	< 0.35 kU/L
REPEAT TESTING INTERVAL	365 Days
UKAS ACCREDITED	Yes
DESCRIPTION	These should be requested on the basis of a clinical history compatible with an IgE mediated allergic reaction. Typically this involves immediate allergy symptoms usually within an hour of exposure to the potential allergen. Testing is rarely of any value in the investigation of chronic urticaria or non-specific symptoms such as abdominal bloating. Test sensitivity and specificity varies between allergens. The presence of allergen specific IgE indicates sensitisation to the culprit allergen but does not necessarily imply clinical allergy. Negative results do not exclude allergy completely. Results should always be interpreted in the context of the clinical history.
REFERENCES	1. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007. 2. Plebani M. Clinical value and measurement of specific IgE. Clin Biochem. 2003. 36(6):453-469.

ISAC

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Multiplexed immunoassay
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	See report for interpretation of results
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	ImmunoCAP ISAC is a biochip based test using multiplexed component resolved diagnostic techniques to measure allergen specific IgE to a fixed panel of 112 components from 51 allergen sources in a semi-quantitative manner. This test can be useful in the investigation of idiopathic anaphylaxis. The test is only available following assessment by an allergist or immunologist and requires a formal cost approval (and purchase order number) from the service manager of the requesting clinician.
REFERENCES	NA

Avian Precipitins - IgG to Pigeon

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	21 days
NORMAL RESULT	0 – 10 mgA/L
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	Yes
DESCRIPTION	Positive levels indicate exposure to pigeon antigens and may be associated with Pigeon Fancier's Lung, a form of extrinsic allergic alveolitis. High levels may be found in severe acute disease. The presence of IgG precipitating antibodies is regarded as evidence of inhalational exposure to these antigens. This test is only indicated in patients with a history of exposure to pigeons or related birds
REFERENCES	1. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007. 2. Ohtani Y, et al. Clinical features of recurrent and insidious chronic bird fancier's lung. Ann Allergy Asthma Immunol. 2003. 90(6):604-610. 3. Mcsharry C, et al. Takes your breath away – the immunology of allergy alveolitis. Clin Exp Imm. 2002. 128:3-9.

Aspergillus Serology
(IgG and IgE antibodies to *Aspergillus* plus total IgE level)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	21 days
NORMAL RESULT	• IgG aspergillus – 0 – 40 mgA/L • IgE to aspergillus 0 – 0.35 kU/L • Total IgE (adults) 0 – 120 kU/L
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	Yes
DESCRIPTION	Aspergillus IgG & IgE antibodies can be associated with aspergilloma, allergic bronchopulmonary aspergillosis (ABPA), extrinsic allergic alveolitis (EAA) and are a known complication of cystic fibrosis (CF). These antibodies indicate immune response to a prior or ongoing exposure to the antigen in question. A positive test should not be, of itself, interpreted as representing a pathologic state. The absence of antibodies does not exclude the diagnosis since antibodies reduce when the disease is not in an acute state. Aspergillus IgG antibodies are sometimes termed Aspergillus precipitins.
REFERENCES	1. Thia LP and Balfour Lynn IM. Diagnosing allergic bronchopulmonary aspergillosis in children with cystic fibrosis. Paed Res Rev. 2009. 10:37-42. 2. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007.

Farmer's Lung Serology

IgG to M Faeni

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence Enzyme Immunoassay (FEIA).
TURN AROUND TIME	21 days
NORMAL RESULT	0 – 22 mgA/L
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	Yes
DESCRIPTION	Positive levels indicate exposure to the fungus *M. faeni* and may be associated with Farmer's Lung. Low titre antibodies to M Faeni (22-60 mgA/L) are of uncertain clinical significance. High levels may be found in severe acute disease. This test is only indicated in patients with a history of exposure to potentially mouldy hay.
REFERENCES	1. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007.

Tryptase

SAMPLE	2 ml Serum (5ml Gold Gel tube) **If samples will not reach the immunology laboratory within 3 days, they should be sent to the local Biochemistry lab to be separated, frozen and forwarded to Immunology lab the next working day**
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	14 days
NORMAL RESULT	2-14 µg/L
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	Yes
ADDITIONAL SAMPLE INFORMATION	Anaesthetic reactions / anaphylaxis **– send 3 timed samples; proforma request form available** Sample 1- at ~30mins (immediately after resuscitation) Sample 2- at 1- 2 hrs (or as soon as possible after this) Sample 3- at ~24hrs after onset of reaction. Post mortem samples – take as soon as possible after death Note, resuscitation ALWAYS takes priority over collection of samples. State the time interval between reaction and blood sample on request form. Please provide information about nature of reaction and potential triggers. Other tests such as IgE to latex, chlorhexidine, ethylene oxide, suxamethonium, penicillins should normally be delayed until 6 weeks after the acute reaction as false negative results have been reported.

DESCRIPTION	Tryptase typically peaks 1-2 hours post reaction returning to normal within 24 hours. However rises are not seen in all anaphylactic reactions especially those triggered by food. Reactions may be caused by a range of agents including anaesthetic drugs, other drugs (e.g. antibiotics, premedication), plasma expanders, chlorhexidine or latex. Results do not affect the immediate management. Persistently elevated tryptase levels may indicate an underlying systemic mast cell disorder. Close liaison with the laboratory is advised in the interpretation of results. West of Scotland patients may be referred to Anaphylaxis Service, West Glasgow Ambulatory Care Hospital. UK guidelines available at www.aagbi.org or www.bsaci.org Post mortem samples Post mortem samples – blood from a peripheral vein (e.g. femoral veins) is preferred. Take the sample as soon as possible after death. Tryptase may be high in intra-cardiac samples after CPR/trauma. In addition tryptase levels tend to rise post mortem. Suspected mastocytosis / other mast cell disorders Please provide clinical details and state clearly on the form if this is a random sample or one taken at the time of a flare in symptoms in which case state interval since flare began (ideally samples should be taken within 3-4 hours of onset of a flare). Normal tryptase levels do not completely exclude mast cell disorders. However lack of a change in tryptase levels between samples taken during a flare and outwith a flare makes a diagnosis of Mast Cell Activation Syndrome much less likely.
REFERENCES	1. Sargur R, et al. Raised tryptase without anaphylaxis or mastocytosis: heterophilic antibody interference in the serum tryptase assay. Clin Exp Imm. 2011. 163(3):339-345. 2. Caughey GH. Tryptase genetics and anaphylaxis. J Allergy Clin Immunol. 2006. 117(6):1411-1414. 3. Payne V and Kam PC. Mast cell tryptase: a review of its physiology and clinical significance. Anaesthesia. 2004. 59(7):695-703. 4. Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematological disorders. Leukaemia research. 2001. 25:553-562. 5. Protein Reference Unit Handbook of clinical immunology. 9th Edition. 2007. 6. Harper NJ, Dixon T, Dugué P, Edgar DM, Fay A, Gooi HC, et al. Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia. 2009 Feb;64(2):199-211. 7. Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Clinical & Experimental Allergy, 2010 (40) 15–31. 8. Valent P et al. Why the 20% +2 tryptase formula is a gold standard for severe mast cell activation and mast cell activation syndrome. In Arch Allergy Immunolol published online 28/06/2019

Autoantibodies

ANA
See under Nuclear Antibodies

ANCA
See under Neutrophil Cytoplasmic Antibodies

Adrenal Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	28 days
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	No
DESCRIPTION	Adrenal antibodies are positive in up to 80% of Addison's disease. Adrenal antibodies may also be detectable prior to development of adrenal failure. Positive adrenal antibodies in the context of autoimmune polyglandular autoimmune syndrome type 1 indicate 92% likelihood of developing of adrenal insufficiency. They may also be found in autoimmune ovarian failure.
REFERENCES	1. Brandao Neto RA, de Carvalho JF. Diagnosis and classification of Addison's disease (autoimmune adrenalitis). Autoimmunity reviews. 2014 Apr-May;13(4-5):408-11 2. Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. Journal of internal medicine. 2014 Feb; 275(2):104-15. 3. PRU Handbook of Autoimmunity. 4th Edition. 2007.

Beta 2-Glycoprotein 1 Antibodies
B2 GP1 antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	0-10 U/mL Negative. >10.0 U/mL Positive.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	The measurement of beta-2-glycoprotein 1 (B2 GP1) antibodies may be useful in patients suspected of having antiphospholipid syndrome who have negative results for lupus anticoagulant and cardiolipin antibodies (see under cardiolipin antibodies)
REFERENCES	NA

C1q Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked Immunosorbent assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative result < 15 U/mL. Positive result > 15 U/mL.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	C1q antibodies may be found in patients with Hypocomplementaemic Urticarial Vasculitis (HUV; C3 & C4 levels also very low). They are also found in patients with SLE and are a marker of renal involvement in SLE. Patients without C1q abs have a low risk of developing lupus nephritis. In contrast, high titres of C1q abs indicate a high risk in developing lupus nephritis. Successful treatment of lupus nephritis typically decreases C1q ab titres.
REFERENCES	1. Holers, VM. Anti-C1q antibodies amplify pathogenic complement activation in systemic lupus erythematosus. J. Clin. Invest. 2004. 114(5):616-619. 2. Flierman R, Daha MR. Pathogenic role of anti-C1q autoantibodies in the development of lupus nephritis – a hypothesis. Mol. Immunol. 2007. 44:133-138.

Cardiac Muscle Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF).
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	These antibodies are of limited clinical significance. Cardiac muscle antibodies are described in patients with Dressler's syndrome after myocardial infarction, cardiomyopathy, myocarditis and in patients who have undergone cardiac surgery or have had rheumatic fever. The presence of these antibodies can occur without Dressler's syndrome. This test is of no value in patients with suspected myositis.
REFERENCES	1. PRU Handbook of Autoimmunity. 4th Edition. 2007. 2. Jahns R, Boivin V, Schwarzbach V et al. Pathological autoantibodies in cardiomyopathy. Autoimmunity. 2008. 41(6):454-461. 3. Okasaki T, Honjo T. Pathogenic roles of cardiac autoantibodies in dilated cardiomyopathy. Trends Mol Med. 2005. 11(7):322-326. 4. Caforio AL, Daliento L, Angelini A et al. Autoimmune myocarditis and dilated cardiomyopathy: focus on cardiac autoantibodies. Lupus. 2005. 14(9):652-655.

Cardiolipin Antibodies (IgG & IgM)

Now measured in Haematology at Glasgow Royal Infirmary

C3 Nephritic Factor

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Immunoelectrophoresis
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	C3 nephritic factor is an IgG autoantibody which stabilises the alternate pathway C3 convertase (C3bBb), thereby permitting continual activation of the alternative complement pathway. Therefore most patients will have a low C3. Conversely, a normal C3 level makes C3 nephritic factor unlikely. The test should only be requested in patients with unexplained low C3, clinical features of partial lipodystrophy or unexplained glomerulonephritis. This test is not indicated in the routine investigation of chronic kidney disease
REFERENCES	1. PRU Handbook of Autoimmunity. 4th Edition. 2007. 2. Tsokos GC. Nephritic factor autoantibodies. Autoantibodies. 2007. 2nd Ed. Elsevier. 561-566 Appel GB, et al. 3. Servais A, Noel L-H, Fremeaux-Bacchi V, Lesavre P. C3 glomerulopathy. Contributions to Nephrology. 2013;181:185-93.

Cyclic citrullinated (CCP) Antibodies

Only available to GG&C Rheumatology Service

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	14 days
NORMAL RESULT	0-7 U/ml
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	Yes
DESCRIPTION	This test is currently only funded for the GGC rheumatology service. NICE guidance recommends rheumatoid factor (RhF) as the initial investigation for rheumatoid arthritis (RA) in adults. CCP antibodies are more specific for RA and may appear early in the disease process. However CCP antibodies can be positive in other settings and negative CCP antibodies do not exclude RA
REFERENCES	1. Aletaha D, et al. 2010 Rheumatoid Arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis and Rheumatism. 2010. 62(9):2569-2581. 2. NICE clinical guideline CG79. Rheumatoid arthritis in adults: management. 2015. 3. PRU Handbook of Autoimmunity. 4th Edition. 2007. 4. Pruijn G, et al. Anti-CCP detection facilitates early diagnosis and prognosis of rheumatoid arthritis. Cur Rhem Rev. 2005. 1:1-7. 5. Mimori T. Clinical significance of CCP antibodies in rheumatoid arthritis. Internal Med. 44(11):1122-1126.

Centromere Antibodies

(Included in ANA Screen)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect immunofluorescence (IIF) microscopy on Hep2 cell line.
TURN AROUND TIME	negative results available in 10 days; samples requiring confirmation take 4 weeks
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	1 Year
UKAS ACCREDITED	Accredited for Zenit platform. Transition to new platform ETS
DESCRIPTION	Performed as part of the standard ANA screen (see under nuclear antibodies) i.e. 'ANA negative' means centromere antibodies are also negative. Centromere antibodies are characteristic of the CREST syndrome, a variant of systemic sclerosis with limited skin involvement but associated with **C**alcinosis, **R**aynaud's phenomenon o**E**sphageal immobility, **S**clerodactyly and **T**elangectasia.
REFERENCES	NA

Diabetic Autoantibodies (GAD, IA-2, ZnT8)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
PAEDIATRIC SAMPLE	1 ml Serum
METHOD	See individual tests
TURN AROUND TIME	See individual tests
NORMAL RESULT	See individual tests
REPEAT TESTING INTERVAL	365 days
UKAS ACCREDITED	See individual tests
DESCRIPTION	Several autoantibodies including GAD, IA-2, pancreatic islet cell and ZnT8 antibodies may be found in type 1 diabetes with levels being at their highest early in the disease course. Individual patients may be positive for any one or more of these autoantibodies. NICE guidelines recommend testing up to 2 antibodies to increase chance of obtaining a positive result. One clearly positive antibody is sufficient to support a diagnosis of T1 diabetes in the appropriate clinical context. There are no particular clinical associations with any of the individual antibodies. Testing is indicated in the following situations:- • Recent onset diabetes if it is unclear if the patient has T1 or T2 diabetes. • Established diabetes (ie >3 years duration) if C-Peptide levels are between 0.2 -0.9 nmol/L and autoantibodies have not been previously assessed. Requests for Diabetic Autoantibodies will be reviewed. If testing is indicated, GAD antibodies will be tested first. If results are negative or equivocal, samples will be sent for IA-2 antibodies (adults) or IA-2 and ZnT8 antibodies (children <16 years of age). ZnT8 antibody tests are currently only funded for paediatric patients. Testing for adult patients is only available with formal cost approval and provision of a purchase order number from the service manager of the requesting clinician.
REFERENCES	1. NICE Guideline NG17. Type 1 diabetes in adults: diagnosis and management.2015. 2. NICE Guideline NG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015.

dsDNA Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	• Fluorescence enzyme immunoassay (FEIA) used to screen samples. • Crithidia Indirect Immunofluorescence (IIF) used for confirmation on new positives
TURN AROUND TIME	21 days for initial FEIA result; further 1 week for confirmatory IIF result
NORMAL RESULT	• FEIA immunoassay for dsDNA abs 0 - 10 IU/mL • Crithidia – normal result is negative
REPEAT TESTING INTERVAL	30 Days
UKAS ACCREDITED	Yes
DESCRIPTION	Antibodies to native double stranded DNA (dsDNA) are characteristic of SLE and titre may vary with disease activity. However they are only found in 40-60% of SLE patients. dsDNA abs may also be found in autoimmune hepatitis, rheumatoid arthritis and sometimes apparently healthy individuals. Confirmatory testing is carried out on new positive samples using indirect immunofluorescence on Crithidia – this test only detects high avidity antibodies to native dsDNA so is more specific but less sensitive than the FEIA method. dsDNA abs are rarely found if ANA is negative. Therefore ANA remains the best screening test for connective tissue disorders. dsDNA abs are added routinely to any new positive ANA with titre of 1/160 or above. dsDNA abs should only be requested for monitoring patients known to have SLE.
REFERENCES	1. Isenberg DA, et al. Fifty years of anti-dsDNA antibodies: are we approaching journey's end? Rheumatology. 2007. 46(7):1052-1056. 2. Deshmukh US, Bagavant H, Fu SM. Role of anti-DNA antibodies in the pathogenesis of lupus nephritis. Autoimmunity Reviews. 2006. 5(6):414-418. 3. Rouquette AM, Desgruelles C. Detection of antibodies to dsDNA:an overview of laboratory assays. Lupus. 2006. 15(7):403-407. 4. Egner W. The use of laboratory tests in the diagnosis of SLE. Journal of Clinical Pathology. 2000. 53:424-432. 5. PRU Handbook of Autoimmunity. 4th Edition. 2007.

Endomysial Antibodies (IgA)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	21 days
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	5 Months
UKAS ACCREDITED	No
DESCRIPTION	IgA TTG antibodies are the first line test for coeliac disease (see under TTG antibodies). IgA endomysial abs cannot be requested directly as they are now only used within the laboratory as a confirmatory follow on test for new positive or equivocal IgA TTG samples.
REFERENCES	1. NICE guidelines [NG20] Coeliac disease: recognition, assessment and management. Published September 2015. 2. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease. JPGN 2012; 54: 136-160

Glutamic Acid Decarboxylase (GAD) Antibodies (Diabetic)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	28 days
NORMAL RESULT	<5 U/mL
REPEAT TESTING INTERVAL	365 days
UKAS ACCREDITED	Yes
DESCRIPTION	Please see section 'Diabetic autoantibodies' for further information regarding overall clinical pathway for autoimmune diabetic serology. GAD antibodies may be found in type 1 diabetes with levels being at their highest early in the disease course. NICE guidelines (2015) recommend diabetes-specific autoantibodies should not be used routinely to confirm type 1 diabetes in adults or children. GAD antibodies are also associated with stiff person syndrome.
REFERENCES	1. NICE Guideline NG17. Type 1 diabetes in adults: diagnosis and management.2015. 2. NICE Guideline NG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015.

Extractable Nuclear Antigens (ENA) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	21 days (screening), further 7 days for identification of positives
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	2 Years
UKAS ACCREDITED	Yes

DESCRIPTION

ENA antibodies are routinely performed on any new positive ANA or 1:160 or above.
Their presence is strongly associated with connective tissue diseases (CTD) although they are only positive in a subset of patients. Positive ENA antibodies are rarely found in the absence of a positive ANA. Therefore ANA is recommended as the initial screening test and ENA should only be requested in selected patients with neonatal heart block or strong suspicion of CTD/dermatomyosistis. Direct requests for ENA abs will be tested ANA instead unless the clinical details provide a clear indication for ENA testing. Please contact laboratory to discuss testing if required.

ENA screen includes antibodies to Ro52, Ro60, La, Sm, RNP, Jo-1, Scl-70 and Centromere B (CENPB). ENA confirmation also includes ribosomal P antibodies. Jo-1 and Ro can be present without a positive ANA.

ENA	Disease Association
Ro52	Isolated Ro52 antibodies are associated with SLE, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, myositis, interstitial lung disease and autoimmune liver disease
Ro60	SLE (particularly photosensitivity), cutaneous lupus, Sjogren's syndrome neonatal lupus and congenital heart block
La	SLE, Sjogren's syndrome
SmD	SLE.
U1-RNP	SLE , Mixed Connective Tissue Disease (MCTD)
Jo-1	Polymyositis or dermatomyositis especially with respiratory involvement
Scl-70	Systemic Sclerosis (generalised scleroderma)
CENPB	CREST syndrome (limited scleroderma)
Ribosomal P	SLE

REFERENCES

1. PRU Handbook of Autoimmunity. 4th Edition. 2007.

Gastric Parietal Cell Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF) on rat liver/stomach/kidney
TURN AROUND TIME	14 days
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	1 Year
UKAS ACCREDITED	Yes*
DESCRIPTION	Occur in 95% of patients with pernicious anaemia and may be detectable prior to the development of clinically apparent disease. They also occur in up to 15% of the normal population. Mitochondrial antibodies may mask gastric parietal cell antibody – in this case intrinsic factor antibodies should be requested if pernicious anaemia is suspected.
REFERENCES	1. Khan S et al. Limited value of testing for intrinsic factor antibodies with negative gastric parietal cell antibodies in pernicious anaemia. J Clin Pathol. 2009. 62. 439-441.

Glomerular Basement Membrane (GBM) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	7 days
NORMAL RESULT	0 – 7 U/mL
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	Yes
DESCRIPTION	GBM abs target the non-collagenous domains of type IV collagen. Positive GBM abs are strongly associated with anti-GBM disease (previously called Goodpasture's syndrome). These antibodies are pathogenic, so GBM ab titres follow disease activity. Patients with GBM antibodies may also have a positive P-ANCA, usually due to myeloperoxidase antibodies although the significance of this is unclear. ANCA and GBM abs should both be requested in patients with glomerulonephritis and/or pulmonary haemorrhage
REFERENCES	1. PRU Handbook of Autoimmunity. 4th Edition. 2007. 2. Sinclair D, Stevens JM. Role of anti-neutrophil cytoplasmic antibodies and glomerular basement membrane antibodies in the diagnosis and monitoring of systemic vasculitides. Annals Clinical Biochemistry. 2007. 44(5): 432-42. 3. Cui Z, Wang HY, Zhao MH. Natural autoantibodies against glomerular basement membrane exist in normal human sera. Kidney Int. 2006. 69:894-899. 4. Levy JB, et al. Clinical features and outcomes of patients with both ANCA and anti-GBM antibodies. Kidney Int. 2004. 66:1535. 5. Pusey CD. Anti-glomerular basement membrane disease. Kidney Int. 2003. 64(4):1535-1550.

Histone Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	<40 U/mL
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Histone antibodies may be found in up to 95% of patients with drug-induced lupus. These patients are usually ANA positive but dsDNA antibody and ENA antibody negative. Histone antibodies may also be found in SLE.
REFERENCES	1. Antonov D et al. Drug-induced lupus erythematosus. Clin Dermatol. 2004. 22(2):157

IA2 Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Clinical Immunology, SNBTS, New Royal Infirmary Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA
NORMAL RESULT	< 10 IU/mL.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Please see section 'Diabetic autoantibodies' for further information regarding overall clinical pathway for autoimmune diabetic serology. Islet antigen2 (IA2) antibodies may be found type 1 diabetes with levels being at their highest early in the disease course. NICE guidelines (2015) recommend diabetes-specific autoantibodies should not be used routinely to confirm type 1 diabetes in adults or children.
REFERENCES	1. NICE Guideline NG17. Type 1 diabetes in adults: diagnosis and management.2015. 2. NICE Guideline NG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015.

Insulin Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	0 - 5 mg/L.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Please see section 'Diabetic autoantibodies' for further information regarding overall clinical pathway for autoimmune diabetic serology. Insulin antibodies may be found in newly diagnosed type 1 diabetes. Insulin antibodies may also be produced as a secondary phenomenon response to exogenous insulin. This test is currently not funded and is only available with formal cost approval and provision of a purchase order number from the service manager of the requesting clinician.
REFERENCES	1. NICE Guideline NG17. Type 1 diabetes in adults: diagnosis and management.2015. 2. NICE Guideline NG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015.

Intrinsic Factor Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	14 days
TURN AROUND TIME	2 Weeks
NORMAL RESULT	0-20 U/ml
REPEAT TESTING INTERVAL	365 Days
UKAS ACCREDITED	Yes
DESCRIPTION	Positive in 50-70% of patients with Pernicious Anaemia. Intrinsic Factor antibodies are more specific for pernicious anaemia than gastric parietal cell abs. Unlike older intrinsic factor antibody assays this method is not affected by treatment with Vitamin B12.
REFERENCES	1. Khan S et al. Limited value of testing for intrinsic factor antibodies with negative gastric parietal cell antibodies in pernicious anaemia. J Clin Pathol. 2009. 62. 439-441.

Liver Antibodies

Comprises Smooth Muscle, Mitochondrial, Liver Kidney Microsomal(LKM)& Liver Cytosol-1(LC1) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF) on rodent liver/stomach/kidney
TURN AROUND TIME	14 days
NORMAL RESULT	Negative (Screening dilution is 1/40)
REPEAT TESTING INTERVAL	1 Year
UKAS ACCREDITED	Yes*
DESCRIPTION	Found in autoimmune liver disease. The different combinations of antibodies are associated with different types of autoimmune liver disease (see below). Unusual staining patterns may be sent to King's College Hospital, London for confirmatory testing, which may include immunoblot for anti-M2, anti-LKM, anti-soluble liver antigen (SLA) and anti-LC1 antibodies. Liver cytosol 1 (LC1) antibodies Found in a sub-group of patients with autoimmune hepatitis. Liver kidney microsomal (LKM) antibodies Found in a sub-group of patients with autoimmune hepatitis and is associated with a particularly aggressive form of the disease, especially in children. Mitochondrial antibodies Occur in 95% of patients with primary biliary cirrhosis and may be detectable prior to the development of abnormal liver function. Low titres may also be found in chronic active hepatitis. Samples with atypical mitochondrial antibody patterns will be referred for immunoblot analysis to King's College Hospital, London. Smooth muscle antibodies Found in autoimmune hepatitis, often in association with positive ANA and occasionally mitochondrial abs. May also occur in other settings eg viral infections especially EBV and Hepatitis A. Only actin pattern smooth muscle antibodies are reported. Anti-nuclear abs (ANA) Found in autoimmune hepatitis, often in association with positive smooth muscle abs and occasionally mitochondrial abs. ANA may be found in connective tissue disease and other settings- see under ANA
REFERENCES	1. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet.2015. 386:1565-75.

Myeloperoxidase (MPO) & Proteinase 3(PR3) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence Enzyme Immunoassay (FEIA)
TURN AROUND TIME	7 days
NORMAL RESULT	MPO <3.5 IU/mL; PR3 <2.0 IU/mL
REPEAT TESTING INTERVAL	90 days
UKAS ACCREDITED	Yes
DESCRIPTION	**Urgent request for ANCA must be discussed with the duty immunologist at the earliest opportunity – 0141 232 8872 or ext 68872.** MPO/PR3 antibodies will be tested first and ANCA is reserved for the confirmatory testing of new positive MPO or PR3 abs. MPO/PR3 should be requested for the investigation and diagnosis of suspected ANCA-associated vasculitis. International consensus guidelines advise testing ANCA in the following situations; outwith these settings it has limited clinical utility. • Glomerulonephritis, especially rapidly progressive glomerulonephritis • Pulmonary haemorrhage, especially pulmonary renal syndrome • Cutaneous vasculitis with systemic features • Multiple lung nodules • Chronic destructive disease of the upper airways • Long-standing sinusitis or otitis • Subglottic tracheal stenoses • Mononeuritis multiplex or other peripheral neuropathy • Retro-orbital mass • Scleritis • Monitoring of known ANCA vasculitis and previous positive MPO or PR3 abs - at diagnosis, relapse, change of therapy (change of drug rather than dose adjustment) every 6 months while on treatment, annually off treatment. ANCA will be tested on all new positive MPO or PR3 abs. If required ANCA can also be tested on MPO/PR3 negative samples if there is a high index of suspicion of ANCA associated vasculitis – in this event, clinicians should phone the laboratory to arrange testing.

Pattern	Antigen	Disease Association
C-ANCA	PR3	Granulomatosis with polyangiitis (Wegener's granulomatosis)
P-ANCA	MPO	Systemic vasculitis eg Microscopic Polyangiitis Eosinophilic granulomatosis with polyangiitis (Churg Strauss) Crescentic glomerulonephritis
Atypical ANCA	various	Wide range of inflammatory, infective & neoplastic diseases but the clinical utility of atypical ANCAs has not yet been established.

REFERENCES

1. Bossuyt X, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nature Reviews Rheumatology. 2017. 13: 683-692
2. Ntatsaki E et al. BSR and BHPR guideline for the management of adults wth ANCA-associated vasculitis. Rheumatology 2014: 53(12): 2306-2309
3. Sinclair D, Stevens JM. Role of antineutrophil cytoplasmic antibodies and glomerular basement membrane antibodies in the diagnosis and monitoring of systemic vasculitides. Ann Clin Biochem. 2007. 44(5):432-442.
4. Lapraik C, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology. 2007. 46 (10):1615-1616.
5. Bosch X, Guilabert A and Font J. Antineutrophil cytoplasmic antibodies. Lancet. 2006. 368(9533):404-418.
6. Seo P and Stone J. The Antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med. 2004. 117:39-50.

Myositis antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Immunoblot
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL.
NORMAL RESULT	Negative
UKAS ACCREDITED	8915
REFERENCES	NA

Nuclear Antibodies (ANA)	
SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect immunofluorescence (IIF) microscopy on Hep2cell line
TURN AROUND TIME	10 days for screening, 14 days if titration required.
NORMAL RESULT	Negative (Screening dilution is 1:80)
REPEAT TESTING INTERVAL	1 Year
UKAS ACCREDITED	Yes*
DESCRIPTION	ANA is indicated in suspected connective tissue disease or autoimmune liver disease. Centromere autoantibodies are detectable on the ANA screen and do not need to be requested separately. ENA and dsDNA autoantibodies will be requested automatically on all new positive ANAs with titre of 1/160 or above. Autoantibody-mediated inflammation and cell destruction may affect many organs of the body. The ANA test identifies autoantibodies that target substances contained inside cells. It can also be used to screen autoantibodies directed against nuclear components and cellular components that are contained within the cell cytoplasm, outside of the nucleus.Hep2 cells contain only small amounts of Jo-1 and Ro antigens so the ANA test may be negative in the minority of patients who only react against these antigens. By itself, a positive ANA test does not indicate the presence of an autoimmune disease or the need for therapy. ANA can be positive in healthy people – in healthy individuals aged 21-60, 13.3% have a positive ANA at 1:80 dilution and in 5% at 1:160 dilution. Positive ANAs are particularly common in the over 65s. However a negative ANA makes connective tissue disease very unlikely. Positive ANA can be associated with the following conditions: 1. Systemic autoimmune diseases - SLE, Sjogren's, Scleroderma, drug-induced lupus, polymyositis, dermatomyositis, rheumatoid arthritis, pauciarticular juvenile chronic arthritis, polyarteritis nodosum, mixed connective tissue disease 2. Organ specific autoimmune diseases - thyroid (Hashimoto's thyroiditis, Grave's disease), gastrointestinal (autoimmune liver disease, inflammatory bowel disease), pulmonary fibrosis 3. Infection - tuberculosis, schistosomiasis, viral hepatitis, parvovirus and other infections. Miscellaneous - neoplastic disease, relative of person with autoimmune disease

REFERENCES	

1. Khan S, et al. The clinical significance of antinucleolar antibodies. J Clin Pathol. 2008. 61:283-286.
2. Tan EM et al. Range of Antinuclear Antibodies in 'Healthy Individuals. Arthritis Rheum 1997: 40: 1601-1611.
3. Koenig M, Diede M, Senecal JL. Predictive value of antinuclear autoantibodies: the lessons of the systemic sclerosis autoantibodies. Autoimmunity Reviews. 2008. 7: 588-593.
4. Muro Y. Antinuclear antibodies. Autoimmunity. 2005. 38(1): 3-9.
5. Kavanagh A, et al. Guidelines for clinical use of antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. American College of Pathologists. Arch Pathol Lab Med. 2000. 124(1):71-81.
6. Agmon-Levin N et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis 2014:73: 17-23
7. Peene I, et al. Detection and identification of antinuclear antibodies (ANA) in a large and consecutive cohort of serum samples referred for ANA testing. Ann Rheum Dis. 2001. 60(12):1131-1136

Neutrophil Cytoplasmic Antibodies - ANCA

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF) on ethanol fixed human neutrophil slides.
TURN AROUND TIME	14 days plus additional 7 days if ANA is needed to confirm pattern
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	30 days
UKAS ACCREDITED	Accredited for Zenit platform. Transition to new platform ETS
DESCRIPTION	MPO/PR3 antibodies will be tested first in patients with suspected ANCA associated vasculitis. Refer to Myeloperoxidase (MPO) & Proteinase 3(PR3) Antibodies section. ANCA by IIF is used for confirmatory testing of new positive MPO/PR3 samples. If required ANCA can also be tested on MPO/PR3 negative samples if there is a high index of suspicion of ANCA associated vasculitis – in this event, clinicians should phone the laboratory to arrange testing. There are three main ANCA patterns – C-ANCA, P-ANCA and atypical ANCA. These patterns relate to different antigenic specificities eg proteinase 3 (PR3), myeloperoxidase (MPO). C-ANCA abs are principally directed against PR3. Other C-ANCA specificities include cationic protein 57 and cathepsin G. P-ANCA abs are principally directed against MPO. Other P-ANCA antigen specificities are elastase and lactoferrin. Strongly positive PR3 or MPO abs with positive C- or P-ANCA is suggestive but not diagnostic of an ANCA associated vasculitis (see table below). However all types of ANCA have been reported in a wide range of other conditions eg infection, neoplasia, inflammatory disease, cocaine use as well as vasculitis. Conversely ANCA is typically negative in other forms of vascultis
REFERENCES	1. Bossuyt X, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nature Reviews Rheumatology. 2017. 13: 683-692 2. Ntatsaki E et al. BSR and BHPR guideline for the management of adults wth ANCA-associated vasculitis. Rheumatology 2014: 53(12): 2306-2309

Ovarian Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	These may be found in premature ovarian failure.

Parathyroid Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Parathyroid antibodies are associated with autoimmune hypoparathyroidism.
REFERENCES	NA

Phospholipid Antibodies

Now measured in Haematology at Glasgow Royal Infirmary

Pituitary Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Pituitary antibodies may be seen in 30% of patients with autoimmune hypopituitarism and 70% of patients with lymphocytic hypophysitis. They may also be seen in a variety of other autoimmune conditions and in some non-autoimmune pituitary conditions including pituitary tumours.
REFERENCES	1. Caturegli P, et al. Pituitary autoimmunity: 30 years later. Autoimmunity Rev . 2008. 7:631–637.

Phospholipase A2 (PLA2) Receptor Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	<14 RU/mL = Negative. 14 - 20 RU/mL = Borderline. >20 RU/mL = Positive.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Indicated in the investigation of primary membranous nephropathy. Primary membranous nephropathy may have an autoimmune component, with 70% of cases positive for PLA2 receptor antibodies. IgG antibody binding to PLA2 receptors on kidney podocytes may result in complement deposition and renal damage. While PLA2 receptor antibody testing may be useful in distinguishing primary from secondary membranous nephropathy and in disease monitoring, it should not be viewed as a replacement for renal biopsy.
REFERENCES	1. Bech L, et al. M- type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. 2009. N Eng J Med. 361: 11-21. 2. Hofstra JM, Wetzels JF. Anti PLA2R antibodies in membranous nephropat hy: Ready for routine clinical practice? Neth J Med. 2012. 70:109-113.

Rheumatoid Factor (RhF)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Latex-enhanced turbidimetry
TURN AROUND TIME	3 Days
NORMAL RESULT	Normal result: 0 – 29 IU/mL Weak positive 30-90 IU/mL
REPEAT TESTING INTERVAL	1 Year
UKAS ACCREDITED	No
DESCRIPTION	Used in the investigation of inflammatory arthropathies to differentiate sero-negative from sero-positive arthritides. In rheumatoid arthritis, high titres may be associated with extra-articular manifestations e.g. vasculitis and nodules. RhF is not useful for monitoring disease activity. RFs may occur in other connective tissue/autoimmune diseases, cryoglobulinaemia (may be very high titre), infections and in some healthy individuals (often low titre). A negative RhF does NOT exclude rheumatoid arthritis
REFERENCES	1. Aletaha D, et al. 2010 Rheumatoid Arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis and Rheumatism. 2010. 62(9):2569-2581. NICE clinical guideline 79. Rheumatoid arthritis: The management of rheumatoid arthritis in adults. 2009. 2. PRU Handbook of Clinical Immunochemistry. 9th Edition. 2007.

Skeletal Muscle Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect immunofluorescence (IIF)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	Skeletal muscle antibodies are typically seen in patients with both thymoma and myasthenia gravis. They may also occur in some patients with hepatitis, acute viral infections and polymyositis. Acetyl choline receptor antibody testing should be performed in the initial investigation of myasthenia gravis.
REFERENCES	NA

Skin Reactive Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Indirect Immunofluorescence (IIF)
TURN AROUND TIME	28 days
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	30 Days
UKAS ACCREDITED	No
DESCRIPTION	Two varieties are recognised: Intercellular substance antibodies - found in Pemphigus Basement zone antibodies - found in Bullous Pemphigoid and Epidermolysis Bullosa Acquista.
REFERENCES	1. Zillikens D. Diagnosis of autoimmune bullous skin diseases, Clin Lab. 2008. 54(11-12):491-503. Langan SM, et al. Bullous pemphigoid and pemphigus vulgaris-incidence and mortality in the UK: population based cohort study. BMJ. 2008. 337(180):a180. 2. PRU Handbook of Autoimmunity. 4th Edition. 2007.

Soluble Liver Antigen (SLA) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Immunoblot
TURN AROUND TIME	THIS IS A REFERRED TEST: Clinical Immunology and Allergy, Kings College Hospital, Denmark Hill, London, SE5 9RS.
NORMAL RESULT	Negative
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8641
DESCRIPTION	May be the only antibody found in some rare forms of autoimmune hepatitis. These may also be seen in hepatitis C. These antibodies are not detected by the conventional liver antibody indirect immunofluorescence screen.
REFERENCES	1. Baeres M, et al. Establishment of standardised SLA/LP immunoassays: s pecificity for autoimmune hepatitis, worldwide occurrence and clinical characteristics. Gut. 2002. 51:259-264.

Thyroid Antibodies

Now measured in Biochemistry

Tissue Transglutaminase Antibodies (IgA TTG)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	14 days
NORMAL RESULT	0 – 7 U/mL
REPEAT TESTING INTERVAL	5 Months (155 Days)
UKAS ACCREDITED	Yes
DESCRIPTION	Please ensure patients have been consuming sufficient gluten at time of testing to ensure reliable results. False negative results may be found if patients have been eating gluten less often than twice a day everyday for the previous 6 weeks. If patients have not been consuming sufficient gluten, advise delay testing. IgA TTG abs are the first line test for coeliac disease (NICE guidance 2015) and have a reported specificity and sensitivity of >95% in untreated coeliac disease, provided patients are consuming sufficient gluten at time of testing. IgA TTG abs may also be found in dermatitis herpetiformis. IgA endomysial antibodies (EMA) will follow automatically in all samples with a new positive or equivocal IgA TTG result. Rarely, IgA TTG can be falsely positive in patients with high total IgA levels due to liver disease or IgA paraproteinaemia; these patients are usually negative for IgA endomysial abs. False negative IgA TTG antibody results may be obtained in IgA deficiency. However the IgA TTG ab assay is able to accurately identify samples with low IgA levels. In these patients, IgA will be measured and if below <0.4g/l, IgG TTG abs will follow. ESPGHAN guidelines advise that an IgA level of 0.2g/l is considered sufficient for reliable IgA TTG antibody assessment. Please note that all coeliac serology is likely to be less reliable in patients with panhypogammaglobulinaemia.

REFERENCES	
	1. NICE guidelines [NG20] Coeliac disease: recognition, assessment and management. Published September 2015. 2. Hopper AD, et al. What is the role of serologic testing in coeliac disease? A prospective, biopsy-confirmed study with economic analysis. Clinical gastroenterology and hepatology. 2008. 6:314-320. 3. Hopper AD, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. BMJ. 2007. 334:729. 4. Rostom A, et al. The diagnostic accuracy of serologic tests for coeliac disease: a systematic review. Gastroenterology. 2005. 128(4):S38-46. 5. Dahlbom D, Olsson M, Forooz NK. Immunoglobulin G (IgG) anti-tissue transglutaminase antibodies used as markers for IgA deficient coeliac disease patients. Clinical and Diagnostic Laboratory Immunology. 2005. 254-258. 6. Villalta D, et al. False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. Clinical Chimica Acta. 2005. 356(1-2):102-109. 7. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease. JPGN 2012; 54: 136-160

Tissue Transglutaminase Antibodies (IgG TTG)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Fluorescence enzyme immunoassay (FEIA)
TURN AROUND TIME	14 days
NORMAL RESULT	0 – 7 U/mL
REPEAT TESTING INTERVAL	5 Months (155 Days)
UKAS ACCREDITED	No
DESCRIPTION	Please ensure patients have been consuming sufficient gluten at time of testing to ensure reliable results. False negative results may be found if patients have been eating gluten less often than twice a day everyday for the previous 6 weeks. If patients have not been consuming sufficient gluten, advise delay testing. IgA TTG antibodies are the first line test for coeliac disease (see under TTG antibodies). IgG TTG abs should only be requested in patients known to have IgA levels below 0.2g/L. They are of no value in patients with higher IgA levels. The sensitivity and specificity of IgG TTG for coeliac disease is less than IgA based tests therefore a negative result does not exclude coeliac disease. Please note that all coeliac serology is likely to be less reliable in patients with panhypogammaglobulinaemia

REFERENCES	1. NICE guidelines [NG20] Coeliac disease: recognition, assessment and management. Published September 2015. 2. Hopper AD, et al. What is the role of serologic testing in coeliac disease? A prospective, biopsy-confirmed study with economic analysis. Clinical gastroenterology and hepatology. 2008. 6:314-320. 3. Hopper AD, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. BMJ. 2007. 334:729. 4. Rostom A, et al. The diagnostic accuracy of serologic tests for coeliac disease: a systematic review. Gastroenterology. 2005. 128(4):S38-46. 5. Dahlbom D, Olsson M, Forooz NK. Immunoglobulin G (IgG) anti-tissue transglutaminase antibodies used as markers for IgA deficient coeliac disease patients. Clinical and Diagnostic Laboratory Immunology. 2005. 254-258. 6. Villalta D, et al. False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. Clinical Chimica Acta. 2005. 356(1-2):102-109. 7. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Diagnosis of Coeliac Disease. JPGN 2012; 54: 136-160

ZnT8 Antibodies	
SAMPLE	2 ml Serum (5ml Gold Gel tube)
PAEDIATRIC SAMPLE	0.5ml Serum
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Clinical Immunology, SNBTS, New Royal Infirmary Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA
NORMAL RESULT	< 15 IU/mL.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Please see section 'Diabetic autoantibodies' for further information regarding overall clinical pathway for autoimmune diabetic serology. Autoantibodies to pancreatic B cell antigens are important serological markers of T1D. The antigens recognised by these autoantibodies include insulin, GAD, IA2 and ZnT8. They are detectable prior to clinical presentation of disease and are therefore considered to be useful clinical markers of disease. ZnT8 can usefully complement GAD and IA2 testing raising detection rates to 93% and up to 98% at disease onset. Prevalence is correlated to disease onset: ZnT8 declined in first years after disease onset and was less persistent than IA2 or GAD in longer term. ZnT8 antibody tests are currently only funded for paediatric patients. Testing for adult patients is only available with formal cost approval and provision of a purchase order number from the service manager of the requesting clinician.
REFERENCES	1. NICE Guideline NG17. Type 1 diabetes in adults: diagnosis and management.2015. 2. NICE Guideline NG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015.

Immunochemistry

Alternate & Classical Path Haemolytic Complement (AP100/CH100)	
SAMPLE	Fresh serum 5 mL clotted blood (Gold top) to reach laboratory on day of venepuncture or separated and frozen on day of venepuncture and transported frozen
METHOD	Radial immunodiffusion haemolytic assay
TURN AROUND TIME	60 days
NORMAL RESULT	**CH100** 392 - 1019 CH100U/mL **AP100** 66 - 129 %
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Complement function tests are useful as a screen for rare inherited deficiencies in the complement pathway. CH100 measures integrity of the classical and terminal pathways and AP100 measures the integrity of the alternate and terminal pathway, therefore the two tests are always done together to identify the presence and location of any deficiency. Since this is a functional assay, attention to sample collection advice is important to avoid in vitro degradation of complement. The test is also best done in convalescence rather than at times of high in vivo complement activity e.g. sepsis, active SLE. Rare inherited deficiencies in the classical pathway predispose to sepsis and immune complex disease and deficiencies in the alternate and common terminal pathways predispose to *Neisserial* infections. Therefore indications for the test are recurrent/atypical meningococcal infection, systemic gonococcal infection, atypical immune complex disorders e.g. early onset atypical SLE or a family history of these. Contact the lab to discuss abnormal results and coordinate further testing at a specialist centre. Normal AP100/ CH100 results may not exclude properdin deficiency or partial Factor H or I deficiency – contact the laboratory for further advice if these are suspected. CH100/AP100 is also useful in monitoring the efficacy of Eculizumab suppression of in vivo complement activity. Very low levels in a correctly handled sample (see sample requirements) suggest effective suppression of complement activity by Eculizumab.
REFERENCES	1. PRU Handbook of Clinical Immunochemistry. 9th Ed. 2007. 2. Mollnes, et al. Complement analysis in the 21st Century. 2007. Mol Imm. 44:3838-3849. 3. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol. 2004. 113(4):585-593.

C1 Inhibitor (Function)

SAMPLE	Fresh blood 9 mL EDTA (purple top) to reach lab on day of venepuncture. **Advise to contact immunology laboratory before sending the sample.**
METHOD	Spectrophotometry
TURN AROUND TIME	60 days
NORMAL RESULT	70 – 130%
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	See comments under C1 inhibitor (quantitative). The functional assay is only required in individuals with a personal or family history of angioedema plus C4 level <0.25g/l and normal C1 inhibitor (quantitative) level. Samples must be separated and frozen within 4 hours of venepuncture
REFERENCES	NA

C1 Inhibitor (Quantitative)

SAMPLE	Fresh Serum 2 ml (5ml Gold Gel tube)(Also request C3 & C4)
METHOD	Immunoturbidimetry
TURN AROUND TIME	14 days
NORMAL RESULT	0.19 – 0.36 g/L
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	Yes
DESCRIPTION	C1 inhibitor measurement is recommended in patients with a personal or family history of isolated angioedema (urticaria is not a typical feature of C1 inhibitor deficiency). C3 & C4 should also be checked as C4 is typically low in all forms of C1 inhibitor deficiency; a C4 level of 0.25g/l or greater essentially excludes this diagnosis. Patients with angioedema, C4 <0.25g/l but normal C1 inhibitor (quantitative) levels should have C1 inhibitor function checked
REFERENCES	1. PRU handbook of Clinical Immunochemistry. 9th Edition. 2007. Gompels MM, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005. 139(3):379-394. 2. Markovic SN, et al. Acquired C1 esterase inhibitor deficiency. Ann Intern Med. 2000. 132(2):144-150. 3. US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency. Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, et al. The Journal of Allergy and Clinical Immunology: In Practice. 2013;1, 5, 458-467.

C1Q

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Radial Immunodiffusion (RID)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	50-250 mg/L.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	C1q measurement is only indicated for the differentiation of hereditary from acquired C1inhibitor deficiency. Note this test measures C1q and NOT anti-C1q antibodies and is of **NO** value in SLE monitoring.
REFERENCES	NA

C1Q Antibodies

See under Autoantibodies

C3 and C4

SAMPLE	5ml Gold Gel tube (clotted, gel activated, blood)
METHOD	Immunoturbidimetry
TURN AROUND TIME	3 Days
NORMAL RESULT	age/sex related ranges in g/L

	C3	C4
Male <14 yrs	0.80 – 1.70	0.14 – 0.44
Female <14 yrs	0.82 – 1.73	0.13 – 0.46
Male >14 yrs	0.82 – 1.85	0.15 – 0.53
Female > 14 yrs	0.83 – 1.93	0.15 – 0.57

REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	C3 and C4 levels measurement is useful in the investigation / monitoring of patients with connective tissue disease/other inflammatory disorders. Serial measurements are typically more useful than single levels.

C3	C4	Association
High	High	Acute phase response
Low	Low	SLE and other immune complex disorders Sepsis (eg subacute bacterial endocarditis) Haemodilution Liver disease Hypocomplementaemic urticarial vasculitis
Low	Normal	Sepsis (eg Gram negative septicaemia) Post-streptococcal nephritis Membranoproliferative glomerulonephritis C3 nephritic factor Inherited deficiency of C3, Factor H or I (rare)
Normal	Low	C1 inhibitor deficiency Cryoglobulinaemia Inherited deficiency of C4 null alleles (common especially in SLE)

REFERENCES	NA

Bence-Jones Protein/Urinary Free Light Chains
SEND DIRECTLY TO BIOCHEMISTRY

SAMPLE	A urine sample should accompany ALL serum samples in cases of suspected myeloma since up to 20% of myeloma patients have no detectable paraprotein in the serum.

C3 Nephritic factor

See under Autoantibodies

Cryoglobulins

Collection / Screening by Biochemistry
Typing of positives by Immunology

SAMPLE	10-20mL clotted blood collected & transported at 37ºC **(contact Biochemistry)**
METHOD	Typing by immunofixation and latex-enhanced turbidimetry (rheumatoid factor)
TURN AROUND TIME	21 days
NORMAL RESULT	Absent
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Cryoglobulin studies are indicated in the investigation of patients with features of hyperviscosity, Raynaud's or unexplained vasculitis. Detectable cryoglobulins are typed within immunology to determine composition, clonality and rheumatoid factor activity.

Functional (Specific) Antibodies

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	21 days
NORMAL RESULT	Depends upon exposure and immunisation history • Hib abs– minimum protective level 0.15 mg/L, optimal protective level 1mg/L • Tetanus abs – minimum protective level 0.15 IU/mL
REPEAT TESTING INTERVAL	20 Days
UKAS ACCREDITED	Yes
DESCRIPTION	Functional antibodies comprise antibodies to tetanus toxoid, pneumococci and Hib and are indicated as part of the investigation of suspected immunodeficiency. Levels of antibodies depend upon both exposure and immunisation. Interpretation of results should be in context of clinical picture, age and exposure/immunisation history. Where levels are low, test immunisation may be carried out to assess response. Post immunisation levels should be checked 4-6 weeks after administration. Please note that Hib refers to Haemophilus influenza b which causes systemic infection e.g. meningitis, epiglottitis and NOT the non-typeable Haemophilus influenzae commonly associated with respiratory infections.
REFERENCES	NA

IgD

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Enzyme Linked ImmunoSorbent Assay (ELISA)
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	2 - 100 KU/L.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	This is only of value in the assessment of rare periodic fever syndromes. Immunofixation vs IgD – see under Paraprotein.
REFERENCES	NA

IgG Subclasses

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Nephelometry
TURN AROUND TIME	THIS IS A REFERRED TEST: Immunology, PRU Procurement, PO Box 894, Sheffield, S5 7YT
NORMAL RESULT	

Age	IgG1	IgG2	IgG3	IgG4
Cord Blood	3.6-8.4	1.2-4.0	0.3-1.5	<0.5
6 months	1.5-3.0	0.3-0.5	0.1-0.6	<0.5
2 Years	2.3-5.8	0.3-2.9	0.1-0.8	<0.5
5 Years	2.3-6.4	0.7-4.5	0.1-1.1	<0.8
10 years	3.6-7.3	1.4-4.5	0.3-1.1	<1.0
15 years	3.8-7.73	1.3-4.6	0.2-1.2	<1.1
Adult	3.2-10.2	1.2-6.6	0.2-1.9	<1.3

REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	8494
DESCRIPTION	IgG subclasses may be requested in patients with suspected IgG4 disorders such as autoimmune pancreatitis.

Immunoglobulins – IgG,IgA, IgM & Electrophoresis
Send via Biochemistry

DESCRIPTION	Immunoglobulins & electrophoresis are useful in the investigation of suspected immunodeficiency and lymphoproliferative diseases. A myeloma screen order set is available in the trakcare and GP order comms systems - search on 'myeloma'.
Immune deficiency	A wide range of immunoglobulin abnormalities can be seen in antibody deficiency and levels may be normal or even raised in other forms of immunodeficiency (eg T cell or neutrophil defects). Therefore suggest discuss further investigation with an immunologist if there are clinical features of immune deficiency – eg unexplained serious, persistent, unusual or recurrent infections
Polyclonal elevations in immunoglobulins	Occur in a variety of disorders including chronic infectious/inflammatory conditions and liver disease
Paraproteins	If a paraprotein is detected, it will be typed and quantified. Immunofixation for IgD & E is available – referral labs requiring this test for further assessment of suspected light chain paraproteins should ensure that they request 'immunofixation for IgD & IgE' to avoid confusion with requests for quantitation of total IgD or IgE.
Malignant Paraproteins	Are usually, but not always, of high concentration, associated with low levels of the non-paraprotein immunoglobulins (immunoparesis) and with the presence of free monoclonal light chains in the urine (Bence-Jones Protein). Most often occur in multiple myeloma but may also be seen in other lymphoproliferative diseases e.g. Waldenstrom's Macroglobulinaemia, Plasmacytosis, AL amyloidosis, Chronic Lymphocytic Leukaemia ,Non-Hodgkin's Lymphoma.
Monoclonal gammopathy of undetermined significance (MGUS)	These are paraproteins found in patients without an identifiable underlying disease. The paraprotein is usually small and not accompanied by immunoparesis or free urinary light chains (BJP). MGUS may be caused by the same group of conditions which cause a polyclonal increase in immunoglobulins. MGUS may ultimately undergo malignant transformation (1-2% per annum).
REFERENCES	1. Bird J et al. Guidelines for the investigation of newly detected M-proteins and the management of Monoclonal Gammopathy of Uncertain Significance (MGUS). British Council for Standards in Haematology. 2009. 2. Dispenzieri A, et al. International Myeloma Working Group guidelines for serum free-light chain analysis in multiple myeloma and related disorders. Leukaemia. 2009. 23:215-224. 3. PRU handbook of Clinical Immunochemistry. 9th Edition. 2007.

Serum Free Light Chains (sFLC)

SAMPLE	2 ml Serum (5ml Gold Gel tube)
METHOD	Turbidimetry
TURN AROUND TIME	7 days
NORMAL RESULT	• serum free kappa 3.3 – 19.4 mg/L • serum free lambda 5.7 – 26.3 mg/L • K/L ratio 0.26 – 1.65 (up to 0.37 - 3.1 in renal impairment)
REPEAT TESTING INTERVAL	18 Days
UKAS ACCREDITED	Yes
DESCRIPTION	SFLC is indicated for monitoring of light chain or non-secretory myeloma, AL-amyloidosis, assessment of prognosis of MGUS. Serum free light chain test is not suitable for routine myeloma screening and a normal result does not exclude myeloma. If screening for myeloma send blood for immunoglobulins & electrophoresis PLUS urine for electrophoresis (BJP) – a myeloma screen order set is available in the trakcare and GP order comms systems (search on 'myeloma'). Serum free light chains are also not indicated for the routine follow up of MGUS. In settings where there is immune stimulation (e.g. sepsis, inflammatory disorders etc) or renal impairment causing reduced clearance of light chains, then both kappa and lambda light chains increase. In this setting the ratio remains similar. SFLC is indicated for monitoring of light chain or non-secretory myeloma, AL-amyloidosis, assessment of prognosis of MGUS. Serum free light chain test is not suitable for routine myeloma screening and a normal result does not exclude myeloma. If screening for myeloma send blood for immunoglobulins & electrophoresis PLUS urine for electrophoresis (BJP) – a myeloma screen order set is available in the trakcare and GP order comms systems (search on 'myeloma'). Serum free light chains are also not indicated for the routine follow up of MGUS. In settings where there is immune stimulation (e.g. sepsis, inflammatory disorders etc) or renal impairment causing reduced clearance of light chains, then both kappa and lambda light chains increase and the ratio may also increase slightly (see 'renal reference range on reports). The individual monoclonal nature of serum free light chains associated with plasma cell dyscrasias means that very high levels can be missed due to antigen excess during testing. The instrument and laboratory have extensive safeguards in place to reduce this risk including mechanisms to ensure that individual patients known to be prone to the antigen excess phenomenon are automatically re-tested with additional dilutions. Thus undetected antigen excess is a rare event but cannot be excluded. Results should always be interpreted in conjunction with other laboratory tests and clinical evidence. If free light chain results do not agree with other clinical or laboratory findings please contact the laboratory to discuss.

REFERENCES	
	1. Bradwell AR. Serum free light chain analysis. 7th Edition. 2015. 2. Hutchison CA, et al. Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. BMC Neph. 2008. 9(11):1-8. 3. Smith A, et al. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haem. 2006. 132:410-451. 4. Bradwell AR. Serum free light chain measurements move to centre stage. Clin Chem. 2005. 51:805-807.

Cellular Studies

Lymphocyte Subsets	
SAMPLE	4ml EDTA blood to reach lab within 20 hours & before 3pm on Fridays. **Do not refrigerate samples as this lowers the CD4 count.**
METHOD	Flow cytometry
TURN AROUND TIME	7 days
NORMAL RESULT	Age specific normal ranges will be provided on the reports
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Indicated in the evaluation and monitoring of primary and secondary immunodeficiency disorders including HIV infections and therapies such as Rituximab and anti-thymocyte globulin. **Please note that a CD4 count is an unreliable and unacceptable alternative to HIV testing.** For suspected immunodeficiency patients, prior discussion with the laboratory is recommended to enable selection of the appropriate panel.
REFERENCES	

Lymphocyte Function / Proliferation

SAMPLE	5-7ml lithium heparin blood from patient **AND** a healthy control from an unrelated person (label this bottle **'CONTROL'**) to reach laboratory before 3.00pm (Tuesday and Friday) on the day of venepuncture. Prior arrangement with the laboratory is recommended. Samples cannot be processed on Monday,Wednesdays or Thursdays**.** **Do not refrigerate samples.** **Samples without controls will not be analysed**.
METHOD	Mitogen driven proliferation assay with thymidine incorporation
TURN AROUND TIME	14 days
NORMAL RESULT	Contact immunologists for advice on the interpretation of individual test results.
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Indication indicated in investigation of suspected cellular immunodeficiency-contact immunologists for advice on the interpretation of individual test results.
REFERENCES	1. Asboe D, Aitken C, Boffito M, Booth C, Cane P, Fakoya A, http://www.ncbi.nlm.nih.gov/pubmed?term=Geretti%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=22171742 et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. HIV Med. 2012 Jan; 13(1):1-44. 2. Ata P, Kara M, Özdemir E, Canbakan M, Gökçe AM, Bayraktar FA, et al. Monitoring of CD3(+) T-cell count in patients receiving antithymocyte globulin induction after cadaveric renal transplantation. Transplant Proc. 2013 Apr; 45(3):929-31. Uber WE, Uber LA, VanBakel AB, Crumbley AJ 3rd, Pereira NL, Ikonomidis JS, 3. Et al. CD3 monitoring and thymoglobulin therapy in cardiac transplantation: clinical outcomes and pharmacoeconomic implications. Transplant Proc. 2004 Dec;36(10):3245-9.

Neutrophil Respiratory Burst (Neutrophil Function)

SAMPLE	4ml EDTA blood from both patient **AND** a healthy control from an unrelated person (label this bottle **'CONTROL'**). Prior arrangement with the laboratory is recommended. **Sample to reach laboratory before 3.00pm on day of venepuncture.** **Do not refrigerate samples.** **Samples without controls will not be analysed.**
METHOD	Dihydrorhodamine flow cytometry based assay
TURN AROUND TIME	7 days
NORMAL RESULT	NA
REPEAT TESTING INTERVAL	NA
UKAS ACCREDITED	No
DESCRIPTION	Neutrophil function test is indicated in suspected Chronic Granulomatous Disease (CGD). Assessment of neutrophil respiratory burst is now undertaken using the flow cytometric dihydrorhodamine assay(replaces the NBT test). This assay checks the respiratory burst activity of neutrophils which is impaired in CGD due to a genetic defect in one of the components of the NADPH-oxidase complex that produces reactive oxygen intermediates. Note - neutrophil function cannot be reliably assessed if the neutrophil count is less than 1×10^9/L.
REFERENCES	1. Mauch L, et al. Chronic Granulomatous Disease (CGD) and complete myeloperoxidase deficiency both yield strongly reduced dihydrorhodamine 123 test signals but can be easily discerned in routine testing for CGD. Clin Chem. 2007. 53:890-896. 2. Heyworth P, Cross A, and Curnutte J. Chronic granulomatous disease. Curr. Opin. Immunology. 2003. 15(5):578-584.

GUIDE TO APPROPRIATE INVESTIGATIONS

Allergy	Allergen specific IgE - must specify allergen(s) Contact lab for list of available allergens if required
Anaesthetic reactions	3 samples ~30 mins, 1-3 hrs, 24 hrs after onset of reaction If not requesting via trakcare, suggest use proforma request form
Angioedema (no urticaria)	C1 inhibitor level (quantitative), C3, C4
Arthritis (inflammatory)	ANA, Rheumatoid factor
Autoimmune liver disease	Liver abs (mitochondrial, smooth muscle, LKM, LC1) ANA, immunoglobulins
Coeliac Disease	Tissue transglutaminase IgA abs (TTG abs)
Connective tissue disease	Initial screen – ANA, C3 & C4 Monitoring SLE - C3 & C4, dsDNA Pregnancy –ANA, C3 & C4, ENA, cardiolipin antibodies
Glomerulonephritis (acute)	MPO/PR3 abs, ANA, GBM, C3 & C4 Consider cryoglobulins, myeloma screen
Immunodeficiency	Contact laboratory / medical staff for advice Immunoglobulins and electrophoresis Functional abs Consider CH100/AP100, Lymphocyte subsets and other cellular assays
Myeloma screen	Immunoglobulins & electrophoresis Urine for Bence Jones Protein
Urticaria	Allergen specific IgE rarely helpful unless intermittent short episodes and possible trigger identifiable from history Investigations are usually for checking the differential diagnoses based on the clinical presentation (e.g. ANA for urticarial vasculitis). Patient leaflet & guidelines available at www.bad.org.uk Guidelines for diagnosis and management
Vasculitis	MPO/PR3 abs, ANA, C3&C4 and consider cryoglobulins If renal involvement -see also 'glomerulonephritis tests' If thrombosis is prominent, also consider cardiolipin antibodies.
MAG neuropathy	Anti-MAG antibodies, immunoglobulins and electrophoresis

Paraneoplastic screen	Anti-neuronal antibodies, ANA, oligoclonal bands
Myasthenia gravis	Anti-AChR antibodies, Anti-MuSK antibodies, Anti-neuronal antibodies
Autoimmune encephalitis	Anti-NMDA receptor antibodies, anti-LGI1 antibodies, anti-Caspr2 antibodies, anti-neuronal antibodies, oligoclonal bands, ANA