Sandwell and West Birmingham Hospitals NHS
NHS Trust

Where EVERYONE Matters

Pathology news

April 2016 – Referral Labs Edition

Moving Forward Together...

We are focussed on offering relevant services in a timely manner that are both beneficial to patients and cost-effective to our users.

This annual "referral laboratory" *Pathology News* updates our service levels and pricing structures. It is an important document to be used in conjunction with the service level agreement which we have recently sent to over 400 referral laboratories. This year, after a thorough cost analysis, we have made some small changes to our price list, including both price reductions and also some increases, to reflect our costs.

We have some new services developed over the last year. Our blood spot serology testing in particular is being used by other trusts and also the prison service. We are at the forefront of legal high analysis and this work continues to make a real difference in clinical care with samples sent to us from all over the United Kingdom. We can see that there are going to be many more requests for tests such as clozapine and have been gearing up our services to ensure we can meet demand.

Joseph Murray, Blood Sciences Lead for NPEX

News in brief

- **Clozapine Analysis**
  We are now running our clozapine assay daily.
  Further details on page 8
- **IT Links**
  NPEX: If you use this IT solution please contact us for further details on how we can work together Email: swbh.pathology-it@nhs.net
- **Service Level Agreements**
  This Pathology News is the appendix to your Service Level Agreement (SLA) and means that we do not need to re-issue SLAs every year unless required.
- **Legal Highs**
  See page 3 inside for the latest updates.
- **Thiopurine Metabolites (6-TGN)**
  Find out more about our service on page 6.
- **Blood Spot Serology**
  This new service which may be of special interest to colleagues in mental health.
  See further details on Page 2.
- **Trace Elements Explained**
  Dr Nicola Barlow, Consultant Clinical Scientist, gives further details on our Trace Elements services.
  See inside, page 4.

Serology Dried Blood Spot Screening

Our work in developing services based on collection of blood samples continues.

In 2015, a major initiative between the Clinical Biochemistry and Microbiology Departments saw the launch of the Serology blood borne virus screening service. This is ideal for taking samples where normal phlebotomy is not available.

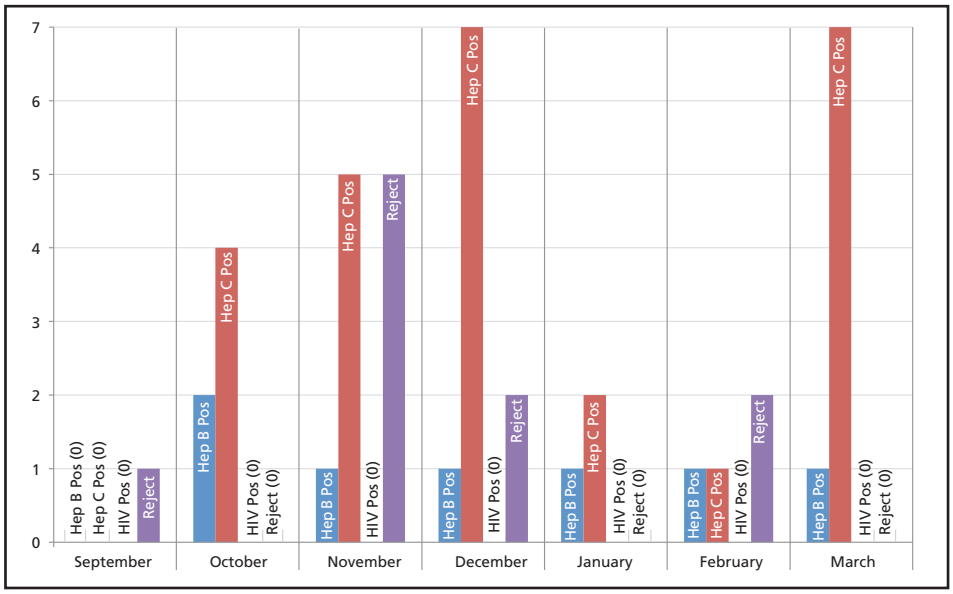
This new test screens for the presence of Hepatitis C, Hepatitis B and HIV from a single dried blood spot obtained from a finger prick sample using a collection device that has been developed in our laboratory. Once collected, the blood spot samples can be immediately sealed and sent back to our laboratory, which gives a significant advantage over other devices.

As part of this service we have produced a collection pack with everything the end user needs to take the sample and return it to the laboratory. This service has been very well received in the mental healthcare setting and also in institutions such as prisons.

Brenda Blundell getting ready to do her daily run of the serology blood spots

Since setting up the service in September 2015, we have received over 300 samples, detecting 7 new Hepatitis B and 26 Hepatitis C infections. These infections may have gone un-diagnosed if it wasn't for this novel test being available to these patient groups.

For more information about this service please email Ashok Dadrah, Serology Section Lead
Email: ashok.dadrah@nhs.net



Data showing dried blood spot samples received for blood borne virus screening between September 2015 – March 2016

Legal Highs Detected on Prison Letters

In 2013 we launched the first NHS clinical service for routine screening of legal highs also known as novel psychotropic substances (NPS).

NPS are designer drugs that mimic classic drugs of abuse such as cocaine, amfetamine and cannabis and are readily available to buy in shops on the high street and on the internet.

Our current NPS service includes:

- Routine urine and oral fluid drug screening by liquid chromatography tandem mass spectrometry (UPLC-MS/MS) for 26 drugs, including five common NPS identified by us from analysis of actual NPS products.
- Time of flight (UPLC-MS/Tof) screening of biological and non-biological materials, including NPS using exact mass libraries capable of detecting over 1,500 drugs and metabolites including 300 NPS.

How big a problem are NPS?

By analysing all the requests for drug screening on patients admitted into our Emergency Medicine Department we have obtained an indication of the impact on hospital admissions and resources.

'Black Mamba' is a popular street name given to any synthetic cannabis (NOID) type NPS. Typically these are prepared by spraying the NOIDS onto herbs which users then incorporate into roll-ups and smoke usually together with tobacco. Using Time of flight (Tof) we have we have identified a marker to test for the third generation adamantyl-type NOIDS such as AKB-48 and its fluoropentyl analogue 5F-AKB-48 which are among the most popular NOIDS currently found in Black Mamba.

Legal Highs Detection on Prison Letters

NPS are a major concern in UK prisons fuelling violence, aggression and disruptive behaviour. In 2015 we were approached by a prison Search Dog Team for advice on which NPS to target. These NPS trained search dogs are now in routine use in UK prisons. In January 2016 we were asked to test five suspicious letters sent to prisoners that the search dogs had positively indicated for NPS and this coincides with reports of prisoners observed, licking, chewing and smoking their letters.

Urvesh Rana preparing a legal high sample

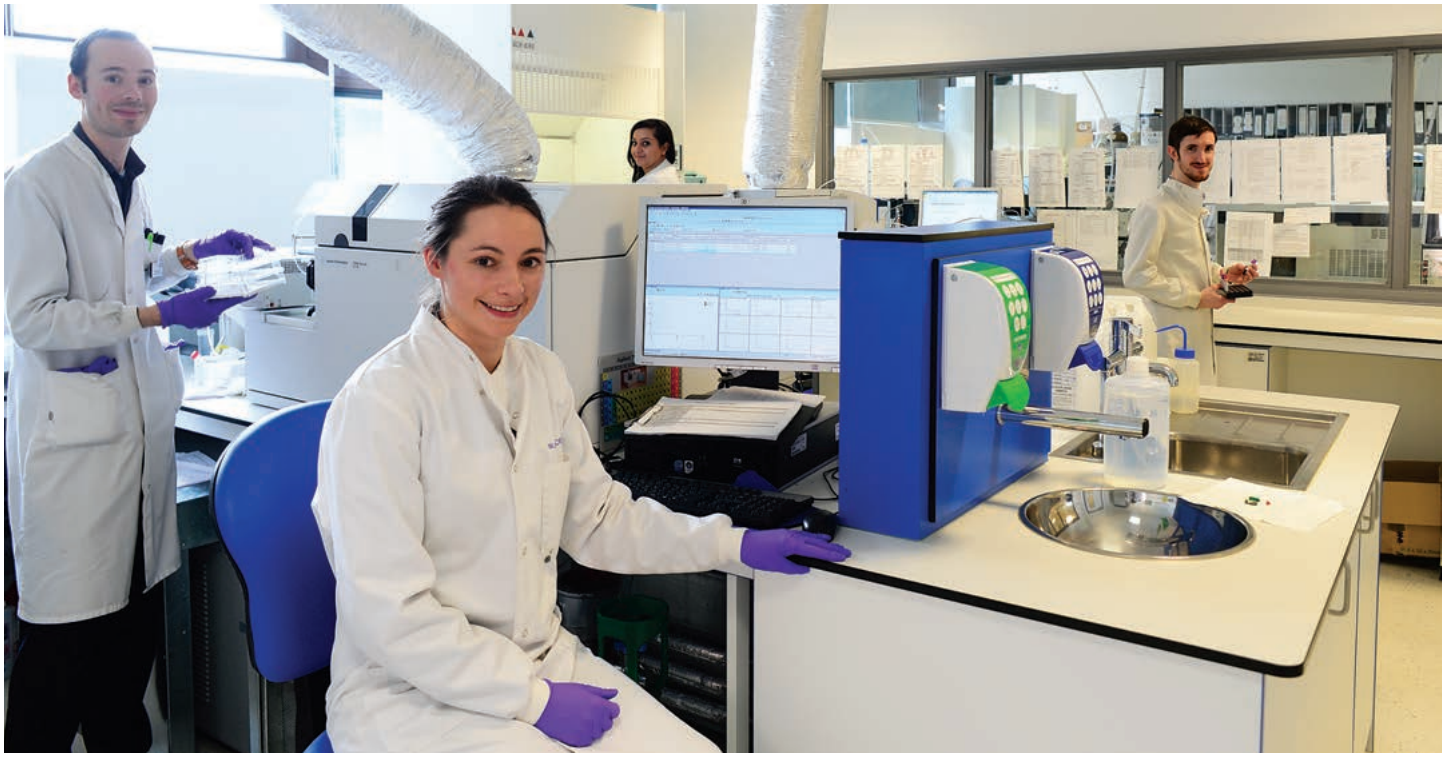
Using the Tof we tested the letters, the contents of which included poems, children's pictures as well as multiple blank A4 sheets. One in particular contained seven blank sheets of paper. The paper had the appearance of being dipped, with watermarks visible. NPS were detected on all five letters, including the third generation synthetic cannabinoids AKB-48, 5F-AKB-48, ethylphenidate (cocaine mimic), methiopropamine (metamfetamine mimic), the benodiazapine analog etizolam and methoxphenidine (MXP), a hallucinogenic.

In addition to enabling HMPS to train search dogs to detect NPS, we have provided analytical proof that letters are being used to smuggle NPS into UK prisons.

Our work features in a BBC 3 TV series, *Drugs Map of Britain; Wolverhampton Getting off Mamba* which can be viewed from the BBC 3 website page for *Drugs Map of Britain*.

Professor Jonathan Berg with a BBC 3 film crew for the Drugs Map of Britain *Series*

Trace Elements Laboratory



Dr Nicola Barlow and some of her colleagues in the Trace Elements Laboratory

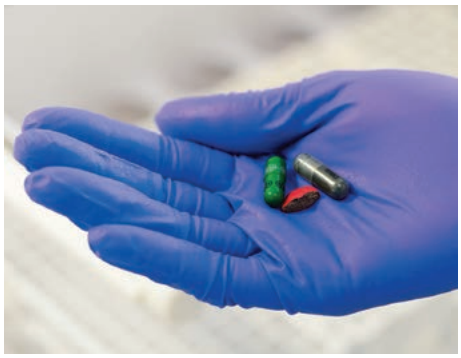
Our Trace Elements Laboratory now boasts three inductively-coupled plasma mass spectrometers, allowing us to achieve even faster turn-around times and further develop our services.

We also made a price reduction in January for our most commonly requested panels (serum copper, zinc and selenium and blood cobalt & chromium) with a discount when requesting more than one element.

This year we have seen some interesting case work – the most unusual was a serious case of mercury poisoning following injection of 4 mL (56 g) elemental mercury into the arm. We played a pivotal role in monitoring the patient and determining the amount of mercury removed during a novel heart aspiration procedure (2.1 mg), excision of the injection site (5.2 g) and the first round of chelation therapy (79.1 mg).

Did you know?

- Herbal remedies may contain marked amounts of heavy metals. Our tablets/powder ICPMS screen identified 4.5 mg lead and 7.0 mg mercury in capsules of Indian origin that had resulted in a clinically significant lead poisoning.
- Fish and seafood contain a non-toxic form of arsenic called arsenobetaine, which can result in raised urine total arsenic. We recommend collecting urine samples for arsenic following at least 5 days abstention from fish/seafood.



- In 2014, CDC lowered the blood lead reference limit for children to 0.24 µmol/L. An audit of paediatric lead results demonstrated that in a 6 month period none of the children with a blood lead 0.24 – 0.48 µmol/L had repeat testing. Report comments have been introduced to address this. All paediatric lead results greater than 0.48 µmol/L are currently reported to Public Health England.
- Blood manganese is monitored in TPN patients to detect excess accumulation; however, many brands of EDTA tubes are contaminated with manganese and so trace element free sodium heparin tubes are the preferred sample type.
- Blood cobalt and chromium levels that exceed the MHRA threshold (120 and 135 nmol/L respectively) for the first time should be followed up by a repeat specimen in 3 months. Our audit data show that 9.8% of samples tested over an 18 month period had concentrations exceeding the threshold and only 23% were repeated.
- Zinc contamination is every-where! We recommend trace element free sodium heparin plasma (or lithium heparin plasma for paediatrics) for zinc and **don't forget to ensure your secondary tubes are zinc free. We are always happy to check!**

For further information contact Dr Nicola Barlow, Consultant Clinical Scientist Email: nicola.barlow1@nhs.net

Adalimumab & Infliximab Service

Infliximab and Adalimumab are two therapeutic drugs approved for the use in the treatment of various chronic inflammatory diseases including Crohn's disease, ulcerative colitis, rheumatoid arthritis and psoriasis.

Both drugs are monoclonal antibodies directed against tumour necrosis factor alpha (TNFα). TNFα belongs to the pro-inflammatory cytokines, which promote and sustain inflammatory reactions and thus plays an important role in both acute and chronic inflammation. A significant proportion of patients on Infliximab or Adalimumab go on to develop antibodies against the drug, leading to loss of therapeutic drug efficacy and increased risk of infusion reactions. Monitoring of TNFα therapy is important in patients.

We measure both serum Infliximab and Adalimumab drug levels, in addition to antibodies against Infliximab and Adalimumab.

Dr Alexandra Thurston-Postle and some of the team

Currently, our antibody-drug antibody assays report qualitative results, but we plan on reporting quantitative results in the very near future. Workload for our Infliximab assay has increased by 38% on the previous year, with our Adalimumab workload increasing by over 200% from when we introduced both the drug and antibody assays a year ago. Our average turnaround time for the last year for all four assays has been maintained at <5 days and these services are complimented by full clinical support on interpretation of results.

For further details contact,
Dr Alexandra Thurston-Postle,
Principal Biochemist at
Email: info@cityassays.org.uk

Gilbert's Syndrome

UDP-glucuronosyltransferase 1A1 (UGT1A1) genotyping

UGT1A1 is an enzyme of the glucuronidation pathway, which transforms exogenous and endogenous lipophilic molecules into water-soluble and excretable molecules.

A reduction of UGT1A1 activity causes unconjugated hyperbilirubinaemia. Several mutations of UGT1A1 have been identified, with UGT1A1*28 being the most common mutation within White and African-American populations.

Clinical use of UGT1A1 genotyping

Mutations of UGT1A1 result in Gilbert's and Crigler-Najjar syndromes.

UGT1A1 is involved in the metabolism of several drugs:

- The published guidelines from Clinical Pharmacogenetics Implementation Consortium (CPIC, 2015) on the use of Atazanavir in patients with UGT1A1 mutations indicate that alternative treatment should be considered due to a significant risk of developing hyperbilirubinaemia.
- Homozygous mutant patients should be started on a reduced dose of Belinostat.
- Studies have showed that the UGT1A1 mutation is associated with hyperbilirubinaemia in patients taking drugs such as Nilotinib and Pazopanib.
- UGT1A1 mutations are associated with adverse events caused by Irinotecan toxicity. This drug is approved worldwide for the treatment of metastatic colorectal cancer.

Practical Details

Analysis of UGT1A1*28 is performed by real-time PCR using FastStart DNA master hybprobe with LightSNiP.

Kate Fitzpatrick-Ellis & Dr Elodie run this service

Our laboratory takes part in the Instand (Germany) EQA scheme for UGT1A1 genotyping.

The average turn-around time is 3 days and the cost is £40 per sample.

Thiopurine Metabolites (6TGN) Service Update

The thiopurine metabolites (6TGN) service has now been established for 10 years.

Due to increasing demand and clinical need our workload has significantly increased during this time (see graph below).

We have identified a number of ways to maintain our high quality of service and make our laboratory processes more efficient to ensure we continue to meet our target turnaround times as the workload increases. This has included the introduction of a new automated analyser for the measurement of RBC, which is required to correct the 6TGN results (expressed as pmol/8X108 RBCs). This new analyser has required us to modify the tube specification for 6TGN analysis, as detailed.

Jenna Waldron and some of the TPMT/TGN laboratory staff

Thiopurine metabolites (6TGN) and TPMT Sample/tube requirements

Due to a change in our analytical platforms and streamlining of our laboratory processes for 6TGN and TPMT analysis, we now require our referral labs to send, where possible, only the smaller 2.7-4mL EDTA tubes for thiopurine metabolites and TPMT analysis.

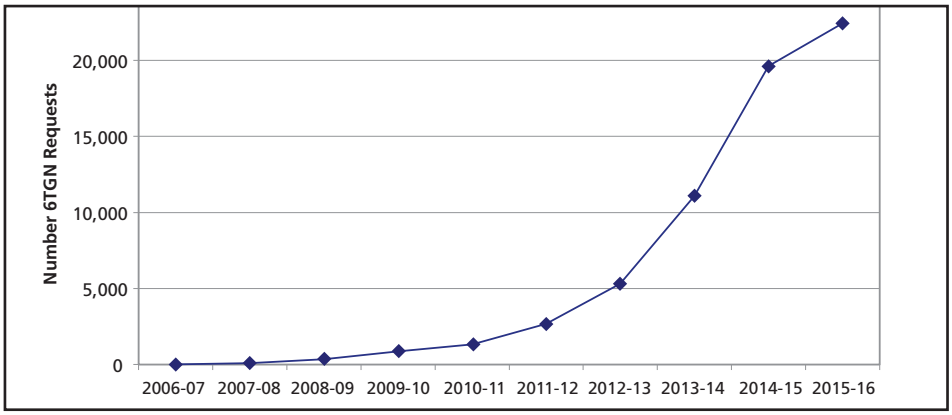
A minimum sample volume of 0.5-2mL only is required for these tests (a single EDTA tube may be sent if both tests are required), therefore the larger 6ml BD vacutainer tubes and 4.5/4.9/7.5mL Starstedt Monovette tubes are not required. The table below provides some examples of the more suitable EDTA containers for thiopurine metabolite and TPMT requests.

Our average monthly turnaround time for the year 2015-16 has been consistently ≤2 days, which is on target for our stated turnaround time of 2 days.

Key Information for 6TGN Service Users

- **Indications for monitoring:** Treating patients with low TPMT activity, suspected non-compliance or treatment with a suboptimal drug dose, or failure to respond to standard doses of thiopurine drugs.
- **Sample Type:** Minimum 0.5 mL EDTA whole blood (for specific tube dimensions refer to separate article).
- **Sample Storage:** Samples should be stored at 4°C prior to dispatch. Please ensure samples are not frozen.
- **Sample stability:** Thiopurine metabolites are stable for at least 7 days at 4°C but for less than 3 days at room temperature. We highlight samples >5 days old on receipt.
- **Sample timing:** We suggest a sample for therapeutic drug monitoring is timed at 4 weeks from the start of treatment or change in drug dose.
- Please provide details of current thiopurine drug regime and patient diagnosis on the request form.
- TPMT activity can also be undertaken on this sample but must be requested on the form.

Manufacturer	Tube vol. (mL)	Minimum sample vol. (mL)
BD Vacutainer/vacuette EDTA	4	0.5-2.0
Starstedt Monovette EDTA	2.7	0.5-2.0



6TGN Workload April 2006 – February 2016

For any queries please contact Jenna Waldron, Principal Clinical Scientist, Email jenna.waldron@nhs.net

Specialist Assays

Prices and turn round targets* offered to NHS Contracts

Biochemistry	Turn round	Cost
ACE	3 days	£15
Bile Acids	1 day	£15
Caeruloplasmin	2 days	£15
Carotenes	5 days	£35
Faecal Calprotectin	3 days	£26
Faecal Elastase	3 days	£36
Fructosamine	1 day	£15
Gilberts Syndrome	3 days	£40
Pro Collagen Type 3 Peptide (P3NP)	7 days	£20
Cholinesterase	within 24 hours	£15
RBC Cholinesterase	within 24 hours	£50
Xanthachromia	2 hours	£35

Pharmacogenomics	Turn round	Cost
Thioguanine Nucleotides	2 days	£30
TPMT Service	1 day	£22
Serum Infliximab	5 days	£25
Anti Infliximab Antibodies	7 days	£35
Adalimumab	5 days	£25
Adalimumab Antibodies	7 days	£35

Fat soluble vitamins	Turn round	Cost
25-hydroxyvitamin D_2 & D_3 Serum/Plasma	2-3 days	£10
Vitamin A	2-3 days	£13
Vitamin E	2-3 days	£13

Blood spot analysis	Turn round	Cost
25-hydroxyvitamin D_2 & D_3	2-3 days	£16
Serology BBV Screening	2-3 days	£35

Stone service	Turn round	Cost
Stone Analysis	5 days	£28
Urine Citrate	5 days	£15
Urine Oxalate	5 days	£15
Urine Stone Screen (calcium, phosphate, citrate, oxalate, magnesium, urate)	5 days	£50

Trace Elements	Turn round	Cost
Aluminium (plasma or water)	2-5 days	£25
Arsenic (blood or urine)	2-5 days	£25
Cadmium (blood or urine)	2-5 days	£25
Chromium (blood)	1-2 days	£15
Chromium (urine)	1-2 days	£20
Cobalt (blood)	1-2 days	£15
Cobalt (urine)	1-2 days	£20
Chromium & Cobalt (blood)	1-2 days	£25
Chromium & Cobalt (synovial fluid)	1-2 days	£40
Copper (urine)	2-3 days	£20
Lead (blood)	2-3 days	£20
Lead HB ZPP	2-3 days	£35
Manganese (blood)	2-3 days	£20
Mercury (blood or urine)	2-5 days	£25
Nickel (blood, serum or urine)	2-5 days	£30
Selenium, Copper & Zinc (serum)	1-2 days	£10 each or for all three £25
Toxic Metals Screen (blood & urine or powders)	1-2 days	£100
Gold	2-3 days	£40
Bromide (serum)	2-3 days	£40
Thalium (blood or urine)	5 days	£40
Other Metals (e.g urine lead, iron, manganese, bismuth, barium, antimony, selenium, tellurium,silver, gallium, indium, blood bismuth, barium, boron, strontium - discounts available on panels)	2-5 days	£40

Therapeutic drugs	Turn round	Cost
Amitriptyline & Nortriptyline	5 days	£22
Caffeine	1-2 days	£20
Clozapine & Norclozapine	2 days	£22
Lamotrigine	2 days	£22
Lithium	1 day	£10
Olanzapine	5 days	£22
Levetiracetam	5 days	£22
Quetiapine	5 days	£22

Toxicology	Turn round	Cost
Caffeine & Paraxanthine	1-2 hours	£20
CDT	5 days	£40
Ethanol (urine & blood)	1 day	£30
Ethylene/Diethylene Glycol	1-2 hours Out of hours:	£200 £400
Methanol (methyl alcohol)	1-2 hours Out of hours:	£100 £200
Sulphonyl Urea, Antidiabetic Drug Screen	2-3 hours	£90
Unknown Drug Screen	3 days	£150
LC-QTOF Screen (urine, blood,stubs,powders,pills, tobacco & paper)	4 hours	£100
Paraquat	1 day	£90
Diaquat	1 day	£90
Urine Diuretic Screen	1-2 days	£90
Urine Laxative Screen	2-3 days	£90
γ-Hydroxy-Butyrate (GHB)	2-3 days	£90
Spiked Drink Screen	5 days	£300

Drugs of abuse screening kits	Cost
Oral fluid collection device without pre-paid postage – pack of 20	£30
Urine & oral fluid reply paid kits – each	£7

Drugs of abuse screen	Turn round	Cost
Oral Fluid (incl Cannabis)	1-2 days	£25
Urine (incl Cannabis)	1-2 days	£25

Current drugs of abuse panel includes 26 classic drugs and common legal highs.

Other drugs of abuse screening	Turn round	Cost
Amfetamine ratio (resolution of D, L isomers)	3 days	£50

Immunology	Turn round	Cost
ANCA abs	1-2 days	£10
Anti-C1INH abs	up to 28 days	£180
Anti-nuclear antibodies	1-3 days	£10
Anti-nuclear antibodies titration	1-3 days	£11.50
Aspergillus IgG	3-7 days	£11
Avian IgG - budgie	3-7 days	£13
Avian IgG - pigeon	3-7 days	£13
Beta 2 Microglobulin	3-7 days	£7
CCP abs	3-5 days	£10
Complement C3	1-2 days	£10
Complement C4	1-2 days	£10
Double Stranded dsDNA screen	1-3 days	£7.50
Double stranded DNA quantitation abs	1-7 days	£11
Endomysial (IgA) abs	3-5 days	£13.50
ENA Screen	3-7 days	£10
ENA Profile	10-14 days	£22
Epidermal abs	3-7 days	£12
GAD abs	10-20 days	£16
Gastric Parietal cell abs	3-5 days	£10
Glomerular Basement Membrane (GBM) abs	3-5 days	£12
IHIB abs	10-14 days	£10.50
IgG/IgM Cardiolipin abs screen	3-7 days	£14
IgG Cardiolipin abs	3-7 days	£6
IgM Cardiolipin abs	3-7 days	£6
Intrinsic Factor abs	3-7 days	£10
ISAC (Specific IgE allergen component panel)	14-21 days	£180
Liver Kidney Microsomal abs	3-5 days	£10
Mitochondrial abs	3-5 days	£10
Mitochondrial abs quantitation	3-7 days	£15
Myeloperoxidase (MPO) abs & Proteinase 3 (PR3) abs	3-7 days	£30
Pneumococcal ABS	10-14 days	£13
Rheumatoid factor	1-2 days	£6
Smooth Muscle abs	3-5 days	£10
Smooth Muscle abs quantitation	3-7 days	£15
Specific IgE single common allergen	3-5 days	£14
Specific IgE single rare allergen	3-5 days	£15
Specific IgE Bee Venom Apim1	3-5 days	£15
Specific IgE Birch, rBetv1	3-5 days	£15
Specific IgE Egg Gald1	3-5 days	£15
Specific IgE Grass – rPhl p7,p12	3-5 days	£15
Specific IgE Hazelnut – Cora1/Cora8	3-5 days	£22
Specific IgE Latex HevB1, B3, B5, B6.01, B6.02, B8	3-5 days	£65
Specific IgE Mixed panel	3-5 days	£15.50
Specific IgE to Mixed Food	3-5 days	£18.50
Specific IgE Peanut Arah1,2,3,8, 9	3-5 days	£55
Specific IgE Wasp Vesv5	3-5 days	£15
Specific IgE Wheat Omega5 gliadin	3-5 days	£15
Tetanus abs	10-14 days	£10.50
Tissue Transglutaminase (IgA) abs	2-4 days	£10
Total IgE	3-5 days	£13
Tryptase	3-5 days	£20
Thyroid Peroxidase abs (TPO)	3-7 days	£10
T spot	24 hours after sample receipt	£75

*Where days are given these are working days.

Clozapine, Olanzapine and Quetiapine

Effective treatment of schizophrenia with antipsychotic medication has many benefits, including allowing patients to live in the community with a reduced risk of re-hospitalisation and lower mortality compared to non-treated patients.

The newer second generation atypical antipsychotics include clozapine, olanzapine and quetiapine have advantages of a lower risk of discontinuation and consequent treatment failure. Monitoring the blood levels of these second generation antipsychotics can increase effectiveness in the following situations:

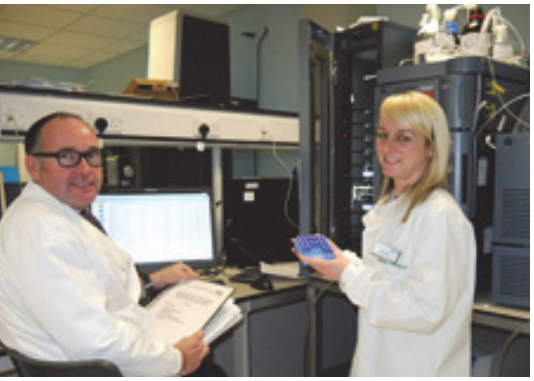
- Identifying/confirm non-compliance
- Minimising toxicity
- Aid the investigation of lack of response to standard doses
- Help investigate altered pharmacokinetics due to hepatic disease, co-administration of drugs or change in smoking habit
- Detecting abuse, especially quetiapine

An EDTA sample is required for analysis, preferably collected pre-dose or minimum 6 hours post dose. Samples can be sent at ambient temperature through the normal postal system. Analysis is performed daily and results can be returned electronically by secure PDF for even faster turn-around time.

Atypical Antipsychotics in More Detail

Clozapine

Clozapine can cause serious side effects including life threatening agranulocytosis (incidence 0.8-0.9%) and for this reason neutrophil monitoring of patients is regularly performed.



Metabolism of clozapine via the cytochrome P450 system is induced by cigarette smoke and smoking 6-7 cigarettes a day can increase clozapine requirement by 50%. Since it is actual tobacco smoke responsible for clozapine induction, clinicians need to be vigilante when treating patients on smoke free wards with replacement therapies such as e-cigarettes, especially if they have access to tobacco products on home release. Carbamazepine and phenytoin treatment will also cause induction, whereas erythromycin, fluvoxamine, fluoxetine and cimetidine all potentiate the action of clozapine by inhibiting metabolism. Age and gender may also have some effect on clozapine concentration, and generally older patients require a lower dose.

Olanzapine & Quetiapine

Both olanzapine and quetiapine are structurally similar to clozapine and are used to treat schizophrenia and manic disorders as well as preventing recurrence of bipolar disorder and associated depression.

Metabolism of olanzapine may be induced by smoking and carbamazepine, resulting in a slight reduction in olanzapine concentrations. Fluvoxamine and ciprofloxacin inhibit olanzapine metabolism.

Quetiapine issues...

Side effects of quetiapine use include drowsiness, sluggishness, fatigue, dry mouth, sore throat, dizziness, abdominal pain, constipation, and orthostatic hypertension. Cases of tardi dyskenia, hyperlipidemia, hyperglycemia, hyperprolactinaemia and weight gain have also been reported. There are reports of recreational abuse of quetiapine, mainly for its euphoric as well as sedative properties, including intravenous co-administration with cocaine known as a "Q-Ball".

Contact Point

General Enquiries
info@cityassays.org.uk
Tel: 0121 507 5348

Trace Elements
elements@cityassays.org.uk
Tel: 0121 507 3517

Toxicology
toxicology@cityassays.org.uk
Tel: 0121 507 4135

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Our website gives basic details for many of our tests.

This includes:

- Downloadable PDF files of user information leaflets
- Relevant information and background details
- Up to date turn round times