The Association for
Clinical Biochemistry &
Laboratory Medicine

The Royal College of Pathologists
Pathology: the science behind the cure

National Minimum Re-testing Interval Project:

A final report detailing consensus recommendations for

minimum re-testing intervals for use in Clinical Biochemistry

Prepared for the Clinical Practice Group of the

Association for Clinical Biochemistry and Laboratory Medicine and

supported by the Royal College of Pathologists.

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These recommendations represent best practice in the opinion of the author(s) and have been reviewed through a consensus approach. However, new evidence at any time can invalidate these recommendations. No liability whatsoever can be taken as a result of using this information.

These recommendations should not be used in paediatric/neonatal patients unless specifically stated.

CONTENTS

Background

There is currently a drive in pathology to harmonise processes and remove unnecessary waste, thereby saving money**.** At a time when many trusts are implementing electronic requesting of laboratory tests, which allows the requestor and the laboratory to manage what is requested, there needs to be a solution to support this process based on the best available evidence. Similar type initiatives have been reported including the work of the Pathology Harmony Group and the recent proposal to standardise test profiles.[1-2] How often a test should be repeated, if at all, should be based upon a number of criteria: the physiological properties, biological half-life, analytical aspects, treatment and monitoring requirements, and established guidance. This report proposes a set of consensus recommendations from the laboratory medicine perspective.

What is a minimal re-testing interval?

Minimal re-testing intervals (MRI) are defined as the minimum time before a test should be repeated, based on the properties of the test and the clinical situation in which it is used**.**

Establishing MRIs

This work was carried out with the support of the Association for Clinical Biochemistry and Laboratory Medicine (ACB). As a first step, a survey was distributed to members of the Clinical Practice Section (CPS) of the ACB to assess their current use of MRIs and implications for their use in practice. This group represents the medically qualified practitioners in clinical biochemistry who are members of the ACB. In addition, a literature search was performed using a strategy previously used in this area.[3] However, little published evidence was identified on the use or production on MRIs in clinical practice.

The next phase of the project was the convening of small groups, made up of invited members of the CPS, to investigate the evidence and existing guidelines and prepare recommendations in a number of selected work streams (Box 1). The method used was an approach based on that used by Glaser *et al* termed 'the state of the art'.[4]

The evidence or source for these recommendations has been taken from a number of authorities such as National Institute for Health and Clinical Excellence (NICE), NHS Clinical Knowledge Summaries (CKS) (formerly PRODIGY) and the Scottish Intercollegiate Guidelines Network (SIGN). The CKS are a reliable source of evidence-based information and practical 'know how' about the common conditions managed in primary care that were identified following a literature search and expert opinion strategy.

When the draft recommendations were completed, they were sent to an independent reviewer for assessment and comment.
The final stage of this project was a review of the prepared recommendations by a panel made up of representatives of the authors from each major region of the UK and invited members from the ACB Executive. The recommendations were discussed and accepted by consensus. Where no evidence-based guidance existed either in the literature or published guidance, recommendations were prepared based on the consensus opinion of the working group. The final document was then sent out for final consultation by the full membership of the Clinical Practice Group and the chairs of each ACB region before submission to the ACB Executive.

Box 1 Minimum Re-testing Interval Work Streams

Renal
Liver and bone
Endocrine
Lipids and diabetes
Specific proteins
Cardiac
Tumour markers
Gastrointestinal
Occupational/toxicology
Therapeutic drug monitoring
Pregnancy and paediatrics

Future Work

It is planned to develop further the scope of these recommendations to include other areas not covered by the initial project. There are a number of specific clinical scenarios that have not been addressed by these recommendation because of their complexity, for example the areas of nutritional support and haemodialysis, where there is already existing guidance. It is also planned to review the current recommendations at timely intervals to ensure that they reflect current and likely future practice.

Using minimum re-testing intervals in practice

The recommendations presented in this document are intended to provide assistance in appropriately managing test requesting at all levels of the request cycle. They are intended to be used in a number of different scenarios, either delivered manually or via a laboratory/remote requesting computer system.

- Education of requesters so that appropriate tests are requested at the right time and in the right patient.
- Information on request cards or in pathology handbooks on when to repeat a test.

- Delivery of prompts to remind requester at point of requesting via remote/ward requesting software that a request is either too soon or inappropriate, with the facility to review previous results or ask questions. There should also be an option to record the reason for overriding a MRI.
- Implementation of logic rules in the laboratory to remove or restrict requests based on previous patient data.

Any MRI being used must also reflect not only the assay being used but also how it is being used – thus the MRI must reflect the local protocol. It should also be implemented following full consultation with the users, ideally supported with an education package if required. It is important to understand the mechanism employed to restrict any test or its request so that it does not appear too restrictive. There must be always the option for the clinicians/requesters to override a rule if they feel that it is clinically appropriate to continue to request the test. How this is managed will reflect the way a test is requested locally. Ideally, there must be an opportunity for requestors to record their reason to override a rule and conversely to inform the requestor, at the earliest opportunity, why it has been rejected. The availability of previously reported laboratory results at or before the time of requesting a new test would greatly assist the requester in deciding whether a test was appropriate. To support this initiative, the availability of up to date clinical history from the requester or the patient's electronic patient record is paramount so that prepared logic rules or MRIs can be correctly implemented. The implementation of electronic requesting of tests provides an opportunity to improve the quality of information received from the requester for the laboratory to use. When a profile is recommended this refers to the standardised profile.[2] It may also be useful to allow the requester to request individual tests from a recognised profile so that only the required and necessary tests are performed. Limiting a test's use may also be achieved by restricting the requesting of a repeat test to a particular grade or level of staff so that only those of an appropriate level may have access to a particular test.

If implementing the MRI into a laboratory information system or remote request system the programmer must be aware of how the system counts time so that the correct unit is used.

REFERENCES

1. Pathology Harmony working towards harmonising standards in UK pathology services http://www.pathologyharmony.co.uk (accessed 11 Jan 2012)
2. Smellie WSA. BMJ 2012;344:e1169
3. Smellie WSA, Finnigan DI, Wilson D, Freedman D, McNulty CAM, Clark G. J Clin Pathol 2005; 58: 249-253.
4. Glaser EM. J App Behavioral Sci 1980; 16: 79-92.
5. Brunton LL, Chabner BA, Knollman BC, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACB	Association for Clinical Biochemistry and Laboratory Medicine
ALP	Alkaline phosphatase
ASCO	American Society of Clinical Oncology
ATPOab	Anti-Thyoid Peroxidase Antibodies
BCSH	British Committee for Standards in Haematology
BMI	Body Mass Index
BNF	British National Formulary
BSPGHAN	British Society of paediatric Gastroenterology, Hepatology and Nutrition
BSH	British Society for Haematology
CA125	Carbohydrate Antigen 125
CA15.3	Carbohydrate 15.3
CA 19.9	Carbohydrate Antigen 19.9
CEA	Carcinoembryonic Antigen
CG	Clinical Guideline
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CKS	Clinical Knowledge Summaries
CPS	Clinical Practice Section
EASL	European Association of the Study of the Liver
e-GFR	Estimated Glomerular Filtration Rate
EGTM	European Group on Tumour Markers
ESC	European of Society of Cardiology
FSH	Follicule Stimulating Hormone
fT3	Free Triiodothyronine
fT4	Free Thyroxine
GAIN	Guidelines and Audit Implementation Network
GGT	Gamma-glutamyltransferase
IGF-1	Insulin-like Growth Factor 1
IHD	Ischaemic Heart Disease
ITU	Intensive Treatment Unit
IV	Intravenous
IVF	*In vitro* Fertilisation
LCMS	Liquid Chromatography Mass Spectrometry
LFT	Liver Function Tests
MDRD	Modification of Diet in Renal Disease
MRI	Minimum Re-testing Intervals
MTC	Medullary Thyroid Carcinoma
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute for Health
NPHS	National Public Health Service
RCOG	Royal College of Obstetricians and Gynaecologists
SIGN	Scottish Intercollegiate Guidelines Network

TFT	Thyroid Function Tests
TPN	Total Parenteral Nutrition
TSH	Thyroid Stimulating Hormone
tTG	Tissue Transglutaminase
U&E	Urea and Electrolytes
UKMI	UK Medicines Information
VP	Venture Publications

RENAL – Refers to the measurement of U&E, unless otherwise stated.

REF	Clinical situation	Recommendation	Source
R1	Normal follow up	A repeat would be indicated on clinical grounds if there were a significant change in that patients condition which indicated an acute renal (or other electrolyte related problem) is developing	Consensus opinion of the working group
R2	Inpatient monitoring of a **stable** patient	An inpatient with an admission sodium within the reference range should not have a repeat sodium within the average length of stay of 4 days	Consensus opinion of the working group
R3	Inpatient monitoring of a **stable** patient on IV fluids, adults as well as children.	Daily monitoring of U&E and glucose	GAIN- Hyponatraemia in Adults 2010
R4	In symptomatic patients or following administering of hypertonic saline	Monitoring should be more frequent, i.e. every 2-4 hr.	GAIN- Hyponatraemia in Adults 2010
R5	Patient diagnosed with acute kidney injury	U&E checked on admission and within 24 hours	Acute Kidney Injury UK Renal Association Clinical Practice Guidelines 5th Edition 2011
R6	Monitoring of ACE inhibitors	Within 1 week of starting and 1 week after each dose titration. Then annually (unless required more frequently because of impaired renal function)	CKS Safe Practice Clinical Answers
R7	Diuretic therapy	Before the initiation of therapy and after 4 weeks, and then 6 monthly/yearly or more frequently in the elderly or in patients with renal disease, disorders affecting electrolyte status or those patients taking other drugs e.g. corticosteroids, digoxin	CKS Safe Practice Clinical Answers
R8	Monitoring of potassium concentrations in patients receiving digoxin	Eight days after initiation or change in digoxin therapy and/or addition/subtraction of interacting drug. Then annually if no change	UKMI. Monitoring Drug Therapy. 2002 PRODIGY. Atrial Fibrillation. 2003, PRODIGY. Heart failure. 2004
R9	Monitoring of potassium concentrations on patients receiving digoxin and diuretics	Regular monitoring	NPHS. Drug Monitoring: A Risk Management System. 2004
R10	Aminosalicylates	In the elderly , every 3 months in first year, then every 6 months for next 4 years then annually after that based on personal risk factors	CKS Safe practice clinical answers
R11	Carbamazepine	6 months	CKS Safe practice clinical answers
R12	Anti-psychotics	12 months	CKS Safe practice clinical answers

RENAL Cont.....

REF	Clinical situation	Recommendation	Source
R13a	eGFR – MDRD – CKD	Repeat in 14 days if new finding of reduced GFR and/or confirmation of eGFR < 60 mL/min/1.73m^2 *eGFR by MDRD not valid in AKI	NICE CG073, 2008
R13b	eGFR – MDRD – Radiological procedures/contrast administration	eGFR or creatinine within previous 7 days in patients with acute illness or renal disease. eGFR for angiography: < 60 mL/min/1.73m^2 should trigger local guidelines for contrast dosage eGFR for Gadolinium: <30 mL/min/1.73m^2 high risk agents contraindicated eGFR 30-59 mL/min/1.73m^2 lowest dose possible can be used and not repeated within 7 days	Royal College of Radiologists Standards for intravascular contrast agent administration to adult patients (2nd Ed) 2010. Ref. No. BFCR(10)4
R13c	eGFR – Cockcroft & Gault	For estimating chemotherapy & drug dosages. Within 24 hours unless rapidly changing creatinine concentrations or fluid balance	None (inferred from BNF)
R13d	Iohexol GFR	72 hours to avoid contamination (based on half life of iohexol of 2 hr)	Krutzen et al. Plasma clearance of a new contrast agent, iohexol: a method for the assessment of glomerular filtration rate. J Lab Clin Med 1984; **104**: 955–961.

BONE - Refers to the measurement of the bone profile, unless otherwise stated.

REF	Clinical situation	Recommendation	Source
B1	Non-acute setting unless there are other clinical indications	Testing at 3 month intervals	Consensus opinion of the working group
B2	Acute settings	Testing at 48 hr intervals	Consensus opinion of the working group
B3	Acute hypo/hypercalcaemia, TPN and ITU patients	May require more frequent monitoring	Consensus opinion of the working group
B4	ALP and total protein in acute setting	Testing at weekly intervals. ALP may need checking more often, but probably only in the context of acute cholestatic changes. *See* Liver recommendations	Consensus opinion of the working group
B5	Vitamin D: no clinical signs and symptoms	Do not retest (whatever the result as there may be no indication to test in first place).	Consensus opinion of the working group.

BONE Cont.....

REF	Clinical situation	Recommendation	Source
B6	Vitamin D: cholecalciferol or ergocalciferol therapy for whatever clinical indication, where baseline vitamin D concentration was adequate	Do not retest, unless otherwise clinically indicated e.g. sick coeliac or Crohn's patient	Sattar *et al*, Increasing requests for vitamin D measurement: costly, confusing, and without credibility. Lancet 2012; **379**:95-96. Sattar *et al*, Vitamin D testing — Authors' reply.Lancet 2012; **379**:1700-1701
B7	Vitamin D: cholecalciferol or ergocalciferol therapy for whatever clinical indication, where baseline vitamin D concentration was low *and* where there is underlying disease that might impact negatively on absorption	Repeat after 3-6 months on recommended replacement dose	Consensus opinion of the working group
B8	Vitamin D: calcitriol or alphacalcidol therapy	Do not measure vitamin D	Consensus opinion of the working group

LIVER - Refers to the measurement of LFTs, unless otherwise stated.

REF	Clinical situation	Recommendation	Source
L1	Non acute setting	Testing at 1-3-month intervals	Primary Care and Laboratory Medicine, Frequently Asked Questions Published 2011, Smellie S, Galloway M, McNulty S. ACB Venture Publications
L2	Acute inpatient setting	Testing at 72 hr intervals in acute setting (apart from those in L4)	Consensus opinion of the working group
L3	GGT and conjugated bilirubin in acute setting	Testing at weekly intervals	Consensus opinion of the working group
L4	Acute poisoning (e.g. paracetamol), TPN, liver unit, acute liver injury and ITU patients	May require more frequent monitoring	Consensus opinion of the working group
L5	Neonatal jaundice	These recommendations must not be used in the management of neonatal jaundice	

LIPIDS – Refers to the measurement of lipid profile (not fasting), unless otherwise stated.

REF	Clinical situation	Recommendation	Source
LP1	LOW risk cases for IHD assessment.	3 years	Bettertesting website
LP2	Higher risk cases for IHD assessment and those on stable treatment.	1 year	Consensus opinion of the working group
LP3	Initiating or changing therapies.	1-3 months	Consensus opinion of the working group
LP4	When assessing triglyceridaemia to see effects of changing diet and alcohol.	1 week	Consensus opinion of the working group
LP5	In patients on TPN or who have hypertriglyceridaemia-induced pancreatitis.	1 day	Consensus opinion of the working group

ENDOCRINE RELATED (for pregnancy-related endocrinology – *see* pregnancy)

REF	Clinical situation	Recommendation	Source
E1	Thyroid function testing in healthy person in absence of any clinical symptoms	Three years	Consensus opinion of the working group
E2	Hyperthyroid - monitoring of treatment in Graves' disease	Follow-up in first 1-2 months after radioactive iodine treatment for Graves' should include fT4 and total T3. If patient remains thyrotoxic then biochemical monitoring to continue at 4-6 wk intervals Following thyroidectomy for Graves' disease (and commencement of levothyroxine), serum TSH to be measured 6-8 wks post-op	Bahn *et al*. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011, **21:**593-646

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E3	Hyperthyroid - monitoring of treatment in toxic multinodular goitre and toxic adenoma	Follow-up in first 1-2 months after radioactive iodine treatment for toxic multinodular goitre and toxic adenoma should include fT4 and total T3 and TSH. Should be repeated at 1-2 month intervals until stable results, and then annually thereafter Following surgery for toxic multinodular goitre and start of thyroxine therapy, TSH should be measured 1-2 monthly until stable and annually thereafter Following surgery for toxic adenoma TSH and fT4 concentrations should be measured 4-6 weeks post op	Bahn *et al*. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011, **21:**593-646
E4	UK Thyroid guidelines	TFTs should be performed every 4-6 wks for at least 6 months following radioiodine treatment. Once fT4 remains in ref range then frequency of testing should be reduced to annually. Life-long annual follow up is required Indefinite surveillance required following radioiodine or thyroidectomy for the development of hypothyroidism or recurrence of hyperthyroidism. TFTs should be assessed 4-8 wks post treatment, then 3 monthly for up to one 1 year, then annually thereafter TFTs should be performed every 4-6 wks after commencing thionamidides. Testing at 3 month intervals is recommended once maintenance dose achieved In patients treated with 'block and replace', assess TSH and T4 at 4-6 wk intervals, then after a further 3 months once maintenance dose achieved, and then 6 monthly thereafter	Association for Clinical Biochemistry and Laboratory Medicine, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry and Laboratory Medicine, British Thyroid Association, British Thyroid Foundation July 2006

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E5	Hypothyroidism - monitoring treatment	The minimum period to achieve stable concentrations after a change of dose of thyroxine is 2 months and TFTs should not normally be assessed before this period has elapsed Patients stabilised on long-term thyroxine therapy should have serum TSH checked annually An annual fT4 should be performed in all patients with secondary hypothyroidism stabilised on thyroxine therapy	Association for Clinical Biochemistry and Laboratory Medicine, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation, July 2006.
E6	Monitoring Adult sub-clinical hyperthyroidism	If a serum TSH below ref range but >0.1 mU/L is found, then the measurement should be repeated 1-2 months later along with T4 and T3 after excluding non-thyroidal illness and drug interferences. This is contradicted later in the guidelines when the authors state that a 3-6 month repeat interval is appropriate unless the patient is elderly or has underlying vascular disease If treatment not undertaken then serum TSH should be measured in the long term every 6-12 months, with follow up with fT4 and fT3 and fT3 if serum TSH result is low	Association for Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation July 2006
E7	Monitoring adult sub-clinical hypothyroidism.	Patients with subclinical hypothyroidism should have the pattern confirmed within 3-6 months to exclude transient causes of elevated TSH Subjects with subclinical hypothyroidism who are ATPOab positive should have TSH and fT4 checked annually Subjects with subclinical hypothyroidism who are ATPOab neg should have TSH and fT4 checked every 3 years	Association for Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation July 2006

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E8	Follow up of patients who have had differentiated (papillary and follicular) thyroid carcinoma and a total thyroidectomy and ^{131}I ablation	TSH and fT4 should be measured as dose of levothyroxine increased (every 6 weeks) until the serum TSH is <0.1 mIU/L. Thereafter annually unless clinically indicated / pregnant Samples for thyroglobulin (Tg) should not be collected sooner than 6 weeks post-thyroidectomy or 131I ablation/therapy. TSH, fT4/fT3 (whichever is being supplemented) and Tg autoantibodies (TgAb) should be requested when Tg is measured. If TgAb are detectable, measurement should be repeated every 6 months	British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer (Perros P, ed) 2nd edition.Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007
E9	Follow up of patients who have had medullary thyroid cancer and surgical resection	A baseline CEA and fasting calcitonin should be taken prior to operation. Postoperative samples should be measured no earlier than 10 days after thyroidectomy and plasma calcitonin concentrations are most informative 6 months after surgery At least 4 measurements of calcitonin over a 2-3 year period can be taken to provide an accurate estimate of the calcitonin doubling time. CEA is elevated in approximately 30% of MTC patients, and in those patients CEA doubling time is comparably informative to calcitonin doubling time Calcitonin monitoring should continue lifelong TFTs should be measured as per guidance for hypothyroidism	British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer (Perros P, ed) 2nd edition.Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007. Eur J Endocrinol 2008; **158**: 239-246
E10	Anaplastic thyroid cancer	There is no need for any monitoring of thyroid function unless patient is on thyroid replacement, then as per hypothyroidism	British Thyroid Association, Royal College of Physicians. Guidelines for the management of thyroid cancer (Perros P, ed) 2nd edition.Report of the Thyroid Cancer Guidelines Update Group. London: Royal College of Physicians, 2007

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E11	Progesterone	Testing weekly in patients with irregular cycle from day 21 until next menstrual period	Fertility: assessment and treatment for people with fertility problems. NICE 2004
E12	FSH.	Two tests 4-8 weeks apart in women with possible early or premature menopause.	AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of menopause
E13	Patients with suspected drug- induced hyperprolactinaemia.	Discontinue medication for 3 days and re-measure prolactin	Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas Clin Endocrino 2006, **65**, 265-273. Diagnosis & Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice J Clin Endocrinol Metab. 2011;**96**:273-288
E14	Patients with hyperprolactinaemia commencing dopamine agonist therapy	Repeat prolactin measurement after 1 month to guide therapy	Diagnosis & Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice J Clin Endocrinol Metab. 2011;**96**:273-288
E15	Diagnosis of male androgen deficiency	Repeat testosterone measurement to confirm diagnosis recommended.	Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes Endocrine Society Clinical Guideline J Clin Endocrinol Metab 2010, **95**:2536-2559.
E16	Monitoring of patient with androgen deficiency on replacement therapy	Measure testosterone value 3 to 6 months after initiation of testosterone therapy Measure testosterone every 3-4 months for first year Measurement of prostate specific antigen (PSA) – Please refer to TM7	Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes Endocrine Society Clinical Guideline J Clin Endocrinol Metab 2010, **95**(6):2536-2559. AACE medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update
E17	Female androgen excess	If measurement found to be raised by an immunoassay method, confirm measurement with a LCMS method: Thereafter 1 year	Evaluation and Treatment of Hirsutism in premenopausal women Endocrine Society guideline The Journal of Clinical Endocrinology & Metabolism 2008; **93**: 1105-1120, 2008. Consensus opinion of the working group

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E18	Oestradiol	No evidence, guideline or consensus exists for repeat frequency For patients undergoing IVF samples may be taken daily For patients receiving implant treatment a pre-implant value is checked to avoid tachyphylaxis. Frequency depends on frequency of implant For patients receiving implant treatment a pre-implant value is checked to avoid tachyphylaxis	
E19	Growth hormone deficiency	IGF-1 is the most useful marker for monitoring and should be measured at least yearly, and assessment should be performed no sooner than 6 weeks following a dose change	Ken K Y Ho (on behalf of the 2007 GH deficiency Consensus Workshop participants. EuropJ Endocrinol 2007; **157**: 695-700
E20	Acromegaly: post surgery medical therapy medical therapy using GH receptor antagonists Postradiotherapy	 Measure both GH and IGF-1 at 3 months. If normal then at annual follow up Measure both GH and IGF-1 at 3 months. If normal then at annual follow up Measure only IGF-1 at 6 monthly intervals after dose titration. Monthly monitoring of LFTs for first six months Measurement of GH and IGF-1 annually	Biochemical Assessment and Long-Term Monitoring in Patients with Acromegaly: Statement from a Joint Consensus Conference of The Growth Hormone Research Society and The Pituitary Society (2004). J Clin Endocrinol Metab 2004; **89**: 3099-3102

ENDOCRINE RELATED Cont.....

REF	Clinical situation	Recommendation	Source
E21	Screening for diabetes in asymptomatic patients: Adults < 45 y with normal weight and no risk factor Adults > 45 y with normal weight (BMI <25 kg/m^2)and no risk factor* Adults >18 y with BMI ≥25 kg/m2 and 1 risk factor*	 Screening not recommended 3 y 3 y, if result is normal.	American Diabetes Association Clinical Practice Recommendations (2012) * Risk[s] factors listed in Table 4 of this document
E22	Diagnosing diabetes using HbA_{1C} in an asymptomatic patient (not to be used in children or young adults	Diagnosis should not be made on the basis of a single abnormal plasma glucose or HbA_{1C} value. At least one additional HbA_{1C} or plasma glucose test result with a value in the diabetic range is required within 2 weeks of the initial measurement, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT)	Use of Glycated Haemoglobin (HbA_{1C}) in the Diagnosis of Diabetes Mellitus - Abbreviated Report of a WHO Consultation 2011
E23	HbA_{1C} monitoring of patients with type 2 diabetes	2–6 monthly intervals (tailored to individual needs), until the blood glucose concentration is stable on unchanging therapy; use a measurement made at an interval of less than 3 months as an indicator of direction of change, rather than as a new steady state Six monthly intervals once the blood glucose concentration and blood glucose lowering therapy are stable	NICE CG66 Type 2 diabetes

CARDIAC

REF	Clinical situation	Recommendation	Source
C1	Using troponin (general)	MRI largely dependent on the assay being used and the clinical scenario. MRIs should be implemented according to the local protocol used	
	Acute coronary syndrome (ACS)	High sensitivity troponin assays will usually require several samples – with a second sample within 3 hr of presentation, the sensitivity for Myocardial infarction approaches 100%	ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation European Heart Journal 2011; **32**, 2999–3054
		For standard troponin assays - If the first blood sample for troponin is not elevated, a second sample should be obtained after 6–9 hr, and sometimes a third sample after 12–24 hr is required	Recommendations for the use of cardiac troponin measurement in acute cardiac care. European Heart Journal doi:10.1093/eurheartj/ehq251
	Cardiac surgery	Single measurement at 24 hr post surgery gives best correlation with outcome. Serial samples justified if clinical condition worsens and /or new ECG changes to assess ACS	Croal BL.The relationship between post-operative cardiac troponin I levels and outcome from cardiac surgery. Circulation 2006; **114**: 1468-1475
	Renal failure	Concentrations usually increased in Chronic kidney diseasee (CKD) patients (especially using high sensitivity assays) – serial samples will be required if suspected ACS as above	Khan et al Prognostic Value of Troponin Enzymes in End-Stage Renal Disease. Circulation. 2005;**112**:3088-3096 Group Consensus Opinion

CARDIAC

REF	Clinical situation	Recommendation	Source
C2	Using BNP (NT-ProBNP) Primary care (Heart failure triage) Secondary care (Acute 'short of breath' triage) Therapeutic guidance in heart failure	 Should only be measured once unless there is a repeat episode of suspected heart failure with a change in clinical presentation and the diagnosis of heart failure has previously been excluded. Single time point use adequate for NICE guidance purposes Should only be measured once per acute episode for diagnosis. Pre-discharge repeat measurement has prognostic significance but has not been shown to alter outcome Not yet accepted in guidelines	 NICE CG 108 Chronic Heart failure Group Consensus Opinion NICE guidelines (2012)

GASTROINTESTINAL

REF	Clinical situation	Recommendation	Source
G1	Coeliac serology in known adult patients on follow up	IgA tTG can be used to monitor response to a gluten-free diet. Retesting at 3–12 months depending on pre-treatment value	www.uptodate.com
G2	Faecal elastase	Minimum retesting interval 6 months	Molinari *et al* Clin Biochem 2004;**37**:758-763
G3	Faecal calprotectin	Minimum retesting interval 6 months	van Rheenen *et al*, BMJ 2010;**341**:c3369
G4	Trace elements (copper, zinc, selenium)	Baseline then every 2 to 4 weeks depending upon results	NICE CG32
G5	Ferritin monitoring for haemochromatosis	EASL 2010 recommend retesting interval initially 3 months but test more frequently as ferritin approaches normal range. BCSH 2000 recommends monthly ferritin during venesection.	European Association for the Study of the Liver. EASL Clinical Practice Guidelines for HFE Hemochromatosis. J Hepatol 2010; **53**(1):3-22 . British Committee for Standards in Haematology: Guidelines on diagnosis and therapy - Genetic Haemochromatosis 2000
G6	Iron deficiency diagnosis	Repeat measurement not required unless doubt regarding diagnosis	British Society of Gastroenterology 2011

GASTROINTESTINAL Cont.....

REF	Clinical situation	Recommendation	Source
G7	Iron profile/ferritin in patients on parenteral nutrition	Minimum retesting interval 3-6 months	NICE CG32
G8	Iron status in chronic kidney disease	Monitor iron status no earlier than 1 week after receiving I.V. iron and at intervals of 4 weeks to 3 months routinely.	NICE CG114
G9	Iron profile/ferritin in a normal patient	Minimum retesting interval 1 year	NICE CG 32 Smellie *et al*, J Clin Pathol 2006; **59:** 781-789
G10	Monitoring vitamin B12 and folate deficiency	Repeat measurement of vitamin B12 and folate is unnecessary in patients with vitamin B12 and folate deficiency	CKS Guidelines: Anaema – Vitamin B12 and Folate Deficiency

For more guidance on the laboratory monitoring of patients on nutritional support, particularly parenteral nutrition and those receiving enteral or oral feeds who are metabolically unstable or at risk of re-feeding syndrome, please refer to the NICE Clinical Guideline 32 - Nutrition support in adults.

SPECIFIC PROTEINS

REF	Clinical situation	Recommendation	Source
SP1	Paraproteins	Testing at 3 months intervals initially	Bettertesting Website, BCSH
SP2	Patients with no features of plasma cell dyscrasia (for example, anaemia, bone fracture or pain located in bone, suppression of other immunoglobulin classes, renal impairment) and a band of <15g/L	Annual serum protein electrophoresis and quantitation by densitometry without need for further immunofixation is recommended	Bettertesting Website
SP3	Monoclonal gammopathy of undetermined significance	Annually	Bettertesting Website
SP4	Immunoglobulins	Patients on immunoglobulin replacement therapy must have trough IgG concentrations and liver function tests performed at least quarterly	UK Primary Immunodeficiency Network Standard of care Version 2, 2011
SP5	Immunoglobulins	For other purposes, testing at minimum interval of 6 months is recommended	Expert opinion
SP6	Myeloma patients on active treatment	Local guidance and treatment regimes should be followed when requesting paraproteins concnetrations for patient on active treatment	Feedback from consultation

SPECIFIC PROTEINS Cont.....

REF	Clinical situation	Recommendation	Source
SP7	C-Reactive protein (CRP)	Not within a 24 hr period following an initial request with the exception of paediatric requests	Hutton *et al*. Ann Clin Biochem 2009; **46**: 155-158.
SP8	Procalcitonin	24 hr	Hochreiter *et al*, Crit Care 2009; **13**:R83, Seguela *et al*, Cardiology in the Young 2011; **21**: 392-399

TUMOUR MARKERS

REF	Clinical situation	Recommendation	Source
TM1	α-Fetoprotein for hepatocellular carcinoma (HCC) surveillance: screening patients at high HCC risk	6 months (UK)	British Society of Gastroenterology, EGTM
TM2	α -Fetoprotein for monitoring disease recurrence in HCC	3-6 months	EGTM 2010
TM3	Screening women with family history of ovarian cancer with CA125	12 months	NIH consensus, EGTM 2010
TM4	Using CA125 in diagnostic strategies.	Retesting CA125 where imaging is negative within 1 month	NICE CG122
TM5	Monitoring CA125 in disease recurrence	1 month	EGTM 2010
TM6	Monitoring disease recurrence with CEA	2-3 months	EGTM 2010, ASCO, The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines use of Tumour Markers in Clinical Practice .Quality Requirements. Clin Chem 2008; **54**: 1935-1939
TM7	Monitoring disease recurrence with CA199	1 month	No available evidence. All Wales consensus
TM8	PSA screening	When first result is raised repeat once in 6 weeks to assess the trend.	Prostate Cancer Risk management programme
TM9	Monitoring disease with PSA	Every 3 months for first 1-2 yrs. Every 6 months for 2 yr. Annual thereafter	Bettertesting.org.uk
TM10	Monitoring disease recurrence with CA15.3	2 months	EGTM 2010
TM11	Serum β-HCG (tumour marker)	After evacuation of a molar pregnancy, the hCG concentration should be monitored every week until normalization and then every month during the first year	Kinetics of Serum Tumour Marker Concentrations and Usefulness in Clinical Monitoring. Bidert J-M *et al*. Clin Chem1999; **45**: 1695-1707
TM12	Serum β-HCG (tumour marker)	After resection,prolonged marker t½ (>3 days for hCG) is a reliable indicator of residual tumor and a significant predictor of survival	

TUMOUR MARKERS Cont.....

REF	Clinical situation	Recommendation	Source
TM13	Serum β-HCG (tumour marker)	If rate of change in tumour marker concentration changes velocity, an urgent repeat to confirm the result is reasonable	The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines use of Tumour Markers in Clinical Practice .Quality Requirements. Clin Chem 2008; 54: 1935-1939

THERAPEUTIC DRUG MONITORING

As drugs are xenobiotics, the time for significant change is based on the kinetics of absorption and clearance. Steady state concentrations on new dose regimens are normally established after five plasma half-lives have elapsed.

For drugs where over 30% of clearance is renal then dosing and half-life are reflected by the creatinine clearance calculated using Cockcroft & Gault formula (eGFR is less reliable though widely used). Tables of half-lives for most drugs are given and referenced in Brunton et al.[5]
Some drugs induce their own metabolism e.g. carbamazepine, or can have hepatic clearance induced by another drug, and specific details need to be checked with the literature; other xenobiotic interactions may significantly affect half-lives e.g. smoking and clozapine.

Depending on the metabolic pathway an individual's pharmacogenetic phenotype may result in more rapid or much slower metabolism than the general population, so the half-lives will be shorter or longer respectively and the 5 half-life rule applies, but using a half-life specific to the individual.

As there are so many different combinations of interaction the advice given above is a general guide and the specific classes discussed below are for high-level guidance.

THERAPEUTIC DRUG MONITORING Cont.....

REF	Clinical situation	Recommendation	Source
TD1	Anticonvulsant drugs (carbamazepine, phenytoin)	Five half-lives after dosage change (4-5 days) during initial dose optimisation, **unless toxicity is suspected**. The kinetics of phenytoin are highly variable between individuals and when metabolism is saturated, a small dose change results in a disproportionate increase in plasma concentration. There is a significant risk of overdose and therefore when titrating dose changes check up to every 12hr depending on clinical condition and therapy. This will be more frequent on iv therapy for status epilepticus. Note: carbamazepine induces its own metabolism and concentrations should be confirmed 2-3 months after commencing therapy	Expert opinion
TD2	Digoxin	Five half-lives after dosage change (i.e. approx 7 days) during initial dose optimisation, unless toxicity is suspected. When renal function has changed significantly recognise the proportionate decrease in clearance. In overdose situations, up to every 4hr depending on clinical condition and therapy	Expert opinion
TD3	Aminoglycoside antibiotics (gentamicin, tobramycin)	Every 24 h at start of therapy on high-dose parenteral regimes, less frequently when stable. Especially important in the elderly, patients with impaired renal function and those with cystic fibrosis	Consult local guidelines
TD4	Immunosuppressive drugs (ciclosporin, tacrolimus, sirolimus)	Initially 3x per week after transplantation, less frequently when stable. Concentrations should also be checked when any medication with possible interactions is prescribed, the dosage is changed, the formulation is changed or when there is unexplained graft dysfunction	Renal Association guidelines: Post-operative Care of the Kidney Transplant Recipient (2011)

THERAPEUTIC DRUG MONITORING Cont.....

REF	Clinical situation	Recommendation	Source
TD5	Theophylline	Five half-lives after dosage change (i.e. approx 2 days) during initial dose optimisation on oral regimes. Note smoking significantly reduces the half-life. Daily on IV aminophylline. In overdose situations requiring haemodialysis, every 4 hr	Expert opinion
TD6	Methotrexate (high dose IV)	24 hr after completion of therapy then every 24 hr until plasma methotrexate is below cut-off concentration for toxicity (1 μmol/L at 48 hr or according to local protocol)	See product literature
TD7	Lithium	Days 4-7 of treatment then every week until dosage has remained constant for 4 weeks, then every 3 months on stabilised regimes. Check concentration when preparation changed, when fluid intake changes or when interacting drugs are added/withdrawn. 100% renal clearance, so dependant on renal function. Up to every 4 hr in overdose situations requiring intensive therapy	BNF (2012)
TD 8	Clozapine	Induces its own metabolism and is induced further by smoking. Approximately 4 days to reach new steady-state after dose change or smoking cessation with potentially fatal consequences due to the rapid increase to toxic concentrations	Expert opinion

OCCUPATIONAL / TOXICOLOGY

REF	Clinical situation	Recommendation	Source
O1	Occupational lead exposure (chronic)	Initial blood lead concentration before commencing work or within 14 days of starting Blood lead concentration monitoring performed at least every 12 months unless significantly exposed to metallic lead and its compounds, in which case the blood lead should be measured every three months If the blood lead is ≥30 µg/dL in adult males (≥20 µg/dL in women of child bearing age) monitor at least every 6 months If the blood lead is ≥40 µg/dL in adult males (≥25 µg/dL in women of child bearing age) monitor at least every 3 months If the blood lead is ≥60 µg/dL in adult males (≥30 µg/dL in women of child bearing age) repeat measurement of blood lead within 2 weeks	Control of Lead at Work Regulations 2002.3rd Edition. Health and Safety Executive Books
O2	Acute lead poisoning in adults	If baseline blood lead concentration is <50 µg/dL, the patient is asymptomatic and not pregnant, repeat blood lead concentration after 2 weeks following removal from exposure If baseline blood lead concentration is ≥ 50 µg/dL, monitor blood lead concentrations daily during chelation therapy and measure 24 hour urine lead excretion to assist in deciding the duration of treatment. Repeat the blood lead measurement 1 week after the end of chelation treatment	TOXBASE

OCCUPATIONAL / TOXICOLOGY Cont.....

REF	Clinical situation	Recommendation	Source
O3	Acute lead poisoning in children	If the baseline blood lead concentration is between 10-50 µg/dL then repeat blood lead measurement in one month following removal from exposure If baseline blood lead concentration is >50 µg/dL, monitor blood lead daily during chelation therapy and measure 24 h urine lead excretion to assist in deciding the duration of therapy. Repeat the blood lead measurement 1 week after the end of treatment	TOXBASE
O4	Amfetamine toxicity	Re-testing is not indicated in the same acute episode	Consensus opinion of the working group
O5	Benzodiazepine toxicity	Re-testing is not indicated in the same acute episode	Consensus opinion of the working group
O6	Cocaine toxicity	Re-testing is not indicated in the same acute episode	Consensus opinion of the working group
O7	Opiate toxicity including morphine, codeine and heroin	Re-testing is not indicated in the same acute episode	Consensus opinion of the working group
O8	Opioid toxicity including methadone	Re-testing is not indicated in the same acute episode	Consensus opinion of the working group

PREGNANCY-RELATED

REF	Clinical situation	Recommendation	Source
P1	Urine βHCG (pregnancy)	Urine pregnancy test can be repeated at 3 days after a negative result or approx 28 days after period commences	Manufacturer's instructions
P2	Serum βHCG (pregnancy)	Serum βHCG test: do not repeat if positive. Repeat after 3 days if negative and no menstrual period has occurred	Serum HCG doubling time = 1.5-2 days.
P3	Serum βHCG (ectopic pregnancy)	48 h repeat interval	RCOG Guideline 21 Implementation of probabilistic decision rule improves the predictive values in algorithms in the diagnostic management of ectopic pregnancy. Mol BWJ *et al*. Hum Reprod 1999. **14**; 2855-2262.

PREGNANCY-RELATED Cont.....

REF	Clinical situation	Recommendation	Source
P4	Serum βHCG (tumour marker)	After evacuation of a molar pregnancy, the hCG concentration should be monitored every week until normalization and then every month during the first year	Kinetics of Serum Tumor Marker Concentrations and Usefulness in Clinical Monitoring. Bidart J-M *et al*. Clinical Chemistry 1999; **45**: 1695-1707.
P5	LFTs in obstetric cholestasis	Once obstetric cholestasis is diagnosed, it is reasonable to measure LFTs weekly until delivery. Postnatally, LFTs should be deferred for at least 10 days	RCOG guidelines for Obstetric Cholestasis (Green Top 43) (2011)
P6	Women with persistent pruritus and normal biochemistry.	LFTs repeated every 1–2 weeks	RCOG guidelines for Obstetric Cholestasis (Green Top 43) (2011)
P7	Bile acids in obstetric cholestasis	Weekly monitoring. Twice weekly monitoring advised in later weeks if clinical state changing	No evidence available but reflects expert opinion and practice
P8	Measurement of urate in pre-eclampsia	Awaiting expert advice whilst not admitted: twice weekly urate	No evidence but reflect practice of tertiary centre of excellent
P9	Urine protein in pre-eclampsia.	At each antenatal visit to screen for pre-eclampsia. Once diagnosed do not repeat quantification of proteinuria. However, daily urine protein recommended in severe hypertension	NICE CG62 – Antenatal care. NICE CG107 - Hypertension in pregnancy
P10	LFT/renal in pre-emclampsia.	At least daily when the results are abnormal but more often if the clinical condition If mild hypertension* then perform tests twice weekly. If moderate hypertension* then perform tests three times a week If severe hypertension* then perform tests three times a week * see source guidelines for definitions of hypertension.	RCOG Severe pre-eclampsia/eclampsia, management (Green-top 10A). NICE CG107 Hypertension in pregnancy

PREGNANCY-RELATED Cont.....

REF	Clinical situation	Recommendation	Source
P11	Pregnant women - monitoring of thyrotoxicosis treatment. (UK)	In women taking anti-thyroid drugs TFTs should be performed prior to conception, at time of diagnosis of pregnancy or at antenatal booking Newly diagnosed hyperthyroid patients require monthly testing during pregnancy until stabilised Pregnant women receiving anti-thyroid drugs should be tested frequently (perhaps monthly)	Association for Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation July 2006
P12	Pregnant women - monitoring thyrotoxicosis treatment. (USA)	It is recommend that women treated with anti-thyroid drugs in pregnancy, fT4 and TSH should be monitored approximately every 2--6 weeks	Stagnaro-Green et al. The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Thyroid 2011 ; **21**:1081-1125
P13	Pregnant women - monitoring thyroxine replacement therapy	Both TSH and fT4 (and fT3 if TSH below detection limit) should be measured to assess thyroid status and monitor thyroxine therapy in pregnancy The thyroid status of hypothyroid patients should be checked with TSH and fT4 during each trimester. Measurement of T3 is not appropriate The following TFT test sequence is recommended by the UK guidelines [ii]: • before conception • at time of diagnosis of pregnancy • at antenatal booking • at least once in second and third trimesters and again after delivery • newly diagnosed hypothyroid patient to be tested every 4-6 wks until stabilised	Association for Clinical Biochemistry, British Thyroid Association and British Thyroid Foundation (2006) UK guidelines for the use of thyroid function tests. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation July 2006

PREGNANCY-RELATED Cont.....

REF	Clinical situation	Recommendation	Source
P14	Pregnancy sub-clinical hypothyroidism	Women with subclinical hypothyroidism who are not initially treated should be monitored for progression to overt hypothyroidism with serum fT4 and TSH every 4 weeks until 16-20 weeks gestation and at least once between 26-32 weeks (Euthyroid women (not receiving LT4) who are antithyroid antibody positive should be monitored during pregnancy - with serum fT4 and TSH every 4 weeks until 16-20 weeks gestation and at least once between 26-32 weeks)	Stagnaro-Greenet *et al*. The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Thyroid. 2011 ; **21**:1081-1125
P15	Women with diabetes who are planning to become pregnant	Monthly measurement of HbA_{1C}	NICE CG063 (2008)
P16	Assessing glycaemic control using HbA_{1c} in pregnancy	HbA_{1C} should not be used routinely for assessing glycaemic control in the second and third trimesters of pregnancy."	NICE CG063 (2008)

PAEDIATRIC-RELATED

REF	Clinical situation	Recommendation	Source
CH1	HbA_{1C} monitoring in children and young people with type 1 diabetes .	2 months	NICE CG15 Type 1 diabetes in children and young people: full guideline
CH2	Coeliac serology in known paediatric patients on follow up	Testing at 6 months in children	BSPGHAN (British Society of paediatric Gastroenterology, Hepatology and Nutrition) Guideline for the diagnosis and managementof coelic disease in children (2006)-Coelic working group of BSPGHAN

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