Pathologist approval for laboratory tests:
Vitamin D, Insulin, DHEAS, Homocysteine, and Lipoprotein(a)

To ensure the optimal use of public laboratory resources consistent with good medical practice, it has been Labplus policy to require pathologist approval before certain laboratory tests are performed. This has proved successful in curbing inappropriate testing and has found wide acceptance in the health care community. This policy has now been extended to the 5 tests listed above. These tests have been carefully selected to ensure that limitations on them will not adversely impact on patient care. This policy is supported by the ADHB Clinical Practice Committee.

Vitamin D

Labplus (Auckland City Hospital's laboratory) has been responsible for doing all vitamin D tests for the Auckland region. Labplus will be introducing a new policy on vitamin D testing in the near future. Vitamin D tests were originally developed for investigation of rickets, osteomalacia and other metabolic bone disorders. In recent years the number of requests for vitamin D tests has increased dramatically. Most of these requests are unrelated to metabolic bone disease, and have arisen because of reported associations between various disease states (cancers, cardiovascular disease, diabetes, autoimmune disorders and infectious diseases) and lower vitamin D concentrations.

However, a causal link has yet to be demonstrated for any of these conditions.[1-3] The Institute of Medicine, following an comprehensive review of the evidence, concluded that " For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements. Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative."[2]

A recent comprehensive literature review for the Ontario Ministry of Health has concluded that there is little evidence that it is useful to test vitamin D concentrations in patients without symptoms of metabolic bone disease. [4]

It is not necessary to routinely measure vitamin D in patients with low bone density. It is reasonable to routinely provide vitamin D supplements (1.25 mg or 50,000IU cholecalciferol per month) without testing vitamin D to frail housebound or institutionalized elderly people, or those in the community who practise sunlight avoidance for cultural or medical reasons.

The following criteria will apply to vitamin D tests at LabPlus. The test will be performed only when:

1. Ordered by an endocrinologist
2. Ordered for specific high risk groups for rickets/osteomalacia (e.g. cystic fibrosis, proven malabsorption)
3. Ordered for the investigation of rickets/osteomalacia, or disorders of calcium and phosphate metabolism
4. Ordered for other patients after discussion with, and approval by, a Labplus Chemical Pathologist

Insulin

Serum insulin measurement is important in determining whether hypoglycemia is due to an insulinoma or exogenous insulin administration. The sample must be taken during a spontaneous hypoglycemic attack or a controlled fast. It may also be useful in classifying some unusual cases of diabetes.

Insulin tests are sometimes requested as a measure of insulin resistance. While it is true that insulin resistance is a feature of the "metabolic syndrome", there is no clinical benefit in measuring insulin resistance in everyday clinical practice.[5] In addition, the fasting serum insulin levels is a poor measure of insulin resistance.[5]

Clinicians should rather identify risk factors such as fasting glucose and lipid levels, central obesity and hypertension. [5]

Criteria for approval of insulin tests

- Investigation for insulinoma
- All requests from endocrinologists will be approved
- Other cases will require discussion with a Labplus chemical pathologist

DHEAS

DHEAS is an androgenic steroid, mainly of adrenal origin. Its main diagnostic use is to exclude an adrenal tumour in the investigation of hirsuitism, virilization or hyperandrogenism in women[6]. Minor elevations of DHEAS are common in polycystic ovary syndrome and idiopathic hirsutism, but its measurement is of little diagnostic value in these conditions. In this context the key androgen to measure is testosterone and a normal testosterone level effectively excludes an adrenal tumour.

DHEAS is also used in the investigation of ambiguous genitalia and congenital adrenal hyperplasia, and may be helpful in differentiating between different types of Cushing's syndrome and in the evaluation of the HPA axis.[7]

DHEAS levels peak in early adulthood and decrease thereafter. This has led to the concept of DHEAS 'deficiency' or 'andropause' in the middle-aged and elderly, which is promoted by manufacturers of DHEA supplements and alternative medicine practitioners. There is no good evidence that a low DHEAS level constitues a deficiency state, or that DHEA supplementation has any benefits, except in patients with proven adrenal insufficiency (Addison's disease or hypopituitarism).[8]

Criteria for approval of DHEAS tests

- Investigation of ambiguous genitalia or congenital adrenal hyperplasia.
- Females with very high testosterone level (total testosterone >5 nmol/L)
- All requests from endocrinologists, gynaecologists and dermatologists will be approved.
- Other cases will require discussion with a Labplus chemical pathologist

Homocysteine

Classical Homocystinuria is a rare genetic condition associated with premature vascular disease and very high homocysteine levels (> 50 umol/L). Plasma homocysteine may be elevated in vitamin B12 or folate deficiency, or genetic defects of B12 or folate metabolic pathways.

In the general population, raised homocysteine levels are associated with increased risk of cardiovascular disease and stroke. However, homocysteine-lowering interventions (e.g. folate and vitamin B6 supplementation) do **not** modify cardiovascular risk, despite the fact that they lower homocysteine levels.[9, 10] This suggests that homocysteine does not have a causative role in vascular disease. Routine homocysteine testing is not recommended as part of cardiovascular risk assessment[11].

Criteria for approval of homocysteine tests

- Diagnosis of genetic classical homocystinuria. Clinical details state "?homocystinuria" or "premature vascular disease" or "thrombotic tendency" or similar.
- Requests from paediatricians, cardiologists, haematologists, specialist lipid, metabolic or cardiovascular disease clinics will be approved.
- Other cases will require discussion with a Labplus chemical pathologist

Lipoprotein(a)

Lipoprotein (a) is an atherogenic lipoprotein and is a modest independent risk factor for premature coronary artery disease. It is thought to have pro-thrombotic effects. Lp(a) levels are mainly genetically determined and are poorly responsive to diet or to lipid-lowering drugs.[12]

Because Lp(a) levels are difficult to alter, there are no clinical trials that have adequately tested whether Lp(a) reduction reduces the incidence of cardiovascular events. Therefore routine measurement of lipoprotein (a) is not indicated as part of a cardiovascular risk assessment in primary

care.[11, 12] If the clinical approach is otherwise clear based on other risk factors, then measuring Lp(a) has little additional value. In borderline cases, where a decision on management is not clear from other risk factors, Lp(a) measurement (once only) may be indicated.

Criteria for approval of Lp(a) tests

- Requests from cardiologists, and from specialist lipid, metabolic or cardiovascular disease clinics will be approved.
- Repeat testing will not be approved.
- Other cases will require discussion with a Labplus chemical pathologist

How to contact a Labplus chemical pathologist

We prefer contact by email: ChemicalPathologist@adhb.govt.nz
If unable to email, call Lablink (09-307-8995), identify yourself as a doctor, and ask to speak to the on-call Chemical Pathologist.

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References

1. Grey A, Bolland M. Vitamin D: a place in the sun? Arch Intern Med. 2010;170:1099-1100
2. Ross AC, Manson JE, Abrams SA et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96:53-58
3. Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer--ready for prime time? N Engl J Med. 2011;364:1385-1387
4. Clinical utility of vitamin D testing: an evidence-based analysis. Ont Health Technol Assess Ser[Internet].www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_vitamin%20d_201002.pdf. Vol. 10: Medical Advisory Secretariat. , 2010:1-95
5. Samaras K, McElduff A, Twigg SM et al. Insulin levels in insulin resistance: phantom of the metabolic opera? Med J Aust. 2006;185:159-161
6. Martin KA, Chang RJ, Ehrmann DA et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:1105-1120
7. Fischli S, Jenni S, Allemann S et al. Dehydroepiandrosterone sulfate in the assessment of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab. 2008;93:539-542
8. Davis SR, Panjari M, Stanczyk FZ. DHEA Replacement for Postmenopausal Women. J Clin Endocrinol Metab;96:1642-1653
9. Marti-Carvajal AJ, Sola I, Lathyris D, Salanti G. Homocysteine lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2009:CD006612
10. Miller ER, 3rd, Juraschek S, Pastor-Barriuso R et al. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. Am J Cardiol;106:517-527
11. Assessing cardiovascular risk: what the experts think. Best Practice Journal (www.BPAC.org.nz) 10-21
12. G.R. Cooper PWFW, G.L. Myers, S.M. Grundy, Labarthe aDR. Lipoprotein (a) and Cardiovascular Disease Risk. Emerging Biomarkers for Primary Prevention of Cardiovascular Disease and Stroke AACC Press, 2009