

Clinical Biochemistry

Ten Things Clinicians and Patients Should Question

by

Canadian Society of Clinical Chemists

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1 **Don't order HFE-related hemochromatosis molecular testing unless BOTH the ferritin (above upper limit of normal), and the transferrin saturation (above 45%) are elevated.**

The overall clinical penetrance in terms of iron overload-related clinical symptoms is less than 30% in HFE-associated hereditary hemochromatosis. Ferritin is the most reliable biomarker to quantify iron load but may be falsely elevated during an acute phase response as in inflammation, stress, or infections. In the investigation of clinical hereditary hemochromatosis, don't order HFE C282Y testing unless BOTH the ferritin and the transferrin saturation are elevated. A normal ferritin rules out a clinically treatable hemochromatosis syndrome and is therefore an appropriate first line test. Transferrin saturation can be added on to the same blood sample if the ferritin is elevated.

2 **Don't repeat HbA1c testing within 3 months of a previous result.**

The lifespan of a red blood cell (RBC) is approximately 90-120 days, thus the effects of a patient's change in behaviour, diet, or newly adjusted medications will not be reflected in the HbA1c measurement until most of the previous RBCs in circulation are replaced (~90 days). Therefore, testing at time intervals earlier than 3 months does not allow enough time to pass to reach the treatment target or new steady-state. Overtesting may lead to unnecessary regimen changes, adverse effects, and higher costs. Testing at 6-month intervals may be considered when glycemic targets are consistently achieved. In pregnant patients with pre-existing diabetes, more frequent HbA1c measurements may be appropriate based on clinical guidelines (i.e. at each trimester).

3 **Don't order tissue transglutaminase IgG antibody or Deamidated Gliadin Peptide (DGP) antibody testing in the initial screening for Celiac Disease.**

Tissue transglutaminase IgA antibody (anti-tTG IgA) is the recommended first-line screening test for celiac disease as it provides the best diagnostic sensitivity and specificity. Serum IgA concentrations should be considered to rule out IgA deficiency. The addition of tissue transglutaminase IgG antibody (anti-tTG IgG), or deamidated gliadin peptide antibodies (anti-DGP IgG or IgA) in the initial screening will reduce the diagnostic performance and may cause misleading results. In particular, testing of anti-DGP antibodies result in a higher false positive rate that can lead to further unnecessary testing and/or endoscopy. Anti-tTG IgG and anti-DGP IgG testing should be reserved for individuals with IgA deficiency. Implementation of an automated reflexive algorithm in the laboratory can streamline the ordering process.

4 **Don't repeat renal calculi analysis within 3 years.**

Renal calculi analysis is a laborious and expensive test. In Alberta, 16% of repeated renal calculi tests occurred within ~5 years (88% were repeated within 3 years). However, the repeated test only rarely demonstrated a change in stone composition (5.5% of all repeats). Similarly, the first epidemiology study of urolithiasis in New Brunswick found that 14% of renal calculi tests were repeated within 3 years, and in all cases, there was no compositional change. Both Canadian Urological Association and American College of Physicians do not recommend routinely monitoring calculi composition for recurrent stones. A calculi analysis may be repeated if there are significant systemic and/or urinary abnormalities, or patients do not respond to treatment.

5 **Don't order random urine protein electrophoresis to screen for a monoclonal gammopathy.**

Screening for monoclonal gammopathies should only be performed in patients with unexplained "CRAB" symptoms (hyperCalcemia, Renal insufficiency, Anemia, or lytic Bone lesions) or diseases associated with monoclonal gammopathies. For such patients, serum protein electrophoresis (SPE) should be the initial screening test with follow-up immunofixation electrophoresis (IFE) if indicated. If SPE is negative, serum free light chain (SFLC) testing may be ordered since SPE/IFE + SFLC offers the best sensitivity for detection of monoclonal proteins. If SFLC testing is not available, or if amyloidosis is suspected, 24-hour urine protein electrophoresis (UPE) may be ordered with follow-up IFE if indicated. Random UPE should not be ordered as there is very limited evidence supporting its sensitivity.

6 Do not routinely order iron profile (iron, UIBC/TIBC, transferrin saturation) in the investigation of iron deficiency. A low ferritin result is highly probable for iron deficiency, and thus, there is no added value in performing an iron profile.

Ferritin is recognized as the most sensitive and specific marker of iron storage, and low ferritin alone is diagnostic of IDA in the general population, i.e. uncomplicated cases of IDA. The measurement of iron is a poor biomarker for IDA as it is susceptible to preanalytical factors such as diurnal variation, diet, and exercise, and ultimately does not represent iron storage. In patients with complicating comorbidities (e.g. infection, autoimmune disease, kidney disease, or cancer), ferritin is an acute phase reactant and may be falsely elevated. In this setting, ordering a fasting transferrin saturation is useful to help diagnose iron deficiency together with the ferritin result.

7 Do not order AST or Urea for routine screening in the initial workup of common diagnostic investigations. Review order sets regularly for diagnostic utility and uncouple low value routine tests (i.e. AST and ALT).

Routine biochemical screening frequently bundles redundant tests when one is sufficient from a screening, diagnostic or monitoring perspective. For example, ALT is a more specific test to detect liver injury compared to AST. AST is rarely needed if the ALT is normal, and AST should only be ordered by physicians with experience in treating liver disorders or monitoring of diagnosed liver fibrosis with a validated score (e.g. FIB-4). Creatinine alone is sufficient to check kidney function because laboratories automatically report estimated GFR; urea is often an unnecessary addition. Uncoupling bundled tests within order sets for initial screening reduces low value testing.

8 Do not routinely order both total and direct bilirubin testing on patients.

Direct bilirubin is a sub-component of total bilirubin. Total bilirubin assays measure both direct (conjugated and delta) and indirect (unconjugated) bilirubin. When total bilirubin is low or undetectable there is no value in measuring the direct bilirubin level. Limiting direct bilirubin testing to individuals with elevated total bilirubin has been demonstrated to decrease unnecessary testing. Additionally, implementation of a laboratory reflexive testing algorithm for infants, where direct bilirubin is automatically tested when total bilirubin is elevated, has been proposed to accelerate the identification of biliary atresia while also reducing the need for additional blood collections.

9 Do not routinely order urine drug screens for evaluation of patients with substance use disorders (1) without a clinical care plan directed by the test results, (2) without laboratory input, especially on the ability of immunoassay results to support the clinical management.

Urine drug tests (UDTs) have a limited but important role in managing patients with substance use disorders and should be guided by a care plan that will be meaningfully changed by the results. The unregulated drug market is encumbered by an evolving milieu of drug additives and contaminants which can complicate the interpretation of simplistic urine drug testing. In particular, testing by immunoassay without confirmation by mass spectrometry can fail to detect potent drugs that can be harmful. Immunoassays are also well known for false positives that can mislead patient management. Mass spectrometry testing delivers the most reliable and comprehensive results, but with delayed turnaround time. Clinicians that are considering drug testing should consider consulting with the laboratory for advice on choosing the best test methodology available and for help interpreting the results.

10 Don't order allergen specific IgE (sIgE) tests unless indicated by the patient's clinical history and correlated to specific exposures.

Positive allergen specific IgE (sIgE) tests represent sensitization and not necessarily clinical allergy. This means that IgE against specific allergens may be detectable even when a patient is clinically tolerant of a given food or environmental allergen. The positive predictive value (PPV) of this testing is low unless the specific allergen tests are carefully chosen based on a review of the patient's clinical history correlated to specific food and/or environmental exposures. Screening panels and indiscriminate batteries of specific allergen tests should be avoided. Positive specific allergen test results in the absence of clinical allergy lead to incorrect diagnosis of allergy, unsuitable treatment and, in the case of food allergies, inappropriate dietary restrictions with potentially negative health consequences.

How the list was created

The list was developed by the Canadian Society of Clinical Chemists (CSCC) membership, as part of the CSCC Utilization Special Interest Group. All CSCC members were invited to participate and a working group of 39 clinical & medical biochemists was created. Members put forth 12 recommendations for discussion and further modifications.

To determine consensus, an anonymous modified Delphi process (via SurveyMonkey) was used. The 39 working group members rated their agreement with each of the 12 recommendations, and provided feedback for improvement during the Delphi process. Ultimately, 10 of the 12 recommendations reached Delphi consensus (>80%) and passed external review.

Members of the Canadian Association of Medical Biochemists (CAMB) participated in developing this list, and we thank the CAMB board of directors for their review and support of these recommendations. The list had final approval by the CSCC Council in December 2023.

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About the Canadian Society of Clinical Chemists

The Canadian Society of Clinical Chemists (CSCC) is a national scientific and professional society representing clinical biochemists across Canada. It provides leadership in the practice of clinical biochemistry and clinical laboratory medicine through service, education and research. The Society establishes standards for diagnostic services and serves as a resource to government, industry and healthcare associations, in the interest of the general public. Clinical Biochemists work in a variety of settings, including hospital, community and reference laboratories and in industry.



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