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Choosing Wisely Canada recommendations for clinical biochemistry: test ordering for sustainable and high-quality patient care☆

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ABSTRACT

Laboratory Medicine is growing at a rapid rate in both the breadth of unique tests and the total number of tests performed per year. Inappropriate overutilization of laboratory tests can lead to patient harm, excessive environmental waste and increased carbon emissions. A focus on reducing inefficiencies in healthcare is needed to ensure a robust and sustainable healthcare system. To promote laboratory sustainability, the Canadian Society of Clinical Chemists (CSCC) has developed ten recommendations related to medical tests within clinical

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biochemistry. These recommendations are designed as 'low-hanging fruit' that should be adopted by both hospital and community laboratories. By implementing automated strategies and/or educational approaches to reduce misuse of laboratory resources, clinical laboratories can move toward a more sustainable model that improves patient care. This list of recommendations, created for Choosing Wisely Canada, covers tests for diabetes, celiac disease, monoclonal gammopathies, iron disorders, liver disorders, kidney disorders, substance use disorders, and allergen testing.

1. Introduction

Clinical laboratory overutilization is a widespread problem in modern medicine that is characterized by unnecessary diagnostic tests, subsequent treatments, and associated harms. These harms are multifaceted impacting patients physically, psychologically, and financially [1]. Overuse also contributes to systemic inefficiencies and broader societal challenges such as the climate crisis [2,3]. These contributions are not insignificant, with healthcare systems or services responsible for 5 % of the net global carbon emissions [2] with significant contributions stemming from laboratory testing and associated processes. Notably, before the COVID-19 pandemic, healthcare expenditures were the leading cause of bankruptcy in the United States [4,5] underscoring the financial impact of such inefficiencies. Reducing the overutilization of laboratory tests provides a unique opportunity to enhance patient care, optimize the healthcare system as a whole, and mitigate the environmental impact.

Choosing Wisely Canada is a national campaign that partners with 88 Canadian clinical societies to identify and develop recommendations to reduce overuse or misuse of tests and treatments that do not add value to patient care (https://choosingwiselycanada.org/about/). Experts in the field rigorously review these recommendations and this allows for the mobilization of clinicians and organizations to implement change into routine practice. Therefore, we convened a Canadian working group to develop and refine recommendations to avoid low-value testing, as well as improve the efficiency and environmental sustainability of clinical biochemistry laboratories. Within this framework, the Canadian Society of Clinical Chemists (CSCC) has developed a list of 10 Choosing Wisely recommendations related to clinical biochemistry laboratory tests, led by the CSCC Utilization Special Interest Group.

2. Methods

All CSCC members were invited to participate and a working group of 39 clinical and medical biochemists was created for this initiative. To ensure diversity and a broad perspective, the working group included members from across Canada and had representation from academic hospitals, community hospitals, and private laboratories. In the initial phase, several working group members with content matter expertise conducted a literature review and put forth evidence-based recommendations. These recommendations were reviewed for quality and strength of evidence, and 12 recommendations advanced to the evaluation stage. The evaluation stage required members to engage in an anonymous, modified Delphi process to determine consensus. This involved all 39 working group members rating their agreement on a 5-point Likert scale (i.e. strongly agree, agree, neutral, disagree, strongly disagree) for each recommendation. Written feedback was encouraged in each Delphi round to help improve the recommendations for subsequent voting rounds. Ultimately, 10 of the 12 recommendations reached Delphi consensus, with a score of 4 or 5 among greater than 80 % of the working group members (consensus score defined a priori). The following 10 recommendations were reviewed and approved by Choosing Wisely Canada and represent excellent 'low-hanging fruit' initiatives to reduce unnecessary testing in the healthcare setting.

3. Recommendations

1. Don't order HFE-related hemochromatosis molecular testing unless BOTH the ferritin (above the 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 [6,7]. 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 [8,9]. In the investigation of clinical hereditary hemochromatosis, don't order HFE C282Y testing unless BOTH the ferritin and the transferrin saturation are elevated [10]. A normal ferritin rules out a clinically treatable hemochromatosis syndrome and is therefore an appropriate first line test [11]. Transferrin saturation can be added 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 hemoglobin A1c (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 [12–14]. 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 [15,16]. In pregnant patients with pre-existing diabetes, more frequent HbA1c measurements may be appropriate based on clinical guidelines (i.e. at each trimester) [17].

3 Don't order tissue transglutaminase IgG antibody (anti-tTG IgG) or Deamidated Gliadin Peptide antibody (anti-DGP) 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 [18–20]. Serum IgA concentrations should be considered to rule out IgA deficiency [18]. 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 results in a higher false positive rate [18] 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 [18–20]. 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) [21]. However, the repeated test only rarely demonstrated a change in stone composition (5.5 % of all repeats) [21]. 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 [22]. Both Canadian Urological Association and American College of Physicians do not recommend routinely monitoring calculi composition for recurrent stones [23,24]. 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 the detection of monoclonal proteins [25–28]. 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 [26]. Random UPE should not be ordered as there is very limited evidence supporting its sensitivity.

6. Do not routinely order iron profile (iron, Total Iron Binding Capacity (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 iron deficient anemia (IDA) in the general population, i.e. uncomplicated cases of IDA [29]. 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 [30]. 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 [31,32].

7. Do not order aspartate aminotransferase (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 alanine transaminase (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) [33]. Creatinine alone is sufficient to check kidney function because laboratories automatically report estimated GFR; urea is often an unnecessary addition [34,35]. Uncoupling bundled tests within order sets for initial screening reduces low value testing [36].

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 [37]. Limiting direct bilirubin testing to individuals with elevated total bilirubin has been demonstrated to decrease unnecessary testing [38]. 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 collection [39].

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 screens 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 [40–43]. The unregulated drug market is encumbered by an evolving milieu of drug additives and contaminates which can complicate the interpretation of simplistic urine drug testing [43]. In particular, testing by immunoassay without confirmation by mass spectrometry can fail to detect potent drugs that can be harmful [43]. Immunoassays are also well known for false positives that can mislead patient management [41]. 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 [44,45]. 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 [46,47]. Screening panels and indiscriminate batteries of specific allergen tests should be avoided [44,45]. Positive specific allergen test results in the absence of clinical allergy led to incorrect diagnosis of allergy, unsuitable treatment and, in the case of food allergies, inappropriate dietary restrictions with potentially negative health consequences [44,45].

4. Discussion

The CSCC has developed 10 utilization recommendations, in collaboration with Choosing Wisely Canada, that have the potential to (i) enhance clinical decision making by eliminating tests of low utility (ii) minimize redundant or unnecessary tests to conserve laboratory resources and limit waste generation (iii) improve patient experience by ensuring fewer false positive or false negative test results and (iv) decreasing the carbon footprint of laboratory operations and downstream healthcare practices to support environmental sustainability. The goal is to encourage all clinical laboratories to adopt and implement these recommendations within their institutions to maximize their impact.

Choosing Wisely Canada has over 550 appropriate utilization recommendations from numerous professional healthcare societies, many of which focus on laboratory testing.

[https://choosingwiselycanada.org/recommendations/]. Over-utilization of laboratory testing is a common, systemic problem in modern-day medicine, with estimates indicating 16 % to 56 % of clinical laboratory tests are unnecessary [48]. Such overuse can lead to a cascade of inefficiencies including follow-up testing, specialist consults, inappropriate treatment, and/or additional procedures. These activities strain healthcare resources and waste valuable time while increasing the risk of false positive or false negative test results. The impact on patients can vary; at minimum, it wastes time and resources, but for some it results in physical, psychological, or financial harms [1]. The impact on the environment is also significant due to unnecessary use of disposable plastics, tubes, syringes, gloves, laboratory-grade water, and/or laboratory reagents. Moreover, the carbon emissions generated by manufacturing, transporting and disposing of these materials exacerbate the healthcare system's ecological footprint. Ultimately, implementation of these Choosing Wisely recommendations will promote a more efficient system that maximizes the benefits and minimizes the risks and waste.

Numerous review articles have highlighted the importance of proper implementation strategies to ensure a successful utilization initiative [49–51]. There is no standardized or singular recommended approach to implementing change in a hospital or community laboratory setting [50]. Many well-designed studies will follow some form of a quality improvement framework that creates a multi-disciplinary team to

identify a problem, analyze the causes and implement a continuous improvement plan as a sustainable solution [51,52]. Arguably, the most important part of the implementation is tracking the outcome measure (s) and any negative consequences that the change may have caused [1]. Follow up analysis and subsequent cycles of improvement would be used to reach an optimal state of change. The following examples below are a few strategies often utilized in practice, along with clinician education, to implement a successful utilization initiative.

Laboratory auto-cancellation rules are one option to help provide efficiency in the clinical laboratory system. Clinicians may find it easier to re-order a test than to look up a previous result. Modern-day laboratory and/or hospital information systems can calculate the time since the previous test result, trigger auto-cancellation rules based on a predefined timeframe, and display the date and the result of the previous test for that patient. These automated solutions can be extremely efficient at controlling unnecessary repeat testing and do not rely on individuals to act as the gatekeeper, nor require consistent educational teaching to ensure success [12,50]. Ideally, such strategies prevent the test order upfront to avoid collection of unnecessary blood from the patient or use of unnecessary supplies such as blood collection tubes. However, flexibility needs to be considered during the implementation stage of such an automated solution. If the auto-cancellation rules are too strict, it may cause unwanted delays and harm to patients. For example, if an auto-cancellation rule is setup for HbA1c at 90 days since the prior result, and a patient arrives at 89 days for blood collection, the system will cancel the collection despite no difference in the result between 89 or 90 days. Thus, flexibility in the form of a bypass mechanism for special cases or a less strict auto-cancellation rule (e.g. 80 days instead of 90 days for HbA1c) can allow for the variability and exceptions that occur in real practice. Setting up a robust, comprehensive strategy will help minimize negative impacts to patients or clinicians, and its success will help promote further quality improvement initiatives.

Another automated strategy that can help to regulate testing is reflex algorithms. The result of an initial 'first-line' test can dictate whether a follow-up test is indicated and processed, or is not indicated and cancelled [53,54]. For example, direct bilirubin testing can be set as a reflex test that will only occur when the total bilirubin result is elevated [37–39]. These automated solutions are helpful in a fast-paced system; they do not require the clinician to check previous results before deciding on subsequent testing, and they avoid the situation of extra tests being ordered and performed upfront to ensure the patient does not have to return for subsequent blood draws. This allows the right test to be completed, for the right patient, at the right time using optimal resources.

Lastly, decoupling of tests from routine order entry, order-sets or panels can be an effective strategy to reduce unnecessary testing. Typical examples of this approach relate to de-coupling tests such as AST and ALT, CK and troponin, as well as urea and creatinine. These tests do not need to be paired in all situations, yet doing so causes a significant amount of unnecessary testing in clinical practice [33–36]. This does not mean that AST, CK, or Urea have no clinical value, rather that they are valuable when ordered thoughtfully under the right circumstance.

The relative contributions of various automated test utilization strategies on the environment have been demonstrated [55–57]. When applying repeat interval limits to high-volume tests, reflex testing and/or decoupling of tests, laboratories were able to directly reduce reagent use, energy consumption, and waste. The carbon footprint, measured as carbon dioxide equivalent (CO_2e) emissions, of a common set of tests (complete blood count, differential, creatinine, urea, sodium, potassium) that were inappropriately ordered in general surgery patients was shown to be 332 g CO_2e per person. Adding a liver panel (liver enzymes, bilirubin, albumin, international normalised ratio (INR)/partial thromboplastin time (PTT)) resulted in an additional 462 g CO_2e per person [56]. Another study showed the overall carbon footprint of five common hospital tests (CBC, coagulation profile, urea/electrolytes, C-reactive protein and arterial blood gases) ranged between 0.5 to 116 g CO_2e per test, equivalent to driving a car between 3 m and 0.8 km per 1,000 tests ordered [57].

Despite the use of automated utilization strategies, each may have unforeseen limitations that warrant discussion. For instance, in practice, some ordering physicians will simply reorder tests that were auto-cancelled, bypass the repeat interval limit rule or request an add-on to an existing specimen by reaching out to the clinical laboratory. This behavior can be a challenge especially in settings where information systems can only cancel once or have limited lookback capabilities. As a result, these tests are performed, undermining the purpose of the cancellation and contributing to increased waste of resources, excessive use of phlebotomy supplies, added patient burden, and potential delays or disruptions in care. These examples highlight that automation alone is not foolproof. To be effective, such strategies must be targeted with a physician champion in each area to help with education, ongoing quality monitoring, peer comparison, and multi-layered interventions that support long-term behaviour change to reinforce responsible test utilization.

The CSCC working group was able to reach consensus on ten recommendations of high value that can improve utilization in clinical laboratories. The main limitation to the Delphi process was that the group was unable to reach consensus on the following two proposed recommendations: a) Do not measure venous blood gases (VBG) in outpatients or as a first-line test for investigation of acid-base abnormalities, and b) Do not order both a serum bicarbonate and chloride except to investigate for a metabolic acidosis. Generally speaking, the working group found the two recommendations contradicted each other and needed clarity, and there was not sufficient evidence to identify these recommendations as wide spread issues that needed to be fixed. In the pediatric setting or rural community, VBG testing may need to be the first-line test to accommodate turnaround time expectations, or a lack of instrumentation. In addition, reducing chloride ordering in (b) may not lead to a real reduction in testing as chloride is analytically measured with other electrolytes simultaneously. Further work on these potential recommendations at local institutions would be needed to identify the impact and benefits.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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