Preamble

The purpose of this guideline is to ensure patient safety and improve patient care by providing guidance on the timeliness of reporting significant, abnormal test results in the field of Metabolics/Biochemical Genetics. This guideline is intended as an aid as laboratories develop or revise their own specific standard operating procedures and policies.

While guidelines for reporting such results exist for other clinical laboratory specialties, there are no consensus guidelines for reporting such results in Metabolics/Biochemical Genetics in Canada. The Centers for Disease Control have recently published good laboratory practice recommendations for Biochemical Genetic laboratories in the United States\(^1\), clearly stated that the Clinical Laboratory Improvement Amendments (CLIA) regulations for postanalytic systems assessment requirements also apply to Metabolics/Biochemical Genetics testing, and should include (among other criteria):

“Procedures for notifying the test requestor about the test results, including routine tests, urgent testing, abnormal results, and critical values or alert values that warrant immediate medical attention”

A recent informal survey of Metabolics/Biochemical Genetics laboratories across Canada shows variation in reporting practices and communications of such results, which is cause for concern. While we assume that patient care and good clinical acumen should guide communications between the laboratory and referring physicians, this guideline seeks to inform a minimum standardized approach.

For most clinical situations, the standard reporting mechanism used by individual laboratories typically meets the needs of patients and clinicians, as it should follow directly from standard operating procedures, defined laboratory workflows and expected turnaround times for routine testing. Certain circumstances, however, do present exceptions to routine reporting practices. In order to facilitate a timely response to one or more actionable results, the circumstances outlined below may require expedited reporting processes.
These circumstances may include:

1. Test results which deviate significantly from reference values that fall within known disease ranges or are unexpected based on the clinical information available to the testing laboratory.

2. Test results that indicate a new diagnosis (an enzyme result or an analyte result with high positive predictive value), whether or not that diagnosis was suspected previously by the requesting physician.

3. Any abnormal test result on a previously undiagnosed patient that is pathognomonic for a known disorder or syndrome.

4. A result that impacts the decision to treat or adjustments to current treatment.

5. Any test result used for monitoring therapy that has immediate treatment implications, or places that patient at increased risk of acute mortality or morbidity.

6. A request to expedite the reporting of a test-specific result to meet a defined clinical need, often based on the result being actionable in the management of the patient.

**Classes of Abnormal Metabolics/Biochemical Genetics Test Results**

The following categories (based on a recent review about the need for harmonizing critical result management in laboratory medicine\(^2\)) represent different classes of abnormal test results commonly used in Laboratory Medicine. The following discussion will use the same terminology to describe how they pertain to the Metabolics/Biochemical Genetics laboratory, while highlighting the required attention needed that is distinct from routine result reporting. In each case, examples are provided regarding the types of Metabolics/Biochemical Genetics test results that would fall into each category, as well as recommendations on the timeliness, means and documentation of such communication.

**A. Critical Results**

In laboratory medicine, a “critical result” is defined as a laboratory result representing a pathophysiologic state so abnormal that it is life-threatening if action is not taken quickly and for which effective action is possible\(^3\). This term has become synonymous with the establishment of a short list of critical limits that automatically trigger the clinical laboratory to urgently and personally communicate the result to the treating physician. In the Metabolics/Biochemical Genetics laboratory, results of this nature may indicate a significant risk of a life-threatening or serious medical event due to an underlying metabolic disease in a previously undiagnosed patient. Prompt medical intervention may therefore be required. As such, these results are generally considered “critical” and should be called directly and immediately to clinicians or the referring laboratory within four (4) hours. As in other laboratory specialties, efforts to communicate these results should not cease until successful, with all attempts made, including the...
actual communication, being clearly and consistently documented in the patient file, laboratory information system or in alignment with some other lab-defined practice.

The full use of the term “critical”, as typically observed in laboratory medicine, may not be warranted however, as the final classification of a laboratory result as critical should be determined by the Laboratory Head (or designate) based on the laboratory reference range(s), the patient’s analytical test history and any other available clinical information. For this reason, not all laboratory results falling into the “critical” result designation will be classified by the laboratory as needing to be immediately communicated. It is strongly recommended that each laboratory, in consultation with clinical staff, develop written policies around reporting critical results including specific examples, with the timing and means of such communication. Furthermore, unlike other laboratory specialties, the specific requirements of the Metabolics/Biochemical Genetics laboratory geneticist/specialist to provide an interpretation of the result may restrict laboratory staff from immediately calling out critical results and delaying the immediacy of such communication. Therefore, policies should include all contingencies including unavailability of the geneticist/specialist to provide an interpretation, and communication of critical preliminary findings by designated laboratory staff. As such, the roles and responsibilities of each individual within the path of reporting out critical results should be clearly defined and stated to ensure communication is consistently and efficiently achievable within all reasonable scenarios.

**Examples of Critical Results**

Any of the findings found within a previously undiagnosed patient should constitute immediate communication:

- the presence of succinylacetone on urine organic acid analysis/quantitative method that is diagnostic of type I tyrosinemia
- increased CSF:plasma glycine ratio diagnostic of nonketotic hyperglycinemia
- any result judged to be of sufficient specificity to diagnose a condition with high likelihood and with immediate treatment implications, for example:
  - elevated branched-chain amino acids with evidence of allo-isoleucine on plasma amino acid profile and/or urine branched-chain keto acids on urine organic acid analysis indicating maple syrup urine disease
  - elevated glutamine ± alanine with high citrulline and low arginine indicating either citrullinemia or argininosuccinic aciduria
  - low or absent galactose-1-phosphate uridylyltransferase enzymatic activity indicating classical galactosemia

**B. Significantly Abnormal Results**

A “significantly abnormal result” in laboratory medicine is defined as a non-emergent, non-life threatening result that needs attention and follow-up action as soon as possible, but for which timing is not as crucial as a critical result\(^2\). Within the Metabolics/Biochemical Genetics laboratory, results of this nature may include:
1. Results diagnostic for a specific disorder where the patient is not at increased risk of acute mortality or morbidity.
2. Results that deviate significantly from the laboratory’s reference ranges but by themselves (or in combination with other known results) are not sufficient to provide a specific diagnosis.
3. Abnormal results that have direct implications for the need for prompt follow-up or reflexive testing. When unexpected, these results suggest the possible need to re-evaluate the patient’s clinical condition without waiting for routine report communication.

These results should be communicated during working hours and within one business day. They may be faxed or phoned to the referring physician or referring laboratory. Such attempts by the laboratory to communicate directly with the clinician’s office or referring laboratory should cease only once the results have been delivered by their routine means (electronic, fax or hard copy).

It is recommended that each laboratory, in consultation with clinical staff, develop written policies around reporting significantly abnormal results including specific examples and the means of communication. Furthermore, the roles and responsibilities of each individual within the path of reporting out significantly abnormal results should be clearly defined and stated.

**Examples of Significantly Abnormal results**

Any of the findings found within a previously undiagnosed patient should prompt communication:

- increased N-acetylaspartic acid on urine organic acid analysis/quantitative method that is diagnostic of Canavan disease
- low or absent enzymatic activity that suggests or indicates a lysosomal storage disorder
- positive MPS spot testing or clearly abnormal urinary oligosaccharides
- positive isoelectric focusing of transferrin

**C. Expedited or Priority Testing/Reporting:**

Results of this nature may include test results for which there is a prior agreement between the clinician and laboratory geneticist/specialist, or where there is a specific clinical need for such testing (often judged by whether the result is actionable in the management of the patient). It is recommended that this be dealt with on a case-by-case basis, or that the laboratory, in consultation with clinical staff, develops written policies around reporting expedited or priority results including specific examples and the means of communication.

**Examples of Expedited or Priority Testing/Reporting**

- follow-up testing of a positive newborn screen result
- tests on an acutely ill patient (either previously undiagnosed, or a known, diagnosed patient)
- carrier testing on a couple in which the woman is currently pregnant

Guideline for the Reporting of Significant Laboratory Results in Metabolics/Biochemical Genetics
Role & Responsibilities of the Laboratory and the Ordering Clinician

Given that critical, significantly abnormal, and expedited or priority test results can have direct and serious consequences to patient welfare, it is mandatory that such results be communicated in a timely and reasonable fashion to ensure appropriate clinical response can occur. The results should be communicated to the ordering and/or treating physician, or the referring laboratory if no referring physician has been clearly stated. The ordering clinician, regardless of scope of practice, has a professional responsibility to provide the testing laboratory with sufficient contact information that will allow direct communication of these results, at any time. It is recommended that there should be a written policy that defines the specific sequence of actions and escalations if contact is not made within the recommended timeframes.

Acknowledgements

Thanks to the CCMG Metabolics committee, and to Drs. Michael Geraghty, David Sinasac, Hilary Vallance and Murray Potter, and Ontario Association of Medical Laboratories.

References