More than half of abnormal results from laboratory tests ordered by family physicians could be false-positive

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Family physicians are becoming more aware that non-selectively ordering a high number of laboratory tests per requisition can be harmful to patients and our health care system, as it leads to an increased number of abnormal test results that will consist of both true- and false-positive results.[1] We know that false-positive test results harm patients by causing unnecessary anxiety and psychosocial issues, as seen in breast cancer,[2] prenatal,[3] and cystic fibrosis[4] screening. Overuse is also harmful to the health care system owing to the billions of dollars in costs associated with repeat and follow-up testing in North America.[5,6] The more laboratory tests are ordered irrationally, the more likely we will see false-positive results within our abnormal test results.

Estimating likelihood of false positives

The likelihood of false-positive test results can be estimated: most laboratory tests that do not have disease-specific cutoff values have a "normal" *reference range,* defined as the central 95% interpercentile range in a Gaussian distribution for a group of healthy volunteers.[7-9] In other words, if healthy individuals were randomly selected from a specific population to receive laboratory tests (eg, for alanine aminotransferase, ferritin, or urea levels), 5% of the test results would be flagged as abnormal. By this definition, one would reason that within the 5% of abnormal test results obtained from healthy individuals, 100% are false-positive. If the same tests were conducted in diseased individuals, one would expect that more than 5% of the test results would be abnormal, as there is a higher pretest probability that the test results would fall outside the normal reference range. We would then expect less than 100% of the abnormal test results to be false-positive, as there should be true-positive test results present to suggest illness. Consequently, if you order laboratory tests inappropriately (eg, order a high number of laboratory tests for a patient who is asymptomatic or has a low pretest probability of disease), you will have a much higher chance of receiving false-positive abnormal test results than if you ordered laboratory tests more selectively (eg, order only the tests necessary to assist in the diagnosis of a clinical presentation). However, what is the extent of false-positive test results in family medicine?

Mean abnormal result rate

Our group recently developed the mean abnormal result rate (MARR) metric,[10] which can also be used to estimate the expected proportion of false-positive and true-positive results within abnormal test results. The principle behind the MARR is that most laboratory tests have a reference range defined by the 95% interpercentile range, as described earlier.[9,10] A higher MARR suggests increased laboratory test ordering selectivity, which in turn would suggest fewer false positives within the abnormal test results. In 2013, 1340 family physicians in Calgary, Alta, had a MARR of 8.6%.[10] Recall that 100% of abnormal results are expected to be false-positive if the physicians only ordered laboratory tests for healthy patients (MARR = 5%). For a patient population that has a higher pretest probability of disease where the ordering physician group had a MARR of 8.6%, approximately 58% of abnormal results are likely false-positive (expected MARR 5%; actual MARR 8.6%), with 42% that are likely true-positive. In fact, we would need to increase our laboratory ordering selectivity to greater than 10% before more than half the abnormal results are expected to be true-positive.

Calculating the MARR is a simplified approach to estimating the expected proportion of false positives within abnormal test results, and we understand that there are caveats. The MARR was calculated based on 39 laboratory analytes that do not have disease-specific cutoffs, instead of including all laboratory analytes available to us. Also, we have only attempted this for one medical specialty, jurisdiction, and patient population. What we see in Calgary might not reflect other jurisdictions. Further research using test results from other regions of Canada would be required to calculate the MARR for other family physicians and ordering groups to estimate the proportions of false-positive versus true-positive test results.

Knowing that there might be a high probability of false-positive test results in Calgary, we remind family physicians across Canada that in addition to ordering laboratory tests appropriately, they should approach all abnormal results with a differential diagnosis. If an abnormal laboratory test result is correct, it might or might not be indicative of disease, as it might be true- or false-positive. If the abnormal test result is unexpected based on the clinical evidence, or is severely abnormal, then the test should be repeated appropriately, or further investigations should be pursued. However, if the abnormal result is marginally outside the normal range, the clinical context and other evidence must be taken into consideration, as this might represent an expected

abnormal result—part of the 5% seen in healthy individuals. Conversely, the result might be owing to an error, and one must consider whether or not the result is from a preanalytical, postanalytical, or analytical error.[11] Therefore, physicians must consider the pretest probability of a positive result in a patient when deciding whether a given test result is likely true or false to prevent harm to patients.

Conclusion

Inappropriate laboratory test ordering leads to a higher probability of false-positive abnormal results. False-positive test results are harmful psychologically and financially to the patients and to the Canadian health care system, respectively. Knowing that there might be a high probability of false-positive test results in family medicine, we remind others to be good stewards of resources by looking critically at our laboratory test ordering practices.

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Competing interests
None declared

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References
1. College of Family Physicians of Canada. *Family medicine. Eleven things physicians and patients should question.* Toronto, ON: Choosing Wisely Canada; 2017. Available from: **http://choosingwiselycanada.org/family-medicine**. Accessed 2018 Jan 26.
2. Brodersen J, Siersma VD. Long-term psychosocial consequences of false-positive screening mammography. *Ann Fam Med* 2013;11(2):106-15.
3. Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med* 2000;154(7):714-8.
4. Tluczek A, Orland KM, Cavanagh L. Psychosocial consequences of false-positive newborn screens for cystic fibrosis. *Qual Health Res* 2011;21(2):174-86. Epub 2010 Sep 17.
5. Morgen EK, Naugler C. Inappropriate repeats of six common tests in a Canadian city: a population cohort study within a laboratory informatics framework. *Am J Clin Pathol* 2015;144(5):704-12.
6. Lyon AW, Greenway DC, Hindmarsh JT. A strategy to promote rational clinical chemistry test utilization. *Am J Clin Pathol* 1995;103(6):718-24.
7. McPherson RA, Mincus MR. *Henry's clinical diagnosis and management by laboratory methods.* 21st ed. Philadelphia, PA: Saunders Elsevier; 2007.
8. Rang M. The Ulysses syndrome. *Can Med Assoc J* 1972;106(2):122-3.
9. Jorgensen LG, Brandslund I, Hyltoft Petersen P. Should we maintain the 95 percent reference intervals in the era of wellness testing? A concept paper. *Clin Chem Lab Med* 2004;42(7):747-51.
10. Naugler CT, Guo M. Mean abnormal result rate: proof of concept of a new metric for benchmarking selectivity in laboratory test ordering. *Am J Clin Pathol* 2016;145(4):568-73. Epub 2016 Apr 26.
11. Naugler CT. *Lab literacy for Canadian doctors: a guide to ordering the right tests for better patient care.* Edmonton, AB: Brush Education; 2014.

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