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To: Hossein Sadrzadeh,
Chief of Clinical Biochemistry Section
South Sector, APL

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Dear Dr. Hossein Sadrzadeh,

I'm one of the leaders of a newly incorporated patient-run federal nonprofit, *Thyroid Patients Canada*. I'm a Calgarian myself, and I needed the Reverse T3 test three times in the past 4 years to manage a health crisis and change in thyroid therapy. I see that our new laboratory system is going forward in Alberta. I would like to help us strengthen our laboratories for thyroid-disabled Albertans' health.

Our community of patients, encompassing 3000+ users Canada-wide on social media, is concerned about the Alberta Precision Laboratory's patient-pay Reverse T3 (RT3) test cancellation policy. It recently came to our attention in early February.

I have published a blog post on our website Thyroidpatients.ca that publicly appeals this decision based on cost, risk, and ethical reasons, backed up with relevant citations. I have also inserted into the post a copy of this open letter.

https://thyroidpatients.ca/2020/02/21/think-twice-about-cancelling-patient-pay-reverse-t3-tests/

My letter today tries to condense its main points.

I conclude with some questions.

Reverse T3's metabolic activity

One of the most frequent arguments against RT3 testing is that it is "inactive."

I'm not sure if you have heard, but in 2019, RT3 was found to have non-genomic activities that mimic those of T4 hormone. T4's activities have been known since 2005, and science has progressed. RT3 appears to have similar actions as T4 at the same "integrin αvβ3" receptor on the cell wall. At concentrations relevant to RT3 levels in Nonthyroidal Illness (NTIS), RT3's pathological activity is implicated in the progress of various diseases such as

- cancer,
- disorders in blood clotting,
- bacterial infections,
- and vascular integrity.

See my public post for more information and various scientific citations.

This exciting development should grant more respect for RT3. Clinicians already using this test can now use it with this new information in mind. It is an inopportune time to phase out the RT3 test.

Thyroid clinical guidelines

As your Laboratory Bulletin dated January 27, 2020 accurately states, the clinical use of Reverse T3 is not yet articulated in guidelines nor guided by clinical studies.

However, the thyroid guidelines' silence on RT3 ought to be understood in light of the unethical gap in scientific literature.

Endocrinologists and other medical specializations have routinely excluded treated thyroid patients from studies of Nonthyroidal Illness (NTIS). Despite hundreds of studies on NTIS that involved RT3 measurements, research has neglected treated thyroid patients' RT3 levels in health and illness.

Therefore, silence in the guidelines regarding the clinical relevance of RT3 testing in the thyroid-disabled population is NOT based on evidence-based dismissal.

Instead, silence is based on decades of irresponsible neglect in research.

NTIS Risks indicated by RT3

According to the theory of the mechanisms involved in NTIS, treated thyroid patients' risk of non-recovery is increased in NTIS.

In NTIS, research places risk of mortality at its peak when RT3 levels are highest and T3 levels are lowest, and after T4 has fallen, before TSH rises.

In recovery, thyroid hormones are replenished as TSH temporarily rises above reference, but RT3 levels remain elevated until they are gradually cleared.

> "A rise in TSH levels precedes the onset of recovery from severe illness." (Van den Berghe et al, 2014).

Therefore, many thyroid patients may lack equipment needed for recovery from NTIS. If inappropriately higher RT3 and lower FT3 continue on a chronic basis (for weeks or months or years), patients at risk during severe illness include:

- The central hypothyroidism (CH) patient.
- The patient on TSH-controlling medications (including thyroid hormones).
- The patient with a very small amount of functional thyroid tissue.
- The patient with an unknown degree of thyroid damage who is only taking LT4 medication. As TSH rises, a higher ratio of T3:T4 is synthesized
- The patient with a history of fluctuating Graves' disease antibodies.

For our population, RT3 testing is more relevant to track NTIS progress so that therapy can be adjusted if or when necessary to aid recovery.

At this time, there is not enough evidence to either forbid changes to our therapy, nor to guide changes by RT3 levels and ratios.

Nevertheless, in light of the likelihood of a higher risk faced by these vulnerable patients, it is wiser to continue access to RT3 testing rather than remove access.

How have we found RT3 useful in monitoring therapy?

Many patients strongly believe RT3 is essential as a thyroid test because they have found increasing concentrations of it harmful to their health.

In light of new knowledge of RT3's activity on the cell wall, doctors should acknowledge the symptoms that line up with this hormone's known effects.

At bare minimum, RT3 has been a valuable troubleshooting test.

Its cost to the patient is a disincentive against overtesting in all but the affluent.

Most often, the TSH, FT3 and FT4 in light of clinical history and presentation is capable of diagnosing thyroid therapy difficulties.

RT3 provides additional metabolic information in our more complicated cases. RT3:FT4 provides an indication of the rate of T4 conversion to RT3, and the loss of T3 indicates the concurrent rate of conversion of T3 to T2 in cells, since the primary enzyme that converts T4 to RT3 prefers T3 as its substrate. The net effect of this metabolic emphasis is depletion of T3 in cells and blood, unless T3 is dosed. Within-reference RT3 is still clinically useful, because it is best interpreted in ratio with T4 its prohormone and T3 its sister hormone.

RT3 testing may be indicated as a metabolic assessment when the FT4 or FT3 loss is abnormal in light of dosing, or when an increase in dose, which we hoped would alleviate symptoms, has backfired and worsened health.

Possible Clinical Responses to RT3 results

Tests are often judged by their utility in modifying therapy in evidence-based ways.

For example, if the patient appears to be undergoing NTIS, the doctor's logical step is to reduce T4 dose, but not too far to entail health risk. This imitates the way the body naturally allows T4 to fall before the turning point of NTIS. Next, wise clinicians then allow time for the body and bloodstream to adjust to the reduced LT4 dose before adding thyroid hormone, given T4's clearance rate. After clearing any excess T4, they integrate T3 in dosing to aid NTIS recovery with both hormones. This is because in normal NTIS recovery, elevations in TSH above reference would naturally increase thyroidal T3:T4 synthesis ratio above the norm, since the secretion ratio is highly flexible and adapts to TSH (Citterio, et al, 2017).

Health benefits from RT3 testing

Our RT3 results keep us safe from harm and optimize our therapy.

Reverse T3 has been an aid to reducing excess T4 medication within reference range when the TSH is artificially suppressed by central hypothyroidism, medications or concurrent illnesses. RT3 levels can be a signal that FT4 in the upper-normal range or higher is too much for the individual to metabolize efficiently to T3.

In our patient community, we have observed that Inappropriately higher RT3 can signal the presence and severity of undiagnosed severe chronic illnesses, especially if the thyroid biochemistry pattern confirms NTIS. One of the body's earliest responses to a severe insult is to elevate RT3 while dropping FT3. This sign is noticeable within hours and remains during the crisis. This can be one of the early

signs that something is very wrong. It can also be slowly encroaching, such as a cancer, or a cardiovascular health problem like endothelial dysfunction.

If more doctors were to understand NTIS, our RT3 levels in context should prevent our distress from being dismissed too easily – and it should justify expenditure to discover the cause so it can be monitored and treated.

Thank you.

I realize this is a long letter, and I appreciate your attention to our health concerns.

Questions

On behalf of our community, I have some questions about going forward:

1) If the issue was one of cost covering the operations, materials, and shipping to the US lab where it was eventually tested, why didn't the price to patients increase to accommodate it instead of cancelling the test orders?

2) Is the decision based on Quality Management criteria such as those articulated in the "Provincial Plan for Integrated Laboratory Services in Alberta, February 2017" pages 33-36? If so, which criterion did it fail, Access, Timeliness, Accuracy and Quality, or Safety?

3) I have an image of an Operational Update in circulation that advises staff that "third party testing" of Reverse T3 will continue. Are there particular clinics or doctors in Alberta that have arranged "third party testing" for Reverse T3, and if so, can you please inform us of who they are so that our patients can access them and thereby access third party testing so that orders do not get cancelled?

4) Since this is a democratic society and we are taxpayers of our healthcare system, what recourse do we have as thyroid patients to appeal this decision regarding our health? Could we have consultations, and could our case be heard with a genuine chance of seeing a policy change? Is there an ethic of patient voice and patient rights in our health care system?

Sincerely,

Tania S. Smith, thyroid patient, researcher and writer, Thyroidpatients.ca