The Canadian Cystic Fibrosis Clinic Directors and other CF clinic physicians believe that it is a very positive step that CADTH has recommended elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) reimbursement for the treatment of some patients 12 years of age and older with cystic fibrosis (CF) with eligible mutations in CFTR.

However, we have some serious concerns about specific conditions for reimbursement that will preclude access for many patients who could greatly benefit from this therapy.

Initiation Reimbursement Condition 3:

The first condition of concern is the recommendation that patients must have a percent predicted FEV1 (ppFEV1) of ≤ 90% for coverage.

Cystic Fibrosis is a genetic, life-long, multi-systemic, and fatal disease. The median age of death of persons with cystic fibrosis (pwCF) over the past few years has ranged in the mid 30s – mid 40s,[1] with most pwCF dying from respiratory disease. However, the development of respiratory disease is a life-long process, and manifestation in other organ systems, such as malabsorption due to digestive system malfunction and cystic fibrosis-related diabetes contribute to the progression of the disease.

We know that physical manifestations of cystic fibrosis start early in life, with some symptoms, such as meconium ileus, pancreatic damage leading to pancreatic insufficiency, and congenital absence of the vas deferens, starting before birth. Lung abnormalities in CF start in early childhood, can be detected before patients become symptomatic and are initially too subtle to be measured by conventional pulmonary function testing (including FEV1) but can be seen on imaging and detected with other measures of lung function.[2,3] These changes are inherently cumulative and progressive. We also know that a significant factor in the decline in lung health over time is related to failure to return to baseline lung function after a pulmonary exacerbation.[4]

As with the management of other chronic diseases, one of the major paradigms of cystic fibrosis care is a strong emphasis on prevention and early treatment to prevent or delay the progression of the disease and the additive effects of chronic organ damage. To this purpose, multiple strategies have been adopted, including newborn screening, enrolment in specialty CF clinics with regular and frequent follow up, prompt treatment with pancreatic enzymes to prevent malnutrition, early initiation of physical therapy for airway clearance, eradication and treatment of initial infection with *Pseudomonas aeruginosa*, annual screening and prompt treatment of cystic fibrosis related diabetes, as examples. Over the years, these proactive strategies have led to increased survival and later development and slower progression of the sequelae of cystic fibrosis.

Although the clinical trials reviewed for the CADTH application for ELX/TEZ/IVA only enrolled patients with ppFEV1 between 40 – 90 %,[5,6] this was due to factors involved in clinical trial design and statistical considerations and was not based on real world clinical indications and clinical practice. FEV1 is only one measure of lung health and is widely recognized as being insensitive to detecting early CF pulmonary disease.[7] Although it is commonly available and has been used as a standard in both clinical

care and clinical trials, it is not the only test for determining lung health nor overall health in pwCF. It has particular and widely recognized limitations in those with early (but still important) lung disease.[8]

With regard to CFTR modulator therapy, ivacaftor (Kalydeco) is indicated and reimbursed for persons with the appropriate CFTR mutations regardless of FEV1, despite the core clinical trial for ivacaftor enrolling only patients with FEV1 of 40 – 90%.[9] For ELX/TEZ/IVA, data from the clinical trial showed that children ages 6-11 years with ppFEV1 ≥ 90% do show an increase in FEV1 when treated with ELX/TEZ/IVA along with improvements in other clinically meaningful outcome parameters.[10] Based on the observations with Ivacaftor, clinical experience in other countries where ELX/TEZ/IVA is currently being widely used, and in the 6–11-year-old study, a similar improvement is clinically plausible in persons ages 12 and older. Post-market approval studies will include persons ≥ 12 years of age with ppFEV1 >90%, so the data in this age group should be available shortly.

However, delaying coverage for those 12 years and older who do not meet this reimbursement condition while further data is reviewed and recommendations are adjusted could put them at an important disadvantage and risk for further irreversible disease progression during this period. During the delay, ongoing disease progression and potential for pulmonary exacerbation, nutritional factors, and effects on quality of life may have both short- and long-term repercussions on health and well-being.[11] It is not clinically reasonable and raises some ethical questions[12] with regards to equitable access if persons with CF covered by provincial and other public medication coverage plans to not have coverage based on the ppFEV1 ≤90% criterion. This inequity is inevitable if specific provinces elect to expand coverage to this group.

Other pwCF at risk for undertreatment using this criterion are adolescents. Due to early diagnosis and other advances in CF treatment, many adolescents with CF will have an FEV1 above the 90% cut off - in fact the median ppFEV1 in 6–17-year-olds with CF in Canada in the 2019 Cystic Fibrosis Canada Annual Data Report was 93.4%.[1] Thus, many adolescents may not be able to benefit from ELX/TEZ/IVA until their lung damage is significant enough to drop the ppFEV1 below the 90% threshold. This is a crucial period of development, both physically and otherwise, for young people with chronic disease. This is the time where there is an increased risk of accelerated decline in lung function (particularly in young women with CF) and development of other important complications of cystic fibrosis including CF-related diabetes. It is also a period where young people are making decisions about education, career, and relationships, all of which are affected by having a chronic disease and will have repercussions on their adult lives. Using ppFEV1 as the sole criteria for initiation reimbursement may prevent many adolescents with CF from benefiting from ELX/TEZ/IVA during this crucial period of growth and development.

There are factors other than CF lung disease that can affect FEV1 values. Genetic factors, ethnicity, height and growth, and other factors can influence where a person's baseline FEV1 falls in the general population distribution used form the equations used to calculate ppFEV1%. For example, due to these factors, someone with relatively mild lung disease could have a stable baseline ppFEV1 of 85% over several years and someone with a ppFEV1% of 95% could be experiencing a decline from their previous baseline of 110% and have a severe acceleration of their lung disease. Using an isolated ppFEV1 alone to determine coverage would not consider that using just a number for ppFEV1 can represent a variety of clinical realities.

We appreciate the statement that those with FEV1 <= 40 % should be included. These represent our most vulnerable patients with broad post hoc clinical trial data and real world experience showing robust positive responses. These patients were intentionally not enrolled in the clinical trials as their ability to demonstrate FEV1 improvement is limited by structural scarring, but clinical experience and study data very strongly supports their inclusion in the reimbursement recommendations. Although other groups of patients were excluded from the clinical trials due to study design factors, such as those colonized with *Burkholderia cepacia* complex or non-tuberculous mycobacteria, we are relieved that they are not also being excluded.

The effect on the mental health and quality of life of pwCF due to this criterion was also not explored in the CADTH report. CF clinicians and other members of the CF community have been discussing another ethical conundrum: whether pwCF and their families may feel forced to make difficult choices such as adjusting their treatments or using other measures to temporarily worsen their lung function to meet the arbitrary ppFEV1 criteria to qualify for coverage and to increase their chances of fulfilling the renewal criteria. Weighing the risks of a short-term drop in lung function versus the potential long-term benefits of therapy with ELX/TEZ/IVA, some may decide to take the risk.

In summary, the ppFEV1 ≤ 90% criterion was based on the design of clinical trials, not on clinical experience with the natural history of cystic fibrosis, the multisystemic nature of the disorder, the experience in other countries where ELX/TEZ/IVA is being used in a wider range of patients, or on experience with other CFTR modulators. These other factors support the use of ELX/TEZ/IVA in a wider range of pwCF, fitting in with the goal of treating and slowing the many manifestations of the disease as early as possible.

Initiation Reimbursement Condition 5:

The stipulation that patients should be stable, not be hospitalized, and not be receiving antibiotic treatment before receiving reimbursement may be unnecessarily restrictive for some patients with severe lung disease. While this recommendation may not be a problem for initiating therapy in patients with mild and moderate lung disease, some persons with CF with severe lung disease may require very frequent antibiotic treatments or may have prolonged hospitalizations. Trying to find a window to start ELX/TEZ/IVA may be difficult and result in an unnecessary delay starting therapy and seeing the potential clinical benefit. The initiation of ELX/TEZ/IVA outside of periods of clinical stability may be necessary to optimize functional status, as shown by clinical (Special Access Program) and research experience with patients with FEV1 <40%. Because prescribing ELX/TEZ/IVA was recommended to be limited to CF specialists, these physicians are able evaluate the risks and potential benefits of starting CFTR modulator therapy during a time of non baseline clinical vulnerability. Lack of coverage for initiating therapy during these situations may be countertherapeutic, leading to poorer outcomes.

Renewal Condition 1 and Renewal Condition 2:

We also have concerns about the requirement of an improvement in ppFEV1 of at least 5% for renewal of therapy after 6 months of treatment and annually.

As discussed above, FEV1 is only one measure of disease severity and response to therapy in cystic fibrosis.

The onset of effect and washout (loss of effect) time periods for CFTR modulators are short and the therapeutic effect is lost after the medication is discontinued. We do not know the potential effects of stopping and starting therapy with ELX/TEZ/IVA if reimbursement is lost and whether this could attenuate the long-term effects of the therapy. Potential adverse effects of discontinuing therapy include pulmonary exacerbation and further lung damage, poorer nutritional status, and destabilization of CF related diabetes, amongst others. In addition, the negative effects on the mental health of pwCF, the stress and insecurity regarding whether coverage will be halted due to falling short of the ppFEV1 cut-off, and the effects of all these factors on the quality of life and productivity was not discussed in the CADTH decision.

There is also the potential of someone with CF with a moderate response to the modulator gradually "losing ground" if ppFEV1 at renewal time is repeatedly compared to the baseline FEV1 response. We know that the decline in ppFEV1 with age is greater in persons with CF than in the non-CF general population. Real world studies have shown that CFTR modulators can decrease the rate of decline but there is still a decline. A person with a moderate response to CFTR modulator with an improvement in ppFEV1 of 6% from baseline, for example, could see this margin eroded with time if the decline in FEV1 on modulator therapy is still greater than the decline in the non-CF population, from which the ppFEV1 are calculated. Although that person with CF could still have a positive therapeutic effect from the medication slowing the ppFEV1 decline and showing improvement in other measures of health, they could lose coverage under the 5% criterion. In addition, complications of CF that can result in a sudden drop in FEV1, such as pneumothorax, massive hemoptysis or allergic bronchopulmonary aspergillosis, could inappropriately exclude a patient from continuing of ELX/TEZ/IVA.

The emphasis on ppFEV1 for renewal ignores other important CF related outcomes such as pulmonary exacerbations that have an impact on survival, quality of life and health care costs as well as impacting the rate of decline in lung function. Cystic fibrosis is a multi-systemic disease, and the systems are interrelated – for example, an improvement in nutritional status due to improved intestinal absorption can also have a positive effect on lung health or CF diabetes management or aspects of CF disease. Taking into account the effect of modulator therapy on the whole person seems a more clinically reasonable and important manner for determining if the therapy is effective.

CF is a complex illness. The determination of the effectiveness of currently available CF treatments (such as mucolytics or inhaled antibiotics) is not limited to a single measure with a strict cut-off value. Use of the 5% criteria alone take the decisions regarding effectiveness and continuation of therapy out of the hands of experienced CF physicians and the physician-patient partnership. Complex treatment analyses and decision making should not be completely taken out of the hands of the care team.

From a practical point of view, there is no guidance for when a patient who had had reimbursement withdrawn for failing to maintain a 5% improvement in ppFEV1 could be reconsidered for restarting

therapy after a further decline in lung function or health. Do patients only have one chance in their lifetime to access ELZ/TEZ/IVA or would they cycle on and off based on lung function values?

Although other measures to evaluate effectiveness and renewal of reimbursement (such as nutritional status, adverse events, and health-related quality of life) are mentioned in the Implementation Guidance section, without inclusion in Table 1 they may be overlooked by provincial or other payers using the CADTH report. The process of including these criteria should not be excessively cumbersome and should be designed to attempt to avoid coverage gaps that could lead to discontinuation of therapy.

Summary

In summary, as Canadian CF specialists, we believe that there are some conditions placed on reimbursement of ELX/TEZ/IVA that will deny therapeutic access for important subsets of Canadians with CF who could benefit from this potentially life changing therapy. Most importantly, the heavy weighting of ppFEV1 in decision-making regarding initiation and continuation of coverage does not take into consideration other important clinical benefits and does not incorporate the natural history of the disease, the multisystemic manifestations of CF, or the potential magnitude of the positive effects of this new therapy for people with CF. The report and the reimbursement criteria have generated uncertainty and concern for some people with CF, their families, and their care teams.

We strongly encourage the provincial, territorial, and federal programs involved in medication reimbursement and coverage to consider these factors to ensure fair, effective, and beneficial access to this medication for persons with cystic fibrosis. We also remain available to work with programs to help establish, maintain, and evaluate these programs as further experience and evidence becomes available.

Signed by 34 CF Clinic directors and physicians from across Canada.

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