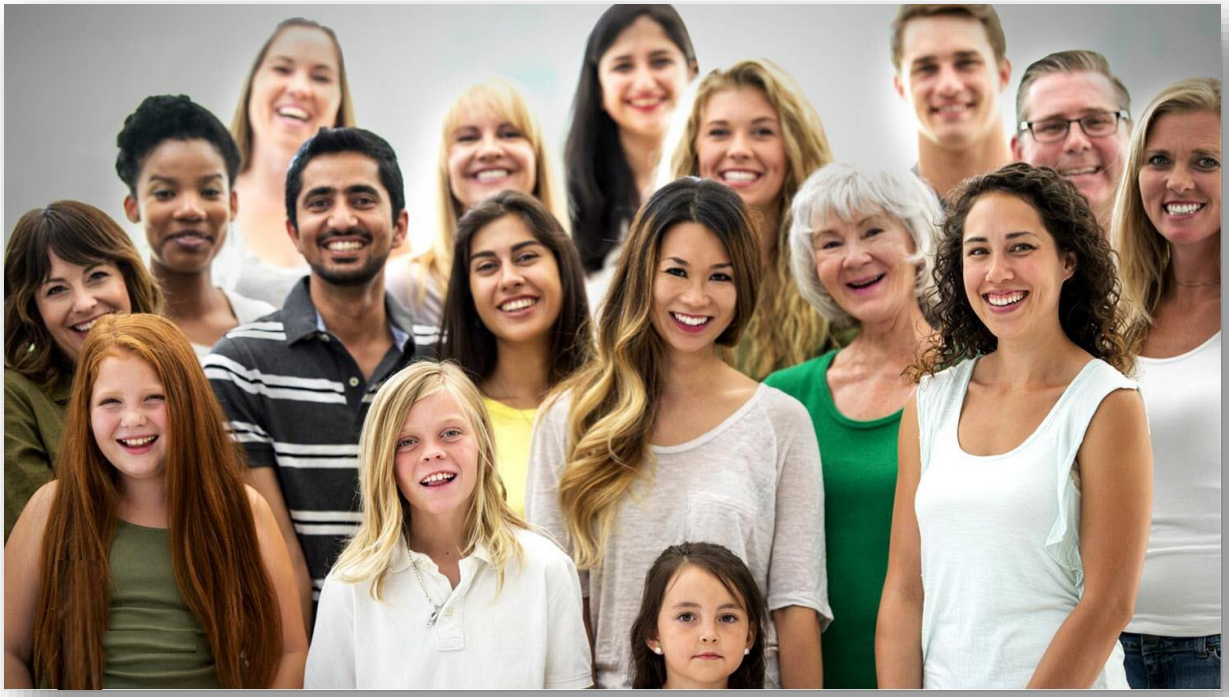
GenomeQuébec

Regroupement en soins de santé personnalisés au Québec (RSSPQ)



Genetics Saving Lives:
The Case of Cancer and 5-Fu

July 2020

Foreword

In the world of medicine, it is possible to have many treatment options for patients affected by the same disease, but also to find that not all patients share the same response to the same therapies. This is the case, for instance, with therapies used to treat certain types of cancers. In the last ten years, researchers have developed diagnostic and molecular tests. These tests are used to match the right treatment with the right patient at the right time, by evaluating additional parameters. This is what we call “personalized medicine” or “precision medicine.” The goal of this approach is to pinpoint the treatment best suited to each patient, thus improving quality of life and life expectancy. Moreover, precision medicine aims to make optimal use of healthcare resources by reducing, among other things, the percentage of people most likely to experience severe adverse effects. Genotype screening of the DPD enzyme, administered before starting the chemotherapy with 5-FU, is a prime example of the value of such tests in reducing the risk of severe toxicity, which in this case, can be fatal.

Background

According to the Canadian Cancer Society, an estimated one in two Canadians is expected to have cancer in their lifetime and one in four will die from it (Canadian Cancer Society, 2019). Following a cancer diagnosis, doctors proceed to prescribe a treatment for their patients. Two common anticancer agents used to treat a number of different solid-tumour cancers (e.g., breast, colon, stomach, head and neck) are fluoropyrimidine-based therapies (Loriot M-A *et al.*, 2018), including 5-fluorouracil (5-FU) (Cancer Research UK, 2019).

How 5-FU works in the body

Once 5-FU is administered orally or by intravenous, the molecule is integrated into the cells of the body – both cancerous and healthy – where it goes to work. However, only a small proportion of the administered dose of 5-FU is converted into an active molecule. It is this tiny amount that will actually reach cancer cells to destroy them or keep them from growing. This is so because over 80% of 5-FU is broken down into an inactive molecule by a liver enzyme called DPD (dihydropyrimidine dehydrogenase). The medicine then undergoes additional changes before being excreted in the urine (Lemaitre F. *et al.*, 2018).

Risks associated with 5-FU

While the efficacy of 5-FU has been demonstrated in clinical trials, severe toxic effects, grade 3 in 5 and above, can occur in 10% to 40% of cases, depending on the chemotherapy protocol used (Loriot M-A *et al.*, 2018), (Institut national d'excellence en santé et en services sociaux (INESSS, 2019). The grade refers to the severity of adverse effects on a scale of 1 to 5. Here are the definitions of grades 3, 4 and 5 (National Cancer Institute, 2017):

- **Grade 3**: Severe or medically significant toxicity, but not life-threatening; hospitalization or extension of hospitalization is indicated; disabling, limiting self-care and activities of daily living.
- **Grade 4**: Life-threatening consequences; urgent care is indicated.
- **Grade 5**: Death related to adverse effects.

In the case of 5-FU, the toxic effects can be lethal in up to 1% of cases (grade 5)[1] (Lemaitre F. *et al.*, 2018).

Why do severe adverse effects occur?

A proportion of 39% to 61% of patients who have developed toxicity following treatment with 5-FU were found to have a partial or complete deficiency of DPD (INESSS, 2019). These patients are unable to metabolize 5-FU because their body does not produce enough DPD to have an impact on the drug. Consequently, 5-FU remains at elevated levels in their bloodstream leading to prolonged exposure, which compromises normal cells. This results in the onset of severe toxic effects (grade ≥ 3). These complications can be life threatening (INESSS, 2019). Patient sensitivity to the toxic effects of 5-FU depends on the activity of his DPD enzyme, which is modulated by genetic mutations (Loriot M-A *et al.*, 2018). With this knowledge, it becomes possible to identify patients at risk for developing toxic effects associated with the use of 5-FU.

[1] A few cases have even been reported in Québec in recent years: Chimiothérapie : des tests génétiques accessibles partout au Québec, M-C Malboeuf, *La Presse,* 2019; Chimiothérapie : un test pour prévenir les complications fatales, M-C Malboeuf, *La Presse* 2017; Chimiothérapie : Combien de morts ça va prendre? M-C Malboeuf, *La Presse, 2015*

Prevention

Genetic or genotype tests can be done on the DPD enzyme gene using blood samples collected from patients. These tests can help identify certain variants or mutations that are responsible for the enzyme's reduced activity and its resulting increase in 5-FU-induced toxicity with the standard-dose treatment (INESSS, 2019). To date, over fifty mutations have been identified (Loriot M-A *et al.*, 2018). Only four are formally and consistently associated with an increased risk for 5-FU toxicity, as found in studies conducted primarily in Caucasian populations (Loriot M-A *et al.*, 2018*)*. For these four DPD enzyme mutations, there are recommended guidelines on the pre-treatment dose adjustment; one is from the Dutch Pharmacogenetics Working Group (Lunenburg C. *et al.*, 2019) and another, from the American Society for Clinical Pharmacology and Therapeutics (Amstutz *et al.*, 2017*)*. Québec laboratories already offer the DPD-mutation screening test for the four mutations that cause the vast majority of DPD deficiencies and secondary complications.

Costs and benefits

Conducting the genetic test to screen for these four mutations prior to treatment with 5-FU enables clinicians to assess a patient's risk of severe toxic effects (INESSS, 2019*)*. The attending clinician can, therefore, opt to lower doses or modify the treatment plan based on the results of the test (Henricks L. M. 2019*)*. If patient tolerance of 5-FU is found to be adequate during treatment, the clinician can subsequently decide to increase the dose.

This is how precision medicine works on reducing the number of cases of severe toxicity. The quality of life of many patients can be significantly improved and, in some cases, death can even be prevented[2] without the need for additional healthcare spending. According to some cost analyses, the genotype screening of DPD enzyme mutations could even generate cost savings per patient (Deenen *et al.*, 2016).

[2]For example, a patient treated for colorectal cancer in 2019 at Pierre-Boucher Hospital survived his treatment thanks to the DPD genetic test. According to the attending oncologist, without a dose reduction, this patient could have succumbed to severe toxic effects (Chimiothérapie: des tests génétiques accessibles partout au Québec, M-C Malboeuf, La Presse, 2019)

Potential economic benefits of genotype testing of four DPD enzyme mutations

In addition to potential improvements in patient safety and life expectancy, many studies have shown various economic benefits associated with the use of genotype screening prior to treatment with 5-FU.

A study conducted by Deenen *et al*. (the Netherlands) found that the use of a strategy involving genotype screening prior to treatment with 5-FU generated savings of Can$81 per patient compared to a non-screening strategy. (Deenen *et al.*, 2016.) While the authors deemed this cost saving to be modest, the study shows that a systematic screening strategy would not require additional healthcare spending.

In another cost analysis, this one carried out by Henricks *et al*. (the Netherlands), the authors determined that genotype-guided dosing cost Can$4,037 for patients compared to Can$4,116 for patients who had received the standard dose of 5-FU (Henricks *et al.*, 2019). This represents savings of Can$80 per patient. In other words, dose individualization based on DPD screening not only improves patient safety, it also saves money. Furthermore, the strategy is not expected to generate any additional costs for the healthcare system.

According to a study by Toffoli *et al*. (Italy), average toxicity management costs for patients carrying a DPD variant was Can$5,350 per patient compared to Can$1,485 for patients with a normally functioning enzyme (Toffoli *et al.*, 2018). This means that managing adverse effects in patients with a deficient DPD enzyme following the administration of the standard dose of 5-FU costs the healthcare system an average of Can$3,865 more. The study determined that 69 patients would need to be genotyped to identify one case of toxicity requiring hospitalization.

Finally, based on research led by Magnes *et al*., in Austria, 1,000 patients need to be genotyped to save one life. The corresponding cost for one death is Can$121,850 (Magnes *et al.*, 2016).

Québec data: Genotype screening of four DPD enzyme mutations and number of patients to be tested.

Screening costs	The genotype screening test for all four mutations costs $40.64 per patient (INESSS, 2019). Approximately 6,000 cancer patients would likely need the test. This estimated figure is based on the number of new cancer cases each year whose treatment plan will involve chemotherapy with 5-FU (INESSS, 2019). The total screening cost for these 6,000 people works out to approximately $244,000 per year.
Screening capacity	In Québec, there are three certified laboratories conducting genotyping of the DPD enzyme (ministère de la Santé et des Services sociaux (MSSS), 2020). According to a 2019 report by the INESSS, an estimated 2,080 tests can be done annually at each of the three laboratories, making the target of 6,000 patients per year achievable.

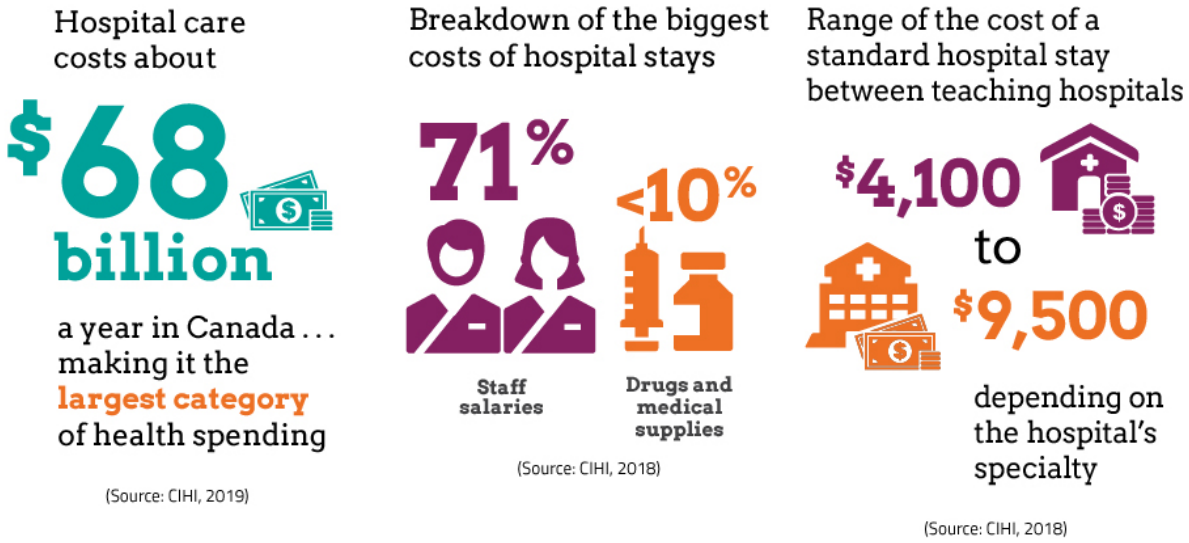
An average of 87 cases of severe toxicity out of 6,000 patients could be prevented each year, keeping in mind that 69 patients need to be tested to identify one case of toxicity requiring hospitalization (Toffoli *et al.*, 2018). Consequently, up to six lives could be saved if we consider that 1,000 genotype tests are needed to avert one death (Magnes *et al.*, 2016).

In addition to the potential benefits in terms of patient safety and improved life expectancy, as demonstrated in the studies presented herein, it could be possible, in Québec, to save at least $80 per patient. These savings are associated with the management of toxic – even life-threatening – effects in patients with a positive test.

A study on the reduction of 5-FU toxicity based on genotype screening of one of the four mutations was carried out following the introduction of the test in clinical practice at the Centre hospitalier de l'Université de Montréal (CHUM, 2019). The study demonstrated that reduced 5-FU toxicity is more than theoretical, since it has a real impact when used right here in Québec. The findings from this study, combined with those of European research on the social profitability previously mentioned, led the MSSS to recognize the expanded screening of the four DPD mutations in 2019.

Conclusion

The case of the DPD genetic testing and 5-FU-based chemotherapy for cancer speaks volumes to the importance of implementing diagnostic screening in the healthcare pathway. Detecting mutations of the DPD enzyme could make it possible to **improve the quality of life and life expectancy of patients, and in certain cases, even save lives, without generating any additional expenses for the healthcare system.** This represents an even more efficient use of health resources, since screening can reduce the number of severe toxicity events through genotype-guided adjustments to patient 5-FU treatment plans or doses. Moreover, treatment cost per patient is expected to be slightly lower due to the improved management of toxicity. It has also been shown that integrating the screening test into clinical practice in Québec would not yield additional healthcare costs for our healthcare system.



List of References

Amstutz U., Henricks L. M., Offer S. M., Barbarino J., Schellens J. H. M., J. Swen J. J., Klein T. E., McLeod H. L., Caudle K. E., Diasio R. B. and Schwab M. (2017) - Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Clinical Pharmacology & Therapeutics*, 103, 2 (210-216). https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.911,

Canadian Cancer Statistics Advisory Committee (2019) - Canadian Cancer Statistics (2019) - Toronto, Ontario, Canadian Cancer Societyhttps://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en

Cancer research UK (2019) - DPD deficiency https://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency

Deenen M. J., Meulendijks D., Cats A., Sechterberger M. K., Severens J. L., Boot H., Smits P. H., Rosing H., Mandigers C. M., Soesan M., Beijnen J. H., Schellens J. H. (2016) - Upfront Genotyping of DYPD*2A to Individualize Fluoropyrimidine Therapy : A Safety and Cost Analysis. *Journal of Clinical Oncology*. 34(3), 227-34. DOI 10.1200/JCO.2015.63.1325

Henricks L. M., Lunenberg L., de Man F., Meulendijks D., Frederix G. W. J., Kienhuis E., Creemers G-J., Dezentjé V. O., Imholz A. L. T., Jeurissen F. J. F., Portielje J. E. A., Jamsen R. L. H., Hamberg P., Ten Tije A. J., Droogendkik H. J., Nieboer P., Schellens J. H. M. (2018) - DPYD genotype-guided dose individualization of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *The Lancet* 19 (11), 1459-1467 https://doi.org/10.1016/S1470-2045(18)30686-7

Henricks L. M., Lunenberg L., de Man F., Meulendijks D., Frederix G. W. J., Kienhuis E., Creemers G-J., Dezentjé V. O., Imholz A. L. T., Jeurissen F. J. F., Portielje J. E. A., Jamsen R. L. H., Hamberg P., Ten Tije A. J., Droogendkik H. J., Nieboer P, Schellens J. H. M. (2019) - A cost analysis of upfront DPYD genotype–guided dose individualization in fluoropyrimidine-based anticancer therapy. *European Journal of Cancer* 107, 60-67 https://doi.org/10.1016/j.ejca.2018.11.010

CIHI (2018) - Information on the Cost of a Standard Hospital Stay - Québec Your Health System - https://yourhealthsystem.cihi.ca/hsp/inbrief?lang=en#!/indicators/015/cost-of-a-standard-hospital-stay/;mapC1;mapLevel2;/

INESSS (2017) - Génotypage de la mutation DPYD*2A du gène de la dihydropyrimidine déshydrogénase (DPYD) par PCR en temps réel, Québec city, Québec https://www.inesss.qc.ca/fileadmin/doc/INESSS/Analyse_biomedicale/Fevrier_2017/01-Genotypage_mutation_DPYD-2A.pdf

INESSS (2019) - Génotypage de la dihydropyrimidine déshydrogénase DPYD*2A, Québec City, Québec https://www.inesss.qc.ca/fileadmin/doc/INESSS/Analyse_biomedicale/Septembre_2019/INESSS_DPYD_CHUS.pdf

INESSS (2019) - Génotypage de la dihydropyrimidine déshydrogénase DPYD (4 variations pathogéniques), Québec City, Québec https://www.inesss.qc.ca/fileadmin/doc/INESSS/Analyse_biomedicale/Septembre_2019/INESSS_DPYD.pdf

INESSS (2019) - Traitement à base de fluoropyrimidine : meilleures stratégies pour réduire le risque de toxicités sévères causées par une déficience en dihydorpyrimidine déshydrogénase. Rapport rédigé par Mélanie Béland, Québec City, Québec https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_DPYD_Traitements.pdf

Jolivet C., Amireault C., M. Ayoub J-P., Beauregard P., Blais N., Carrier C., Cloutier A-S., Desnoyers A., Jolivet J., Lemay A-S., Lemay F., Letendre F., Loungnarath R., Soulières D., Tehf M.,

Viens D., Weng X. ry Aubin F. (2019) - Implementing DPYD*2A Genotyping in clinical practice, the Québec experience. *Journal of Clinical Oncology*. 37 (4) 650-650 https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.4_suppl.650

Lemaitre F., Goirand F., Launay M., Chetelut E., Boyer J-C., Evrard A., Paludetto M-N., Guilhaumou R., Ciccolini J. et Schmitt A., 2018 - Suivi thérapeutique pharmacologique du 5-fluorouracile : Mise au point et recommandations du groupe STP-PT de la SFPT et du GPCO-Unicancer. *Bulletin du cancer*, 105(9), 790-803 https://doi.org/10.1016/j.bulcan.2018.06.008

Loriot M-A., Ciccolini J., Thomas F., BlE-Guellec C., Royer B., Milano G., Picard N., Becquemont L., Verstuyft C., Narjoz C., Schmitt A., Bobin0Dubugeon C., Harle A., Paci A., Poinsignon V., Quaranta S., Evrard A., Hennart B., Etienne-Grimaldi M-C, 2018 - Dépistage du déficit en dihydropyrimidine déshydrogénase (DPD) et sécurisation des chimiothérapies à base de fluoropyrimidines : mise au point et recommandations nationales du GPCO-Unicancer et du RNPGx. *Bulletin du Cancer*, 105 (4), 397-407 https://doi.org/10.1016/j.bulcan.2018.02.001

Lunenburg, C.A.T.C., Van der Wouden, C.H., Nijenhuis, M. *et al.* 2019 - Dutch Pharmacogenetics Working Group (DPWG) - Guideline for the gene–drug interaction of DPYD and fluoropyrimidines. *European Journal of Human Genetics* https://doi.org/10.1038/s41431-019-0540-0

Magnes T., Melchardt T., Weiss L., Hufnagl C., Greil R., Egle A. (2016) - Fluorouracil and Dihydropyrimidine Dehydrogenase Genotyping. *Journal of Clinical Oncology* 34(20), 2433-2434 DOI : 10.1200/JCO.2016.66.6057

MSSS (2020) - Répertoire des procédures suprarégionales de biologie médicale : Laboratoires certifiés du Québec. 65036 – Dihydropyrimidine déshydrogénase (DPYD) (mutations DPYD*2A, c.2846A>T, c.1679T>G, c.1236G>A) (TAAN). https://www.msss.gouv.qc.ca/repertoires/biomed/fiche.php?id=65036

National Cancer Institute (2017) - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Toffoli G., Giodini L., Buonadonna A., Berretta M., De Paoli A., Scalone S, Miolo G, Mini E, Nobili S, Lonardi S, Pella N, Lo Re G, Montico M, Roncato R, Dreussi E, Gagno S, Cecchin E, (2015) - Clinical Validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. *International Journal of Cancer* 137(12), 2971-2980 https://doi.org/10.1002/ijc.29654

U.S. Department of Health & Human Services (2017) - Common Terminology Criteria for Adverse Events (CTCAE) - Version 5.0., National Cancer Institute https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf