

A Systematic Mapping Study of Tumor Cell Released by Enzymes and Toxins

Abstract

Cancers, especially of the neural tissue, are often deemed a death sentence. However, neither the cellular and molecular mechanisms nor the underlying causes are fully defined. Despite what is currently known about various types of brain tumors, it remains poorly understood how they spread and cause collateral damage to other parts of the brain. This research focuses the cerebrospinal fluid (CSF) leakage and enzymes from brain cancer cases and various secreted proteins and enzymes within the following hypothesis responsible for the breach of the blood-brain barrier. This research investigated the role of CSF in brain cancer and BBB. The research provides evidence that the leakage typically occurs at the spine level, especially in the thoracic spine region and the cardiothoracic connection at the base of the brain. The aim is to determine the various proteins and enzymes contained within the CSF and investigated how to evaluate and specifically examine: (a) protein, (b) identity of these proteins/enzymes, (c) sequence of proteins/enzymes, and (d) identify the genes encoding these proteins/enzymes. Furthermore, the evidence that the function of CSF is breached by the components released from the tumorous tissue identifies the precise foci of this leakage and various proteins and enzymes that may be responsible for this damage. These observations perform a novel role in the detection of enzymes and toxins released by tumor cells, and a new component recognizes the type of CSF, whether it is normal CSF and proteolysis components of CSF related to tumor cells.

Keywords: *Cerebrospinal fluid, Enzymes, Blood brain barrier, Brain cancer*

Introduction

The human brain is one of the most complex organs and consists of myriad neuronal networks that are responsible for maintaining processes like homeostasis, cognition, behavior, and emotions, among others. There is an ongoing quest to understand the brain's intricacies, so we can take a step forward in the clinic to treat debilitating neurological disorders. The cells that make up those interfaces are also websites of complete change mechanisms (transporters) that manage the access and exit of the brain to a wide variety of molecules. An essential mechanism for controlling the one-of-a-kind shape of the interstitial fluid of the brain is the secretion of cerebrospinal fluid by way of choroid plexuses, which glides through the ventricular gadget and exchange materials between the cerebrospinal fluid and the brain. Understanding the complexity of barrier mechanisms is important in an effort to evaluate the effects of inflammatory conditions on the brain, each in adults and at some stage in the boom. The exhaustion of the cerebrospinal fluid may also occur due to leakage, a shunt, insufficient

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production, or very rapid absorption. There are also several related syndromes where the intracranial conformity is very excessive; producing similar effects as the head shrinks and floats upward again. Cerebrospinal fluid (CSF) has been investigated widely for the identification of cancer molecules. This research explores the contemporary clinical awareness of the CSF's biochemical elements mentioned in the literature as brain cancer and its cell toxin emitted by enzymes.

Cancer will begin in the human frame consisting of billions of cells, almost anywhere. Human cells normally expand and separate to create new cells, which the body requires. Enzymes are biological catalysts (additionally referred to as organic catalysts) that increase biochemical reactions in dwelling organisms. They can be extracted from the cells; after which they can be used to stimulate an extensive variety of commercially vital strategies.

RQ1: What are the common signs of cerebrospinal fluid (CSF) leakage, enzymes from brain cancer, and various secreted proteins?

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RQ2: What are the key venues for publications on the breached blood vessel and enzymes of brain cancer?

RQ3: Which research targets genes encoding proteins/enzymes and the breakdown of enzymes in the selected studies?

RQ4: What are the common bacteria sampling of brain cancer in CSF discussed in the literature?

Literature review

A brain tumor is a collection of abnormal cells or a mass of ordinary cells in your brain. Any increase in this constrained area can be elaborated.^[1] Brain tumors can be cancerous (malignant) or not (benign), similar to most cancers. If the developed tumors are benign or malignant, intracranial stress might also grow. This can bring about brain harm which can be life-threatening. Brain tumors are classified as both primary and secondary, and many tumors of the brain are benign. Secondary brain tumors are also referred to as metastatic brain tumors, which occur while cancer cells from any other organs progress to the brain,^[2] including the lung or the breast. Brain tumors seldom progress to other components of the body, but most can progress via the brain tissue. Even so-called benign tumors can compress and spoil the brain's regular tissues as they develop, frequently inflicting adverse and, on occasion, deadly damage. This is why doctors often talk of brain tumors in place of most brain cancers.^[3] The fundamental worries related to brain and spinal twine tumors are the ease with which they can spread to the rest of the brain or spinal cord, and whether or not or now not they can be removed. Tumors of the brain and the spinal cord tend to differ between adults and kids. They are often shaped in various regions, expand from one kind variety of cells, and have exclusive views and treatments. It is beneficial to know the normal shape of the critical nervous system (CNS), the scientific name of the brain, and the spinal cord to recognize brain tumors and spinal wires.^[3]

Cerebrospinal fluid (CSF) leaks

Cerebrospinal fluid (CSF) leakage is one of the maximum tough complications in neurosurgery. The cerebrospinal fluid (CSF) is the fluid that travels via the brain's ventricles (cavities or voids) and across the surface of the brain and spine. CSF leakage is a situation that happens when the CSF leaks through deformity within the Dura or head and exits through the nose or ear.^[4] CSF leakage results from a hollow or tear of the Dura which is the topmost layer of the meninges. The cause at the back of the hollow or tear consolidates head damage and brain or sinus medicinal machine. Cerebrospinal fluid leakage is often misdiagnosed as migraine, other headache conditions, or sinusitis. The symptoms of CSF leakage generally consist of a headache that is severe inside the upright function and is perceived at the supine below the chest (Trendelenburg). Horizontal artery changes into tinnitus, blurred vision and perception, facial numbness, nausea, and radicular signs (tingling) within the top limbs. These symptoms are not specific, as they are commonly discovered in migraines and severe headaches. Cognitive decline has also been mentioned.^[4]

RQ1: What are the common sign of cerebrospinal fluid

(CSF) leakage?

A CSF disorder is caused by the diagnosis of psychiatric conditions that affect the central nervous system. Any such cases include various cases of sclerosis, a degenerative nerve disorder that occurs in the loss of myelin covering the mental and spinal wire nerve fibers. Starting with the lateral ventricles, CSF flows into the 0.33 ventricle through two passages. Firstly, from the 0.33 ventricle, it flows down into the fourth ventricle through a long, narrow passageway (Sylvius' aqueduct). CSF is absorbed back into the blood-stream through blood vessels over the brain's surface. Cerebrospinal fluid (CSF) has been particularly focused on the discovery of molecules that are known to be useful indicators for cancer diagnosis. However, so far, only a handful of these markers have been systematically analyzed. This study explores the current biochemical components within the CSF, referred to in the literature as biomarkers of brain cancer and focuses on the explanations for the role of specific markers in the treatment of CNS tumors.^[5]

RQ2: What are the key venues for publications on breach the blood vessel and Enzymes of Brain Cancer?

Blood vessel breach the blood-brain barrier

The brain is isolated from the rest of the body by the blood-brain barrier. This compact combination of cells is determined between the main blood vessels in the brain and the brain tissue itself. The blood-brain barrier facilitates and protects the brain from threats, including contamination. Nevertheless, it could also block useful medicinal drugs from reaching the brain when needed. Researchers realize that the blood-brain barrier is not entirely locked, for example, cancer cells can penetrate and set up metastatic tumors (from other web sites) in the brain.^[6]

If scientists can understand how most cancer cells acquire this intersection of leakage, they can broaden methods to prevent it. Many cells, consisting of most cancer cells, launch small cysts known as extracellular vehicles (EVs). EVs can affect other cells by transporting proteins and genetic material to them. Tumor ECVs, for example, can enter the circulatory system and regulate distant organs to cause extra susceptibility to metastatic cancer. This is because of their capacity to disrupt cells. This will permit more significant EVs to make their way through barrier cells into the brain safely. EVs can control endothelial cells to make it easier for them to move through the blood-brain barrier.^[7]

Enzymes of brain cancer

Enzymes are organic catalysts (additionally referred to as organic that accelerate biochemical reactions in the residing organisms, which may be extracted from cells and then used to simulate a wide variety of commercially vital strategies.

One of the most common varieties of brain tumors in adults is polymorphous glioblastoma, which is one of the most devastating tumors and also with the latest advances in surgical operation, radiation, and chemotherapy, competitive

and intrusive assaults become the remedy, and the average affected person will approximately 15 months. The researcher determined an important relationship between natural enzymes and brain tumors. If brain tumors return after treatment, this is due to cancer stem cells that were not affected by the treatment.^[8]

In many cancers, treatments exclusively divide the tumor cells that make up the large mass of the tumor. On the other hand, neoplastic stem cells are hardly divided and resistant to chemotherapy and radiation. Worse yet, it is activated by treatments and then responsible for the tumor’s return.^[9] This is especially true for glioblastoma, which is the most aggressive brain tumor. The only way to prevent glioblastoma relapse after treatment is an effective treatment against the brain’s tumor stem cells. Therefore, they pledged to identify specific marker molecules for brain tumor stem cells. They

began their search for mouse glioblastomas to investigate whether the detected structures also play a role in human brain tumors.^[10]

There are multiple enzymes are involved in enhancing human brain cancers, which are given below:

1. Acetyl-Coa Synthetase 2 (Acss2)
2. Kallikrein 6
3. Marker Enzymes
4. CDK5

Existing work

The following table summarizes the list of enzyme performance in the brain:

Table 1. Details of brain tumor enzymes mechanisms

SNO.	Type of cancer	Name of Enzymes	Key Finding point	Detection Method
1	Brain Cancer	Acetyl-Coa Synthetase-2 (ACSS2)	To offer the facts of an enzyme referred to as Acetyl-CoA synthetase 2 (ACSS2) is at the center of imparting tumors with a path to continue to exist. ACSS2 complements the tumor’s ability to use acetate, a cell salt, as a carbon-primarily based supply of meals, as opposed to glucose. Acetate presents the cancer cells which are placed on the core of the tumor with a lifeline to now, not handiest survive whilst suffering from nutrient deficiency, however additionally a method to develop. ^[11]	We know that ACSS2 is a bidirectional enzyme in cancer cells and that ACSS2 may play a temporary role in tumor Acetyl-CoA / acetate metabolism. The researcher used quantitative real-time PCR (qRT-PCR) to quantify ACSS2 expression in most adjacent tissues. Inhibition of ACSS2 expression was achieved by RNA interference, which was observed with the help of qRT-PCR and <i>Western blot 16</i> . ^[12]
2	Brain Cancer	kallikrein 6 (KLK6)	To provide the information of enzyme known as KLK6. KLK6 receptor was blocked on tumor cells; the cells became more sensitive to <i>cytotoxic drugs</i> . Grade IV glioblastoma tumors had the highest levels of KLK6 compared with grade III tumors. In sufferers, higher ranges of KLK6 correlated with shorter survival—the one’s sufferers with the best stages of the enzyme lived for 276 days as compared with 408 days in patients with decreased stages. ^[13, 14]	The researchers also used a tissue culture model of glioblastoma to demonstrate that the cells become both chemotherapy and radiation-resistant when the KLK6 enzyme was added to the culture. KLK6 functions like a hormone, activating a signaling cascade within the cell that promotes tumor cell survival. ^[14]
3	Brain Cancer	Marker enzyme	In the PET images, the cells and molecular basis of choline uptake and the choline-containing compounds seen in MRS are not well understood. Choline kinase alpha (ChoKα) is an enzyme that acts on choline phosphorylation, an important step in the synthesis of membranes. ^[10] In human glioma, the investigator examines the choline tissue metabolism of 18F-fluoromethylcholine (18F-FMC), MRS, and ChoKα. ^[9, 15, 16]	The researcher uses the notion of an enzyme profile such as PET-choline and choline-containing compounds visible in MRS that was determinants of human glioma. We are aware that 18F-FMC / PET ranged from grade II and III to grade IV tumors, while MRS separated grade III / IV tumors of grade II. ^[17]
4	Brain Cancer	Cyclin-dependent kinases (CDK)	Researchers were able to stop the development of glioblastoma, an active type of brain cancer, by inhibiting an enzyme called CDK5. The discovery of the regulatory effect of this enzyme on glioblastoma can also open the door to an extended-anticipated advancement following current therapies. ^[15, 16]	We have used a gene screen tissue culture variant on <i>Drosophila</i> fashions with brain tumors to prove that the tumors decreased in size due to the use of the <i>Drosophila</i> fashions gene display screen and attempted to decrease the number of cancer stem cells after silencing the gene that coded for CDK5. ^[18] In humans, after examining glioblastoma patient genetic data, they found a large number of patients with glioblastoma still had elevated levels of the enzyme.

Table 1 shows a different kind of enzymes released by the tumor cell inside of the brain and supports the growth of the tumor cell to migrate from other parts of the human body.

RQ3: Which research targets genes encoding proteins/enzymes and breaking down the enzymes in the selected studies?

Breakdown enzymes

Any normal cell produces chemical compounds called enzymes to break down cells and tissues. Cells use enzymes to devastate infectious bacteria and viruses. They regularly go through it to break and scrub damaged regions of the body. This is a consequence of the regular recuperating measure. Numerous tumors contain a lot of these enzymes. A few sorts of malignancies additionally contain different typically

normal white blood cells that produce enzymes. It is a piece of the body's immune reaction to malignancy. Researchers are still uncertain about the source of the enzymes, but they are likely to facilitate the spread of healthy tissue cancer. When cancer passes and breaks normal tissue, the blood vessels in the vicinity can cause bleeding.^[15] As the tumor grows, its middle movements are far from the blood vessels in the place in which it grows. Therefore, the tumor center receives a decreasing amount of oxygen and vitamins. Cancer cells are unable to live without oxygen and vitamins like healthy cells. They then transport alerts, called angiogenic elements (angiogenesis is the formation of the latest blood vessels), which involve the migration, growth, and differentiation of endothelial cells, which line the inner wall of the blood vessels.^[16]

RQ4: What are the common bacteria sampling of brain cancer in CSF discussed in the literature?

Bacteria sampling of brain cancer in CSF

The microorganism or different germs in the pattern may be a signal of meningitis. This is an infection of the membranes masking the brain and spinal cord. The contamination can be caused by bacteria, fungi, and viruses, and it is the infectious illnesses of the brain and spinal wire, along with meningitis and encephalitis. The CSF assessments for infection examine white blood cells, bacteria, and different materials in the CSF and autoimmune disorders, including Guillain-Barré syndrome and more than one sclerosis (MS). Lymphoma occurs while cancer cells migrate from the breast, lung, or every other part of the body into the cerebrospinal fluid (CSF).

Once most cancer cells enter the cerebrospinal fluid, they settle in a single location within the brain and/or spinal cord and develop. The scientist carries out a bacterial test to determine the disorder and to research it using CSF. This check is particularly used to search for cancerous cells inside the CSF, the fluid that surrounds the brain and spinal wire. It is most often used if the tumor has already been diagnosed as a kind that can usually spread through CSF, which includes endometriosis. This check is carried out to measure the pressure within the CSF and collect a pattern of the liquid for further tests. The CSF evaluation may be used to diagnose a few neurological disorders. These can consist of infections (consisting of meningitis) and brain or spinal cord damage.^[19]

Materials and Methods

The reasons for preferring theoretical mapping are fundamental. It is a theoretical-based technique for defining, comparing, and interpreting all related data on a particular study topic, target area, or fascinating phenomena. Systematic mapping is well-established and is a systematic method of researching and synthesizing scientific data regarding a methodology or procedure, finding relevant regions and discrepancies in contemporary studies, and providing specific information to researchers or clinicians to support a new inquiry. A comprehensive mapping analysis differs from a conventional literature review in that it takes extra time and effort, and it also provides a broader understanding of the subject and a good foundation for generating data on issues concerning the studies reviewed.^[20-22] This systematic procedure for mapping have five steps are shown in **Figure 1**.

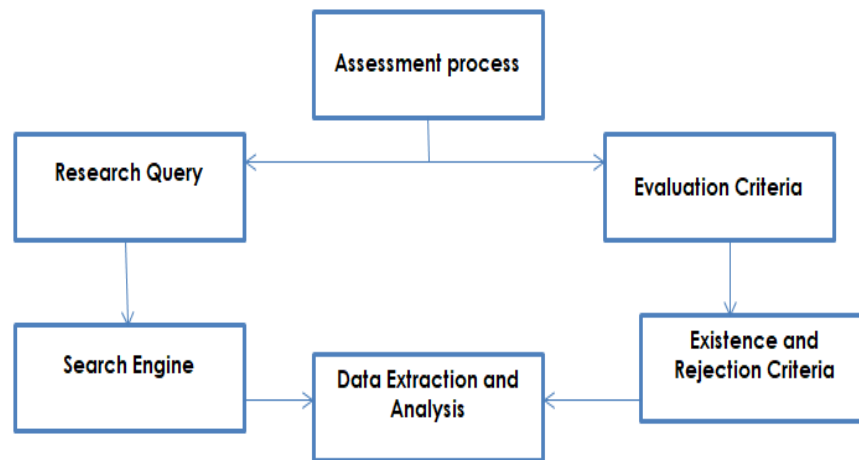


Figure 1. Stages of a systematic mapping study

Figure 1 shows the conceptual framework of data collection for different journal publishing houses. The manuscripts give brief information about enzymes and CSF detecting brain cancer using a variety of well-indexed journal materials.

Publication selection

This section includes information on the criteria of inclusion and exclusion used to select publications and the process used

to pick relevant articles based on the study questions. Subsequent requirements for inclusion were developed:

The study period comprised almost a decade of publication, which involved articles conducted between 2007 and 2022. The date of commencement was selected because most cancer enzymes were initially reported from 2007 onward. However, the studies were carried out in early 2018, so the nearest publication corresponding to the end of 2017 had been taken

into consideration within the systematic mapping to take a look at:

- Experimental studies specializing in most cancers-concentrated on enzymes.
- Studies that focused on supplying treatment for brain tumors, a way to spot cancer-related enzymes, and locate symptoms of cerebrospinal fluid (CSF).

The following exclusion criteria were used:

- Articles without focusing on the field of neuroscience.
- Articles that only provide guidelines, recommendations, or descriptions of multiple brain tumor enzymes.
- Articles not written in English.

Categorization of enzymes

This segment provides the effects of systematic mapping. The general wide variety of studies selected within the number of studies segment becomes 162. Based on the inclusion and exclusion criteria, 44 articles in the last generation were identified. Details of each generation are illustrated in **Table 1**. The selected articles were studied and analyzed in detail to answer the research questions. The following sources are used to evaluate this study which is given below:

Table 2. Study selection

Source	Retrieved	Initial selection	Final selection
IEEE	98	10	6
ACM	20	9	3
Science Direct	120	100	20
Springer Link	40	20	5
SAGE	30	25	10
Total	308	164	44

Table 2 illustrates the selection criteria of the articles in the publishing database of the recognized indexing services. We can see the distribution of the information from the retrieved manuscripts and the initial and final selection of the manuscripts which are targeted by gathering detailed information about cancer and enzymes.

Table 4. Targeting CSF for the discovery of brain cancer biomarkers

Approach	Method	Pros	Cons
Detection of cancer cells in the CSF	CSF cytoanalysis - CSF is tested underneath a microscope to search for cancerous cells	Highly specific ^[23]	Low sensitivity and fake bad consequences are common place ^[24]
	Cytometry Analysis: They can provide information on the expression of cell surface proteins	An automated method allowing for rapid analysis. ^[25] A smaller size of the CSF is needed ^[26, 27]	False negative and false positive results may occur (especially with a decrease in the number of cells, <25 cells / UL). ^[28]
Detection of biochemical molecules discharged by malignancy for CSF	CSF Protein Analysis: Normal character and measurement of entire protein supplementation in CSF	Explicit protein examples can separate among subtypes or degrees of special cerebrum tumors ^[29, 30]	Limited sensitivity and specificity ^[28, 31]

Table 3. Publication venues with more than one selected study

Library	Type	Frequency
Science Direct	Journal	5
Science Direct	Journal	3
ACM	Journal	2
IEEE	Journal	2
IEEE	Journal	2
SAGE	Journal	1
Springer	Journal	1

Table 3 demonstrated the Libraries' information such as Science Direct, SAGE Online, and Springer, and excerpts for courses related to the evolving field of testing that had been published in journals. Among these three libraries, the frequency of books on Science Direct changed for the better, forming 25% of articles within the collection. Springer and SAGE ranked second and third within the group, respectively. **Table 3** shows unusual peaks for study number one with two or more repeats. The results indicate that most articles are published in journals. The journal Appropriateness Science via Science Direct has the best articles (20 out of 120), although Information Science via Science Direct ranks second with two articles out of 20.

Results and Discussion

This section shall discuss the results in detail and map them in line with the proposed study inquiries to fully understand the ability of the readers.

RQ1: What are the common sign of cerebrospinal fluid (CSF) leakage and enzymes from brain cancer cases and various secreted proteins?

To solve RQ1, all retrieved articles have been meticulously studied, and the primary weaknesses mentioned in those articles have been extracted. **Table 4** lists these common signs of a CSF leak which encompass: complications, which become worse whilst sitting or enhanced while lying down; it happens regularly or suddenly. The consequences of the present-day mapping suggest that the enzymes are investigated extra frequently, with many researchers treating these concerns as shown in **Table 4**.

Table 4 shows a brief discussion about cancer and CSF detection in the edema or peritumoral cyst.

RQ2: What are the key venues for publications on Enzymes and Enzymes of Brain Cancer?

Five foremost fact-mining libraries specifically, IEEE, ACM, Science Direct, SAGE, and Springer had been used, to determine the primary places of eBooks. Moreover, the outcomes in **Table 2** show that the guides extracted from IEEE and ACM libraries are specifically convention articles; only 6 out of 98 articles found inside the IEEE library within the virtual library-ACM are journaled articles. On the other hand, all guides retrieved from the remaining 3 libraries (Science Direct, SAGE, and Springer) are mostly articles in clinical journals, except for one article posted in Springer journal. This suggests that IEEE and ACM are the principal websites for convention courses in the region, similar to Science Direct, SAGE, and Springer, which are the primary sites for journal publications. In addition, to discover the most important journals and meetings that publish articles on enzymes for brain cancers, we listed journals that have posted a couple of articles from the Retrospective List of Studies in **Table 3**.

RQ3: Which researches are the targets of genes encoding proteins/enzymes and breakdown enzymes in the selected studies?

Detection of cancer cell enzymes in the CSF

The statistics acquired from the selected research reply to the research question; Central nervous system cancer (CNS) is a devastating disease that requires treatment. It is extremely important to create biomarkers that can lead to an accurate diagnosis of central nervous system cancer or that are useful in predicting disease progression or responding to treatment. Cerebrospinal fluid has been widely targeted to detect molecules that could have beneficial signs of cancer detection. However, to date, only a few of those signs have found a standardized recurring medical utility. This study examines cutting-edge scientific knowledge about the biochemical elements in CSF which have been pronounced within the literature as critical indicators of brain cancer. It highlights why many markers have not been diagnosed within the control of tumors.^[28]

RQ4: What are the common Bacteria sampling of brain cancer in CSF discussed in the literature?

According to the information acquired from the chosen studies, cancer cells changed the metabolism of cells. Mutations in genes related to the principal metabolic pathways (for an instance, Isocitrate dehydrogenase 1 and a pair of IDH1/IDH2) are vital cancer-causing agents, inclusive of critical nervous system tumors (CNS). Therefore, we hypothesize that the abnormal metabolic state of CNS cancer cells ends up in foreign levels of metabolites in the cerebrospinal fluid, and certain important types of systemic cancers of concern are associated with unique changes within the ranges of the cerebrospinal fluid metabolite. We analyzed

the contrasts in the abundance of 43 metabolites between the cerebrospinal fluid of control patients and the CSF of patients with essential or metastatic anxiety tumors.^[28]

Research and practical implications

This map observes both accurate and studied implications. We categorized the primary properties of enzymes and brain cancer and determined their frequency of occurrence in selected studies. This will help researchers to figure out the enzymes targeted for creating brain cancer toxins. In the future, researchers may target those cells that migrate from one part to another, which requires more research for future implementation. Therefore, the study of the systematic maps and empirical effects will help to practitioners to decide where to invest, develop equipment and strategies by becoming aware of information about the enzymes and their functionalities.

Conclusion

This research offers scientific mapping by investigating the effects of enzymes and toxins released by tumor cell leakage in cerebrospinal cancer. A total of 44 articles were selected using a specific search series for this systematic mapping study. Each publication was analyzed in detail, and this study focuses on the six types of enzymes that are discussed in the selected publications. According to analysis, kallikrein 6 (KLK6) and acetyl-CoA synthetase-2 (ACSS2) were the most frequently used and cited enzymes of brain tumors/carcinomas. These methods are most commonly used in the detection of enzymes, as detailed in the selected research including the purpose of infiltration detection and solutions to treat it with the help of enzymes analysis. These results are expected to help the cancer community better understand the diseases that exist in a variety of cancer conditions and strategies for mitigating them.

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Conflict of interest

None.

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Ethics statement

The study received ethical approval from the Human Research Ethics Committee of the University of Calgary, Canada, and was conducted according to the good clinical practice guideline, as well as the Declaration of Prof. Dr. Naweed. I. Syed, University of Calgary, 2500- NW, Calgary, AB T2N 1N4, Canada. The project number of ethical approval was School of Cuming, cell Biology Department and special

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