Metabolic biomarkers in cancer

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Abstract

Over the course of years healthcare systems have utilized various ‘–omics’ approaches to prognose, diagnose and evaluate the treatment efficacy of cancer diseases. Metabolomics is one of the latest prominent additions to the –omics approaches, characterized by its versatile methodology. Owing to constant improvements in the field, a metabolomic aims to provide a faster and a more accurate diagnosis, as well as personalized and optimal strategies of treatment. In recent years, a growing number of studies have utilized metabolomics approach to find new disease-related biomarkers of cancer diseases. Here we present the summary of recent advances in biomarker discovery for various types of cancers such as leukemia, ovarian, lung, breast and liver cancers as well as cancer-related cachexia.

Keywords: metabolomics; cancer diseases; biomarkers; personalized treatments; personalized medicine; protein
**Introduction**

Disease prognosis, diagnosis, and treatment efficacy can be improved significantly if a comprehensive system of all human metabolic pathways and metabolic balance is monitored (1-4). A comprehensive dataset of the healthy human metabolic status of a specific population can be used to distinguish abnormal states and predict disease onset, guide food intake and adapt choices for a healthy lifestyle (5-7).

Metabolomics is a dynamic and emerging field of new ‘-omics’ science, which joins proteomics, transcriptomics, and genomics (Figure 1, Figure 2), and affords a global understanding of biological systems (8-11) (Figure 1). Metabolomics provides a snap-shot of the metabolic composition of studied samples, which reflects both internal effects (such as a genetic function) and external influences (such as food intake and drug administration) (5, 12-14). Thus, metabolomics approaches provide significant details for medical applications including disease diagnoses, discovering new drugs, assessing drug toxicity, or even uncover new drug targets.

Small changes in protein concentration level due to disease onset lead to significant changes in the metabolites balance. The unbalance of certain metabolites can be indicative of the development and progression of different cancer types. For instance, an increase in taurine concentration is associated with the survival rate for prostate cancer (15); an increase in lactate concentration is considered a biomarker in a wide range of cancers (16, 17). Thus, monitoring the metabolite's concentration is a novel approach to cancer prognosis, diagnosis, and personalized treatment. The importance of creating new ways to monitor the prevalence of cancers worldwide is further highlighted by the incidence and number of deaths related to them (Figure 3).
Figure 1. Fields of study consisting within system biology.
Figure 2. Number of published papers from 1984 to 2021 for the published papers of biomarker diseases, based on a search conducted on Scopus (keywords: biomarker, disease, non-infection). The topic biomarker non-infection diseases have grown exponentially since the turn of the century (21st century), with an $R^2=0.98$ and a total of 28753 papers.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
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<td>684996</td>
</tr>
<tr>
<td>Lung</td>
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<td>1796144</td>
</tr>
<tr>
<td>Liver</td>
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<td>Leukemia</td>
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<td>311594</td>
</tr>
<tr>
<td>Ovary</td>
<td>313959</td>
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</tbody>
</table>

Figure 3. Comparison of incidence and mortality of various types of cancer. Data obtained from (18, 19).

Pharmacometabolomics is an emerging sub-metabolomics field, which has gained attention in the recent years (9, 20, 21). Its main focus is to establish personal and optimal strategies of treatment by the use of biomarkers of potential response to the administered drug. Even of pharmacometabolomics is a new field, it has already proven to be applicable in many cancer studies including, breast cancer (22, 23), pancreatic cancer (24), and lung cancer (25).

Metabolomics, similarly to other “-omics” disciplines, is a technology-driven field, where different analytical tools are applied, including nuclear magnetic resonance (NMR) (26, 27), Fourier-transform infrared spectroscopy (FT-IR) (28-34), high-performance liquid chromatography (HPLC) (35) and mass spectrometry (MS) (36, 37). NMR spectroscopy and MS...
spectrometry, which is usually combined with liquid chromatography (38) or gas chromatography (37, 39-41), are the most frequently used platforms in metabolomic studies (27, 42, 43).

In the current chapter we present the progress of the recent metabolomics approaches in cancer research, with particular attention to diseases biomarkers search. Different types of cancer including leukemia, ovarian, lung, breast and liver cancers, and cancer-related cachexia have been discussed as examples of recent metabolomics/proteomics applications in medical research. Numerous examples of recently found biomarkers are summarized in Table 1.

Leukemia Cancer

Leukemia was the sixth most common cause of cancer death in males and the seventh most common cause of death in females in the US between 2013 and 2017. (44). Leukemia is a cancer of the blood and bone marrow characterized by rapid, out-of-control growth of abnormal cells. These abnormal cells start in the blood-forming cells of the bone marrow and can spread through the blood to other organs (45). Unlike other cancers, leukemia generally does not form into a mass (tumor) that can be seen in imaging tests, such as X-rays.

There are many types of leukemia, and the classification depends on the blood cell type involved. Leukemia can be defined as acute or chronic, depending on cancer prevalence in the body. Acute leukemia has a fast rate and happens when most of the abnormal blood cells do not mature and cannot carry out physiological functions. Chronic leukemia has a slower rate with respect to the acute form and occurs when there are some immature cells, but others are normal and function normally. Specific leukemia types are more common in children; other in adults. Acute lymphocytic leukemia (ALL) is the most common form of childhood leukemia, and it can spread to lymph nodes and the central nervous system. Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia. Some kinds of CLL can be stable for years and do not require treatments. Acute myeloid leukemia (AML) is the second most common form of childhood leukemia and one of the most common forms of adult leukemia. Chronic myeloid leukemia (CML) is prevalent in subjects aged over 65. It has no noticeable symptoms and the
diagnosis depends on a routine blood test. People 65 and older have a higher risk of this type (46).

Symptoms vary according to the type of leukemia, but in general, patients may experience extreme tiredness, unexplained bruising or bleeding, weight loss, and infections that last longer or happen more often than normal (47).

Accurate diagnosis and classification of leukemias are the bases for the appropriate management of patients. The diagnostic accuracy and efficiency of present methods may be improved by the use of microarrays for gene expression profiling and the identification of specific biomarkers. In general, the diagnosis may rely on the simultaneous application of multiple techniques. Cytomorphology and histomorphology are combined with cytochemistry and multiparameter flow cytometry to assign the diagnostic sample to the correct entity. Furthermore, chromosomal analysis, often supplemented by fluorescence in situ hybridization (FISH), and molecular techniques, such as polymerase chain reaction (PCR), is needed to definitively confirm the diagnosis. A comprehensive and standardized algorithm for a diagnostic workflow and an effective and carefully designed combination of methods is essential to guarantee that all the required diagnostic information is gathered (48).

Novel technologies, which detect biomarkers and molecular markers (such as point mutations), and characterize epigenetic and proteomic profiles, have begun to play an important role in approaching disease in a personalized way (49). Several tests are needed for the diagnosis of leukemia and include blood tests of full blood count (the number of red blood cells, white blood cells, and platelets) and a bone marrow biopsy (microscope imagining analysis, and scanning tests: MRI, CT, PET, ultrasound scans) (50). In addition, immunophenotype analysis and/or flow cytometry, genetic tests, and/or cytogenetics can be done (51). Many studies highlight the need to develop a biomarkers panel for diagnosis and treatment (52, 53). A list of the most common and promising biomarkers is presented in Table 1.

**Ovarian Cancer**

Although in 2008 ovarian cancer constituted the 3% of cancers in women, in 2020, the number has increased to 3.5% (not including non-melanoma skin cancer cases) with more than
60% of diagnosed cases resulting in death (18, 19, 54). Most cases of ovarian cancer occur in women older than 50 years old, even if it can be diagnosed at any age, including infancy (55). According to the most recent findings of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute in 2020, about 21,750 new cases of ovarian cancer were diagnosed, among which 13,940 women are expected to die in the United States. The SEER program reported that in the United States in 2016 approximately 229,875 women are living with the diagnosis of ovarian cancer (including those who are already under therapy) (56). The ovarian cancer mortality rates showed lower reduction rates compared with other cancer types, due to the fact that ovarian cancer at the early stages rarely has symptoms (57). Ovarian cancer has often been called the "silent killer" because symptoms are not thought to develop until advanced stages when the chance of cure is poor.

The main symptoms of ovarian cancer include bloating, lack of appetite, abdominal pain, fatigue, urinary frequency, and frequent constipation. Among women with the early stage of the disease, bloating was the most common symptom, followed by gastrointestinal tract disturbances (58). Such symptoms are unspecific for ovarian cancer and other pathologies could be misdiagnosed.

Early diagnosis of ovarian cancer is essential for efficient treatment. Up to date, there is no unique screening method and/or early detection tests for ovarian cancer. In clinical practice, several exams are used when the symptoms of ovarian cancer appear, namely a complete pelvic exam, a transvaginal or pelvic ultrasound, radiological tests (transvaginal ultrasound or CT scan), and a CA-125 blood test (59). In addition, some genetic mutations can be screened. According to literature, mutations in the BRCA 1 gene are associated with an 80-90% lifetime risk of breast cancer (60) and are strongly linked to ovarian cancer (61). The most significant risk factor for ovarian cancer is an inherited genetic mutation in one of two genes: breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2). These genes are responsible for about 10 to 15 percent of all ovarian cancers.

The research interest in ovarian cancer biomarkers has grown in recent years (Table 1), with particular emphasis on early detection biomarkers. For instance, CA125 level in blood is a highly specific biomarker of epithelial ovarian cancer, but it lacks sensitivity. However, the lack of
sensitivity at the early stages of the pathology can be ameliorated by the addition of HE4, CA 72.4, anti-TP53 autoantibodies, and other biomarkers (62). Recent literature reviews have mentioned some other promising biomarkers for the early detection of ovarian cancer include KLK6/7, GSTT1, PRSS8, FOLR1, ALDH1, and miRNAs (63-66).

Early disease detection requires the development not only of biomarker panels, but also more sensitive and specific imaging strategies (62). Effective biomarker panels are already available for distinguishing between benign and malignant pelvic masses, but their use by gynecologic oncologists in diagnosis needs to be encouraged (67).

**Lung Cancer**

Lung cancer (LC) persisted as the main cause of cancer mortality worldwide, with an estimated 2.2 million new cases (11.4%) and 1.8 million deaths (18%) in 2020 (18). Traditionally, lung cancer has been classified into two histologic groups; small and non-small cell lung cancer (NSCLC) (68). NSCLC represent 80-85% of all lung cancer cases and includes forms such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (69).

There are several risk factors for lung cancer, including lifestyle, environmental, and occupational exposures (70). The effective therapy of LC varies with a number of significant factors such as histologic subtype, molecular characterization, and stage at diagnosis (71). The choice of adequate treatment is a major challenge due to the very heterogeneous nature of lung cancer, and its prognosis within the same stage of development. In spite of innovations in early detection and conventional treatments, around 57 percent of patients are identified at a developed phase with a bad prognosis, and with only a 5-year survival rate of 10–15 percent overall (72). In addition, the failure of treatment is mostly because the disease has already achieved metastasis. To this concern, biomarkers have been shown to be beneficial in detecting and screening for the disease, in high-risk populations of lung cancer (73).

Low-dose computed tomography of the chest (LDCT) is commonly used to screen and diagnose early lung cancer. However, both benign and malignant lung nodules could be identified by LDCT which can expose a healthy patient to possibly risky procedures. In addition, other procedures such as biopsy could be used to diagnose the disease; however they may not be
appropriate for all patients due to other pathologies or complications (74). Therefore, biomarkers which can be rapidly processed without surgical intervention are very helpful in the prediction, diagnosis, prognosis, and development of personalized therapy for lung cancer (73).

A number of biomarkers have been established from different biospecimen samples to measure molecular targets, including circulating cancer cells tumor, DNA methylation, immune antigens, miRNA, and autoantibodies (73). Blood is considered the best biomarker source that gives a global view on patient body, including tumor stage and immune response (75).

Epidermal growth factor receptor (EGFR), neuron-specific enolase (NSE), progastrin-releasing peptide (ProGRP), carcinoembryonic antigen (CEA), CYFRA 21-1, and squamous cell carcinoma (SCC) are protein biomarkers for lung cancer, widely discussed in publications and are currently clinically used for detection, diagnosis, and prognosis of LC (76) (Table 1).

EGFR, which is the most common target molecule in NSCLC, is a member of the family of receptor tyrosine kinases (77). Up to 85% of patients with NSCLC have EGFR expression, which has been linked to a poor prognosis. Gene sequencing and reaction-based polymerase chain reactions are highly used approaches for discovering EGFR mutations (68). Currently, patients must be examined for EGFR sensitizing mutations before administration of anti-EGFR medicines such as Afatinib, Gefitinib, Erlotinib, and Osimertinib. The investigations of mutated EGFR can be accomplished on tumor tissue or plasma (78).

Neuron-specific Enolase (NSE) was found in neuronal cells and was subsequently detected in cells with neuroendocrine differentiation. Because SCLC might be of neuroendocrine origin, NSE levels in SCLC patient serum are typically increased. NSE has a sensitivity of 74% for detecting (76, 79). In addition, the neuroendocrine origin SCLC cells generate ProGRP, a more stable biochemical precursor to GRP.

SCLC diagnosis is more accurate with Pro-GRP due to its high sensitivity. It is considered a valuable diagnostic tool for distinguishing between SCLC and NSCLC. Pro-GRP may have a negative prognostic relevance since high marker levels are linked with a greater disease charge. Research on its function in clinical practice, such as monitoring treatment responses and early relapses, is necessary (80). NSE and ProGRP have traditionally been used as diagnostic and
prognostic indicators in the diagnosis and treatment of SCLC. However, in certain NSCLC patients, increased ProGRP and NSE levels have also been found (75).

Adult tissues do not often express the oncofetal CEA protein that is normally generated in the digestive tract through embryonic development. Because of this, higher levels of CEA in the blood can be employed as a clinical cancer marker in examinations (76). The CEA serum level provides prognostic and predictive information about the possibility of recurrence and mortality in NSCLC, regardless of study design or medication (81).

CYFRA 21-1, a protein tumor marker, is typically linked with squamous cell lung carcinoma. Degradation of cytokeratin, which is an intermediate filament protein present in the epithelial cells, creates soluble fragments that may be identified in the blood of a patient with lung cancer and could be used as a biomarker. CYFRA 21-1 is recognized to be linked with LC diagnosis. Nevertheless, it cannot be utilized to distinguish patients with cancer from those with respiratory illness (76).

Human blood specimen has a large number of stable miRNAs, which are used as an effective biomarker in several illnesses (82). miRNAs could be a disease biomarkers due to their biological relevance, presence in bodily fluids, and ability to be qualified and quantified accurately. While miRNA are implicated in all phases of carcinogenesis, they can be employed not only as diagnostic biomarkers but also as a dynamic tumor predictor before and during treatment (83). The miRNA-34 has been extensively investigated in lung tumors. The study on miRNA-34 extends from its development and confirmation to its clinical implications in diagnosis and treatment (75, 84).

Recently, Zhang et al., found and validated novel circulating biomarkers including E-cadherin, brain angiogenesis inhibitor 1 (BAI-1), integrin-binding sialoprotein (IBSP), and thrombospondin-1 (TSP-1) that perform an important role in early diagnosis of lung cancer (85). In the coming years, the number of predictive biomarkers will expand as a consequence of multiple ongoing research to identify new possible biomarkers and the new clinical trials that include these results (71).

Breast Cancer
Breast cancer is a life-threatening disease that affects women and is the main cause of death among them. According to the World Health Organization (WHO), breast cancer affected 2.3 million women globally in 2020, with over 685,000 fatalities (18). Breast cancer had been diagnosed in 7.8 million women in the previous five years as of the end of 2020, making it the most common cancer in the world. It causes more disability-adjusted life years (DALYs) in women around the world than any other type of cancer. Breast cancer strikes women at any age after puberty in every country on the planet, with rates rising as they become older. From the 1930s until the 1970s, breast cancer mortality did not alter much (86). Survival rates began to improve in the 1990s in countries where early detection programs were combined with various treatment options to eradicate invasive illnesses (86). Studies on breast cancer have led to incredible advancements in our understanding of the disease over the last two decades, leading in more effective treatments (87). The foundation of breast cancer regulations is improving breast cancer outcomes and survival through early detection. Breast cancer is treated with a variety of contemporary medications. Antiestrogen medication for breast cancer, such as raloxifene or tamoxifen, may prevent breast cancer in people who are at a higher risk of acquiring it (88).

Although there are many symptoms associated with breast cancer, most women feel a lump or an area of swollen tissue in their breast as the first sign of the disease. Most breast lumps are not malignant; nevertheless it is always a good idea to have them examined by a doctor. Symptoms of breast cancer include new lumps or thicker tissue area in either breast that was not there previously; a change in the size or shape of one or both breasts, a fluid discharge from one or both of the nipples, a lump or swelling in either of the armpits, a change in the look or feel of the skin, such as puckering or dimpling, a rash or redness, a rash, crusting, scaly or itchy skin, or redness on or around the nipple (like eczema), and a change in the appearance of the nipples. It is worth to mention that breast pain isn't usually a sign of cancer in the breast (89).

In general, breast cancer prognosis and treatment options are generally based on tumor-node-metastasis staging (90). Lymphocytic spread, histologic grade, hormone receptor status, ERBB2 (previously HER2 or HER2/neu) overexpression, comorbidities, patient menopausal status, and age are all essential aspects and factors needed to consider (91). Therefore, typical treatment options depend on the cancer stage and type of breast cancer (92, 93). For example, a recent
metabolomic study done by Jobard et al., have showed a set of 10 metabolites that could be used to predict the cancer onset in the premenopausal subgroup with modest accuracy. However, those metabolites could not serve as biomarkers when considered the overall group or postmenopausal women (94).

Liver Cancer

Primary liver cancer that is one of the most common malignant cancer, has a high incidence and fatality rate and poses a major threat to human health (95). In 2020, about 905,677 new cases (4.7%) were diagnosed and 830,180 liver cancer deaths (8.3 %) was estimated (18). Liver Tumor is classified as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined HCC cholangiocarcinoma (cHCC-CC), according to the histological type (95, 96). Hepatocellular carcinoma (HCC) is the most frequent primary malignant liver tumor, with incidences of 75-85% (95). It is generally found in the setting of chronic liver illness, such as hepatitis B or C virus infection, alcohol use, or the metabolic syndrome (97). HCC is characterized with a high degree of heterogeneity, both molecularly and histologically (97). Therefore, using liver tumor biomarkers including blood and histochemical biomarkers is critical in the early detection and identification of cancers, as well as in the assessment of therapy options, recurrence, and prognosis (95, 98). The most utilized primary liver cancer biomarker for early detection and diagnosis of liver cancer is the glycoprotein biomarker, α-fetoprotein (AFP). It comprises 591 amino acids and is an alpha globulin generated by the yolk sac and released by fetal hepatocytes (99). Adult hepatocytes have extremely low levels (25 ng ml−1) of this biomarker; nevertheless, the concentration of AFP rises dramatically when some of these adult hepatocytes develop malignancy (99). However, the level of AFP can additionally rise during pregnancy and for patients with trisomy 18, 21 and breast tumor (99). Although AFP levels were considerably elevated in 60 percent of patients with liver cancer, the remaining 40 percent of patients had levels within the normal range, according to some research (100). Patients with ICC have relatively stable AFP levels, making AFP a useful diagnostic for separating ICC from HCC (95). For patients that present lower level of AFP, the use of an additional biomarker is common to improve the detection of HCC (95). AFP-L3, lens culinaris agglutinin-reactive AFP, has been shown
to be more specific for HCC since it is only derived from cancerous cells (101). Choi et al has shown that the combination of AFP and AFP-L3 enhanced the sensitivity to 79% and the specificity to 87% (102). Des-gamma-carboxyprothrombin (DCP), an abnormal prothrombin produced by malignant hepatocytes, is a common blood test (103). DCP was initially shown to be extremely sensitive for the diagnosis of hepatocellular carcinoma was in 1984 by Liebman (104). It has been tested for its diagnostic precision in numerous research, and the findings have been conflicting (95, 101). Osteopontin (OPN) is a common valuable blood biomarker used for early diagnosis and treating of HCC (105). OPN is a secretory extracellular matrix protein that participates in a number of physiological and pathological processes (106). In addition, Golgi protein 73 (GP73), Gamma Glutamyl Transferase (GGT) and α-L-fucosidase (AFU) have been shown to be a valuable biomarker for the detection of HCC. In ICC patients, Carbohydrate antigen 19-9 (CA19-9) is beneficial in predicting not only lymph node metastases but also prognosis following curative surgical resection (107). Biomarkers of tissue structure and cell morphology are more accurate than other imaging and chemical investigations. Tissue biomarkers are critical in the evaluation of patients with benign tumors, HCC, ICC and cHCC-CC as well as the prognosis and therapy of these conditions (95). Glypican-3 (GPC-3), Heat Shock Protein 70 (HSP70), Hepatocyte paraffin 1 (Hep Par 1), Glutamine synthetase (GS) and Arginase-1 (Arg-1) are frequently used as histochemical biomarkers in HCC. For ICC patients, CK7 and CK19 are common employed. Therefore, to distinguish HCC from ICC and initial HCC from metastatic HCC, an appropriate combination of immunohistochemistry markers is required (95). Numerous studies have shown in HCC, the dysregulation of a several miRNAs, and thus their levels can be used as potential biomarkers for liver cancer. As example, miR-21 is frequently reported as diagnostic markers in HCC (108). Early diagnosis of liver cancer is related to effective cancer biomarkers. Given that the limitation of individual biomarker, the combination of liver cancer markers is considered essential to achieve early diagnosis with high sensitivity and specificity.

Cancer Cachexia
Cachexia is a highly destructive, multifactorial process that involves a set of complex changes in metabolic pathways. The main outcome of those changes is weight reduction influenced by the loss of skeletal muscle with or without a loss of body fat mass (109, 110). This process is distinct from starvation, age-related changes in the body mass, or endocrine disorders, as it occurs regardless of the calorie intake and is an important sign of underlying diseases such as cancer (109, 110). The cancer cachexia is diagnosed when patients record a weight loss of more than 5% of their stable weight over the course of the past 6 months or when the weight loss of more than 2% occurs in patients with BMI less than 20 (110). Currently, half of the cancer deaths are credited to cancer types associated with cachexia such as pancreatic, oesophageal, gastric, hepatic, pulmonary, and colorectal (111).

The loss of body mass acts as a consequence of metabolic changes, particularly increased levels of energy expenditure, excessive catabolic processes, and inflammation (111). Till now, the diagnosis of cachexia is ambiguous as the disease itself has shown heterogeneous development (depending on the type of cancer) (111, 112). Additionally, the lack of specific diagnostic criteria adds another complexity as some drugs used in cancer treatment show catabolic effects on skeletal muscle (111). Although improvements have been made recently to standardize the procedures of diagnosis and treatments such as the consensus on a definition of cancer cachexia (110), there are still many issues to be resolved. One of them is the lack of clinically significant biomarkers that could assess both the prediction of disease and the effects of treatment (111, 112). So far, several potential biomarkers have been identified but none of them have been widely accepted as a clinical diagnostic standard.

The complexity of finding a potent biomarker for cancer-induced cachexia comes for a variety of reasons. As mentioned before, each cancer type is unique and imposes a distinctive set of changes on the organ/organism that is particular for its type – meaning that the indicators of potential cachexia can vary between the patients with e.g. pancreatic cancer and breast cancer. Factors such as age, sex, and body composition are also complicating the search for biomarkers, and even diagnosis itself (e.g. age-related loss of muscle, sexual dimorphism of muscle mass amount/loss) (113, 114). All of it means that cachexia development can be variable based on the tumor and host type, which makes it even more difficult to find universal biomarkers.
Nevertheless, many tries have been made and a few examples are explained below. Since the topic of cancer cachexia-related biomarkers is broad, the reader is referred to (115-118) for more detailed examples and their explanation.

Since one of the main changes in cachexia is the reduction of muscle mass, many have focused on molecules indicating muscle degradation. For example, a recent study by Stephens et al., has shown that levels of β-dystroglycan are higher in cachectic compared to non-cachectic patients with upper gastrointestinal cancer (UGIC) (119). Additionally, low levels of two proteins - MyHC and dystrophin have been shown to be indicators of reduced survival chance (119). In another study made by Kunz et al., it was observed that mice injected with LLC1 tumor cells (exhibiting cachexia) have increased concentrations of two methylarginines: asymmetric dimethylarginine (ADMA) and N\(^G\)-monomethyl-l-arginine (L-NMMA) in the plasma and skeletal muscles (120). Interestingly, human cancer patients had also been observed to have higher levels of ADMA in the skeletal muscle (120). One more example of a study describing potential biomarkers was made by Judge et al., in which patients with pancreatic ductal adenocarcinoma (PDAC) have been observed to have increased collagen content when compared with control subjects (121). The increased levels of collagen were also positively correlated with bodyweight loss, lymph node metastasis and decreased survival chances (121).

As for inflammatory factors, the most prominent example is the widely studied IL-6 cytokine. In a recent paper, Han et al., have observed an increased level of IL-6 in the plasma levels of both male and female patients having either gastric or colorectal cancer (122). Additionally, a positive correlation was established between IL-6 and free fatty acid in female Cachexic patients meaning that IL-6 may play an important role in promoting lipolysis (122). Indeed, the previous study on human and mice models has proven the association between IL-6 and free fatty acid and its effect on white adipose tissue lipolysis and browning (123). However, other studies have shown no association between IL-6 and cachexia and reduce its value as a biomarker whatsoever (124-126).

Summary
The fact that human diseases such as cancer initiate biochemical adaptations during carcinogenesis leading to changes in metabolite concentrations reflects the potential role metabolomics can play in medical applications (127, 128) (Figure 4). For example, it has been repeatedly reported that an increase in lactate concentration is a biomarker indication for a wide range of cancers and in particular, certain types of neoplasms whereas the increase in taurine concentration is associated with prostate cancer and liver metastasis (129, 130). Thus monitoring the metabolite's concentration could be an effective and reliable method for cancer prognosis. Moreover, metabolomics research is not only focused on disease diagnosis but also on chemotherapy interventions including the development of new chemotherapies and the evaluation of the toxic response to drug therapy.

Figure 4. Types of potential compounds (yellow circles) that have been described to serve a potential role of cancer biomarker, along the various techniques used to study them (green circles represent techniques used for metabolomic studies). Created with biorender.com.
### Table 1. Summary of potential biomarkers for cancer treatment.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker</th>
<th>Application</th>
<th>Sample</th>
<th>Ref</th>
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<tbody>
<tr>
<td>Acute B lymphoblastic leukemia</td>
<td>↑ CD34 and CD38</td>
<td>Prognostic</td>
<td>Blood</td>
<td>(131-133)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ Adenylate kinase 1 (AK1)</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(134, 135)</td>
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<td>Acute myeloid leukemia (AML)</td>
<td>↑ Kynurenine, ↓ Glutamic acid, oleic acid</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(136)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>↓ Protein tyrosine phosphatase (Ptptb)</td>
<td>Predictive</td>
<td>Bone marrow–derived macrophage (BMDM)</td>
<td>(137)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ Phenylalanine, tyrosine, N-acetyl-glycoproteins (NAG), citrate, mannose, glucose, ↓ Choline, glycerophosphorylcholine (GPC), phosphorylcholine (PC), acetylcarnitine, unsaturated fatty acids, HDL, valine, isoleucine, leucine, lysine, arginine, glutamine, alanine, histidine, scyllitol, and lactate</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(138)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ Isoleucine, leucine, valine, glutamine, glutamate, lysine, arginine, phenylalanine, histidine, myoinositol, choline, PC/GPC, lactate and HDL, ↓ VLDL, LDL</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(138)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>↑ CD23</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(139)</td>
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</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>↑ miR-29a, miR-150-5p, hsa-miR-155-5p</td>
<td>Predictive</td>
<td>Serum</td>
<td>(140)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ B-cell translocation gene 1 (BTG1)</td>
<td>Prognostic</td>
<td>Bone marrow mononuclear cells</td>
<td>(141)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ Esterase D, gamma 1 actin</td>
<td>Prognostic</td>
<td>Peripheral blood and/or bone marrow samples</td>
<td>(142)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ 5hmC levels</td>
<td>Prognostic</td>
<td>Bone marrow and peripheral blood</td>
<td>(143)</td>
</tr>
<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>↑ Heat shock proteins (HSPs)</td>
<td>Prognostic</td>
<td>Bone marrow (BM) and peripheral blood (PB)</td>
<td>(144)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>↓ Afamin</td>
<td>Predictive</td>
<td>Serum/Plasma</td>
<td>(145)</td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>↑ CA125</td>
<td>Predictive</td>
<td>Serum</td>
<td>(146)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>↑ miR-21, miR-200a, miR-200b, miR-200c, miR-141, miR-429, miR-205, miR-10a, miR-346, ↓ miR-122, miR-193a, miR-223, miR-126, miR-106b</td>
<td>Predictive</td>
<td>Plasma/Serum</td>
<td>(147)</td>
</tr>
<tr>
<td>Tumor Type</td>
<td>Change to Control</td>
<td>Diagnostic/Prognostic</td>
<td>Sample Type</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>↑ Galectin-1</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(148)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>↑ miR-6131, miR-1305, miR-197-3p, miR-3651 ↓ miR-3135b, miR-4430, miR-664b-5p, miR-766-3p</td>
<td>Diagnostic/Prognostic</td>
<td>Peripheral blood samples</td>
<td>(149)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>↑ CA-125, Human epididymis protein 4 (HE4) ↓ Vascular cell adhesion protein 1 (VCAM-1)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(150)</td>
</tr>
<tr>
<td>Epithelial ovarian cancer (EOC)</td>
<td>↑ HE4</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(151)</td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>↑ miR-7, miR-429 ↓ miR-25, miR-93</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(152)</td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>↑ Mesothelin</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(153)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>↑ ALDH1 (Aldehyde Dehydrogenase 1)</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(154)</td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>↑ FOLR1 (folate receptor alpha)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(155)</td>
</tr>
<tr>
<td>Condition</td>
<td>Marker</td>
<td>Type</td>
<td>Location</td>
<td>Reference</td>
</tr>
<tr>
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<tr>
<td>Ovarian Cancer</td>
<td>↑ Human kallikrein 4 (KLK4)</td>
<td>Diagnostic/Prognostic</td>
<td>Tumor tissue</td>
<td>(156)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>↑ Prostasin</td>
<td>Diagnostic</td>
<td>Tumor tissue</td>
<td>(157)</td>
</tr>
<tr>
<td>Ovarian epithelial cancer</td>
<td>↑ Multidrug resistance-associated protein 1 (MRP1), glutathione S-transferase π (GST-π), glycogen synthase kinase-3β (GSK3β)</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(158)</td>
</tr>
<tr>
<td>Lung cancers (non-SQ NSCLC)</td>
<td>↑ Thyroid transcription factor-1 (TTF-1)</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(159)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↑ Cytokeratin 19 fragment (CYFRA 21-1), Carcinoembryonic antigen (CEA), Squamous cell carcinoma antigen (SCCA)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(160)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↑ SCCA</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(161)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↓ Hypoxanthine, inosine, L-tryptophan, indoleacrylic acid, lysoPC (18:2), acyl-carnitine C10:1</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(162)</td>
</tr>
<tr>
<td>Lung cancer (SCLC)</td>
<td>↑ Neuron specific enolase (NSE), lactate dehydrogenase (LDH)</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(163)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>↑ Acetoacetate, β-hydroxybutyrate, glutamine, glutamate, asparagine, aspartate, tyrosine histidine, cysteine, isoleucine, leucine ↓ β-glucose, α-glucose, unsaturated lipids, LDL/VLDL, glycerophosphocholine, phosphocholine, choline, TMAO, betaine, tryptophan, methionine</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(164)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Lung cancer (SCLC)</td>
<td>↑ ProGRP</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(165, 166)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↑ miR-21, miR-221, miR-222, miR-191, miR-149 ↓ miR-101, miR-130a, miR-200, miR-128, miR-34, miR-15a, miR-16</td>
<td>Predictive/Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(82, 167, 168)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↑ Epidermal growth factor receptor (EGFR)</td>
<td>Predictive/Prognostic</td>
<td>Tumor tissue/Plasma</td>
<td>(169, 170)</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>↑ Programmed death-ligand 1 (PD-L1)</td>
<td>Predictive</td>
<td>Tumor tissue</td>
<td>(171)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>↑ miR-9</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(172)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>↑ Human epidermal growth factor receptor-2 - extracellular domain (HER2- ECD)</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(173)</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ Hypoxanthine 5-oxoproline ↓ L-octanoylcarnitine, docosahexaenoic acid</td>
<td>Diagnostic</td>
<td>Plasma</td>
<td>(174)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>↑ N-acetyl glycoproteins, ethanol, histidine, glycerol, ornithine, leucine, albumin, glutamine, glutamate, pyruvate ↓ Histidine</td>
<td>Predictive</td>
<td>Plasma</td>
<td>(94)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>↑ Acetoacetate, glycerol, pyruvate, N-acetylglycoproteins, mannose, glutamate, phenylalanine ↓ Histidine</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(175)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ Glycine, lactate</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(176)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ Lactate, tyrosine ↓ Choline, formate, histidine, glutamic acid, proline, 2-methyl,3-hydroxybutanoic acid, nonanedioic acid, 3-hydroxybutyrate</td>
<td>Predictive</td>
<td>Serum</td>
<td>(177)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ Carnitine palmitoyl transferase 1A (CPT1A)</td>
<td>Prognostic/Diagnostic</td>
<td>Serum</td>
<td>(178)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ Carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3)</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(179)</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Markers</td>
<td>Type</td>
<td>Sample</td>
<td>Refs</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------</td>
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</tr>
<tr>
<td>Breast cancer</td>
<td>↑Glucose, lipids, ↓Histidine</td>
<td>Predictive</td>
<td>Serum</td>
<td>(180)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC) Combined HCC cholangiocarcinoma (cHCC-CC)</td>
<td>↑Alpha-fetoprotein (AFP)</td>
<td>Predictive/Prognostic</td>
<td>Serum</td>
<td>(108, 181)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑Bile acid, choline, phosphorylethanolamine, phosphocholine, glycerophosphocholine, glutamate, glutamine, glycine, alanine, leucine, ↓Lipids, glucose, glycogen</td>
<td>Diagnostic</td>
<td>Tumor tissue</td>
<td>(182)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑Tyrosine, phenylalanine, glutamate, acetate, citrate, glucose, propylene glycol, ethanol, ↓Unsaturated lipids, VLDL, N-acetyl glycoproteins, choline, glutamine, acetone, mannose, valine, leucine, isoleucine</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(183)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑Des-gamma-carboxyprothrombin (DCP)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(103, 104)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑Osteopontin (OPN)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(184)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑α-L-fucosidase (AFU)</td>
<td>Diagnostic/Prognostic</td>
<td>Serum</td>
<td>(185, 186)</td>
</tr>
<tr>
<td>Condition</td>
<td>Biomarker</td>
<td>Type</td>
<td>Sample</td>
<td>Reference</td>
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</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ Golgi protein 37 (GP73), Midkine (MDK), Dickkopf-1 (DKK-1)</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(187)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ Gamma-glutamyltransferase (GGT)</td>
<td>Prognostic</td>
<td>Blood</td>
<td>(188)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ Heat-shock protein 70</td>
<td>Diagnostic</td>
<td>Tumor tissue</td>
<td>(189, 190)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ α-Glucose, β-Glucose, galactose, N-acetylglycoproteins and glycine ↓</td>
<td>Prognostic</td>
<td>Serum</td>
<td>(191)</td>
</tr>
<tr>
<td></td>
<td>Alanine, glutamine, 1-methylhistidine, lactate, valine, tyrosine, lysine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ Glutamine synthetase</td>
<td>Diagnostic</td>
<td>Tumor tissue</td>
<td>(189)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>↑ 2-hydroxybutyric acid ↓ Tryptophan, glutamine</td>
<td>Diagnostic</td>
<td>Serum</td>
<td>(192)</td>
</tr>
<tr>
<td>Intrahepatic cholangiocarcinoma (ICC)</td>
<td>↑ Cytokeratin 7 (CK7), cytokeratin 19 (CK19)</td>
<td>Prognostic</td>
<td>Tumor tissue</td>
<td>(193)</td>
</tr>
<tr>
<td>Cachexia (UGIC)</td>
<td>↑ β-dystroglycan, ↓ MyHC, Dystrophin</td>
<td>Prognostic/Diagnostic</td>
<td>Muscle tissue (Rectus abdominis)</td>
<td>(119)</td>
</tr>
<tr>
<td>Cachexia</td>
<td>↑ Asymmetric dimethylarginine (ADMA)</td>
<td>Diagnostic</td>
<td>Muscle tissue (Vastus lateralis)</td>
<td>(120)</td>
</tr>
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<td>-------------------------------------------</td>
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<td>-------------</td>
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<tr>
<td>Cachexia (PDAC)</td>
<td>↑ Collagen</td>
<td>Prognostic</td>
<td>Muscle tissue (Rectus abdominis)</td>
<td>(121)</td>
</tr>
<tr>
<td>Cachexia (PDAC) (UGIC)</td>
<td>↑ Translational activation of mast cells</td>
<td>Predictive/Diagnostic/Prognostic</td>
<td>Muscle tissue (Quadriiceps (UGIC), Rectus abdominis (PDAC))</td>
<td>(194)</td>
</tr>
<tr>
<td>Cachexia (gastric/colorectal cancer)</td>
<td>↑ IL-6</td>
<td>Diagnostic</td>
<td>Plasma</td>
<td>(122, 123)</td>
</tr>
<tr>
<td>Cachexia (pancreatic/colorectal cancer)</td>
<td>↑ miR-3184-3p, miR-423-5p, let-7d-3p, miR-1296-5p, miR-345-5p, miR-532-5p, miR-423-3p, and miR-199a-3p</td>
<td>Predictive/Prognostic</td>
<td>Muscle tissue (Rectus abdominis)</td>
<td>(195)</td>
</tr>
<tr>
<td>Cachexia (pancreatic cancer)</td>
<td>↑ Monocyte chemoattractant protein-1 (MCP-1)</td>
<td>Diagnostic</td>
<td>Plasma</td>
<td>(124)</td>
</tr>
<tr>
<td>Cachexia (gastrointestinal tumors)</td>
<td>↑ circPTK2</td>
<td>Diagnostic</td>
<td>Adipose tissues</td>
<td>(196)</td>
</tr>
<tr>
<td>Cachexia (gastrointestinal/non-small cell lung cancer)</td>
<td>↑ IL-1β</td>
<td>Diagnostic</td>
<td>Plasma</td>
<td>(126)</td>
</tr>
</tbody>
</table>
Acknowledgments

We would like to thank King Abdullah University of Science and Technology for financial support.

References


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