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Clinical use of tumor biomarkers: An overview

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SUMMARY
Tumor biomarkers play an important role in cancer detection and guiding patient management. In healthy asymptomatic individuals, biomarkers may be used in the identification of those at increased risk of developing malignancy and in screening for early cancer. Following a diagnosis of malignancy, biomarkers can be used in determining prognosis, upfront therapy prediction, postoperative surveillance and monitoring response to ongoing therapy. Amongst the most widely used serum biomarkers are PSA in screening for prostate cancer, CEA in surveillance of patients with diagnosed CRC, both AFP and HCG in the management of patients with non-seminomatous germ cell tumors, CA 125 for monitoring therapy in patients with ovarian cancer. Mandatory tissue biomarkers include estrogen receptors (ER) and HER2 in breast cancer for predicting response to endocrine and anti-HER2, respectively, KRAS/NRAS genotyping for selecting patients with CRC likely to be resistant to treatment with anti-EGFR antibodies, BRAF genotyping for predicting response to anti-BRAF therapies in melanoma and EGFR genotyping for predicting response to EGFR TKI in patients with non-small cell lung cancer. In the future, mutation testing of plasma DNA is likely to complement or possibly replace some of the existing biomarkers.
Keywords: tumor markers, biomarkers, CEA, PSA, CA 15-3, CA 125, ER, HER2.

SOUHRN
Duffy M. J.: Klinické využití nádorových marker: přehled
Nádorové biomarkery hrají významnou roli v detekci nádorů a řízení péče o nemocné. U zdravých asymptomatických jedinců mohou být biomarkery využity k identifikaci osob se zvýšeným rizikem rozvoje malignity a pro screening časných nádorů. Po stanovení diagnózy malignity mohou být biomarkery následně použity pro určení prognózy, predikci efektu terapie, pooperační sledování a monitoraci odpovědi na probíhající terapii. Nejčastěji používanými sérovými biomarkery jsou PSA pro screening karcinomu prostaty, CEA při sledování pacientů s diagnostikovaným kolorektálním karcinomem (CRC), AFP a HCG v péči o nemocné s non-seminomatózními nádory ze zárodečných buněk a CA 125 pro monitoraci léčby nemocných s ovariálním karcinomem. Nezbytné tkáňové biomarkery zahrnují estrogenové receptory (ER) a HER2 u karcinomu prsu pro predikci odpovědi na endokrinní, resp. anti-HER2 léčbu, KRAS/NRAS genotypizace pro selekci pacientů s CRC, který bude pravděpodobně rezistentní na léčbu anti-EGFR protilátkami, BRAF genotypizace pro predikci odpovědi na anti-BRAF terapii u melanomu a EGFR genotypizace pro predikci odpovědi na EGFR TKI u pacientů s nemalobuněčným plicním nádorem. Testování mutací plazmatické DNA v budoucnu pravděpodobně doplní či případně nahradí některé z existujících biomarkerů.
Klíčová slova: nádorové markery, biomarkery, CEA, PSA, CA 15-3, CA 125, ER, HER2.

Introduction

Cancer markers or biomarkers are defined as molecules which indicate the presence of cancer or provides information about the likely future behaviour of a cancer (i.e., likelihood of progression or response to therapy) [1]. In recent years, biomarkers have begun to play an increasingly important role in cancer detection, treatment and patient follow-up (Table 1). Indeed, currently, the measurement of specific biomarkers is mandatory in patients with several different malignancies. The aim of this article is to discuss the use of biomarkers in cancer detection and management of patients with different diagnosed cancers.

Clinical Uses of Biomarkers

Identification of Subjects at Increased Risk of Developing Malignancy

The aim of risk assessment is to identify individuals who are at an increased risk of developing malignancy. This is now possible with genetic testing for several cancer-related syndromes. Within the past decade, the identity of many of the genes predisposing to hereditary cancer syndromes has been established [2, 3] (Table 2). Consequently, genetic testing for cancer susceptibility can now be carried out within high-risk families. For most hereditary cancer syndromes, a positive test for a known disease-causing mutation indicates that the individual has an increased risk of developing malignancy. However, it is not a guarantee that the individual will succumb to cancer. On the other hand, a negative result in a family with a known harmful mutation signifies that the individual has the same probability of developing cancer as a similar sex and age-matched subject in the community.

Since genetic testing for inherited cancer susceptibility may have adverse consequences, it is recommended that subjects considering such testing should receive both pre-test and post-test genetic counselling. This counselling must include discussion of possible risks and benefits of cancer early detection and prevention modalities [4].

Table 1: Cancer biomarkers used in clinical practice. *relates to mutational status; **relates to gene translocation; ***differentiated thyroid cancer. ER, estrogen receptor; PR progesterone receptors; PHI, Prostate Health Index; NSC, non-small cell; TKI, tyrosine kinase inhibitor such as gefitinib and erlotinib.

Cancer	Biomarker	Use
Breast	ER, PR	Predicting endocrine sensitivity
	HER2	Predicting anti-HER2 sensitivity
	CA 15-3	Monitoring therapy
	Oncotype DX	Prognosis and therapy prediction
	MammaPrint	Prognosis
	uPA/PAI-1	Prognosis
Colorectal	FOBT	Screening
	CEA	Surveillance and monitoring therapy
	KRAS/NRAS*	Predicting response to anti-EGFR therapy
Prostate	PSA	Screening, diagnostic aid, prognosis, surveillance and therapy monitoring
	PHI	Diagnostic aid, prognosis
Ovarian	CA 125	Differential diagnosis of pelvic masses, therapy monitoring
	HE4	Differential diagnosis of pelvic masses
Germ cell	AFP, HCG	Prognosis, surveillance, and therapy monitoring
Pancreatic	CA 19-9	Diagnostic aid and therapy monitoring
Melanoma	BRAF*	Predicting response to anti-BRAF therapy
Lung (NSC)	EGFR*	Predicting response to anti-EGFR TKIs
Lung (NSC)	ALK**	Predicting response to anti-ALK therapy
Thyroid***	Thyroglobulin	Surveillance, monitoring therapy

Table 2: Examples of hereditary cancer syndromes and their predisposing genes.

Hereditary Cancer Syndrome	Predisposing gene(s)
Hereditary breast and ovarian cancer	BRCA1, BRCA2
Familial adenomatous polyposis	APC
Hereditary non-polyposis colorectal cancer	MLH1, MSH2, MSH6, PMS1,
Multiple endocrine neoplasia type1	MEN1
Multiple endocrine neoplasia type 2	RET
Retinoblastoma	RB
Familial melanoma	CDK4, CDKN2A

Potential benefits of undergoing testing for inherited cancer susceptibility may include a more accurate risk assessment for the individual as well as their family, with the possibility of early cancer detection or indeed prevention. Thus, possible options for decreasing the risk of breast cancer in BRCA1/2 mutation carriers include surveillance with mammography and magnetic resonance imaging (MRI), prophylactic bilateral mastectomy, oophorectomy or administration of prophylactic tamoxifen [2, 3]. Recommended interventions for individuals at increased risk of familial adenomatous polyps (FAP) and hereditary non-polyposis coli colorectal cancer (HNPCC) include colectomy and regular colonoscopy, respectively [2, 3].

Screening and Early Detection of Cancer

Detecting cancer at an early and potentially treatable stage is one of the greatest challenges in medicine today. Indeed, the development of biomarkers for this purpose is currently one of the top priorities in cancer research. Unfortunately, most of the available biomarkers are unsuitable for early detection as they possess inadequate sensitivity for small cancers or premalignant lesions and lack specificity for malignancy [5, 6]. These twin problems of limited sensitivity and specificity, especially when combined with the low prevalence of most cancers in the community, limit the use of most of the available biomarkers in population-based screening for early malignancy [5, 6].

However, as biomarkers are usually easy and relatively cheap to measure, several have undergone evaluation for cancer screening [5, 6]. Indeed, two biomarkers are currently widely used in asymptomatic subjects to screen for early cancer, i.e., PSA for prostate cancer [7] and fecal occult testing (FOBT) for colorectal cancer [8]. Although widely performed, screening for prostate cancer is controversial, mainly because it is unclear whether the practice does more good than harm [7]. Consequently, guidelines on PSA screening vary, with some expert panels opposed to the practice and other

recommending it, following a discussion with the man's doctor regarding benefits and harms of the testing [9]. In contrast, population-based screening for CRC with FOBT especially using the fecal immunochemical test (FIT) is widely recommended [8] and is ongoing in many countries.

A biomarker used to screen for cancer in high-risk individuals is AFP in detecting hepatocellular cancer [10]. Thus, according to guidelines published by the National Academy of Clinical Biochemistry (NACB) (US), AFP should be measured and abdominal ultrasound performed at 6-month intervals in patients at high risk of HCC, especially in those with liver cirrhosis related to hepatitis B and hepatitis C virus. AFP concentrations that are >20 μg/L and increasing should prompt further investigation even if ultrasound is negative [11].

Diagnostic Aids for Cancer

Diagnosis, in contrast to screening, involves patients with specific symptoms which may or may not be due to cancer. In general, serum biomarkers contribute little to the early diagnosis of cancer, mainly due to lack of specificity and sensitivity. In a small number of situations however, biomarkers may aid in the differential diagnosis of benign and malignant disease. Thus, serum CA 125 is used as an adjunct in differentiating between benign and malignant pelvic masses in postmenopausal women [12-14]. Thus, according to the guidelines of the European Group on Tumor Markers (EGTM), the Risk of Malignancy Index, which includes CA125, transvaginal ultrasound, and menopausal status, is recommended for the differential diagnosis of a pelvic mass [14]. Similarly, HE4 may be used as a diagnostic aid in women with pelvic masses as it has superior specificity to CA125, especially in premenopausal women [14].

Another biomarker that can aid cancer diagnosis is AFP for detection of hepatocellular cancer. According to the NACB guidelines [11], "sustained increases in serum AFP may be used in conjunction with ultrasound to aid early detection of HCC in patients at high-risk for HCC. Ultrasound detected nodules < 1 cm should be monitored at 3-month intervals with ultrasound. Nodules of 1–2 cm in cirrhotic liver should be investigated by two imaging modalities (e.g. CT and MRI). If the appearance of the nodules is consistent with HCC, they should be treated as such, with biopsy required if not. If lesions are > 2 cm in size, AFP is > 200 μg/L, and the ultrasound appearance is typical of HCC, results may be considered diagnostic of HCC and biopsy is not necessary".

Assessing Prognosis

Following diagnosis and surgical removal of a primary cancer, the key questions to be addressed for patient management are: how aggressive is the tumor and, is administration of adjuvant systemic therapy necessary. Thus, if a tumor is deemed to be indolent, the patient may be able to avoid having to receive adjuvant systemic treatment. On the other hand, if identified as being potentially aggressive and life threatening, he/she would be advised to have additional therapy, such as adjuvant chemotherapy.

Historically, histological (tumor size, tumor grade, status of local lymph nodes) and clinical (patient age, co-morbidity) criteria were used as aids for addressing the above questions. Although these clinical and histological factors are still universally used, in recent years a limited number of biomarkers have become available that supplement the traditional criteria for determining prognosis in patients with cancer. These include the tissue-based biomarkers, urokinase type plasminogen activator (uPA), PAI-1, Oncotype DX and MammaPrint for assessing prognosis in patients with breast cancer [15, 16]. All these tests can help identifying lymph node-negative patients whose prognosis is so good that they may not require adjuvant chemotherapy. Other biomarkers widely used for aiding prognosis include AFP, HCG and LDH in patients with testicular cancer (non-seminomatous type) [17] and PSA in patients with prostate cancer [18].

Therapy Predictive Markers in Cancer

Therapy predictive biomarkers prospectively identify patients who are likely to respond or be resistant to specific treatments. Predictive biomarkers are necessary as patients with malignancies of the same organ type respond very differently to a specific drug. Thus, response rates for unselected patients with different types of advanced cancer to currently available systemic treatments vary from < 10 % to > 90 % [15, 19]. Many of the newer biological or molecular therapies, in particular, have efficacy in only a minority of unselected patients (< 10 %). This finding, when combined with the high costs of some of these drugs, illustrates the importance of having accurate therapy predictive biomarkers.

In recent years, several new therapy predictive biomarkers entered clinical use (Table 3) [15, 19]. Measurement of the therapy predictive biomarkers listed in Table 3 is indeed mandatory prior to administering the relevant therapy. Although an increasing number of therapy predictive biomarkers have recently become available, many more are necessary in order to progress toward personalized treatment for patients with cancer. New predictive biomarkers are especially required for the identification of patients likely to benefit from specific cytotoxic drugs (taxanes, anthracyclines, platinums), anti-angiogenic therapy (bevacizumab, aflivercept) and immunotherapies (ipilumumab, anti PD-1 antibodies).

As well as assessing efficacy, predictive biomarkers may also potentially identify optimum drug dose and predict severe toxicity. However, currently, there are few validated biomarkers for upfront determining drug dose or predicting likely severe toxicity.

Overall, therapy predictive biomarkers are important in patient management and personalizing treatment. Their measurement can increase drug efficacy and result in decreased toxicity. This in turn, should reduce overall health care costs and lead to an enhanced quality of life for patients.

Table 3: Routinely used predictive biomarkers for therapies in oncology. NSCLC, non-small cell lung cancer. *refers to mutational status; EML4-ALK translocation.

Therapy	Marker	Cancer
Hormone (tamoxifen, aromatase inhibitors)	Estrogen receptor	Breast
Anti HER2 (trastuzumab, lapatinib, pertuzumab, TDM-1)	HER2	Breast
Trastuzumab	HER2	Gastric
Anti EGFR (cetuximab, panitumumab)	KRAS*	Colorectal
EGFR TKIs (gefitinib, erlotinib, afatinib)	EGFR*	NSCLC
Anti ALK (crizotinib, ceritinib)	EML4-ALK**	NSCLC
Anti KIT (imatinib)	KIT*	GIST
Anti BRAF (vemurafenib, dabrafenib)	BRAF*	Melanoma

Surveillance Following Treatment for Cancer

The primary aim of postoperative surveillance is to detect recurrent/metastatic disease at a potentially curable stage, the assumption being that early detection followed by the initiation of treatment will result in better outcome than starting treatment when a recurrence is clinically evident. Indeed, in several cancer types, serial levels of biomarkers cancer can predict the presence of early recurrent/metastatic disease, i.e., provide a lead-time vis-à-vis clinical and radiological finding. Biomarkers that can identify early recurrences and are in routine clinical use for this purpose include HCG in trophoblastic malignancy, PSA in prostate cancer, CEA in colo-rectal cancer, AFP and HCG in patients with germ cell tumors of the testis (non-seminomatous type), CA 15-3 in breast cancer and CA 125 in ovarian cancer [20-30]. However, apart from CEA in colorectal cancer, there is little evidence that the early detection of recurrent disease and the initiation of new treatment enhances patient outcome [20, 21].

Monitoring Systemic Therapy

Another frequent use of tumor biomarkers is in monitoring patients with advanced cancer receiving systemic therapy. Although radiological imaging is the gold standard method for monitoring response to therapy, the use of blood-based biomarkers is more convenient for patients and less expensive. Generally, decreasing blood levels of biomarkers following the initiation of therapy correlates with tumor regression and increasing levels predict progressive disease. Biomarkers widely used in monitoring therapy include the bcr-abl translocation in chronic myeloid leukemia, AFP and HCG in testicular germ cell cancers, CA 125 in ovarian cancer, PSA in prostate cancer, CEA in colorectal cancer and CA 15-3 in breast cancer [20-30].

With most, if not these biomarkers, transient increases or spikes in serum levels may occur within the first month or two of starting treatment, especially in patients with large tumor volume [1]. These short-term increases are believed to result from tumor cell death (necrosis or apoptosis) in response to the initial treatment with the cytotoxic drugs and are not associated with disease progression. Such transient increases have not yet been reported with biological therapies such as therapeutic monoclonal antibodies (e.g., trastuzumab, cetuximab or panitumumab).

Conclusion

From above, it is clear, that certain tumor biomarkers are making a major contribution to cancer detection and patient management. Indeed, in some situations, biomarkers can be used as the only available criterion for clinical decision making. This applies especially for all the therapy predictive biomarkers listed in Table 3. Other mandatory biomarkers are the use of both HCG and AFP treatment in patients with germ cell tumors of testis. In this situation, doctors are recommended to initiate or change therapy based solely on serum levels of these biomarkers, i.e., irrespective of radiological or clinical findings. In other situations, however, the clinical use of biomarkers is less certain. Thus, although PSA is widely used in screening for prostate cancer, the impact of this practice on decreasing mortality or indeed doing more good than harm is uncertain [7]. Similarly, the clinical value of serial determinations of biomarkers (e.g., CA 15-3 or CEA) in the surveillance of patients who have undergone curative surgery is unclear.

In the future, the trend will be to simultaneously measure multiple biomarkers with technologies such as microarray, multiplex PCR, multigene sequencing and eventually whole genome analysis. The use of multiple markers can potentially capture more fully, intra-tumor heterogeneity and provide more comprehensive clinical information than is currently available with only one or two biomarkers.

References

1. **Duffy, M. J.** Tumor markers in clinical practice: A review focusing on common solid cancers. *Med. Princ. Pract.*, 2013, 22, p. 4-11.
2. **Sifri, R., Gangadharappa, S., Acheson, L.** Identifying and testing for hereditary susceptibility to cancer. *CA Cancer J. Clin.*, 2004, 54, p. 309-326.
3. **Lerman, C., Shields, A. E.** Genetic testing for cancer susceptibility. Nature Rev. *Cancer*, 2004, 4, p. 235-241.
4. **Robson, M. E., Bradbury, A. R., Arun, B., Domchek, S. M., Ford, J. M., Hampel, H. L., Lipkin, S. M., Syngal, S., Wollins, D. S., Lindor, N. M.** American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin. Oncol.*, 2015, 33, p. 3660-36607.
5. **Duffy, M. J.** Use of Biomarkers in screening for cancer. Duffy MJ1. EJIFCC. 2010, 21, p. 1-12. *eCollection* 2010 Mar.

6. **Duffy, M. J.** Use of biomarkers in screening for cancer. Adv. Exp. Med. Biol., 2015, 867, p. 27-39.
7. **Duffy, M. J.** PSA in screening for prostate cancer: more good than harm or more harm than good? *Adv. Clin. Chem.*, 2014, 66, p. 1-23.
8. **Duffy, M. J., van Rossum, L. G., van Turenhout, S. T., Malminiemi, O., Sturgeon, C., Lamerz, R., Nicolini, A., Haglund, C., Holubec, L., Fraser, C. G., Halloran, S. P.** Use of faecal markers in screening for colorectal neoplasia: a European group on tumor markers position paper. *Int. J Cancer*, 2011, 128, p. 3-11.
9. **Pinsky, P. F., Prorok, P. C., Kramer, B. S.** Prostate Cancer Screening - A Perspective on the Current State of the Evidence. *N Engl. J Med.*, 2017, 376, p. 1285-1289.
10. **Sauzay, C., Petit, A., Bourgeois, A. M., Barbare, J. C., Chauffert, B., Galmiche, A., Houessinon, A.** Alpha-foetoprotein (AFP): A multi-purpose marker in hepatocellular carcinoma. *Clin. Chim. Acta*, 2016, 463, p. 39-44.
11. **Sturgeon, C. M., Duffy, M. J., Hofmann, B. R. et al.** National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers. *Clin. Chem.*, 2010, 56, e1-48.
12. **Sturgeon, C. M., Duffy, M. J., Stenman, U. K. et al.** National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast and Ovarian Cancers. *Clin. Chem.*, 2008, 54, e11-79.
13. **Duffy, M. J., Bonfrer, J. M., Kulpa, J. et al.** CA125 in ovarian cancer: European Group on Tumor Markers (EGTM) guidelines for clinical use. *Int J Gynecol. Cancer*, 2005, 15, p. 679-691.
14. **Sölétormos, G., Duffy, M. J., Othman, A. H. S., Verheijen, R. H., Tholander, B., Bast, R. C. Jr., Gaarenstroom, K. N., Sturgeon, C. M., Bonfrer, J. M., Petersen, P. H., Troonen, H., CarloTorre, G., Kanty, K. J., Tuxen, M. K., Molina, R.** Clinical Use of Cancer Biomarkers in Epithelial Ovarian Cancer: Updated Guidelines From the European Group on Tumor Markers. *Int. J Gynecol. Cancer*, 2016, 26, p. 43-51.
15. **Duffy, M. J., Crown, J.** Precision treatment for cancer: role of prognostic and predictive markers. *Crit. Rev. Clin. Lab. Sci.*, 2014, 51, p. 30-45.
16. **Duffy, M. J., Harbeck, N., Nap, M., Molina, R., Nicolini, A., Senkus, E., Cardoso, F.** Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur. J Cancer*, 2017, 75, p. 284-298.
17. **Steyerberg, E. W., Pencina, M. J., Lingsma, H. F., Kattan, M. W., Vickers, A. J., Van Calster, B.** Assessing the incremental value of diagnostic and prognostic markers: a review and illustration. *Eur. J Clin. Invest.*, 2012, 42, p. 216-28.
18. **Kontos, C. K., Adamopoulos, P. G., Scorilas, A.** Prognostic and predictive biomarkers in prostate cancer. *Expert Rev. Mol. Diagn.*, 2015, 15, p. 1567-76.
19. **Duffy, M. J., Crown, J.** Companion biomarkers: paving the way to personalized treatment for cancer. *Clin. Chem.*, 2013, 59, p. 1447-56.
20. **Renehan, A. G., Egger, M., Saunders, M. P., O'Dwyer, S. T.** Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ*, 2002, 324, p. 813-20.
21. **Figueredo, A., Rumble, R. B., Maroun, J. et al.** Follow-up of patients with curatively resected colorectal cancer: a practice guideline. *BMC Cancer*, 2003, 3, p. 26-38.
22. **Duffy, M. J., van Dalen, A., Haglund, C. et al.** Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. *Eur. J Cancer*, 2007, 43, p. 1348-1360.
23. **Duffy, M. J., Lamerz, R., Haglund, C., Nicolini, A., Kalousová, M., Holubec, L., Sturgeon, C.** Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European Group on Tumor Markers 2014 guidelines update. *Int. J Cancer*, 2014, 134, p. 2513-22.
24. **Locker, G. Y., Hamilton, S., Harris, J. et al.** ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin. Oncol.*, 2006, 24, p. 5313-27.
25. **Gilligan, T. D., Seidenfeld, J., Basch, E. M. et al.** American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin. Oncol.*, 2010, 28, p. 3388-404.
26. **Diniz, C. P., Landis, P., Carter, H. B., Epstein, J. I., Mamawala, M.** Comparison of biochemical recurrence free survival after radical prostatectomy triggered by grade reclassification on active surveillance, and men newly diagnosed with similar grade disease. *J Urol.*, 2017, S0022-5347(17)42184-7.
27. **Tuxen, M. K., Soletormos, G., Dombernowsky, P.** Serum tumour marker CA 125 in monitoring of ovarian cancer during first-line chemotherapy. *Br. J Cancer*, 2001, 84, p. 1301-1307.
28. **Rustin, G. J., van der Burg, M. E., Griffin, C. L., Guthrie, D., Lamont, A., Jayson, G. C., Kristensen, G., Mediola, C., Coens, C., Qian, W., Parmar, M. K., Swart, A. M.,** MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet*, 2010, 376, p. 1155-63.
29. **Duffy, M. J., Walsh, S., McDermott, E. W., Crown, J.** Biomarkers in breast cancer: where are we and where are we going? *Adv. Clin. Chem.*, 2015, 71, p. 1-23.
30. **Duffy, M. J., Evoy, D., McDermott, E. W.** CA 15-3: Uses and limitation as a biomarker for breast cancer. *Clin. Chim. Acta*, 2010, 411, p. 1869-74.

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