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Chapter

lncRNAs in Hallmarks of Cancer and Clinical Applications

Leandro Garcia, Erika Zambalde, Carolina Mathias, Jéssica Barazetti, Daniela Gradia and Jaqueline Oliveira

Abstract

Long noncoding RNAs (lncRNAs) are transcripts longer than 200 nucleotides in length that, in general, do not appear to have protein-coding potential. lncRNAs act in gene regulation involved with several biological processes. Furthermore, lncRNAs have been associated with a significant number of cancers, suggesting a potential role in tumorigenesis and progression. For example, HOTAIR regulates proliferation processes and other lncRNAs like highly upregulated in liver cancer (HULC), H19, PTENP1, HEIH, and antisense noncoding RNA in the INK4 locus (ANRIL). Other lncRNAs as AFAP1-AS1 and lincRNA-p21 can interact with *BCL-2* and *TP53*, acting in apoptosis. Moreover, NORAD plays a vital role in genomic stability. Additionally, due to deregulated expression and high tissue specificity level, lncRNAs exhibit great potential as prognostic markers. In this chapter, we review the most highlighted lncRNAs acting in hallmarks of cancer and clinical application.

Keywords: cancer, hallmarks, lncRNAs, ncRNAs, tumor

1. Introduction

The landscape of human transcriptome is more complicated than was imagined. In the last decade, the technology of RNA sequencing reveals more than 100,000 different RNA molecules produced by mammalian organisms [1, 2], most of them, without protein-coding potential, named as noncoding RNAs (ncRNAs). These molecules called the attention for their multiple roles in cell physiology. NcRNAs are classified, by the size, as small (microRNAs 22~25 bp) or long, with more than 200 nucleotides [3]. Previously, it was considered that lncRNAs were "dark matter" or "transcriptional noise" of the human transcriptome, with no biological functions. Recently, lncRNAs were found in all the branches of the tree of life, and their amount and diversity are more correlated with organismal complexity than protein-coding genes [4].

The majority of lncRNAs is transcribed by RNA polymerase II, capped and polyadenylated with some lncRNAs being also spliced. They are described as noncoding RNAs. New studies have shown functional micropeptides derived from some of the lncRNAs [5]. Until now, 16,000 lncRNAs were identified in the human genome with approximately 30,000 distinct lncRNA transcripts according to the Encyclopedia of DNA Elements (ENCODE) Project Consortium (GENCODE release 30). This number continues to increase, mainly through sensitive RNA sequencing and advanced

bioinformatics pipelines. lncRNAs have a lower expression level than other RNAs, and they show specific expression in tissues [6, 7], cell types, and subcellular compartments [8]. lncRNAs are classified according to their relative position to protein-coding genes in a sense, antisense, bidirectional, intronic, and intergenic [9]. Also, lncRNAs can be regulated by well-established transcription factors and associated with epigenetic signatures that modify chromatin states, making the lncRNA loci more accessible in the cell [10].

The current knowledge about lncRNAs is essential to understand cell biology, especially in cancer cells. Cancer is a complex disease characterized by extreme genetic and epigenetic changes that can fundamentally alter cell homeostasis to promote uncontrolled cell growth. Emerging evidence suggests that lncRNAs are involved with cancer-associated phenotypes like resisting cell death, invasion, proliferation, gene deregulation, and genomic instability and evade growth suppressors [11]. lncRNAs also interact with transcriptional regulation of tumor suppressors or oncogenes [12, 13]. One example is lincRNA-p21 that acts as a repressor in p53-dependent transcriptional responses [12]. Alternatively, HOTAIR can increase metastasis in primary breast tumors and hepatocellular carcinomas [14].

lncRNAs can participate in gene regulation at transcriptional and posttranscriptional levels [15]. For example, related to epigenetic mechanisms, lncRNAs can recruit methyltransferases [16] and polycomb complex [17] to prevent DNA accessibility through histone modification. lncRNAs are also involved in several posttranscriptional processes, such as splicing and nuclear export, mRNAs localization and stability, and in protein translation process [18–22].

lncRNAs can serve as a molecular scaffold, enhancing the interactions between protein-protein, protein-RNA, and protein-DNA, by base complementarity or interaction by secondary structures [23]. Alternatively, lncRNAs can function as a decoy when they titrate transcription molecules and other proteins away from the target [24]. Additionally, lncRNAs can work as binding platforms regulating miRNAs competing with mRNAs for miRNA response elements, known as competitive endogenous [25].

The development of several discoveries about the role of lncRNAs, especially in cancer, highlighted the importance of gene regulation in cellular functions. The evidence that we show here supports the idea that lncRNAs have an essential role in tumorigenesis and are associated with several cellular processes. Here, we review the current knowledge about lncRNAs in hallmarks of cancer and their potential for clinical application.

2. lncRNAs act in hallmarks of cancer

The transformation of a regular cell into cancer involves several processes, including molecular and environmental alterations [26]. The healthy cells must acquire different abilities to change the cell physiology and dictate malignant growth. The hallmarks of cancer comprise the biological capabilities acquired during the multistep development of human tumors. These changes include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion/metastasis [27]. Additionally, genomic instability, inflammation, reprogramming of energy metabolism, and evading immune destruction were also included [28]. There are many lncRNAs well described associated with cancer [29], and, herein, we highlighted some lncRNAs with strong evidence for cancer process association and with molecular details, for exemple (**Figure 1**). The influence of those long noncoding RNAs in hallmarks of cancer is due to the regulation of different pathways.

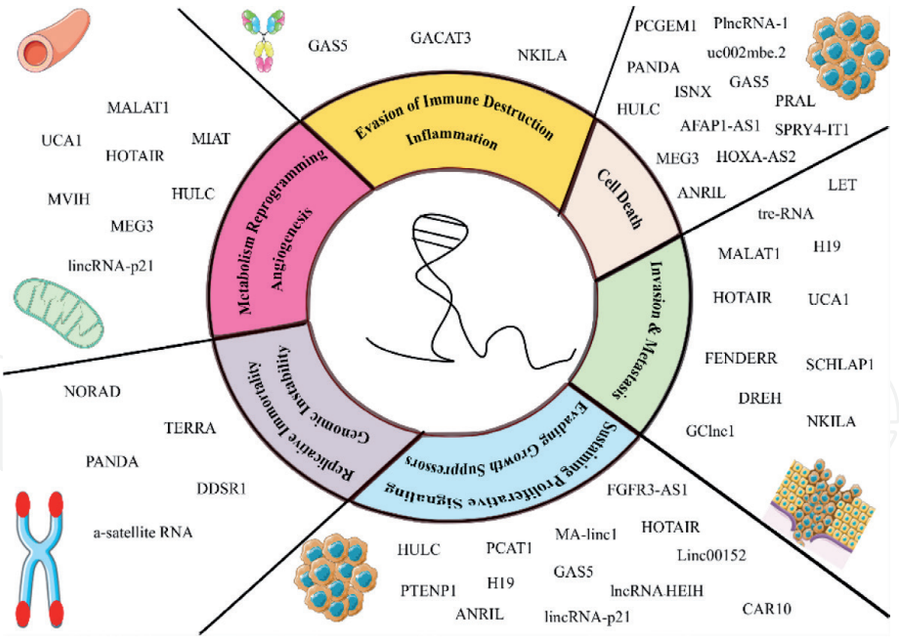

Figure 1.
lncRNAs in hallmarks of cancer.

lncRNAs have virtual association in all the hallmarks of cancer, some of them linked with more than one hallmark. For example, the expression of ANRIL, growth arrest-specific transcript 5 (GAS5), urothelial cancer-associated 1 (UCA1), and HULC regulates the resistance to cell death. Also, ANRIL, HULC, and H19 are associated with the evasion of growth suppressors, GAS5, and H19, sustaining cell proliferation. UCA1 and H19 are also associated with invasion and metastasis. Moreover, UCA1 is associated with metabolism reprogramming and GAS5 with an inflammatory process.

In more detail, ANRIL may inhibit apoptosis by silencing *KFL2* and *p21* genes, involved in cell proliferation. Moreover, regulating MET and MMP3 proteins that facilitate cell migration and invasion [30–34].

The lncRNA GAS5 can sustain proliferation by regulating glucocorticoid receptors (GR), with strong influences in cell growth and repression of anti-apoptosis genes. lncRNA binds to the DNA-binding domain of GR, competing with glucocorticoid response element [35].

lncRNA is also observed in cell cycle regulation, whereas it arrests cells in the G0/G1 phase. In stomach cancer, GAS5 binds to YBX1 to regulate *p21* expression, enhancing G1 arrest. In bladder cancer, GAS5 associates with CDK6 and reduces both *CDK6* mRNA and protein levels, resulting in the inhibition of cell proliferation. Besides, GAS5 acts in the immune response by NF-κB and ERK1/2 pathways. The knockdown of *GAS5* increases expression and secretion of interleukin-10 (*IL-10*) and vascular endothelial growth factor (*VEGF-A*), the essential cytokines involved in inflammation [36].

Due to its oncogenic regulatory potential, the lncRNA UCA1 regulates the proliferation and migration targeting the transcription factor KLF832 in pancreatic cancer. UCA1 also promotes invasion and metastasis through activation of *MMP14*, *FGFR1/ERK*, and *ZEB1/2-FSCN1* [37–40]. In hypoxic conditions, *HIF-1α* effectively activates UCA1 transcription by binding in the *UCA1* promoter, inducing proliferation, migration, invasion, and apoptosis resistance of cancer cells [41].

Several pathways regulate the switch of oxidative phosphorylation to aerobic glycolysis, such as the PI3K, AMPK, p53, and HIF-1 pathways. These pathways

are involved in metabolism deregulation associated with the Warburg effect, which consists in the special metabolism of glucose in the cytosol even in the presence of oxygen [42, 43], and UCA1 acts indirectly in genes involved in this process [44, 45].

HULC contributes to malignant phenotypes by, at least, three mechanisms. The first is regulating the expression of P18, an auxiliary protein of cell cycle that inhibits the tumor suppressors *CDK4* and *CDK6*. Also, hepatitis B virus infection activates the *HULC* promoter and induces cell cycle progression by downregulation of *P18* [46]. The other two mechanisms are related to angiogenesis. In breast and liver cancer, HULC sequesters miR-107 and regulates the transcription factor *E2F1/SPHK1* [47, 48]. In glioma, HULC acts through PI3K/Akt/mTOR signaling pathway, inducing *ESM-1/VEGF-A* and affecting vascular permeability and cell mobilization [49].

Some lncRNAs have been described more exclusively in only one hallmark, for example, telomeric repeat-containing RNA (TERRA) associated with replicative immortality. We know that cells have a limited survival rate that can be explained by telomere end loss, which generate a waste of genetic conservation, restricting the number of mitosis in a tissue. Thus, neoplastic cells can escape this telomere process with the help of telomerase. This enzyme can increase the size of telomere adding repeats on the edge 3′ in chromosomes [50]. TERRA comprises a heterogeneous class of lncRNAs transcribed from telomeric regions [51]. TERRA transcripts negatively regulate the activity of telomerase, acting as a tumor suppressor. Besides acting as telomere maintenance and genome stability, TERRA is also regulated by genes, such as *TP53* and *RB*, highlighting that TERRA transcripts can be crucially involved in tumorigenesis [52–54].

Another critical feature of neoplastic cells is in genomic instability, which can be related to defects in the DNA repair machinery. Activation of telomerase, following by individual DNA variations, activating proto-oncogenes or deactivating tumor suppressor genes, conferring a selective advantage on subclones of tumor cells, enabling their survival and outgrowth [28].

One lncRNA that is important in this tumor cell feature is NORAD. lncRNA protects the cells against aneuploidy by binding to *PUM1/PUM2* proteins and suppressing their binding to other targets, including those that maintain genomic stability [55, 56]. An alternative mechanism to define the relationship among NORAD and genomic stability is that a nuclear ribonucleoprotein complex, named NORAD-activated ribonucleoprotein complex 1 (NARC1), is joined by NORAD, recruiting proteins known to act as suppressors of genomic instability, such as topoisomerase I (*TOP1*), *ALYREF*, and the *PRPF19-CDC5L* [57].

The implication of lncRNAs in cancer development and progression has been proved in the last decade and indicates that those new class of RNAs has a great potential as biomarkers on cancer and a future perspective to targeted specific therapies.

3. Clinical application for lncRNAs

As we discussed in earlier topics, we have examples of lncRNAs that participate in essential processes in tumor development. Many of them have great potential as diagnostic/prognostic markers and therapeutic targets. A great example is the lncRNA prostate cancer antigen 3 (PCA3), already used as a molecular marker in prostate cancer [58, 59]. PCA3 is a prostate-specific lncRNA overexpressed in 95% of prostate cancer cases. PCA3 may be detected by *in vitro* nucleic acid amplification

in urine specimens, and the US Food and Drug Administration approved the test in 2012 [60].

In cases of suspicion of prostate cancer, the PCA3 test is recommended, based on prostate-specific antigen (PSA) level and post-digital rectal examination with biopsy results. PCA3 has a high expression in prostate cancer without any correlation to prostatic volume and other prostatic diseases. This feature makes a PCA3 an attractive biomarker [61], but some recent studies question the use of this isolated biomarker and propose that the test should be carried out in association with another test, like *TMPRSS2:ERG* quantification [58].

Although there are few lncRNAs used in medical practice, many are being discovered and tested. For example, a treatment protocol for triple-negative high-risk breast cancer predicted by the integrated mRNA-lncRNA signatures is initiated in the clinical trials evaluated, to validate the efficacy of lncRNA signature [62].

Also, in clinical trials, there is an early phase study to evaluate the HOTAIR as a potential lncRNA biomarker in thyroid cancer. Many lncRNAs have a different expression in tumors when compared to healthy tissues and are strongly associated with clinical parameters, making them a candidate for tumor markers or even therapeutic targets [63].

A study found the downregulation of expression of downregulated in liver cancer (DILC) in colorectal cancer tissues compared to their adjacent healthy tissues and the normal colorectal tissues. The downregulation of DILC was associated with aggressive clinical characteristics, including depth of invasion and advanced TNM stage, and the lower expression of DILC was associated with more reduced survival and disease-free survival. With multivariate analyses, the authors confirmed that the expression of DILC was an independent prognostic factor in colorectal cancer [64]. Most of lncRNA papers characterize biomarkers that are specific to one type of cancer, such as those cited above. However, some lncRNAs are found differentially expressed in several types of cancer compared with healthy tissues, like the loc285194 lncRNA [65].

In addition to the association of lncRNAs with stage and prognosis, their association with drug resistance is also possible [66]. Several works have tried to reallocate the lncRNAs in the mechanism of resistance to the primary drugs used in the treatment of cancer. For example, Campos-Parra et al. [67] have identified several lncRNAs that participate in resistance mechanisms to several drugs utilized in the therapy of breast cancer. Most studies with lncRNAs measure their expression in tissues, but it is possible to detect and quantify their presence in other types of samples, like whole blood, plasma, urine, gastric acid, and saliva [68].

Within the use of lncRNAs as biomarkers in cancer, these molecules have applications as therapeutic targets in the development of new treatments and drugs. New therapeutic strategies are already focusing on noncoding RNAs, such as silencing via small interfering RNA (siRNA), an antisense oligonucleotide (ASO)-based strategies and other molecular inhibitors further modulating lncRNA expression by gene editing [69, 70]. An experimental model that aims to modulate lncRNAs in cancer cells is the use of siRNAs, which can decrease the amount of a target lncRNA, since they are complementary molecules to the sequence of lncRNA, promoting lncRNA binding and subsequent degradation. Although this methodology may be functional in many studies, some lncRNAs are not efficiently reduced by siRNA [70]. This methodology is efficient for cytoplasmic lncRNAs since the siRNA mechanism is located predominantly in the cytoplasm. In this case, siRNA does not silence nuclear lncRNAs [11, 71].

Another mechanism used to block lncRNAs activity relies on the ability of lncRNAs to bend and create secondary structures and on the ability of protein

interactions in lncRNAs. RNAi molecule can compete with the protein for the binding site; or when it binds to the target lncRNA, it changes the structure of the RNA, disrupting the binding site of the protein [72, 73].

For nuclear lncRNAs, an alternative strategy is the use of antisense oligonucleotides, which function predominantly in the nucleus [71]. ASOs modulate gene expression by inducing ribonuclease H cleavage of the duplex DNA-RNA. A limitation of the ASO and siRNA strategies is the possibility of non-specific targets, as well as the inconvenience of incomplete knockdown and transient modulation [74]. One method that has shed light on ncRNA-based cancer therapy and solves the problem of target specificity is genome editing by clustered regularly interspaced short palindromic repeats-associated endonuclease 9 (CRISPR/Cas9). The Cas9 nuclease can act guided to generate site-specific DNA cleavage in the genome, by an optimized equivalent single-guide RNA (sgRNA) [75]. That is, it can delete lncRNA genes or introduce RNA-destabilizing elements into their locus.

A limitation to apply CRISPR/Cas9 system to noncoding genes is that tiny indels may not necessarily generate a functional loss of a specific noncoding gene and the most protocols can perform small point mutations; plus not all lncRNAs CRISPR can be applied. Another limitation is that, although it is more specific than other systems, this technique may still have off-target effects [76, 77].

Currently, many studies performed lncRNA modulation technologies, both *in vitro* and *in vivo*. Moreover, while these models may resemble reality, the clinical use of modulation technology has a barrier that still needs to be broken: an efficient delivery to the target. There are some techniques for delivering lncRNA modulation systems to live cells, based on viral and non-viral methods, but both ways have limitations and problems to be solved before the utilization in clinical practice.

The main advantage of viral vectors is their innate ability to efficiently transfer the genetic material into the cell and the possibility of infecting specific cells. However, this technique also has a significant disadvantage, which is relatively high immunogenicity and toxicity. The possibility of generating an immune response is the main challenge for the use of this tool [78, 79].

Non-viral vectors are becoming recognized as an alternative to the immunogenicity of viral vectors, although their transfection capabilities usually do not reach such levels. Besides its main strengths are the low capacity to generate an immune response and the relatively easy and inexpensive synthesis with large-scale production and safety, which make them very attractive delivery systems for *in vivo* application. However, the target specification still needs to be better developed [79].

In order to choose the best delivery system, it is necessary to consider the type of cell/tissue, since some tissues are more accessible than others. When the target of therapy is a difficult-to-access tissue, some strategies may improve delivery efficiencies, such as binding to specific targeting elements like antibodies, carbohydrates, and synthetic peptides. These molecules also have their advantages and limitations; for example, although antibodies have a high recognition specificity and interaction with different receptors on target cells, they may be immunogenic and chemically unstable. Peptides and carbohydrates, on the other hand, demonstrate low immunogenicity, but the binding affinity to the target is lower [79, 80].

All the techniques cited in this topic have their limitations. Although *in vitro* studies present satisfactory results that have the potential to use in clinical aspects. However, these techniques require better improvements, especially in the delivery of drugs in specific targets. Despite this, our knowledge of lncRNAs linked with clinical applications creates hope for the development of better biomarkers and therapeutic targets. In **Table 1**, we list the main lncRNAs that have excellent potential for biomarker and therapeutic target.

	Cancer															
lncRNAs	**Head/ neck**	**Gastric**	**Lung**	**Breast**	**Pancreas**	**Liver**	**Colon**	**Uterine**	**Ovarian**	**Osteosarcoma**	**Prostate**	**Bladder**	**Renal**	**SNC**	**Leukemia**	**Refs.**
AFAP1-AS1	x	x	x	x	x	x	x		x			x	x			[81]
ANRIL	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	[82, 83]
CCAT1/ CCAT2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	[84]
CRNDE		x	x	x	x	x	x	x	x			x	x	x	x	[85]
DANCR		x	x	x		x	x			x	x		x			[85]
GAS5		x	x	x	x	x	x	x	x	x	x	x	x	x	x	[86]
H19	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	[87]
HOTAIR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	[88]
HULC	x	x		x	x	x	x	x	x	x	x	x		x	x	[89]
LINC00152	x	x	x	x	x	x	x		x			x	x	x		[90]
LincRNA-p21		x	x			x	x				x				x	[91]
Linc-RoR	x		x	x	x	x	x		x					x		[92]
MALAT1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	[93]
MALAT2		x														[94]
MEG3	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	[95]
MIAT		x	x	x	x		x		x		x		x		x	[96]
NEAT1	x	x	x	x	x	x	x	x	x	x	x		x	x	x	[97]
PANDA		x	x	x	x	x	x			x			x			[98]

	Cancer															
lncRNAs	**Head/ neck**	**Gastric**	**Lung**	**Breast**	**Pancreas**	**Liver**	**Colon**	**Uterine**	**Ovarian**	**Osteosarcoma**	**Prostate**	**Bladder**	**Renal**	**SNC**	**Leukemia**	**Refs.**
PCA3									x		x					[99, 100]
PCAT-1	x	x	x	x		x	x	x		x	x	x		x		[101, 102]
TUG1	x	x	x	x		x	x	x	x	x	x	x	x	x	x	[103, 104]
XIST	x	x	x	x		x	x	x	x	x	x	x		x	x	[105]

Table 1.
lncRNAs with potential to be used as biomarkers, in several types of cancer.

4. Conclusion

The vast number of studies describing lncRNAs associated with several tumor types and regulating several processes of cancer cells is shown here. The great advance in RNA sequencing technology allows us to identify new molecules and characterized better lncRNAs. From the discovery of these molecules, in the beginning, they appeared to have no important functions; however, today many researches in this area propose that more information about these molecules may help us understand numerous characters of tumor cells that are still unknown. Some lncRNAs are associated with several hallmarks of cancer demonstrating the importance of these molecules in the mechanism of disease, like MALAT and HOTAIR. Other are already utilized as biomarker in prostate cancer like PCA3. Considering the challenges for *in vivo* experimental designs, lncRNAs continue to be promising as biomarkers and potential therapeutic targets.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;**458**(7235):223

[2] Hu W, Alvarez-Dominguez JR, Lodish HF. Regulation of mammalian cell differentiation by long non-coding RNAs. EMBO Reports. 2012;**13**(11):971-983

[3] Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes & Development. 2011;**25**(18):1915-1927

[4] Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nature Reviews. Genetics. 2016;**17**(1):47

[5] Anderson DM, Anderson KM, Chang C-L, Makarewich CA, Nelson BR, McAnally JR, et al. A micropeptide encoded by a putative long noncoding RNA regulates muscle performance. Cell. 2015;**160**(4):595-606

[6] Clark MB, Mercer TR, Bussotti G, Leonardi T, Haynes KR, Crawford J, et al. Quantitative gene profiling of long noncoding RNAs with targeted RNA sequencing. Nature Methods. 2015;**12**(4):339

[7] Salviano-Silva A, Lobo-Alves S, Almeida R, Malheiros D, Petzl-Erler M. Besides pathology: Long non-coding RNA in cell and tissue homeostasis. Non-Coding RNA. 2018;**4**(1):3

[8] Mercer TR, Dinger ME, Sunkin SM, Mehler MF, Mattick JS. Specific expression of long noncoding RNAs in the mouse brain. Proceedings of the National Academy of Sciences. 2008;**105**(2):716-721

[9] Ma Y, Ma W, Huang L, Feng D, Cai B. Long non-coding RNAs, a new important regulator of cardiovascular physiology and pathology. International Journal of Cardiology. 2015;**188**:105-110

[10] Yao RW, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. Nature Cell Biology. 2019;**21**(5):542-551. DOI: 10.1038/s41556-019-0311-8

[11] Huarte M. The emerging role of lncRNAs in cancer. Nature Medicine. 2015;**21**(11):1253-1261. DOI: 10.1038/nm.3981

[12] Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, et al. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell. 2010;**142**(3):409-419

[13] Zheng GX, Do BT, Webster DE, Khavari PA, Chang HY. Dicer-microRNA-Myc circuit promotes transcription of hundreds of long noncoding RNAs. Nature Structural & Molecular Biology. 2014;**21**(7):585

[14] Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;**464**(7291):1071

[15] Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. Cellular and Molecular Life Sciences. 2016;**73**(13):2491-2509. DOI: 10.1007/s00018-016-2174-5

[16] Zhao Y, Sun H, Wang H. Long noncoding RNAs in DNA methylation:

New players stepping into the old game. Cell & Bioscience. 2016;**6**:45. DOI: 10.1186/s13578-016-0109-3

[17] Achour C, Aguilo F. Long non-coding RNA and polycomb: An intricate partnership in cancer biology. Frontiers in Bioscience. 2018;**23**:2106-2132

[18] Dykes IM, Emanueli C. Transcriptional and post-transcriptional gene regulation by long non-coding RNA. Genomics, Proteomics & Bioinformatics. 2017;**15**(3):177-186

[19] Noh JH, Kim KM, McClusky WG, Abdelmohsen K, Gorospe M. Cytoplasmic functions of long noncoding RNAs. Wiley Interdisciplinary Reviews: RNA. 2018;**9**(3):e1471

[20] Rashid F, Shah A, Shan G. Long non-coding RNAs in the cytoplasm. Genomics, Proteomics & Bioinformatics. 2016;**14**(2):73-80. DOI: 10.1016/j.gpb.2016.03.005

[21] Weil TT. Post-transcriptional regulation of early embryogenesis. F1000Prime Reports. 2015;**7**:31. DOI: 10.12703/P7-31

[22] Yoon JH, Abdelmohsen K, Gorospe M. Posttranscriptional gene regulation by long noncoding RNA. Journal of Molecular Biology. 2013;**425**(19):3723-3730. DOI: 10.1016/j.jmb.2012.11.024

[23] Kopp F, Mendell JT. Functional classification and experimental dissection of long noncoding RNAs. Cell. 2018;**172**(3):393-407. DOI: 10.1016/j.cell.2018.01.011

[24] Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Molecular Cell. 2011;**43**(6):904-914

[25] Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? Cell. 2011;**146**(3):353-358. DOI: 10.1016/j.cell.2011.07.014

[26] Herceg Z, Hainaut P. Genetic and epigenetic alterations as biomarkers for cancer detection, diagnosis and prognosis. Molecular Oncology. 2007;**1**(1):26-41. DOI: 10.1016/j.molonc.2007.01.004

[27] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;**100**(1):57-70

[28] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;**144**(5):646-674. DOI: 10.1016/j.cell.2011.02.013

[29] de Oliveira JC, Oliveira LC, Mathias C, Pedroso GA, Lemos DS, Salviano-Silva A, et al. Long non-coding RNAs in cancer: Another layer of complexity. The Journal of Gene Medicine. 2019;**21**(1):e3065. DOI: 10.1002/jgm.3065

[30] Yap KL, Li S, Munoz-Cabello AM, Raguz S, Zeng L, Mujtaba S, et al. Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. Molecular Cell. 2010;**38**(5):662-674. DOI: 10.1016/j.molcel.2010.03.021

[31] Naemura M, Murasaki C, Inoue Y, Okamoto H, Kotake Y. Long noncoding RNA ANRIL regulates proliferation of non-small cell lung cancer and cervical cancer cells. Anticancer Research. 2015;**35**(10):5377-5382

[32] Nie FQ, Sun M, Yang JS, Xie M, Xu TP, Xia R, et al. Long noncoding RNA ANRIL promotes non-small cell lung cancer cell proliferation and inhibits apoptosis by silencing KLF2 and P21 expression. Molecular Cancer Therapeutics. 2015;**14**(1):268-277. DOI: 10.1158/1535-7163.Mct-14-0492

[33] Qiu JJ, Lin YY, Ding JX, Feng WW, Jin HY, Hua KQ. Long non-coding RNA ANRIL predicts poor prognosis and promotes invasion/metastasis in serous ovarian cancer. International Journal of Oncology. 2015;**46**(6):2497-2505. DOI: 10.3892/ijo.2015.2943

[34] Kotake Y, Nakagawa T, Kitagawa K, Suzuki S, Liu N, Kitagawa M, et al. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene. Oncogene. 2011;**30**(16):1956-1962. DOI: 10.1038/onc.2010.568

[35] Lucafo M, De Iudicibus S, Di Silvestre A, Pelin M, Candussio L, Martelossi S, et al. Long noncoding RNA GAS5: A novel marker involved in glucocorticoid response. Current Molecular Medicine. 2015;**15**(1):94-99

[36] Li S, Zhou J, Wang Z, Wang P, Gao X, Wang Y. Long noncoding RNA GAS5 suppresses triple negative breast cancer progression through inhibition of proliferation and invasion by competitively binding miR-196a-5p. Biomedicine & Pharmacotherapy. 2018;**104**:451-457. DOI: 10.1016/j.biopha.2018.05.056

[37] Zhang X, Gao F, Zhou L, Wang H, Shi G, Tan X. UCA1 regulates the growth and metastasis of pancreatic cancer by sponging miR-135a. Oncology Research. 2017;**25**(9):1529-1541. DOI: 10.3727/096504017x14888987683152

[38] Xue M, Pang H, Li X, Li H, Pan J, Chen W. Long non-coding RNA urothelial cancer-associated 1 promotes bladder cancer cell migration and invasion by way of the hsa-miR-145-ZEB1/2-FSCN1 pathway. Cancer Science. 2016;**107**(1):18-27. DOI: 10.1111/cas.12844

[39] Cheng N, Cai W, Ren S, Li X, Wang Q, Pan H, et al. Long non-coding RNA UCA1 induces non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway in EGFR-mutant non-small cell lung cancer. Oncotarget. 2015;**6**(27):23582-23593. DOI: 10.18632/oncotarget.4361

[40] Wang F, Ying HQ, He BS, Pan YQ, Deng QW, Sun HL, et al. Upregulated lncRNA-UCA1 contributes to progression of hepatocellular carcinoma through inhibition of miR-216b and activation of FGFR1/ERK signaling pathway. Oncotarget. 2015;**6**(10):7899-7917. DOI: 10.18632/oncotarget.3219

[41] Xue M, Li X, Li Z, Chen W. Urothelial carcinoma associated 1 is a hypoxia-inducible factor-1alpha-targeted long noncoding RNA that enhances hypoxic bladder cancer cell proliferation, migration, and invasion. Tumour Biology. 2014;**35**(7):6901-6912. DOI: 10.1007/s13277-014-1925-x

[42] Ramapriyan R, Caetano MS, Barsoumian HB, Mafra ACP, Zambalde EP, Menon H, et al. Altered cancer metabolism in mechanisms of immunotherapy resistance. Pharmacology & Therapeutics. 2019;**195**:162-171. DOI: 10.1016/j.pharmthera.2018.11.004

[43] Warburg O. Origin of cancer cells. Oncologia. 1956;**9**(2):75-83

[44] Yu C, Xue J, Zhu W, Jiao Y, Zhang S, Cao J. Warburg meets non-coding RNAs: The emerging role of ncRNA in regulating the glucose metabolism of cancer cells. Tumour Biology. 2015;**36**(1):81-94. DOI: 10.1007/s13277-014-2875-z

[45] Wu W, Zhang S, Li X, Xue M, Cao S, Chen W. Ets-2 regulates cell apoptosis via the Akt pathway, through the regulation of urothelial cancer associated 1, a long non-coding RNA, in bladder cancer cells. PLoS One. 2013;**8**(9):e73920. DOI: 10.1371/journal.pone.0073920

[46] Du Y, Kong G, You X, Zhang S, Zhang T, Gao Y, et al. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. The Journal of Biological Chemistry. 2012;**287**(31):26302-26311. DOI: 10.1074/jbc.M112.342113

[47] Lu Z, Xiao Z, Liu F, Cui M, Li W, Yang Z, et al. Long non-coding RNA HULC promotes tumor angiogenesis in liver cancer by up-regulating sphingosine kinase 1 (SPHK1). Oncotarget. 2016;7(1):241-254. DOI: 10.18632/oncotarget.6280

[48] Nagahashi M, Ramachandran S, Kim EY, Allegood JC, Rashid OM, Yamada A, et al. Sphingosine-1-phosphate produced by sphingosine kinase 1 promotes breast cancer progression by stimulating angiogenesis and lymphangiogenesis. Cancer Research. 2012;**72**(3):726-735. DOI: 10.1158/0008-5472.Can-11-2167

[49] Zhu Y, Zhang X, Qi L, Cai Y, Yang P, Xuan G, et al. HULC long noncoding RNA silencing suppresses angiogenesis by regulating ESM-1 via the PI3K/Akt/mTOR signaling pathway in human gliomas. Oncotarget. 2016;7(12):14429-14440. DOI: 10.18632/oncotarget.7418

[50] Hayflick L. The limited in vitro lifetime of human diploid cell strains. Experimental Cell Research. 1965;**37**:614-636

[51] Azzalin CM, Reichenbach P, Khoriauli L, Giulotto E, Lingner J. Telomeric repeat containing RNA and RNA surveillance factors at mammalian chromosome ends. Science. 2007;**318**(5851):798-801. DOI: 10.1126/science.1147182

[52] Bettin N, Oss Pegorar C, Cusanelli E. The emerging roles of TERRA in telomere maintenance and genome stability. Cell. 2019;**8**(3):E246. DOI: 10.3390/cells8030246

[53] Tutton S, Lieberman PM. A role for p53 in telomere protection. Molecular & Cellular Oncology. 2017;**4**(6):e1143078. DOI: 10.1080/23723556.2016.1143078

[54] Redon S, Reichenbach P, Lingner J. The non-coding RNA TERRA is a natural ligand and direct inhibitor of human telomerase. Nucleic Acids Research. 2010;**38**(17):5797-5806. DOI: 10.1093/nar/gkq296

[55] Lee S, Kopp F, Chang TC, Sataluri A, Chen B, Sivakumar S, et al. Noncoding RNA NORAD regulates genomic stability by sequestering PUMILIO proteins. Cell. 2016;**164**(1-2):69-80. DOI: 10.1016/j.cell.2015.12.017

[56] Liu H, Qu Q, Warrington R, Rice A, Cheng N, Yu H. Mitotic transcription installs Sgo1 at centromeres to coordinate chromosome segregation. Molecular Cell. 2015;**59**(3):426-436. DOI: 10.1016/j.molcel.2015.06.018

[57] Munschauer M, Nguyen CT, Sirokman K, Hartigan CR, Hogstrom L, Engreitz JM, et al. The NORAD lncRNA assembles a topoisomerase complex critical for genome stability. Nature. 2018;**561**(7721):132-136. DOI: 10.1038/s41586-018-0453-z

[58] Osses DF, Roobol MJ, Schoots IG. Prediction medicine: Biomarkers, risk calculators and magnetic resonance imaging as risk stratification tools in prostate cancer diagnosis. International Journal of Molecular Sciences. 2019;**20**(7):E1637. DOI: 10.3390/ijms20071637

[59] Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, Schalken JA, et al. DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Research. 1999;**59**(23):5975-5979

[60] Sartori DA, Chan DW. Biomarkers in prostate cancer: What's new? Current Opinion in Oncology.

2014;**26**(3):259-264. DOI: 10.1097/cco.0000000000000065

[61] Bourdoumis A, Papatsoris AG, Chrisofos M, Efstathiou E, Skolarikos A, Deliveliotis C. The novel prostate cancer antigen 3 (PCA3) biomarker. International Brazilian Journal of Urology. 2010;**36**(6):665-668. DOI: 10.1590/s1677-55382010000600003

[62] ClinicalTrials.gov. TA(E)C-GP Versus A(E)C-T for the High Risk TNBC Patients and Validation of the mRNA-lncRNA Signature. 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT02641847 [Accessed: 23-June-2019]

[63] ClinicalTrials.gov. Long Non Coding RNA HOTAIR and Midkine as Biomarkers in Thyroid Cancer. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03469544?term=lncRNA+cancer [Accessed: 23-June-2019]

[64] Li QG, Xu XQ, Zhou DY, Jia ZB, Yu BF, Xu FG, et al. Long non-coding RNA DILC as a potentially useful biomarker for the diagnosis and prognosis of colorectal cancer. European Review for Medical and Pharmacological Sciences. 2019;**23**(8):3320-3325. DOI: 10.26355/eurrev_201904_17694

[65] Mehrad-Majd H, Ravanshad S, Moradi A, Khansalar N, Sheikhi M, Akhtari J. Decreased expression of lncRNA loc285194 as an independent prognostic marker in cancer: A systematic review and meta-analysis. Pathology, Research and Practice. 2019;**215**(6):152426. DOI: 10.1016/j.prp.2019.04.018

[66] Malek E, Jagannathan S, Driscoll JJ. Correlation of long non-coding RNA expression with metastasis, drug resistance and clinical outcome in cancer. Oncotarget. 2014;**5**(18):8027-8038. DOI: 10.18632/oncotarget.2469

[67] Campos-Parra AD, Lopez-Urrutia E, Orozco Moreno LT, Lopez-Camarillo C, Meza-Menchaca T, Figueroa Gonzalez G, et al. Long non-coding RNAs as new master regulators of resistance to systemic treatments in breast cancer. International Journal of Molecular Sciences. 2018;**19**(9):E2711. DOI: 10.3390/ijms19092711

[68] Shi T, Gao G, Cao Y. Long noncoding RNAs as novel biomarkers have a promising future in cancer diagnostics. Disease Markers. 2016;**2016**:9085195. DOI: 10.1155/2016/9085195

[69] Wu X, Tudoran OM, Calin GA, Ivan M. The many faces of long noncoding RNAs in cancer. Antioxidants & Redox Signaling. 2018;**29**(9):922-935. DOI: 10.1089/ars.2017.7293

[70] Feng Y, Hu X, Zhang Y, Zhang D, Li C, Zhang L. Methods for the study of long noncoding RNA in cancer cell signaling. Methods in Molecular Biology. 2014;**1165**:115-143. DOI: 10.1007/978-1-4939-0856-1_10

[71] Lennox KA, Behlke MA. Cellular localization of long non-coding RNAs affects silencing by RNAi more than by antisense oligonucleotides. Nucleic Acids Research. 2016;**44**(2):863-877. DOI: 10.1093/nar/gkv1206

[72] Bobbin ML, Rossi JJ. RNA interference (RNAi)-based therapeutics: Delivering on the promise? Annual Review of Pharmacology and Toxicology. 2016;**56**:103-122. DOI: 10.1146/annurev-pharmtox-010715-103633

[73] Shortridge MD, Varani G. Structure based approaches for targeting non-coding RNAs with small molecules. Current Opinion in Structural Biology.

2015;**30**:79-88. DOI: 10.1016/j.sbi.2015.01.008

[74] Kole R, Krainer AR, Altman S. RNA therapeutics: Beyond RNA interference and antisense oligonucleotides. Nature Reviews. Drug Discovery. 2012;**11**(2):125-140. DOI: 10.1038/nrd3625

[75] Han J, Zhang J, Chen L, Shen B, Zhou J, Hu B, et al. Efficient in vivo deletion of a large imprinted lncRNA by CRISPR/Cas9. RNA Biology. 2014;**11**(7):829-835. DOI: 10.4161/rna.29624

[76] Yang J, Meng X, Pan J, Jiang N, Zhou C, Wu Z, et al. CRISPR/Cas9-mediated noncoding RNA editing in human cancers. RNA Biology. 2018;**15**(1):35-43. DOI: 10.1080/15476286.2017.1391443

[77] Goyal A, Myacheva K, Gross M, Klingenberg M, Duran Arque B, Diederichs S. Challenges of CRISPR/Cas9 applications for long non-coding RNA genes. Nucleic Acids Research. 2017;**45**(3):e12. DOI: 10.1093/nar/gkw883

[78] Hosseinahli N, Aghapour M, Duijf PHG, Baradaran B. Treating cancer with microRNA replacement therapy: A literature review. Journal of Cellular Physiology. 2018;**233**(8):5574-5588. DOI: 10.1002/jcp.26514

[79] Slaby O, Laga R, Sedlacek O. Therapeutic targeting of non-coding RNAs in cancer. The Biochemical Journal. 2017;**474**(24):4219-4251. DOI: 10.1042/bcj20170079

[80] Matsui M, Corey DR. Non-coding RNAs as drug targets. Nature Reviews. Drug Discovery. 2017;**16**(3):167-179. DOI: 10.1038/nrd.2016.117

[81] Zhou Y, Chen S, Cheng S, Wei Q, Fathy AH, Shan T. The prognostic value of high LncRNA AFAP1-AS1 expression in various cancers: A systematic review and meta-analysis containing 21 studies. Clinica Chimica Acta. 2018;**481**:147-153. DOI: 10.1016/j.cca.2018.03.006

[82] Wang H, Liu Y, Zhong J, Wu C, Zhong Y, Yang G, et al. Long noncoding RNA ANRIL as a novel biomarker of lymph node metastasis and prognosis in human cancer: A meta-analysis. Oncotarget. 2018;**9**(18):14608-14618. DOI: 10.18632/oncotarget.21825

[83] Liu FT, Zhu PQ, Luo HL, Zhang Y, Hao TF, Xia GF, et al. Long noncoding RNA ANRIL: A potential novel prognostic marker in cancer: A meta-analysis. Minerva Medica. 2016;**107**(2):77-83

[84] Guo X, Hua Y. CCAT1: An oncogenic long noncoding RNA in human cancers. Journal of Cancer Research and Clinical Oncology. 2017;**143**(4):555-562. DOI: 10.1007/s00432-016-2268-3

[85] Thin KZ, Liu X, Feng X, Raveendran S, Tu JC. LncRNA-DANCR: A valuable cancer related long non-coding RNA for human cancers. Pathology, Research and Practice. 2018;**214**(6):801-805. DOI: 10.1016/j.prp.2018.04.003

[86] Gao Q, Xie H, Zhan H, Li J, Liu Y, Huang W. Prognostic values of long noncoding RNA GAS5 in various carcinomas: An updated systematic review and meta-analysis. Frontiers in Physiology. 2017;**8**:814. DOI: 10.3389/fphys.2017.00814

[87] Yoshimura H, Matsuda Y, Yamamoto M, Kamiya S, Ishiwata T. Expression and role of long non-coding RNA H19 in carcinogenesis. Frontiers in Bioscience. 2018;**23**:614-625

[88] Tang Q, Hann SS. HOTAIR: An oncogenic long non-coding RNA in human cancer. Cellular Physiology and

Biochemistry. 2018;**47**(3):893-913. DOI: 10.1159/000490131

[89] Ding Y, Sun C, Li J, Hu L, Li M, Liu J, et al. The significance of long non-coding RNA HULC in predicting prognosis and metastasis of cancers: A meta-analysis. Pathology Oncology Research. 2019;**25**(1):311-318. DOI: 10.1007/s12253-017-0351-y

[90] Zhang J, Yin M, Huang J, Lv Z, Liang S, Miao X, et al. Long noncoding RNA LINC00152 as a novel predictor of lymph node metastasis and survival in human cancer: A systematic review and meta-analysis. Clinica Chimica Acta. 2018;**483**:25-32. DOI: 10.1016/j.cca.2018.03.034

[91] Chen S, Liang H, Yang H, Zhou K, Xu L, Liu J, et al. LincRNA-p21: Function and mechanism in cancer. Medical Oncology. 2017;**34**(5):98

[92] Pan Y, Li C, Chen J, Zhang K, Chu X, Wang R, et al. The emerging roles of long noncoding RNA ROR (lincRNA-ROR) and its possible mechanisms in human cancers. Cellular Physiology and Biochemistry. 2016;**40**(1-2):219-229. DOI: 10.1159/000452539

[93] Li J, Cui Z, Li H, Lv X, Gao M, Yang Z, et al. Clinicopathological and prognostic significance of long noncoding RNA MALAT1 in human cancers: A review and meta-analysis. Cancer Cell International. 2018;**18**:109. DOI: 10.1186/s12935-018-0606-z

[94] Chen F, Tian Y, Pang EJ, Wang Y, Li L. MALAT2-activated long noncoding RNA indicates a biomarker of poor prognosis in gastric cancer. Cancer Gene Therapy. 2015. p. 1-7. DOI: 10.1038/cgt.2015.6

[95] He Y, Luo Y, Liang B, Ye L, Lu G, He W. Potential applications of MEG3 in cancer diagnosis and prognosis. Oncotarget. 2017;**8**(42):73282-73295. DOI: 10.18632/oncotarget.19931

[96] Sun C, Huang L, Li Z, Leng K, Xu Y, Jiang X, et al. Long non-coding RNA MIAT in development and disease: A new player in an old game. Journal of Biomedical Science. 2018;**25**(1):23. DOI: 10.1186/s12929-018-0427-3

[97] Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: A novel cancer-related long non-coding RNA. Cell Proliferation. 2017;**50**(2):e12329. DOI: 10.1111/cpr.12329

[98] Zou Y, Zhong Y, Wu J, Xiao H, Zhang X, Liao X, et al. Long non-coding PANDAR as a novel biomarker in human cancer: A systematic review. Cell Proliferation. 2018;**51**(1):e12422. DOI: 10.1111/cpr.12422

[99] Liu Y, Zong ZH, Guan X, Wang LL, Zhao Y. The role of long non-coding RNA PCA3 in epithelial ovarian carcinoma tumorigenesis and progression. Gene. 2017;**633**:42-47. DOI: 10.1016/j.gene.2017.08.027

[100] de Kok JB, Verhaegh GW, Roelofs RW, Hessels D, Kiemeney LA, Aalders TW, et al. DD3(PCA3), a very sensitive and specific marker to detect prostate tumors. Cancer Research. 2002;**62**(9):2695-2698

[101] Ma T, Zhou L, Xia J, Shen Y, Yan Y, Zhu R. LncRNA PCAT-1 regulates the proliferation, metastasis and invasion of cervical cancer cells. European Review for Medical and Pharmacological Sciences. 2018;**22**(7):1907-1913

[102] Liu L, Liu Y, Zhuang C, Xu W, Fu X, Lv Z, et al. Inducing cell growth arrest and apoptosis by silencing long non-coding RNA PCAT-1 in human bladder cancer. Tumour Biology. 2015;**36**(10):7685-7689. DOI: 10.1007/s13277-015-3490-3

[103] Gradia DF, Mathias C, Coutinho R, Cavalli IJ, Ribeiro E,

de Oliveira JC. Long non-coding RNA TUG1 expression is associated with different subtypes in human breast cancer. Noncoding RNA. 2017;**3**(4):E26. DOI: 10.3390/ncrna3040026

[104] Li N, Shi K, Kang X, Li W. Prognostic value of long non-coding RNA TUG1 in various tumors. Oncotarget. 2017;**8**(39):65659-65667. DOI: 10.18632/oncotarget.20025

[105] Zhou Q, Hu W, Zhu W, Zhang F, Lin-Lin L, Liu C, et al. Long non coding RNA XIST as a prognostic cancer marker—A meta-analysis. Clinica Chimica Acta. 2018;**482**:1-7. DOI: 10.1016/j.cca.2018.03.016