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CA-125:CA72-4 ratio – towards a promising cost-effective tool in ovarian cancer diagnosis and monitoring of post-menopausal women under hormone treatment

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Abstract

Ovarian cancer (OC) is the most lethal gynecological cancer in the developed world. Most cases are diagnosed at late stage III-IV with a very low 5-year overall survival rate. Several studies revealed an elevated risk of OC in users of hormone treatment (HT) compared with non-users. The extended duration of HT is a statistically significant risk factor. Carbohydrate antigen or cancer antigen 125 (CA-125) remains the best screening tool for OC; however, its value is limited due to low specificity, leading to unnecessary interventions, surgeries, and psychological harm. Additionally, the variability of ultrasound interpretation highlights the urgent need to develop a univariate index with higher sensitivity and specificity for early diagnosis of OC in women under HT. Herein we critically review the limitations of biomarkers for the detection of OC aiming to suggest an accurate and cost-effective diagnostic ratio that eliminates the impact of body mass index, age, HT, smoking, and benign ovarian diseases on measurements. Numerous studies combine biomarkers such as CA-125, human epididymis protein 4, and thymidine kinase 1 into diagnostic algorithms. Data suggest that the expression of estrogen receptors may have diagnostic and prognostic value, as the estrogen receptor α (ERα):estrogen receptor β (ERβ) ratio is significantly higher in OC than in normal tissue due to ERβ downregulation. A high positive correlation between expression of CA-125 and carbohydrate antigen or cancer antigen 72−4 (CA72-4) with ERα and ERβ, respectively, poses that a novel ratio CA-125:CA72-4 could be nodal for monitoring post-menopausal women under HT.

Keywords Ovarian cancer, Hormone treatment, Estrogen receptor ratio, Biomarkers, Post-menopausal women, Diagnostic algorithm

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Introduction

Ovarian cancer (OC) is the leading cause of cancer-related death among gynecological cancers due to its insidious onset, asymptomatic nature, and lack of an organ-specific biomarker with high sensitivity and diagnostic value [1]. Aproximately 60% of patients have stage III-IV at initial diagnosis, which is associated with a low 5-year survival rate of 27% and 13%, respectively. More than 80% of women have a 5-year survival rate if diagnosed in stage I-II, underlying the challenge of early detection [1–4]. Ovarian cancers are influenced by steroid hormones [4–7]. Recent studies showed that post-menopausal women who use hormone treatment (HT) are at elevated risk of OC compared with never users [5]. The duration of therapy significantly augmented the risk after two years, with an overall increased risk of 30–40% found in two prospective studies [1, 5]. Although there is a differential influence of HT on different subtypes of OC, the highest risk was for serous tumors and the lowest for mucinous tumors. Estrogen-only therapy is more strongly associated with the risk of endometrioid OC than other types. The incident rate ratios for serous OC increased with the duration of therapy [5]. Therefore, further research should be performed to develop an effective screening index for monitoring and early diagnosis of OC in post-menopausal women under long-term HT. Several studies explore a predictive index to distinguish OC from benign ovarian masses combining epidemiological risk factors, ultrasound, and carbohydrate antigen or cancer antigen 125 (CA-125), such as the Risk Malignancy Index (RMI) [8, 9]. Although CA-125 has the highest specificity in post-menopausal women, it is frequently elevated in benign gynecological conditions and mainly in endometriosis. The need to discriminate benign or malignant masses in the preoperative period led to a dual marker algorithm termed the Risk of Ovarian Malignancy Algorithm (ROMA), which combined CA-125 and human epididymis protein 4 (HE4) [8]. Although HE4 and ROMA were less sensitive in pre-menopausal women, they were of comparable sensitivity and higher specificity in post-menopausal women [9]. Combination of several biomarkers was investigated to reduce the missed diagnosis. The Risk of Ovarian Malignancy Index (ROMI) is a novel algorithm that added thymidine kinase 1 (TK1) into ROMA, which appeared to have a better diagnostic value than ROMA [8]. Recent studies uncovered the strong association of estrogen and the development of OC and suggest that estrogen receptors (ERs) play a crucial role in ovarian carcinogenesis [10]. Estrogen receptor α (ERα) mediates estrogen effects and promotes tumor growth, whereas estrogen receptor β (ERβ) has a tumor-suppressive role in OC. Low expression of ERβ is associated with OC and seems to have prognostic value [11–13]. Therefore, it is very challenging to investigate an association among the levels of different serum biomarkers and expression of ERs (ERα, ERβ) that might lead to a new both diagnostic and prognostic algorithm [4, 13].

CA-125 guides the surveillance for OC leading to RMI and ROMA algorithms

CA-125 is a large transmembrane glycoprotein, member of the mucin family, and normally expressed in Mullerian and coelomic epithelial tissue derivatives [6]. It is a non-specific marker that is overexpressed in the majority of serous tumors, the most common type of OC [7]. CA-125 is used extensively in standard clinical practice for OC surveillance and prognostic prediction as it is a cost-effective, non-invasive method and a very sensitive biomarker. Half of patients at an early stage have elevated serum concentrations (>35 U/mL), whereas CA-125 elevation reaches 80–90% of late-stage patients [14]. However, CA-125 is characterized by low diagnostic specificity as abnormally high levels can be found in non-ovarian gynecological cancers (endometrial, pancreatic, breast, and colorectal cancer) and various benign conditions [14].

Endometriosis is a common disease that affects 5–10% of women in reproductive age. Elevated levels of CA-125 are observed in more than 50% of women with endometriosis [14]. Thus, CA-125 has a limited role in the differential diagnosis between OC and ovarian endometriosis [15–17]. Additionally, abnormally high concentrations of CA-125 occur in diseases such as liver cirrhosis, pelvic inflammatory disease, uterine fibroid, tuberculosis, or normal conditions such as pregnancy and different phases of the menstrual cycle. Personal characteristics such as age, body mass index (BMI), menstrual cycle, hysterectomy, age at menopause, late menopause, smoking status, and duration of HT also affect CA-125 levels [16]. Therefore, the need for developing a non-invasive, organ-specific method with higher sensitivity and diagnostic specificity led to the identification of the RMI. RMI was set up in 1999 and it combines CA-125 levels, menopausal score, and ultrasound score [18, 19].

The variability of CA-125 levels in addition to the differential interpretation of ultrasound scan images led Moore et al. in 2009 to combine two biomarkers, CA-125 and HE4, and propose a dual marker algorithm, known as ROMA [20, 21]. ROMA has been proved to be a widely useful clinical tool which was established due to its diagnostic efficiency. In post-menopausal women, ROMA shows a significantly higher sensitivity in detecting OC compared to the measurement of a single biomarker CA-125 (89%, 84.1%), whereas ROMA index and CA-125 have comparable specificity (95.9%, 96.7%, respectively), in post-menopausal women (Table 1) [22].

A novel formula that adds the new parameter, TK1, in the ROMA algorithm, claims to have a better diagnostic

Table 1 Diagnostic accuracy for differential diagnosis between benign ovarian diseases and ovarian cancer of CA-125, HE4, ROMA, ROMI algorithm in pre- and post-menopausal women[#]

Biomarkers	Cut off Optimal/Preferred	Sensitivity (%) Optimal/Preferred	Specificity (%) Optimal/Preferred	PPV (%) Optimal/Preferred	NPV (%) Optimal/Preferred
Pre-menopausal CA-125	64.6/35 (U/mL)	87.0/86.6	84.1/70.9	44.8/33.6	94.8/96.1
HE4	70.3/140 (pmol/L)	83.5/68.2	89.9/98.6	46.2/86.4	96.7/94.4
ROMA	14.9/11.4%	86.8/86.2	89.1/88.8	42.1/39.6	97.2/98.7
ROMI	53,54%	84.6	93.9	92.8	86.8
Post-menopausal CA-125	39.4/35 (U/mL)	84.1/91.9	96.7/89.8	91.7/83.2	92.8/94.4
HE4	109.1/140 (pmol/L)	83.8/87.1	96.9/94.2	86.8/92.8	89.6/86.2
ROMA	33.4/29.9%	89.0/86.8	95.9/92.2	91.9/89.4	94.2/94.9
ROMI	44.56%	98.2	97.0	99.1	94.1

#This Table provides a synopsis of cut offs, sensitivity, specificity, positive and negative predictive values for all biomarkers and algorithms clinically used in pre- and post-menopausal women for discriminating ovarian cancer from normal conditions

CA-125: carbohydrate antigen or cancer antigen 125, HE4: human epididymis protein 4, ROMA: Risk of Ovarian Malignancy Algorithm, ROMI: Risk of Ovarian Malignancy Index

performance than ROMA due to its higher sensitivity, specificity, and accuracy for both pre- and post-menopausal women. The correct cut-offs to reduce missed diagnosis of benign and non-benign masses are yet to be validated, to increase sensitivity without reducing specificity [8]. This new combined measurement of CA-125, HE4, and TK1 is called ROMI [4]. TK1 is a DNA precursor enzyme and plays a crucial role in both DNA synthesis and DNA repair. It is regarded as a proliferation marker and given the high proliferation characteristic of malignancy, TK1 may be a reliable marker for malignancy prediction [8]. Serum TK1 exhibits higher expression in ovarian tumors than in non-benign masses and normal tissue. Moreover, TK1 levels are positively correlated with the stage of OC, intrapelvic metastasis, lymphatic metastasis, and distant metastasis, indicating that TK1 may be used as a predictive and preoperative diagnostic test as well as a tumor marker for OC detection [8].

In summary, CA-125 compared to HE4 has the highest sensitivity in the total population but also in the pre-menopausal age group (87% and 83%, respectively). Nevertheless, as presented in Table 1, CA-125 in post-menopausal women has a lower sensitivity than ROMA and ROMI indexes (84.1%, 89%, and 98.2%, respectively). Thus, in post-menopausal women, CA-125 specificity rises to 96.7% compared with 95.9% for the ROMA algorithm and 97% for the RMI index [14, 20, 21].

HE4

HE4 is a small, secreted glycoprotein that is overexpressed in endometrioid OC (100%) but also in serous OC (93%). HE4 is rarely increased in benign gynecological conditions, and this finding supports its complementary role to ROMA index. Compared to CA-125, HE4 levels display no significant variations at different phases of the menstrual cycle [23, 24]. Additionally, HE4 levels in women who use contraceptives or different types of HT have no significant difference compared to non-users. Therefore, serum HE4 may be measured regardless of menstrual phase or hormonal mediation, explaining its high specificity in pre-menopausal women. In post-menopausal women, its specificity remains higher than CA-125, while its sensitivity is lower than CA-125. The combination of these two biomarkers significantly increases sensitivity in post-menopausal women but fails to increase specificity compared to CA-125 and HE4 separately [1, 25].

Although the combination of HE4 and CA-125 increases the accuracy of OC diagnosis and helps in the differential diagnosis between ovarian tumors and ovarian endometriosis cysts, there are some cases of high HE4 levels in endometriosis [6, 17]. HE4 levels are also elevated in other cancer types such as lung cancer and adenocarcinoma, while smoking status, age, and BMI affect its levels. Nonetheless, impaired renal function may also provoke HE4 levels elevation [14]. HE4 has recently been approved by the Food and Drug Administration (FDA) as a tumor marker for monitoring the recurrence or progression of epithelial OC [26, 27]. It is widely measured due to its significant contribution to OC diagnosis via the ROMA algorithm.

The upcoming goal will be to develop a combination of markers with a dual role of screening and detecting recurrence as early as possible. Although CA-125 has been widely used to monitor response to treatment and to detect recurrence, that is possible only 4.8 months before signs and symptoms. Thus, HE4 serum levels have received growing interest in OC follow-up, and the FDA recently approved the use of HE4 only as a biomarker for the surveillance of patients who show a possible recurrence [20]. Detection of CA-125 and HE4 in urine samples is a promising screening test for OC, however measurements of these biomarkers in saliva showed no diagnostic value [28, 29].

Carbohydrate antigen or cancer antigen 72 – 4 (CA72-4): potential role of a non-FDA approved marker

CA72-4 is a mucin-like, cell-surface glycoprotein known as TAG72, which is selectively expressed in OC. In contrast to HE4, CA72-4 is highly detectable in all histological subtypes of OC [8, 30]. CA72-4 is increased in gastric, colon, breast, and ovarian adenocarcinomas and especially in advanced metastatic tumors. Among patients with serous OC, the most common type of OC, there is a positive correlation between calcineurin (CaN) and CA72-4 expression [31]. CaN is an important prognostic factor as it is upregulated in later-stage metastatic OC. Elevated levels of CaN, CA-125, and CA72-4 are an index of poor prognosis for OC, underscoring the prognostic value of CA72-4. Measurement and evaluation of CA72-4 levels are done in combination with other cancer markers (CA-125 and HE4) for the differential diagnosis of adnexal masses.

CA72-4 is less sensitive than CA-125 for OC but is not influenced by pregnancy or the phase of the menstrual cycle [17]. Compared to CA-125, whose levels are higher in the follicular than in the luteal phase, CA72-4 exhibits extreme stability at the fluctuations in estrogen and progesterone levels [30]. Like HE4, CA72-4 measurement can be carried out irrespective of hormone medication with either combined estrogen/progestin or estrogen-only therapy in post-menopausal women [10]. Furthermore, CA72-4 levels are not affected by BMI, smoking status, and age [32]. This stability in epidemiological personal characteristics reflects its usefulness as a biomarker compared to the widely used CA-125 and HE4, which are influenced by age, BMI, and smoking. The serum concentration of CA72-4 gradually decreases in women with the increase in age; however, no statistical difference was found in females aged 16–60 years in recent studies [11, 32]. An adjustment in cut-offs should be made for women above 60 years old.

CA72-4 is measured in human sera and plasma by an automated chemiluminescent immunoassay, an accurate, widely used method that ensures the precision of results [33, 34]. Additionally, the fact that CA72-4 is measured with a simple blood collection performed by an automated cost-effective method supports its clinical usefulness as a diagnostic and prognostic marker. CA-125 shows significantly higher sensitivity than CA72-4 in the total population. In post-menopausal women, an elevation in CA-125 specificity is also observed (96.7%). It seems that CA-125 and CA72-4 have comparable sensitivity in all types of OC, but CA-125 shows the best sensitivity for serous types, while CA72-4 shows higher sensitivity in mucinous tumors [35]. CA72-4 also has a higher value in predicting overall survival (OS) [36]. Several studies revealed the variability of CA-125 due to the age factor, BMI, menstrual cycle, and non-benign conditions, and the variability of HE4 due to personal characteristics such as age, BMI, and smoking habits that reduce the sensitivity and specificity of these markers. Therefore, we strongly support the promising diagnostic and prognostic role of CA72-4 as a univariate cost-effective screening index in post-menopausal women at elevated risk [20, 37].

Role of ERs in diagnosis / prognosis of OC

Estrogens are the main female sex steroid hormones with a decisive role in the regulation of growth and differentiation in the human ovary. The effects of estrogen are mediated by estrogen receptors ERα and ERβ [38]. ERα and ERβ act as ligand-activated transcription factors that directly bind to DNA at specific estrogen response elements (EREs), regulating the transcription of their target genes. They also interfere with gene regulation by triggering the potentiation of cytoplasmic kinase signaling cascades. It is well established that steroid hormones play an important role in carcinogenesis and particularly in OC [5, 39, 40]. This is further supported by the effect of anti-estrogenic treatment, which hinders the growth of OC in vitro and in vivo. Numerous studies support the important role of ERs in OC, while growing evidence suggests their role in tumor development, progression, and metastasis [41].

More than two-thirds of OC cases display an overexpression in ER proteins [10, 38]. ERα functions as a transcription factor, whilst ERβ is a DNA-binding protein with a multi-level inhibitory effect on the expression of ERα [42]. ERα has a tumor-promoting role in many estrogen-dependent cancers, mediating estrogen effects such as the activation of cell proliferation. In contrast, the role of ERβ in OC is less understood, but alterations in ERβ expression were found to be involved in the pathophysiology of various tumors. Additionally, ERβ acts as an ERα antagonist in certain situations, and their ratio impacts their carcinogenic effects. However, ERs have different mechanisms of carcinogenesis in different types of OC, and their regulation of OC growth requires further elucidation.

The functions of later discovered estrogen-related receptors (ERRs) are less understood, but in vitro studies reveal the tumor-promoting role of ERRα and ERRγ [38]. Recent studies have performed immunohistochemical analyses in 208 OC samples and found positive staining for ERRα, ERRβ, and ERRγ at 91.8%, 82.2%, and 96.6%, respectively. ERRα acts as a modulator of metabolism and stimulates tumor growth. A positive correlation between carcinoembryonic antigen (CEA) and ERRα was found, supporting their oncogenic features and role in the migration and metastasis of cancer cells. The overall staining intensities were highest for ERRγ, followed by ERRα, and lowest for ERRβ in all OC samples and in

the serous subtype. ERRγ was predominant in late-stage OC and is significantly associated with shortened OS in patients with OC [4, 13, 38, 43, 44]. Multivariate survival analysis points out ERRγ as an independent prognostic marker for survival in patients with serous OC. ERRγ was also positively correlated with CA-125, as high levels of CA-125 were detected in the subgroup where ERRγ levels were statistically increased [38, 45]. Therefore, a strong correlation between the expression of ERRs and serum biomarkers was proved.

ERα to ERβ ratio: unraveling a diagnostic and prognostic index

After the initial controversial studies, the tumor-suppressive role of ERβ has been revealed. ERβ is the predominant ER in normal ovarian tissue. In OC tissue, several studies found a significantly lower ERβ expression compared to normal tissue. ERβ signaling reduces proliferation, migration, and activates apoptosis of OC cells [46]. Specific ERβ agonists significantly hamper the growth of different OC cell lines and may be a promising therapeutic strategy in the future [4, 39]. Moreover, the levels of ERβ expression have an impact on OS and progression-free time (PFT), with higher ERβ levels showing increased OS and PFT [38, 47, 48].

On the contrary, ERα has a well-established tumor-promoting role, but the impact of ERα expression on OS has been discussed controversially. Notably, the two ERs, ERα and ERβ, have a tightly balanced interaction, with ERβ affecting the transcriptional activity of ERα. Recent studies have shown increased interest in the ratio of ERα to ERβ, as small changes in the expression of the two ERs have a significant impact on cellular regulatory mechanisms [40, 43, 46, 49]. The ratio of ERα to ERβ is significantly augmented in OC compared with normal ovarian tissue, mainly due to the downregulation of ERβ [12, 42].

Another interesting correlation was revealed between the cancer biomarkers CEA, CA-125, and CA72-4 and the expression of ERs and ERRs. Several studies support a significant positive correlation among ERα, ERRα, and ERRγ with CA-125, whereas ERβ is significantly positively correlated with CA72-4. CA-125 is overexpressed in the majority of OC cases, mainly in serous tumors. It regulates cell adhesion and the metastatic process, while also promoting proliferation and migration. A significant positive correlation was found between CA-125 levels and ERα expression. On the other hand, CA72-4 is a highly detectable marker in all subtypes of OC. A highly significant correlation was observed between ERβ and CA72-4 in all OC specimens, as well as in the serous type [4].

Based on the strong correlation of these markers with the expression of ERs, which have a major impact on cellular metabolism, cell proliferation, and migration, we are proposing a new ratio that may be a cost-effective diagnostic and prognostic index: the ratio of CA-125 to CA72-4 [50].

Discussion – conclusions

OC is one of the leading causes of death in the western world. OC is lower in prevalence than breast and cervical cancer but higher than gastric, colon, and pancreatic cancer in women. Most of patients are diagnosed at late stage that leads to an extremely low 5-year OS, as the therapeutic strategies followed globally remain unsatisfactory. The incidence rate of OC is higher in post-menopausal women [5, 42] and that rises significantly after systematic use of hormone therapy [5, 8, 11]. Clinical studies have proved that women under hormone therapy, irrelevant the kind of treatment, are at elevated risk of developing OC. There is a positive correlation between the duration of treatment and the incidence ratio, posing that treatment above two years is an independent risk factor for OC [3]. The most accurate procedure to confirm diagnosis is laparoscopy and histological confirmation of cancer cells in ovary tissue, however the risk of damage to healthy ovarian tissue, the post-surgical complications and the phycological harm highlights the need for non-invasive diagnostic approaches. Using ultrasound scanning does not eliminate the variability of interpretation by less experienced scientists. Until now, the best available biomarker for screening population was CA-125 with the odds of screening with CA-125 resulting in four surgeries to diagnose only one cancer. The high sensitivity of CA-125 is limited by its low specificity as benign conditions seem to increase its levels. Therefore, a co-evaluation of CA-125, ultrasound score, and age of menopause led to RMI Index in 1999. Moore et al. proposed the combination of two different serum biomarkers, CA-125 and HE4, that exhibited high sensitivity and specificity. ROMA was well established and worldwide used in clinical practice for differential diagnosis between normal conditions and OC [9]. A later study [8] suggested that ROMA did not add clinical benefit over CA-125 and HE4 measurements and insisted on the need of incorporating different biomarkers to minimize the false positive cases and define ovarian malignancy at early stages. It seems that an accurate and sensitive multimarker index has a dual role, as an OC early diagnosis leads to better prognosis. In post-menopausal women, CA-125 seems to decline in sensitivity compared to HE4, but it rises in specificity. It is known that endometriosis, non-gynecological cancers, age, BMI, smoking, menstrual cycle, and HT affect CA-125 levels. Although HE4 is regarded a highly specific marker as it is irrelevant to menstrual cycle and estrogen/progestin levels, it is still affected by age, BMI, renal dysfunction, and smoking. CA72-4 is selectively expressed in OC and highly detectable

in all OC subtypes [8, 9], whereas CA-125 is expressed only in serous tumors, the most common OC type. The menstrual cycle and HT have no significant impact on CA72-4. Neither BMI, age, smoking nor the use of combined estrogen/progestin therapy influence CA72-4 levels [10, 11]. Its stability in all previous factors suggests the reconsideration of adding CA72-4 into an algorithm for screening and monitoring post-menopausal women under HT. A positive correlation between levels of serum biomarkers CA-125, CA72-4 and ERs ERα and ERβ, respectively, reveals a promising potential algorithm in early diagnosis. Novel studies found that not only estrogens are associated with OC, but ERs and ERRs play a pivotal role in carcinogenesis. ERα has a well-established tumor-promoting role, while ERRγ is predominant in late OC stage and serves as a bad prognostic marker. ERβ has a tumor-suppressive role and is downregulated in OC tissue compared to normal. There is a highly balanced crosstalk between ERα and ERβ, as the latter inhibits the transcriptional potential of ERα. ERα to ERβ ratio is significantly increased in OC compared to normal. Given the tumor-suppressive role of ERβ, a low ERα to ERβ ratio is associated with a better progression-free time and OS [4]. This dual diagnostic and prognostic role of ERα to ERβ is very promising but rather expensive for a broad use as a screening test. However, ERα, ERRα, and ERRγ displayed a significant positive correlation with the most frequently used CA-125 biomarker. Furthermore, ERβ expression attenuates tumor growth, proliferation, and migration, and is positive correlated with CA72-4 levels. Based on these strong positive correlations we propose the utmost need to intensify the evaluation of a CA-125 to CA72-4 ratio as a diagnostic and prognostic tool at elevated risk post-menopausal women under HT. CA-125 to CA72-4 ratio is a cost-effective, non-invasive index, as it only needs blood collection, and is performed with an automated chemiluminescent immunoassay, a highly sensitive and precise method. CA72-4 invariability in age, BMI, and HT increases the specificity of the ratio, while CA-125 maximizes its sensitivity. The absence of an organ-specific biomarker with high sensitivity and specificity underlines the need to incorporate CA-125:CA72-4 and ERα:ERβ ratios for monitoring women at elevated risk, as early diagnosis at stage I-II increases OS by timely surgical and/or chemotherapeutic treatment.

Conclusively, CA-125:CA72-4 ratio may serve as a risk prediction classifier for identifying post-menopausal users of HT at elevated risk of OC. To our knowledge, we are the first to propose CA-125:CA72-4 ratio as a diagnostic and prognostic index; further studies will be necessary to evaluate this ratio in the clinical setting.

Author contributions

A.M., A.N.G. and A.G.P. establish review idea, information collection and writing. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

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