SPi	Journal Code				Article ID				Dispatch: 27.03.14	CE: Sapon, Abbey Valerie
	P	O	N		3	5	4	0	No. of Pages: 7	ME:

Psycho-Oncology
Psycho-Oncology (2014)
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3540

Validation of the Freund Clock Drawing Test as a screening tool to detect cognitive dysfunction in elderly cancer patients undergoing comprehensive geriatric assessment

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Received: 17 January 2014
Revised: 13 March 2014
Accepted: 13 March 2014

Abstract

***Objective*: We aimed to validate the Freund Clock Drawing Test (CDT), with its predefined cutoff score of ≤4, as a screening tool to detect elderly cancer patients in need of a more in-depth cognitive evaluation within a comprehensive geriatric assessment (CGA).**

***Methods*: Patients aged 70 years or older with a histologically confirmed diagnosis of cancer were evaluated with a full CGA, including CDT and Folstein Mini Mental State Examination (MMSE) as gold standard. Validation of the Freund CDT was defined in terms of diagnostic accuracy of the test through receiver operating characteristics (ROC)-analysis. To accept the Freund CDT as a screening tool, we estimated that the area under the ROC curve (AUC) had to differ significantly from 0.70 with an AUC of at least 0.85.**

***Results*: Two hundred elderly cancer patients with a mean age of 79.0 years were included. Four patients were excluded from the analyses because of invalid results. Potential cognitive impairment (MMSE ≤23) was observed in 27.0% of patients. On the basis of the AUC ± SE, the Freund CDT showed excellent diagnostic performance (0.95 ± 0.17). Furthermore, it provided excellent sensitivity (94.3%) and high specificity (87.4%).**

***Conclusions*: Our results indicate that the Freund CDT can be used as an initial screening tool to detect elderly cancer patients in need of a more in-depth cognitive assessment within CGA, instead of the MMSE.**

Introduction

As a result of the aging of populations, there is currently a demographic evolution particularly in Western countries. These demographic changes have triggered an increased interest in the multidisciplinary management of elderly patients ~~because~~ the latter is a heterogeneous group that is in need of a more individualized treatment approach [1,2]. Tailored care can be facilitated through a comprehensive geriatric assessment (CGA), which has been the cornerstone in the management of geriatric patients for years [3]. A CGA is a multidisciplinary evaluation assessing medical, psychosocial, and functional capabilities and limitations in elderly cancer patients. It aims at predicting the functional age of patients including the risk on morbidity and mortality through assessing a wide range of domains including functional status, cognition, nutrition, emotional status, polypharmacy, comorbidities, and geriatric syndromes, each evaluated with a commonly used validated tool [2,4–6]. In addition, it reveals unknown problems and predicts toxicity from treatment and quality of life. During the past years, efforts have been made to

implement a CGA in an elderly oncology population, with success, as it has now been proposed as the key treatment approach [7,8].

The Folstein Mini Mental State Examination (MMSE) is a standard validated measure to screen cognitive function within a CGA. Studies have noted that up to 40% of elderly cancer patients present with cognitive abnormalities that warranted further evaluation. Cognitive dysfunctions can influence the ability to weigh the risks and benefits of cancer therapy, comply with the suggested treatment plan, and decrease the ability to recognize the symptoms of toxicity that need medical attention [9]. The MMSE can be used to screen for dementia and to estimate the severity of cognitive impairment in a general population and in elderly cancer patients [10–12]. However, in an oncogeriatric population, where the majority of patients has a normal cognitive function, such assessment can be experienced as tedious and time-consuming, as it may take up to 10–15 min to carry out [13,14]. More recently, the Clock Drawing Test (CDT) has been proposed as a quick and simple screening tool to assess cognitive dysfunction as it can be completed in only 5 ~~min~~ [15]. The CDT evaluates multiple domains of cognition including memory, comprehensive and executive function, visuo-spatial ability, and abstract thinking [16,17]. Furthermore, when given a pre-drawn circle, the CDT is not influenced by education age [18]. Although the CDT has the characteristics of an attractive screening tool, an easy and straightforward scoring method and validated cutoff scores were still lacking. Therefore, our research group retrospectively reviewed the Freund scoring system, as it has been reported in literature as a fast, easy, and trustworthy scoring method [18]. A retrospective analysis on 105 elderly cancer patients at the General Hospital Groeninge showed that a cutoff score of ≤4 for the CDT had a good area under the curve (AUC), sensitivity (Se), and specificity (Sp). The same cutoff score appeared optimal in a general geriatric population. Furthermore, the Freund scoring system demonstrated high interrater reliability [11,19].

In this prospective trial, our primary endpoint was to prospectively validate the Freund CDT, with its predefined cutoff score of ≤4, as a screening tool to detect cognitive deterioration in elderly cancer patients within a CGA.

Methods

Patient selection

This prospective study (PROACTIVE trial, ClinicalTrials.gov identifier: NCT01749995) was conducted from November 2012 till December 2013 in patients aged 70 years or older with a histologically confirmed diagnosis of a solid cancer or hematologic malignancy at all four sites of the General Hospital Groeninge (Kortrijk, Belgium). Patients, receiving their primary oncology care (surgery, course of (neo)adjuvant or palliative chemotherapy, radiotherapy, targeted therapy, palliative care, experimental treatment as part of a clinical trial,…) could be included before or at the start of a line of treatment but not during a line of treatment. Eligible patients were screened with the G8-questionnaire before or after they had received their cancer diagnosis, as part of routine clinical practice [20]. Patients who screened positive on the G8 (cutoff ≤14) were evaluated with a full CGA and were subsequently invited to participate in this trial. In a limited number of cases, a CGA was performed irrespective of the G8 test score because of a referral by the treating physician on the basis of clinical suspicion of vulnerability or frailty. This trial was approved by the ethical committee of the General Hospital Groeninge (Kortrijk, Belgium).

Comprehensive geriatric assessment and cognitive ~~assessments~~

Cognitive function was assessed as part of a routine oncogeriatric assessment or CGA. The CGA comprised several domains, each assessed with a standard validated measure: nutrition (Mini Nutritional Assessment-Short Form [21]), functional status (activities of daily living, instrumental activities of daily living [22,23]), physical status (number of falls, JAMAR® Hydraulic Hand Dynamometer [24]), depression (Geriatric Depression Scale-15 [25]), cognition (MMSE, Freund CDT [12,19]), polypharmacy (number of drugs), and comorbidities (Charlson Comorbidity Index [26]). In accordance with previous reports, patients were deemed vulnerable if they presented with impairments in two or more domains within the CGA [3,27]. The CGA, including MMSE and Freund CDT, was conducted by an oncopsychologist or research associate with experience in the field of oncogeriatrics. Both had received training from an occupational therapist, enabling them to conduct and score the Folstein MMSE according to international guidelines [28]. Patients were considered to be potentially cognitively impaired if they presented with a test score of 23 or less [13]. Potentially cognitively impaired means that a patient has to be referred to a neurologist or memory clinic for a more in-depth cognitive assessment. For the CDT, patients were given a pre-drawn circle and were verbally instructed to put all the numbers of a clock on it and set the time at ten past eleven, as this has been reported to be the most sensitive for detecting neurocognitive impairments [29]. The Freund scoring system uses a 7-point rating scale ranging from 0 to 7, indicating a potentially very poor to excellent cognitive function, respectively. The scoring system is divided into three categories, namely, the ability to correctly reproduce all numbers, to position them accurately in the circle, and to appropriately replicate the hands at the indicated time (Table 1). For every item,**T1**

DOI: 10.1002/pon

Table 1. Clock Drawing Test: Freund scoring system [19] and examples

Time (0–3 points)	– One hand points 2 (or symbol representative of 2) – Exactly two hands – Absence of intrusive marks, for example, writing or hands indicating incorrect time, hand points to number 10, tic marks, time written in text
Numbers (0–2 points)	– Numbers are inside the clock circle – All numbers 1–12 are present, no duplicates or omissions
Spacing (0–2 points)	– Numbers spaced equally or nearly equally from each other – Numbers spaced equally or nearly equally from the edge of the circle
Examples	

Excellent clock drawing followed by two poor drawings

one point can be awarded [11,19]. According to our predefined cutoff score, patients were considered to be potentially cognitively impaired if they had a score of 4 or less [11].

Statistical analyses

All statistical analyses were performed by using SPSS software (version 21; IBM SPSS Statistics, Chicago, IL). Descriptive statistics were conducted to present patient and tumor characteristics and CGA and cognitive test results. Scatter graphs were plotted to evaluate if a linear relationship was present between education age and MMSE and CDT test scores. ~~On the basis of~~ the linearity of this association, Pearson or Spearman's correlation coefficients were calculated to examine the association between age, education age, and MMSE and CDT test scores. Education age can be defined as the number of years that patients went to school, starting from primary education. In advance, sample size calculations were based on the hypothesis of equality with 0.70 of the area under the receiver operating characteristics (ROC) curve (ClinicalTrials.gov identifier: NCT01749995). In our scenario, a sample with an unequal allocation ratio of four, consisting of a sample of at least 32 from the positive group and at least 128 from the negative group, would achieve at least 80% power to detect a difference of 0.15 between the area under the ROC curve under the null hypothesis of 0.70 and an AUC under the alternative hypothesis of 0.85 using a two-sided z-test at a significance level of 5%. ROC curves were plotted to evaluate the diagnostic performance, in terms of AUC, of the Freund CDT in determining patients who are potentially cognitively impaired compared with the Folstein MMSE as gold standard. The cutoff for determining impairment was defined as having a MMSE score of 23 or less [13]. Se and Sp with 95% ~~CIs~~ (95%CI) were calculated at our predefined cutoff score of ≤4. Positive and negative predictive values were also determined (PPV and NPV, respectively).

Results

Patient characteristics

During the inclusion period, 490 patients were evaluated a routine oncogeriatric screening at the General Hospital Groeninge. Of those, 320 (65%) patients needed an additional full CGA. Two hundred elderly cancer patients consented to participate in this trial. Four patients were excluded from analyses ~~because of~~ an incomplete cognitive assessment. Patients presented with a mean age of 79.0 years (range 70.0–93.0 years) and a mean education age of 10.3 years (range 4.0–22.0 years). The study population comprised slightly more male patients (52.6%). Patients presented with cancer of the following regions: digestive (30.6%), genitourinary (22.4%), gynecologic (13.3%), breast (8.7%), hematological malignancies (8.7%), thorax (5.6%), head and neck (5.6%), skin (2.0%), musculoskeletal (2.0%), and central nervous system (1.0%). More than half of patients were treated with curative intent (55.1%) (Table 2). T2

Comprehensive geriatric assessment and cognitive measures

Three patients (1.5%) screened negative on the G8-questionnaire (cutoff ≤14) and were evaluated with a full CGA ~~on the basis of~~ a referral from their treating

DOI: 10.1002/pon

Table 2. Patient and tumor characteristics

Characteristic ($n = 196$)	Mean (range)	N (%)
Age	79.0 (70.0–93.0)	
Gender		
Male		103 (52.6)
Female		93 (47.4)
Marital Status		
Single		13 (6.6)
Married		107 (54.6)
Divorced		3 (1.5)
Widow-er		69 (35.2)
Other		4 (2.1)
Level of education		
Age	10.3 (4.0–22.0)	
Less than primary education		2 (1.0)
Primary education		11 (5.6)
Lower secondary education		109 (55.6)
Higher secondary education		51 (26.0)
Higher education		23 (11.8)
Cancer site		
Digestive		60 (30.6)
Genitourinary		44 (22.5)
Gynecologic		26 (13.3)
Breast		17 (8.7)
Hematologic malignancies		17 (8.7)
Head and neck		11 (5.6)
Thorax		11 (5.6)
Skin		4 (2.0)
Musculoskeletal		4 (2.0)
Central nervous system		2 (1.0)
Treatment intent		
Curative		108 (55.1)
Palliative		77 (39.3)
No active treatment		11 (5.6)

physician. On the basis of the CGA outcome, 89.8% of patients were deemed vulnerable as they presented with a potential impairment in two or more domains (data not shown). Potential cognitive deficits were identified in 27.0% of patients according to the MMSE. The CDT selected 68 (34.7%) patients with a potential cognitive impairment. Median MMSE and CDT scores were 27 and 5, respectively (Table 3). Scatter graphs did not detect a linear association between age, education age, and MMSE test scores nor was this the case for the CDT test results. Spearman's correlation coefficient showed a significant negative correlation between MMSE and age ($p < 0.01$; $r_s = -0.23$) and a significant positive association between MMSE scores and the years of education ($p < 0.01$; $r_s = 0.24$). We did not find a significant association between age, education age, and CDT test results ($p = 0.07$; $r_s = -0.13$ and $p = 0.07$; $r_s = 0.13$, respectively) (data not shown). At our predefined cutoff score of ≤4, the area under the ROC curve (AUC ± SE) of the CDT showed excellent diagnostic accuracy (0.95 ± 0.17) (Figure 1). Furthermore, it provided a Se of 94.3% (95% CI [83.4-98.5]) and Sp of 87.4% (95% CI [80.6–92.2]). The PPV and NPV were 73.5% (95% CI [61.2–83.2]) and 97.7% (95% CI [92.8–99.4]), respectively (Table 3).

Table 3. Cognitive test results, performance measures, and predictive values

Cognitive test results ($n = 196$)	
MMSE score (0–30)	
Median	27
IQR	23–29
Impairment (%)	27.0
CDT score (0–7)	5
Median	5
IQR	3–7
Impairment (%)	34.7%
Performance measures (cutoff ≤4)	% [95% CI]
Se	94.3% [83.4–98.5]
Sp	87.4% [80.6–92.2]
AUC	0.95 [0.92–0.98]
Predictive values (cutoff ≤4)	
PPV	73.5% [61.2–83.2]
NPV	97.7% [92.8–99.4]

MMSE, Mini Mental State Examination; CDT, Clock Drawing Test; IQR, interquartile range; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristics; AUC, area under the receiver operating characteristics curve.

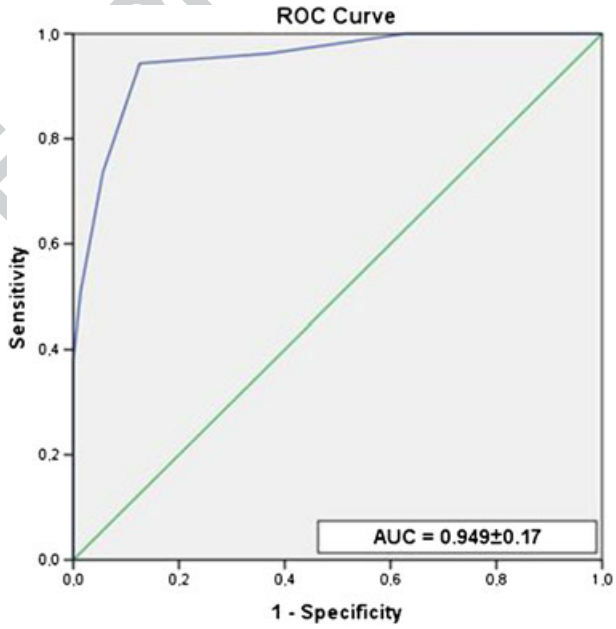

Figure 1. Receiver operating characteristics (ROC) curve of the Clock Drawing Test compared with the Mini Mental State Examination as gold standard. AUC, area under the (ROC) curve

When subdividing patients into groups by age and education age according to Crum *et al.* (1993), the cutoff remained optimal (data not shown) [30].

Discussion

Assessing cognitive function provides health care workers valuable information on the mental reserve of the patient as patients presenting with memory impairment can have difficulties understanding treatment instructions and may

DOI: 10.1002/pon

not be alert for the signs and symptoms of treatment related toxicities that need further evaluation [31]. The Folstein MMSE is a commonly used instrument to screen for dementia and is validated for use in several patient populations. Nevertheless, the MMSE is time-consuming and confronting in the many cognitively fit patients that undergo a CGA as part of their cancer care. Previous work from our group suggested that the Freund CDT with a cutoff score of ≤4 could replace the MMSE within the CGA, resulting in gain in time for health providers and increased comfort for patients [11]. The current study was able to prospectively validate the retrospectively identified cutoff score and could therefore be practice changing.

A good screening tool needs a high Se and high NPV as it reduces the number of false–negative cases. Our results show that the Freund CDT, with a cutoff score of ≤4, has indeed the properties of an excellent screening instrument as we have found a Se of 94.3% and NPV of 97.7%. Further, the Freund CDT provided a high Sp of 87.4%. In this trial, our primary endpoint was to validate the CDT on the basis of the diagnostic accuracy of the test. We stated that a sample with an unequal allocation ratio of four, consisting of a sample of at least 32 from the positive group and at least 128 from the negative group, would achieve at least 80% power to detect a difference of 0.15 between the AUC under the null hypothesis of 0.70 and an AUC under the alternative hypothesis of 0.85 using a two-sided z-test at a significance level of 5%. In our sample, results show an AUC (AUC ± SE) under the ROC curve of 0.95 ± 0.17. Hereby, we can accept the alternative hypothesis as an AUC under the ROC curve, of at least 0.85 was achieved. As this cutoff score was also determined in our previous retrospective study (in oncogeriatric and general geriatric patients) and in the original paper by Freund *et al*., we can assume the robustness of this cutoff score [11,19]. Further, we can state that the cutoff score of ≤4 is the most optimal cutoff score for use in an oncogeriatric population.

In our sample, 27.0% of patients presented with a potential cognitive deficit that needed further evaluation on the basis of the MMSE. This is in line with previous research reporting cognitive deterioration in up to 50% of patients [9]. Further, it has been noted that the Folstein MMSE can be influenced by education age, whereas the CDT is less dependent of education age when given a pre-drawn circle [18,30]. Spearman's correlation coefficients showed a significant statistical association between MMSE test scores and education age. This was not the case for the Freund CDT.

Initially, it was our objective to validate the Freund CDT as a pre-screener within a CGA. Because results show such an excellent AUC of 0.95 with Se of 94.3% and Sp of 87.4%, we could assume that an assessment with the MMSE may be redundant and that results on both screening tools will be nearly equal. However, McNemar test revealed a significant difference between both test outcomes disputing the latter statement ($p = 0.001$; data not shown). This highly significant result reflects a minor discordance in 21 out of 196 patients, of which 18 are considered fit by MMSE were classified vulnerable by CDT and 3 out of 196 are considered vulnerable by MMSE were classified as by CDT. Nevertheless, selecting the Freund CDT above the Folstein MMSE has some advantages. First, the Freund CDT defined more patients as vulnerable leading to a more sensitive test. Second, within a CGA, we try to select those domains that can influence and increase the risk on morbidity and mortality. As it is not our intention to diagnose patients but merely to detect potential vulnerabilities, we need a screening tool that gives us valuable information in less time. The Freund CDT can be administered in approximately 5 ~~min~~ and has been previously reported as a good screening tool in other populations that can be carried out in very little time [15]. Third, the Freund scoring system is user-friendly and has been reported with a high interrater reliability [11,19]. Fourth, in our and other patient populations, the MMSE can be experienced as tedious and annoying, whereas the CDT has been described previously as a non-threatening cognitive assessment [32]. Last, it has been noted that the MMSE can be influenced by education age, whereas the CDT—when given a pre-drawn circle—is not influenced by education age [18,30]. Our results support this statement.

The results of this trial need to be interpreted with caution because of some limitations. We considered the Folstein MMSE as the gold standard against the Freund CDT. Although the MMSE is a commonly used validated measure, it is not a diagnostic test. Cognitive malfunction detected by the CDT may slightly differ from that detected by our gold standard. Therefore, it is important to remember that both MMSE and CDT are screening tools and that they should always be followed by an intensive diagnostic neuropsychological assessment when a potential cognitive impairment is detected [33]. Further, the MMSE cutoff of ≤23 may not be sufficient for detecting mild cognitive impairment nor may it be sufficient for detection dysfunctions in patients with less than 9 years of education [30,34]. Although our population has a mean education age of 10.3 years, 6.6% of patients received less than lower secondary education (Table 2). However, in our study, we did not intend to diagnose patients but to select those who may present with a potential vulnerability that needs closer evaluation. Next, this study was conducted in oncogeriatric patients receiving a routine oncogeriatric assessment. Most patients consenting for this trial had been assessed with a CGA because of a positive test score on the G8-questionnaire. In our clinic, patients deemed fit —on the basis of their G8 screening score—are only evaluated with a CGA when required by the physician. Therefore, this trial includes only a minority of fit patients. The

DOI: 10.1002/pon

cutoff score achieved may thus not be representative for patients who screened negative on the G8 or patients who are evaluated with other screeners such as VES-13. However, the G8-questionnaire contains seven items from the Mini Nutritional Assessment and age. One of the items included in the G8-questionnaire concerns cognition and depression. This item has previously shown to correlate with MMSE test scores [35,36]. Last, we did not consider the chronobiology [37]. However, in our sample, as patients were seen throughout the day, we suggest a minimal bias by biological rhythms.

Overall, we can conclude that in this prospective trial, we were able to validate the Freund CDT with a cutoff score of ≤4 as a screening tool to detect cognitive dysfunction in elderly cancer patients undergoing a CGA. Our results indicate that it could potentially replace the MMSE as a stand-alone screening instrument, leading to a more time-efficient CGA.

Acknowledgement

Our work was supported by the Belgian Federal Government, National Cancer Plan (NKP_24_018, NKP_2122C_044, and NKP_24_A_025).

Conflict of interest

The authors have declared no conflicts of interest.

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- If you intend to annotate your proof electronically, please refer to the E-annotation guidelines.
- If you intend to annotate your proof by means of hard-copy mark-up, please refer to the proof mark-up symbols guidelines. If manually writing corrections on your proof and returning it by fax, do not write too close to the edge of the paper. Please remember that illegible mark-ups may delay publication.

Whether you opt for hard-copy or electronic annotation of your proofs, we recommend that you provide additional clarification of answers to queries by entering your answers on the query sheet, in addition to the text mark-up.

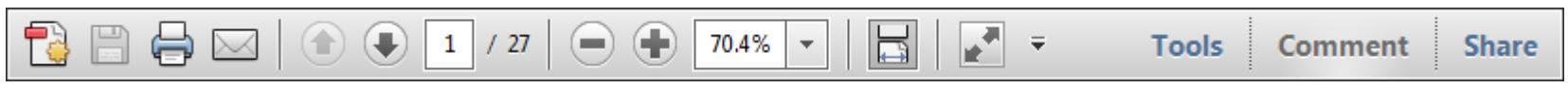
Query No.	Query	Remark
Q1	AUTHOR: Please check affiliations if captured and presented correctly.	
Q2	AUTHOR: 'level years of education' has been changed to 'years of education'. Please check if correct.	
Q3	AUTHOR: Please check journal titles abbreviation if captured correctly.	
Q4	AUTHOR: If this reference has now been published in print, please add relevant page information.	

WILEY-BLACKWELL

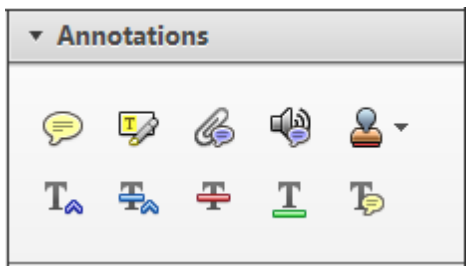
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 7.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/uk/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

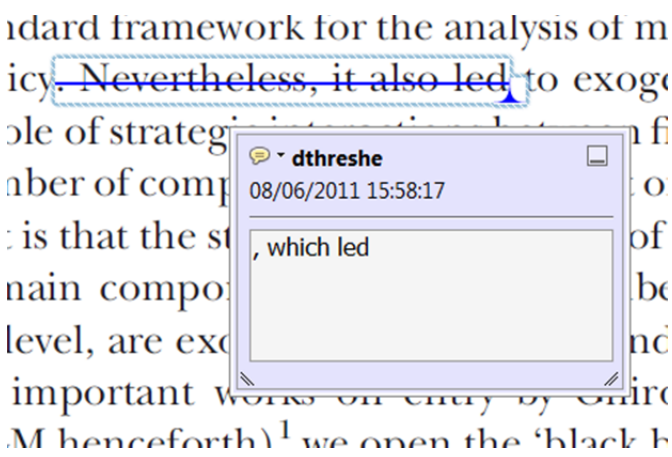


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

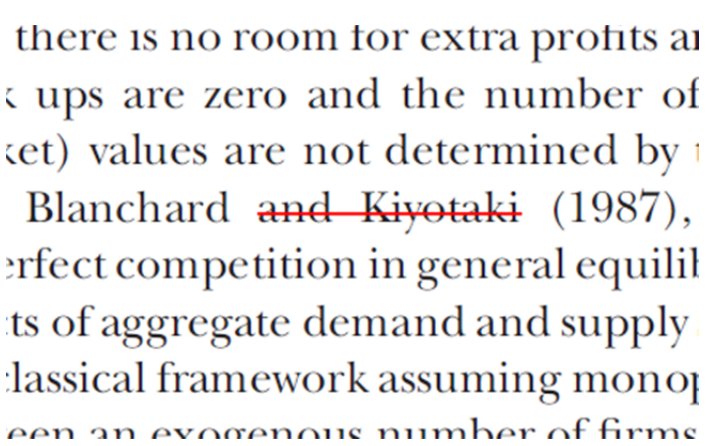


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

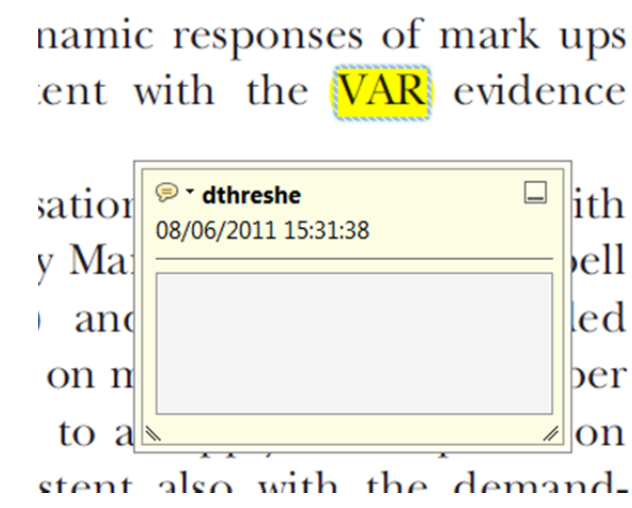


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

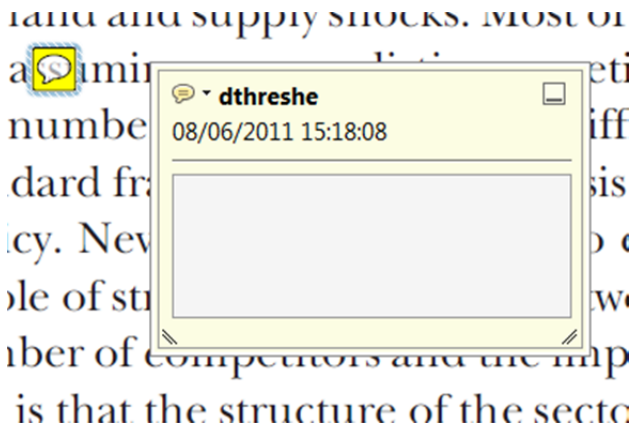


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



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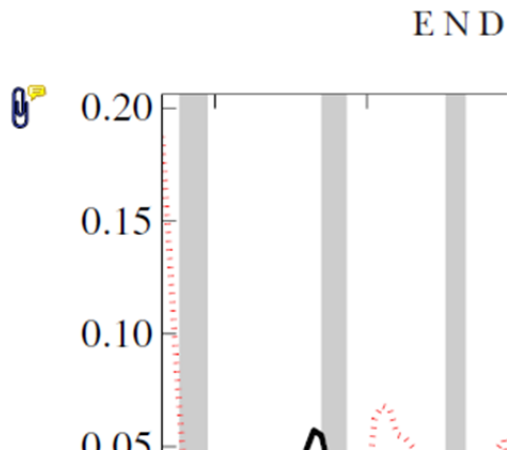
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

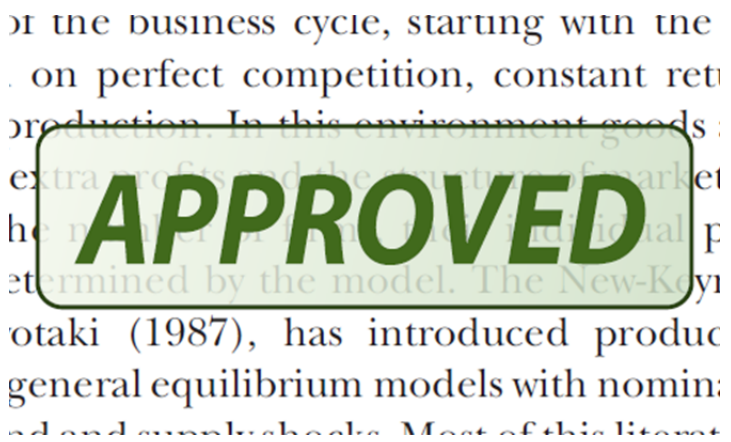


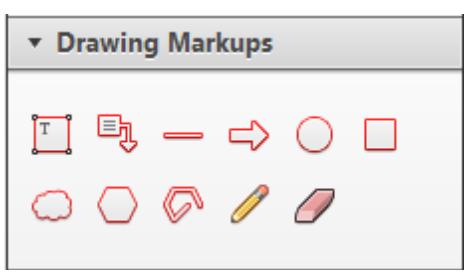
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).



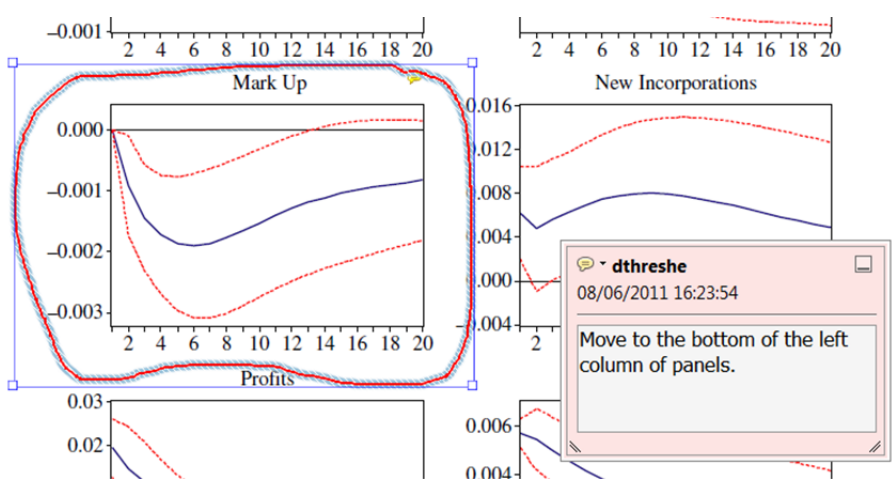


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: