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Acute respiratory distress syndrome and the promise of driving pressure

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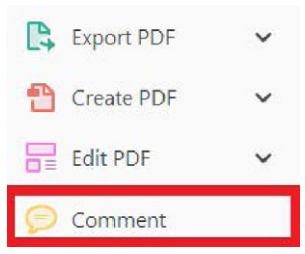

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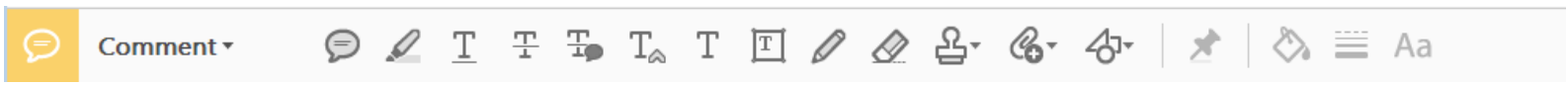
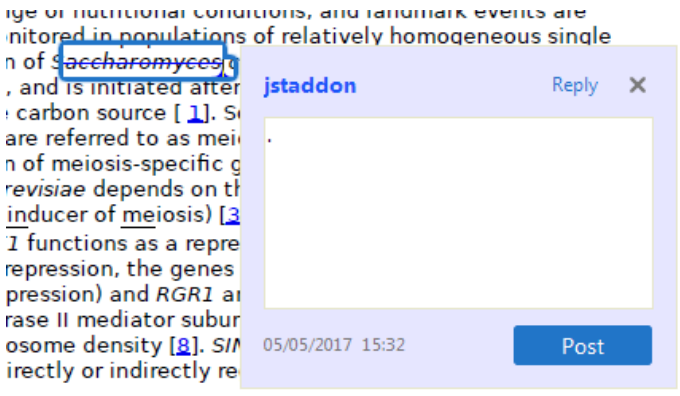


1. Replace (Ins) Tool – for replacing text.

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 .
- Type the replacement text into the blue box that appears.

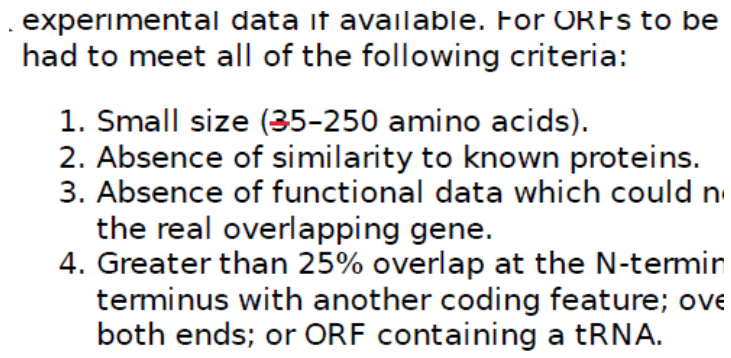


2. Strikethrough (Del) Tool – for deleting text.

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

How to use it:

- Highlight a word or sentence.
- Click on .
- The text will be struck out in red.


experimental data if available. For ORFs to be had to meet all of the following criteria:

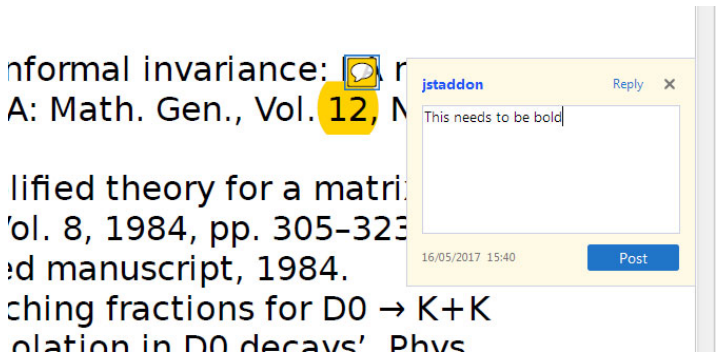
1. Small size (~~3~~5–250 amino acids).
2. Absence of similarity to known proteins.
3. Absence of functional data which could n the real overlapping gene.
4. Greater than 25% overlap at the N-termir terminus with another coding feature; ove both ends; or ORF containing a tRNA.

3. Commenting Tool – for highlighting a section to be changed to bold or italic or for general comments.

Use these 2 tools to highlight the text where a comment is then made.

How to use it:

- Click on .
- Click and drag over the text you need to highlight for the comment you will add.
- Click on .
- Click close to the text you just highlighted.
- Type any instructions regarding the text to be altered into the box that appears.

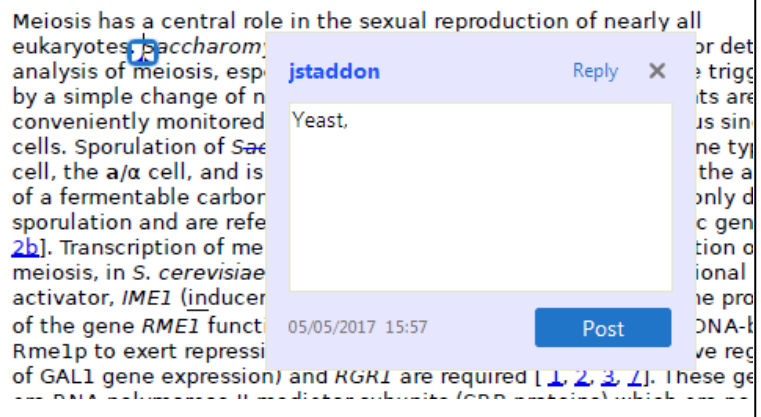


4. Insert Tool – for inserting missing text at specific points in the text.

Marks an insertion point in the text and opens up a text box where comments can be entered.

How to use it:

- Click on .
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the box that appears.



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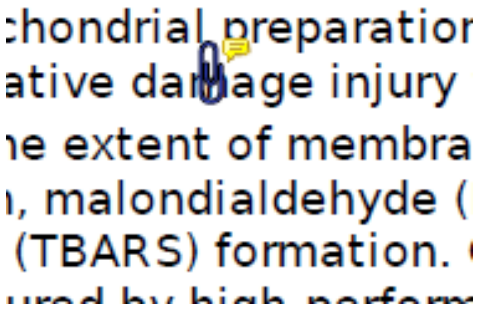
5. Attach File Tool – for inserting large amounts of text or replacement figures.

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

How to use it:

- Click on .
- 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.

  The attachment appears in the right-hand panel.

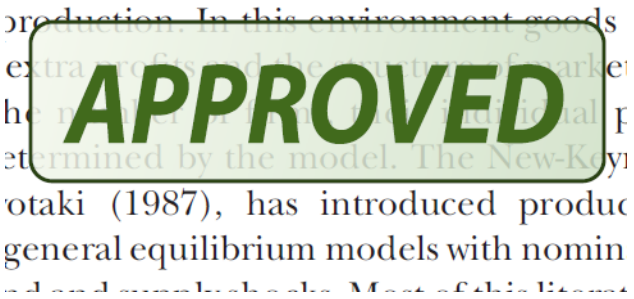


6. Add stamp Tool – for approving a proof if no corrections are required.

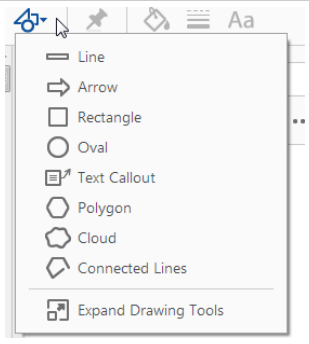
Inserts a selected stamp onto an appropriate place in the proof.

How to use it:

- Click on .
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears. Others are shown under *Dynamic*, *Sign Here*, *Standard Business*).
- Fill in any details and then 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).



Drawing tools available on comment ribbon

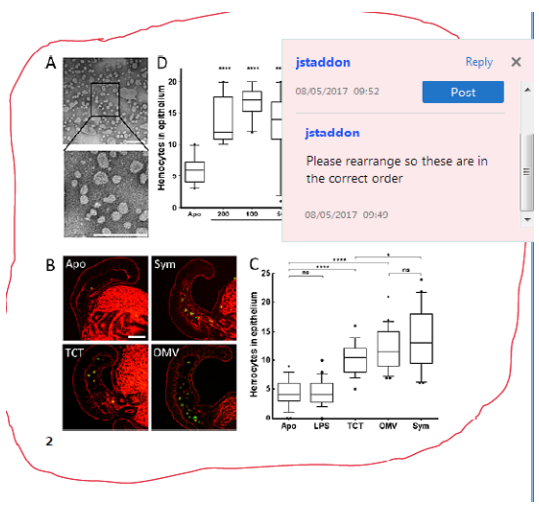


7. Drawing Markups Tools – for drawing shapes, lines, and freeform annotations on proofs and commenting on these marks.

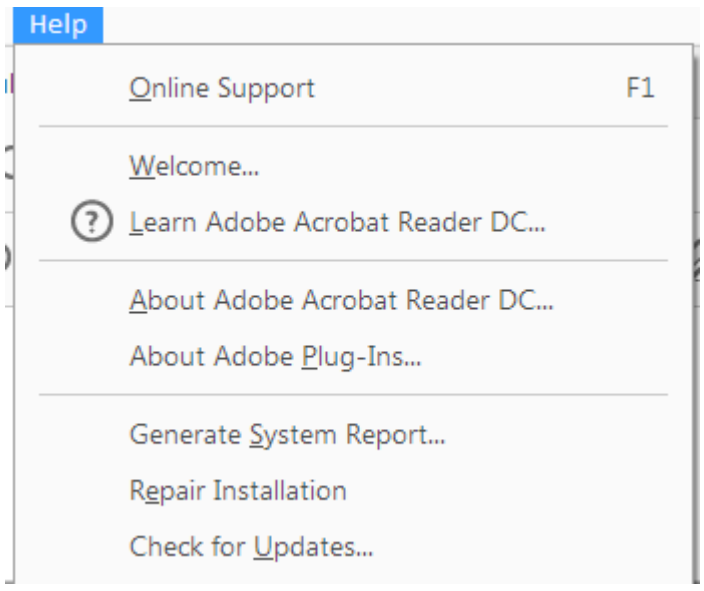
Allows shapes, lines, and freeform annotations to be drawn on proofs and for comments to be made on these marks.

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, right-click on shape and select *Open Pop-up Note.*
- 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:



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EDITORIAL

Acute respiratory distress syndrome and the promise of driving pressure

Key words: adult respiratory distress syndrome, lung injury, ventilation.

A recent meta-analysis advanced the concept that driving pressure (plateau minus PEEP) is a useful parameter in determining outcome in patients with established acute respiratory distress syndrome (ARDS).[1] Indeed, Amato *et al.* showed that driving pressure was an independent predictor of survival when data were aggregated from nine major ARDS trials including over 3000 patients. Driving pressure had predictive value independent of major covariates, including PEEP, tidal volume, plateau pressure, severity of illness and other important parameters. The concept is appealing as driving pressure is a function of the delivered tidal volume and the compliance of the respiratory system, thus providing some scaling of ventilatory parameters based on the patient's underlying physiology.[2] Driving pressure is easily assessed and thus easily implemented in the clinical setting. Driving pressure was subsequently validated prospectively in the Lung Safe Study in which high driving pressure predicted poor outcomes.[3]

Driving pressure, however, has some limitations, in part because of statistical issues.[4] Although driving pressure had independent predictive value in meta-analysis, many of the studies were designed with relatively fixed tidal volumes, limiting tidal volume's ability to predict clinical outcomes. There are other points regarding driving pressure for consideration:

1. Lung stress is governed by transpulmonary pressure, that is, the pressure difference between the airway and the pleural space.[5] This concept has been used to guide mechanical ventilation with modest success. However, the concept is sometimes confused by use of the term 'delta pressure' in which people may conflate the terms transpulmonary pressure and driving pressure.
2. Although driving pressure is thought to be helpful due to its simplicity, the correct interpretation of this parameter can be more complex; for example, a reduction of driving pressure may be very different from standpoint of haemodynamics, mechanics and gas exchange if it was achieved by raising PEEP versus lowering plateau pressure.
3. Driving pressure is thought to be valid in passively ventilated patients without respiratory effort.[2] In our experience, the presence or absence of respiratory effort is not always obvious at the bedside. Spontaneous respiratory efforts may complicate interpretation of driving pressure and its predictive value.[2]

Although mechanical ventilation can be life saving, the ventilator can be damaging to the lung when set inappropriately. Thus, data are compelling that lung stress can worsen outcomes in established ARDS, and increasingly, data suggest that minimizing lung stress can prevent ARDS development in patients at risk. In a recent publication in *Respirology*, Blondonnet *et al.*[6] report results from a secondary analysis of a prospective multicentre observational intensive care unit (ICU) study. Although the stated goal of the authors was to define the role of driving pressure in determining incident ARDS, of note, the baseline characteristics show PaO_2/FIO_2 values of <300 suggesting established ARDS was already present based on the Berlin definition.[7] Despite this caveat, the authors observed that driving pressures were higher in patients who developed clinician-diagnosed ARDS than in those who did not develop ARDS, even when adjusted for baseline tidal volume, respiratory rate, PEEP, severity of illness and other comorbidities. Although the statistical issues are complex, the authors attempted to separate the influence of driving pressure from its components, including PEEP and plateau pressure. A baseline driving pressure of >16.5 cm H_2O was highly specific for predicting incident ARDS, whereas a baseline driving pressure of <7.5 cm H2O was highly sensitive in predicting those who would not develop ARDS. The findings add to the literature regarding the potential utility of driving pressure and the notion that mechanical ventilation settings can worsen the risk of lung injury.

Although we advocate for further research on driving pressure, we believe that a definitive randomized trial would be challenging to design given the difficulty in dissociating driving pressure from other important parameters such as tidal volume, lung compliance and $PaCO_2$. Several alternative strategies to guide mechanical ventilation have been proposed:

1. Scaling ventilator settings based on imaging. Advances in technology including electrical impedance tomography and other imaging modalities may allow real-time adjustment of mechanical ventilator settings based on assessments of lung collapse and/or stretch.
2. Optimizing ventilator settings based on sizing the 'baby lung'. Gattinoni *et al.*[8] described the ARDS lung as small with many alveoli either collapsed or flooded and unable to participate in gas exchange. As such, Beitler *et al.*[9] have quantified the amount of lung available for gas exchange in ARDS and have used this value to scale tidal volume. Using this concept, the patients with smaller baby lungs in ARDS would ostensibly need smaller tidal volumes than those with more lung units available for gas exchange. This concept has not been tested

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definitively, but the analyses performed provide rationale for this strategy.

3. The measurement of oesophageal pressure allows estimation of transpulmonary pressure (airway pressure minus pleural).[5] This strategy was tested in a small pilot study in which PEEP and tidal volume were applied to optimize transpulmonary pressure (i.e. to prevent lung collapse at end-exhalation and overdistension at peak inflation). A multicentre randomized trial testing this approach has recently completed enrolment.

We applaud the authors for making an important contribution. Questions remain about how to optimize mechanical ventilator settings and how these decisions may be influenced by adjunctive therapies such as prone positioning, extra-corporeal support, etc. Moreover, Calfee *et al.*[10] have proposed the concept of phenotypically distinct sub-types of ARDS that respond differentially to various interventions (including statins, high PEEP, etc.). Thus, further research into the biology and physiology of lung injury is required for meaningful progress to occur.

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