



An introduction to eLife's peer-review process

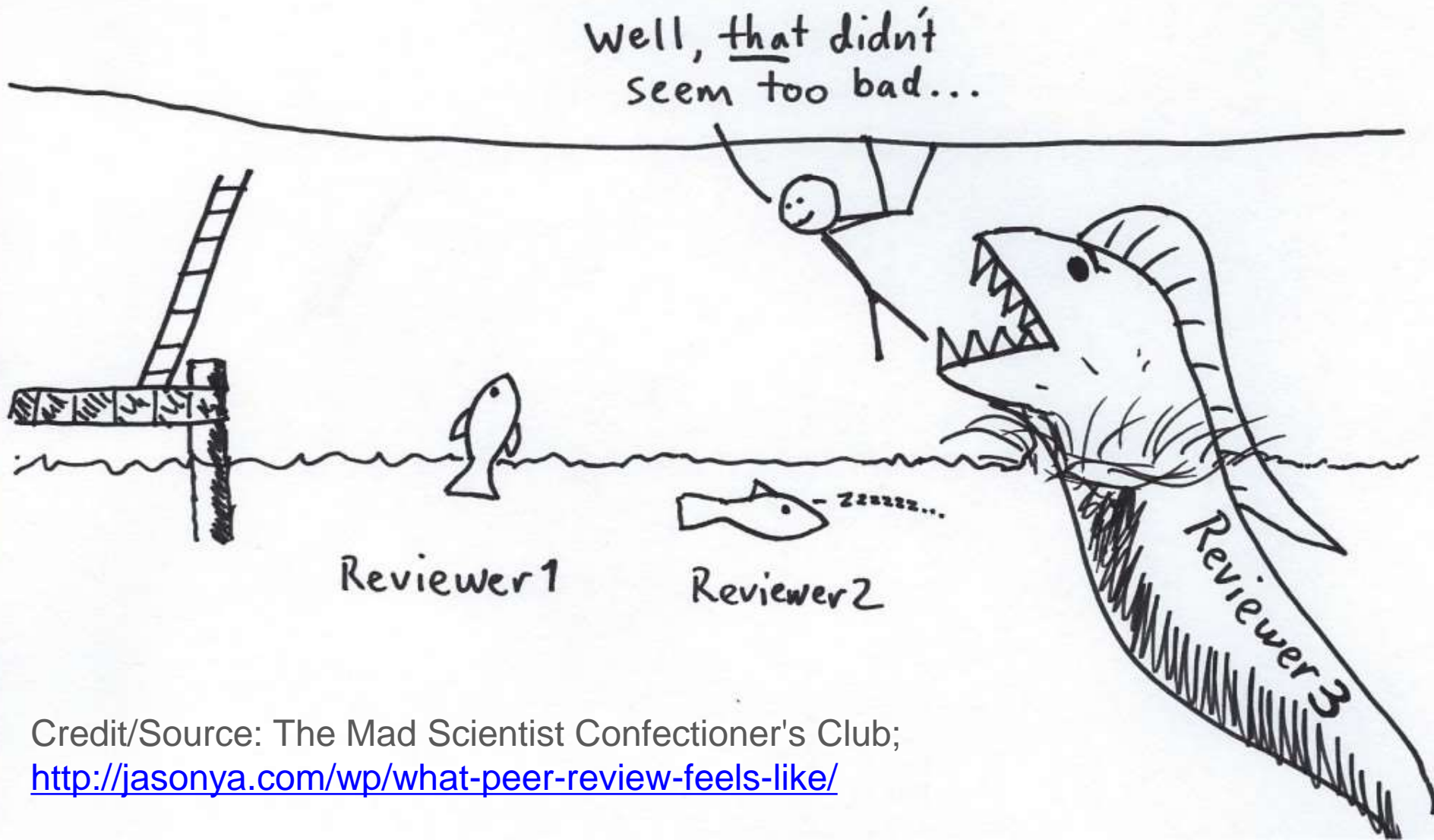
Andy Collings, Executive Editor

"Peer review is faith-, not evidence-based; ineffective; a lottery; slow; expensive; wasteful; ineffective; easily abused; biased; doesn't detect fraud; irrelevant. Apart from that, it's perfect."



Dr Richard Smith, Future of Scholarly Scientific Communication Conference, Royal Society, London, April 20 2015

What Peer Review Feels Like (sometimes)



Credit/Source: The Mad Scientist Confectioner's Club;
<http://jasonya.com/wp/what-peer-review-feels-like/>

Martin Raff, Alexander Johnson
and Peter Walter

Science

"The stress associated with publishing experimental results... can drain much of the joy from practicing science."

End the wasteful tyranny of reviewer experiments



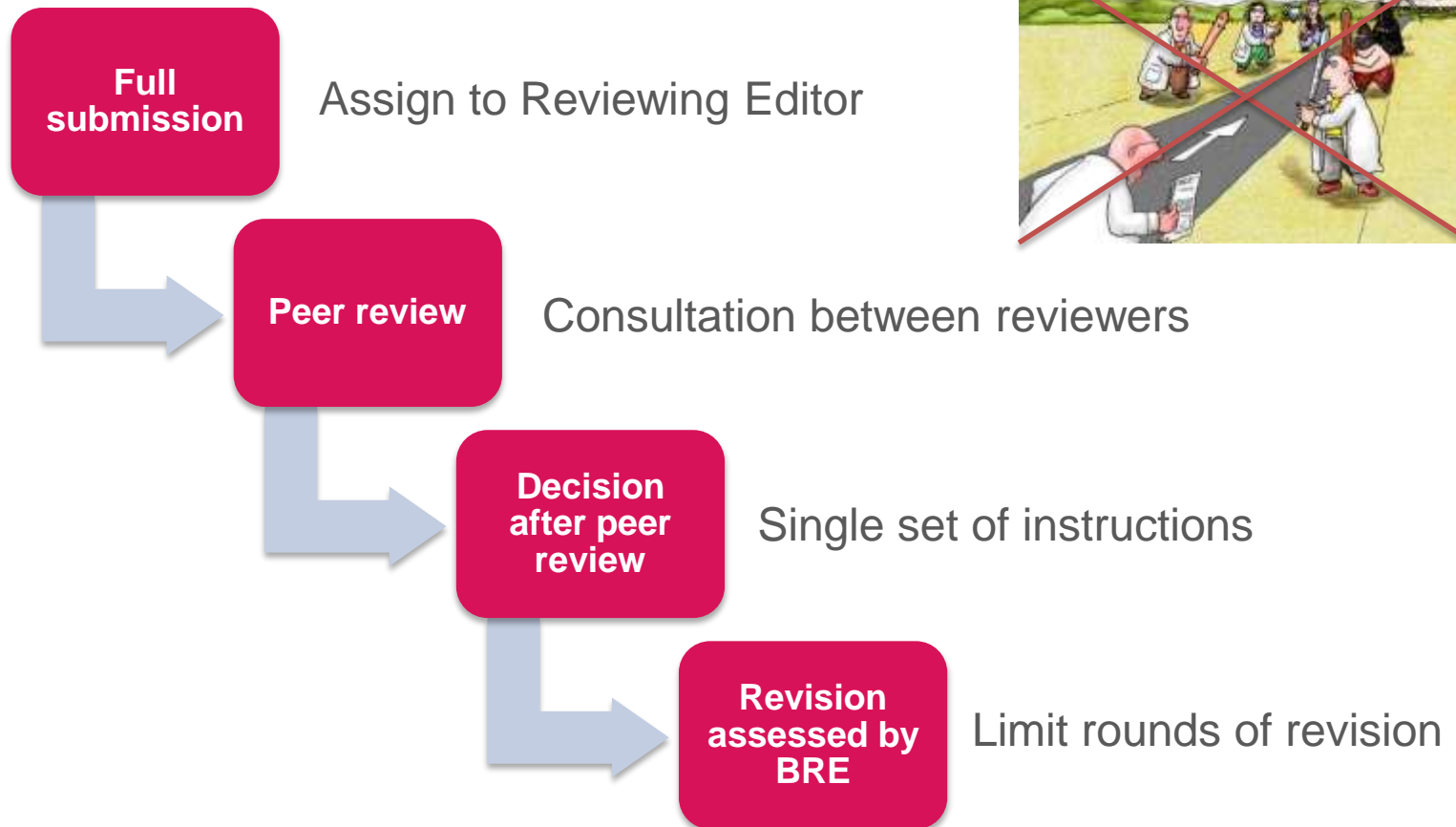
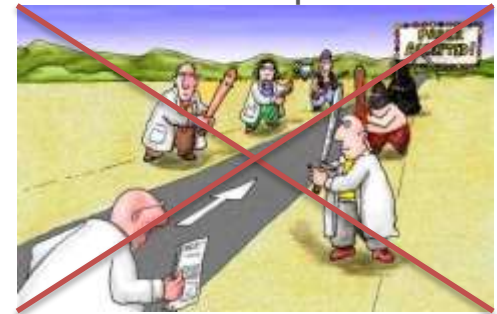
Peer review of scientific papers in top journals is bogged down by unnecessary demands for extra lab work, argues Hidde Ploegh.

Hidde Ploegh

nature

Editorial process at eLife

Adapted from/credit to:
GenomicEnterprise.com



Consultation between reviewers

I agree that this is an important contribution that provides new insight into congenital heart disease.

I do not think they need to perform any new wet lab experiments. I am willing to waive the functional testing of the inappropriately activated GRNs, but the findings therefore need to be more conservatively discussed.

I fully agree with the previous comments with respect to revisions. The study makes a number of important and novel points about mechanisms of congenital heart disease.

Transparency: decision letter

1-1 Decision letter

Margaret Buckingham, Reviewing editor, Institut Pasteur, France



eLife posts the editorial decision letter and author response on a selection of the published articles (subject to the approval of the authors). An edited version of the letter sent to the authors after peer review is shown, indicating the substantive concerns or comments; minor concerns are not usually shown. Reviewers have the opportunity to discuss the decision before the letter is sent (see [review process](#)). Similarly, the author response typically shows only responses to the major concerns raised by the reviewers.

Thank you for sending your work entitled "NKX2-5 mutations causative for congenital heart disease retain functionality and are directed to hundreds of targets" for consideration at *eLife*. Your article has been favorably evaluated by Janet Rossant (Senior editor) and four reviewers, one of whom is a member of our Board of Reviewing Editors.

This paper makes an important contribution to the field of cardiogenesis and to understanding NKX2-5 driven mechanisms underlying congenital heart disease. It leads to a shift in the conceptual framework, from the conventional view that mutations in NKX2-5 result in a failure of the transcription factor to correctly activate its downstream targets to the idea that the mutant factor participates in promiscuous interactions that lead to inappropriate activation of genes that are not normally NKX2-5 targets. This is a very data rich study that represents a technical tour de force. The results are complex and the manuscript densely written. In order to make it more accessible, some simplifications and clarifications are required in the text. Further experimentation is not required. However the authors should strengthen the validation of their results by more comparative analyses of data and tone down some of their conclusions. Specific points to be taken into account when modifying the text are as follows:

- 1) The results are based on the Dam-ID approach to discover transcription factor binding sites. It is essential to compare the findings with available published ChIP-Seq data. The authors compared their DamID peaks with NKX2-5 ChIP-Seq from HL-1 cells ([He et al., 2011](#)) mentioning 77.8% overlap but commenting that genes associated with ChIP-Seq peaks overwhelmed DamID targets, making comparison difficult. However, since a high quality ChIP-Seq dataset provides genome-wide TF occupancy information with higher resolution, the authors should show the percentage of ChIP-Seq peaks that are overlaid for the DamID data. This will serve as a validation.
- 2) The enzymatic function of Dam is supposed to be local. The authors should indicate the average distance from NKE to the nearest (predicted) methylated *DpnI* sites in the enriched DamID peaks and should discuss whether the requirement for *DpnI* sites introduces bias.
- 3) The experiments were performed using overexpression in cell culture and the data should also be compared with results obtained by others on NKX2-5 chromatin interactions using endogenous NKX2-5 (ex. [Van den Boogaard et al., 2012](#)).

Transparency: author response

1-1 Author response



1) *The results are based on the Dam-ID approach to discover transcription factor binding sites. It is essential to compare the findings with available published ChIP-Seq data. The authors compared their DamID peaks with NKX2-5 ChIP-Seq from HL-1 cells (He et al., 2011) mentioning 77.8% overlap but commenting that genes associated with ChIP-Seq peaks overwhelmed DamID targets, making comparison difficult. However, since a high quality ChIP-Seq dataset provides genome-wide TF occupancy information with higher resolution, the authors should show the percentage of ChIP-Seq peaks that are overlaid for the DamID data. This will serve as a validation.*

We agree that this is an important issue. In response to the reviewer's request, we calculated the overlap of NKX2-5 DamID peaks (this study) and ChIP-seq peaks (He et al., 2011), both data sets generated in HL-1 cells. A proportional Venn diagram is now included in a new figure (Figure 1-figure supplement 9). We also included in this figure a comparison of NKX2-5 ChIP-seq peaks generated from total adult hearts by van den Boogaard and colleagues (van den Boogaard et al., 2012), as requested below (point 3). Figure legends and the Materials and methods section have been adjusted accordingly. Since our DamID peaks were detected on Affymetrix promoter microarrays (average -6kb to +2.5kb relative to TSS), we limited the comparison to genomic regions covered by the microarray.

The overlap between our DamID data and the ChIP-seq data of He et al. data, both generated in HL-1 cells, was relatively low (18% of DamID peaks and 6.8% of ChIP-seq peaks). Importantly, the overlap between the He et al. peaks and those of van den Boogaard peaks, both established using ChIP-seq, was similarly low (15.6% of the van en Boogaard et al. peaks and 7.6% of the He et al. peaks).

We note the following observations that relate to these specific comparisons of NKX2-5 targets:

A) Previous studies comparing DamID and ChIP-chip experiments performed in *Drosophila* reported "a high degree of overlap" (Negre et al., 2006, Moorman et al., 2006, Tolhuis et al., 2006, van Bemmelen et al., 2010, Yin et al., 2011). Although we did not compare DamID with ChIP-chip directly, 10/11 DamID targets were confirmed using ChIP-PCR.

B) Contrary to the understanding of one of the reviewers (point 3 and response below), in DamID experiments extremely low, undetectable, levels of NKX2-5 were expressed from the uninduced heat shock protein68 promoter (*hsp68*). The He et al. data was generated from stable HL-1 cell lines over-expressing *bio*-tagged NKX2-5 protein (4-5x based on RNA detection). As highlighted by the editor, overexpression may lead to a larger number of apparent target peaks and we note that in the He et al. study, >20,000 peaks were detected.

C) We performed DamID using 3-4 biological replicates for each experiment. It is known that ChIP-seq experiments can be noisy (Yang et al., 2014); therefore replication is an essential design element for ChIP-seq experiments. The ChIP-seq experiments of He et al. and van den Boogaard et al. were performed with no biological or technical replicates.

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REVIEWS

Total: 102

TOP REVIEWERS



Jacques Fellay

ENDORSED BY



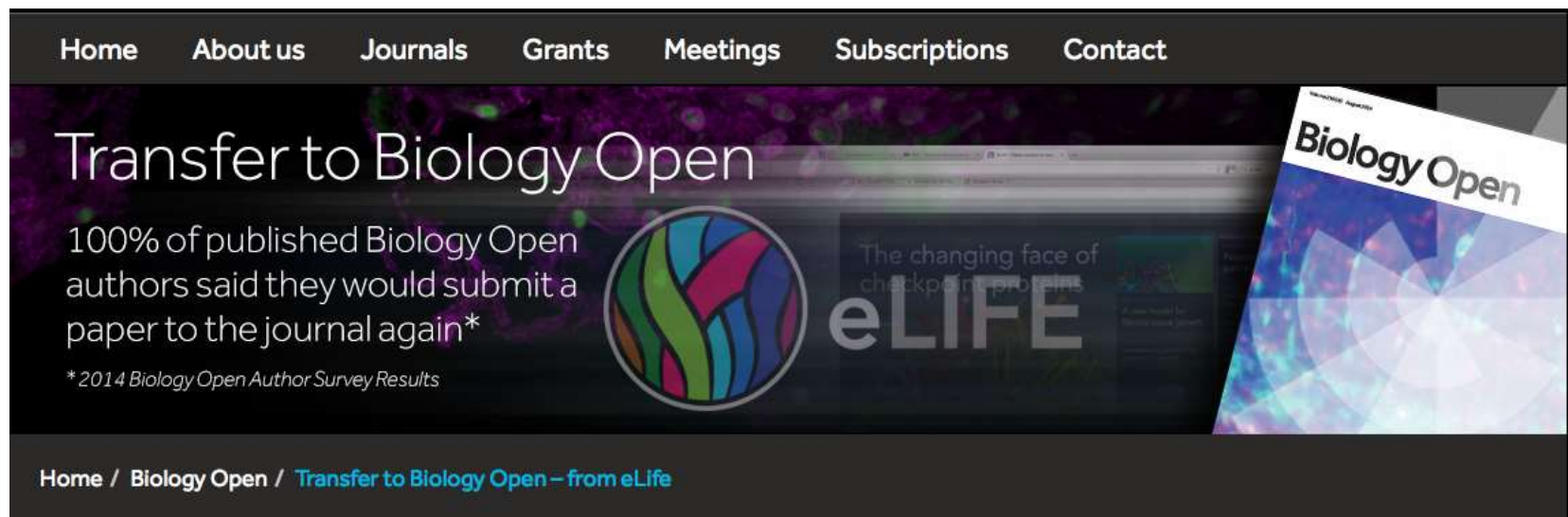
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The changing face of checkpoint proteins

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REPRODUCIBILITY PROJECT Cancer Biology

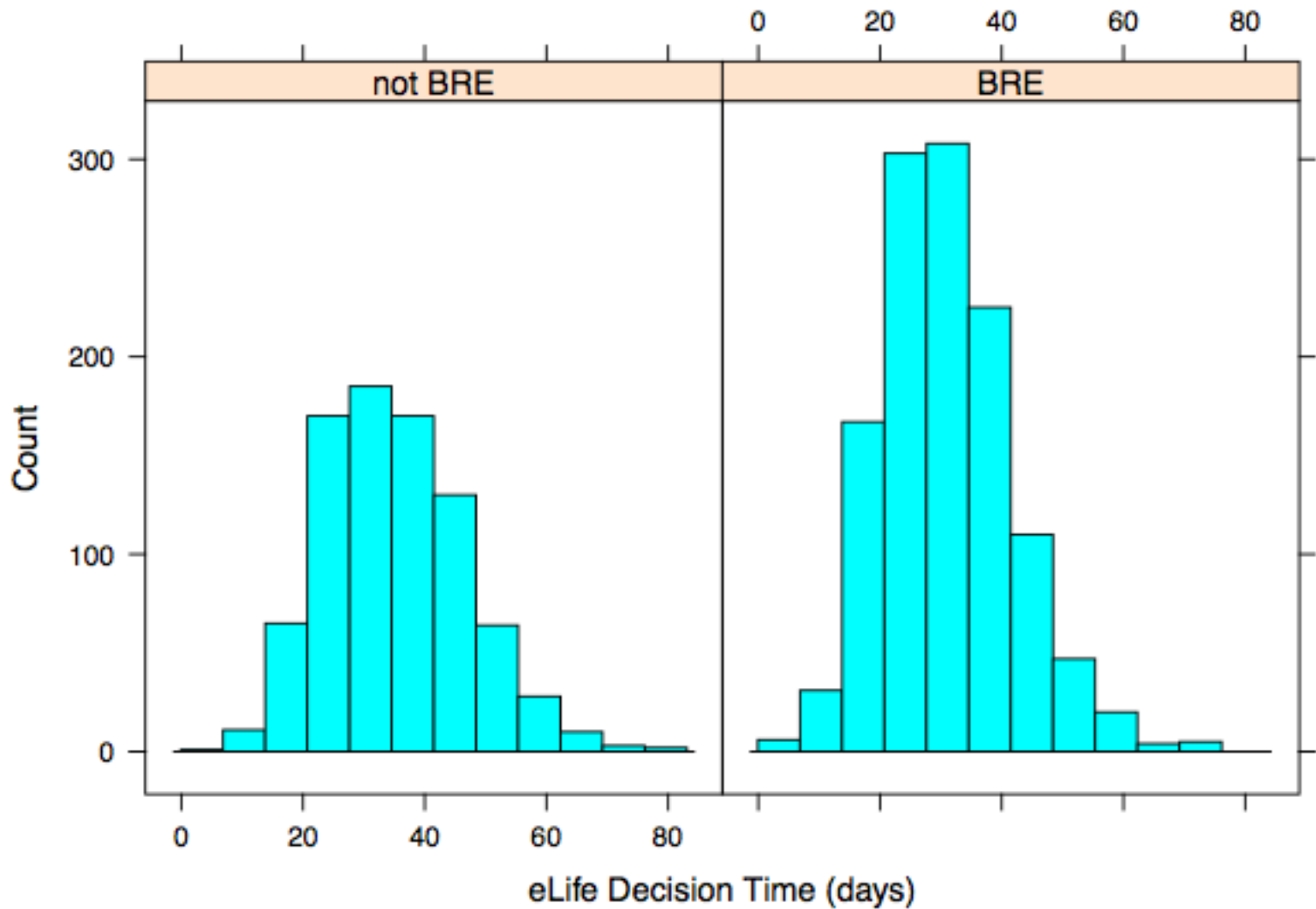
Details of the Reproducibility Project: Cancer Biology

The Reproducibility Project: Cancer Biology is a collaboration between the Center for Open Science (a non-profit foundation dedicated to promoting openness, integrity, and reproducibility in scientific research) and the Science Exchange (a network of laboratories that performs assays on a fee-for-service basis, often in core facilities at academic institutions or in contract research organizations).

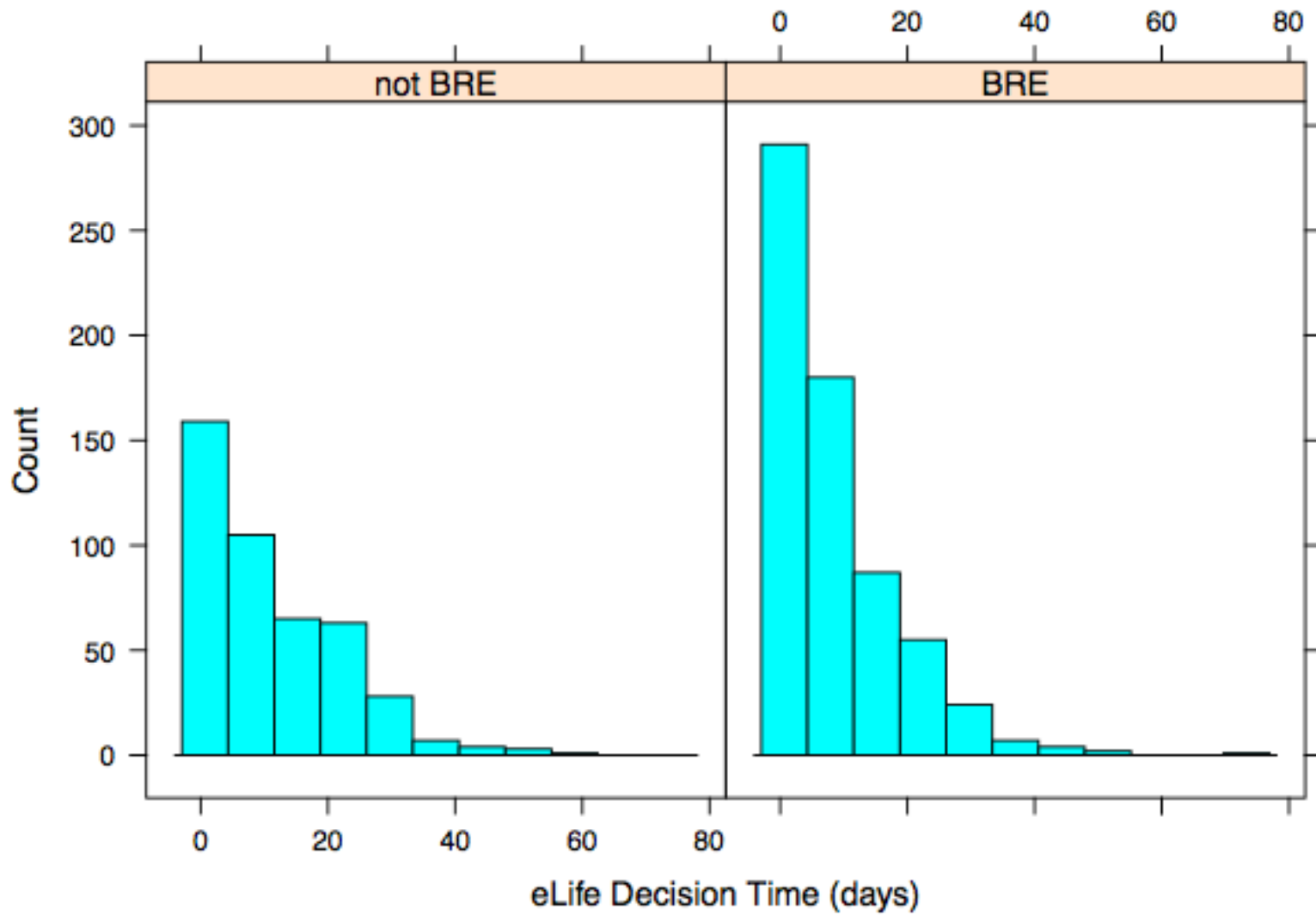
The Reproducibility Project is using a Registered Report/Replication Study approach to publish its work and results. The team replicating the study first submits a Registered Report that explains how it intends to replicate selected experiments from the original paper. The corresponding author of the original paper is contacted to suggest potential referees, to identify referees who should be excluded and, if they wish, to submit a review of the Registered Report.

Each Registered Report will be peer reviewed by several experts, including a statistician. Once the reviews have been received, a Reviewing Editor oversees a consultation between the referees and a decision letter listing essential revisions is sent to the authors of the report. The author of the original paper is not involved in the consultation process, but the Reviewing Editor can decide to consult him/her on specific points.

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Credit: Federico Vaggi



Credit: Federico Vaggi

Future possibilities

- Can we be more transparent?
- More Registered Reports?
- More consultation?
- Integration with pre-print servers to allow authors to submit for review?